RESEARCH ARTICLE

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Influence of Proton Pump Inhibitor on clinical outcomes in Post Percutaneous Coronary Intervention Patients Receiving Clopidogrel-Meta Analysis

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Abstract

Background and Aim: Proton Pump Inhibitors (PPIs) are frequently advised to cardiac patients as part of their polypharmacy regimen to reduce gastrointestinal bleeding. Clopidogrel and PPIs are both prodrugs that exploit the cytochrome P450 enzyme system, notably P450 (CYP2C19) leading to inadequate antiplatelet action in response to clopidogrel which may potentially lead to severe cardiovascular events. **Methods:** We conducted a meta-analysis study which included papers from EMBASE, WOS, PubMed, The Cochrane Library, and The Chinese Biomedical Medical Literature Database that were published up to December 2019. The Cochrane Review Manual 5.0.2 criteria were used to assess the studies' quality. The complete statistical study was carried out using the RStudio package version 1.3.1073. The assumption of heterogeneity was tested using a chi-square test based on a Q-test. **Results:** We selected 16 studies with 61,835 patients for our meta-analysis, comprising 33,964 non-PPI patients and 27,871 PPI patients who also took clopidogrel. Forest plots were built for each of the outcomes to gather the results. **Conclusion:** According to the study, individuals who had PPI and clopidogrel had an increased risk of major adverse cardiovascular events (MACE), MI recurrence, stent thrombosis, and stroke. As with bleeding, there is no statistical significance, indicating that the two groups are equivalent. Several peer-reviewed studies contradicted these conclusions.

Major Findings: 1. Patients consuming proton pump inhibitors and clopidogrel after PCI exhibited higher risk of major adverse cardiovascular events, myocardial infarction recurrence, stent thrombosis and stroke. 2. PPIs inhibit CYP2C19 enzyme which is crucial for clopidogrel activation. This interaction reduces clopidogrel's anti platelet efficacy resulting in positive cardiovascular events. 3. No statistical difference for bleeding risk in post PCI patients consuming clopidogrel with or without PPI.

Keywords: Cardiovascular Disease, Clopidogrel, Meta-Analysis, Percutaneous Proton Pump, Percutaneous Coronary Interventions

1. Introduction

The first-line treatment for cardiovascular events in people with coronary artery disease is the antiplatelet drug clopidogrel. To avoid gastrointestinal problems, including ulceration and bleeding, Proton Pump Inhibitors (PPIs) are frequently recommended in addition to clopidogrel[1]. Clopidogrel is generally given to post-PCI patients to reduce recurrent cardiac events and mortality[2]. Although PPIs are frequently prescribed with clopidogrel to reduce the risk of bleeding, there is a growing concern that this practice is decreasing the efficacy of clopidogrel[3]. The prodrug clopidogrel is transformed into thiol-containing active metabolites, which have anti-platelet aggregation

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capabilities, in the liver by the CYP450 (CYP2C19) isoenzymes. By binding to the P2Y12 receptor, clopidogrel blocks the activation of the ADP glycoprotein IIa-IIIb pathway[4]. The same isoenzymes also metabolize PPIs. PPIs suppress the CYP2C19 enzyme, which may reduce the conversion of clopidogrel to its active metabolite, decreasing the drug and anti-platelet effectiveness and leading to unfavorable clinical outcomes[5]. When given alongside PPI, clopidogrel's effectiveness is claimed to have decreased significantly in several pharmacodynamic trials. Numerous observational studies and Randomized Controlled Trials (RCTs) have produced conflicting findings that these two medications may interact metabolically, raising the risk of cardiovascular outcomes[6]. In comparison to patients who use clopidogrel alone, post-PCI patients who concurrently took clopidogrel and proton pump inhibitors had a greater risk of adverse cardiovascular events like bleeding, stroke, myocardial reinfarction, stent thrombosis, and rehospitalization[7]. And hence, the study was proposed and carried out by the use of systematic review and meta-analysis techniques to assess the impact of concurrent use of PPIs and clopidogrel on the cardiovascular outcomes in patients with post-percutaneous coronary interventions and atherosclerotic heart disease.

2. Methods

2.1 Eligibility Criteria

Meta-analysis and RCT studies published in peer-reviewed publications were considered, with no restrictions on language or structure. Patients who have had atherosclerotic heart disease and PCI (Percutaneous Coronary Intervention) were included. Animal studies, studies involving additional anti-platelet medications like aspirin and anticoagulants, cross-over studies, self-controlled case series studies, studies with a substantial difference in baseline analysis groups, and studies with no baseline analysis were all omitted. Meta-analysis studies have been undertaken based on the interaction of clopidogrel with PPIs.

