

Truth or Fiction: PPIs Inhibit Clopidogrel Effectiveness?

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Studies showing a decrease in clopidogrel's active metabolite and effect on platelets of patients taking clopidogrel with proton pump inhibitors (PPI) prompted the FDA to issue a public health advisory warning that omeprazole may reduce the antithrombotic effects of clopidogrel.^{1,2} Still at issue is whether this interaction affects clinical outcomes for patients at risk of myocardial infarction (MI) or stroke.

Some observational studies have indicated patients taking clopidogrel with a PPI versus those taking clopidogrel without a PPI are at greater risk of cardiovascular events.^{3,4,5} However, the validity of these studies is uncertain because of difficulty controlling for confounders that may affect the actions of clopidogrel or have an association with both increased risk of repeat MI and PPI use. Since these observational studies were published, other studies have cast doubt on the clinical significance of the reported interaction between clopidogrel and PPIs.^{15, 18}

Clopidogrel is an antithrombotic agent indicated for the reduction of atherothrombotic events in patients with a history of recent myocardial infarction (MI), recent stroke, established peripheral arterial disease (PAD), or acute coronary syndrome (ACS).⁶ The American College of Cardiology (ACC) and the American Heart Association (AHA) recommend dual therapy with aspirin and clopidogrel for many patients who have a history of ACS.⁷ Clopidogrel also is recommended in those with a history of PAD or stroke who are intolerant to aspirin.^{8, 9} PPIs often are prescribed in these patients to reduce the risk of gastrointestinal bleeding. The ACC Foundation, American College of Gastroenterology, and AHA consensus document on reducing the gastrointestinal risks of using antiplatelet therapy and NSAIDs supports this strategy.¹⁰

Clopidogrel is a prodrug whose active metabolite inhibits platelet activation by irreversibly preventing adenosine diphosphate (ADP) from binding to the P2Y₁₂ receptor on platelets. Cytochrome P450 enzymes, most notably CYP2C19, convert clopidogrel to its active metabolite. Therefore, PPIs that are substrates and inhibitors of CYP2C19 could attenuate clopidogrel's activity by mitigating conversion of the prodrug into its active metabolite.¹¹

Two types of studies have predominated in the literature suggesting a drug interaction between clopidogrel and proton pump inhibitors:

- (1) *ex vivo* pharmacodynamic studies that measure the effect of PPIs on clopidogrel's ability to inhibit platelet aggregation; and
- (2) observational studies comparing the risk of adverse clinical outcomes for patients treated with clopidogrel with and without a PPI, including adverse cardiovascular events, revascularization, and death.

The Omeprazole Clopidogrel Aspirin (OCLA) study has been the only randomized, double-blind, placebo-controlled trial to assess whether clopidogrel's actions would be reduced in coronary stent implantation patients also receiving omeprazole.¹² The study measured subjects' mean platelet reactivity index (PRI), a surrogate endpoint that correlates with platelet aggregation inhibition.

One hundred forty patients receiving clopidogrel (300 mg loading dose followed by 75 mg daily) and aspirin (75 mg daily) were randomized 1:1 to receive omeprazole 20 mg or placebo for 7 days. Mean PRI on day 1 was compared with mean PRI on day 7 for 124 patients. Results revealed an attenuated response to clopidogrel in omeprazole-treated patients as measured by PRI. On day 1, mean PRI was 83.9 ± 4.6% and 83.2 ± 5.6% for omeprazole and placebo groups, respectively, while on day 7, mean PRI was 51.4% ± 16.4 and 39.8 ± 15.4% ($p < 0.0001$).

Though the OCLA study demonstrated a pharmacodynamic interaction between omeprazole and clopidogrel, it could not address whether the interaction impacted clinical outcomes. Three published observational studies are commonly cited as evidence for the existence of an association between

increased incidence of cardiovascular events and the use of clopidogrel with a PPI: two retrospective cohort studies and a population-based, nested-case control study.

