Conflicting Results Between Randomized Trials and Observational Studies on the Impact of Proton Pump Inhibitors on Cardiovascular Events When Coadministered With Dual Antiplatelet Therapy

Systematic Review

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Background—Discordant results have been reported on the effects of concomitant use of proton pump inhibitors (PPIs) and dual antiplatelet therapy (DAPT) for cardiovascular outcomes. We conducted a systematic review comparing the effectiveness and safety of concomitant use of PPIs and DAPT in the postdischarge treatment of unstable angina/non–ST-segment–elevation myocardial infarction patients.

Methods and Results—We searched for clinical studies in MEDLINE, EMBASE, and the Cochrane Database of Systematic Reviews, from 1995 to 2012. Reviewers screened and extracted data, assessed applicability and quality, and graded the strength of evidence. We performed meta-analyses of direct comparisons when outcomes and follow-up periods were comparable. Thirty-five studies were eligible. Five (4 randomized controlled trials and 1 observational) assessed the effect of omeprazole when added to DAPT; the other 30 (observational) assessed the effect of PPIs as a class when compared with no PPIs. Random-effects meta-analyses of the studies assessing PPIs as a class consistently reported higher event rates in patients receiving PPIs for various clinical outcomes at 1 year (composite ischemic end points, all-cause mortality, nonfatal MI, stroke, revascularization, and stent thrombosis). However, the results from randomized controlled trials evaluating omeprazole compared with placebo showed no difference in ischemic outcomes, despite a reduction in upper gastrointestinal bleeding with omeprazole.

Conclusions—Large, well-conducted observational studies of PPIs and randomized controlled trials of omeprazole seem to provide conflicting results for the effect of PPIs on cardiovascular outcomes when coadministered with DAPT. Prospective trials that directly compare pharmacodynamic parameters and clinical events among specific PPI agents in patients with unstable angina/non–ST-segment–elevation myocardial infarction treated with DAPT are warranted. (Circ Cardiovasc Qual Outcomes. 2015;8:47-55. DOI: 10.1161/CIRCOUTCOMES.114.001177.)

Key Words: acute coronary syndrome • proton pump inhibitors

Proton pump inhibitors (PPIs) are often prescribed together with antiplatelet therapy to prevent gastrointestinal complications, such as ulceration and bleeding. Clopidogrel, a potent antiplatelet used in the treatment of patients with coronary artery disease,1 is a prodrug that requires metabolic transformation in the liver by cytochrome P-450 isoenzyme (CYP2C19) to acquire its antiaggregation properties. PPIs are also metabolized by CYP enzymes, leading to a potential competitive inhibition of CYP2C19 and reduced activation of clopidogrel when used together.

Several pharmacodynamic studies have reported a significant decrease in the effect of clopidogrel on platelet aggregation when coadministered with omeprazole.2-5 These observations led the US Food and Drug Administration and the European Medicines Agency in 2009 to discourage the combination of clopidogrel and PPIs (in particular, omeprazole).6,7 Effects of concomitant administration on clinical outcomes have been discordant; some studies report an increased risk of major cardiovascular events whereas others report no difference.6-10

We conducted this systematic review to evaluate the comparative effectiveness and safety of concomitant use of PPIs
WHAT IS KNOWN

• A significant decrease in the effect of clopidogrel on platelet aggregation when coadministered with proton pump inhibitor (PPI) omeprazole has been reported in several pharmacodynamic studies. The clinical effect of the pharmacodynamic interaction between PPIs and clopidogrel remains unclear because results from observational studies have been discordant.

• The Food and Drug Administration and EMEA discourage the combination of clopidogrel and omeprazole

WHAT THE STUDY ADDS

• Using a systematic review approach, we evaluated the effectiveness and safety of PPIs when coadministered with clopidogrel in unstable angina/non–ST-segment–elevation myocardial infarction population.

• Omeprazole was the only PPI studied in randomized controlled trials. Results from randomized controlled trials did not show increased risk of ischemic events when omeprazole was coadministered with clopidogrel.

• A systematic assessment of the data obtained from observational studies suggested increased risk of cardiovascular outcomes when PPIs (as a class) were coadministered with clopidogrel. However, questions remain on the causality of this association, and even models and propensity scores adopted in observational data may have not fully addressed biases in patients selection. Overall, the systematic review of available evidence suggests the need of future randomized studies combining the assessment of pharmacodynamic parameters and their association with clinical outcomes.

and dual antiplatelet therapy (DAPT) among patients with unstable angina/non–ST-segment–elevation myocardial infarction (UA/NSTEMI).

Methods

This analysis was part of a broader systematic review assessing the effectiveness and safety of antiplatelet and anticoagulant medications used to treat patients with UA/NSTEMI. The full evidence report\(^4\) contains a detailed description of the methods and results, including evidence tables.

Study Selection

We searched for clinical studies in MEDLINE, EMBASE, and the Cochrane Database of Systematic Reviews, from January 1, 1995, to July 30, 2012. We also searched the gray literature of study registries and conference abstracts for relevant articles from completed trials and reviewed reference lists of relevant review articles to provide additional citations. Figure 1 depicts the flow of articles through the literature search and screening process.

Data Extraction and Quality Assessment

Two investigators independently reviewed titles, abstracts, and full-text articles for eligibility. We included original studies that were comparative assessments of strategies for treating patients with UA/NSTEMI with an indication for DAPT and who were discharged on PPIs. For this analysis, we excluded studies if (1) the population was composed entirely of STEMI or stable angina patients, (2) all patients included in the study received PPIs, (3) the outcomes of interest were not reported, or (4) the studies were nonclinical (eg, editorial, letter to the editor, and case series).

One investigator abstracted data on general study characteristics, study population, eligibility criteria, treatment strategy, clinical outcomes, and safety using standardized forms. A second investigator over-read the abstraction to check for accuracy and completeness. We used predefined criteria\(^1\) to assess study quality using the summary ratings of good (low risk of bias), fair (moderate risk), or poor (high risk). To assess study applicability, we evaluated the study eligibility criteria, study population demographics, clinical relevance, and timing of the outcome measures.

Data Synthesis and Analysis

We synthesized the primary literature by continuous data (eg, age and event rates) and categorical data (eg, race/ethnicity). Feasibility of completing a quantitative synthesis (meta-analysis) was based on the volume of relevant literature, conceptual homogeneity of the studies, and completeness of the reporting of results. We considered meta-analysis for comparisons where ≥3 separate studies reported data for the same outcome at a similar time of follow-up. Meta-analyses were based on the nature of the outcome variable, but random-effects models were used for all outcomes to accommodate the heterogeneity of the studies. Dichotomous outcome measures comparing 2 treatments were combined using hazard ratios (HRs) and a random-effects model using Comprehensive Meta-Analysis version 2 software (Biostat; Englewood, NJ).

Some studies reported only standard-adjusted results, others only propensity-adjusted results, and some reported both. For each outcome evaluated, we first performed a meta-analysis comparing the 2 types of estimates and looked for potential differences. As a second step, we did a meta-analysis using the propensity-adjusted HR (P) when it was available and the standard-adjusted HR (A) when the propensity-adjusted ratio was not available. We tested for statistical heterogeneity between studies (Q and F statistics) while recognizing that the power to detect such heterogeneity may be limited. Potential heterogeneity between studies was determined by evaluating the range of confidence intervals (CIs) of the random-effects summary statistics.

