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Clinical relevance of clopidogrel-proton pump inhibitors interaction

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Abstract

Clopidogrel is a widely used antiplatelet agent for the secondary prevention of cardiovascular events in patients with stable coronary heart disease, acute coronary syndromes and ischemic stroke. Even though clopidogrel is safer than aspirin in terms of risk for gastrointestinal (GI) bleeding, the elderly, and patients with a history of prior GI bleeding, with *Helicobacter pylori* infection or those who are also treated with aspirin, anticoagulants, corticosteroids or nonsteroidal anti-inflammatory drugs are at high risk for GI complications when treated with clopidogrel. Accordingly, proton pump inhibitors are frequently administered in combination with clopidogrel to reduce the risk for GI bleeding. Nevertheless, pharmacodynamic studies suggest that omeprazole might attenuate the antiplatelet effect of clopidogrel. However, in observational studies, this interaction does not appear to translate into increased cardiovascular risk in patients treated with this combination. Moreover, in the only randomized, double-blind study that assessed the cardiovascular implications of combining clopidogrel and omeprazole, patients treated with clopidogrel/omeprazole combination had reduced risk for GI events and similar risk for cardiovascular events than patients treated with clopidogrel and placebo. However, the premature interruption of the study and the lack of power analysis in terms of the cardiovascular endpoint do not allow definite conclusions regarding the cardiovascular safety of clopidogrel/omeprazole combination. Other proton pump inhibitors do not appear to interact with clopidogrel. Nevertheless, given the limitations of existing observational and interventional studies, the decision to administer proton pump inhibitors to patients treated with clopidogrel should be individualized based on the patient's bleeding and cardiovascular risk.

Key words: Clopidogrel; Esomeprazole; Lansoprazole; Pantoprazole; Rabeprazole; Omeprazole; Cardiovascular risk; Proton pump inhibitors

Core tip: Even though pharmacodynamic studies suggest that omeprazole can attenuate the antiplatelet effect of clopidogrel, this interaction does not appear to translate into increased cardiovascular risk in patients treated with this combination in observational studies. In the only randomized, double-blind, placebo-controlled study that assessed the cardiovascular implications of combining clopidogrel and omeprazole, patients treated with clopidogrel/omeprazole combination had reduced risk for

gastrointestinal events and similar risk for cardiovascular events. Other proton pump inhibitors also do not appear to interact with clopidogrel. However, given the limitations of existing studies, the decision to administer proton pump inhibitors to patients treated with clopidogrel should be individualized based on the patient's bleeding and cardiovascular risk.

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INTRODUCTION

Clopidogrel is a first-line antiplatelet agent for the secondary prevention of cardiovascular events in patients with stable coronary heart disease or with a history of non-cardioembolic ischemic stroke[1,2]. In addition, clopidogrel is recommended in combination with aspirin for up to 12 mo in patients with acute coronary syndrome (ACS) treated either medically or invasively[3,4]. Even though clopidogrel is safer than aspirin in terms of risk for gastrointestinal (GI) bleeding, the risk of GI bleeding is not negligible in patients treated with this agent[5,6]. Moreover, the risk of GI bleeding further increases in patients who receive clopidogrel in combination with aspirin as well as in the elderly, in patients with a history of prior GI bleeding or with *Helicobacter pylori* infection, and in those who are also treated with anticoagulants, corticosteroids or nonsteroidal anti-inflammatory drugs (NSAIDs)[7,8]. In these patients, administration of proton pump inhibitors (PPIs) significantly reduces the risk of GI bleeding associated with clopidogrel treatment[9,10]. Accordingly, PPIs are commonly prescribed in patients treated with clopidogrel to reduce the risk of GI bleeding[11,12].

