Influence of proton pump inhibitors on clinical outcomes in coronary heart disease patients receiving aspirin and clopidogrel
A meta-analysis

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Abstract

Background: Proton pump inhibitors (PPIs) are usually prescribed to protect against gastrointestinal bleeding in patients on dual antiplatelet therapy. This meta-analysis reviewed clinical outcomes in patients taking aspirin and clopidogrel, with and without concomitant PPIs to address concerns of adverse reactions.

Methods: We searched PubMed, Embase, and the Cochrane Library for articles published between January 1, 2010 and April 11, 2017. The primary end points were major adverse cardiovascular events and gastrointestinal bleeding. Secondary end points were myocardial infarction, stent thrombosis, revascularization, cardiogenic death, and all-cause mortality.

Results: The meta-analysis included 33,492 patients in 4 randomized controlled trials and 8 controlled observational studies. Overall, patients taking PPIs had statistical differences in major adverse cardiovascular events [odds ratio (OR) 1.17 (95% confidence interval [CI] 1.07–1.28); $P = .001$; $I^2 = 28.3\%$], gastrointestinal bleeding [OR 0.58 (95% CI 0.36–0.92); $P = .022$; $I^2 = 80.6\%$], stent thrombosis [OR 1.30 (95% CI 1.01–1.68); $P = .041$; $I^2 = 0\%$], and revascularization [OR 1.20 (95% CI 1.04–1.38); $P = .011$; $I^2 = 5.1\%$], compared those not taking PPIs. There were no significant differences in myocardial infarction [OR 1.03 (95% CI 0.87–1.22); $P = .742$; $I^2 = 0\%$], cardiogenic death [OR 1.09 (95% CI 0.83–1.43); $P = .526$; $I^2 = 0\%$], or all-cause mortality [OR 1.08 (95% CI 0.93–1.25); $P = .329$; $I^2 = 0\%$].

Conclusions: Among the patients taking aspirin and clopidogrel, the results indicated that the combined use of PPIs increased the rates of major adverse cardiovascular events, stent thrombosis, and revascularization.

Abbreviations: ACS = acute coronary syndrome, CI = confidence interval, CYP = hepatic cytochrome P-450, DAPT = dual antiplatelet therapy, GI = gastrointestinal, MACE = major adverse cardiovascular events, MI = myocardial infarction, OR = odds ratio, PPIs = proton pump inhibitors, PCI = percutaneous coronary intervention, RCT = randomized controlled trial.

Keywords: aspirin, clopidogrel, coronary heart disease, coronary stenting, percutaneous coronary intervention, proton pump inhibitors

1. Introduction

Dual antiplatelet therapy (DAPT), especially combination therapy with aspirin and clopidogrel, is recommended for the treatment of acute coronary syndrome (ACS) and patients with percutaneous coronary intervention (PCI).[1,2] Antiplatelet drugs significantly reduce the risk of cardiovascular events, but also

have side effects involving the gastrointestinal (GI) mucous membrane such as GI bleeding, peptic ulcer, perforated peptic ulcer, and digestive tract obstruction.[3,4] Proton pump inhibitors (PPIs) are usually prescribed for patients on DAPT to attenuate the side effects,[5–7] but there are concerns of adverse interactions of antiplatelet drugs and PPIs.[8,9] Current guidelines do not recommend the routine use of PPIs by patients with a low risk of GI bleeding[1] and advise that combination therapy with DAPT and PPIs has the potential of adverse drug interactions.[7–9]

Aspirin absorption is dependent on gastric pH, and the secretion of gastric acid may be decreased by PPIs. Consequently, long-term use of PPIs might reduce the antiplatelet activity of aspirin.[10,11] Clopidogrel is a prodrug that needs undergo metabolic transformation to generate its active metabolite. The transformation depends on the hepatic cytochrome P-450 (CYP) enzyme system, which is also responsible for the metabolism of PPIs. The competitive inhibition and adverse interactions of clopidogrel and PPIs have been confirmed by pharmacokinetics and platelet aggregation studies.[12–15] Few meta-analyses of the impact of PPIs on aspirin or clopidogrel monotherapy have been published,[16–19] but GI adverse events are more common in people on DAPT, and PPIs are more often prescribed for people on DAPT than for those on aspirin or clopidogrel monotherapy. Reports of the clinical outcomes of patients undergoing combination therapy with DAPT and PPIs have been published,

Table 1

The quality outcomes of assessed cohort studies based on the Newcastle-Ottawa Scale.

Author	Selection	Comparability	Outcomes available	Total, n	Outcomes available	Study design
Yasu[25]	****	**	***	9	MACE, GB, ST, R, CD	Retrospective cohort
Zairis[26]	***	**	***	8	MACE, MI, ST, R, CD	Retrospective cohort
Tentzeris[27]	***	*	**	6	MACE, ST, CD, M	Prospective cohort
Rossini[28]	****	**	***	9	MACE, GB, ST, M	Cohort
Harjai[29]	****	*	***	8	MACE, GB, MI, ST, R, M	Prospective cohort
Zou[9]	***	**	***	8	MACE, MI, ST, R, M	Retrospective cohort
Weisz[13]	***	*	***	7	MACE, GB, MI, ST, R, CD, M	Prospective cohort
Chandrasekhar[7]	***	*	***	7	MACE, GB, MI, ST, R, M	Prospective cohort

CD = cardiogenic death, GB = gastrointestinal bleeding, M = all-cause mortality, MACE = major adverse cardiovascular events, MI = myocardial infarction, n = number, R = revascularization, ST = stent thrombosis.

but the results are either inconsistent,[5–9] or the eligibility was not restricted to patients with coronary heart disease. This meta-analysis evaluated the clinical outcomes of patients on combination therapy with aspirin and clopidogrel with or without PPIs.

2. Methods

This meta-analysis was performed following the PRISMA checklist. Ethical approval and patient consent were not required because our study was retrieved from previous published studies.

2.1. Search strategy and selection criteria

We searched PubMed, Embase, and the Cochrane Library for articles published between January 1, 2010 and April 11, 2017 using the terms "proton pump inhibitors," "aspirin," "clopidogrel," "acute coronary syndrome," "percutaneous coronary intervention," and "coronary stenting." Eligible studies were those that included ACS, PCI, or coronary stenting patients given combination therapy with aspirin and clopidogrel, compared a PPI with a placebo group, reported a primary end point of major adverse cardiovascular events (MACE), and had at least 3 months of follow-up. Nonclinical studies (e.g., editorials or letters to the editor), reports of case series, different reports of the same trial, reports of incomplete, interim, or duplicate data, or trials with patient samples of 100 or fewer were excluded.

