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Efficacy and Safety of Proton Pump Inhibitors in Patients With Coronary Artery Diseases Receiving Oral Antiplatelet Agents and/or Anticoagulants: A Systematic Review and Meta-Analysis

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Abstract: The purpose of this meta-analysis was to evaluate the efficacy and safety of proton pump inhibitors (PPIs) plus antithrombotic strategy in patients with coronary artery diseases compared with antithrombotic strategy alone. We searched PubMed, EMBASE, Cochrane Library, and Chinese Biomedical Medical Literature databases to retrieve randomized controlled trials investigating PPIs combined with antithrombotic strategy in coronary artery diseases. The primary efficacy outcome was major adverse cardiovascular and cerebrovascular events (MACCE). The primary safety outcome was gastrointestinal events. Secondary outcomes included all-cause death, cardiovascular death, myocardial infarction, stent thrombosis, significant bleeding from gastroduodenal lesions, and gastroduodenal ulcer. Overall, 43,943 patients were enrolled from 19 trials. The incidence of MACCE [relative risk (RR) 1.05; 95% confidence interval (CI) 0.96–1.15], all-cause death (RR 0.84; 95% CI 0.69–1.01), cardiovascular death (RR 0.88; 95% CI 0.69–1.12), myocardial infarction (RR 0.98; 95% CI 0.88–1.09), stent thrombosis (RR 1.01; 95% CI 0.76–1.34), and gastroduodenal ulcer (RR 0.40; 95% CI 0.13–1.29) did not increase significantly in patients receiving PPIs compared with patients without those. There were significant differences in the risk of gastrointestinal events (RR 0.34; 95% CI 0.21–0.54) and significant bleeding from gastroduodenal lesions (RR 0.09; 95% CI 0.03–0.28) between the 2 groups. In patients with coronary artery diseases, PPIs plus antithrombotic strategy could reduce the risk of gastrointestinal events and significant bleeding from gastroduodenal lesions but may not affect the incidence of MACCE, all-cause death, cardiovascular death, myocardial infarction, stent thrombosis, and gastroduodenal ulcer (PROSPERO: CRD42021277899, date of registration October 10, 2021).

Key Words: coronary artery diseases, proton pump inhibitors, anticoagulants, dual antiplatelet therapy, gastrointestinal bleeding, meta-analysis

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INTRODUCTION

The mortality of coronary artery disease (CAD) has increased rapidly since 2000, with an increase of more than 2 million in 2019.[1] To reduce this situation, the guidelines recommend dual antiplatelet therapy after percutaneous coronary intervention in patients with CAD. For patients with non–ST-segment elevation, acute coronary syndrome and atrial fibrillation undergoing stent implantation, novel oral anticoagulants, and clopidogrel are recommended.[2,3] However, these antithrombotic strategies significantly reduce the incidence of ischemic events and increase the risk of gastrointestinal (GI) bleeding.[4–8] GI bleeding can be treated prophylactically with proton pump inhibitors (PPIs).[9]

PPIs affect the bioavailability of aspirin and the antiplatelet effect of clopidogrel,[10,11] which may affect the improvement of ischemic events. The CREDO trial showed that PPIs combined with aspirin and clopidogrel increased the incidence of ischemic events in patients with stent implantation,[12] whereas the COGENT trial demonstrated that PPIs reduced the risk of GI bleeding without increasing cardiovascular events.[13] Moayyedi et al[14] found that pantoprazole plus rivaroxaban and/or aspirin reduced the upper GI events in patients with stable cardiovascular disease, but it was not statistically significant.

Previous meta-analyses evaluated the strategy of PPIs combined with aspirin and $P2Y_{12}$ receptor inhibitors, but the results were inconsistent.[6,15–17] Meanwhile, with the update of guidelines, more antithrombotic strategies have been

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Y.-S. Shang, P.-Y. Zhong, Y. Ma, N. Bai, and Y. Niu contributed equally to this work.

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The data can be availability on the request from the authors.

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proposed. We performed this meta-analysis and hypothesized that PPIs plus antithrombotic strategy can reduce the risk of GI bleeding without increasing ischemic events in patients with CAD.

METHODS

Literature Selection

This meta-analysis followed the guidelines of Cochrane Collaboration and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist.[18,19] PubMed, EMBASE, Cochrane Library, and the Chinese Biomedical Medical Literature databases were systematically searched from inception to August 15, 2021. Moreover, other sources of related literature were also manually searched. The search terms included as follows: "Cardiovascular Disease," "Coronary Artery Diseases," "Acute Coronary Syndrome," "unstable angina," "ST-segment-elevation myocardial infarction," "non-ST-segment-elevation myocardial infarction," "Proton Pump Inhibitors," "Omeprazole," "Pantoprazole," "Lansoprazole," "Esomeprazole," "Rabeprazole," "Ilaprazole," "Dual Antiplatelet Therapy," "Anticoagulants," "Novel Oral Anticoagulant," "Aspirin," "Clopidogrel," "Prasugrel," "Ticagrelor," "Rivaroxaban," "Apixaban," "Edoxaban," "Dabigatran," "Argatroban," "Warfarin" AND "Randomized Controlled Trial" without language and country or region restriction. A PubMed update reminder was set up to continuously identify the latest relevant publications and inform us by e-mail. The search strategies are shown in **Supplemental Digital Content 1** (see **Appendix 1**, http://links.lww.com/JCVP/A824). The eligible trials met the following inclusion criteria: (1) randomized controlled trials (or post hoc analysis of randomized controlled trial) investigating PPIs combined with antithrombotic strategy (oral antiplatelet agents and/or anticoagulants) in patients with CAD; (2) included outcomes data of interest for patients aged 18 years or older; and (3) the control arm was only treated with antithrombotic strategy. The exclusion criteria included the following: (1) oral gastric acid–suppressive drugs other than PPIs from the study group; (2) children and healthy human beings as participants; and (3) repeated report. All titles, abstracts, and full text of the retrieved literature were reviewed independently and manually by 2 authors (Y.-S.S. and P.-Y.Z.) to determine whether these articles met the inclusion and exclusion criteria. The discrepancy between the reviewers was resolved by mutual discussion with the third party (N.B., Y.M., and Y.N.). All eligible trials have been published. Consequently, local ethics committees' approval and patient informed consents were not required. The meta-analysis protocol has been registered in PROSPERO (CRD42021277899).

