Antiplatelet Therapy and Proton Pump Inhibition

Clinician Update

George V. Moukarbel, MD; Deepak L. Bhatt, MD, MPH

A 77-year-old man with history of diabetes mellitus and coronary artery disease presented with angina and evidence of ischemia despite maximal medical therapy. He underwent a percutaneous coronary intervention with a drug-eluting stent and was started on long-term dual antiplatelet therapy with aspirin and clopidogrel. His medical history was significant for an episode of gastrointestinal (GI) bleeding in the setting of using nonsteroidal antiinflammatory drugs.

Dual antiplatelet therapy, typically the addition of an ADP receptor antagonist to aspirin, has become the cornerstone of management of patients with acute coronary syndromes and after percutaneous coronary intervention. However, along with the reduction of thrombotic outcomes, this therapeutic strategy has the untoward effect of increasing the risk of bleeding events, including GI bleeding. The use of gastroprotective strategies, most notably proton pump inhibitors (PPIs), has become a widely adopted and recommended practice in this patient population. Currently, the most commonly prescribed ADP receptor antagonist is clopidogrel, a prodrug that undergoes activation by the cytochrome P450 system, in particular CYP2C19. The importance of this reaction on the overall platelet inhibitory effects of clopidogrel is highlighted by the fact that patients with reduced-function CYP2C19 alleles exhibit a reduced response to clopidogrel compared with those with the wild-type alleles. This finding might translate into increased risk of adverse events after acute coronary syndromes and percutaneous coronary intervention. Given that PPIs are inhibitors of CYP2C19, coupled with reports suggesting a clinically significant interaction, regulatory agencies issued a cautionary statement advising against the combined use of PPIs (specifically omeprazole and esomeprazole) and clopidogrel.

Risk of GI Bleeding With Antiplatelet Therapy and Effect of Gastroprotective Strategies

Aspirin causes direct damage to the gastric epithelium and inhibits prostaglandin production by the gastric mucosa, leading to ulcerations and an estimated 2-fold increased risk of GI bleeding with low-dose aspirin alone. The risk increases with the additional use of antiplatelet and antithrombotic agents, as well as steroidal and nonsteroidal antiinflammatory drugs. In patients with heart disease, several clinical characteristics that confer added risk of GI bleeding such as older age, male sex, nonwhite race, diabetes mellitus, history of alcohol abuse, heart failure symptoms, and renal insufficiency can be identified. History of ulcers and prior GI bleeding events are also very important risk factors. The risk of bleeding appears to be highest in the early period after a cardiac event but continues to be present on long-term follow-up (Figure 1). Gastroprotective strategies to reduce the risk of GI bleeding in patients taking antiplatelet agents have been tested in several settings. Both H2 receptor antagonists and PPIs reduce stomach acid production, thus allowing gastric ulcers and erosions to heal. Use of PPIs in patients taking antiplatelet therapy has been associated with a significant reduction in the risk of GI bleeding, ulcers, and erosions in data from observational and randomized clinical trials. Although there is no large clinical trial with a head-to-head comparison with PPIs, H2 re-
Receptor antagonists appear to confer a more modest protection from GI events in this setting according to observational and retrospective studies. Clinical characteristics can be used to guide the need for PPIs in patients taking antiplatelet therapy (Figure 2).

The weight of the evidence for and against a clinically significant interaction between antiplatelet agents and PPIs comes mostly from retrospective cohort studies or secondary analyses of randomized controlled trials. Inherent to the design of such studies, the main issue is the inability to adjust for residual confounding factors that might drive the decision to initiate PPI therapy in patients who are at high risk. Additionally, patients could have been prescribed PPIs for symptoms that were misdiagnosed as having a GI rather than a cardiac origin. Such an occurrence would be captured in these nonrandomized studies and could lead to an erroneous association of PPI use with increased cardiac events.

**PPIs and Aspirin Interaction**

There have been recent concerns that PPIs may interfere with the absorption and bioavailability of aspirin by altering gastric acidity. Small platelet aggregation studies in patients treated with low-dose aspirin (75–100 mg) and concomitant PPI showed opposing results. A propensity score-matched study in 20,000 patients with first myocardial infarction who were not treated with clopidogrel showed that treatment with a PPI was associated with up to 60% increased risk of cardiovascular death, myocardial infarction, or stroke. There was no increased risk noted with H2 receptor antagonists. This study had 2 major specific limitations: it relied on prescription-filling data from a national registry, and it was uncertain why these patients were not treated with dual antiplatelet therapy.

