Pharmacogenomics and Personalized Medicine

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REVIEW

# Antiplatelet agents and proton pump inhibitors – personalizing treatment



This article was published in the following Dove Press journal:
Pharmacogenomics and Personalized Medicine
26 June 2010
Number of times this article has been viewed

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**Introduction:** Antiplatelet therapy remains one of the cornerstones in the management of non-cardioembolic ischemic stroke. However, a significant percentage of patients have concomitant gastroesophageal reflux or peptic ulcer disease that requires acid-reducing medications, the most powerful and effective being the proton pump inhibitors (PPIs). Antiplatelet efficacy, at least *in vivo*, and particularly for clopidogrel, has been shown to be reduced with concomitant proton pump inhibitor use. Whether this is clinically relevant is not clear from the limited studies available.

**Methods:** We conducted an extensive review of studies available on Medline related to pharmacodynamic interactions between the antiplatelet medications and proton pump inhibitors as well as clinical studies that addressed this potential interaction.

**Results:** Based on the present pharmacodynamic and clinical studies we did not find a significant interaction that would reduce the efficacy of antiplatelet agents with concomitant user of proton pump inhibitors.

**Conclusions:** Patients on antiplatelet agents after a transient ischemic attack or ischemic stroke can safely use aspirin, and extended release dipyridamole/aspirin with proton pump inhibitors. Patients on clopidogrel may use other acid-reducing drugs besides proton pump inhibitors. In rare cases where proton pump inhibitors and clopidogrel have to be used concurrently, careful close monitoring for recurrent vascular events is required.

**Keywords:** proton pump inhibitors, antiplatelet medications, clopidogrel, ischemic stroke, cardiovascular events

## Introduction

Antiplatelet agents are the mainstay of primary and secondary prevention of vascular events including myocardial infarction, stroke, and peripheral artery disease. While aspirin was the first to be widely used in prevention, it was soon joined by other agents including Dipyridamole. More recently, clopidogrel has seen increased use in treatment of both cardiovascular (CV) events in combination with aspirin, and for cerebrovascular risk factor reduction as a monotherapy treatment, according to current consensus recommendations.[1] However, several studies have prompted the Food and Drug Administration (FDA) to issue a public health advisory regarding clopidogrel and omeprazole as a result of drug interaction and blockade of CYP2C19.[2] This FDA recommendation came despite recent studies that have questioned the clinical relevance of drug interaction in causing increased risk of myocardial infarction (MI) or death.[3] The review discusses the indications of aspirin, dipyridamole, and clopidogrel use along with individual metabolism with a focus on the potential for

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interaction between clopidogrel and proton pump inhibitors (PPIs), and relevant conclusions and suggestions. Medline was searched for the terms 'aspirin', 'dipyridamole', 'clopidogrel', and 'proton pump inhibitors' up till March 2010. Further manual search of studies referenced by the articles were also conducted.

The initial widely-used antiplatelet agent was aspirin as it was shown to have protective benefits in patients at increased risk of vascular occlusive events and is effective at a low dose (50–325 mg) for long term use.[4] However, the need for further risk reduction led to the consideration of other antiplatelet medications including extended release dipyridamole [ERDP], clopidogrel and most recently prasugrel. The benefits of extended release dipyridamole were explored in the second European Stroke Prevention Study (ESPS2)which revealed a very significant relative risk reduction of stroke with a combination of (ERDP/ASA) compared to aspirin alone and replicated in the European/Australian Stroke Prevention in Reversible Ischemia Trial (ESPRIT) comparing (ERDP/ASA) to aspirin alone.[5] Recent studies including the Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) trial have compared aspirin and dipyridamole with clopidogrel which showed equal efficacy in ischemic stroke patients.[6]

The use of thienopyridines, specifically clopidogrel, has been approved for reduction of atherothrombotic events in patients with recent stroke, recent MI, acute coronary syndrome, and peripheral arterial disease. After an acute stroke, clopidogrel monotherapy can be used as secondary prevention of vascular events according to recent guidelines.[1] For acute MI and coronary syndrome clopidogrel is used in combination with aspirin as randomized controlled trials have shown significant relative risk reductions of 9% compared to aspirin alone.[7,8] Recent guidelines recommend clopidogrel for at least one month after implantation of a bare metal coronary stent (BMS), and for 12 months after a drug eluting stent and ideally 1 year in those with ST elevation MI (STEMI) or non-STEMI patients who did not undergo intervention. This should be used in conjunction with indefinite aspirin therapy. In patients with high risk of bleeding, dual therapy is still recommended for an abbreviated duration of 2 weeks after BMS and 3–6 months after drug eluting stent[9] while continuing aspirin indefinitely. Furthermore, recent studies have supported the guideline update of an alternative thienopyridine, prasugrel, in patients with acute coronary syndrome and undergoing percutaneous intervention (PCI). However, given the increased bleed risk it is contraindicated in patients with prior strokes or transient ischemic attacks.[10]