2.2. Data extraction and quality assessment

Data extraction was performed independently by 2 investigators (W.H. and J.T.) following the predefined inclusion and exclusion criteria. Differences in opinion were resolved by discussion, with a final decision by a third investigator if necessary. The baseline patient characteristics included first author, year of publication, study population, sex, proportion of patients with diabetes mellitus, hypertension and ACS, the mean follow-up period, type of PPIs, and study sample.

The quality of each controlled observational study was assessed using the Newcastle–Ottawa Scale, which includes patient selection, comparability of groups, and evaluation of outcomes. A maximum of 4 stars were possible for patient selection, 2 for group comparability, and 3 for evaluation of outcomes.[20] The star scores of the controlled observational studies are shown in Table 1. High-quality studies had 6 or more stars.[21] The quality of each randomized controlled trial (RCT) was assessed by the modified Jadad scale, which includes randomization, allocation concealment, blinding, and loss to follow-up.[22] High-quality studies had 4 or more scores.[23] The scores of the RCTs are shown in Table 2.

2.3. End points

The primary end points were MACE (defined as ACS, stent thrombosis, revascularization, stroke, and all-cause mortality) and GI bleeding (overt and occult). Secondary end points were myocardial infarction (MI), stent thrombosis, revascularization, cardiogenic death, and all-cause mortality. Stent thrombosis included both definite and probable. If revascularization was not reported, then target vessel revascularization was used as the most preferred alternative; target lesion revascularization was the least preferred. If different reports of the same trial were retrieved, then the publication with the most complete data was abstracted.

2.4. Statistical analysis

The results were analyzed with Stata 12.0 and fixed-effects (Mantel–Haenszel) or random-effects (M-H heterogeneity) models. We computed the pooled odds ratios (ORs) for dichotomous end points with 95% confidence intervals (CIs). The level of statistical significance was $\alpha = 0.05$. A fixed-effects model was used to analyze studies with an acceptable heterogeneity of $P > .1$ or $I^2 < 50\%$. If substantial heterogeneity ($P < .1$ or $I^2 > 50\%$) was indicated, then a random-effects model was used, and the possible sources of heterogeneity were analyzed

Table 2

The quality outcomes of assessed randomized controlled trials based on the modified Jadad scale.

Author	Randomization	Allocation concealment	Blinding	Loss to follow-up	Jadad score	Outcomes available	Study design
Bhatt[5]	2	1	1	0	4	MACE, GB, MI, R, CD, M	RCT
Zhang[30]	1	1	1	1	4	MACE	RCT
WEI[6]	2	2	0	1	5	MACE, GB, MI, CD	RCT
Vaduganathan[8]	1	1	1	1	4	MACE, GB, MI, R, CD ,M	RCT

CD = cardiogenic death, GB = gastrointestinal bleeding, M = all-cause mortality, MACE = major adverse cardiovascular events, MI = myocardial infarction, R = revascularization.

by a statistician.[24] Publication bias was estimated using a funnel plot by checking whether the trials were symmetrically distributed.

3. Results

3.1. Search results

A total of 295 articles were initially retrieved from PubMed, 501 from Embase, and 107 from the Cochrane Library; 576 duplicates were excluded, leaving 327 potentially relevant articles. An additional 302 articles were excluded after reading the titles and abstracts. Of the 25 remaining articles, 12 studies including 33,492 patients were selected for analysis. A flowchart of the trial selection process is shown in Figure 1.

3.2. Baseline characteristics

The baseline characteristics of the patients in the 4 RCTs[5,6,8,30] and 8 controlled observational studies[7,9,13,25–29] are shown in Table 3. The study sample sizes ranged from 104 to 8582

patients. PPIs were used by 16,845 of the 33,492 patients (50.29%); 16,647 patients did not use PPIs. The mean age of the patients enrolled in the 12 studies ranged from 58 to 69 years, the majority were men, and the majority had hypertension. The proportion of patients with diabetes mellitus ranged from 18% to 39%, but 1 trial[6] did not report the number of patients with diabetes. The proportion of patients with ACS varied widely; mean follow-up duration ranged from 3.5 to 24 months.

