Review of the Clopidogrel-Proton Pump Inhibitor Interaction

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Upon completing this article the pharmacist should be able to:

OBJECTIVES
1. Describe the proposed mechanism of the interaction between clopidogrel and proton pump inhibitors.
2. Summarize the pharmacologic/pharmacodynamic evidence for the interaction between clopidogrel and proton pump inhibitors.
3. Summarize the clinical evidence for the interaction between clopidogrel and proton pump inhibitors.
4. Describe the Food and Drug Administration’s updated warning on the interaction between clopidogrel and proton pump inhibitors.
5. Describe how to counsel patients and advise prescribers regarding this interaction.

INTRODUCTION
Clopidogrel (Plavix), a thienopyridine, is an established antiplatelet agent used in the prevention and treatment of cardiovascular diseases. Because clopidogrel is a prodrug, it requires hepatic metabolism by CYP450 isozymes to its active compound. The P450 isozymes involved in clopidogrel activation are CYP1A2, 2B6, 2C9, 3A4, and 2C19. Clopidogrel’s active metabolite irreversibly and selectively inhibits adenosine diphosphate (ADP) from binding to its P2Y12 receptor and subsequently inhibits ADP-mediated activation of the glycoprotein GPIIb/IIIa complex which is critical for platelet aggregation.

Variability in clopidogrel responsiveness is well established. It is estimated that as many as one-third of pa-
<table>
<thead>
<tr>
<th>Study</th>
<th>Platelet Function Assay</th>
<th>Sample Size</th>
<th>Study Population</th>
<th>Clopidogrel Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gilard et al., 2006</td>
<td>VASP at least 48 hours</td>
<td>105</td>
<td>High-risk patients on clopidogrel and aspirin undergoing</td>
<td>Esomeprazole</td>
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<tr>
<td></td>
<td></td>
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<td></td>
<td>N/A</td>
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<tr>
<td>Gilard et al., 2008</td>
<td>VASP on day 1 and day 7. Good responder if PRI &lt; 50%; poor responder if PRI &gt; 50%</td>
<td>No PPI 70 Omeprazole 70</td>
<td>Recent elective coronary stent implantation</td>
<td>N/A</td>
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<tr>
<td>Small et al., 2008</td>
<td>Turbidometric platelet aggregometry before and 2–24 h after dose, 5 µM and 20 µM ADP as agonist. Maximum platelet aggregation values were converted to inhibition of platelet aggregation (IPA).</td>
<td>26</td>
<td>Healthy volunteers</td>
<td>N/A</td>
</tr>
<tr>
<td>Siller-Matula et al., 2009</td>
<td>VASP assay within 24 hours after blood sampling &amp; ADP-induced platelet impedance aggregometry (reference 29–118 U). Poor responder if PRI ≥ 69%</td>
<td>No PPI 74 Esomeprazole 74 Pantoprazole 154</td>
<td>Coronary heart disease undergoing PCI</td>
<td>↓</td>
</tr>
<tr>
<td>Sibbing et al., 2009</td>
<td>Impedance platelet aggregometry using multiplate analyzer (Dynabyte, Munich, Germany) during angiography. Low-response defined as upper 20% of patients using multiple electrode aggregometry.</td>
<td>Esomeprazole 42 Omeprazole 64 Pantoprazole 162</td>
<td>Patients with coronary artery disease admitted for a control coronary angiography</td>
<td>↓</td>
</tr>
</tbody>
</table>
patients are resistant to clopidogrel. “Resistance” has been described as the failure to achieve the expected degree of platelet inhibition assessed by platelet function testing. Although most acknowledge the existence of clopidogrel resistance, there is no clear agreement as to what it is and what it means clinically.

The exact mechanism for clopidogrel resistance is not yet clear. Possible mechanisms are genetic polymorphism, decreased clopidogrel absorption, and limited biotransformation to its active compound as a result of cytochrome P450 (CYP) drug interactions. Recent studies suggest that CYP2C19 variants may lead to clopidogrel resistance. A study showed that carriers of at least one CYP2C19 reduced-function allele had lower levels of clopidogrel’s active metabolite, diminished platelet inhibition, and a higher rate of death from cardiovascular cause, myocardial infarction (MI), or stroke than noncarriers. Another study in patients with MI showed that patients carrying two CYP2C19 loss-of-function alleles had a higher rate of death from any cause, nonfatal stroke, or MI than those who were not carriers. In a different study, CYP2C19*2 genotype was associated with diminished platelet response to clopidogrel and poorer cardiovascular outcomes. Moreover, drugs that inhibit the biotransformation of clopidogrel to its active metabolite could reduce clopidogrel responsiveness.

Clopidogrel is currently FDA-indicated for the reduction of atherothrombotic events in patients with recent MI, stroke, and peripheral arterial disease. Dual antiplatelet therapy with aspirin and clopidogrel reduces cardiac events, and the American College of Cardiology and American College of Chest Physicians recommend dual antiplatelet therapy for patients with non-ST-elevation myocardial infarction (NSTEMI), ST-elevation myocardial infarction (STEMI), and after coronary stent implantation. In 2008, the American College of Cardiology Foundation, American College of Gastroenterology, and American Heart Association published an expert consensus document on reducing the gastrointestinal (GI) risks of antiplatelet and non-steroidal, anti-inflammatory drug (NSAID) use.

Protein Pump Inhibitors (PPIs) are preferred for the treatment and prophylaxis of NSAID- and aspirin-associated GI injury. Dual antiplatelet therapy provides more effective platelet inhibition, but increases the risk for bleeding. When dual antiplatelet therapy is used, PPIs are recommended for prophylaxis against medication-induced GI risk.