Pazella et al. conducted a retrospective cohort study by examining medical and pharmacy claims databases for acute MI rates in members younger than age 65 receiving clopidogrel with and without a PPI.³ Patients were assigned to no, low or high PPI exposure based on adherence rates; however, the study left the adherence rates undefined. The study concluded one year acute MI rates were higher for patients exposed to PPIs than patients not exposed to PPIs: 1.38% for patients without PPI ($n=4800$), 3.08% for those with low PPI exposure ($n=712$), and 5.03% for those with high PPI exposure (n not published) ($p < 0.05$ for the high exposure group versus no PPI). This study was published as a correspondence and did not delineate methods, population demographics, baseline characteristics, or clopidogrel indication.

Juurlink et al. conducted a population-based, nested case-control study using linked hospital admission, medical claims, and prescription records of Ontario residents.⁴ The population was comprised of patients aged 66 years or older who received clopidogrel following hospital discharge after MI. The cases were patients who were readmitted for acute MI or had died within 90 days of discharge ($n=734$). Controls ($n=2057$) were patients without an MI, were matched to cases on age, receipt of percutaneous coronary intervention (PCI), date of hospital discharge, and predicted probability of short-term mortality. The study concluded patients diagnosed with MI who received a clopidogrel prescription and a PPI had increased odds of reinfarction versus those not taking a PPI. The odds ratio, adjusted using conditional logistic regression, was 1.27 (CI 1.03–1.57). The study did not control for previous MI, history of PAD, and cardiac risk factors such as tobacco use, BMI, hypertension, family history of coronary artery disease, and hypercholesterolemia.

Ho et al. conducted a retrospective cohort study of patients discharged from 127 Veterans Affairs hospitals with ACS (acute MI or unstable angina).⁵ The study compared the rates of all cause mortality and rehospitalization for ACS between patients taking clopidogrel with PPI ($n=5244$) versus those taking clopidogrel without PPI ($n=2961$). The study concluded patients taking clopidogrel plus a PPI were at increased risk of death or rehospitalization for ACS, with a median follow-up 521 days after hospital discharge. The odds ratio adjusted by multivariable analysis was 1.25 (CI 1.11–1.41). This study adjusted for demographics, comorbidities, and ACS presentation and treatment but not cardiac risk factors.

The Ho and Juurlink studies also looked at death as an outcome in their secondary analyses. Neither showed an increased risk of death among patients taking clopidogrel with a PPI.

For each of the aforementioned observational studies, patients in the group receiving PPIs had significantly higher rates of comorbidities—such as diabetes, renal insufficiency, and prior MI—than patients not receiving PPIs. Significant differences between groups with regard to comorbid conditions confound conclusions, as the results may be due to comorbidities rather than PPIs. Each study adjusted for an array of investigator-identified confounders. However, control of confounders may have been incomplete.

Since these studies were published, five more studies (two in one article) have been published. Two of the studies affirmed evidence PPIs weaken clopidogrel's ability to inhibit platelet aggregation as measured *ex vivo*: an observational monocenter study by Zuern et al.¹³ and a randomized prospective study by Cuisset et al.¹⁴ However, one study "observed a trend towards a modest attenuation" of the antiplatelet effects of clopidogrel by PPIs, and two cast doubt on whether PPI attenuation of clopidogrel activity is clinically relevant. These latter three studies are described below.

O'Donoghue et al. performed post-hoc analyses of the PRINCIPLE-TIMI 44 and TRITON-TIMI 38 trials to assess whether the use of a PPI plus clopidogrel or prasugrel affects measures of platelet function or clinical outcomes.¹⁵ In both studies, PPI use was at the discretion of the physician.

PRINCIPLE-TIMI 44—a double-blind, two-phase crossover study in subjects undergoing cardiac catheterization with planned PCI—randomized 201 subjects 1:1 to receive prasugrel (60 mg loading, 10 mg daily maintenance) or high-dose clopidogrel (600 mg loading dose, 150 mg daily maintenance).¹⁶ The primary end point of the loading-dose phase was inhibition of platelet aggregation (IPA) with 20 μ M ADP at 6 hours. The primary endpoint of the maintenance-dose phase, with PCI patients, was IPA after 14 days. In this trial, 53 (26.4%) patients were recorded as using a PPI at randomization.

