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ORIGINAL RESEARCH

Comparison of prophylactic effect of UGIB and effects on platelet function between PPIs and H_2RAs combined with DAPT: systematic review and meta-analysis

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Zhan-Miao Yi[1]
Ting-Ting Qiu[1,2]
Yuan Zhang[3]
Zhi-Yan Liu[1]
Suo-Di Zhai[1]

[1]Department of Pharmacy, Peking University Third Hospital, Beijing, [2]Department of Pharmacy, China Pharmaceutical University, Nanjing, People's Republic of China; [3]Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, ON, Canada

Objective: We compared prophylactic effects of proton pump inhibitors (PPIs) and histamine-2 receptor antagonists (H_2RAs) on upper gastrointestinal bleeding (UGIB) associated with dual antiplatelet therapy (DAPT) and explored this influence on platelet function.

Methods: Randomized controlled trials and cohort studies comparing PPIs with H_2RAs in adults receiving DAPT were collected from PubMed, EMBASE and Cochrane databases. Dichotomous data were pooled to obtain risk ratios (RRs) for UGIB, major adverse cardiovascular events (MACEs), poor responders to clopidogrel and rehospitalization, and continuous data were pooled to obtain mean differences (MDs) for $P2Y_{12}$ reaction units (PRUs), with 95% confidence intervals (CIs).

Results: Twelve clinical trials (n=3,301) met the inclusion criteria. Compared to H_2RAs, PPIs lessened UGIB (RR =0.16, 95% CI: 0.03–0.70), and there was no significant difference in the incidence of PRUs (MD =18.21 PRUs, 95% CI: −4.11–40.54), poor responders to clopidogrel (RR =1.21, 95% CI: 0.92–1.61), incidence of MACEs (RR =0.89, 95% CI: 0.45–1.75) or rehospitalization (RR =1.76, 95% CI: 0.79–3.92). Subgroup analysis confirmed fewer PRUs in the H_2RAs group compared to the omeprazole group (2 studies, n=189, MD =31.80 PRUs, 95% CI: 11.65–51.96). However, poor responder data for clopidogrel and MACEs might be unreliable because few studies of this kind were included.

Conclusion: Limited evidence indicates that PPIs were better than H_2RAs for prophylaxis of UGIB associated with DAPT and had no effect on platelet function. Further study is needed to confirm these observations.

Keywords: proton pump inhibitors, histamine-2 receptor antagonists, dual-antiplatelet therapy, upper gastrointestinal bleeding, platelet function, meta-analysis

Introduction

Dual antiplatelet therapy (DAPT; clopidogrel and aspirin) is commonly used for primary and secondary prevention of cardiovascular (CV) and cerebrovascular diseases. DAPT can reduce the risk of subsequent stroke for a year after the first event.[1] In a randomized controlled trial (RCT), DAPT was confirmed to reduce the risk of stroke by 32% compared to aspirin alone in patients with minor stroke or transient ischemic attacks.[2]

As DAPT use increases, the incidence of DAPT-associated upper gastrointestinal (GI) injuries, including gastric mucosal erosions, peptic ulcers and bleeding, also rises. Morneau et al reported that DAPT therapy could increase twofold the risk of

Correspondence: Suo-Di Zhai
Department of Pharmacy, Peking University Third Hospital, No 49 North Garden Road, Haidian District, Beijing 100191, People's Republic of China
Tel +86 10 8226 6686
Fax +86 10 8226 5740
Email zhaisuodi@163.com

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GI bleeding (GIB), especially in patients with multiple risk factors.[3] Thus, GIB prophylaxis was suggested for patients receiving DAPT therapy.

In 2007, the American College of Cardiology recommended antiulcer drugs for patients with a history of GIB, and proton pump inhibitors (PPIs) effectively lowered the adjusted risk of aspirin-induced GIB by 28%.[4] Meanwhile, histamine-2 receptor antagonists (H_2RAs) therapy can prevent ulcers for patients receiving low-dose aspirin.[5]

Studies suggest that combination treatment with PPIs plus clopidogrel is associated with high platelet reactivity and more adverse events during long-term follow-up.[6,7] PPIs were also shown to reduce responsiveness to standard clopidogrel doses and increased CV events for patients with the cytochrome P450 (CYP) 2C19 loss-of-function allele.[8] Moreover, H_2RAs may be as effective as PPIs plus DAPT for patients with no prior history of upper GI bleeding (UGIB).[9] Therefore, H_2RAs might be a reasonable alternative to PPIs, as they do not affect CYP 2C19 genotypes. Therefore, we conducted a systematic review and meta-analysis to compare the efficacy and safety of PPIs compared with H_2RAs for preventing UGIB associated with DAPT, and offered a foundation of evidence for clinical decision-making.