3.3. Primary endpoints

All 12 articles[5–9,13,25–30] reported MACE as a primary endpoint. It occurred in 1580 of the 16,839 patients (9.38%) in the PPI group, and 1281 of 16,632 patients (7.70%) in the placebo group. As a forest plot showed acceptable heterogeneity ($I^2 =$ 28.3%; $P = .167$), a fixed-effects model was used to evaluate the occurrence of MACE. Compared with placebo, PPIs increased the occurrence of MACE [OR 1.17 (95% CI 1.07–1.28); $P = .001$; Fig. 2]. Because MACE is of key clinical significance and was reported in all the included trials, publication bias was
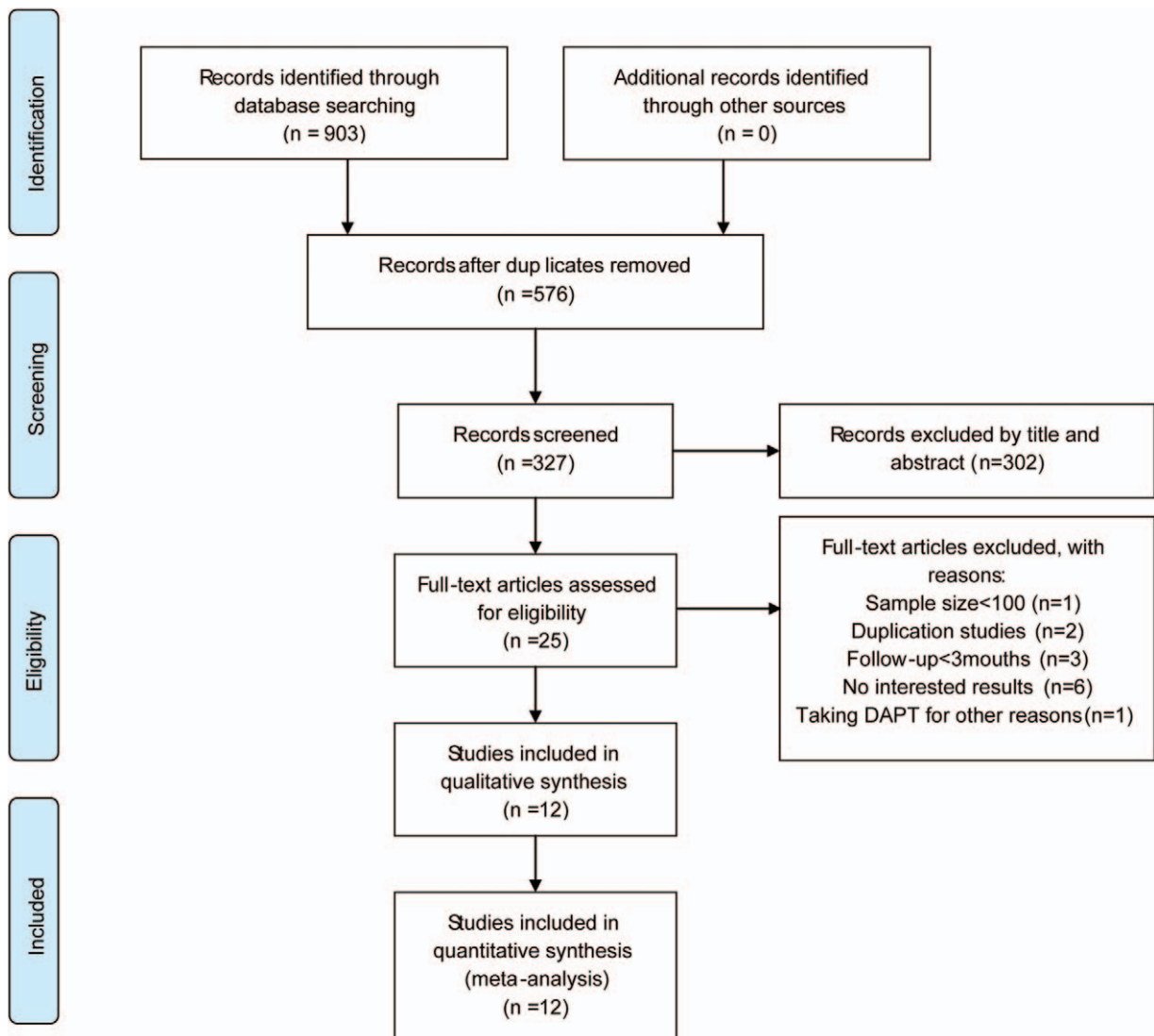

Figure 1. A flowchart of the trial selection. DAPT = dual antiplatelet therapy.

Table 3

The baseline characteristics of the included studies.

Author	Year	Population	Men, %	DM, %	HP, %	ACS, %	FU	PPIs	Patients, n
Yasu[25]	2010	CS	67.0/72.4	35.0/39.7	64.1/64.8	27.2/27.1	13	R	302
Zairis[26]	2010	CS	82.4/81.9	30.2/26.2	50.9/46.4	77.4/76.2	12	O	588
Tentzeris[27]	2010	CS	65.4/72.6	18.7/26.0	73.7/78.2	52.2/34.3	7.8	NA	1210
Bhatt[5]	2010	ACS or CS	66.9/69.5	31.7/28.6	80.1/81.4	42.2/42.6	6	O	3761
Rossini[28]	2011	CS	75.6/81.2	27.1/28.0	63.6/65.2	69.3/67.4	12	L,P,O	1328
Harjai[29]	2011	CS	61.7/71.9	30.0/26.6	73.0/65.0	NA	6	NA	1370
Zou[9]	2014	CS	73.5/73.9	25.8/23.6	71.3/70.4	NA	12	NA	7653
Weisz[13]	2015	CS	70.1/75.9	34.8/31.4	83.7/77.8	57.4/49.0	24	NA	8582
Zhang[30]	2015	ACS with CS	45.3/43.1	18.9/27,5	50.9/49.0	100/100	6	L	104
Chandrasekhar[7]	2016	CS	30.5/24.7	32.9/32.8	79.8/80.4	43.1/41.3	24	NA	4635
WEI[6]	2016	MI with PCI	56.1/57.1	NA	NA	100/100	6	P	207
Vaduganathan[8]	2016	ACS or PCI	68.1/71.2	32.2/28.8	79.2/80.7	41.4/42.2	3.5	O	3752

Data are mean (SD) or n (%), unless otherwise indicated.

ACS = acute coronary syndrome, CS = coronary stenting, DM = diabetes mellitus, FU = follow-up (months), HP = hypertension, L = lansoprazole, MI = myocardial infarction, n = number, NA = not available, O = omeprazole, P = pantoprazole, PCI = percutaneous coronary intervention, PPI = proton pump inhibitor, R = rabeprazole.

estimated in the funnel plot (Fig. 3), which showed a symmetrical distribution of the trials indicating that publication bias was not likely to have influenced the analysis.

GI bleeding was reported in 8 articles,[5–8,13,25,28,29] and was reported in 315 of 9038 patients (3.49%) in the PPI group, and 608 of 14,898 patients (4.08%) in the placebo group. As significant heterogeneity was found for the articles reporting GI bleeding ($I^2 = 80.6\%$; $P < .001$), a random-effects model was used to evaluate its occurrence. The rate of GI bleeding was lower in the PPI group than in the placebo group [OR 0.58 (95% CI 0.36–0.92); $P = .022$; Fig. 4]. The possible sources of heterogeneity are discussed below.

3.4. Secondary endpoints

The secondary endpoints were MI, stent thrombosis, revascularization, cardiogenic death, and all-cause mortality. Heterogeneity of the 8 articles[5–9,13,26,29] reporting MI was not detected ($I^2 = 0\%$; $P = .804$); a fixed-effects model was used for analysis. A total of 265 of 14,816 patients (1.79%) in the PPI group, and 391 of 15,684 patients (2.49%) in the placebo group experienced an MI. The rates of MI in the PPI and placebo groups were not significantly different [OR 1.03 (95% CI 0.87–1.22); $P = .724$; Fig. 5].

