REVIEW

Proton Pump Inhibitor and Clopidogrel Interaction: Fact or Fiction?

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Current consensus recommendations state that patients prescribed clopidogrel plus aspirin should receive a proton pump inhibitor (PPI) to reduce gastrointestinal bleeding. Clopidogrel is converted to its active metabolite by cytochrome P450 (CYP) enzymes. Clopidogrel users with decreased CYP2C19 function have less inhibition of platelet aggregation and increased cardiovascular (CV) events. As PPI metabolism also involves CYP2C19, it was hypothesized that competition by PPIs might interfere with clopidogrel's action. Omeprazole, but not other PPIs, worsens surrogate markers of clopidogrel efficacy. Some (but not all) observational studies show that clopidogrel users prescribed PPIs have increased risks of CV events (hazard/odds ratios = 1.25–1.5). When effect sizes are small to moderate (relative risks < 1.5–2.0), however, it is only possible to conclude whether statistical associations are valid in randomized trials. A randomized trial of omeprazole vs. placebo in clopidogrel users showed no difference in CV events (hazard ratio = 1.02,0.70–1.51). Thus, current evidence does not justify a conclusion that PPIs are associated with CV events among clopidogrel users, let alone a judgment of causality. Nonetheless, positive results from some observational studies and biological plausibility have led some health-care providers to accept that PPIs reduce clopidogrel's efficacy. The US Food and Drug Administration (FDA) recommends that "concomitant use of drugs that inhibit CYP2C19 (e.g., omeprazole) should be discouraged." As the presence of PPIs and clopidogrel in plasma is short lived, separation by 12–20 h should in theory prevent competitive inhibition of CYP metabolism and minimize any potential, though unproven, clinical interaction. PPI may be given before breakfast and clopidogrel at bedtime, or PPI may be taken before dinner and clopidogrel at lunchtime.

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Clopidogrel is an antiplatelet agent widely used in combination with aspirin to reduce cardiovascular (CV) events and is the second leading prescription drug sold worldwide, with global sales of $8.6 billion in 2008 (1). Proton pump inhibitors (PPIs) are also widely used, with worldwide sales of $26.5 billion in 2008 (2), and current consensus recommendations state that patients prescribed clopidogrel plus aspirin should receive a PPI to reduce gastrointestinal (GI) bleeding (3).

Recent studies and the ensuing media coverage have raised concerns among health-care providers and patients that an interaction of PPIs and clopidogrel could increase CV events such as coronary artery stent thrombosis and myocardial infarction (MI). This review discusses the indications for clopidogrel and PPIs, their metabolism, and the evidence regarding a potential interaction, and provides recommendations for health-care providers. MEDLINE was searched for the terms "clopidogrel" plus "proton pump inhibitors" from 1996 to July 2009; separate searches of these individual terms with the term "metabolism" and the term "pharmacokinetics" were also performed. In addition, Google was searched for the phrase "clopidogrel and proton pump inhibitors" to identify recent studies or recommendations.

WHAT IS THE ROLE OF CLOPIDOGREL IN CV DISEASE?

Clopidogrel is approved in the United States for reduction of atherothrombotic events in patients with recent MI, recent stroke, established peripheral arterial disease, or acute coronary syndrome (4). Although guidelines suggest clopidogrel as an alternative to aspirin for patients with unstable angina or non-ST-segment elevation MI who are intolerant of aspirin

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(5), clopidogrel is used primarily in combination with low-dose aspirin. Several randomized trials in patients with acute coronary syndrome or atrial fibrillation have shown that clopidogrel plus aspirin produces small but significant relative risk (RR) reductions of ~10–20% in CV events compared with aspirin alone (6–8). Current guidelines recommend clopidogrel plus aspirin for ≥1 month after a bare metal coronary artery stent, ≥1 year after a drug-eluting stent, ≥1 month and ideally 1 year after unstable angina or non-ST-elevation MI managed without intervention, and 1 year after ST-elevation MI (5,9,10). As dual antiplatelet therapy is most critical early after stent implantation, guidelines recommend that patients at high risk of bleeding should be given dual therapy for a minimum of 2 weeks after a bare metal stent and 3–6 months after a drug-eluting stent (9).