2.2 Search Strategy

To find the pertinent studies, a review of PubMed, EMBASE, WOS, The Chinese Biomedical Medical Literature Database, and The Cochrane Library was done. Up till December 2019, articles published were included in our meta-analysis. The search strategy for the meta-analysis included the terms clopidogrel, Proton Pump Inhibitors (PPIs), *pantoprazole, ilaprazole, esomeprazole, lansoprazole*, and *omeprazole*. It also included the phrase "interaction between the PPI and clopidogrel in individuals with coronary artery disease".

2.3 Selection of Study

Two reviewers checked the articles' titles and abstracts to see if they complied with the requirements, and those that didn't were rejected. Full reports of possibly pertinent publications were acquired by two reviewers, who then independently examined the relevant articles. The study site, drug exposure, research design, participant characteristics, and relevant outcomes were collected and entered into a table. The two reviewers discussed the papers to decide whether or not the study should be included if there was any disagreement. When there were questions that needed answers or instances where the data was incorrect, we got in touch with the writers. The flow diagram for the selection of articles for the analysis is shown in Figure 1.

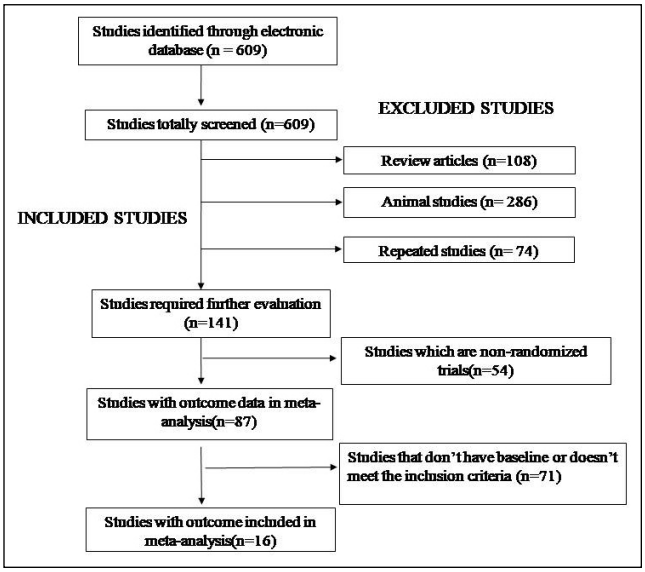


Figure 1. Flow diagram for selection of the articles.

2.4 Extraction of Data and Evaluation of Quality

The quality of the identified studies that satisfied the inclusion criteria for our meta-analysis was assessed using the Cochrane Review Manual 5.0.2 criteria. We evaluated possible sources of bias as yes, no, or uncertain

for each individual publication using the criteria specified in the review manual (i.e., the result is unclear or the insufficient information in the articles). MACE (Major Acute Cardiovascular Events), recurrence of myocardial infarction, and Stent thrombosis are the primary outcomes of our meta-analysis. Stroke and bleeding events were secondary outcomes in our meta-analysis.

2.5 Statistical Analysis

The RStudio software package version 1.3.1073 was used for all statistical analysis. The association between PPI and NON-PPI was measured using an OR (Odd Ratio) and a 95% confidence interval.

2.6 Statistical Heterogeneity

A chi-square test based on a Q-test was used to examine the assumption of heterogeneity. Low, moderate, and high degrees of heterogeneity, respectively, are indicated by I^2 figures of 25, 50, and 75%. If $p<0.05$ and/or $I^2> 50\%$, a random-effect model with a 95 percent Confidence Interval (CI) was employed to calculate the pooled Odd Ratio (OR).

3. Results

Using precise search criteria, 609 articles were identified. Based on the titles and abstracts of each published paper 108 review papers, 286 non-clinical trials, and 74 repeated studies were excluded. Further assessment of articles was performed, 54 non-randomized controlled trials and 71 studies with unfulfilled inclusion criteria were removed. Thus, a total of 16 randomized controlled trials were included in the meta-analysis, which comprised 61,835 patients of which 33,964 were non-PPI patients and 27,871 patients received PPI with clopidogrel. To obtain the results, forest plots were created for each of the outcomes. The demographic details of the study population are depicted in Table 1. The study outcome and its validity have been demonstrated in Table 2.