We assessed the strength of evidence using the 4 required domains: risk of bias, consistency, directness, and precision.\(^1\) We graded the strength of evidence for each outcome; thus, a given study may be of different quality for 2 individual outcomes reported within that same study. The studies were evaluated for the presence of confounders that would diminish an observed effect, strength of association (magnitude of effect), and publication bias. These domains were considered qualitatively, and a summary rating of high, moderate, or low strength of evidence was assigned.

Results

Thirty-five studies (4 randomized controlled trials [RCTs] and 31 observational) assessed the effect of antiplatelet therapy coadministered with PPI compared with DAPT alone (ie, no PPI) in the postdischarge treatment of patients with UA/NSTEMI (Appendix Table 1 in the Data Supplement).\(^5\) We stratified the studies for the presence of confounders that would diminish an observed effect, strength of association (magnitude of effect), and publication bias. These domains were considered qualitatively, and a summary rating of high, moderate, or low strength of evidence was assigned.
Effect of PPIs as a class compared with no PPI in the setting of DAPT. The summary results and strength of evidence ratings are shown in the Table.

**Effect on Composite Ischemic End Point at ≈1 Year**

The RCT comparing omeprazole with famotidine reported a nonsignificant difference in the rate of composite outcomes (cardiovascular mortality, nonfatal MI, or stroke) at 4 months between the 2 groups (4.3% versus 3.4%; \( P=0.7788 \)). Another RCT comparing omeprazole with placebo reported a nonsignificant difference in the rate of composite outcomes (cardiovascular mortality, nonfatal MI, stroke, or revascularization) at 6 months between the 2 arms (4.9% versus 5.7%; HR, 0.99; 95% CI, 0.68–1.44; \( P=0.96 \)). Similarly, an observational study comparing omeprazole versus no omeprazole reported a nonsignificant difference in the rate of composite outcomes (cardiovascular mortality or nonfatal MI) at 12 months between the 2 groups (10% versus 9.7%; unadjusted HR, 1.1; 95% CI, 0.6–1.8; \( P=0.89 \)).

Twenty observational studies reported the effect of any PPI on the composite end point of all-cause mortality, stroke, or MI at 6 to 18 months. Ten reported only standard-adjusted results, 3 only propensity-adjusted results, and 7 reported both. The overall estimate for the standard-adjusted HRs was 1.40, whereas the estimate for the propensity-adjusted HRs was 1.34 (\( \chi^2=0.111 \) for 1 degree of freedom; \( P=0.739 \)). Figure 2A shows the propensity-adjusted HR (P) when it was available and the standard-adjusted HR (A) when the propensity-adjusted HR was not available. The random-effects combined estimate was 1.35 (95% CI, 1.18–1.54; \( P<0.001 \); low-strength evidence).

Three observational studies with 60,389 patients reported the effect of any PPI on all-cause mortality or MI at 6 to 18 months. One reported only standard-adjusted results, and 2 reported both standard and propensity-adjusted results. The overall estimate for the standard-adjusted HRs was 1.23, the estimate for the propensity-adjusted HRs was 1.31 (\( \chi^2=0.265 \) for 1 degree of freedom; \( P=0.607 \)). Figure 2B shows that the random-effects combined estimate was 1.27 (95% CI, 1.12–1.43; \( P<0.001 \); moderate-strength evidence).

Three studies of omeprazole (2 RCTs and 1 observational) reported all-cause or cardiovascular mortality within at 6 to 18 months. One RCT comparing omeprazole with placebo in 237 patients with acute MI reported a significant difference in all-cause mortality at 14 days favoring omeprazole (3.5% versus 10.6%; \( P=0.035 \)). One RCT comparing omeprazole with placebo in a mixed population of 3873 acute coronary syndrome and percutaneous coronary intervention (PCI) patients reported a nonsignificant difference in all-cause mortality at 6 months between omeprazole and placebo (4% versus 5%). Similarly, an observational study comparing omeprazole versus no omeprazole in a mixed population of 558 stable angina and patients with acute coronary syndrome reported a nonsignificant difference in cardiovascular mortality at 1 year between omeprazole and placebo (3.5% versus 3.2%; unadjusted HR, 1.10; 95% CI, 0.44–2.84; \( P=0.84 \)).

Of the 17 observational studies that reported the effect of any PPI on all-cause mortality at 6 to 18 months, 11 reported only standard-adjusted results, 2 only propensity-adjusted results, and 4
**Table. Summary Results by Outcome for Patients With Unstable Angina/Non–ST-Segment–Elevation Myocardial Infarction Treated With Dual Antiplatelet Therapy With and Without Proton Pump Inhibitors**

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<th>Outcome and Timing</th>
<th>SOE* and Effect Estimate (95% CI)</th>
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<tbody>
<tr>
<td><strong>Composite ischemic end points at =1 y</strong></td>
<td>SOE=low (2 RCTs and 21 observational studies; 272311 patients) RCTS of omeprazole showed no difference; however, meta-analysis of observational studies of any PPI showed adj HR 1.35 (1.18–1.54), which favors no PPI. The discrepancy between the RCTs and the observational studies makes it difficult to draw a firm conclusion about the effect</td>
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<tr>
<td><strong>Composite of all-cause mortality or MI at about 1 y</strong></td>
<td>SOE=moderate (3 observational studies; 60389 patients) Adj HR 1.27 (1.12–1.43); favors no PPI</td>
</tr>
<tr>
<td><strong>All-cause mortality at about 1 y</strong></td>
<td>SOE=moderate (2 RCTs and 18 observational studies; 264172 patients) RCTS of omeprazole showed no difference or favored omeprazole, and the meta-analysis of observational studies of any PPI showed adj HR 1.17 (0.92–1.48); no difference</td>
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<tr>
<td><strong>All-cause mortality at 6 y</strong></td>
<td>SOE=low (1 observational study; 23200 patients) Adj HR 1.32 (1.00–1.73); favors no PPI</td>
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<tr>
<td><strong>Cardiovascular mortality at 1 y</strong></td>
<td>SOE=insufficient (3 observational studies; 76184 patients) Insufficient evidence due to inconsistency and imprecision: 2 of 3 studies showed statistically significant increase in CV mortality in PPI group</td>
</tr>
<tr>
<td><strong>Nonfatal MI at about 1 y</strong></td>
<td>SOE=low (1 RCT and 11 observational studies; 225687 patients) The RCT and observational study of omeprazole showed no difference; however, the meta-analysis of observational studies of any PPI showed adj HR 1.33 (1.15–1.55), which favors no PPI. The discrepancy between the omeprazole studies and the observational studies of any PPI makes it difficult to draw a firm conclusion about the effect</td>
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<tr>
<td><strong>Stroke at about 1 y</strong></td>
<td>SOE=low (2 RCTS and 5 observational studies; 165212 patients) RCTS of omeprazole showed no difference; however, the meta-analysis of observational studies of any PPI showed adj HR 1.49 (1.20–1.84), which favors no PPI. The discrepancy between the RCTs and the observational studies makes it difficult to draw a firm conclusion about the effect</td>
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<td><strong>Revascularization at 6 mo</strong></td>
<td>SOE=low (1 RCT and 1 observational study; 22326 patients) Both studies showed no difference in revascularization rates; no difference</td>
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<tr>
<td><strong>Revascularization at 1 y</strong></td>
<td>SOE=low (5 observational studies; 53164 patients) Observational study of omeprazole showed no difference; meta-analysis of observational studies of any PPI showed adj OR 1.48 (1.21–1.82); favors no PPI</td>
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<tr>
<td><strong>Revascularization at 4 y</strong></td>
<td>SOE=insufficient (1 observational study; 315 patients) Insufficient evidence because of imprecision; no statistically significant difference in revascularization rate between groups</td>
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**Table. Continued**

