

# Treatment with clopidogrel and proton pump inhibitors in combination: a review of emerging evidence

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## ABSTRACT

**Proton pump inhibitors often are prescribed in combination with clopidogrel to decrease risk of gastrointestinal bleeding after acute coronary syndrome. Clopidogrel is a prodrug that has to be metabolized in the liver to generate the active metabolite. Both medications are metabolized largely by the CYP2C19 enzyme; therefore, concerns exist that a drug-drug interaction during concomitant treatment with clopidogrel and a proton pump inhibitor may result in reduction of platelet inhibition. We have reviewed observational and randomized control studies that have evaluated the potential influence of proton pump inhibitors on the platelet inhibitory effect of clopidogrel, along with cardiovascular outcomes. We also have summarized regulatory and academic guidelines for treatment of patients in which concomitant therapy with clopidogrel and proton pump inhibitors may be indicated. Confounding issues, including differential effects of individual proton pump inhibitors on the pharmacodynamics of clopidogrel and variation in clopidogrel metabolism mediated by CYP2C19 gene polymorphisms, also are discussed.**

**Keywords:** Proton Pump Inhibitors; Clopidogrel; Dual Antiplatelet Therapy; Drug-Drug Interaction; Gastrointestinal Bleeding; Myocardial Infarction; Percutaneous Coronary Intervention

## 1. INTRODUCTION

Clopidogrel is recommended for inhibition of platelet activation and aggregation in patients who are unable to take aspirin or in combination with aspirin in patients with unstable angina or myocardial infarction (MI) or who undergo percutaneous coronary intervention (PCI) [1,2]. Gastrointestinal (GI) bleeding occurs in approximately 2% of patients who are administered dual antiplatelet therapy after PCI [3]; proton pump inhibitors (PPIs) of-

ten are prescribed to decrease this risk [2]. Addition of a PPI to treatment with aspirin and clopidogrel alone or in combination is recommended for patients with unstable angina or non-ST elevation MI and history of GI bleeding [1]. Of the 4162 patients enrolled in the Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction (PROVE IT-TIMI) 22 trial who had been hospitalized for acute coronary syndrome (ACS), 781 (18.8%) received treatment with a PPI [4]. Moreover, PPI use increased with increased number of GI risk factors such as prior GI events and use of anticoagulants [4].

Concomitant treatment with clopidogrel and PPI has been shown to be beneficial for the prevention of GI bleeding. A case-control study of 2777 patients with upper GI peptic ulcer bleeding and 5532 control subjects without GI bleeding showed that the addition of a PPI to treatment with clopidogrel or ticlopidine was associated with a reduction in bleeding (adjusted relative risk, 0.19; 95% confidence interval [CI], 0.07 - 0.49) compared with clopidogrel or ticlopidine treatment alone [5]. A six-month, open-label trial of 165 patients with atherosclerosis, a history of peptic ulcer, and clopidogrel treatment for at least two weeks who were randomized to receive clopidogrel (75 mg/d) alone or in combination with esomeprazole (20 mg/d) demonstrated that fewer patients treated with clopidogrel plus esomeprazole (1.2%) had recurrent gastric or duodenal ulcers compared with clopidogrel treatment alone (11.0%;  $p = 0.009$ ) [6]. In addition, a retrospective cohort study of 347 patients treated with dual antiplatelet therapy showed that the addition of a PPI decreased the risk for a major bleed (defined as a bleed resulting in death, transfusion, or hospitalization) in patients with an additional risk factor for bleeding ( $p = 0.05$ ) compared with patients not on a PPI [7].

Concerns have been raised that a drug-drug interaction during concomitant treatment with clopidogrel and a PPI may result in the reduction of platelet inhibition. Clopidogrel is metabolized by CYP450 enzymes to pro-

duce the active metabolite that inhibits platelet aggregation [8]. Metabolism of clopidogrel occurs through two distinct pathways: esterase-mediated hydrolysis into an inactive derivative and activation by multiple cytochrome P450 (CYP) enzymes, including CYP2C19, CYP3A, CYP2B6, and CYP1A2 [8]. Inhibitors of the CYP enzymes that metabolize clopidogrel may decrease production of active clopidogrel metabolite in some patients. PPIs also are metabolized extensively by CYP2C19 and inhibit CYP2C19 active sites competitively [9-13] with varying degrees of potency (Table 1) [14]. This review summarizes the key studies that have been designed to examine the potential pharmacodynamic effect of PPIs on clopidogrel efficacy and clinical outcomes. We searched the PubMed database on April 14, 2011, using the term "clopidogrel and proton pump inhibitor."