WHAT IS THE RISK OF GI BLEEDING WITH CLOPIDOGREL?

Clopidogrel-associated GI bleeding seems to be related to its potent antiplatelet activity—presumably causing clinically silent GI lesions (e.g., ulcers because of *Helicobacter pylori* or nonsteroidal antiinflammatory drugs) to bleed. Induction of upper GI tract mucosal injury was not identified in an 8-day double-blind endoscopic trial (11), although, based solely on experimental models, some have suggested that antiangiogenic effects of clopidogrel could potentially impair healing of ulcers or erosions already present due to other causes (3).

The magnitude of the GI bleeding risk with clopidogrel is uncertain as no randomized, placebo-controlled trials that address this question are available. A case–control study showed a significant association between patients prescribed clopidogrel or ticlopidine and upper GI bleeding (RR = 2.8; 95% confidence interval = 1.9–4.2); the RR for patients taking aspirin ≤300 mg daily in this study was 3.7 (3.0–4.5) (12). In one randomized trial, clopidogrel showed a trend to less major GI bleeding than low-dose aspirin (RR = 0.69, 0.48–1.00) (13), whereas in two other randomized trials, the combination of clopidogrel plus aspirin significantly increased the RR of major GI bleeding by ~80–95% as compared with aspirin alone (6,8).

DO PPIS DECREASE GI BLEEDING IN PATIENTS TAKING CLOPIDOGREL?

A case–control study found that patients with bleeding ulcers prescribed clopidogrel or ticlopidine had a significantly lower rate of current PPI use than controls prescribed clopidogrel or ticlopidine (RR = 0. 19, 0.07–0.49) (14). Preliminary analysis of a randomized double-blind trial of omeprazole vs. placebo in patients taking clopidogrel plus aspirin, which was terminated before the pre-specified sample size and duration were reached due to bankruptcy of the sponsor, revealed a significant decrease in a composite of GI events (overt or occult GI bleeding, symptomatic gastroduodenal ulcers or erosions) (hazard ratio = 0.55, 0.36–0.85) (15).

In randomized trials, PPIs seem to decrease recurrent ulcer bleeding in patients who bled on low-dose aspirin and continue aspirin (16–19). In addition, randomized, placebo-controlled trials show that both PPIs and histamine-2 receptor antagonists decrease the development of endoscopic ulcers in low-dose aspirin users (20–22). Current consensus recommendations do not specifically address clopidogrel monotherapy, but do state that patients taking dual antiplatelet therapy should receive a PPI (3).

CLOPIDOGREL METABOLISM

Clopidogrel is an inactive prodrug that is converted to its active metabolite by cytochrome P450 (CYP) enzymes, leading to inhibition of ADP-induced platelet aggregation by irreversible blockade of the platelet $P2Y_{12}$ receptor (4,23,24). Both clopidogrel and its active metabolite are relatively short lived in plasma. With repeated 75 mg daily doses, plasma concentrations of the parent compound and its active metabolite fall below the lower limit of quantification after 2 h (4,25). Despite a short half-life, the irreversible binding of clopidogrel's active metabolite to the platelet receptor leads to a prolonged pharmacodynamic effect. Inhibition of platelet aggregation by clopidogrel lasts for several days, with platelet function returning to baseline about 5 days after stopping the drug (4,26).