Data Extraction, Outcomes, and Quality Assessment

Data were collected independently by 2 authors (Y.-S.S. and P.-Y.Z.), and conflicts were resolved by negotiating with a third author (Z.-L.W.). The data were extracted and summarized in a spreadsheet, including baseline characteristics of included patients, intervention methods, number of events, the total number of trials, follow-up duration, and definition of interested outcomes. If necessary, intention-to-treat analysis was implemented.

The primary efficacy outcome was major adverse cardiovascular and cerebrovascular events (MACCE), the composite of death, myocardial infarction, revascularization, angina readmission, stent thrombosis (definite or probable), or stroke. The primary safety outcome was GI events, the composite of significant bleeding from gastroduodenal lesions, overt upper GI bleeding of unknown origin, occult bleeding, gastroduodenal ulcer, gastroduodenal erosions, upper GI obstruction, or perforation. The secondary outcome included all-cause death, cardiovascular death, myocardial infarction, stent thrombosis (definite or probable), significant bleeding from gastroduodenal lesions, and gastroduodenal ulcer.

The Cochrane Collaboration risk of bias 2 (RoB 2) tool was performed to assess the risk of bias for each included trial, and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system was adopted to evaluate certainty of evidence at each outcome level.[20,21]

Statistical Analysis

The effect size was expressed by relative risk (RR) and 95% confidence interval (CI) after the pool of outcomes of the original 4-table data. For several trials with confounding factors, adjusted hazard ratio (HR) and 95% CI should be used. We pooled HR and RR based on rare incidence rates. Both DerSimonian and Laird method and Mantel–Haenszel method were applied in random and fixed effect model, respectively. The sensitivity analysis of the primary efficacy and safety outcomes was conducted on patients after percutaneous coronary intervention. Considering the inconsistency of follow-up durations, we used incidence rate ratios (IRR) as the effect size of sensitivity analysis. Prespecified subgroup analysis of the primary outcomes was performed on individual PPIs, different races, and various antithrombotic strategies. $P < 0.05$ was suggested as a significant difference. Heterogeneity was assessed by Cochrane Q statistic with Pearson's χ^2 test and the Higgins I^2 test. $I^2 > 50\%$ with $P < 0.10$ was regarded as significant heterogeneity. "Leave-one-out" method, meta-regression analyses, and subgroup analyses were performed to find the potential influencing factors. If heterogeneity exists, a random effect model should be employed; otherwise, a fixed effect model should be adopted. Funnel plot, Begg's test, and Egger's test were used to evaluate the publication bias for outcomes of interest. If publication bias exists, the meta-trim operation will be performed to determine whether additional trials are needed to reduce the bias. Trial Sequential Analysis version 0.9.5.10 software [Copenhagen Trial Unit (CTU)] was implemented to evaluate the statistical reliability of results (based on α of 5% and power of 80%). This meta-analysis was performed using Review Manager version 5.3 software (The Nordic Cochrane Centre, Copenhagen, Denmark), Stata software (ersion 14.1 (StataCorp LP, College Station, TX), and GRADE profiler version 3.6.1 software.

RESULTS

Search Results and Study Characteristics

A total of 1114 literatures are retrieved after a systematic search from the 4 databases, and 29 publications are initially extracted for full-text review (Fig. 1). Finally, 19 eligible randomized controlled trials were identified for this meta-analysis.[12–14,22–37] A total of 43,943 patients with CAD were enrolled. Among them, 19,313 patients (44%) were divided into the PPIs arm, and 24,630 patients (56%) were divided into the non-PPIs arm. The details of included trials and patients are summarized (Tables 1 and 2).

The Primary Efficacy and Safety Outcomes

The outcome of MACCE was reported in 15 included trials. The incidence of MACCE in patients receiving PPIs is increased by 5% without statistical significance compared with non-PPIs arm. Meanwhile, there is no heterogeneity in the trials included (I^2 = 0.0%, P = 0.673) (Fig. 2). Exploratory meta-regression analyses show that PPIs type, different race, antithrombotic strategy, bias risk of included trial, year of publication, follow-up duration, and sample size are not the potential influencing factors of MACCE (see **Table S1**, **Supplemental Digital Content 2**, http://links.lww.com/JCVP/A825). After sensitivity analysis, there is no significant difference in the incidence of MACCE for patients undergoing percutaneous coronary intervention between the 2 arms (IRR 1.06; 95% CI, 0.69–1.62) (see **Table S2**, **Supplemental Digital Content 2**, http://links.lww.com/JCVP/A825).

The GI events were evaluated in 14 trials. Compared with the non-PPIs arm, the PPIs arm significantly reduces the risk of GI events by 66% with a significant heterogeneity (I^2 = 72.3%, P = 0.000) (Fig. 3). The result of the "leave-one-out" method shows that Moayyedi 2019 trial may be the source of heterogeneity (see **Figure S1**, **Supplemental Digital Content 2**, http://links.lww.com/JCVP/A825). After removing this trial, the PPIs arm can significantly reduce the risk of GI events by 71%, and the heterogeneity is slightly reduced (I^2 = 67.1%, P = 0.000) (see **Figure S2**, **Supplemental Digital Content 2**, http://links.lww.com/JCVP/A825). Exploratory meta-regression analyses show that the heterogeneity of GI events may be related to different race (P = 0.037) and different antithrombotic strategy (P = 0.000) (see **Table S1**, **Supplemental Digital Content 2**, http://links.lww.com/JCVP/A825). Meanwhile, the type of PPIs, the bias risk of included trial, the year of publication, follow-up duration, and sample size are not the potential influencing factors (see **Table S1**, **Supplemental Digital Content 2**, http://links.lww.com/JCVP/A825). The sensitivity analysis shows that there is a significant difference in the risk of GI events in