Post-hoc analysis of the PRINCIPLE-TIMI trial revealed the mean IPA was significantly lower in subjects treated with a PPI at 2, 6, and 18 to 24 hours post clopidogrel loading dose when data were unadjusted for baseline characteristics but not at 6 and 18 to 24 hours when they were adjusted. Mean IPA (%) (SD) for patients without PPI and with PPI, respectively, were: •24.2 (20.5) versus 10.4 (16.2) ($p < 0.003$, adjusted $p < 0.005$) at 2 hours; •35.2 (20.9) versus 23.2 (19.5) ($p < 0.02$, adjusted $p < 0.08$) at 6 hours; and •36.1 (20.8) versus 23.8 (14.4) ($p < 0.03$, adjusted $p < 0.16$) for 18 to 24 hours. Significance also was not achieved after 15 days of clopidogrel maintenance therapy without and with PPI, respectively: 48.8 (17.6) v. 29.4 (23.7) ($p = 0.06$).

The proportion of patients hyporesponsive, defined as an IPA < 20% to 20 μ M ADP, to clopidogrel also was calculated for 6 hours following loading dose and 15 days following maintenance therapy. The proportion of patients hyporesponsive to clopidogrel at 6 hours was more than two-fold higher for patients on a PPI (50% v. 18.2%, $p = 0.009$) and at 15 days was more than six-fold higher (50% v. 7.9%, $p = 0.012$).

TRITON-TIMI 38—a double-blind phase 3 trial in patients with ACS undergoing planned PCI—randomized 13,608 patients 1:1 to prasugrel (60 mg loading, 150 mg daily maintenance) or clopidogrel (300 mg loading, 75 mg daily maintenance).¹⁷ The primary endpoint was the composite of cardiovascular death, non-fatal MI, or non-fatal stroke. Clinical endpoints were assessed at hospital discharge, 30 and 90 days, and every 3 months up to 15 months. In this trial, 4529 (33.3%) of patients were recorded as being on a PPI at randomization.

Post-hoc analysis of TRITON-TIMI revealed no association between PPI use and risk of the primary endpoint for patients treated with clopidogrel. The rate of the primary endpoint throughout long-term follow-up was 11.8% for those with a PPI and 12.2% for those without a PPI. The unadjusted and adjusted hazard ratios were 0.98 (CI 0.84–1.14, $p = 0.08$) and 0.94 (CI 0.80–1.11, $p = 0.46$), respectively. Additional analyses showed no association between different types of PPIs and the risk of MI or the composite endpoint.

Unlike the previously described observational studies, the investigators performing the TRITON-TIMI post hoc analysis were able to control not only for demographics, comorbidities, and ACS presentation and treatment but also cardiac risk factors as well as history of peptic ulcer disease, history of carotid or vertebral artery disease, baseline hemoglobin, heart rate, and ethnicity. The study also used a propensity score for the decision to treat with a PPI.

Raseen et al. conducted a retrospective cohort study using the insurance records of 18,565 patients from three North American populations: British Columbia ($n = 10,391$), Pennsylvania ($n = 4176$), and New Jersey ($n = 3998$).¹⁸ The patients had undergone PCI or had been hospitalized from ACS between 2001 and 2005 and had used clopidogrel with or without a PPI. The primary endpoint was combined MI hospitalization and death over up to 180 days of follow up.

The study was initiated with the express intent to adjust for confounders. In addition to using multivariate analysis, the study employed high-dimensional propensity scores, which not only controlled for investigator-identified covariates but also 400 more variables empirically identified from claims codes in the databases used for the study.

For the primary endpoint, the pooled unadjusted, multivariate-adjusted, and propensity score-adjusted rate ratios for PPI users versus nonusers were 1.74 (CI 1.44–2.1), 1.32 (CI 1.08–1.61), and 1.22 (CI 0.99–1.51), respectively. The propensity score-adjusted rate ratios for the secondary endpoints—MI hospitalization, death, and revascularization—also were not significant. The study's authors concluded that no conclusive evidence of a clopidogrel-PPI interaction of major clinical significance was observed and the effect, if it exists, is unlikely to exceed a 20% risk increase.

To date, observational studies and post hoc analyses have been unable to provide clarity on whether a clinically relevant interaction between clopidogrel and PPIs exists. Furthermore, observational studies and post hoc analyses can only identify potential associations and cannot establish cause or exclude unmeasured confounders. Thus, based on *ex vivo* studies, the FDA has recommended avoiding the use of omeprazole and esomeprazole with clopidogrel and has suggested the H2 blockers ranitidine, famotidine, and nizatidine as alternative stomach acid reducers.² Some studies have suggested pantoprazole, a less potent CYP2C19 inhibitor than omeprazole, may be a reasonable alternative.¹⁴ As always, the benefits of using a PPI with clopidogrel versus the risks must be assessed for each patient.