Recent studies have raised concerns that PPIs may inhibit CYP2C19 and affect the bioactivation of clopido-

Table 1. Summary of Pharmacologic/Pharmacodynamic Evidence (continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Platelet Function Assay</th>
<th>Sample Size</th>
<th>Study Population</th>
<th>Clopidogrel Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zuern et al, 2009</td>
<td>Residual platelet aggregation by turbidometric aggregometry</td>
<td>Esomeprazole 108</td>
<td>Coronary stenting</td>
<td>↓</td>
</tr>
<tr>
<td>Cuisett et al, 2009</td>
<td>VASP</td>
<td>Omeprazole 52</td>
<td>Coronary stenting for non-ST elevation ACS</td>
<td>N/A</td>
</tr>
</tbody>
</table>

*a= Similar for clopidogrel alone and with lansoprazole except IPA decrease of 10% with clopidogrel and lansoprazole at 24 hour assessment only.

ACS=acute coronary syndrome
ADP=adenosine diphosphate
PCI=percutaneous coronary intervention
PPI=proton pump inhibitor
PRI=platelet reactivity index
VASP=vasodilator-stimulator phosphoprotein

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grel. This drug interaction could reduce clopidogrel’s platelet inhibitory effect. As a result of emerging data, in January 2009 the FDA issued an early communication on the potential interaction between clopidogrel and PPIs. It discussed the potential for this drug interaction to increase the risk for adverse cardiac events, which can be clinically important for patient care. In November 2009, the FDA released a new public health warning on the possible interaction between clopidogrel and omeprazole. The warning states, “New data show that when clopidogrel and omeprazole are taken together, the effectiveness of clopidogrel is reduced. Patients at risk for heart attacks or strokes who use clopidogrel to prevent blood clots will not get the full effect of this medicine if they are also taking omeprazole.” This article will review the evidence for the interaction between clopidogrel and PPIs.

**WHAT IS THE PHARMACOLOGIC/PHARMACODYNAMIC EVIDENCE FOR THIS INTERACTION?**

Many studies have evaluated the potential interaction with combined clopidogrel and PPI therapy by measuring platelet aggregation ex vivo. (See table 1.) An observational study first reported that omeprazole may diminish the antiplatelet effect of clopidogrel. This study evaluated the influence of omeprazole on the antiplatelet effect of clopidogrel. Platelet aggregation was measured using vasodilator-stimulator phosphoprotein (VASP) phosphorylation, which provides an index of platelet reactivity specific to clopidogrel but not other antiplatelet drugs. A higher platelet reactivity index (PRI) indicates greater risk for thrombosis on clopidogrel. Patients on omeprazole had significantly higher VASP values compared with the control group (p=0.007), indicating decreased platelet inhibition in patients taking omeprazole. The study investigators hypothesized that omeprazole inhibits the activation of clopidogrel by inhibiting CYP2C19.

As a follow-up study, the same authors conducted a prospective, double-blind, placebo-controlled, randomized trial to assess the influence of omeprazole on the antiplatelet action of clopidogrel plus aspirin. All patients received aspirin 75 mg/day and clopidogrel 75 mg/day following a 300 mg loading dose. Patients also received either omeprazole 20 mg/day or placebo for seven days. The PRI at baseline was similar for both groups; however, the mean PRI on day seven was 39.8 ± 15.4 percent and 51.4 ± 16.4 percent in the placebo and omeprazole groups, respectively (p<0.0001). The omeprazole group had a statistically significant higher PRI, indicating reduced platelet inhibition. On day seven, 39 patients (60.9 percent) in the omeprazole group were poor responders compared with 16 patients (26.7 percent) in the placebo group (p<0.0001). The authors concluded that omeprazole significantly decreased clopidogrel’s antiplatelet activity as tested by VASP phosphorylation.

Additional studies have evaluated the potential interaction of clopidogrel with other PPIs. In an open-label, randomized, crossover study that investigated the effect of lansoprazole on the pharmacokinetics and pharmacodynamics of prasugrel and clopidogrel, the treatment groups received single doses of prasugrel 60 mg or clopidogrel 300 mg with or without lansoprazole 30 mg. For the treatment groups who received clopidogrel ± lansoprazole, the only significantly different point was the 24-hour assessment of IPA (inhibition of platelet aggregation), which showed an IPA decrease of 10 percent in the group treated with lansoprazole. In comparing all groups, mean IPA levels of prasugrel ± lansoprazole were significantly higher than those treated with clopidogrel ± lansoprazole.

Another study evaluated the antiplatelet action of clopidogrel when co-administered with esomeprazole and pantoprazole. The PRI (VASP assay) and ADP-induced platelet aggregation did not differ significantly in the control or PPI groups. The mean PRI was 51 percent (95 percent CI 48–54 percent) in the PPI group and 49 percent (95 percent CI 43–55 percent) in the control group. Moreover, the mean ADP-mediated platelet aggregation in the PPI and control groups was similar (p=0.619). The authors concluded that neither esomeprazole nor pantoprazole is associated with diminished antiplatelet effects of clopidogrel.

Sibbing and colleagues studied the impact of omeprazole, esomeprazole, and pantoprazole on clopidogrel action. ADP-mediated platelet aggregation was assessed by multiple-electrode platelet aggregometry using...
Multiplate analyzer. Platelet aggregation was significantly higher in patients on omeprazole compared with patients not taking a PPI (p=0.001). Platelet aggregation was similar in patients on pantoprazole or esomeprazole, compared with patients not on a PPI (p=0.69 and p=0.88, respectively). While pantoprazole and esomeprazole were not independently associated with reduced platelet response to clopidogrel, multivariate analysis showed that omeprazole was associated with a reduced platelet response. Significantly more patients on concurrent omeprazole (32.8 percent) had low response to clopidogrel, compared with patients on clopidogrel alone (19.1 percent; p=0.008).