Of ten studies, 5 studies statistically demonstrated significant MACE outcomes on PPI administration with clopidogrel (Figure 2). The 95% confidence intervals of four studies overlap at 1, however, the random effect's 95% confidence intervals do not overlap at 1. As a result, both the meta-analysis and the study level ($p<0.01$) showed statistical significance. The overall effect estimate and its 95% confidence intervals are at the left of the line of effect showing MACE outcomes in the PPI-added clopidogrel

Table 1. Baseline characteristics of the study population

S No	Included Studies	Age		Male		Hyper Tension		Diabetes Mellitus	
		NON-PPI	PPI	NON-PPI	PPI	NON-PPI	PPI	NON-PPI	PPI
1.	Jian Jun Zou – 2014	65.7	66.2	73.9%	73.5%	70.4%	71.3%	23.6%	25.8%
2.	Robert.A.Rossini 2010	63	64	81.2%	75.6%	65.2%	63.6%	28.0%	27.1%
3.	Michael-2010	63.7	63.8	64.1%	61.9%	74.8%	78.5%	33.1%	36.3%
4.	Bukard – 2011	63.3	66.5	79.9%	68.8%	65.0%	72.5%	17.2%	29.6%
5.	Ekta.G. – 2010	62	61.7	N/A	N/A	68%	76%	30%	36%
6.	Ayub – 2016	69.4	64.7	89.5%	77.2%	N/A	N/A	N/A	N/A
7.	Bhatt – 2010	68.7	68.5	69.5%	66.9%	81.4%	80.1%	28.6%	31.57%
8.	Simon T – 2011	65	64	N/A	N/A	53%	52%	35%	30%
9.	Takeo – 2010	67.4	69.0	72.4%	67.0%	64.8%	64.1%	39.7%	35.0%
10.	Subash – 2010	64.5	63.8	98.3%	98.2%	92.4%	88.9%	51.4%	45.1%
11.	R.P.kreutz – 2010	65.2	67.5	73.9%	62%	46.5%	50.6%	22.7%	25.9%
12.	O.Donoghue – 2009	60	62	74.7%	70.3%	63.5%	65.9%	22.5%	24.2%
13.	Rassen – 2010	74.3%	75.7%	64.0%	53.9%	60.4%	65.9%	26.4%	27.6%
14.	Goodman – 2012	62	63	N/A	N/A	65.4%	65.6%	24.7%	25.8%
15.	Hiroshi Y - 2009	67	71	82.2%	66.7%	N/A	N/A	N/A	N/A
16.	Rahel H - 2012	64	68	74.3%	70.1%	62.1%	79.3%	15.8%	12.6%

Table 2. Various study outcomes and their duration

Authors	Group (Non PPI Use)	Group (PPI Use)	Patient Type	Outcome	Follow Up
Jian Jun Zou-2014	1456	6188	Post PCI	MACE, MI, stent thrombosis	5 years
Takeo -2010	119	103	Post PCI	Bleeding, stent thrombosis, MACE	3 years
Robert.A. Rossini 2010	170	1158	Post PCI	MACE, bleeding events, stent thrombosis	1 year
Hiroshi Y -2009	135	108	Post PCI	Bleeding	2 years
Michael- 2010	502	318	Post PCI	MI, stent thrombosis, MACE	1 year
Rahel H- 2012	631	87	Post PCI	Bleeding	23 months
Subash 2010	3678	867	Post PCI	MACE, stent thrombosis	6 year
Burkard 2011	692	109	Post PCI	MACE, MI, stent thrombosis	3 years
Ekta G- 2009	243	72	Post PCI	MACE	50 months
O Donoghue 2009	4538	2257	Post PCI	MI, stent thrombosis, bleeding	1 year
Ayub 2016	287	453	Post PCI	MACE	1 year
Bhatt 2010	1885	1876	Post PCI	Stroke, MACE, MI	6 months
Simon T 2011	900	1453	Post PCI	MACE, MI	3 years
Rassen 2009	2845	2739	Post PCI	MI	1 year
Goodman 2012	6021	3255	Post PCI	MI, stent thrombosis	6 months
Rolf P.kreutz 2010	9862	6828	Post PCI	Stroke MI	12 months

