

Review Article

Lack increased evidence of cardiovascular events in patients receiving clopidogrel with proton-pump inhibitors: a meta-analysis and system review

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Abstract: Recently, cardiologists raised concerns about the adverse cardiovascular outcomes meta-analysis to further evaluate the cardiovascular effect in patients receiving clopidogrel, with and without concomitant treatment with proton pump inhibitors. A multitude of studies published up to July 2017 that investigated the association of concomitant therapy of proton pump inhibitor and clopidogrel in patients with cardiovascular effects were collected from MEDLINE, Cochrane, EMBASE, Chinese Biomedical Literature Database (CBM), and the conference proceedings from important cardiology and gastroenterology meetings. To ensure the rigor of the research, we only included original studies published in English and Chinese. This meta-analysis was performed with the random-effect or fixed-effect models according to the presence or absence of significant heterogeneity. A total of 9 placebo-control RCTs were involved in this study. A total of 22,890 patients aged 40 years or older were available for analyses. Among the included studies, three studies were from multi-country, one study was in American and Canada; five studies were from Asian. The number of participants ranges from 30 to 9191, including men and women. The types of PPI included omeprazole, lansoprazole, pantoprazole, esomeprazole, and rabeprazole. Our meta-analysis of the studies assessing PPIs as a class compared with placebo showed no difference in composite ischemic endpoints, all-cause mortality, nonfatal MI, stroke, despite a reduction in upper gastrointestinal bleeding with omeprazole (RR 1.06, 95% confidence interval [CI] 0.95-1.18; P=0.27, with heterogeneity among trials ($I^2=57\%$). We did subgroup analysis, pooling data of five RCTs from Asia showed no increased risk of MACE in patients administered PPIs with clopidogrel and aspirin (RR 0.81, 95% confidence interval [CI] 0.58-1.13; P=0.21). There was no statistical heterogeneity among the five subgroup studies ($I^2=0\%$). At present, data from pharmacokinetic and pharmacodynamics studies have indicated that there might be an adverse interaction between clopidogrel and proton pump inhibitor. Therefore, the clinical validity or possible relevance to the hypothesized the interaction of clopidogrel and PPI need further investigation and discussion.

Keywords: Proton pump inhibitors, clopidogrel, adverse cardiovascular event, meta-analysis

Introduction

It has been recognized that platelet activation and aggregation play a critical role in the pathogenesis of thrombosis and atherosclerotic process [1]. Platelet activation and aggregation may cause not only acute coronary syndrome (ACS) but also major adverse cardiac events (MACE) in patients following coronary angioplasty [2, 3]. Several international guidelines [4-8] have already recommended dual usage of aspirin and clopidogrel for the prevention of ACS and MACE after percutaneous coronary

intervention (PCI). However, patients receiving this dual antiplatelet therapy (DAPT) showed an increased risk of gastrointestinal hemorrhage. Data from several trials have proved the concept that prophylactic use of proton-pump inhibitors (PPIs) may decrease the rate of gastrointestinal bleeding. Clopidogrel, a thienopyridine, is a prodrug. In liver, about 15% absorbed clopidogrel converted to an active metabolite by hepatic cytochromes (CYP450) enzymes in a 2-step process. It has demonstrated that CYP2C19, CYP1A2, CYP2B6 isoenzymes have a crucial role in the first step, and CYP2C19,

CYP3A4, CYP2C9 play a vital role in the second phase. Of note, PPIs are extensively metabolized by competitively inhibiting CYP2C19 and CYP3A4 and therefore interfere with clopidogrel metabolites [9, 10]. Gilard [11] firstly proposed that the drug interactions might occur with concomitant use of clopidogrel and PPIs. Later, multiple pharmacodynamics and pharmacodynamics trials have pointed out the influence of PPIs treatment on the antiplatelet action of dual therapy with clopidogrel and aspirin [12]. Increasing evidence suggests the concomitant use of clopidogrel and PPIs might induce negative cardiovascular events. Pharmacokinetic and pharmacodynamics studies have found that the postulated adverse interaction between proton pump inhibitors (PPIs) and clopidogrel may not represent a class side-effect, i.e. individual PPIs (particularly omeprazole and esomeprazole) have a demonstrable communication, while pantoprazole appears to be few problematic [13-16]. However, some RCTs did not find such a correlation. Up to now, whether the concomitant treatment of proton pump inhibitors and clopidogrel might induce adverse cardiovascular events remains controversial. For lacking high-quality articles in the previous meta-analysis, We, therefore, performed this meta-analysis of the randomized controlled trials (RCTs) to evaluate whether the concomitant use of clopidogrel plus PPIs may increase the incidence of major adverse cardiovascular events (MACE), ACS, stent thrombosis and stroke, et al.