Zuern and colleagues analyzed the effect of co-medication with PPIs on post-interventional residual platelet aggregation. All patients received dual antiplatelet therapy with clopidogrel and aspirin. PPI intake was determined based on patient or physician reporting. Residual platelet aggregation (RPA) was measured around 20 to 24 hours after clopidogrel loading. The RPA was statistically higher in patients who were treated with a PPI (34.0±21.4 vs. 29.8±20.2, p<0.001), but the differences among the three PPIs were not significant. The authors concluded that peri-procedural co-administration of esomeprazole, omeprazole, and pantoprazole significantly decreases the effect of clopidogrel, as assessed by RPA.

The Proton Pump Inhibitors And Clopidogrel Association (PACA) prospective randomized study compared the effect of omeprazole and pantoprazole on platelet response to 150 mg clopidogrel maintenance dose. Platelet reactivity was assessed using VASP and PAP4 Aggregometer. Data on maximal intensity of ADP-induced platelet aggregation (ADP-Ag) was reported. The primary endpoint was clopidogrel response one month after discharge, assessed using VASP. Antiplatelet response to clopidogrel was significantly better with pantoprazole as assessed with VASP. There were more clopidogrel nonresponders in the omeprazole group (44 percent) than in the pantoprazole group (23 percent; p=0.04). However, platelet reactivity with ADP-Ag between omeprazole and pantoprazole did not differ.

**DISCUSSION OF PHARMACOLOGIC/PHARMACODYNAMIC EVIDENCE**

As summarized previously, numerous studies have raised concerns about the potential interaction between clopidogrel and PPIs. The existing data and its limitations must be critically evaluated. Ex-vivo platelet aggregation studies, which used diverse methods for assessing platelet aggregation, showed varying results for each PPI (table 1). For example, omeprazole was shown to decrease the antiplatelet to clopidogrel compared with placebo in four different studies, and with pantoprazole in another study. One study showed that lansoprazole decreased IPA by 10 percent at 24 hour assessment. Although two studies showed that pantoprazole or esomeprazole had no effect on clopidogrel response, one study showed decreased antiplatelet response for both. Platelet aggregation studies for rabeprazole have not been conducted.

An important limitation to these studies is the use of different methods to assess platelet aggregation. Although turbidometric aggregometry is considered the gold standard for assessing platelet function, methodological standardization for this testing is not available. Moreover, there is no consensus on a clinically meaningful, evidence-based, standardized definition of clopidogrel resistance. The studies described were mostly conducted at single centers, included small numbers of patients, and used different methods to assess platelet function. Each study defined non-responsiveness or resistance to clopidogrel differently. Because inconsistent findings could be explained by methodological differences, interpreting and comparing these studies become problematic.

The timing of laboratory assessment and duration of antiplatelet therapy may also affect platelet aggregation response. All studies evaluated platelet response during a few time points, but this methodology may be inaccurate due to intra-patient variability. In patients who had inadequate response to clopidogrel initially, studies suggest that clopidogrel response may improve over time without any intervention. Some studies assessed platelet response after a short course of clopidogrel therapy, which precludes extrapolation of data to patients on chronic therapy.

Other limitations to the pharmacologic evidence exist. For example, regardless of PPI use, a subset of clopi-
dogrel-treated patients will be resistant to therapy. The number of clopidogrel non-responders in these studies is unknown and may have led to selection bias. Also, none of these studies investigated the mechanism of the interaction. Finally, the critical question is whether ex vivo assessment of platelet function correlates
with clinical outcomes. These studies evaluated the pharmacodynamics of clopidogrel plus PPIs, but they did not assess clinical outcomes or risk of thrombosis. Although the data are intriguing, the clinical relevance of these pharmacologic findings is unknown and can be clarified only in prospective randomized studies.

**WHAT IS THE CLINICAL EVIDENCE FOR THIS INTERACTION?**

In response to initial reports of this potential drug-drug interaction, Aetna Health Insurance analyzed the medical and pharmacy databases for MI rates in members receiving clopidogrel with or without a PPI. Based on adherence rates, patients were stratified into a high PPI exposure group, a low PPI exposure group, or an inside control group (if they had no exposure to a PPI). One-year acute MI rate was 1.38 percent (66 of 4800) in the control group, 3.08 percent (22 of 712) in the low PPI exposure group, and 5.03 percent in the high PPI exposure group. Patients in the high PPI exposure group had a statistically significantly higher rate of MI (p<0.05). Although slightly more people in the high PPI exposure group had pre-existing hypertension, diabetes, and a slightly higher severity of illness when clopidogrel was initially prescribed, the differences in acute MI rates remained significant (p<0.05) after multivariable adjustment. Moreover, the relative risk for acute MI was more than three times greater in the high exposure group than in the control group.

A population-based, nested, case-control study evaluated the drug interaction between PPIs and clopidogrel in 13,636 patients who were prescribed and filled a prescription for clopidogrel within three days after discharge for acute MI. A total of 734 patients were identified as the cases for this study and had been readmitted for MI within 90 days after initial discharge; the control group comprised 2,057 patients who were comparable in age, PCI, and validated risk scores. Exposure to PPI was defined as current (within the past 30 days), previous (31–90 days), and remote (91–180 days). After adjustment for concurrent medical conditions and other CYP2C19 inhibitors and inducers, current use of a PPI was associated with an adjusted odds ratio (OR) of 1.27 (95 percent confidence interval [CI] 1.02–1.57) for re-infarction. Compared with the control group, there was a relative 40 percent increase in the risk of recurrent MI. This excess risk was not observed in clopidogrel nonusers or in patients taking pantoprazole or H2 receptor antagonists. The authors advise caution with the concurrent use of CYP2C19 inhibiting PPIs and clopidogrel and suggest the use of pantoprazole or H2 receptor antagonists with clopidogrel.

