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Proton Pump Inhibitors in Cardiovascular Disease: Drug Interactions with Antiplatelet Drugs

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Abstract

Aspirin and $P2Y_{12}$ receptor antagonists are widely used across the spectrum of cardiovascular diseases. Upper gastrointestinal complications, including ulcer and bleeding, are relatively common during antiplatelet treatment and, therefore, concomitant proton pump inhibitor (PPI) treatment is often prescribed.

PPIs provide gastroprotection by changing the intragastric milieu, essentially by raising intragastric pH. In recent years, it has been heavily discussed whether PPIs may reduce the cardiovascular protection by aspirin and, even more so, clopidogrel. Pharmacodynamic and pharmacokinetic studies suggested an interaction between PPIs and clopidogrel, and subsequent clinical studies were conducted to evaluate the clinical impact of this interaction. More recently, it was reported that PPIs may also attenuate the antiplatelet effect of aspirin. This may be clinically important, because a fixed combination of aspirin and a PPI (esomeprazole) has recently been approved and because aspirin is the most widely used drug in patients with cardiovascular disease. The antiplatelet effect of the new $P2Y_{12}$ receptor antagonists, ticagrelor and prasugrel, seems less influenced by PPI co-treatment.

Given the large number of patients treated with antithrombotic drugs and PPIs, even a minor reduction of platelet inhibition potentially carries considerable clinical impact. The present book chapter summarizes the evidence regarding the widespread use of platelet inhibitors and PPIs in combination. Moreover, it outlines current evidence supporting or opposing drug interactions between these drugs and discusses clinical implications.

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1 Introduction

In 2009, European and American regulatory authorities issued public warnings discouraging co-prescription of clopidogrel and proton pump inhibitors (PPIs) "unless absolutely necessary" [1, 2]. These recommendations were based on pharmacological studies suggesting that platelet inhibition with clopidogrel was reduced by PPIs and by observations of increased coronary event rates in patients taking both drugs. In 2010, the European Medicines Agency amended its statement to include only omeprazole and esomeprazole [3], and according to current clinical guidelines, PPIs are still recommended in combination with clopidogrel and other antiplatelet drugs in patients at high risk of gastrointestinal complications [4, 5].

Given the vast use of polypharmacy in the treatment of cardiovascular disease, insight into drug interactions is pivotal. When a doctor prescribes two drugs or more at the same time, each drug potentially loses efficacy due to a reduction in bioavailability, chelation of compounds, altered cytochrome P450 (CYP) enzyme activity, altered protein binding, *etc*. [6]. A strong relationship exists between the number of dispensed drugs and the occurrence of drug interactions [7], and drug interactions are a common cause of treatment failure and adverse drug reactions [8].

The number of patients treated with platelet inhibitors and PPIs is high, so even modest drug interactions may have considerable clinical impact. The present book chapter summarizes the evidence regarding the widespread use of platelet inhibitors and PPIs. Moreover, it outlines current evidence supporting or opposing drug interactions between these drugs and discusses clinical implications.

2 Aspirin: Pharmacology and Clinical Use

2.1 Pharmacology

Platelet inhibition by aspirin results from irreversible blockage of the cyclooxygenase (COX)-1 enzyme. COX-1 is responsible for converting arachidonic acid to thromboxane A_2, which is a potent platelet activator and vasoconstrictor. By acetylating a serine moiety in COX-1, aspirin prevents arachidonic acid from accessing the catalytic site of the enzyme thereby lowering the production of thromboxane A_2 [9]. The inhibition of COX-1 is virtually complete even at low doses (30 mg/day). In addition, the inhibition is rapid, dose-independent, and largely irreversible because mature platelets retain only limited capacity to re-synthesize COX-1 [10]. Aspirin also inhibits endothelial COX-dependent synthesis of prostacyclin, which, contrary to TXA_2, acts as a vasodilator and inhibitor of platelet aggregation. However, once aspirin has been cleared from the circulation, nucleated endothelial cells readily produce new unacetylated COX-1. Importantly, this does not occur in platelets due to their lack of a nucleus. Overall, this yields an antithrombotic net result of treatment with low-dose aspirin [6]. Aspirin has a higher affinity for COX-1 than for COX-2 inhibiting COX-1 50–100 times more potently than COX-2 [11]. Sufficient COX-2 inhibition requires considerably larger doses and a shorter dosing interval because COX-2 is expressed by nucleated cells capable of re-synthesizing COX-2 [12]. Accordingly, aspirin must be administered in analgesic or anti-inflammatory doses (500–1000 mg) several times daily to sustainably inhibit the COX-2 system [13].

2.2 Clinical Use

In cardiology, the therapeutic utility of aspirin spans the continuum from primary prevention through stable coronary artery disease to acute coronary syndrome (ACS). A widespread appreciation of aspirin in secondary cardiovascular prevention was founded during the 1980s. The landmark ISIS-2 trial convincingly demonstrated the superiority of aspirin over placebo in patients with suspected acute ST elevation MI [14]. At 15-month follow-up, 1 month of low-dose aspirin (162.5 mg, enteric-coated), either alone or in combination with fibrinolytic streptokinase, conferred a relative risk reduction of non-fatal reinfarction (23 %) and death (42 %). The benefit was sustained at 10 years [15]. During the same period, four clinical trials documented the benefit of aspirin in the setting of non-ST elevation ACS [16–19]. Today, aspirin is a first-line antiplatelet drug for secondary cardiovascular prevention conferring a 25 % reduction in serious vascular events compared to placebo [20].

3 ADP Receptor Antagonists: Pharmacology and Clinical Use

ADP receptor antagonists target the $P2Y_{12}$ receptor on the platelet membrane thereby inhibiting ADP-mediated platelet activation. Four different oral ADP receptor antagonists are approved for clinical use: ticlopidine, clopidogrel, prasugrel, and ticagrelor. Due to its poor safety profile and the need for twice-daily dosing, ticlopidine has been almost completely replaced by clopidogrel, prasugrel, and ticagrelor. Therefore, ticlopidine will not be reviewed herein, while the characteristics of clopidogrel, prasugrel, and ticagrelor are provided in Table 1.

3.1 Pharmacology

Clopidogrel is a second-generation thienopyridine, which became available in its generic form in 2012. Clopidogrel is a prodrug, which is well absorbed from the gut, but remains pharmacologically inert until activated in the liver through the CYP system (Fig. 1). The majority of administered clopidogrel is metabolized by an esterase pathway not resulting in active drug metabolites, and only 15 % reaches the liver for active metabolite transformation [14]. This is mediated by a two-step oxidative process regulated by the CYP system. Ultimately, as little as 2 % ends up irreversibly inhibiting the $P2Y_{12}$ receptor [21]. Among the different CYP variants involved in the hepatic conversion of clopidogrel, CYP2C19 is the major variant responsible for approximately 45 % [21].

Prasugrel is activated in a one-step oxidative process and, unlike clopidogrel, none of the drug is shunted to an inactive pathway (Fig. 1). Compared to clopidogrel, the hepatic conversion of prasugel is less dependent on CYP2C19 [22]. Ticagrelor is an adenosine triphosphate analogue not belonging to the thienopyridine family. Ticagrelor inhibits the $P2Y_{12}$ receptor reversibly and does not require hepatic bioactivation (Table 1 and Fig. 1). Prasugrel and ticagrelor are more potent platelet function inhibitors than clopidogrel and are now being widely used in combination with aspirin in the setting of ACS.

