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Review Article

Analyzing the Safety of Esomeprazole in Patients with Comorbidities

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Abstract

The increasing prevalence of comorbidities such as cardiovascular disease (CVD), diabetes, chronic kidney disease, and liver disorders in ageing populations has led to an increase in the use of medications such as proton pump inhibitors (PPIs) for gastrointestinal (GI) protection. Peptic ulcer disease and gastroesophageal reflux disease (GERD), which are common among patients with comorbid conditions, are frequently managed with PPIs to reduce the risk of GI injury, particularly in those on antithrombotic therapy. Among PPIs, Esomeprazole has gained prominence due to its potent acid-suppressive effects, minimal drug interactions, and favorable pharmacokinetic profile. This review examines the role of esomeprazole in managing GI complications in patients with comorbidities, including diabetes, CVD, and chronic kidney and liver diseases. Esomeprazole has been shown to effectively prevent GI bleeding in patients on dual or triple antiplatelet therapy and offer protection against acid-related disorders in patients with diabetes, including those with diabetic nephropathy. Moreover, studies have demonstrated its safety and efficacy in managing GI symptoms without significantly altering the metabolic effects of other therapies. Esomeprazole has been shown to provide gastroprotection in individuals with CVD, renal disorders, and diabetes, highlighting its importance in managing GI symptoms and preventing complications in these populations. In conclusion, Esomeprazole remains a promising therapeutic option for gastroprotection, particularly in older patients and those with complex comorbid conditions.

Key words: Cardiovascular disease, Chronic kidney disease, Comorbidities, Esomeprazole, Gastroesophageal reflux disease, Liver disease, Safety, Type 2 diabetes mellitus

INTRODUCTION

The probability of having multiple comorbidities, such as cardiovascular disease (CVD), cerebral vascular disease, diabetes, chronic kidney disease, and degenerative joint disease, increases with age. This has increased the tendency to prescribe medications such as aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) that can increase the risk of upper gastrointestinal (GI) injury.[1]

Peptic ulcer disease (PUD) frequently co-exists with comorbidities such as cardiovascular (CV), pulmonary, metabolic, or renal conditions, which can worsen disease prognosis. Furthermore, old age and the presence of comorbidities have been consistently shown to be risk factors for poor outcomes in patients with complicated PUD.[1]

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Patients with type 2 diabetes mellitus (T2DM) are commonly reported to have a greater risk of gastro-esophageal reflux secondary to decreased GI motility. Therefore, PPIs are often prescribed in this population because patients with diabetic nephropathy may experience GI symptoms such as nausea and/or vomiting, necessitating the use of a PPI for safe and effective treatment outcomes.[2] PPIs can improve glycemic control and alleviate gastro-esophageal symptoms in patients with diabetes mellitus (DM). Therefore, a risk–benefit assessment for long-term use of the right PPIs in DM is the need of the hour.[2]

While proton pump inhibitors (PPIs) are typically considered safe and well-tolerated, recent studies have

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raised concerns about their potential association with renal dysfunction, including acute interstitial nephritis (AIN) and chronic kidney disease. The first case of omeprazole-induced AIN was reported in 1992, and over the next 12 years, 29 additional cases were documented, 23 of which were confirmed through biopsy.[2]

PPIs ASSOCIATED WITH GASTROPROTECTION IN PATIENTS WITH COMORBIDITIES

PPIs are widely prescribed for managing PUD, healing erosive esophagitis, and alleviating symptoms of gastroesophageal reflux disease (GERD) in both adults and children.[3-5] PPIs, which effectively reduce gastric acid, have seen a significant increase in usage, particularly among patients receiving medications such as acetylsalicylic acid or NSAIDs.[5,6]