The search results were limited to articles reporting data from clinical trials and randomized controlled trials in the English language. We selected articles based on study design and included other relevant articles as appropriate.

## 2. EVALUATION OF CONCOMITANT TREATMENT WITH CLOPIDOGREL AND PPIs

### 2.1. Retrospective Studies

Blood samples collected immediately after PCI for coronary artery disease from 300 patients treated with aspirin (100 mg/d) and clopidogrel (600-mg loading dose followed by 75 mg/d) for at least five days (mean time, three months) before intervention showed that platelet reactivity index (PRI) and platelet aggregation was similar in patients who were or were not treated concomitantly with a PPI [15]. The effect of PPI use on platelet

**Table 1.** Inhibitory potency of proton pump inhibitors for human cytochrome P450 2C19 [14].

PPI	$K_i$ Values ( $\mu$ M) for CYP2C19 <sup>a</sup>	
	<i>S</i> -mephenytoin	4'-hydroxylation
Lansoprazole	0.45 $\pm$ 0.07	0.74 $\pm$ 0.09
Rabeprazole thioether <sup>b</sup>	2.4 $\pm$ 0.1	2.8 $\pm$ 0.1
Omeprazole	6.2 $\pm$ 0.8	2.4 $\pm$ 0.05
Esomeprazole	8.6 $\pm$ 1.0	7.9 $\pm$ 0.5
Rabeprazole	21.3 $\pm$ 2.8	18.8 $\pm$ 1.3
Pantoprazole	69.4 $\pm$ 9.2	15.3 $\pm$ 1.1

<sup>a</sup>All  $K_i$  values were calculated for inhibition of CYP2C19 *in vitro* using marker substrates *S*-mephenytoin and 4'-hydroxylation [14]. Smaller  $K_i$  values correlate with increased potency for enzyme inhibition. <sup>b</sup>Rabeprazole also is metabolized by systemic non-enzymatic reduction to a thioether analog [9, 14]. CYP = cytochrome P450;  $K_i$  = inhibition constant; PPI = proton pump inhibitor. Adapted with permission from Li, X.-Q., Andersson, T.B., Ahlström, M., Weidolf, L. (2004) Comparison of inhibitory effects of the proton pump-inhibiting drugs omeprazole, esomeprazole, lansoprazole, pantoprazole, and rabeprazole on human cytochrome p450 activities. *Drug Metabolism and Disposition: The Biological Fate of Chemicals*, 32, 821-827 [14].

reactivity also was evaluated in a study of 230 patients on dual antiplatelet therapy (aspirin 100 mg/d and clopidogrel 75 mg/d with a 300- or 600-mg loading dose for patients initiating therapy) after PCI with endovascular stent implantation; 135 patients (58.7%) were treated continuously with a PPI for at least three months before PCI [16]. Platelet function tests performed  $\geq$  24 hours after PCI (mean time, 38 hours after loading dose) showed no attenuation of platelet reactivity with PPI use compared with clopidogrel alone ( $p \geq 0.06$ ) [16].

Retrospective analyses also have evaluated the effect of treatment with clopidogrel and a PPI on clinical outcomes in patients with acute MI or undergoing PCI (Table 2). In these studies, clopidogrel was used concomitantly with a PPI in approximately 15% - 64% of patients [17-30]. Several studies have shown that concomitant use of a PPI with clopidogrel is associated with increased risk of cardiovascular complications (including MI) compared with those receiving clopidogrel alone; however, associations were not reported consistently for all end points [17,18,20-23,25,26,29]. In contrast, other studies have demonstrated no association between concomitant PPI use with clopidogrel and adverse cardiovascular outcomes in patients with cardiovascular or cerebrovascular disease [19,24,27,28,30].

### 2.2. Randomized Controlled Trials

Results from randomized controlled studies are now emerging to inform the evidence base regarding treatment with clopidogrel in combination with PPIs (Table 3). In a double-blind study of patients undergoing coronary artery stent implantation receiving aspirin (75 mg/d) and clopidogrel (loading dose 300 mg followed by 75 mg/d), concomitant treatment with omeprazole (20 mg/d) resulted in decreased clopidogrel platelet inhibitory effect on day seven ( $p < 0.0001$ ) [31]. However, a randomized, double-blind, placebo-controlled, multi-center study of patients treated with dual antiplatelet therapy with aspirin (75-325 mg/d) and clopidogrel (75 mg/d) found no association between treatment with omeprazole (20 mg/d) and a composite end point of death from cardiovascular causes, nonfatal MI, coronary revascularization, or ischemic stroke ( $p = 0.98$  by log-rank test) [32].

