

More data support adverse clopidogrel and proton-pump inhibitor interaction

MARCH 3, 2009 | [Michael O'Riordan](#)

Denver, CO - More evidence published this week suggests that the concomitant use of clopidogrel (Plavix, Bristol-Myers Squibb/Sanofi-Aventis) and proton-pump inhibitors (PPIs) attenuates the benefits of antiplatelet therapy and increases the risk of future events. Among discharged acute coronary syndrome (ACS) patients prescribed the two drugs, there was an increased risk of adverse clinical outcomes compared with clopidogrel alone, including higher rates of death or rehospitalization for ACS [[1](#)].

"I don't think our study changes the guidelines or the recommendations for clopidogrel use after ACS hospitalization," lead investigator Dr P Michael Ho (Denver Veterans Affairs Medical Center, CO) told *heartwire*, "but it does suggest, along with other studies, that proton-pump inhibitors shouldn't be prescribed prophylactically just because the patient is on aspirin and clopidogrel. Given the accumulating evidence, this study suggests that unless there is a clear indication for the PPI medication, there might be other stomach medications that patients can take."

The results of the study are published in the March 4, 2009 issue of the *Journal of the American Medical Association*.

FDA issued an early communication about safety review

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 alter the effectiveness of clopidogrel and potentially lead to an increased risk of adverse cardiovascular outcomes. As noted by the investigators, many patients treated with clopidogrel and aspirin following ACS are also treated with PPIs to reduce the risk of gastrointestinal bleeding with dual antiplatelet therapy.

In January, the Food and Administration (FDA) announced it was continuing to study the effectiveness of clopidogrel in patients taking other medications, particularly PPIs, as well as in those with genetic variants linked with clopidogrel resistance. Despite the early communication from the FDA, the existing data were insufficient to make firm recommendations, leading investigators to analyze the interaction in a large cohort of Veterans Affairs patients.

In this retrospective cohort study, 8205 patients with ACS taking clopidogrel after discharge from the hospital between 2003 and 2006 were identified. Of these patients, 64% were prescribed a PPI at discharge or during follow-up, while 36% were not prescribed a PPI. Those prescribed a PPI tended to be older and have more comorbid disease, including higher rates of diabetes, prior MI, previous CABG surgery, peripheral vascular disease, and lung and renal disease.

Concomitant use of clopidogrel and a PPI was associated with a 25% greater risk of death or rehospitalization for ACS, the primary end point in this analysis. Individual end points, including rehospitalization for ACS and revascularization procedures, were also significantly increased with the combination, although all-cause mortality was not significantly different between the two treatment regimens.

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)

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Various sensitivity analyses examining time periods of use, as well as a nested case-control analysis, confirmed the findings and suggested it was the interaction of the medications responsible for the increased risk. The increased risk of an adverse outcome associated with the use of clopidogrel and PPI remained statistically significant after researchers excluded those with a history of gastrointestinal bleeding prior to hospitalization for ACS, those who had a bleeding event during hospitalization, and those prescribed an H₂-antagonist.

Speaking with *heartwire*, Ho noted that the risk appears primarily due to recurrent hospitalization for ACS, which is consistent with mechanistic studies suggesting an increased prothrombotic state due to the inhibition of platelet activity with clopidogrel and PPIs. He noted that 8% of patients in this study had a previous history of gastrointestinal bleeding, while 25% had an in-hospital bleed or during follow-up, making them eligible for a PPI. Still, with 64% prescribed a PPI in this study, "it suggests there are a large number of patients prescribed the drug prophylactically," said Ho.

Regarding the lack of mortality risk associated with the interaction, Ho said that researchers had access only to all-cause mortality data and that more detailed causes of death might show a signal, particularly with cardiovascular death.

The researchers also note that 60% of patients taking a PPI were prescribed omeprazole, a drug available over the counter since 2003, and that there was a strong association between its use with clopidogrel and adverse clinical outcomes. Overall, said Ho, the findings highlight the importance of a drug interaction not observed in large clinical trials and suggest that drug surveillance is critical after drug approval to monitor unintended side effects and interactions.

SCAI issues a statement

In light of the findings, the Society for Cardiovascular Angiography and Interventions (SCAI) issued a statement that patients prescribed clopidogrel and other antiplatelet medications after undergoing interventional cardiology procedures should continue taking the drugs unless told to stop by their physician.

An expert consensus document developed by the American College of Cardiology, American Heart Association, and American College of Gastroenterology and published in 2008 notes that PPIs should be the mainstay of treatment and prevention of gastrointestinal ulcers and bleeding in patients on antiplatelet therapy who are at increased risk for the gastrointestinal complications. High-risk patients who might benefit from a PPI include patients with a history of ulcer disease, gastrointestinal bleeding, a need for dual antiplatelet therapy, or an indication for warfarin or other anticoagulants, according to the report.

SCAI recommends physicians continue prescribing dual antiplatelet therapy after stent implantation according to the guidelines and prescribe a PPI medication when there is a clinical indication for it.

Source

1. Ho PM, Maddox TM, Wang L, et al. Risk of adverse outcomes associated with concomitant use of clopidogrel and proton pump inhibitors following acute coronary syndrome. *JAMA* 2009; 301:937-944. 

Related links

- [Increased risk of reinfarction with clopidogrel and proton-pump inhibitors](#)
[Acute Coronary Syndrome > Acute coronary syndromes; Jan 29, 2009]
- [Genetic variant linked with worse clinical outcomes in MI patients treated with clopidogrel](#)
[Acute Coronary Syndrome > Acute coronary syndromes; Dec 24, 2008]
- [Testing and acting on clopidogrel nonresponsiveness: Intense interest and confusion](#)
[Acute Coronary Syndrome > Acute coronary syndromes; Dec 18, 2008]
- [Aspirin resistance linked to worse outcomes](#)
[Prevention > Prevention; Jan 18, 2008]
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