In patients with comorbidities, particularly those with CVD receiving antithrombotic therapy, PPIs play a crucial role in gastroprotection. This is particularly important for those undergoing dual antiplatelet therapy (DAPT) or even triple therapy, where DAPT is combined with oral anticoagulants such as Vitamin K antagonists or direct oral anticoagulants. The use of these therapies in combination significantly raises the risk of upper GI bleeding, making PPIs an essential component of preventive treatment.[6] A similar trend of gastroprotection with PPI, such as esomeprazole, has been observed in patients with diabetes and kidney disease.[7,8]

ESOMEPRAZOLE: A PROMISING PPI

Esomeprazole suppresses gastric acid secretion through irreversible inhibition of the H^+/K^+-ATPase enzyme in gastric parietal cells. The blockage in the last stage of acid production is dose-dependent, typically with a daily dose of 20–40 mg, leading to decreased gastric acidity.[9]

A study analyzing the pharmacokinetic profile of esomeprazole in 36 patients with symptomatic GERD who received repeated once-daily doses of esomeprazole 20 and 40 mg capsules for 5 days revealed area under the curve (AUC), C_{max}, T_{max}, and half-life of esomeprazole [Table 1].[9]

Table 1: Pharmacokinetic parameters of esomeprazole[9]

Parameter	Esomeprazole 40 mg	Esomeprazole 20 mg
AUC (µmol·h/L)	12.6	4.2
Median C_{max} (µmol/L)	5.1	2.4
Median T_{max} (h)	1.2	1.0
Median $t_{1/2}$ (h)	1.6	1.3

AUC: Area under the plasma concentration-time curve, C_{max}: Maximum plasma concentration, T_{max}: Time to reach maximum concentration, $t_{1/2}$: Elimination half-life

DRUG-DRUG INTERACTIONS OF ESOMEPRAZOLE

Esomeprazole exhibits a low risk of drug interactions, particularly with medications metabolized by cytochrome P450 (CYP) enzymes, including CYP1A2, 2A6, 2C9, 2D6, and 2E1.[10] Drug interaction studies with diazepam, phenytoin, and (R)-warfarin have shown that esomeprazole primarily affects CYP2C19, causing a slight alteration in the metabolism of cisapride. This suggests that Esomeprazole inhibits a minor metabolic pathway mediated by CYP2C19.[10] The effects observed with diazepam, phenytoin, (R)-warfarin, and cisapride are generally minor and unlikely to have clinical significance, supporting the safety of esomeprazole in terms of drug interactions.[9,10] Importantly, esomeprazole does not interact with substrates of CYP3A4, such as clarithromycin or quinidine, confirming that it does not inhibit this enzyme.[10]

EFFICACY AND SAFETY OF ESOMEPRAZOLE

The safety of esomeprazole was evaluated in multiple large clinical trials, involving 15,000–2,900 patients. Clinical studies evaluating 6–12 month use demonstrated that esomeprazole maintains good tolerability in both short-term and extended therapy.[9]

In a meta-analysis, the standard-dose esomeprazole had substantial advantages over other licensed PPIs in mucosal erosion healing and heartburn relief.[11] Another recent meta-analysis demonstrated the efficacy and safety of esomeprazole in the treatment of patients with GERD across 8 randomized controlled trials. Esomeprazole was shown to be consistently more effective than placebo and had a placebo-like safety profile, suggesting that esomeprazole is a promising anti-GERD medication that would address the need to treat acid-related disorders and GERD symptoms specifically and efficiently.[12]

ESOMEPRAZOLE VERSUS OTHER PPIs: A COMPARATIVE OVERVIEW

Esomeprazole was found to exhibit intragastric pH >4.0 for a significantly greater number of hours than other PPIs [Figure 1]. In addition, a greater percentage of Esomeprazole-treated patients maintained an intragastric pH above 4.0 for more than 12 h compared to other PPIs [Figure 2].[13]