Table 1 Pharmacology and dosing of aspirin and ADP receptor antagonists

Drug	Primary mode of action	Metabolism and platelet inhibition	Platelet inhibition	Dosing
Aspirin	COX-1 inhibition	Prodrug	Irreversible	Once daily
Clopidogrel	$P2Y_{12}$ receptor antagonism	Prodrug	Irreversible	Once daily
Prasugrel	$P2Y_{12}$ receptor antagonism	Prodrug	Irreversible	Once daily
Ticagrelor	Allosteric $P2Y_{12}$ receptor antagonism	Direct-acting	Reversible	Twice daily

ADP adenosine diphosphate, *COX* cyclooxygenase

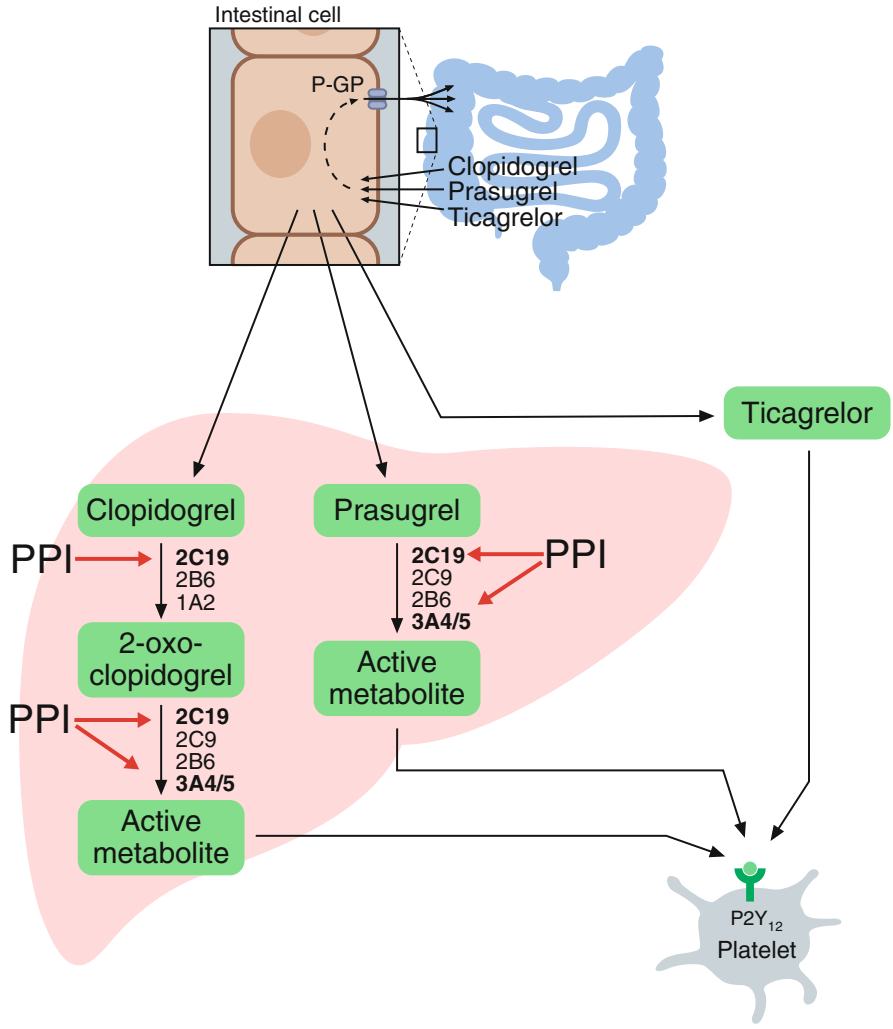

Fig. 1 A schematic presentation of the absorption and metabolism of clopidogrel, prasugrel, and ticagrelor (Adapted from Würtz et al. [112]). Clopidogrel is activated by a two-step oxidative process in the liver, whereas only one oxidative step is needed for the activation of prasugrel. The most important CYP enzymes mediating hepatic bioactivation of clopidogrel and prasugrel are depicted. CYP2C19 and CYP3A4/A5 are highlighted because they are strongly involved in the metabolism of certain PPIs, in particular omeprazole, thereby competitively inhibiting the bioactivation of clopidogrel and prasugrel. Ticagrelor does not require hepatic bioactivation. *CYP* cytochrome P450, *P-GP* P-glycoprotein (multidrug resistance protein), *PPI* proton pump inhibitor

3.2 Clinical Use

The CURE trial from 2001 documented the benefit of clopidogrel in addition to aspirin in patients with non-ST elevation MI [23]. The relative risk for the primary end point (cardiovascular death, non-fatal MI, or stroke) with aspirin and clopidogrel was 0.80 (95 % confidence interval [CI] 0.72–0.90) compared to aspirin alone. Since then, clopidogrel has been used in combination with aspirin in the setting of percutaneous coronary intervention (PCI), especially in the treatment of ACS. In 2005, a similar benefit was documented in patients with ST elevation MI [24, 25]. Overall, dual antiplatelet therapy with aspirin and clopidogrel in patients with ACS reduced cardiovascular risk by approximately 10 % compared to aspirin alone

[23–25]. Documenting its widespread use, clopidogrel was the second most prescribed drug worldwide in 2010 (atorvastatin was the most prescribed) [26].

From 2009 to 2011 ticagrelor and prasugrel received authorization from European and American authorities for use in combination with aspirin for prevention of atherothrombotic events in patients with ACS undergoing PCI. Approvals were based on two phase III trials, TRITON-TIMI 38 (prasugrel) [27] and PLATO (ticagrelor) [28], documenting significant reductions in cardiovascular death, non-fatal MI, or stroke when using prasugrel or ticagrelor instead of clopidogrel. In TRITON-TIMI 38 the hazard ratio with prasugrel was 0.81 (95 % CI 0.73–0.90), and in PLATO the hazard ratio with ticagrelor was 0.84 (95 % CI 0.77–0.92). Although prasugrel and ticagrelor increased the risk of non-coronary artery bypass grafting-related major bleeding according to the Thrombolysis in Myocardial Infarction criteria (by 32 % and 25 %, respectively), both drugs are now widely used as treatment and short-term prevention of atherothrombotic events in patients with ACS [4].

4 Antiplatelet Treatment and Gastrointestinal Bleeding

Cardiovascular protection by aspirin and ADP receptor antagonists accrue at the expense of an increased risk of upper gastrointestinal bleeding [29, 30]. Gastrointestinal bleeding is life-threatening, especially in patients presenting with ACS [31] and documenting this, aspirin remains the dominant contributor to gastrointestinal bleeding-related mortality [32].

The gastrotoxic effects of aspirin that cause ulceration and bleeding have been attributed to (1) topical mucosal injury caused by inhibition of prostaglandin and (2) systemic antiplatelet effects driven by inhibition of thromboxane A_2 generation [33, 34]. Prostaglandins are essential in protecting the gastric mucosa. They increase mucosal blood flow, promote proliferation of gastric epithelial cells, and stimulate mucus and bicarbonate secretion. Therefore, inhibition of prostaglandin synthesis by aspirin makes the gastric mucosa susceptible to ulcer formation and bleeding in the highly acidic environment. Furthermore, platelet inhibition with aspirin impairs healing of the vulnerable gastric mucosa [33, 34].

Unlike aspirin, ADP receptor antagonists do not cause injury of the gastric mucosa, but their inhibition of platelet aggregation are likely to impair healing and aggravate already existing gastric injuries caused by acidic drugs such as aspirin [33, 34].

5 Proton Pump Inhibitors: Pharmacology and Clinical Use

Strategies to prevent gastrointestinal discomfort, ulceration, and bleeding during antiplatelet treatment include the identification and modification of associated risk factors as well as concomitant treatment with gastroprotective agents, mainly histamine H_2 receptor antagonists and PPIs [33, 35]. For more than two decades, PPIs have been used extensively for the treatment of gastric acid-related disorders. Even though H_2 receptor antagonist are effective in preventing gastrointestinal complications [36], PPIs produce a higher degree and longer duration of gastric acid suppression than H_2 receptor antagonists leading to higher healing rates [8]. Although PPIs have widely been considered harmless, there are studies associating these drugs with serious adverse effects such as pneumonia, interstitial nephritis, osteoporotic fractures, and intestinal *Clostridium difficile* infections [37].