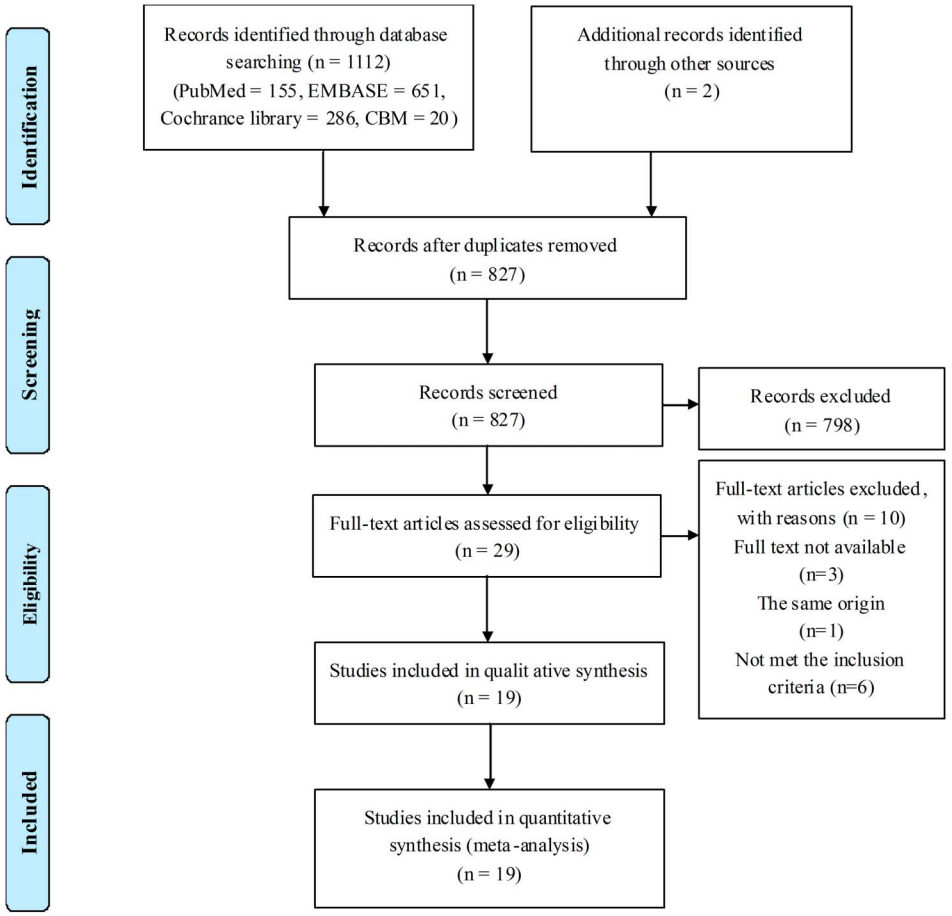

FIGURE 1. Flow diagram of literature review.

TABLE 1. Baseline Characteristics of Trials Included

Trial	Publication Year	Country	Design	No. of Study Patients	No. of Patients in Meta-Analysis	Type of Included Patients	Follow-up Duration	Experiment Treatment	Ischemic Events	Bleeding Events
O'Donoghue et al[31]	2009	United States and Europe	RCT (post hoc analysis)	13,608	13,608	ACS undergoing PCI	15 mo	Aspirin + prasugrel/ clopidogrel + PPIs	The composite of CV death, MI, or stroke; all-cause death; CV death; MI; stent thrombosis (definite or probable)	TIMI major or minor bleeding (non-CABG); TIMI major bleeding (non-CABG)
Bhatt et al[13]	2010	393 sites in 15 countries	RCT	3873	3761	ACS or undergoing placement of a coronary stent	106 d	Omeprazole + clopidogrel + aspirin	Death from cardiovascular causes, nonfatal myocardial infarction, revascularization, or stroke	The composite of overt or occult bleeding, symptomatic gastroduodenal ulcers or erosions, obstruction, or perforation
Cai et al[33],	2010	China	RCT	60	60	Coronary artery disease undergoing PCI	1 mo	Pantoprazole/ omeprazole + aspirin + clopidogrel	MACE (cardiac death, non-fatal MI, urgent target vessel revascular-ization, subacute instent thrombosis, and stroke)	Massive haemorrhage; small haemorrhage; GI bleeding
Nikcevic et al[28]	2011	Serbia	RCT	300	300	Patients with ACS	Not given*	Pantoprazole + antithrombotic drugs*	Mortality; recurrent MI and stroke	GI bleeding
Ren et al[27]	2011	China	RCT	172	172	ACS undergoing elective PCI	1 mo	Omeprazole + aspirin + clopidogrel	Coronary artery ischemia, cerebral artery events	GI bleeding
Wu et al[24]	2011	China	RCT	665	665	High-risk patients with ACS	1 mo	Aspirin + clopidogrel + pantoprazole	Not given	GI bleeding
Chang et al[37]	2013	China	RCT	120	120	ACS undergoing PCI	3 mo	Rabeprazole + aspirin + clopidogrel	MACE (cardiac death, nonfatal MI, target vessel revascularization, or rehospitalization)	GI bleeding; the change of hemoglobin; occult blood situation
Dunn et al[12]	2013	United States and Canada	RCT (post hoc analysis)	2116	2116	Coronary artery disease patients at high likelihood of undergoing PCI	1 y	PPIs + aspirin + clopidogrel/PPIs + clopidogrel	All-cause death, MI, or stroke	Not given
Wang et al[34]	2013	China	RCT	85	85	ACS undergoing PCI	12 mo	Esomeprazole/ rabeprazole + aspirin + clopidogrel	MACE(cardiac death, nonfatal MI, target vessel revascularization, sub-acute in-stent thrombosis and stroke)	Bleeding events according to GUSTO

