

Safety of Concomitant Use of Proton Pump Inhibitors and Clopidogrel

To The Editor:

We read with interest the article by Ali et al,¹ “Long-term Safety Concerns with Proton Pump Inhibitors.” The article is a comprehensive review of potential safety concerns about proton pump inhibitors. However, the authors did not discuss the potential effect of proton pump inhibitors on concomitant use of clopidogrel, a medication that is widely used in patients with coronary artery disease, stroke, and other atherosclerotic diseases. Recently, there have been multiple conflicting reports about potential increase in cardiovascular events in patients taking these medications concomitantly.²⁻⁵

A study by Ho et al² of 8025 patients demonstrated increased death or rehospitalization for acute coronary syndrome occurring in concomitant clopidogrel and proton pump inhibitors use (29.8% vs 20.8%, respectively). Simon et al³ demonstrated similar findings (13% adverse events on concomitant clopidogrel and proton pump inhibitors vs 2.9% of patients on clopidogrel alone). In contrast, O’Donoghue et al⁴ did not show any significant difference in 6795 patients. Adverse cardiovascular events and deaths were seen in 11.29% on concomitant clopidogrel and proton pump inhibitors vs. 11.59% of patients on clopidogrel alone. Recently, Bhatt et al⁵ demonstrated adverse cardiovascular events and death in 3.8% of patients on concomitant clopidogrel and proton pump inhibitors, and in 3.67% of those on clopidogrel alone.

One of the proposed mechanisms of action has been the inhibition of the enzyme CYP2C19 responsible for the metabolism of clopidogrel. Certain proton pump inhibitors not

only serve as a substrate for this enzyme but also can inhibit the enzyme CYP2C19.^{6,7} Proton pump inhibitors differ in their effect on the inhibition of the enzyme, which is potentially something to be looked for when selecting a proton pump inhibitor to be used in patients on clopidogrel.

We believe that a dedicated powered randomized clinical trial is needed to answer this important clinical question.

Owais Khawaja, MD^{a,b}

Mouaz H. Al-Mallah MD, MSc^{b,c}

^aDepartment of Internal Medicine
 Providence Hospital
 Southfield, Mich

^bDepartment of Internal Medicine
 Wayne State University School of Medicine
 Detroit, Mich

^cHenry Ford Health System
 Detroit, Mich

doi:10.1016/j.amjmed.2009.10.010

References

1. Ali T, Roberts DN, Tierney WM. Long-term safety concerns with proton pump inhibitors. *Am J Med.* 2009;122:896-903.
2. Ho PM, Maddox TM, Wang L, et al. Risk of adverse outcomes associated with concomitant use of clopidogrel and proton pump inhibitors following acute coronary syndrome. *JAMA.* 2009;301:937-944.
3. Simon T, Verstuyft C, Mary-Krause M, et al. Genetic determinants of response to clopidogrel and cardiovascular events. *N Engl J Med.* 2009;360:363-375.
4. O’Donoghue ML, Braunwald E, Antman EM, et al. Pharmacodynamic effect and clinical efficacy of clopidogrel and prasugrel with or without a proton-pump inhibitor: an analysis of two randomised trials. *Lancet.* 2009;374:989-997.
5. Bhatt DL, Cryer B, Contant CF, et al. The COGENT Trial; Transcatheter Cardiovascular Therapeutics; 2009: San Francisco, CA.
6. Li XQ, Andersson TB, Ahlström M, Weidolf L. Comparison of inhibitory effects of the proton-pump-inhibiting drugs omeprazole, esomeprazole, lansoprazole, pantoprazole, and rabeprazole on human cytochrome P450 activities. *Drug Metab Dispos.* 2004;32:821-827.
7. Furuta T, Ohashi K, Kamata T, et al. Effect of genetic differences in omeprazole metabolism on cure rates for *Helicobacter pylori* infection and peptic ulcer. *Ann Intern Med.* 1998;129:1027-1030.

Funding: None.

Conflict of Interest: There is no potential conflict of interest in the preparation of this manuscript.

Authorship: All authors had access to data and had role in manuscript writing.