Comparison of prophylactic effect of UGIB and effects on platelet function between PPIs and H₂RAs 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 (H₂RAs) 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 H₂RAs 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 P2Y₁₂ reaction units (PRUs), with 95% confidence intervals (CIs).

Results: Twelve clinical trials (n=3,301) met the inclusion criteria. Compared to H₂RAs, 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 H₂RAs 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 H₂RAs 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 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_{2}RAs; 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, 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 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 predefined 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 F 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. 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$_2$RAs, 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$_2$RAs, 1 studied prescription rates of PPIs and H$_2$RAs, 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$_2$RAs 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 1 Characteristics of included studies

<table>
<thead>
<tr>
<th>Studies</th>
<th>Type of studies</th>
<th>Inclusion criteria</th>
<th>Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arbel et al13</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>
</tr>
<tr>
<td>Furtado et al14</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>
</tr>
<tr>
<td>Moceri et al15</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>
</tr>
<tr>
<td>Ng et al16</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>
</tr>
<tr>
<td>Parri et al17</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>
</tr>
<tr>
<td>Tunggal et al18</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>
</tr>
<tr>
<td>Uosaki et al19</td>
<td>RCT</td>
<td>Healthy subjects with different CYP 2C19 genotypes, received DAPT</td>
<td>Rabeprazole N=20 A = NR M = NR</td>
</tr>
<tr>
<td>Yano et al20</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>
</tr>
<tr>
<td>Cappelletti et al</td>
<td>Cohort study</td>
<td>Patients undergone PCI, treated with DAPT</td>
<td>Omeprazole N=977 A = 63±12 M = 62 (64%)</td>
</tr>
</tbody>
</table>
decreased UGIB compared to H₂RAs. Ng et al conducted a cohort study to measure UGIB events and treatment effect of PPIs and H₂RAs, and the risk of UGIB was marginally reduced by H₂RAs (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 al¹³ was 2 weeks; blood samples were collected and results were analyzed in the manner of a parallel-group trial. Arbel et al’s¹³ study data were divided into two groups of similar subject size; Arbel et al 2013a compared omeprazole and H₂RAs and Arbel et al 2013b compared pantoprazole and H₂RAs. Heterogeneity of included trials was significant, and there were no statistically significant differences among PRUs between the PPIs and H₂RAs groups (Figure 3). Subgroup analysis of the omeprazole group (n=163, 2 studies) indicated no significant heterogeneity between trials (P = 0.16, I² = 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 H₂RAs group compared to the omeprazole group. The pantoprazole subgroup (1 study) had more PRUs compared to the H₂RAs 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 RCTs¹⁵,¹⁸,¹⁹ reported of poor responders to clopidogrel (75 mg). The washout period in the study by Moceri et al¹⁵ 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 H₂RAs 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

<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</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</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</td>
<td>Unclear (not stated)</td>
<td>High (not stated)</td>
<td>Unclear (not stated)</td>
<td>Low (not stated)</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Ng et al</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</td>
<td>Moderate</td>
</tr>
<tr>
<td>Parri et al</td>
<td>Unclear (not stated)</td>
<td>High (not stated)</td>
<td>High (open label)</td>
<td>Low (not stated)</td>
<td>High</td>
<td>Low</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Tunggal et al</td>
<td>Low (shuffling envelopes)</td>
<td>Low (identical blinded sealed envelopes)</td>
<td>Low (double blind)</td>
<td>Unclear (not stated)</td>
<td>Low (88/107)</td>
<td>Low</td>
<td>Unclear</td>
<td>High</td>
</tr>
<tr>
<td>Uotani et al</td>
<td>Unclear (not stated)</td>
<td>High (not stated)</td>
<td>Unclear (not stated)</td>
<td>Unclear (not stated)</td>
<td>Unclear</td>
<td>Low</td>
<td>Unclear</td>
<td>High</td>
</tr>
<tr>
<td>Yano et al</td>
<td>Low (computer-generated randomization sequence)</td>
<td>Low (central concealment)</td>
<td>High (open label)</td>
<td>Unclear (not stated)</td>
<td>High</td>
<td>Low</td>
<td>Unclear</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 not present at start of study</th>
<th>Comparability of cohorts on important factors</th>
<th>Outcome assessment</th>
<th>Follow-up long enough for outcomes to occur</th>
<th>Complete accounting for cohorts</th>
<th>Total NOS scores</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cappellotti</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</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>NR</td>
<td>NR</td>
<td>NR</td>
<td>Y</td>
<td>NR</td>
<td>5</td>
</tr>
<tr>
<td>Macaione et al</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>NR</td>
<td>N'</td>
<td>N'</td>
<td>Y</td>
<td>Y</td>
<td>7</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>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>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.

The patients of proton pump inhibitor group had significantly higher proportion of anemia \( (P=0.048) \).

