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## Proton Pump Inhibitors and Clopidogrel: Bad Company?

*In a large observational cohort of ACS patients, this drug combination was associated with poorer outcomes than was clopidogrel alone.*

Proton pump inhibitors (PPIs) are often prescribed to minimize gastrointestinal bleeding in patients taking clopidogrel (Plavix) after acute coronary syndromes (ACS). However, findings from small studies suggest that PPIs may reduce clopidogrel's efficacy. To determine whether such an interaction could have important clinical effects, investigators assessed outcomes in 8025 patients with ACS who were discharged from Veterans Affairs hospitals nationwide and who received clopidogrel with or without a PPI. The primary outcome was the composite of all-cause mortality and rehospitalization for ACS.

A majority (63.9%) of the patients were prescribed a PPI in conjunction with clopidogrel. In multivariable analysis, the use of a PPI with clopidogrel was associated with a significantly increased risk for the primary outcome compared with clopidogrel alone (odds ratio, 1.25; 95% confidence interval, 1.11–1.41). Secondary analyses suggested that these findings were driven by increases in hospitalization for recurrent ACS and in revascularization procedures but not in all-cause mortality. Use of clopidogrel without a PPI was not associated with adverse outcomes.

**Comment:** In this large, retrospective study, the use of PPIs appeared to attenuate the benefits of clopidogrel, resulting in increased rates of recurrent ACS and revascularization. Although these results bear the limitations of all

observational studies, they support the hypothesis that PPIs inhibit the anti-platelet effects of clopidogrel. Pending further research, clinicians should consider this potential interaction when they weigh the pros and cons of prescribing a PPI with clopidogrel for ACS patients.

— JoAnne M. Foody, MD

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### Citation(s):

Ho, P.M., et al. Risk of adverse outcomes associated with concomitant use of clopidogrel and proton pump inhibitors following acute coronary syndrome.

*JAMA* March 4, 2009; 301:937-944.



All of the above, including the title, appeared in *Journal Watch Cardiology*. This *Heartbeat* will propose a plan to handle this

issue until further data are available.

Clopidogrel is a prodrug converted in the liver to its active form by cytochrome P450 isoenzymes, with P450 2C19 playing a particularly important role. There is evidence suggesting that various PPIs can inhibit P450 2C19, which would decrease the effectiveness of clopidogrel and potentially lead to an increased risk of adverse cardiovascular outcomes. This study adds to other recent studies that suggest PPIs like

Aciphex (raberprazole), Nexium (esomeprazole magnesium), Prevacid (lansoprazole), Protonix (pantoprazole sodium), and Prilosec (omeprozole) OTC reduce the effectiveness of clopidogrel, resulting in a 25% increase in the risk of death and ACS.

**Adverse outcomes following hospital discharge for ACS**

Outcome	Clopidogrel without PPI (n=2961), %	Clopidogrel with PPI (n=5244), %	Adjusted odds ratio (95% CI)
Death or rehospitalization for ACS	20.8	29.8	1.25 (1.11-1.41)
Rehospitalization for ACS	6.9	14.6	1.86 (1.57-2.20)
Revascularization procedures	11.9	15.5	1.49 (1.30-1.71)
All-cause mortality	16.6	19.9	0.91 (0.80-1.05)

Ho, P.M., et al. *JAMA* 2009; 301: 937-944.

Dr. P. Michael Ho, a cardiologist at the Denver VA Medical Center and the lead author, states, "A lot of patients are on Plavix and also a lot of patients are being prescribed PPI medication just prophylactically to prevent a stomach bleed." He said that the "study doesn't change the reasons for prescribing Plavix," but he added that "both clinicians and patients should look at why the PPI is being prescribed. It shouldn't be prescribed prophylactically just to prevent a GI bleed, because there might be an interaction between the PPI and Plavix." Dr. Ho said a PPI "should only be prescribed to patients who have had a stomach bleed, since they are at higher risk of another bleed."