In a *post hoc* analysis of the randomized, double-blind Platelet Inhibition in Children on Clopidogrel (PICOLO) study, platelet aggregation was evaluated in children aged 0-24 months with cardiac disease who received PPI and clopidogrel ( $n = 5$ ) versus clopidogrel alone ( $n = 44$ ). In a subgroup of clopidogrel responders, a lower percent inhibition of maximum extent of aggregation was observed in patients who received PPI plus clopidogrel versus those who received clopidogrel alone ( $p = 0.04$ ), but this effect did not reach significance in the overall

**Table 2.** Observational studies assessing the effect of treatment with clopidogrel and proton pump inhibitors on clinical outcomes in patients with cardiovascular disease.

Study	Design	End Point by PPI Exposure	Adjusted Ratio (95% CI)
Juurlink <i>et al.</i> (2009) [17]	Population-based, nested case-control (3:1) study of patients ( $\geq 66$ years) who filled a prescription for clopidogrel after hospitalization for acute MI (N = 2791)	Recurrent MI in < 90 days (n = 734 cases) <sup>a</sup>	OR
		Current PPI use	1.27 (1.03 - 1.57)
		Previous PPI use	0.86 (0.63 - 1.19)
		Remote PPI use	0.81 (0.46 - 1.41)
Ho <i>et al.</i> (2009) [18]	Retrospective cohort study of patients prescribed clopidogrel at hospital discharge after acute MI or unstable angina (N = 8205; n = 5244 with PPI)	Combined end point of all-cause mortality or re-hospitalization for ACS	OR
		Re-hospitalization for ACS	1.25 (1.11 - 1.41)
		Revascularization procedures <sup>b</sup>	1.86 (1.57 - 2.20)
		All-cause mortality	1.49 (1.30 - 1.71)
Rassen <i>et al.</i> (2009) [19]	Retrospective cohort study (pooled from three databases) of patients who initiated clopidogrel therapy $\leq 7$ days after PCI or re-hospitalization after ACS (N = 18,565; n = 3996 with PPI)	MI hospitalization and death	RR
		MI hospitalization	1.22 (0.99 - 1.51); p=0.31
		All-cause mortality	1.22 (0.95 - 1.57); p=0.32
		Revascularization	1.20 (0.84 - 1.70); p=0.36
Evanchan <i>et al.</i> (2010) [20]	Retrospective observational study of patients discharged on clopidogrel after hospitalization for acute MI with PCI and coronary stent placement (N = 5794; n = 1369 with PPI)	Recurrent acute MI	OR
			1.78 (1.55 - 2.07)
Gaglia <i>et al.</i> (2010) [29]	Retrospective database analysis of patients who underwent PCI with drug-eluting stents discharged with 325 mg/d aspirin and clopidogrel for $\geq 6$ months (N = 820; n = 318 with PPI)	Major adverse cardiac events (including death from all causes, Q-wave myocardial infarction, target vessel revascularization, and stent thrombosis) at 1 year	HR
			1.8 (1.1 - 2.7); p=0.01
Gupta <i>et al.</i> (2010) [21]	Retrospective cohort study of patients treated with 75 mg/d clopidogrel at discharge following PCI (N = 315; n = 72 with PPI)	Composite end point of major adverse CV events <sup>c</sup>	OR
		Death	1.95 (1.09 - 3.49)
		Target lesion revascularization	1.20 (0.53 - 2.70)
		Target vessel failure	1.57 (0.80 - 3.03)
Huang <i>et al.</i> (2010) [22]	Retrospective cohort study of patients treated with clopidogrel after PCI (N = 3278; n = 572 with PPI)	Re-hospitalization	HR
		Revascularization	1.23 (1.07 - 1.41); p = 0.003
		All-cause mortality	1.02 (0.86 - 1.21); p = 0.825
Kreutz <i>et al.</i> (2010) [23]	Retrospective cohort analysis of patients ( $\geq 18$ years) who initiated clopidogrel therapy $\leq 1$ month after hospitalization for PCI with coronary stent placement (N = 16,690; n = 6828 with PPI)	Composite of major adverse CV events <sup>d</sup> in patients	HR
		Individual components	1.51 (1.39 - 1.64); p < 0.001
		Stroke or transient ischemic attack	1.48 (1.08 - 2.01); p = 0.0135
		MI or unstable angina	1.70 (1.53 - 1.89); p < 0.001
Ray <i>et al.</i> (2010) [24]	Retrospective cohort study of patients ( $\geq 30$ years) treated with clopidogrel after hospitalization for serious coronary heart disease (N = 20,596; n = 7953 with PPIs)	Coronary revascularization	1.35 (1.22 - 1.50); p < 0.001
		CV death	1.10 (0.51 - 2.40); p = 0.8041
		Acute MI/sudden cardiac death	HR
		Stroke	0.91 (0.75 - 1.09)
Stockl <i>et al.</i> (2010) [25]	Retrospective cohort study of patients (18 - 84 years) who filled prescriptions for clopidogrel after hospital discharge for MI or coronary stent placement (N = 7049; n = 1033 with PPI)	Other CV death	1.21 (0.82 - 1.78)
		All serious CV disease <sup>e</sup> (composite)	1.06 (0.65 - 1.74)
		Re-hospitalization for MI	HR
		Re-hospitalization for MI or coronary stent placement	0.99 (0.82 - 1.19)
van Boxel <i>et al.</i> (2010) [26]	Retrospective cohort study of patients ( $\geq 18$ years) treated with clopidogrel (N = 18,139; n = 5734 with PPI <sup>f</sup> )	Composite end point	HR
		Individual components	1.75 (1.58 - 1.94)
		MI	1.93 (1.40 - 2.65)
		Unstable angina pectoris	1.79 (1.60 - 2.03)
		Stroke	1.13 (0.78 - 1.65)
	All-cause mortality	1.79 (1.44 - 2.22)	