Materials and methods

Search strategy and inclusion criteria

We searched PubMed (January 1966 to August 2016), EMBASE (January 1974 to August 2016) and the Cochrane Collaboration's Central Register of Controlled Trials (CENTRAL) (2016 Issue 8) to identify clinical trials comparing the efficacy of PPIs to H_2RAs for patients treated with DAPT consisting of aspirin and clopidogrel. The following search terms were used: aspirin, acetylsalicylic, clopidogrel, proton pump inhibitors, PPIs, esomeprazole, pantoprazole, omeprazole, rabeprazole, lansoprazole, histamine receptor blocker, H_2 receptor antagonists, H_2 blocker, H_2RA, cimetidine, ranitidine, famotidine, roxatidine, nizatidine and lafutidine. Reference lists of original articles and reviews were manually searched for additional relevant studies. Experts in this field of study were consulted.

For this review, inclusion criteria included 1) RCTs (parallel or crossover design) and cohort studies; 2) patients treated with aspirin and clopidogrel; 3) PPIs versus H_2RAs; 4) primary outcome of UGIB; secondary outcomes were $P2Y_{12}$ reaction units (PRUs), number of poor responders to clopidogrel, major adverse CV events (MACEs) and rehospitalization frequency. All manuscripts were in English. UGIB referred to hematemesis, melena or a hemoglobin decrease of >2 g/dL, with or without endoscopy. Poor clopidogrel responder was defined by a PRU value >240 or a PRU% <20% or a platelet reactivity index >50%. MACEs referred to death from CV causes, spontaneous myocardial infarction, unstable angina, stent thrombosis, target vessel revascularization, nontarget vessel revascularization and ischemic stroke. The systematic review with meta-analysis was registered on PROSPERO (No CRD42015030158).

Study selection and quality assessment

Two authors (ZMY and TTQ) independently selected potentially eligible studies from the literature according to title and abstracts. Then, full-text versions were screened for potentially eligible studies to determine eligibility based on inclusion criteria.

Two authors (ZMY and TTQ) independently assessed the risk of bias in included studies. The methodological quality of eligible RCTs was evaluated with the Cochrane risk of bias assessment tool,[10] in which critical quality assessments are made separately for different domains including method of randomization, concealment of allocation, blinding, incomplete outcome data, selective reporting and other biases. Considering that the observational studies were more vulnerable to the potential selection bias than RCTs, the methodological quality of eligible cohort studies was evaluated with the Newcastle–Ottawa scale.[11] Three domains including selection, comparability and outcome were assessed. All disagreements about study selection and quality assessment were resolved through discussion.

Data extraction and synthesis

Data extraction was performed by each author (ZMY and TTQ) according to a predesigned review form, and study characteristics (author, publication year and type of study), participant characteristics (inclusion criteria, sample size, age and sex), intervention information (dosage, administration route and duration) and outcome measures (primary and secondary outcomes) were collected. All disagreements were resolved through discussion.

Meta-analyses were performed with RevMan 5.3. Dichotomous and continuous outcomes were expressed with random effect model as the risk ratio (RR) with 95% confidence interval (CI) and mean difference (MD) with 95% CI, respectively. Statistical heterogeneity was assessed with the Mantel–Haenszel chi-square test and quantified using an I^2 test (P-value of heterogeneity was 0.10). Subgroup analyses among different PPIs were conducted to explore sources of clinical heterogeneity in data regarding PRUs. According to the guidance in Chapter 16 of *Cochrane*

Handbook for Systematic Reviews of Interventions, when carryover or period effects were not serious for crossover studies, all measurements were analyzed as if the trials were parallel-group trials.[12] Sensitivity analysis was conducted by changing the random-effects methods to fixed-effects methods to pool the trials.

Results

Search results and study characteristics

Studies identified are depicted in Figure 1 along with strategies for including relevant papers. Among studies that retrieved full text for inspection, 20 studies were excluded, and the details were as following: 4 had no comparisons between PPIs and H_2RAs, 4 were duplications, patients did not meet inclusion criteria in 3 studies, 2 were case series, 1 presented no separate data on the PPIs and H_2RAs, 1 studied prescription rates of PPIs and H_2RAs, 1 was a review, 1 was a commentary, 1 was an animal experiment, 1 was a case–control study and 1 was a Chinese article with English abstract (Figure 1).

Table 1 depicts study characteristics, and bias risk data are shown in Tables 2 and 3. A total of 12 studies containing 3,301 patients (2,068 in the PPIs group, 1,233 in H_2RAs group) were included in the analysis.[13–24] The risk of bias for all included RCTs is high except the low risk of bias for Furtado et al[14] and moderate risk of bias for Ng et al.[16] For cohort studies, the risk of bias for Cappelletti Galante et al,[21] Ng et al[23] and Yew et al[24] is moderate and the risk of bias for Macaione et al[22] is high.

