Comparison of prophylactic effect of UGIB and effects on platelet function between PPIs and H\textsubscript{2}RAs combined with DAPT: systematic review and meta-analysis

Objective: We compared prophylactic effects of proton pump inhibitors (PPIs) and histamine-2 receptor antagonists (H\textsubscript{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\textsubscript{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\textsubscript{12} reaction units (PRUs), with 95% confidence intervals (CIs).

Results: Twelve clinical trials (n=3,301) met the inclusion criteria. Compared to H\textsubscript{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\textsubscript{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\textsubscript{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.\textsuperscript{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.\textsuperscript{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 (H₂RAs) 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, H₂RAs may be as effective as PPIs plus DAPT for patients with no prior history of upper GI bleeding (UGIB).

Therefore, H₂RAs 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 H₂RAs 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 H₂RAs 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, H₂ receptor antagonists, H₂ blocker, H₂RA, 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 H₂RAs; 4) primary outcome of UGIB; secondary outcomes were P2Y₁₂ 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 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 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 and moderate risk of bias for Ng et al. For cohort studies, the risk of bias for Cappelletti Galante et al, Ng et al and Yew et al is moderate and the risk of bias for Macaione et al is high.

Incidence of UGIB
Three RCTs 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$_2$RAs, histamine-2 receptor antagonists; PPIs, proton pump inhibitors.
<table>
<thead>
<tr>
<th>Studies</th>
<th>Type of studies</th>
<th>Inclusion criteria</th>
<th>Participants</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>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>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>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>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>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>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>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>Omeprazole 10 mg daily</td>
<td>At least 4 weeks</td>
<td>PRL, poor responders to clopidogrel, adverse CV events, non-CABG-related bleeding, symptoms of upper GI damage Rehospitalization, death</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>Omeprazole Ranitidine</td>
<td>6 months</td>
<td>Rehospitalization, death</td>
</tr>
</tbody>
</table>

**Table 1** Characteristics of included studies.
decreased UGIB compared to H$_2$RAs. Ng et al conducted a cohort study to measure UGIB events and treatment effect of PPIs and H$_2$RAs, and the risk of UGIB was marginally reduced by H$_2$RAs (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.\textsuperscript{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.\textsuperscript{13,14,18} The washout period for the study by Arbel et al\textsuperscript{15} was 2 weeks; blood samples were collected and results were analyzed in the manner of a parallel-group trial. Arbel et al\textsuperscript{15} study data were divided into two groups of similar subject size; Arbel et al 2013a compared omeprazole and H$_2$RAs and Arbel et al 2013b compared pantoprazole and H$_2$RAs. Heterogeneity of included trials was significant, and there were no statistically significant differences among PRUs between the PPIs and H$_2$RAs 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$_2$RAs group compared to the omeprazole group. The pantoprazole subgroup (1 study) had more PRUs compared to the H$_2$RAs 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).\textsuperscript{15}

Three RCTs\textsuperscript{15,18,20} reported of poor responders to clopidogrel (75 mg). The washout period in the study by Moceri et al\textsuperscript{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$_2$RAs 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.\textsuperscript{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 al13</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 al14</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 al15</td>
<td>Unclear (not stated)</td>
<td>High (not stated)</td>
<td>Unclear (not stated)</td>
<td>Low</td>
<td>Low (21/21)</td>
<td>Low</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Ng et al16</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>Unclearb</td>
<td>Moderate</td>
</tr>
<tr>
<td>Parri et al17</td>
<td>Unclear (not stated)</td>
<td>High (not stated)</td>
<td>High (not stated)</td>
<td>Low</td>
<td>High (not stated)</td>
<td>Low</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Tunggal et al18</td>
<td>Low (shuffling envelopes)</td>
<td>Low (identical blinded sealed envelopes)</td>
<td>Low (double blind)</td>
<td>Low</td>
<td>Low (88/107)</td>
<td>Low</td>
<td>Unclearb</td>
<td>High</td>
</tr>
<tr>
<td>Uotani et al19</td>
<td>Unclear (not stated)</td>
<td>High (not stated)</td>
<td>Unclear (not stated)</td>
<td>Unclear</td>
<td>Low (not stated)</td>
<td>Low</td>
<td>Uncleara</td>
<td>High</td>
</tr>
<tr>
<td>Yano et al20</td>
<td>Low (computer-generated randomization sequence)</td>
<td>Low (central concealment)</td>
<td>Low (open label)</td>
<td>Low</td>
<td>Low (130/180)</td>
<td>Low</td>
<td>Unclearc</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.
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 MACEs16,20 and there was no heterogeneity between the trials (P=0.44, I²=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).

