

# Review of recent evidence: Potential interaction between clopidogrel and proton pump inhibitors

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Clopidogrel is a thienopyridine platelet-aggregation inhibitor that acts by preventing adenosine diphosphate (ADP) from binding to ADP receptors on platelets.<sup>1</sup> Clopidogrel is indicated for the secondary prevention of atherothrombotic events in patients with a recent myocardial infarction, a recent stroke, an established peripheral arterial disease, or a history of acute coronary syndrome. Dual antiplatelet therapy with clopidogrel and aspirin is recommended by the American College of Cardiology (ACC) and American Heart Association (AHA) for patients who have experienced unstable angina or non-ST-segment-elevated myocardial infarction and either are managed medically or have undergone bare-metal or drug-eluting stent placement.<sup>2,3</sup> In addition, joint recommendations from the ACC Foundation, American College of Gastroenterology (ACG), and AHA state that for patients receiving aspirin therapy, proton pump inhibitors (PPIs) are the preferred agents for the treatment and prevention of gastrointestinal (GI) injury.<sup>4</sup> Other

**Purpose.** Recent evidence of a potential interaction between clopidogrel and proton pump inhibitors (PPIs) is discussed.

**Summary.** The American College of Cardiology and the American Heart Association recommend use of gastroprotective agents, specifically PPIs, in patients receiving aspirin, a thienopyridine, or the combination who have an increased risk for recurrent gastrointestinal bleeding. Available evidence from one small, short-term, randomized, double-blind trial evaluating platelet aggregation and several observational studies suggests that there is a potential for a clinically significant interaction between clopidogrel and PPIs. A post hoc analysis of a large, randomized, double-blind trial found no evidence of a clinically significant drug interaction at 28 days, though a significant difference was observed at one year. The authors

concluded that the use of PPIs, regardless of clopidogrel use, increases the risk of adverse cardiovascular events.

**Conclusion.** Although data are limited, observational studies and prospective trials involving surrogate markers of platelet reactivity suggest a clinically significant interaction between clopidogrel and PPIs. Until further studies are completed to delineate the specifics of the interaction between clopidogrel and PPIs, the risks and benefits of concomitant treatment should be carefully weighed to determine the most appropriate treatment for each individual patient.

**Index terms:** Cardiovascular diseases; Clopidogrel; Drug interactions; Gastrointestinal drugs; Platelet aggregation inhibitors; Toxicity

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medications available for the treatment and prevention of GI injury with aspirin use are misoprostol, sucralfate, and histamine H<sub>2</sub>-receptor antagonists.<sup>4</sup> The usefulness of these agents is limited by adverse effects, as with misoprostol, or inferior efficacy in both prevention and treatment

of GI injury, as with sucralfate. Although high-dose H<sub>2</sub>-receptor antagonists have been used to prevent the GI injury that occurs with nonsteroidal antiinflammatory drugs, no evidence-based recommendations for their use are made in current ACG guidelines.<sup>5</sup> Results from one small

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recent trial evaluating the use of oral famotidine 20 mg twice daily showed that famotidine effectively prevented GI injury in patients receiving low-dose aspirin.<sup>6</sup> There is little conclusive evidence that supports the use of PPIs to reduce the risk of GI bleeding in patients receiving dual antiplatelet therapy who have a history of upper GI bleeding or ulceration. However, ACC and AHA recommend the use of gastroprotective agents, specifically PPIs, in patients receiving aspirin, a thienopyridine derivative, or the combination who have an increased risk for recurrent GI bleeding.<sup>2</sup> Therefore, the use of clopidogrel and PPIs in combination has become common practice.<sup>7</sup>

