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.

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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.2-3 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).4,5 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.4-10

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

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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 observation 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 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.

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 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 ≥2 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. 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 I in the Data Supplement). Four studies, consisting of 3 RCTs and 1 observational study in 5183 patients with UA/NSTEMI, assessed the effect of omeprazole added to DAPT; and 1 RCT compared esomeprazole with famotidine for the prevention of gastrointestinal bleeding. The other 30 studies, all observational, assessed the
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\(^1\) 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\(^4\) 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.\(^5,8,13,17,18,22,23,25,27,30–32,34,37,39,42,43\)

- Not English language: 1
- Not a clinical study: 102
- Not a full publication, not original data, not peer reviewed literature, or not gray literature meeting specified criteria: 56
- Study population did not have UA/NSTEMI: 256
- Did not include an active comparator: 576
- Did not include primary or secondary outcomes of interest: 281

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 overall estimate for the propensity-adjusted HRs was 1.34. \( (\chi^2 = 0.111 \text{ for } 1 \text{ degree of freedom}; \ P = 0.739) \). Figure 2A shows the random-effects combined estimate was 1.27 (95% CI, 1.12–1.43; \( P < 0.001 \); moderate-strength evidence).

### Effect on Composite End Point of All-Cause Mortality or Nonfatal MI at ≈1 Year

Three observational studies with 60,389 patients reported the effect of any PPI on all-cause mortality or MI at 6 to 18 months.\(^13,23,31\) One reported only standard-adjusted results, and 2 reported both standard and propensity-adjusted results. The overall estimate for the standard-adjusted HRs was 1.21, the estimate for the propensity-adjusted HRs was 1.31 (\( \chi^2 = 0.265 \text{ for } 1 \text{ degree of freedom}; \ P = 0.607 \)). Figure 2B shows that the random-effects combined estimate was 1.27 (95% CI, 1.12–1.43; \( P < 0.001 \); moderate-strength evidence).

### Effect on All-Cause Mortality at ≈1 Year

Three studies of omeprazole (2 RCTs and 1 observational) reported all-cause or cardiovascular mortality within at 6 to 18 months.\(^21\) 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\(^1\) 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\(^4\) 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,\(^5,8,9,13,17,18,22,23,25,27,30–32,34,37,39,42\) 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

<table>
<thead>
<tr>
<th>Outcome and Timing</th>
<th>SOE* and Effect Estimate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite ischemic endpoints at ≈1 y</td>
<td>SOE=low (2 RCTs and 21 observational studies; 272,311 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>
</tr>
<tr>
<td>Composite of all-cause mortality or MI at about 1 y</td>
<td>SOE=moderate (3 observational studies; 60,389 patients) Adj HR 1.27 (1.12–1.43); favors no PPI</td>
</tr>
<tr>
<td>All-cause mortality at about 1 y</td>
<td>SOE=moderate (2 RCTs and 18 observational studies; 264,172 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>
</tr>
<tr>
<td>All-cause mortality at 6 y</td>
<td>SOE=low (1 observational study; 23,200 patients) Adj HR 1.32 (1.00–1.73); favors no PPI</td>
</tr>
<tr>
<td>Cardiovascular mortality at 1 y</td>
<td>SOE=insufficient (3 observational studies; 76,184 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>Nonfatal MI at about 1 y</td>
<td>SOE=low (1 RCT and 11 observational studies; 225,567 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 study 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>Stroke at about 1 y</td>
<td>SOE=low (2 RCTs and 5 observational studies; 165,212 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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<tr>
<td>Revascularization at 6 mo</td>
<td>SOE=low (1 RCT and 1 observational study; 22,326 patients) Both studies showed no difference in revascularization rates; no difference</td>
</tr>
<tr>
<td>Revascularization at 1 y</td>
<td>SOE=low (5 observational studies; 53,164 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>
</tr>
<tr>
<td>Revascularization at 4 y</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>
<th>SOE* and Effect Estimate (95% CI)</th>
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<tbody>
<tr>
<td>Stent thrombosis at about 1 y</td>
<td>SOE=low (1 RCT and 7 observational studies; 45,198 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>
</tr>
<tr>
<td>Major bleeding at 30 d</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>
</tr>
<tr>
<td>Major bleeding at about 1 y</td>
<td>SOE=low (4 observational studies; 36,231 patients) Adj HR 1.26 (1.12–1.41); favors no PPI</td>
</tr>
<tr>
<td>GI bleeding</td>
<td>SOE=moderate (4 RCTs and 4 observational studies; 28,032 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>Minor bleeding</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>Rehospitalization at 3 mo</td>
<td>SOE=low (1 observational study; 5862 patients) Significant increase in rehospitalization in PPI group at 3 mo: adj HR 1.32 (1.00–1.73); favors no PPI</td>
</tr>
<tr>
<td>Rehospitalization at about 1 y</td>
<td>SOE=insufficient (4 observational studies; 16,925 patients) Insufficient because of inconsistency and imprecision: adj HR 1.70 (0.86–3.34)</td>
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</table>

