The Clinical Significance of the Interaction Between Proton Pump Inhibitors and Clopidogrel

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Objective: To determine whether the interaction between omeprazole and clopidogrel is a proton pump inhibitor (PPI) class effect or a drug-specific effect.

Data Sources: A MEDLINE search for primary literature was completed (through August 2009) using the search terms proton pump inhibitors and clopidogrel. Additional data obtained from references and abstracts presented at clinical meetings were included when appropriate.

Study Selection: Nine primary literature articles were identified and reviewed. This included only one prospective, double-blind, placebo-controlled, randomized trial. The remainder were prospective and retrospective cohort studies and a population-based nested case-control study.

Data Extraction: Omeprazole, a CYP2C19 inhibitor, has been shown to increase the platelet reactivity index (PRI) when combined with clopidogrel (52.4% vs 39.8%; $p < 0.0001$), leading to an increased risk of thrombosis. This combination was also shown to cause a 25% increase in the risk of mortality or rehospitalization for acute coronary syndrome (ACS), with a significantly higher risk for each 10% increase in time on this combination therapy (odds ratio [OR] 1.07; CI 1.05 to 1.09). Conversely, combination therapy with pantoprazole or esomeprazole and clopidogrel caused a nonsignificant increase in PRI ($p = 0.382$) and adenosine diphosphate–induced platelet aggregation ($p = 0.69$ and 0.88, respectively). Similarly, the combination of pantoprazole and clopidogrel was not associated with an increased risk of myocardial infarction (OR 1.02 [0.70–1.47]) when patients were followed for 90 days following hospital discharge for ACS. One study has shown a class effect when PPIs are combined with clopidogrel, leading to an increased risk of a major adverse cardiovascular event (hazard ratio 1.51; 1.39 to 1.64). Histamine$_2$ (H_2)–receptor antagonists have not been associated with a significant interaction with clopidogrel in any study.

Conclusions: The use of PPIs with clopidogrel may be warranted, based on comorbid disease states for many patients, but H_2-receptor antagonists should be considered when appropriate, due to their lack of interaction with clopidogrel.

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Pharmacologic inhibition of platelets with a combination of aspirin and clopidogrel, a thienopyridine, is a currently recommended approach to preventing recurrent ischemic events in patients with acute coronary syndrome (ACS) who are undergoing percutaneous coronary intervention. Clopidogrel therapy is usually recommended as a long-term option in patients with coronary artery disease. Specifically, current guidelines recommend clopidogrel for a minimum of 12 months in patients (without contraindications) with stent placement (drug-eluting and bare metal), ST-elevation myocardial infarction (MI), non-ST elevation MI, and unstable angina (UA).[1-3] Further, dual antiplatelet therapy with aspirin is recommended for patients without a corresponding allergy. Current guidelines also recommend proton pump inhibitor (PPI) therapy for the prevention of gastrointestinal (GI) ulcers in patients on dual antiplatelet therapy.[4] With the increasing use of clopidogrel, there have been reports of clopidogrel resistance in 4–30% of patients.[5] Mechanisms of resistance are largely focused on genetic resistance through decreased activation of clopidogrel because it is a prodrug. Clopidogrel requires cytochrome P450 (CYP450) enzymes for activation, specifically CYP2C19, 3A4/5, 1A2, 2B6, and 2C9.[6] Because of the dependence on CYP3A4 and 2C19 for activation, other medications that inhibit these enzymes have been investigated as a cause of nongenetic clopidogrel

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resistance. Most recently, the use of omeprazole, a CYP2C19 inhibitor, has been shown to decrease clopidogrel effectiveness.

To review the potential significance of the proposed interaction between omeprazole, or all PPIs, and clopidogrel, a MEDLINE search for primary literature was completed (through August 2009) using the search terms proton pump inhibitors and clopidogrel. Additional data obtained from references and abstracts presented at clinical meetings were included for a full analysis.