In a joint statement issued in November 2008, ACC, ACG, and AHA stated that the results of an outcomes study exploring a possible interaction between clopidogrel and PPIs did not provide sufficient evidence to warrant a change in practice.<sup>8,9</sup> However, additional concerns have recently been raised about a possible interaction between clopidogrel and PPIs.<sup>10</sup> Clopidogrel is a prodrug that must be metabolized to its active form by cytochrome P-450 (CYP) isoenzymes; underexpression of CYP 2C19 has been linked to decreased clopidogrel activity and increased cardiovascular events.<sup>11</sup> Because PPIs, including lansoprazole, omeprazole, esomeprazole, pantoprazole, and rabeprazole, are metabolized by CYP 2C19 to various extents, competitive inhibition may explain an interaction between clopidogrel and PPIs.<sup>12</sup> While CYP 2C19 inhibition is the most likely

mechanism, other possible theories have been identified.<sup>13</sup>

### Literature review

A PubMed search was conducted using the keywords “clopidogrel” and “proton pump inhibitors” to identify studies that evaluated a potential drug interaction between clopidogrel and PPIs. Reference lists of recent publications on this topic were also evaluated for relevant publications. Press releases were used to identify information presented in abstracts or popular media concurrent with scientific meeting presentations. Studies involving healthy subjects were excluded.

**Effect on platelet inhibition.** After results from a small observational study demonstrated decreased clopidogrel response in patients receiving PPIs,<sup>14</sup> the Omeprazole Clopidogrel Aspirin (OCLA) study was conducted to further evaluate the effect of omeprazole on the antiplatelet action of clopidogrel.<sup>15</sup> This was a randomized, double-blind, placebo-controlled study that included 140 patients undergoing coronary artery stent placement. Enrolled patients were receiving dual antiplatelet therapy and were randomized to receive either omeprazole 20 mg orally daily or placebo for seven days. The primary endpoint of the trial was the platelet reactivity index (PRI), a measure of platelet reactivity to clopidogrel for which a higher value indicates more frequent thrombosis with clopidogrel treatment (i.e., decreased clopidogrel response). The results indicated that omeprazole significantly decreased the antiplatelet activity of clopidogrel compared with placebo. The mean  $\pm$  S.D. PRI at baseline, as measured by platelet-phosphorylated vasodilator-stimulated phosphoprotein (VASP), was  $83.2\% \pm 5.6\%$  in the placebo group and  $83.9\% \pm 4.3\%$  in the omeprazole-treated group. After seven days of treatment, the mean  $\pm$  S.D. PRI was  $39.8\% \pm 15.4\%$  in the placebo group and  $51.4\% \pm 16.4\%$  in

the omeprazole-treated group ( $p < 0.0001$ ). Poor response was defined as a PRI of  $>50\%$ . The authors classified 26.7% of placebo-treated patients and 60.9% of omeprazole-treated patients as poor responders to clopidogrel. The PRI is a more specific method for measuring clopidogrel response compared with other measures. However, there was considerable variability in platelet response in both treatment groups of the OCLA trial.<sup>15</sup> Factors that may contribute to variability in clopidogrel response include compliance with therapy, variable intestinal absorption, differences in platelet response to ADP, and genetic differences in CYP metabolic activity.<sup>8</sup> Although the groups evaluated had similar PRIs at baseline, the results could have been affected by failure to exclude clopidogrel nonresponders, as a subset of patients may not have a therapeutic response to clopidogrel, regardless of PPI use.<sup>11</sup> The clinical implications of this trial are limited by the short study duration and the use of surrogate laboratory endpoints.

Siller-Matula et al.<sup>16</sup> assessed the effects of pantoprazole and esomeprazole on the antiplatelet action of clopidogrel. In this study, the mean PRIs, as measured by VASP, were recorded for 300 patients undergoing percutaneous coronary intervention (PCI) who had received dual antiplatelet therapy for an average of 90 days. The mean PRI for patients treated with any PPI was 51% (95% confidence interval [CI], 48–54%), while patients not treated with a PPI had a mean PRI of 49% (95% CI, 43–55%). The mean PRI for the PPIs studied was 50% for pantoprazole ( $n = 152$ ) and 54% for esomeprazole ( $n = 74$ ). The authors concluded that the interaction previously reported between omeprazole and clopidogrel<sup>14,15</sup> was not observed with esomeprazole or pantoprazole.<sup>16</sup> The authors further suggested that the drug interaction may be specific to omeprazole and is likely

not a class effect. However, the lack of baseline PRI data severely limits conclusions about the similarity in PRIs between the two groups. In addition, the mean PRI for patients receiving any PPI in this trial (51%) was similar to the PRI reported for the omeprazole-treated group in the OCLA trial (51.4%),<sup>15</sup> implying a similar effect among the different PPIs (omeprazole, esomeprazole, and pantoprazole) and suggesting that the observed findings represent a class drug interaction.