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REFERENCES

1. Food and Drug Administration. Public Health Advisory: Updated Safety Information about a drug interaction between Clopidogrel Bisulfate (marketed as Plavix) and Omeprazole (marketed as Prilosec and Prilosec OTC). 11/17/2009. (accessed 2010 Mar. 11) <http://www.fda.gov/Drugs/DrugSafety/PublicHealthAdvisories/ucm190825.htm>
2. Food and Drug Administration. Information for healthcare professionals: Update to the labeling of clopidogrel bisulfate (marketed as Plavix) to alert healthcare professionals about a drug interaction with omeprazole (marketed as Prilosec and Prilosec OTC). 11/17/1009. (accessed 2010 Mar. 11) <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHealthcareProfessionals/ucm190787.htm>
3. Pezalla E, Day D, Pulliathath I. Initial assessment of clinical impact of a drug interaction between clopidogrel and proton pump inhibitors. *J Am Coll Cardiol*. 2008; 52(12):1037–9.
4. 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):713–8.
5. 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(9):937–944.
6. Plavix[®] prescribing information. Bridgewater, NJ: Bristol-Myers Squibb/Sanofi Pharmaceuticals Partnership; 2009 Oct.
7. Anderson JL, Adams CD, Antman EM et al. ACC/AHA 2007 Guidelines for the management of patients with unstable angina/non–ST-elevation myocardial infarction—executive summary. *J Am Coll Cardiol*. 2007; 50(7): 652–726.
8. Sacco RL, Adams R, Albers G et al. Guidelines for prevention of stroke in patients with ischemic stroke or transient ischemic attack: A statement for healthcare professionals from the American Heart Association/American Stroke Association Council on Stroke Co-Sponsored by the Council on Cardiovascular Radiology and Intervention. *Stroke*. 2006; 37:577–617.
9. Hirsch AT, Haskal ZJ, Hertzler NR et al. ACC/AHA 2005 guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): A collaborative report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2006; 47:e1–e192.
10. Bhatt DL, Scheiman J, Abraham NS et al. ACCF/ACG/AHA 2008 expert consensus document on reducing the gastrointestinal risks of antiplatelet therapy and NSAID use: A report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents. *Circulation* published online Oct 3, 2008 from <http://circ.ahajournals.org>.
11. Laine L and Hennekens C. Proton pump inhibitor and clopidogrel interaction: fact of fiction? *Am J Gastroenterol*. 2010; 105:34–41.
12. Gilard M, Arnaud B, Comily JC, et al. Influence of omeprazole on the antiplatelet action of clopidogrel associated with aspirin in the randomized, double-blind OCLA (Omeprazole CLopidogrel Aspirin) study. *J Am Coll Cardiol*. 2008; 51(3):256–60.
13. Zuern CS, Geisler T, Lutinsky N et al. Effect of comedication with proton pump inhibitors (PPIs) on post-interventional residual platelet aggregation in patients undergoing coronary stenting treated by dual antiplatelet therapy. *Thromb Res*. 2010; 125:e51–e54.
14. Cuisset T, Frere C, Quilici J, et al. Comparison of omeprazole and pantoprazole Influence on a high 150-mg clopidogrel maintenance dose: The PACA (Proton Pump Inhibitors and Clopidogrel Association) prospective randomized study. *J Am Coll Cardiol*. 2009; 54(13):1149–53.
15. 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 randomised trials. *Lancet* 2009; 374:989–97.
16. Wiviott SD, Trenk D, Frelinger AL et al. Prasugrel compared with high loading- and maintenance-dose clopidogrel in patients with planned percutaneous coronary intervention: The Prasugrel in Comparison to Clopidogrel for Inhibition of Platelet Activation and Aggregation—Thrombolysis in Myocardial Infarction 44 Trial. *Circulation*. 2007; 116:2923–2932.
17. Wiviott SD, Braunwald E, McCabe CH et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2007. 357:2001–15.
18. Rassen JA, Choudhry NK, Avorn J et al. 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.