Published in final edited form as:

Expert Opin Drug Metab Toxicol. 2014 February ; 10(2): 175–189. doi:10.1517/17425255.2014.856883.

Antiplatelet drug interactions with proton pump inhibitors

Stuart A Scott, PhD^{†,1}, Aniwa Obeng, PharmD^{2,3}, and Jean-Sébastien Hulot, MD, PhD^{4,5}

¹Assistant Professor, Icahn School of Medicine at Mount Sinai, Department of Genetics and Genomic Sciences, One Gustave L. Levy Place, Box 1497, New York, NY 10029, USA

²The Charles Bronfman Institute for Personalized Medicine, Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA

³Mount Sinai Medical Center, Department of Pharmacy, New York, NY 10029, USA

⁴Icahn School of Medicine at Mount Sinai, Cardiovascular Research Center, New York, NY 10029, USA

⁵Université Pierre et Marie Curie-Paris 6, Pitié-Salpêtrière University Hospital, INSERM UMR S 956, Pharmacology Department, Paris, France

Abstract

Introduction—Non-aspirin antiplatelet agents (e.g., clopidogrel, prasugrel, ticagrelor) are commonly prescribed for the prevention of recurrent cardiovascular events among patients with acute coronary syndromes (ACS) and/or those undergoing percutaneous coronary intervention (PCI). In addition, combination therapy with proton pump inhibitors (PPIs) is often recommended to attenuate gastrointestinal bleeding risk, particularly during dual antiplatelet therapy (DAPT) with clopidogrel and aspirin. Importantly, a pharmacological interaction between clopidogrel and some PPIs has been proposed based on mutual CYP450-dependent metabolism, but available evidence is inconsistent.

Areas covered—This article provides an overview of the currently approved antiplatelet agents and PPIs, including their metabolic pathways. Additionally, the CYP450 isoenzyme at the center of the drug interaction, CYP2C19, is described in detail, and the available evidence on both the potential pharmacological interaction and influence on clinical outcomes are summarized and evaluated.

Expert opinion—Although concomitant DAPT and PPI use reduces clopidogrel active metabolite levels and *ex vivo*-measured platelet inhibition, the influence of the drug interaction on

© 2014 Informa UK, Ltd.

[†]Author for correspondence: Icahn School of Medicine at Mount Sinai, Department of Genetics and Genomic Sciences, New York, NY, USA; Tel: +1 212 241 3780; Fax: +1 212 241 0139; stuart.scott@mssm.edu.

Declaration of interest

S Scott receives support from NIH for antiplatelet pharmacogenomics research, is a consultant to USDS, Inc., and is an assistant director of a clinical laboratory that performs *CYP2C19* testing. J-S Hulot has received research grant support from Biotronik and Medco Research Institute, and consulting fees from Biotronik and Medco Health Solutions. This research was supported in part by the National Center for Research Resources (NCRR) and the National Center for Advancing Translational Sciences (NCATS), and the National Institute of General Medical Sciences (NIGMS) of the National Institutes of Health (NIH), through grants KL2TR000069 and K23GM104401 (S Scott). A Obeng has no conflicts of interest to declare.

clinical outcomes has been conflicting and largely reported from non-randomized observational studies. Despite this inconsistency, a clinically important interaction cannot be definitively excluded, particularly among patient subgroups with higher overall cardiovascular risk and potentially among *CYP2C19* loss-of-function allele carriers.

Keywords

antiplatelet agents; clopidogrel; CYP2C19; drug interaction; omeprazole; proton pump inhibitors

1. Introduction

Antiplatelet agents are widely prescribed anti-thrombotics that reduce cardiovascular events in patients with acute coronary syndromes (ACS) and/or those undergoing percutaneous coronary intervention (PCI). One of the most common among them is the second generation thienopyridine clopidogrel, typically used in conjunction with aspirin as dual antiplatelet therapy (DAPT). DAPT significantly reduces the risk of stroke, myocardial infarction (MI), and/or death in ACS patients; however, the risk of major gastrointestinal (GI) hemorrhage is also increased [1]. This increased bleeding risk prompted guidelines recommending concomitant administration of a proton pump inhibitor (PPI), particularly advised in high-risk patients with a prior history of bleeding and/or other risk factors [e.g., ancillary use of nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids and anticoagulants] [2,3].

PPIs have been widely available for ~ 30 years as treatment for acid-peptic disorders by inhibiting the parietal cell proton pump (H^+/K^+ ATPase) and suppressing gastric acid secretion. As such, they are effective for the prevention and treatment of ulcers, gastroesophageal reflux disease (GERD) and Zollinger–Ellison syndrome, as well as for eradicating *Helicobacter pylori* in combination with antibiotics. Although a number of PPIs with shared mechanism of action are available (e.g., omeprazole, esomeprazole, pantoprazole, lansoprazole and rabeprazole), meta-analyses suggest that esomeprazole has a modest benefit in efficacy compared to the first generation PPIs (omeprazole, pantoprazole and lansoprazole) [4,5].

Importantly, hepatic metabolism of clopidogrel and several of the PPIs are dependent on the cytochrome-P450 (CYP450) enzymes CYP2C19 and CYP3A4, suggesting the potential for drug interaction. This fact prompted concerns for potential adverse cardiovascular outcomes when co-administered and ultimately a 2009 warning by the US Food and Drug Administration (FDA) against concomitant administration of clopidogrel and omeprazole due to their mutual dependence on CYP2C19-mediated metabolism. Since then, a number of groups have studied this potential drug interaction, both pharmacologically and clinically, which frequently concluded with conflicting results. This manuscript aims to provide an overview of the currently approved non-aspirin antiplatelet agents and PPIs, as well as a critical review of the available antiplatelet and PPI drug interaction literature with emphasis on clinical relevance and utility.

2. Antiplatelet agents

2.1 Clopidogrel

Clopidogrel is a second generation thienopyridine that is bio-transformed in the liver to an active metabolite that binds specifically and irreversibly to the purinergic P2Y₁₂ receptor, inhibiting ADP-mediated platelet activation and aggregation for the platelet lifespan. The majority of the prodrug (~ 85%) is hydrolyzed to inactive metabolites by esterases, leaving only ~ 15% available for transformation to the active agent (Figure 1). Two sequential oxidative reactions are necessary to form the active metabolite, involving several CYP450 enzymes: CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP3A4 and CYP3A5 (Table 1) [6,7].

Clopidogrel and aspirin are widely used antiplatelet agents that together reduce cardiovascular death and ischemic complications in patients with ACS and those undergoing PCI. However, wide inter-individual variability (~ 8-fold) in platelet aggregation is commonly observed before and after clopidogrel treatment [8] and some patients can experience thrombotic events (including stent thrombosis) following DAPT. Moreover, persistent high platelet reactivity is associated with more frequent adverse cardiovascular events [9]. Approximately 20 – 40% of coronary patients are classified as clopidogrel non-responders, poor-responders or resistant because of reduced inhibition of ADP-induced platelet aggregation [10]. Non-genetic factors influencing clopidogrel response include age, diabetes, renal failure and cardiac failure.

Candidate gene studies have been performed to identify genes and variants associated with poor platelet inhibition following DAPT. Consistent among these studies has been the association between *CYP2C19* loss-of-function alleles (e.g., *2 – *8) and poor platelet inhibition in healthy individuals and ACS patients [8,10,11]. Specifically, *CYP2C19* loss-of-function alleles have reproducibly been associated with lower active metabolite levels [10,12], decreased platelet inhibition [8,11,13,14] and increased adverse cardiovascular event rates among clopidogrel-treated ACS patients undergoing PCI [8,10,13–22]. Moreover, large meta-analyses [17,19,23] have shown that in ACS/PCI patients receiving clopidogrel, *CYP2C19**2 carriers have a ~ 30% increased risk of major adverse cardiovascular events (MACE) compared to non-carriers [17] and increased risks of stent thrombosis in both hetero- and homozygous patients [19]. However, another meta-analysis suggests that *CYP2C19* may not be clinically relevant for all clopidogrel-treated patients [24], underscoring the importance of indication (i.e., ACS/PCI) when assessing the pharmacogenetic effect of *CYP2C19* [25]. Together, these data prompted a 2009 product insert label revision by the US FDA to include a boxed warning detailing the increased risk among ACS/PCI patients who carry *CYP2C19* loss-of-function alleles, particularly for *CYP2C19* poor metabolizers (PM).

2.2 Prasugrel

Prasugrel is a third-generation thienopyridine approved for use in ACS patients undergoing PCI. Like clopidogrel, prasugrel is a prodrug that requires biotransformation to generate its active metabolite (R-138727) (Figure 1), which can irreversibly inhibit platelet function for the duration of its life-span by antagonizing the P2Y₁₂ receptor and impairing the ADP-

mediated activation of the glycoprotein GPIIb/IIIa complex. In contrast to clopidogrel, following esterification to an intermediate metabolite, only one hepatic CYP450-dependent metabolism step is necessary for conversion to its active metabolite, involving CYP2B6, CYP2C9, CYP2C19, CYP2D6 and CYP3A4 (Table 1) [26,27].