Stent thrombosis was reported in 8 articles.[7,9,13,25–29] It occurred in 182 of 12,924 patients (1.41%) in the PPI group, and
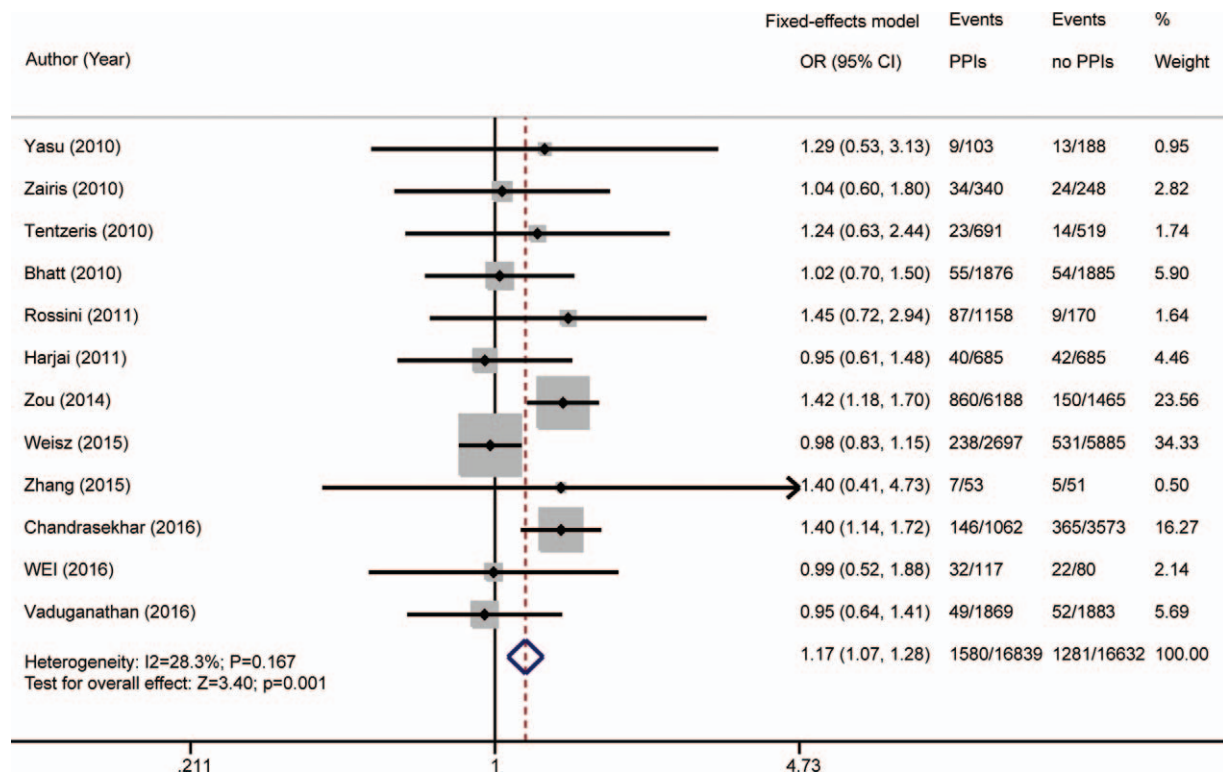

Figure 2. Risk estimates of major adverse cardiovascular events (MACE). CI = confidence interval, OR = odds ratio, PPI = proton pump inhibitor.
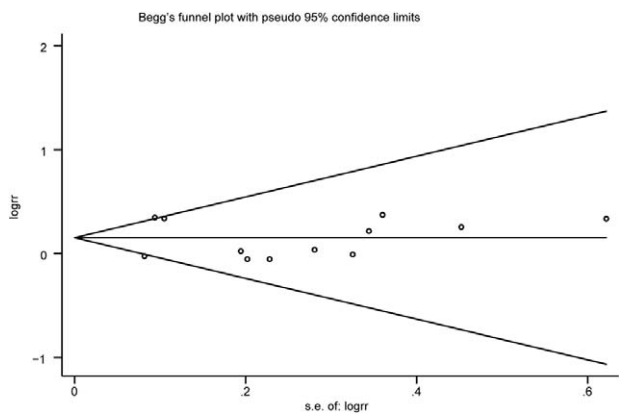
Figure 3. Funnel plot indicating major adverse cardiovascular events (MACE) among patients taking aspirin and clopidogrel with or without proton pump inhibitors (PPIs).

145 of 12,733 patients (1.14%) in the placebo group. No heterogeneity was found ($I^2 = 0\%$; $P = .561$); a fixed-effects model was used. The occurrence of stent thrombosis was higher in the PPI group than in the placebo group [OR 1.30 (95% CI 1.01–1.68); $P = .041$; Fig. 6].

Eight articles[5,7–9,13,25,26,29] reported revascularization. There were 662 events in the 14,820 PPI patients (4.47%) and 455 events in the 15,812 placebo patients (2.88%). Heterogeneity was acceptable ($I^2 = 5.1\%$; $P = .391$); a fixed-effects model was used. The occurrence of revascularization [OR 1.20 (95% CI 1.04–1.38); $P = .011$; Fig. 7] was higher in the PPI than in the placebo group.

Seven articles[5,6,8,13,25–27] reported cardiogenic death. It occurred in 91 of 7693 patients (1.18%) in the PPI group and

139 of 10,688 patients (1.30%) in the placebo group. Study heterogeneity was not detected ($I^2 = 0\%$; $P = .823$); a fixed-effects model was used. The occurrence of cardiogenic death in the PPI group was not significantly different from that in the placebo group [OR 1.09 (95% CI 0.83–1.43); $P = .526$; Fig. 8].

All-cause mortality was reported in 8 articles.[5,7–9,13,27–29] It occurred in 459 of 16,226 patients (2.83%) in the PPI group and 463 of 16,065 patients (2.88%) in the placebo group. Study heterogeneity was not detected ($I^2 = 0\%$; $P = .433$); a fixed-effects model was used. The difference in all-cause mortality in the PPI and placebo groups was not significant [OR 1.08 (95% CI 0.93–1.25); $P = .329$; Fig. 9].

4. Discussion

Few meta-analyses have assessed the impact of PPIs on antiplatelet drugs, but they selected studies that included patients on aspirin or clopidogrel monotherapy or studies that did not restricted eligibility to patients with coronary heart disease.[16–19] Patients with a high risk of MACE are often given aspirin and clopidogrel combination therapy. The concomitant use of PPIs by those patients may multiply their occurrence of MACE compared with patients on aspirin or clopidogrel monotherapy and PPIs. However, meta-analyses of the outcomes of aspirin, clopidogrel, and PPIs combination therapy are lacking. This analysis found that the concomitant use of aspirin, clopidogrel, and PPIs decreased the rate of GI bleeding but increased the rates of MACE, stent thrombosis, and revascularization. There were no differences in the risks of MI, cardiogenic death, and all-cause mortality.