CYP2C19 has an important function in the metabolism of clopidogrel to its active metabolite, although other members of the CYP family also are involved (e.g., CYP3A4, CYP3A5, CYP2B6, CYP1A2) (27–32). Patients with reduced-function genetic polypmorphisms of CYP2C19 have less exposure to clopidogrel's active metabolite (32,33) and a reduction in clopidogrel's inhibition of ADP-induced platelet aggregation (26,30,33–35). The clinical consequences of these pharmacokinetic and pharmacodynamic findings have been assessed in observational studies. Several cohort studies show that patients with prior MI, acute coronary syndrome, or percutaneous coronary intervention who are prescribed clopidogrel have significantly increased RRs of CV events (from ~1.5 to 4) with CYP2C19 reduced-function genetic variants (32,35–37). Importantly, this increased risk was apparent even among patients who were heterozygous for reduced-function allelic variants (32,36,37). Although homozygotes for reduced-function alleles (poor metabolizers) are seen primarily in Asian populations (e.g., 12–23% of Asians vs. 1–4% of Caucasians, and 2–7% of African-Americans (38)), heterozygotes are not uncommon in other groups (e.g., 16–37% of Caucasians and African-Americans (39–41)).

PPI METABOLISM

PPIs are also prodrugs transformed in the acid environment of gastric parietal cells nonenzymatically to active derivatives, which bind covalently to H^+K^+-ATPase (proton pump) (38,42). This irreversible inhibition of the proton pump leads to long-term acid suppression for up to 36 h, despite very short plasma half-lives of ~0.5–2 h (38).

CYP2C19 is also a principal enzyme in PPI metabolism (along with CYP3A4) (38,43). In contrast to the situation with clopidogrel, reduced CYP2C19 function results in less "inactivation" of PPI and an increase in pharmacodynamic effect (greater acid inhibition). Poor CYP2C19 metabolism has been associated with improved clinical outcomes such as healing of esophagitis or eradication of *H. pylori* (43)—and also theoretically could increase toxicity. All PPIs have increased plasma concentration and improved acid inhibition in poor CYP2C19 metabolizers (42–44).

PPIs also may competitively inhibit CYP2C19 metabolism. *In vitro* testing of a model substrate showed that lansoprazole and omeprazole were the most potent inhibitors, whereas pantoprazole and rabeprazole were the least potent, with inhibition constants (K_i) for the latter PPIs above their pharmacologically relevant concentrations generally achieved *in vivo* (44). The *in vitro* inhibition constant reported for esomeprazole (~8–9 μM) was close to its reported peak plasma concentration (~5–7 μM) (44). Inhibition constants for all PPIs for CYP3A4 *in vitro* metabolism of a model substrate were shown to be above plasma concentrations achieved *in vivo* for PPIs (44).

DO PPIS INFLUENCE CLOPIDOGREL'S PHARMACODYNAMIC EFFECTS?

As metabolism of both PPIs and clopidogrel involves CYP2C19 (and CYP3A4), and decreased metabolism of clopidogrel to its active metabolite is associated with poorer clinical outcomes, the potential influence of PPIs on the pharmacodynamic and clinical effects of clopidogrel were explored.

Pharmacodynamic studies are summarized in **Table 1**. In a 2006 letter, Gilard *et al.*, (45) using a novel surrogate marker for CV events (vasodilator-stimulated phosphoprotein phosphorylation platelet reactivity index (PRI)), reported higher PRI in patients taking clopidogrel plus PPI than in those taking clopidogrel without PPI. In a subsequent 7-day randomized, double-blind, placebo-controlled trial of omeprazole in clopidogrel users, these authors found significantly more poor responders, as measured by PRI, in the omeprazole group than in the placebo group (46). A randomized, crossover trial found that ADP-induced platelet aggregation was not significantly different with lansoprazole added to clopidogrel vs. clopidogrel alone (47). In a cohort of patients who received clopidogrel for a mean of 3 months, the PRI and ADP-induced platelet aggregation were not significantly different among those on no PPI, pantoprazole, and esomeprazole (48), whereas in another cohort of patients on clopidogrel maintenance therapy, ADP-induced platelet aggregation was significantly higher in patients on omeprazole but not significantly different in patients taking esomeprazole or pantoprazole when compared with those not prescribed a PPI (49). Finally, a *post hoc* nonrandomized subgroup analysis within the clopidogrel arm of a double-blind randomized trial showed that PPI users had significantly less inhibition of ADP-induced platelet aggregation than nonusers (50).

