Proton Pump Inhibitors and Myocardial Infarction: The Current Perspective

Proton pump inhibitors (PPI) are perennially among the most prescribed drugs in all of medicine, and are the single most prescribed class of gastrointestinal drugs.[1] Because PPI use is widespread, even a very modest increase in the absolute risk for an adverse effect can impact large numbers of patients. Overall, the safety profile of PPIs is excellent. However, PPI use has been associated with several potential adverse effects including increased risk for *Clostridium difficile* infection, bone fracture, and vitamin deficiencies. Drug–drug interactions related to PPIs have been identified, with particular attention paid to possibly decreased efficacy of clopidogrel in the setting of PPI use. A recent paper by Shah et al[2] reported an increase in risk for myocardial infarction (MI) in patients with gastroesophageal reflux disease who take PPIs.[2] The study was designed primarily to identify loose associations or "signals" regarding adverse drug effects. Nonetheless, their findings have received considerable attention in the lay press and have caused understandable concern among gastroenterologists and patients taking PPIs. Given the potential importance of this result, we review the existing literature related to PPIs and cardiovascular outcomes, with a focus on the paper by Shah et al,[2] as well as the biological mechanisms that may underlie this association.

Existing Literature on PPIs and Cardiovascular Outcomes

Previous concern regarding PPIs and cardiovascular risk has centered on the potential interaction between PPIs and clopidogrel. In brief, clopidogrel irreversibly binds the $P2Y_{12}$ receptor for adenosine diphosphate on platelet cell membranes to inhibit platelet aggregation. Clopidogrel is metabolized from a prodrug to the active drug through the cytochrome P450 enzyme superfamily, specifically through isoenzyme CYP2C19.[3] Patients who carry CYP2C19 loss-of-function alleles have increased ex vivo platelet aggregation while taking clopidogrel.[4] Because PPIs are also metabolized by CYP2C19, competitive inhibition of CYP2C19 by PPIs could cause loss of clopidogrel's antiplatelet effects.[5] Initial epidemiologic studies supported the hypothesis that PPIs interact with clopidogrel to increase risk for cardiovascular events,[6] and the US Food and Drug Administration (FDA) issued a safety communication in 2009 regarding PPIs and increased cardiovascular risk in patients concurrently taking clopidogrel.[7]

Soon after the FDA safety communication, conflicting evidence emerged.[8] When data from trials with randomization of patients to clopidogrel were analyzed, the conclusions led many to question the initial mechanistic basis for the PPI–clopidogrel interaction. In a study of 5059 patients who were genotyped for CYP2C19 and randomized to clopidogrel versus placebo, clopidogrel was equally beneficial regardless of CYP2C19 carrier status.[9] This result suggested that it was unlikely that PPIs could influence the effectiveness of clopidogrel by interacting with CYP2C19.

The conclusion that PPIs do not increase risk for cardiovascular events in those taking clopidogrel was also supported by findings from the COGENT study, which remains the single most important piece of evidence related to PPIs and adverse cardiovascular events.[10] COGENT used a randomized study design to test whether a combination pill containing omeprazole 20 mg and clopidogrel 75 mg was more effective than clopidogrel alone at preventing upper gastrointestinal bleeding in patients who were also receiving daily aspirin. When results from 3761 patients were analyzed, there was decreased bleeding on PPIs and no difference in the combined cardiovascular event rate between omeprazole–clopidogrel (4.9%) compared with clopidogrel alone (5.7%). The study was closed prematurely owing to loss of funding and did not reach its target sample size; the lack of an association between omeprazole and cardiovascular events thus depends on 109 patients who met criteria for the combined cardiovascular outcome, with wide 95% confidence estimates for the risk associated with omeprazole. The question remains whether a larger study would have found a similar "negative" result.

Two other randomized studies testing PPIs versus placebo also found no increase in risk for death or cardiovascular events after exposure to PPIs, but the studies were very small with only 56 total events over 14–30 days of follow-up.[11,12] Now >5 years after the publication of COGENT's results, our understanding of the PPI–clopidogrel interaction remains substantially the same. Randomized trial data argue against a large increase in cardiovascular risk associated with PPIs in those taking clopidogrel, but cannot exclude the possibility that PPIs confer a small but significant increase in risk in this population.

Novel Potential Mechanism Linking PPIs and MI

Most gastroenterologists are familiar with the potential interaction between PPIs and clopidogrel, but relatively few are aware that there are alternative, relatively novel mechanisms that directly link PPIs to increased risk for MI.[13] These mechanisms posit that PPIs alter vascular reactivity and theoretically apply to all patients who are taking PPIs, regardless of whether or not they are taking clopidogrel. The leading hypothesis linking PPIs and MI is as follows: PPIs inhibit dimethylarginine dimethylaminohydrolase (DDAH), leading to increased levels of asymmetrical dimethylarginine (ADMA), blockade of vascular nitric oxide synthase activity, and enhanced contractivity with loss of