<table>
<thead>
<tr>
<th>Outcome and Timing</th>
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<tbody>
<tr>
<td><strong>Stent thrombosis at about 1 y</strong></td>
<td>SOE=low (1 RCT and 7 observational studies; 45198 patients) The RCT and observational study of omeprazole showed no difference; however, the meta-analysis of observational studies of any PPI showed adj HR 1.34 (1.17–1.55), which favors no PPI. The discrepancy between the RCT and the observational studies makes it difficult to draw a firm conclusion about the effect</td>
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<tr>
<td><strong>Major bleeding at 30 d</strong></td>
<td>SOE=insufficient (3 observational studies; 7498 patients) Insufficient evidence because of inconsistency and imprecision: adj HR 1.73 (0.61–4.88)</td>
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<tr>
<td><strong>Major bleeding at about 1 y</strong></td>
<td>SOE=low (4 observational studies; 36231 patients) Adj HR 1.26 (1.12–1.41); favors no PPI</td>
</tr>
<tr>
<td><strong>GI bleeding</strong></td>
<td>SOE=moderate (4 RCTs and 4 observational studies; 28032 patients) 3 of 4 RCTS of omeprazole and 2 of 4 observational studies of any PPI showed statistically significant lower rates of GI bleed in the PPI group; favors PPI</td>
</tr>
<tr>
<td><strong>Minor bleeding</strong></td>
<td>SOE=insufficient (1 observational study; 1346 patients) Insufficient evidence because of imprecision: no difference in minor bleed in-hospital or at 1 y</td>
</tr>
<tr>
<td><strong>Rehospitalization at 3 mo</strong></td>
<td>SOE=low (1 observational study; 5662 patients) Significant increase in rehospitalization in PPI group at 3 mo; adj HR 1.32 (1.00–1.73); favors no PPI</td>
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<tr>
<td><strong>Rehospitalization at about 1 y</strong></td>
<td>SOE=insufficient (4 observational studies; 16925 patients) Insufficient because of inconsistency and imprecision: adj HR 1.70 (0.86–3.34)</td>
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*Adj indicates adjusted; CI, confidence interval; CV, cardiovascular; GI, gastrointestinal; HR, hazard ratio; MI, myocardial infarction; OR, odds ratio; PPI, proton pump inhibitor; RCT, randomized controlled trial; and SOE, strength of evidence.

*All strength of evidence ratings of insufficient (ie, no evidence is available or available evidence is imprecise or too inconsistent to reach a conclusion) are shaded.

†HRs <1 favor PPI use; ORs >1 favor no PPI use.

reported both. The overall estimates for the standard-adjusted HRs and propensity-adjusted HRs were 1.18 and 1.44, respectively (χ²=1.271 for 1 degree of freedom; P=0.258). Figure 2C shows that the random-effects combined estimate was 1.17 (95% CI, 0.92–1.48; P=0.20; moderate-strength evidence).

**Effect on Nonfatal MI at ≈1 Year**

Two studies (1 RCT and 1 observational) of omeprazole reported nonfatal MI within the first year. The RCT found a nonsignificant reduction of nonfatal MI at 6 months (1.2% versus 1.5%; HR, 0.92; 95% CI, 0.44–1.90; P=0.81) with omeprazole. Similarly, the observational study found no effect of omeprazole versus no omeprazole on nonfatal MI (6.5% versus 6.5%; HR, 1.0; 95% CI, 0.5–1.9).

Ten observational studies reported the effect of any PPI use on nonfatal MI at 6 to 18 months. Six
reported only standard-adjusted results, 3 both standard and propensity-adjusted results, and 1 reported only propensity-adjusted results. The overall estimate for the standard-adjusted and propensity-adjusted HRs was 1.35 and 1.33, respectively ($\chi^2=0.005$ for 1 degree of freedom; $P=0.941$). Figure 2D shows that the random-effects combined estimate was 1.33 (95% CI, 1.15–1.55; $P<0.001$; low-strength evidence).

**Effect on Stroke at 30 Days and at ≈1 Year**
Nonsignificant differences were found in the rate of both transient ischemic attacks at 30 days (2.3% versus 1.0%)\(^{13}\) and stroke events at 6 months (stroke 0.2% versus 0.3%)\(^{15}\) between patients treated with omeprazole compared with those receiving placebo. Five observational studies reported the effect of any PPI on stroke at 6 to 18 months.\(^{17,18,27,32,42}\) Four reported only standard-adjusted results, and one reported both standard and propensity-adjusted results. Figure 2E shows that the random-effects combined estimate was 1.49 (95% CI, 1.20–1.84; $P<0.001$; low-strength evidence).

**Effect on Revascularization at ≈1 Year**
One RCT\(^{15}\) found a similar rate of revascularization at 6 months among patients discharged on omeprazole compared with those discharged without (4.0% versus 4.6%). One observational study\(^{31}\) similarly found no difference in the risk of revascularization at 6 months among 22,326 patients with UA/NSTEMI treated at discharge with PPI compared with those not treated with PPI (adjusted HR, 0.97; 95% CI, 0.79–1.21; low-strength evidence).

One observational study\(^{44}\) found a similar rate of revascularization at 1 year for 588 patients with UA/NSTEMI discharged on omeprazole compared with those discharged without omeprazole (9.4% versus 8.9%).

A random-effects meta-analysis of 4 observational studies of any PPI,\(^{8,11,27,36}\) including 52,576 patients with UA/NSTEMI assessing revascularization at 1 year reported standard-adjusted results, and 1 study additionally reported propensity-adjusted results.\(^{13}\) Figure 2F shows that the random-effects combined estimate was 1.48 (95% CI, 1.21–1.82; low-strength evidence). There was evidence of heterogeneity that seemed to be because of the Banerjee study.\(^{13}\) As a sensitivity analysis, we performed a meta-analysis where we used only the adjusted HR from the Banerjee study.\(^{13}\) For propensity-adjusted HRs was 1.35 and 1.33, respectively ($\chi^2=0.005$ for 1 degree of freedom; $P=0.941$).\(^{15,21,28,33}\) Figure 2G shows that the random-effects combined estimate was 1.34 (95% CI, 1.17–1.55; $P<0.001$; low-strength evidence).

**Effect on Stent Thrombosis at ≈1 Year**
Two studies (1 RCT and 1 observational) of omeprazole reported stent thrombosis (definite, possible, and probable) within 1 year. In the RCT,\(^{15}\) 2 cases of definite or probable stent thrombosis occurred at 6 months in the placebo group, and no cases occurred in the omeprazole group. A nonsignificant difference in stent thrombosis was found among patients discharged on omeprazole compared with those discharged without (8.8% versus 5.8%; HR, 1.1; 95% CI, 0.7–1.8) at 1 year in the observational study.\(^{44}\)

Six observational studies reported the effect of any PPI use on stent thrombosis at 6 to 18 months.\(^{5,23,25,34,35,39}\) Four reported only standard-adjusted results, and 2 only propensity-adjusted results. The overall estimate for the standard-adjusted and propensity-adjusted HRs was 1.35 and 1.33, respectively ($\chi^2=0.005$ for 1 degree of freedom; $P=0.941$).\(^{15,21,28,33}\) Figure 2G shows that the random-effects combined estimate was 1.34 (95% CI, 1.17–1.55; $P<0.001$; low-strength evidence).