Study	Design	Outcomes	HR
Banerjee <i>et al.</i> (2011) [27]	Retrospective cohort study of patients treated with clopidogrel after hospitalization for uncomplicated PCI with coronary stent implantation (N = 23,200; n = 3712 with continuous clopidogrel ± PPI use at ≤ 6 years <sup>a</sup> )	Outcomes within 1 year of PCI	
		Death	1.16 (0.87 - 1.55)
		Death or MI	1.20 (1.02 - 1.41)
		Repeat vascularization	1.18 (1.01 - 1.30)
		Major adverse CV events	1.19 (1.06 - 1.33)
		Outcomes within 6 years of PCI	
		Death	1.32 (1.00 - 1.73)
		Death or MI	1.26 (1.08 - 1.48)
		Repeat vascularization	1.22 (1.05 - 1.42)
		Major adverse CV events	1.24 (1.11 - 1.38)
Juurlink <i>et al.</i> (2011) [30]	Population-based, nested case-control study of Ontario residents (≥ 66 years) treated with clopidogrel after stroke (N = 2765)	Outcomes within 180 days of event	
		Recurrent stroke	1.05 (0.60 - 1.82)
		All-cause mortality	1.84 (0.88 - 3.89)
		In-hospital outcomes	OR
		Death	1.04 (0.61 - 1.77)
Simon <i>et al.</i> (2011) [28]	Retrospective cohort study of patients (> 18 years) admitted to an intensive care unit with definite MI within 48 hours of symptom onset and were prescribed clopidogrel at discharge (N = 2353; n = 1453 with PPI <sup>b</sup> )	Reinfarction	1.15 (0.57 - 2.32)
		Stroke	0.33 (0.12 - 0.92)
		Major bleed	0.87 (0.44 - 1.74)
		Transfusion	0.79 (0.47 - 1.32)
		Outcomes at 1 year	
		Death, MI, or stroke	0.98 (0.90 - 1.08)
		Death	0.97 (0.87 - 1.08)

<sup>a</sup>Exposure to PPIs was defined as current, within 30 days before index date; previous, 31 - 90 days before index; remote, 91 - 180 days before index date; <sup>b</sup>Includes PCI or CABG; <sup>c</sup>Defined as the composite of death (cardiac and noncardiac), nonfatal MI, and target vessel failure (cardiac death, MI, clinically driven target lesion, or target vessel vascularization); <sup>d</sup>Defined as hospitalization for a cerebrovascular event (stroke or transient ischemic attack), ACS (MI or unstable angina), CV death (cardiac arrest or sudden death), or coronary revascularization (CABG or PCI); <sup>e</sup>Acute MI or sudden cardiac death, nonfatal or fatal stroke, or other CV death; <sup>f</sup>Defined as a minimum of 80% overlap between PPI and clopidogrel use or concurrent use of both medications within 7 days before or at the time of a possible event; <sup>g</sup>Exposure derived from dispensing records using prescription release dates and days of supply. Continuous exposure was defined as consistent and uninterrupted exposure to clopidogrel and consistent use of a PPI; <sup>h</sup>Defined as receipt of PPI therapy at 48 hours after MI symptom onset and at discharge; ACS = acute coronary syndrome; CABG = coronary artery bypass graft; CI = confidence interval; CV = cardiovascular; HR = hazard ratio; MI = myocardial infarction; OR = odds ratio; PCI = percutaneous coronary intervention; PPI = proton pump inhibitor; RR = risk ratio.