With the development of clinical research regarding the application of clopidogrel, it has been found that the reduced drug metabolism of clopidogrel is a common phenomenon in Asian populations compared with regions for other international, on account of the prevalence of CYP2C19 loss-of-function alleles in Asian patients. Previous meta-analyses were lacking high-quality papers, the included studies are very mixed, and no published researchers specifically explored the potential drug-drug interactions between PPIs and clopidogrel in Asian populations. So we also did subgroup to analysis whether cardiovascular risks exist in Asian populations. To make rational clinical decisions for individual patients as well as policy decisions for the health of the general public. The present meta-analysis attempts to use all relevant evidence to answer the question of

whether concomitant use of PPIs and clopidogrel is related to the increased risks of major cardiovascular events (MACE), ACS, all-cause mortality, cardiovascular death, stent thrombosis and stroke. We also tried to clarify whether the potential risk is the same among Asian populations.

Materials and methods

Eligibility criteria

The search strategy focus on RCTs studies. In the RCT studies, patients receiving clopidogrel were classified into two groups that are those who were PPI users or non-PPI users. Outcomes of the interests included MACE (defined as death, ACS, cerebrovascular accident, stent thrombosis, revascularization, etc.), ACS, all-cause mortality, cardiovascular death, stent thrombosis, and stroke. Reviews, nonclinical investigations, letters, comments, articles with data of platelet activity only or no available data and articles published other than in Chinese or English were excluded.

Search strategy and selection criteria

We performed comprehensive literature retrieve to search all published randomized controlled trials (RCT) up to July 1, 2017, which concerned PPI treatment to prevent gastrointestinal hemorrhage in patients receiving this dual antiplatelet therapy (DAPT), using searching engines such as Medline (<http://www.nlm.nih.gov/bsd/pmresources.html>), Embase (<http://www.elsevier.com/solutions/embase-biomedical-research>) and Cochrane (<http://uk.cochrane.org/>).

Data sources and searches

An electronic search of EMBASE (1996 to 2017), MEDLINE (1948 to 2017), Cochrane (1996 to 2017), and Chinese Biomedical Literature Database (CBM, 1990 to 2017), were performed using the search Clopidogrel/Plavix and PPI/omeprazole/lansoprazole/pantoprazole/esomeprazole/rabeprazole. Search strategies were developed according to the characteristics of the different database. Bibliographies from included articles and review articles were hand-searched, and experts in this field were consulted to ensure our inclusion of all pertinent studies.

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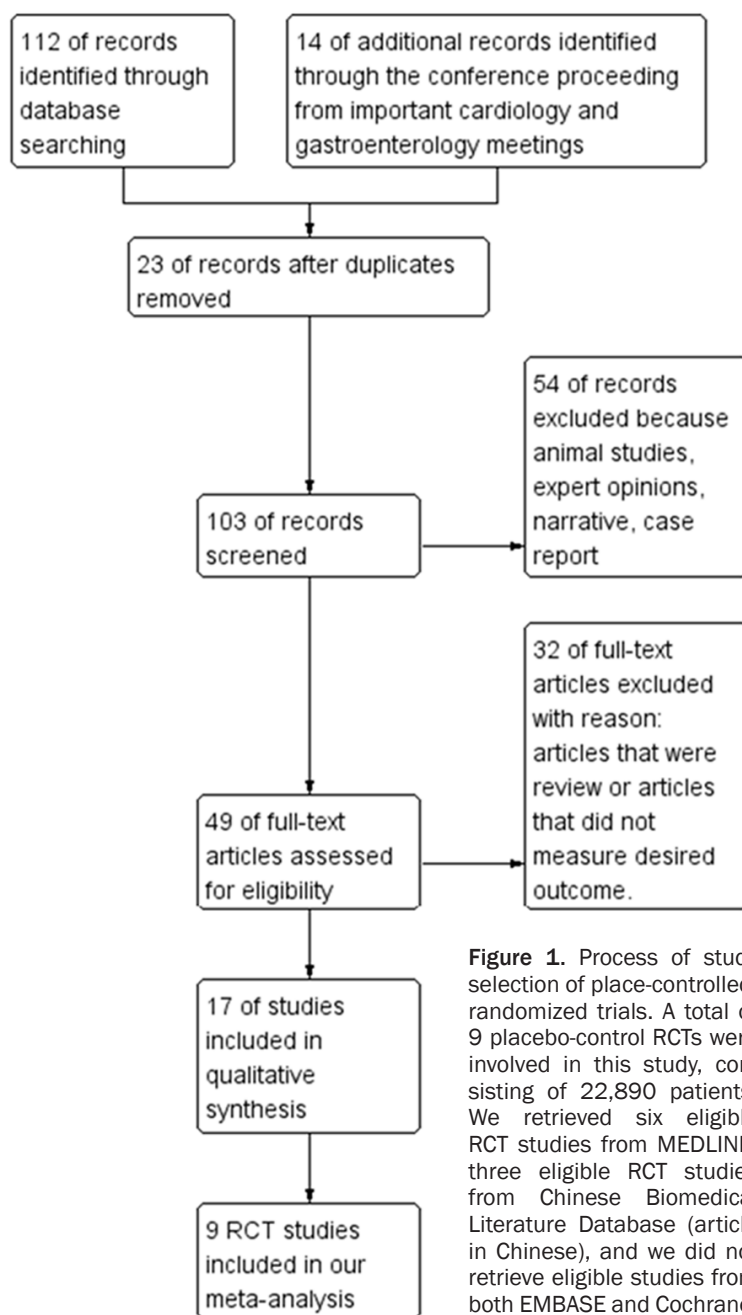


Figure 1. Process of study selection of place-controlled, randomized trials. A total of 9 placebo-control RCTs were involved in this study, consisting of 22,890 patients. We retrieved six eligible RCT studies from MEDLINE, three eligible RCT studies from Chinese Biomedical Literature Database (article in Chinese), and we did not retrieve eligible studies from both EMBASE and Cochrane.