Sibbing et al.<sup>17</sup> examined the effects of concomitant clopidogrel and PPI use (pantoprazole, omeprazole, and esomeprazole) on ADP-induced platelet aggregation assessed using multiple-electrode platelet aggregometry. This study included 1000 patients with coronary artery disease who had undergone PCI and were receiving chronic dual antiplatelet therapy. While a significant increase in platelet aggregation ( $p = 0.001$ ) was demonstrated in patients receiving omeprazole ( $n = 64$ ) compared to those not receiving a PPI ( $n = 732$ ), no significant difference was seen between patients receiving pantoprazole ( $n = 162$ ) or esomeprazole ( $n = 42$ ) and those not receiving a PPI ( $p = 0.69$  and  $p = 0.88$ , respectively). In addition, a higher percentage of patients receiving omeprazole (32.8%) were classified by the authors as having a low response to clopidogrel compared with patients not receiving omeprazole (19.1%,  $p = 0.008$ ). When patients receiving either pantoprazole or esomeprazole were compared with patients not treated with the medications, no significant differences in the number of low responders were found. Further analysis revealed that diabetes mellitus, body mass index, renal insufficiency, active smoking, previous myocardial infarction, and platelet count were independently associated with decreased platelet response. The small numbers of patients receiving omeprazole and esomeprazole versus

pantoprazole limit the interpretation of these results.

**Effect on patients' clinical outcomes.** Four observational studies and one post hoc analysis of a prospective trial were conducted to examine the clinical relevance of an interaction between clopidogrel and PPIs.<sup>18-24</sup> Pezalla et al.<sup>18</sup> used data from medical and pharmacy databases to conduct a retrospective cohort study of patients younger than 65 years old who were adherent to clopidogrel therapy for 1 year. Patients were divided into three treatment groups: clopidogrel with no PPI ( $n = 4800$ ), clopidogrel with low PPI exposure ( $n = 712$ ), and clopidogrel with high PPI exposure ( $n$  not given). Low and high PPI exposures were not defined, and the specific PPIs included were not stated. One-year acute myocardial infarction (AMI) rates were 1.38% for the control group, 3.08% for patients with low PPI exposure, and 5.03% for patients with high PPI exposure ( $p < 0.05$  versus control). Significant differences between groups with regard to comorbid conditions may limit the applicability of these findings. For example, patients with high PPI exposure were generally more ill, with a greater number of patients having hypertension or diabetes, compared with the other patient groups. However, a significant difference in event rates was still found between the high PPI exposure group and the control group after statistically controlling for these patient differences.

Juurink et al.<sup>19</sup> conducted a population-based, nested case-control study of patients over age 66 years in Ontario, Canada, discharged from the hospital with a diagnosis of acute coronary syndrome (ACS) between April 1, 2002, and December 31, 2007. The authors examined prescription records from the Ontario Public Drug Program and included patients who received a clopidogrel prescription within 3 days of discharge and were followed for 90 days