**Table 3.** Prospective randomized clinical trials evaluating the potential drug-drug interaction between clopidogrel and PPI use.

Study	Design	Study Groups	End Point	Results
Gilard <i>et al.</i> (2008) [31]	Randomized, double-blind, 7-day, placebo-controlled study of patients undergoing elective coronary stent implantation and treated with aspirin (75 mg/d) and clopidogrel (loading dose of 300 mg followed by 75 mg/d)	Omeprazole 20 mg/d, aspirin, and clopidogrel (n = 64)	Mean (SD) PRI on day 7	Omeprazole: 51.4% (16.4) Placebo: 39.8% (15.4), p < 0.001
		Placebo, aspirin, and clopidogrel (n = 60)	Percentage of poor responders to clopidogrel <sup>a</sup>	Omeprazole: 60.9% Placebo: 26.7%, p < 0.001
Bhatt <i>et al.</i> (2010) [32]	Randomized, double-blind, placebo-controlled, multi-center study (COGENT) of patients (≥ 21 years) who anticipated treatment with clopidogrel and aspirin <sup>b</sup> for ≥ 12 months <sup>c</sup>	Omeprazole 20 mg/d and clopidogrel 75 mg/d (n = 1876) <sup>c</sup>	Composite of CV events <sup>d</sup>	HR for omeprazole users: 0.99 (95% CI, 0.68 - 1.44; p = 0.96)
		Placebo and clopidogrel 75 mg/d (n = 1885)	MI Revascularization	HR: 0.92 (0.44-1.90; p = 0.81) HR: 0.91 (0.59 - 1.38; p = 0.64)

<sup>a</sup>Defined as PRI > 50%; <sup>b</sup>All patients were treated with enteric-coated aspirin (75 - 325 mg/d); <sup>c</sup>Includes patients who presented with ACS or PCI with stent implantation; <sup>d</sup>Composite end point included death from CV causes, nonfatal MI, coronary revascularization, or ischemic stroke; ACS = acute coronary syndrome; CI = confidence interval; CV = cardiovascular; HR = hazard ratio; MI = myocardial infarction; PCI = percutaneous coronary intervention; PPI = proton pump inhibitor; PRI = platelet reactivity index; SD = standard deviation.

cohort [33]. A *post hoc* analysis of randomized, double-blind studies of patients treated with clopidogrel in the Prasugrel in Comparison to Clopidogrel for Inhibition of Platelet Activation and Aggregation trial (PRINCIPLE-TIMI 44) and Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel (TRITON-TIMI 38) assessed the association between PPI use, measures of platelet function, and clinical outcomes [34]. In the PRINCIPLE-TIMI 44 trial, 28 of 99 patients (28.3%) undergoing cardiac catheterization with

planned PCI randomized to receive high-dose clopidogrel (600-mg loading dose followed by 150 mg/d) also were treated with a PPI. Inhibition of platelet aggregation was lower in patients treated with a PPI 2, 6, and 18-24 hours after administration of the clopidogrel loading dose (p ≤ 0.03); no significant differences were observed 0.5 hours after the loading dose or after 15 days of maintenance therapy with clopidogrel. Thienopyridine hyporesponsiveness was more frequent with PPI versus no PPI treatment 24 hours after the clopidogrel loading



12.04%, respectively;  $p = 0.141$ ). No significant differences were seen in the percentages of patients who did not respond to clopidogrel treatment [42].

Several retrospective studies evaluating the interaction between clopidogrel and PPIs as a class has included sub-analyses comparing the effects of individual PPI medications. A stratified analysis of the type of PPI used from a case-control study of patients who filled a prescription for clopidogrel after discharge for acute MI demonstrated that pantoprazole was not associated with recurrent MI (adjusted odds ratio, 1.02; 95% CI, 0.70 - 1.47), whereas patients taking other PPIs were collectively associated with 40% increase in risk of recurrent MI (adjusted odds ratio, 1.40; 95% CI, 1.10 - 1.77) [17]. However, there is no significant difference between the effect of pantoprazole and the effect of the other PPIs [43]. In another study, a subgroup of 659 patients who were treated with pantoprazole and clopidogrel had an increased risk of recurrent hospitalization for MI (adjusted hazard ratio, 2.18; 95% CI, 0.88 - 5.39;  $p = 0.09$ ) or for MI or coronary stent placement (adjusted hazard ratio, 1.91; 95% CI, 1.19 - 3.06;  $p = 0.008$ ) compared with matched pairs who were not treated with a PPI [25]. No differences were observed among the use of omeprazole, pantoprazole, esomeprazole, or rabeprazole in another study of patients treated with clopidogrel concurrently; however, all individual PPIs were predictors of cardiovascular events (hazard ratios, 1.622 - 1.833) [26]. An analysis of 16,690 patients who underwent PCI with stent placement who received clopidogrel plus a PPI ( $N = 6828$ ) showed a similar increased risk of major cardio- or cerebrovascular events with each PPI (omeprazole, esomeprazole, pantoprazole, and lansoprazole) [23].