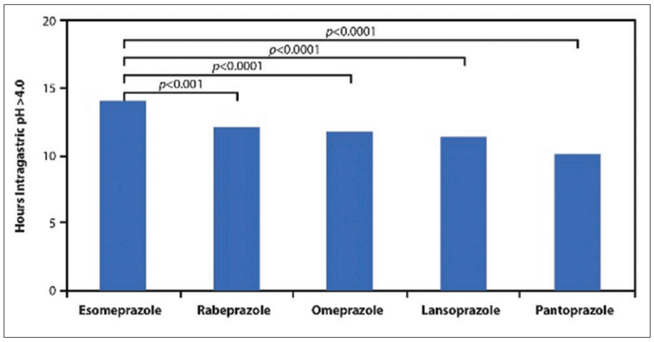

Figure 1: Mean number of hours on day 5 that intragastric pH was >4.0 by the treatment group[13]

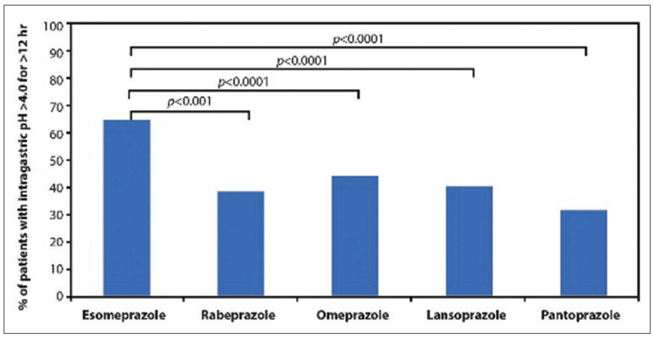

Figure 2: Percentage of subjects with intragastric pH >4.0 for >12 h[13]

Like other PPIs, esomeprazole is generally well-tolerated, with side effects such as diarrhea, nausea, abdominal pain, flatulence, and headache reported in <5% of patients.[1]

GI DAMAGE AND COMORBIDITIES: A COMPLEX RELATIONSHIP

Patients with CVD and cerebrovascular diseases are typically on long-term aspirin and/or other antithrombotic drug therapy, placing them at high risk for GI complications. To reduce the risk of upper GI bleeding in aspirin users, the main strategies include eliminating risk factors and co-administering gastroprotective agents.[1]

PPIs are frequently used for patients on antiplatelet agents and anticoagulants and those with additional risk factors to help minimize bleeding risks.[6] An increasing body of evidence suggests that esomeprazole is effective and safe in different patient populations such as geriatric, pediatric, and patients with diabetes, CVD, and renal/liver diseases.[1,5,7,8,14]

CURRENT LITERATURE ON ESOMEPRAZOLE USE IN PATIENTS WITH COMORBIDITIES

Esomeprazole in Patients with CVD

An investigational study found an increased risk of CV events in 6,757 patients with diabetes after bare-metal stent (BMS) deployment, but no evidence of an increased risk of CV events among concomitant users of clopidogrel and PPIs. The results indicate that the use of PPIs may not modify the protective effect of clopidogrel following BMS implantation.[15] Clinical trials (PRINCIPLE-TIMI 44 and TRITON-TIMI 38) on the co-administration of clopidogrel and PPI demonstrated no significant increase in the risk of adverse clinical outcomes in patients with acute coronary syndrome undergoing percutaneous coronary intervention (PCI).[15]

In a comparative study analyzing, the impact of concomitant treatment with three different PPIs, including pantoprazole, omeprazole, and esomeprazole, on platelet response to clopidogrel treatment in a large cohort of CAD patients with previous PCI revealed no attenuating effects on platelet response to clopidogrel with esomeprazole.[16]

In primary-care patients with unexplained chest pain but infrequent or no heartburn/regurgitation, high-dose esomeprazole (40 mg twice daily) provided statistically significant relief. However, no significant reduction was observed in patients who experienced frequent reflux symptoms. Among 617 patients, adverse events (AEs) were reported in 37% of esomeprazole recipients and 30% of placebo recipients, with 3% discontinuing due to AEs in each group. There were no deaths reported, and no serious AEs were attributed to the trial medication.[17]

