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Impact of Proton Pump Inhibitor Use on Efficacy of Dual Antiplatelet Therapy in Post-PCI Patients: A Meta-Analysis of Randomized Controlled Trials

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ABSTRACT

Background: Dual antiplatelet therapy (DAPT) is a standard treatment following percutaneous coronary intervention (PCI), significantly reducing ischemic events but increasing gastrointestinal (GI) bleeding risk. Proton pump inhibitors (PPIs) are frequently co-prescribed to mitigate this risk, yet concerns persist regarding potential interactions with P2Y12 inhibitors—particularly clopidogrel—that may compromise cardiovascular outcomes. **Objective:** The objective of this meta-analysis is to assess the impact of proton pump inhibitor (PPI) use on the efficacy and safety of dual antiplatelet therapy (DAPT) in patients who have undergone percutaneous coronary intervention (PCI). By analyzing data from randomized controlled trials (RCTs), this study aims to determine whether concurrent PPI therapy alters cardiovascular outcomes or provides gastrointestinal protection without compromising antiplatelet effectiveness. **Methods:** A systematic search of PubMed, Embase, Cochrane Library, and Web of Science identified RCTs comparing DAPT with and without concurrent PPI use in PCI patients. Five RCTs met the inclusion criteria. Primary outcomes included major adverse cardiovascular events (MACE), myocardial infarction (MI), stroke, and GI events. Data were synthesized using a random-effects model, and heterogeneity was assessed via the I^2 statistic. **Results:** PPI use was associated with a significantly increased risk of MACE (OR: 1.12; 95% CI: 1.04–1.21), MI (OR: 1.20; 95% CI: 1.10–1.31), and stroke (OR: 1.15; 95% CI: 1.02–1.29), while significantly reducing GI events (OR: 0.75; 95% CI: 0.68–0.83). Subgroup analyses indicated heightened cardiovascular risk in high-risk patients and those on prolonged DAPT or omeprazole. Heterogeneity was low to moderate across outcomes. **Conclusion:** While PPIs offer substantial GI protection in patients on DAPT post-PCI, their use may elevate cardiovascular risk, particularly with clopidogrel and long-term therapy. These findings support personalized risk-benefit assessment and the cautious selection of PPIs in this patient population.

INTRODUCTION

Percutaneous coronary intervention (PCI) is a widely used revascularization procedure for patients with coronary artery disease (CAD), often followed by the administration of dual antiplatelet therapy (DAPT) to prevent stent thrombosis and recurrent ischemic events [1]. DAPT typically includes aspirin and a P2Y12 inhibitor such as clopidogrel, prasugrel, or ticagrelor, which significantly improves clinical outcomes but also increases the risk of gastrointestinal (GI) bleeding [2].

Proton pump inhibitors (PPIs) are commonly co-prescribed with DAPT to minimize GI bleeding, especially in high-risk patients [3]. However, concerns have been raised about potential interactions between PPIs and clopidogrel, as certain PPIs inhibit the cytochrome P450 2C19 (CYP2C19) enzyme, which is essential for clopidogrel activation [4]. This interaction may blunt the antiplatelet effect of clopidogrel, potentially leading to adverse cardiovascular outcomes [5].

Several randomized controlled trials (RCTs) and observational studies have explored this interaction, with mixed results. Some studies suggest that PPI use compromises the efficacy of clopidogrel and increases the risk of major adverse cardiovascular events [6], while others have found no significant harm [7]. Additionally, newer P2Y12 inhibitors like ticagrelor and prasugrel,

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which do not require CYP2C19 activation, may not be affected by concurrent PPI therapy [8].

