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Original Research

Proton Pump Inhibitor Therapy in Metabolic Syndrome and Gastroesophageal Reflux Disease: Expert Opinion and the Role of Rabeprazole

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ABSTRACT

Aim: To analyse the efficacy of proton pump inhibitors (PPIs) in patients with metabolic syndrome (MetS) and provide guidance on selecting the most appropriate PPI to minimise drug interactions.

Background: Gastroesophageal reflux disease (GERD) and MetS share a common pathophysiological framework, with MetS increasing the risk of GERD. PPIs are critical for managing GERD, gastritis and peptic ulcers, especially in patients receiving anti-coagulants or anti-diabetics or in those with coronary heart disease. However, PPIs can inhibit hepatic cytochrome P450 (CYP450) enzymes, potentially leading to significant drug interactions. Thus, selecting PPIs with minimal CYP450 interactions is essential.

Results: This survey highlights the consensus among physicians regarding Rabeprazole's efficacy and suitability as the preferred PPI for patients with MetS.

Discussion: Rabeprazole, which minimally inhibits CYP450 enzymes, is effective in gastro protection and may be beneficial in improving glycaemic control in patients with diabetes, reducing blood pressure in individuals with hypertension and achieving positive outcomes in patients with cardiovascular disease, all while maintaining favourable safety profile. Due to its lack of CYP2C19 inhibition or induction, Rabeprazole may not interact with drugs such as Theophylline, Phenytoin, Warfarin or Diazepam. Additionally, it may reduce the risk of major adverse cardiovascular events when used in conjunction with Clopidogrel.

Clinical Significance: GERD and MetS are linked to each other. A PPI with minimal drug–drug interactions and pleiotropic benefits can be effective for GERD. Rabeprazole, due to its certain pleiotropic benefits and minimal drug–drug interaction can be recommended as the preferred PPI for managing GERD in patients with MetS.

Keywords: Cytochrome P450 enzymes, Diabetes, Dual antiplatelet therapy, Gastrointestinal bleeding, Hypertension, Metabolic syndrome, Proton pump inhibitors, Rabeprazole

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INTRODUCTION

Gastroesophageal reflux disease (GERD), which involves the reflux of gastric contents into the oesophagus,[1] is characterised by heartburn, regurgitation and chest pain. The prevalence of GERD has been reported to be increasing in recent years, affecting around 13% of people globally and ~15% of Indians.[1-3]

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Metabolic syndrome (MetS) encompasses a group of common metabolic disorders, including obesity, dyslipidaemia, elevated blood glucose levels and high blood pressure. MetS is also a high-risk factor for cardiovascular and other atherosclerotic diseases.[4] Indian Council of Medical Research–India Diabetes suggests that the prevalence of metabolic non-communicable diseases in India is considerably higher than previously estimated.[5] MetS including abdominal obesity, hypertriglyceridemia, hyperglycaemia and hypertension are also considered to berisk factors for GERD.[3]

Proton pump inhibitors (PPIs) play a key role in treating GERD. PPIs are frequently used to prevent GERD, gastritis and peptic ulcers caused by corticosteroids, anti-coagulants, anti-diabetics, chemotherapy and coronary heart disease.[6,7] In addition, PPIs are reported to improve

glycaemic control in patients with diabetes and lower blood pressure in patients with hypertension.[6,8]

PPIs are also prescribed with anti-thrombotic agents to reduce gastrointestinal (GI) bleeding risk.[9] However, several PPIs can inhibit hepatic cytochrome P450 (CYP450) enzymes, leading to potentially significant drug interactions.[10] Thus, it is crucial to choose PPIs with minimal CYP450 interaction and a favourable drug interaction profile.

This manuscript critically examines the evidence on the efficacy of PPIs in patients with metabolic disorders including diabetes, hypertension and coronary artery disease (CAD). Moreover, it offers guidance on choosing the best PPI considering polypharmacy in patients with metabolic disorders. It underscores the need for consensus among clinicians on prescribing PPIs with a positive impact on metabolic disorders and having minimal CYP450 inhibition to mitigate drug interactions.

Forty-seven experts from across India participated in the survey. Following this survey, expert opinions were recorded. Then, the insights gathered were compiled to finalise the expert opinions, which all participating experts unanimously endorsed.

