Comparison of prophylactic effect of UGIB and effects on platelet function between PPIs and \(H_2\)RAs combined with DAPT: systematic review and meta-analysis

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Objective: We compared prophylactic effects of proton pump inhibitors (PPIs) and histamine-2 receptor antagonists (H\(_2\)RAs) 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\(_2\)RAs 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\(_2\)RAs, 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\(_2\)RAs 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\(_2\)RAs 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...
GI bleeding (GIB), especially in patients with multiple risk factors. 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%. Meanwhile, histamine-2 receptor antagonists (H$_2$RAs) therapy can prevent ulcers for patients receiving low-dose aspirin.

Studies suggest that combination treatment with PPIs plus clopidogrel is associated with high platelet reactivity and more adverse events during long-term follow-up. 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. Moreover, H$_2$RAs may be as effective as PPIs plus DAPT for patients with no prior history of upper GI bleeding (UGIB).

Therefore, H$_2$RAs 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$_2$RAs 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$_2$RAs 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$_2$RA, cimetidine, ranitidine, famotidine, roxatidine, nizatidine and lafutidine. Reference lists of original articles and reviews were searched for potentially eligible studies to determine eligibility based on inclusion criteria.

Methodological quality of eligible RCTs was evaluated with the Cochrane risk of bias assessment tool, 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. Three domains including selection, comparability and outcome measures (primary and secondary outcomes) were collected. 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 I$^2$-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...
**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 H₂RAs, 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 H₂RAs, 1 studied prescription rates of PPIs and H₂RAs, 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 H₂RAs group) were included in the analysis. 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
<table>
<thead>
<tr>
<th>Studies</th>
<th>Type of studies</th>
<th>Inclusion criteria</th>
<th>Participants</th>
<th>H, RAs</th>
<th>Intervention</th>
<th>Duration</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arbel et al(^{13})</td>
<td>RCT</td>
<td>Patients ≥18 years, undergone PCI for stable/unstable CAD, treated with DAPT for at least 1 month</td>
<td>Omeprazole/ pantoprazole N=52 A = 57.6±9.3 M = 46 (88.46%)</td>
<td>Famotidine N=52 A = 57.6±9.3 M = 46 (88.46%)</td>
<td>Omeprazole/ pantoprazole 20 mg twice a day</td>
<td>1 month</td>
<td>PRUs</td>
</tr>
<tr>
<td>Furtado et al(^{14})</td>
<td>RCT</td>
<td>Patients ≥18 years, with stable CAD treated with DAPT</td>
<td>Omeprazole N=41 A = 62.6±10.9 M = 32 (78.0%)</td>
<td>Ranitidine N=44 A = 62.5±8.9 M = 30 (68.2%)</td>
<td>Omeprazole 20 mg twice a day</td>
<td>1 week</td>
<td>IPA, PRUs</td>
</tr>
<tr>
<td>Moceri et al(^{15})</td>
<td>RCT</td>
<td>Patients with history of CAD with DAPT</td>
<td>Esomeprazole N=21 A = 65±14.3 M = 15 (71.5%)</td>
<td>Famotidine N=21 A = 65±14.3 M = 15 (71.5%)</td>
<td>Esomeprazole 20 mg daily</td>
<td>7 days</td>
<td>ARUs, PRU%, number of poor responders to clopidogrel</td>
</tr>
<tr>
<td>Ng et al(^{16})</td>
<td>RCT</td>
<td>Patients admitted for ACS or acute STEMI, received DAPT and either enoxaparin or thrombolytic</td>
<td>Esomeprazole N=163 A = 64.3±13.8 M = 126 (77.3%)</td>
<td>Famotidine N=148 A = 63.1±13.2 M = 107 (72.3%)</td>
<td>Esomeprazole 20 mg daily</td>
<td>4–52 weeks</td>
<td>UGIB, occult bleeding of unknown origin</td>
</tr>
<tr>
<td>Parri et al(^{17})</td>
<td>RCT</td>
<td>Patients with STEMI undergone primary PCI, received DAPT</td>
<td>Pantoprazole N=55 A = 59.4±10.6 M = 41 (75%)</td>
<td>Ranitidine N=50 A = 60.7±9.9 M = 41 (82%)</td>
<td>Pantoprazole 40 mg daily</td>
<td>30 days</td>
<td>Platelet function, residual platelet reactivity</td>
</tr>
<tr>
<td>Tunggal et al(^{18})</td>
<td>RCT</td>
<td>Age ≥18 years, patients with unstable angina, MI or elective PCIs, treated with DAPT</td>
<td>Esomeprazole N=44 A = 63.2±13.0 M = 37 (84%)</td>
<td>Famotidine N=44 A = 63.4±11.8 M = 37 (84%)</td>
<td>Esomeprazole 20 mg daily</td>
<td>28 days</td>
<td>PRU, poor responders to clopidogrel, UGIB</td>
</tr>
<tr>
<td>Uotani et al(^{19})</td>
<td>RCT</td>
<td>Healthy subjects with different CYP 2C19 genotypes, received DAPT</td>
<td>Rabeprazole N=20 A = NR M = NR</td>
<td>Famotidine N=20 A = NR M = NR</td>
<td>Rabeprazole 10 mg</td>
<td>7 days</td>
<td>Antiplatelet function test, modified Lanza score, 24-h intragastric pH</td>
</tr>
<tr>
<td>Yano et al(^{20})</td>
<td>RCT</td>
<td>Patients with ACS scheduled for coronary stent implantation, received DAPT</td>
<td>Omeprazole N=65 A = 67±11 M = 50 (77%)</td>
<td>Famotidine N=65 A = 66±11 M = 53 (81%)</td>
<td>Omeprazole 20 mg daily</td>
<td>4 weeks</td>
<td>PRL, poor responders to clopidogrel, adverse events, non-CABG-related bleeding, symptoms of upper GI damage</td>
</tr>
<tr>
<td>Cappelletti et al(^{21})</td>
<td>Cohort study</td>
<td>Patients undergone PCI, treated with DAPT</td>
<td>Omeprazole N=977 A = 63±12 M = 625 (64%)</td>
<td>Ranitidine N=222 A = 63±12 M = 142 (64%)</td>
<td>Omeprazole Ranitidine</td>
<td>6 months</td>
<td>Rehospitalization, death (1–34.6 months)</td>
</tr>
</tbody>
</table>
Macaione et al\textsuperscript{22} & Cohort study & Patients with ACS, undergoing PCI with drug eluting & PPIs & H$_2$RAs & Esomeprazole, omeprazole, pantoprazole, ranitidine & 12–18 months & Rehospitalization, cardiac death, TVR \\
Ng et al\textsuperscript{23} & Cohort study & Patients discharged from hospital or outpatient, received DAPT & PPIs & H$_2$RAs & H$_2$RAs & 5.8±6.5 months & UGIB, significant occult bleeding \\
Yew et al\textsuperscript{24} & Cohort study & Patients undergone PCI with DAPT & Omeprazole & H$_2$RAs & Omeprazole, H$_2$RAs & 12 months & Incidence of CV complications (CV death, nonfatal MI), need for urgent TVR and IS \\