**SCAI issues a statement**

In light of the findings, the Society for Cardiovascular Angiography and Interventions (SCAI) issued a statement that patients taking dual anti-platelet therapy after undergoing PCI should continue taking their medications unless instructed to stop by their physicians.

Highlights from an expert consensus document developed by the American College of Cardiology (ACC), American Heart Association (AHA), and American College of Gastroenterology (ACG) <sup>1</sup> published in 2008 include the following:

1. Patients with a history of previous ulcer, gastrointestinal tract bleeding and who are to receive dual anti-platelet therapy or an anti-platelet medication plus an anticoagulant are considered high-risk and should receive gastrointestinal tract prophylaxis during treatment with an anti-platelet medication.
2. In addition, lower-risk patients with 2 or more of the following risk factors should receive gastrointestinal tract prophylaxis during anti-platelet therapy:
  - Age 60 years or older
  - Corticosteroid use
  - Dyspepsia or symptoms of gastroesophageal reflux disease
3. PPIs are the preferred medications and mainstay of treatment and prevention of gastrointestinal ulcers and bleeding in patients on anti-platelet therapy for the therapy and prophylaxis of NSAID- and ASA-associated gastrointestinal tract injury. Misoprostol is associated with adverse effects, which often lead to treatment discontinuation. Sucralfate and H2 receptor antagonists are not adequately effective in the prevention of NSAID and ASA-related gastric ulcers.
4. In patients with ulcer histories who are starting chronic anti-platelet therapy, clinicians should test for and eradicate *Helicobacter pylori* infections.

SCAI recommends physicians continue prescribing dual anti-platelet therapy after PCI according to the guidelines and **prescribe a PPI medication only when there is a significant high-risk clinical indication.** *The assumption here is that the risk of using PPI therapy in the lower- risk setting (#2 above) may be greater than the possible benefit. The ACC/AHA/ACG consensus guideline statement will have to be adjusted to reflect this recent information as millions of patients will be taking clopidogrel in combination with a PPI with resultant increased risk of CV events.*

### **Are All PPIs Equal?**

Recent findings from a large Canadian trial, reported in late January, suggest that all PPIs are not equal when it comes to inhibiting the anti-platelet activity of clopidogrel.<sup>2</sup> The study, conducted over 6 years in thousands of MI patients aged 66 years and older, found a significantly increased risk of readmission for MIs if patients were taking one of several PPIs, including omeprazole, lansoprazole, or rabeprazole. The investigators found no such association with pantoprazole or with H2 receptor antagonists.

In this study, according to study researcher David N. Juurlink, MD, PhD, "although most PPIs did appear to interact with Plavix, one – protonix (pantoprazole) – showed no evidence of reducing the effectiveness of the anti-platelet drug." He added, "Literally millions of people who are taking Plavix and aspirin are also taking a PPI," and "If a patient on Plavix requires a PPI, it would seem to make sense to preferentially give them pantoprazole."

### **Conclusions:**

Given the accumulating evidence, this study suggests that unless there is a clear high-risk indication for a PPI medication—where Protonix

would be the PPI of choice—other stomach medications (antacids) should be considered if patients are taking clopidogrel.

Patients should be cautioned about taking OTC Prilosec while taking clopidogrel post PCI unless instructed by a physician in this setting for a high-risk indication.

Consideration should be given to discontinuing clopidogrel in PCI patients after one year if the need for a PPI continues.

Overall, our review suggests that indiscriminate treatment with a PPI could result in thousands of additional cases of recurrent MI each year. This can be avoided simply by selectively prescribing pantoprazole in high-risk patients who require treatment with a PPI and avoiding their use in the lower risk patients receiving clopidogrel.

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<sup>1</sup> ACCF/ACG/AHA 2008 Expert Consensus Document on Reducing the Gastrointestinal Risks of Antiplatelet Therapy and NSAID Use. A Report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents. *Circulation* October 28 2008; 118: 1894-1909.

<sup>2</sup> Juurlink D N et al. Certain PPIs Increase Risk of Heart Attacks for Patients on Clopidogrel. *Canadian Medical Association Journal* March 2009 Online.