Editorial

Revisiting the Clopidogrel–Proton Pump Inhibitor Interaction
From Bench to Bedside

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Dual antiplatelet therapy (DAPT) with aspirin and a P2Y₁₂ antagonist represents the mainstay of therapy for prevention of ischemic events in high-risk patients after acute coronary syndrome (ACS) and in those undergoing percutaneous coronary intervention (PCI). Over the last 2 decades, the arsenal of antithrombotic agents available to clinicians has rapidly expanded, contributing to step-wise declines in cardiovascular mortality after ACS and PCI.¹ In this setting, clinically significant bleeding complications, particularly gastrointestinal bleeding, remain a major barrier to intensifying antiplatelet inhibition.² Strategies to attenuate this excess gastrointestinal risk are limited. Proton pump inhibitors (PPI) have been demonstrated to reduce gastrointestinal bleeding³ and patient-reported dyspepsia⁴ in patients receiving DAPT. As such, gastroprotection with PPIs in patients requiring DAPT at high risk for bleeding events is supported by consensus guidelines.⁵,⁶

See Article by Weisz et al

Clopidogrel remains the most widely prescribed P2Y₁₂ inhibitor worldwide, largely related to clinician familiarity and affordability. Given frequent co-administration of clopidogrel and PPI therapy, their common hepatic metabolism, and the consequences of suboptimal therapeutic effects, clarifying a possible adverse pharmacological interaction between these agents has been an ongoing substantial research effort. Indeed, regulatory agencies have issued formal statements highlighting the potential safety hazards of concurrent use of clopidogrel and certain PPIs (namely, omeprazole and esomeprazole). Despite new data generated in this space and increased attention from regulatory and research fronts, it remains unclear whether the pharmacokinetic and pharmacodynamic interaction between clopidogrel and PPIs has any real-world clinical implications.

Biological Plausibility of the Clopidogrel–PPI Interaction?
PPIs may reduce the availability of the biologically active metabolite of clopidogrel by competitively inhibiting cytochrome P450 2C19 (CYP2C19), one of the isozymes responsible for the step-wise hepatic oxidation and subsequent hydroxylation of the thienopyridine prodrug.⁷ Heterogeneity exists in the inhibitory effects of specific PPIs on CYP2C19 isozymes. Supporting the dose-dependency of PPI-related enzymatic inhibition, omeprazole and esomeprazole, which exhibit more potent CYP2C19 effects, attenuate clopidogrel’s antiplatelet activity to a greater degree than dexlansoprazole, for example.⁸

Several converging lines of data, however, call the clinical relevance of this theoretical mechanism into question. First, PPI use has been associated with excess adverse cardiovascular events in patients on aspirin and ticagrelor, neither of which require biotransformation by the CYP2C19 isozyme.⁹ Second, although CYP2C19 polymorphism status may influence levels of active clopidogrel metabolite, it does not seem to modulate clopidogrel’s safety or efficacy.¹⁰ Thus, it follows that pharmacological inhibition of CYP2C19 with PPI therapy would not directly influence clopidogrel’s antiplatelet benefits.

It is also unlikely that modulation of gastric pH and impaired initial absorption are major drivers of this interaction. Levels of inactive clopidogrel metabolites remain unaltered with PPI therapy, suggesting intact gastric absorption. Furthermore, histamine-2 blockers, which also suppress gastric acid, have not been proven to reduce clopidogrel’s antiplatelet efficacy. More recently, other preclinical mechanisms underlying the adverse effects of PPIs in cardiovascular disease (independent of clopidogrel) have been postulated related to nitric oxide availability, but additional clinical data are required to substantiate these hypotheses.

