INDIAN SOCIETY OF HYPERTENSION

HYPERTENSION JOURNAL
www.hypertensionj.com

Original Research

# Optimising Proton Pump Inhibitor Therapy in Cardiovascular Polypharmacy: Expert Opinion and the Role of Rabeprazole

Krishnakumar P[1], Sankar Chandra Mondal[2], Hema Rath[3], Kamaldeep Chawla[4*]

[1]Medical College Hospital, Kerala, India
[2]Institute of Post Graduate Medical Education & Research, Kolkata, WB, India
[3]Woodland's Hospital, Kolkata, WB, India
[4]Ayushman heart and wellness, Vadodara, Gujarat, India

## ABSTRACT

**Aim:** To analyse the cardiovascular risks related to proton pump inhibitors (PPIs) in patients with coronary artery disease (CAD) and provide assistanceinchoosing the most suitable PPI to minimise drug interactions.

**Background:** Globally, cardiovascular disease (CVD) is a leading cause of morbidity and mortality, with marked prevalence in India. Anti-thrombotic therapy, including anti-platelet drugs and oral anti-coagulants, is standard for patients with CVD but is linked to a risk of gastrointestinal (GI) bleeding. Identifying high-risk patients and employing gastroprotective agents are critical in mitigating this risk. PPIsare commonly used for gastro protection along with anti-thrombotic therapy, particularly in patients undergoing dual anti-platelet therapy (DAPT) during acute coronary syndrome (ACS) and having a history of GI issues. However, PPIs can inhibit hepatic cytochrome P450 (CYP450) enzymes, potentially causing significant drug interactions. Therefore, selecting PPIs with minimal CYP450 interaction and monitoring patient compliance are essential for optimising therapy and reducing adverse interactions.

**Review Results:** This survey highlights the consensus among physicians regarding Rabeprazole's safety, efficacy and suitability as the preferred PPI for patients with CVD undergoing anti-platelet therapy.

**Discussion:**This manuscript evaluates the cardiovascular risks associated with PPIs in patients with CAD and guides in choosing the most appropriate PPI, emphasising the importance of choosing agents with minimal CYP450 suppression to lower the risk of adverse interactions.

**Clinical Significance:** A PPI with limited drug–drug interactions is advisable, particularly for patients receiving Clopidogrel or multiple medications. Rabeprazole is a suitable choice in such cases due to its effective acid suppression and limited interaction with other medications.

**KEYWORDS:** Cardiovascular disease, proton pump inhibitors, dual anti-platelet therapy, cytochrome P450 enzymes.

**doi:** 10.61081/htnj/24v10i403

## INTRODUCTION

Globally, cardiovascular disease (CVD) is a major contributor to morbidity and mortality, with the World Health Organisation estimating nearly 18 million deaths in 2019.[1] India, which accounts for one-fifth of these deaths, has seen a dramatic rise in CVD prevalence, rising from 25.7 million in 1990 to 54.5 million in 2016, with urban prevalence increasing from 2.0% in 1960 to approximately 14.0% by 2013 and rural prevalence increasing from 1.7% in 1970 to 7.4% in 2013.[2]

Anti-thrombotic therapy with anti-platelet drugs and oral anti-coagulants is thecornertsone of treatment for patients with CVD, but is linked to a risk of gastrointestinal (GI) bleeding.[2,3]Identifying patients at high risk of GI bleeding, using gastroprotective agents to manage bleeding risk and selecting the appropriate anti-thrombotic therapy are essential for preventing bleeding.[4]

Proton pump inhibitors (PPIs) are administered with anti-thrombotic agents to lower GI bleeding risk. Guidelines and consensus documents recommend PPIs for patients receivingdual anti-platelet therapy (DAPT) during acute coronary syndrome (ACS), especially those with a history of GI bleeding or peptic ulcer.[5]However, PPIs can inhibit hepatic cytochrome P450 (CYP450) enzymes, leading to potentially significant drug interactions. Thus, it is crucial to choose PPIs with minimal CYP450 interaction and a favourable drug interaction profile while also implementing regular monitoring to enhance patient compliance.[2]

This manuscript critically examines the evidence on cardiovascular risks of PPIs in patients with coronary artery disease (CAD) and

**Corresponding author**
Dr. Kamaldeep Chawla, Ayushman heart and wellness, Vadodara, Gujarat, India.
**Email:** kychawla@rediffmail.com

offers assistancein choosing the best PPI considering cardiovascular polypharmacy. It also underscores the need for consensus among clinicians on prescribing PPIs with minimal CYP450 inhibition to mitigate drug interactions.