In some studies, PPIs reduced the occurrence of GI bleeding in patients on DAPT,[5,6,8] but other results were contradictory.[7,13,25,28,29] Many studies did not stratify the participants by risk of GI bleeding, with the use of PPIs was determined by
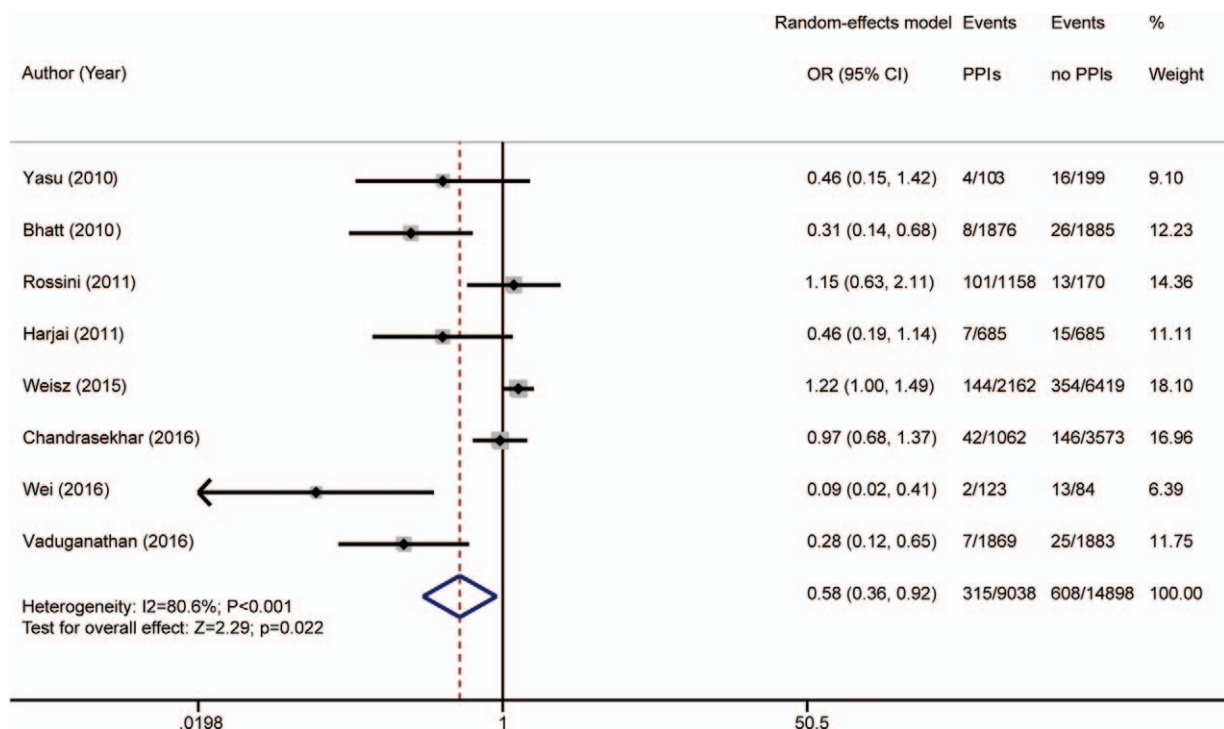

Figure 4. Risk estimates of gastrointestinal (GI) bleeding. CI = confidence interval, OR = odds ratio, PPI = proton pump inhibitor.

Author (Year)	Fixed-effects model OR (95% CI)	Events PPIs	Events no PPIs	% Weight
Zairis (2010)	1.00 (0.52, 1.95)	22/340	16/248	6.82
Bhatt (2010)	0.94 (0.45, 1.95)	14/1876	15/1885	5.85
Harjai (2011)	1.00 (0.53, 1.87)	20/667	20/665	7.65
Zou (2014)	1.82 (0.91, 3.66)	69/6188	9/1465	5.67
Weisz (2015)	0.90 (0.69, 1.18)	79/2697	190/5885	45.66
Chandrasekhar (2016)	1.12 (0.78, 1.60)	41/1062	124/3573	21.52
WEI (2016)	1.03 (0.28, 3.76)	6/117	4/80	1.78
Vaduganathan (2016)	1.09 (0.51, 2.32)	14/1869	13/1883	5.06
	1.03 (0.87, 1.22)	265/14816	391/15684	100.00

Heterogeneity: I2=0%; P=0.804
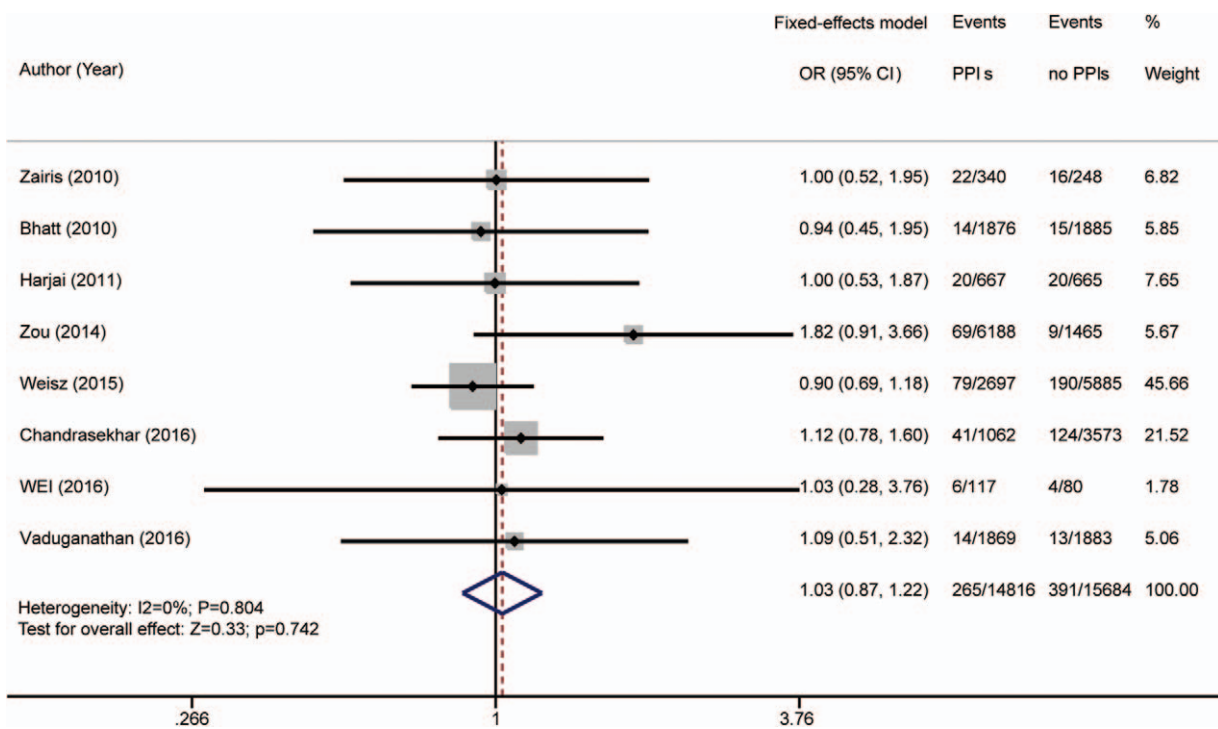Test for overall effect: Z=0.33; p=0.742