Other subgroup analyses from retrospective studies found no link between the use of a specific PPI and the pharmacodynamics or clinical efficacy of clopidogrel. Patients treated with dual antiplatelet therapy and concomitant PPI exhibited similar levels of platelet activity, regardless of individual PPI used in studies by Siller-Matula *et al.* (pantoprazole and esomeprazole) and Gremmel *et al.* (pantoprazole, esomeprazole, omeprazole, and lansoprazole) [15,16]. In a cohort of 20,596 clopidogrel users, individual PPI (esomeprazole, omeprazole, pantoprazole, rabeprazole, or lansoprazole) use was not associated with a statistically significant increase in serious cardiovascular disease, defined as acute MI, coronary artery revascularization, or unstable angina pectoris [24]. Also, no increased risk of in-hospital or one-year cardiovascular events were observed in patients treated with clopidogrel and omeprazole, esomeprazole, lansoprazole, or pantoprazole after acute MI [28]. In addition, no significant risk of major adverse cardiac events, death, Q-wave MI, target vessel vascularization, or cumulative stent

thrombosis was reported in a population of 820 patients undergoing PCI and treated with dual antiplatelet therapy concomitantly with esomeprazole, lansoprazole, omeprazole, pantoprazole, or rabeprazole [29].

#### 4. CLOPIDOGREL AND PPI COMBINATION THERAPY BY CYP2C19 GENOTYPE

Several pharmacokinetic and antiplatelet tests have shown that clopidogrel levels and antiplatelet effects differ with CYP2C19 enzyme genotype, and additional studies are ongoing [44,45]. Specifically, the CYP2C19\*1 allele allows for fully functional metabolism of clopidogrel, while CYP2C19\*2 and CYP2C19\*3 have no functional metabolism. Alleles CYP2C19\*4-\*8 occur less frequently but may be associated with absent or reduced metabolism of the drug, and patients with two loss-of-function alleles will be poor metabolizers of clopidogrel [44]. The US Food and Drug Administration (FDA) added a boxed warning to the label for clopidogrel in March 2010 that warns about reduced effectiveness in patients who are poor metabolizers, informs that tests are available to identify genetic differences in CYP2C19 function, and advises consideration of other antiplatelet medications or alternative clopidogrel dosing strategies for poor metabolizers [44].

The clinical effects of clopidogrel in combination with PPIs are now being investigated in patients with loss-of-function CYP2C19 alleles. Response to induced platelet aggregation was examined in 15 healthy subjects with CYP2C19\*1\*1 alleles and 15 subjects with heterozygous CYP2C19\*1\*2 alleles who were treated with clopidogrel (75 mg/d) for seven days [46]. After a two-week washout, poor responders to clopidogrel (<40% inhibition to induced platelet aggregation) were treated with an increased clopidogrel maintenance dose of 150 mg/d for seven days. After a one-week washout, responders received lansoprazole (30 mg/d) for seven days followed by lansoprazole (30 mg/d) in combination with clopidogrel (75 mg/d) for an additional seven days. Of the nine subjects who were classified as poor responders, all were carriers of the CYP2C19\*2 allele. Treatment with 150 mg/d clopidogrel resulted in all poor responders becoming responders with a mean induced platelet aggregation increasing from 26.4% to 54.5% ( $p < 0.0001$ ). Mean induced platelet aggregation in responders was similar with seven days of lansoprazole and clopidogrel treatment (52.1%) compared with clopidogrel treatment alone (58.3%;  $p = 0.094$ ), although 3 of 21 subjects became poor responders. Concomitant treatment with lansoprazole decreased the mean PRI compared with clopidogrel treatment alone (55.3% versus 46.9%;  $p = 0.001$ ); however, this effect was not significant in CYP2C19\*2 carriers compared with CYP2C19\*1/\*1 ( $p = 0.11$ ) [46].

**Table 4.** Summary of recent guidelines and recommendations regarding treatment with clopidogrel and PPIs in combination.