## Interplay between Cardiac and GI Disorders

Gastroesophageal reflux disease (GERD) has been traditionally regarded as either a cause of non-cardiac chest pain or a comorbidity in patients with CVD. However, recent studies have identified GERD and its treatments as potential risk factors for CVD.[6] In patients with CAD undergoing percutaneous coronary intervention, antithrombotic therapy is essential for preventing stent thrombosis and recurrent cardiovascular events, but this therapy is related to a high risk of GI bleeding. This augmented bleeding risk can elevate the likelihood of cardiovascular events, mortality and prolonged hospital stays.[2] Research has also explored the link between GI disorders, such as GERD and inflammatory bowel diseases (IBDs), and the development of CVD and arrhythmias such as atrial fibrillation, revealing an unexpected association with the onset of CVD.[7]

## Polypharmacy Increases Risk of Drug Interactions in Patients with CVD

Patients with CVD often require multiple essential medications, which can lead to drug interactions. Although polypharmacy is sometimes necessary, it is significantly associated with the risk of side effects.[8] The most critical interactions are between Aspirin and Clopidogrel (46.8%) and between Omeprazole and Clopidogrel (32.4%). Combining a PPI with Clopidogrel can lead to serious interactions. However, PPIs are recommended to reduce GI bleeding risk after DAPT. It is important to assess the patient's risk of GI bleeding and select PPIs with minimal interaction with Clopidogrel.[9]

## PPIs and Anti-platelet Drugs: Common CYP450 Metabolic Pathways

Several PPIs and anti-platelet agents are metabolised by hepatic CYP450 enzymes, particularly CYP2C19 and CYP3A4, raising the potential for drug–drug interactions (DDIs). Clopidogrel,a prodrug, gets activated *via* CYP450 enzyme-dependent metabolism, but PPIs can inhibit CYP2C19, the enzyme crucial for converting Clopidogrel into its active form. This competitive inhibition can diminish Clopidogrel's anti-platelet effect, increasing cardiovascularrisk in patients using both medications.[2] All PPIs, with the exception of Rabeprazole, undergo significant metabolism by and competitively inhibit the activity of the CYP2C19 and CYP3A4 enzymes. Lansoprazole and Omeprazole are among the most potent inhibitors of these enzymes. In contrast, Rabeprazole has a lower inhibitory effect on these enzymes. Its hepatic metabolism is extensive, predominantly through non-enzymatic reduction to thioether, with CYP2C19 and CYP3A4 playing a minor role.[10]Consequently, Rabeprazole is less likely to be influenced by CYP2C19 genetic variations or other drug interactions compared with other PPIs (Figure 1).[2]

## Rabeprazole: A Distinctive PPI with Minimal Drug Interactions

### *Rabeprazole Shows Lesser Interactions with Clopidogrel Compared to Other PPIs*

Extensive evidence suggests that Rabeprazole—a PPI with weak inhibition of CYP2C19—has the lowest likelihood of causing clinically