.266   1   3.76

Figure 5. Risk estimates of myocardial infarction (MI). CI = confidence interval, OR = odds ratio, PPI = proton pump inhibitor.

clinicians. In many studies, the PPI users had a higher risk of GI events than nonusers. Even though the difference in GI bleeding in the PPI and placebo groups was not significant, that may have attributed to the protective effect of PPIs on the GI mucous membrane. This may have contributed to study heterogeneity.[7]

Previous studies found that when DAPT and PPIs were used in combination, the risks of MACE, stent thrombosis, and revascularization were increased.[7,9] PPIs inhibit gastric acid secretion, which increases the gastric pH and can alter the pharmacokinetics of aspirin. This might account for a decline in
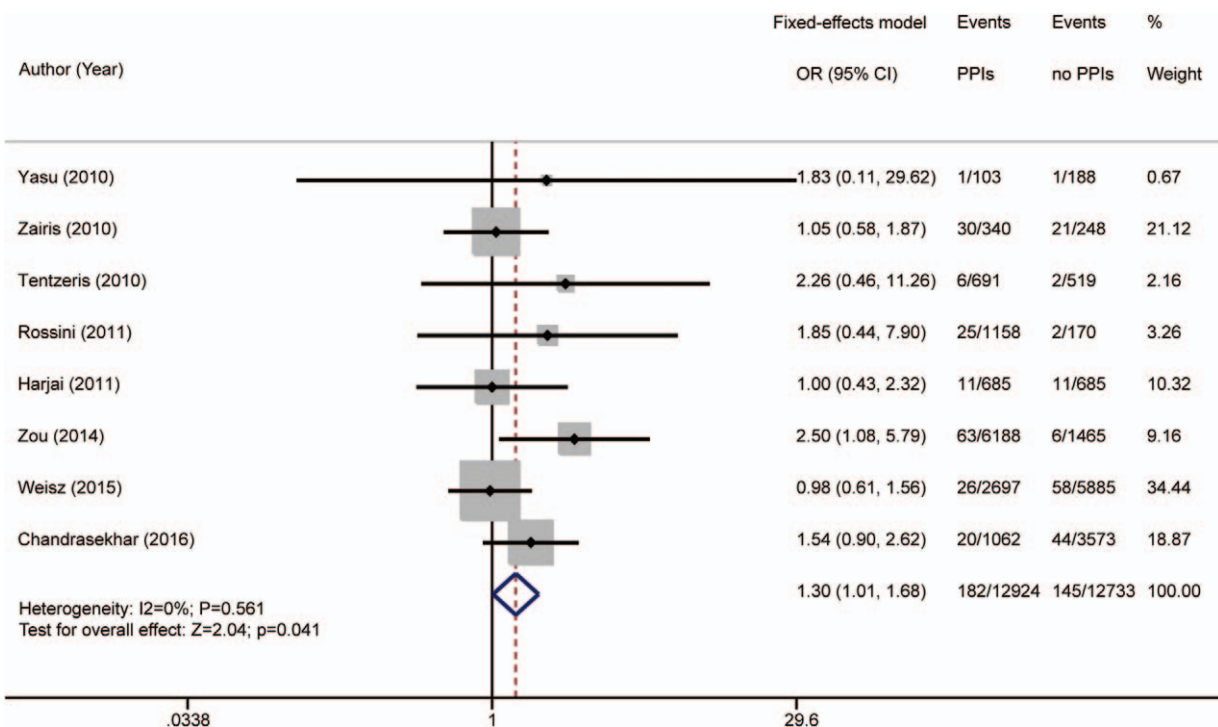
Author (Year)	Fixed-effects model OR (95% CI)	Events PPIs	Events no PPIs	% Weight
Yasu (2010)	1.83 (0.11, 29.62)	1/103	1/188	0.67
Zairis (2010)	1.05 (0.58, 1.87)	30/340	21/248	21.12
Tentzeris (2010)	2.26 (0.46, 11.26)	6/691	2/519	2.16
Rossini (2011)	1.85 (0.44, 7.90)	25/1158	2/170	3.26
Harjai (2011)	1.00 (0.43, 2.32)	11/685	11/685	10.32
Zou (2014)	2.50 (1.08, 5.79)	63/6188	6/1465	9.16
Weisz (2015)	0.98 (0.61, 1.56)	26/2697	58/5885	34.44
Chandrasekhar (2016)	1.54 (0.90, 2.62)	20/1062	44/3573	18.87
	1.30 (1.01, 1.68)	182/12924	145/12733	100.00