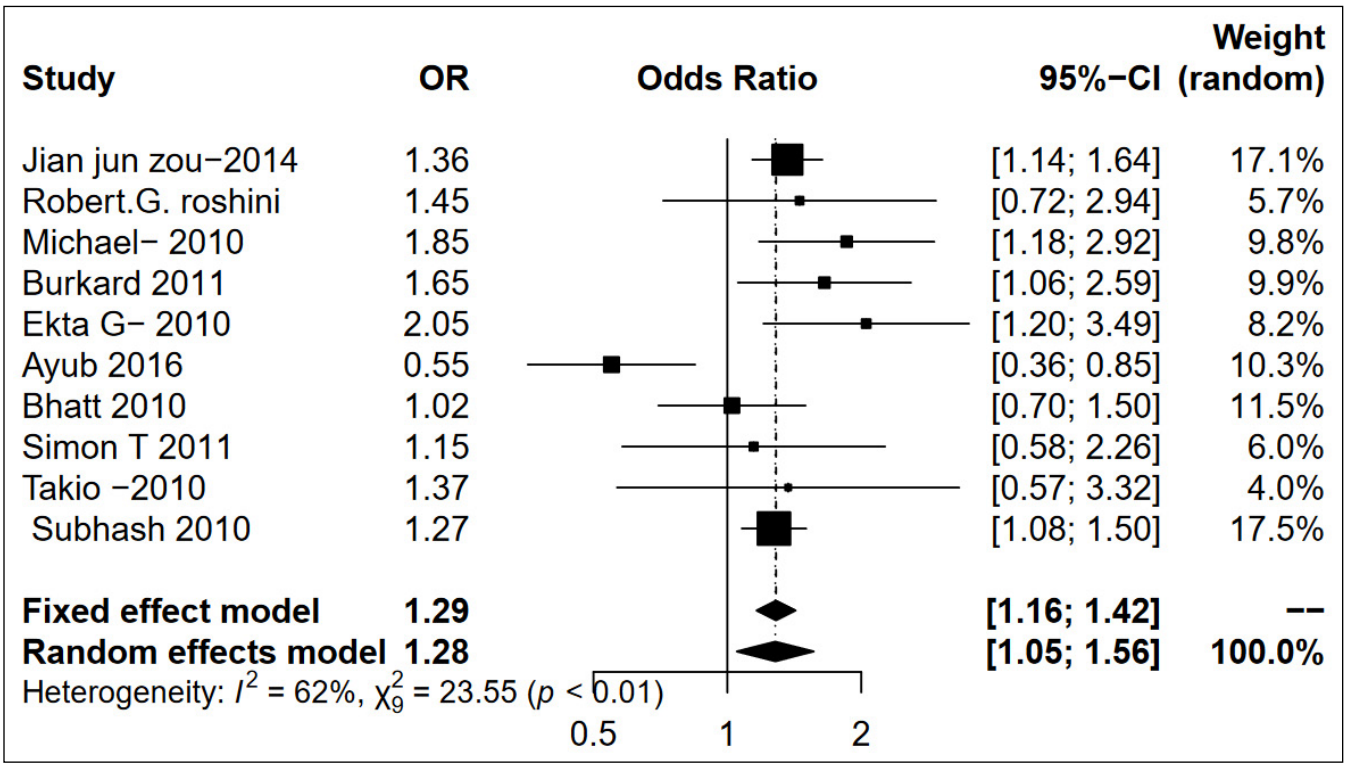


Figure 2. Major Adverse Cardiovascular Events (MACE) as an outcome of the interaction between Clopidogrel and Proton Pump Inhibitors.