Clopidogrel also theoretically might increase the pharmacological effect of PPIs through CYP2C19. Chen *et al.* (51) reported that clopidogrel significantly inhibited CYP2C19-dependent hydroxylation of omeprazole and increased plasma concentration of omeprazole in CYP2C19 wild-type metabolizers.

Newer more potent inhibitors of the platelet $P2Y_{12}$ receptor may mitigate potential but unproven concerns regarding an interaction with PPIs. Prasugrel, recently approved by the US Food and Drug Administration (FDA), also requires CYP metabolism to its active metabolite, but does not show a decrease in its active metabolite or its inhibition of ADP-induced platelet aggregation in patients with CYP2C19 reduced-function genetic variants (33). In addition, nonrandomized subgroup analysis found that an inadequate response in inhibition of ADP-induced platelet aggregation was less common with prasugrel than clopidogrel among PPI users (50). Although prasugrel is more effective than clopidogrel in reducing CV events in patients with moderate-to-high risk acute coronary syndromes, its use is currently recommended only in selected patients because it causes significantly more major bleeding than clopidogrel (52,53). Newer reversible inhibitors of the platelet $P2Y_{12}$ receptor that do not require metabolism to an active metabolite are under investigation. One such agent (ticagrelor) was recently shown to significantly decrease CV events in patients with acute coronary syndrome without significantly increasing major bleeding as compared with clopidogrel (54).

DO PPIS INFLUENCE CLOPIDOGREL'S CLINICAL EFFICACY?

Recent studies examining the influence of PPIs on clinical outcomes with clopidogrel therapy are summarized in **Table 1**. Preliminary analysis of a randomized double-blind trial of omeprazole vs. placebo in patients taking clopidogrel and aspirin, which was terminated before the pre-specified sample size and duration were reached due to bankruptcy of the sponsor, revealed no significant difference in CV events (hazard ratio = 1.02, 0.70–1.51) (15). A 2008 letter reported that clopidogrel users with high PPI exposure had significantly higher crude rates of MI than those without PPI exposure, but indicated that the difference could be accounted for by significant differences in comorbidities (55). Three large observational studies reported that patients prescribed clopidogrel who also took PPIs had small but significant increases in CV events (odds and hazard ratios = 1.25–1.5) (56–58). If one were to accept these point estimates from observational studies as true, they would indicate that the negative impact of PPIs was greater than the incremental benefit of clopidogrel plus aspirin over aspirin alone in randomized trials. A nonrandomized subgroup analysis within a randomized trial found that patients prescribed PPIs had similar increases in the risk of CV events in the clopidogrel and placebo groups (59). The findings in all of these observational studies (56–59) could be due to confounding by indication (e.g., more PPI use in "sicker" patients) and/or chance, and are even compatible with the possibility

Table 1. Summary of studies assessing effect of PPI on pharmacodynamic outcomes in clopidogrel users