In 2006, Gilard and colleagues were the first to report a change in vasodilator-stimulated phosphoprotein (VASP) assay in patients taking both clopidogrel and omeprazole.[7] The VASP assay provides an index of platelet reactivity to clopidogrel. The greater the VASP value, the more likely thrombosis will occur. Patients treated with PPIs and clopidogrel had significantly higher VASP results of 61.4 ± 23.2 versus 49.5 ± 16.3 in non-PPI users ($p = 0.007$). Although Gilard et al. did not specify which PPIs were used in this cohort, it was the first analysis of this potential interaction. These study results were among the first to show this potential interaction, but the clinical significance of the VASP assay is difficult to assess since this test is not used clinically and is reserved for the research setting. The VASP assay correlates to a measure of platelet reactivity to clopidogrel, with a platelet reactivity index (PRI) value of greater than 50% often considered resistant to clopidogrel.

The first outcomes studies of this interaction were presented at the American Heart Association (AHA) Scientific Sessions in 2008. Dunn and colleagues presented the results of a subgroup analysis of the CREDO study, which included 2,116 patients and showed an increased risk of death/MI/stroke composite endpoint at 1 year in patients taking a PPI with clopidogrel (odds ratio [OR] 1.63; 1.01 to 2.63; $p = 0.043$) or without clopidogrel (OR 1.56; 1.03 to 2.34; $p = 0.035$).[8] At the same time, Aubert and colleagues presented the results of the Clopidogrel Medco Outcomes Study.[9] Although the initial presentation of this study was only available in limited abstract form at the AHA Scientific Sessions, more complete results were later presented at the Society for Cardiovascular Angiography and Interventions (SCAI) Scientific Sessions in May 2009. The Clopidogrel Medco Outcomes Study is a retrospective analysis of 14,383 patients within the Medco database who had a coronary stent placed during 2005–2006. These patients were then assessed at 1 year for the occurrence of a major adverse cardiac event (MACE) and compared, based on the concurrent use of a PPI and clopidogrel. During the follow-up period, the incidence of a MACE was significantly higher in patients taking clopidogrel plus PPI versus clopidogrel alone (25.1% vs 17.9%, respectively; hazard ratio [HR] 1.51; 1.39 to 1.64; $p < 0.0001$). Excluding rabeprazole due to an insufficient number of patients for statistical power, the Clopidogrel Medco Outcomes Study showed a significant risk of a MACE for those taking all other PPIs (Table 1).[10] Conversely, at the American College of Cardiology (ACC) Scientific Session in 2009, Ramirez et al. presented their cohort analysis, which showed that concomitant PPI and clopidogrel use did not increase the rates of death ($p = 0.18$), MI ($p = 0.83$), death/MI ($p = 0.32$), or repeat revascularization ($p = 0.65$) at 1 year.[11]

The results of these studies of a potential clopidogrel–PPI interaction were concerning and conflicting, but the question remained whether this interaction was a class effect or specific to one PPI. Aside from the Clopidogrel Medco Outcomes Study and the results from Ramirez et al., current published information has largely separated the PPI effects on clopidogrel to omeprazole versus all other PPIs.

Omeprazole

In 2008, results of the OCLA (Influence of Omeprazole on the Antiplatelet Action of Clopidogrel Associated with Aspirin) study, a double-blind, placebo-controlled, randomized trial of 140 consecutive patients undergoing elective coronary stent placement, were released.[12] Following dual aspirin (75 mg) and clopidogrel (300 mg loading dose, then 75 mg daily) therapy, patients were assigned to either omeprazole 20 mg daily or placebo for 7 days. At baseline and at the end of 7 days, all patients were assessed for their PRI, with a comparison of the PRI between patients treated with omeprazole versus those treated with placebo. Gilard et al. reported that, at the end of 7 days, patients treated with omeprazole had a significantly higher PRI than did those treated with placebo (52.4% vs 39.8%, respectively; $p < 0.0001$).[12] Similarly, patients treated with omeprazole had a significantly lower change from baseline in their PRI (43.3% vs 32.6%, respectively; $p < 0.0001$). The percentage of patients classified as poor responders (PRI >50%) was also significantly higher in patients treated with omeprazole than in those receiving placebo (60.9% vs 26.7%, respectively; OR 4.31; $p < 0.0001$).