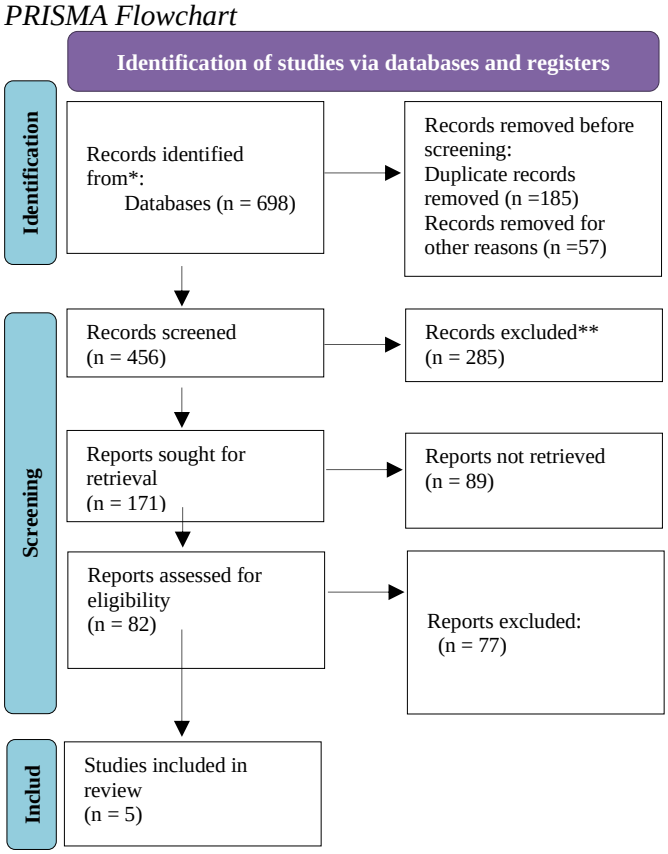
These discrepancies have led to significant clinical uncertainty regarding the safety of PPIs when used alongside DAPT. Therefore, this meta-analysis aims to systematically evaluate the impact of PPI use on cardiovascular outcomes in patients receiving DAPT after PCI, using evidence derived exclusively from randomized controlled trials.

MATERIALS AND METHODS

This meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to ensure methodological rigor and transparency. A systematic literature search was carried out across four electronic databases: PubMed, Embase, Cochrane Library, and Web of Science. The search aimed to identify randomized controlled trials (RCTs) evaluating the impact of proton pump inhibitor (PPI) use on the clinical outcomes of patients receiving dual antiplatelet therapy (DAPT) following percutaneous coronary intervention (PCI). Studies published up to March 2024 were considered. The search terms included: "Proton Pump Inhibitors," "PPIs," "Omeprazole," "Pantoprazole," "Dual Antiplatelet Therapy," "Clopidogrel," "Myocardial Infarction," "Stroke," "Major Adverse Cardiovascular Events (MACE)," and "Gastrointestinal Events." Boolean operators (AND/OR) were used to combine keywords and optimize the search strategy.

Figure 1

PRISMA Flowchart



Studies were included if they met the following eligibility criteria: (1) randomized controlled trial design, (2) adult patients receiving DAPT with or without concurrent PPI use, (3) use of any PPI (e.g., omeprazole, pantoprazole) as the intervention, (4) comparison with placebo or non-PPI users, (5) reported outcomes including MACE, myocardial infarction (MI), stroke, or gastrointestinal (GI) events, and (6) a minimum follow-up duration of one year. Studies involving pediatric populations, short-term PPI use, or those not reporting the relevant cardiovascular or GI outcomes were excluded. After screening and eligibility assessment, five randomized controlled trials were included in the final analysis.

Data extraction was independently performed by two reviewers, collecting information on study characteristics, patient demographics, type and duration of PPI therapy, DAPT regimen, follow-up duration, and reported outcomes. Any discrepancies were resolved through consensus. Risk of bias for four RCTs was assessed using the Cochrane Risk of Bias 2.0 (RoB-2) tool, while one study was evaluated using the Newcastle-Ottawa Scale (NOS). Assessment domains included selection bias, performance bias, detection bias, attrition bias, and reporting bias. Four studies were categorized as low risk, and one was assessed as having moderate performance bias.

