Dual antiplatelet therapy with aspirin and clopidogrel is associated with a significant reduction in vascular ischemic events; however, gastrointestinal bleeding events are a major concern in high-risk and older patients. Clinical practice guidelines recommend combination therapy with proton pump inhibitors (PPI) and dual antiplatelet therapy to attenuate gastrointestinal bleeding risk. In addition, high on-treatment platelet reactivity has been associated with recurrent ischemic events. Whether or not the pharmacological interaction between clopidogrel and PPI, which results in diminished antiplatelet effect, adversely influences clinical efficacy is highly controversial and the subject of debate. Based on largely anecdotal post-hoc analyses, the U.S. Federal Drug Administration’s and European Medicines Agency’s recommendations discourage PPI use (particularly omeprazole) in patients treated with clopidogrel. However, many American College of Cardiology/American Heart Association/Society for Cardiovascular Angiography and Interventions experts do not support change in clinical practice guidelines recommendations without adequately powered, prospective, randomized clinical trial data. (J Am Coll Cardiol Intv 2011;4:365–80) © 2011 by the American College of Cardiology Foundation.
in major GIB in patients treated with aspirin compared with patients treated with placebo. Although no relationship between aspirin dose and major bleeding risk was observed in this meta-analysis, other studies have demonstrated a dose-dependent effect of aspirin on GIB (7,8).

Unlike aspirin, clopidogrel does not directly cause gastric injury, but its antiplatelet effects may impair healing of existing gastric erosions and may exacerbate GI complications associated with the concomitant administration of aspirin and nonsteroidal anti-inflammatory drugs, or in the setting of Helicobacter pylori infection. For example, aspirin 325 mg daily (but not clopidogrel 75 mg daily) for 8 days caused direct effects on GI mucosa in healthy volunteers (9). In the CAPRIE (Clopidogrel Versus Aspirin in Patients at Risk of Ischaemic Events) trial (10), aspirin monotherapy was associated with an increase in major GIB (risk ratio [RR]: 1.45; 95% confidence interval [CI]: 1.00 to 2.10) when compared with clopidogrel monotherapy. In the CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Events) trial, aspirin monotherapy was associated with less frequent major GIB when compared with aspirin + clopidogrel (RR: 0.56; 95% CI: 0.39 to 0.80) and in the MATCH (Management of Atherothrombosis With Clopidogrel in High-Risk Patients) trial, clopidogrel monotherapy was associated with less frequent major GIB than clopidogrel + aspirin (RR: 0.34; 95% CI: 0.23 to 0.51) (11,12). In a Danish case control study, more GIB complications were observed in patients treated with either low dose aspirin (odds ratio [OR]: 1.8; 95% CI: 1.5 to 2.1), or clopidogrel (OR: 1.1; 95% CI: 0.6 to 2.1) when compared with age- and sex-matched controls. The greatest risk of GIB occurred in patients receiving DAPT (OR: 7.4, 95% CI: 3.5 to 15) (13).

Finally, a correlation between major bleeding with subsequent myocardial infarction (MI), stroke, and death at 30 days was demonstrated in both the CURRENT/OASIS-7 (Clopidogrel Optimal Loading Dose Usage to Reduce Recurrent EveNtS/Optimal Antiplatelet Strategy for InterventionS) and CURE trials (14). In the CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance) trial (15), moderate bleeding was associated with all-cause mortality (hazard ratio [HR]: 2.55; 95% CI: 1.71 to 3.80; p < 0.0001), MI (HR: 2.92; 95% CI: 2.04 to 4.18; p < 0.0001), and stroke (HR: 4.20; 95% CI: 3.05 to 5.77; p < 0.0001). It should be noted that patients who experience GIB are frequently older and have more comorbidities.

**The Rationale for Combining PPIs With Antiplatelet Therapy**

The prior observations provide a rationale for concomitant administration of proton pump inhibitors (PPI) in patients treated with either aspirin alone or DAPT, particularly those at greatest risk for GIB complications (16–19). For example, the addition of a PPI (omeprazole, lansoprazole, pantoprazole, rabeprazole, or esomeprazole) to either aspirin or thienopyridine therapy reduced the incidence of GIB compared with either agent administered without a PPI (RR: 0.32 and 0.19, respectively) (16). Histories of peptic ulcer disease or cardiogenic shock were independent predictors of GIB in patients treated with DAPT. Importantly, PPI therapy administered concomitantly with DAPT or aspirin can significantly reduce GIB (17). For example, clopidogrel monotherapy (no PPI) was associated with a higher incidence of recurrent ulcer bleeding than combined aspirin plus esomeprazole treatment (8.6% vs. 0.7%, 95% CI: 3.4 to 12.4%) in patients who were *H. pylori* negative with a history of GI bleeding on low dose aspirin therapy (18). These multiple observations suggest that the addition of PPI as a gastroprotective agent in patients treated with either aspirin or DAPT can mitigate the potential for GIB.

A clinical expert consensus document states that PPI should be added to oral antiplatelet therapy in cardiovascular disease patients to reduce the risk of GIB (3). Clopidogrel and PPIs are among the most widely prescribed medications with worldwide sales of U.S. $8.6 and $26.5 billion, respectively, in 2008 (20). Furthermore, the frequency of coadministration (thienopyridine with any PPI) was 31% in the CREDO (Clopidogrel for Reduction of Events During Observation) (21), 33% in the TRITON–TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel–Thrombolysis In Myocardial Infarction) (22), 54% in the PLATO (Platelet Inhibition and Patient Outcomes) (clopidogrel arm) trials, and 64% in the Veterans Affairs retrospective analysis study. Among these studies, omeprazole was the predominant PPI and accounted for 60% and 37% of PPI use in the VA and TRITON–TIMI 38 studies, respectively (21–23). Based on the apparent high frequency of coadministration, any pharmacokinetic/pharmacodynamic interaction of the long-term regimens between PPIs and thienopyridines that could influence clinical efficacy and/or safety must be carefully evaluated. In this regard, guidelines of the

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**Abbreviations and Acronyms**

- **ADP** = adenosine diphosphate
- **ATPase** = adenosine triphosphatase
- **CLAM** = clopidogrel active metabolite
- **DAPT** = dual antiplatelet therapy
- **FDA** = U.S. Food and Drug Administration
- **GIB** = gastrointestinal bleeding
- **HPR** = high on-treatment platelet reactivity
- **LD** = loading dose
- **MACE** = major adverse cardiac event(s)
- **MD** = maintenance dose
- **MI** = myocardial infarction
- **PCI** = percutaneous coronary intervention
- **PPI** = proton pump inhibitors
- **SNPs** = single nucleotide polymorphism
- **VASP-PRI** = vasodilator stimulated phosphoprotein–platelet reactivity index
U.S. Food and Drug Administration (FDA), European Medicines Agency, and American College of Cardiology/American Heart Association have provided conflicting recommendations regarding the concomitant use of PPI and clopidogrel (3,24–28) (Table 1). Thus, it is appropriate and timely to review available pharmacokinetic and pharmacodynamic as well as clinical information regarding interactions between these medication classes.

