



---

# NATIONAL PBM BULLETIN

FEBRUARY 12, 2010

---

VETERANS HEALTH ADMINISTRATION (VHA) PHARMACY BENEFITS MANAGEMENT SERVICES (PBM),  
MEDICAL ADVISORY PANEL (MAP), & CENTER FOR MEDICATION SAFETY (VA MEDSAFE)

## CLOPIDOGREL AND OMEPRAZOLE DRUG INTERACTION

### I. ISSUE

The FDA recently released an alert regarding new safety information concerning an interaction between clopidogrel and omeprazole, a proton pump inhibitor (PPI). Trials completed by the manufacturer of clopidogrel demonstrate that when clopidogrel and omeprazole are taken together, the effectiveness of clopidogrel based on platelet aggregation profiles, and area under the concentration time curve, or AUC is reduced, although the clinical effects are unclear.

### II. BACKGROUND

Clopidogrel is a prodrug, and requires biotransformation to the active compound. This bioactivation occurs via the hepatic cytochrome P450 (CYP) enzyme system, which is the same metabolic pathway used by PPIs. Theoretically, the 2C19 pathway may display competitive inhibition when both clopidogrel and a PPI are given concurrently. This may result in a decreased concentration of the active clopidogrel moiety resulting in less effect on platelet aggregation factors. Another mechanism for this potential decreased effect may be the genetic polymorphisms displayed in the cytochrome P450 system, resulting in insufficient 2C19 activity.

New studies cited in the FDA alert compared the amount of clopidogrel's active metabolite in the blood and its effect on platelets in healthy volunteers who took clopidogrel plus omeprazole versus those who took clopidogrel alone. A reduction of about 45% in active metabolite levels (with similar reduction in the effect on platelets) was found in people who received clopidogrel with omeprazole compared to those taking clopidogrel alone. These reductions were seen whether the drugs were given at the same time or 12 hours apart. The dose of omeprazole used in these investigations was 80 mg daily, higher than the doses employed in actual patients.

Overall, the clinical relevance of a PPI-clopidogrel interaction remains unclear. Retrospective reviews and prescription database studies have demonstrated variable and inconsistent effects on outcomes compared to a control group. Various studies have provided contradictory results in terms of which PPI are implicated in the designated adverse outcome. Currently, the best available evidence (post-hoc analyses of intervention trials, TRITON-TIMI & CREDO; modified assessment of an RCT outcome assessment in COGENT) suggest that PPI-clopidogrel combinations do not have clinically-relevant adverse outcomes. All of the analyses have limitations however. For example, while some retrospective reviews have suggested that combined use of clopidogrel and PPI may result in an increased risk of coronary events compared to groups that do not take a PPI with clopidogrel therapy, these studies are limited by their ability to fully control for known variables that may confound the results (i.e., years of risk factor presence, weight gain, smoking history, family history of coronary artery disease).

### III. SUMMARY POINTS

1. Clopidogrel requires bioactivation by cytochrome P450 isoenzymes in the liver in order to exert its inhibitory effect on platelet aggregation.
2. Polymorphisms resulting in decreased enzymatic expression of cytochrome P450 2C19 and competitive inhibition of this isoenzyme by proton pump inhibitors impair activation of clopidogrel.
3. Up to 33% of patients have an inadequate response to clopidogrel (measured by platelet aggregation studies) due to polymorphisms.
4. All the PPI have some degree of involvement with the 2C19 pathway. It is unclear which agent(s) may have the least effect on the conversion of clopidogrel.
5. Judgments regarding causality (e.g., do PPIs decrease clopidogrel's clinical efficacy) must be made by critically assessing the totality of available evidence. The available evidence on the interaction contains many levels; retrospective database reviews, retrospective case series, prospective trials with surrogate (not clinical) outcomes, subgroup analysis from major clinical trials and one incomplete randomized trial.

6. The FDA alert bases its warning on new studies conducted by clopidogrel's manufacturer that compared the amount of clopidogrel's active metabolite in the blood of healthy volunteers and its effect on platelets in people who took clopidogrel plus omeprazole vs. those who took clopidogrel alone.
7. These trials used omeprazole 80 mg per day (a higher dose than used in the majority of patients).
8. Whether clopidogrel plus omeprazole was given concomitantly or administered 12 hours apart did not seem to result in significant differences in terms of potency of antiplatelet effect.
9. Because of potential unknown effects or interactions, it is not always possible to extrapolate an altered response to a drug in an in vitro test of platelet reactivity to clinical events or outcomes.
10. The currently available evidence does not justify a conclusion that PPI use increases the risk of cardiovascular events in patients who are also taking clopidogrel.