Note: 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); GL, gastrointestinal; H$_2$RAs, 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.
### Table 2 ROB of randomized controlled trials

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

**Notes:**
- n, number of patients whose data were included in the final analysis; N, number of patients who were recruited into the study.
- Although information on blinding of outcome assessors was not stated, the outcomes were objective and not affected by subjective factors.
- Impact of genetic polymorphism of cytochrome P450 2C19 on platelet inhibition was not studied.
- The information of washout period was not mentioned.
- 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

<table>
<thead>
<tr>
<th>Studies</th>
<th>Selection</th>
<th>Representativeness of the intervention cohort</th>
<th>Nonexposed cohort drawn from the same community as the exposed cohort</th>
<th>Ascertainment of exposure from a secure record</th>
<th>Demonstration that outcome of interest was present at start of study</th>
<th>Comparability of cohorts comparable on important factors*</th>
<th>Cohorts comparable on other factors*</th>
<th>Outcome</th>
<th>Assessment of outcome of record linkage or independent blind assessment</th>
<th>Follow-up long enough for outcomes to occur</th>
<th>Complete accounting for cohorts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cappelletti et al</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Y</td>
<td>NR</td>
<td>5</td>
</tr>
<tr>
<td>Galante et al</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>N*</td>
<td>Y</td>
<td>N*</td>
<td>NR</td>
<td>Y</td>
<td>NR</td>
<td>7</td>
</tr>
<tr>
<td>Macaione et al</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Y</td>
<td>NR</td>
<td>6</td>
</tr>
<tr>
<td>Ng et al</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Y</td>
<td>NR</td>
<td>6</td>
</tr>
<tr>
<td>Yew et al</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Y</td>
<td>NR</td>
<td>6</td>
</tr>
</tbody>
</table>

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.
*Important factors are previous peptic ulcer, previous upper gastrointestinal bleeding, Helicobacter pylori infection, dose of aspirin, smoking and alcohol use. Other factors are age, sex, weight, cytochrome P450 2C19 gene polymorphism, concurrent corticosteroid and concurrent non-steroidal anti-inflammatory drugs.