Evidence Underlying Pharmacological Interaction: More Data, Less Definitive Answers

In this issue of Circulation: Cardiovascular Interventions, Weisz et al¹¹ provide further insight into the complex interplay between this pharmacological interaction, platelet function testing, and clinical outcomes. The investigators analyzed data from 8582 patients treated with DAPT after successful drug-eluting stent placement enrolled from 11 centers in the US and Germany in the prospective Assessment of Dual Antiplatelet Therapy With Drug-Eluting Stents (ADAPT-DES; ClinicalTrials.gov Identifier NCT00433966) registry from 2008 to 2010.¹¹ PPI use at

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enrollment was independently associated with a \( \approx 10\% \) greater rate of high on-treatment platelet reactivity (HTPR), defined by the VerifyNow P2Y\textsubscript{12} assay (Accumetrics, San Diego, CA), but not with in-hospital clinical events. At 2-year follow-up, discharge PPI use was not associated with a difference in the primary end point of stent thrombosis, but was independently associated with major adverse cardiac events. Counterintuitively, PPI use was associated with directionally greater, albeit nonsignificant, out-of-hospital bleeding events at 2 years.\textsuperscript{11}

The clopidogrel–PPI interaction has been the focus of numerous nonrandomized observational studies varying widely by design, study population, setting, pattern of drug administration, follow-up duration, and clinical end points, producing largely conflicting data.\textsuperscript{3} Systematic reviews and meta-analyses of these nonrandomized experiences have not consistently shown an association between PPI use and adverse clinical events in DAPT-treated patients.\textsuperscript{13} Furthermore, these studies have demonstrated marked heterogeneity in clinical outcomes and instability of point estimates based on imbalances in underlying patient profiles.\textsuperscript{15}

As recognized by the study authors,\textsuperscript{11} despite well-intentioned and rigorous study designs, careful statistical accounting, and large robust clinical experiences, the observational nature of these studies invariably introduces substantial bias related to selection and indication. As nicely demonstrated by Weisz et al,\textsuperscript{11} PPI therapy is commonly administered in higher-risk patients who are older with more extensive comorbid disease burden. In addition, PPIs may be prescribed to patients with angina (misdiagnosed as GI-related dyspepsia) and, thus, inappropriately linked with increased cardiovascular events in some of these observational analyses.\textsuperscript{14}

Prospective investigations and studies in which PPI use was randomly allocated do not support a clinically significant clopidogrel–PPI interaction.\textsuperscript{15} Clopidogrel and the Optimization of Gastrointestinal Events Trial (COGENT; ClinicalTrials.gov Identifier NCT00557921) represents the only large randomized controlled trial examining the safety and efficacy of prophylactic PPIs in patients with high coronary risk and low gastrointestinal bleeding risk requiring DAPT.\textsuperscript{3} The trial was prematurely terminated because of bankruptcy of the sponsor and, therefore, did not reach its desired target enrollment (though it did reach the initially planned sample size). It may not have had sufficient power to exclude with absolute certainty a small excess of cardiovascular events related to PPI therapy. Regardless, in the 3761 randomized patients, PPI therapy was not associated with any cardiovascular safety signal in the early, high-risk time frame after ACS or stenting, but did significantly reduce rates of gastrointestinal events compared with placebo at 180 days (1.1\% versus 2.9\%, \( P<0.001 \)).\textsuperscript{3} It is true that COGENT tested a fixed-dose combination of clopidogrel and omeprazole that is not used in clinical practice, but there is no good evidence that the results of clopidogrel and omeprazole given separately would differ.

Is Platelet Function Testing a Reliable Surrogate End Point?

Point-of-care testing, including the VerifyNow P2Y\textsubscript{12} assay, has matured in recent years and can rapidly and reliably assess ex vivo platelet aggregability. Studies of ex vivo testing have shown that clopidogrel is subject to widespread variability in antiplatelet responses in real-world populations with rates of HTPR ranging from 5\% to 40\%.\textsuperscript{15} HTPR has been consistently linked to excess cardiovascular events in patients treated with DAPT, and standardized cut offs defining HTPR have been established for various platelet function assays.\textsuperscript{16}

