Interaction between clopidogrel and proton-pump inhibitors and management strategies in patients with cardiovascular diseases

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Abstract: Dual antiplatelet therapy (DAPT) with clopidogrel and aspirin has been successful in reducing ischemic events in a wide range of patients with cardiovascular diseases. However, the anti-ischemic effects of DAPT may also be associated with gastrointestinal (GI) complications including ulceration and bleeding particularly in ‘high risk’ and elderly patients. Current guidelines recommend the use of proton-pump inhibitors (PPIs) to reduce the risk of GI bleeding in patients treated with DAPT. However, pharmacodynamic studies suggest an effect of PPIs on clopidogrel metabolism with a resultant reduction in platelet inhibitory effects. Similarly, several observational studies have demonstrated reduced clopidogrel benefit in patients who coadministered PPIs. Although recent US Food and Drug Administration and European Medicines Agency statements discourage PPI (particularly omeprazole) and clopidogrel coadministration, the 2009 AHA/ACC/SCAI PCI guidelines do not support a change in current practice in the absence of adequately powered prospective randomized clinical trial data. The data regarding pharmacologic and clinical interactions between PPI and clopidogrel therapies are herein examined and treatment strategies are provided.

Keywords: cardiovascular disease, gastrointestinal, proton-pump inhibitor, antiplatelet therapy

Introduction

Platelet activation and reactivity play an important role in the occurrence of ischemic events during acute coronary syndromes (ACS) and following percutaneous intervention (PCI). The two important secondary agonists, thromboxane and particularly adenosine diphosphate (ADP) are released upon platelet activation and are responsible for the sustained platelet activation and aggregation and the generation of subsequent thrombus at the site of vascular injury. Therefore, inhibition of these two major pathways, thromboxane synthesis by aspirin and ADP (P2Y12) receptor activation by P2Y12 receptor blockers constitutes a major strategy to attenuate ischemic events. Moreover, this strategy has been shown to be effective in attenuating atherothrombotic events across a wide range of patients with cardiovascular disease.1 However, the benefit of antiplatelet therapy may be associated with gastrointestinal (GI) complications including ulceration and bleeding.2 Current guidelines recommend the use of proton pump inhibitors (PPIs) to reduce the risk of gastrointestinal bleeding (GIB) in patients treated with dual antiplatelet therapy (DAPT). However, pharmacodynamic studies suggest an effect of PPIs on clopidogrel metabolism with a resultant reduction in platelet inhibitory effects. Similarly, several observational studies have demonstrated reduced clopidogrel benefit in patients who coadministered PPIs. Although recent US Food and...
Drug Administration (FDA) and European Medicines Agency (EMEA) statements discourage PPI (particularly omeprazole) and clopidogrel coadministration, the 2009 American Heart Association/American College of Cardiology/Society for Cardiac Angiography and Interventions (AHA/ACC/SCAI) PCI guidelines do not support a change in current practice in the absence of adequately powered prospective randomized clinical trial data. The data regarding pharmacologic and clinical interactions between PPI and clopidogrel therapies are herein examined and treatment strategies are provided.

**Rationale for coadministration of clopidogrel and PPIs**

Prostaglandins, especially prostaglandin E₁ (PGE₁) and thromboxane A₂, are involved in the regulation of gastric mucosal blood flow, stimulation of mucosal and bicarbonate secretions, and the proliferation of gastric epithelial cells. Thus, inhibition of prostaglandin synthesis by aspirin may impair the protective barrier for gastric mucosa making it more susceptible to ulceration induced by endogenous acid, pepsin, and bile salts. In addition, inhibition of platelet aggregation along with various growth factors released from activated platelets at the site of vascular injury during aspirin therapy can attenuate gastric healing and increase susceptibility to GIB. In patients treated with low-dose aspirin alone (OR 1.8; 95% CI: 1.5–2.1) compared to age- and sex-matched controls, and the greatest risk was observed in patients receiving DAPT when compared to age- and sex-matched controls (OR 7.4; 95% CI: 3.5–15). In the CHARISMA trial, an increased risk of GUSTO bleeding (mostly GIB) was observed during long-term DAPT compared with aspirin monotherapy. Interestingly, the relative risk of bleeding on DAPT was greatest during the first year of therapy. Furthermore, the relative risk of GI complications observed during DAPT compared with aspirin monotherapy was increased two- to threefold in randomized clinical trials and sevenfold in observational studies. In addition to DAPT, other factors such as older age, male sex, advanced heart failure symptoms, and diabetes were independently associated with GIB. Finally, a history of prior ulcer disease as well as concomitant therapy with NSAID, anticoagulants, and/or aspirin has been associated with an increased risk of GIB in clopidogrel-treated patients.