Authors	Study type	Population	End point	*N*	Results
Gilard *et al.* (45)	Cohort	High-risk coronary angioplasty	Platelet reactivity index	PPI: 24 No PPI: 81	PPI: 61.4% No PPI: 49.5% (P=0.007)
Gilard *et al.* (46)	Double-blind placebo-controlled randomized trial	Elective coronary stent implantation	Platelet reactivity index	Omeprazole: 64 Placebo: 60	Poor responders (index>50%) Omeprazole: 39 (61%) Placebo: 16 (27%) (P<0.0001)
Small *et al.* (47)	Randomized open-label crossover study	Healthy volunteers	Inhibition of 5 and 20 μM ADP-induced platelet aggregation at 4, 8, 12, and 24 h	Clopidogrel: 24 Clopidogrel + lansoprazole: 24	"Similar for clopidogrel alone and with lansoprazole, except with 5M ADP at 24 h": 49% vs. 39% (P=0.046)
Siller-Matula *et al.* (48)	Cohort	Undergoing percutaneous coronary intervention	Platelet reactivity index; ADP-induced platelet aggregation	Pantoprazole: 152 Esomeprazole: 74 No PPI: 74	Platelet reactivity index: pantoprazole: 50%, esomeprazole: 54%, no PPI: 49% Platelet aggregation: pantoprazole: 47U, esomeprazole: 42U, no PPI: 41U
Sibbing *et al.* (49)	Cohort	Prior coronary stent placement	ADP-induced platelet aggregation	Pantoprazole: 162 Omeprazole: 64 Esomeprazole: 42 No PPI: 732	Pantoprazole: 226.0 AU*min Esomeprazole: 209.0 AU*min Omeprazole: 295.5 AU*min No PPI: 220.0 AU*min (P=0.001 vs. omeprazole)
O'Donoghue *et al.* (50)	Retrospective cohort within randomized trial	Planned percutaneous coronary intervention	Inhibition of 20 μM ADP-induced platelet aggregation at 0.5, 2, 6, 24 h and 15 days; nonresponders (<20% inhibition) at 6 h, 15 days	PPI: 28 No PPI: 71	Lower mean inhibition with PPI at 2, 6, 24 h; Nonresponders (PPI vs. no PPI): 6 h: 50% vs. 18% (P=0.009) 15 days: 50% vs. 8% (P=0.012)

PPI, proton pump inhibitor.

that PPIs alone increase CV events. In two observational studies, however, patients prescribed PPI without clopidogrel had no significant increase in CV events (56,60).

A *post hoc* nonrandomized analysis of the clopidogrel arm of a double-blind randomized trial showed no association between PPIs and CV events in the overall clopidogrel group nor in the subgroups with and without a reduced-function CYP2C19 allele (50). Finally, in univariate analyses of two cohort studies, patients prescribed clopidogrel had no increase in CV events with PPIs (36,61). In multivariable analysis in one of these studies, the increased risk of CV events with CYP2C19 reduced-function genetic variants was not modified by PPIs (36). In another cohort study of patients prescribed clopidogrel, there was no association between use of PPIs and CV events (37) (**Table 2**).

The potential for differential effects of different PPIs has also been explored. One observational study of clopidogrel users found no significant association between prescription of pantoprazole and CV events, a finding attributed by the authors to pantoprazole's lesser CYP2C19 inhibition (57). In this study, however, the difference in the risk of CV events between patients prescribed pantoprazole and those prescribed other PPIs was not significant. Two observational studies of clopidogrel users showed that patients prescribed pantoprazole, rabeprazole, or esomeprazole had increased risks of CV events at least as large as the risks in those prescribed omeprazole or lansoprazole (56,58), whereas in another observational study of clopidogrel users, no increased risk of CV events was seen in patients prescribed omeprazole, lansoprazole, esomeprazole, or pantoprazole (50) (**Table 2**).

RECOMMENDATIONS TO HEALTH-CARE PROVIDERS

The available data regarding whether PPIs influence the clinical efficacy of clopidogrel are primarily observational. In observational studies, the exposure being studied (e.g., PPI use) is not assigned at random, but rather is related to patient characteristics and/or clinical decisions of health-care providers (e.g., PPI prescribed because of older age, reflux symptoms, aspirin use). As a result, all observational studies have differences between the exposed and nonexposed groups in known and unknown factors that confound the results (62). Because of the presence of these factors, when effect sizes are small to moderate (RR < 1.5–2.0), it is not possible to conclude whether any observed statistical association is valid, even after the most careful statistical adjustment for all known factors (62). Only randomized trials of sufficient size and duration can adequately control for known and unknown confounding variables (62).