TABLE 1. (*Continued*) Baseline Characteristics of Trials Included

Trial	Publication Year	Country	Design	No. of Study Patients	No. of Patients in Meta-Analysis	Type of Included Patients	Follow-up Duration	Experiment Treatment	Ischemic Events	Bleeding Events
Zhang et al[25]	2015	China	RCT	104	104	Non–ST-segment elevated ACS who underwent PCI	6 mo	Aspirin + clopidogrel + lansoprazole	Death, stroke, MI, angina rehospitalization, and cardiovascular revascularization	Not given
Zhao et al[36]	2015	China	RCT	300	300	Elderly coronary artery disease patients undergoing PCI	12 mo	Pantoprazole + aspirin + clopidogrel	MACE (death, nonfatal MI, target vessel revascularization, and stroke)	GI bleeding and GI adverse reactions
Gargiulo et al[22]	2016	Italy	RCT (post hoc analysis)	1970	1970	Stable coronary artery disease or ACS undergoing PCI	24 mo	Aspirin + clopidogrel + PPIs	The composite of death, MI, or cerebrovascular accident	Bleeding Academic Research Consortium type 2, 3, or 5 bleeding
Wei et al[32]	2016	China	RCT	207	207	STEMI undergoing emergent percutaneous coronary intervention	6 mo	Aspirin + clopidogrel + pantoprazole	MACE (secondary onset of heart failure, severe arrhythmias, infarction after angina, recurrent MI, and cardiac death)	GI bleeding events
Feng et al[35]	2017	China	RCT	160	160	Coronary artery disease undergoing PCI	12 mo	Pantoprazole + aspirin + clopidogrel	MACE (death, nonfatal MI, target vessel revascularization, and stroke)	Digestive tract discomfort and bleeding
Huang et al[29]	2017	China	RCT	90	90	Coronary artery disease undergoing PCI	1 y	Lansoprazole + aspirin + clopidogrel	MI; revascularization	GI bleeding
Jensen et al[26]	2017	Western Denmark	RCT	2009	2009	Coronary artery disease undergoing PCI	1 y	Pantoprazole + aspirin + clopidogrel/ ticagrelor	Cardiovascular events (unstable angina pectoris, MI), all-cause mortality	Upper GI bleeding; uncomplicated ulcer; and upper GI endoscopy
Moayyedi et al[14]	2019	580 centers in 33 countries	RCT	15,703	15,703	Stable coronary artery disease	3.02 y	Pantoprazole + rivaroxaban and aspirin/rivaroxaban/ aspirin	Not given	The composite of overt bleeding with a gastroduodenal lesion, overt upper GI bleeding of unknown origin, occult bleeding, symptomatic gastroduodenal ulcer, GI pain or more gastroduodenal erosions, upper GI obstruction or perforation

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TABLE 1. (*Continued*) Baseline Characteristics of Trials Included

Trial	Publication Year	Country	Design	No. of Study Patients	No. of Patients in Meta-Analysis	Type of Included Patients	Follow-up Duration	Experiment Treatment	Ischemic Events	Bleeding Events
Nicolau et al[30]	2020	414 sites in 41 countries	RCT (post hoc analysis)	2678	2427	Nonvalvular atrial fibrillation and had successfully undergone PCI	14 mo	PPIs + dabigatran+ clopidogrel/ ticagrelor; PPIs + warfarin + aspirin + clopidogrel/ticagrelor	Thromboembolic events (MI, stroke, or systemic embolism), all-cause mortality, or unplanned revascularization	Major bleeding events or clinically relevant non-major bleeding events: all GI bleeding
Zhang et al[23]	2020	China	RCT	86	86	Acute myocardial infarction undergoing primary PCI	6 mo	Aspirin + ticagrelor + omeprazole	MACE (recurrent stent thrombosis, recurrent MI, revascularization, malignant arrhythmia, cerebral infarction, and cardiac death)	Major bleeding events, such as gastrointestinal hemorrhage and cerebral hemorrhage, and minor bleeding events, such as bleeding in the gums of the oral cavity, nasal bleeding, hematoma at the puncture site, and skin ecchymosis

*This trial was report as an abstract form. Therefore, some details cannot be found.

ACS, acute coronary syndrome; CABG, coronary artery bypass graft surgery; CV, cardiovascular; GUSTO, global use of strategies to open occluded coronary arteries; MACE, major adverse cardiovascular and cerebrovascular events; MI, myocardial infarction; PCI, percutaneous coronary intervention; RCT, randomized controlled trial; STEMI, ST-segment elevation myocardial infarction; TIMI, thrombolysis in myocardial infarction.

TABLE 2. Baseline Characteristics of the Patients Included

Trial	O'Donoghue et al[31]		Bhatt et al[13]		Cai et al[33]*		Nikcevic et al[28],†		Ren et al[27]		Wu et al[24]		Chang et al[37]	
	PPIs	Non-PPIs	PPIs	Non-PPIs	PPIs	Non-PPIs	PPIs	Non-PPIs	PPIs	Non-PPIs	PPIs	Non-PPIs	PPIs	Non-PPIs
Age (y)	62	60	69	69	NG	NG	NG	NG	62	62	NG	NG	67	68
Male (%)	71.6%	75.3%	66.9%	69.5%	NG	NG	NG	NG	72.1%	73.3%	73.9%	73.5%	65.0%	60.0%
Hypertension (%)	65.3%	63.7%	80.1%	81.4%	NG	NG	NG	NG	NG	NG	NG	NG	66.7%	71.7%
Diabetes (%)	23.9%	22.7%	31.7%	28.6%	NG	NG	NG	NG	NG	NG	33.6%	32.5%	45.0%	46.7%
Current tobacco use (%)	37.6%	38.5%	12.5%	14.1%	NG	NG	NG	NG	NG	NG	20.7%	20.2%	40.0%	36.7%
Hyperlipidemia (%)	56.8%	55.1%	79.1%	77.1%	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG
BMI	28	28	28	28	NG	NG	NG	NG	26	26	NG	NG	26	26
Previous MI (%)	17.4%	18.1%	30.5%	28.5%	NG	NG	NG	NG	NG	NG	14.4%	9.6%	NG	NG
Previous stroke (%)	NG	NG	7.3%	8.1%	NG	NG	NG	NG	NG	NG	7.8%	8.4%	NG	NG
Previous PCI (%)	NG	NG	71.7%	71.4%	NG	NG	NG	NG	NG	NG	53.2%	55.4%	NG	NG
Previous CABG (%)	7.8%	7.6%	NG	NG	NG	NG	NG	NG	NG	NG	6.6%	6.3%	NG	NG
Previous CHF (%)	4.2%	3.6%	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	15.0%	13.3%
Previous peptic ulcer (%)	9.7%	4.1%	4.2%	4.1%	NG	NG	NG	NG	NG	NG	12.6%	12.9%	NG	NG
β Blocker	88.7%	87.9%	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	76.7%	83.3%
Statin	93.0%	91.7%	67.9%	66.5%	NG	NG	NG	NG	100.0%	100.0%	NG	NG	98.3%	96.7%