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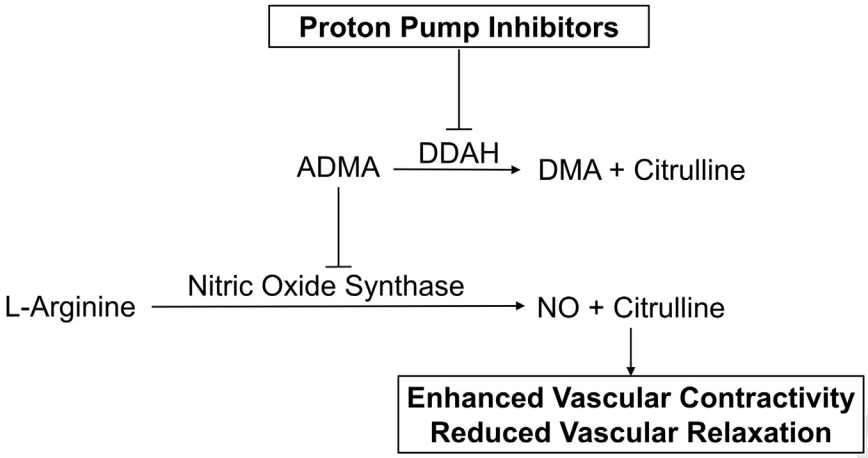

Figure 1. Putative mechanism linking proton pump inhibitors with enhanced vascular contractivity and reduced vascular relaxation. ADMA, asymmetrical dimethylarginine; DDAH, dimethylarginine dimethylaminohydrolase; DMA, dimethylarginine; NO, nitric oxide. Adapted from Ghebremariam et al.[13]

normal relaxation (Figure 1). Compelling evidence in support of this hypothesis was described in a series of experiments by Ghebremariam et al published in *Circulation* in 2013, which showed that PPIs can increase intracellular ADMA levels in animal and ex vivo human models.[13] In prospective studies of patients with coronary disease, baseline ADMA levels predicted cardiovascular death after adjusting for other factors.[14] In the Framingham Offspring Study, ADMA concentrations associated with increased risk for cardiovascular death in a population free from cardiovascular disease at baseline.[15] Therefore, a PPI-induced increase in plasma ADMA levels seems to have the theoretical potential to affect cardiovascular risk in humans.

However, it is unclear whether PPIs, given at physiologic doses, can achieve an increase in ADMA levels that is relevant in human coronary disease. In a dilution assay performed by Ghebremariam et al,[13] there was significant inhibition of DDAH activity at omeprazole concentrations of 60 μmol/L but not 6 μmol/L; in isolated human saphenous venous grafts, nitrite concentration was decreased significantly by omeprazole only when concentrations exceeded 50 μmol/L.[13] In contrast, in humans—even in poor metabolizers of PPIs—oral PPIs do not achieve peak plasma concentrations of >5 μmol/L.[16] PPIs have a long effective half-life because they irreversibly bind and inactivate H^+/K^+-ATPases on gastric parietal cells. The plasma half-life of PPIs is about 1 hour and, unlike the binding between PPIs and H^+/K^+-ATPases, binding between PPIs and DDAH is fully reversible.[13] When oral lansoprazole 30 mg was given daily for 4 weeks to volunteers with and without cardiovascular disease, there was no change in plasma ADMA levels or in flow-mediated vasodilation.[17] Because plasma binding of standard dose oral PPIs to DDAH is of limited duration, any window for adverse cardiovascular effects may be very narrow. These data suggest that oral PPIs are unlikely to have clinically meaningful adverse cardiovascular effects in humans through binding of DDAH, although it does not exclude the possibility that alternative mechanisms underlie the PPI–MI association, if in fact PPIs do increase the risk for MI.

Large Observational Studies of PPI Use and MIs

Shah et al[2] recently performed a large, retrospective study to pursue clinical evidence related to whether PPIs increase risk for cardiovascular events in patients who are or are not taking clopidogrel. To perform their study, the authors extracted data for adult patients with a diagnosis of gastroesophageal reflux disease from 3 sources describing nearly 3 million patients who were 94% clopidogrel free: an institutional data warehouse, data from a free electronic medical record, and comprehensive data for 1503 patients who underwent coronary angiography. Recording of PPI use and MI was not readily apparent in all 3 datasets, so the authors used a computer science-derived algorithm for extracting data. This algorithm uses methods from natural language processing to identify key data from codes or from written text and places this information in context to classify each variable. Within each dataset, exposure to PPIs was classified as yes versus no and the type of PPI was captured. Time stamps were captured from medical records and other data to determine whether the outcome of MI preceded or followed recording of PPI exposure.

In both the institutional dataset and the electronic medical record–derived dataset, the authors found that exposure to PPIs was associated with a modest but significant increased risk for MI (excess relative risk of 9%–16%). Because these populations had a relatively low baseline risk for MI, this translates into approximately 1-2 additional MIs for every 1000 patients taking PPIs over a median period of 4 years. In the dataset of patients undergoing coronary angiograms, PPIs were associated with a 2-fold increased hazard for cardiovascular death, with 58 total cardiovascular deaths over a median follow-up period of 5.2 years. Exposure to all types of PPIs was associated with MI, suggesting a class effect, but there was no association between exposure to histamine-2 receptor antagonists (H2RAs) and MI. The relationship between PPIs and MI was unchanged after excluding from the analysis patients who received clopidogrel.

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