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The Impact of Proton Pump Inhibitors on the Efficacy of Dual Antiplatelet Therapy in Patients Following Percutaneous Coronary Intervention: A Systematic Review and Network Meta-Analysis.

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Abstract

To investigate the effects of proton pump inhibitors (PPIs) on the efficacy of dual antiplatelet therapy (DAPT) in patients following percutaneous coronary intervention (PCI). A computer-based search was conducted in the Cochrane Library, ClinicalTrials.gov, and PubMed databases up to September 30, 2024. Randomized controlled trials (RCTs) evaluating the application of DAPT in conjunction with PPIs in post-PCI patients were included. This network meta-analysis included a total of 6 RCTs with 2,826 participants. The direct meta-analysis of the incidence of major adverse cardiovascular events (MACE) yielded a combined effect size of OR 0.87 (95% CI: 0.71, 1.06). Subgroup analyses by PPI type revealed an OR of 0.85 (95% CI: 0.70, 1.05) for pantoprazole, 0.49 (95% CI: 0.04, 5.59) for lansoprazole, and 1.83 (95% CI: 0.51, 6.53) for omeprazole. For gastrointestinal event incidence, the direct meta-analysis resulted in a combined effect size of OR 0.22 (95% CI: 0.10, 0.46). The ORs for pantoprazole, lansoprazole, and omeprazole were 0.23 (95% CI: 0.07, 0.70), 0.18 (95% CI: 0.02, 1.62), and 0.13 (95% CI: 0.02, 0.73), respectively. The network meta-analysis indicated that the preferred hierarchy for reducing MACE risk is lansoprazole, followed by pantoprazole and omeprazole. In contrast, for minimizing gastrointestinal event risk, the preferred order was omeprazole, followed by lansoprazole and pantoprazole. For patients after PCI, the combination of DAPT and PPIs is recommended to reduce the risks of cardiovascular and gastrointestinal events. Strong CYP2C19 inhibitors such as omeprazole and esomeprazole should be avoided.

Keywords: Percutaneous Coronary Intervention; Dual Antiplatelet Therapy; Proton Pump Inhibitors; Network Meta-Analysis

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1 Introduction

Dual Antiplatelet Therapy (DAPT) is recognized for its efficacy in reducing the incidence of stent thrombosis and ischemic events in patients undergoing Percutaneous Coronary Intervention (PCI) [1]. However, this therapeutic approach is concomitantly associated with an elevated risk of bleeding complications, particularly gastrointestinal bleeding, which may necessitate the cessation of DAPT and consequently increase the likelihood of adverse cardiovascular outcomes [2]. Proton Pump Inhibitors (PPIs) play a pivotal role in mitigating these risks by inhibiting the gastric proton pump (H+/K+ ATPase), thereby decreasing gastric acid secretion, stabilizing the gastrointestinal milieu, facilitating ulcer healing, and reducing the incidence of acid-related hemorrhage [3]. PPIs are widely utilized for the prophylaxis of gastrointestinal bleeding and are indicated for a range of acid-related gastrointestinal disorders, including gastroesophageal reflux disease, Zollinger-Ellison syndrome, peptic ulcers, and acute upper gastrointestinal bleeding [4].

In clinical settings, the co-prescription of PPIs with DAPT is common practice aimed at minimizing gastrointestinal complications. The COGENT study has demonstrated that the concurrent administration of PPIs during DAPT is associated with a statistically significant reduction in gastrointestinal events [5]. Notwithstanding the protective effect of PPIs against upper gastrointestinal bleeding (UGIB), concerns have emerged surrounding their potential impact on the antiplatelet efficacy of clopidogrel. Multiple studies have reported no statistically significant differences in major adverse cardiovascular events (MACE) between patients who are PPI users and those who are not [6,7]. Conversely, some investigations have suggested that the concomitant use of omeprazole and esomeprazole with clopidogrel after drug-eluting stent implantation may be associated with an increased risk of adverse clinical outcomes [8]. A meta-analysis that included 52 studies found no significant correlation between the combination of PPIs and DAPT and adverse clinical outcomes based on randomized controlled trial (RCT) data; however, observational studies have indicated an increased risk of adverse events associated with PPI use among patients receiving DAPT [9].