Increasingly, ex vivo point-of-care platelet function assays have been used as surrogate end points in clinical investigations. Unfortunately, although useful in hypothesis generation, platelet function testing generally does not serve as an adequate surrogate end point, as in the case of the clopidogrel–PPI interaction, for several reasons. First, the risk conferred by HTPR determined by platelet function testing does not seem modifiable with tailored management strategies. In clinical trials, therapeutic modulation of clopidogrel dosing based on baseline HTPR status in stable patients undergoing elective PCI did not influence cardiovascular end points versus standard therapy.\textsuperscript{17} Second, static single time-point measurement of ex vivo platelet function at the time of PCI may not capture the evolving post-ACS platelet aggregation profile over time.\textsuperscript{18} Third, other CYP450 drug–drug interactions with antiplatelet therapy (eg, statin–clopidogrel) based on ex vivo mechanistic studies have not shown clinical significance.\textsuperscript{19} Fourth, variability in clopidogrel’s antiplatelet effects is only partially explained by known genetic, environmental, and clinical factors even in well-phenotyped populations.\textsuperscript{20} As such, ascribing the relative influence of drug–drug interactions in the background of this wide and unmapped variability is challenging. Finally, if platelet function assays do indeed suggest reduced clopidogrel antiplatelet efficacy, one would expect not only increased ischemic events, but also decreased bleeding events. Paradoxically, in multiple clopidogrel–PPI interaction observational investigations, PPI use is associated with increased ischemic and bleeding events,\textsuperscript{11} suggestive of residual confounding by indication (ie, sicker patients get prescribed PPIs).

**PPIs in Cardiovascular Disease: Marker of Risk or Mediator of Harm?**

Worldwide, over 100 million PPIs are prescribed annually, a figure that is likely underestimated given high over-the-counter utilization. In general cardiovascular populations, PPI use may be even more robust, ranging from 25\% to 40\% in most contemporary series. Consistent with these estimates, Weisz et al report rates of PPI use of 31\% at the time of PCI and 25\% at discharge in their registry-based study.\textsuperscript{11}

Based on the totality of evidence, PPI use serves as a marker of risk and as a proxy for underlying cardiometabolic disease burden. Few high-quality clinical studies support that PPI use itself drives excess cardiovascular risk in this population.

Choice of specific PPI should be guided by local formulary availability and costs. If these issues do not pose significant barriers to access, then it may be prudent to use PPIs with less inhibitory effect on the CYP2C19 isozyme. Newer P2Y\textsubscript{12} antagonists, including prasugrel (given its more efficient hepatic metabolism) in ACS patients undergoing PCI\textsuperscript{21} and ticagrelor (given its direct action largely bypassing CYP
activation) in ACS patients treated invasively or noninvasively, may circumvent this theoretical drug–drug interaction altogether. Staggering the timing of administration of clopidogrel and PPI dosing does not seem to alter the apparent pharmacodynamic interaction compared with concomitant use. Histamine-2 receptor antagonists may be considered, but are less efficacious at preventing gastrointestinal bleeding complications compared with PPI therapy.

Clinician concerns regarding a potential adverse DAPT–PPI interaction will likely persist in the near future because of the (1) aging cardiovascular population with numerous medical comorbidities requiring concomitant PPI use; (2) advent of newer, more potent antithrombotic combinations which amplify bleeding risk; and (3) accumulating data to support prolonged DAPT in ACS patients. Ongoing data collection will continue to inform the risk-benefit profile of concurrent administration of PPIs with longer durations of more potent antithrombotic regimens in the contemporary cardiovascular patient. We eagerly await randomized data from Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS; ClinicalTrials.gov Identifier NCT01776424), which will provide further insight into PPI effects in this population, albeit not directly related to clopidogrel.

In an era of increasing polypharmacy, clinicians and researchers should continue to evaluate for potential drug–drug interactions that may compromise DAPT therapy. Pharmacokinetic and pharmacodynamic interactions based solely on ex vivo platelet function testing have not been reliably correlated with clinical outcomes. Thus, based on available data and consistent with expert consensus guidelines, continued judicious use of PPIs in patients on DAPT is warranted in appropriately selected high-risk patients.

Disclosures

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References


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