The role of esomeprazole in preventing GI complications is particularly relevant in patients with CVD on antithrombotic therapy, such as aspirin or clopidogrel.[3,14,18] A study by Ng *et al.* (2011) demonstrated that low-dose esomeprazole (20 mg) did not increase the risk of major adverse CV events, while providing sustained protection against GI bleeding. . This suggests that low-dose esomeprazole is a viable option for managing the risk of clopidogrel-PPI interaction and preventing GI bleeding.[14,18]

Furthermore, a randomized, double-blind trial investigating aspirin and esomeprazole therapy versus clopidogrel in patients with a history of aspirin-induced ulcer bleeding found that the combination of aspirin and esomeprazole resulted in significantly fewer instances of recurrent bleeding. After 12 months, the recurrence rate of bleeding was 0.7% in the aspirin plus Esomeprazole group compared to 8.6% in the clopidogrel group ($P = 0.001$), indicating that esomeprazole offers superior protection against ulcer bleeding in these high-risk patients.[19] Overall, the available evidence supports the safe and effective use of csomeprazole in patients with CVD, especially those at risk for GI bleeding, while also providing reassurance regarding its lack of interaction with clopidogrel.

ESOMEPRAZOLE IN PATIENTS WITH LIVER AND KIDNEY DISEASE

In patients with mild or moderate hepatic impairment, the metabolism of esomeprazole may be decreased. Patients with severe liver dysfunction exhibit significantly impaired esomeprazole metabolism, resulting in a two-fold increase in systemic exposure (AUC) compared to those with normal hepatic function. Therefore, it is advised not to exceed the maximum dose of 20 mg in patients with severe hepatic impairment. Esomeprazole and its main metabolites do not tend to accumulate with once-daily dosing.[20]

In renal transplant recipients, GI complications are a significant concern, with up to 12% of these patients experiencing upper GI bleeding episodes. PPIs, such as esomeprazole, are commonly used to treat acid-related disorders and prevent gastroduodenal toxicity in these patients. A study comparing the effects of pantoprazole and esomeprazole on renal function in stable kidney transplant recipients receiving a triple immunosuppressive regimen (cyclosporine A, mycophenolate mofetil, and corticosteroids) found that esomeprazole was more effective. It resulted in continuously decreasing serum creatinine levels, suggesting better renal function, whereas pantoprazole had no significant effect on serum creatinine levels.[8]

For patients with cirrhosis, especially those with Child–Turcotte–Pugh Class C (CTP C) cirrhosis, esomeprazole is the only recommended PPI at a maximum dose of 20 mg per day. Other PPIs, such as pantoprazole and lansoprazole, have been classified as unsafe due to their 4–8-fold increased exposure in these patients. Esomeprazole, omeprazole, or rabeprazole can be administered in patients with CTP A or B cirrhosis, but only esomeprazole is advised for patients with CTP C. Given its pharmacokinetic profile, esomeprazole's use in patients with cirrhosis should follow specific guidelines to avoid exacerbating underlying conditions.[20]

Although evidence regarding the safety of esomeprazole in patients with advanced cirrhosis (CTP C) is limited, the current recommendation is to limit its dose to no more than 20 mg per day in these patients to mitigate the risk of excessive exposure. Based on the available data, esomeprazole is generally considered to present "no additional risks," although careful monitoring is advised in patients with severe hepatic or renal conditions.[20]

ESOMEPRAZOLE IN PATIENTS WITH DIABETES

PPIs with lower potency, such as pantoprazole, need higher doses to produce the same anti-acid effect as more potent PPIs such as esomeprazole. At equipotent doses (20 mg esomeprazole ≈ 120 mg pantoprazole), the increased drug load from lower-efficacy PPIs may underlie their stronger correlation with diabetes development compared to more potent alternatives.[3]