The impact of PPIs on the therapeutic efficacy of DAPT in PCI patients remains a subject of considerable debate, characterized by a lack of high-quality RCTs and an absence of comparative assessments among various PPIs, such as omeprazole, lansoprazole, and pantoprazole. This study aims to explore the effects of PPI co-administration with DAPT on the incidence of MACE and gastrointestinal events post-PCI through both direct and network meta-analyses, while also elucidating the differential impacts of various PPI formulations.

2 Methods

This meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for network meta-analyses. As this study does not involve clinical trials, it is exempt from ethical approval and the requirement for informed consent.

2.1 Search Strategy

A systematic search was performed across the Cochrane Library, ClinicalTrials.gov, and PubMed databases using the following keywords: "Dual Antiplatelet Therapy," "PCI,"

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"Proton Pump Inhibitors," "omeprazole," "lansoprazole," "pantoprazole," and "randomized controlled trial." The search was limited to English-language articles published up to September 30, 2024.

2.2 Inclusion Criteria

Two authors independently screened the literature. After an initial review of titles and abstracts to exclude irrelevant studies, the full texts of potentially eligible articles were assessed. Studies were selected based on the PICOS framework: (i) Population (P): patients aged 18 years or older with coronary artery atherosclerosis undergoing PCI; (ii) Intervention (I): DAPT combined with any type of PPI; (iii) Comparator (C): DAPT without PPI; (iv) Outcomes (O): incidence of MACE and gastrointestinal complications; (v) Study Design (S): randomized controlled trials only.

The following studies were excluded from the analysis: (i) patients receiving aspirin or clopidogrel as stand-alone treatments; (ii) studies lacking information on the number of events (e) and total sample size (n); (iii) duplicate publications or overlapping data from the same trial; (iv) case reports.

2.3 Data Extraction

Two researchers independently extracted relevant data according to a pre-specified Excel template, including the first author's name, publication year, sample size, duration until randomization, intervention methods, follow-up duration, and outcome measures. Any disagreements between the two researchers were resolved through discussion with a third researcher.

2.4 Quality Assessment

The quality of the included studies was assessed independently by two researchers using the Cochrane Risk of Bias Tool. This assessment covered seven domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, handling of incomplete outcome data, selective reporting, and any other potential biases. Each domain was categorized as low risk, unclear risk, or high risk of bias, and a summary risk of bias graph was created.

2.5 Statistical Analysis

Network meta-analysis was performed utilizing the R package 'gemtc' alongside the Network module in STATA. Odds ratios (OR) and 95% confidence intervals (CI) were calculated to evaluate the efficacy and safety of various interventions, with a CI excluding 1 indicating statistical significance. Additionally, we computed the surface under the cumulative ranking curve (SUCRA) probabilities and treatment rankings as secondary endpoints for each intervention's effect. SUCRA values range from 0 to 100%, with higher values signifying better efficacy outcomes and lower risks for safety outcomes. Prior to conducting the network meta-analysis, inconsistency testing was performed; if inconsistencies were detected, an inconsistency model was employed; otherwise, a consistency model was applied.

3 Results

3.1 Literature Screening Process

A total of 8,632 studies were identified through computer searches in the databases. After removing duplicate entries, 5,026 articles were screened based on titles and abstracts. Following this screening, 4,924 articles were excluded, leaving 102 articles for full-text review. Of these, 96 were further excluded, resulting in the inclusion of 6 RCTs for analysis. (Figure 1)