**Effect on Gastrointestinal Bleeding**
Four RCTs of omeprazole reported gastrointestinal bleeding.\(^{15,21,28,33}\) Three found that the use of omeprazole significantly reduced the rates of upper gastrointestinal bleeding at 14 days and at 4 and 6 months.

Four observational studies of any PPIs reported on gastrointestinal bleeding.\(^{14,19,29,32}\) One\(^{14}\) found no difference in the rate of in-hospital gastrointestinal bleeding between patients discharged with and without PPI (0.7% versus 0.6%; $P=0.88$). Another\(^{19}\) found a significant increase in the rate of in-hospital gastrointestinal bleeding among patients not receiving PPI compared with those treated with PPI (4.8% versus 0.6%; $P=0.001$). The 2 studies reporting gastrointestinal events at longer follow-up found dissimilar results. One\(^{19}\) found no differences in gastrointestinal bleeding at 18 months between patients with UA/NSTEMI treated with or without PPI (3.5% versus 3.8%; HR, 0.39; 95% CI, 0.04–3.26; $P=0.38$). The other\(^{29}\) found a significant reduction in gastrointestinal bleeding at 1 year among patients treated with PPI compared with those not treated with PPI (HR, 0.50; 95% CI, 0.39–0.65).

Given the differences in the duration of follow-up both in the RCTs and observational studies, a meta-analysis was not performed; however, there is moderate-strength evidence that favors use of PPIs for reducing gastrointestinal bleeding.

**Discussion**
Using a systematic review approach, we found that among patients with UA/NSTEMI with an indication for DAPT, the concomitant administration of PPIs (as a class) was associated with worse clinical outcomes in observational studies; however, 4 RCTs of omeprazole versus placebo report no difference in ischemic outcomes despite reducing upper gastrointestinal bleeding with omeprazole administration.

Several studies assessing platelet aggregation inhibition have shown how PPIs may significantly reduce the antiplatelet effect of clopidogrel when the 2 drugs are coadministered.\(^{2–5}\) This effect is attributed to an important pharmacokinetic interaction between the 2 drugs, where clopidogrel needs metabolic transformation to its active form by CYP2C19 enzyme, and PPIs inhibit this enzyme to different extents.

The findings from pharmacodynamic studies have not fully translated into a difference in clinical outcomes because multiple studies exploring the effect of concomitant use of PPIs and clopidogrel on major cardiovascular outcomes have found contrasting results.\(^{5,9,45,46}\)

In our analysis of the use of PPIs with DAPT, we identified 35 studies, of which only 4 were RCTs. All RCTs investigating the effect of omeprazole compared with placebo or esomeprazole compared with famotidine (1 study) on cardiovascular outcomes showed no difference in ischemic events. The use of omeprazole
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Figure 2. Meta-analyses of dual antiplatelet therapy with and without proton pump inhibitor (PPI). A, Composite end point at about 1 year. Q=196.64 for 19 degrees of freedom (P<0.001), I²=90.34: indicate very significant heterogeneity. B, All-cause mortality and nonfatal myocardial infarction at about 1 year. Q=0.466 for 2 degrees of freedom (P=0.792), I²=0.00: indicate no heterogeneity. C, All-cause mortality at ≥1 year. Q=243.34 for 16 degrees of freedom (P<0.000), I²=93.452: indicate extreme heterogeneity. D, Nonfatal myocardial infarction at =1 year. Q=54.103 for 9 degrees of freedom (P<0.001), I²=83.365: indicate extreme heterogeneity. E, Stroke at ≥1 year. Q=16.258 for 4 degrees of freedom (P=0.001), I²=70.230: indicate extreme heterogeneity. F, Revascularization at ≥1 year. Q=11.092 for 3 degrees of freedom (P=0.001), I²=72.955: indicates heterogeneity. G, Stent thrombosis at ≥1 year. Q=14.845 for 5 degrees of freedom (P=0.011), I²=66.318: indicate heterogeneity. A standard-deviation-adjusted hazard ratio; CI, confidence interval; P, propensity-adjusted hazard ratio; and UA/NSTEMI, unstable angina/non–ST-segment-elevation myocardial infarction.

did result in a significant reduction in gastrointestinal bleeding; however, given the differences in the timing of follow-up (from 14 days to 6 months), a meta-analysis was not considered applicable. Although a net clinical benefit analysis was not performed, these data suggest that omeprazole and clopidogrel can be safely coadministered. These findings all based on RCTs call into question the Food and Drug Administration warning against the concomitant use of clopidogrel plus omeprazole.

Data obtained from the remaining 30 studies (all observational) comparing PPI medication (as a class) with no PPI...
medication suggest that event rates are higher in patients who receive any type of PPI medication for the composite outcome (all-cause mortality or nonfatal MI) at 1 year, and nonfatal MI, all-cause mortality, and revascularization after 1 year.

The potential for selection bias in observational trials is not negligible. Sicker patients, with more comorbidities and at higher baseline risk for adverse outcomes, are preferentially treated with PPI therapy, and as a result this cohort seems to have more adverse clinical outcomes.\textsuperscript{8,17} In an attempt to account for some of these baseline differences between patients who received PPI and those who did not, we used the results for standard and propensity score–matched HRs for each study. Also, when possible, we ran separate meta-analyses to assess the effect of adjustment on the clinical outcomes. For a majority of analyses, there was no statistically significant difference in the summary estimate for the standard-adjustment compared with the propensity-adjusted HRs. Many of the meta-analyses showed evidence of heterogeneity that is likely because of the variation in the clinical factors used to calculate the standard and propensity-adjusted HRs. The summary estimates for the standard/propensity-adjusted results showed HRs that were closer to 1, but for many outcomes the summary estimate still favored the no PPI group.

Aside from the underlying differences in patients’ baseline characteristics and comorbidities that were observed in the analysis population of the observational studies, there are other important factors to consider when comparing results from RCTs and observational studies. Among them, we found that observational studies lacked information on the PPI regimen, such as the dose and frequency of administration, the duration of treatment, concomitant medications, new prescription versus chronic therapy, and patients’ medication adherence.

Although we attempted to control for some of these confounding factors inherent to patient and clinical characteristics, it is highly probable that unmeasurable confounding still remains, and the effect of PPIs analyzed as a class in this analysis is not based on strong evidence.\textsuperscript{47} It is also unclear whether genetic resistance to clopidogrel is a causal factor, or whether the negative interaction may be drug specific or class specific. Those variables were not included in the studies we reviewed. The overall strength of evidence rating was downgraded because the findings from observational studies on PPI as a class conflicted with the few RCTs of omeprazole.

Study type and method of analysis can explain some variation in the relative hazard associated with the coadministration of PPI with clopidogrel; the risk of error is mitigated as the methodological rigor increases.\textsuperscript{42,47,48}

A recent update of the American Heart Association/American College of Cardiology guidelines has removed the recommendation to administer PPI to patients with a history of gastrointestinal bleeding, and in its place suggests that healthcare providers evaluate the need for starting or continuing PPI treatment in patients taking clopidogrel. Their statement does not prohibit the use of PPIs in appropriate clinical settings; however, they describe the potential risks and benefits from PPIs in combination with clopidogrel.\textsuperscript{1} Our findings also support a cautious approach to PPI use with DAPT therapy in patients with UA/NSTEMI.

Further research—preferably additional RCTs of specific PPI agents or prospective propensity score–matched cohort studies—is warranted on whether the detrimental effect of PPIs is because of comorbid conditions of the patient population, to the specific PPI agent used, or to genetic predisposition for reduced clopidogrel responsiveness.

