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The Reply:

We appreciate the thoughtful comments and critical appraisal by Khawaja et al of our article.[1] We agree with the authors about the growing concern about the potential interaction between proton pump inhibitors (PPIs) and clopidogrel. However, our article was focused on long-term side effects of the medications and not the drug interactions and related complications. Also, our article was submitted for publication in January 2009, when articles about this potential interaction, as mentioned in Khawaja et al's references, were just being published.

The antiplatelet activity of clopidogrel is determined by the vasodilator-stimulated phosphoprotein phosphorylation test-derived platelet reactivity index (PRI). Patients responding adequately to clopidogrel have a PRI under 50%. Recently, the potential interaction between clopidogrel and PPIs has gained attention. The milestone of this issue is the prospective, randomized, placebo-controlled, double-blind ex vivo study by Gilard et al,[2] in which patients taking 75 mg aspirin and 75 mg clopidogrel after percutaneous coronary intervention received either 20 mg omeprazole or placebo for 7 days. PRI was calculated on the first and the 7th day of omeprazole therapy. Both the omeprazole and placebo groups presented PRIs of approximately 80% on the first day. However, on day 7, PRI was significantly higher ($P < .0001$) in the omeprazole group than in the placebo arm (51.4% and 39.8%, respectively), referring to a significantly lower clopidogrel effect.

The Food and Drug administration (FDA) is now recommending avoiding omeprazole with clopidogrel, according to a public health advisory issued in November 2009. Separating the dose of clopidegrol and omeprazole in time will not reduce this drug interaction. At this time, the FDA does not have enough information about drug interactions between clopidogrel and PPIs other than omeprazole and esomeprazole to advise on their use together. Patients who use clopidogrel and need a medication to reduce stomach acid can use antacids and most H_2 blockers such as Zantac (Boehringer Ingleheim Pharmaceuticals Inc., Ridgefield, Conn) (ranitidine), Pepcid (Merck & Co. Inc., Whitehouse Station, NJ) (famotidine), and Axid (Braintree Laboratories Inc., Braintree, Mass) (nizatidine), but not Tagamet and Tagamet HB (GlaxoSmithKline, Clifton, NJ) (cimetidine) (www.fda.gov).

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The FDA advisory was based primarily on recent laboratory data and observational studies that suggested decreased activity of clopidogrel in people taking omeprazole.[2-4] Laboratory data can raise important questions; however, decreased activity in the blood does not always cause a meaningful clinical effect. The data from the COGENT randomized controlled trial, which did use clinical end points, failed to reveal a difference in cardiovascular end points (cardiovascular death, myocardial infarction, and revascularization) among those patients prescribed clopidogrel with PPI when compared with those prescribed clopidogrel with placebo. These results were presented at the 21st annual Transcatheter Cardiovascular Therapeutics Scientific Symposium, sponsored by the Cardiovascular Research Foundation (www.theheart.org/article/1007145.do).

Pantoprazole may have some advantage because there is little if any metabolism via this pathway.[5] However, physicians must decide upon the best treatment for their patients. As far as PPI-clopidogrel co-therapy is concerned, they must weigh the risks of gastrointestinal bleeding with clopidogrel (and aspirin) against the potential (but unproven) risk of worse cardiovascular outcomes. While not all patients taking clopidogrel require a PPI, it remains appropriate for those with additional risk factors for upper gastrointestinal bleeding. Physicians should carefully read the FDA's recommendations and select an agent based on all currently available information.

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