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. 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.” 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.

The authors did not address studies that have reported results that contradict theirs. Although they correctly indicated that Simon and colleagues 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 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. 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. 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. 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. Given these differences, it is far from clear that rabeprazole would exhibit an interaction potential with clopidogrel comparable to that of omeprazole and lansoprazole.

Mark H. Friesen BScPharm PharmD
Clinical Pharmacist, Health Sciences Centre, Winnipeg, MB

Competing interests: None declared.

REFERENCES
1. Juurlink DN, Gomes T, Ko DT, et al. A population-based study of the drug interaction between proton pump inhibitors and clopidogrel. CMAJ 2009;180:713-8.
2. Levine M, Waite S, Lee H, et al. Users’ guides to the medical literature IV. How to use an article about harm. JAMA 1994;271:1615-9.
3. Simon T, Verstuyft C, Mary-Krause M, et al. Genetic determinants of response to clopidogrel and cardiovascular response. N Engl J Med 2009;360: 363-75.
4. Aubert RE, Epstein RS, Teagarden JR, et al. Proton pump inhibitors effect on clopidogrel effectiveness: the Clopidogrel Medco Outcomes Study. Circulation 2008;118:S_815.
5. Dunn SP, Macaulay TL, Brennan DM, et al. Baseline proton pump inhibitor use is associated with increased cardiovascular events with and without the use of clopidogrel in the CREDO trial. Circulation 2008;118:S_815.
6. Small DS, Farid NA, Payne CD, et al. Effects of the proton pump inhibitor lansoprazole on the pharmacokinetics and pharmacodynamics of prasugrel and clopidogrel. J Clin Pharmacol 2008;48:475-84.