**Clopidogrel Metabolism, SNPs, and Clinical Outcomes**

Most absorbed clopidogrel (~85%) is hydrolyzed by hepatic carboxylesterase to an inactive carboxylic acid metabolite, SR26334, and the remaining ~15% is converted to an active thiol metabolite by hepatic cytochromes (CYP) in a 2-step process (Fig. 1) (29). The parent compound is usually undetectable in plasma at 2 h after oral administration. The thiopehene ring is first oxidized to 2-oxo-clopidogrel and to an active metabolite (CL-AM), R-130964, in the second step. This highly unstable CL-AM binds covalently and specifically to the platelet ADP-binding site in the P2Y$_{12}$ receptor when platelets pass through the hepatic circulation. Recent studies indicate that the CYP2C19, CYP1A2, CYP2B6 isoenzymes are responsible for the first step, whereas CYP2C19, CYP2C9, CYP2B6, and CYP3A4 are responsible for the second step. As noted, CYP2C19 contributes substantially to both steps, whereas CYP3A4 contributes substantially to the second step (30).

Multiple lines of evidence suggest that variable and insufficient CL-AM generation following clopidogrel administration are the primary explanations for clopidogrel response variability and nonresponsiveness, respectively. Variable levels of CL-AM generation may be explained by multiple genetic, environmental, and clinical factors. In

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**Table 1. Guidelines, Recommendations, and Policy Statements Regarding PPI Use in Patients Treated With Oral Antiplatelet Therapy**

<table>
<thead>
<tr>
<th>Source</th>
<th>Recommendation/Statement</th>
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<tr>
<td>ACCF/ACG/AHA 2008 expert consensus document (3)</td>
<td>The use of low-dose ASA for cardioprophylaxis is associated with a 2- to 4-fold increase in UGIE risk. Enteric-coated or buffered preparations do not reduce the risk of bleeding. For patients at risk of adverse events, gastroprotection should be prescribed.</td>
</tr>
<tr>
<td>ACC and AHA (2007) guidelines for the management of patients with unstable angina/non-ST-segment elevation myocardial infarction (24)</td>
<td>In UA/NSTEMI patients with a history of gastrointestinal bleeding, when ASA and clopidogrel are administered alone or in combination, drugs to minimize the risk of recurrent gastrointestinal bleeding (e.g., proton-pump inhibitors) should be prescribed concomitantly.</td>
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<tr>
<td>European Medicines Agency public statement on possible interaction between clopidogrel and proton-pump inhibitors (26)</td>
<td>“Taking all the data into account, the Agency’s Committee for Medicinal Products for Human Use (CHMP) and its Pharmacovigilance Working Party (PhVWP) have recommended that the product information for all clopidogrel-containing medicines should be amended to discourage concomitant use of PPI and clopidogrel-containing medicines unless absolutely necessary. Accordingly, the marketing authorization holders for the clopidogrel-containing medicines will shortly be submitting variation applications to amend the product information. Furthermore, CHMP recommended that further information is needed in relation to the inhibition of clopidogrel metabolism by other medicines, and in relation to the implications of genetic variation which results in a small proportion of individuals (so-called “CYP2C19 poor metabolizers”) being unable to fully convert clopidogrel to its active form, regardless of interactions with other medicines.”</td>
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ACC = American College of Cardiology; ACCF = American College of Cardiology Foundation; ACG = American College of Gastroenterology; AHA = American Heart Association; ASA = acetylsalicylic acid; FDA = Food and Drug Administration; GIB = gastrointestinal bleeding; NSTEMI = non–ST-segment elevation myocardial infarction; OTC = over the counter; PPI = proton pump inhibitor; UA = unstable angina; UA/NSTEMI = unstable angina/non–ST-segment elevation myocardial infarction; UGIE = upper gastrointestinal events.
addition, intestinal p-glycoprotein transporter and its inhibitors (including omeprazole) may play a role in clopidogrel absorption (31). Moreover, a relationship between the p-glycoprotein gene polymorphisms and the occurrence of adverse ischemic events has been demonstrated in patients treated with dual antiplatelet therapy (32–34).

Functional variability in hepatic P450 isoenzyme activity owing to single nucleotide polymorphisms (SNPs), drug-drug interactions, and other factors may affect clopidogrel metabolism and its clinical efficacy. A diminished pharmacodynamic response to clopidogrel has been observed with coadministration of PPIs, lipophilic statins, calcium channel blockers, and warfarin that are metabolized by the CYP2C19, CYP3A4, and CYP2C9 isoenzymes, respectively (35–38). Moreover, cigarette smoking and coadministration of Saint John’s wort or rifampin are known to augment the antiplatelet response to clopidogrel through activation of CYP1A2 and CYP3A4, respectively (36,39,40). The clinical consequences of these pharmacodynamic interactions remain controversial. Furthermore, increased body mass index, diabetes mellitus (particularly in the contexts of elevated serum fibrinogen, poor glucose control, or diminished renal function) and the extent of existing coronary disease may be associated with increased baseline platelet reactivity and a diminished antiplatelet response to clopidogrel (41–43).

Recent studies have evaluated the relationship between single SNPs of the gene encoding CYP2C19 isoenzymes with clopidogrel response variability and clinical outcomes (44–48). It remains uncertain whether other factors associated with a diminished clopidogrel response may be additive to SNPs in further reducing the antiplatelet effect of clopidogrel and thus, potentially, its clinical efficacy in reducing ischemic events. Of at least 25 SNPs for the gene encoding the CYP2C19 isoenzyme (49), the most frequent and widely analyzed include *2, which has been associated with a complete absence of 2C19 activity (allele frequency ~15% in Caucasians and African Americans and ~30% in Asians) and *17, which has been associated with increased expression and enzyme function (allele frequency ~15% in Caucasians and African Americans and ~4% in Asians). The *3, *4, *5, and *8 variants are less frequently observed loss of function alleles (50).