Trial	Dunn et al[12]		Wang et al[34]		Zhang et al[25]		Zhao et al[36]		Gargiulo et al[22]		Wei et al[32]		Feng et al[35],*	
	PPIs	Non-PPIs	PPIs	Non-PPIs	PPIs	Non-PPIs	PPIs	Non-PPIs	PPIs	Non-PPIs	PPIs	Non-PPIs	PPIs	Non-PPIs
Age (y)	62	62	59	60	65	61	62	62	71	68	59	58	NG	NG
Male (%)	70.3%	71.6%	64.3%	75.9%	45.3%	43.1%	56.7%	57.3%	72.5%	79.2%	56.1%	57.1%	NG	NG
Hypertension (%)	69.0%	68.4%	55.4%	51.7%	50.9%	49.0%	14.0%	14.7%	72.5%	71.3%	NG	NG	NG	NG
Diabetes (%)	27.3%	26.3%	NG	NG	18.9%	27.5%	6.0%	6.7%	23.3%	24.8%	NG	NG	NG	NG
Current tobacco use (%)	28.9%	30.9%	42.9%	58.6%	39.6%	41.2%	NG	NG	22.6%	24.4%	NG	NG	NG	NG
Hyperlipidemia (%)	79.1%	73.4%	23.2%	27.6%	39.6%	39.2%	13.3%	12.7%	53.8%	55.3%	NG	NG	NG	NG
BMI	NG	NG	NG	NG	NG	NG	NG	NG	26	27	NG	NG	NG	NG
Previous MI (%)	37.2%	33.2%	8.9%	17.2%	NG	NG	NG	NG	27.0%	26.1%	NG	NG	NG	NG
Previous stroke (%)	6.1%	6.8%	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG
Previous PCI (%)	35.3%	26.3%	NG	NG	NG	NG	NG	NG	16.1%	18.6%	NG	NG	NG	NG
Previous CABG (%)	18.4%	15.3%	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG
Previous CHF (%)	8.8%	8.7%	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG
Previous peptic ulcer (%)	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG
β Blocker	NG	NG	87.5%	96.6%	50.9%	47.1%	NG	NG	NG	NG	NG	NG	NG	NG
Statin	NG	NG	100.0%	100.0%	100.0%	100.0%	NG	NG	90.9%	90.3%	NG	NG	NG	NG

Trial	Huang et al[29]		Jensen et al[26]		Moayyedi et al[14]		Nicolau et al[30]		Zhang et al[23]	
	PPIs	Non-PPIs	PPIs	Non-PPIs	PPIs	Non-PPIs	PPIs	Non-PPIs	PPIs	Non-PPIs
Age (y)	69	68	65	65	68	68	71	70	60	60
Male (%)	55.6%	60.0%	73.1%	74.9%	78.0%	79.0%	74.3%	78.4%	72.1%	67.4%
Hypertension (%)	NG	NG	NG	NG	NG	NG	55.6%	46.2%	53.5%	55.8%
Diabetes (%)	NG	NG	NG	NG	38.0%	38.0%	37.5%	34.5%	48.8%	53.5%
Current tobacco use (%)	NG	NG	25.4%	27.6%	23.5%	23.0%	13.0%	11.6%	46.5%	41.9%
Hyperlipidemia (%)	NG	NG	NG	NG	NG	NG	NG	NG	67.4%	76.7%
BMI	24	24	NG	NG	28	28	NG	NG	27	27
Previous MI (%)	NG	NG	NG	NG	61.5%	61.0%	27.9%	22.1%	NG	NG
Previous stroke (%)	NG	NG	NG	NG	4.0%	4.0%	NG	NG	11.6%	14.0%
Previous PCI (%)	NG	NG	NG	NG	NG	NG	35.6%	30.0%	NG	NG

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TABLE 2. (*Continued*) Baseline Characteristics of the Patients Included

	Huang et al[29]		Jensen et al[26]		Moayyedi et al[14]		Nicolau et al[30]		Zhang et al[23]	
Trial	**PPIs**	**Non-PPIs**	**PPIs**	**Non-PPIs**	**PPIs**	**Non-PPIs**	**PPIs**	**Non-PPIs**	**PPIs**	**Non-PPIs**
Previous CABG (%)	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG
Previous CHF (%)	NG	NG	NG	NG	25.0%	24.0%	34.7%	33.8%	NG	NG
Previous peptic ulcer (%)	NG	NG	10.8%	9.7%	3.0%	2.5%	8.2%	4.2%	NG	NG
β Blocker	NG	NG	NG	NG	70.0%	70.0%	84.5%	81.4%	81.4%	79.1%
Statin	NG	NG	NG	NG	88.0%	89.0%	88.7%	84.8%	97.7%	95.3%

*The baseline information for these trials is not available.
†This trial was report as an abstract form without baseline data.
BMI, body mass index; CABG, coronary artery bypass graft surgery; CHF, chronic heart failure; MI, myocardial infarction; NG, not given; PCI, percutaneous coronary intervention.

patients undergoing percutaneous coronary intervention between the 2 arms (IRR 0.21; 95% CI 0.14–0.32) (see **Table S2**, **Supplemental Digital Content 2**, http://links.lww.com/JCVP/A825).