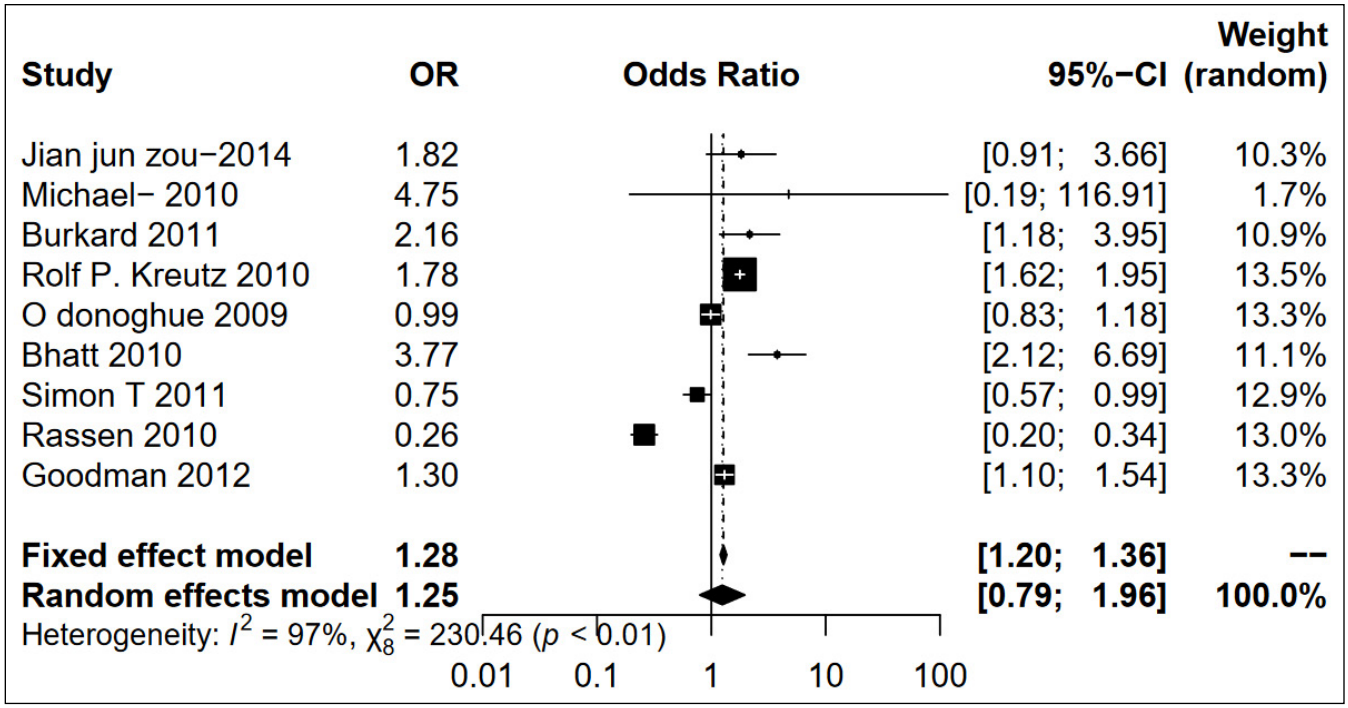


Figure 3. Myocardial infarction recurrence as an outcome of interaction between clopidogrel and Proton Pump Inhibitors.