Regulatory Agency/Society	Publication Date	Summary of Recommendations/Statements
European Medicines Agency [48]	May 2009	<p>“Product information for all clopidogrel-containing medicines should be amended to discourage concomitant use of PPI and clopidogrel-containing medicines unless absolutely necessary.”</p> <p>“Further information is needed in relation to the inhibition of clopidogrel metabolism by other medicines, and in relation to the implications of genetic variation which results in a small proportion of individuals (so called “CYP2C19 poor metabolisers”) being unable to fully convert clopidogrel to its active form, regardless of interactions with other medicines.”</p>
Society for Cardiovascular Angiography and Interventions [49]	May 2009	<p>“More research is needed on this topic.”</p> <p>“SCAI recommends the use of alternative medications<sup>a</sup> for GI symptoms in patients with stents when appropriate.”</p> <p>“In some patients the use of PPIs may still be warranted based on the patient’s medical problems and should be taken at the direction of the patient’s cardiologist, gastroenterologist or primary physician.”</p>
US Food and Drug Administration [50]	November 2009	<p>“The concomitant use of omeprazole and clopidogrel should be avoided because of the effect on clopidogrel’s active metabolite levels and anti-clotting activity. Patients at risk for heart attacks or strokes, who are given clopidogrel to prevent blood clots, may not get the full protective anti-clotting effect if they also take prescription omeprazole or the OTC form.”</p> <p>“Separating the dose of clopidogrel and omeprazole in time will not reduce this drug interaction.”</p> <p>Other drugs should be avoided in combination with clopidogrel because they may have a similar interaction<sup>b</sup>.</p>
American College of Cardiology Foundation, American Heart Association, and Society for Cardiovascular Angiography and Interventions [2] <sup>c</sup>	December 2009	<p>“Although there are studies that show a pharmacodynamic interaction on <i>ex vivo</i> platelet function testing, to date there are no convincing randomized clinical trial data for an important clinical drug-drug interaction.”</p> <p>“Additional data, notably randomized controlled clinical trial data that have been peer reviewed and published, are needed before an official recommendation can be made about the use of dual antiplatelet therapy with PPIs in the setting of ACS.”</p>
European Medicines Agency [51]	March 2010	<p>“The class warning for all PPIs has been replaced with a warning stating that only the concomitant use of clopidogrel and omeprazole or esomeprazole should be discouraged.”</p> <p>“A description of the results of the two recent studies that show the interaction between clopidogrel and omeprazole be added to the product information.”</p>
American College of Cardiology Foundation, American College of Gastroenterology, and American Heart Association (consensus document) [52]	December 2010	<p>“Clinical decisions regarding concomitant use of PPIs and thienopyridines must balance overall risks and benefits, considering both CV and GI complications.”</p> <p>“Pharmacokinetic and pharmacodynamic studies, using platelet assays as surrogate endpoints, suggest that concomitant use of clopidogrel and a PPI reduces the antiplatelet effects of clopidogrel. The strongest evidence for an interaction is between omeprazole and clopidogrel. It is not established that changes in these surrogate endpoints translate into clinically meaningful differences.”</p> <p>“Observational studies and a single randomized clinical trial have shown inconsistent effects on CV outcomes of concomitant use of thienopyridines and PPIs. A clinically important interaction cannot be excluded, particularly in certain subgroups, such as poor metabolizers of clopidogrel.”</p> <p>“The role of either pharmacogenomic testing or platelet function testing in managing therapy with thienopyridines and PPIs has not yet been established.”</p>
American College of Cardiology Foundation and American Heart Association [1] <sup>d</sup>	May 2011	<p>“In UA/NSTEMI patients with a history of gastrointestinal bleeding, when ASA and clopidogrel are administered alone or in combination, drugs to minimize the risk of recurrent gastrointestinal bleeding (e.g., proton-pump inhibitors) should be prescribed concomitantly.”</p>

<sup>a</sup>Other effective treatments for heartburn and ulcers include histaminergic blockers or antacids; <sup>b</sup>These include esomeprazole, cimetidine, fluconazole, ketoconazole, voriconazole, etravirine, felbamate, fluoxetine, fluvoxamine, and ticlopidine; <sup>c</sup>American College of Cardiology Foundation and American Heart Association guidelines for the management of patients with ST-elevation MI (updating the 2004 guideline and 2007 focused update) and American College of Cardiology Foundation, American Heart Association, and Society for Cardiovascular Angiography and Interventions guidelines on percutaneous coronary intervention (updating the 2005 guideline and 2007 focused update); <sup>d</sup>Guidelines for management of patients with unstable angina/non-ST elevation MI. ACS = acute coronary syndrome; ASA = aspirin; CV = cardiovascular; GI = gastrointestinal; MI = myocardial infarction; OTC = over the counter; PPI = proton pump inhibitor; UA/NSTEMI = unstable angina/non-ST-segment elevation myocardial infarction.