The meta-analysis including ten RCTs by Mo et al showed that PPIs reduced LDA-associated UGIB, and no differences were found in PRUs, poor responders to clopidogrel, or incidence of rehospitalization between the PPIs and H2RAs groups. Two RCTs reported the incidence of MACEs (22) and there were no heterogeneity between the trials \( (P=0.44, I^2=0\%) \) as well as no difference in the incidence of MACEs between PPIs and H2RAs therapy \( (RR=0.89, 95\% CI 0.45–1.75) \). Two cohort studies reported the incidence of rehospitalization \( (22,24) \) and these data agreed with our results.22 Only two trials were included in comparisons between PPIs and H2RAs by Mo et al. and no comparisons of this nature were made by Cardoso et al.22,24 A meta-analysis of MACs and rehospitalization among the PPIs subgroup analyses suggested that omeprazole may increase PRUs, poor responders to clopidogrel, or incidence of rehospitalization between the PPIs and H2RAs groups (Figure 5). Two RCTs reported the incidence of MACEs between PPIs and H2RAs therapy \( (RR=0.89, 95\% CI 0.45–1.75) \). Two cohort studies reported the incidence of rehospitalization \( (22,24) \) and these data agreed with our results.22 Only two trials were included in comparisons between PPIs and H2RAs by Mo et al. and no comparisons of this nature were made by Cardoso et al.22,24 A meta-analysis of MACs and rehospitalization among the PPIs subgroup analyses suggested that omeprazole may increase PRUs, poor responders to clopidogrel, or incidence of rehospitalization between the PPIs and H2RAs groups (Figure 5).
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<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>PPIs Events</th>
<th>Total H$_2$RAs</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>9</td>
<td>53.1</td>
</tr>
<tr>
<td>Tunggal et al$^{16}$</td>
<td>0</td>
<td>44</td>
<td>2</td>
<td>24.8</td>
</tr>
<tr>
<td>Yano et al$^{18}$</td>
<td>0</td>
<td>65</td>
<td>1</td>
<td>22.1</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>272</td>
<td>257</td>
<td>100</td>
<td>0.16 (0.03–0.70)</td>
</tr>
</tbody>
</table>

Total events 12
Heterogeneity: $r^2=0.00; \chi^2=0.43, df=2 (P=0.81); I^2=9%$
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$_2$RAs, histamine-2 receptor antagonists; PPIs, proton pump inhibitors.

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>PPIs Mean</th>
<th>SD</th>
<th>Total H$_2$RAs Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th>Mean difference IV, random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arbel et al 2013a</td>
<td>217</td>
<td>12</td>
<td>52</td>
<td>11</td>
<td>26</td>
<td>31.4</td>
<td>38.00 (32.66–43.34)</td>
</tr>
<tr>
<td>Arbel et al 2013b</td>
<td>187</td>
<td>12</td>
<td>52</td>
<td>11</td>
<td>26</td>
<td>31.4</td>
<td>8.00 (2.66–13.34)</td>
</tr>
<tr>
<td>Furtado et al$^{18}$</td>
<td>173.54</td>
<td>72.28</td>
<td>41</td>
<td>158.8</td>
<td>76.4</td>
<td>44</td>
<td>19.5</td>
</tr>
<tr>
<td>Tunggal et al$^{18}$</td>
<td>24.26</td>
<td>89.7</td>
<td>44</td>
<td>237.5</td>
<td>79.2</td>
<td>44</td>
<td>17.7</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>189</td>
<td>140</td>
<td>100</td>
<td>18.21 (~4.11–40.54)</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Heterogeneity: $r^2=406.03; \chi^2=61.84, df=3 (P<0.00001); I^2=95%$
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$_2$RAs, histamine-2 receptor antagonists; PPIs, proton pump inhibitors; SD, standard deviation.

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>PPIs Events</th>
<th>Total H$_2$RAs</th>
<th>Weight (%)</th>
<th>Risk ratio M–H, random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moceri et al$^{18}$</td>
<td>7</td>
<td>21</td>
<td>2</td>
<td>3.7</td>
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<tr>
<td>Tunggal et al$^{18}$</td>
<td>23</td>
<td>44</td>
<td>19</td>
<td>33.9</td>
</tr>
<tr>
<td>Yano et al$^{20}$</td>
<td>40</td>
<td>65</td>
<td>35</td>
<td>62.4</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>130</td>
<td>130</td>
<td>100</td>
<td>1.21 (0.92–1.61)</td>
</tr>
</tbody>
</table>

Total events 70
Heterogeneity: $r^2=0.01; \chi^2=2.31, df=2 (P=0.32); I^2=13%$
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$_2$RAs, histamine-2 receptor antagonists; PPIs, proton pump inhibitors.

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>PPIs Events</th>
<th>Total H$_2$RAs</th>
<th>Weight (%)</th>
<th>Risk ratio M–H, random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cappelletti Galante et al$^{15}$</td>
<td>336</td>
<td>977</td>
<td>86</td>
<td>222</td>
</tr>
<tr>
<td>Maceinae et al 2012a</td>
<td>22</td>
<td>52</td>
<td>2</td>
<td>16</td>
</tr>
<tr>
<td>Maceinae et al 2012b</td>
<td>8</td>
<td>14</td>
<td>2</td>
<td>13</td>
</tr>
<tr>
<td>Maceinae et al 2012c</td>
<td>5</td>
<td>13</td>
<td>2</td>
<td>13</td>
</tr>
<tr>
<td>Maceinae et al 2012d</td>
<td>3</td>
<td>42</td>
<td>1</td>
<td>13</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>1,098</td>
<td>277</td>
<td>100</td>
<td>1.76 (0.79–3.92)</td>
</tr>
</tbody>
</table>

Total events 374
Heterogeneity: $r^2=0.45; \chi^2=9.93, df=4 (P=0.04); I^2=60%$
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$_2$RAs, 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_{2} RAs,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 PPIs29 and CV outcomes,
and a systematic review by Focks et al challenged the valid-
ity 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_{2} RAs. This
suggested that the safety profile of PPIs were comparable
with H_{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,32 while benefit overcame the
risk for some subgroups 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_{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 out-
comes 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 scarce36 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 *Helicobacter pylori* status could not be per-
formed 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_{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_{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