Under acidic conditions, PPIs are protonated and converted to cyclic sulphenamides. These active PPI metabolites reduce gastric acid production by irreversibly inhibiting the enzyme responsible for gastric acid secretion: the H^+/K^+-exchanging adenosine triphosphatase, often referred to as "the proton pump" [8]. The proton pump, which is located on gastric parietal cells, is directly responsible for H^+ secretion into the gastric lumen. It follows that PPIs, as opposed to

H_2 receptor antagonists, target the terminal step in gastric acid secretion making the gastric acid suppression particularly strong. PPIs have a short plasma half-life of 30–120 min depending on pH level, yet the antacid effect is sustained for days due to the irreversible inhibition as well as accumulation of the drug in parietal cells [8].

6 Biochemical Background for Putative Drug Interactions Between Proton Pump Inhibitors and Antiplatelet Drugs

Under physiological conditions, aspirin is absorbed in its non-ionized lipid state across the gastric mucosal barrier. A pH-dependent mechanism has been suggested to explain a drug interaction between aspirin and PPIs. PPI reduce gastric acid production by inhibiting the enzyme responsible for gastric acid secretion from gastric parietal cells: the H^+/K^+-exchanging adenosine triphosphatase (Fig. 2) [103]. According to the pH partition hypothesis [38], modifying the intragastric milieu by raising pH potentially reduces the bioavailability of drugs, in particular those being absorbed across the gastric mucosal membrane, such as aspirin [39]. During PPI treatment, intragastric pH does indeed rise above the pK_a (3.5) of aspirin potentially reducing its lipophilicity and gastric absorption [39, 40].

The activity of CYP2C19 is altered by PPIs, which are CYP2C19 substrates and thus may interact with clopidogrel and prasugrel metabolism through competitive antagonism. It follows that the interaction between PPIs and thienopyridines depends on the capacity of each PPI subtype to inhibit CYP2C19. Omeprazole, esomeprazole, and lansoprazole have a relatively high potency towards CYP2C19, while rabeprazole and pantoprazole have less potency.

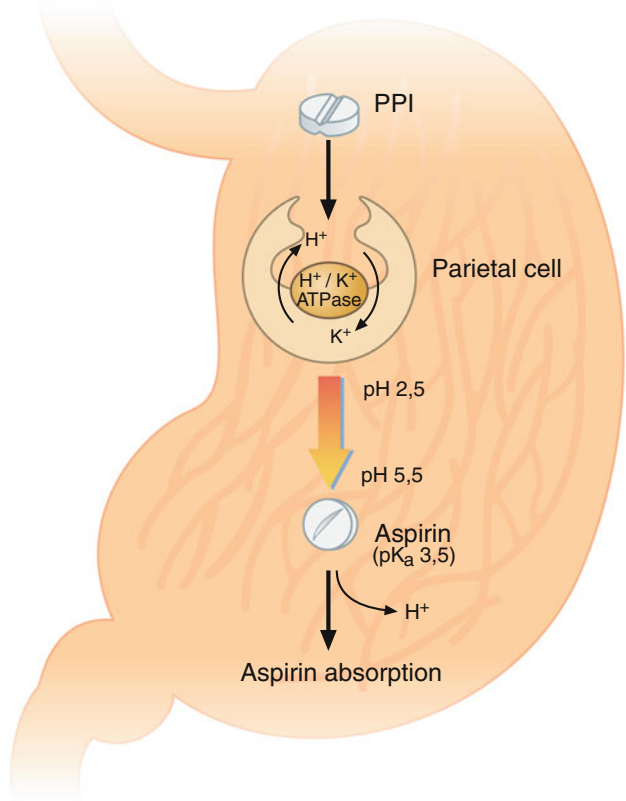

Fig. 2 Suggested biochemical background for a drug interaction between aspirin and proton pump inhibitors (Adapted from Würtz and Grove [113]). Under normal physiological conditions, aspirin is absorbed in its non-ionized lipid state across the gastric mucosal barrier. Proton pump inhibitors inhibit the H^+/K^+-exchanging ATPase of the gastric parietal cells. Intragastric pH rises above the pK_a (3.5) of aspirin and reduces the lipophilicity of aspirin thereby lowering its gastric absorption. *ATP* adenosine triphosphate, *PPI* proton pump inhibitor

Accordingly, PPIs with low inhibitory effect on CYP219 are recommended if combined treatment with a thienopyridine and a PPI is required [35].

7 Interactions Between Proton Pump Inhibitors and Aspirin

The number of studies addressing a drug interaction between PPIs and aspirin remains relatively sparse (Table 2). Evidence is gathered from statistical modeling [41], pharmacokinetic measurements [42–44], large observational studies with clinical end points [45, 46], *post-hoc* analyses of large clinical trials [47], smaller interventional studies with clinical end points [48], or derived from studies utilizing *ex vivo* platelet function tests as a marker for the clinical effect of aspirin [49–53].

In previous animal studies, omeprazole reduced the analgesic and antipyretic effects of aspirin, which was measured by means of reduced gastric aspirin absorption [40, 54]. Similar findings were reported from a study of humans [55]. On the other hand, Iñarrea et al. measured the antiplatelet effect of aspirin in 14 healthy individuals before and after 4 days of 20 mg/day omeprazole treatment. Bleeding time and platelet aggregation levels were both unaffected by omeprazole [49]. In a randomized cross-over study of 24 healthy individuals, 100 mg of enteric-coated aspirin was given for 4 weeks with or without concomitant 30 mg/day lansoprazole. Thereafter, participants were switched to the other treatment regimen for another 4 weeks. Platelet function assessed by light transmittance aggregometry (APACT 4) and shear stress-stimulated closure time (Platelet Function Analyzer-100) suggested no difference in antiplatelet potency between aspirin with lansoprazole and aspirin alone [51]. Another study showed no pharmacokinetic interaction based on measurements of acetylsalicylic acid plasma concentrations in 55 healthy volunteers subjected to three treatment periods comprising esomeprazole, aspirin, and both [42]. Subsequently, the authors evaluated the bioequivalence between 40 mg esomeprazole and 325 mg aspirin given separately and as a single-tablet formulation including both agents. Analyzing the same end point of acetylsalicylic acid maximal plasma concentration, the two treatment schemes remained bioequivalent [43]. In a randomized cross-over study, 29 healthy individuals received low-dose aspirin with or without esomeprazole 20 mg once daily for 5 days followed by 14-day washout and subsequent treatment cross-over. Platelet aggregation evaluated with the VerifyNow® Aspirin test did not differ between the two treatment regimens, neither did levels of serum thromboxane B_2 [53].

In a pharmacodynamic study by Würtz et al., we included 418 aspirin-treated patients with stable coronary artery disease, of whom 54 were PPI users. In multivariable adjusted analyses, platelet aggregation (median 180 [interquartile range 119–312] vs. 152 [84–226] aggregation units*minute, $p = 0.013$) and platelet activation measured by soluble serum P-selectin (88.5 [65.2–105.8] vs 75.4 [60.0–91.5] ng/ml, $p = 0.013$) were significantly higher in patients treated with a PPI. In contrast to many other pharmacodynamic studies, a non-enteric coated formulation of aspirin was used in this study, which may be important given that gastric absorption of enteric-coated aspirin has been shown to increase during omeprazole-treatment [56]. The findings by Würtz et al. were supported by a large Danish register-based study of 19,925 patients suffering a first-time MI. All patients were treated with aspirin, while almost 30,000 patients treated with clopidogrel were excluded. The risk of cardiovascular death, recurrent MI, or stroke was increased in patients receiving a PPI (adjusted hazard ratio 1.46, 95 % CI 1.33–1.61), but not in patients receiving a gastroprotective H_2 receptor antagonist [45].