In another study, mean IPA induced by clopidogrel was not significantly decreased by omeprazole (20 mg/d), lansoprazole (30 mg/d), or rabeprazole (20 mg/d) in healthy subjects ( $n = 39$ ); however, in subjects with CYP2C19\*1\*1 alleles (rapid metabolizers;  $n = 15$ ) concomitant administration of omeprazole or rabeprazole attenuated inhibition of induced platelet aggregation by clopidogrel compared with clopidogrel alone ( $p = 0.015$  and  $p = 0.035$ , respectively) [47]. In patients with genotypes associated with decreased metabolism of clopidogrel (CYP2C19\*1\*2 and CYP2C19\*2\*3) concomitant administration of PPIs did not decrease inhibition of clopidogrel-induced platelet aggregation, but were more likely to convert from “responder” to “non-responder” to clopidogrel with concomitant PPI use [47]. Also, separating dosing of a PPI (e.g., clopidogrel in the morning and PPI in the evening) did not prevent the interaction between clopidogrel and PPI, although the effect was improved in rapid metabolizers [47].

A sub-analysis evaluating the risk of in-hospital and one-year clinical events after MI by number of CYP2C19 loss-of-function alleles demonstrated that PPI use with clopidogrel was not associated with in-hospital death, MI, or stroke in patients with zero, one, or two variant alleles (adjusted odds ratios [95% CI]: 0.68 [0.37 - 1.25], 0.34 [0.11 - 1.08], and 1.05 [0.03 - 34.6], respectively) [28]. No effects were observed in hospital survivors at one year of clopidogrel and PPI treatment, regardless of variant alleles (adjusted hazard ratios [95% CI]: 1.13 [0.74 - 1.74], 1.02 [0.44 - 2.40], and 0.25 [0.02 - 3.58] for patients with zero, one, or two variant alleles, respectively) [28].

## 5. GUIDELINES AND RECOMMENDATIONS REGARDING TREATMENT WITH CLOPIDOGREL AND PPIs

Considering the varied evidence from observational and prospective randomized studies regarding pharmacodynamics and clinical outcomes resulting from clopidogrel-PPI interactions, regulatory organizations as well as cardiovascular and GI societies have made conflicting recommendations about concomitant use of these medications (Table 4) [48-52]. The FDA and European Medicines Agency have recommended that the use of clopidogrel in combination with omeprazole or omeprazole/ esomeprazole, respectively, should be avoided [50,51]. A consensus statement by the American College of Cardiology Foundation, American College of Gastroenterology, and American Heart Association reported that existing studies have shown inconsistent effects on cardiovascular outcomes of concomitant use of clopidogrel and PPIs; therefore, clinical decisions regarding concomitant use of PPIs and clopidogrel should balance overall risks and

benefits while considering both cardiovascular and GI complications. Concomitant therapy with aspirin, clopidogrel, and a PPI continues to be recommended in patients with unstable angina or non-ST elevation MI and history of GI bleeding to minimize the risk of recurrent GI bleeding [1].

## 6. CONCLUSIONS

New data continues to emerge regarding cardiovascular outcomes during treatment with clopidogrel and PPIs in combination. Data from retrospective studies regarding *in vitro* pharmacodynamic effects of PPIs on clopidogrel are more consistent than data from studies with clinical end points; however, it is unknown if effects of PPIs on clopidogrel-induced inhibition of platelet activation and aggregation translate to differences in clinical outcomes. Retrospective studies examining the cardiovascular effects of treatment with clopidogrel and a PPI in combination have yielded conflicting results, and more recent studies have shown a lack of effect. The only randomized controlled trial evaluating clinical cardiovascular outcomes in patients on standard dual antiplatelet therapy found no effect with concomitant PPI treatment [32].

In 2009, the FDA published statements recommending that physicians avoid the prescription of omeprazole in combination with clopidogrel [50]; however, since the publication of these statements, a wealth of data has been published on this topic, which has been summarized herein. Further research is needed to make a definitive statement about the clinical effects of individual PPIs, or their effect as a class, on the clinical efficacy of clopidogrel, although caution should be exercised when considering treatment with a PPI for any patient for whom treatment with clopidogrel or dual antiplatelet therapy is indicated. Additionally, it is unknown how concomitant administration of additional medications prescribed for treatment of cardiovascular disease may confound the pharmacodynamic effects of PPIs on clopidogrel. Genetic polymorphisms, particularly of the CYP2C19 allele, also may contribute to differences in clopidogrel and/or PPI metabolism in some patients. Additional studies are warranted that investigate more novel antiplatelet therapies in development, which may be appropriate for treatment of patients in whom PPI therapy is indicated.

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