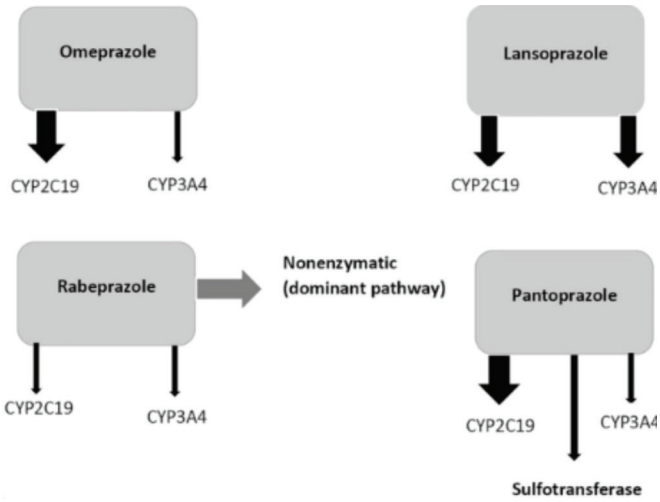


**Figure 1:** Major metabolic pathways for proton pump inhibitors and their associated cytochrome P450 enzymes. *(Adapted from Dalal J, Dutta AL, Hiremath J, et al. CardiolTher. 2023;12(4):557-570)*

[Arrow thickness represents the contribution of each isoenzyme (thick arrows designate the dominant pathway; thin arrows designate the non-dominant pathway.)]

significant drug interactions among PPIs, particularly in cardiac patients taking Clopidogrel and Aspirin. According to Sarnaik *et al.*, the strength of interaction between the drug and CYP2C19 increases in the following order: Rabeprazole, Pantoprazole, Lansoprazole, Esomeprazole and Omeprazole.[11] Additionally, a recent meta-analysis examining the risk of major adverse cardiovascular events (MACEs) in patients with CAD using Clopidogrel and PPIs foundthe risk of MACEs was negligible in the Rabeprazole group as compared to other PPIs.[2]

### *No Elevated Risk of MACE Noted with Rabeprazole in Cardiac Patients Receiving DAPT*

A study comparing 199 patients receiving DAPT alone with 103 patients receiving DAPT plus Rabeprazole found no significant increase in MACEs with Rabeprazole use. MACEs occurred in 8.7% and 6.9% of patients in the Rabeprazole and control groups, respectively. Cardiac deaths were 1.1% in the control group and 0% in the Rabeprazole-treated group. ACS was observed in 1.0% of patients in the Rabeprazole group and 0% of patients in the control group, with stent thrombosis in 1.0% and 0.5% of patients, respectively. Thus, Rabeprazole did not elevate MACE risk in these patients.[12]

### *When using a PPI in combination with Clopidogrel, Rabeprazole May Offer a Safer Profile for MACE Risk Compared to Other PPIs*

Several studies have consistently indicated an augmented risk of MACEs associated with Omeprazole, Esomeprazole, Lansoprazole, and Pantoprazole usein patients taking the Clopidogrel–PPI combination, although no such increase was observed with Rabeprazole. With Rabeprazole, the odds ratio for MACE risk was the least (1.03) compared to Pantoprazole, Lansoprazole, Esomeprazole, and Omeprazole. Additionally, a pilot randomised trial found that when Pantoprazole was used alongside Clopidogrel and Aspirin in

patients with ACS, it significantly increased adenosine diphosphate-maximal aggregation (ADP-MA).[13]

A 2021 meta-analysis, including6 randomised controlled trials (RCTs) with 6,930 patients and 16 observational studies with 1,83,546 patients, showed that PPIs substantially reduced the likelihood of gastrointestinal bleeding, with Rabeprazole showing no association with MACE.[14] This suggests that Rabeprazole does not compromise the anti-platelet efficacy of Clopidogrel and may be safer than other PPIs.

## RESULTS

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

1. **Which among the following in your opinion can be the appropriate evidence for the association between GI disorders and CVD?**

   Approximately, 75% of the doctors agreed that multiple factors highlight the relation between GI disorders and CVD (BOX-1). Around 12.5% of the doctors specifically pointed to GERD contributing to increased ischaemic events, highlighting the association between them. Additionally, three doctors highlighted two points each: 1) the correlation between augmented GI bleeding and risk of cardiovascular events;2) the elevated risk of GI bleeding caused by administering anti-thrombotic agents.

**BOX-1**

- GERD is linked to an increased occurrence of ischaemic events in patients with CVD.
- Anti-thrombotic therapy carries a high risk of GI bleeding.
- Elevated GI bleeding is associated with an augmented risk of CV events, death and an extended hospitalisation.
- Bleeding episodes after the procedure are associated with an elevated risk of in-hospital mortality.