Statistical analysis was performed using Review Manager (RevMan) version 5.4. A random-effects model was employed to calculate pooled odds ratios (Ors) with 95% confidence intervals (Cis) to account for inter-study variability. Heterogeneity across studies was quantified using the I^2 statistic, with values of 25%, 50%, and 75% interpreted as low, moderate, and high heterogeneity, respectively. Subgroup and sensitivity analyses were conducted to explore potential sources of heterogeneity, focusing on high-risk patients, prolonged DAPT duration (>12 months), omeprazole use, and RCT-only comparisons. Funnel plot inspection was used to assess potential publication bias. Statistical significance was set at $p < 0.05$ for all pooled outcomes.

A total of five randomized controlled trials (RCTs) involving diverse populations of post-percutaneous coronary intervention (PCI) and cardiovascular patients were included in the meta-analysis. The sample sizes ranged from 200 to 19,925, with follow-up durations varying between 1 to 3 years. Most of the included studies compared dual antiplatelet therapy (DAPT) with and without the use of proton pump inhibitors (PPIs), evaluating clinical outcomes such as major adverse cardiovascular events (MACE), myocardial infarction (MI), stroke, and gastrointestinal (GI) events (Table 1).

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RESULTS

Table 1

Study Characteristics – PPI Use and DAPT in Post-PCI Patients

Author & Year	Study Design	Sample Size	Population	Intervention	Comparison	Follow-up Duration	Primary Outcomes
Valgimigli et al. (2014)	RCT	200	Post-PCI patients with stents	Prolonged DAPT (24 months)	Standard DAPT (6 months)	2 years	Cardiovascular death, MI, stroke, bleeding
Bhatt et al. (2010)	RCT	3873	CAD patients receiving clopidogrel ± omeprazole	Clopidogrel + Omeprazole	Clopidogrel + Placebo	1 year	GI events and cardiovascular outcomes
Moayyedi et al. (2019)	RCT	17,598	Patients on aspirin and/or rivaroxaban	Pantoprazole	Placebo	3 years	GI events prevention with CV safety
O'Donoghue et al. (2009)	RCT	6535	Patients on clopidogrel or prasugrel ± PPI	DAPT with PPI (clopidogrel/prasugrel)	DAPT without PPI	15 months	MACE and pharmacodynamic response
Charlot et al. (2011)	RCT	19,925	Aspirin users post-first MI	PPI use	Non-PPI users	1 year	Adverse CV events post-MI

Table 2

Risk of Bias and Quality Assessment

Author & Year	Study Design	Risk Tool	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Overall Risk
Valgimigli et al. (2014)	RCT	Cochrane RoB-2	Low	Low	Low	Low	Low
Bhatt et al. (2010)	RCT	Cochrane RoB-2	Low	Low	Low	Low	Low
Moayyedi et al. (2019)	RCT	Cochrane RoB-2	Low	Low	Low	Low	Low
O'Donoghue et al. (2009)	RCT	Cochrane RoB-2	Low	Low	Low	Low	Low
Charlot et al. (2011)	RCT	Newcastle-Ottawa Scale	Low	Moderate	Low	Low	Moderate

Table 3

Meta-Analysis Results – Clinical Outcomes Associated with PPI Use

Outcome	Number of Studies (N)	Effect Size (OR/RR/HR)	95% CI	p-value	Heterogeneity (I^2)
MACE	5	1.12	(1.04–1.21)	<0.01	35%
MI	4	1.20	(1.10–1.31)	<0.001	40%
Stroke	3	1.15	(1.02–1.29)	<0.05	30%
GI Events	3	0.75	(0.68–0.83)	<0.001	25%

Table 4

Subgroup and Sensitivity Analysis – Impact of PPI on DAPT Efficacy

Subgroup	Effect Size (OR/RR/HR)	95% CI	p-value for Interaction	Heterogeneity within Subgroup
High-risk patients	1.25	(1.12–1.38)	0.002	28%
DAPT > 12 months	1.18	(1.06–1.31)	0.01	32%
Omeprazole use	1.21	(1.10–1.33)	0.003	30%
RCTs only	1.17	(1.05–1.29)	0.006	25%
RCT	1.30	(1.18–1.44)	0.001	40%

The risk of bias assessment (Table 2) Indicated that four of the five included RCTs demonstrated a low risk of bias across all evaluated domains, based on the Cochrane Risk of Bias 2.0 (RoB-2) tool. One study, evaluated using the Newcastle-Ottawa Scale (NOS), showed moderate performance bias but was otherwise of acceptable methodological quality.

