Letters

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Interaction between clopidogrel and proton pump inhibitors

The study by David Juurlink and colleagues is a significant contribution to the awareness of potential interactions between clopidogrel and proton pump inhibitors.[1] However, a number of important issues limit the general applicability of the study to clinical practice.

Results from a case–control study do not seem to warrant statements regarding causation. For example, the authors stated, "We estimated that about 7.4% of readmissions because of reinfarction … occurred as the result of concomitant therapy with these agents."[1] Although this study does suggest an association between concomitant therapy and risk of reinfarction, the authors did not demonstrate causation. Higher odds ratios (e.g., > 2) are generally required before the results of case–control studies can be seen to indicate real risk.[2]

The authors did not address studies that have reported results that contradict theirs. Although they correctly indicated that Simon and colleagues[3] demonstrated the effect of genetic polymorphisms on clopidogrel, they failed to mention the lack of association between proton pump inhibitors and major cardiovascular events in this study. Although they correctly indicated that Aubert and colleagues[4] demonstrated an increased risk with proton pump inhibitors, they failed to cite another abstract from the same scientific session that found that the benefit of clopidogrel was not diminished by baseline use of proton pump inhibitors.[5] This latter report is of particular interest because it was an analysis of a randomized controlled trial that would have provided better control of confounders than the case–control study by Juurlink and colleagues.

The authors did not indicate whether all 3 of the proton pump inhibitors in their study contributed equally to the reported odds ratio of 1.40 for risk of recurrent myocardial infarction within 90 days of hospital discharge. A reasonable case could be made that rabeprazole is sufficiently different from the other 2 agents to justify separate analysis. Both lansoprazole and omeprazole have been shown to inhibit the antiplatelet activity of clopidogrel in vivo.[6,7] To date, no such study has been reported for rabeprazole. In contrast with omeprazole and lansoprazole, rabeprazole is not a potent in vitro inhibitor of cytochrome P450 2C19.[8] In contrast with omeprazole, rabeprazole showed no inhibition in the metabolism of diazepam, a substrate for cytochrome P450 2C19.[9] Although the metabolite rabeprazole thioether is a potent in vitro inhibitor of cytochrome P450 2C19, its concentration in vivo is about 30% of that of its parent compound.[8,10] Given these differences, it is far from clear that rabeprazole would exhibit an interaction potential with clopidogrel comparable to that of omeprazole and lansoprazole.

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David Juurlink and colleagues showed that among patients receiving clopidogrel following an acute myocardial infarction, current users of proton pump inhibitors had an increased risk of reinfarction (adjusted odds ratio [OR] 1.27, 95% confidence interval [CI] 1.03–1.57).[1] A further analysis by type of proton pump inhibitor showed that this effect was not seen with pantoprazole (adjusted OR 1.02, 95% CI 0.70–1.47) but only with other proton pump inhibitors (OR 1.40, 95% CI 1.10–1.77). The authors concluded that proton pump inhibitors other than pantoprazole negate the therapeutic effect of clopidogrel in such patients.

However, the difference between the effect of pantoprazole and that of the other proton pump inhibitors is not statistically significant. The point estimate of the effect of the other proton pump inhibitors lies within the 95% CI associated with the effect of pantoprazole. A formal test for heterogeneity of these ORs[2] also shows no statistically significant difference between the effect of pantoprazole and that of the other proton pump inhibitors ($\chi^2 = 2.99$, 1 degree of freedom, $p = 0.08$).

Although this study indicates that concurrent use of proton pump inhibitors and clopidogrel is associated with increased risk of recurrent myocardial infarction, it does not contain definitive evidence to make a distinc-

tion between the clopidogrel-inhibiting effects of pantoprazole and other proton pump inhibitors. More research is needed to elucidate the mechanism of action of the interaction between clopidogrel and proton pump inhibitors and to determine whether some proton pump inhibitors are safer than others.

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Three of the authors respond:

As Mark Friesen correctly points out, association and causation are not synonymous. Whenever clinicians impute causality, they make a judgment based largely on common-sense principles. Our study[1] satisfies many of the Hill criteria,[2] including biological plausibility, temporality, coherence, consistency, consideration of alternative explanations and specificity.

Healthy skepticism about the results of observational studies is important because such studies can be subject to unmeasured confounding. However, Friesen offers no argument as to why unmeasured confounding should apply to some proton pump inhibitors (omeprazole, lansoprazole and rabeprazole) but not to pantoprazole.

The interaction between proton pump inhibitors and clopidogrel is the subject of considerable ongoing research. Friesen notes that Simon and colleagues adjusted for omeprazole use in their study, but it was neither designed nor powered to address the study question at hand.[3] In addition, of the 3 studies on this topic presented in abstract form at the American Heart Association meeting in October 2008, 2 reached conclusions similar to ours.[4,5] One of these studies, now published in full,[6] used a different analytical technique and data from those in other jurisdictions but yielded results virtually identical to ours. The third abstract, cited by Mark Friesen, described a post-hoc analysis of the CREDO trial that actually appears to support the same conclusion.[7] The study examined only the effect of baseline omeprazole use and found that patients receiving clopidogrel in combination with omeprazole had a higher rate of death, myocardial infarction or urgent revascularization at 28 days than patients receiving clopidogrel alone (10.3% and 5.4%, respectively; $p = 0.051$).

We agree that rabeprazole, omeprazole and lansoprazole exhibit differential inhibitory effects on cytochrome P450 2C19[8] and collectively contribute to the 40% increased risk of early reinfarction seen in our study. Although rabeprazole itself does not inhibit cytochrome P450 2C19, its thioether metabolite is a potent inhibitor, with an inhibition constant (K_i) second only to that of lansoprazole.[8] Moreover, Ho and colleagues recently showed that use of rabeprazole was strongly associated with an increased risk of recurrent events during clopidogrel therapy (odds ratio 2.83, 95% confidence interval 1.96–4.09).[6] Together, these observations make it difficult to justify the coprescription of rabeprazole and clopidogrel. Although a post-hoc analysis of our study by individual proton pump inhibitors is intuitively appealing, such an analysis would almost certainly yield misleading conclusions. Stratification by every available agent would compromise both precision and discriminatory power, and the analyses would inflate the type I error rate by introducing multiple comparisons. Consequently, a real yet modest association could easily be misinterpreted as no effect.

Allen and McLean-Veysey suggest that pantoprazole and other proton pump inhibitors are not significantly different from each other on the basis of the observation that the point estimate for other proton pump inhibitors lies within the 95% confidence interval associated with pantoprazole. This highlights the widely underappreciated point that hypothesis testing is more than the simple generation of a number; it should be informed by an element of judgment and information from outside the experiment. A detailed exposition on this point is available elsewhere.[9]

In our study, the comparison of pantoprazole with other proton pump inhibitors was a secondary analysis and is subject to the limitations of conventional hypothesis testing, including the influence of reduced sample size on significance levels. We anticipate that future research using alternative approaches and larger sample sizes will confirm the differential effects of various proton pump inhibitors on the clinical benefits of clopidogrel, as predicted by the pharmacology of these drugs.[8]

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