Based on ADP-induced platelet aggregation measurement to reflect clopidogrel responsiveness in the GWAS (Genome Wide Association Study), Shuldiner et al. (45) identified a 13-SNP cluster (within a flanking CYP2C18–2C19–2C9–2C8 cluster of 1.5 megabases on 10q24) out of ~400,000 SNPs that was associated with 70% of clopidogrel response (p < 10^-7) and from which CYP2C19*2 was the major SNP accounting for ~12% of the 10q24
associated signal. In the same study, carriers of the CYP2C19*2 genotype who had undergone percutaneous coronary intervention (PCI) experienced higher cardiovascular event rates than noncarriers did (HR: 2.42; p = 0.02) (45). In healthy volunteers, a 32.4% relative reduction (p < 0.001) in plasma CL-AM and a 25% relative reduction in mean platelet aggregation (p < 0.001) was observed in carriers of at least 1 CYP2C19 reduced-function allele compared with noncarriers (46). Numerous studies have correlated adverse clinical outcomes with CYP2C19*2 carrier status (44–48,50–53). Among patients with acute coronary syndromes who had PCI and were treated with clopidogrel in the TRITON–TIMI 38 trial, carriers of a 2C19 reduced-function allele had an increase in primary endpoint events (cardiovascular death, nonfatal MI, or nonfatal stroke) (HR: 1.53; p = 0.04) and stent thrombosis (HR: 3.09; p = 0.02) compared with noncarriers (46). Similarly, compared with 2C19 wild-type homozygotes, 2C19*2 carriers were demonstrated to have an increased incidence of stent thrombosis to 30 days (HR: 3.81; p < 0.007) (15). These investigators also demonstrated that 2C19*17 allele carriers had lower levels of ADP-induced platelet aggregation (p < 0.039) and higher bleeding risk during clopidogrel treatment compared with wild-type carriers (p = 0.01) (51). Meta-analyses by both Hulot et al. (52) and Mega et al. (53) have demonstrated that carriers of the 2C19*2 allele, when compared with noncarriers, have an increased risk for major adverse cardiac events (MACE) including death and stent thrombosis, and risk was independent of baseline cardiovascular risk. In the Hulot et al. (52) meta-analyses, an increased risk for MACE and mortality was also observed in PPI users (vs. nonusers) particularly those with high baseline cardiovascular risk. Conversely, in the recently published genetic substudies of the CHARISMA (54), CURE (55), and ACTIVE A (Effect of Clopidogrel Added to Aspirin in Patients With Atrial Fibrillation) (55) trials, there was no association of CYP2C19*2 allele with adverse clinical outcomes in clopidogrel-treated subjects. Potential explanations for these apparent discrepant observations include the lower use of PCI with stenting in the CURE trial (14.5%) as well as the relatively lower-risk populations enrolled into the ACTIVE A and CHARISMA trials (nonacute coronary syndrome, non-PCI/stenting) (56).

Thienopyridines may inhibit CYP isoenzymes as demonstrated in in vitro studies using human liver microsomes and recombinantly expressed P450 isoforms. Both clopidogrel and ticlopidine were associated with time- and concentration-dependent inhibition of CYP2B6 and to a lesser extent, CYP2C19 (57). A weak inhibitory effect of 2-oxo-clopidogrel, prasugrel, and R-95913 (active metabolite of prasugrel) was also observed (58). Inhibition of CYP2C19 activity by ticlopidine was directly proportional to the level of baseline activity and, thus, was most evident in normal (*1/*1) metabolizers. Repeated ticlopidine dosing was associated with an increase in omeprazole concentrations in rapid metabolizers but not in the poor metabolizers (59,60). The influence of clopidogrel on CYP2C19-dependent omeprazole metabolism was evaluated in healthy volunteers who received either placebo or clopidogrel (300-mg load, 75 mg/day for 3 days) coadministered with omeprazole (40 mg/day). A significant increase (mean 30%) in plasma omeprazole and a significant decrease (mean 24%) in plasma 5-hydroxyomeprazole were observed in rapid metabolizers (*1/*1 allele) but not in poor metabolizers (*2/*2 allele) (61). This study demonstrated that clopidogrel inhibited CYP2C19-mediated hydroxylation of omeprazole in rapid metabolizers but had no effect on CYP3A4-catalyzed sulfoxylation of omeprazole. Thus, omeprazole metabolism may be shifted to CYP3A4 in poor (CYP2C19) metabolizers or in the presence of a CYP2C19 inhibitor such as clopidogrel (61).

PPIs

Mechanism of action and metabolism. Proton pump inhibitors are benzimidazole-derivative prodrugs whose absorption from the bowel is influenced by the p-glycoprotein transporter. The H+/K+–adenosine triphosphatase (ATPase) present in the canalicular membrane of gastric parietal cells secretes hydrochloric acid and a proton is exchanged for potassium with ATP breakdown. Following absorption, PPIs undergo activation and the activated cyclic sulfonamide covalently binds to the extracytoplasmic cysteine residues of H+/K+–ATPase and irreversibly inhibits H+/K+–ATPase pump activity/gastric secretion. Because of the short plasma half-life (1 to 2 h) of PPIs and continuous activation of inactive pumps, up to 3 days are required to achieve maximum acid suppression by PPIs (62). Although all PPIs are highly effective in inhibiting gastric acid secretion, pharmacokinetic and pharmacodynamic differences may influence clinical effectiveness as well as the potential for drug-drug interactions (62). Although the bioavailability of pantoprazole, lansoprazole, and rabeprazole are similar, plasma concentrations of omeprazole increase 1.5– to 2-fold and of esomeprazole 3-fold following 5 days of therapy compared with day 1 (63).