Ho et al. published results of a large retrospective cohort of all patients with an MI or UA who were discharged from a Veterans Affairs Medical Center (VAMC) over about 2.5 years.[13] Within this period, 8,205 patients who filled a prescription for clopidogrel at a VAMC pharmacy were identified. The primary outcome was a composite of all-cause mortality or rehospitalization for ACS (MI or UA) in patients taking clopidogrel with or without concurrent PPI therapy. Secondary outcomes in-

Table 1. PPI Major Adverse Cardiovascular Event Risk[10]

PPI	MACE (%)	HR	p VALUE
Omeprazole	25.1	1.39	<0.0001
Esomeprazole	24.9	1.57	<0.0001
Pantoprazole	29.2	1.61	<0.0001
Lansoprazole	24.3	1.39	<0.0001

HR = hazard ratio; MACE = major adverse cardiovascular event; PPI = proton pump inhibitor.

cluded rehospitalization for ACS, revascularization procedures, and all-cause mortality following hospitalization for ACS. Of the 8,205 patients who filled a prescription for clopidogrel, 63.9% were prescribed concomitant PPI therapy, with omeprazole prescribed most commonly (59.7%). The rate of the primary endpoint was significantly higher in the group with clopidogrel and PPI (mainly omeprazole) combination therapy (29.8% vs 20.8%, respectively; OR 1.25; 1.11 to 1.41). Similarly, the rate of recurrent hospitalization for ACS and revascularization procedures was significantly higher in the combination PPI and clopidogrel group (OR 1.86; 1.57 to 2.20 and 1.49; 1.30 to 1.71, respectively). All-cause mortality was not significantly different (OR 0.91; 0.80 to 1.05). Despite the increased risk associated with concurrent PPI and clopidogrel therapy, there was no dose-response relationship between PPI dose and any of the outcomes. Also, it was concluded that there was a significant increase in the risk of the primary outcome for each 10% increase in the length of time the patient was on PPI and clopidogrel combination therapy (OR 1.07; 1.05 to 1.09).

Other PPIs

In addition to the interaction between omeprazole and clopidogrel, other PPIs have been investigated for a similar effect. Siller-Matula et al. were among the first to publish the effects of other PPIs, specifically pantoprazole and esomeprazole, on clopidogrel platelet inhibition.[14] In their study, 300 consecutive patients undergoing percutaneous coronary intervention (PCI) were given a 600-mg loading dose of clopidogrel followed by 75 mg daily and aspirin 100 mg daily for 5 months. The primary endpoint was a comparison of PRI between patients taking esomeprazole or pantoprazole versus patients without PPI treatment. The average PRI for patients without concomitant PPI treatment was 49%, which did not significantly differ from that of patients on pantoprazole or esomeprazole (50% and 54%, respectively; p = 0.382). Due to differences in the number of patients within each treatment group, subgroup analyses found that the PRI was not influenced by male sex, statins, angiotensin-converting enzyme inhibitors, or calcium-channel blockers.

More recently, Sibbing et al. published results that supported the lack of a significant interaction between clopidogrel and esomeprazole or pantoprazole.[6] This study evaluated 1000 consecutive patients with coronary artery disease who were admitted for a control coronary angiography. The adenosine diphosphate (ADP)–induced platelet aggregation was compared in patients taking clopidogrel with or without concomitant PPI therapy. Similar to previously published results, omeprazole combined with clopidogrel resulted in increased ADP-induced platelet aggregation compared with no concomitant PPI treatment (p = 0.0001). Pantoprazole and esomeprazole were not associated with a significant difference in ADP-induced platelet aggregation (p = 0.69 and 0.88, respectively). Of note, this study was only prospectively powered to detect a difference between the pantoprazole group and the no PPI group. Sibbing et al. also noted an attenuated platelet response in patients who were active smokers, had diabetes, increased body mass index, renal insufficiency, previous MI, or increased platelet count, which may warrant further investigation as a potential independent factor of platelet response.