The occurrence of GIB is associated with morbidity and mortality in patients with underlying cardiovascular disease and following PCI. A correlation between the occurrence of major bleeding events and subsequent MI, stroke, or death was observed in both the OASIS and CURE trials. In the CHARISMA trial, moderate severity bleeding events were associated with all-cause mortality (hazard ratio [HR] 2.92; 95% CI: 1.71–3.80; P < 0.001), MI (HR 2.92; 95% CI: 2.04–4.18; P < 0.001), and stroke (HR 4.20; 95% CI: 3.05–5.77; P < 0.001), and the occurrence of GIB was associated with all-cause mortality (HR 1.82; 95% CI: 1.24–2.69). Similarly, a multivariate analysis of the ACUITY trial demonstrated that GIB was associated with all-cause mortality, cardiac mortality, and a composite ischemic endpoint to both 30 days and 1 year as well as with stent thrombosis to 1 year. GIB was the most frequent cause of bleeding in medically managed patients and the second most frequent cause of non-CABG-related bleeding (following access site bleeding) in the entire study population. Finally, GIB was an important correlate of premature antiplatelet therapy cessation, and 20.8% of GIB patients were discharged without aspirin or thienopyridine therapy.

Obviously, a balance between cardiovascular risk (the major rationale for DAPT) and risk for GIB must be established. Current guidelines recommend uninterrupted DAPT for ‘at least 1 year’ in patients presenting with ACS and/or those treated with drug-eluting stents. Multiple data sources provide a rationale for the concomitant administration of PPIs in patients treated with either aspirin alone or with DAPT especially those at greatest risk for GIB complications. Lanas et al demonstrated that the addition of a...
interaction between clopidogrel and PPIs

Clopidogrel metabolism

Clopidogrel is administered orally as a prodrug and only 10%–15% of absorbed clopidogrel is available for hepatic conversion to an active metabolite in a two-step process. Metabolic conversion occurs rapidly and neither native clopidogrel nor active metabolites are detectable in plasma beyond 2 h following oral clopidogrel administration. Recent studies suggest that hepatic cytochrome P450 (CYP) isoenzymes CYP2C19, CYP1A2, and CYP2B6 are responsible for the first step of metabolic conversion, whereas CYP2C19, CYP2C9, CYP2B6, and CYP3A4 are responsible for the second step. CYP2C19 contributes prominently to both steps and CYP3A4 substantially to the second step. Clopidogrel therapy is associated with a wide response variability/nonresponsiveness that is mostly attributed to variable/insufficient active metabolite generation. Variability in intestinal absorption, drug–drug interactions at the CYP isoenzyme level, and genetic polymorphisms of CYP isoenzymes (particularly CYP2C19*2) which lead to CYP functional variability are major contributors to variability in clopidogrel response. A diminished pharmacodynamic response (inhibition of platelet aggregation) to clopidogrel has been observed following coadministration of PPIs, lipophilic statins, calcium channel blockers, and warfarin which are metabolized by the CYP2C19, CYP3A4, and CYP2C9 isoenzymes. Importantly, clopidogrel nonresponsiveness or high ‘on-treatment’ platelet reactivity has been correlated with adverse ischemic events in multiple independent studies.