RESULTS

The survey indicated unanimous agreement among experts on the connection between metabolic disorders and GERD, with patients experiencing MetS frequently suffering from GERD (Box-1). Experts concurred that Rabeprazole can be a preferred PPI for patients receiving anti-hypertensive medications, those with diabetes (Figure1) and individuals with cardiovascular disease (CVD). Experts agree that it is important to consider CYP450 enzymes in drug prescriptions(Box-2). Rabeprazole is comparatively safe for use in conjunction with drugs such as statins (which share CYP450 enzyme pathways) (Box-3), dual anti-platelet therapy (including Clopidogrel and Aspirin) (Figure2) and other medications for MetS. In addition to alleviating GI symptoms, experts believe that Rabeprazole may provide several additional benefits, as follows: help lower blood pressure in patients receiving anti-hypertensive drugs, improve glycaemic control when used with Metformin and enhance cardiovascular outcomes by improving adherence to anti-platelet therapy.

SURVEY QUESTIONS AND EXPERT OPINION:

1. In your opinion, what symptoms might link metabolic disorders and GERD?

The majority of the experts (~85.1%) opined that there are multiple symptoms, as mentioned in Box-1, which might link metabolic disorders and GERD. The literature also suggests that GERD andMetS share similar risk factors (abdominal obesity, hypertriglyceridemia, hyperglycaemia and hypertension) and common pathogenesis.

2. Rabeprazole is effective in patients with GERD taking anti-hypertensive drugs. Which of the following statements do you believe best supports the efficacy of Rabeprazole in this context?

A majority of the experts (~72.3%)believed that following statements best supports the efficacy of rabeprazole in patients with GERD taking anti-hypertensive drugs

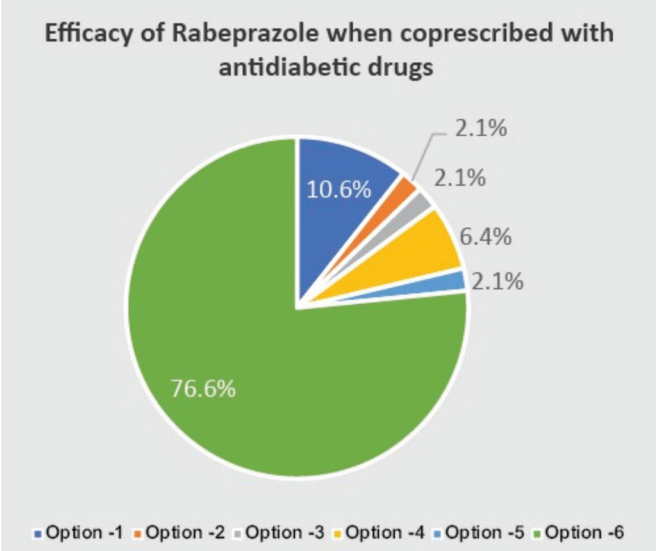

Figure 1: Rabeprazole when co-prescribed with anti-diabetic drugs.

Option 1: Rabeprazole shows the least effect on glucose disposition when used with sulfonylureas such as Glibenclamide and Glipizide, meglitinides and thiazolidinediones.

Option 2: Hyperglycaemia is one of the manifestations of insulin resistance, which may cause lower oesophageal sphincter dysfunction, leading to increased acid exposure of the oesophageal mucosa.

Option 3: Patients with diabetes are often accompanied by autonomic nerve damage, which may cause vagus nerve dysfunction, leading to lower oesophageal sphincter dysfunction followed by the appearance of gastroesophageal reflux disease.

Option 4: The percentage change in glucose levels, as indicated by % area under the curve and $\%C_{max}$, was found to be lower with Rabeprazole co-administration than with Pantoprazole co-administration with Metformin.

Option 5: The percentage change in the area under the curve for glucose concentration versus time for Metformin plus Rabeprazole was significantly lower than that for Metformin plus Pantoprazole.

Option 6: All of the above.