Juurlink and colleagues published the results of a large, population-based, nested case-control study examining the effects of the PPI–clopidogrel interaction.[15] Patients who filled a prescription for clopidogrel within 3 days of hospital discharge were followed for 90 days for an MI. Juurlink and colleagues then stratified all patients with a clopidogrel prescription based on their exposure to a PPI. PPI exposure was classified as current PPI use (within the past 30 days), previous PPI use (within the past 31–90 days), or remote PPI use (within the past 91–180 days). Over a 69-month period, 13,636 patients who filled a clopidogrel prescription were identified. Of these patients, 2,682 (19.7%) were considered current PPI users and 4,224 (31.0%) were previous users. In total, 782 patients were readmitted due to an acute MI. When the data were stratified based on PPI exposure, the risk of recurrent MI within 90 days was only significant for patients who were currently taking both clopidogrel and a PPI (OR 1.27; 1.03 to 1.57). Previous and remote PPI use were not associated with an increased risk (OR 0.86; 0.63 to 1.19 and 0.81; 0.46 to 1.41, respectively). Similar to results in trials by Siller-Matula et al.[14] and Sibbing et al.,[6] pantoprazole in combination with clopidogrel was not associated with an increased risk of MI (OR 1.02; 0.70 to 1.47).[15] However, esomeprazole alone was not included for analysis in this study. The significant interaction found between current PPI use and clopidogrel was due to the significant increase in recurrent MI within 90 days when all other PPIs (excluding pantoprazole) were grouped together (OR 1.40; 1.10 to 1.77). Juurlink et al. also noted that histamine$_2$ (H_2)–blockers were not associated with an increased MI risk when used with clopidogrel (OR 0.94; 0.63 to 1.40). Overall, information regarding the interaction between dexlansoprazole, lansoprazole, or rabeprazole and clopidogrel is lacking at this point. However, in vitro studies have shown that lansoprazole does not significantly alter the pharmacokinetics or pharmacodynamics of clopidogrel.[16]

Discussion

Current literature suggests that the interaction between clopidogrel and PPIs appears to be mainly a drug-specific effect with omeprazole. Gilard et al.[12] showed that clopidogrel and omeprazole combination therapy was associated with a significantly higher PRI. Similarly, Ho and colleagues[13] were able to correlate this combination with an increased risk of a composite endpoint of mortality or rehospitalization for ACS. The OCLA study is the only prospective, double-blind, randomized, placebo-controlled

trial available regarding this drug interaction.[12] However, the baseline clopidogrel response level and CYP2C19 activity were not assessed in this study and could have led to bias in the treatment groups. In addition to the significant effect on the nonclinical endpoint of PRI shown by Gilard and colleagues,[12] Ho and colleagues were able to correlate omeprazole and clopidogrel combination therapy with a significant increase in cardiovascular outcomes in a much larger patient population of more than 8,000 people. However, patients who were prescribed a PPI were older and had a higher incidence of other cardiovascular risk factors, including diabetes, previous MI, previous coronary bypass surgery, lung disease, renal disease, and peripheral vascular disease. It also appears that the risk associated with this combination was primarily due to recurrent hospitalization for ACS, and not an increase in mortality. The higher incidence of comorbid risk factors in the PPI group makes generalizing these results to all PPI users more difficult.

Juurlink et al.,[15] Siller-Matula et al.,[14] and Sibbing et al.[6] have shown that other PPIs, specifically esomeprazole or pantoprazole, were not associated with a significant interaction with clopidogrel. Juurlink et al. provided a large patient population in examination of this medication interaction, and even though patients taking PPIs tended to have more risk factors, the use of pantoprazole was still not associated with an increased risk of recurrent MI. The results of this study provide significant evidence to support the use of pantoprazole in combination with clopidogrel. Siller-Matula et al. provided additional evidence that pantoprazole and esomeprazole did not significantly affect the PRI of clopidogrel, but due to the study design and lack of adequate power, they were unable to compare these results with results of omeprazole trials. This study was also a cohort study with the potential for bias due to lack of randomization. The study by Sibbing and colleagues offers additional non–outcome-based evidence supporting the use of pantoprazole and esomeprazole, using a different platelet assay than that used in the OCLA study. However, this study was only powered to consider pantoprazole treatment. Due to the nonrandomized design of all of these studies and the lack of power for direct comparison with omeprazole, the results should be considered for potential bias or confounders that may have been present in the treatment groups.

