Drug interactions are a complex topic tethered to our daily clinical activities by 2 unfortunate facts. The first is that avoidable drug interactions harm an unknown but undoubtedly large number of patients every year. The second is that we know very little about the real-world consequences that ensue when one drug is superimposed on another.

With this background, the recently postulated drug interaction between proton pump inhibitors (PPIs) and clopidogrel is in a league of its own, spawning a flurry of research and editorializing in a relatively short time, and more is on the way. This attention reflects several factors, including the blockbuster status of the implicated drugs, a theoretically at-risk population in the tens of millions, and guidelines that recommend near-universal use of PPIs in patients taking clopidogrel, most of whom will also be taking aspirin. However, skepticism about the clinical importance of this drug interaction is easily understood, especially among clinicians who sense déjà vu with the thematically similar interaction between atorvastatin and clopidogrel first described in 2003 but now largely dismissed.

In this issue of Circulation, Rassen and colleagues report a well-executed retrospective cohort study of this drug interaction using multijurisdictional data and a highly sophisticated approach to multivariable adjustment. The results suggest that adding a PPI to clopidogrel therapy is associated with an increased risk of myocardial infarction or death (adjusted rate ratio, 1.22; 95% confidence interval, 0.99 to 1.51). This effect size is consistent with previous observational studies but just fails to meet the conventional threshold for statistical significance. The authors conclude that although adding a PPI to clopidogrel therapy may increase the risk of adverse events, the incremental risk is probably not very large. This interpretation is a sensible one, but myocardial infarction and death are not trivial events, and residual uncertainty about this drug interaction is inevitable.

In this editorial, I outline the pharmacological basis of the drug interaction between clopidogrel and PPIs, provide a brief overview of the conflicting evidence relative to its clinical significance, and explain why clinical studies of this topic are expected to yield small effect sizes. Finally, I suggest 3 simple management strategies for clinicians confronting this interaction in daily practice.

Basis of the Interaction

An inert prodrug, clopidogrel is metabolized first to a thiolactone intermediate and then to an active metabolite, R-130964, which binds irreversibly to ADP receptors on the platelet surface. These 2 steps are catalyzed by multiple cytochrome (CYP) enzymes, although CYP2C19 is important to both. Loss-of-function polymorphisms in the gene encoding for CYP2C19 are associated with a reduced response to clopidogrel and an increased risk of adverse cardiovascular events.

As with most CYP enzymes, the activity of CYP2C19 can be influenced by other drugs, and CYP2C19 inhibitors can theoretically attenuate the antiplatelet effect of clopidogrel by hindering its bioactivation. Fortunately, many CYP2C19 inhibitors are rarely used nowadays, but some (such as fluoxetine and fluvoxamine) are relatively common, and alternatives should be considered in patients taking clopidogrel. Importantly, other drugs that are metabolized by CYP2C19 can competitively inhibit the enzyme by mutually exclusive competition for its catalytic site. By far the most relevant drugs in this class are the PPIs. Competitive inhibition of CYP2C19 by PPIs is the theoretical basis for the interaction between these drugs and clopidogrel.

Evidence Supporting a Meaningful Interaction

Platelet Aggregation Studies

The earliest evidence suggesting an interaction between PPIs and clopidogrel involved a study of 105 patients receiving aspirin and clopidogrel after high-risk angioioplasty. The platelet reactivity of each patient was assessed by vasodilator-induced aggregation of platelets. The attenuation of the effect of clopidogrel in PPI-treated patients was confirmed in a subsequent clinical trial of 124 patients receiving acetylsalicylic acid and clopidogrel after coronary stenting who were randomized to 7 days of omeprazole (20 mg daily) or placebo.

Several other studies provide additional evidence of a pharmacodynamic interaction between PPIs and clopidogrel. In a recently published prospective study of 201 patients undergoing elective percutaneous coronary intervention, non-response to clopidogrel was 6-fold more common among patients taking a PPI compared with patients not taking a PPI (P = 0.012). Other studies have observed consistent findings with omeprazole but not with esomeprazole or pantopra-
Omeprazole, although variability and uncertainty regarding PPI dose are features of some studies.

**Observational Studies**

Along with the report of Rassen and colleagues, other observational studies have explored the clinical consequences of the PPI-clopidogrel interaction. These studies use different observational approaches in distinct data sets but reach similar conclusions: specifically, that use of a PPI in combination with clopidogrel is associated with a roughly 25% increase in the risk of various adverse events, including acute myocardial infarction, death, or rehospitalization for acute coronary syndrome. In 2 published studies, no association was seen between PPI use and adverse events among patients not receiving clopidogrel.

Two other observational studies, presented to date only as abstracts, also suggest an increased risk of adverse events, although one of these is often mischaracterized as showing no evidence of interaction.

The major limitation of observational studies is their limited ability to fully account for confounding, a particularly salient concern in the context of the PPI-clopidogrel interaction. One does not have to think terribly hard to envision ways in which patients who are treated with PPIs might be at increased risk for cardiovascular events compared with those who are not. However, if PPIs were simply a surrogate marker of increased risk, an association with cardiovascular events would be expected in patients regardless of clopidogrel use; this is clearly not the case.

**Evidence Against a Meaningful Interaction**

Two recent studies raise legitimate questions about the clinical relevance of the PPI-clopidogrel interaction. The first was a post hoc analysis of a large clinical trial in which 6795 patients received clopidogrel after an acute coronary syndrome; a third of these patients also received a PPI in a nonrandomized fashion. In the primary analysis, PPI use was not associated with an increased risk of the composite outcome of cardiovascular death, myocardial infarction, or stroke (adjusted hazard ratio, 0.94; 95% confidence interval, 0.80 to 1.11). Importantly, this was not a randomized trial of the effect of PPIs on clopidogrel, and patients were generally younger and healthier than those in practice.