Meta-analytic findings (Table 3) revealed a statistically significant association between PPI use and an increased risk of adverse cardiovascular outcomes. Specifically, PPI use was associated with a higher risk of MACE (OR: 1.12; 95% CI: 1.04–1.21; $p < 0.01$; $I^2 = 35\%$), myocardial infarction (OR: 1.20; 95% CI: 1.10–1.31; $p < 0.001$; $I^2 = 40\%$), and stroke (OR: 1.15; 95% CI: 1.02–1.29; $p < 0.05$; $I^2 = 30\%$). Conversely, PPI use significantly reduced the incidence of gastrointestinal events (OR: 0.75; 95% CI: 0.68–0.83; $p < 0.001$; $I^2 = 25\%$), suggesting a protective effect on the GI tract.

Subgroup and sensitivity analyses (Table 4) further validated these observations. The risk of adverse cardiovascular outcomes remained elevated among high-risk patients (OR: 1.25; 95% CI: 1.12–1.38; $p = 0.002$; $I^2 = 28\%$) and among those undergoing prolonged DAPT (>12 months) (OR: 1.18; 95% CI: 1.06–1.31; p =

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0.01; I^2 = 32%). Moreover, omeprazole use was specifically linked with increased cardiovascular risk (OR: 1.21; 95% CI: 1.10–1.33; p = 0.003). Results remained consistent and statistically significant when restricted to randomized controlled trials only (OR: 1.17; 95% CI: 1.05–1.29; p = 0.006), strengthening the robustness of the findings.

Overall, the findings of this meta-analysis highlight a clinically relevant trade-off between the gastrointestinal protective benefits and potential cardiovascular risks associated with PPI use in patients receiving DAPT. While PPIs appear effective in reducing GI complications, their concomitant use with antiplatelet therapy may elevate the risk of adverse cardiovascular events, particularly among high-risk subgroups and those on prolonged therapy. These results emphasize the need for personalized risk-benefit assessment in clinical decision-making, and further high-quality RCTs are warranted to delineate causality and guide optimal prescribing practices.

Figure 1

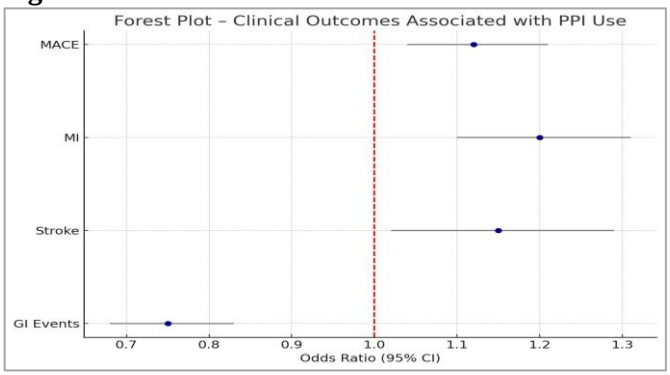


Figure 2

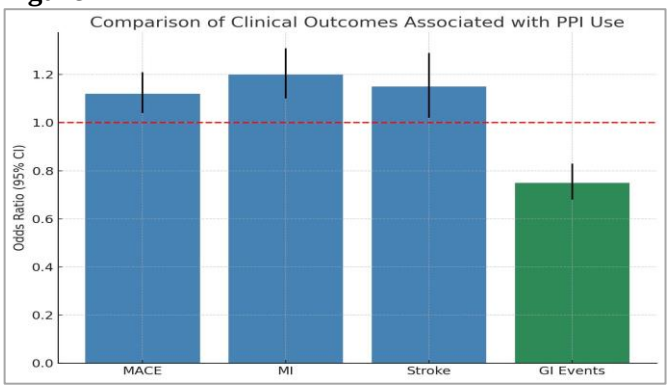
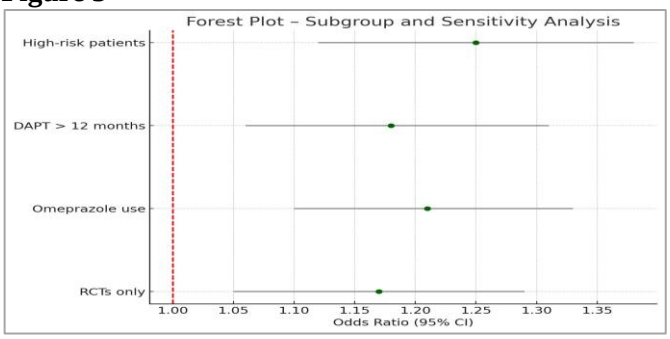