## Mechanism of action and interaction of aspirin

Aspirin exhibits its antiplatelet effect by irreversibly inhibiting cyclooxygenase-1 enzyme and prevents the production of thromboxane $A_2$ (TXA2).[11] It is rapidly converted in the plasma to salicylic acid and subsequently metabolized in the liver to form phenolic glucorinide. However, this is a separate pathway from that of PPIs and thus does not have any interaction. Instead, aspirin resistance, an *in vitro* measure of the inability of aspirin to reduce platelet activation and aggregation by failure to suppress the platelet production of TXA2 has been studied extensively.[12] The large meta-analyses have found low-dose aspirin to be as effective as high-dose aspirin in preventing vascular events and thus showing clinical irrelevance of an *in vitro* response.[11]

Despite the benefits of aspirin, long-term it has been found to increase the incidence of gastrointestinal hemorrhage.[13] Given the increased risk of major bleeding, the concurrent use of proton pump inhibitors (PPI) have also been studied and various reviews have shown their efficacy and safety in preventing aspirin-induced GI injury.[14] For those with previous complications of ulcers, a PPI such as lansoprazole has been found to reduce the rates of ulcer complications for those taking aspirin.[15] In addition, there is little evidence of impaired aspirin pharmacodynamics with the use of PPI, as a study of healthy patients has shown that when the serum levels of aspirin and platelet aggregation were measured, with and without previous use of omeprazole, there was no noted decrease in effectiveness.[16] These outcomes are likely due to aspirin metabolism that, unlike clopidogrel, does not occur through the cytochrome isoenzymes that govern the metabolism of PPI and clopidogrel.

## Mechanism of action and interaction of extended release dipyridamole

Dipyridamole is an alternative antiplatelet agent that inhibits the uptake of adenosine into platelets, endothelial cells, and erythrocytes increasing local concentrations of adenosine that acts on TXA2. This results in inhibition of platelet aggregation. It is metabolized in the liver; primarily by conjugation with glucuronic acid in a pathway that does not interact with PPIs. While studies have been conducted which showed that the bioavailability of the dipyridamole is affected by the increased pH due to concurrent use of PPIs there have been no

randomized studies directly exploring clinical implications of dipyridamole use with proton pump inhibitors.[17]

## Mechanism of action and interaction of clopidogrel

Finally, clopidogrel through a CYP450-dependent pathway is metabolized into metabolite 2-oxo-clopidogrel at an efficiency of 15%.[18] It is then hydrolyzed to 2-{1-[(1S)-1-(2-chlorophenyl)-2-methoxy-2-oxoethyl]-4-sulfanyl-3-piperidinyli-diene}3 acetic acid. This active metabolite affects the binding of [$^{32}$P]2MeSADP by selectively inhibiting platelet ADP receptors P2Y12 in a noncompetitive irreversible manner.[19] This leads to a prolonged inhibition of platelet aggregation lasting for up to 7 days after the last clopidogrel dose.[20] However, the CYP enzymes are polymorphic and it has been shown that reduced enzymatic function can be conferred by certain alleles.[21] In the Trial to assess Improvement in Therapeutic Outcomes by optimizing platelet Inhibition with prasugrel Thrombolysis In Myocardial Infarction 38 (TRITON-TIMI 38), the CYP2C events 19 reduced function variant was found to have reduced pharmacokinetic and pharmacodynamic responses to clopidogrel by one quarter to one third and was associated with adverse clinical outcomes from cardiovascular events.[22] Several cohort studies have further shown that the CYP2C19 genotype is associated with diminished platelet response to clopidogrel treatment and places those patients with this autosomal recessive trait at increased risk of a cardiovascular ischemic event.[23,24] In addition, prior studies have explored the population at risk for having homozygous alleles for poor metabolism and found that Asians were more than twice as likely as either Caucasians or African Americans to carry both homozygous alleles and that there was high individual and ethnic variation even for homozygotes.[25]

As with the previously-discussed antiplatelet agents, clopidogrel also increases the risk of gastrointestinal injury (GI) as it impairs repair of GI mucosal injuries, and when taken with aspirin as dual antiplatelet therapy, expert consensus recommends the use of a proton pump inhibitor (PPI).[26] The benefits of PPI and clopidogrel monotherapy are only supported through observational studies showing some benefit of PPI use in reducing the bleeding risk of clopidogrel monotherapy; however there have been no randomized control studies. A case-control study found that bleeding ulcers were more common in patients taking clopidogrel or ticlopidine and lower rate of PPI use (RR = 0.19, (0.07–0.49).[27] PPIs achieve their efficacy within the acidic environment of the parietal cells in the gastric lining, as they are converted into their active derivatives that interfere with H+, K+—ATPase molecule and irreversibly inhibit gastric acid secretion. While the half lives for the various PPIs range from 0.5 to 1.5 hours, their effects may last from 15 to 46 hours.[28] However, these PPIs are competitive inhibitors of the CYP2C19 isoenzymes, which result in varying antiplatelet effects.[29]