Heterogeneity: I2=0%; P=0.561
Test for overall effect: Z=2.04; p=0.041

.0338   1   29.6

Figure 6. Risk estimates of stent thrombosis. CI = confidence interval, OR = odds ratio, PPI = proton pump inhibitor.
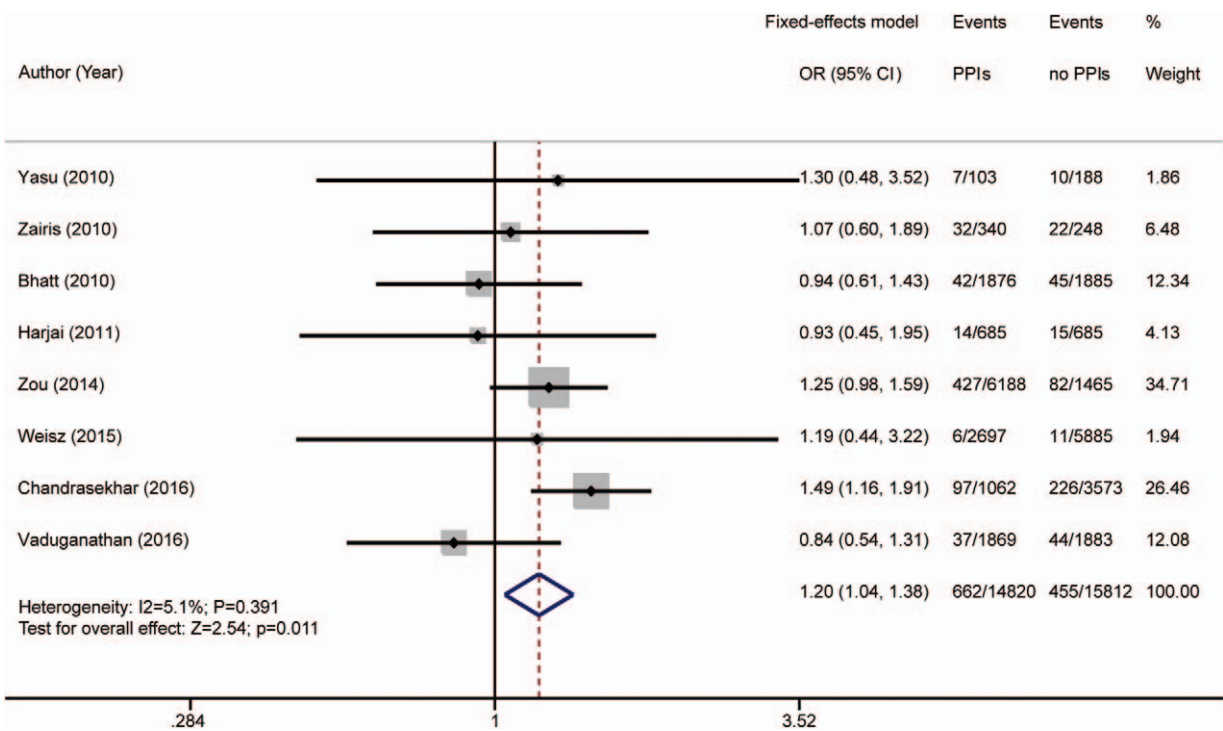
Figure 7. Risk estimates of revascularization. CI = confidence interval, OR = odds ratio, PPI = proton pump inhibitor.

bioavailability and therapeutic effects of combination therapy with aspirin and PPIs.[10,11]

Another underlying mechanism involves interaction of metabolic pathways that requires CYP enzymes. Clopidogrel is a prodrug that undergoes CYP-dependent metabolic transformation to generate its active metabolite.[12–15] CYP2C19 is the predominant enzyme in this conversion, but CYP3A4/5, CYP2B6, and CYP1A2/1 may be involved. PPIs are also metabolized by the CYP enzyme system, but different PPIs require different isoenzymes. Omeprazole/esomeprazole is metabolized by CYP2C19 to 5-hydroxyomeprazole, which is converted to 5-hydroxyomeprazole sulfone by CYP3A4.
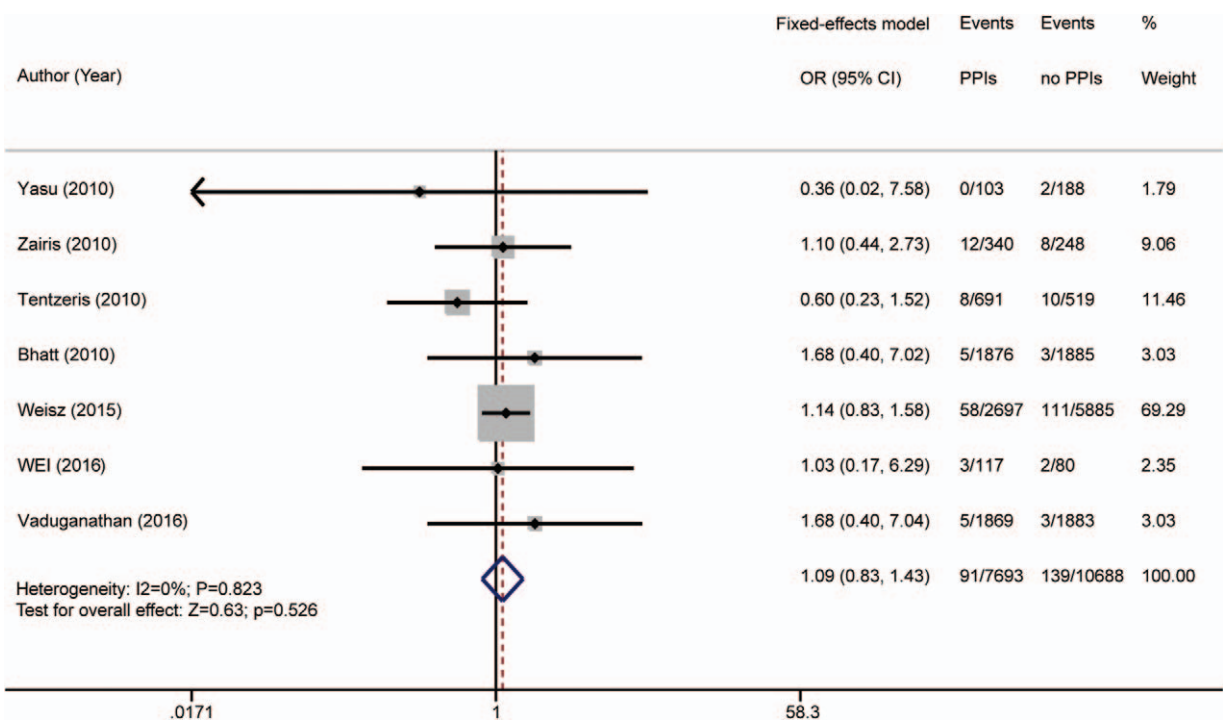