*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.

report 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 RCT35 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 study44 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.5,9,17,18,23,27,31,35,41,42 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,$^{8,11,12,27,36}$ 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.$^{13}$ As a sensitivity analysis, we performed a meta-analysis where we used only the adjusted HR from the Banerjee study.$^{13}$ As a sensitivity analysis, we performed a meta-analysis where we used only the adjusted HR from the Banerjee study.$^{13}$ As a sensitivity analysis, we performed a meta-analysis where we used only the adjusted HR from the Banerjee study.$^{13}$

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.

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$^{20}$ 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 different 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$^{20}$ 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**
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 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).
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<0.001), I²=83.425: 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 indicates standard-adj usted hazard ratio; CI, confidence interval; P, propensity-adjusted hazard ratio; and UA/NSTEMI, unstable angina/non–ST-segment–elevation myocardial infarction.

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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 concurrent 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. 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. 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. In the above example of the comparison of the risk of adverse events with and without PPI treatment, the summary estimate for the standard-adjusted HRs is closer to 1 than the 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.

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.

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Disclosures
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References


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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## Appendix Table. Study Characteristics

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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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</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  
Individual Total mortality  
Revascularization | 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>
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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>
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<tr>
<td></td>
<td>Population NR Total N: 3,761 Median Age: 69 Female: 32% Race: NR</td>
<td>Duration: 12 months</td>
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<td>Bhurke, 2012²</td>
<td>Observational Multiple sites in US Funding: Government Timeframe: 01/2001–12/2008</td>
<td>Clopidogrel + PPI (N=2,674)</td>
<td>Clopidogrel (N=2,674)</td>
<td>NR</td>
<td>Timing: 1 year Composite (primary) Nonfatal MI Stents Nonstenting revascularization Intermediate coronary syndrome Individual Nonfatal MI Stents</td>
<td>Fair</td>
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<td></td>
<td>Population 100% ACS Total N: 5,348 Mean Age: 61 Female: 30 % Race: NR</td>
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<td>Charlot, 2010&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Observational NR sites in Europe Funding: Private foundation Timeframe: 2000–2006</td>
<td>No PPI (N=22,815)</td>
<td>No PPI (N=17,949)</td>
<td>No clopidogrel</td>
<td>Timing: 1 year Composite (primary) CV mortality Nonfatal MI Stroke Individual Total mortality CV mortality Nonfatal MI Stroke</td>
<td>Good</td>
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<tr>
<td></td>
<td>Population: NR</td>
<td>PPI (N=8,889)</td>
<td>PPI (N=6,753)</td>
<td>Clopidogrel</td>
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<td>Total N: 56,406 Mean Age: 68.5 Female: 41% Race: NR</td>
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<td>Population: ACS N=19,925</td>
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<td></td>
<td>Total N: 49,452 Mean Age: 64 to 73 Female: 76% Race: NR</td>
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<td>Chitose, 2012(I) KICS Study</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>Gaspar, 201010</td>