## Pharmacodynamic effects of clopidogrel and proton pump inhibitors

Initial studies focused on the pharmacodynamic effects of various PPIs and clopidogrel through measurements of platelet reactivity and aggregation. The first biological evidence of an interaction of clopidogrel and a PPI was reported through a brief letter to the editor showing that there was variation in platelet reactivity to clopidogrel when combined with the use of a PPI in an observational study.[30] This was followed by the Omeprazole Clopidogrel Aspirin study (OCLA), a prospective randomized trial again measuring platelet reactivity index (PRI) over 7 days that further raised the concern that omeprazole significantly decreased clopidogrel inhibitory effect as measured by Vasoactive stimulated phosphoprotein (VASP) phosphorylation, a standardized cytometric assay that measures the amount of VASP dephosphorylation that occurs when clopidogrel binds to the $P2Y_{12}$ platelet receptor.[31] They measured 124 patients with similar baseline characteristics who were undergoing elective coronary stent placement without prior use of clopidogrel or PPI use. Poor responders were defined by a PRI less than 50% and while no difference was noted on Day 1 between the placebo and omeprazole group, on Day 7, 60.9% in the omeprazole group were identified as poor responders compared to 26.7% in the placebo group. This indicated that the concurrent use of omeprazole and clopidogrel decreased the antiplatelet response of clopidogrel (OR = 4.31, CI: 2.0–9.2).[31] However, the small study group size may be a limitation as evidenced by the wide confidence interval.

Subsequent studies explored the effects on platelet aggregation of other PPIs and helped to explore whether a class effect was present. One randomized study of prasugrel, clopidogrel, and lansoprazole noted a decrease in the inhibition of platelet aggregation when the PPI was used in conjunction with clopidogrel, but they had not been able to measure the active metabolite of clopidogrel directly.[32] In addition, this study was limited by the small sample size of 24 healthy subjects that reduces its applicability to the general population. A following study was focused on clopidogrel and PPIs including esomeprazole or pantoprazole that again measured PRI through VASP phosphorylation. Three hundred patients with coronary artery disease who had been taking aspirin and

clopidogrel for an average of 3 months and were undergoing PCI were included in the study. This study involving two alternative PPIs did not duplicate the decrease in PRI noted earlier with omeprazole, but it is important to note the limitations.[33] These included the nonrandomized nature of the study, the difference of baseline characteristics among the three groups including a predominance of male patients, decreased statin use, decreased ace inhibitor use, and decreased myocardial infarction hospitalizations seen in the no-PPI group compared to the groups on either pantoprazole or esomeprazole. While a multivariable analysis was used to adjust for confounding factors, there is still the potential that all variables were not accounted for.

A study comparing clopidogrel along with pantoprazole, esomeprazole, and omeprazole might clarify whether a class effect is present in the interactions among PPIs and clopidogrel. This was explored in an observational study involving patients undergoing PCI who had coronary artery disease receiving dual antiplatelet therapy for a median of 7 months who did not have acute coronary syndrome. The measured primary endpoint involved ADP-induced platelet aggregation with low clopidogrel responders defined as patients in the upper 20% quintile. After multivariable analysis was conducted to account for confounders, it was noted that patients with concurrent use of omeprazole were significantly higher than those in the non-PPI group taking clopidogrel.[34]

The possibility that the observed drug interaction might not be a class effect is further supported by the recent PACA trial examining platelet reactivity for patients on clopidogrel and aspirin. In the prospective randomized study, 104 patients undergoing coronary stenting for ACS were followed for 1 month and randomized to omeprazole and pantoprazole with clopidogrel response measured by PRI through VASP. They identified more clopidogrel nonresponders in the omeprazole group compared to pantoprazole (44% vs 23%, $P = 0.04$).[35] While similar to several studies exploring this biological interaction, the applicability to the general population is limited by the small sample size. However, it further supports evidence of a biological effect between clopidogrel and proton pump inhibitors such as omeprazole.

## Clinical effects of clopidogrel and proton pump inhibitors

Based on the prior biological studies, clinical studies have been conducted to further elucidate the interaction of clopidogrel and a PPI; however, they have mainly involved cohort studies. One of the latest retrospective cohort studies involved 20,596 Tennessee Medicaid patients of whom 7593 were concurrently using clopidogrel and PPIs (majority pantoprazole 62%). They evaluated the hospitalizations for gastroduodenal bleeding and serious cardiovascular disease and found the hazard ratio for being on both medications for serious cardiovascular disease was 0.99 (95% CI: 0.82–1.19).[36] The noted limitations included difficulty in verifying medication exposure, confounding not adjusted for in the analysis, and classification of end points from computerized review. Another retrospectively-designed cohort study had also evaluated the risk of adverse cardiovascular events while on a PPI and clopidogrel with pooled data from patients enrolled in 3 large health insurance programs. While there was a slightly-increased risk of MI or death, there was no conclusive evidence of major clinical relevance (pooled RR 1.22, CI: 0.99–1.51).[3] However the noted limitations were the nonrandomized study, difficulty in accounting for the use of omeprazole over the counter, and that the PPIs were grouped during analysis.

Further studies that have not found clinically-significant risk include the retrospective cohort study of TRITON TIMI 38 which involved a total of 13,608 patients with ACS who had been randomly assigned to receive prasugrel and clopidogrel, of which 4529 patients had been taking a PPI at the time of randomization. This also did not demonstrate an association between use of a PPI and increased risk of the primary endpoint even after adjustment for potential confounders (HR 0.94, CI: 0.89–1.11, $P = 0.58$).[37] However, the observational nature of the study limits the study and its ability to address comorbidities.

