In January 2009, the FDA issued an alert regarding the potential for differences in effectiveness of clopidogrel due to genetic differences in clopidogrel metabolism or the interference of therapeutic effect due to drug-drug interaction. Several reports have been published indicating that PPIs may make clopidogrel less effective. This issue of CLIPs reviews two clinical trials that have been published evaluating the potential for drug-drug interactions between PPIs and clopidogrel. If you need further information, please contact the Samford University Global Drug Information Service at (205) 726-2659.


**Study Question:** Does concomitant administration of clopidogrel with or without a PPI after hospitalization increase the risk of acute coronary syndrome (ACS) or rehospitalization for ACS?

**Primary Endpoint:** Combined endpoint of all-cause mortality or rehospitalization for ACS.

**Secondary Endpoint:** Rehospitalization for ACS; revascularization procedures; percutaneous coronary intervention (PCI) or coronary artery bypass graft surgery; and all cause mortality following index ACS hospitalization.

**Methods:** A retrospective, cohort study was conducted to assess the outcomes of patients receiving clopidogrel with (n=5244) or without (n=2961) a proton pump inhibitor after hospitalization for an ACS. Clopidogrel and PPI use were based on pharmacy refill data.

**Results:**
- The majority of patients in the study were > 65 years, male, presented with NSTEMI, and were prescribed aspirin, a β blocker, ACE inhibitor, and statin at discharge.
- The median follow up time after hospital discharge was 521 days.
- There were 3132 (59.7%) patients prescribed omeprazole, 151 (2.9%) prescribed rabeprazole, 22 (0.4%) prescribed lansoprazole, and 15 (0.2%) prescribed pantoprazole.
- The primary endpoint occurred in 20.8% (n=1561) of patients prescribed clopidogrel with a PPI and 29.8% (n=1561) of patients prescribed clopidogrel plus a PPI (adjusted OR [AOR], 1.25; 95% CI, 1.11-1.41).
- Statistically significant differences for the secondary outcomes were reported (e.g., rates of recurrent hospitalization for ACS (14.6% vs. 6.9%, p<0.001); revascularization procedures (15.5% vs. 11.9%; p<0.001) and death (19.9% vs. 16.6%; p<0.001)) in patients receiving clopidogrel plus PPI compared with those taking clopidogrel without PPI.

**Conclusion:** The investigators’ concluded that concomitant use of clopidogrel and a PPI after hospital discharge for ACS resulted in a significantly increased risk of adverse effects compared to patients who received clopidogrel therapy alone.

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Juurlink DN, Gomes T, Ko DT. A population-based study of the drug interaction between proton pump inhibitors and clopidogrel. CMAJ. 2009;180(7):713-718.

Study Question: Does concomitant use of clopidogrel and PPIs increase the risk of adverse outcomes among older patients discharged from the hospital after acute myocardial infarction?

Primary Endpoint: Reinfarction and exposure to a PPI.

Secondary Endpoint: Recurrent MI with previous or remote PPI use, death < 90 days, and PPI use.

Methods: A population-based study of the drug interaction between PPIs and clopidogrel received after hospital discharge after treatment of acute myocardial infarction. Ontario residents ≥ 66 years discharged from the hospital after treatment for AMI and filled a prescription for clopidogrel within 3 days of hospital discharge were included. Patients in the study were matched to cases (patients who died or were readmitted for MI within 90 days after the initial hospital discharge). PPI use was evaluated by obtaining prescription records of the Ontario Public Drug Program. PPI use was categorized according to the most proximate prescription as either current (within 30 days before the index date), previous (31-90 days before the index date), or remote (91-180 days before the index date).

Results:
- A total of 13,636 patients ≥ 66 years who filled a prescription for clopidogrel within 3 days following hospital discharge for AMI were identified over the 69-month study period.
- The mean age of patients was 76 years, the median length of stay during hospital admission was 5 days, and 4022 (29.5%) of patients underwent PCI.
- Approximately 19.7% of patients received a prescription for a PPI within 30 days of discharge and 4224 (31%) of patients received a prescription for a PPI within 90 days.
- A significant association between readmission because of MI and current use of a PPI was found (AOR 1.27, 95% CI [1.03-1.57], but not with earlier use of PPIs.
- Previous or remote PPI use was not associated with recurrent MI (OR 0.86 [95%CI 0.63-1.19]; OR 0.81 [95% CI 0.57-1.18]).
- Death < 90 days was not significant between groups (OR 0.82, 0.57-1.18).
- In a subgroup analysis, pantoprazole was not associated with recurrent MI among patients receiving clopidogrel (OR 1.02, [95% CI, 0.70-1.47]) compared to other PPIs (AOR, 1.40 [95% CI 1.1-1.77]).

Conclusion: The investigators’ concluded that among older patients receiving clopidogrel following acute MI, concomitant use of a PPI was associated with an increased risk of reinfarction.

COMMENTARY
An association between use of clopidogrel and PPIs and risk for reinfarction after myocardial infarction exists; however, neither of these studies can be considered a controlled clinical trial (CCT). CCTs are the best study design to determine a cause and effect relationship between an intervention and outcome of interest and should be conducted to quantify the cardiovascular risks of this combined therapy.

The absolute risk increase (ARI) of the primary endpoint between the two groups was 9.8% in the trial by Ho et al compared to an ARI of 4.8% in the Juurlink et al study. Although a statistically significant increase in events was reported by Ho et al, this may be an underestimation of the effect since PPIs are available OTC and the patients in this study received their medications via the VA hospital and may not be as willing to purchase OTC medications. Cardiovascular risk factors were not assessed and imbalances existed between the measured characteristics of the cases and controls in the study by Jurrlink et al. Genetic polymorphisms of 2C19 were not assessed and ethnicity was not readily discussed in either study. Pantoprazole may be less inhibited by CYP450 2C19 and may be a better option for patients receiving clopidogrel. Other alternatives may need to be considered when patients are receiving clopidogrel after an AMI including H2 antagonists (with the exception of cimetidine).

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