Whellan et al. tested the hypothesis that a single-tablet formulation (PA32540) [57] of enteric-coated aspirin (325 mg) and immediate-release omeprazole (40 mg) would reduce gastrointestinal complications without promoting thrombotic complications compared to aspirin

Table 2 Studies evaluating the association between proton pump inhibitor use and the antiplatelet effect of aspirin

Study	Participants (n)	Antiplatelet treatment	PPI type (n)	Design	Test/end point	Main results
Iñarrea et al. [49]	Healthy volunteers (14)	Non enteric-coated ASA 125 mg ± PPI	Omeprazole	Cross-over study	Skin bleeding time, light transmittance aggregometry (Aggrecorder), plasma levels of ASA and salicylic acid	Omeprazole did not affect bleeding time, platelet aggregation, or plasma levels of ASA and salicylic acid
Adamopoulos et al. [51]	Hypertensive subjects with indication for primary prophylaxis with aspirin	Enteric-coated ASA 100 mg ± PPI	Lansoprazole	Cross-over study	Light transmittance aggregometry (APACT4) and closure time (PFA-100)	Platelet aggregation and closure time during ASA treatment were unaffected by lansoprazole
Niazi et al. [42]	Healthy volunteers (55)	Non enteric-coated ASA 325 mg ± PPI	Esomeprazole	Cross-over study	Maximum ASA plasma concentration and steady-state area under the concentration-time curve	Pharmacokinetic measures of ASA were unaffected by esomeprazole
Kasprzak et al. [50]	PCI for ACS (31)	Enteric-coated ASA 75 mg ± PPI	Pantoprazole	Cross-over study	Platelet aggregometry (Multiplate Analyzer)	Reduced platelet aggregation in PPI users compared to non-users
Andersson et al. [53]	Healthy volunteers (29)	ASA 81 mg (coating not specified) ± PPI	Esomeprazole	Cross-over study	Optical aggregometry (VerifyNow Aspirin) and thromboxane B_2	The drop in platelet aggregation and thromboxane B_2 from baseline (no aspirin) to post-treatment was equal whether treatment was ASA + PPI or ASA alone
Würtz et al. [52]	Coronary artery disease (418)	Non enteric-coated ASA 75 mg PPI: 54 users, 364 non-users	Pantoprazole, esomeprazole, omeprazole, and lansoprazole	Cohort study	Platelet aggregometry (Multiplate Analyzer) and platelet activation level (soluble P-selectin)	Increased platelet aggregation, platelet activation, and thromboxane B_2 levels in PPI users compared to non-users

Charlot et al. [45]	30-day survivors of a first-ever MI between 1997 and 2006 (19,925)	ASA (dose and coating not specified), clopidogrel users excluded	Pantoprazole, omeprazole, lansoprazole, and esomeprazole	Retrospective nationwide register-based study	1-year composite of cardiovascular death, MI, or stroke	PPI use, but not H_2 receptor antagonist use, at any time following discharge associated with increased risk of the composite end point compared with non-use in the multivariable adjusted (multivariable adjusted hazard ratio 1.46, 95 % CI 1.33–1.61; propensity score-matched hazard ratio 1.61, 95 % CI 1.45–1.79)
Dunn et al. [47]	*Post-hoc* analysis of the CAPRIE trial Previous MI, ischemic stroke, or peripheral vascular disease (ASA arm, 9586)	ASA 325 mg or CLO 75 mg	Omeprazole and lansoprazole	*Post-hoc* analysis of a clinical trial	1-year composite of ischemic stroke, MI, or vascular death	In ASA-treated patients, PPI use was not associated with an increased risk of the composite end point compared to non-use (adjusted hazard ratio 1.04, 95 % CI 0.70–1.57)
Whellan et al. [48]	Users of ASA for secondary cardiovascular prevention (1049)	Enteric-coated ASA 325 mg ± PPI PPI was given as a single-tablet combination of ASA and omeprazole	Omeprazole	Randomized PPI assignment	6-month major adverse cardiovascular events and upper gastrointestinal symptoms	The rate of cardiovascular events was equal between treatment arms, but upper gastrointestinal symptoms were reduced with the combination tablet compared to ASA alone
Garcia Rodriguez et al. [46]	Users of ASA for secondary cardiovascular prevention (39,513) or in patients with previous ACS (42,542) between 2000 and 2007	ASA 75–300 mg (>85 % received 75 mg, coating not specified)	Not specified	Cohort study	Composite of non-fatal MI or coronary death	PPI use not associated with increased risk of non-fatal MI or coronary death in neither of the study cohorts (pooled relative risk 0.96, 95 % CI 0.62−1.48)

ACS acute coronary syndrome, *ASA* acetylsalicylic acid (aspirin), *CI* confidence interval, *CLO* clopidogrel, *MI* myocardial infarction, *PPI* proton pump inhibitor

alone. A coordinated-delivery tablet was used, in which omeprazole is embedded within a film coat enabling instantaneous dissolution, whereas aspirin release occurs only when gastrointestinal pH reaches a level of 5.5 [48]. The primary end point of endoscopically verified gastric ulcer at 6 months occurred less frequently among users of the combined formulation (3.2 % vs. 8.6 %, $p < 0.001$), while the rate of major adverse cardiovascular events did not differ between treatment arms (1.7 % vs. 2.5 %, $p > 0.05$). Importantly, the study had a low rate of cardiovascular events, for which the study was underpowered [48].

Most recently, the combined analysis of coronary event rates in two large cohorts of first-time users of aspirin for secondary prevention was published [46]. The first cohort included first-time users of aspirin for any secondary prevention indication, while the second cohort consisted of patients who initiated aspirin treatment following an acute coronary event. Looking at the cohorts separately or combined, PPI treatment was not associated with an increase in the risk of non-fatal MI or coronary death [46], and the results thus contrast those of the above mentioned large registry-based study [45].

A recent analysis showed that co-prescription of low-dose aspirin and a PPI turned out to be cost-effective by reducing gastrointestinal as well as cardiovascular events [41]. This cost-effectiveness analysis was based on previously published clinical studies, and the cardiovascular benefit appeared to be partly driven by increased adherence to aspirin in PPI users. Furthermore, even in patients with cardiovascular disease who continue aspirin treatment after suffering a gastrointestinal bleeding event, aspirin seems to confer a net clinical benefit because the risk of bleeding is outbalanced by improved cardiovascular outcome [58]. This was shown in a small randomized study, in which aspirin users who suffered a peptic ulcer bleeding were given either aspirin or placebo on top of pantoprazole. While increasing the risk for recurrent gastrointestinal bleeding, continued aspirin treatment reduced mortality [58]. Although these interesting results should be confirmed in larger studies, they stress that discontinuing aspirin upon gastrointestinal events should be carefully considered in patients with increased risk of cardiovascular events.

Altogether, studies exploring whether PPIs reduce the effect of aspirin are sparse. Studies are small and relatively heterogeneous and this, coupled with the fact that only one randomized, yet underpowered, study has been performed makes it premature to change clinical recommendations at present as reflected in current guidelines [4, 5, 35].

