Aspirin and proton-pump inhibitors: interpreting the interplay

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This editorial refers to ‘Proton pump inhibitor use by aspirin-treated coronary artery disease patients is not associated with increased risk of cardiovascular events’, by L.A. Fortuna et al., on page 13.

Aspirin has a well-established role in secondary prevention of cardiovascular disease, but increases gastrointestinal bleeding, especially when used in high-risk patients. Unfortunately, gastrointestinal bleeding in patients after acute coronary syndrome portends poor prognosis and is independently associated with increased risk for adverse cardiovascular events and mortality.1 Proton-pump inhibitors (PPIs) have been shown to effectively reduce the risk of gastrointestinal bleeding in patients requiring dual antiplatelet therapy (DAPT)2 and may improve aspirin adherence due to reduction in dyspepsia.3,4 Multidisciplinary consensus guidelines thus recommend the prophylactic use of PPIs in high-risk patients requiring antiplatelet therapy.5 However, there has been growing interest in possible adverse drug interactions between aspirin and PPIs compromising the antiplatelet efficacy of aspirin. Early preclinical studies have supported a potential gastric acid-mediated drug–drug interaction.6 Two subsequent ex vivo platelet function studies provided conflicting data.7,8 A small, cross-over study of 24 patients with hypertension demonstrated no effect of 4 weeks of lansoprazole on antiplatelet efficacy of low-dose aspirin determined by light-transmission aggregometry.7 In contrast, a larger study of 418 patients with stable coronary artery disease (CAD) showed that PPI use increased on-treatment platelet aggregation (multiplate whole blood aggregometry) and activation (soluble serum P-selectin levels) in low-dose aspirin-treated patients.8 These preclinical studies provided limited foundation for a potential gastric acid-mediated drug–drug interaction. Inconsistently, H2-receptor blockers which also influence gastric acid production do not appear to be associated with excess risk of adverse cardiovascular events in aspirin-treated patients.9 It is plausible that PPIs may augment cardiovascular risk, regardless of interactions with concurrently administered antiplatelet agents, via platelet-independent biological pathways.10

Aspirin–proton-pump inhibitor interaction: clinical correlation

There are unfortunately no clinical trials to evaluate the potential interaction between PPIs and antiplatelet monotherapy with aspirin. A single, retrospective, administrative study investigated this issue in almost 20 000 patients in Denmark receiving aspirin therapy who had experienced first-time myocardial infarction from 1997 to 2006.9 At 1-year follow-up, PPI use was associated with increased risk of major adverse cardiovascular events. This excess risk was not modulated by PPI subtype, PPI dose, or aspirin dose.9

In this issue, Fortuna et al.11 report electronic health record-linked data from a retrospective cohort study of 2011 aspirin-treated patients with established CAD from 2007 to 2009. Roughly 50% of patients at baseline were on concomitant antithrombotic therapies (in addition to aspirin) and were excluded from the analyses. Approximately 15% of patients in the final cohort were prescribed a PPI, primarily omeprazole. Proton-pump inhibitor use was associated with advanced age, female sex, and increased comorbid disease burden. At 3-year follow-up, PPI users experienced numerically greater major adverse cardiovascular events (21.4 vs. 13.5%) and all-cause mortality (15.9 vs. 9.0%) compared with non-PPI users. No residual excess risk associated with PPI use was observed, however, after accounting for baseline risk imbalances using propensity-score matching.11

The opinions expressed in this article are not necessarily those of the Editors of the European Heart Journal – Cardiovascular Pharmacotherapy or of the European Society of Cardiology.

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This is an important clinical study that reinforces that PPI therapy in the CAD population represents a strong marker of risk. Proton-pump inhibitor therapy may be prescribed appropriately (e.g. in patients at high-risk for bleeding with advanced age and multiple medical comorbidities) or inappropriately (e.g. in patients with escalating cardiovascular symptoms, misdiagnosed as gastrointestinal-related dyspepsia). Both scenarios would elevate the risk attributed to PPI therapy in observational studies. As acknowledged by the authors, the study findings are restricted to low—moderate risk, insured CAD patients who are not on DAPT. It is noteworthy that PPI use in this study was relatively lower (~15%) compared with other contemporary, ‘real-world’ CAD populations at higher risk for bleeding (25–40%). Other limitations of this clinical investigation include reliance on prescription claims data and lack of data regarding drug adherence and bleeding events.

Although limited direct clinical data are available to evaluate the implications of the aspirin—PPI interaction, one randomized controlled trial did not demonstrate significant excess risk associated with PPIs in patients on DAPT. Clopidogrel and the Optimization of Gastrointestinal Events Trial (COGENT) demonstrated that omeprazole significantly reduced gastrointestinal bleeding without increasing cardiovascular events in 3761 patients with CAD requiring DAPT.

The use of prophylactic PPIs reduces gastrointestinal bleeding and may improve adherence to low-dose aspirin therapy, thus representing a cost-effective strategy of gastroprotection in appropriately selected patients. Incremental cost-effectiveness ratios were <$50,000 per life-year saved in average-risk patients at over-the-counter PPI costs and in high-risk patients at prescription PPI costs. Despite this, prophylactic PPI use in appropriate clinical settings appears to be underutilized in large, nationwide studies.

**Approaches to reducing aspirin-related gastrointestinal bleeding**

Low-dose aspirin (75–100 mg daily) is preferred given that upper gastrointestinal bleeding risk increases at higher doses. Similarly, clinicians should restrict adjunctive therapies that augment bleeding risk profile, including second antiplatelet agents, non-steroidal anti-inflammatory agents, corticosteroids, and anticoagulants, to appropriately selected patients. Buffered and enteric-coated aspirin appear to carry a similar risk of upper gastrointestinal bleeding as non-coated preparations. Decisions regarding temporary discontinuation of aspirin in patients who have experienced upper gastrointestinal bleeding should be tailored based on an individual patient’s risk for ischemic and gastrointestinal events. A small non-inferiority trial has suggested that continuation of low-dose aspirin after endoscopic control of acute peptic ulcer bleeding increased short-term endoscopy—confirmed recurrent bleeding, but decreased all-cause mortality. Other pharmacotherapies including prostaglandin replacement, sucralfate, and H$_2$-receptor antagonists have not been shown to be as efficacious at attenuating gastrointestinal bleeding risk as PPI therapy. Novel preparations of aspirin may preserve aspirin’s oral bioavailability while limiting endoscopy—confirmed gastrointestinal mucosal damage, though further data are needed.

**Aspirin and proton-pump inhibitors**

Fortuna et al. add to the available clinical data that are reassuring against a clinically significant pharmacological interaction between these two commonly administered drugs. At this juncture, prophylactic therapy with PPIs in appropriately selected, high-risk patients requiring low-dose aspirin represents a potentially underutilized, guideline supported, and cost-effective strategy of gastroprotection.

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