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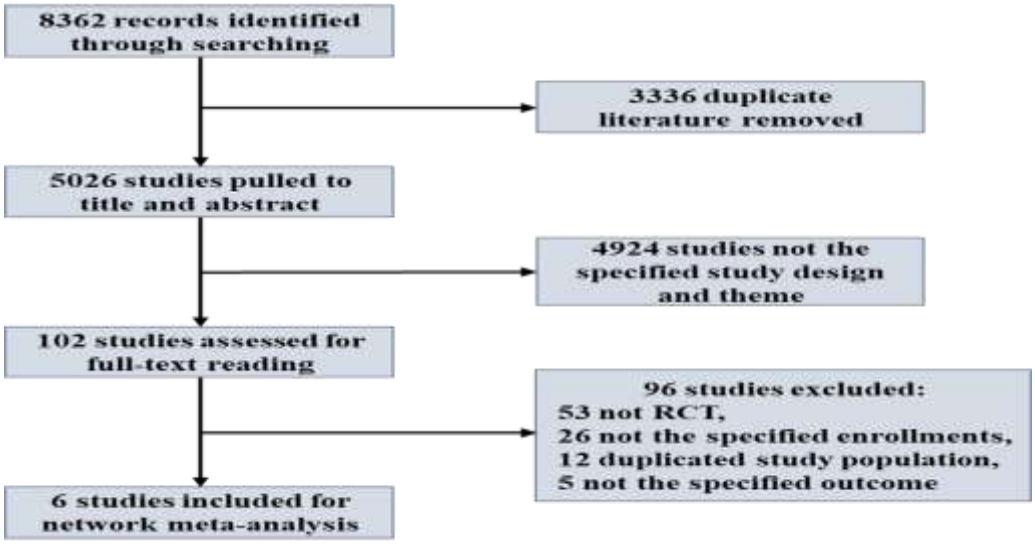

Figure 1: Flowchart of the literature screening process.

3.2 Basic Characteristics of Included Studies

This network meta-analysis included 6 RCTs with a total of 2,826 participants. All included studies were dual-arm trials, examining four treatment modalities: DAPT, DAPT combined with pantoprazole, DAPT combined with lansoprazole, and DAPT combined with omeprazole. Among the study population, 1,270 participants received DAPT with pantoprazole, 45 with lansoprazole, 129 with omeprazole, and 1,420 received DAPT without PPIs. (Table 1 and Figure 2)

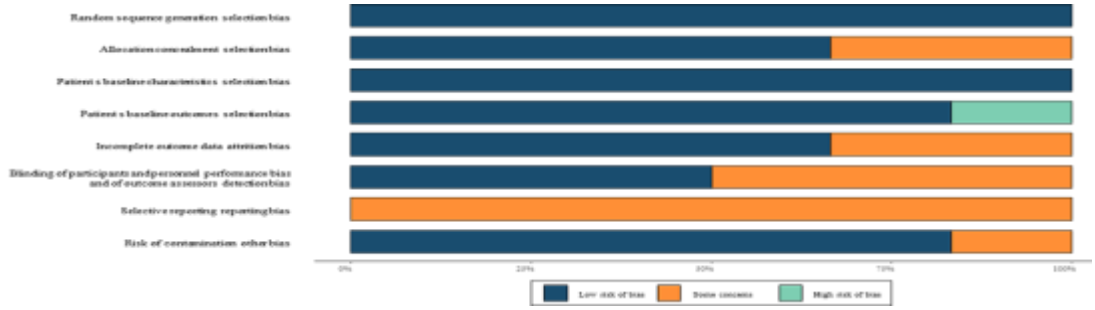

Figure 2: Risk of Bias (ROB) Graph for Publication Bias

3.3 Direct Meta-Analysis

3.3.1 Incidence of MACE

All 6 studies reported the incidence of MACE following intervention, and no consistency was found among the studies. The direct meta-analysis yielded an overall OR for MACE of 0.87 (95% CI: 0.71, 1.06). Subgroup analyses by PPI type revealed an OR of 0.85 (95% CI: 0.70, 1.05) for pantoprazole, 0.49 (95% CI: 0.04, 5.59) for lansoprazole, and 1.83 (95% CI: 0.51, 6.53) for omeprazole. The forest plot comparing MACE incidence after intervention is shown in Figure 3, indicating that the use of PPIs does not significantly affect the incidence of MACE. A contour-enhanced funnel plot was employed to assess publication bias, with missing studies distributed within the area of non-significance (the white area in Figure 4), indicating some degree of publication bias that necessitates additional studies. The funnel plot for publication bias is presented in Figure 4.