8 Interaction Between Proton Pump Inhibitors and Clopidogrel

8.1 Pharmacological Studies

Since 2006, several observational studies have reported an attenuation of the antiplatelet effect of clopidogrel when given concomitantly with PPI, particularly omeprazole (Table 3). Gilard et al. used the vasodilator-stimulated phosphoprotein (VASP) phosphorylation assay to assess platelet function 48 h after treatment initiation in 105 patients undergoing angiography. All patients were treated with aspirin and clopidogrel, and 24 patients were also treated with a PPI. PPI users had a significantly higher platelet reactivity index than non-users (61.4 ± 23.2 % vs. 49.5 ± 16.3 %, $p = 0.007$) [59]. Indeed, the VASP assay reflects the extent of intracellular $P2Y_{12}$ pathway inhibition and is therefore considered the pharmacologically most specific test of platelet inhibition by ADP receptor antagonists [60]. Pursuing more firm documentation, the authors conducted the double-blind placebo-controlled OCLA trial published in 2008 [61]. A total of 124 patients undergoing PCI received standard doses of aspirin and clopidogrel and were randomized to either omeprazole 20 mg/day or placebo for 7 days. Platelet inhibition was assessed at days one and seven using the platelet reactivity VASP index. On day seven, the omeprazole-arm had significantly higher platelet reactivity than the placebo-arm (51.4 ± 16.4 % vs. 39.8 ± 15.4 %,

Table 3 Studies with pharmacokinetic and/or pharmacodynamic end points suggesting an association between proton pump inhibitor use and the antiplatelet effect of clopidogrel

Study	Participants (n)	Antiplatelet treatment	PPI type (n)	Random PPI assignment?	Test	Main results
Gilard et al. [59]	High-risk coronary angioplasty (105)	ASA and CLO for a minimum of 48 h	Not specified	No	VASP-PRI	Increased PRI in PPI users (61.4 ± 23.2 vs. 49.5 ± 16.3, p = 0.007)
	PPI: 24 users, 81 non-users					No association found with statins, angiotensin converting enzyme inhibitors, angiotensin II receptor antagonist, or beta blockers
Gilard et al. [61]	Elective PCI (124)	ASA and CLO + PPI or placebo (7 days)	Omeprazole	Yes	VASP-PRI	Increased PRI in the PPI-arm at day 7 (39.8 ± 15.4 % vs. 51.4 ± 16.4 %), but not at day 1 (83.2 ± 5.6 % vs. 83.9 ± 4.6 %, not significant)
Small et al. [63]	Healthy volunteers (24)	CLO 300 mg or PRA 60 mg ± PPI	Lansoprazole	Yes (cross-over design)	Pharmacokinetics: Maximum CLO plasma concentration and area under the concentration-time curve	PPI use did not affect the pharmacokinetics of CLO, but tended to reduce maximal inhibition of platelet aggregation, which was most pronounced in subjects with aggregation levels
					Pharmacodynamics: Optical platelet aggregometry	
O'Donoghue et al. [64]	Elective PCI (201). *Post-hoc* analysis of PRINCIPLE-TIMI 44	Random assignment to CLO 600 mg LD/300 mg MD or PRA 60 mg LD/10 mg MD	Not specified	No	Light transmittance aggregometry	Reduced platelet inhibition in CLO-treated PPI users compared to non-users 2, 6, and 18–24 h after PCI
						2 h: 10.4 ± 16.2 % vs. 24.2 ± 20.5 %, p = 0.003
						6 h: 23.2 ± 19.5 % vs. 35.2 ± 20.9 %, p = 0.02
						18–24 h: 23.8 ± 14.4 % vs. 36.1 ± 20.8 %, p = 0.03
						No differences 30 min nor 15 days after PCI

(continued)

Table 3 (continued)

Study	Participants (n)	Antiplatelet treatment	PPI type (n)	Random PPI assignment?	Test	Main results
Sibbing et al. [65]	Scheduled for control angiography after PCI (1000)	ASA 75 mg and CLO 75 mg	Pantoprazole, omeprazole, and esomeprazole	No	Platelet aggregometry (Multiplate Analyzer)	Increased platelet aggregation in omeprazole users compared to non-users (295.5 [IQR 193.5–571.2] aggregation units*min vs. 220.0 [IQR 143.8–388.8] aggregation units*min; $p = 0.001$). No differences between pantoprazole/esomeprazole users and PPI non-users
Zuern et al. [67]	Elective or urgent PCI (1425)	ASA 100 mg and CLO 600 mg LD/75 mg MD	Pantoprazole, esomeprazole, and omeprazole	No	Optical aggregometry (Chronolog Lumi Aggregometer)	Increased platelet aggregation in PPI users compared to non-users (34.0 ± 21.4 % vs. 29.8 ± 20.2 %, $p < 0.001$). PPI use was an independent predictor of residual platelet aggregation
Cuisset et al. [66]	PCI for non-ST elevation MI (104)	ASA 250 mg LD/75 mg MD and CLO 600 mg LD/150 mg MD plus PPI	Omeprazole and pantoprazole	Yes	VASP-PRI and optical aggregometry (PAP4 Aggregometer)	12–24 h after LD: No differences in terms of PRI or aggregation 1 month after discharge: Increased PRI in omeprazole users compared to pantoprazole users (36 ± 20 % vs. 48 ± 17 %, $p = 0.007$). Using PRI, more CLO non-responders among omeprazole users than pantoprazole users (44 % vs. 23 %, $p = 0.04$. Odds ratio 2.6, 95 % CI 1.2–6.2). No differences found by aggregometry

Fontes-Carvalho et al. [68]	PCI for MI (34)	ASA 150 mg and CLO 75 mg plus PPI	Omeprazole or pantoprazole (cross-over, 1 month washout)	Yes (cross-over design)	Optical aggregometry (VerifyNow P2Y12)	1 month after PCI: Significant increase in platelet aggregation during omeprazole-treatment compared to PPI non-use (235 ± 58 PRU vs. 201 ± 48, $p < 0.001$). The number of clopidogrel non-responders almost doubled during omeprazole-treatment. No differences seen with pantoprazole compared to PPI non-use
Angiolillo et al. [69]	Healthy volunteers (282)	CLO 300 mg LD/75 mg MD	Omeprazole or pantoprazole	Yes (cross-over design)	VASP-PRI and platelet aggregometry	Significant increase in platelet aggregation and PRI during omeprazole-treatment compared to PPI non-use. The drug interaction was not mitigated by increasing clopidogrel dose or administering clopidogrel and omeprazole apart (spaced administration). Pantoprazole only affected platelet aggregation and VASP-PRI sparsely compared to omeprazole
Parri et al. [73]	Primary PCI for ST elevation MI (105)	ASA 100 mg and CLO 300 mg LD/75 mg MD and optional glycoprotein IIb/IIIa inhibition	Pantoprazole or ranitidine (H_2 receptor antagonist)	Yes	Light transmittance aggregometry and closure time (PFA-100)	Increased maximal platelet aggregation stimulated with ADP in pantoprazole users compared to ranitidine users after correction for CYP2C19*2 genotype both five (median 29 % vs. 19 %, $p = 0.01$) and 30 days (median 35 % vs. 27 %, $p = 0.03$) after PCI. No difference observed with other agonists or with the PFA-100

ACS acute coronary syndrome, *ASA* acetylsalicylic acid (aspirin), *CI* confidence interval, *CLO* clopidogrel, *LD* loading dose, *MD* maintenance dose, *MI* myocardial infarction, *PPI* proton pump inhibitor, *VASP-PRI* vasodilator-stimulated phosphoprotein platelet reactivity index

$p < 0.0001$) [61]. Given the rigorous design of the OCLA trial, the results were convincing, and many, but not all [62], subsequent studies supported the findings [63–69].