A retrospective cohort study evaluated adverse outcomes of patients taking clopidogrel with or without a PPI following hospitalization for ACS. The study population consisted of 8,205 patients with acute MI or unstable angina taking clopidogrel after discharge from any of the 127 Veterans Affairs hospitals between Oct. 1, 2003, and Jan. 31, 2006. Pharmacy refill data were used to determine concomitant clopidogrel and PPI use. The primary outcome was the combined endpoint of all-cause mortality or rehospitalization for ACS following the index hospitalization. Approximately 64 percent of patients (n=5244) were on concomitant PPI and clopidogrel therapy, and these patients were older and had more co-morbid conditions. The primary outcome occurred in 20.8 percent (n=615) and 29.8 percent (n=615) in patients on clopidogrel alone and with PPI, respectively. In multivariable analysis, patients taking clopidogrel plus PPI had a higher risk of the primary outcome compared with those taking clopidogrel alone (adjusted odds ratio [AOR], 1.25; 95 percent confidence interval [CI], 1.11–1.41). Additionally, use of clopidogrel plus PPI, compared with use of clopidogrel alone, was associated with a higher risk for recurrent ACS (AOR, 1.86; 95 percent CI, 1.57–2.20) and revascularization procedures (AOR, 1.49; 95 percent CI, 1.30–1.71), but not all-cause mortality (AOR 0.91; 95 percent CI, 0.80–1.05). A consistent association between omeprazole and rabeprazole with adverse outcomes was seen, but the small number of patients taking other PPIs prohibited exploring these specific agents. PPI use by itself was not associated with death or recurrent ACS (AOR, 0.98; 95 percent CI, 0.85–1.13).

Gupta and colleagues evaluated the incidence of major adverse cardiovascular events (MACE; composite of MI, cardiovascular death and target vessel failure) in patients...
who were post-percutaneous coronary intervention (PCI).

Although baseline characteristics of these patients were generally similar, the use of bare metal stents was higher among patients on combined clopidogrel-PPI therapy. Rabeprazole was the most often used PPI (78 percent of patients). The rate of MACE in the clopidogrel monotherapy group was 38 percent (92/243) compared with 56 percent (40/72) in the clopidogrel and PPI group (p=0.025).

O’Donoghue and colleagues analyzed two large randomized trials to assess the association between PPI use, measures of platelet function, and clinical outcomes for patients treated with clopidogrel and prasugrel. PRINCIPLE (Prasugrel In Comparison to Clopidogrel for Inhibition of Platelet Activation and Aggregation) TIMI 44 was a double-blind, two-phase, crossover study that randomly assigned patients to either prasugrel (60 mg load, 10 mg daily maintenance) or clopidogrel (600 mg load, 150 mg daily maintenance dose). At day 15, patients were transferred to the alternate antiplatelet. Platelet function was measured on day 1, 15, and 29 using light transmission aggregometry. The primary endpoint of PRINCIPLE-TIMI was to determine any differences in antiplatelet effect. Fifty-three patients (26.4 percent) reported PPI use on the day of platelet function assessment. At baseline, platelet aggregation was similar for PPI users and nonusers. For the clopidogrel group, the mean inhibition of platelet aggregation was significantly lower in PPI users at 2, 6, and 18–24 hours after the study drug administration. In the prasugrel group, the mean inhibition of platelet aggregation was significantly lower in PPI users at 30 minutes after the loading dose. After 15 days of treatment with prasugrel, the mean inhibition of platelet aggregation was significantly lower in PPI users than nonusers. The Trial to assess Improvement in Therapeutic Outcomes by optimizing platelet inhibition with Prasugrel (TRITON-TIMI) 38 was a double-blind trial that randomized 13,608 patients to prasugrel (60 mg load, 10 mg daily maintenance) or clopidogrel (300 mg load, 75 mg daily maintenance dose). The primary endpoint was the composite of CV death, nonfatal MI, or nonfatal stroke. No significant difference in the primary endpoint was noted for patients on clopidogrel or prasugrel, even after adjustment for potential confounders. Use of a PPI was also not associated with any increased risk of MI, stent thrombosis, or a decreased risk of bleeding with patients on either prasugrel or clopidogrel.

Rassen and colleagues evaluated three cohorts of patients (n=18,565) 65 years or older who received clopidogrel and were post-PCI or hospitalized for ACS. Three different geographic areas were represented: British Columbia, Pennsylvania, and New Jersey. The primary endpoint was hospitalization for MI, revascularization, or death. Baseline characteristics were different among cohorts with respect to age, gender, and risk factors; PPI users generally had more comorbidities. In a pooled analysis, 2.6 percent of PPI users compared with 2.1 percent of PPI nonusers had an MI hospitalization. Similar modest increases in death (1.5 percent versus 0.9 percent) and revascularization (3.4 percent versus 3.1 percent) were observed. Crude rates of MI hospitalization or death were higher for PPI users than PPI nonusers among the three cohorts. After propensity score rate ratios were adjusted, none of the primary endpoints were statistically significant.

In addition to the published literature, numerous studies with conflicting findings have been presented at scientific meetings. Four other studies showed negative outcomes with this interaction. For example, Aubert and colleagues used the National Medco Integrated Database and examined the impact of PPIs on the effectiveness of clopidogrel to prevent coronary artery stent restenosis in patients (n=14,383) who had stent placement. For patients with no preceding CV events, the incidence of major CV event within one year was 32.5 percent in patients on concurrent PPI and clopidogrel, and 21.2 percent in patients on clopidogrel alone (adjusted OR 1.79, CI 1.62–1.97). For patients with a preceding CV event, the incidence of major CV events within one year was 39.8 percent in the PPI and clopidogrel group, and 26.2 percent in patients on clopidogrel alone (adjusted OR 1.86, CI 1.63–2.12). Other studies showed similar negative outcomes with concurrent PPI and clopidogrel. In contrast, two studies reported conflicting findings. Data from the Clopidogrel for the Reduction of Events During Observation (CREDO) trial was presented at the AHA Scientific Sessions 2008. This study assessed whether baseline PPI use would increase 28-day and one-year composite end-
points in patients undergoing, or at high likelihood of undergoing PCI. The primary endpoints were 28-day death, MI, or urgent target-vessel revascularization and one-year death, MI, or stroke. At one year, clopidogrel reduced adverse events to a similar degree, regardless of PPI use. The incidence of the 28-day endpoint in patients receiving clopidogrel or placebo was higher with PPI use, but this difference was not statistically significant. PPI use was independently associated with the 28-day (HR 1.6, 95 percent CI 1.08–2.5, p=0.022) and one-year (HR 1.5, 95 percent CI 1.1–2.1, p=0.012) endpoints in the overall trial population.