Table 2. Summary of studies assessing effect of PPI on clinical outcomes in clopidogrel users

Authors	Study type	Population	End point	*N*	Results
Bhatt *et al.* (15)	Double-blind randomized	Acute coronary syndrome; coronary stent placement	MI, stroke, CABG, PCI, CV death	PPI: 1,801 Placebo: 1,826	HR=1.02 (0.70–1.51)
Pezalla *et al.* (55)	Retrospective cohort	<65 Years; adherent to clopidogrel	MI (1 year)	No PPI: 4,800 Low PPI: 712 High PPI: ?	No PPI: 1.38%; low PPI: 3.08%; high PPI: 5.03% ("Significant comorbidity differences could account for findings," so looked at subgroup (n=1,010) with comorbid conditions: No PPI: 2.60%; low PPI: 10.0%; high PPI: 11.38%) (P<0.05 high vs. no PPI in overall and subgroup)
Juurlink *et al.* (57)	Nested case–control	>65 Years; discharged after MI hospitalization	Death or readmitted for MI (90 days) (adjusted for age, sex, income, comorbidity index, length of hospitalization, nine comorbidities, dozens of medications)	Cases: 734 (PPI: 194) Controls: 2,057 (PPI: 424)	OR=1.27, 1.03–1.57 Pantoprazole OR=1.02, 0.70–1.47 Other PPIs OR=1.40, 1.10–1.77
Ho *et al.* (56)	Retrospective cohort	Discharged after MI or unstable angina hospitalization	Death or rehospitalization for MI or unstable angina (adjusted for 24 variables)	PPI: 5,244 No PPI: 2,961	OR=1.25, 1.11–1.41 Omeprazole OR=1.24, 1.08–1.41 Rabeprazole OR=2.83, 1.96–4.09
Stanek *et al.* (58)	Retrospective cohort	Adherent to clopidogrel after coronary stent	MI, unstable angina, stroke, TIA, coronary revascularization, CV death (1 year) (adjusted for age, sex, comorbidity)	PPI: 6,828 No PPI: 9,862	HR=1.51, 1.39–1.64 Omeprazole HR=1.39, 1.22–1.57 Esomeprazole HR=1.57, 1.40–1.76 Pantoprazole HR=1.61, 1.41–1.88 Lansoprazole HR=1.39, 1.16–1.67
Dunn *et al.* (59)	Retrospective cohort within RCT	Undergoing PCI or high likelihood of PCI	Death, MI, stroke (1 year) ("multivariate" models)	PPI: 366 No PPI: 1,750	Clopidogrel + PPI vs. clopidogrel OR=1.63, 1.02–2.63 Placebo + PPI vs. placebo OR=1.55, 1.03–2.34
O'Donoghue *et al.* (50)	Retrospective cohort within RCT	Acute coronary syndrome undergoing PCI	MI, stroke, CV death (adjusted for 28 variables)	PPI: 2,257 No PPI: 4,538	HR=0.94 (0.80–1.11) Omeprazole (n=1,675) HR=0.91 (0.72–1.15) Lansoprazole (n=441) HR=1.00 (0.63–1.59) Esomeprazole (n=613) HR=1.07 (0.75–1.52) Pantoprazole (n=1,844) HR=0.97 (0.75–1.24) Patients with reduced-function CYP2C19 allele (n=357) HR=0.76 (0.39–1.48) Patients without reduced-function allele (n=1,064) HR=0.90 (0.55–1.48)
Simon *et al.* (36)	Cohort	Acute MI	MI, stroke, death (1 year); (1) Adjusted for ~46 variables (includes PPI). (2) Propensity analysis for CYP2C19 genotype, using multivariable model, and developed matched cohort of 5 controls for each patient with 2 variant alleles, on basis of the propensity analysis score	PPI: 1,606; (Omeprazole: 1,147) No PPI: 602	Univariate analysis (CV event with PPI vs. no PPI): PPI: RR=0.92 (0.73–1.16); Omeprazole: RR=0.85 (0.69–1.05) Multivariable analysis: PPIs "had no significant effects" on hazard ratios for CV events with 2 loss-of-function alleles vs. wild type
Collet *et al.* (37)	Cohort	MI	MI, CV death, urgent revascularization	PPI: 83 No PPI: 176	Multivariable analysis: "no significant effect of use of PPIs"
Ramirez *et al.* (61)	Retrospective cohort	PCI	MI, death, CABG or repeat PCI (1 year)	PPI: 397 No PPI: 138	MI/death (PPI vs. no PPI): 6.7% vs. 9.6%; P=0.32 CABG/repeat PCI: 15.8% vs. 14.2%; P=0.65

CABG, coronary artery bypass graft; CV, cardiovascular; HR, hazard ratio; MI, myocardial infarction; OR, odds ratio; PCI, percutaneous coronary intervention; PPI, proton pump inhibitor; RCT, randomized, controlled trial; RR, relative risk; TIA, transient ischemic attack.