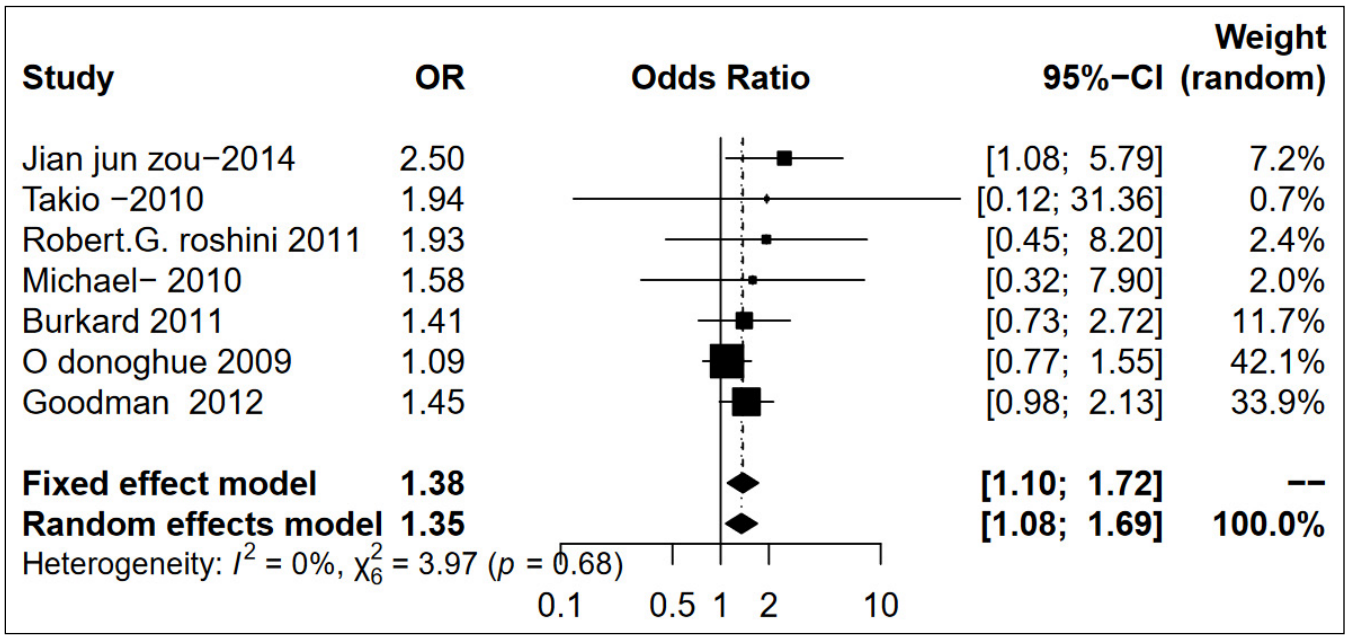


Figure 4. Stent thrombosis as an outcome of the interaction between Clopidogrel and Proton Pump Inhibitors.

group, making interpretation easier. (OR1.29; 95% CI ;1.16-1.42) significant heterogeneity (I^2=62%)

Of ten studies, four studies statistically demonstrated significant myocardial infarction outcomes on PPI administration with clopidogrel (Figure 3). The 95% confidence intervals of the three studies overlap at 1, however, the random effect's 95% confidence intervals do not overlap at 1. As a result, both the meta-analysis and the study level (p<0.01) showed statistical significance. The overall effect estimate and its 95% confidence intervals are at the left of the line of effect showing myocardial reinfarction outcomes in the PPI-added

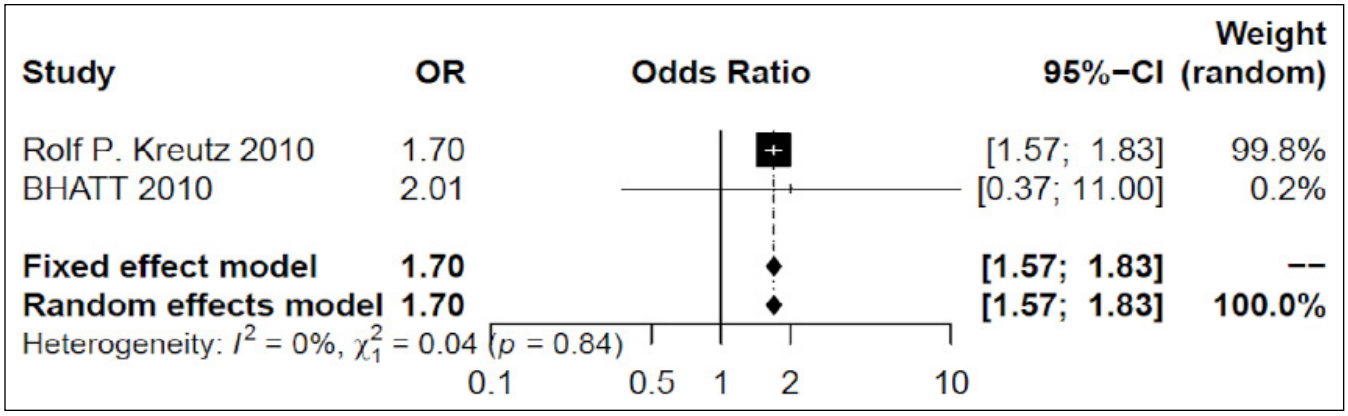


Figure 5. Stroke as an outcome of the interaction between Clopidogrel and Proton Pump Inhibitors