Results from the only randomized trial were presented at the late-breaking clinical-trial session during the Transcatheter Cardiovascular Therapeutics 2009 meeting. The clopidogrel and the Optimization of Gastrointestinal Events (COGENT-1) study was aborted after the trial sponsor declared bankruptcy. This study was a phase three trial testing a combination product known as CGT-2168—a once-daily pill that combined clopidogrel 75 mg with omeprazole 20 mg. Patients requiring clopidogrel for at least 12 months, typically following NST ACS, ST-elevation MI, or stent implantation were enrolled. Roughly 3,600 patients were enrolled, and mean follow up was 133 days. The outcome measure was a composite of CV death, nonfatal MI, coronary artery bypass graft or PCI, or ischemic stroke. There were no differences in outcome (67 CV events in the placebo group compared with 69 events in the omeprazole group). Gastrointestinal events were significantly reduced in the omeprazole group (p=0.007).

**DISCUSSION OF CLINICAL EVIDENCE**

Published studies that have evaluated the potential interaction with clopidogrel and PPIs on clinical outcomes are summarized in table 2. The results of clinical outcome studies are also contradictory. While nine studies showed an increase in adverse outcomes, four other studies did not. Interestingly, Dunn and colleagues found that PPI use was independently associated with adverse outcomes. All these studies, with the exception of one, were retrospective analyses that suggest an association but not causality. The retrospective nature of the data, the inability to determine nonprescription medication use, and lack of assessment for adherence with clopidogrel or PPIs are additional limitations to these studies. Each PPI was evaluated in different studies, although some reported on PPIs as a class and did not provide data on specific PPIs. Moreover, the study and control groups were not well matched in baseline characteristics in many studies, and these discrepancies could have affected results. As mentioned previously, the number of clopidogrel nonresponders in the study population was also unknown.

Randomized controlled trials provide the most rigorous information. TRITON-TIMI 38 was a retrospective analysis of a randomized control trial, and COGENT is the one prospective, double-blind study that evaluated this interaction. Both studies showed no effect of combined PPI-clopidogrel therapy on clinical outcomes.