The more rapid generation of a higher level of active metabolite results in prasugrel having a more effective and rapid platelet inhibition compared to clopidogrel [28–31] and a reduction in the incidence of cardiac death, and non-fatal MI or stroke among ACS/PCI patients [9.9 vs 12.1%, respectively; hazard ratio (HR) = 0.81 (0.73 – 0.94)] [32]. However, this is balanced by an increased risk in major bleeding complications compared to clopidogrel, including fatal bleeding [32]. Of note, the benefit of prasugrel over clopidogrel was found to be greater in patients with a *CYP2C19* loss-of-function allele [31], and clinical trials consequently are underway to determine the utility of *CYP2C19*-genotype directed antiplatelet therapy. Pharmacokinetic analyses have also identified higher prasugrel active metabolite exposure in patients > 75 years and in patients weighing < 60 kg [33], indicating reduced maintenance dosing or alternative antiplatelet agent for these patient subgroups.

Despite the pharmacodynamic advantages of prasugrel over clopidogrel, high-platelet reactivity can also occur among prasugrel-treated patients following PCI, which has been associated with higher rates of thrombotic events [34]. Moreover, like clopidogrel, prasugrel causes irreversible platelet inhibition with a slow offset of antiplatelet efficacy (5 – 7 days) [35]. To reduce bleeding complications when surgical procedures are scheduled following thienopyridine discontinuation, reversible P2Y₁₂ receptor antagonists with a more rapid onset and offset of antiplatelet action could be beneficial.

2.3 Ticagrelor

Ticagrelor is a reversible, non-thienopyridine recently approved for use in ACS patients. Unlike clopidogrel and prasugrel, ticagrelor binds the ADP receptor at a different site than ADP and, therefore, acts as an allosteric antagonist [36]. It inhibits ADP-induced P2Y₁₂ receptor signaling in a non-competitive manner and does not require metabolic activation to generate its active metabolite (Figure 1) [36,37]. After oral administration, ticagrelor undergoes rapid absorption and subsequent degradation to its primary active (AR-C124910XX) and inactive (AR-C133913XX) metabolites through CYP3A4/5-mediated metabolism (Table 1).

Ticagrelor achieves a greater and more consistent platelet inhibition compared to clopidogrel, with a faster onset (observed within 30 min of loading) and offset of action [38]. Additionally, among patients with ACS, ticagrelor achieved greater suppression of platelet reactivity compared with clopidogrel after loading dose administration and during maintenance therapy [39]. Moreover, ticagrelor was superior to clopidogrel in a large-scale randomized trial of ACS patients with a HR for cardiovascular death, MI, or stroke for ticagrelor versus clopidogrel of 0.84 (95% CI 0.77 – 0.92, $p < 0.001$), including a 26% reduction in stent thrombosis and 18% reduction in all-cause mortality [40].

No significant difference in the rates of major bleeding were found between ticagrelor and clopidogrel (11.6 and 11.2%, respectively; $p = 0.43$), but ticagrelor was associated with a

higher rate of major bleeding not related to coronary-artery bypass grafting (4.5 vs 3.8%, $p = 0.03$), including more instances of fatal intracranial bleeding and fewer of fatal bleeding of other types [40]. Unlike prasugrel, there was no increase in major bleeding with ticagrelor in patients > 75 years or in those with a history of stroke or transient ischemic attack [41,42]. However, ticagrelor is contraindicated in patients with active bleeding, a history of intracranial hemorrhage or liver failure. Additionally, although there is no dependency on CYP2C19 for metabolic activation, coadministration with strong CYP3A inhibitors or inducers may influence ticagrelor metabolism and efficacy.

3. Proton pump inhibitors

3.1 PPI mechanism of action

PPIs are substituted benzimidazole compounds that act by blocking hydrogen–potassium adenosine triphosphatase (H^+/K^+ ATPase) in the cell lining of the gastric mucosa [43]. Although the parent compounds are inactive, PPIs are activated on ingestion by the low pH environment inside the canaliculus of parietal cells to form tetracyclic sulfenamide metabolites [43,44]. These metabolites form covalent bonds with the H^+/K^+ ATPase to suppress gastric acid secretion. The pronounced acid suppression induced by PPIs makes them one of the most effective treatments for hypersecretory disorders such as GERD and Zollinger–Ellison syndrome [45].

Both the ionization constant (pK_a) and target cell pH influence PPI activation [43]. Kromer *et al.* reported activation half-lives of 1.3 – 4.6 min when PPI agents were subjected to a pH of 1.2 [44]. Conversely, at a higher pH of 5.1, their activation half-lives increased to 0.12 h for rabeprazole; 1.4 h for omeprazole; 1.5 h for lansoprazole and 4.7 h for pantoprazole. Moreover, Besancon and colleagues observed that rabeprazole had the most rapid inhibition of the H^+/K^+ ATPase system *in vitro* followed by lansoprazole, omeprazole and finally pantoprazole [46]. Despite their relatively short half-lives, the duration of their activity extends up to 3 days post administration, which is attributed to the irreversible nature of their inhibition on H^+/K^+ ATPase pumps. The generation of new pumps or activation of resting pumps by the parietal cells is needed for continued acid secretion [47]. Despite the individual differences, PPIs are similar with respect to half-lives, time to maximum plasma concentration and safety [43].

PPIs are considered safe and tolerable with only 1 – 3% of patients experiencing minor adverse effects, including nausea, abdominal pain, constipation, flatulence and diarrhea. Potential long-term consequences of these agents due to their prolonged and sometimes indefinite use are currently unknown but may include increased fracture risk, community acquired pneumonia, iron deficiency, hypomagnesemia, cancer and birth defects. Although these concerns have yet to be substantiated, risk–benefit evaluation and/or increased monitoring of patients at risk for vitamin B₁₂ deficiency, gastric polyps and enteric infections have been recommended [48], which includes the elderly, malnourished, immunocompromised, osteoporotic and chronically ill. In general, the benefits of acid suppression achieved by PPIs far offset the potential safety concerns for the majority of patients.

3.2 PPI metabolism

Prior to elimination, PPIs undergo hepatic biotransformation, which is primarily mediated by CYP2C19 and CYP3A4 [43,49]. The metabolism of each PPI agent differs in terms of the identity and degree of involvement of the specific CYP450 isoenzyme(s) (Table 2). Regarding PPI pharmacogenetics, the effects of *CYP2C19* variant alleles (e.g., *2), if any, on PPI metabolism can be summarized in the following order: omeprazole and esomeprazole > pantoprazole > lansoprazole > rabeprazole [47].

3.2.1 Omeprazole and esomeprazole—Omeprazole is the most studied PPI and likely the PPI most affected by variation in CYP450 activity. The major enzyme responsible for its biotransformation is CYP2C19, which has approximately ten times higher affinity for omeprazole than CYP3A4 (Figure 2) [47]. The polymorphic CYP2C19 enzyme converts omeprazole to 5-hydroxy-omeprazole, which is subsequently transformed into 5-hydroxy-omeprazole sulfone by CYP3A4. A minor alternative pathway for omeprazole metabolism is through CYP3A4 directly, which converts the parent drug to sulfide and omeprazole sulfone prior to CYP2C19-mediated conversion of the latter into 5-hydroxy-omeprazole sulfone [43,47]. Notably, *CYP2C19* genotype has reproducibly been shown to influence the clinical outcomes of omeprazole, as demonstrated by reduced effectiveness among extensive metabolizers (EMs) compared to intermediate metabolizers (IMs) and PMs [50–59].

Esomeprazole is the S-enantiomer of the racemic omeprazole. Apart from a slower 5'-hydroxylation step observed *in vitro* among esomeprazole studies [60], the metabolic pathway of esomeprazole is similar to that of omeprazole (Figure 2) [43]. At equal doses, esomeprazole appears to produce a higher AUC among *CYP2C19* EMs as compared to omeprazole [60].

3.2.2 Pantoprazole—Pantoprazole is primarily metabolized by CYP2C19 to desmethyl pantoprazole (5-hydroxy-pantoprazole), and to a lesser extent, by CYP3A4 to pantoprazole sulfone and sulfide (Figure 2). The 5-hydroxy-pantoprazole product of pantoprazole is quickly converted into pantoprazole sulfate by sulfotransferase, which is the major plasma metabolite [47]. This conversion by sulfotransferase into the sulfate product may minimize the potential for significant drug–drug interactions with antiplatelet or other agents metabolized by CYP2C19. Additionally, the influence of *CYP2C19* variant alleles on pantoprazole pharmacokinetics and clinical efficacy is an area of active research, with available data on healthy subjects suggesting that *CYP2C19* genotype may be a potential determinant of pantoprazole pharmacokinetics [61].

