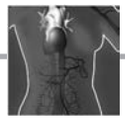
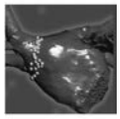
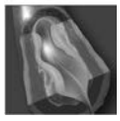

Concomitant use of clopidogrel and proton-pump inhibitor: a reality check

There are emerging reports supporting the fact that proton-pump inhibitors competitively inhibit the metabolism of clopidogrel to its active metabolite and diminish its clinical efficacy, especially in patients on long-term dual antiplatelet therapy. In this article, we examine the current evidence and provide interpretation of the results along with practical recommendations for healthcare providers.

KEYWORDS: cardiovascular outcome ■ clopidogrel ■ proton-pump inhibitor

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Consensus guidelines from the American College of Gastroenterology, the American College of Cardiology and the American Heart Association endorse the use of proton-pump inhibitor(s) (PPI) in patients judged to be at higher risk for gastrointestinal (GI) ulceration and related complications [1]. This recommendation is largely based on an observational study reporting PPI cotherapy to be beneficial in reducing the risk of upper GI bleed in patients on clopidogrel monotherapy [2]. This effect is possibly due to inhibition of the gastric parietal cell proton pump and suppression of gastric acid production by PPI, especially in aspirin-treated patients [3–5]. This recommendation has in turn fuelled widespread empiric use of PPIs, especially omeprazole in patients on dual antiplatelet therapy (DAPT) with aspirin and clopidogrel [5,6].

Mechanism

Recent studies have reported significant reduction in the antiplatelet effect of clopidogrel in patients on omeprazole [7]. *Ex vivo* studies have demonstrated an attenuated antiplatelet effect, measured by ADP-induced platelet aggregation and elevated residual platelet activity [8,9]. These studies are supported by some large retrospective analyses demonstrating excess cardiovascular events in patients taking clopidogrel with any PPI versus clopidogrel alone [10–13]. The mechanism of this adverse interaction is possibly due to competitive interference of the hepatic cytochrome P450 (CYP450) pathway by PPIs. PPIs are metabolized using the same pathway responsible for biotransformation of clopidogrel, a prodrug, into its biologically active metabolite. This may in turn lead to reduced amounts of active clopidogrel metabolite and a resultant reduction in platelet inhibition [14–15].

Current evidence

The Omeprazole Clopidogrel Aspirin (OCLA) study randomized 140 patients undergoing percutaneous coronary intervention (PCI) on clopidogrel to omeprazole 20 mg daily or placebo [16]. The primary end point was platelet reactivity index (PRI) after 7 days of concomitant exposure. A higher PRI designates lower clopidogrel response on platelet aggregation. The mean ± standard deviation PRI was measured by platelet phosphorylated vasodilator-stimulated phosphoprotein (VASP). At 7 days, PRI for the placebo group was 39.8 ± 15.4% and 51.4 ± 16.4% in the omeprazole-treated group ($p < 0.0001$). There was no significant difference in baseline PRI. Siller-Matula *et al.* then reported PRI in 300 PCI patients on clopidogrel maintenance therapy, exposed to pantoprazole and esomeprazole [8]. The mean PRI in the clopidogrel and PPI group was 51% (95% CI: 48–54%) and for the clopidogrel-only group the mean PRI was 49% (95% CI: 43–55%), indicating that pantoprazole and esomeprazole may not be competitive inhibitors of clopidogrel, unlike omeprazole. No baseline PRI was reported, and the PRI values for pantoprazole and esomeprazole were similar to that reported in the OCLA trial for omeprazole. Another study attempting to compare clopidogrel response on platelet aggregation by impedance aggregometry in 1000 PCI patients treated with omeprazole (n = 64), esomeprazole (n = 42) or pantoprazole (n = 162), was limited by having only a small number of patients on these individual PPIs [9]. Even though patients on omeprazole had a reduced response to clopidogrel compared with other PPIs (32.8 vs 19.1%; $p = 0.008$), prior myocardial infarction, diabetes, BMI and smoking were also predictors of increased aggregation.

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Table 1. Clinical trials of proton-pump inhibitor use with clopidogrel and its effect on cardiovascular outcomes.