**Strengths and Limitations**

Some considerations should be taken into account while interpreting these data. The strength of this review is its focus on comparative studies of antiplatelet and anticoagulant treatments; any studies that reported noncomparative findings were excluded. To review adequate numbers of studies to address the safety and effectiveness of PPIs when coadministered with DAPT in patients with UA/NSTEMI, we had to broaden our eligible patient population to include studies of either UA/NSTEMI or acute coronary syndrome (STEMI, NSTEMI, and unstable angina). Also, some PPI studies included patients with acute coronary syndrome or stable angina. To improve the applicability of our findings to the UA/NSTEMI population, we did exclude studies that focused exclusively on the STEMI or stable angina population.

In addition, different composite end point definitions made quantitative analysis less feasible. Information on adherence to clopidogrel or PPI treatment, dose of PPI, or switching between one PPI and another was not available. Finally, an analysis of the net benefit was not conducted (ie, assessing the effectiveness while accounting for the risk of these therapies).

**Conclusions**

Although the use of PPIs as a class was associated with worse clinical outcomes in observational studies of patients with UA/NSTEMI receiving DAPT, the results from a small number of RCTs of omeprazole showed no significant difference in clinical events. Prospective trials directly comparing pharmacodynamic parameters and clinical events of different PPIs in patients with UA/NSTEMI treated with DAPT are warranted.

**Acknowledgments**

We thank Dr. Kato, Agency for Healthcare Research and Quality Task Order Officer and Dr. Bass for their suggestions on improving the clarity of the report; Megan von Isenburg, MSLS, for help with the literature search and retrieval; R. Julian Irvine, MCM, for project coordination; and Liz Wing, MA, for editorial assistance. The authors of this report are responsible for its contents; particularly, Dr Melloni had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Drs Melloni and Dolor helped in concept and design. Drs Melloni, Dolor, and Hasselblad helped in acquisition of data. Drs Melloni, Dolor, and Hasselblad helped in analysis and interpretation of data. Dr Melloni helped in drafting of the article. Dr Dolor, J.B. Washam, Dr Mayer, and Dr Jones helped in critical revision of the article for important intellectual content. Drs Hasselblad and Dolor helped in statistical analysis. Dr Heidenfelder helped in provision of study materials. Dr Dolor helped in obtaining funding. Dr Heidenfelder helped in administrative, technical, or logistic support. Dr Dolor helped in supervision.
Sources of Funding

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Disclosures

Dr Jones reports research grants to the Duke Clinical Research Institute from the American Heart Association, AstraZeneca and Bristol-Myers Squibb, and consultant/honoraria from the American Physician Institute and the American College of Physicians. The Dr Mayer reports grant funding from NIH T32 grant (NIH 5T32DK007012 Endocrinology and Metabolism Research Training Program).

References


3. Small DS, Farid NA, Payne CD, Weerakkody GJ, Li YG, Brandt JT, Salazar DE, Winters KJ. Effects of the proton pump inhibitor lan索投稿 to the pharmacokinetics and pharmacodynamics of prasugrel and clopi-


efficacy of clopidogrel and prasugrel with or without a proton-pump


8. Ho PM, Maddox TM, Wang L, Fihn SD, Jesse RL, Peterson ED, Rumtsfeld JS. Risk of adverse outcomes associated with concomitant use of clopi-
dogrel and proton pump inhibitors following acute coronary syndrome. JAMA. 2009;301:937–944.


on=display produceton=0id=318. Accessed January 5, 2012.


16. Blomback SM, Martin BJ, Bili B, Yeh F, Ahlehoff O, Selmer C, Said Q. Effect of the clopidogrel-proton pump inhibitor drug interaction on adverse cardiovas-

17. Charron M, Ahlehoff O, Norgaard ML, Jørgensen CH, Sørensen R, Ahlbildt SZ, Hansen PK, Madsen JK, Køber L, Tørp-Pedersen C, Gislason G. Proton-pump inhibitors are associated with increased cardio-


21. Gao QY, Sun Y, Sun YX, Wang LF, Fu L. Early use of omeprazole ben-


25. Harjai KJ, Shneyer C, Oreshaw P, Usmani S, Boura J, Mehta RH. Clinical outcomes in patients with concomitant use of proton pump inhibitor and pro-

26. Hsiao FY, Mullins CD, Wen YW, Huang WF, Chen PF, Tsai YW. Relationship between cardiovascular outcomes and proton pump inhibi-


Conflicting Results Between Randomized Trials and Observational Studies on the Impact of Proton Pump Inhibitors on Cardiovascular Events When Coadministered With Dual Antiplatelet Therapy: Systematic Review

Chiara Melloni, Jeffrey B. Washam, W. Schuyler Jones, Sharif A. Halim, Victor Hasselblad, Stephanie B. Mayer, Brooke L. Heidenfelder and Rowena J. Dolor

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http://circoutcomes.ahajournals.org/content/9/5/614.full.pdf

Data Supplement (unedited) at:
http://circoutcomes.ahajournals.org/content/suppl/2015/01/14/CIRCOUTCOMES.114.001177.DC1

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In the article by Melloni et al, “Conflicting Results Between Randomized Trials and Observational Studies on the Impact of Proton Pump Inhibitors on Cardiovascular Events When Coadministered With Dual Antiplatelet Therapy: Systematic Review,” which initially published online January 13, 2015 and which appeared in the January 2015 issue of the journal (Circ Cardiovasc Qual Outcomes. 2015;8:47–55. doi: 10.1161/CIRCOUTCOMES.114.001177), a correction to the Disclosures section is needed; additional funding needed to be reported.

The original text read:

“Dr Jones reports research grants to the Duke Clinical Research Institute from the American Heart Association, AstraZeneca and Bristol-Myers Squibb, and consultant/honoraria from the American Physician Institute and the American College of Physicians. The other authors report no conflicts.”

It should read:

“Dr Jones reports research grants to the Duke Clinical Research Institute from the American Heart Association, AstraZeneca and Bristol-Myers Squibb, and consultant/honoraria from the American Physician Institute and the American College of Physicians. Dr Mayer reports grant funding from NIH T32 grant (NIH 5T32DK007012 Endocrinology and Metabolism Research Training Program).”

The correction has been made to the final version of the article, which is available at http://circoutcomes.ahajournals.org/content/8/1/47.