The Secondary Outcomes

All-Cause Death and Cardiovascular Death

Seven trials evaluated all-cause death outcome in this meta-analysis. No significant difference is observed between patients with PPIs combined with antithrombotic strategy and patients without those (RR 0.84; 95% CI 0.69–1.01). There is no heterogeneity in the trials included (I^2 = 0.0%, P = 0.750) (see **Figure S3**, **Supplemental Digital Content 2**, http://links.lww.com/JCVP/A825).

In 5 trials, PPIs combined with antithrombotic strategy reduce the incidence of cardiovascular death by 12% without significant difference and heterogeneity (I^2 = 0.0%, P = 0.601) (see **Figure S4**, **Supplemental Digital Content 2**, http://links.lww.com/JCVP/A825).

Myocardial Infarction and Definite or Probable Stent Thrombosis

In 11 trials, there is no significant difference in the incidence of myocardial infarction between PPIs arm and non-PPIs arm (RR 0.98; 95% CI 0.88–1.09) without heterogeneity (I^2 = 0.0%, P = 0.999) (see **Figure S5**, **Supplemental Digital Content 2**, http://links.lww.com/JCVP/A825).

Three included trials provided data on the outcome of definite or probable stent thrombosis. Compared with non-PPIs arm, no significant difference is found in patients with PPIs combined with antithrombotic strategy (RR 1.01; 95% CI 0.76–1.34). No heterogeneity is detected (I^2 = 0.0%, P = 0.771) (see **Figure S6**, **Supplemental Digital Content 2**, http://links.lww.com/JCVP/A825).

Significant Bleeding from Gastroduodenal Lesions and Gastroduodenal Ulcer

The data on significant bleeding from gastroduodenal lesions were reported in 4 trials. The concomitant strategy of PPIs and antithrombotic strategy significantly reduces the risk of significant bleeding by 91% compared with non-PPIs arm. No heterogeneity is observed (I^2 = 0.0%, P = 0.757) (see **Figure S7**, **Supplemental Digital Content 2**, http://links.lww.com/JCVP/A825).

PPIs combined with antithrombotic strategy significantly reduce the risk of gastroduodenal ulcer by 60% without significant difference and heterogeneity in 2 trials (I^2 = 0.0%, P = 0.700) (see **Figure S8**, **Supplemental Digital Content 2**, http://links.lww.com/JCVP/A825).

Subgroup Analysis

As for individual PPIs, no significant difference in the incidence of MACCE is observed between PPIs arm and non-PPIs arm (see **Figure S9**, **Supplemental Digital Content 2**, http://links.lww.com/JCVP/A825). All PPIs significantly reduce the risk of GI events (see **Figure S10**, **Supplemental Digital Content 2**, http://links.lww.com/JCVP/A825).

Compared with non-PPIs arm, PPIs combined with antithrombotic strategy have no effect on the incidence of MACCE when the factor of race is considered (see **Figure S9**, **Supplemental Digital Content 2**, http://links.lww.com/JCVP/A825). However, the combination strategy can reduce the risk of GI events by 59% in non-Asian and 81% Asian patients ($P_{interaction}$ = 0.016) (see **Figure S10**, **Supplemental Digital Content 2**, http://links.lww.com/JCVP/A825).

The subgroup analysis of different antithrombotic strategies shows that no significant difference is observed in the incidence of MACCE (see **Figure S9**, **Supplemental Digital Content 2**, http://links.lww.com/JCVP/A825). The reduction in the risk of GI events is associated with PPI combined with aspirin and clopidogrel (RR 0.23; 95% CI 0.16–0.33). PPI combined with other antithrombotic strategies does not significantly reduce the risk of GI events (RR 0.90; 95% CI 0.60–1.34) (see **Figure S10**, **Supplemental Digital Content 2**, http://links.lww.com/JCVP/A825).

Quality Assessment, Trial Sequential Analysis, and Publication Bias

The risk of bias assessments shows that the risk of attrition bias, reporting bias, and other bias is low in all eligible trials. Two trials are considered "low risk of bias." Twelve trials are considered "some concerns" and do not report the detailed processes of random sequence generation and allocation concealment. Five trials are considered "high risk of bias" because of the detection bias or performance bias. The details were shown in **Supplemental Digital**