2. **Do you think polypharmacy (prescription of two or more essential drugs) can cause significant DDIs in patients with CVD?**

   The majority of doctors (90%) believe that polypharmacy can lead to significant DDIs in patients with CVD. However, a small percentage (10%) of doctors does not share this view.

3. **Which of the following do you think can be true for PPI metabolism?**

   The majority of doctors (~77%) agree that all the statements in BOX-2 are accurate regarding PPI metabolism. However, six doctors believe that the statement, 'All PPIs, except Rabeprazole, competitively inhibit CYP2C19' is true. Additionally, three doctors supported the statement,'Over 80% of the metabolism of Lansoprazole, Omeprazole, and Pantoprazole relies on CYP2C19,' whereas two doctors also considered this statement to be true.

**BOX-2**

- All PPIs, except Rabeprazole, competitively inhibit CYP2C19.
- Over 80% of the metabolism of Lansoprazole, Omeprazole, and Pantoprazole relies on CYP2C19.
- Attenuation of the GI bleeding risk with common cardiac drugs such as Clopidogrel, Aspirin and Warfarinhas led to the recommendation of co-prescription of PPIs.
- Clopidogrel is a prodrug that is activated through CYP450 enzyme-dependent metabolism, primarily involving CYP2C19.
- Rabeprazole experiences extensive hepatic metabolism, primarily through non-enzymatic reduction to thioether, with a lesser involvement of CYP2C19.

4. **In your opinion, why Rabeprazole, a weak inhibitor of CYP2C19, is the PPI of choicein patients with CVD receiving Clopidogrel and Aspirin?**

   Most doctors (~69%) consider Rabeprazole as the PPI of choice for patients with CVD receiving Clopidogrel and Aspirin for all aspects noted in BOX-3. Some believe that Rabeprazole's primarily non-enzymatic metabolism, which minimises the impact of CYP2C19 genetic variations and medication interactions compared to other PPIs, is a key factor in their preference. A smaller group of doctors highlight Rabeprazole's remarkable ability to inhibit acid secretion, irrespective of CYP2C19 genotypes and its effectiveness in reducing Aspirin-related mucosal injury, making it their preferred PPI (Figure 2).

**BOX-3**

- Rabeprazole's metabolism is primarily non-enzymatic; making it less influenced by CYP2C19 genetic variations or drug interactions compared to other PPIs.
- Rabeprazole markedly inhibits acid secretion, irrespective of CYP2C19 genotypes, and lowers the occurence of aspirin-related mucosal injury.
- A PPI with minimal DDI is recommended, particularly for patients using Clopidogrel or those on polypharmacy.
- Rabeprazole helps avert therecurrence of peptic ulcers in patients undergoing low-dose aspirin (LDA) therapy.
- The mean ratios of the 24-hour pH ≥3 holding time were seen to be significantly longer, and the inhibition of gastric acid was superior with Rabeprazole due to its higher pKa than other PPIs.

5. **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 majority of doctors (~75%) believe that Rabeprazole's safety is supported by multiple factors (BOX-4). About 14.60%

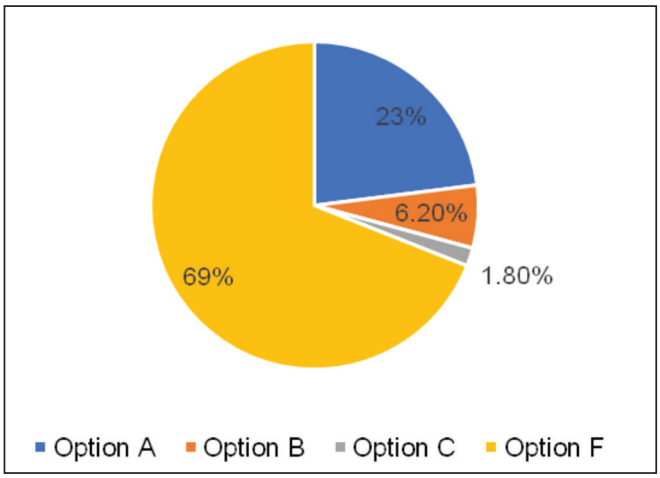


**Figure 2:** Rabeprazole is the proton pump inhibitor of choice in patients with cardiovascular disease receiving Clopidogrel and Aspirin.*

