

**American College of Cardiology (ACC)/American College of Gastroenterology
(ACG)/American Heart Association (AHA) Joint Comment on Studies Regarding Possible
Interaction of Clopidogrel and Proton Pump Inhibitors**

Two studies released today at the American Heart Association Scientific Sessions 2008 came to opposite conclusions in studying whether a class of heartburn drugs called proton pump inhibitors (PPIs) alter the ability of clopidogrel, an anti-platelet drug, to prevent cardiovascular events after stent placement. American College of Cardiology (ACC)/American Heart Association (AHA) guidelines and statements recommend dual anti-platelet therapy (aspirin plus a thienopyridine such as clopidogrel) following stent placement. Previous research shows that combining a PPI with clopidogrel lessens the risk of GI bleeding. However, other recent studies have suggested that adding a PPI could blunt clopidogrel's anti-platelet effect. This interaction has not been studied in large numbers of patients, so there is no definitive evidence that the use of PPIs will keep clopidogrel from working to prevent cardiac events.

Neither of the studies presented today provides sufficient evidence to change clinical practice. In the interest of patient safety, the AHA/ACC and the American College of Gastroenterology (ACG) advise that patients who are currently taking these medications should not change their medication regimen unless advised by their healthcare provider.

The first study (Abstract # 3998) reviewed major adverse cardiac events (hospitalization for stroke, heart attack, angina or bypass surgery) over one year in patients prescribed clopidogrel after stent placement. The study group included 14,383 patients in the Medco Integrated Database who were at least 80 percent compliant with refilling their medication. Patients who took clopidogrel alone were compared with those taking clopidogrel and PPIs.

The study found that patients receiving both medications had significantly more major cardiovascular events in a year than patients taking clopidogrel alone. However, the patients taking both medications had a higher cardiovascular risk factor profile (age, gender, diabetes, hypertension, chronic kidney disease). There are several significant limitations to this type of study, as acknowledged by the authors. The database did not include information about participants' use of over-the-counter drugs (including aspirin or omeprazole) and could not account for other cardiovascular risk factors such as family history, smoking status, blood pressure levels and lipid values. As the authors themselves concluded, further investigation should focus on prospective study of this interaction.

The second study (Abstract #3999) reported no adverse effect of combining a PPI with clopidogrel. CREDO previously found a benefit of one year vs. one month of treatment with clopidogrel after coronary stenting. The sub-group analysis reported today assessed the endpoint of death, MI or stroke in patients on clopidogrel or placebo with or without a PPI, and showed no adverse effect of combining a PPI with clopidogrel. Patients treated with a PPI were at higher baseline risk and had a worse outcome compared to those who were not, whether they were given placebo or clopidogrel.

The ongoing COGENT-1 study should help answer some of these questions – this trial is randomizing patients with coronary artery disease to ASA plus clopidogrel in combination with 20 mg of omeprazole (a PPI) or placebo and should provide further evidence to help address these issues. Other clinical trials are needed to fully explore this issue.

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