The proposed mechanism for the clopidogrel and PPI interaction is inhibition of CYP2C19, which is involved in the activation of clopidogrel. Based on this mechanism, PPIs that minimally inhibit CYP2C19 should not interact with clopidogrel. However, results from available studies are conflicting. Omeprazole and esomeprazole are inhibitors of CYP2C19 and have the greatest potential to cause CYP450-mediated drug interaction. Lansoprazole also inhibits CYP2C19, while pantoprazole and rabeprazole minimally inhibit CYP2C19. Pantoprazole should neither interact with clopidogrel nor affect clinical outcomes, because it minimally inhibits CYP2C19. Two ex vivo platelet aggregation studies showed that pantoprazole may not interact because it is metabolized to a significant extent by a conjugating enzyme, a cytosolic sulfotransferase. However, Zuern and colleagues showed that clopidogrel response was reduced with pantoprazole. While Juurlink and colleagues showed that pantoprazole was not associated with reinfarction, Stanek and colleagues showed that pantoprazole was associated with adverse clinical outcomes. Theoretically, esomeprazole can interact with clopidogrel because it inhibits CYP2C19, but the data is conflicting here, as well. Ex vivo, esomeprazole was shown to reduce the antiplatelet response of clopidogrel in one study and to not interfere with platelet aggrega-
<table>
<thead>
<tr>
<th>Brand (Generic)</th>
<th>Dosage Forms</th>
<th>Isomer of existing product?</th>
<th>How to take?</th>
<th>Special Administration Instructions</th>
<th>Pregnancy category</th>
<th>Metabolism/ Selected Drug Interactions</th>
</tr>
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<tbody>
<tr>
<td>Kapidex (dexlansoprazole) Delayed-release capsules 30 mg, 60 mg</td>
<td>R-isomer of lansoprazole</td>
<td>Take without regard to food.</td>
<td>• Capsule contents can be sprinkled on applesauce and taken immediately. • Swallow delayed-release capsules intact; do not chew or crush.</td>
<td>B</td>
<td>Metabolism • CYP2C19, CYP3A4 Selected Drug Interactions • Azole antifungals, protease inhibitors, tacrolimus, warfarin</td>
<td></td>
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<tr>
<td>Nexium (esomeprazole) Delayed-release capsules 20 mg, 40 mg Delayed-release oral suspension 10 mg, 20 mg, 40 mg Injection 20 mg, 40 mg</td>
<td>S-isomer of omeprazole</td>
<td>Take at least 1 hour before eating.</td>
<td>• Capsule can be swallowed whole or can be opened and mixed with applesauce and taken immediately; do not crush or chew granules. • Can be given through NG tube.</td>
<td>B</td>
<td>Metabolism • CYP2C19, CYP3A4 • Inhibits CYP2C19 Selected Drug Interactions • Azole antifungals, protease inhibitors, warfarin</td>
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<tr>
<td>Prevacid®, Prevacid SoluTab®, Prevacid® 24HR (OTC) (lansoprazole) Capsules 15 mg, 30 mg Orally-disintegrating tablet 15 mg, 30 mg Injection 30 mg</td>
<td>N/A</td>
<td>Take 30 minutes before meals. Do not crush or chew.</td>
<td>• Place orally disintegrating tablet on the tongue and allow the tablet to disintegrate with or without water until the particles can be swallowed. • Capsule contents can be sprinkled on applesauce and taken immediately. • Can be given through a NG tube.</td>
<td>B</td>
<td>Metabolism • CYP2C19 and CYP3A4 • Inhibits CYP2C19 and CYP2C9 Selected Drug Interactions • Azole antifungals, protease inhibitors, tacrolimus, warfarin</td>
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<td>Brand (Generic) Dose Adjustments</td>
<td>Isomer of existing product?</td>
<td>How to take?</td>
<td>Special Administration Instructions</td>
<td>Pregnancy category</td>
<td>Metabolism/Selected Drug Interactions</td>
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<td>Prilosec, Prilosec-OTC (omeprazole) Capsules 10 mg, 20 mg, 40 mg Suspension 2.5 mg, 10 mg Available brand, generic, and OTC</td>
<td>N/A</td>
<td>Take on an empty stomach at least 1 hour before a meal.</td>
<td>• Capsule can be swallowed whole or can be opened and mixed with applesauce; swallow immediately and do not crush or chew granules. • Can be given through a NG tube.</td>
<td>C</td>
<td>Metabolism • CYP2C19, CYP3A4 • Inhibits CYP2C19 Selected Drug Interactions • Azole antifungals, clopidogrel, protease inhibitors, tacrolimus, warfarin</td>
<td></td>
</tr>
<tr>
<td>Zegerid, Zegerid OTC (omeprazole and sodium bicarbonate) Capsules 20 mg, 40 mg (1,100 mg sodium bicarbonate) Oral Suspension 20 mg, 40 mg (1,680 mg sodium bicarbonate) Available brand, generic, and OTC</td>
<td>N/A</td>
<td>Take on an empty stomach at least 1 hour before a meal.</td>
<td>• Capsule can be swallowed whole or can be opened and mixed with applesauce; swallow immediately and do not crush or chew granules. • Can be given through a NG tube.</td>
<td>C</td>
<td>Metabolism • CYP2C19, CYP3A4 • Inhibits CYP2C19 Selected Drug Interactions • Azole antifungals, clopidogrel, protease inhibitors, tacrolimus, warfarin</td>
<td></td>
</tr>
<tr>
<td>Protonix (pantoprazole) Delayed-release tablets 20 mg, 40 mg Delayed-release oral suspension 40 mg Injection 40 mg Available brand and generic</td>
<td>N/A</td>
<td>Delayed release tablets: Take without regard to meals. Delayed-release oral suspension: Take approximately 30 minutes before a meal.</td>
<td>• Delayed release tablets: Do not chew, crush, or split. Food delays, but does not affect the extent of absorption. • Delayed release oral suspension: The granules may be sprinkled on applesauce or put in apple juice. • Can be given through a NG tube.</td>
<td>B</td>
<td>Metabolism • CYP2C19, CYP3A4 • Minimally inhibits CYP2C19 Selected Drug Interactions • Azole antifungals, protease inhibitors, warfarin</td>
<td></td>
</tr>
<tr>
<td>AcipHex (rabeprazole) Tablets 20 mg Available brand only</td>
<td>N/A</td>
<td>Take without regard to meals.</td>
<td>• Swallow tablets whole; do not chew, crush, or split.</td>
<td>B</td>
<td>Metabolism • CYP2C19, CYP3A4 • Minimally inhibits CYP2C19 Selected Drug Interactions • Azole antifungals, protease inhibitors, cyclosporine, warfarin</td>
<td></td>
</tr>
</tbody>
</table>

NG = nasogastric tube; OTC = over-the-counter
tion in two other studies. Clinically, esomeprazole was not associated with any increased risk of MI or stent thrombosis.

Other potential drug interactions with clopidogrel have been suggested previously. Because CYP3A4 also metabolizes clopidogrel to its active compound, the influence of CYP3A4 inhibitors on the antiplatelet effects of clopidogrel has been investigated. CYP3A4 inhibitors such as ketoconazole, calcium channel blockers, and statins have been shown to reduce the concentration of clopidogrel’s active metabolite and reduce platelet aggregation. However, post hoc analyses failed to find a statistically significant clinical interaction. The CREDO study, for example, found no evidence that statins affect clopidogrel response. As a result of these findings, interest in these interactions has since dissipated.

In summary, the evidence regarding the potential interaction between clopidogrel and PPIs is conflicting. Much of the current evidence comes primarily from observational, retrospective, or laboratory-based studies, which do not provide the luxury of establishing or refuting a cause-and-effect relationship between PPIs and adverse outcomes. These studies can only suggest an association. Changes in platelet aggregability have been observed with various platelet aggregation assays, but this ex vivo data has not been correlated to adverse patient events. More recent data suggest that this combination does not increase CV risk. PRINCIPLE-TIMI 44 and TRITON-TIMI 38 showed that PPIs can reduce the platelet inhibition response to clopidogrel, but did not worsen clinical outcomes. Definitive evidence of the interaction requires large prospective trials. COGENT-1, the only prospective, randomized, double-blind study, provides some insight. Preliminary reports from this study indicated no differences in the incidence of CV events (including MI) with combined PPI-omeprazole therapy, and GI outcomes were reduced with PPI therapy.

HOW SHOULD THIS INTERACTION BE MANAGED?

In early January 2009, the FDA released an early communication about the safety of clopidogrel. The makers of clopidogrel agreed to work with the FDA to promptly conduct additional studies on this drug interaction. At that time, the FDA made several recommendations: 1) clopidogrel should be continued when indicated; 2) health care providers should reevaluate the need for starting or continuing treatment with a PPI, including Prilosec OTC, in patients taking clopidogrel; and 3) patients should consult their health care provider before taking a PPI, including OTC omeprazole.