A. Rabeprazole's metabolism is primarily non-enzymatic; hence, it is less affected by cytochrome P2C19 genetic variation or medication interactions than other PPIs.
B. Rabeprazole remarkably inhibits acid secretion, regardless of cytochrome P2C19 genotypes, and reduces the incidence of Aspirin-related mucosal injury.
C. A proton pump inhibitor with minimal drug–drug interaction is recommended, especially in patients requiring Clopidogrel or polypharmacy.
D. Rabeprazole prevents the recurrence of peptic ulcers in patients on low-dose aspirin therapy.
E. The mean ratios of the 24-hour pH ≥ 3 holding time were seen to be significantly longer, and the inhibition of gastric acid was superior with Rabeprazole due to its higher pKa than other proton pump inhibitors.
F. All of the above.

**Options D and E have been excluded from the pie chart due to negligible response.*

of doctors consider the risk of MACEs to be low when using the Clopidogrel–PPI combination with Rabeprazole. A smaller group of doctors emphasise that Rabeprazole's lack of interaction with drugs such as Theophylline, Phenytoin, Warfarin or Diazepam makes it a safe option for patients with CVD receiving anti-platelet therapy (Figure 3).

**6. Clinical evidence indicates that there is no augmented risk of MACE when Rabeprazole is administered in cardiac patients undergoing DAPT (Clopidogrel and Aspirin). Which of the following statements do you believe best supports the safety of Rabeprazole in this context?**

The majority of doctors (~77%) agreed with all the statements provided in BOX-5. Some doctors specifically highlighted that Rabeprazole's primarily non-enzymatic metabolism makes it minimally affected by CYP2C19 genetic variations or medication interactions compared to other PPIs, leading to no increased risk of MACE. A small percentage of doctors chose statements emphasising that Rabeprazole does not interact with drugs like Theophylline, Phenytoin, Warfarin or Diazepam. Additionally, they noted that patients undergoing combination therapy with Clopidogrel and PPIs face an elevated risk of MACE, especially rapid metabolisers, due to increased platelet reactivity. However, this risk is evident with Omeprazole, Lansoprazole, Esomeprazole and Pantoprazole but not in the case of Rabeprazole (Figure 4).

**BOX-4**

- With Rabeprazole, there is a low risk of MACEs in patients on the clopidogrel–PPI combination.
- Rabeprazole is not associated with drug interactions with drugs such as,Theophylline, Warfarin, Phenytoin, or Diazepam.
- Rabeprazole did not affect the Clopidogrel efficacy in a patient with reduced CYP2C19 function and was 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.

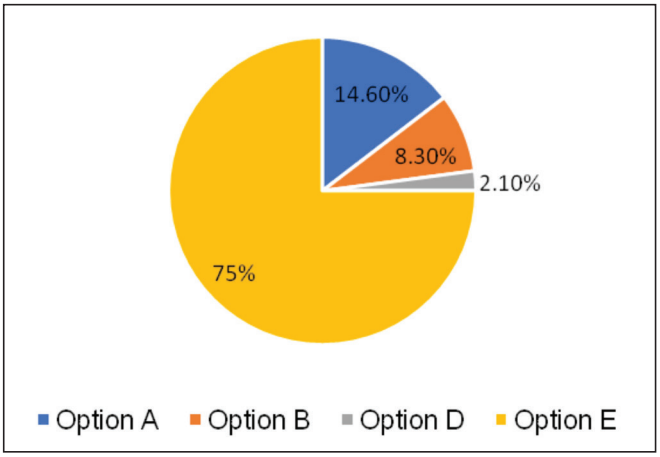


**Figure 3:** Rabeprazole is safe in patients with cardiovascular disease receiving anti-platelet therapy.*

A. There is a low risk of major adverse cardiovascular events with Rabeprazole in patients receiving the clopidogrel–proton pump inhibitor combination.
B. Rabeprazole is not associated with drug interactions with drugs like Theophylline, Phenytoin, Warfarin or Diazepam.
C. Rabeprazole (10 mg) did not affect the Clopidogrel efficacy in a patient with reduced cytochrome P2C19 function and was as potent as 20 mg Omeprazole.
D. 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.
E. All of the above.