3.2.3 Lansoprazole—Lansoprazole is primarily metabolized by both CYP2C19 and CYP3A4 into 5-hydroxy-lansoprazole and lansoprazole sulphone or sulfide, respectively (Figure 2), which subsequently are converted into 5-hydroxy-lansoprazole sulfone and sulfide through CYP3A4 and CYP2C19 [43,49,62]. Furata and colleagues conducted a study in healthy volunteers to assess the influence of *CYP2C19* genotype on the acid-inhibitory effects of lansoprazole [63]. The mean 24-h intragastric pH values after once daily dosing for 8 days among *CYP2C19* EM, IM and PM were 4.5, 4.9 and 5.5, respectively ($p < 0.005$) [63]. The investigators attempted to overcome the genotype effects by increasing dosing

frequency to four times daily dosing (lansoprazole 30 mg four times daily) in EMs; however, this was not successful at increasing the intragastric pH. As such, it was concluded that the effect of lansoprazole on intragastric pH was significantly dependent on *CYP2C19* genotype status.

3.2.4 Rabeprazole—Rabeprazole primarily undergoes non-enzymatic degradation into thioether rabeprazole (Figure 2). In addition to the non-enzymatic pathway, a small amount of rabeprazole is converted into desmethyl rabeprazole and rabeprazole sulfone by CYP2C19 and CYP3A4, respectively [43,49,62]. Consequently, a number of studies have reported similar values for drug exposure, efficacy and clearance in both healthy volunteers and patients regardless of *CYP2C19* genotype status [47,51,55,64,65].

3.2.5 Other considerations regarding PPI metabolism—PPIs can also have significant effects on the metabolism of other medications based on CYP450 enzyme inhibition. For example, in addition to being a CYP2C19 substrate, omeprazole is also a CYP2C19 inhibitor, which is evident following multiple omeprazole doses. Specifically, among *CYP2C19* EM healthy volunteers, a significant increase in mean intra-gastric pH, AUC, C_{max} and half-life, and decreased omeprazole clearance has been reported after repeated dosing compared to after a single dose [66]. This observation can be explained, in part, by omeprazole-mediated inhibition of CYP2C19 and a subsequent reduction in omeprazole clearance. Competitive inhibition of CYP2C19 has also been reported *in vitro* for both omeprazole and lansoprazole [67]. In this study, lansoprazole was also five times more potent than omeprazole at inhibiting CYP2D6, which is an important CYP450 isoenzyme involved in the metabolism of ~ 25% of all commonly prescribed medications [68]. These data suggest that further studies are warranted that evaluate the interaction between selected PPIs and concomitant administration with CYP2D6-metabolized drugs, in addition to those metabolized primarily by CYP2C19.

4. Cytochrome P450-2C19

The hepatic CYP450 superfamily of hemoproteins are the principal enzymes involved in human drug metabolism and bioactivation. Over 50 human CYP450 isozymes have been identified; however, members of the CYP2 and CYP3 families have significant importance as they contribute to the metabolism of the majority of drugs [69]. One of the most notable CYP2C subfamily enzymes is CYP2C19, which is involved in the metabolism of a large number of clinically relevant drugs and drug classes [70,71]. A large portion of the literature on CYP2C19 and drug response variability focuses on the pharmacogenetic influence of variant *CYP2C19* alleles. Many of these alleles encode reduced or complete loss-of-function enzyme variants, and their frequencies can significantly differ between racial and ethnic groups [72–74]. The most commonly tested loss-of-function alleles are *2 and *3; however, some studies include *4 – *8 based on extensive *in vitro* evidence for their respective complete loss-of-function, despite low frequencies in the general population. In addition, the common *17 gain-of-function allele [75] is also frequently interrogated in *CYP2C19* pharmacogenetic studies.

Based on the predicted ability to metabolize CYP2C19 substrates, individuals can be classified as ultrarapid metabolizer (UM), EM, IM or PM [71]. EM individuals are homozygous for the wild-type *CYP2C19*1* allele, which is associated with functional CYP2C19-mediated metabolism. The IM genotype consists of one wild-type allele and one loss-of-function allele, resulting in decreased CYP2C19 activity. PM individuals have two loss-of-function alleles, resulting in markedly reduced or absent CYP2C19 activity. Individuals who carry one or two **17* gain-of-function alleles may be categorized as UMs; however, the phenotypic consequences of a loss-of-function allele and a **17* compound heterozygous genotype (e.g., **2/*17*) is currently unclear but is likely substrate-dependent and more consistent with an IM phenotype [76,77].

5. Drug interactions

A drug interaction is defined as a pharmacologic or clinical response to the administration of a drug combination different from that anticipated from the known effects of the two agents when given alone [78]. Importantly, this interaction can be synergistic, antagonistic or a new effect can be produced that neither drug produces independently. In addition, drug interactions can be defined at different physiological levels and with different relevance. A pharmacokinetic interaction occurs when one drug alters the concentration of another by altering its absorption, distribution, metabolism or excretion, which is often mediated by the CYP450 system. A pharmacodynamic interaction occurs when one drug modulates the pharmacologic effect of another through a specific transducer, which is often mediated by a mutual drug receptor, effector or signaling pathway.

One well-known illustration of a beneficial and desirable pharmacodynamic drug–drug interaction is DAPT, combining aspirin and a thienopyridine for improved antiplatelet response among ACS/PCI patients [79]. However, a pharmacological interaction does not always necessarily translate into a significant effect on clinical response. Changes in drug concentration are mostly well-tolerated for many medications due to large safety indexes. Drugs with narrow therapeutic indexes are, therefore, the medications with higher risk for clinically significant drug interaction. As such, experimental confirmation of a pharmacologic drug interaction, on its own, is not adequate evidence to establish clinical relevance.

6. Antiplatelet and PPI drug interactions

6.1 Pharmacologic drug interaction

The 2009 drug interaction warning by the US FDA was largely based on initial pharmacokinetic and pharmacodynamic studies that reported impaired platelet inhibition following concomitant administration of DAPT and PPIs [80–83]. Different mechanisms have been proposed as responsible for this drug interaction, including decreased absorption of clopidogrel due to PPI-mediated elevated gastric pH, and competitive inhibition of CYP2C19 by PPIs themselves. However, plasma unchanged clopidogrel levels are not lower during PPI administration [84], which indicates that clopidogrel absorption is not affected by PPI use. Furthermore, given that the most potent CYP2C19 inhibitor among the PPIs (omeprazole) consistently has shown the strongest effect on platelet inhibition [85–91], it is

most likely that the drug interaction is mediated by competitive CYP2C19 inhibition (Figure 3).

The pharmacologic drug interaction effect has been observed by both reduced clopidogrel metabolite levels and higher on-treatment *ex vivo* platelet reactivity when compared to individuals not concomitantly administered PPIs. Evidence suggests that a drug interaction may also exist to a lesser degree with esomeprazole and lansoprazole, but not pantoprazole or rabeprazole. Together, these data support an ‘agent-specific’ rather than ‘class-specific’ drug interaction between clopidogrel and PPIs. Of note, many of the early studies did not account for the additional influence of interindividual *CYP2C19* genetic variability, which is also potentially relevant given its established effect on platelet inhibition following clopidogrel treatment [8,10,11,13]. Moreover, the ultimate effect of this drug interaction on clinical outcomes has been conflicting and, therefore, extensively debated.

In an effort to attenuate the negative metabolic interaction between clopidogrel and omeprazole, a split dosage strategy with the two agents previously has been suggested. However, given the short half-life of most PPIs (~ 1 – 2 h) [92] and the longer half-life of clopidogrel (> 300 h) [93], this strategy is unlikely to overcome any interaction. This is further evidenced by a randomized, placebo-controlled, healthy subject crossover study, which concluded that clopidogrel metabolites and platelet inhibition were both decreased by co-administration of omeprazole with clopidogrel regardless of the timing of omeprazole administration [90]. Notably, this study also reported that pantoprazole did not influence the antiplatelet effects of clopidogrel [90].

6.2 Clinical significance

Cardiovascular clinical outcome data from studies on the clopidogrel and PPI drug interaction have been inconsistent, with evidence both for and against a clinically significant effect [94]. Evidence supporting a clinically meaningful interaction has largely been derived from non-randomized observational studies that reported increased risks of recurrent MI/ACS [85,95–97] and MACE [98] among coronary patients treated with clopidogrel and a PPI, as well as a case–control study that identified PPI use as a significant determinant of early stent thrombosis [99]. In contrast, *post hoc* analyses of randomized-controlled trials [86] and a large retrospective cohort study [100] have failed to identify an increased risk of cardiovascular events among patients taking PPIs, suggesting the possibility of confounding in the non-randomized studies. Of note, pantoprazole was the predominant PPI in the cohort study (62%), which has been reported to have limited influence on clopidogrel metabolite levels [90,101] and on-treatment platelet aggregation [87,90]. A single prospective clinical trial designed to directly test the clinical relevance of the clopidogrel and omeprazole interaction (COGENT) was unfortunately prematurely terminated, but also failed to find a significant cardiovascular interaction between clopidogrel and omeprazole based on the available data [102]. Consequently, a clinically meaningful difference in cardiovascular events due to use of a PPI cannot be definitively ruled out.