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). Some of the clinical follow-up data were collected through telephone calls.

Abbreviation: NOS, Newcastle–Ottawa scale.

Discussion

We included studies that compared the effectiveness and safety of PPIs to HRAs for patients receiving DAPT, as assessed in RCTs and cohort studies. Limited evidence suggested that compared with HRAs, PPIs decreased the risk of UGIB for patients taking clopidogrel. A meta-analysis including ten RCTs by Mo et al suggested that PPIs reduced LDA-associated UGIB. A meta-analysis of MACs and rehospitalization suggested that PPIs reduced MACs and rehospitalization among the PPI subgroups, which were included in comparisons between PPIs and HRAs by Mo et al and these data agreed with our results. Only two trials were included in comparisons between PPIs and HRAs by Mo et al, and no comparisons of this nature were made by them.

Sensitivity analysis and publication bias

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

Rehospitalization

Two cohort studies reported the incidence of rehospitalization. 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 2012a depicted results of lansoprazole versus HRAs; Macaione et al 2012b included results of pantoprazole versus HRAs; and Macaione et al 2014d included results of pantoprazole versus HRAs. Macaione et al 2012b reported that PPIs reduced UGIB, and no differences were found in MACs and rehospitalization between the PPI and HRAs groups (Figure 5).

Cardiovascular events

Two RCTs reported the incidence of MACEs, and there were no heterogeneity between the trials (P=0.41, P=0.31) as well as no difference in the incidence of MACEs between PPIs and HRAs therapy (RR = 0.89, 95% CI 0.65–1.21). Yew et al published retrospective cohort study in Singapore that included post-PCI patients who received either omeprazole or a HRAs and DAPT and they confirmed that significantly more CV complications occurred in the omeprazole group (P=0.042).

Prophylactic effect of UGIB and effects on platelet function

and reported that rabeprazole plus DAPT did not attenuate antiplatelet function compared with DAPT.
### Table 1: Incidence of Upper Gastrointestinal Bleeding

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>PPIs Events</th>
<th>H$_2$RAs Events</th>
<th>Weight (%)</th>
<th>Risk ratio M–H, random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ng et al$^{16}$</td>
<td>1</td>
<td>163</td>
<td>953.1</td>
<td>0.10 (0.01–0.79)</td>
</tr>
<tr>
<td>Tunggal et al$^{18}$</td>
<td>0</td>
<td>44</td>
<td>244.8</td>
<td>0.20 (0.01–4.05)</td>
</tr>
<tr>
<td>Yano et al$^{20}$</td>
<td>0</td>
<td>65</td>
<td>22.1</td>
<td>0.33 (0.01–8.03)</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>272</strong></td>
<td><strong>257</strong></td>
<td><strong>100</strong></td>
<td><strong>0.16 (0.03–0.70)</strong></td>
</tr>
</tbody>
</table>

Total events: 12

Heterogeneity: $I^2=0.00$; $χ^2=0.43$, df=2 ($P=0.81$); $I^2=0$

Test for overall effect: $Z=2.44$ ($P=0.01$)

### Abbreviations:
- CI: confidence interval
- M–H: Mantel–Haenszel chi-square test
- H$_2$Ras: histamine-2 receptor antagonists
- PPis: proton pump inhibitors

#### Figure 2: Incidence of upper gastrointestinal bleeding.

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### Table 2: P2Y$_{12}$ Reaction Units

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>PPIs Mean SD</th>
<th>H$_2$RAs Mean SD</th>
<th>Weight (%)</th>
<th>Mean difference IV, random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arbel et al 2013a</td>
<td>217 12 52</td>
<td>179 11 26</td>
<td>31.4</td>
<td>38.00 (32.66–43.34)</td>
</tr>
<tr>
<td>Arbel et al 2013b</td>
<td>187 12 52</td>
<td>179 11 26</td>
<td>31.4</td>
<td>8.00 (2.66–13.34)</td>
</tr>
<tr>
<td>Furtado et al$^{18}$</td>
<td>158.8 72.8 41</td>
<td>158.8 76.4 44</td>
<td>19.5</td>
<td>14.74 (~16.87–46.35)</td>
</tr>
<tr>
<td>Tunggal et al$^{18}$</td>
<td>242.6 89.7 44</td>
<td>237.5 79.2 44</td>
<td>17.7</td>
<td>5.10 (~30.26–40.46)</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>189</strong></td>
<td><strong>140</strong></td>
<td><strong>100</strong></td>
<td><strong>18.21 (~4.11–40.54)</strong></td>
</tr>
</tbody>
</table>