**Option C has been excluded from the pie chart due to negligible response.*

**7. Pantoprazole increases ADP-MA in patients with ST-elevation myocardial infarction on DAPT and considerablyhinders the anti-platelet effects of Clopidogrel. Thus, it can be considered that Pantoprazole may not be a safe option for patients receiving DAPT. What do you think?**

About 52% of the doctors agreed that Pantoprazole may not be a safe option for patients receiving DAPT, whereas approximately, 39.6% agreed with some reservations. About 8.4% disagreed with the statement.

**BOX-5**

- Rabeprazole does not need any adjustments in dosage, and the lack of drug accumulation prevents the occurrence of adverse effects due to toxicity.
- Rabeprazole is not associated with drug interactions with drugs such asTheophylline, Phenytoin, Warfarin or Diazepam.
- Rabeprazole's metabolism is primarily non-enzymatic; hence, it is minimally affected by CYP2C19 genetic variation or medication interactions compared to other PPIs.
- Patients undergoing combination therapy with Clopidogrel and PPIs face an elevated risk of MACEs, particularly rapid metabolisers, due to increased platelet reactivity levels. This risk is evident with Omeprazole, Lansoprazole, Esomeprazoleand Pantoprazole, but not in the case of Rabeprazole.

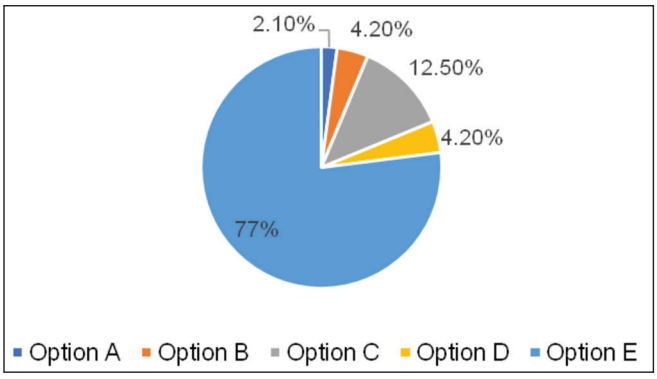


**Figure 4:** Safety of Rabeprazole in patients receiving dual anti-platelet therapy.

A. Rabeprazole does not need any adjustments in dosage, and the lack of drug accumulation prevents the occurrence of adverse effects due to toxicity.
B. Rabeprazole is not associated with drug interactions with drugs such as Theophylline, Phenytoin, Warfarin or Diazepam.
C. Rabeprazole's metabolism is primarily non-enzymatic; hence, it is less affected by cytochrome P2C19 genetic variation or medication interactions compared to other proton pump inhibitors.
D. Patients undergoing combination therapy with Clopidogrel and proton pump inhibitors face an elevated risk of major adverse cardiovascular events, particularly rapid metabolisers, due to increased platelet reactivity levels. This risk is evident with Omeprazole, Lansoprazole, Esomeprazole and Pantoprazole, but not with Rabeprazole.
E. All of the above.

8. In your clinical experience, which of the following options do you believe is the most appropriate medication for decreasing GI bleeding in patients with CVD?

   The majority of doctors (~90%) believe that Rabeprazole is the most suitable medication for decreasing GI bleeding in patients with CVD. However, a few doctors consider Esomeprazole and Pantoprazole to be appropriate alternatives for managing GI bleeding in these patients.

9. **PPIs may prevent the conversion of Clopidogrel to its active metabolite, thereby lowering its clinical efficacy due to mutual CYP450-dependent metabolism. Do you agree or disagree?**

   Approximately, 73% of doctors agreed that PPIs could prevent the conversion of Clopidogrel to its active metabolite, potentially reducing its clinical efficacy due to shared CYP450-dependent metabolism. Meanwhile, about 27.1% agreed but expressed some reservations.