Several meta-analyses of the clinical outcome studies have been reported and they are summarized in Table 3. Consistent with the literature detailed above, general findings across most of the meta-analyses suggest an increased risk for MI/ACS and MACE, but not

mortality, with concomitant PPI use; however, these conclusions were limited to observational studies and not identified in the clinical trial analyses. When analyzed (and as expected), a reduction in GI bleeding risk was also associated with PPI use. An additional challenge with inference from the meta-analyses is the widespread heterogeneity identified across the majority of clinical studies, making definitive conclusions challenging. Of note, sensitivity analyses from one meta-analysis suggested that the clinical influence of PPI use may depend, in part, on baseline cardiovascular risk, as the PPI effect was only significant among patients with an annual rate of MACE greater than 10% and not among those with a rate below 10% [17]. These data suggest that the influence of PPI use may be most prominent when considered in conjunction with other known risk factors for poor clopidogrel response (e.g., age, diabetes, renal failure, etc.). This is further evidenced by a case-control multivariable analysis that identified PPI use, together with other clinical and genetic variables, as a significant risk factor for early stent thrombosis [99].

6.3 Drug interaction and *CYP2C19* pharmacogenetics

Given the importance of *CYP2C19* loss-of-function alleles in clopidogrel metabolite levels, platelet aggregation and clinical outcomes in ACS/PCI patients, assessing the clopidogrel and PPI interaction in conjunction with *CYP2C19* metabolizer status is warranted. Although it is conceivable that reduced *CYP2C19* function and PPI use have an additive effect on diminished clopidogrel response, a recent registry study using a propensity-matched analysis reported that PPI use was not associated with increased cardiovascular events among *CYP2C19* loss-of-function allele carriers [103]. Similarly, a subgroup analysis of the TRITON-TIMI 38 trial found that PPI use was not associated with an increased risk of cardiovascular events in *CYP2C19* loss-of-function allele carriers compared to EMs (i.e., **1/*1*) [86]. Unfortunately pharmacodynamic platelet aggregation data were not available in either study. One recent pharmacodynamic study on clopidogrel and esomeprazole/rabeprazole did include *CYP2C19* genotyping but found that neither PPI use nor *CYP2C19* loss-of-function allele status influenced high on-treatment platelet reactivity [104]; however, this may have been confounded by the mixed indications that were included in the study (cardiac, neurologic and peripheral arterial).

In contrast, a small study of healthy subjects reported that PPI coadministration resulted in attenuated platelet inhibition, which differed between *CYP2C19* genotype groups [105]. In this study, decreased platelet inhibition to 'low-responder' status (< 30% inhibition) due to PPI use was more likely to occur among *CYP2C19**2 and/or *3 carriers than EMs (i.e., **1/*1*), suggesting that *CYP2C19* loss-of-function allele carriers may be more sensitive to the PPI drug interaction. In a larger study of coronary artery disease patients, platelet inhibition was further reduced by concomitant administration of a PPI and/or a calcium-channel blocker among *CYP2C19**2 carriers compared to non-carriers and the risk of an adverse cardiovascular event increased in the presence of more than one of these three independent risk factors [106]. Taken together, these data suggest that further studies are warranted to investigate the clopidogrel and PPI drug interaction in the context of *CYP2C19* genotype status, as an additive effect of these risk factors cannot currently be ruled out. Although *CYP2C19* poor metabolizers (i.e., **2/*2*) may biologically not be effected by further

CYP2C19 inhibition due to complete genetic loss-of-function [107], heterozygotes may still be sensitive to the PPI interaction.

7. Expert opinion

The increased risk of GI bleeding associated with DAPT prompted recommendations for concomitant PPI use for patients with additional risk factors (advanced age, concomitant use of anticoagulants or NSAIDs, etc.) who require anti-platelet therapy. However, the pharmacokinetic and pharmacodynamic evidence for a negative clopidogrel and PPI drug interaction prompted the 2009 US FDA warning and ultimately lead to the 2010 ACCF/ACG/AHA Expert Consensus Document on the Concomitant Use of PPIs and Thienopyridines [3]. As stated in the consensus document, clinical decisions regarding concomitant use of PPIs and thienopyridines must balance overall risks and benefits, considering both cardiovascular and GI complications. This leaves the therapeutic strategy ultimately up to the prescribing physician.

Concomitant use of DAPT and selected PPIs (primarily omeprazole) reduces clopidogrel active metabolite levels and *ex vivo*-measured platelet inhibition, which can be attributed to competitive inhibition of CYP2C19. However, the available data on clinical outcomes has been inconsistent, with positive studies being largely non-randomized and observational. Although prospective randomized clinical trials could clarify the relevance of this drug interaction on cardiovascular outcomes, it is unlikely that such studies would now be launched given the possibility of an extended harmful exposure. As such, assessment of the clinical relevance of the clopidogrel and PPI interaction must be made with the available cohort studies, *post hoc* analyses of randomized trials and healthy subject studies. Unfortunately these study designs each come with inherent limitations, including potential for confounding, adequate power to specifically interrogate the drug interaction, and generalizability, respectively.

The available evidence for the relevance of the DAPT and PPI interaction indicates that a clinically important interaction cannot be definitively ruled out, particularly with omeprazole. Additionally, there is emerging evidence for an increased sensitivity for the interaction among specific patient subgroups, including those with higher baseline cardiovascular risk (i.e., an annual rate of MACE > 10%) [17] and/or those who carry a *CYP2C19* loss-of-function allele [106]. Although further studies are needed to confirm the role these cofactors potentially play in the DAPT and PPI interaction, the significant variability in platelet aggregation observed across DAPT-treated coronary patients suggests a multifactorial origin likely influenced by a number of factors, including drug interactions, baseline clinical risk and genetic susceptibility.

As such, if assessment of the cardiovascular and GI risks and benefits prompts consideration of individualized antiplatelet and PPI therapy, alternative options include third-generation thienopyridines and non-thienopyridines (i.e., prasugrel and ticagrelor) as well as PPIs with weaker evidence for interference with clopidogrel metabolism (e.g., pantoprazole, rabeprazole) (Figure 4). To date, the pharmacologic effect of PPI coadministration on platelet aggregation appears limited for both prasugrel and ticagrelor, with little evidence of

a clinically meaningful interaction [39,82,108]; however, any consideration of an alternative therapeutic strategy must take into account the additional practice guidelines and established contraindications for prasugrel and ticagrelor. Although histamine H₂ receptor antagonists (H₂RAs) also decrease GI bleeding in patients using thienopyridines, available data suggest that PPIs are superior to H₂RAs. Additionally, one of the common H₂RAs, cimetidine, is a potent CYP2C19 inhibitor. Consequently, their use as a replacement to PPIs should likely be avoided, instead opting for a PPI with lower potential for clopidogrel drug interaction.

Balancing the cardiovascular and GI risks and benefits for such multifactorial outcomes is challenging. Consequently, further studies are warranted to better determine the utility of alternative antiplatelet and PPI management strategies to reduce thrombotic risk while at the same time providing adequate gastroprotection when clearly needed.

Acknowledgments

A Owusu Obeng would like to thank JA Johnson, PharmD, K Weitzel, PharmD and I Hamadeh, PharmD, all from the UF Health Personalized Medicine Program, for their useful discussions and comments.

Bibliography

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Yusuf S, Zhao F, Mehta SR, et al. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med*. 2001; 345(7):494–502. [PubMed: 11519503]
2. Bhatt DL, Scheiman J, Abraham NS, et al. ACCF/ACG/AHA 2008 expert consensus document on reducing the gastrointestinal risks of antiplatelet therapy and NSAID use: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents. *Circulation*. 2008; 118(18):1894–909. [PubMed: 18836135]
- 3••. Abraham NS, Hlatky MA, Antman EM, et al. ACCF/ACG/AHA 2010 expert consensus document on the concomitant use of proton pump inhibitors and thienopyridines: a focused update of the ACCF/ACG/AHA 2008 expert consensus document on reducing the gastrointestinal risks of antiplatelet therapy and NSAID use. A Report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents. *J Am Coll Cardiol*. 2010; 56(24):2051–66. The most recent ACCF/ACG/ AHA guidelines on concomitant use of PPIs and thienopyridines. [PubMed: 21126648]
4. Gralnek IM, Dulai GS, Fennerty MB, Spiegel BM. Esomeprazole versus other proton pump inhibitors in erosive esophagitis: a meta-analysis of randomized clinical trials. *Clin Gastroenterol Hepatol*. 2006; 4(12):1452–8. [PubMed: 17162239]
5. Edwards SJ, Lind T, Lundell L. Systematic review: proton pump inhibitors (PPIs) for the healing of reflux oesophagitis - a comparison of esomeprazole with other PPIs. *Aliment Pharmacol Ther*. 2006; 24(5):743–50. [PubMed: 16918878]
6. Kazui M, Nishiya Y, Ishizuka T, et al. Identification of the human cytochrome P450 enzymes involved in the two oxidative steps in the bioactivation of clopidogrel to its pharmacologically active metabolite. *Drug Metab Dispos*. 2010; 38(1):92–9. [PubMed: 19812348]
7. Sangkuhl K, Klein TE, Altman RB. Clopidogrel pathway. *Pharmacogenet Genomics*. 2010; 20(7): 463–5. [PubMed: 20440227]
8. Shuldiner AR, O'Connell JR, Bliden KP, et al. Association of cytochrome P450 2C19 genotype with the antiplatelet effect and clinical efficacy of clopidogrel therapy. *JAMA*. 2009; 302(8):849–57. [PubMed: 19706858]