<td>Observational&lt;br&gt;Single site in Europe&lt;br&gt;Funding: NR&lt;br&gt;Timeframe: 12/2004–03/2008&lt;br&gt;Population&lt;br&gt;65% UA/NSTEMI&lt;br&gt;35% STEMI&lt;br&gt;Total N: 876&lt;br&gt;Mean Age: 61 to 65&lt;br&gt;Female: 24%&lt;br&gt;Race: NR</td>
<td>PPI (N=274)</td>
<td>No PPI (N=528)</td>
<td>Clopidogrel, aspirin, GPIs</td>
<td>Timing: 6 months&lt;br&gt;Composite (primary)&lt;br&gt;Total mortality&lt;br&gt;Nonfatal MI&lt;br&gt;Unstable angina&lt;br&gt;Individual&lt;br&gt;Total mortality</td>
<td>Good</td>
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<td>Goodman, 201211</td>
<td>Observational&lt;br&gt;43 sites in US, Canada, UK, Europe, South America, Central America, Asia, Africa, Australia/New Zealand&lt;br&gt;Funding: Industry&lt;br&gt;Timeframe: 10/2006–07/2008&lt;br&gt;Population&lt;br&gt;N=3,111 unstable angina&lt;br&gt;N=7,950 NSTEMI&lt;br&gt;N=7,023 STEMI&lt;br&gt;Total N: 18,624&lt;br&gt;Median Age: 62 to 63&lt;br&gt;Female: 28%&lt;br&gt;Race: Black 1%, Asian 6%, White 92%</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)&lt;br&gt;Clopidogrel (N=9,291; 300 mg loading, 75 mg/day maintenance)</td>
<td>Timing: 1 year&lt;br&gt;Composite (primary)&lt;br&gt;CV mortality&lt;br&gt;Nonfatal MI&lt;br&gt;Stroke&lt;br&gt;(secondary)&lt;br&gt;CV mortality&lt;br&gt;Nonfatal MI&lt;br&gt;Individual&lt;br&gt;Total mortality&lt;br&gt;CV mortality&lt;br&gt;Nonfatal MI&lt;br&gt;Major bleeding&lt;br&gt;Stent thrombosis</td>
<td>Good</td>
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<td>Gupta, 2010¹²</td>
<td>Observational&lt;br&gt;Single site in US&lt;br&gt;Funding: NR&lt;br&gt;Timeframe: 01/2003–08/2004&lt;br&gt;Population: NR&lt;br&gt;Total N: 315&lt;br&gt;Mean Age: 62&lt;br&gt;Female: NR&lt;br&gt;Race: NR</td>
<td>PPI (N=72)</td>
<td>No PPI (N=243)</td>
<td>Clopidogrel 75 mg/day</td>
<td>Timing: 4 years&lt;br&gt;Composite (primary)&lt;br&gt;Total mortality&lt;br&gt;Nonfatal MI&lt;br&gt;Target vessel failure&lt;br&gt;Individual&lt;br&gt;Total mortality&lt;br&gt;Target lesion revascularization&lt;br&gt;Target vessel failure</td>
<td>Fair</td>
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<td>Harjai, 2011¹³</td>
<td>Observational&lt;br&gt;NR sites in US&lt;br&gt;Funding: NR&lt;br&gt;Timeframe: 07/2001–12/2007&lt;br&gt;Population&lt;br&gt;39% NSTEMI&lt;br&gt;Total N: 2,653&lt;br&gt;Mean Age: 64 to 66&lt;br&gt;Female: 31%&lt;br&gt;Race: NR</td>
<td>PPI (N=1,902)</td>
<td>No PPI (N=751)</td>
<td>Aspirin</td>
<td>Timing: 6 months&lt;br&gt;Composite (primary)&lt;br&gt;Total mortality&lt;br&gt;Nonfatal MI&lt;br&gt;Revascularization&lt;br&gt;Stent thrombosis&lt;br&gt;Individual&lt;br&gt;Total mortality&lt;br&gt;Nonfatal MI&lt;br&gt;Revascularization&lt;br&gt;Stent thrombosis&lt;br&gt;Major bleeding</td>
<td>Good</td>
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<td>Ho, 2009(^{14})</td>
<td>Observational 127 sites in US Funding: Government Timeframe: 10/2003–12/2006 Population 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 Composite (primary) Total mortality Rehospitalization Individual Rehospitalization Revascularization Total mortality</td>
<td>Good</td>
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<tr>
<td>Hsiao, 2011(^{15})</td>
<td>Observational NR sites in Asia Funding: Private foundation Timeframe: 01/2001–12/2006 Population N=9,753 ACS 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 Individual Rehospitalization</td>
<td>Good</td>
</tr>
<tr>
<td>Juurlink, 2009(^{16})</td>
<td>Observational NR sites in Canada Funding: Government, private foundation Timeframe: 04/2002–12/2007 Population: NR Total N: 2,791 Median 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 Individual Total mortality Nonfatal MI</td>
<td>Good</td>
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<td>Ng, 2008</td>
<td>Observational&lt;br&gt;38 sites in Asia&lt;br&gt;Funding: None&lt;br&gt;Timeframe: 01/2002–12/2006&lt;br&gt;Population&lt;br&gt;N=375 unstable angina&lt;br&gt;Total N: 666&lt;br&gt;Mean Age: 72&lt;br&gt;Female: NR&lt;br&gt;Race: NR</td>
<td>PPI (N=336)</td>
<td>No PPI (N=290)</td>
<td>Clopidogrel, aspirin, enoxaparin</td>
<td>Timing: 7 days&lt;br.Individual GI bleeding&lt;br.GI bleeding/occult bleeding</td>
<td>Good</td>
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<tr>
<td>Ng, 2012⁹</td>
<td>RCT</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 (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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Population