Even though the administration of PPIs in patients treated with clopidogrel reduces the risk for GI bleeding, some pharmacodynamic studies suggested that the antiplatelet effect of clopidogrel is also attenuated by PPIs[13-15]. This interaction is due to the inhibition by PPIs of the cytochrome (CYP) P450 isoenzyme 2C19, which converts clopidogrel to its active metabolite[16]. Notably, PPIs differ in their ability to inhibit CYP2C19, omeprazole being a more potent inhibitor than the other members of the class[17,18]. Accordingly, some studies showed that omeprazole attenuates the antiplatelet effect of clopidogrel[13-15] but others did not confirm these findings[19,20]. In contrast, esomeprazole, lansoprazole, pantoprazole and rabeprazole did not affect platelet function in patients treated with clopidogrel[13,15,19-22].

However, it is unclear whether these *ex vivo* findings have clinical importance, *i.e.*, if the co-administration of clopidogrel with omeprazole or other PPIs will result in reduced protection against cardiovascular events. Notably, earlier studies suggested that atorvastatin attenuates the antiplatelet effects of clopidogrel *ex vivo* but this interaction did not translate into higher cardiovascular morbidity in patients receiving this combination[23-25]. Indeed, observational studies that evaluated the effect of administering PPIs in combination with clopidogrel on cardiovascular events in patients who suffered an ACS or underwent percutaneous coronary intervention (PCI) reported conflicting results. In two early retrospective studies, patients treated with clopidogrel and either omeprazole or pantoprazole had higher risk of recurrent cardiovascular events than those who were given clopidogrel alone[11,26] (Table 1). In contrast, several other retrospective studies reported that neither omeprazole nor pantoprazole increase cardiovascular morbidity when combined with clopidogrel[10,12,27-30] (Table 1). A post-hoc analysis of the randomized controlled Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction 38 also reported similar findings[31] (Table 1). In the same post-hoc analysis and in more recent observational studies, treatment with esomeprazole or lansoprazole was also not associated with increased cardiovascular risk when combined with clopidogrel[29-31] (Table 1).

Given the well-known limitations of observational studies, these results should be interpreted with caution. Patients who are given PPIs are frequently older and have more comorbidities and despite the adjustment for these differences there is always potential for residual confounding[10-12,26-31]. Indeed, some studies reported that PPI use is associated with increased risk for cardiovascular events regardless of the use of clopidogrel and in patients treated with ticagrelor, which does require activation by CYP2C19, suggesting that PPI use is a marker of increased cardiovascular risk and frailty[12,30,32,33]. Moreover, none of the above-mentioned studies could adjust for over-the-counter use of PPIs and adherence to treatment[10-12,26-31]. Many patients used PPIs intermittently, a parameter which was not considered in most studies[10-12,26-31]. Finally, most studies evaluated very-high risk patients, *i.e.*, with a recent ACS or PCI, and it is unclear whether these results are applicable to lower-risk patients, *e.g.*, those with stable angina or history of ischemic stroke[10-12,26-31]. Finally, the antiplatelet activity of clopidogrel is affected by several polymorphisms (Table 2)[34] and none of these studies evaluated this parameter[10-12,26-31]. However, both pharmacodynamic and clinical studies suggest that there is no association between CYP2C19 genotype and the impact of PPIs on the antiplatelet effect of clopidogrel[35-37].

The only randomized, double-blind, placebo-controlled study that assessed the cardiovascular implications of combining clopidogrel and omeprazole is the Clopidogrel and the Optimization of Gastrointestinal Events Trial[9]. In this trial, 3761 patients with an indication for dual antiplatelet treatment with aspirin and clopidogrel were randomly assigned to a fixed-dose combination of

Table 1 Major observational studies that evaluated the effects of coadministration of clopidogrel and proton pump inhibitors on cardiovascular events