9. Buonamici P, Marcucci R, Migliorini A, et al. Impact of platelet reactivity after clopidogrel administration on drug-eluting stent thrombosis. *J Am Coll Cardiol.* 2007; 49(24):2312–17. [PubMed: 17572245]
10. Brandt JT, Close SL, Iturria SJ II, et al. Common polymorphisms of CYP2C19 and CYP2C9 affect the pharmacokinetic and pharmacodynamic response to clopidogrel but not prasugrel. *J Thromb Haemost.* 2007; 5(12):2429–36. [PubMed: 17900275]
11. Hulot JS, Bura A, Villard E, et al. Cytochrome P450 2C19 loss-of-function polymorphism is a major determinant of clopidogrel responsiveness in healthy subjects. *Blood.* 2006; 108(7):2244–7. The first study to identify CYP2C19 variants as determinants of clopidogrel response. [PubMed: 16772608]
12. Collet JP, Hulot JS, Anzaha G, et al. High doses of clopidogrel to overcome genetic resistance: the randomized crossover CLOVIS-2 (Clopidogrel and Response Variability Investigation Study 2). *JACC Cardiovasc Interv.* 2011; 4(4):392–402. [PubMed: 21511218]
13. Giusti B, Gori AM, Marcucci R, et al. Cytochrome P450 2C19 loss-of-function polymorphism, but not CYP3A4 IVS10 + 12G/A and P2Y₁₂ T744C polymorphisms, is associated with response variability to dual antiplatelet treatment in high-risk vascular patients. *Pharmacogenet Genomics.* 2007; 17(12):1057–64. [PubMed: 18004210]
14. Mega JL, Close SL, Wiviott SD, et al. Cytochrome p-450 polymorphisms and response to clopidogrel. *N Engl J Med.* 2009; 360(4):354–62. [PubMed: 19106084]
15. Simon T, Verstuyft C, Mary-Krause M, et al. Genetic determinants of response to clopidogrel and cardiovascular events. *N Engl J Med.* 2009; 360(4):363–75. [PubMed: 19106083]
16. Collet JP, Hulot JS, Pena A, et al. Cytochrome P450 2C19 polymorphism in young patients treated with clopidogrel after myocardial infarction: a cohort study. *Lancet.* 2009; 373(9660):309–17. [PubMed: 19108880]
17. Hulot JS, Collet JP, Silvain J, et al. Cardiovascular risk in clopidogrel-treated patients according to cytochrome P450 2C19*2 loss-of-function allele or proton pump inhibitor coadministration: a systematic meta-analysis. *J Am Coll Cardiol.* 2010; 56(2):134–43. One of the first meta-analyses of CYP2C19 variants plus PPI use and cardiovascular risk in clopidogrel-treated patients. [PubMed: 20620727]
18. Mega JL, Close SL, Wiviott SD, et al. Genetic variants in ABCB1 and CYP2C19 and cardiovascular outcomes after treatment with clopidogrel and prasugrel in the TRITON-TIMI 38 trial: a pharmacogenetic analysis. *Lancet.* 2010; 376(9749):1312–19. [PubMed: 20801494]
19. Mega JL, Simon T, Collet JP, et al. Reduced-function CYP2C19 genotype and risk of adverse clinical outcomes among patients treated with clopidogrel predominantly for PCI: a meta-analysis. *JAMA.* 2010; 304(16):1821–30. [PubMed: 20978260]
20. Fontana P, Hulot JS, De Moerloose P, Gaussem P. Influence of CYP2C19 and CYP3A4 gene polymorphisms on clopidogrel responsiveness in healthy subjects. *J Thromb Haemost.* 2007; 5(10):2153–5. [PubMed: 17697139]
21. Simon T, Verstuyft C, Mary-Krause M, et al. Genetic determinants of response to clopidogrel and cardiovascular events. *N Engl J Med.* 2009; 360(4):363–75. [PubMed: 19106083]
22. Delaney JT, Ramirez AH, Bowton E, et al. Predicting clopidogrel response using DNA samples linked to an electronic health record. *Clin Pharmacol Ther.* 2012; 91(2):257–63. [PubMed: 22190063]
23. Sofi F, Giusti B, Marcucci R, et al. Cytochrome P450 2C19(*) 2 polymorphism and cardiovascular recurrences in patients taking clopidogrel: a meta-analysis. *Pharmacogenomics J.* 2011; 11(3):199–206. [PubMed: 20351750]
24. Holmes MV, Perel P, Shah T, et al. CYP2C19 genotype, clopidogrel metabolism, platelet function, and cardiovascular events: a systematic review and meta-analysis. *JAMA.* 2011; 306(24):2704–14. [PubMed: 22203539]
25. Johnson JA, Roden DM, Lesko LJ, et al. Clopidogrel: a case for indication-specific pharmacogenetics. *Clin Pharmacol Ther.* 2012; 91(5):774–6. [PubMed: 22513313]
26. Rehmel JL, Eckstein JA, Farid NA, et al. Interactions of two major metabolites of prasugrel, a thienopyridine antiplatelet agent, with the cytochromes P450. *Drug Metab Dispos.* 2006; 34(4):600–7. [PubMed: 16415119]

27. Farid NA, Kurihara A, Wrighton SA. Metabolism and disposition of the thienopyridine antiplatelet drugs ticlopidine, clopidogrel, and prasugrel in humans. *J Clin Pharmacol.* 2010; 50(2):126–42. [PubMed: 19948947]
28. Brandt JT, Payne CD, Wiviott SD, et al. A comparison of prasugrel and clopidogrel loading doses on platelet function: magnitude of platelet inhibition is related to active metabolite formation. *Am Heart J.* 2007; 153(1):66 e9–16. [PubMed: 17174640]
29. Payne CD, Li YG, Small DS II, et al. Increased active metabolite formation explains the greater platelet inhibition with prasugrel compared to high-dose clopidogrel. *J Cardiovasc Pharmacol.* 2007; 50(5):555–62. [PubMed: 18030066]
30. Wallentin L, Varenhorst C, James S, et al. Prasugrel achieves greater and faster P2Y₁₂receptor-mediated platelet inhibition than clopidogrel due to more efficient generation of its active metabolite in aspirin-treated patients with coronary artery disease. *Eur Heart J.* 2008; 29(1):21–30. [PubMed: 18055486]
31. Mega JL, Close SL, Wiviott SD, et al. Cytochrome P450 genetic polymorphisms and the response to prasugrel: relationship to pharmacokinetic, pharmacodynamic, and clinical outcomes. *Circulation.* 2009; 119(19):2553–60. [PubMed: 19414633]
32. Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med.* 2007; 357(20):2001–15. [PubMed: 17982182]
33. Wrishko RE, Ernest CS II, Small DS, et al. Population pharmacokinetic analyses to evaluate the influence of intrinsic and extrinsic factors on exposure of prasugrel active metabolite in TRITON-TIMI 38. *J Clin Pharmacol.* 2009; 49(8):984–98. [PubMed: 19546250]
34. Bonello L, Pansieri M, Mancini J, et al. High on-treatment platelet reactivity after prasugrel loading dose and cardiovascular events after percutaneous coronary intervention in acute coronary syndromes. *J Am Coll Cardiol.* 2011; 58(5):467–73. [PubMed: 21777742]
35. Price MJ, Walder JS, Baker BA, et al. Recovery of platelet function after discontinuation of prasugrel or clopidogrel maintenance dosing in aspirin-treated patients with stable coronary disease: the recovery trial. *J Am Coll Cardiol.* 2012; 59(25):2338–43. [PubMed: 22698488]
36. Htun WW, Steinhubl SR. Ticagrelor: the first novel reversible P2Y₁₂ inhibitor. *Expert Opin Pharmacother.* 2013; 14(2):237–45. [PubMed: 23268703]
37. Iyu D, Glenn JR, White AE, et al. Mode of action of P2Y₁₂ antagonists as inhibitors of platelet function. *Thromb Haemost.* 2011; 105(1):96–106. [PubMed: 20941457]
38. Gurbel PA, Bliden KP, Butler K, et al. Randomized double-blind assessment of the ONSET and OFFSET of the antiplatelet effects of ticagrelor versus clopidogrel in patients with stable coronary artery disease: the ONSET/ OFFSET study. *Circulation.* 2009; 120(25):2577–85. [PubMed: 19923168]
39. Storey RF, Angiolillo DJ, Patil SB, et al. Inhibitory effects of ticagrelor compared with clopidogrel on platelet function in patients with acute coronary syndromes: the PLATO (PLATElet inhibition and patient Outcomes) PLATELET substudy. *J Am Coll Cardiol.* 2010; 56(18):1456–62. [PubMed: 20832963]
40. Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med.* 2009; 361(11):1045–57. [PubMed: 19717846]
41. Husted S, James S, Becker RC, et al. Ticagrelor versus clopidogrel in elderly patients with acute coronary syndromes: a substudy from the prospective randomized PLATElet inhibition and patient Outcomes (PLATO) trial. *Circulation Cardiovasc Qual Outcomes.* 2012; 5(5):680–8.
42. James SK, Storey RF, Khurmi NS, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes and a history of stroke or transient ischemic attack. *Circulation.* 2012; 125(23):2914–21. [PubMed: 22572911]
43. Robinson M, Horn J. Clinical pharmacology of proton pump inhibitors: what the practising physician needs to know. *Drugs.* 2003; 63(24):2739–54. [PubMed: 14664653]
44. Kromer W, Kruger U, Huber R, et al. Differences in pH-dependent activation rates of substituted benzimidazoles and biological in vitro correlates. *Pharmacology.* 1998; 56(2):57–70. [PubMed: 9494064]
45. Sachs G. Proton pump inhibitors and acid-related diseases. *Pharmacotherapy.* 1997; 17(1):22–37. [PubMed: 9017763]

