Impact of PPIs on Clopidogrel Activity Uncertain

BY MITCHEL L. ZOLER

NEW ORLEANS — A possible interaction between proton pump inhibitors and the antiplatelet drug clopidogrel remains a potential concern and became a muddled issue when findings from two independent studies produced diametrically opposed results.

A review of more than 16,000 patients who were prescribed clopidogrel (Plavix) after they had undergone a percutaneous coronary intervention (PCI) found that the patients who were also taking a proton pump inhibitor (PPI) had a significantly higher risk of having a major adverse cardiovascular event, compared with patients not on a PPI, according to a study from Medco Health Solutions Inc. reported at the annual scientific sessions of the American Heart Association.

'There is nothing to warrant changing clinical practice, or hesitating to administer a PPI.'

DR. BHATT

In contrast, a second report at the same session of a post hoc analysis of data collected in a trial of clopidogrel in more than 2,000 patients undergoing PCI found no indication of any interaction between clopidogrel and concurrent PPI use, according to Steven P. Dunn, Pharm.D., a researcher at the University of Kentucky, Lexington.

Given these two conflicting findings, "at this time there is nothing to warrant changing clinical practice, or hesitating to administer a PPI and clopidogrel to patients when clinically indicated," commented Dr. Deepak L. Bhatt, chief of cardiology for the VA Boston Healthcare System, who chaired the session where the two reports were presented.

A similar call for not changing current practice on the basis of the two reports came in a joint statement issued by the American Heart Association, American College of Cardiology, and American College of Gastroenterology. "Neither of the studies presented today provides sufficient evidence to change clinical practice," said the statement. "Patients currently taking these medications should not change their medication regimen unless advised by their health care provider."

The idea that treatment with a PPI could blunt the action of clopidogrel originated with French researchers, who realized that PPIs such as omeprazole exert competitive metabolic effects on one of the main liver enzymes that converts clopidogrel, a prodrug, into its active form. Hence, concurrent treatment with both drugs could result in reduced clopidogrel activity and enhanced platelet activity despite clopidogrel treatment. The ability of omeprazole to decrease clopidogrel's effect on platelets was shown in studies done at Brest (France) University Hospital (J. Am Coll. Cardiol. 2008; 51:256-60), but those studies did not examine the impact of the PPI on clinical outcomes in patients on clopidogrel.

To answer the clinical question, Ronald E. Aubert, Ph.D., and his associates at Medco retrospectively studied patients who had undergone a PCI and were using prescribed drugs provided through Medco. The group included 9,862 patients treated with clopidogrel only and 6,828 patients taking both clopidogrel and a PPI. Concurrent PPI therapy was defined as any PPI prescription record that overlapped with the clopidogrel prescription record during the 12 months following the index PCI. The study was funded entirely by Medco.

During this follow-up, the relative risk for a major cardiovascular event, such as MI, stroke, or hospitalization for angina, was 50% higher among patients on both a PPI and clopidogrel, compared with those on clopidogrel alone, in an analysis that adjusted for baseline differences among the patients in the two groups, Dr. Aubert reported.

Medco plans to assess the feedback it is receiving based on its report at the meeting, prepare a final manuscript of its findings for publication, and then alert physicians about the study findings

and their implications, a company spokesperson said.

The second study reported at the meeting used data collected in the Clopidogrel for the Reduction of Events During Observation (CREDO) trial, which compared clopidogrel with placebo for reducing the risk of adverse ischemic events in patients the first year after PCI. The primary finding showed that clopidogrel treatment cut the combined ischemic event rate by an absolute 3% (relative risk reduction was 27%), compared with placebo (JAMA 2002;288:2411-20).

The new post hoc analysis compared the 374 patients in the study who were prescribed a PPI at the time they entered the study with 1,742 patients without a PPI prescription. This analysis showed that during both 28-day and 1-year follow-up, patients who received PPI treatment had no statistically significant difference in their relative rate of ischemic events in both the clopidogrel and the placebo arms of the study, compared with patients not on a PPI. Patients on a PPI had higher rates of ischemic events, but this increase was seen in both the clopidogrel and the placebo arms, suggesting that while the patients on a PPI were more susceptible to ischemic events overall, there was no link between PPI use and a blunting of clopidogrel's efficacy, Dr. Dunn said.

This new analysis received no commercial funding, and Dr. Dunn said that he had no financial disclosures to report.

"The event rates were higher in the patients on PPIs, but there is no indication that it was because of the PPIs. It may be because they are sicker patients," Dr. Bhatt commented.

"I do not think there is enough evidence yet to change practice. Patients who have a clinical indication to be on clopidogrel should certainly remain on it. Likewise, patients who have a good reason to be on a PPI should stay on it," Dr. Bhatt said in an interview.

He added that a study now in progress should be able to more definitely address this issue because it is prospectively randomizing and comparing post-PCI patients treated with aspirin and clopidogrel alone and those treated with these two drugs plus omeprazole. The Clopidogrel and Optimization of Gastrointestinal Events (COGENT-1) trial has enrolled about 5,000 patients, and is planned to be complete by the end of 2009. ■