The Clopidogrel Medco Outcomes Study is the only trial to date that identifies the interaction between clopidogrel and PPIs as a class effect.[9] This study was a retrospective analysis that did not include analyses of over-the-counter medications (including aspirin and omeprazole), family history of cardiovascular disease, smoking status, blood pressure, lipids, or other potentially confounding variables. The authors also acknowledged that there was potential bias within this patient population, due to the presence or absence of these confounders within each PPI group as well as the different number of people receiving each PPI.

Although their results are only available as an abstract, Ramirez and colleagues[11] had results opposite of those of the Clopidogrel Medco Outcomes Study,[9] with no significant interaction between PPIs and clopidogrel. However, this abstract did not specify which PPIs were included in the analysis but did identify, as potential confounders, that the baseline prevalence of diabetes, hypertension, renal dysfunction, smoking habits, and PCI procedural success was similar between PPI users and nonusers.[11]

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Esomeprazole and pantoprazole were not associated with a significant interaction with clopidogrel.

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The difference in the effects between omeprazole and the rest of the PPIs is thought to be through the affinity for CYP2C19. Although esomeprazole and pantoprazole are both metabolized to some extent by CYP2C19 and 3A4, omeprazole has the greatest affinity for CYP2C19, thus resulting in the greatest inhibition of this enzyme of all the PPIs. Also, pantoprazole is metabolized by a cytosolic sulfotransferase, which is independent of the CYP450 pathway.[6] If this interaction is indeed the root of the reduced effectiveness of clopidogrel, the possibility of the effect being unique to omeprazole is plausible.

In response to the ongoing controversy about PPI and clopidogrel interactions, in January 2009, the FDA released an "Early Communication about an Ongoing Safety Review of Clopidogrel Bisulfate (marketed as Plavix)."[17] In this communication, the FDA highlighted that some of the differences in effectiveness of clopidogrel seen in previous trials have been attributed to genetics. Similarly, genetic analysis has not been completed in any of the PPI trials. Also noted in the FDA report is that the interaction between clopidogrel and PPIs appears to be largely a specific reaction with omeprazole. In this release, the FDA recommends that prescribers continue to prescribe clopidogrel as directed, reevaluate the need for starting or continuing PPI therapy, and remind patients taking PPIs to consult their healthcare providers about any concerns. It is also highlighted that H_2-blockers have not been associated with a significant interaction with clopidogrel and may be an appropriate option in certain patients. Following the release of the FDA communication, the clopidogrel product information was updated to warn providers about potential increased MI risk with reduced CYP2C19 function as well as to discourage concurrent use of drugs that inhibit CYP2C19, specifically omeprazole.[18]

The AHA, ACC, and American College of Gastroenterology (ACG) have released a joint statement reminding practitioners that PPIs are the mainstay of treatment and

prevention of GI ulcers and bleeding.[4] Their statement identifies the high-risk patients who would benefit most from PPI therapy as those with a history of GI bleed ing, with a history of ulcer disease, on dual antiplatelet therapy, or taking other anticoagulants. The SCAI reiterated that patients should "continue taking the drugs [clopidogrel and PPI] unless told to stop by their physician."[1] Following the SCAI Scientific Sessions in May 2009, the SCAI released a more specific statement reminding providers to consider H_2-blockers or antacids in appropriate patients, as these medications have not been associated with significant interactions with clopidogrel.[10]

Summary

Patients taking dual antiplatelet therapy with clopidogrel and aspirin generally should be on a PPI for prevention of GI ulcers. However, it should be carefully decided as to which PPI should be used. Based on current evidence and the revised clopidogrel labeling, the use of omeprazole should be avoided due to the risk of decreased clopidogrel effectiveness. Similarly, the use of rabeprazole, lansoprazole, or dexlansoprazole is questionable due to the lack of data regarding their potential interaction. Esomeprazole or pantoprazole appear to be the safest options in this patient population and should likely be used as first-line PPI therapy in patients who require dual antiplatelet therapy. However, the use of these 2 PPIs (esomeprazole and pantoprazole) should be examined carefully and consideration given to the high-risk patient populations outlined by the AHA, ACC, and ACG joint statement, as the studies comparing them did not include adequate power for direct comparison with omeprazole. Based on recommendations by the FDA, evidence presented by Juurlink et al., and results from the SCAI Scientific Sessions in 2009, H_2-receptor antagonists are an appropriate option to prevent GI symptoms for many patients taking clopidogrel and have not been associated with an interaction with clopidogrel. Overall, further investigation is needed to better determine the clinical significance of all PPI and clopidogrel interactions. Randomized controlled trials should be completed to provide the strongest evidence on this interaction. Patients should continue to take both clopidogrel and PPIs as directed, but be familiar with this risk and ask their physicians before making any change to their therapy. ≏