BOX-1

- The diagnostic criteria of both conditions include obesity, dyslipidemia, abnormal blood glucose and abnormal blood pressure.
- Abdominal obesity can elevate intra-abdominal pressure, leading to GERD via increased gastric emptying obstruction, lower oesophageal sphincter(LES) relaxation and reflux frequency.
- Adipose tissue accumulation triggers increased secretion of inflammatory factors like IL-1, IL-6 and TNFα, potentially chronically stimulating the oesophageal mucosa.
- Hyperglycaemia is one of the manifestations of insulin resistance, which may cause LES dysfunction, leading to increased acid exposure of the oesophageal mucosa.Bs) used to treat hypertension or high blood pressure are considered to be
- Calcium channel blockers (CCthe cause of the increased risk of GERD.

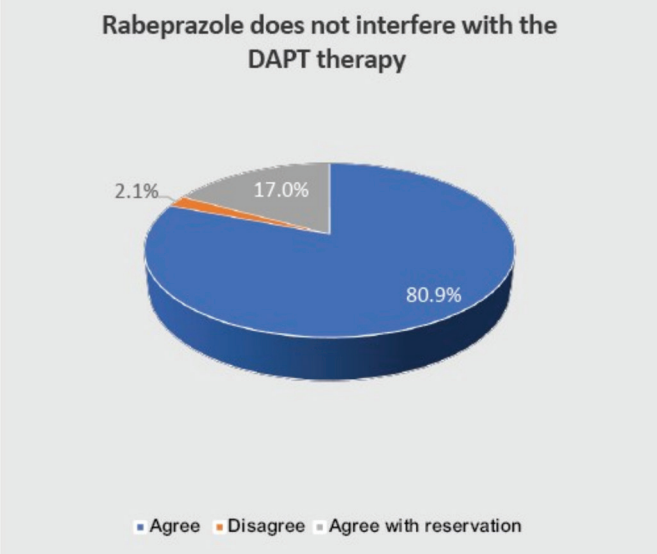

Figure 2: Rabeprazole does not interfere with the dual anti-platelet therapy.

- CCBs particularly nifedipine, increase the risk of GERD by significantly reducing the tone of the LES, increasing esophageal exposure to gastric acid and reducing the amplitude and duration of esophageal peristalsis.
- Antiacid drug therapy with Rabeprazole could reduce systolic and diastolic BP of patients with both GERD and hypertension.
- The mean ratios of 24-hour 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.

3. Clinical evidence suggests that Rabeprazole is effective when prescribed with glycaemic control drugs. Which of the following statements do you believe best supports the efficacy of Rabeprazole in this context?

A majority of the experts (76.6%) opined that increased glucose levels in patients with diabetes may cause vagus nerve dysfunction, leading to LES dysfunction, followed by the appearance of GERD. These experts agreed that the percentage change in glucose levels (indicated by % area under the curve [AUC] and % Metformin maximum concentration [C_{max}]) and percentage change in the AUC for glucose concentration vs. time were lower with Rabeprazole co-administration with Metformin compared to those with Pantoprazole co-administration with Metformin.They also agreed that Rabeprazole may demonstrate the least effect on glucose disposition when used with sulfonylureas such as Glibenclamide and Glipizide, Meglitinides and Thiazolidinediones (Figure 1).

4. Clinical evidence suggests that Rabeprazole is safe in patients co-prescribed with drugs sharing CYP450 enzymes. Which of the following statements do you believe best supports the safety of Rabeprazole in this context?

A majority (68.0%) of the experts believed that all the below-mentioned pharmacological and pharmacokinetic properties of Rabeprazole make it a safe PPI to be co-prescribed with drugs sharing CYP450 enzymes:

1. Minimal or no drug interactions owing to CYP2C19 enzyme inhibition or induction.
2. May not interact with drug interactions with drugs such as Theophylline, Phenytoin, Warfarin, Tacrolimus, Diazepam or Antacids.
3. May not have systemic effects on the central nervous, lymphoid, hematopoietic, renal, hepatic, cardiovascular or respiratory systems in humans treated for up to 1-year.
4. Minimal or no significant accumulation of the drug after repeated administration, and there may be no dosage adjustment needed in patients with renal failure.

About 17% of the rest of the experts believe that Rabeprazole may show no drug interactions owing to CYP2C19 enzyme inhibition or induction, making it a comparatively safe drug to be co-administered with drugs sharing CYP450 enzymes.

5. Information on the CYP450 inhibitory or inducing potential of the drug needs to be on every drug approved by the Food and Drug Administration since 1997. In your clinical experience, what is the importance of considering CYP450 enzymes in drug prescription?