Unpublished observational studies have also supported the limited clinical risk for taking both a PPI and clopidogrel. A retrospective cohort of 535 patients showed no adverse effects although the study was not sufficiently powered.[38] This conclusion was also shared by preliminary results of an incomplete randomized double-blind trial (COGENT study), stopped due to sponsor bankruptcy, of omeprazole vs placebo in patients on clopidogrel and aspirin, which also demonstrated no significant difference in CV events (HR 1.02 CI: 0.70–1.51).[39] However, it was not powered to evaluate differences in CV events and did not meet target sample size, putting it at risk of a Type 2 error.

In contrast to the studies that have not found any clinically-significant effects, there have been several retrospective studies that have raised the concern of increased CV risk from taking both PPIs and clopidogrel. This included an analysis of the Clopidogrel for the reduction of events during observation (CREDO) trial that concluded that use of PPI increased the risk of CV events, but that clopidogrel

**Table 1** Pharmacodynamic Studies involving clopidogrel

| Authors | Study type and population | Outcome | N | Significance | Results |
|---|---|---|---|---|---|
| Gilard et al[31] | Double-blind placebo-controlled randomized trial<br>Elective coronary stent implantation | Platelet Reactivity Index | Omeprazole = 64<br>Placebo = 60 | $P < 0.0001$ | Poor responders in:<br>Omeprazole: 60.9% (39)<br>Placebo: 26.7% (16)<br>OR for poor reactivity = 4.31(2.0–9.2) |
| Cuissett et al[35] | Prospective randomized trial<br>Planned coronary stenting after ACS | Platelet Reactivity Index | Omeprazole = 52<br>Pantoprazole = 52 | $P = 0.04$ | Poor responders in:<br>Omeprazole: 44%<br>Pantoprazole: 22%<br>OR for poor reactivity = 2.6(1.2–6.2) |
| Small et al[32] | Randomized open label crossover<br>Healthy volunteers | Inhibition of ADP-induced platelet aggregation | Clopidogrel = 24<br>Clopidogrel and Lansoprazole = 24 | $P = 0.046$ | Statistically similar for clopidogrel alone and with lansoprazole<br>Except with 5 micrometer ADPat 24 hrs (reduced to 39% from 49%) |
| O'Donoghue et al[37] | Retrospective cohort within Principle TIMI and TRITON Timi<br>Planned percutaneous coronary intervention | ADP-induced platelet aggregation at 6 hours | PPI = 28<br>No PPI = 71 | $P = 0.50,0.051,0.11$ (respectively)<br>$P = 0.009$ | Lower mean inhibition in those taking PPI at 2, 6 and 18–24 h<br>Nonresponders at 6 h 50.0% on PPI compared to 18.2% without PPI |
| Collet et al[23] | Prospective cohort | CV death, nonfatal MI, urgent revascularization | Any PPI = 83<br>No PPI = 176 | $P = 0.40$ | No significant differences according to CYP2C19*2 genotype with PPI |
| Gilard et al[30] | Prospective cohort<br>High risk coronary angioplasty | Platelet Reactivity Index | PPI = 24<br>No PPI = 81 | $P = 0.007$ | VASP = 61.4%<br>No PPI VASP = 4.95% |
| Siller-Matula et al[33] | Prospective cohort<br>Undergoing percutaneous coronary intervention | Platelet Reactivity Index<br>ADP-induced aggregation | PPI = 226<br>(Pantoprazole = 152<br>Esomeprazole = 74)<br>No PPI = 74 | $P = 0.724$ | Platelet Reactivity Index<br>pantoprazole = 50%<br>Esomeprazole = 54%<br>No PPI = 49% |
| Sibbing et al[34] | Prospective cohort<br>Prior coronary stent placement | ADP-induced platelet aggregation | Pantoprazole = 162<br>Omeprazole = 64<br>Esomeprazole = 42<br>No PPI = 732 | $P = 0.001$<br>$P = 0.69$<br>$P = 0.88$ | Pantoprazole 226.0 AU*min<br>Omeprazole 295.5 AU*min<br>Esomepraozle 209.0 AU*min<br>No PPI = 220.0 AU*min |

**Abbreviations:** ADP, adenosine diphosphate; ACS, acute coronary syndrome; CV, cardiovascular; MI, myocardial infarction; PPI, proton pump inhibitor; N, total number.

reduced adverse events to the same degree with or without PPI.[40] Further studies have included a retrospective cohort by Pezalla in an initial 2008 letter that observed a slight increase in MI rates in those on PPI, even after accounting for significant comorbidity differences.[41] Three subsequent retrospective studies further examined PPIs and found an OR of 1.25–1.51 when taking a PPI, and further analyzed individual usage of PPIs including Pantoprazole, omeprazole, rabeprazole, lansoprazole and esomeprazole, but found that they all increased risk to some degree.[42–44] These retrospective studies have a number of limitations, including lack of controlling for risk factors, making it difficult to form valid conclusions from such analyses and to determine if a class effect for the various PPIs exist.