Incidence of UGIB

Three RCTs[16,18,20] reported the incidence of UGIB, and Figure 2 depicts the lack of heterogeneity between included trials and the pooled RR, confirming that PPIs

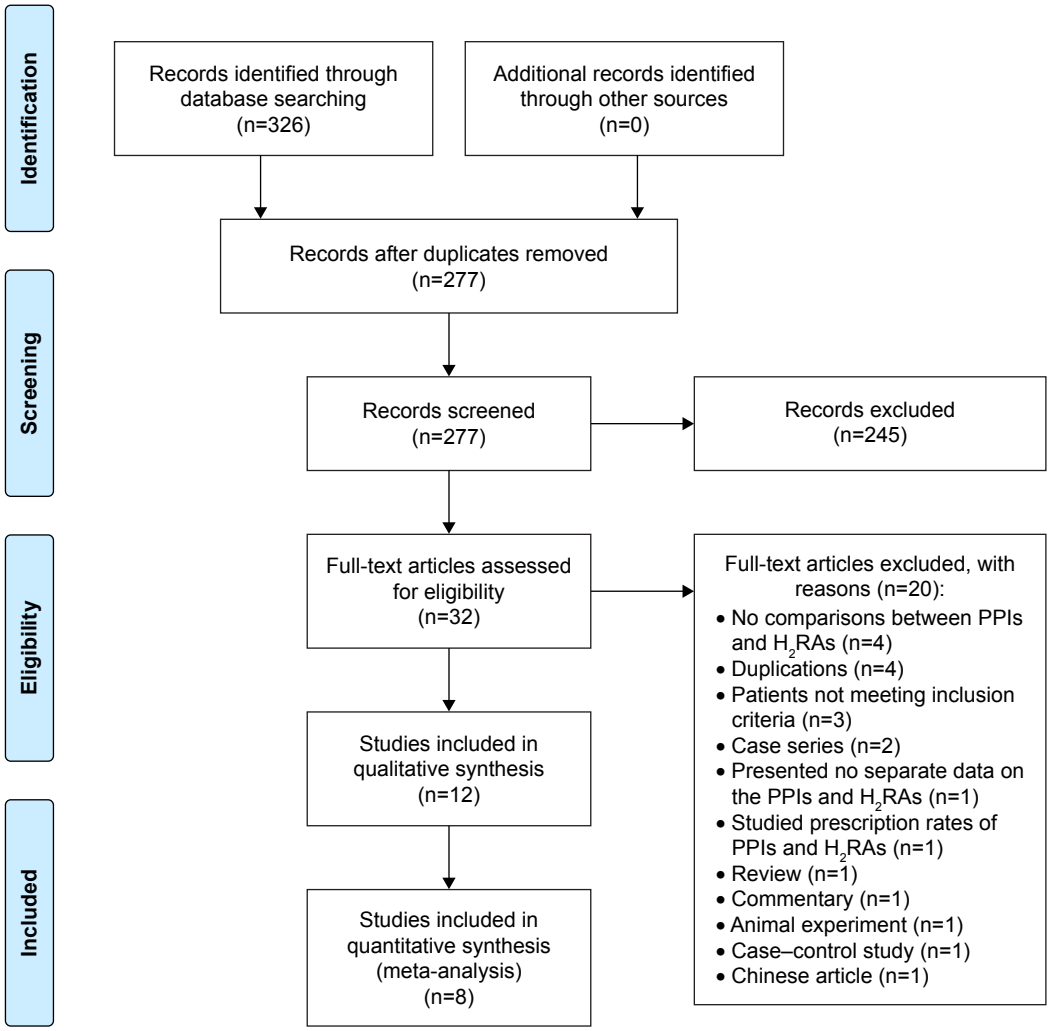

Figure 1 Flow diagram for study selection.
Abbreviations: H_2RAs, histamine-2 receptor antagonists; PPIs, proton pump inhibitors.