Heterogeneity: $r^2=406.03$; $χ^2=11.84$, df=3 ($P=0.0001$); $I^2=95$

Test for overall effect: $Z=1.60$ ($P=0.11$)

#### Figure 3: P2Y$_{12}$ reaction units.

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### Table 3: Incidence of Poor Responders to Clopidogrel

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>PPIs Events</th>
<th>H$_2$RAs Events</th>
<th>Weight (%)</th>
<th>Risk ratio M–H, random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moceri et al$^{13}$</td>
<td>7</td>
<td>21</td>
<td>3.7</td>
<td>3.50 (0.82–14.93)</td>
</tr>
<tr>
<td>Tunggal et al$^{18}$</td>
<td>23</td>
<td>44</td>
<td>33.9</td>
<td>1.21 (0.78–1.88)</td>
</tr>
<tr>
<td>Yano et al$^{20}$</td>
<td>40</td>
<td>65</td>
<td>62.4</td>
<td>1.14 (0.85–1.54)</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>130</strong></td>
<td><strong>130</strong></td>
<td><strong>100</strong></td>
<td><strong>1.21 (0.92–1.61)</strong></td>
</tr>
</tbody>
</table>

Total events: 70

Heterogeneity: $r^2=0.01$; $χ^2=2.31$, 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.

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### Table 4: Incidence of Rehospitalization

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>PPIs Events</th>
<th>H$_2$RAs Events</th>
<th>Weight (%)</th>
<th>Risk ratio M–H, random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cappelletti Galante et al$^{11}$</td>
<td>336</td>
<td>977</td>
<td>86 222</td>
<td>36.7 0.89 (0.74–1.07)</td>
</tr>
<tr>
<td>Macaione et al 2012a</td>
<td>22</td>
<td>52</td>
<td>2 16</td>
<td>18.4 3.38 (0.89–12.86)</td>
</tr>
<tr>
<td>Macaione et al 2012b</td>
<td>8</td>
<td>14</td>
<td>2 13</td>
<td>18.1 3.71 (0.96–14.37)</td>
</tr>
<tr>
<td>Macaione et al 2012c</td>
<td>5</td>
<td>13</td>
<td>2 13</td>
<td>16.8 2.50 (0.59–10.64)</td>
</tr>
<tr>
<td>Macaione et al 2012d</td>
<td>3</td>
<td>42</td>
<td>1 13</td>
<td>10.0 0.93 (0.11–8.18)</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>1,098</strong></td>
<td><strong>277</strong></td>
<td><strong>100</strong></td>
<td><strong>1.76 (0.79–3.92)</strong></td>
</tr>
</tbody>
</table>

Total events: 374

Heterogeneity: $r^2=0.45$; $χ^2=9.93$, df=4 ($P=0.04$); $I^2=60$

Test for overall effect: $Z=1.38$ ($P=0.17$)

#### Figure 5: Incidence of rehospitalization.

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Cardoso et al.\textsuperscript{26} Regarding CV events, Yasuda et al reported significantly more coronary stenotic lesions after treatment with PPIs compared with H\textsubscript{2}RAs,\textsuperscript{27} whereas the CALIBER study confirmed that both PPIs and ranitidine were associated with higher incidence of death or myocardial infarctions.\textsuperscript{28} A meta-analysis of RCTs and observational studies by Melloni et al had conflicting results regarding PPIs\textsuperscript{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.\textsuperscript{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.\textsuperscript{31} We found no difference in the incidence of MACEs and between PPIs and H\textsubscript{2}RAs. This suggested that the safety profile of PPIs were comparable with H\textsubscript{2}RAs. 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,\textsuperscript{32} while benefit overcame the risk for some subgroups at higher risk.\textsuperscript{33} Thus, more studies are needed to draw firm conclusions.

Our report is the first of its kind to directly compare PPIs with H\textsubscript{2}RAs 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.\textsuperscript{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,\textsuperscript{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.\textsuperscript{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\textsuperscript{36} or unjustified based on current evidence.\textsuperscript{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 RR.s. 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 Helicobacter 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\textsubscript{2}RAs 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\textsubscript{2}RAs 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.

References