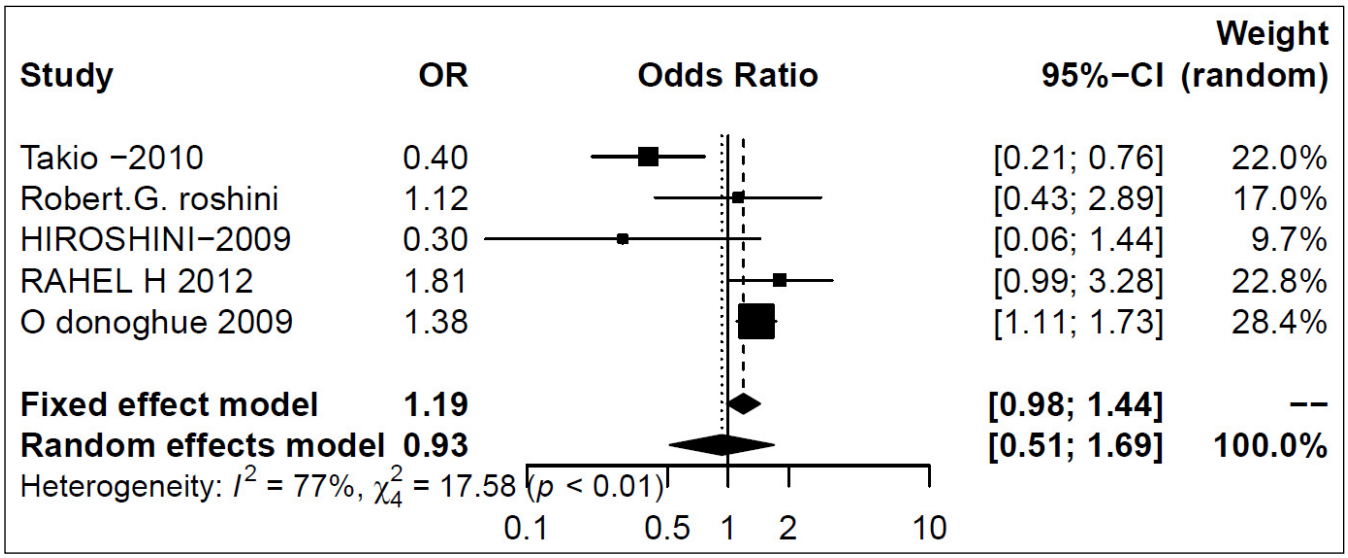


Figure 6. Bleeding as an outcome of interaction between Clopidogrel and Proton Pump Inhibitors.

clopidogrel group, making interpretation easier. (OR1.20; 95% CI ;1.20-1.36) significant heterogeneity (I^2=97%).

Of seven studies, one study statistically demonstrated significant stent thrombosis outcome on PPI administration with clopidogrel (Figure 4). The 95% confidence intervals of six studies overlap at 1, however, the random effect's 95% confidence intervals do not overlap at 1. As a result, both the meta-analysis and the study level (p<0.01) showed statistical significance except for one study (p=0.68). The overall effect estimate and its 95% confidence intervals are at the left of the line of effect showing stent thrombosis outcomes in the PPI-added clopidogrel group, making interpretation easier. (OR1.38; 95% CI; 1.10-1.72) significant heterogeneity (I^2=0%).

Of two studies, one study statistically demonstrated significant stroke outcomes on PPI administration with clopidogrel (Figure 5). The 95% confidence intervals of one study overlap at 1, however, the random effect's 95% confidence intervals do not overlap at 1. As a result, both the meta-analysis and the study level (p<0.01) showed statistical significance except for one study (p=0.84). The overall effect estimate and its 95% confidence intervals are at the left of the line of effect showing stroke outcomes in the PPI-added clopidogrel group, making interpretation easier. (OR 1.70; 95% CI; 1.57-1.83) significant heterogeneity (I^2=0%).

Of five studies, two studies statistically demonstrated significant bleeding outcomes on PPI administration with clopidogrel (Figure 6). The 95% confidence intervals of the two studies overlap at 1. As a result, both the meta-analysis and the study level (p<0.01) showed no statistical significance. Because the overall impact estimate and

its 95% confidence intervals overlap the line of effect, indicating a reduced risk of bleeding, the interpretation is incoherent. (OR 1.19; 95% CI; 0.98-1.44) significant heterogeneity (I^2=77%).

4. Discussion

According to the meta-analysis, the incidence of MACE, myocardial infarction recurrence, stroke, and stent thrombosis was lower in Non-PPI patients compared to patients taking PPI along with clopidogrel. Since there is no statistical significance in bleeding, the two groups are comparable. These findings were found to be contraindicated in numerous previously published study articles.