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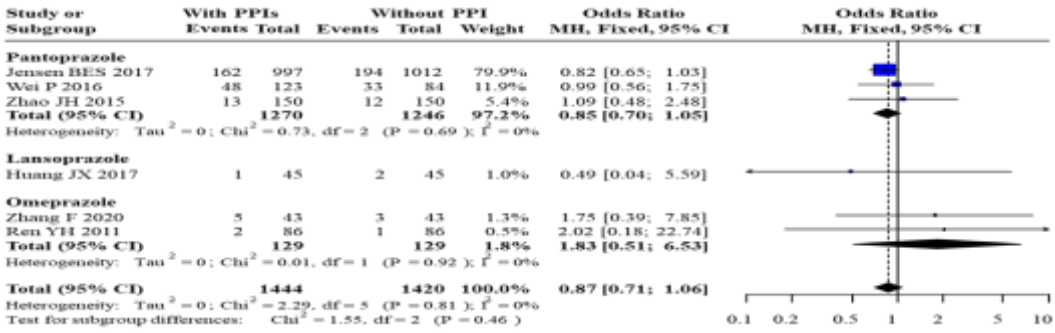

Figure 3: Forest Plot for Direct Comparison of Major Adverse Cardiovascular Events (MACE) Indicators.

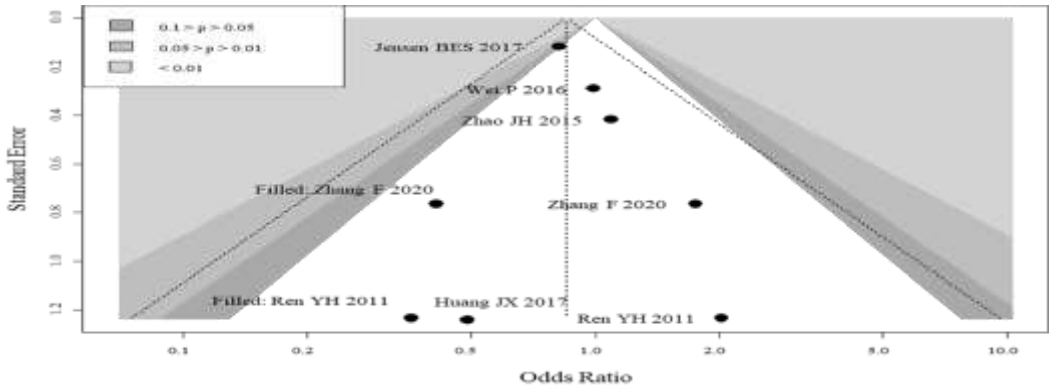

Figure 4: Funnel Plot for Publication Bias of MACE Incidence.

3.3.2 Incidence of Gastrointestinal Events

All 6 studies reported the incidence of gastrointestinal events post-intervention, revealing mild heterogeneity among the studies. A fixed-effects model was employed for analysis. The direct meta-analysis of gastrointestinal event incidence resulted in an OR of 0.22 (95% CI: 0.10, 0.46). Subgroup analysis by PPI type indicated significant heterogeneity in the pantoprazole subgroup, necessitating a random-effects model, yielding an OR of 0.23 (95% CI: 0.07, 0.70). For lansoprazole, the OR was 0.18 (95% CI: 0.02, 1.62), while for omeprazole, it was 0.13 (95% CI: 0.02, 0.73). The forest plot comparing gastrointestinal event incidence after intervention is shown in Figure 5, indicating that the use of PPIs significantly reduces the risk of gastrointestinal events, although this was not statistically significant for lansoprazole. A contour-enhanced funnel plot was again used to evaluate publication bias, with missing studies distributed within the area of non-significance (the white area in Figure 6), suggesting some publication bias that requires further investigation. The funnel plot for publication bias is shown in Figure 6.