Yew et al published a retrospective cohort study in Singapore that included post-PCI patients who received either omeprazole or a H₂RAs and DAPT and they confirmed that significantly more CV complications occurred in the omeprazole group (P=0.042).21

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 al22 2012a depicted omeprazole versus H₂RAs; Macaione et al 2012b reported esomeprazole versus H₂RAs; Macaione et al 2012c included results of lansoprazole versus H₂RAs; and Macaione et al 2012d included results of pantoprazole versus H₂RAs.22 Heterogeneity of included trials was substantial and there were no statistically significant differences among incidence of rehospitalization between the PPIs and H₂RAs 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 H₂RAs for patients receiving DAPT, as assessed in RCTs and cohort studies. Limited evidence suggested that compared to H₂RAs, 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.23 Another meta-analysis of 39 studies by Cardoso et al indicated that PPIs reduced LDA-associated UGIB.24 This review compared the effectiveness and safety of PPIs to H₂RAs for patients receiving DAPT, as assessed in RCTs and cohort studies. Limited evidence suggested that compared to H₂RAs, 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.23 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.24 Only two trials were included in comparisons between PPIs and H₂RAs by Mo et al,25 and no comparisons of this nature were made by

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>Non-exposed cohort drawn from the same community</th>
<th>Ascertained exposure</th>
<th>Outcome</th>
<th>Assessment of outcome of interest</th>
<th>Cohorts comparable on important factors</th>
<th>Blind assessment</th>
<th>Follow-up complete enough for outcomes of interest</th>
<th>Total NOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cappelletti et al21</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>7</td>
</tr>
<tr>
<td>Galante et al22</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>7</td>
</tr>
<tr>
<td>Macaione et al22</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>7</td>
</tr>
<tr>
<td>Ng et al23</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>7</td>
</tr>
<tr>
<td>Yew et al24</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>7</td>
</tr>
</tbody>
</table>

Notes: Y, related content conforms to the item; N, related content does not conform to the 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 drug. The patients of proton pump inhibitor group had significantly higher proportion of anemia (P=0.019) and previous coronary artery bypass grafting (P=0.048). Some of the clinical follow-up data were collected through telephone calls.

Abbreviation: NOS, Newcastle–Ottawa scale.
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 Events</th>
<th>Total</th>
<th>H$_2$RAs Events</th>
<th>Total</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>148</td>
<td>53.1</td>
<td>0.10 (0.01–0.79)</td>
</tr>
<tr>
<td>Tunggal et al$^{18}$</td>
<td>0</td>
<td>44</td>
<td>2</td>
<td>44</td>
<td>24.8</td>
<td>0.20 (0.01–4.05)</td>
</tr>
<tr>
<td>Yano et al$^{19}$</td>
<td>0</td>
<td>65</td>
<td>1</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>1.06 (0.30–1.70)</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $r^2=0.00; \chi^2=0.43, df=2 (P=0.81); I^2=0%$
Test for overall effect: $Z=2.44 (P=0.01)$

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 Mean, SD</th>
<th>Total</th>
<th>H$_2$RAs Mean, SD</th>
<th>Total</th>
<th>Mean difference IV, random, 95% CI</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</td>
<td>11, 26</td>
<td>31.4</td>
<td>38.00 (32.66–43.34)</td>
<td></td>
</tr>
<tr>
<td>Arbel et al 2013b</td>
<td>187, 12, 52</td>
<td>179</td>
<td>11, 26</td>
<td>31.4</td>
<td>8.00 (2.66–13.34)</td>
<td></td>
</tr>
<tr>
<td>Furtado et al$^{18}$</td>
<td>173.54, 72.28</td>
<td>158.8</td>
<td>76.4, 44</td>
<td>19.5</td>
<td>14.74 (–16.87–46.35)</td>
<td></td>
</tr>
<tr>
<td>Tunggal et al$^{18}$</td>
<td>242.6, 89.7</td>
<td>237.5</td>
<td>79.2, 44</td>
<td>17.7</td>
<td>5.10 (–30.26–40.46)</td>
<td></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>
<td></td>
<td></td>
</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 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</th>
<th>H$_2$RAs Events</th>
<th>Total</th>
<th>Weight (%)</th>
<th>Risk ratio M–H, random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moceri et al$^{12}$</td>
<td>7</td>
<td>21</td>
<td>2</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>19</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>35</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>
<td></td>
<td></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 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.
Of 28 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, yet while benefit overcame the risk for some subgroups at higher risk. 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 outcomes when coadministered with DAPT. 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, 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. 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 or unjustified based on current evidence. 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 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$_2$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.

Acknowledgments
The project was supported by Award Number 2016B-YX007 from the Chinese Medical Association. We extend our special thanks to Hua Zhang from the Research Center of Clinical Epidemiology, Peking University Third Hospital for clarifying types of included studies. We thank Prof Shu-Sen Sun from the College of Pharmacy, Western New England University for editing assistance.

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