## Personalizing treatment

Based on a thorough review of literature in Medline, the authors wish to make the following conclusions and suggestions regarding the use of antiplatelet agents with proton pump inhibitors:

- Our review of literature on the use of aspirin with PPIs has shown no significant interactions on a pharmacody-

**Table 2** Clinical studies involving clopidogrel

| Authors | Study type and population | Outcome | N | Significance | Results |
|---|---|---|---|---|---|
| Bhatt et al[39] | Double-blind randomized incomplete (COGENT) ACS and coronary stent placement | Stroke, MI, CABG, PCI and CV death | PPI = 1878<br>Placebo = 1895 | $P = 0.007$ | HR 0.55(0.36–0.85) |
| Dunn et al[40] | Retrospective cohort within CREDO trial (RCT) High likelihood of PCI or undergoing PCI | Death, MI, stroke at 1 year | PPI = 366<br>No PPI = 1750 | $P = 0.043$<br>$P = 0.035$ | Clopidogrel and PPI OR = 1.633(1.015–2.627)<br>Placebo and PPI OR = 1.554(1.031–2.341) |
| Ho et al[43] | Retrospective cohort Discharged after MI or unstable angina | Mortality or rehospitalization for ACS | PPI = 5244<br>Omeprazole = 3132(59.7%)<br>Rabeprazole = 22(0.4%)<br>No PPI = 2961 | $P = 0.46$ | Adjusted OR = 1.25 (1.11–1.41)<br>OR = 1.24(1.08–1.41)<br>OR = 2.83(1.96–4.09) |
| O'Donoghue et al[37] | Retrospective cohort Principle-TIMI 44 and TRITON-TIMI 38 RCT ACS undergoing PCI | CV death, MI or stroke | No PPI = 4538<br>PPI = 2257 | | Pantoprazole 1844 0.94 (0.74–1.18)<br>Omeprazole 1675 0.91 (0.72–1.15)<br>Esomeprazole 613 1.07 (0.75–1.52)<br>Lansoprazole 441 1.00 (0.63–1.59)<br>Rabeprazole 66 no calculations<br>Overall 0.94 (0.80–1.11) |
| Pezalla et al[41] | Retrospective cohort Younger than 65 years and taking clopidogrel | MI within 1 year | Low PPI = 712<br>No PPI = 4800<br>Subset of all risk factors = 1010 | $P < 0.05$<br>$P < 0.05$ | Unadjusted comorbidities MI Rates low PPI = 3.08%, no PPI = 1.38%, high PPI = 5.03%<br>MI Rates low PPI = 10.0%, no PPI = 2.60%, high PPI = 11.38% |
| Ramirez et al[38] | Retrospective cohort PCI | MI, death, CABG or repeat PCI | PPI = 138<br>No PPI = 397 | $P = 0.32$ | Death/MI for PPI = 6.7% vs no PPI 9.6%<br>Repeat vascularization PPI = 15.8% vs no PPI 14.2% |
| Rassen et al[3] | Retrospective cohort Older than 65 years old with PCI or ACS and had started clopidogrel | MI, death | PPI = 3996<br>No PPI = 14659 | | Pooled RR = 1.22 (0.99–1.51) |
| Ray et al[36] | Retrospective cohort Hospitalized for MI, revascularization or unstable angina | Gastroduodenal bleeding or serious CV disease | PPI = 7593<br>(Omeprazole 9%)<br>(Pantoprazole 62%) | | HR = 0.99 (95% CI, 0.82–1.19) |
| Stanek et al[44] | Retrospective cohort Consistent use of clopidogrel after coronary stent | Stroke, TIA, MI, coronary revascularization, Death (adjusted risk for age/sex/comorbidity) | PPI = 6826 (25.1%)<br>Omeprazole = 2307<br>Esomeprazole = 3257<br>Pantoprazole = 1653<br>Lansoprazole = 785<br>No PPI = 9862 (17.9%)<br>No PPI = 602 | <br>$P < 0.0001$<br>$P < 0.0001$<br>$P < 0.0001$<br>$P < 0.0004$ | Adjusted HR = 1.51 (1.39–1.64)<br>HR = 1.39(1.22–1.57)<br>HR = 1.57(1.40–1.76)<br>HR = 1.61(1.41–1.88)<br>HR = 1.39(1.16–1.67) |
| Juurlink et al[42] | Population-based nested case-control study Older than 65 years old with discharge after MI | Died or readmitted for MI within 90 days after initial hospital discharge Controls matched for age, PCI, date of discharge, comorbidities, medications | Cases on PPI = (26.4%)<br>Controls on PPI = (20.6%) | | OR = 1.25 (1.03–1.57)<br>Pantoprazole = 1.02 (0.70–1.47)<br>All other PPI = 1.40 (1.10–1.77) |

**Abbreviations:** CV, cardiovascular, MI, myocardial infarction; TIA, transient ischemic attack; PCI, percutaneous intervention; PPI, proton pump inhibitor; N, total number.

namic or clinical basis. At the present time, the use of aspirin should be continued regardless of whether there is concomitant use of PPIs. Concurrent use of aspirin and PPI has been found to be both safe and effective and PPIs are the drug on choice for treating and preventing aspirin-induced GI injury.