Clopidogrel is an anti-platelet medication that undergoes metabolism in the liver by hepatic cytochrome P450 enzymes, especially with CYP2C19 polymorphism. Clopidogrel inhibits fibrinogen polymerization by binding to the ADP Receptor P2Y12[8,9]. PPIs form an irreversible bond with the proton pumps in the parietal cells of the stomach thus lowering gastric acid secretion. The same CYP2C19 enzyme is also involved in the metabolism of proton pump inhibitors. Proton pump inhibitors are used to alleviate GI bleeding caused by the long-term use of clopidogrel, which otherwise causes gastric bleeding[10,11]. By competitively inhibiting the CYP2C19 enzyme, PPI may affect clopidogrel activity and result in drug interactions. As a result of this drug interaction, the risk of cardiovascular events and mortality is increased[12–14]. The final results of the meta-analysis illustrate that there is a possibility of high chance of MACE, myocardial infarction recurrence, stroke, and stent thrombosis.

Our study concentrated on individuals who had undergone PCI and had concurrent administration of clopidogrel and Proton Pump Inhibitors (PPIs), which raised the risk of death and cardiovascular events. On estimating the forest plot there was a significant chance of MACE outcome with OR 1.29; 95% CI:1.16-1.42 with significant heterogeneity and I^2=62%. The outcome for myocardial infarction recurrence was OR 1.20; 95% CI: 1.20-1.36 with significant heterogeneity I^2=97%. The chances of stent thrombosis were OR 1.38; 95% CI 1.10-1.72 significant heterogeneity I^2=0% and stroke showed OR 1.70; 95% CI 1.57-1.83 significant heterogeneity I^2=0%. Whereas there was no significant statistical difference seen for the outcome of bleeding OR 1.19; 95% CI 0.98-1.44 with significant heterogeneity I^2=77%.

Gilard M *et al.,*[15] found that concurrent treatment of PPI's resulted in a significant decrease in clopidogrel's inhibitory action on platelets when phosphoprotein phosphorylation was increased by a vasodilator, which indicates the mechanism behind PPI's influence on clopidogrel. According to the findings, the groups receiving PPIs in addition to clopidogrel differed significantly from those receiving clopidogrel alone. PPIs are frequently used in clinical practice to prevent bleeding, yet several included studies found no appreciable decline in bleeding episodes[16]. Because only a small proportion of patients using clopidogrel had a higher risk of gastrointestinal bleeding, there was no statistically significant difference between the clopidogrel-supplemented PPI group and the clopidogrel alone group. All patients' bleeding episodes were minimal[17,18].

According to several pharmacokinetic studies, clopidogrel and PPIs have competitive drug interactions. When taken simultaneously, the pharmacological impact of PPI reduces the effectiveness of clopidogrel, which reduces the gastrointestinal protective role of PPIs[19].

Several randomized studies have been conducted that demonstrated the effect of PPIs influence clopidogrel pharmacokinetics. According to the findings, lansoprazole, pantoprazole, and dexlansoprazole had less of an inhibitory effect on the active metabolite of clopidogrel and platelet function, whereas administration of esomeprazole or omeprazole with clopidogrel led to a competitive drug interaction that affected the pharmaceutical activity of clopidogrel[20].

A black box warning by the US FDA was announced regarding patients who have CYP2C19 poor metabolizers, the co-administration of clopidogrel along with PPIs such as omeprazole or esomeprazole should not be used whereas PPIs such as pantoprazole and lansoprazole who are not much dependent on CYP2C19 can be administered with clopidogrel as they have fewer drug interactions[21].

This study validated several previous studies on concomitant use of clopidogrel with PPIs. Major Cardiovascular events such as myocardial infarction recurrence, stent thrombosis, stroke, and rehospitalization

were found to be associated with concomitant use of clopidogrel with PPIs.

5. Conclusion

The findings of this meta-analysis concluded that post-PCI patients receiving clopidogrel along with PPI had a distinct risk of cardiovascular events such as MACE, myocardial infarction recurrence, stroke, and stent thrombosis compared to non-PPI patients.

6. Abbreviations

Mace- Major Adverse Cardiovascular Event, PCI-Percutaneous Coronary Intervention, PPI-Proton Pump Inhibitor, USFDA- United States Food and Drug Administration, CYP2C19 Cytochrome P450 Isoenzyme, OR-Odds Ratio, CI- Confidence Interval, I^2-Substantial Heterogeneity.

7. Authors Contribution

All of the authors contributed significantly to the study's conception, design, and execution. Data collection, analysis, and interpretation were done by Nezamuddin, Sujit, Laxman, Srivarshn, and Sukesh. Nezamuddin, Balavigneshwaran, and Benil wrote the manuscript. Sarumathy S provided a critical assessment of the article and provided final approval.

Each author has reviewed the final manuscript and given their approval.

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