References

1. King SB, Smith SC, Hirshfield JW, et al. 2007 Focused update of the ACC/AHA/SCAI 2005 guideline update for percutaneous coronary intervention: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines: 2007 Writing Group to Review New Evidence and Update the ACC/AHA/SCAI 2005 Guideline Update for Percutaneous Coronary Intervention, writing on behalf of the 2005 writing committee. Circulation 2008;117:261-95.
2. Antman EM, Hand M, Armstrong PW, et al. 2007 Focused update of the ACC/AHA 2004 guidelines for the management of patients with ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the Canadian Cardiovascular Society, endorsed by the American Academy of Family Physicians: 2007 writing group to review new evidence and update the ACC/AHA 2004 guidelines for the management of patients with ST-elevation myocardial infarction, writing on behalf of the 2004 writing committee. Circulation 2008;117: 296-329.
3. 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: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (writing committee to revise the 2002 guidelines for the management of patients with unstable angina/non ST-elevation myocardial infarction): developed in collaboration with the American College of Emergency Physicians, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons: endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation and the Society for Academic Emergency Medicine. Circulation 2007;116:e148-304.
4. 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;52:1502-17.
5. Nappi J. Benefits and limitations of current antiplatelet therapies. Am J Health Syst Pharm 2008;65:S5-10.
6. Sibbing D, Morath T, Stegharr J, et al. Impact of proton pump inhibitors on the antiplatelet effects of clopidogrel. Thromb Haemost 2009;101:714-9.
7. Gilard M, Arnaud B, Le Gal G, Abgrall JF, Boschat J. Influence of omeprazole on the antiplatelet action of clopidogrel associated to aspirin. J Thromb Haemost 2006;4:2508-9.
8. Dunn SP, Macaulay TE, Brennan DM, et al. Baseline proton pump inhibitor use is associated with increased cardiovascular events with and without the use of clopidogrel in the CREDO trial (abstract 3999). Circulation 2008;118:S815.
9. Aubert RE, Epstein RS, Teagarden JR, et al. Proton pump inhibitor effect on clopidogrel effectiveness: the Clopidogrel Medco Outcomes Study (abstract 3998). Circulation 2008;118:S815.
10. Wood S. Possible "class effect" for proton-pump inhibitors on top of clopidogrel therapy. www.theheart.org/article/967075.do (accessed 2009 Jun 16).
11. Ramirez JF, Selzer F, Chakaprani R, et al. Proton pump inhibitor and clopidogrel combination is not associated with adverse clinical outcomes after PCI: the NHLBI dynamic registry. J Am Coll Cardiol 2009;53:A27.
12. Gilard MG, Arnaud B, Cornily JC, et al. Influence of omeprazole on the antiplatelet action of clopidogrel associated with aspirin. J Am Coll Cardiol 2008;51:256-60.
13. 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;301:937-44.
14. Siller-Matula JM, Spiel AO, Lang IM, Kreiner G, Christ G, Jilma B. Effects of pantoprazole and esomeprazole on platelet inhibition by clopidogrel. Heart J 2009;157:148.e1-e5.
15. Juurlink DN, Gomes T, Ko DT, et al. A population-based study of the drug interaction between proton pump inhibitors and clopidogrel. CMAJ 2009;180:713-8. DOI 10.1503/cmaj.082001
16. 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 2008;48;475-84.
17. US Food and Drug Administration. Early communication about an ongoing safety of clopidogrel bisulfate (marketed as Plavix). January 26, 2009. http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHealthcareProfessionals/ucm079520.htm (accessed 2010 Jan 12).
18. Prescribing information. Clopidogrel bisulfate (Plavix). Bridgewater, NJ: Bristol-Myers Squibb/Sanofi Pharmaceuticals, May 2009.