The authors regret the error.
## Supplemental Material

### Appendix Table. Study Characteristics

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Details</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Cointervention</th>
<th>Timing Outcomes Reported</th>
<th>Quality</th>
</tr>
</thead>
</table>
| Banerjee, 2011¹ | Observational NR sites in US  
Funding: NR  
Timeframe: 01/2003–12/2008  
Population:  
89% ACS  
Total N: 23,200  
Mean Age: 64 to 65  
Female: 1.7%  
Race: Hispanic 4%, Black 6%, White 54%, Other 37% | No PPI (N=3,678) | PPI (N=867) | Clopidogrel  
All patients received clopidogrel | Timing: 1 year, 6 years  
Composite (primary)  
Total mortality  
Nonfatal MI  
Revascularization (secondary)  
Total mortality  
Nonfatal MI  | Good |
| Barada, 2008²  | Observational Single site in Africa  
Funding: None  
Population:  
NR  
Total N: 1,023  
Mean Age: 63 to 64  
Female: 26%  
Race: NR | No PPI (N=705) | PPI (N=318) | Clopidogrel, aspirin | Timing: In-hospital  
Individual  
Upper GI bleeding | Poor |
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<th>Study</th>
<th>Study Details</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Cointervention</th>
<th>Timing Outcomes Reported</th>
<th>Quality</th>
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<tr>
<td>Bhatt, 2010¹</td>
<td>RCT 393 sites location NR Funding: Industry Timeframe: 01/2008–12/2008</td>
<td>Omeprazole 20 mg (N=1,876)</td>
<td>Placebo (N=1,885)</td>
<td>Aspirin 75–325 mg Clopidogrel 75 mg</td>
<td>Timing: 6 months Composite: (primary) CV mortality Nonfatal MI Stroke Revascularization Individual Upper GI events Overt gastroduodenal or upper GI bleeding Nonfatal MI Revascularization Stroke Total mortality CV mortality</td>
<td>Good</td>
</tr>
<tr>
<td>COGENT study</td>
<td>Population NR Total N: 3,761 Median Age: 69 Female: 32% Race: NR</td>
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<tr>
<td></td>
<td>Population 100% ACS Total N: 5,348 Mean Age: 61 Female: 30 % Race: NR</td>
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| Charlot, 2010<sup>5</sup> | Observational NR sites in Europe Funding: Private foundation Timeframe: 2000–2006  
Population: NR  
Total N: 56,406  
Mean Age: 68.5  
Female: 41%  
Race: NR | No PPI (N=22,815)  
PPI (N=8,889) | No PPI (N=17,949)  
PPI (N=6,753) | No clopidogrel  
Clopidogrel | Timing: 1 year  
Composite (primary)  
CV mortality  
Nonfatal MI  
Stroke  
Individual  
Total mortality  
CV mortality  
Nonfatal MI  
Stroke | Good |
Population  
N=19,925 ACS  
Total N: 49,452  
Mean Age: 64 to 73  
Female: 76%  
Race: NR | No PPI (N=15,619)  
PPI (N=4,306) | Aspirin 75 mg/day |  | Timing: 1 year  
Composite (primary)  
CV mortality  
Stroke  
Rehospitalization  
Individual  
Total mortality  
CV mortality  
Nonfatal MI  
Stroke | Fair |
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<th>Study</th>
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<tr>
<td>Chitose, 2012</td>
<td>Observational 16 sites in Asia Funding: Private foundation Timeframe: 06/2008–03/2009 Population N=621 ACS Total N: 1,270 Mean Age: 69 to 72 Female: 30% Race: Asian 100%</td>
<td>PPI (N=171)</td>
<td>No PPI (N=450)</td>
<td>Clopidogrel, aspirin Aspirin 100 mg/day thienopyridine agent (75 mg/day clopidogrel or 200 mg/day ticlopidine)</td>
<td>Timing: 18 months Composite (primary) CV mortality Nonfatal MI Stroke Individual CV mortality Nonfatal MI Stroke GI event</td>
<td>Good</td>
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<td>Study</td>
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<tr>
<td>Gaspar, 2010¹</td>
<td>Observational Single site in Europe Funding: NR Timeframe: 12/2004–03/2008</td>
<td>PPI (N=274)</td>
<td>No PPI</td>
<td>Clopidogrel, aspirin, GPIs</td>
<td>Timing: 6 months Composite (primary) Total mortality Nonfatal MI Unstable angina</td>
<td>Good</td>
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<td>Population 65% UA/NSTEMI 35% STEMI</td>
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<td>Individual Total mortality</td>
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<td></td>
<td>Total N: 876 Mean Age: 61 to 65 Female: 24% Race: NR</td>
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<td>Goodman, 2012¹</td>
<td>Observational 43 sites in US, Canada, UK, Europe, South America, Central America, Asia, Africa, Australia/New Zealand Funding: Industry Timeframe: 10/2006–07/2008</td>
<td>PPI (N=6,538)</td>
<td>No PPI (N=12,062)</td>
<td>Clopidogrel (N=9,291; 300 mg loading, 75 mg/day maintenance) Clopidogrel (N=9,291; 300 mg loading, 75 mg/day maintenance)</td>
<td>Timing: 1 year Composite (primary) CV mortality Nonfatal MI Stroke (secondary) CV mortality Nonfatal MI Individual Total mortality CV mortality Nonfatal MI Major bleeding Stent thrombosis</td>
<td>Good</td>
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<td>PLATO</td>
<td>Population N=3,111 unstable angina N=7,950 NSTEMI N=7,023 STEMI</td>
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<td></td>
<td>Total N: 18,624 Median Age: 62 to 63 Female: 28% Race: Black 1%, Asian 6%, White 92%</td>
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<td>Gupta, 2010</td>
<td>Observational Single site in US</td>
<td>PPI (N=72)</td>
<td>No PPI</td>
<td>Clopidogrel 75 mg/day</td>
<td>Timing: 4 years Composite (primary) Total mortality Nonfatal MI Target vessel failure Individual Total mortality Target lesion revascularization Target vessel failure</td>
<td>Fair</td>
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<td>Funding: NR</td>
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<td>(N=243)</td>
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<td>Timeframe: 01/2003–08/2004</td>
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<td>Population: NR</td>
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<td>Total N: 315</td>
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<td>Mean Age: 62</td>
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<td>Race: NR</td>
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<td>Harjai, 2011</td>
<td>Observational NR sites in US</td>
<td>PPI (N=1,902)</td>
<td>No PPI</td>
<td>Aspirin</td>
<td>Timing: 6 months Composite (primary) Total mortality Nonfatal MI Revascularization Stent thrombosis Individual Total mortality Nonfatal MI Revascularization Stent thrombosis Major bleeding</td>
<td>Good</td>
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<td>Funding: NR</td>
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<td>(N=751)</td>
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<td>Population 39% NSTEMI</td>
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<td>Total N: 2,653</td>
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<td>Mean Age: 64 to 66</td>
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<td>Female: 31%</td>
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<td>Race: NR</td>
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<td>Ho, 2009&lt;sup&gt;14&lt;/sup&gt;</td>
<td>Observational 127 sites in US Funding: Government Timeframe: 10/2003–12/2006 Population&lt;br&gt;Total N: 8,790 Mean Age: 66 to 68 Female: 1% Race: NR</td>