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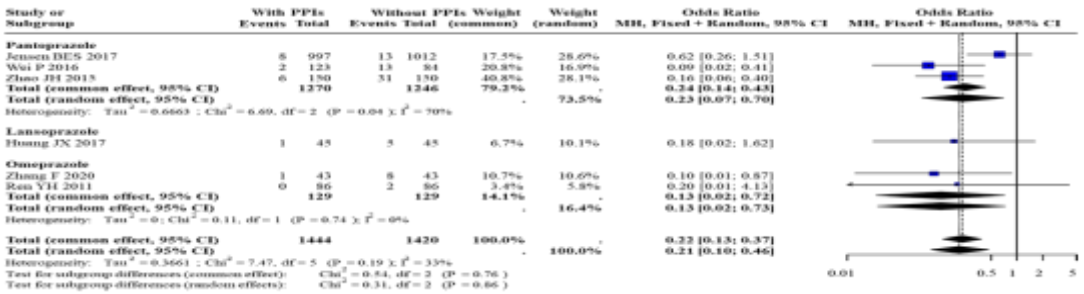

Figure 5: Forest Plot for Direct Comparison of Gastrointestinal Event Incidence

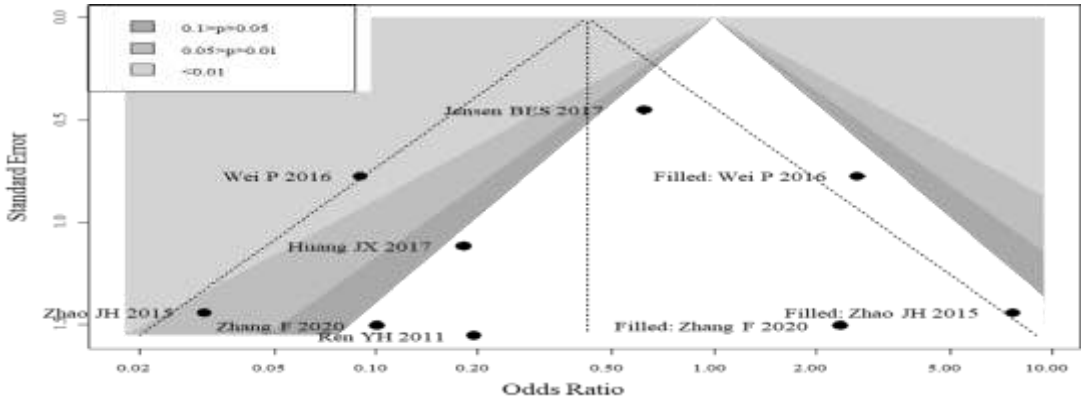

Figure 6: Funnel Plot for Publication Bias of Gastrointestinal Event Incidence.

3.4 Network Meta-Analysis

3.4.1 Network Diagram

To further assess the effects of different PPIs on MACE and gastrointestinal event incidence, a network meta-analysis was performed. Among the 6 included studies, 3 utilized pantoprazole, 1 utilized lansoprazole, and 2 utilized omeprazole (Figure 7), where the size of the nodes reflects the number of patients involved, and the thickness of the lines indicates the number of RCTs.

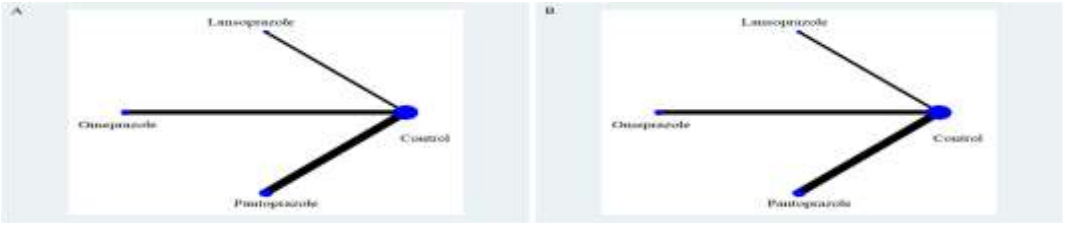

Figure 7: Network Diagram (A represents MACE indicators, B represents gastrointestinal event indicators).