or until readmission. The use of PPIs, including omeprazole, rabeprazole, lansoprazole, and pantoprazole, was also recorded. Aspirin usage was unknown. A total of 734 patients either died or were readmitted for AMI within 90 days after their initial hospital discharge, and 2057 patients were not readmitted within 90 days (control group). Matching criteria included age (within 3 years), receipt of PCI, date of discharge (within 4 days), and predicted probability of short-term mortality. The authors reported that current use of a PPI was associated with increased odds of reinfarction versus no PPI (adjusted odds ratio [OR], 1.27; 95% CI, 1.03–1.57).<sup>19</sup> No association was found between pantoprazole use and reinfarction when pantoprazole was analyzed separately (adjusted OR, 1.02; 95% CI, 0.7–1.47); a further evaluation revealed increased odds of reinfarction in patients receiving any of the other PPIs (adjusted OR, 1.40; 95% CI, 1.10–1.77). The authors concluded that pantoprazole was not associated with a significant drug interaction with clopidogrel and that pantoprazole should be used when PPI therapy is necessary in a patient receiving clopidogrel. As demonstrated in the study by Pezalla et al.,<sup>18</sup> there were significant differences between study groups in the rates of comorbid conditions, such as acute renal insufficiency (6.1% cases versus 3.3% controls), congestive heart failure (27.7% cases versus 18.0% controls), and diabetes with complications (28.3% cases versus 19.9% controls) ( $p < 0.001$  for all comparisons). Previous research has revealed that diabetes mellitus and renal insufficiency are associated with decreased platelet response to clopidogrel.<sup>17</sup> No information on cardiovascular disease risk factors, including smoking, was reported.<sup>19</sup> It is also important to note that the subgroup analysis of patients treated with pantoprazole was likely underpowered ( $n = 46$  cases,  $n = 125$  controls) to determine

an association between pantoprazole and clopidogrel use and reinfarction. Subgroup analyses examining each of the other PPIs individually in combination with clopidogrel were not performed.

Ho et al.<sup>20</sup> conducted a retrospective study of patients with documented AMI or unstable angina discharged from 1 of 127 Veterans Affairs facilities with a prescription for clopidogrel between October 2003 and January 2006. The investigators identified 8205 patients who received a prescription for clopidogrel with or without a PPI at discharge or during follow-up as determined from pharmacy refill data. The PPIs evaluated in this study included omeprazole ( $n = 3132$ , 59.7%), rabeprazole ( $n = 151$ , 2.9%), lansoprazole ( $n = 22$ , 0.4%), and pantoprazole ( $n = 15$ , 0.2%), with 1924 patients (36.7%) receiving more than one PPI. Approximately 90% of patients also received aspirin at discharge. Of the 5244 patients who received clopidogrel with a PPI, 3291 received the PPI at discharge and 1953 received it during follow-up. The authors also identified 2961 patients who received clopidogrel without a PPI. The results indicated an increased risk of death or rehospitalization for ACS with clopidogrel in combination with a PPI after discharge (adjusted OR, 1.25; 95% CI, 1.11–1.41). In addition, periods of concomitant clopidogrel and PPI use were associated with a higher risk of death or rehospitalization for ACS than periods without concomitant use (adjusted OR, 1.27; 95% CI, 1.10–1.46). As with other observational studies, patients in the group that received PPIs had significantly higher rates of comorbidities at discharge than did patients who did not receive PPIs: diabetes mellitus (45.5% versus 38%), prior myocardial infarction (26.4% versus 20.1%), previous coronary artery bypass graft (26.3% versus 19.8%), heart failure (26.2% versus 16.1%), peripheral vascular disease (25.6%

versus 16.2%), chronic obstructive pulmonary disease (25.7% versus 17%), and renal disease (17.4% versus 9.9%). Because of these differences, it is unclear if the adverse outcomes observed were related to PPI use or to comorbidities. In analyses of patients using individual PPIs, the rates of adverse outcomes were significantly higher with omeprazole (OR, 1.24; 95% CI, 1.08–1.41) and rabeprazole (OR, 2.83; 95% CI, 1.96–4.09) versus no PPI use. Other PPIs were not analyzed individually due to limited usage.

The results of a retrospective cohort study evaluating the effect of PPIs on patients after stent implantation were recently presented by multiple sources.<sup>21–23</sup> Patients were identified using the National Medco Integrated Database and were included if they received clopidogrel post-PCI and submitted a prescription claim for a PPI during the 12-month post-PCI period (from October 1, 2005, through September 30, 2006). The PPIs included in the analysis were esomeprazole ( $n = 3257$ ), omeprazole ( $n = 2307$ ), pantoprazole ( $n = 1653$ ), lansoprazole ( $n = 785$ ), and rabeprazole ( $n = 298$ ). The median duration of overlapping therapy between clopidogrel and a PPI in the patients studied was 293 days (interquartile range, 160–365 days). The authors reported an increased risk of major adverse cardiovascular events over 12 months associated with use of clopidogrel in combination with a PPI (25.1%) versus the use of clopidogrel without a PPI (17.9%) (hazard ratio [HR], 1.51; 95% CI, 1.39–1.64). A subgroup analysis found that each individual PPI was associated with a statistically significant increase in the risk for a major adverse cardiovascular event ( $p \leq 0.004$  for each PPI versus placebo). The rates of such adverse events among patients receiving each PPI and the HRs compared with the group not receiving a PPI were 29.2% for pantoprazole (HR, 1.61; 95% CI, 1.44–1.81), 25.1%