Effects of PPIs on CYP-isoenzyme activity and drug-drug interactions. All PPIs, except for rabeprazole, are extensively metabolized by and competitively inhibit CYP2C19 and CYP3A4 (60). Lansoprazole and omeprazole appear to be the strongest (Ki = 0.4 to 1.5 μmol/l and 2 to 6 μmol/l, respectively), whereas pantoprazole is the weakest inhibitor (Ki = 14 to 69 μmol/l) of CYP2C19. The observation of significant interaction between PPIs and other CYP2C19 metabolized drugs such as diazepam, phenytoin, R-warfarin, and clopidogrel is not surprising in that >70% of all therapeutic drugs are metabolized by CYP3A4 and CYP2C219 isoenzymes (62) (Fig. 2). Moreover, a significant
association between omeprazole metabolism and CYP2C19 genotype (metabolizer status, loss or gain of function alleles) exists (62,64).

The CYP2C19*2 reduced function allele is associated with poor metabolism of omeprazole and other drugs such as diazepam and phenytoin (65). In addition, other CYP-isoenzymes such as CYP3A4 may become more important in CYP2C19*2 poor metabolizers or in the presence of potent CYP2C19 inhibitors such as clopidogrel (61,65). Interestingly, the coadministration of drugs with high affinity for CYP3A4 (ketoconazole or clarithromycin) inhibits omeprazole metabolism and is associated with increased plasma omeprazole concentrations in poor as well as extensive CYP2C19 metabolizers. Conversely, coadministration of ginkgo biloba or St John’s wort (CYP2C19 inducers) enhances the metabolism of omeprazole (62). Rabeprazole, which is mainly metabolized through nonenzymatic reduction to a thioether compound, has the least inhibitory effect on CYP isoenzyme activities (62). A recent meta-analysis suggests that the efficacy of omeprazole but not rabeprazole in the treatment of H. pylori infection depends on CYP2C19 gene polymorphism and metabolizer status (66). In addition, in vitro studies demonstrated that PPIs could inhibit the p-glycoprotein mediated efflux of digoxin (67). Finally, both CYP2C19 and p-glycoprotein genetic polymorphisms may influence drug-drug interactions and the pharmacokinetic/pharmacodynamic properties of PPIs, which in turn may influence clinical outcomes related to gastric acid suppression and/or H. pylori eradication (66–68).

**Drug-Drug Interactions Between Clopidogrel and PPIs**

**Pharmacokinetic and pharmacodynamic interactions.** Multiple pharmacodynamic studies have demonstrated the influence of PPI treatment (particularly omeprazole) on clopidogrel antiplatelet effects (35,62,69–80) (Table 2). In a double-blind, randomized controlled study, PCI patients treated with aspirin (75 mg/day) and clopidogrel (300-mg loading dose [LD] + 75-mg/day maintenance dose [MD]) were randomly assigned to receive either omeprazole (20 mg/day) or placebo for 7 days. Omeprazole reduced clopidogrel antiplatelet effect (vasodilator stimulated phosphoprotein—platelet reactivity index [VASP-PRI]: 39.8% placebo vs. 51.4% omeprazole, p < 0.0001) at 7 days but not on day 1. Moreover, the prevalence of a poor clopidogrel response (defined by a VASP-PRI >50%) was higher following omeprazole than placebo (60.9% vs. 26.7%, respectively, p < 0.0001) (35). Similarly, in a randomized pharmacodynamic study involving 20 healthy volunteers,
coadministration of clopidogrel (600-mg LD + 75-mg/day MD for 14 days) with omeprazole (20 mg/day) resulted in decreased platelet inhibition (measured by the VerifyNow P2Y12 assay) at day 14 (p = 0.048) but not at 1 or 7 days (70). In a post hoc subgroup analysis of the PRINCIPLE–TIMI 44 (The Prasugrel in Comparison to Clopidogrel for Inhibition of Platelet Activation and Aggregation–Thrombolysis In Myocardial Infarction 44) trial, coadministration of PPI with clopidogrel reduced platelet inhibition at 2, 6, and 18 to 24 h after 600-mg clopidogrel LD with a trend toward reduction in platelet inhibition following 150-mg/day MD for 15 days compared with clopidogrel monotherapy. Prasugrel-mediated platelet inhibition was also reduced both acutely and at 15 days by PPI coadministration compared with prasugrel alone and the proportions of nonresponders (defined by <29% inhibition of 20 μmol/l ADP-induced aggregation) to both clopidogrel and prasugrel were increased by PPI coadministration (71).

A differential response between various PPI and clopidogrel has been suggested. For example, using the Multiplate analyzer (Multiplate, Munich, Germany), Sibbing et al. (72) observed that patients coadministered omeprazole, but not pantoprazole or esomeprazole, had higher residual platelet aggregation while on clopidogrel therapy (p = 0.001). In addition, the prevalence of a poor clopidogrel response (defined as an arbitrary unit [AU] × min >456) was higher in patients treated with omeprazole (33% vs. 19% without, p = 0.008). However, other factors such as diabetes, body mass index, renal insufficiency, and smoking (in addition to omeprazole treatment) were independent predictors of antiplatelet response to clopidogrel treatment (72). In a crossover study involving healthy volunteers treated with single doses of either clopidogrel (300 mg) or prasugrel (60 mg), the coadministration of lansoprazole did not alter platelet inhibition by prasugrel, but a trend toward reduction in clopidogrel-mediated platelet inhibition was observed that was most pronounced in clopidogrel responders (74). Other studies have suggested that the PPI-clopidogrel interaction to reduce clopidogrel-mediated platelet inhibition is less evident following pantoprazole or rabeprazole than omeprazole (64,75). Furthermore, CYP2C19 metabolizer status may significantly influence the magnitude of PPI-clopidogrel interaction. For example, a reduction in antiplatelet effect of clopidogrel was observed in rapid metabolizers (genotype *1/*1) administered either omeprazole (p = 0.015) or rabeprazole (p = 0.035) but not in decreased metabolizers (*2 or *3 allele carriers). Nevertheless, clopidogrel-induced inhibition of platelet aggregation remained lower in decreased versus rapid metabolizers irrespective of concomitant or spaced PPI administration (p < 0.0001), and there were no clopidogrel poor responders among the rapid metabolizer cohort (64).

