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ARTICLE (starts on next page)

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PPI Interactions with Clopidogrel

Clopidogrel *(Plavix),* which prevents arterial thrombosis by inhibiting platelet activation, is commonly prescribed (usually with aspirin) for months after acute coronary syndromes and stent implantation.[1] It may also, however, increase the risk of bleeding.[2] Therefore, a proton pump inhibitor (PPI) such as omeprazole (*Prilosec*, and others) is often given concurrently to decrease the risk of gastrointestinal (GI) bleeding.[2] Some reports have suggested that omeprazole may interfere with the antiplatelet effect of clopidogrel.

PHARMACOKINETICS — Clopidogrel is a prodrug that is activated by CYP450 enzymes in the liver, principally (it is thought) by CYP2C19. Omeprazole is a strong inhibitor of CYP2C19, but all PPIs may inhibit CYP2C19 to some extent.[3] Patients who are carriers of CYP2C19 loss-of-function polymorphisms (common in East Asians) show a marked decrease in platelet responsiveness to clopidogrel.[4]

AN *EX VIVO* STUDY — A randomized, double-blind study in 124 patients taking aspirin-clopidogrel antiplatelet therapy after coronary stent implantation compared the effects of omeprazole or placebo on the ability of clopidogrel to inhibit platelet activation in blood samples from the patients. After 7 days of use, omeprazole decreased the antiplatelet effect of clopidogrel.[5] A similar study found no such interaction between esomeprazole or pantoprazole and clopidogrel.[6]

CLINICAL STUDIES — In a retrospective cohort study using an administrative claims database and published only as a letter to the editor, the Aetna Insurance Company compared myocardial infarction (MI) rates in members receiving clopidogrel with or without a PPI for one year. MIs occurred in 1.38% (66/4800) with clopidogrel alone, in 3.08% (22/712) with "low" PPI exposure, and in 5.03% with "high" PPI exposure (not defined). Among the subset of patients who had significant risk factors such as hypertension or diabetes, MIs occurred in 2.6% (10/384) on clopidogrel alone, 10.0% (9/90) with low PPI exposure, and 11.4% (61/536) with high PPI exposure. The high PPI exposure group had a greater number of patients with pre-existing hypertension and diabetes. Which PPIs were used was not specified.[7]

A retrospective cohort study, published only as an abstract, of more than 14,000 patients who took clopidogrel for 1 year after stent placement (and were at least

Table 1. Proton Pump Inhibitors for Peptic Ulcers/GERD

Drug	Dosage[1]	Tablet/Capsule Size	Cost[2]
Esomeprazole – *Nexium* (AstraZeneca)	20-40 mg once daily	20, 40 mg caps[3]	$172.80
Lansoprazole – *Prevacid* (TAP)	15-30 mg once daily[4]	15, 30 mg tabs, ODT	156.30
Omeprazole – generic	20-40 mg once daily[4]	10, 20, 40 mg caps	92.10
Prilosec (AstraZeneca)			141.90
Prilosec OTC		20 mg tabs	26.99[5]
generic			21.99[5]
Zegerid		20, 40 mg caps[3,6]	150.60
Pantoprazole – generic	20-40 mg once daily	20, 40 mg tabs	112.50
Protonix (Wyeth)			133.80
Rabeprazole – *Aciphex* (Janssen)	20 mg once daily	20 mg tabs	179.70

OTC = Over the counter; ODT = orally disintegrating tabs.
1. The lower end of the range is generally used for initial treatment of GERD. Customary doses of antisecretory drugs may not be effective in patients with peptic ulcers due to hypersecretory states like Zollinger-Ellison Syndrome.
2. Cost for 30 days' treatment at the lowest dosage, according to the most recent data (November 30, 2008) from retail pharmacies nationwide available from Wolter's Kluwer Health.
3. Also available as an oral suspension, syrup or solution.
4. Lower dose is for GERD and duodenal ulcer; higher dose is for gastric ulcer.
5. Cost of a box of 42 tablets from drugstore.com (accessed December 19, 2008).
6. Both strengths contain sodium bicarbonate 1.1 g; therefore, two 20-mg caps are not equivalent to a 40-mg cap.

80% adherent) compared the incidence of major cardiovascular events in those who took clopidogrel alone (n >9000) with those who also took a PPI (n >4000). Patients taking both drugs had more cardiovascular risk factors and more major cardiovascular events.[8]

A sub-set analysis, also published only as an abstract, of an earlier study (CREDO) that compared clopidogrel with placebo for 1 year after stenting found that patients randomized to clopidogrel who also received a PPI at the discretion of their physician had a higher incidence of cardiovascular events after 1 year compared to those not receiving a PPI, but the same was true of those randomized to placebo.[9]

A prospective, randomized, placebo-controlled trial (COGENT) of clopidogrel plus omeprazole is in progress.

CONCLUSION — Whether omeprazole or other PPIs could interfere with the antiplatelet effect of clopidogrel enough to increase the incidence of cardiovascular events after coronary stenting is unclear. The increased incidence of such events reported retrospectively could also reflect increased risk factors among PPI users. Patients taking both drugs concurrently should probably continue to do so until more data become available.

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