In a study by Lin *et al.* (2016) involving 388,098 patients, it was found that the use of PPIs in patients older than 60 years resulted in a lower risk of developing diabetes (hazard ratio, 0.73; 95% confidence interval [CI], 0.63–0.83), whereas those under 40 years of age showed a higher risk. Moreover, in patients with upper GI disease, PPI therapy was linked to a significantly reduced risk of T2DM compared to those not receiving such treatment.[7] Study by Abrignani *et al.* (2023) describes a retrospective cohort study conducted using the National Health Insurance Research Database in patients with T2DM treated with Clopidogrel after BMS deployment. There was no significant increase in adverse CV events among patients who received PPIs, including esomeprazole, compared to those who did not receive PPIs within 1 year. These results suggest that esomeprazole does not modify the CV protective effects of clopidogrel, which is a key finding for patients with diabetes and CVD.[6]

Regarding the risk of DM, a dose-dependent increase in risk was observed among patients with upper GI disease who used PPIs. Kuo *et al.* (2022) analyzed analyzed data from 41,880 patients and found that pantoprazole, lansoprazole, and omeprazole were associated with the development of diabetes, while no relationship with esomeprazole was noted [Table 2].[3]

CONCLUSION

Esomeprazole is an effective and safe therapeutic option for gastroprotection in patients with multiple comorbidities, including CVD, diabetes, chronic kidney disease, and liver disorders. Its favorable pharmacokinetic profile, minimal drug interactions, and proven efficacy in managing upper GI symptoms and preventing complications, particularly in high-risk populations, make

Table 2: Risk of type 2 diabetes among patients who were exposed to PPI[3]

PPI	With subsequent type 2 diabetes (*n*, %)	Without subsequent type 2 diabetes (*n*, %)	Adjusted OR (95% CI)
Pantoprazole	2,472 (11.8)	2,206 (10.5)	1.14 (1.07–1.21)
Lansoprazole	5,697 (27.2)	5,407 (25.8)	1.08 (1.03–1.12)
Omeprazole	5,015 (23.9)	4,658 (22.2)	1.11 (1.06–1.16)
Esomeprazole	3,858 (18.4)	3,808 (17.7)	1.05 (1.00–1.10)
Rabeprazole	1,364 (6.5)	1,411 (6.7)	0.96 (0.89–1.04)

PPI: Proton pump inhibitor, OR: Odds ratio, CI: Confidence interval it a valuable tool in clinical practice. Despite concerns regarding its potential association with renal dysfunction, existing evidence supports its safety, especially when used at recommended doses in patients with hepatic or renal impairment. Moreover, Esomeprazole's role in managing GI complications in patients receiving antithrombotic therapy further reinforces its importance in preventing adverse outcomes such as GI bleeding. However, due to the evolving nature of research regarding PPIs, careful patient selection and monitoring are crucial, particularly for those with advanced liver or kidney conditions. Given its benefits, esomeprazole continues to be an essential component in the management of patients with comorbidities, with proper clinical vigilance to ensure its safe and effective use in these vulnerable populations.

EXPERT OPINION

The Drug–Drug Interaction Profile of Esomeprazole Compared to Other Drugs

Among 190 healthcare professionals (HCPs) surveyed, the majority (68.9%) acknowledged that Esomeprazole has a superior drug–drug interaction profile, highlighting its minimal interactions with diazepam, phenytoin, and (R)-warfarin as well as with amoxicillin and clarithromycin. It also demonstrates long-term safety and tolerability, and safety in paediatric patients. In addition, 19.5% emphasized its long-term safety and tolerability. A few (8.9%) noted no potential interaction with diazepam, phenytoin, and (R)-warfarin, whereas 2.1% considered it safe for paediatric use.

Esomeprazole Demonstrated a Favorable Safety Profile in Patients with Comorbid CVD

Around 68.9% of HCPs agreed that Esomeprazole reduces recurrent peptic ulcers and is safe for patients on acetylsalicylic acid for cardio-protection. Approximately one-fifth (17.9%) of HCPs suggested esomeprazole's neutral safety profile regarding mortality, CV outcomes, and treatment-related tolerability issues.