Table 1 Characteristics of included studies

Studies	Type of studies	Inclusion criteria	Participants		Intervention		Duration	Outcomes
			PPIs	H_2RAs	PPIs	H_2RAs		
Arbel et al[13]	RCT	Patients ≥18 years, undergone PCI for stable/unstable CAD, treated with DAPT for at least 1 month	Omeprazole/ pantoprazole N=52 A =57.6±9.3 M =46 (88.46%)	Famotidine N=52 A =57.6±9.3 M =46 (88.46%)	Omeprazole/ pantoprazole 20 mg twice a day	40 mg famotidine twice a day	1 month	PRUs
Furtado et al[14]	RCT	Patients ≥18 years, with stable CAD treated with DAPT	Omeprazole N=41 A =62.6±10.9 M =32 (78.0%)	Ranitidine N=44 A =62.5±8.9 M =30 (68.2%)	Omeprazole 20 mg twice a day	Ranitidine 150 mg twice a day	1 week	IPA, PRUs
Moceri et al[15]	RCT	Patients with history of CAD with DAPT	Esomeprazole N=21 A =65±14.3 M =15 (71.5%)	Ranitidine N=21 A =65±14.3 M =15 (71.5%)	Esomeprazole 20 mg daily	Ranitidine 150 mg daily	7 days	ARUs, PRU%, number of poor responders to clopidogrel
Ng et al[16]	RCT	Patients admitted for ACS or acute STEMI, received DAPT and either enoxaparin or thrombolytic	Esomeprazole N=163 A =64.3±13.8 M =126 (77.3%)	Famotidine N=148 A =63.1±13.2 M =107 (72.3%)	Esomeprazole 20 mg daily	Famotidine 40 mg daily	4–52 weeks	UGIB, occult bleeding of unknown origin
Parri et al[17]	RCT	Patients with STEMI undergone primary PCI, received DAPT	Pantoprazole N=55 A =59.4±10.6 M =41 (75%)	Ranitidine N=50 A =60.7±9.9 M =41 (82%)	Pantoprazole 40 mg daily	Ranitidine 150 mg daily	30 days	Platelet function, residual platelet reactivity
Tunggal et al[18]	RCT	Age ≥18 years, patients with unstable angina, MI or elective PCIs, treated with DAPT	Esomeprazole N=44 A =63.2±13.0 M =37 (84%)	Famotidine N=44 A =63.4±11.8 M =37 (84%)	Esomeprazole 20 mg daily	Famotidine 40 mg daily	28 days	PRU, poor responders to clopidogrel, UGIB
Uotani et al[19]	RCT	Healthy subjects with different CYP 2C19 genotypes, received DAPT	Rabeprazole N=20 A = NR M = NR	Famotidine N=20 A = NR M = NR	Rabeprazole 10 mg	Famotidine 40 mg	7 days	Antiplatelet function test, modified LANZA score, 24-h intragastric pH
Yano et al[20]	RCT	Patients with ACS scheduled for coronary stent implantation, received DAPT	Omeprazole N=65 A =67±11 M =50 (77%)	Famotidine N=65 A =66±11 M =53 (81%)	Omeprazole 10 mg daily	Famotidine 20 mg daily	At least 4 weeks	PRI, poor responders to clopidogrel, adverse CV events, non-CABG-related bleeding, symptoms of upper GI damage
Cappelletti Galante et al[21]	Cohort study	Patients undergone PCI, treated with DAPT	Omeprazole N=977 A =63±12[a] M =625 (64%)[a]	Ranitidine N=222 A =63±12[a] M =142 (64%)[a]	Omeprazole	Ranitidine	6 months (1–34.6 months)	Rehospitalization, death

Macaione et al[22]	Cohort study	Patients with ACS, undergoing PCI with drug eluting	PPIs N=121 A =63.66±10.56 M =97 (82.38%)	H_2RAs N=55 A =65.75±8.85 M =48 (87.27%)	Esomeprazole, omeprazole, lansoprazole, pantoprazole	Ranitidine	12–18 months	Rehospitalization, cardiac death, TVR
Ng et al[23]	Cohort study	Patients discharged from hospital or outpatient, received DAPT	PPIs N=213 A =66.9±12.1[a] M =161 (75.6%)[a]	H_2RAs N=287 A =66.9±12.1[a] M =217 (75.6%)[a]	PPIs	H_2RAs	5.8±6.5 months	UGIB, significant occult bleeding
Yew et al[24]	Cohort study	Patients undergone PCI with DAPT	Omeprazole N=296 A = NR M = NR	H_2RAs N=318 A = NR M = NR	Omeprazole	H_2RAs	12 months	Incidence of CV complications (CV death, nonfatal MI), need for urgent TVR and IS

Note: [a]Information of total population.