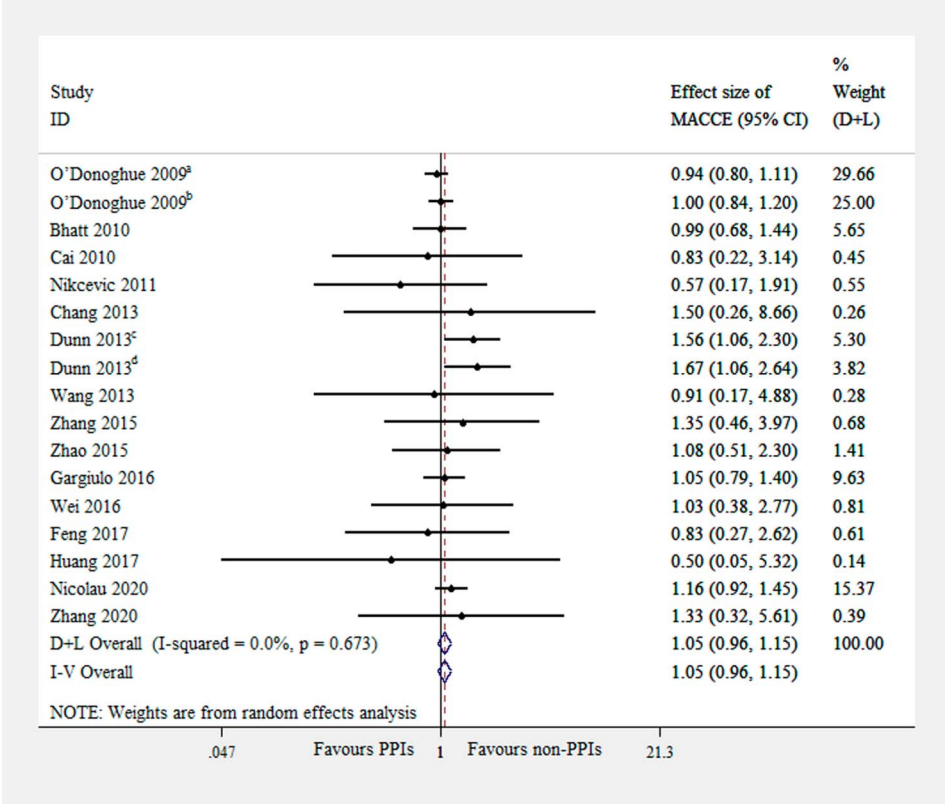

FIGURE 2. Effect of PPIs combined with antithrombotic strategy on the incidence of MACCE in patients with coronary artery diseases. Study ID indicates the name of trials included; a, aspirin plus clopidogrel in the O'Donoghue trial; b, aspirin plus prasugrel in the O'Donoghue trial; c, aspirin alone in the Dunn trial; d, aspirin plus clopidogrel in the Dunn trial; D + L, the DerSimonian and Laird random effects model; I-V, the inverse-variance fixed effect model.

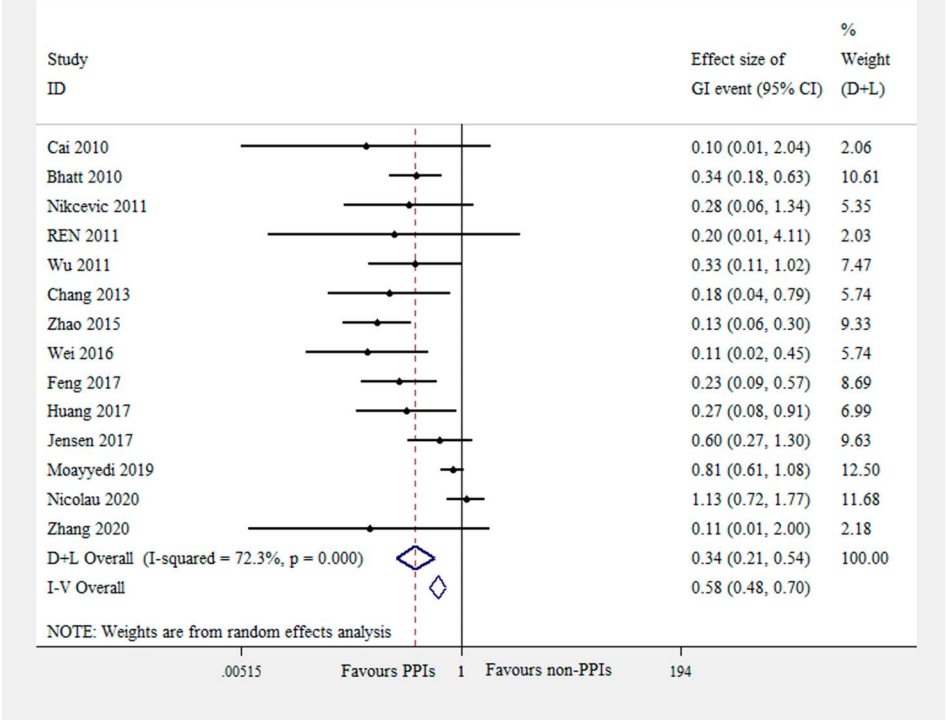

FIGURE 3. Effect of PPIs combined with antithrombotic strategy on the risk of GI events in patients with coronary artery diseases. Study ID indicates the name of trials included; D + L, the DerSimonian and Laird random effects model; I-V, the inverse-variance fixed effect model.

Content 2 (see **Figure S11**, http://links.lww.com/JCVP/A825).

The quality of evidence is determined to be very low for GI events and moderate for MACCE, all-cause death, cardiovascular death, myocardial infarction, definite or probable stent thrombosis, gastroduodenal ulcer, and significant bleeding from gastroduodenal lesions (see **Table S3**, **Supplemental Digital Content 2**, http://links.lww.com/JCVP/A825).

The Trial Sequential Analysis shows that the cumulative Z curves of MACCE, all-cause death, cardiovascular death, myocardial infarction, definite or probable stent thrombosis, and gastroduodenal ulcer do not exceed any boundary, which indicates that the sample sizes of these outcomes do not reach the anticipated sample size. It suggests that no significant difference is observed in the above outcomes between PPIs and non-PPIs arms, and these results need to be confirmed by a larger population. Concerning outcomes of GI events and significant bleeding from gastroduodenal lesions, the cumulative Z curves are beyond the conventional and trial sequential analysis boundaries and the sample sizes reach the anticipated values, which indicate that the results are reliable (see **Figures S12 and S13**, **Supplemental Digital Content 2**, http://links.lww.com/JCVP/A825).

According to the funnel plot and mathematical examination by Begg's test and Egger's test, no publication bias is found for all outcomes ($P > 0.1$), except for GI events ($P = 0.002$) (see **Figures S14 and S15**, **Supplemental Digital Content 2**, http://links.lww.com/JCVP/A825, and see **Table S4**, **Supplemental Digital Content 2**, http://links.lww.com/JCVP/A825). A meta-trim operation is conducted, which demonstrates that no additional trial is needed to fill the analysis (see **Figure S16**, **Supplemental Digital Content 2**, http://links.lww.com/JCVP/A825).

DISCUSSION

The meta-analysis shows that the strategy of PPIs combined with antithrombotic strategy could reduce the risk of GI events and significant bleeding from gastroduodenal lesions. However, the regimen may not affect the incidence of MACCE, all-cause death, cardiovascular death, myocardial infarction, stent thrombosis, and gastroduodenal ulcer in patients with CAD. This strategy could reduce the risk of GI events for patients with percutaneous coronary intervention. Meanwhile, this benefit was observed in patients receiving omeprazole, pantoprazole, rabeprazole, or lansoprazole, Asian or non-Asian patients, or patients with aspirin combined with clopidogrel. The GRADE evidence intensity is moderate for all outcomes, except for GI events. The quality of evidence is very low for GI events.