for omeprazole (HR, 1.39; 95% CI, 1.22–1.57), 24.9% for esomeprazole (HR, 1.57; 95% CI, 1.40–1.76), and 24.3% for lansoprazole (HR, 1.39; 95% CI, 1.16–1.67). These data, which are available only in abstract, press release, and slide presentation form, suggest that there may be a class effect interaction between PPIs (including pantoprazole) and clopidogrel. The investigators also examined records of patients who had stents implanted but did not receive clopidogrel ( $n = 1641$ ) to evaluate the risk of major adverse cardiovascular events with PPIs alone. The risk in patients receiving any PPI ( $n = 234$ ) did not differ significantly from that of patients not receiving a PPI ( $n = 1407$ ) (HR, 1.19; 95% CI, 0.84–1.70).

Dunn et al.<sup>24</sup> reported information from a post hoc analysis of data from the Clopidogrel for the Reduction of Events During Observation (CREDO) trial. Data from patients who received clopidogrel plus aspirin with or without a PPI were analyzed. PPI use at baseline was associated with increased cardiovascular events in patients receiving clopidogrel and in all patients included in the trial. PPI use, independent of clopidogrel use, was associated with increased adverse cardiovascular outcomes. The rate of events at 28 days was higher in the clopidogrel plus PPI group (10.3%) than in patients receiving clopidogrel without a PPI (5.4%) but did not differ significantly between groups (OR, 1.794; 95% CI, 0.997–3.227); however, the rate did significantly differ at one year (13.4% versus 7.7%, respectively) (OR, 1.633; 95% CI, 1.015–2.627). These data were available only in abstract form. Further, the small numbers of patients in the groups who received PPIs and the lack of information about baseline characteristics in these patient groups limit the conclusions that may be drawn.

## Discussion

Available evidence from one small,

short-term, randomized, double-blind trial evaluating platelet aggregation and several observational studies indicates that there is the potential for a clinically significant interaction between clopidogrel and PPIs. A post hoc analysis of the CREDO trial—a large, randomized, double-blind trial—suggests that the use of PPIs, regardless of whether they are combined with clopidogrel, increases patients' risk of cardiovascular events. While these findings offer valuable insight, several questions remain. It is unclear if the available data indicate that the observed drug interaction represents a class effect between all PPIs and clopidogrel. Results from platelet-aggregation studies<sup>15,17</sup> and some observational studies<sup>20,23</sup> suggest that an interaction occurs when omeprazole is used concomitantly with clopidogrel. However, in one of the larger observational outcome trials,<sup>23</sup> all PPIs evaluated, including pantoprazole and esomeprazole, were associated with increased adverse cardiovascular events when used concomitantly with clopidogrel. It should also be noted that earlier studies demonstrating no interaction between pantoprazole or esomeprazole and clopidogrel<sup>16,17,19,20</sup> included small numbers of patients receiving these two PPIs, limiting the ability to demonstrate statistical significance.

Limitations of current observational trials are numerous. Significant differences in comorbidities between study groups at baseline could have affected the findings of the studies. Factors that may independently increase platelet aggregation, such as renal insufficiency and diabetes mellitus, were present in more patients in groups that received PPIs than in those that did not. In addition, information about cardiovascular risks, smoking habits, and nonprescription PPI use was not uniformly reported in the available studies.