Metabolism of PPIs

PPIs (with the exception of rabeprazole) are absorbed efficiently and metabolized rapidly by CYP isoenzymes, especially CYP2C19 and CYP3A4. Although PPIs differ with regard to pharmacokinetic and pharmacodynamic properties, they are equally potent in inhibiting gastric secretion when administered with proper dosing. In addition to being metabolized by CYP isoenzymes, PPIs (similar to clopidogrel) also competitively inhibit CYP2C9, CYP2D6, CYP3A4, and particularly CYP2C19. The half-life of PPIs is 1–2 h. PPIs may affect the metabolism of other drugs metabolized by CYP2C19 such as diazepam, phenytoin, and R-warfarin. The magnitude of PPI inhibitory effect (particularly omeprazole) on the metabolism of other drugs is more pronounced in extensive metabolizers of 2C19 isoenzyme with gain-of-function allele (2C19*17) compared to poor metabolizers with 2C19 loss-of-function allele (2C19*2). Furthermore, metabolism of omeprazole may shift to CYP3A4 from CYP2C19 in poor metabolizers. In addition to drug–drug interactions between clopidogrel and
PPIs, genetic polymorphisms of both CYP2C19 as well as the ABCB1 gene may be responsible for a differential pharmacokinetic/pharmacodynamic response to both PPIs as well as clopidogrel. The latter mechanisms may thus influence clinical outcomes related to acid suppression, *H. pylori* eradication, and the mitigation of ischemic events associated with PPIs and clopidogrel therapy, respectively.\(^\text{30,32}\)

**Pharmacodynamic interaction between clopidogrel and PPIs**

As omeprazole is the most frequently prescribed PPI, the pharmacodynamic interaction between omeprazole and clopidogrel has been most extensively characterized. For example, vasodilator-stimulated phosphoprotein (VASP)-phosphorylation levels (a direct reflection of P2Y\(_{12}\) receptor activity) were significantly increased after at least 48 h following the addition of PPI in subjects treated with aspirin and clopidogrel compared with those receiving aspirin and clopidogrel alone \((P = 0.007)\). Similarly, in a randomized, double-blind, placebo-controlled study, the concomitant administration of omeprazole with clopidogrel significantly increased the VASP-phosphorylation index \((51.4\% \text{ versus } 39.8\% \text{ placebo, } P < 0.0001)\) at day 7 of therapy but not on day 1. This observation suggests that the effect of omeprazole to reduce the level of clopidogrel active metabolite and thus clopidogrel-mediated platelet inhibition is dynamic over time.\(^\text{33,34}\) A variable effect of lanospazole on platelet inhibition by prasugrel or clopidogrel and on the active metabolite generation of both thienopyridines has been described.\(^\text{35}\)

In a post-hoc subgroup analysis of the PRINCIPLE-TIMI 44 study, the coadministration of PPI with either clopidogrel or prasugrel was associated with reduced inhibition of platelet aggregation measured early and late \((15 \text{ days})\) on treatment. This observation suggests that PPIs are effective in reducing the level of active metabolite generation for both clopidogrel and prasugrel.\(^\text{36}\)

Differences between PPIs with regard to their influence on antiplatelet effect of clopidogrel may exist. For example, in a cross-sectional study of patients \((n = 1000)\) scheduled for PCI, significantly higher levels of on-treatment ADP-induced platelet aggregation \((\text{using Multiplate}^\text{\textregistered} \text{ analyzer, Munich, Germany})\) were observed in patients receiving omeprazole \((\text{mean } \text{AU*min} = 295, \ P = 0.001)\), but not pantoprazole or esomeprazole \((\text{mean range} = 134–226 \text{ AU*min})\) when compared to patients not receiving PPI in conjunction with clopidogrel therapy \((\text{mean} = 220 \text{ AU*min})\). In addition, the prevalence of low responders to clopidogrel \( (>456 \text{ AU*min, upper quintile})\) was significantly higher following omeprazole treatment \( (33\% \text{ versus } 19\%, \ P = 0.008)\).\(^\text{37}\) However, in another study of patients \((n = 1425)\) undergoing PCI, on-treatment platelet aggregation \((-20 \text{ h after a } 600-\text{mg clopidogrel oral loading dose})\) was significantly higher in patients receiving concomitant PPI \(\text{(similar for omeprazole, esomeprazole, and pantoprazole) compared to patients not treated with PPI} \ (P < 0.001)\).\(^\text{38}\) In additional, nonrandomized analysis of 300 patients undergoing PCI following a 600-mg oral clopidogrel loading dose, no apparent interaction between pantoprazole or esomeprazole with clopidogrel with regard to platelet inhibition was observed.\(^\text{39}\)