Of interest, some studies suggested a differential impact of proton pump inhibitors on the antiplatelet effect of clopidogrel. Four studies independently argued in favor of preferentially using non-omeprazole PPIs, namely pantoprazole, to avoid a drug interaction [65, 66, 68, 69]. In the PACA study, a total of 104 patients with non-ST elevation ACS were randomized to omeprazole or pantoprazole on top of aspirin and clopidogrel. After 1 month, platelet inhibition assessed by the VASP index was significantly greater with clopidogrel in patients receiving pantoprazole (36 ± 20 % vs. 48 ± 17 %, $p < 0.007$) [66].

Angiolillo et al. performed a complex study including four randomized, placebo-controlled, cross-over studies among 282 healthy individuals. The purpose was (1) to explore any drug interaction between clopidogrel and omeprazole, (2) to test if such interaction could be mitigated by administering clopidogrel and omeprazole 12 h apart, (3) or by doubling the clopidogrel maintenance dose to 150 mg daily, and (4) to compare the drug interaction caused by omeprazole with that caused by pantoprazole. Essentially, the study showed that omeprazole, but not pantoprazole, reduced the pharmacodynamic effect of clopidogrel through a pH-independent mechanism mediated by the CYP2C19 enzyme [69]. Since all PPIs lower gastric pH to roughly the same extent at equipotent doses [70, 71], the differential impact of PPIs on the platelet inhibitory effect of clopidogrel may rather be attributable to differences in the inhibitory potency towards CYP2C19. In particular, pantoprazole seems to interfere little, if at all, with the metabolism of clopidogrel and is known to have very little affinity for CYP2C19 [72]. Notwithstanding, a recent study suggested that pantoprazole increases platelet aggregation irrespective of *CYP2C19*2* genotype in clopidogrel-treated patients with ST elevation MI undergoing PCI [73]. According to a *post-hoc* subgroup analysis of the PRINCIPLE-TIMI 44 trial, treatment with a PPI and clopidogrel increased the number of non-responders to a clopidogrel loading dose in the acute phase and to a 150 mg daily maintenance dose 15 days after PCI [64].

Few studies have investigated to what extent the influence of PPIs on clopidogrel's antiplatelet potency differs according to *CYP2C19* genotype, however there is evidence suggesting that *CYP2C19* inhibition is the main cause of drug-drug interaction between clopidogrel and PPIs, especially omeprazole [74]. Furuta et al. reported that the likelihood of converting from clopidogrel responder to non-responder during PPI treatment (omeprazole, lansoprazole, rabeprazole) was much higher in slow metabolizers carrying the *CYP2C19*2* and/or **3* allele [75]. Based on these findings, which were derived from healthy volunteers only, PPI treatment seems to be particularly problematic in patients carrying a *CYP2C19 *2* and/or **3* allele, as supported by a very recent clinical study [76]. Depta et al. showed that among PPI users, *CYP2C19*2* and *CYP2C19*17* carriers tended to have a poorer 1-year clinical outcome, while carriers of *CYP2C19*1* did not. However, there are contrasting reports. One study showed no difference between *CYP2C19* genotypes [77], while two studies showed that fast metabolizers (*CYP2C19 *1* homozygotes) experienced the largest reduction in clopidogrel's antiplatelet potency [78, 79].

In summary, there is quite strong evidence that PPIs reduce the pharmacodynamic effect of clopidogrel. This has been documented with conventional aggregometry as well as with VASP assays. However, pharmacodynamic end points do rarely translate directly into comparable clinical end points.

8.2 Clinical Studies

Since 2008, numerous studies investigating hard clinical end points have been performed to determine if the drug interaction documented in pharmacological studies would affect the risk of adverse clinical outcomes (Table 4). Most

Table 4 Studies with clinical end points suggesting an association between proton pump inhibitor use and the antiplatelet effect of clopidogrel

Study	Participants (n)	Antiplatelet treatment	PPI generic (n)	Random PPI assignment?	End point	Main results
Juurlink et al. [84]	Acute MI (13,636). Cases (734) = patients who died or were readmitted for MI within 90 days after hospital discharge. Controls (2057) = patients at risk who were not readmitted for MI	CLO at discharge (dose not specified) Among cases, 26.4 % were current PPI users Among controls, 20.6 % were current PPI users	Not specified	No	90-day and 1-year readmission for acute MI	Current PPI use associated with increased risk of reinfarction compared with non-use (adjusted odds ratio 1.27, 95 % CI 1.03–1.57). Former PPI use showed no association
Ho et al. [85]	ACS (8205).	CLO at discharge (dose not specified). 90 % received ASA 63.9 % were prescribed PPI a at discharge, during follow-up, or both and 36.1 % were not	Omeprazole, rabeprazole, lansoprazole, and pantoprazole. One third received more than one PPI type	No	All-cause mortality or rehospitalization for ACS	PPI use at any time following discharge associated with increased risk of the composite end point compared with non-use (adjusted odds ratio 1.25, 95 % CI 1.11–1.41). The risk for rehospitalization for ACS alone was increased by 86 % PPI use not associated with clinical outcomes in patients not taking CLO
Kreutz et al. [83]	Previous PCI (16,690).	CLO 75 mg (0.3 % received 150 mg). ASA use not specified 40.9 % were prescribed a PPI during the 1-year study period	Omeprazole, esomeprazole, pantoprazole, lansoprazole, and rabeprazole	No	1-year composite of hospitalization for a cerebrovascular event or ACS, cardiovascular death, or coronary revascularization	PPI use at any time following discharge associated with increased risk of the composite end point compared with non-use (adjusted hazard ratio 1.51, 95 % CI 1.39–1.64). No differences between PPI generics PPI use not associated with clinical outcomes in patients not taking CLO

(continued)

Table 4 (continued)

Study	Participants (n)	Antiplatelet treatment	PPI generic (n)	Random PPI assignment?	End point	Main results
Siller-Matula et al. [114]	Meta-analysis of randomized studies, *post-hoc* analyses of randomized studies, and observational studies with data on PPI exposure in CLO-treated patients (159,138)	CLO ± PPI	Omeprazole, esomeprazole, pantoprazole, lansoprazole, and rabeprazole	No	Major adverse cardiac events, MI, stent thrombosis, death, and gastrointestinal bleeding	Overall conclusion: PPI use might be associated with increased risk of cardiovascular events, but does not seem to influence mortality
Dunn et al. [47]	*Post-hoc* analyses of the CAPRIE and CREDO trials	CAPRIE: ASA 325 mg or CLO 75 mg	CAPRIE: Lansoprazole and omeprazole	No	CAPRIE: 1-year composite of ischemic stroke, MI, or vascular death	CAPRIE: In CLO-treated patients, PPI use associated with an increased risk of the composite end point compared to non-use (adjusted hazard ratio 2.39, 95 % CI 1.74–3.28)
	CAPRIE: Previous MI, ischemic stroke, or peripheral vascular disease (CLO arm, 9599)	CREDO: CLO 300 mg LD/75 mg MD for 1 year or CLO 75 mg for 28 days (placebo thereafter)	CREDO: Lansoprazole, omeprazole, pantoprazole, and rabeprazole		CREDO: 1-year composite of all-cause death, MI, or stroke	CREDO: In CLO-treated patients, PPI use associated with an increased risk of the composite end point compared to non-use (hazard ratio 1.67, 95 % CI 1.06–2.64). PPI use associated with a similar risk in patients not treated with CLO
	CREDO: Planned to undergo PCI (CLO arm, 1053)					
Kwok et al. [90]	Meta-analysis of randomized and non-randomized studies with data on PPI exposure in CLO-treated patients (222,311)	CLO ± PPI	Omeprazole, esomeprazole, lansoprazole, pantoprazole, and rabeprazole	No	Major adverse cardiovascular events or MI	Overall conclusion: PPI use seems to be associated with clinical outcome, but also in the absence of CLO. Uncontrolled confounding is an important limitation of studies investigating the influence of PPI use on cardiovascular outcome in CLO-treated patients