Although there is a need for information from randomized, controlled

outcomes trials addressing this topic, there are currently no studies of this type in progress. The Clopidogrel and the Optimization of Gastrointestinal Events (COGENT-1) trial was a randomized, double-blind, interventional study designed to compare the use of a combination clopidogrel–omeprazole pill plus aspirin with the use of clopidogrel plus aspirin; however, this study was terminated by the sponsor due to bankruptcy in January 2009.<sup>25</sup> The Evaluation of the Influence of Statins and Proton Pump Inhibitors on Clopidogrel Antiplatelet Effects (SPICE) trial will assess the effect of statins and commonly used PPIs with concomitant dual antiplatelet therapy on the surrogate endpoint of platelet aggregation.<sup>26</sup> This trial is currently recruiting participants and is not expected to be completed until April 2011.

In a May 2009 press release, the Society for Cardiovascular Angiography and Interventions recommended that H<sub>2</sub>-receptor antagonists be considered for the treatment or prevention of GI injury in patients requiring dual antiplatelet therapy.<sup>22</sup> Although the efficacy of H<sub>2</sub>-receptor antagonists in the prevention of GI injury with aspirin use has not been demonstrated in large randomized trials, these agents may be viable alternatives to PPIs for patients receiving aspirin and clopidogrel.<sup>6</sup> In addition, the clopidogrel package insert was updated in May 2009 to include a statement discouraging the concomitant use of clopidogrel and medications that inhibit CYP 2C19, including omeprazole.<sup>1</sup>

### Conclusion

Although data are limited, observational studies and prospective trials involving surrogate markers of platelet reactivity suggest a clinically significant interaction between clopidogrel and PPIs. Until further studies are completed to delineate the specifics of the interaction between

clopidogrel and PPIs, the risks and benefits of concomitant treatment should be carefully weighed to determine the most appropriate treatment for each individual patient.

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### Addendum

Since the time of manuscript preparation, one new publication describing the association between concomitant thienopyridine and PPI use and pharmacodynamic and clinical outcomes has become available. O'Donoghue et al.<sup>1</sup> performed post hoc analyses on data from the PRINCIPLE (Prasugrel In Comparison to Clopidogrel for Inhibition of Platelet Activation and Aggregation)–TIMI 44 and TRITON (Trial to Assess Improvements in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel)–TIMI 38 trials. Both studies included patients assigned to receive either clopidogrel or prasugrel who were to undergo PCI; neither study controlled PPI use. Findings from the PRINCIPLE–TIMI 44 post hoc analysis demonstrated that inhibition of platelet aggregation (IPA) was significantly lower at 2, 6, and 24 hours after a 600-mg clopidogrel loading dose in patients receiving a PPI ( $n = 28$ ), compared with patients not receiving a PPI ( $n = 71$ ,  $p < 0.05$ ). After 15 days of maintenance therapy with 150 mg clopidogrel daily, no significant difference in IPA was noted between these groups. Among patients receiving a 60-mg prasugrel loading dose and a PPI ( $n = 25$ ), IPA was significantly lower at 30 minutes after the loading dose than in patients not receiving a PPI ( $n = 77$ ,  $p < 0.05$ ); however, no significant differences were found at other time points evaluated during the first 24 hours after the loading dose was administered. In contrast to clopidogrel-treated patients, after 15 days of maintenance therapy with prasugrel 10 mg, patients receiving concomitant PPI treatment had significantly decreased IPA ( $p = 0.01$ ).

The post hoc analysis of TRITON–TIMI 38 showed no significant differences in the composite outcome of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke between clopidogrel-treated patients who received a PPI ( $n = 2257$ ) and those who did not receive a PPI ( $n = 4538$ ) or between prasugrel-treated patients who received a PPI ( $n = 2272$ ) and those who did not receive a PPI ( $n = 4541$ ). Additional analyses of each PPI alone demonstrated no association between the concomitant use of any PPI and a thienopyridine and major cardiovascular events.

Although these analyses are limited by their post hoc nature, the results serve to confound the question of the overall clinical significance of an interaction between thienopyridines and PPIs. Therefore, until randomized controlled trials are available to evaluate a potential causal association, the risks and benefits of concomitant clopidogrel and PPI use must be carefully evaluated on an individual patient basis.

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