3.4.2 Results of Network Meta-Analysis

The network meta-analysis results indicated no significant differences in the effects on MACE incidence among pantoprazole, lansoprazole, omeprazole, and the control group. However, both omeprazole and pantoprazole interventions were found to significantly reduce the risk of gastrointestinal events, while lansoprazole showed no significant effect. Additionally, there were no notable differences in gastrointestinal event risk among the different PPIs. The OR for the risk of MACE and gastrointestinal events across different interventions are summarized in Table 2.

Subsequently, we calculated the SUCRA values for different interventions regarding the risks of MACE and gastrointestinal events, presented in a SUCRA plot. For MACE

incidence, the SUCRA values were as follows: lansoprazole (73.9%), pantoprazole (71.4%), control (39.4%), and omeprazole (15.3%). For gastrointestinal event incidence, the SUCRA values were: omeprazole (74.5%), lansoprazole (63.4%), pantoprazole (57.9%), and control (4.2%). Higher SUCRA values indicate a lower risk of MACE and gastrointestinal events. The SUCRA results for MACE and gastrointestinal event incidence risks are illustrated in Figure 8.

Table 2: League Table for Network Meta-Analysis of MACE and Gastrointestinal Events.

Control	0.08 (0.02, 1.62)	**0.13 (0.02, 0.73)**	**0.24 (0.14, 0.43)**
2.56 (0.2, 74.53)	Lansoprazole	0.45 (0.01, 20.6)	1.70 (0.2, 52.04)
0.55 (0.13, 2.07)	0.21 (0.01, 3.83)	Omeprazole	3.75 (0.52, 109.6)
1.13 (0.72, 1.64)	0.44 (0.01, 5.96)	2.07 (0.51, 9.37)	Pantoprazole

Note: The cells below contain the Odds Ratios (OR) and 95% Confidence Intervals (CI) for the incidence of Major Adverse Cardiovascular Events (MACE), while the cells above contain the OR and 95% CI for the incidence of gastrointestinal events.

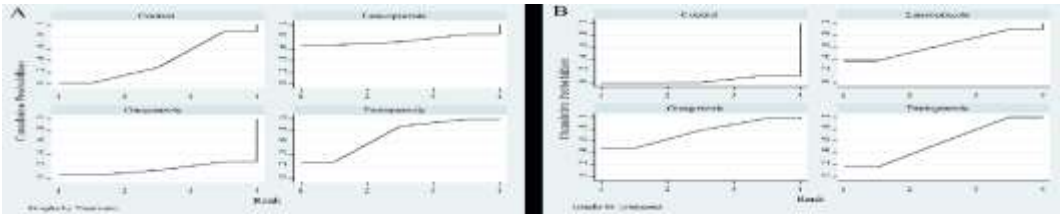

Figure 8: SUCRA Plot for Risk of MACE and Bleeding Incidence (A represents MACE indicators, B represents gastrointestinal event indicators).

4 Discussion

This systematic review and network meta-analysis evaluated the efficacy and safety profile of PPIs in conjunction with DAPT following PCI. The results from the direct meta-analysis indicate that the concurrent administration of PPIs significantly mitigates the risk of gastrointestinal complications without adversely affecting the incidence of MACE. The network meta-analysis further elucidated a preferred hierarchy for reducing MACE risk: lansoprazole emerged as the most effective, followed by pantoprazole and omeprazole. Conversely, for minimizing gastrointestinal event risk, omeprazole was the most effective, followed by lansoprazole and pantoprazole.