Study selection

Two reviewers independently screened the abstracts and titles of the studies from the electronic search to identify all potential qualified studies. We retrieved relevant kinds of literature for further assessment of the eligibility. Any discrepancies or uncertainties between reviewers were resolved by consultation or consensus with the third reviewer. We also contacted the authors if any areas of

uncertainty wanted to clarify.

Data extraction

Two investigators independently did extract data on study and patient characteristics, outcomes, exposure factors, and study quality for each study using the standardized data extraction form. Any discrepancies were resolved by consultation or consensus. We did extract the following information from every study: first author, year of publication, location, study design and number of patients; mean age (and standard deviation), gender, underlying disease; types of PPI used; duration of follow-up, outcomes definition, effect size (OR, HR), and adjusted variables and so on.

Quality assessment

Quality assessment of all the included RCTs was done by using the following six domains of the Cochrane tool for the assessing risk of bias: sequence generation, allocation concealment, blinding, selective reporting, incomplete outcome data, et al. Each entry was assessed as yes (low risk of bias), no (high risk of bias), or unclear (lack of relevant information or uncertainty of bias) based on the information of included studies. Disagreements regard to the methodological quality were

resolved by consulting with the third reviewer or discussion between the reviewers.

Data analysis

Extracted information of the included studies was entered into a table to help us browse the study subjects, exposure factors, outcomes, quality and design of each study and then to evaluate the heterogeneity of each included study.

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Table 1. Study design and characteristics of included studies

Study	Location	Design	No. of subjects	Mean age	PPIs studied	Mean Follow-up	Selection criteria	Refs
Bhatt et al, 2010 COGENT study	Multicentre	RCT	3761 Male: 2563 Female: 1198	68	Omeprazole	106 days	Age >21 years with ACS or coronary stent requiring clopidogrel and aspirin for next 12 months. Excluded those with significant GI or bleeding history, current use of gastroprotective drugs or anticoagulants.	17
Cai et al, 2010	China	RCT	406	40-70	Omeprazole Pantoprazole	30 days	Age 40-70 year with ACS or coronary stent requiring clopidogrel and aspirin for 30 days. Excluded those with risk of bleeding, current GI disorder, bleeding disorder, allergy to study drug, current use of PPI.	19
Peng et al, 2010	China	RCT	90 Male: 48 Female: 42	60	Omeprazole Pantoprazole	6 months	Age 50-72 year with DES stent requiring clopidogrel and aspirin for 6 month; omeprazole or pantoprazole for 15 days. Excluded those with risk of bleeding, current GI disorder, bleeding disorder, allergy to study drug, current use of PPI.	21
Cao et al, 2011	China	RCT	800 Male: 393 Female: 407	60-81	Esomeprazole	18 months	Age 60-81 year with coronary stent requiring clopidogrel and aspirin; esomeprazole for 12 months. Excluded those with history of GI bleeding, et al.	20
TRITON-TIMI38 2009	Multicentre	RCT	6795 Male: 4977 Female: 1818	60	Omeprazole Pantoprazole Esomeprazole Rabeprazole Lansoprazole	15 months	Age about 60 year with coronary stent requiring clopidogrel and aspirin. Excluded an increased risk of bleeding, a history of anaemia, thrombocytopenia, pathological intracranial findings or the use of a thienopyridine within 5 days before randomization.	18
Gao et al, 2009	China	RCT	237 Male: 126 Female: 111	58	Omeprazole	14 days	Patients with acute myocardial infarction. Excluded: the patients who did not accept recanalization therapy, had presented upper gastrointestinal bleeding in half a year before.	25
Ren et al, 2011	China	RCT	172 Male: 125 Female: 47	62	Omeprazole	30 days	Patients with acute coronary syndrome undergoing elective percutaneous coronary intervention. Excluded severe bleeding.	23
Dunn et al, 2013 [CREDO]	American and Canada	RCT	2116	61	Lansoprazole Omeprazole Pantoprazole Rabeprazole	1 year	Age >21 years with stent requiring clopidogrel and aspirin. Excluded constrain to study drug, coronary anatomy no amenable to stent placement, et al.	22
Dunn et al, 2013 CAPRIE steering committee 1996 CAPRIE	Multicentre	RCT	19185	62	Omeprazole Lansoprazole	1 to 3 years	Age >21 years requiring clopidogrel. Excluded constrain to study drug.	24