#### IV. PROVIDER RECOMMENDATIONS

1. Patients should first be evaluated for the necessity of PPI therapy.
2. Consideration should be given to using alternative anti-secretory agents. Histamine-2-receptor antagonists (H2 blockers) have demonstrated a decrease in endoscopic ulcers in low dose aspirin users. Patients taking clopidogrel plus aspirin, especially with other GI risk factors such as prior ulcer or bleeding and concomitant nonsteroidal anti-inflammatory (NSAID) drug or anticoagulant therapy, should receive GI-protective therapy. H2 blockers (other than cimetidine) may be an appropriate alternative.
3. If continuing PPI therapy is deemed necessary, a discussion should be held with the patient about the potential risks and benefits of PPIs and clopidogrel, and this should include information about the FDA warning on omeprazole.
4. If a provider or patient feels uncomfortable with continuing omeprazole, and a PPI is deemed necessary, then an alternate PPI, such as pantoprazole, should be made available.

#### V. REFERENCES

1. MedWatch: The FDA Safety Information and Adverse Event Reporting Program  
<http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHealthcareProfessionals/ucm190787.htm>  
(Posted 11-17-09)
2. PBM response to the clopidogrel-omeprazole FDA Alert.  
[http://www.nationalcmop.va.gov/PBM/Clinical%20Guidance/Clinical%20Recommendations/PBM%20Response%20clopidogrel-omeprazole%20FDA%20alert%20\(1%202023%202010\).doc](http://www.nationalcmop.va.gov/PBM/Clinical%20Guidance/Clinical%20Recommendations/PBM%20Response%20clopidogrel-omeprazole%20FDA%20alert%20(1%202023%202010).doc) ( updated Jan 23, 2010)
3. Juurlink DN, Gomes T, Ko DT, et al. A population-based study of the drug interaction between proton pump inhibitors and clopidogrel. *CMAJ*. 2009;180(7). Epub 28 Jan 2009.
4. 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.
5. Pezella E, Day D, Pulliathath I. Initial assessment of clopidogrel impact of a drug interaction between clopidogrel and proton pump inhibitors. *JACC*. 2008;52:1038-1039.
6. Stanek EJ, Aubert RE, Flockhart DA, et al. Abstract O-11: A national study of the effect of individual proton pump inhibitors on cardiovascular outcomes in patients treated with clopidogrel following coronary stenting: *The Clopidogrel Medco Outcomes Study*. Presented at: The Society for Cardiovascular Angiography and Interventions, 2009; Las Vegas, NV.
7. Sibbing D, Kastrati A. Risk of combining PPIs with thienopyridines: fact or fiction? *Lancet*. 2009 Sep 19;374(9694):952-4.
8. O'Donoghue ML, Braunwald E, Antman EM, et al. Pharmacodynamic effect and clinical efficacy of clopidogrel and prasugrel with or without a proton-pump inhibitor: an analysis of two randomized trials. *Lancet*. 2009; Early access..
9. Bhatt DL, Cryer B, Contant CF, et al. The COGENT Trial. Presented at Transcatheter Cardiovascular Therapeutics, 2009; San Francisco, CA. Available at [http://assets.cardiosource.com/Bhatt\\_COGENT.ppt](http://assets.cardiosource.com/Bhatt_COGENT.ppt). Accessed on September 28, 2009
10. PLAV 010, Bristol-Myers Squibb Company, Princeton, NJ.
11. PLAV 011, Bristol-Myers Squibb Company, Princeton, NJ.
12. Norgard NB, Mathews KD, and Wall GC. Drug-Drug Interaction Between Clopidogrel and the ProtonPump Inhibitors *Ann Pharmacother* 2009;43:1266-74.
13. Rassen, JA, Choudhry, NK; Avorn, J; Schneeweiss, S. Cardiovascular Outcomes and Mortality in Patients Using Clopidogrel With Proton Pump Inhibitors After Percutaneous Coronary Intervention or Acute Coronary Syndrome (*Circulation*. 2009;120:2322-2329)
14. Laine L, Hennekens C. Proton pump inhibitor and clopidogrel interaction: fact or fiction? *Am J Gastroenterol*. 2010 Jan;105(1):34-41.

#### **ACTIONS:**

- **Facility COS and Chief Nurse Executives:** Forward this document to all appropriate providers who prescribe/use/handle this agent (e.g., **primary care providers, Cardiology, and Neurology, including contract providers, etc.**). In addition, forward to the Associate Chief of Staff (ACOS) for Research and Development (R&D). Forward to other VA employees as deemed appropriate.
- **ACOS for R&D:** Forward this document to Principal Investigators (PIs) who have authority to practice at the facility and to your respective Institutional Review Board (IRB).