A randomized trial of omeprazole vs. placebo showed no difference in CV events among clopidogrel users (hazard ratio = 1.02, 0.70–1.51) (15). Thus, the current evidence does not justify a conclusion that there is a valid statistical association of PPIs with CV events among clopidogrel users.

Judgments regarding causality (e.g., do PPIs decrease clopidogrel's clinical efficacy) must be made by critically assessing the totality of available evidence (62). Criteria supporting causality include *strength of association* (larger associations are more likely causal), *consistency* (different investigators using different study designs in different populations find similar results), and *biologic credibility* (a biologically plausible mechanism adds support to a judgment of causality) (62).

Some health-care providers and regulatory authorities have judged that PPIs reduce the clinical efficacy of clopidogrel, based on positive results in some (but not all) observational studies and the biological plausibility of the proposed mechanism. Regulatory authorities have recently issued recommendations regarding use of PPIs with clopidogrel. The FDA suggests that "health-care providers should re-evaluate the need for starting or continuing treatment with a PPI in patients taking clopidogrel" (63), and has revised clopidogrel labeling to state "concomitant use of drugs that inhibit CYP2C19 (e.g., omeprazole) should be discouraged" (64). The FDA's European counterpart, European Medicines Agency, also discourages "concomitant use of PPI and clopidogrel-containing medicines unless absolutely necessary" (65).

In fact, the current totality of evidence does not justify a conclusion that PPIs are associated with CV events among clopidogrel users, let alone support a judgment of causality. Yet, health-care providers must make decisions for their patients even in the face of conflicting evidence. We suggest the following guidance.

First, patients who require clopidogrel should start and continue their therapy. Second, patients taking clopidogrel plus aspirin, especially with other GI risk factors such as prior ulcer or bleeding and concomitant nonsteroidal antiinflammatory drug or anticoagulant therapy, should receive GI-protective therapy (3).

Histamine-2-receptor antagonist therapy significantly decreases endoscopic ulcers in low-dose aspirin users and may be an alternative to PPIs (22). Randomized trials, however, are not available documenting that this therapy decreases GI bleeding with aspirin use.

The current clinical evidence does not indicate that one PPI is clearly different from another, so merely switching PPIs cannot be viewed as sufficient to avoid any potential risk. If PPIs decrease clopidogrel's efficacy, the postulated mechanism is competitive inhibition of clopidogrel metabolism. As PPIs and clopidogrel are each given once daily and their presence in the bloodstream is short lived, separation by 12–15 h should in theory prevent any competitive inhibition of CYP metabolism and any clinical effect. In the occasional poor CYP2C19 metabolizer, low plasma concentrations of PPIs potentially may still be present 12 h after dosing (43,66,67) but should be extremely low or absent at ~20 h (43,51), whereas clopidogrel concentrations should be very low or unmeasurable 4–6 h after ingestion (34). In addition, PPIs are most effective when taken before meals. Therefore, we suggest that PPIs be given before breakfast and clopidogrel at bedtime, or, to minimize concern about poor CYP2C19 metabolizers, PPIs may be taken before dinner and clopidogrel at lunchtime.

The current evidence does not justify the conclusion that PPIs decrease the clinical efficacy of clopidogrel. Nonetheless, until further reliable data become available, wide separation of PPI and clopidogrel dosing should in theory minimize any potential, though unproven, clinical interaction between these two widely used medications.

CONFLICT OF INTEREST

Guarantor of the article: Loren Laine, MD.
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