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Table 2. Validity assessment of the studies

Study (y)	PPI exposure (daily dose and duration) and verification of exposure	Antiplatelet exposure (daily dose and duration) and verification of exposure	Event/Total		Definition of outcome and ascertainment
			T: PPI	C: no PPI	
Bhatt et al [17] 2010	Omeprazole 20 mg	CLOD 75 mg maintenance with aspirin 75 to 325 mg	T: 55/1876	C: 54/1885	MACE defined as CV death, nonfatal MI, CABG, or PCI, or ischemic stroke, et al.
Cai et al [19] 2010	Omeprazole 40 mg Pantoprazole 40 mg	CLOD 75 mg maintenance with aspirin 100 mg	T: 23/280	C: 10/120	MACE defined as cardiac death, non-fatal MI, urgent target vessel revascularization, sub-acute. In-stent thrombosis, stroke, hemorrhagic complication et al.
Peng et al [21] 2010	Omeprazole 20 mg Pantoprazole 40 mg	CLOD 300 mg LD, 75 mg maintenance with aspirin 100 mg	T: 2/60	C: 0/30	MACE defined as all-cause death, target vessel revascularization (PCI, CABG), cerebrovascular event et al.
Cao et al [20] 2011	Esomeprazole 40 mg/d for 4 weeks, 40 mg/2 d maintain for 12 months	CLOD 300 mg LD, 75 mg maintenance with aspirin 100 mg	T: 11/397	C: 14/395	MACE defined as mortality, refraction and revascularization.
O'Donoghue TRITON-TIMI38 2009 [18]	Omeprazole Pantoprazole Esomeprazole Rabeprazole Lansoprazole	CLOD 300 mg LD, 75 mg maintenance with aspirin 100 mg	T: 255/2257	C: 526/4538	Cardiovascular death, non-fatal myocardial infarction or non-fatal stroke.
Gao et al [25] 2009	Omeprazole 40 mg loading, 20 mg maintain	Not reported	T: 4/114	C: 13/123	Over mortality, total mortality upper GI bleeding.
Ren et al [23] 2011	Omeprazole	Aspirin 300 mg LD, 100 mg maintenance and CLOD 600 mg LD, 75 mg maintenance	T: 22/86	C: 24/86	Slight chest pressure, occasional angina, transient ischemic attack, major bleeding.
Dunn et al [22] 2013 [CREDO]	Lansoprazole Omeprazole Pantoprazole Rabeprazole	CLOD 300 mg LD, 75 mg maintenance; with aspirin 325 mg for 28 days and 80 mg maintenance	T: 36/301	C: 53/752	All-cause death, MI, stroke.
Dunn et al [24] 2013 CAPRIE steering committee 1996 CAPRIE	Omeprazole Lansoprazole	Monotherapy with either aspirin 325 mg daily or clopidogrel 75 mg	T: 57/408	C: 882/9191	Ischemic stroke, myocardial infarction, vascular death.

Figure 2. Risk-of-bias analysis. The selected trials in our meta-analysis were well-designed and reasonably conducted, implementing the randomized sequence generation adequately and participants among them were blinded.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Bhatt 2010	+	?	+	?	+	+	?
Cai 2010	+	?	?	?	+	?	?
Cao 2011	+	?	?	?	+	?	?
Dunn [CAPRIE] 2013	+	?	?	?	+	?	?
Dunn [CREDO] 2013	+	?	?	?	+	?	?
Gao 2009	+	?	+	?	?	?	?
O'Donoghue 2009	+	?	+	?	?	+	?
Peng 2010	+	?	?	?	+	?	?
Ren 2011	+	?	?	?	?	?	?

Data were expressed as hazard ratio (HR) or odds ratio (OR) with 95% confidence interval (CI) for binary outcomes. Statistical heterogeneity was assessed by using the χ^2 test and was quantified by using the I^2 statistic. When there was a significant heterogeneity with p values <0.1 , random-effects model was used with DerSimonian and Laird method. Otherwise, we will use a fixed-effects model with Mantel-Haenszel method. We assessed the association between concomitant use of clopidogrel

with individual PPIs and primary cardiovascular events. The primary cardiovascular events was a composite of all-cause mortality, nonfatal myocardial infarction, or stroke. Sensitivity analyses of primary outcomes were conducted after eliminating the maximum or minimum of effect size to explore the stability of the results. Finally, we assessed the small study bias and publication bias using visual inspection of a funnel plot and Egger' test.

Results

Description of the studies

Nine placebo-control RCTs were involved in our meta-analysis [17-25]. The range of participant number was 30-9191, including male and female. A total of 22,890 patients aged 40 years or older were available for analyses. The types of PPI included omeprazole, lansoprazole, pantoprazole, esomeprazole, and rabeprazole. We showed the flow of identified studies and the selection process in **Figure 1**. The characteristics of baseline and design of the selected studies are shown in **Tables 1** and **2**. Articles reported MACE, all-cause mortality, cardiovascular death, stroke, non-fatal myocardial infarction, Slight chest pressure, occasional angina, transient ischemic attack, major bleeding.