Abbreviations: A, age; ACS, acute coronary syndrome; ARUs, aspirin reaction units; CABG, coronary artery bypass graft; CAD, coronary artery disease; CV, cardiovascular; CYP, cytochrome P450; DAPT, dual antiplatelet therapy (clopidogrel and aspirin); GI, gastrointestinal; H_2RAs, histamine-2 receptor antagonists; IPA, inhibition of platelet aggregation; IS, ischemic stroke; M, male; MI, myocardial infarction; NR, not reported; PCI, percutaneous coronary intervention; PPIs, proton pump inhibitors; PRI, platelet reactivity index; PRUs, $P2Y_{12}$ reaction units; RCT, randomized controlled trial; STEMI, ST elevation myocardial infarction; TVR, target vessel revascularization; UGIB, upper gastrointestinal bleeding.

decreased UGIB compared to H_2RAs. Ng et al conducted a cohort study to measure UGIB events and treatment effect of PPIs and H_2RAs, and the risk of UGIB was marginally reduced by H_2RAs (odds ratio [OR] =0.43, 95% CI: 0.18–0.91), but significantly reduced by PPIs (OR =0.04, 95% CI: 0.002–0.21) compared to controls.[23]

Antiplatelet effects

For antiplatelet effects, three outcomes were studied: PRUs, poor responders to clopidogrel (75 mg) and ADP-induced maximal amplitude (ADP-MA). Three RCTs reported the results of PRUs.[13,14,18] The washout period for the study by Arbel et al[13] was 2 weeks; blood samples were collected and results were analyzed in the manner of a parallel-group trial. Arbel et al's[13] study data were divided into two groups of similar subject size; Arbel et al 2013a compared omeprazole and H_2RAs and Arbel et al 2013b compared pantoprazole and H_2RAs. Heterogeneity of included trials was significant, and there were no statistically significant differences among PRUs between the PPIs and H_2RAs groups (Figure 3). Subgroup analysis of the omeprazole group (n=163, 2 studies) indicated no significant heterogeneity between trials (P=0.16, I^2=50%). At endpoint, the pooled MD of the subgroup was 31.82 PRUs (95% CI: 11.70–51.94), indicating that PRUs were fewer in the H_2RAs group compared to the omeprazole group. The pantoprazole subgroup (1 study) had more PRUs compared to the H_2RAs group (MD =8.00 PRUs, 95% CI: 2.66–13.34).

Moceri et al reported a decreased mean PRU% for those treated with esomeprazole compared to those treated with no drug ($P<0.0001$), but no statistical difference was found in the ranitidine group (P=0.97).[15]

Three RCTs[15,18,20] reported of poor responders to clopidogrel (75 mg). The washout period in the study by Moceri et al[15] was 48 h, and blood samples were collected at the end of each phase. This washout period was sufficient to eliminate the effect of clopidogrel for poor responders and data were assessed as if this was a parallel-group trial. Heterogeneity of included trials was insignificant (see Figure 4 for data), and there were no statistically significant differences among numbers of poor responders to clopidogrel between the PPIs and H_2RAs groups (Figure 4).

Parri et al reported that pantoprazole plus DAPT significantly increased ADP-MA compared with ranitidine at 5 and 30 days' follow-ups (P=0.01 and P=0.03, respectively), indicating that pantoprazole interfered with antiplatelet effects of clopidogrel.[17] Uotani et al conducted a three-way randomized crossover study including 20 Japanese subjects

Table 2 ROB of randomized controlled trials

Studies	Bias in random sequence generation	Bias in allocation concealment	Bias in blinding (participants/ investigators)	Bias in blinding (outcome assessors)	Bias due to incomplete outcome data (n/N for final analysis)	Bias in selective reporting	Other bias	Overall ROB judgment
Arbel et al[13]	Unclear (not stated)	Low (closed envelope)	High (single blind)	Low (blind)	Low (52/62)	Low	Low	High
Furtado et al[14]	Low (computer program)	Low (sealed envelope)	Low (double blind)	Low (blind)	Low (85/92)	Low	Low	Low
Moceri et al[15]	Unclear (not stated)	High (not stated)	Unclear (not stated)	Low[a] (not stated)	Low (21/21)	Low	Low	High
Ng et al[16]	Low (shuffling envelopes)	Low (identical blinded sealed envelopes)	Low (double blind)	Low (blind)	Low (311/313)	Low	Unclear[b]	Moderate
Parri et al[17]	Unclear (not stated)	High (not stated)	High (open label)	Low (not stated)	High (not stated)	Low	Low	High
Tunggal et al[18]	Low (shuffling envelopes)	Low (identical blinded sealed envelopes)	Low (double blind)	Unclear (not stated)	High (88/107)	Low	Unclear[b]	High
Uotani et al[19]	Unclear (not stated)	High (not stated)	Unclear (not stated)	Unclear (not stated)	Unclear (not stated)	Low	Unclear[c]	High
Yano et al[20]	Low (computer-generated randomization sequence)	Low (central concealment)	High (open label)	Unclear (not stated)	High (130/180)	Low	Unclear[d]	High

Notes: n, number of patients whose data were included in the final analysis; N, number of patients who were recruited into the study. [a]Although information on blinding of outcome assessors was not stated, the outcomes were objective and not affected by subjective factors. [b]Impact of genetic polymorphism of cytochrome P450 2C19 on platelet inhibition was not studied. [c]The information of washout period was not mentioned. [d]The work was supported by a grant from Daiichi Sankyo Co, Ltd.