Similarly, Cuisset et al demonstrated a better antiplatelet effect of clopidogrel following pantoprazole as measured by the VASP-phosphorylation assay \((\text{but not ADP-induced platelet aggregation})\) in a randomized comparison with omeprazole among 104 patients undergoing stenting for NSTE ACS who were treated with DAPT of 150-mg clopidogrel plus 75-mg aspirin.\(^\text{40}\)

In summary, the major site of drug–drug interaction between clopidogrel and PPIs appears to involve the CYP2C19 isoenzyme pathway. Although the PK/PD interaction between clopidogrel and PPIs has not been demonstrated to significantly influence the clinical efficacy of either drug, coadministration of omeprazole with clopidogrel was demonstrated to decrease \((\text{up to } 20\%)\) clopidogrel-mediated platelet inhibition. This effect was more pronounced at 7–14 days compared with 1 day of treatment after a clopidogrel loading dose and translated into both an increased prevalence of clopidogrel nonresponders as well as more patients with ‘high on-treatment platelet reactivity’, an established cardiovascular risk factor. Among these studies, the absolute decrease in clopidogrel-mediated platelet aggregation attributable to PPIs was in the magnitude of 20% by light transmission aggregometry 41–76 PRU by VerifyNow P2Y\(_{12}\) assay, ∼95 units AU*min by Multiplate analyzer and up to 12% by VASP-P PRI. These results were associated with a significant increase in the prevalence of ‘nonresponders’ as defined by the respective assay.

**Influence of coadministration of PPI with clopidogrel on clinical outcome**

Numerous observational studies and meta-analyses have suggested an influence of PPI coadministration on the clinical efficacy of clopidogrel. Although these studies reflect the real-world scenario, these studies are associated with inherent deficiencies such as selection bias, variable effects of various comedations, compliance, and so on. A retrospective insurance claim-based study reported that rates of MI to 1 year
were significantly higher in clopidogrel-treated patients who had high PPI exposure compared with those having either low PPI exposure or treated with clopidogrel alone (5.03%, 3.08%, and 1.38%, respectively, \( P < 0.05 \)). In the MEDCO Outcomes study among patients, a higher incidence of major CV events (hospitalization for stroke, MI, angina, or CABG) was observed to 1 year following coronary stent deployment in patients taking concomitant PPI versus those who were not (32.5% versus 21.2%, adjusted OR 1.79; 95% CI: 1.62–1.07). This difference remained significant even after adjusting for baseline differences in age, gender, and measured comorbidities. Conversely, the primary outcome measurement at 28 days (death/MI/urgent target vessel revascularization) and 1 year (death/MI/stroke) was increased in those patients who were treated with PPIs at baseline, regardless of subsequent clopidogrel treatment strategy in a retrospective analysis of the CREDO trial. Furthermore, treatment with clopidogrel reduced cardiovascular events at 1 year to a similar degree whether or not patients were receiving concomitant PPI.