Quality assessment of the trials and publication bias

The selected trials in our meta-analysis were well-designed and reasonably conducted, implementing the randomized sequence generation adequately and participants among them were blinded. All of the selected studies had a low to moderate risk bias, and the details

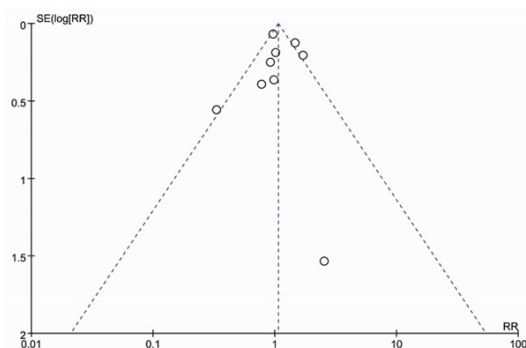


Figure 3. Test for publication bias for the relationship between clopidogrel and PPIs. SE, standard error; RR, relative risk.

are shown in **Figure 2**. The publication bias assessed by the Egger's test was shown in **Figure 3**.

Effect on composite ischemic end point of all-cause mortality or nonfatal MI, Stroke

Nine randomized controlled trials assessed the effect of PPIs in patients receiving clopidogrel and aspirin. Our meta-analysis of the studies evaluating PPIs as a class compared with placebo showed no difference in composite ischemic endpoints, all-cause mortality, nonfatal MI, stroke (RR 1.06, 95% confidence interval [CI] 0.95-1.18; $P=0.27$, with heterogeneity among trials ($I^2=57\%$). We also did the subgroup analysis to assess the effect on the composite of all-cause mortality or nonfatal myocardial infarction or stroke. The results showed no increased risk of all-cause mortality (OR 0.78, 95% confidence interval [CI] 0.58-1.04; $P=0.09$), nonfatal MI (OR 0.99, 95% confidence interval [CI] 0.84-1.17; $P=0.90$), stroke (OR 2.02 95% confidence interval [CI] 0.50-8.09; $P=0.32$). **Figure 4**. Furthermore, we did subgroup analysis, pooling data of five RCTs from Asia showed no increased risk of MACE in patients administered PPIs with clopidogrel and aspirin (RR 0.81, 95% confidence interval [CI] 0.58-1.13; $P=0.21$). There was no statistical heterogeneity among the five studies ($I^2=0\%$) **Figure 5**.

Discussion

Firstly, the results from our meta-analysis of clinical outcome study demonstrate that there are no interactions between administration of PPIs and clopidogrel in adverse cardiovascular

events. Secondly, the results from our subgroup analysis do not support the opinion that PPIs confer risk for side-effect events in Asian populations. These findings are inconsistent with the result of pharmacokinetic and pharmacodynamic investigations which points out the speculation of their interaction.

Dual antiplatelet therapy with aspirin and clopidogrel is universally acknowledged to be a cornerstone of treatment for the prevention of ischaemic events and improving outcomes following the acute coronary syndromes (ACS) and percutaneous coronary intervention (PCI) with stenting. Increasing their use of antiplatelet agents had apparently cut down the occurrence of recurrent ischemic events or death in the patients with acute coronary syndrome (ACS). However, bleeding complications may also increase at the same time. The most often gastrointestinal (GI) bleeding might be treating and preventing by PPIs therapies [26]. It is well known that gastrointestinal complications are the adverse effects on the average life of patients who take antiplatelet agents [27]. The mechanisms which result in the recurrent ulcer bleeding among these patients receiving clopidogrel are still unclear. Nonetheless, it has been pointed out in the vitro research that clopidogrel lead to the impairment of the healing of gastric ulcer by decreasing the release of plate-derived growth factors. So we presumed that clopidogrel might also inhibit ulcer healing in human beings. Recently, the American college of cardiology/American college of gastroenterology/American heart association guideline recommends that patients who are taking dual antiplatelet therapy with clopidogrel and aspirin should also receive PPI to reduce the risk of gastric side-effects. Proton pump inhibitors (PPIs) have been applied in the setting of ACS to prevent GI bleeding in many medical centers, particularly for those patients thought to be at high risk of GI bleeding. It has been pointed out that approximately half of patients receiving dual antiplatelet treatment were prescribed with a PPI in real world clinical practice. Clopidogrel, a thienopyridine, is a well-known prodrug. In liver, approximately 15% absorbed clopidogrel is metabolized to an active metabolite by hepatic cytochromes (CYP450) enzymes in a 2-step enzyme conversion process. It has been proven that CYP2C19, CYP1A2, CYP2B6 isoenzymes have a critical role in the first step,