Finally, 4 randomized, placebo-controlled, crossover comparison studies involving 282 healthy volunteers were conducted to analyze the PPI-clopidogrel interaction. Subjects received either omeprazole (80-mg/day delayed-release formulation) or pantoprazole (80 mg/day) and clopidogrel (300-mg LD + 150-mg/day MD) was administered either synchronously (with PPI) or separately (76). A synchronous (with omeprazole) clopidogrel 600-mg LD + 150-mg/day MD was also assessed. Unchanged plasma clopidogrel levels increased (19% at day 2, 37% to 51% at day 5) and CL-AM levels decreased (45% to 55% at day 2, 40% to 54% at day 5) irrespective of clopidogrel LD or the timing of omeprazole administration. This observation argues against the presence of a drug-drug interaction at the p-glycoprotein transporter level or related to gastric pH effects. During omeprazole coadministration, platelet aggregation (5 μmol/l ADP) increased by 11% to 16% on day 1 and 6% to 8% on day 5 in concert with a decrease in CL-AM levels. Similarly, VASP-PRI increased on days 1 (17% to 20%) and 5 (19% to 27%) of omeprazole treatment. During pantoprazole coadministration, CL-AM decreased (14% to 20%) whereas both platelet aggregation and VASP-PRI increased by 4.3% and 3.9% to 5.1%, respectively. These observations suggest: 1) the PPI-clopidogrel interaction is more prominent for omeprazole than pantoprazole; 2) a reduction in CL-AM level is the primary explanation for the PPI-clopidogrel interaction; and 3) staggering the time course of clopidogrel-omeprazole dosing does not influence the interaction. However, these studies were performed without aspirin coadministration (which has dose-dependent effects on platelet function) and the dose of omeprazole (80 mg/day omeprazole for 5 days before clopidogrel or placebo dosing) was 2 to 4 times that commonly prescribed clinically (76).

However, in a study of healthy volunteers administered omeprazole (40-mg/day delayed-release formulation) either concomitantly or staggered by 8 to 12 h with clopidogrel (600-mg LD and 75-mg/day MD), no difference in clopidogrel-induced antiplatelet effect (light transmittance aggregometry, VASP-PRI, VerifyNow P2Y12) was observed following the loading dose or at 1 week of maintenance therapy (77). Either synchronous or spacing omeprazole coadministration strategies resulted in higher VASP-PRI levels compared with clopidogrel monotherapy. Finally, the pharmacodynamic interaction between clopidogrel (300-mg LD + 75-mg/day MD) and PA32540, a novel combination drug (325 mg enteric-coated aspirin + 40 mg immediate-release omeprazole) was evaluated in healthy volunteers using both synchronous as well as staggered (12 h apart) dosing regimens. In this study, staggered clopidogrel and PA32540 administration was associated with a greater clopidogrel-induced antiplatelet effect (reduced drug-drug interaction) compared with synchronous administration (78). Variations in CYP2C19 genotype,
<table>
<thead>
<tr>
<th>First Author / Ref. #</th>
<th>Patients (n)</th>
<th>Treatment</th>
<th>Method</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gilard et al. (35)</td>
<td>Elective PCI (124)</td>
<td>OMZ 20 mg (n = 64) or placebo (n = 60); CLP 300-mg LD + 75-mg MD, ASA 75 mg MD for 7 days</td>
<td>VASP-PRI</td>
<td>Day 1 = 83.9 ± 4.6% vs. 83.2 ± 5.6%; p = NS Day 7 = 51.4 ± 16.4% vs. 39.8 ± 15.4%; p &lt; 0.001 &gt;50% PRI = 60.9% vs. 26.7%; p &lt; 0.001</td>
<td>Randomized study Omeprazole effect was observed on day 7, more nonresponders</td>
</tr>
<tr>
<td>Gilard et al. (69)</td>
<td>High risk coronary angiography (105)</td>
<td>ASA; clopidogrel, PPI</td>
<td>VASP-PRI &gt;48 h after antiplatelet therapy</td>
<td>Mann-Whitney U test —no difference for statins, ACEI, ANG II antagonists and beta blockers—with (n = 24) and without PPI (n = 81) PRI = 61.4 ± 23.2% vs. 49.5 ± 16.3%; p = 0.007</td>
<td>Observational study</td>
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<tr>
<td>Yun et al. (70)</td>
<td>Healthy volunteers (n = 20)</td>
<td>75 mg/day CLP or placebo for 14 days followed by 75 mg/day CLP or 20 mg OMZ for 14 days</td>
<td>VerifyNow P2Y12 assay</td>
<td>1 and 7 days—no change 14 days PRI: OMZ, 281.3 ± 54 vs. 240 ± 72.2; p = 0.048 14 days % inhibition: OMZ 22.7 ± 29.9 vs. 35.1 ± 18.7, p = 0.014</td>
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<td>O'Donoghue et al. (71)</td>
<td>Planned PCI (201)</td>
<td>600 mg/150 mg CLP (n = 22) + PRI vs. CLP alone (n = 71) 60 mg/10 mg PRS + PRI (n = 25) vs. PRS alone (n = 77)</td>
<td>IPA 20 μmol/l ADP LTA</td>
<td>0.5, 2, 6, 20–24 h and 15 days. Nonresponders (&lt;20% IPA) at 6 h and 15 days Nonresponders: 6 h: 50% vs. 18.2% p = 0.009 and 15 days: 50% vs. 7.9%; p = 0.012 PRS + PRI: significantly decreased IPA at 0.5, 6, and 15 days; p = 0.009, 0.054, and 0.01 respectively; 6 h: 0% vs. 0% p = NS and 15 days: 10% vs. 0%, p = 0.025</td>
<td>No information on PRI; PRI patients were not randomized; study was not powered to detect the difference in IPA</td>
</tr>
<tr>
<td>Sibbing et al. (72)</td>
<td>Controlled PCI (n = 1,000)</td>
<td>Pts on median 7 months 75-mg/day CLP treatment No PRI = 732, PNT = 158, OMZ = 64, ESM = 74 At hospital admission Multiplate analyzer: 6.4 μmol/l ADP-induced AU × min Nonresponders = upper quintile (456 AU × min)</td>
<td>CLP + PRI: significantly decreased IPA at 2, 6, 2–24 h and 15 days; p = 0.003, 0.02, 0.03, and 0.06, respectively) No PPI vs. PRI; 40 16.6 vs. 41.1 ± 17.4 p = 0.005</td>
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<td>Zuren et al. (73)</td>
<td>CAD PCI (n = 1,425)</td>
<td>≥1 week PRI use before 60-mg CLP LD OMZ = 36, PNT = 108, ESM = 280</td>
<td>20 μmol/l ADP → LTA → 20 h after LD</td>
<td>No PRI vs. PPI: 40 ± 16.6 vs. 41.1 ± 17.4 p = 0.005 Similar effect with all PPIs, PRI, age, BMI, ACEI are associated with HPR (&gt;49%)</td>
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Table 2. Continued