Study (year)	Type	PPI used	Number of patients	OR/RR (end point)	95% CI	Ref.
Pezalla *et al.* (2008)	Retrospective	All	920	4.37 (MI)	–	[10]
Aubert *et al.* (2008)	Retrospective	All	14,383	1.79 (MACE)	–	[13]
Juurlink *et al.* (2009)	Retrospective	Except pantoprazole	13,636	1.27 (MI)	1.03–1.57	[11]
Ho *et al.* (2009)	Retrospective	All	8205	1.25 (Death/ACS)	1.11–1.14	[12]
Rassen *et al.* (2009)	Retrospective	All	18,565	1.22 (MACE)	0.99–1.51	[17]
O'Donoghue *et al.* (2009)	Prospective	All	6795	0.94(MACE)	0.80–1.11	[21]
Bhatt *et al.* (2009)	Prospective	Omeprazole	3627	1,02 (MACE)	0.70–1.51	[22]

MACE refers to either hospitalization for stroke, MI, angina or coronary artery bypass grafting (CABG) for Aubert et al.*; cardiovascular death, nonfatal myocardial infarction, CABG or percutaneous coronary intervention, or confirmed ischemic stroke for COGENT; a composite of cardiovascular death, myocardial infarction or stroke for O'Donoghue* et al. *and myocardial infarction or death for Rassen* et al. *ACS: Acute coronary syndrome; MACE: Major adverse cardiovascular events; MI: Myocardial infarction; OR: Odds ratio; RR: Relative ratio.*

A retrospective cohort study by Pezalla *et al.* reported 3.08 and 5.03% 1-year myocardial infarction (MI) rates for low and high PPI exposure compared with 1.38% in non-PPI exposed patients in the control group (Table 1) [10]. Juurlink *et al.*, in a case–control study from Canada, examined death and readmission for MI of 734 patients with an acute coronary syndrome (ACS) discharged on clopidogrel with or without a PPI [11]. PPI use was associated with an increased odds of MI compared with the no-PPI group (adjusted odds ratio [OR]: 1.27; 95% CI: 1.03–1.57). The study, for the first time, also examined the risk associated with specific PPIs and concluded that pantoprazole was not associated with this elevated risk of MI when used concomitantly with clopidogrel. Both studies by Pezalla and Juurlink were associated with significant differences in the comorbid conditions between the study groups. Moreover, the pantoprazole analysis by Juurlink was based upon 46 patients treated with the drug in the study cohort. Ho *et al.* have, thus far, performed the most comprehensive analysis from a Veterans Affairs database of ACS patients treated conservatively with medical therapy only, or with revascularization in addition to medical therapy [12]. In this large study sample of 5244 patients exposed to clopidogrel and a PPI, the OR of death and readmission for ACS was 1.25 (95% CI: 1.11–1.41) compared with those treated only with clopidogrel (n = 2961). Over 59% of patients in the study received omeprazole and its use was associated with an increased risk of death and readmission for ACS (OR: 1.24; 95% CI: 1.08–1.41). Importantly, this increased risk for cardiovascular events was not evident in nonclopidogrel-treated patients. A more recent analysis by Rassen *et al.* used a sophisticated multivariate analysis to report an OR of 1.22; 95% CI: 0.99–1.51, for death or MI associated with PPI use [17]. Researchers from the Medco study used data from 16,690 patients taking clopidogrel after stenting and found that the risk of major adverse cardiovascular events (MACE; hospitalization for stroke, MI, angina or coronary bypass surgery) was raised from 17.9 to 25.1% in patients also taking PPIs [13]. This study has only been presented as an abstract in the annual scientific session of the Society of Coronary Angiography and Interventions (SCAI). Another study by Dunn *et al.*, also published only as an abstract, has reported an increased risk of cardiovascular events in PPI-treated patients from the Clopidogrel for the Reduction of Events During Observation (CREDO) trial [18]. However, this substudy also demonstrated that there was no

significant difference in the therapeutic effect of clopidogrel in PPI-treated patients compared with non-PPI-treated patients. Our own data of clopidogrel and PPI use, recently presented at the European Society of Cardiology national meeting in 2009, showed an increased risk of death and MI in a small cohort of patients treated exclusively with drug-eluting coronary stents [19]. A similar, yet unpublished outcome analysis of 32,946 post-PCI patients from the Veterans Affairs National Pharmacy Management Database has shown no evidence of an adverse association with concomitant exposure to clopidogrel and PPIs [20]. Most of these high-profile studies have been retrospective and based upon discharge medications and prescription data obtained at any time during the follow-up period without an assessment of drug exposure at the time of MACE and without adequate adjustments for confounding variables. Furthermore, the studies do not account for interruption in clopidogrel or PPI use during the follow-up period and nor do they present exposure analysis at the end point. They do not account for additional factors that may contribute to variability in clopidogrel response, such as compliance with therapy, variable intestinal absorption, differences in platelet response to ADP, and genetic differences in CYP metabolic activity [15].