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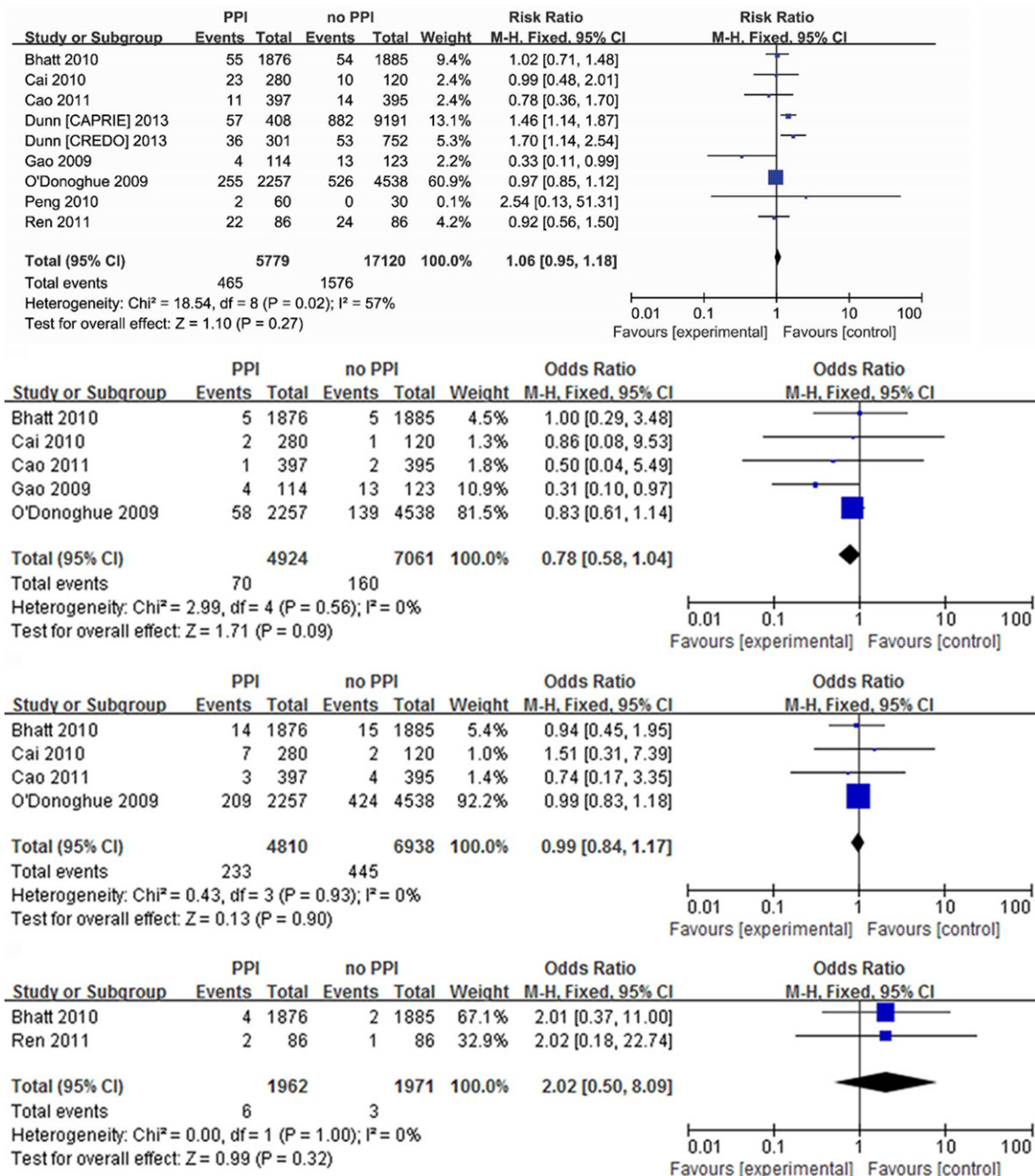


Figure 4. Meta-analysis results of primary cardiovascular events for the incidence of all-cause mortality, nonfatal MI or stroke. All included studies, RR (fixed effect model). Nine randomized controlled trials assessed the effect of PPIs in patients receiving clopidogrel and aspirin. Our meta-analysis of the studies evaluating PPIs as a class compared with placebo showed no difference in composite ischemic endpoints, all-cause mortality, nonfatal MI, stroke (RR 1.06, 95% confidence interval [CI] 0.95-1.18; $P=0.27$, with heterogeneity among trials ($I^2=57\%$). Subgroup analysis to assess the effect on the composite of all-cause mortality or nonfatal myocardial infarction or stroke. The results showed no increased risk of all-cause mortality (OR 0.78, 95% confidence interval [CI] 0.58-1.04; $P=0.09$), nonfatal MI (OR 0.99, 95% confidence interval [CI] 0.84-1.17; $P=0.90$), stroke (OR 2.02 95% confidence interval [CI] 0.50-8.09; $P=0.32$).

and CYP2C19, CYP3A4, CYP2C9 play a crucial role in the second phase. As noted, almost proton-pump inhibitors (PPIs) are also metabolized

by competitively inhibiting CYP2C19 and CYP3A4 and therefore possibly interfere with the process of clopidogrel metabolism. From a