46. Besancon M, Simon A, Sachs G, Shin JM. Sites of reaction of the gastric H,K-ATPase with extracytoplasmic thiol reagents. *J Biol Chem.* 1997; 272(36):22438–46. [PubMed: 9278394]
47. Vanderhoff BT, Tahboub RM. Proton pump inhibitors: an update. *Am Fam Physician.* 2002; 66(2): 273–80. [PubMed: 12152963]
48. Sheen E, Triadafilopoulos G. Adverse effects of long-term proton pump inhibitor therapy. *Dig Dis Sci.* 2011; 56(4):931–50. [PubMed: 21365243]
49. Ishizaki T, Horai Y. Review article: cytochrome P450 and the metabolism of proton pump inhibitors—emphasis on rabeprazole. *Aliment Pharmacol Ther.* 1999; 13(Suppl 3):27–36. [PubMed: 10491726]
50. Zendejdel N, Biramijamal F, Hossein-Nezhad A, et al. Role of cytochrome P450 2C19 genetic polymorphisms in the therapeutic efficacy of omeprazole in Iranian patients with erosive reflux esophagitis. *Arch Iran Med.* 2010; 13(5):406–12. [PubMed: 20804307]
51. Zhang L, Mei Q, Li QS, et al. The effect of cytochrome P2C19 and interleukin-1 polymorphisms on H. pylori eradication rate of 1-week triple therapy with omeprazole or rabeprazole, amoxycillin and clarithromycin in Chinese people. *J Clin Pharm Ther.* 2010; 35(6):713–22. [PubMed: 21054464]
52. Miehlke S, Lobe S, Madisch A, et al. Intragastric acidity during administration of generic omeprazole or esomeprazole - a randomised, two-way crossover study including CYP2C19 genotyping. *Aliment Pharmacol Ther.* 2011; 33(4):471–6. [PubMed: 21175704]
53. Furuta T, Ohashi K, Kamata T, et al. Effect of genetic differences in omeprazole metabolism on cure rates for *Helicobacter pylori* infection and peptic ulcer. *Ann Intern Med.* 1998; 129(12):1027–30. [PubMed: 9867757]
54. Hunfeld NG, Mathot RA, Touw DJ, et al. Effect of CYP2C19*2 and *17 mutations on pharmacodynamics and kinetics of proton pump inhibitors in Caucasians. *Br J Clin Pharmacol.* 2008; 65(5):752–60. [PubMed: 18241283]
55. Shirai N, Furuta T, Moriyama Y, et al. Effects of CYP2C19 genotypic differences in the metabolism of omeprazole and rabeprazole on intragastric pH. *Aliment Pharmacol Ther.* 2001; 15(12):1929–37. [PubMed: 11736724]
56. Shimatani T, Inoue M, Kuroiwa T, et al. Effect of omeprazole 10 mg on intragastric pH in three different CYP2C19 genotypes, compared with omeprazole 20 mg and famotidine 20 mg, a new H₂-receptor antagonist. *Aliment Pharmacol Ther.* 2003; 18(11–12):1149–57. [PubMed: 14653835]
57. Sugimoto M, Furuta T, Shirai N, et al. Initial 48-hour acid inhibition by intravenous infusion of omeprazole, famotidine, or both in relation to cytochrome P450 2C19 genotype status. *Clin Pharmacol Ther.* 2006; 80(5):539–48. [PubMed: 17112810]
58. Gawronska-Szklarz B, Wrzesniewska J, Starzynska T, et al. Effect of CYP2C19 and MDR1 polymorphisms on cure rate in patients with acid-related disorders with *Helicobacter pylori* infection. *Eur J Clin Pharmacol.* 2005; 61(5–6):375–9. [PubMed: 15976989]
59. Furuta T, Shirai N, Xiao F, et al. Polymorphism of interleukin-1beta affects the eradication rates of *Helicobacter pylori* by triple therapy. *Clin Gastroenterol Hepatol.* 2004; 2(1):22–30. [PubMed: 15017629]
60. Andersson T, Hassan-Alin M, Hasselgren G, et al. Pharmacokinetic studies with esomeprazole, the (S)-isomer of omeprazole. *Clin Pharmacokinet.* 2001; 40(6):411–26. [PubMed: 11475467]
61. Gawronska-Szklarz B, Adamiak-Giera U, Wyska E, et al. CYP2C19 polymorphism affects single-dose pharmacokinetics of oral pantoprazole in healthy volunteers. *Eur J Clin Pharmacol.* 2012; 68(9):1267–74. [PubMed: 22418828]
62. Hagymasi K, Mullner K, Herszenyi L, Tulassay Z. Update on the pharmacogenomics of proton pump inhibitors. *Pharmacogenomics.* 2011; 12(6):873–88. [PubMed: 21692617]
63. Furuta T, Shirai N, Xiao F, et al. Effect of high-dose lansoprazole on intragastric pH in subjects who are homozygous extensive metabolizers of cytochrome P4502C19. *Clin Pharmacol Ther.* 2001; 70(5):484–92. [PubMed: 11719736]
64. Lee YC, Lin JT, Wang HP, et al. Influence of cytochrome P450 2C19 genetic polymorphism and dosage of rabeprazole on accuracy of proton-pump inhibitor testing in Chinese patients with gastroesophageal reflux disease. *J Gastroenterol Hepatol.* 2007; 22(8):1286–92. [PubMed: 17559380]

65. Lee JH, Jung HY, Choi KD, et al. The influence of CYP2C19 polymorphism on eradication of helicobacter pylori: a prospective randomized study of lansoprazole and rabeprazole. *Gut Liver*. 2010; 4(2):201–6. [PubMed: 20559522]
66. Wang Y, Zhang H, Meng L, et al. Influence of CYP2C19 on the relationship between pharmacokinetics and intragastric pH of omeprazole administered by successive intravenous infusions in Chinese healthy volunteers. *Eur J Clin Pharmacol*. 2010; 66(6):563–9. [PubMed: 20414645]
67. Ko JW, Sukhova N, Thacker D, et al. Evaluation of omeprazole and lansoprazole as inhibitors of cytochrome P450 isoforms. *Drug Metab Dispos*. 1997; 25(7):853–62. [PubMed: 9224780]
68. Zhou SF. Polymorphism of human cytochrome P450 2D6 and its clinical significance: part I. *Clin Pharmacokinet*. 2009; 48(11):689–723. [PubMed: 19817501]
69. Daly AK. Pharmacogenetics of the cytochromes P450. *Curr Top Med Chem*. 2004; 4(16):1733–44. [PubMed: 15579105]
70. Desta Z, Zhao X, Shin JG, Flockhart DA. Clinical significance of the cytochrome P450 2C19 genetic polymorphism. *Clin Pharmacokinet*. 2002; 41(12):913–58. [PubMed: 12229994]
71. Scott SA, Sangkuhl K, Shuldiner AR, et al. PharmGKB summary: very important pharmacogene information for cytochrome P450, family 2, subfamily C, polypeptide 19. *Pharmacogenet Genomics*. 2012; 22(2):159–65. [PubMed: 22027650]
72. Sim SC, Ingelman-Sundberg M. The Human Cytochrome P450 (CYP) Allele Nomenclature website: a peer-reviewed database of CYP variants and their associated effects. *Hum Genomics*. 2010; 4(4):278–81. [PubMed: 20511141]
73. Martis S, Peter I, Hulot JS, et al. Multi-ethnic distribution of clinically relevant CYP2C genotypes and haplotypes. *Pharmacogenomics J*. 2013; 13(4):369–77. [PubMed: 22491019]
74. Scott SA, Sangkuhl K, Gardner EE, et al. Clinical pharmacogenetics implementation consortium guidelines for cytochrome P450–2C19 (CYP2C19) genotype and clopidogrel therapy. *Clin Pharmacol Ther*. 2011; 90(2):328–32. [PubMed: 21716271]
75. Sim SC, Risinger C, Dahl ML, et al. A common novel CYP2C19 gene variant causes ultrarapid drug metabolism relevant for the drug response to proton pump inhibitors and antidepressants. *Clin Pharmacol Ther*. 2006; 79(1):103–13. [PubMed: 16413245]
76. Li-Wan-Po A, Girard T, Farndon P, et al. Pharmacogenetics of CYP2C19: functional and clinical implications of a new variant CYP2C19*17. *Br J Clin Pharmacol*. 69(3):222–30. [PubMed: 20233192]
77. Lewis J, Stephens S, Horenstein R, et al. The CYP2C19*17 variant is not independently associated with clopidogrel response. *J Thromb Haemost*. 2013; 11(3):1640–6. [PubMed: 23809542]
78. Tatro, DS. Drug interaction facts 2013: the authority on drug interactions. Lippincott Williams & Wilkins; Philadelphia: 2012.
79. Herbert JM, Dol F, Bernat A, et al. The antiaggregating and antithrombotic activity of clopidogrel is potentiated by aspirin in several experimental models in the rabbit. *Thromb Haemost*. 1998; 80(3):512–18. [PubMed: 9759636]
80. Gilard M, Arnaud B, Le Gal G, et al. Influence of omeprazole on the antiplatelet action of clopidogrel associated to aspirin. *J Thromb Haemost*. 2006; 4(11):2508–9. [PubMed: 16898956]
81. Gilard M, Arnaud B, Cornily JC, et al. Influence of omeprazole on the antiplatelet action of clopidogrel associated with aspirin: the randomized, double-blind OCLA (Omeprazole CLopidogrel Aspirin) study. *J Am Coll Cardiol*. 2008; 51(3):256–60. [PubMed: 18206732]
82. Small DS, Farid NA, Payne CD, et al. Effects of the proton pump inhibitor lansoprazole on the pharmacokinetics and pharmacodynamics of prasugrel and clopidogrel. *J Clin Pharmacol*. 2008; 48(4):475–84. [PubMed: 18303127]
83. Siller-Matula JM, Spiel AO, Lang IM, et al. Effects of pantoprazole and esomeprazole on platelet inhibition by clopidogrel. *Am Heart J*. 2009; 157(1):148, e1–5. [PubMed: 19081411]
84. Ferreiro JL, Ueno M, Capodanno D, et al. Pharmacodynamic effects of concomitant versus staggered clopidogrel and omeprazole intake: results of a prospective randomized crossover study. *Circ Cardiovasc Interv*. 2010; 3(5):436–41. Important study showing the negative pharmacodynamic effects of omeprazole and clopidogrel co-administration, irrespective of timing. [PubMed: 20858862]