Esomeprazole is Associated with Superior Outcomes in Post-PCI Patients Compared to Pantoprazole

Esomeprazole was recognized by 82.1% of HCPs for preventing GI bleeding, lowering cardiac risks, and reducing clopidogrel interaction concerns in PCI patients, showing superiority over Pantoprazole. Furthermore, 9.5% highlighted its role in protecting against GI bleeding, 6.3% recognized its ability to reduce the risk of major adverse cardiac events, and 2.1% emphasized its advantage in minimizing clopidogrel interaction concerns [Figure 3].

Efficacy of Esomeprazole in Maintaining Platelet Aggregation Response in Post-stent Patients with Comorbidities

The majority of HCPs (77.9%) agreed that esomeprazole consistently supports platelet aggregation, does not interfere with Clopidogrel's effects, and is a suitable PPI for patients on long-term Clopidogrel therapy. Furthermore, 8.9% supported its role in maintaining platelet aggregation, whereas another 8.9% favored its use in chronic Clopidogrel therapy. A smaller group (7 HCPs [3.7%]) believed that it did not interfere with platelet response to Clopidogrel, whereas one HCP (0.5%) did not respond. These results highlighted strong support for esomeprazole's efficacy in post-stent patients with comorbidities.

Recommendation of Esomeprazole as the Preferred PPI for Patients with Cirrhosis and Child–Pugh C Classification

A significant majority of HCPs (91.6%) agreed that esomeprazole is the recommended PPI for patients with cirrhosis and a Child–Pugh C classification. As few as 7.9% disagreed with it, whereas 0.5% did not respond [Figure 4].

Risk of Developing T2DM in Patients with Upper GI Disease

Out of 190 HCPs surveyed, 58.4% believed that

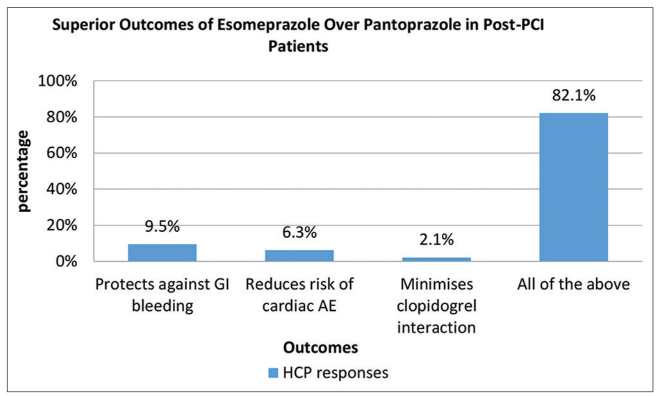

Figure 3: Outcomes of esomeprazole in post-PCI patients compared to pantoprazole. PCI: Percutaneous coronary intervention, GI: Gastrointestinal, HCPs: Healthcare professionals.

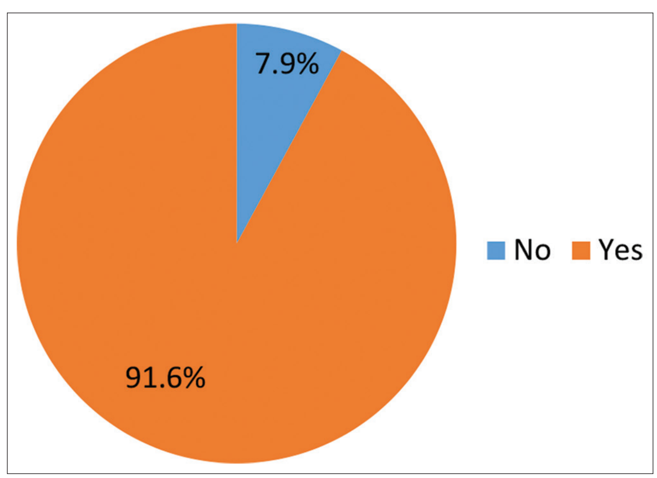

Figure 4: Esomeprazole as the preferred PPI for patients with cirrhosis and child-pugh C. PPI: Proton pump inhibitor