**PPIs and Clopidogrel:** Evidence for and Against a Clinically Significant Interaction

Only 1 randomized controlled trial, Clopidogrel and the Optimization of Gastrointestinal Events (COGENT), has addressed treatment with PPIs in patients with coronary artery disease treated with dual antiplatelet therapy. Unfortunately, the trial was stopped prematurely owing to loss of funding by the sponsor. Nevertheless, important lessons can be learned from the results. In the 3761 patients analyzed, treatment with omeprazole was associated with a significant 66% reduction in the incidence of GI events at 6 months (Figure 3A). COGENT was the first large randomized trial to find that prophylactic PPI use reduced clinical (as opposed to endoscopic) GI end points. Additionally, there was no difference in the occurrence of cardiovascular events in the 2 groups in the early period after acute coronary syndromes or percutaneous coronary intervention.
when risk of cardiac events would be expected to be highest (Figure 3B). The Table summarizes the large non-randomized published studies examining this issue in different patient populations. These studies vary in terms of patient inclusion criteria, outcomes measured, and analysis methods. In general, studies reporting a positive association found 25% to 80% increased risk of cardiovascular events in patients treated with a PPI in addition to dual antiplatelet therapy. Interestingly, 2 recent meta-analyses of published studies found no association between PPI use and mortality. A significant association with cardiovascular events was found in observational studies but not in those using propensity matching or participants of randomized trials. The presence of significant heterogeneity again indicates the biased and confounded nature of the evidence.

**Strategies to Avoid the Effects of an Interaction**

Several approaches to circumvent the potential for significant interference with clopidogrel effect have been suggested. Pantoprazole and rabeprazole interfere minimally with the cytochrome P450 system and may potentially not exhibit a similar interaction. The use of prasugrel instead of clopidogrel in acute coronary syndromes patients undergoing percutaneous coronary intervention can be considered and has been shown to cause platelet inhibition even in the face of clopidogrel nonresponsiveness, albeit at the expense of increased bleeding. Newer antiplatelet agents that are not dependent on the cytochrome P450 isoenzymes such as ticagrelor could be used in acute coronary syndromes treated invasively or conservatively. Administration of the PPI at a different time than the administration of clopidogrel showed inconsistent results in the studies that evaluated this strategy. It is unclear whether the release pharmacokinetics of the particular omeprazole formulation used in COGENT had any impact on the results of the trial. Finally, different gastroprotective drugs such as H2 receptor antagonists can be used, although they have been shown to confer a somewhat more modest protective effect than PPIs.

**Conclusions and Summary of Recommendations**

The totality of evidence available to date does not support a clinically significant impact of any pharmacokinetic or pharmacodynamic interactions between PPIs and the current widely used antiplatelet agents. Further evidence that will shed more light on this matter should come only from randomized clinical trials because new retrospective studies, no matter how statistically sound, will only add confusion to the matter. Until then, the benefit of PPIs in reducing bleeding events (and treating GI symptoms) must be factored into decision making when faced with patients with high GI bleeding risk requiring antiplatelet therapy.

Our patient was treated with 20 mg omeprazole once per day, given the history of prior GI bleeding events, other risk factors, and the need for...
long-term dual antiplatelet therapy. For this patient, omeprazole was the cheapest option because it was on the hospital formulary. If cost were not an issue, it would have been reasonable to initiate therapy with a PPI that has less effect on CYP2C19 in case future studies show that the pharmacokinetic and pharmacodynamic interactions with clopidogrel translate into clinical events.

Disclosures
Dr Bhatt receives research grants from Amarin, AstraZeneca, Bristol-Myers Squibb, Eisai, Ethicon, Medtronic, Sanofi-aventis, and The Medicines Company. He has collaborated with Takeda and PLx Pharma on research studies. He was the chair of the COGENT trial. Dr Moukarbel reports no conflicts.

References

### Table. Summary of Recent Large (n >1000), Nonrandomized Studies Looking at Clinical Evidence of an Interaction Between Clopidogrel and Proton Pump Inhibitors