Figure 8. Risk estimates of cardiogenic death. CI = confidence interval, OR = odds ratio, PPI = proton pump inhibitor.
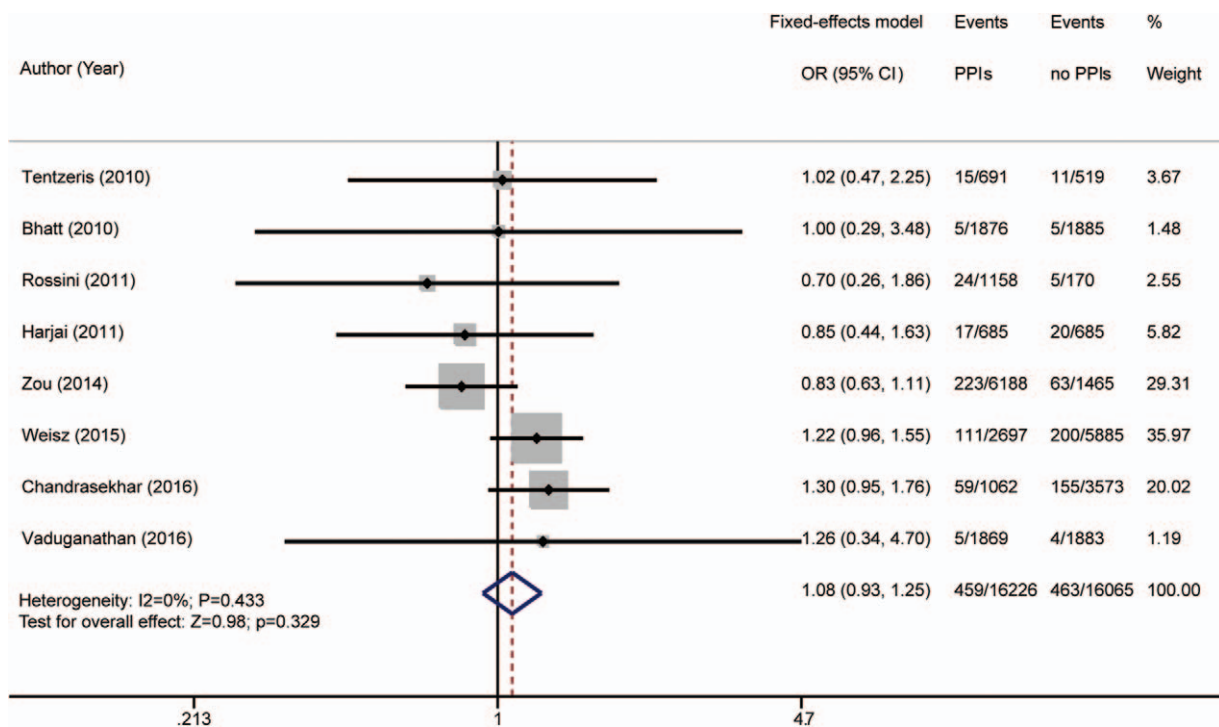
Figure 9. Risk estimates of all-cause mortality. CI = confidence interval, OR = odds ratio, PPI = proton pump inhibitor.

Lansoprazole is metabolized by CYP2C19 and CYP3A4 to 5-hydroxy lansoprazole, lansoprazole sulfone, or lansoprazole sulfide. Pantoprazole is metabolized by CYP2C19 and CYP3A4 to hydroxy pantoprazole or pantoprazole sulfone. Rabeprazole is primarily metabolized nonenzymatically, and a portion is metabolized by CYP2C19.[31,32] The interaction of clopidogrel and PPIs thus involves competitive inhibition.[12–15] In patients carrying hypofunctional CYP2C19 alleles, the active metabolites of clopidogrel and platelet inhibition are significantly decreased,[33] and combination therapy might not effectively reduce the occurrence of MACE. Patients with genetic polymorphisms involving hypofunctional CYP2C19 alleles might benefit more from DAPT–PPI combination therapy with clopidogrel and rabeprazole rather than one of the other PPIs,[31] or from ticagrelor, a potent antiplatelet drug that is not affected by CYP2C19 polymorphisms.[34]

Aspirin directly damages the GI mucous membrane, and clopidogrel delays the healing of peptic ulcers. Antiplatelet drugs thus have side effects such as acute GI hemorrhage, and perforated peptic ulcer, and these stressful events may increase the occurrence of cardiovascular events. A 2008 ACCF/ACG/AHA expert consensus panel recommended routine use of PPIs for patients on DAPT.[35] Subsequent studies reported that patients on combination therapy with DAPT and PPIs increased the incidence of MACE, compared those not taking PPIs,[7,9] and led to revisions of the treatment recommendations. The 2016 American College of Cardiology and American Heart Association guidelines recommend PPIs for patients with a history of prior GI bleeding or the potential for GI bleeding. The routine use of PPIs is currently not suggested patients at low risk of GI bleeding,[1] and it is important to identify patients at risk of GI events. This includes those older than 65 years of age, a history of prior GI bleeding, or peptic ulcer, with *Helicobacter pylori* infection, concomitant use of anticoagulants, steroids, or

nonsteroidal anti-inflammatory drugs.[35] Patients with a history of prior GI bleeding should be treated with caution. For prompt detection of bleeding, patients should check their stool color, and fecal occult blood testing and hemoglobin testing should be done at routine evaluation visits. The ^{13}C-urea breath test can be used to screen for *Helicobacter* infection in high-risk patients, and those taking DAPT should be given anti-*Helicobacter* therapy if positive.[36] PPIs are often given to patients at high risk of GI events, but long-term use of PPIs is discouraged because inhibition of gastric acid secretion and loss of pepsin activity can lead to development of GI disorders.[37] It may be more reasonable to prescribe PPIs for patients at high risk of GI events in the first 3 months after ACS or PCI. PPIs can then be replaced by H$_2$-receptor antagonists or gastric mucosa protective agents. The time of peak risk of DAPT-induced digestive tract bleeding could be used to guide the timing and duration of PPI use, but published recommendations are lacking. On the contrary, prevention should precede treatment. Carotid artery wall motion helps to diagnose atherosclerosis at a preclinical stage, and can be assessed by nonlinear state-space models constructed from ultrasound sequences[38] or elasticity-based state-space models.[39] The recovery of myocardial motor function could be used to evaluate the impact of PPIs on cardiovascular events.[40] Hemodynamics analysis of narrowed coronary arteries[41] and visualization based on 3D printed models[42] provide noninvasive assessments of coronary conditions that can aid in the medical decision-making process.

The limitations of this meta-analysis included the selection of non-RCTs, which are subject to selection bias, confounding bias, and baseline differences of the experimental and control groups. Moreover, PPIs differ in the CYP isoenzymes required for metabolism[31,32] and have different levels of impact on clopidogrel activity.[13–15] But subgroup analyses of PPI–DAPT were not possible because of limited patient data. Consequently,

which of the available PPIs is safer when combined with aspirin and clopidogrel could not have been determined.

5. Conclusion

Combination therapy with aspirin, clopidogrel, and PPIs decreased GI bleeding and potentially increased MACE. The GI benefits should be weighed against the MACE risks when prescribing PPIs to patients taking aspirin and clopidogrel. The meta-analysis included nonrandomized controlled studies, which are subject to selection bias or baseline study group differences. The results should be interpreted with caution.

Acknowledgments

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