In an epidemiologic case-control study, the concurrent use of PPIs with clopidogrel was associated with recurrent MI (adjusted OR 1.27; 95% CI: 1.03–1.57) after multivariate adjustment among 13,636 patients who filled prescriptions for clopidogrel within 3 days of hospital discharge following acute MI. In this study, although pantoprazole (a relatively weak inhibitor of CYP2C19) was not associated with increased risk (OR 1.02; 95% CI: 0.70–1.47), other PPIs (omeprazole, lansoprazole, and rabeprazole) were collectively associated with a 40%-relative increase in risk of recurrent MI (OR 1.40; 95% CI: 1.10–1.77) compared to no PPI treatment. These authors estimated that about 14% of all recurrent MI could be attributed to a clopidogrel–PPI interaction. In a retrospective analysis of 8205 ACS patients discharged from hospital on clopidogrel treatment (64% treated with PPIs), the addition of PPI to clopidogrel therapy was associated with increased risks for death or rehospitalization (adjusted OR 1.25; 95% CI: 1.11–1.41), hospitalization for recurrent ACS (adjusted OR 1.86; 95% CI: 1.57–2.20), and revascularization (adjusted OR 1.49; 95% CI: 1.30–1.71) compared with clopidogrel alone. Interestingly, all-cause mortality did not differ by PPI treatment. In a post-hoc analysis of the TRITON–TIMI 38 study, no relation between PPI use and primary endpoint events was evident among patients treated with either clopidogrel or prasugrel. However, PPI therapy was not randomly assigned and could have been initiated or discontinued during follow-up, as compliance records were lacking.

In the COGENT (Clopidogrel and the Optimization of Gastrointestinal Events) study, 3672 patients (from an originally protected 5000 patient study population) who required clopidogrel therapy following non-STEMI, STEMI, or coronary stent implantation were randomly assigned to receive CGT-2168 (75-mg clopidogrel + 20-mg omeprazole) or 75-mg clopidogrel. The primary outcome measure of clinically significant GI events after 362 days of follow-up (mean 133 days) was significantly lower following combination therapy compared to clopidogrel monotherapy (38 events versus 67 events; \( P = 0.007 \)). The secondary outcome measure of all cardiovascular events (composite of cardiac death, nonfatal MI, CABG, PCI, or ischemic stroke) and the individual endpoints of MI or revascularization were similar between randomly assigned treatments. These results suggest that there is no clinically relevant adverse interaction between clopidogrel and PPI treatment despite the results of ex vivo platelet function studies as well as observational clinical studies. However, numerous limitations to the COGENT study have been noted and include premature study termination (for financial reasons), the poorly characterized antiplatelet effect of the study drug (combination omeprazole + clopidogrel), the exclusion of high risk and older patients, and a low-cardiovascular event rate (only 3.75%; 136 events/3627 patients) compared to a ~10% event rate in recent randomized trials such as PLATO and TRITON–TIMI 38.

Finally, in a retrospective analysis of 18,565 patients who had either undergone PCI or been hospitalized for ACS and were subsequently treated with clopidogrel, the addition of PPI to clopidogrel was associated with an increased risk of MI or death (OR 1.22; 95% CI: 0.99–1.51): death (OR 1.20; 95% CI: 0.84–1.70) and revascularization (OR 0.97; 95% CI: 0.79–1.21) compared with clopidogrel alone. On the basis of this propensity-score adjusted rate ratio analysis, the authors suggest that the clopidogrel–PPI interaction does not have major clinical relevance and that the increased risk of recurrent ischemic events attributable to an interaction does not exceed 20%.

Significant heterogeneity in the risk of cardiovascular outcomes including MI was observed in a meta-analysis of 23 studies involving 93,278 patients receiving clopidogrel with or without concomitant PPI which suggests that the data are inconsistent and/or confounded. Moreover, no measurable association was observed in the analysis of propensity-matched and/or randomized trial participants, whereas the observational studies more often demonstrated an association. Furthermore, the effect of clopidogrel and PPI interaction on clinical outcome measures steadily diminished from risk ratios observed in crude raw data to observational studies that adjusted for confounders and then
to randomized trials or propensity-matched studies. Indeed, recent studies demonstrated an elevated risk of adverse cardiovascular outcomes with PPI alone compared to no PPI in the absence of concomitant clopidogrel therapy indicating a potentially harmful effect of PPI (adjusted risk ratios 1.55 and 1.38).43,49,50