Rassen et al. [82]	Previous PCI or previous hospitalization for ACS (18,565, pooled from 3 cohort studies)	CLO (dose not specified). ASA use not specified, but likely to be almost 100 % 21.5 % were prescribed a PPI during the 6-month study period	Omeprazole, esomeprazole, lansoprazole, pantoprazole, and rabeprazole	No	6-month composite of hospitalization for MI and all-cause mortality	PPI use associated with an increased risk of the composite end point compared to non-use after multivariable adjustment (relative risk 1.32, 95 % CI 1.08–1.61). In propensity score-matched analyses, results were not significant
Burkard et al. [88]	ACS or stable coronary artery disease undergoing PCI (801)	ASA 250–500 mg LD/100 mg MD and CLO 300 mg LD/75 mg MD 13 % were prescribed a PPI at discharge	Omeprazole, esomeprazole, pantoprazole, and lansoprazole	No	3-year composite of cardiac death, non-fatal MI, and target vessel revascularization	PPI use associated with an increased risk of the composite end point compared to non-use (30.3 % vs. 20.8 %, $p = 0.027$) and MI (14.7 % vs. 7.4 %, $p = 0.01$), but not target vessel revascularization or cardiac death
Gaglia et al. [86]	ACS or stable coronary artery disease undergoing PCI (820)	ASA 325 mg LD/325 mg MD and CLO 300–600 mg LD/MD not specified 38.8 % were prescribed a PPI at discharge	Omeprazole, esomeprazole, lansoprazole, pantoprazole, and rabeprazole	No	1-year composite of all-cause mortality, MI, target vessel revascularization, and stent thrombosis	PPI use associated with an increased risk of the composite end point compared to non-use (adjusted hazard ratio 1.8, 95 % CI 1.1–2.7). No differences between PPI generics
Bhurke et al. [87]	ACS (10,101)	CLO (dose not specified). ASA use not specified 41.4 % were prescribed a PPI during the study period	Omeprazole, esomeprazole, lansoprazole, pantoprazole, and rabeprazole	No	Rehospitalization or emergency department visit for MI, PCI, or intermediate coronary syndrome	PPI use at any time following ACS diagnosis associated with an increased risk of the composite end point compared to non-use (propensity score-matched hazard ratio 1.4, 95 % CI 1.2–1.7)

(continued)

Table 4 (continued)

Study	Participants (n)	Antiplatelet treatment	PPI generic (n)	Random PPI assignment?	End point	Main results
Bhatt et al. [80]	ACS or elective PCI (3761)	ASA 75–325 mg MD and CLO 75 mg MD Patients were randomized to a fixed-dose separate-release combination of clopidogrel (75 mg) and omeprazole (20 mg) or clopidogrel alone	Omeprazole	Yes	Primary cardiovascular end point: 6-month composite of cardiovascular death, non-fatal MI, revascularization, or stroke. The study was powered for the primary gastrointestinal end point of overt or occult bleeding, symptomatic gastroduodenal ulcers or erosions, obstruction, or perforation	PPI use reduced the 6-month rate of gastrointestinal events (hazard ratio 0.34, 95 % CI 0.18–0.63) and upper gastrointestinal bleeding (hazard ratio 0.13, 95 % CI 0.03–0.56) without increasing the rate of cardiovascular events (hazard ratio 0.99, 95 % CI 0.68–1.44)

ACS acute coronary syndrome, *ASA* acetylsalicylic acid (aspirin), *CI* confidence interval, *CLO* clopidogrel, *LD* loading dose, *MD* maintenance dose, *MI* myocardial infarction, *PCI* percutaneous coronary intervention, *PPI* proton pump inhibitor

studies are register-based studies or *post-hoc* sub-analyses of clinical trials, in which PPI treatment was not randomly assigned, which potentially introduces confounding by indication. So far, only one large randomized placebo-controlled trial has been performed showing no interaction [80]. In general, some studies suggest an interaction [47, 81–88], whereas others do not [47, 64, 80, 82, 89, 90].

Ho et al. performed a retrospective study of 8205 ACS patients treated with clopidogrel, of which two-thirds were prescribed a PPI at discharge, during follow-up, or both. Upon adjustment, any PPI prescription during follow-up (n = 5244) was associated with an increased risk of death or ACS rehospitalization compared with the use of clopidogrel only (odds ratio 1.25, 95 % CI 1.11–1.41) [85]. In a population-based case-control study of 734 cases and 2057 controls, Juurlink et al. found that in clopidogrel-treated patients suffering an MI, the 90-day risk of re-infarction was increased by 40 % in current users of a non-pantoprazole PPI, whereas the risk was unchanged in pantoprazole users. Importantly, PPI use did not affect mortality risk [84]. In the Clopidogrel Medco Outcomes Study, including 16,690 clopidogrel-treated patients undergoing PCI, a more than 50 % increased risk of major adverse cardiovascular events was found in patients receiving adjunctive PPI treatment with whatever type of PPI. A subgroup analysis of PPI treatment before PCI among 1641 patients showed that the cardiovascular risk was not associated with PPI exposure in the absence of clopidogrel treatment [83].

Dunn et al. looked at data from the well-known CAPRIE (aspirin vs. clopidogrel in ACS) and CREDO (clopidogrel vs. placebo in PCI) trials. These are the only two placebo-controlled trials using clopidogrel as an active comparator, in which PPI use was documented [47]. In CAPRIE, clopidogrel increased the 1-year risk for the primary end point (ischemic stroke, MI, or vascular death) among PPI users (estimated hazard ratio 2.66, 95 % CI 0.94–7.50), while lowering it for non-users (0.90, 95 % CI 0.83–0.99). Furthermore, PPI use was associated with worse outcomes in patients treated with clopidogrel (estimated hazard ratio 2.39, 95 % CI 1.74–3.28), but not with aspirin (1.04, 95 % CI 0.70–1.57). In CREDO, clopidogrel did not influence the risk of the primary end point (all-cause death, MI, or stroke) after 1 year among PPI users (0.82, 95 % CI 0.48–1.40), while lowering it for PPI non-users (0.71, 95 % CI 0.52 to 0.98) [47].

Charlot et al. performed a nationwide cohort study of Danish patients with a first-ever MI (n = 56,406). Among clopidogrel-treated patients, PPI use was associated with a 29 % increased risk of cardiovascular death or re-hospitalization for MI or stroke. Interestingly, no statistically significant interaction between clopidogrel and PPI use was found, and PPI use also increased cardiovascular risk by 29 % in patients not treated with clopidogrel [89]. This premise, that PPI use may be a marker of increased cardiovascular risk rather than the actual cause of this risk, is consistent with other studies [47, 91–94]. Importantly, this highlights unmeasured confounding as an important limitation of studies, in which PPI treatment is not assigned randomly.

Among three randomized placebo-controlled trials to address this topic [80, 95, 96], the trial that most soundly appraised and defined the impact of PPI treatment on cardiovascular protection accounted for by clopidogrel is the COGENT trial, published in 2010 [80]. In this trial, 3873 patients undergoing PCI were randomized to receive either clopidogrel and omeprazole (administered as a combination tablet of clopidogrel 75 mg and omeprazole 20 mg) or clopidogrel only on top of aspirin. As expected, PPI reduced upper gastrointestinal events (1.1 % vs. 2.9 %; hazard ratio 0.34, 95 % CI 0.18–0.63) and upper gastrointestinal bleeding (0.2 % vs. 1.2 %; hazard ratio 0.13, 95 % CI 0.03–0.56) at 6 months, and this was achieved without increasing cardiovascular event rates or mortality (4.9 % vs. 5.7 %, hazard ratio 0.99, 95 % CI 0.68–1.44) [80]. The primary limitation of COGENT was that the trial was halted prematurely due to lack of funding, thus making it underpowered for cardiovascular end

points. Furthermore, event rates were very low, and no genotyping was performed. Finally, the investigators employed a proprietary formulation of omeprazole and clopidogrel intended for the separated release of the two drugs. In theory, this would tend to attenuate a potential drug interaction [97, 98], although this hypothesis was discredited in a meticulous pharmacodynamic study [99]. Despite these important limitations, the key lesson learned from COGENT is that a clinically meaningful interaction between PPIs (omeprazole) and clopidogrel is unlikely, and even if PPIs reduce the antiplatelet effect of clopidogrel and/or aspirin, such effects seem to be outweighed by a reduction in bleeding events, presumably by increased adherence to antiplatelet medications. The results of two other randomized trials, although underpowered for clinical end points, suggest no increased cardiovascular risk in PPI users compared to non-users [95, 96].