Total N: 311
Mean Age: 63 to 64
Female: 25%
Race: NR
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<tr>
<td>O’Donoghue, 2009²⁰</td>
<td>Observational 707 international sites Funding: Industry Timeframe: 11/2004–1/2007 Population 74% UA/NSTEMI 26% STEMI Total N: 13,608 Median Age: 61 Female: 26% Race: 93% White</td>
<td>PPI</td>
<td>No PPI</td>
<td>Aspirin 75–162 mg/day 3% of patients received bivalirudin 55% of patients received GPs</td>
<td>Timing: 3 months, 6 months Composite (primary) CV mortality Nonfatal MI Stroke (secondary) Major bleeding Minor bleeding Individual Total mortality CV mortality Nonfatal MI Stent thrombosis Major bleeding</td>
<td>Good</td>
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| Ortolani, 2012<sup>21</sup> | 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<sup>22</sup> | 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>
<td>Ray, 2010²³</td>
<td>Observational Study Details: NR sites in US Funding; Government Timeframe: 01/1999–12/2005; Population: NR; Total N: 20,596; Mean Age: 60 to 61; Female: 50%; Race: White 78%</td>
<td>No PPI (N=13,003)</td>
<td>PPI (N=7,593)</td>
<td>Clopidogrel</td>
<td>Timing: 1 year; Composite (primary); Total mortality; CV mortality; Nonfatal MI Stroke (secondary); Nonfatal MI; CV mortality</td>
<td>Good</td>
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<tr>
<td>Ren, 2011²⁴</td>
<td>RCT Study Details: Single site in Asia; Funding: NR; Timeframe: NR; Population: 100% ACS; Total N: 168; Mean Age: 62; Female: 28%; Race: White 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; Individual; Slight chest pressure; Occasional angina; Transient ischemic attack; Major bleeding</td>
<td>Poor</td>
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| Rossini, 201125  | 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 | PPI  
(N=1,158) | No PPI  
(N=170) | Aspirin 100 mg/day Clopidogrel 75 mg/day GPIs | Timing: 1 year  
Composite Total mortality  
Nonfatal MI  
Stroke  
Rehospitalization  
Individual Major bleeding Minor bleeding Total mortality Stent thrombosis | Good     |
| Sarafoff, 201026 | Observational 2 sites in Europe  
Funding: NR  
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 | PPI  
(N=698) | No PPI  
(N=2,640) | Clopidogrel, aspirin Clopidogrel 75 mg 2 times/day together with aspirin 100 mg 2 times/day | Timing: 30 days  
Composite (secondary)  
Nonfatal MI  
Stent thrombosis  
Individual  
Stent thrombosis  
Total mortality  
Nonfatal MI  
Major bleeding | Good     |
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<td>Schmidt, 2012&lt;sup&gt;27&lt;/sup&gt;</td>
<td>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</td>
<td>PPI (N=2,742)</td>
<td>No PPI (N=10,259) Clopidogrel 75 mg maintenance</td>
<td>Timing: In-hospital Composite (primary) CV mortality Nonfatal MI Stroke Stent thrombosis Target lesion revascularization Individual CV mortality Nonfatal MI Target lesion revascularization</td>
<td>Poor</td>
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<td>Simon, 2011&lt;sup&gt;28&lt;/sup&gt; FAST-MI Study</td>
<td>Observational 223 sites in Europe Funding: Private foundation, Industry Timeframe: 10/2005–11/2005 Population NSTE: % unreported STEMI: % unreported Unstable angina: 0% Total N: 2,744 Mean Age: 64 to 74 Female: 29.8% Race: NR</td>
<td>Clopidogrel at 48 hrs No PPI (N=900) PPI (N=1,453) No clopidogrel No PPI (N=233) PPI (N=158)</td>
<td>Clopidogrel</td>
<td>Timing: In-hospital, 1 year Composite Total mortality Nonfatal MI Stroke Individual Total mortality Nonfatal MI Stroke Major bleeding</td>