All trials in this meta-analysis were randomized controlled trials with a low risk of selection and reporting bias. Not all trials were double-blind designs, and the performance and detection bias may affect the quality of the included trial. However, some trials accessed outcomes by independent committees to reduce the risk of detection bias. In addition, the data of all outcomes of interest were evaluated directly. To decrease the random error, trial sequential analysis was performed. It showed that the cumulative Z curves of GI events and significant bleeding from gastroduodenal lesions reach the trial sequential analysis boundaries and anticipated sample size. Therefore, PPIs combined with antithrombotic strategy reduces the risk of GI events, and significant bleeding from gastroduodenal lesions should be regarded as a true-positive conclusion. Although publication bias was found in this meta-analysis, no additional trial needs to be added after the meta-trim operation. Meanwhile, all eligible trials were searched systematically without language and region restriction. The process of data search and trial inclusion can be repeated. In short, despite some shortcomings, the results of this meta-analysis are reliable.

How to balance ischemic and bleeding events is the key to the application of antithrombotic strategy. Our meta-analysis showed that the combination of PPIs and antithrombotic strategy could reduce the risk of GI events and significant bleeding from gastroduodenal lesions. However, it may not affect the incidence of MACCE, all-cause death, cardiovascular death, myocardial infarction, stent thrombosis, and gastroduodenal ulcer. A meta-analysis by Li et al compared the efficacy and safety of PPIs arm (PPIs combined with aspirin and $P2Y_{12}$ receptor inhibitor) and non-PPIs arm (aspirin combined with $P2Y_{12}$ receptor inhibitor) in patients with CAD. The result showed that there was no significant difference in the incidence of adverse ischemic events between the 2 arms. Compared with non-PPIs arm, the PPIs arm reduced the risk of GI complications.[16] Similar views were reported in both meta-analyses. However, there are some differences in our meta-analysis. Our meta-analysis included more antithrombotic agents and randomized controlled trials. Meanwhile, more ischemic and bleeding outcomes were evaluated. Sensitivity analysis was conducted on patients after percutaneous coronary intervention, and subgroup analysis was performed on individual PPIs, different races, and antithrombotic strategies.

A meta-analysis published in 2018 found that compared with aspirin combined with clopidogrel, PPIs combined with aspirin and clopidogrel increase the incidence of major adverse cardiovascular events, stent thrombosis, and revascularization and reduce the risk of GI bleeding.[38] The different results of ischemic events may be due to this meta-analysis included observational studies, which have some confounding factors and imbalanced baseline characteristics. In the observational study, patients treated with PPIs were high-risk groups, mostly older, female, with lower creatinine clearance and with a history of hypertension, diabetes mellitus, myocardial infarction, and percutaneous coronary intervention.[39] A meta-analysis demonstrated that PPIs combined with dual antiplatelet therapy significantly increased the incidence of major adverse cardiac events in high-risk patients [odds ratio (OR) 1.49; 95% CI 1.41–1.57] but not in low-risk individuals (OR 1.01; 95% CI 0.88–1.16). The low-risk patients were defined as the incidence of major adverse cardiac events less than 10% in the non-PPIs arm.[15] Therefore, PPIs themselves may be a marker of higher incidence of MACCE rather than trigger factor.

The results of this meta-analysis should be interpreted with caution. On the one hand, a previous study proved that PPIs competitively inhibit the cytochrome P450 enzyme system, especially lansoprazole and omeprazole, to interfere with the antiplatelet effect of clopidogrel and increase the incidence of ischemic events.[11] Our subgroup analysis of individual PPIs showed that no significant difference in the incidence of MACCE is observed between PPIs arm and non-PPIs arm. Due to the limited sample size, further clinical trials should be conducted to determine which PPIs are most likely to benefit patients with CAD. On the other hand, Asians are characterized by low ischemic risk and high bleeding risk.[40] PPIs combined antithrombotic strategy may be more suitable for Asians than non-Asians. This conclusion was confirmed by subgroup analysis of race in our meta-analysis.

Limitation

The present meta-analysis has some limitations. First, compared with patients with stable CAD, patients with acute coronary syndrome have a higher risk of recurrent adverse cardiovascular events. However, the subgroup analysis of the disease cannot be performed due to the incomplete data. Second, several included trials are post hoc analyses of randomized controlled trials, and some trials are not included in the sensitivity and subgroup analysis because of unavailable data, which may lead to bias and affect the accuracy of the results. In addition, our meta-analysis included some small sample trials, which will inevitably produce small study effects/selective reporting. Publication bias is only one of the potential reasons for the small study effects shown by funnel plots and Egger's tests. Therefore, it is necessary to perform a large randomized trial to evaluate the efficacy and safety of PPIs plus antithrombotic strategy in patients with CAD. Finally, the cumulative Z curves of MACCE, all-cause death, cardiovascular death, myocardial infarction, definite or probable stent thrombosis, and gastroduodenal ulcer did not reach the anticipated sample size; false-negative results may exist, and more clinical trials are needed to increase the reliability of results.

CONCLUSIONS

In patients with CAD, the regimen of combined use of PPIs and antithrombotic strategy could reduce the risk of GI events and significant bleeding from gastroduodenal lesions. However, it may not increase the incidence of MACCE, all-cause death, cardiovascular death, myocardial infarction, stent thrombosis, and gastroduodenal ulcer. Therefore, we recommended that PPIs combined with antithrombotic strategy can be used in patients with CAD in routine clinical practice, especially those with a history of GI bleeding or high risk of GI bleeding. In addition, the GRADE evidence intensity of most outcomes was moderate. Therefore, a large-scale, randomized, double-blind, controlled trial is needed to evaluate the efficacy and safety of PPIs combined with antithrombotic strategy in patients with CAD.

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