Abbreviation: ROB, risk of bias.

Table 3 Risk of bias of cohort studies

Studies	Selection				Comparability		Outcome			Total NOS scores
	Representativeness of the intervention cohort	Nonexposed cohort drawn from the same community as the exposed cohort	Ascertainment of exposure from a secure record	Demonstration that outcome of interest not present at start of study	Cohorts comparable on important factors[a]	Cohorts comparable on other factors[b]	Assessment of outcome of record linkage or independent blind assessment	Follow-up long enough for outcomes to occur	Complete accounting for cohorts	
Cappelletti Galante et al[21]	Y	Y	Y	Y	NR	NR	NR	Y	NR	5
Macaione et al[22]	Y	Y	Y	Y	N[c]	Y	N[d]	Y	Y	7
Ng et al[23]	Y	Y	Y	Y	NR	NR	Y	Y	NR	6
Yew et al[24]	Y	Y	Y	Y	NR	NR	Y	Y	NR	6

Notes: Y, related content conforms to this item; N, related content does not conform to this item; NR, information related to this item was not reported. [a]Important factors are previous peptic ulcer, previous upper gastrointestinal bleeding, *Heliobacter pylori* infection, dose of aspirin, smoking and alcohol use. [b]Other factors are age, sex, weight, cytochrome *P450 2C19* gene polymorphism, concurrent corticosteroid and concurrent non-steroidal anti-inflammatory drugs. [c]The patients of proton pump inhibitor group had significantly higher proportion of anemia (P=0.019) and previous coronary artery bypass graft (P=0.048). [d]Some of the clinical follow-up data were collected through telephone calls.

Abbreviation: NOS, Newcastle–Ottawa scale.

and reported that rabeprazole plus DAPT did not attenuate antiplatelet function compared with famotidine combined with DAPT.[19]

Cardiovascular events

Two RCTs reported the incidence of MACEs[16,20] and there was no heterogeneity between the trials (P=0.44, I^2=0%) as well as no difference in the incidence of MACEs between PPIs and H_2RAs therapy (RR =0.89, 95% CI 0.45–1.75). Yew et al published a retrospective cohort study in Singapore that included post-PCI patients who received either omeprazole or a H_2RAs and DAPT and they confirmed that significantly more CV complications occurred in the omeprazole group (P=0.042).[24]

Rehospitalization

Two cohort studies reported the incidence of rehospitalization.[21,22] Macaione et al's study was divided into four groups (Figure 5) and each subgroup consisted of one-fourth of all patients. Macaione et al[22] 2012a depicted omeprazole versus H_2RAs; Macaione et al 2012b reported esomeprazole versus H_2RAs; Macaione et al 2012c included results of lansoprazole versus H_2RAs; and Macaione et al 2012d included results of pantoprazole versus H_2RAs.[22] Heterogeneity of included trials was substantial and there were no statistically significant differences among incidence of rehospitalization between the PPIs and H_2RAs groups (Figure 5).

Sensitivity analysis and publication bias

All pooled results were not affected by the different methods used. Due to a limited number of included studies for each outcome, we could not assess the risk of publication bias.

Discussion

This review compared the effectiveness and safety of PPIs to H_2RAs for patients receiving DAPT, as assessed in RCTs and cohort studies. Limited evidence suggested that compared to H_2RAs, PPIs decreased UGIB, and no differences were found in PRUs, poor responders to clopidogrel, or incidences of MACEs and rehospitalization. Among the PPIs, subgroup analyses suggested that omeprazole may increase PRUs.

A meta-analysis including ten RCTs by Mo et al showed that PPIs reduced LDA-associated UGIB.[25] Another meta-analysis of 39 studies by Cardoso et al indicated that PPIs decreased the risk of UGIB for patients taking clopidogrel and these data agreed with our results.[26] Only two trials were included in comparisons between PPIs and H_2RAs by Mo et al,[25] and no comparisons of this nature were made by

Study or subgroup	PPIs Events	Total	H_2RAs Events	Total	Weight (%)	Risk ratio M–H, random, 95% CI
Ng et al[16]	1	163	9	148	53.1	0.10 (0.01–0.79)
Tunggal et al[18]	0	44	2	44	24.8	0.20 (0.01–4.05)
Yano et al[20]	0	65	1	65	22.1	0.33 (0.01–8.03)
Total (95% CI)		**272**		**257**	**100**	**0.16 (0.03–0.70)**
Total events	1		12			