- Studies on dipyridamole are limited, with an insufficient level of evidence to suggest or refute the potential for interaction of extended release aspirin/dipyridamole combination drug with PPIs, based solely on the question of bioavailability from alterations in gastric pH. Since no clinical studies have been undertaken, discontinuation of extended release aspirin/dipyridamole in patients on PPIs may seem unwarranted until further studies become available. Nevertheless, it is the recommendation of the authors to carefully consider the need for extended release aspirin/dipyridamole in patients needing PPIs who may otherwise benefit from aspirin alone.
- Clopidogrel has received considerable attention due to several level 1 studies showing a statistically-significant pharmacodynamic interaction of clopidogrel with proton pump inhibitors. Studies point towards a potential for decreased efficacy *in vivo* of clopidogrel from likely metabolism via a common CYP2C19 pathway. At the current time there exists no clinical outcome trial outlining the effective therapeutic dose based on differential metabolism via the CYP2C19 pathway.
- Many observational and retrospective studies have shown statistically-significant clinical interaction when both PPIs and clopidogrel are used concurrently (Tables 2 and 3). These have included 4 out of 8 retrospective studies, raising serious concerns for the possibility of a decrease in protection against recurrent cardiovascular or cerebrovascular events that would be clinically relevant. Those studies that have shown nonsignificance do have varied limitations, some of which include the lack of adjustment for risk factors between the two arms and one incomplete randomized double blind study (COGENT) with limited sample size and thus limited power to detect differences. Thus, based on the current level of evidence, the authors suggest avoiding concurrent use of PPIs (especially omeprazole) and clopidogrel, until such time as level 1 evidence, based on a prospectively designed randomized double blind controlled trial, quantifies these clinical implications after appropriately controlling for vascular risk factors such as diabetes, hypertension, age and body mass index. Further, studies should also be designed to take into account a subgroup analysis of PPIs in order to confirm whether a class effect exists.
- Unlike with aspirin, since there is no clinical evidence to support the use of PPIs with clopidogrel in patients on GI prophylaxis, an individual case-based decision should be made to change to H2 receptor blockers other than cimetidine in patients on clopidogrel until such time as a prospective study is done to confirm (or refute) the existence of a net clinical benefit of using PPIs for GI indications in patients needing clopidogrel. This is especially applicable to stroke prophylaxis requiring prolonged monotherapy with clopidogrel. If PPIs are found to be the only option for GI protection, and where both clopidogrel and a PPI are indicated, pantoprazole could be used, since it is the PPI found least likely to interact with clopidogrel (PACA study). Until randomized trials are completed, in patients requiring both aspirin and clopidogrel such as with coronary stents, discontinuation of PPIs and replacement with H2 receptor blockers may be considered where feasible for the limited duration of clopidogrel use (2 weeks after BMS and 3–6 months for drug eluting stent). Once again the risk of GI bleed has to be considered on an individual basis. There is limited clinical evidence regarding the class effect of PPIs and hence where a PPI is absolutely necessary, pantoprazole (based on the prospective evidence from the PACA trial) could be used since it is the PPI least likely to interact with clopidogrel. In such instances, frequent reevaluations should be undertaken to consider the need of continued PPI use since there is a potential for interaction (see Table 3), and thus there is the potential for adverse clinical outcomes, regardless of the choice of PPI.
- The impact of indiscriminate use of PPIs cannot be discounted due to the fact that many patients are inappropriately continued on PPIs after hospital discharge. Such patients should be reevaluated for the need to be on continued doses of PPIs and should discontinue them where they are unnecessary. A more thorough review of the GI symptoms should be undertaken in all patients requiring clopidogrel to assess whether they may need to be continued on PPI or whether the use of H-2 receptor blockers suffice.
- Our study and conclusions have several limitations including the lack of literature on well designed prospective trials with clopidogrel and PPIs. Unlike aspirin, the interaction of PPI with extended release aspirin/dipyridamole has not been well studied either and hence the potential for a clinically-significant interaction cannot be completely ruled out to recommend its use in patients on PPIs. Finally, further well designed prospectively controlled studies are

**Table 3** Odds and hazard ratio for increased risk of adverse outcome when on concurrent proton pump inhibitors and clopidogrel

| Proton pump inhibitor | O'Donoghue et al[37] | Ho et al[43] | Stanek et al[44] PPI = 6826 | Juurlink et al[42] |
|---|---|---|---|---|
| Pantoprazole | 1844 OR = 0.94 (0.74–1.18) | | 24.2% HR = 1.61(1.41–1.88) | OR = 1.02 (0.70–1.47) |
| Omeprazole | 1675 OR = 0.91 (0.72–1.15) | 59.7% OR = 1.24(1.08–1.41) | 33.8% HR = 1.39(1.22–1.57) | |
| Esomeprazole | 613 OR = 1.07 (0.75–1.52) | | 47.7% HR = 1.57(1.40–1.76) | |
| Lansoprazole | 441 OR = 1.00 (0.63–1.59) | | 11.5% HR = 1.39(1.16–1.67) | |
| Rabeprazole | 66 no calculations | 0.4% OR = 2.83(1.96–4.09) | | |

**Abbreviations:** OR, odds ratio; HR, hazard ratio.

required to explore the clinical ramifications for patients taking both PPIs and clopidogrel or dipyridamole.