BOX-2

- Inter-individual variability in drug response is a major problem in clinical practice.
- About 60%–80% of commercialised drugs are metabolized by polymorphic enzymes. The occurrence of adverse drug reactions as well as therapeutic failure may therefore be attributed to genetic variations in the drug-metabolizing enzymes.
- The role of CYP in drug metabolism has gained renewed interest in precision medicine and pharmacogenetic testing because one in every five Asian is a poor metabolizer of drugs dependent on the enzyme.
- Knowledge of this aspect can help with substitution of the drug or adjustment of the dosage required in any individual.
- Co-prescription of drugs sharing CYP450 enzymes can have effect on the pharmacokinetics of drugs with a narrow therapeutic index and can lead to significant toxicity and even death.

According to clinical experience, a majority of the experts (78.7%) agreed that all the points mentioned in Box-2 are the reasons for considering CYP450 enzymes in drug prescription. The literature also supports that all the pointers mentioned in Box-2warrant considering CYP450 enzymes in drug prescription.

6. Clinical evidence suggests that Rabeprazole is effective when prescribed with statins in cardiac patients. Which of the following statements do you believe best supports the efficacy of Rabeprazole in this context?

As evidenced from the literature, all the panellists agree that Rabeprazole is effective when prescribed with statins in cardiac

patients. The majority of the panellists (74.5%) believe that statins are metabolized by the CYP450 enzymes, and Rabeprazole shows minimal or no drug interactions owing to CYP2C19 enzyme inhibition or induction. They also believe that Rabeprazole may not reduce the efficacy of Clopidogrel during the co-prescription of statins, may not accumulate on repeated administration and requires no dose adjustments in patients with renal failure (Box-3). These properties make it a suitable PPI in cardiac patients receiving statin therapy.

BOX-3

- Like PPIs, statins are metabolized by the CYP450 enzymes.
- Rabeprazole shows minimal or no drug interactions owing to CYP2C19 enzyme inhibition or induction.
- Rabeprazole did not reduce the efficacy of Clopidogrel during the co-prescription of statins and Clopidogrel in the cardiac patient.
- PPIs other than Rabeprazole are inhibitors of CYP450 enzymes causing skeletal muscle or liver toxicity by increasing the plasma concentrations of statins.
- There is no significant accumulation of the drug after repeated administration, and no dosage adjustment is needed in patients with renal failure.

7. Clinical evidence suggests that Rabeprazole is safe in patients with CVD receiving anti-platelet therapy. Which of the following statements do you believe best supports the safety of Rabeprazole in this context?

The survey revealed that the majority of the experts (70%) believe that all the below-mentioned statements best support the safety of Rabeprazole in patients with CVD receiving anti-platelet therapy**:**

- There is a low risk of major adverse cardiovascular events (MACEs) with Rabeprazole in patients receiving the clopidogrel–PPI combination.
- Rabeprazole may not be associated with drug interactions with drugs like Theophylline, Phenytoin, Warfarin or Diazepam.
- Rabeprazole may not affect the efficacy of Clopidogrel in a patient with reduced CYP2C19 function and is as potent as Omeprazole.
- Delayed cardiac tamponade and haemothorax emerged as complications in the Lansoprazole group in a study, whereas there were no such reports of delayed bleeding in the Rabeprazole group.

8. Please indicate your level of agreement with the following statement: Rabeprazole does not interfere with the DAPT therapy (Clopidogrel and Aspirin) and can be considered more efficacious than other PPIs.

All the experts, except one, agree (80.9%) or agree with the reservation (17%) that Rabeprazolemay not interfere with the DAPT therapy (Clopidogrel and Aspirin) and can be considered an efficacious option vs. other PPIs. Literature also supports that compared to other PPIs, Rabeprazolemay not interfere with DAPT therapy (Figure 2).

9. Which of the following do you think can be true for the co-prescription of Rabeprazole with other MetSdrugs?

The majority of the experts (~66.0%) agree that all the below-mentioned statements are true for co-prescription of Rabeprazole with other MetSdrugs:

- Rabeprazole, in addition to reducing GI complications, may improve cardiovascular outcomes by optimising compliance with anti-platelet therapy.
- In patients with atherosclerotic CVD, combination therapy with statins and other cardiovascular medications is highly prone to drug–drug interactions. This risk may be alleviated using Rabeprazole.
- Rabeprazole may inhibit acid secretion, regardless of CYP2C19 genotypes, and it reduces the incidence of aspirin-related mucosal injury.
- Antacid drug therapy with Rabeprazole could reduce the systolic and diastolic blood pressure of patients with both GERD and hypertension.