<td>PPI (N=5,244)</td>
<td>No PPI (N=2,961)</td>
<td>Clopidogrel, aspirin</td>
<td>Timing: 18 months&lt;br&gt;Composite (primary)&lt;br&gt;Total mortality&lt;br&gt;Rehospitalization&lt;br&gt;Individual Rehospitalization&lt;br&gt;Revascularization&lt;br&gt;Total mortality</td>
<td>Good</td>
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<tr>
<td>Hsiao, 2011&lt;sup&gt;15&lt;/sup&gt;</td>
<td>Observational NR sites in Asia Funding: Private foundation Timeframe: 01/2001–12/2006 Population&lt;br&gt;N=9,753 ACS&lt;br&gt;Total N: 9,753 Mean Age: 62 to 66 Female: 23% Race: NR</td>
<td>PPI (N=622)</td>
<td>No PPI (N=9,131)</td>
<td>Clopidogrel, aspirin</td>
<td>Timing: 6 months&lt;br&gt;Individual Rehospitalization</td>
<td>Good</td>
</tr>
<tr>
<td>Juurlink, 2009&lt;sup&gt;16&lt;/sup&gt;</td>
<td>Observational NR sites in Canada Funding: Government, private foundation Timeframe: 04/2002–12/2007 Population: NR&lt;br&gt;Total N: 2,791 Mean Age: 77 Female: 46% Race: NR</td>
<td>Clopidogrel + nonfatal MI in 90 days (N=734)</td>
<td>Clopidogrel (N=2,057)</td>
<td>PPI (intervention 39%, comparator 36%)</td>
<td>Timing: 3 months, 1 year&lt;br&gt;Individual&lt;br&gt;Total mortality&lt;br&gt;Nonfatal MI</td>
<td>Good</td>
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<td>Study</td>
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<tr>
<td>Ng, 2008&lt;sup&gt;18&lt;/sup&gt;</td>
<td>Observational 38 sites in Asia Funding: None Timeframe: 01/2002–12/2006 Population N=375 unstable angina Total N: 666 Mean Age: 72 Female: NR Race: NR</td>
<td>PPI (N=336)</td>
<td>No PPI (N=290)</td>
<td>Clopidogrel, aspirin, enoxaparin</td>
<td>Timing: 7 days Individual GI bleeding GI bleeding/occult bleeding</td>
<td>Good</td>
</tr>
<tr>
<td>Study</td>
<td>Study Details</td>
<td>Intervention</td>
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<td>Ng, 2012¹⁹</td>
<td>RCT Single site in Asia Funding: Private foundation Timeframe: 07/2008–09/2010</td>
<td>Esomeprazole 20 mg (N=163) Duration: 16 weeks</td>
<td>Famotidine 40 mg (N=148) Duration: 16 weeks</td>
<td>Aspirin 80–160 mg Clopidogrel 75 mg</td>
<td>Timing: 4 months Composite (secondary) CV mortality Nonfatal MI Stroke (secondary) GI events Occult bleeding of unknown origin Individual GI events</td>
<td>Good</td>
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<td>Study</td>
<td>Study Details</td>
<td>Intervention</td>
<td>Comparator</td>
<td>Cointervention</td>
<td>Timing Outcomes Reported</td>
<td>Quality</td>
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<td>O’Donoghue, 2009²⁰</td>
<td>Observational 707 international sites Funding: Industry Timeframe: 11/2004–1/2007 Population 74% UA/NSTEMI 26% STEMI</td>
<td>PPI</td>
<td>No PPI</td>
<td>Aspirin 75–162 mg/day 3% of patients received bivalirudin 55% of patients received GPls</td>
<td>Timing: 3 months, 6 months Composite (primary) CV mortality Nonfatal MI Stroke (secondary) Major bleeding Minor bleeding (secondary) Mortality MI Stroke Major bleeding Individual Total mortality CV mortality Nonfatal MI Stent thrombosis Major bleeding</td>
<td>Good</td>
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<td>Study</td>
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<td>Intervention</td>
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</table>
| Ortolani, 2012\(^{21}\)      | Observational
NR sites in Europe
Funding: Private foundation
Timeframe: 01/2008–08/2008
Population
N=1,141 unstable angina
N=1,377 NSTEMI
N=1,378 STEMI
Total N: 3,896
Mean Age: 63 to 69
Female: 30%
Race: NR | PPI (N=3,519) | No PPI (N=377) | Clopidogrel, aspirin | Timing: 1 year
Composite (secondary)
Total mortality
Revascularization
Rehospitalization
Individual Rehospitalization
Revascularization
Total mortality | Good |
| Rassen, 2009\(^{22}\)         | Observational
NR sites in US, Canada
Funding: Government
Timeframe: 01/2001–12/2005
Population:
NR
Total N: 18,565
Mean Age: NR
Female: 20%
Race: NR | PPI (N=3,996) | No PPI (N=14,569) | Clopidogrel | Timing: 6 months
Composite (primary)
Total mortality
Nonfatal MI
Individual Nonfatal MI
Total mortality
Revascularization | Good |
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<tr>
<th>Study</th>
<th>Study Details</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Cointervention</th>
<th>Timing Outcomes Reported</th>
<th>Quality</th>
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<tbody>
<tr>
<td>Ray, 201023</td>
<td>Observational NR sites in US Funding: Government Timeframe: 01/1999–12/2005</td>
<td>No PPI (N=13,003)</td>
<td>PPI (N=7,593)</td>
<td>Clopidogrel</td>
<td>Timing: 1 year&lt;br&gt;Composite (primary)&lt;br&gt;Total mortality&lt;br&gt;CV mortality&lt;br&gt;Nonfatal MI Stroke&lt;br&gt;(secondary)&lt;br&gt;Nonfatal MI&lt;br&gt;CV mortality&lt;br&gt;Individual&lt;br&gt;CV mortality&lt;br&gt;Stroke&lt;br&gt;Gastroduodenal bleeding&lt;br&gt;Other bleeding</td>
<td>Good</td>
</tr>
<tr>
<td>Ren, 201124</td>
<td>RCT Single site in Asia Funding: NR Timeframe: NR</td>
<td>Omeprazole 20 mg (N=86) Duration: 30 days</td>
<td>Placebo (N=82)</td>
<td>Aspirin 100 mg Clopidogrel 75 mg</td>
<td>Timing: 30 days&lt;br&gt;Individual&lt;br&gt;Slight chest pressure&lt;br&gt;Occasional angina&lt;br&gt;Transient ischemic attack&lt;br&gt;Major bleeding</td>
<td>Poor</td>
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<td>Study</td>
<td>Study Details</td>
<td>Intervention</td>
<td>Comparator</td>
<td>Cointervention</td>
<td>Timing Outcomes Reported</td>
<td>Quality</td>
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<td>Rossini, 2011&lt;sup&gt;25&lt;/sup&gt;</td>
<td>Observational 2 sites in Europe Funding: NR Timeframe: NR Population 18% unstable angina 22% NSTEMI 29% STEMI 31% stable coronary artery disease Total N: 1,346 Mean Age: 63 to 64 Female: 24% Race: NR</td>
<td>PPI (N=1,158)</td>
<td>No PPI (N=170)</td>
<td>Aspirin 100 mg/day Clopidogrel 75 mg/day GPIs</td>
<td>Timing: 1 year Composite Total mortality Nonfatal MI Stroke Rehospitalization Individual Major bleeding Minor bleeding Total mortality Stent thrombosis</td>
<td>Good</td>
</tr>
<tr>
<td>Sarafoff, 2010&lt;sup&gt;26&lt;/sup&gt;</td>
<td>Observational 2 sites in Europe Funding: NR Timeframe: 07/2002–12/2006 Population N=781 unstable angina N=2,208 stable coronary artery disease Total N: 3,408 Mean Age: 66 to 69 Female: 24% Race: NR</td>
<td>PPI (N=698)</td>
<td>No PPI (N=2,640)</td>
<td>Clopidogrel, aspirin Clopidogrel 75 mg 2 times/day together with aspirin 100 mg 2 times/day</td>
<td>Timing: 30 days Composite (secondary) Nonfatal MI Stent thrombosis Individual Stent thrombosis Total mortality Nonfatal MI Major bleeding</td>
<td>Good</td>
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<td>Study</td>
<td>Study Details</td>
<td>Intervention</td>
<td>Comparator</td>
<td>Cointervention</td>
<td>Timing Outcomes Reported</td>
<td>Quality</td>
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</tbody>
</table>
| Schmidt, 2012^{27} | Observational
NR sites in Europe
Funding: Private foundation
Timeframe: 01/2002–06/2005