While antiplatelet therapy is fundamental in preventing cardiovascular events, it is also associated with an increased risk of gastrointestinal bleeding [16]. Consequently, clinical guidelines advocate for the use of PPIs to provide gastric protection for patients undergoing antiplatelet therapy, particularly those with identifiable bleeding risk factors, as this practice can attenuate the effects of aspirin and clopidogrel on platelet aggregation [17, 18]. Clopidogrel is a prodrug that necessitates metabolic conversion to its active form via the CYP2C19 enzyme [19]. Both omeprazole and esomeprazole are known inhibitors of CYP2C19, and their concomitant use with clopidogrel could lead to competitive inhibition, consequently heightening the risks of ischemic stroke, composite stroke, and myocardial infarction [20]. Pharmacokinetic studies suggest that omeprazole may diminish the efficacy of clopidogrel; however, large-scale clinical investigations have not definitively established that PPIs increase the risk of cardiovascular events or mortality in patients treated with clopidogrel [21]. Furthermore, the interaction potential of different PPIs with CYP2C19 varies, with

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evidence indicating that omeprazole poses the highest risk for clinically significant interactions, followed by lansoprazole, while pantoprazole and rabeprazole exhibit the lowest probabilities [22, 23]. Some studies have linked the use of omeprazole or esomeprazole in conjunction with clopidogrel to an elevated risk of adverse outcomes following PCI with drug-eluting stents [8]. Our findings corroborate this perspective, as the preferred hierarchy for reducing MACE risk was lansoprazole, pantoprazole, and omeprazole, with SUCRA values of 73.9%, 71.4%, and 15.3%, respectively. However, it is noteworthy that only one RCT was included regarding lansoprazole, necessitating further investigation to validate the observed differences compared to pantoprazole.

We juxtaposed our findings with those of previous meta-analyses. Liang et al. [24] conducted a meta-analysis involving 8 RCTs that assessed the effects of PPIs combined with DAPT in patients post-acute coronary syndrome (ACS) and PCI, confirming that this combination reduces the risk of gastrointestinal complications without influencing cardiovascular event rates—aligning with our study's focus on post-PCI patients. Khan et al. [25] performed a meta-analysis of 5 RCTs and demonstrated that the simultaneous use of PPIs with P2Y12 inhibitors provides protective effects against gastrointestinal events, consistent with our conclusions, though they did not differentiate among various PPIs. Luo et al. [26] found that in patients with coronary heart disease (CHD), the combination of PPIs and DAPT was associated with a reduction in gastrointestinal complications but an increase in MACE risk among those using esomeprazole during PCI. This meta-analysis primarily included observational studies, leading to conclusions that differ somewhat from our findings. Khan et al. [27] noted that RCT-based meta-analyses indicated no increased risk of all-cause mortality associated with PPIs; however, contradictory findings emerged from observational studies.

This study does have several limitations. First, the number of studies included is relatively limited, particularly concerning lansoprazole, which was represented by only one publication. Second, the small sample sizes of the included studies may bias the quality of the evidence. Lastly, some degree of publication bias was observed among the literature, indicating that further research is warranted to solidify our conclusions.

Conclusion

For patients undergoing PCI, the combination of DAPT and PPIs is advised to reduce the risks of both cardiovascular and gastrointestinal events. However, careful consideration must be given to the differential effects of various PPIs on the antiplatelet activity of clopidogrel. It is prudent to avoid strong CYP2C19 inhibitors such as omeprazole and esomeprazole, while alternatives such as pantoprazole and rabeprazole may be more appropriate.

Declarations

Ethics approval and consent to participate: This meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for network meta-analyses. As this study does not involve clinical trials, it is exempt from ethical approval and the requirement for informed consent.

Consent for publication: Not applicable.

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Conflicts of Interest: The authors declare that they have no conflict of interest.

Author Contributions: JZ is responsible for the guarantor of integrity of the entire study, study concepts & design, definition of intellectual content, literature research, clinical studies, data acquisition & analysis, statistical analysis, manuscript preparation & editing & review; XLH is responsible for the guarantor of integrity of the entire study, study concepts & design, definition of intellectual content, statistical analysis, manuscript preparation & editing; WXM is responsible for the guarantor of integrity of the entire study, study concepts & design, data analysis, manuscript review. All authors read and approved the final manuscript.

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