Heterogeneity: τ^2=0.00; χ^2=0.43, *df*=2 (*P*=0.81); I^2=0%
Test for overall effect: *Z*=2.44 (*P*=0.01)

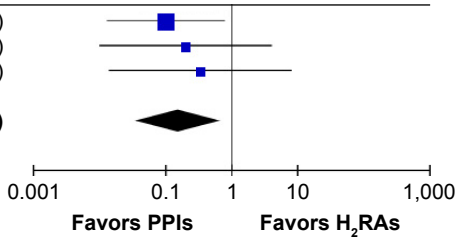

Figure 2 Incidence of upper gastrointestinal bleeding.
Abbreviations: CI, confidence interval; M–H, Mantel–Haenszel chi-square test; H_2RAs, histamine-2 receptor antagonists; PPIs, proton pump inhibitors.

Study or subgroup	PPIs Mean	SD	Total	H_2RAs Mean	SD	Total	Weight (%)	Mean difference IV random, 95% CI
Arbel et al 2013a	217	12	52	179	11	26	31.4	38.00 (32.66–43.34)
Arbel et al 2013b	187	12	52	179	11	26	31.4	8.00 (2.66–13.34)
Furtado et al[14]	173.54	72.28	41	158.8	76.4	44	19.5	14.74 (–16.87–46.35)
Tunggal et al[18]	242.6	89.7	44	237.5	79.2	44	17.7	5.10 (–30.26–40.46)
Total (95% CI)			**189**			**140**	**100**	**18.21 (–4.11–40.54)**

Heterogeneity: τ^2=406.03; χ^2=61.84, *df*=3 (*P*<0.00001); I^2=95%
Test for overall effect: *Z*=1.60 (*P*=0.11)

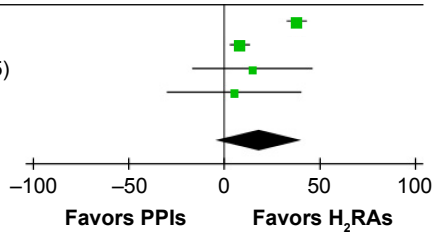

Figure 3 $P2Y_{12}$ reaction units.
Abbreviations: CI, confidence interval; M–H, Mantel–Haenszel chi-square test; H_2RAs, histamine-2 receptor antagonists; PPIs, proton pump inhibitors; SD, standard deviation.

Study or subgroup	PPIs Events	Total	H_2RAs Events	Total	Weight (%)	Risk ratio M–H, random, 95% CI
Moceri et al[15]	7	21	2	21	3.7	3.50 (0.82–14.93)
Tunggal et al[18]	23	44	19	44	33.9	1.21 (0.78–1.88)
Yano et al[20]	40	65	35	65	62.4	1.14 (0.85–1.54)
Total (95% CI)		**130**		**130**	**100**	**1.21 (0.92–1.61)**
Total events	70		56			

Heterogeneity: τ^2=0.01; χ^2=2.31, *df*=2 (*P*=0.32); I^2=13%
Test for overall effect: *Z*=1.35 (*P*=0.18)

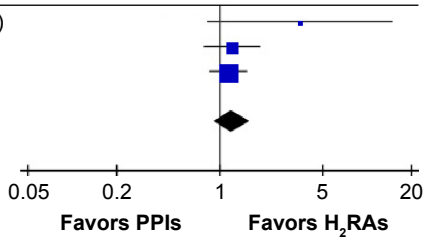

Figure 4 Incidence of poor responders to clopidogrel.
Abbreviations: CI, confidence interval; M–H, Mantel–Haenszel chi-square test; H_2RAs, histamine-2 receptor antagonists; PPIs, proton pump inhibitors.

Study or subgroup	PPIs Events	Total	H_2RAs Events	Total	Weight (%)	Risk ratio M–H, random, 95% CI
Cappelletti Galante et al[21]	336	977	86	222	36.7	0.89 (0.74–1.07)
Macaione et al 2012a	22	52	2	16	18.4	3.38 (0.89–12.86)
Macaione et al 2012b	8	14	2	13	18.1	3.71 (0.96–14.37)
Macaione et al 2012c	5	13	2	13	16.8	2.50 (0.59–10.64)
Macaione et al 2012d	3	42	1	13	10.0	0.93 (0.11–8.18)
Total (95% CI)		**1,098**		**277**	**100**	**1.76 (0.79–3.92)**
Total events	374		93			

Heterogeneity: τ^2=0.45; χ^2=9.93, *df*=4 (*P*=0.04); I^2=60%
Test for overall effect: *Z*=1.38 (*P*=0.17)

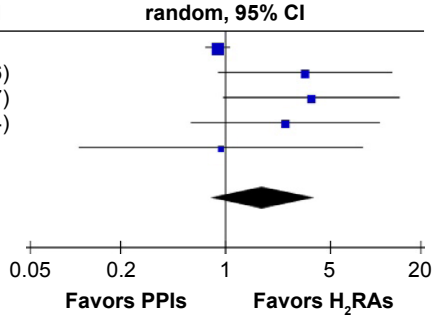

Figure 5 Incidence of rehospitalization.
Abbreviations: CI, confidence interval; M–H, Mantel–Haenszel chi-square test; H_2RAs, histamine-2 receptor antagonists; PPIs, proton pump inhibitors.