Finally, two recent retrospective studies suggest that pantoprazole may influence the clinical efficacy of clopidogrel. In one study in which 64% of clopidogrel-treated patients were coadministered with pantoprazole, an increased risk of rehospitalization for MI or coronary stent placement (adjusted HR 1.91; 95% CI: 1.19–3.06; P = 0.008) was observed in pantoprazole-treated patients.49 In the other study, although concomitant use of PPIs (62% pantoprazole) with clopidogrel was associated with 50% fewer hospitalizations for GIB compared with patients not treated with PPIs, the 95% CI for risk of cardiovascular events attributable to PPI included the potential for clinically important increased risk.50

Treatment strategies
Small pharmacodynamic studies have indicated a potential influence of PPIs on antiplatelet effects of clopidogrel whereas retrospective, observational, and also meta-analyses indicated that influence of PPIs comedication on clinical benefits of clopidogrel may be present only in high-risk patients and may be more pronounced in patients treated with CYP2C19-metabolized PPIs such as omeprazole. Therefore, alternative strategies may be considered in high-risk patients. In the contexts that PPIs have equal efficacy for gastric acid suppression with appropriate dosing and that the PK/PD interaction with clopidogrel is in large part mediated by hepatic CYP-450 isoenzymes (CYP2C19 and CYP3A4), rabeprazole (not CYP metabolized) may be a reasonable alternative for omeprazole. Another option may be to increase the maintenance dose of clopidogrel during long-term therapy although the safety and efficacy of dose escalation have not been established. Moreover, in the PRINCIPLE TIMI 44 study, a significant pharmacodynamic interaction between clopidogrel (150 mg/day) and PPI was demonstrated on day 14 of treatment. Similarly, a significant interaction between PPIs and prasugrel (a third-generation thienopyridine) was observed through 14 days of maintenance dose (10 mg/day) treatment. As the plasma half-lives of both clopidogrel and omeprazole are short (1–2 h), the potential for drug–drug competition at either the P-glycoprotein or CYP2C19 level may be attenuated by separating the timing of clopidogrel and omeprazole administration. However, as omeprazole bioavailability is increased by repeated dosing (maximum at 5 days), such a ‘dose separation’ strategy may have diminishing advantage during the chronic coadministration of clopidogrel and omeprazole. Furthermore, the FDA statement mentions that dose separation does not prevent the interaction between omeprazole and clopidogrel. This statement was based on data from crossover study of 72 healthy volunteers treated with clopidogrel (300-mg load followed by 75 mg/day for 5 days) and coadministered omeprazole (80 mg/day). The coadministration of omeprazole either with clopidogrel or 12 h apart from clopidogrel resulted in the same decrease in clopidogrel active metabolite and the same decrease in platelet inhibition by clopidogrel at both 24 h and 5 days. However, it should be noted that the clopidogrel loading dose of 300 mg is associated with insufficient/variable active metabolite generation as well as widely variable antiplatelet response, and the omeprazole dose of 80 mg/day is significantly higher than commonly prescribed daily doses of 20–40 mg/day.25 These facts raise questions regarding the validity of the study which forms the basis of the FDA statement which also recommends use of alternatives to PPIs such as H2 receptor blockers and antacids.25 Finally, a non-thienopyridine, ticagrelor currently in clinical trial evaluation, does not require metabolic conversion by hepatic CYP-450 isoenzymes and is not influenced by genetic polymorphisms or known drug–drug interactions. Thus, ticagrelor (not yet US FDA approved) may offer an effective alternative strategy for P2Y12 receptor inhibition. Large-scale prospective randomized clinical trials are needed to demonstrate safety and efficacy of alternative strategies to address the potential interaction between clopidogrel and PPIs.

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