Population
30.7% unstable angina
Total N: 13,001
Mean Age: NR
Female: 28%
Race: NR | PPI
(N=2,742) | No PPI
(N=10,259) | Clopidogrel 75 mg maintenance | Timing: In-hospital
Composite
(primary)
CV mortality
Nonfatal MI
Stroke
Stent thrombosis
Target lesion
revascularization
Individual
CV mortality
Nonfatal MI
Target lesion
revascularization | Poor |
| Simon, 2011^{28} | Observational
223 sites in Europe
Funding: Private foundation, Industry
Population
NSTEMI: % unreported
STEMI: % unreported
Unstable angina: 0%
Total N: 2,744
Mean Age: 64 to 74
Female: 29.8%
Race: NR | Clopidogrel at 48 hrs
No PPI
(N=900) | No clopidogrel
No PPI
(N=233) | Clopidogrel | Timing: In-hospital, 1 year
Composite
Total mortality
Nonfatal MI
Stroke
Individual
Total mortality
Nonfatal MI
Stroke
Major bleeding | Good |
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<th>Study</th>
<th>Study Details</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Cointervention</th>
<th>Timing Outcomes Reported</th>
<th>Quality</th>
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<tr>
<td>Stockl, 2010۵۹</td>
<td>Observational&lt;br&gt;NR sites in US&lt;br&gt;Funding: NR&lt;br&gt;Timeframe: 01/2004–12/2006 &lt;br&gt;Population: NR &lt;br&gt;Total N: 2,066 &lt;br&gt;Mean Age: 69 &lt;br&gt;Female: 44% &lt;br&gt;Race: NR</td>
<td>PPI (N=1,033)</td>
<td>No PPI (N=1,033)</td>
<td>Clopidogrel</td>
<td>Timing: 1 year&lt;br&gt;Individual&lt;br&gt;Rehospitalization</td>
<td>Good</td>
</tr>
<tr>
<td>Tentzeris, 2010۵۰</td>
<td>Observational&lt;br&gt;Single site in Europe Funding: Private foundation Timeframe: 01/2003–12/2006 &lt;br&gt;Population 45% ACS &lt;br&gt;Total N: 1,210 &lt;br&gt;Mean Age: 64 &lt;br&gt;Female: 31% &lt;br&gt;Race: NR</td>
<td>PPI (N=691)</td>
<td>No PPI (N=519)</td>
<td>Clopidogrel, aspirin (Aspirin (100 mg/day after loading of 250 mg intravenously), clopidogrel (75 mg/day after loading of 300 mg or 600 mg))</td>
<td>Timing: 1 year&lt;br&gt;Composite Total mortality&lt;br&gt;Rehospitalization&lt;br&gt;Stent thrombosis&lt;br&gt;Individual Total mortality&lt;br&gt;CV mortality&lt;br&gt;Rehospitalization&lt;br&gt;Stent thrombosis</td>
<td>Good</td>
</tr>
<tr>
<td>Tsai, 2011۵۱</td>
<td>Observational&lt;br&gt;NR sites in Asia&lt;br&gt;Funding: NR&lt;br&gt;Timeframe: 01/2001–12/2006 &lt;br&gt;Population: NR &lt;br&gt;Total N: 3,580 &lt;br&gt;Mean Age: 71 &lt;br&gt;Female: 38% &lt;br&gt;Race: NR</td>
<td>Clopidogrel + PPI (N=1,052) 3rd treatment arm: aspirin + PPI (N=1,203)</td>
<td>Clopidogrel (N=1,325)</td>
<td>NR</td>
<td>Timing: 1 year&lt;br&gt;Composite (primary)&lt;br&gt;Nonfatal MI&lt;br&gt;Stroke&lt;br&gt;Rehospitalization&lt;br&gt;Individual&lt;br&gt;GI events</td>
<td>Good</td>
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<td>Study</td>
<td>Study Details</td>
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<td>Cointervention</td>
<td>Timing Outcomes Reported</td>
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</table>
| Valkhoff, 2011 | Observational  
Single site in Europe  
Funding:  
Private foundation  
Timeframe:  
01/1999–12/2008  
Population:  
NR  
Total N: 23,655  
Mean Age: 65  
Female: 33%  
Race: NR | PPI  
(N=NR)  
No PPI  
(N=NR)  
Clopidogrel | Timing: 1 year  
Individual  
Nonfatal MI | Poor |
| Van Boxel, 2010 | Observational  
Multiple sites in Europe  
Funding:  
Industry  
Timeframe:  
01/2006–12/2007  
Population:  
NSTEMI % unknown  
STEMI % unknown  
Total N: 18,139  
Mean Age: 66 to 69  
Female: 36%  
Race: NR | Clopidogrel + PPI  
(N=5,734)  
Clopidogrel  
(N=12,405) | NR | Timing: 30 days, 1 year  
Composite  
(primary)  
Total mortality  
Nonfatal MI  
Stroke  
Unstable angina  
Individual  
Nonfatal MI  
Unstable angina  
Stroke  
Total mortality  
Peptic ulcer disease | Fair |
<table>
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<tr>
<th>Study</th>
<th>Study Details</th>
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<th>Cointervention</th>
<th>Timing Outcomes Reported</th>
<th>Quality</th>
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<tbody>
<tr>
<td></td>
<td>Population: N=5,862 ACS</td>
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<td>Composite (primary)</td>
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<td>Total N: 6,300</td>
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<td>Total mortality</td>
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<td>Mean Age: 66</td>
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<td>Rehospitalization</td>
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<td></td>
<td>Female: NR</td>
<td></td>
<td></td>
<td></td>
<td>Individual</td>
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<td></td>
<td>Race: NR</td>
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<td>Rehospitalization</td>
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<td>Revascularization</td>
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<td></td>
<td></td>
<td></td>
<td>Total mortality</td>
<td></td>
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<tr>
<td>Zairis, 2010³⁵</td>
<td>Observational Single site in Europe Funding: NR Timeframe: 04/2003–01/2005</td>
<td>Omeprazole (N=340)</td>
<td>No PPI (N=248)</td>
<td>Aspirin 100–325 mg Clopidogrel 75 mg</td>
<td>Timing: 1 year</td>
<td>Good</td>
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<td></td>
<td>Population: 37% STEMI, 23% Stable angina, 40% UA/NSTEMI</td>
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<td>Composite (primary)</td>
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<td>Total N: 588</td>
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<td>CV mortality</td>
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<td></td>
<td>Mean Age: 62</td>
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<td></td>
<td>Rehospitalization</td>
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<td></td>
<td>Female: 18%</td>
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<td></td>
<td>Individual</td>
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<td></td>
<td>Race: NR</td>
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<td>Rehospitalization</td>
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<td>Revascularization</td>
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<td>Stent thrombosis</td>
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Abbreviations: ACS=acute coronary syndrome; CV=cardiovascular; GI=gastrointestinal; GPI=glycoprotein inhibitor; mg=milligram/milligrams; MI=myocardial infarction; NR=not reported; PPI=proton pump inhibitor; RCT=randomized controlled trial; STEMI=ST segment elevation myocardial infarction; UA/NSTEMI=unstable angina/non-ST segment elevation myocardial infarction
REFERENCES CITED IN APPENDIX TABLE


13. Harjai KJ, Shenoy C, Orshaw P, Usmani S, Boura J, Mehta RH. Clinical outcomes in patients with the concomitant use of clopidogrel and proton pump inhibitors after


31. Tsai YW, Wen YW, Huang WF, Chen PF, Kuo KN, Hsiao FY. Cardiovascular and gastrointestinal events of three antiplatelet therapies: clopidogrel, clopidogrel plus


