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-