## Disclosure

The authors reports no conflicts of interest in this work.

## References


1. Adams RJ, Albers G, Alberts MJ, et al. Update to the AHA/ASA Recommendations for the Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack. *Stroke*. 2008;39(5):1647–1652.
2. FDA. 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). 2009. Accessed Nov 18, 2009,
3. 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(23):2322–2329.
4. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ*. 2002; 324(7329):71–86.
5. ESPRIT Study Group; Halkes PH, van Gijn J, Kappelle LJ, Koudstaal PJ, Algra A. Aspirin plus dipyridamole versus aspirin alone after cerebral ischaemia of arterial origin (ESPRIT): randomised controlled trial. *Lancet*. 2006;367(9523):1665–1673.
6. Diener HC, Sacco RL, Yusuf S, et al. Effects of aspirin plus extended-release dipyridamole versus clopidogrel and telmisartan on disability and cognitive function after recurrent stroke in patients with ischaemic stroke in the Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) trial: a double-blind, active and placebo-controlled study. *Lancet Neurol*. 2008;7(10):875–884.
7. Chen ZM, Jiang LX, Chen YP, et al. Addition of clopidogrel to aspirin in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. *Lancet*. 2005;366(9497):1607–1621.
8. Yusuf S, Zhao F, Mehta SR, et al. Effects of Clopidogrel in Addition to Aspirin in Patients with Acute Coronary Syndromes without ST-Segment Elevation. *N Engl J Med*. 2001;345(7):494–502.
9. Becker RC, Scheiman J, Dauerman HL, et al. Management of Platelet-Directed Pharmacotherapy in Patients With Atherosclerotic Coronary Artery Disease Undergoing Elective Endoscopic Gastrointestinal Procedures. *J Am Coll Cardiol*. 2009;54(24):2261–2276.
10. Kushner FG, Hand M, Smith SC Jr. et al. 2009 Focused Updates: ACC/AHA Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction (Updating the 2004 Guideline and 2007 Focused Update) and ACC/AHA/SCAI Guidelines on Percutaneous Coronary Intervention (Updating the 2005 Guideline and 2007 Focused Update): A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Catheter Cardiovasc Interv*. 2009;74(7):E25–E68.
11. Patel D, Moonis M. Clinical implications of aspirin resistance. *Expert Rev Cardiovasc Ther*. 2007;5(5):969–975.
12. Krasopoulos G, Brister SJ, Beattie WS, Buchanan MR. Aspirin 'resistance' and risk of cardiovascular morbidity: systematic review and meta-analysis. *BMJ*. 2008;336(7637):195–198.
13. Derry S, Loke YK. Risk of gastrointestinal haemorrhage with long term use of aspirin: meta-analysis. *BMJ*. 2000;321(7270):1183–1187.
14. Arora G, Singh G, Triadafilopoulos G. Proton Pump Inhibitors for Gastroduodenal Damage Related to Nonsteroidal Anti-inflammatory Drugs or Aspirin: Twelve Important Questions for Clinical Practice. *Clin Gastroenterol Hepatol*. 2009;7(7):725–735.
15. Lai KC, Lam SK, Chu KM, et al. Lansoprazole for the Prevention of Recurrences of Ulcer Complications from Long-Term Low-Dose Aspirin Use. *N Engl J Med*. 2002;346(26):2033–2038.
16. Iñarrea P, Esteva F, Cornudella R, Lanas A. Omeprazole Does Not Interfere with the Antiplatelet Effect of Low-Dose Aspirin in Man. *Scand J Gastroenterol*. 2000;35:242–246.
17. Derendorf H, VanderMaelen CP, Brickl RS, MacGregor TR, Eisert W. Dipyridamole Bioavailability in Subjects With Reduced Gastric Acidity. *J Clin Pharmacol*. 2005;45(7):845–850.
18. Savi P, Combalbert J, Gaich C, et al. The antiaggregating activity of clopidogrel is due to a metabolic activation by the hepatic cytochrome P450–1A. *Thromb Haemost*. 1994;72(2):313–317.
19. Savi P, Pereillo JM, Uzabiaga MF, et al. Identification and Biological Activity of the Active Metabolite of Clopidogrel. *Thromb Haemost*. 2000;84(5):891–896.
20. Weber AA, Braun M, Hohlfeld T, Schwippert B, Tschöpe D, Schrör K. Recovery of platelet function after discontinuation of clopidogrel treatment in healthy volunteers. *Br J Clin Pharmacol*. 2001;52(3): 333–336.
21. Ingelman-Sundberg M, Sim SC, Gomez A, Rodriguez-Antona C. Influence of cytochrome P450 polymorphisms on drug therapies: Pharmacogenetic, pharmacoepigenetic and clinical aspects. *Pharmacol Ther*. 2007;116(3):496–526.
22. Mega JL, Close SL, Wiviott SD, et al. Cytochrome P-450 Polymorphisms and Response to Clopidogrel. *N Engl J Med*. 2009;360(4):354–362.
23. Collet JP, Hulot JS, Pena A, et al. Cytochrome P450 2C19 polymorphism in young patients treated with clopidogrel after myocardial infarction: a cohort study. *Lancet*. 2009;373(9660):309–317.
24. Shuldiner AR, O'Connell JR, Bliden KP, et al. Association of Cytochrome P450 2C19 Genotype With the Antiplatelet Effect and Clinical Efficacy of Clopidogrel Therapy. *JAMA*. 2009;302(8):849–857.
25. Desta Z, Zhao X, Shin JG, Flockhart DA. Clinical Significance of the Cytochrome P450 2C19 Genetic Polymorphism. *Clin Pharmacokinet* 2002;41(12):913–958.
26. 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. *J Am Coll Cardiol*. 2008;52(18): 1502–1517.
27. Lanas A, Garcia-Rodriguez LA, Arroyo MT, et al. Effect of Antisecretory Drugs and Nitrates on the Risk of Ulcer Bleeding Associated With Nonsteroidal Anti-Inflammatory Drugs, Antiplatelet Agents, and Anticoagulants. *Am J Gastroenterol*. 2007;102(3):507–515.