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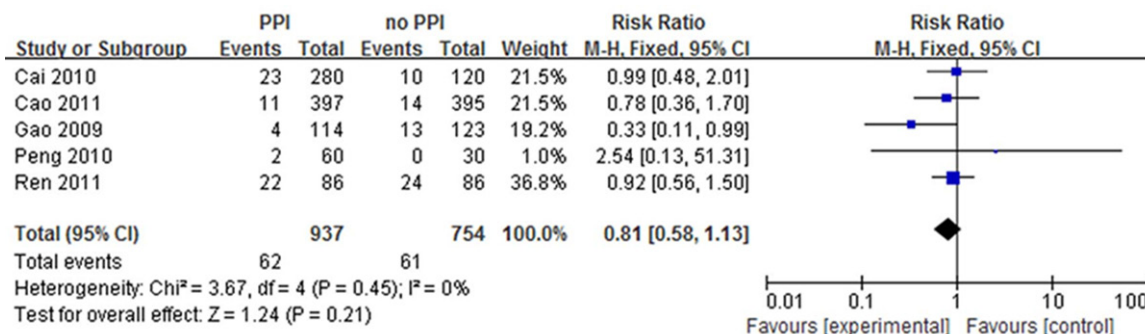


Figure 5. Subgroup analysis pooling data of five RCTs from Asia. We did subgroup analysis, pooling data of five RCTs from Asia showed no increased risk of MACE in patients administered PPIs with clopidogrel and aspirin (RR 0.81, 95% confidence interval [CI] 0.58-1.13; P=0.21). There was no statistical heterogeneity among the five studies (I²=0%).

pharmacological point of view, the impacts of PPIs on the metabolism of clopidogrel seems plausible and could affect the clinical efficacy of clopidogrel. Pharmacokinetic and pharmacodynamics studies have revealed that the postulate adverse effect between proton pump inhibitors (PPIs) and clopidogrel might not represent to be a class effect, i.e. particular PPI (particularly omeprazole and esomeprazole) have a demonstrable interaction, while pantoprazole seems to be less problematic. The US Food and Drug Administration has already indicated a warning specifically against omeprazole and esomeprazole because these particular drugs are regarded to have a severe adverse effect on the bioactivation of clopidogrel (through cytochrome P450 2C19), whereas pantoprazole might have limited side-effect on P450 2C19. According to these data, both the EMEA (European Medicine Agency) and the FDA (US Food and Drug Administration) have put forward the public statements on probably untoward effects between clopidogrel and PPIs [28-30]. However, the results from the COGENT trial comparing omeprazole versus placebo in patients receiving clopidogrel has found no difference in the risk of cardiovascular events in patients who use omeprazole. The COGENT trial [17], included 3873 patients, with a median follow-up 106 days, and reported no significant difference in cardiovascular outcome for adjunctive use of omeprazole in clopidogrel treatment groups. The result is fascinating since omeprazole has most often implicated about warnings according to its laboratory findings and observational data on clinical results. The performance of TRITON-TIMI 38 trial also

revealed no influence of concomitant PPI use on clinical outcome parameters for clopidogrel [31]. Chen et al. 2011 [32], showed in three RCTs, the combination use of clopidogrel and PPIs compared with the use of clopidogrel alone was associated with no detectable the difference in the cardiovascular event. Although the design of RCT might minimize the influence of several confounders and treatment selection bias, the size of RCTs employed in his study is small and not convincing to assess the hard clinical endpoints. Chun et al. 2012, the meta-analysis of two randomized controlled trials did not find a noticeable adverse cardiovascular effect from omeprazole or esomeprazole. And he also did a meta-analysis of adverse cardiovascular risk in seven observational studies reporting on PPI therapy alone (without concomitant clopidogrel) also showed an increased odds ratio of 1.28 compared with no clopidogrel/no PPI exposure. The data from those large scale observational studies have pointed out the concomitant use of clopidogrel plus PPIs after hospital discharge associated with an increased risk of adverse outcomes than use of clopidogrel without PPIs. From the viewpoint of observational studies, the nonrandomized coadministration of clopidogrel with PPIs versus without PPIs associated with about 50% increased the risk of cardiovascular death, readmission for MI/ACS, and nonfatal stroke. For the reasons that the observational studies on clinical outcome are with signs of not well designed, prescription bias and apparently imbalances in baseline characteristic, which may account for the significant variability in the observed results. So we did not analyze the