Ref.	Population	*n*	Hazard ratio in patients who received clopidogrel and proton pump inhibitors *vs* patients treated with clopidogrel alone
[10]	Patients hospitalized for ACS or coronary revascularization	20596	0.99 (95%CI: 0.82-1.19, *P* = NS)
[11]	Patients hospitalized for ACS	8205	1.25 (95%CI: 1.11-1.41, *P* = NR)
[12]	Patients hospitalized for ACS	56406	0.98 (95%CI: 0.88-1.10, *P* = NS)
[26]	Patients hospitalized for ACS or coronary stent placement	2066	1.64 (95%CI: 1.16-2.32, *P* = 0.005)
[27]	Patients hospitalized for ACS or coronary stent placement	18565	1.22 (95%CI: 0.99-1.51 *P* = NS)
[28]	Patients hospitalized for ACS	13636	1.27 (95%CI: 1.03-1.57, *P* = NR)
[29]	Patients hospitalized for ACS	24471	0.75 (95%CI: 0.55-1.01, *P* = NS)
[30]	Patients who underwent coronary stent placement	13001	1.20 (95%CI: 0.91-1.58, *P* = NS)
[31]	Patients with ACS undergoing coronary stent placement	6795	0.94 (95%CI: 0.80-1.11, *P* = NS)

ACS: Acute coronary syndrome; NS: Non-significant; NR: Not reported.

Table 2 Polymorphisms that potentially affect the antiplatelet effect of clopidogrel

Polymorphism	Mechanism of reduced antiplatelet effect of clopidogrel
CYP2C19*2, CYP2C19*3, CYP2C19*4, CYP2C19*5, CYP2C19*6, CYP2C19*7, CYP2C19*8	Reduced metabolism of clopidogrel to its active metabolite
C3435T polymorphism of the *ABCB1* gene	Overexpression of the drug efflux pump P-glycoprotein leading to reduced intestinal absorption of clopidogrel
Q192R polymorphism of the *paraoxonase-1* gene	Reduced metabolism of clopidogrel to its active metabolite

clopidogrel/omeprazole (75/20 mg) or clopidogrel plus placebo[9]. The study was designed to end once 143 GI events (primarily bleeding) had occurred but ended prematurely due to interruption of funding after only 55 GI events had occurred[9]. Sample size calculation was not performed for the cardiovascular endpoint (nonfatal myocardial infarction, ischemic stroke, coronary revascularization or cardiovascular death)[9]. Patients treated with clopidogrel/omeprazole combination had reduced risk for GI events (1.1% *vs* 2.9% in patients treated with clopidogrel plus placebo; $P < 0.001$) and similar risk for cardiovascular events (4.9% *vs* 5.7%, respectively; $P = 0.98$)[9]. Unfortunately, the premature interruption of the study and the lack of power analysis in terms of the cardiovascular endpoint do not allow definite conclusions regarding the cardiovascular safety of clopidogrel/omeprazole combination[9]. In addition, the pharmacokinetics of the combined omeprazole-clopidogrel pill might be different from free combinations, even though data suggest that spacing the two medications does not affect the inhibitory effect of omeprazole on the antiplatelet action of clopidogrel[9,15,38].

In light of these conflicting data, the American Heart Association, American College of Cardiology and the American College of Gastroenterology issued an expert consensus document recommending that PPIs should be considered only in those patients treated with clopidogrel who are at high-risk for GI bleeding, including those with a previous history of GI bleeding, with *Helicobacter pylori* infection, who are treated with NSAIDs, corticosteroids or anticoagulants, and the elderly[16]. On the other hand, the United States Food and Drug Administration and the European Medicines Agency revised the labelling of clopidogrel, which now mentions that omeprazole and esomeprazole should be avoided in patients treated with clopidogrel, that other acid-lowering agents with minimal or no inhibitory effects on CYP2C19 should be considered and that lansoprazole and pantoprazole have less inhibitory effect on the antiplatelet action of clopidogrel than omeprazole and esomeprazole[39,40].

In conclusion, even though pharmacodynamic studies suggest that omeprazole can attenuate the antiplatelet effect of clopidogrel, this interaction does not appear to translate into increased cardiovascular risk in patients treated with this combination. Other PPIs also do not appear to interact with clopidogrel. However, given the limitations of existing studies, the decision to administer PPIs to patients treated with clopidogrel should be individualized based on the patient's bleeding and cardiovascular risk.

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