<td>Good</td>
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<td>Tentzeris, 2010&lt;sup&gt;30&lt;/sup&gt;</td>
<td>Observational Study, Single site in Europe, Funding: Private foundation, Timeframe: 01/2003–12/2006, Population 45% ACS, Total N: 1,210, Mean Age: 64, Female: 31%, Race: NR</td>
<td>PPI (N=691)</td>
<td>No PPI (N=519)</td>
<td>Clopidogrel, 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, Individual, Total mortality CV, Rehospitalization, Stent thrombosis</td>
<td>Good</td>
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<tr>
<td>Valkhoff, 2011(^2)</td>
<td>Observational Single site in Europe Funding: Private foundation Timeframe: 01/1999–12/2008</td>
<td>PPI (N=NR)</td>
<td>No PPI (N=NR)</td>
<td>Clopidogrel</td>
<td>Timing: 1 year</td>
<td>Poor</td>
</tr>
<tr>
<td></td>
<td>Population: NR</td>
<td></td>
<td></td>
<td></td>
<td>Individual Nonfatal MI</td>
<td></td>
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<tr>
<td></td>
<td>Total N: 23,655 Mean Age: 65 Female: 33% Race: NR</td>
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<tr>
<td>Van Boxel, 2010(^3)</td>
<td>Observational Multiple sites in Europe Funding: Industry Timeframe: 01/2006–12/2007</td>
<td>Clopidogrel + PPI (N=5,734)</td>
<td>Clopidogrel (N=12,405)</td>
<td>NR</td>
<td>Timing: 30 days, 1 year</td>
<td>Fair</td>
</tr>
<tr>
<td></td>
<td>Population: NSTEMI % unknown STEMI % unknown</td>
<td></td>
<td></td>
<td></td>
<td>Composite (primary)</td>
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<tr>
<td></td>
<td>Total N: 18,139 Mean Age: 66 to 69 Female: 36% Race: NR</td>
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<td></td>
<td></td>
<td>Total mortality</td>
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<td>Nonfatal MI</td>
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<td>Stroke</td>
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<td>Unstable angina</td>
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<td></td>
<td>Individual Nonfatal MI</td>
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<td>Unstable angina</td>
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<td>Stroke</td>
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<td></td>
<td>Total mortality</td>
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<td></td>
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<td></td>
<td>Peptic ulcer disease</td>
<td></td>
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<tr>
<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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<tr>
<td>Wu, 2010&lt;sup&gt;14&lt;/sup&gt;</td>
<td>Observational NR sites in Asia Funding: Government Timeframe: 07/2002–06/2005</td>
<td>PPI (N=311)</td>
<td>No PPI (N=5,551)</td>
<td>Clopidogrel</td>
<td>Timing: 3 months Composite (primary) Total mortality Rehospitalization Individual Rehospitalization Revascularization Total mortality</td>
<td>Good</td>
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<td>Population N=5,862 ACS</td>
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<td>Total N: 6,300 Mean Age: 66 Female: NR Race: NR</td>
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<td>Population 37% STEMI 23% Stable angina 40% UA/NSTEMI</td>
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<td></td>
<td>Total N: 588 Mean Age: 62 Female: 18% Race: NR</td>
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</table>

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