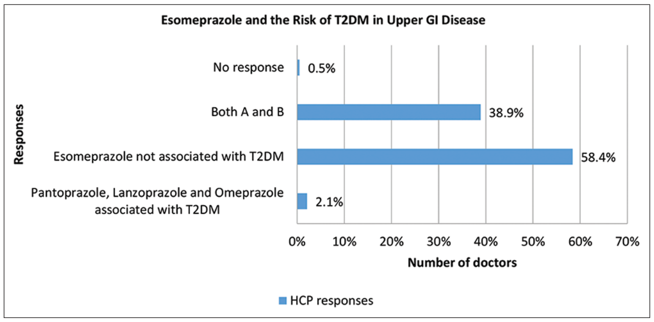

Figure 5: The risk of type 2 diabetes in patients with upper GI disease. T2DM: Type 2 diabetes mellitus, HCP: Healthcare professional, GI: Gastrointestinal

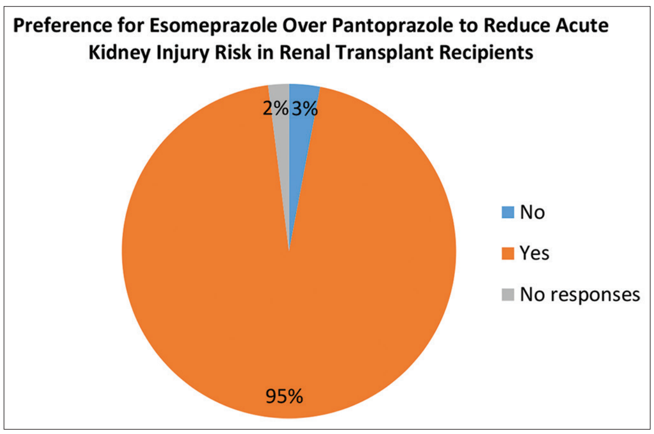

Figure 6: Esomeprazole preferred over pantoprazole to reduce acute kidney injury risk in renal transplant recipients

esomeprazole is not associated with the risk of developing T2DM in patients with upper GI disease [Figure 5]. In addition, 38.9% acknowledged that Esomeprazole is not linked to T2DM risk, whereas pantoprazole, lansoprazole, and omeprazole are associated with T2DM development. A smaller group (2.1%) believed that pantoprazole, lansoprazole, and omeprazole contribute to T2DM development.

Pharmacokinetic Properties of Esomeprazole in Managing Patients with Comorbid Cirrhosis (CTP C)

Regarding esomeprazole's pharmacokinetic profile in patients with cirrhosis, 59.5% of HCPs agreed that esomeprazole and its main metabolites do not accumulate with once-daily dosing and that its metabolism may be decreased in mild-to-moderate hepatic impairment (CTP C). Furthermore, 25.8% supported only the non-accumulation statement, whereas 12.6% acknowledged the potential decrease in metabolism.

Preference of Esomeprazole Over Pantoprazole in Reducing Acute Kidney Injury Risk in Renal Transplant Recipients

The majority of HCPs (180 [95%]) agreed that Esomeprazole is preferred over Pantoprazole in reducing the risk of acute kidney injury in renal transplant recipients based on renal diagnostic biomarkers [Figure 6]. In contrast, 6 (3%) disagreed and 4 (2%) did not respond. These results indicate a strong preference for esomeprazole among HCPs for this patient population.

Esomeprazole Over Pantoprazole in Patients with Comorbid GERD

The majority of HCPs (87.3%) agreed that esomeprazole is superior to Pantoprazole for patients with comorbid GERD, citing its ability to maintain a higher intragastric pH >4.0, promote better oesophagitis healing, and provide more effective heartburn relief. In addition, 14 (7.4%) reported prolonged intragastric pH >4 duration, 7 (3.7%) emphasized improved oesophagitis healing rates, and 2 (1.1%) highlighted enhanced heartburn relief. Only 1 (0.5%) HCP did not respond. These findings provide strong support for esomeprazole in managing GERD.

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