The FDA issued a new public-health warning on the possible interaction between clopidogrel and omeprazole in November 2009, with the following recommendations for health care providers regarding this interaction:

- Avoid the concomitant use of omeprazole and clopidogrel as clopidogrel’s anticlotting activity may be reduced.
- Separating the dose of clopidogrel and omeprazole in time will not reduce this drug interaction.
- Some medications (esomeprazole, cimetidine, fluconazole, ketoconazole, voriconazole, etravirine, felbamate, fluoxetine, fluvoxamine, and ticlopidine) may have a similar interaction and combined use with clopidogrel should be avoided.
- There is insufficient information at this time to make recommendations about drug interactions between clopidogrel and PPIs other than omeprazole and esomeprazole.
- Cimetidine may interfere with the anticlotting activity of clopidogrel. The other H2 blockers such as ranitidine, famotidine, and nizatidine do not.
- Talk with your patients about the OTC medicines they take. Be aware that patients may be taking non-prescription forms of omeprazole and cimetidine.

Despite the conflicting data and newer findings from TRITON-TIMI 38 and COGENT-1, the FDA recommends that “concomitant use of omeprazole and clopidogrel should be avoided.” In contrast to the FDA, some experts have stated that “the current evidence does not justify the conclusion that PPIs decrease the clinical efficacy of clopidogrel.”

How clinicians should respond to this interaction remains a topic of debate. Clinicians may follow the recommendations of the
FDA. Juurlink proposes three steps: 1) evaluate the necessity of PPI therapy and consider an H2 antagonist or antacid, if appropriate; 2) consider using pantoprazole when a PPI is indicated; and 3) stagger the dosing of medications. Another source also endorses pantoprazole or staggering doses of PPI and omeprazole to mitigate this reaction. The FDA, however, does not endorse staggering doses. Unfortunately, a definitive answer to how clinicians should respond to this interaction is unknown. Additional prospective randomized trials are necessary to clarify this important clinical question.

**HOW SHOULD PATIENTS BE COUNSELED?**

Pharmacists will encounter opportunities to counsel patients on this potential interaction. A brief summary of the data and the quality of the data are topics to discuss with patients. The FDA also recommends the following information for patients using clopidogrel:

- Patients using clopidogrel should consult with their health care provider if they are currently taking or considering taking omeprazole, including Prilosec OTC or Zegerid OTC.
- Both clopidogrel and omeprazole can provide significant benefits to patients, and patients should always consult with their health care professional before starting or stopping any medication.
- It is very important that patients talk with their health care professional about any OTC drugs they are taking before starting or while using clopidogrel.
- Talk with your patients about the OTC medicines they take. Be aware that patients may be taking nonprescription forms of omeprazole and cimetidine.

Pharmacists can also guide patients on the proper selection of PPIs, especially if an OTC product is necessary. There is no clinically significant difference among PPIs, but there are some minor differences. Table 3 is a comparison chart of the available PPIs. For patients who require a PPI for the treatment of heartburn or gastroesophageal reflux disease, pharmacists can suggest the following non-pharmacologic strategies to manage heartburn:

- Do not eat for at least two to three hours before lying down or going to bed.
- Try smaller portions of food eaten more frequently throughout the day instead of eating large portions two or three times per day.
- Wear loose fitting clothes.
- Lose weight if overweight.
- Stop smoking and avoid alcohol.
- Avoid foods and beverages that may worsen or trigger heartburn symptoms such as fatty foods, chocolate, peppermint, spicy foods, orange juice, and coffee.
- Keep a heartburn diary that can help determine which foods worsen symptoms.
- Raise the head of the bed so that your head and chest are elevated higher than your feet. 

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**Editor’s Note:** To obtain the complete list of references used in this article, contact Chris Linville, managing editor of America’s Pharmacist, at 703-838-2680, or e-mail chris.linville@ncpanet.org.
CONTINUING EDUCATION QUIZ
Select the correct answer.

1. Which statement is true?
   a. Clopidogrel inhibits ADP from binding to its P2Y1 receptor.
   b. Clopidogrel inhibits ADP from binding to its P2Y12 receptor.
   c. Clopidogrel enhances ADP-mediated activation of the glycoprotein GPIIb/IIIa complex.
   d. Clopidogrel inhibits cyclo-oxygenase 1.

2. Which statement is true?
   a. Clopidogrel resistance does not exist.
   b. Clopidogrel resistance occurs in 10 percent of patients.
   c. Clopidogrel resistance occurs in about one-third of patients.
   d. Clopidogrel resistance occurs in about one-fourth of patients.

3. All of the following are possible mechanisms of clopidogrel resistance, except:
   a. Presence of CYP2C19 reduced-function or loss-of-function allele.
   c. Decreased absorption of clopidogrel.
   d. Drugs that inhibit clopidogrel biotransformation.

4. All the following are FDA approved indications for clopidogrel, except:
   a. Reduction of atherothrombotic events in patients with recent myocardial infarction.
   b. Reduction of atherothrombotic events in patients with atrial fibrillation.
   c. Reduction of atherothrombotic events in patients with recent stroke.
   d. Reduction of atherothrombotic events in patients with established peripheral arterial disease.

5. All of the following CYP isozymes are involved in this biotransformation of clopidogrel to its active metabolite, except:
   a. 2C8
   b. 2C9
   c. 2C19
   d. 3A4

6. In platelet aggregation studies, which proton pump inhibitor has repeatedly been shown to decrease clopidogrel response?
   a. Esomeprazole
   b. Omeprazole
   c. Pantoprazole
   d. Rabeprazole

7. Studies on ex vivo platelet aggregation of ______ ________ with clopidogrel have not reported.
   a. Esomeprazole
   b. Omeprazole
   c. Pantoprazole
   d. Rabeprazole

8. Which statement is true?
   a. A higher PRI (platelet reactivity index) has been used to define poor response to clopidogrel.
   b. A lower PRI (platelet reactivity index) has been used to define poor response to clopidogrel.
   c. The PRI (platelet reactivity index) cut-off point that was used to separate good responders from poor responders to clopidogrel was consistent among studies.
   d. Platelet reactivity tests have been shown to correlate with the risk for clinical thrombotic events.