observational studies. We also excluded several trials published in the prior meta-analysis due to the flaws in their study methodology per our inclusion criteria. In Kwok CS meta-analysis [33], the result of adverse cardiovascular risk almost deduced from observations studies, only two randomized controlled trials for omeprazole or esomeprazole that is Bhatt 2010 and Hsu 2011. Based on the above mentioned reasons for the observational studies on clinical outcomes, we did not analyze the observational studies. In Huang B meta-analysis [34], the results obtained from not only observation but also five abstract. For the purpose of being rigorous, we did not include abstract and observations. And the results deduced from Huang B's paper, he concluded that pantoprazole is associated with MACE risk, however it is different from those previous studies, so we did our meta-analysis. In Chen M meta-analysis [35], he did analysis the studies before the deadline of October 2010. It is so long ago and the author included from confounding studies, for example RCT, RCS, COS, NCS, et al. So we updated the meta-analysis till 2017 and included research from RCTs. In Focks JJ meta-analysis [36], he did the analysis the studies before the deadline of June 2012, and the type of studies also included from confounding studies, such as RCT, prospective data collection, post hoc analysis of prospective research and retrospective studies and case-control studies. Based on these previous studies, we focus on RCTs studies in which patients are receiving clopidogrel classified into those who were PPI users or non-PPI users and adverse cardiovascular outcomes reported. And we search all published randomized controlled trials (RCT) up until July 1, 2017. Our review increased new evidence to the existing meta-analyses because this is a study with the most famous ethnic backgrounds, which increases the resulting credibility and takes the ethnic differences into account. Studies have demonstrated that clopidogrel resistance is related to gene polymorphism. About the metabolism of clopidogrel in healthy individuals, carriers of a reduced-function allele of CYP2C19 had 30% lower levels of the active clopidogrel metabolite and a 25% relative reduction in platelet inhibition *ex vivo*. It points out that CYP2C19 has a very significant impact on the pharmacodynamics of clopidogrel in patients as well. In one clinical research, patients with acute MI on clinical who sus-

tained subsequent cardiovascular events were more likely to carry CYP2C19 loss-of-function alleles compared to control group, showing an increased influence particularly in patients who underwent PTCA [37]. In another study [38] including patients treated with clopidogrel, carriers of a reduced-function CYP2C19 allele had significantly lower levels of the active metabolite concentration of clopidogrel with diminished platelet inhibition and a higher rate of MACE (major adverse cardiovascular events). The percentage of poor CYP2C19 metabolizer subjects is about 2-4.8% worldwide, with an unusually high incidence of 22.5% among East Asians [39-41]. Five studies from China included into our meta-analysis, which might compensate for the limits on races. We did subgroup analysis, pooling data of five RCTs from Asia showed no increased risk of MACE in patients administered PPIs with clopidogrel and aspirin. There has been substantial controversy regarding the risk of cardiovascular adverse events from a potential interaction between proton pump inhibitors and clopidogrel. The earliest studies based on platelet function tests, such as LTA and Verifynow analysis et al. which subsequently followed by studies evaluating clinical outcomes such as myocardial function, major cardiac adverse events, and death. The correlation between platelet function analysis and clinical cardiovascular outcomes with PPIs also remains an uncertainty. Despite pharmacokinetic and platelet function data to the contrary, our meta-analysis did not identify any significant differences in the clinical adverse events of PPIs on clopidogrel.

Limitation

Our meta-analysis has several potential limitations. Many studies were at moderate or uncertain risk of bias. The heterogeneity may partly be due to the variability in the definition of MACE across studies. We also lacked information on the baseline characteristics of participants with regards to key variables such as left ventricular ejection fraction, diabetes, smoking, body mass index, use of implantable defibrillators, and the function of CYP2C19 allele et al, which could have been important confounders. Equally, clopidogrel is converted to an active metabolite by 2 step hepatic mechanism involving several different isoenzymes. Differential exposure to other medications (e.g., lipophilic statins, calcium channels blockers, warfarin and so on) which are metabolized by the

same isoenzymes could influence the amount of active metabolite generated. Instead, much of the data are searching from computerized databases, which may not provide sufficiently accurate and complete information with recording and classifying outcomes and exposures.

For future studies, investigators should document the standardized individual cardiovascular outcomes based on hard endpoints such as MI and death. Only in this way, it might be easier to apply composite results with higher event rates. It seems that a very large RCT with broad, rather than restrictive selection criteria may be the only method of arriving at a definitive answer in real-world clinical practice. Moreover, the clinical relevance of further research into clopidogrel might rapidly diminish in the light of promising new antiplatelet drugs such as prasugrel and ticagrelor that do not appear to be affected by drug interactions to the same extent as clopidogrel [42, 43]. Based on the above, only well-designed, randomized trial powered to evaluate the effect on cardiac outcomes can address the potential side-effect of adjunctive PPIs use in patients on clopidogrel.

Conclusion

The results from our meta-analysis showed that there is lack evidence of cardiovascular events for patients who underwent PCI receiving clopidogrel combine with PPIs. Also, we did not find that PPIs confer more dangerous for adverse cardiovascular events in Asian populations. Discordance with the result of pharmacokinetic-pharmacodynamic studies which prompt us the plausibility of their interaction. We should weight against the evidence for GI benefits for clopidogrel-treated patients following percutaneous coronary intervention, as well as the observational studies and pharmacokinetic-pharmacodynamic studies. For clinical practice, our findings pointed out that there is no main reason to choose or avoid one particular PPI over another in clopidogrel-treated patients, who are at high risk of GI event. Therefore, further well-designed, randomized trials are needed to confirm the rational concomitant usage of clopidogrel and PPIs on cardiovascular outcomes.

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Disclosure of conflict of interest

None.

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