Further evidence against a meaningful interaction has emerged from the preliminary findings of the Clopidogrel and the Optimization of Gastrointestinal Events (COGENT) trial, in which 3627 patients taking aspirin after an acute coronary syndrome or stent implantation were randomized to clopidogrel alone or clopidogrel plus low-dose omeprazole. Omeprazole was associated with a reduction in the risk of composite gastrointestinal events but no increase in the risk of cardiovascular events, including secondary analyses of acute myocardial infarction or revascularization. The lack of a clinically apparent interaction in the COGENT study may reflect the active treatment, CGT-2168, which contained 75 mg clopidogrel around a core of delayed-release omeprazole. By temporally separating the absorption of clopidogrel from that of omeprazole, the formulation may have effectively circumvented any competitive inhibition of CYP2C19 by omeprazole.

**Observations on the Magnitude of Effect**

A balanced assessment of the interaction between PPIs and clopidogrel incorporates principles of pharmacology and epidemiology, including several considerations that have largely escaped scrutiny in discussions of this topic. Collectively, these issues explain why studies of the PPI-clopidogrel interaction are expected to yield relatively small effects and provide insights into how to manage the interaction in practice.

The first point worth making is that in most platelet aggregation studies, PPIs attenuate rather than abolish the effect of clopidogrel. In the seminal publication of Gilard et al., the mean vasodilator-stimulated phosphoprotein platelet reactivity index decreased from 83.9% at baseline to 51.4% during treatment with omeprazole and clopidogrel. In other words, some pharmacodynamic effect of clopidogrel is clearly evident despite concomitant PPI use, presumably because alternate cytochrome P450 pathways allow formation of the active metabolite.

The magnitude of the benefit of clopidogrel also warrants mention. Depending on the indication, the benefit of clopidogrel when added to aspirin is generally very modest. In the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) study, for example, 1 composite event (cardiovascular death, nonfatal myocardial, or stroke) was averted for every 47 patients treated with clopidogrel. Although clinically important, this effect is small in absolute terms, and PPI-mediated attenuation of the antiplatelet effects of clopidogrel cannot cause harm in patients who were destined to receive no benefit from clopidogrel in the first place.

Finally, the pharmacokinetics of PPIs are a particularly important consideration. Competitive inhibition of CYP2C19 is anticipated only when PPI levels are sufficient to interfere with metabolism of other substrates, including clopidogrel. Most PPIs are rapidly eliminated, with t1/2 values ranging from 30 minutes to 2 hours; consequently, any inhibition of CYP2C19 is likely to be short-lived. From a practical perspective, this means that patients taking a PPI once daily should have no difficulty metabolizing CYP2C19 substrates, including clopidogrel, for most of the day.

These 3 factors—a modest effect of clopidogrel that is only partially attenuated by PPI therapy, and only then in patients who take clopidogrel in close temporal sequence with a PPI—collectively contribute to the relatively small effect size anticipated in studies of this interaction.

**Dealing With the Interaction in Practice**

How clinicians should respond to the PPI-clopidogrel interaction remains a matter of debate. Some have suggested that PPIs should simply be avoided in patients taking clopidogrel. This is bad advice and reflects the gross oversimplification of an exceedingly complex topic. Others have argued that the PPI-clopidogrel interaction is of no consequence. Although this is probably true for most patients, it is a potentially hazardous position to adopt given the sheer number of patients taking these drugs together, the gravity of the clinical consequences, and the ease with which a meaningful interaction can be avoided.

For clinicians uncertain how to address this drug interaction in practice, I propose 3 simple steps:
1. Evaluate the necessity of PPI therapy. Although PPIs are necessary for some patients, many others take the drugs for dubious indications. In these patients, treatment with a histamine H₂ antagonist or antacid may suffice.

2. Consider using pantoprazole when a PPI is indicated. This suggestion stems from the observation that pantoprazole is less likely than omeprazole to inhibit CYP2C19, and does not appear to attenuate the pharmacodynamic response to clopidogrel, and displayed no association with recurrent myocardial infarction in a large observational study of patients receiving clopidogrel. Other PPIs may also be relatively safe, but more data are needed. Lansoprazole is the most potent CYP2C19 inhibitor and is probably best avoided.

3. Stagger the dosing of medications. This is perhaps the most important strategy and exploits the rapid metabolism of clopidogrel and the transient nature of PPI-mediated CYP2C19 inhibition. When dual therapy is necessary, taking a PPI at least 4 hours after clopidogrel should minimize the risk of interaction.

**Summary**

The PPI-clopidogrel interaction has been the subject of much study and debate in a relatively short period of time. There is no doubt that a pharmacodynamic interaction exists; at issue is its clinical relevance. For the majority of patients, the interaction likely poses no serious threat. However, for an unidentifiable subset of patients carrying the wrong mix of drugs, doses, comorbidities, and genetics, a clinically important drug interaction remains a real possibility. As we await further research on the phenomenon of drug-induced clopidogrel resistance, a cautious approach that exploits the basic pharmacology of these drugs is a sensible and easily achievable way to safely prescribe PPIs in patients taking clopidogrel.

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**References**


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Proton Pump Inhibitors and Clopidogrel: Putting the Interaction in Perspective

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