10. **Clinical evidence suggests that Rabeprazole is effective in patients with CVD receiving anti-platelet therapy. Which of**

**BOX-6**

- Rabeprazole, in addition to reducing GI complications, may improve cardiovascular outcomes by optimizing compliance with anti-platelet therapy.
- Rabeprazole markedly suppresses acid secretion, independent of CYP2C19 genotypes, and lowers the occurrence of aspirin-induced mucosal damage.
- Interaction strength of various PPIs, ranked from the weakest to the strongest affinitytowards CYP2C19, is as follows: Rabeprazole, Pantoprazole, Lansoprazole, Esomeprazole and Omeprazole.
- Rabeprazole has the highest pKa of ~5.0. As a result, it can be activated more quickly at higher pH levels compared to other PPIs.

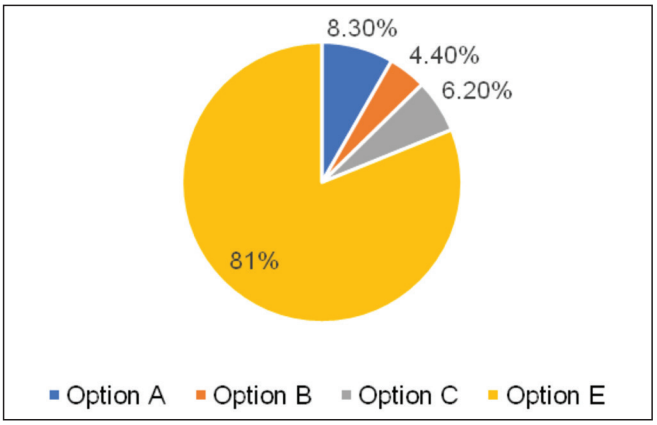


**Figure 5:** Efficacy of Rabeprazole in patients with cardiovascular disease receiving anti-platelet therapy.

A. Rabeprazole, in addition to reducing gastrointestinal complications, may improve cardiovascular outcomes by optimising compliance with anti-platelet therapy.
B. Rabeprazole remarkably inhibits acid secretion, regardless of cytochrome P2C19 genotypes, and reduces the incidence of aspirin-related mucosal injury.
C. Interaction strength of different proton pump inhibitors, from lowest to highest affinity towards cytochrome P2C19, is as follows: Rabeprazole, Pantoprazole, Lansoprazole, Esomeprazole and Omeprazole.
D. Rabeprazole has the highest pKa (~5.0, the pH at which a drug becomes 50% protonated); hence, the molecule can be activated at higher pH levels much faster than other proton pump inhibitors.
E. All of the above.

**Option D has been excluded from the pie chart due to negligible response*

**the following statements do you believe best supports the efficacy of Rabeprazole in this context?**

The majority of doctors (~81%) believe that all statements in BOX-6 support the efficacy of Rabeprazole in patients with CVD receiving anti-platelet therapy. However, about 8.3% of doctors think that, in addition to reducing GI complications, Rabeprazole may also improve cardiovascular outcomes by enhancing compliance with anti-platelet therapy. A few doctors further supported the idea that Rabeprazole has the weakest interaction with CYP2C19 compared to Pantoprazole, Lansoprazole, Esomeprazole and Omeprazole, making it particularly effective for patients with CVD receivinganti-platelet therapy (Figure 5).

## DISCUSSION

The survey results indicate that the majority of doctors perceive Rabeprazole as the preferred PPI for patients with CVD receiving anti-platelet therapy owing to its primarily non-enzymatic metabolism and minimal drug interactions. Rabeprazole's efficacy in reducing GI complications while maintaining the safety profile without compromising cardiovascular outcomes is widely acknowledged. Most respondents believe that Rabeprazole's reduced interaction with CYP2C19, and minimal impact on the efficacy of anti-platelet therapy makes it the safest choice for managing GI bleeding in these patients.

## CONCLUSION

In managing patients with CVD requiring multiple essential drugs, PPIs with minimal CYP450 enzyme interaction and a favourable drug interaction profile, such as Rabeprazole, should be preferred. Long-term unsupervised use of PPIs beyond prescribed dosages must be avoided, with potential DDIs carefully considered to ensure optimal outcomes.