<table>
<thead>
<tr>
<th>Reference (Year)</th>
<th>Design</th>
<th>Population</th>
<th>Treatment, n</th>
<th>Follow-Up</th>
<th>End Point</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence for</td>
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<tr>
<td>Pezalla et al(^{17}) (2008)</td>
<td>Retrospective cohort</td>
<td>Heart disease and or risk factors</td>
<td>PPI, 626; no PPI, 384</td>
<td>1 y</td>
<td>MI</td>
<td>OR, 4.3 (95% CI, 2.2–8.4)</td>
</tr>
<tr>
<td>Ho et al(^{18}) (2009)</td>
<td>Retrospective cohort</td>
<td>Post-MI, ACS</td>
<td>PPI, 5244; no PPI, 2961</td>
<td>~3 y</td>
<td>Death, ACS</td>
<td>OR, 1.25 (95% CI, 1.11–1.41)</td>
</tr>
<tr>
<td>Juurlink et al(^{19}) (2009)</td>
<td>Nested case-control</td>
<td>Cases, 734 (PPI, 194); controls, 2057 (PPI, 424)</td>
<td>3 mo</td>
<td>Death, MI</td>
<td>OR, 1.27 (95% CI, 1.03–1.57)</td>
<td></td>
</tr>
<tr>
<td>Kreutz et al(^{20}) (2010)</td>
<td>Retrospective cohort</td>
<td>Poststenting</td>
<td>PPI, 6828; no PPI, 9802</td>
<td>1 y</td>
<td>CVA, ACS, Revascularization, CV death</td>
<td>HR, 1.51 (95% CI, 1.39–1.64)</td>
</tr>
<tr>
<td>Huang et al(^{21}) (2010)</td>
<td>Registry</td>
<td>Post-PCI</td>
<td>PPI, 572; no PPI, 2706</td>
<td>6 y</td>
<td>ACS, death</td>
<td>HR, 1.23 (95% CI, 1.07–1.41) and 1.65 (95% CI, 1.35–2.01)</td>
</tr>
<tr>
<td>Stockl et al(^{22}) (2010)</td>
<td>Retrospective propensity matching</td>
<td>Post-MI or stent</td>
<td>PPI, 1033; no PPI, 1033</td>
<td>1 y</td>
<td>MI, stent</td>
<td>HR, 1.64 (95% CI, 1.16–2.32)</td>
</tr>
<tr>
<td>Van Boxel et al(^{23}) (2010)</td>
<td>Retrospective cohort</td>
<td>Clopidogrel use</td>
<td>PPI, 5734; no PPI, 12 405</td>
<td>2 y</td>
<td>Death, ACS, CVA</td>
<td>HR, 1.75 (95% CI, 1.58–1.94)</td>
</tr>
<tr>
<td>Munoz-Torrero et al(^{24}) (2011)</td>
<td>Registry</td>
<td>Vascular disease</td>
<td>PPI, 519; no PPI, 703</td>
<td>15 mo</td>
<td>MI, CVA, CLI, death</td>
<td>HR, 1.8 (95% CI, 1.1–2.7)</td>
</tr>
<tr>
<td>Evidence against</td>
<td></td>
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<tr>
<td>O’Donoghue et al(^{25}) (2009)</td>
<td>Post hoc analysis of RCT</td>
<td>ACS and PCI</td>
<td>PPI, 2257; no PPI, 4,538</td>
<td>Up to 15 mo</td>
<td>MI, CVA, CV death</td>
<td>No effect</td>
</tr>
<tr>
<td>Rassen et al(^{26}) (2009)</td>
<td>Retrospective cohort</td>
<td>ACS or PCI</td>
<td>PPI, 3996; no PPI, 14 569</td>
<td>6 mo</td>
<td>MI, death, revascularization</td>
<td>No effect</td>
</tr>
<tr>
<td>Ray et al(^{27}) (2010)</td>
<td>Retrospective cohort</td>
<td>MI, revascularization, UA</td>
<td>PPI, 7593; no PPI, 13 003</td>
<td>1 y</td>
<td>MI, CVA, CV death</td>
<td>No effect</td>
</tr>
<tr>
<td>Charlot et al(^{28}) (2010)</td>
<td>Registry</td>
<td>MI</td>
<td>PPI, 6753; no PPI, 17 949</td>
<td>1 y</td>
<td>MI, CVA, CV death</td>
<td>No effect</td>
</tr>
<tr>
<td>Sarafoff et al(^{29}) (2010)</td>
<td>Retrospective cohort</td>
<td>Poststent</td>
<td>PPI, 698; no PPI, 2640</td>
<td>1 mo</td>
<td>Stent thrombosis</td>
<td>No effect</td>
</tr>
<tr>
<td>Tentzeris et al(^{30}) (2010)</td>
<td>Registry; propensity matching</td>
<td>Poststent</td>
<td>PPI, 691; no PPI, 519</td>
<td>1 y</td>
<td>Death, ACS</td>
<td>No effect</td>
</tr>
<tr>
<td>Banerjee et al(^{31}) (2011)</td>
<td>Retrospective propensity matching</td>
<td>Post-PCI</td>
<td>PPI, 867; no PPI, 3678</td>
<td>6 y</td>
<td>MACE</td>
<td>No effect</td>
</tr>
<tr>
<td>Simon et al(^{32}) (2011)</td>
<td>Registry</td>
<td>MI</td>
<td>PPI, 1453; no PPI, 900</td>
<td>1 y</td>
<td>MI, CVA, Death</td>
<td>No effect</td>
</tr>
<tr>
<td>Harjai et al(^{33}) (2011)</td>
<td>Registry; propensity matching</td>
<td>Post-PCI</td>
<td>PPI, 751; no PPI, 1900</td>
<td>6 mo</td>
<td>MACE</td>
<td>No effect</td>
</tr>
</tbody>
</table>

ACS indicates acute coronary syndrome; CI, confidence interval; CLI, chronic limb ischemia; CV, cardiovascular; CVA, cerebrovascular accident; HR, hazard ratio; MACE, major adverse cardiac events (death, myocardial infarction, revascularization); MI, myocardial infarction; OR, odds ratio; RCT, randomized controlled trial; and UA, unstable angina.


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