Most recently, a meta-analysis scrutinized the conflicting results between randomized trials and observational studies [100]. In particular, co-treatment with dual antiplatelet therapy (aspirin and clopidogrel) and PPIs as a class was associated with a poor clinical outcome in patients with unstable angina or non-ST elevation MI. PPIs increased the 1-year composite end point (all-cause mortality and non-fatal MI) as well as the 1-year rates of all-cause mortality, non-fatal MI, and revascularization. In contrast, four randomized trials (omeprazole versus placebo) found no differences in terms of ischemic events. The authors conclude that unmeasured confounding in observational studies is the likely explanation of the discordant results between randomized trials and observational studies [100, 101].

9 Interaction Between Proton Pump Inhibitors and Prasugrel or Ticagrelor

Pharmacodynamic studies have shown that PPIs (lansoprazole, pantoprazole, and esomeprazole) do not reduce the antiplatelet effect of prasugrel among healthy individuals [63] or patients with ACS [102]. In a *post-hoc* analysis of PRINCIPLE-TIMI 44, in which platelet inhibition with clopidogrel vs. prasugrel was evaluated by platelet aggregometry, a modest difference was seen between patients with and without PPI treatment in the prasugrel-arm (69.6 ± 13.5 % vs. 76.7 ± 12.4 %, $p = 0.054$) [64]. However, in the TRITON-TIMI 38 trial comparing clopidogrel vs. prasugrel in ACS, PPI use was not associated with the occurrence of the primary end point for patients treated with prasugrel (adjusted hazard ratio 1.00, 95 % CI 0.84–1.20) [64].

Ticagrelor is not a prodrug (Table 1), and the antiplatelet effect of this drug is not dependent on the hepatic CYP system. Intuitively, a drug interaction between ticagrelor and PPIs is therefore unlikely. According to a *post-hoc* analysis of PLATO, the use of PPIs in the ticagrelor-arm was associated with increased risk of cardiovascular events. However, a similar association was seen with non-PPI antacid drugs (H_2 receptor antagonists) [94]. Non-use of gastroprotective agents (PPIs or H_2 receptor antagonists) was associated with a significantly better cardiovascular prognosis, which may indicate that the association between PPI use and cardiovascular events merely represents confounding rather than a true drug interaction [94].

10 Discussion

PPIs should be reserved for patients at increased risk of gastrointestinal complications, as reflected by European and American recommendations on the combined use of antiplatelet agents and PPIs [4, 5]. Patients at increased risk are those with previous ulcer or bleeding, but other important risk factors to consider are *Helicobacter pylori* colonization, hemorrhagic diathesis, high age (≥65 years), and concomitant use of drugs that may increase the risk of bleeding risk, such as anticoagulant drugs, non-steroidal anti-inflammatory drugs, steroids, *etc*. In the presence of these risk factors, PPIs should always be considered, simply because they are the most effective means to prevent gastrointestinal bleeding in high-risk patients [103]. PPIs with low potency towards

CYP2C19 (*e.g.* pantoprazole) may preferably be used with clopidogrel, although the clinical support for this recommendation is rather weak [35]. Concerning aspirin, low doses should be used. In the setting of ACS, cardiovascular protection with aspirin doses <100 mg is just as effective as higher doses, but with reduced risk of gastrointestinal bleeding [104].

Gastrointestinal discomfort is an important cause of non-adherence to antiplatelet medications, especially aspirin. This was reflected in the pivotal CAPRIE trial (aspirin 325 mg vs. clopidogrel 75 mg in cardiovascular high-risk patients), in which 40 % of patients who discontinued aspirin treatment did so because of dyspepsia [41, 105]. The importance of this can hardly be overestimated, as premature discontinuation of antiplatelet treatment in patients with cardiovascular disease dramatically increases the risk of adverse outcomes [106, 107]. This obviously argues in favor of concomitant PPI treatment to avoid gastrointestinal complications during antiplatelet treatment. On the other hand, the number of prescribed medications [108] and the dosing frequency [109] are known to be inversely related to treatment adherence. In essence, this means that the more medications prescribed by the doctor, the less likely the patient will be to adhere to drug therapy. Nonetheless, continued aspirin treatment in patients suffering aspirin-related gastrointestinal bleeding reduces overall mortality [58], and PPI co-treatment likely carries a beneficial risk-to-benefit profile in patients at risk of gastrointestinal complications [41]. In this context it is interesting that single pill combinations (aspirin + esomeprazole) have been developed and likely provide a level of platelet inhibition equal to that provided by aspirin alone [43]. Indeed, single pill combinations have been shown to increase treatment adherence by 30 % compared to the same drugs given as free-drug combinations [110]. A combination tablet containing aspirin and omeprazole (PA32540) has recently been tested in two phase III trials [48] and an open-label safety trial [57] for secondary cardiovascular prevention, while formulations combining an ADP receptor antagonist with a PPI have not been developed.

The intense debate throughout the last decade has been nourished mainly by studies, of which the design, end point, and/or statistical power was insufficient to definitively determine the clinical impact of combining PPIs with antiplatelet drugs. Extrapolating from surrogate end points (*e.g.* *ex vivo* platelet function) to hard clinical end points (*e.g.* MI or death) carries a considerable risk of reaching faulty conclusions. As documented in a recent systematic review, there are strong indications of reduced antiplatelet activity *ex vivo* in clopidogrel users taking a PPI, while data on the clinical consequences are controversial [111]. In conclusion, there is no one-to-one translation of impaired *ex vivo* platelet inhibition into adverse clinical outcome. In observational studies, statistical methods like multivariable adjustment and propensity score-matching may reduce, yet never eliminate the risk of residual confounding. The main problem is that cohort studies and registries are inherently limited by the fact that PPIs were not randomly assigned in the study population. True cause-and-effect relationships thus cannot be inferred. This, however, does not mean that non-randomized studies are redundant. They are inexpensive, practically feasible, and hypothesis-generating, and they often serve as precursors for randomized studies with more solid conclusions. Reflecting the suboptimal evidence in this field, the only large randomized clinical trial, the COGENT trial [80], was underpowered for its cardiovascular end point, thus leaving us with few definitive answers. Of particular importance, as suggested in several studies [47, 89, 91–94], we cannot exclude that PPI use merely represents a marker of increased cardiovascular risk rather than the actual cause of the risk.

11 Conclusion

Current evidence argues in favor of continued use of PPIs in patients at risk of gastrointestinal complications, particularly bleeding [4, 5, 35]. However, more studies are warranted, preferably randomized placebo-controlled trials, and we should embrace any attempt to advance our understanding of PPIs and antiplatelet drugs. Prasugrel and ticagrelor have recently been

introduced, but evidence is particularly sparse for these drugs. At present, clinically important drug interactions do not seem to exist between PPIs and antiplatelet drugs, but given the vast number of patients treated with these drugs, even minor drug interactions in subsets of patients may have profound clinical impact.

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