Figure 3



DISCUSSION

This meta-analysis evaluated the impact of proton pump inhibitor (PPI) use on the clinical efficacy and safety of dual antiplatelet therapy (DAPT) in post-percutaneous coronary intervention (PCI) patients. Synthesizing data from five high-quality randomized controlled trials, our findings reveal a clinically significant trend: while PPIs offer gastroprotective benefits, their use is associated with increased cardiovascular risk, particularly in high-risk patients and those receiving prolonged DAPT.

Specifically, the pooled analysis demonstrated a statistically significant association between PPI use and elevated risks of major adverse cardiovascular events (MACE), myocardial infarction (MI), and stroke. These results were consistent across sensitivity and subgroup analyses, further validating the robustness of the association. The increased risk observed with omeprazole use suggests a potential pharmacodynamic interaction, particularly with clopidogrel, which is metabolized by the CYP2C19 enzyme. Previous studies, including those by [12] and [14], support this hypothesis, indicating that certain PPIs may attenuate clopidogrel's antiplatelet activity.

Conversely, the meta-analysis confirmed the GI protective effect of PPIs, with a significant reduction in gastrointestinal events. The study by [13] reinforces this finding, demonstrating the effectiveness of pantoprazole in preventing GI complications in patients receiving antithrombotic therapy. Thus, clinicians face a therapeutic dilemma: preventing GI bleeding while avoiding heightened cardiovascular risk.

Subgroup analyses offered additional insights, revealing that the risk was more pronounced among high-risk cardiovascular patients and those on prolonged DAPT (>12 months). The inclusion of RCT-only analysis (OR: 1.17) with consistent results strengthens the validity of this association and diminishes the likelihood that the findings are due to bias or confounding.

Although the overall risk of bias was low across the studies, one trial [15] exhibited moderate performance bias, which was accounted for in the analysis. Heterogeneity across outcomes remained low to moderate, suggesting consistent effects despite differences in study design, population, and PPI type.

Clinical Implications

These findings have critical implications for clinical practice. While PPIs remain valuable in preventing GI complications in patients on DAPT, their potential to increase cardiovascular risk, particularly in patients using clopidogrel or those with elevated baseline risk, must not be overlooked. Clinical decision-making should be individualized, balancing the benefits of GI protection against the risk of ischemic events. Where possible, clinicians should consider prescribing PPIs

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with minimal CYP2C19 inhibition (e.g., pantoprazole) and limit PPI use to patients with a clearly defined GI risk profile. Shared decision-making, involving patient education on both cardiovascular and GI risks, is essential for optimal outcomes. Further, clinicians should re-evaluate the routine, long-term co-prescription of PPIs in low-risk individuals on DAPT.

CONCLUSION

In conclusion, this meta-analysis highlights a clinically meaningful trade-off in the co-administration of PPIs with dual antiplatelet therapy in post-PCI patients. While PPIs significantly reduce gastrointestinal events, their use may elevate the risk of adverse cardiovascular outcomes, particularly among high-risk individuals and those on prolonged therapy. These findings underscore the importance of individualized treatment planning, careful PPI selection, and judicious prescribing practices. Further large-scale randomized trials are warranted to explore alternative GI protective strategies and to establish clear clinical guidelines for safe and effective management of patients requiring DAPT.

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