9. Which statement is true?
   a. Single isolated measurement of platelet function is useful to assess antiplatelet action of drugs.
   b. A clinically meaningful, evidence-based, standardized definition of clopidogrel resistance has been developed by the International Society of Thrombosis and Hemostasis (ISTH).
   c. Platelet aggregation studies that evaluated the pharmacodynamics of clopidogrel plus PPI did not assess clinical outcomes or risk of thrombosis.
   d. Platelet aggregation studies that evaluated the pharmacodynamics of clopidogrel plus PPI have shown an increased risk of thrombosis with the combination.
10. Which statement is true?
a. Studies showed that the use of clopidogrel plus PPI increases the risk of MACE.
b. Studies showed that the use of clopidogrel plus PPI is associated with a higher risk of MACE.
c. Studies showed that the use of clopidogrel plus PPI decreases the risk of MACE.
d. Studies showed that the use of clopidogrel plus PPI is associated with a lower risk of MACE.

11. Which of the following PPIs is least likely to inhibit CYP2C19?
a. Esomeprazole
b. Lansoprazole
c. Omeprazole
d. Pantoprazole

12. Which of the following PPIs may inhibit CYP2C19?
a. Esomeprazole
b. Lansoprazole
c. Omeprazole
d. All of the above

13. According to the FDA, what other drugs could potentially interact with clopidogrel?
a. Cimetidine
b. Fluvoxamine
c. Fluoxetine
d. All of the above

14. Which of the following is a controversial strategy for managing the PPI-clopidogrel interaction?
a. Clinicians should evaluate the necessity of PPI therapy in patients on clopidogrel.
b. Clinicians may stagger the dosing of PPI and clopidogrel.
c. Clinicians may consider histamine 2 antagonists or antacid, if appropriate.
d. Clinicians may consider pantoprazole when a PPI is indicated.

Use this case to answer Questions 15–16

A.S. is a 76-year-old woman who has a past medical history of hypertension, type 2 diabetes, and osteoarthritis. Her current medications included aspirin 81 mg daily, acetaminophen 1,000 mg twice daily, lisinopril/hydrochlorothiazide 20 mg/25 mg daily, glyburide 10 mg daily, and metformin XR 1,000 mg twice daily. She presented to the emergency department with complaints of chest pain, shortness of breath, nausea, and vomiting. She was diagnosed with ST-myocardial infarction and was taken to the catheterization laboratory upon admission. She underwent drug eluting stent implantation. Her home medications were continued, and clopidogrel 75 mg daily, omeprazole 20 mg daily and simvastatin 20 mg daily were prescribed upon discharge.

15. The following statements are correct, except:
a. Aspirin is clinically necessary in this patient.
b. Omeprazole is clinically necessary in this patient.
c. Omeprazole is not clinically necessary in this patient.
d. Clopidogrel is clinically necessary in this patient.

16. What is the best approach to manage this interaction in this patient?
a. Instruct patient to take omeprazole in the morning and clopidogrel in the evening.
b. Switch to an alternative PPI.
c. Increase the dose of clopidogrel to 150 mg daily.
d. Switch from clopidogrel to prasugrel.

Use the following case to answer questions 17–18

A.T. is a 60-year-old man with a history of hypertension and gastroesophageal reflux disease (GERD). His reflux symptoms are generally mild and can be avoided with nonpharmacologic measures. His current medications include lisinopril 10 mg daily and clopidogrel 75 mg daily. He comes to your pharmacy to purchase omeprazole OTC.

17. What patient counseling is appropriate?
a. Advise the patient against the use of omeprazole OTC.
b. Advise the patient to take omeprazole OTC regularly.
c. Suggest the use of cimetidine for heartburn.
d. Both A and C
18. Which alternative OTC heartburn medication can be recommended for this patient?
   a. Antacids  
   b. Famotidine  
   c. Nizatidine  
   d. All of the above

19. A patient calls your pharmacy because he just heard on the news that Plavix and omeprazole should not be used together. The patient has been taking Plavix and omeprazole for the past six months, and he is quite alarmed by the news report. What is the best approach to this patient’s concerns?
   a. Provide brief information on the interaction, and counsel the patient to stop omeprazole.
   b. Provide brief information on the interaction, and counsel the patient to stop clopidogrel.
   c. Provide brief information on the interaction, and counsel the patient to contact his physician.
   d. Provide brief information on the interaction, and counsel the patient to take aspirin.

20. A physician wants to initiate a PPI for a patient already on clopidogrel and asks you for a recommendation. Which PPI is the best choice?
   a. Esomeprazole  
   b. Omeprazole  
   c. Lansoprazole  
   d. Pantoprazole

Review of the Clopidogrel-Proton Pump Inhibitor Interaction
Apr. 1, 2010 (expires Apr. 1, 2013)
Activity Type: Knowledge-based

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Quiz: Shade in your choice
1. a  b  c  d  e
2. a  b  c  d  e
3. a  b  c  d  e
4. a  b  c  d  e
5. a  b  c  d  e
6. a  b  c  d  e
7. a  b  c  d  e
8. a  b  c  d  e
9. a  b  c  d  e
10. a  b  c  d  e

Quiz: Circle your choice
21. Is this program used to meet your mandatory C.E. requirements?
   a. Yes  b. No
23. Age group: a. 21–30  b. 31–40  c. 41–50  d. 51–60  e. Over 60
24. Did this article achieve its stated objectives?
   a. Yes  b. No
25. How much of this program can you apply in practice?
   a. All  b. Some  c. Very little  d. None

How long did it take you to complete both the reading and the quiz? ______ minutes

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