DISCUSSION

Link between MetS and GERD

GERD and MetS are considered to share the same pathogenesis. Both share common risk factors, including abdominal obesity, hypertriglyceridemia, hyperglycaemia and hypertension. Abdominal obesity raises intra-abdominal pressure, which can obstruct gastric emptying and increase LES relaxation, and frequency of reflux, leading to GERD. Additionally, excess adipose tissue boosts inflammatory factors such asIL-1, IL-6 and TNFα, potentially contributing to chronic oesophageal mucosa irritation. Hyperglycaemia, a sign of insulin resistance, can impair LES function, resulting in greater acid exposure to the oesophageal lining. Hypertension, frequently seen in MetS, is often managed with CCBs. However, these medications can relax the LES, potentially disrupting the anti-reflux mechanism and increasing the risk of GERD.[3]

Link between Diabetes and GERD

Diabetes can lead to autonomic nerve damage, including vagus nerve dysfunction, which may impair the LES and result in reflux.[3] GERD in patients with diabetesis also linked to inadequate glycaemic control and related complications, with a higher prevalence among patients treated with oral hypoglycemics.[11] Therefore, co-administration of PPIs with oral anti-diabetic drugs is necessary to treat GERD and control blood glucose levels effectively. However, the other concern remains that PPIs can impact the GI absorption of oral anti-diabetic drugs by changing stomach pH and inhibiting transporters involved in their disposition.[12]

Link between Cardiac and GI Disorders

GERD should be recognised not merely as benign comorbidity butalsoas a potential risk factor for the onset and progression of CVD.[13] Commonly used anti-hypertensive drugs, i.e., CCBs, especially

Nifedipine, can increase the risk of GERD by significantly lowering the LES tone. This results in greater exposure of the oesophagus to gastric acid and a reduction in both the amplitude and duration of oesophageal contractions.[14] Inadequate diagnosis and management of GERD, an often underestimated condition, may exacerbate the severity of CVD and its impact.[13]

Recent studies have identified GERD and its treatments as potential risk factors for CVD.[6] In patients with CAD undergoing percutaneous coronary intervention, anti-thrombotic therapy is essential for preventing stent thrombosis and recurrent cardiovascular events, but it is associated with a high risk of GI bleeding. This increased bleeding risk can elevate the likelihood of cardiovascular events, mortality and prolonged hospital stays.[9]

Link betweenCYP450 and Co-administration of Drugs

CYP450 enzymes are crucial for metabolising up to 90% of medications. Polymorphism of these enzymes is responsible for inter-individual variability in drug response. Drugs either inhibit or induce CYP450 enzymes, leading to significant drug–drug interactions, resulting inside effects or treatment failures. Physicians should be cautious when prescribing drugs known to affect CYP450 activity as this may necessitate dose adjustments or substitution of the medication. Poor metabolisers (one in five Asians) or those receiving CYP450 inhibitors may experience adverse effects from standard doses due to increased drug levels, especially if the drug has a narrow therapeutic range or relies on a single enzyme for metabolism.[15]

Rabeprazole: An Efficacious PPI in the Management of Metabolic Disorders

Rabeprazole and Anti-diabetic Drug

A study by Kim *et al.*,[12] demonstrated that the percentage change in glucose levels, as indicated by %AUC and $\%C_{max}$, was lower when Rabeprazolewas co-administered with Metformin compared to when Pantoprazole was co-administered with Metformin. The percentage change in the AUC for glucose concentration versus time for Metformin + Rabeprazolewas significantly lower than that for Metformin + Pantoprazole.[12] Also, the 24-hour pH >4 holding time was significantly longer with Rabeprazolevs. Other PPIs, resulting in superior inhibition of gastric acid.[16] In addition, Rabeprazoledoes not show significant accumulation after repeated administration, and no dosage adjustment is needed in patients with renal failure.[17,18]