### Clinical Significance

A PPI with the least DDIs is advisable, particularly for patients receiving Clopidogrel or multiple medications. Rabeprazole is a suitable choice in such cases due to its effective acid suppression and least interaction with other drugs.

**Acknowledgement:** We would like to acknowledge Scientimed Solutions Pvt. Ltd. for their assistance in developing this manuscript.

**Funding:** None.

**Conflict of interest:** None declared.

**Ethical approval:** Not required.

## REFERENCES

1. Zhang H, Dhalla NS. The Role of Pro-Inflammatory Cytokines in the Pathogenesis of Cardiovascular Disease. Int J MolSci 2024;25(2):1082.
2. Dalal J, Dutta AL, Hiremath J, *et al.* Cardiovascular Compatibility of Proton Pump Inhibitors: Practice Recommendations. Cardiol Ther 2023;12(4):557-570.
3. Dahiya DS, Kichloo A, Amir R, *et al.* When should antithrombotic therapy be resumed after gastrointestinal bleeding? Cleve Clin J Med 2022;89(11):630-633.
4. Talasaz AH, Sadeghipour P, Ortega-Paz L, *et al.* Optimizing antithrombotic therapy in patients with coexisting cardiovascular and gastrointestinal disease. Nat Rev Cardiol 2024;21(8):574-592.
5. Agewall S, Cattaneo M, Collet JP, *et al.;* ESC Working Group on Cardiovascular Pharmacology and Drug Therapy and ESC Working Group on Thrombosis. Expert position paper on the use of proton pump inhibitors in patients with cardiovascular disease and antithrombotic therapy. Eur Heart J 2013;34(23):1708-13, 1713a-1713b.
6. Gries JJ, Chen B, Virani SS, *et al*. Heartburn's Hidden Impact: A Narrative Review Exploring Gastroesophageal Reflux Disease (GERD) as a Cardiovascular Disease Risk Factor. J Clin Med2023;12(23):7400.
7. Gesualdo M, Scicchitano P, Carbonara S, *et al.* The association between cardiac and gastrointestinal disorders: causal or causal link? J Cardiovasc Med (Hagerstown) 2016;17(5):330-338.
8. Sheikh-Taha M, Asmar M. Polypharmacy and severe potential drug-drug interactions among older adults with cardiovascular disease in the United States. BMC Geriatr 2021;21(1):233.
9. Al-Amin MM, Rana AZ, Uddin MM, *et al.* Study on polypharmacy in patients with cardiovascular diseases. J App Pharm Sci2012;2(12):053-60.
10. Tantry US, Kereiakes DJ, Gurbel PA. Clopidogrel and proton pump inhibitors: influence of pharmacological interactions on clinical outcomes and mechanistic explanations. JACC CardiovascInterv 2011;4(4):365-380.
11. Sarnaik MK, Modi S, Pisipati Y, *et al.* Proton Pump Inhibitors: Exploring Cardiovascular Complications and Prescription Protocol. Cureus 2021;13(7):e16744.
12. Yasu T, Ikee R, Miyasaka Y, *et al.* Efficacy and safety of concomitant use of rabeprazole during dual-antiplatelet therapy with clopidogrel and aspirin after drug-eluting stent implantation: a retrospective cohort study. YakugakuZasshi2010;130(12):1743-1750
13. Parri MS, Gianetti J, Dushpanova A, *et al.* Pantoprazole significantly interferes with antiplatelet effect of clopidogrel: results of a pilot randomized trial. Int J Cardiol 2013;167(5):2177-2181.
14. Guo H, Ye Z, Huang R. Clinical outcomes of concomitant use of proton pump inhibitors and dual antiplatelet therapy: a systematic review and meta-analysis. Front Pharmacol 2021;12:694698.

**How to cite this article:** Dr. Kamaldeep Chawla . Optimising Proton Pump Inhibitor Therapy in Cardiovascular Polypharmacy: Expert Opinion and the Role of Rabeprazole. Hypertens J. 2024;10(4):94-99

**Source of support:** Nil, **Conflicts of interest:** None