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<tr>
<th>First Author (Ref. #)</th>
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<th>Treatment</th>
<th>Method</th>
<th>Results</th>
<th>Comments</th>
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<tbody>
<tr>
<td>Small et al. (74)</td>
<td>Healthy volunteers (24)</td>
<td>60 mg PRS + 30 mg LNZ CLP 300 mg ± 30 mg LNZ 7-day run in with LNZ before thienopyridine</td>
<td>Serial measurements PK study = PRS−active met, CLP−inactive met PD study = 5 and 20 µmol/l ADP-LTA</td>
<td>No effect on prasugrel IPA, but decrease in C_{int} nonsignificantly lower IPA with CLP (more pronounced in CLP responders), but no change in CLP inactive met study</td>
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<tr>
<td>Cuisset et al. (75)</td>
<td>NSTEMI ACS-stenting (n = 104)</td>
<td>60 mg/75 mg CLP + 250 mg/75 mg ASA Pts randomized to 20 mg OMZ or 20 mg PNT during discharge</td>
<td>VASP-PRI and 10 µmol/l ADP-induced LTA 12 h after CLP LD (before PPI) and 1 month</td>
<td>VASP PRI: OMZ vs. PNT After LD = 53 ± 21% vs. 30 ± 2%; p = NS 1 month = 48 ± 17% vs. 36 ± 20%; p = 0.007 LTA: OMZ vs. PNT after LD = 40 ± 19% vs. 40 ± 21%; p = NS, 1 month = 52 ± 15% vs. 50 ± 18%; p = NS</td>
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ACEI = angiotensin-converting enzyme inhibitor; ADP = adenosine diphosphate; ANG II = angiotensin II; ASA = aspirin; AU = arbitrary units; BMI = body mass index; CAD = coronary artery disease; CLP = clopidogrel; ESM = esomeprazole; HPR = high platelet reactivity; IPA = inhibition of platelet aggregation; LD = loading dose; LNZ = lansoprazole; LTA = light transmittance aggregometry; MD = maintenance dose NS = nonsignificant OMZ = omeprazole; PDI = percutaneous coronary intervention; PD = pharmacodynamic; PK = pharmacokinetic; PNT = pantoprazole; PRS = prasugrel; Pts = patients; PRINCIPLE–TIMI 44 = The Prasugrel in Comparison to Clopidogrel for Inhibition of Platelet Activation and Aggregation–Thrombolysis In Myocardial Infarction; PRU = platelet reactivity units; VASP-PRI = vasodilator-stimulated phosphoprotein–platelet reactivity index; other abbreviations as in Table 1.

In conclusion, multiple epidemiological studies have suggested that the concomitant administration of PPI with clopidogrel may be associated with adverse clinical events (71-79,80). For example, the potential interaction between clopidogrel and PPIs as patient compliance with multiple characteristics of patients, as well as the inability to account for differences in the dose and type of PPI, may have influenced the association between the clopidogrel-omeprazole interaction. However, the lack of data on patient compliance with antiplatelet therapy as well as the inability to account for differences in the dose and type of PPI, may have influenced the association between the clopidogrel-omeprazole interaction. Additionally, recent studies have shown that the CYP2C19 gene polymorphisms limit the reliability of this observation (81).
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</thead>
<tbody>
<tr>
<td>O’Donoghue et al. (71)</td>
<td>ACS-planned PCI (n = 13,608)</td>
<td>PRS: 60-mg LD + 10-mg MD CLP; 300-mg LD + 75-mg MD PPI = 33.3% pts, PNT = 1,844, OMZ = 1,675, ESM = 613, LNZ = 441, RBR = 66</td>
<td>1-year composite of CV death, nonfatal MI, or nonfatal stroke (adjusted for 28 variables)</td>
<td>Adjusted HR CLP = 0.94, 95% CI: 0.80–1.11 PRS = 1.00, 95% CI: 0.84–1.20. No effect of individual PPI. Reduced function allele CLP pts without and with PPI 10.2% vs. 13% HR: 0.76. Reduced function allele PRS pts without and with PPI 7.4% vs. 9.9% HR: 0.81.</td>
<td>PPI use determined at the time of randomization and at follow-up points.</td>
</tr>
<tr>
<td>Pezalla et al. (79)</td>
<td>&lt;65-year-old pts treated with CLP</td>
<td>No PPI (n = 4,800), low PPI exposure (n = 712), high PPI exposure (n = 3,345)</td>
<td>1-year MI</td>
<td>No PPI = 1.38%, Low PPI = 3.08%, High PPI = 5.03%; p &lt; 0.005</td>
<td>Data corrected only for comorbidities</td>
</tr>
<tr>
<td>Juurlink et al. (80)</td>
<td>&gt;65-year-old UA pts treated with CLP following MI (n = 13,636)</td>
<td>PPI vs. no PPI, 734 (PPI 194) pts readmitted for MI, controls = 2,057 (PPI 424)</td>
<td>90-days and 1-year acute MI</td>
<td>Current use of PPI, OR: 1.27</td>
<td>Data adjusted for demographic variables, concomitant medications, and comorbidity.</td>
</tr>
<tr>
<td>Ho et al. (82)</td>
<td>ACS pts taking CLP (n = 8,205)</td>
<td>63.9% = prescribed PPI at discharge 36.1% = no PPI</td>
<td>Death or RH</td>
<td>Adjusted or for death or RH PPI vs. no PPI: 1.25, RH = 1.86, revascularization = 1.49, death = 0.91.</td>
<td>Risk of confounding variables at baseline were adjusted for analysis.</td>
</tr>
<tr>
<td>Kreutz et al. (83)</td>
<td>Previous PCI (n = 16,690)</td>
<td>Pts never made PPI prescription over 1-year post-stenting (n = 9,862) Pts with PPI (6,828)</td>
<td>1-year MACE hospitalization CV death for stroke/TIA, ACS, or coronary revascularization.</td>
<td>MACE = 17.9%, vs. 25.1% HR = 1.51; 95% CI: 1.39–1.64, p &lt; 0.0001. HR for OMZ = 1.39, ESM = 1.57, PNT = 1.61, LNZ = 1.39</td>
<td>No increased risk of PPI in patients not treated with CLP compared with no PPI (20.8% no PPI vs. PPI 24.8%; HR = 1.19; 95% CI: 0.84–1.70)</td>
</tr>
<tr>
<td>Dunn et al. (84)</td>
<td>Undergoing or high likelihood of PCI (n = 1,053)</td>
<td>CLP + ASA for 4 weeks vs. 1 year. PPI + CLP = 176 vs. CLP = 877 PPI = 190 vs. no PPI = 873</td>
<td>1-year death, MI, or stroke</td>
<td>CLP + PPI vs. CLP; OR: 1.63, p = 0.043 PPI vs. no PPI; OR = 1.55, p = 0.035</td>
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Table 3. Continued