85. Juurlink DN, Gomes T, Ko DT, et al. A population-based study of the drug interaction between proton pump inhibitors and clopidogrel. *CMAJ*. 2009; 180(7):713–18. [PubMed: 19176635]
86. O'Donoghue ML, Braunwald E, Antman EM, et al. Pharmacodynamic effect and clinical efficacy of clopidogrel and prasugrel with or without a proton-pump inhibitor: an analysis of two randomised trials. *Lancet*. 2009; 374(9694):989–97. [PubMed: 19726078]
87. Sibbing D, Morath T, Stegherr J, et al. Impact of proton pump inhibitors on the antiplatelet effects of clopidogrel. *Thromb Haemost*. 2009; 101(4):714–19. [PubMed: 19350116]
88. Hulot JS, Wuerzner G, Bachelot-Loza C, et al. Effect of an increased clopidogrel maintenance dose or lansoprazole co-administration on the antiplatelet response to clopidogrel in CYP2C19-genotyped healthy subjects. *J Thromb Haemost*. 2010; 8(3):610–13. [PubMed: 20040040]
89. Yun KH, Rhee SJ, Park HY, et al. Effects of omeprazole on the antiplatelet activity of clopidogrel. *Int Heart J*. 2010; 51(1):13–16. [PubMed: 20145345]
90. Angiolillo DJ, Gibson CM, Cheng S, et al. Differential effects of omeprazole and pantoprazole on the pharmacodynamics and pharmacokinetics of clopidogrel in healthy subjects: randomized, placebo-controlled, crossover comparison studies. *Clin Pharmacol Ther*. 2011; 89(1):65–74. [PubMed: 20844485]
91. Frelinger AL III, Lee RD, Mulford DJ, et al. A randomized, 2-period, crossover design study to assess the effects of dexlansoprazole, lansoprazole, esomeprazole, and omeprazole on the steady-state pharmacokinetics and pharmacodynamics of clopidogrel in healthy volunteers. *J Am Coll Cardiol*. 2012; 59(14):1304–11. [PubMed: 22464259]
92. Shin JM, Sachs G. Pharmacology of proton pump inhibitors. *Curr Gastroenterol Rep*. 2008; 10(6):528–34. [PubMed: 19006606]
93. Lins R, Broekhuysen J, Necciari J, Deroubaix X. Pharmacokinetic profile of 14C-labeled clopidogrel. *Semin Thromb Hemost*. 1999; 25(Suppl 2):29–33. [PubMed: 10440420]
94. Shah BS, Parmar SA, Mahajan S, Mehta AA. An insight into the interaction between clopidogrel and proton pump inhibitors. *Curr Drug Metab*. 2012; 13(2):225–35. [PubMed: 22300021]
95. Ho PM, Peterson ED, Wang L, et al. Incidence of death and acute myocardial infarction associated with stopping clopidogrel after acute coronary syndrome. *JAMA*. 2008; 299(5):532–9. [PubMed: 18252883]
96. Pezalla E, Day D, Pulliath I. Initial assessment of clinical impact of a drug interaction between clopidogrel and proton pump inhibitors. *J Am Coll Cardiol*. 2008; 52(12):1038–9. author reply 39. [PubMed: 18786491]
97. Stockl KM, Le L, Zakharyan A, et al. Risk of rehospitalization for patients using clopidogrel with a proton pump inhibitor. *Arch Intern Med*. 2010; 170(8):704–10. [PubMed: 20421557]
98. Kreutz RP, Stanek EJ, Aubert R, et al. Impact of proton pump inhibitors on the effectiveness of clopidogrel after coronary stent placement: the clopidogrel Medco outcomes study. *Pharmacotherapy*. 2010; 30(8):787–96. [PubMed: 20653354]
99. Cayla G, Hulot JS, O'Connor SA, et al. Clinical, angiographic, and genetic factors associated with early coronary stent thrombosis. *JAMA*. 2011; 306(16):1765–74. Case-control study of stent thrombosis showing independent effects of both CYP2C19 variants and PPI use. [PubMed: 22028352]
100. Ray WA, Murray KT, Griffin MR, et al. Outcomes with concurrent use of clopidogrel and proton-pump inhibitors: a cohort study. *Ann Intern Med*. 2010; 152(6):337–45. [PubMed: 20231564]
101. Harmsze AM, van Werkum JW, Taubert D, et al. Esomeprazole but not pantoprazole is associated with lower plasma concentrations of clopidogrel's active metabolite. *Ann Pharmacother*. 2011; 45(4):542–3. [PubMed: 21487078]
102. Bhatt DL, Cryer BL, Contant CF, et al. Clopidogrel with or without omeprazole in coronary artery disease. *N Engl J Med*. 2010; 363(20):1909–17. [PubMed: 20925534]
103. Simon T, Steg PG, Gilard M, et al. Clinical events as a function of proton pump inhibitor use, clopidogrel use, and cytochrome P450 2C19 genotype in a large nationwide cohort of acute myocardial infarction: results from the French Registry of Acute ST-Elevation and Non-ST-Elevation Myocardial Infarction (FAST-MI) registry. *Circulation*. 2011; 123(5):474–82. [PubMed: 21262992]