Cardoso et al.[26] Regarding CV events, Yasuda et al reported significantly more coronary stenotic lesions after treatment with PPIs compared with H_2RAs,[27] whereas the CALIBER study confirmed that both PPIs and ranitidine were associated with higher incidence of death or myocardial infarctions.[28] A meta-analysis of RCTs and observational studies by Melloni et al had conflicting results regarding PPIs[29] and CV outcomes, and a systematic review by Focks et al challenged the validity of conclusions about PPI–clopidogrel interactions on platelet function and MACEs based on quantitative analyses of predominantly nonrandomized data.[30] A recent published RCT by Gargiulo et al also indicated that DAPT concomitant with PPIs did not increase death for myocardial infarction or cerebrovascular accident.[31] We found no difference in the incidence of MACEs and between PPIs and H_2RAs. This suggested that the safety profile of PPIs were comparable with H_2RAs. However, the small number of included studies might compromise the validity of this conclusion.

Patients with increased upper GI risk are more likely to receive PPIs and patients with increased CV risk are more likely to receive DAPT instead of aspirin or clopidogrel alone, and DAPT treatment is more likely to be paired with PPIs due to increased UGIB risk compared to aspirin or clopidogrel alone. Therefore, in cohort studies, imbalances in baseline characteristics and prescription bias may affect observed outcomes; patient prognostic factors at the RCT baseline may differ from a cohort study. Here, we noted conflicting results between RCTs and cohort studies for ADP-MA and MACEs and these results may be biased due to inherent difference in study characteristics (study designs, study population and different treatment durations from 7 days to 35 months). DAPT length may influence the bleeding risk; the PRODIGY study suggested an increase in bleeding risk without benefit from ischemic adverse events,[32] while benefit overcame the risk for some subgrousps at higher risk.[33] Thus, more studies are needed to draw firm conclusions.

Our report is the first of its kind to directly compare PPIs with H_2RAs for prophylaxis and safety when used with DAPT and we included RCTs and cohort studies. A recent meta-analysis to compare the effects of concomitant use of PPIs and DAPT concluded that observational studies and RCTs have conflicting outcomes regarding PPIs on CV outcomes when coadministered with DAPT.[27] Thus, the results of both RCTs and cohort studies can decrease potential reporting bias. Subgroup analyses of four different types of PPIs to explore the potential effect differences indicate that omeprazole modified CYP 2C19 metabolism and reduced antiplatelet effects,[34] and this was consistent with our results. Since 2009, the US FDA recommended against concomitant use of clopidogrel and omeprazole and suggested, instead, the use of a weak CYP 2C19 inhibitor, pantoprazole.[35] However, in our study, two reports (one RCT and one cohort study) indicate that pantoprazole may have antiplatelet effects; so, we compared "poor responders to clopidogrel", which was a more direct indicator of antiplatelet activity compared to PRUs.

Our study has some limitations. First, our topic has few reports in the literature and so clinical guidelines are similarly scarce[36] or unjustified based on current evidence.[37,38] Thus, high-quality research is required to assess clinical practices and support guideline recommendations. Second, in this systematic review, we could not combine RCTs with observational studies due to lack of matching propensity scores or reporting adjusted RRs. Although 12 studies were included in the review, only 8 RCTs were included in our meta-analysis. Additionally, aggregate sample sizes of all included studies were small and this decreased precision of estimates. Subgroup analysis based on individual CYP 2C19 genotypes and *Heliobacter pylori* status could not be performed because few studies reported these data. Furthermore, only English-language studies were included and conference abstracts were not manually searched, although important conference abstracts were included in databases searched and included in our review.

Conclusion

The available evidence suggests that PPIs outperformed H_2RAs for prophylaxis of UGIB associated with DAPT, and no differences in platelet function were observed. Likely, differences in antiplatelet activity are caused by omeprazole, but larger randomized controlled studies are required to compare PPIs with H_2RAs for preventing UGIB during DAPT treatment.

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Author contributions

All authors contributed toward data analysis, drafting and revising the paper and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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