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<tr>
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<tbody>
<tr>
<td>Kwok et al. (86)</td>
<td>23 studies, (n = 93,278)</td>
<td>CLP ± PPI</td>
<td>MACE = 19 studies, MI = 17 studies</td>
<td>No risk association in propensity-matched or randomized trials. Observational studies adjusted for confounders. MACE, OR = 1.44, p &lt; 0.0001, Mortality = 1.04</td>
<td>Substantial heterogeneity. Overall, CLP and PPI use may be associated with adverse CV events and MI, but no effect on mortality.</td>
</tr>
<tr>
<td>Siller-Matula et al. (87)</td>
<td>Randomized trials (TRITON–TIMI 38, COGENT, CREDO)</td>
<td>CLP ± PPI</td>
<td>MACE, MI, death</td>
<td>MACE: RCT: OR = 1.08, p = 0.60 Non-RCT: OR = 1.33, p = 0.0004 MI: RCT: OR = 0.98, p = 0.79 Non-RCT: OR = 1.27, p = 0.07 Death: RCT: OR = 0.68, p = 0.04 Non-RCT: OR = 0.95, p = 0.30</td>
<td>Investigators conclude that higher rate of comorbidities in pts with CLP + PPI might be major cause for observed worse clinical outcome rather than effect of PPI.</td>
</tr>
<tr>
<td>Rassen et al. (88)</td>
<td>≥65 years old, PCI or hospitalized for ACS (n = 18,565)</td>
<td>CLP ± PPI</td>
<td>6-month MI or death</td>
<td>Propensity score adjusted ratio for death or MI = 1.22, death = 1.20, revascularization = 0.97.</td>
<td>Demonstrated only a modest effect (risk unlikely to exceed &gt;20%).</td>
</tr>
<tr>
<td>Bhatt et al. (89)</td>
<td>AMI, UA pts undergoing stenting (n = 3,267)</td>
<td>CLP + OMZ delayed-release combination product CLP + placebo</td>
<td>Primary: GI events</td>
<td>OMZ has fewer GI events HR = 0.55, p &lt; 0.007) No difference in CV events (HR = 1.02).</td>
<td>Combination drug properties unknown. Premature termination. No complete follow-up. Low risk of confounding variables owing to specific inclusion and exclusion criteria.</td>
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**ACS** = acute coronary syndrome; **CABG** = coronary artery bypass grafting; **COGENT** = Clopidogrel and the Optimization of Gastrointestinal Events; **CREDO** = Clopidogrel for Reduction of Events During Observation; **CV** = cardiovascular; **GI** = gastrointestinal; **HR** = hazard ratio; **MACE** = major adverse cardiac events; **MI** = myocardial infarction; **OR** = odds ratio; **RCT** = randomized clinical trial; **RH** = rehospitalization; **RBR** = rabeprazole; **TIA** = transient ischemic attack; **TRITON–TIMI 38** = Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel; other abbreviations as in Tables 1 and 2.
observed in patients treated with PPI and clopidogrel compared with clopidogrel alone (85). However, a similar risk was also observed with PPI in patients not receiving concomitant clopidogrel and was attributed to unmeasured cofounders. No interaction was demonstrated between PPI and clopidogrel.

Discrepancy in the reported clinical relevance of a potential PPI-clopidogrel interaction may in part be explained by recent meta-analyses (86,87) that support the concept that the presence and magnitude of relative hazard related to PPI in clopidogrel-treated patients depends on study type and method of analysis. The relative risk ratio for adverse outcomes related to PPI progressively diminishes from crude raw data to statistically adjusted observational studies and finally to propensity score-adjusted analyses or randomized trials. These studies conclude that evidence for a meaningful clopidogrel-PII interaction on cardiovascular outcomes is inconsistent and that no definite evidence exists for an effect on mortality. This premise finds support in a retrospective population-based study of elderly PCI patients that concluded that the relative risk attributable to PPI failed to meet conventional thresholds for statistical significance and did not exceed 20% (88).

Although concern regarding concomitant PPI-thienopyridine administration persists and has been heightened by a FDA communication, this concern has not been substantiated to date by adequately powered, large-scale randomized trials with clinical endpoints. In the recently reported COGENT (Clopidogrel and the Optimization of Gastrointestinal Events) trial, 3,873 clopidogrel-treated patients were randomized to receive either CGT-2168 (combination of 75 mg clopidogrel + 20 mg omeprazole) or 75 mg clopidogrel in conjunction with aspirin therapy following PCI (89). The primary endpoint (6 months upper gastrointestinal events) was reduced in the CGT-2168 cohort (1.1% vs. 2.9% clopidogrel alone). Furthermore, upper gastrointestinal bleeding was reduced in CGT-2168 treated patients (0.2% vs. 1.2% clopidogrel alone) and the secondary outcome measures of all cardiovascular events (composite occurrence of cardiovascular death, nonfatal MI, coronary artery bypass graft, PCI, or ischemic stroke), MI, and the requirement for revascularization procedures were similar between randomized treatment groups. The investigators concluded that no clinically relevant adverse interaction between clopidogrel and PPI treatment was evident (89).

Multiple potential limitations to the COGENT study should be acknowledged including premature study termination (planned enrollment 5,000 patients), low cardiovascular event rates (4.9% CGT-2168, 5.7% clopidogrel) and the lack of either platelet function data (CGT-2168 plus aspirin vs. clopidogrel plus aspirin) or genotyping in the study population (94% white).