Nevertheless, on the basis of these early reports, over-the-counter availability of PPIs, their widespread use in patients on DAPT and the potential for harm, many national and international organizations and regulatory bodies rushed to issue position statements, warnings or guidelines on the use of PPIs and clopidogrel. The US FDA has also recently issued a warning stating, "new data show that when clopidogrel and omeprazole are taken together, the effectiveness of clopidogrel is reduced. Patients at risk for heart attacks or strokes who use clopidogrel to prevent blood clots will not get the full effect of this medicine if they are also taking omeprazole" [101]. It would not be an exaggeration to state that these recommendations have been received with great skepticism and confusion by providers and patients alike, and have ignited significant debate.

Much of the confusion arises from the fact that the above position statements disregard data from *post hoc* analysis of large randomized controlled trials that report no adverse outcome in patients exposed to clopidogrel and PPI. Data from the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel - Thrombolysis in Myocardial Infarction (TRITON-TIMI) 38 trial do not demonstrate an increased risk for MI, stroke or death in patients treated with a thienopyridine and PPI, despite inadequate inhibition of platelet aggregation observed in Prasugrel In Comparison to Clopidogrel for Inhibition of Platelet Activation and Aggregation (PRINCIPLE)-TIMI 44 study with PPI exposure [21]. In addition, the reduction in platelet inhibition in the TRITON-TIMI 38 trial is thought to be due to the presence of prevalent reduction-in-function polymorphisms of the specific CYP450 gene (*CYP2C19*) that may result in decreased efficiency of clopidogrel biotransformation to its active metabolite. In the Clopidogrel and the Optimization of Gastrointestinal Events (COGENT) trial, 3627 patients with an ACS and/or PCI were randomized to clopidogrel alone or a combined pill containing a delayed-release omeprazole core with surrounding clopidogrel 75 mg [22]. The study was terminated early for financial reasons; however, there was no increased risk of cardiovascular events observed in the clopidogrel and PPI group. Again, these studies are *post hoc* analyses of randomized trials. It can also be argued that the results from the COGENT trial merely reflect the temporal separation of pharmacodynamic effects of both the drugs released at different time points. Most PPIs have a short half-life (30 min–2 h) and separating them over time may minimize the chance of adverse interactions.

Recommendations

In terms of practical recommendations for prescribing clopidogrel and PPIs, it would be fair to say that the effect is, at best, modest; however, not trivial since it relates to death and MI. This issue has gained much traction as it does have a pharmacodynamic basis. In addition, the fact that PPIs are available over-the-counter, makes the true estimate of its effect on cardiovascular outcomes hard to assess in real time, along with increasing the potential for widespread uncontrolled use by patients, which make this an issue of great importance to resolve. Therefore, the evidence for the FDA position on the concomitant use of clopidogrel and PPI can be challenged, yet it is understandable from a public health policy perspective. Our primary recommendations for practitioners at this given time are first to avoid empiric use of PPIs with clopidogrel. Second, it might be logical to prefer pantoprazole to other PPIs. Although the FDA recommendation states that separating the dose of clopidogrel and omeprazole in time, will not reduce this drug interaction, we still advocate temporally separating the two drugs by advising

patients to take them at least 4–6 h apart. This takes into consideration the mechanism of interaction (competitive interference in metabolism of clopidogrel) and the pharmacokinetics of both drugs as most PPIs have a short half-life (30 min–2 h). We believe that these common sense measures might minimize the risk of potential adverse interaction between clopidogrel and PPIs, until more conclusive evidence on this ongoing question are presented.

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Executive summary

- There is widespread empiric prescription of proton-pump inhibitors (PPIs) to patients on clopidogrel and aspirin therapy.
- Adverse interactions are observed between PPIs and clopidogrel.
  - PPIs competitively inhibit the conversion of the clopidogrel, a prodrug to its biologically active metabolite.
- There are clinical evidence for the adverse effect of PPI coadministration with clopidogrel.
  - Retrospective analyses are limited, confounded and not supported by data from *post hoc* analysis of prospective trials.
  - Data from large randomized controlled trials report no adverse outcome in patients exposed to clopidogrel and PPIs (the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel – Thrombolysis in Myocardial Infarction [TRITON-TIMI] 38 and the Prasugrel In Comparison to Clopidogrel for Inhibition of Platelet Activation and Aggregation [PRINCIPLE]-TIMI 44 studies).
- As PPIs are available over-the-counter, US FDA warnings on concomitant use of PPIs and clopidogrel are justified, but may be overstated.

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