104. El-Halabi MM, Zgheib N, Mansour NM, et al. CYP2C19 genetic polymorphism, rabeprazole and esomeprazole have no effect on the antiplatelet action of clopidogrel. *J Cardiovasc Pharmacol*. 2013; 62(1):41–9. [PubMed: 23474843]
105. Furuta T, Iwaki T, Umemura K. Influences of different proton pump inhibitors on the anti-platelet function of clopidogrel in relation to CYP2C19 genotypes. *Br J Clin Pharmacol*. 2010; 70(3): 383–92. [PubMed: 20716239]
106. Harmsze AM, van Werkum JW, Souverein PC, et al. Combined influence of proton-pump inhibitors, calcium-channel blockers and CYP2C19*2 on on-treatment platelet reactivity and on the occurrence of atherothrombotic events after percutaneous coronary intervention. *J Thromb Haemost*. 2011; 9(10):1892–901. [PubMed: 21854540]
107. O'Donoghue ML. CYP2C19 genotype and proton pump inhibitors in clopidogrel-treated patients: does it take two to tango? *Circulation*. 2011; 123(5):468–70. [PubMed: 21262991]
108. Aradi D, Kuliczowski W, Atar D, Serebruany VL. Inter-patient variability and impact of proton pump inhibitors on platelet reactivity after prasugrel. *Thromb Haemost*. 2012; 107(2):338–45. [PubMed: 22186910]
109. Kwok CS, Loke YK. Meta-analysis: the effects of proton pump inhibitors on cardiovascular events and mortality in patients receiving clopidogrel. *Aliment Pharmacol Ther*. 2010; 31(8): 810–23. [PubMed: 20102352]
110. Kwok CS, Nijjar RS, Loke YK. Effects of proton pump inhibitors on adverse gastrointestinal events in patients receiving clopidogrel: systematic review and meta-analysis. *Drug Saf*. 2011; 34(1):47–57. [PubMed: 21047145]
111. Siller-Matula JM, Jilma B, Schror K, et al. Effect of proton pump inhibitors on clinical outcome in patients treated with clopidogrel: a systematic review and meta-analysis. *J Thromb Haemost*. 2010; 8(12):2624–41. Large meta-analysis of PPI effect on cardiovascular outcomes. [PubMed: 20831618]
112. Chen M, Wei JF, Xu YN, et al. A meta-analysis of impact of proton pump inhibitors on antiplatelet effect of clopidogrel. *Cardiovasc Ther*. 2012; 30(5):e227–33. [PubMed: 21884023]
113. Gerson LB, McMahon D, Olkin I, et al. Lack of significant interactions between clopidogrel and proton pump inhibitor therapy: meta-analysis of existing literature. *Dig Dis Sci*. 2012; 57(5): 1304–13. [PubMed: 22198703]
114. Huang B, Huang Y, Li Y, et al. Adverse cardiovascular effects of concomitant use of proton pump inhibitors and clopidogrel in patients with coronary artery disease: a systematic review and meta-analysis. *Arch Med Res*. 2012; 43(3):212–24. [PubMed: 22564422]
115. Kwok CS, Jeevanantham V, Dawn B, Loke YK. No consistent evidence of differential cardiovascular risk amongst proton-pump inhibitors when used with clopidogrel: meta-analysis. *Int J Cardiol*. 2013; 167(3):965–74. [PubMed: 22464478]

Article highlights

- DAPT with clopidogrel and aspirin significantly reduces the risk of stroke, MI, and/or death in patients with an ACS and/or undergoing PCI; however, the risk of major GI hemorrhage is also increased.
- PPIs are often concomitantly administered to attenuate the GI bleeding risk, yet their inhibition of CYP2C19, an enzyme crucial to clopidogrel bioactivation, is at the center of the proposed clopidogrel and PPI drug interaction.
- The pharmacologic drug interaction reduces clopidogrel metabolite levels and results in higher on-treatment *ex vivo* platelet reactivity, which is most prominent for the PPI omeprazole.
- The relevance of the drug interaction on clinical outcomes has been inconsistent and largely reported from non-randomized observational studies; however, patient subgroups with higher overall cardiovascular risk and/or those who are *CYP2C19* loss-of-function allele carriers may be more sensitive to the interaction.
- As the clinical significance of the clopidogrel/omeprazole interaction cannot be completely excluded by the available data, consideration of alternative antiplatelet agents (e.g., prasugrel, ticagrelor) and/or other PPIs (e.g., pantoprazole, rabeprazole) may be considered for patients with a higher overall cardiovascular risk when concomitant PPI use is warranted.

This box summarizes key points contained in the article.

Figure 1.

Schematic illustration of antiplatelet metabolism for (A) clopidogrel, (B) prasugrel, and (C) ticagrelor. The thickness of the arrows represents the relative contribution of the respective pathway.

Figure 2.

Schematic illustration of proton pump inhibitor (PPI) metabolism for (A) omeprazole/esomeprazole, (B) pantoprazole, (C) lansoprazole, and (D) rabeprazole. The thickness of the arrows represents the relative contribution of the respective pathway.

Figure 3. Simplified illustration of the hypothesized mechanism for drug interaction between clopidogrel and selected proton pump inhibitors (PPIs).

Figure 4.
Flowchart of the antiplatelet and PPI co-administration recommendations.

Table 1

Non-aspirin antiplatelet agent metabolism and potential for interaction with proton pump inhibitors (PPIs).

Antiplatelet agent	Metabolism	Interaction potential [*]
Clopidogrel	Major: CES1 Minor: CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP3A4, CYP3A5	High
Prasugrel	CES2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP3A4	Low
Ticagrelor	CYP3A4, CYP3A5	Low

* See text for further details on interaction potential.

Table 2

Proton pump inhibitor (PPI) metabolism and potential for interaction with clopidogrel.

Proton pump inhibitor (PPI)	Cytochrome P450 metabolism	Interaction potential [*]
Omeprazole	Major: CYP2C19 Minor: CYP3A4	High
Esomeprazole	Major: CYP2C19 Minor: CYP3A4	Moderate
Pantoprazole	Major: CYP2C19 Minor: CYP3A4	Low
Lansoprazole	CYP2C19 CYP3A4	Moderate
Rabeprazole	Major: Non-enzymatic Minor: CYP2C19 Minor: CYP3A4	Low

* See text for further details on interaction potential.

Table 3

Summary of clinical outcome meta-analyses of clopidogrel and proton pump inhibitor (PPI) drug interactions.

Ref.	Study inclusion end date	Sample size	Results	Comments
Kwok and Loke [109]	October 2009	23 studies; 93,278 total patients	MI: RR: 1.43, 95% CI: 1.15 – 1.77, $p = 0.001$ MACE: RR: 1.25, 95% CI: 1.09 – 1.42, $p = 0.001$ Mortality: RR: 1.09, 95% CI: 0.94 – 1.26, $p = 0.27$	Heterogeneity noted Significant CV risk only observed in observational data, not in matched or trial participants
Hulot <i>et al.</i> [17]	October 2009	13 studies; 48,674 total patients	MACE: OR: 1.41, 95% CI: 1.34 – 1.48, $p < 0.001$ Mortality: OR: 1.18, 95% CI: 1.07 – 1.30, $p < 0.001$	Heterogeneity noted Omeprazole most common PPI prescribed, followed by pantoprazole and esomeprazole Stronger effect in high CV risk patients
Kwok <i>et al.</i> [110]	March 2010	9 studies; 71,277 total patients	GI events: RR: 0.38, 95% CI: 0.21 – 0.68, $p = 0.001$	Risk based on upper GI bleeding Reduced risk not seen with clopidogrel monotherapy
Siller-Matula <i>et al.</i> [111]	April 2010	25 studies; 159,138 total patients	MI: RR: 1.31, 95% CI: 1.12 – 1.53, $p < 0.001$ MACE: RR: 1.29, 95% CI: 1.15 – 1.44, $p < 0.001$ ST: RR: 1.88, 95% CI: 0.97 – 3.62, $p = 0.06$ GI bleeding: RR: 0.50, 95% CI: 0.37 – 0.69, $p < 0.001$ Mortality: RR: 1.04, 95% CI: 0.93 – 1.16, $p = 0.53$	Heterogeneity noted
Chen <i>et al.</i> [112]	October 2010	13 studies	Clinical endpoints: RCTs: RR: 1.20, 95% CI: 0.82 – 1.76, $p = 0.34$ Observational studies: RR: 1.40, 95% CI: 1.15 – 1.70, $p < 0.001$	Heterogeneity noted Increased CV risk not observed in RCTs
Gerson <i>et al.</i> [113]	October 2010	26 studies	Primary outcomes: RD: 0.02, 95% CI 0.01 – 0.03 Secondary outcomes: RD: 0.02, 95% CI 0.01 – 0.04	Heterogeneity noted 2 – 3% risk difference only observed in cohort studies, not RCTs
Huang <i>et al.</i> [114]	June 2011	32 studies; 159,998 total patients	MACE: HR: 1.40, 95% CI: 1.19 – 1.64 OR: 1.27, 95% CI: 1.13 – 1.42 Mortality: HR: 1.30, 95% CI: 0.91 – 1.86 OR: 0.92, 95% CI: 0.82 – 1.04 Cardiovascular death: HR: 1.21, 95% CI: 0.60 – 2.43 ST: HR: 1.52, 95% CI: 1.18 – 1.94	Heterogeneity noted Increased risk of MACE not observed in RCTs Did not observe association between increased risk of MACE and individual PPIs except for pantoprazole
Kwok <i>et al.</i> [115]	December 2011	23 studies; 222,311 total patients	Adverse CV events: Omeprazole: OR: 1.24, 95% CI: 1.07 – 1.43 Esomeprazole: OR: 1.32, 95% CI: 1.09 – 1.60 Lansoprazole: OR: 1.39, 95% CI: 1.23 – 1.57 Pantoprazole: OR: 1.41, 95% CI: 1.21 – 1.64 Rabeprazole: OR: 1.38, 95% CI: 0.78 – 2.45 PPIs alone (without clopidogrel): OR: 1.28, 95% CI: 1.14 – 1.44	Heterogeneity noted No difference in CV risk between PPIs Risk for adverse events with PPIs in the absence of clopidogrel

CV: Cardiovascular; GI: Gastrointestinal; HR: Hazard ratio; MACE: Major adverse cardiovascular event; MI: Myocardial infarction; OR: Odds ratio; PPI: Proton pump inhibitor; RCT: Randomized controlled trial; RD: Risk differences; RR: Relative risk; ST: Stent thrombosis.