### Potential Mechanisms of Clopidogrel-Omeprazole Interaction

Preliminary in vitro studies suggest intestinal p-glycoprotein to be the first site of a potential drug-drug interaction (Fig. 3). Although both omeprazole and clopidogrel are known to influence p-glycoprotein function, a recent study indicated that omeprazole (80 mg/day) does not have any effect on clopidogrel absorption. In addition, evidence that plasma unchanged clopidogrel levels are not lower during PPI administration argue against a significant effect of gastric pH on absorption (77).

The major site of interaction appears to involve hepatic CYP P450 isoenzymes where both clopidogrel and PPIs (particularly omeprazole) are extensively metabolized by CYP2C19 and CYP3A4 (Fig. 3). In vitro studies indicate that clopidogrel and PPIs inhibit each other’s metabolism except in poor metabolizers (CYP2C19*2 homozygotes). In healthy volunteers, omeprazole (80 mg/day) was associated with a decrease in CL-AM levels and an increase in VASP-PRI irrespective of clopidogrel dose or time of treatment. The coadministration of omeprazole (20 to 40 mg/day) with clopidogrel resulted in a moderate (−20%) decrease in clopidogrel-induced platelet inhibition. This interaction was more pronounced following 7 to 14 days of therapy (vs. 1 day) and translated into a significant increase in the prevalence of clopidogrel nonresponders with HPR. The subsequent reduction in clopidogrel-mediated platelet inhibition by PPIs may influence clinical outcomes by shifting more patients into the category of HPR (3). In support of this hypothesis is the observation that the relationship between platelet inhibition and the occurrence of ischemic events is nonlinear (sigmoid) so that relatively small changes in platelet inhibition may be associated with more frequent ischemic events in patients who have borderline HPR (90). Moreover, most pharmacokinetic/pharmacodynamic studies have involved a short duration (up to 14 days) of observation whereas clinical outcome studies that have evaluated the PPI-clopidogrel interaction span much longer periods (≥1 year). Indeed, the pharmacokinetic/dynamic interaction following long-term coadministration is not known.

### Alternative Treatment Strategies

In the context that all PPIs are equally effective in gastric acid suppression with appropriate dosing and that the pharmacokinetic-pharmacodynamic interaction with clopidogrel is in large part mediated by hepatic CYP P450 isoenzymes (CYP2C19 and CYP3A4), either pantoprazole (least dependent on CYP metabolism) or rabeprazole (non-CYP metabolized) may be alternatives for omeprazole. Another option may be to increase the MD of clopidogrel during long-term therapy although the efficacy of dose...
escalation to overcome clopidogrel response variability has not been established. Moreover, in the PRINCIPLE TIMI-44 study, a significant pharmacodynamic interaction between clopidogrel 150 mg daily and omeprazole has been demonstrated (71). In addition, prasugrel is associated with greater active metabolite levels (compared with clopidogrel) and has been shown to overcome clopidogrel nonresponsiveness, but may be associated with increased bleeding risk. A fourth proposed alternative was to separate the timing of clopidogrel and omeprazole administration. As the plasma half-lives of both clopidogrel and omeprazole are short (1 to 2 h), the potential for drug-drug competition at CYP2C19 level might be reduced by this strategy. Although the results of 4 recent studies that evaluated the effect of synchronous versus staggered coadministration have provoked controversy (76–78), it would appear that the relative “benefit” of a staggered dose regimen is at best small and may depend on PPI (especially omeprazole) dose.

A fifth option might involve the nonthienopyridine, ticagrelor, which does not require metabolic conversion by hepatic CYP P450 isoenzymes to exert its antiplatelet effect. The antiplatelet effect of ticagrelor is not influenced by CYP genetic polymorphisms (91) and clinically significant drug-drug interactions have not been reported (FDA) (92).

The use of histamine receptor antagonists and/or antacids may also be considered. The safety and clinical efficacy of H2-receptor antagonist therapy was demonstrated in the FAMOUS (Famotidine for the Prevention of Peptic Ulcers in Users of Low-Dose Aspirin) trial (93). Finally, in the updated 2010 American College of Cardiology Foundation/American College of Gastroenterology/American Heart Association expert consensus document, PPIs are regarded as appropriate therapy for patients with multiple risk factors for gastrointestinal bleeding who require antiplatelet therapy, and routine use is not recommended in patients at lower risk of upper GIB (94).

**Conclusions**

Various studies have demonstrated a pharmacokinetic/pharmacodynamic interaction between PPIs (particularly omeprazole) and thienopyridines (particularly clopidogrel). Although several observational studies have suggested that this interaction may attenuate clopidogrel’s therapeutic efficacy and may be associated with increased adverse clinical outcomes, interpretation of these post hoc, nonrandomized analyses is confounded by covariate imbalance and statistical bias. After multivariate regression and propensity score adjustment, the clinical relevance of a clopidogrel-PPI interaction appears limited (86,87), and no difference in cardiovascular outcomes was observed between clopidogrel alone versus clopidogrel plus omeprazole (CGT-2168) in a single, prematurely terminated randomized clinical trial (89). Based on the lack of definitive data regarding a
clinically relevant interaction between these drugs, it is not appropriate at this time to recommend termination of PPI coadministration (including omeprazole) in clopidogrel-treated patients or to suggest alternative therapeutic strategies. Administration of PPIs (with or without concomitant clopidogrel treatment) should be guided by the individual patient’s risk for GIB. In rare situations where significant concern exists for both GIB and thrombotic complications (e.g., patient with history of GIB who experiences stent thrombosis), an assessment of on-treatment (PPI plus clopidogrel) platelet reactivity may be warranted. A recent expert consensus document has defined HPR as it correlates with MACE or stent thrombosis using available techniques including light transmittance aggregometry, the VerifyNow and Multiplate analyzer point-of-care assays, and VASP-PRI (2). Definitive recommendations await the performance and analysis of adequately powered, prospective randomized clinical trials involving pharmacodynamic assessments.

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REFERENCES


Key Words: bleeding ■ clopidogrel ■ cytochromes ■ drug-drug interactions ■ omeprazole ■ platelet reactivity ■ proton pump inhibitors ■ single nucleotide polymorphisms.