Rabeprazole and Hypertension

In a study, researchers observed that concurrent PPI therapy in patients with hypertension may decrease the systolic and diastolic blood pressure of patients with both GERD and essential hypertension.[8] The potential mechanisms by which PPI therapy may lower BP are unknown. However, experimental data suggest that PPIs exert a vasorelaxant effect, which may help lower blood pressure in patients with hypertension.[19]

Rabeprazole and the CYP450 Metabolic Pathways

Rabeprazole with statin and/or anti-platelet drugs

Several PPIs, statins and anti-platelet agents are metabolised by CYP450 enzymes, especially CYP2C19 and CYP3A4, raising the risk of drug interactions. Clopidogrel, activated by CYP2C19, can have its effectiveness reduced by PPIs that inhibit this enzyme, increasing cardiovascular risk. Although PPIs are used to prevent GI bleeding during DAPT, selecting a PPI with minimal interaction with Clopidogrel is crucial.[9,20]

All PPIs, except Rabeprazole, are extensively metabolised by and competitively inhibit CYP2C19 and CYP3A4 enzymes. Rabeprazole undergoes extensive hepatic metabolism, primarily through non-enzymatic reduction to thioether, with a lesser contribution from CYP2C19 and CYP3A4.[9,21] Consequently, Rabeprazole may be less likely to be influenced by CYP2C19 genetic variations or other drug interactions compared to other PPIs.[9] Rabeprazole is less likely to interact with Clopidogrel or statin or be affected by CYP2C19 variations compared to other PPIs such as Omeprazole and Lansoprazole, which are stronger enzyme inhibitors.[9,21]

Kenngott *et al.*[22] conducted a study, to assess the impact of co-administering 20 mg of Omeprazole or 10 mg of Rabeprazole with 75 mg of Clopidogrel on the inhibition of platelet aggregation induced by Clopidogrel. The results indicated that co-administration of Omeprazole, whether taken concurrently or separately, attenuated the anti-platelet effect of Clopidogrel. In contrast, simultaneous administration of Rabeprazole did not diminish the anti-platelet efficacy of Clopidogrel.[22]

Literature also suggests that in addition to mitigating GI complications, Rabeprazole may be an optimal treatment for patients with CVD.[10]

Rabeprazole with Clopidogrel or DAPT therapy may be a safe PPI with no major increase in the risk of MACEs vs. other PPIs.[9,23] A 2021 meta-analysis, which included six randomised controlled trials with 6,930 patients and 16 observational studies with 183,546 patients, showed that PPIs significantly reduced the risk of GIbleeding, and Rabeprazole was not associated with MACE.[24] This suggests that Rabeprazole may not compromise the anti-platelet efficacy of Clopidogrel and may be a safer PPI option compared to other PPIs.

Evidence also reports delayed cardiac tamponade and haemothorax occurrence with co-administration of Lansoprazole and Warfarin. However, no such complications are reported in patients taking Rabeprazole concomitantly with Warfarin.[25]

Moreover, PPIs other than Rabeprazole are inhibitors of CYP450 enzymes causing skeletal muscle or liver toxicity by increasing the plasma concentrations of statins.[26]

Sugimoto *et al.*[9] found that Rabeprazole effectively inhibits acid secretion, irrespective of CYP2C19 genotype variations, and significantly decreases the incidence of mucosal injury associated with Aspirin use.

Rabeprazole with other drugs

Minimal or no drug–drug interaction is reported between Rabeprazole and drugs like Theophylline, Phenytoin, Warfarin, Tacrolimus, Diazepam or Antacids.[27]

Rabeprazole and organ system

Rabeprazole may not have systemic effects on the central nervous, lymphoid, hematopoietic, renal, hepatic, cardiovascular or respiratory systems in humans treated for up to 1-year.[28]

CONCLUSION

In managing patients with MetS and associated GERD, PPIs with minimal CYP450 enzyme interaction, with some pleiotropic benefits and a minimal or no drug interaction profile, such as Rabeprazole, can be preferred. Unsupervised long-term use of PPIs outside prescribed dosages should be avoided, and drug–drug interaction should be considered for optimal outcomes.

Clinical Significance

A PPI with minimal drug–drug interactions along with some pleiotropic benefits is advisable, particularly for patients with metabolic disorders. Rabeprazole can be a suitable choice in such cases due to its effective acid suppression, minimal interaction with other drugs and some pleiotropic benefits.

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