28. Kwong Ming F, Tiing Leong A, Lean Choo B, Edmund Jon Deon L. Proton Pump Inhibitors: Do Differences in Pharmacokinetics Translate into Differences in Clinical Outcomes? *Clin Pharmacokinet*. 2008; 47:1–6.
29. Norgard NB, Mathews KD, Wall GC. Drug-Drug Interaction Between Clopidogrel and the Proton Pump Inhibitors. *Ann Pharmacother*. 2009;43(7):1266–1274.
30. Gilard M, Arnaud B, Gal GL, Abgrall JF, Boschat J. Influence of omeprazol on the antiplatelet action of clopidogrel associated to aspirin. *J Thromb Haemost*. 2006;4(11):2508–2509.
31. Gilard M, Arnaud B, Cornily JC, et al. Influence of Omeprazole on the Antiplatelet Action of Clopidogrel Associated With Aspirin: The Randomized, Double-Blind OCLA (Omeprazole CLopidogrel Aspirin) Study. *J Am Coll Cardiol*. 2008;51(3):256–260.
32. Small DS, Farid NA, Payne CD, et al. Effects of the Proton Pump Inhibitor Lansoprazole on the Pharmacokinetics and Pharmacodynamics of Prasugrel and Clopidogrel. *J Clin Pharmacol*. April 1, 2008 2008;48(4): 475–484.
33. Siller-Matula JM, Spiel AO, Lang IM, Kreiner G, Christ G, Jilma B. Effects of pantoprazole and esomeprazole on platelet inhibition by clopidogrel. *Am Heart J*. 2009 Jan;157(1):148.e1–e5. Epub 2008 Nov 6.
34. Sibbing DM, Tanja, Stegherr, Julia et al. Impact of proton pump inhibitors on the antiplatelet effects of clopidogrel. *Thromb Haemost*. 2009;101(4):714–719.
35. Cuissett 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):1149–1153.
36. Ray WA, Murray KT, Griffin MR, et al. Outcomes With Concurrent Use of Clopidogrel and Proton-Pump Inhibitors. *Ann Intern Med*. 2010; 152(6):337–345.
37. 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(9694):989–997.
38. Ramirez JF. Proton pump inhibitor and clopidogrel combination is not associated with adverse clinical outcomes after PCI: The NHLBI Dynamic Registry. Presented at: American College of Cardiology Session/i2 Summit, March 29, 2009; Orlando, FL.; http://www.tctmd.com/show.aspx?id=77266
39. Bhatt DL, Cryer MM, Byron MD, Contant CF, et al. COGENT: A prospective, randomized, placebo-controlled trial of omeprazole in patients receiving aspirin and clopidogrel. Transvascular Cardiovascular Therapeutics Annual Meeting. Sept 2009.
40. Dunn SP, Macaulay TE, Brennan DM, et al. Abstract 3999: Baseline Proton Pump Inhibitor Use is Associated with Increased Cardiovascular Events With and Without the Use of Clopidogrel in the CREDO Trial. *Circulation*. 2008;118(18_MeetingAbstracts):S_1458.
41. Pezalla E, Day D, Pulliadath I. Initial Assessment of Clinical Impact of a Drug Interaction Between Clopidogrel and Proton Pump Inhibitors. *J Am Coll Cardiol*. 2008;52(12):1038–1039.
42. Juurlink DN, Gomes T, Ko DT, et al. A population-based study of the drug interaction between proton pump inhibitors and clopidogrel. *CMAJ*. 2009 Mar 31. 2009;180(7):713–718.
43. 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.
44. Stanek EJ, Aubert RE, Flockhart DA, et al. 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. 2009. http://www.theheart.org/article/967075.do.