EDITORIAL COMMENT

A COGENT Argument for Gastrointestinal Protection With Low-Dose Aspirin*

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Dual antiplatelet therapy with aspirin and P2Y₁₂ inhibitors, such as clopidogrel, have become the mainstay of patients undergoing percutaneous coronary intervention (PCI) either for acute coronary syndromes or for stable coronary artery disease. Recent evidence suggests that low-dose aspirin defined as ≤100 mg daily is as effective as high-dose aspirin in secondary cardiovascular prevention (1). One may question why some still continue to prescribe high-dose aspirin in the setting of dual antiplatelet therapy (DAPT).

However, many cardiologists may not be aware of the association of low-dose aspirin with a wide variety of gastrointestinal (GI) side effects, including upper and lower GI bleeding, peptic ulcers, and dyspepsia. In 2010, the American College of Cardiology, the American College of Gastroenterology, and the American Heart Association recommended that beyond the debate of a potential interaction between proton pump inhibitors (PPIs) and clopidogrel in patients receiving a coronary stent, upper GI bleeding also must be taken into account in the overall safety profile (2). They identified that factors such as the concomitant use of anticoagulant agents, steroids, or nonsteroidal anti-inflammatory drugs; advanced age; and H. pylori infection were associated with an increased risk of GI bleeding. The association of high-dose aspirin and upper GI bleeding is well documented, but earlier studies have suggested that low-dose aspirin was not associated with these risks (3). Yu et al. (4) compared the relative safety of high- versus low-dose aspirin after PCI in ST-segment elevation myocardial infarction from the HORIZONS (Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction) trial and found that high-dose aspirin was an independent predictor of major bleeding with a hazard ratio of 2.8 (95% confidence interval [CI]: 0.13 to 5.99). Similarly, the CURRENT-OASIS-7 (Clopidogrel Optimal Loading Dose Usage to Reduce Recurrent EveNTs/Optimal Antiplatelet Strategy for InterventionS) trial showed excess bleeding in the group randomized to high-dose aspirin compared with the low-dose arm (1). These findings led many cardiologists to believe that the use of low-dose acetysalicylic acid (ASA) would be associated with significantly reduced rates of gastrointestinal bleeding particularly when used with DAPT strategies.

For clinicians, the current analysis by the Vaduganathan et al. and the COGENT (Clopidogrel and the Optimization of Gastrointestinal Events Trial) investigators (5) in this issue of the Journal provides important insights into patients treated with DAPT with clopidogrel and aspirin. First, patients on low-dose compared with high-dose aspirin do not have an increased risk of cardiovascular events. Secondly, they confirm that patients taking low-dose aspirin are at risk for significant upper GI events including gastroduodenal bleeding and symptomatic gastroduodenal ulcers. However, the low-dose aspirin group had comparable primary GI events to the high-dose ASA group in the non-PPI patient population (3.08% vs. 2.61%).

There are a number of strategies to restratify patients and reduce the risk of GI bleeding in patients receiving DAPT. Over the years, the use of H₂ receptor antagonists has gained popularity particularly in the era when there was a concern about the clopidogrel-
PPI interaction. A recent meta-analysis evaluated 10 randomized trials and showed that PPIs decreased the risk of low-dose aspirin-associated upper GI bleeding in patients treated with DAPT by 64% (odds ratio 0.36; 95% CI: 0.15 to 0.87) without any increase in the risk of major cardiovascular events, with an odds ratio of 1.0 (95% CI: 0.76 to 1.31) (6). This study also confirmed the superiority of PPIs over H₂ receptor antagonists.

What remains concerning is the apparent lack of enthusiasm for the use of PPIs in patients on low-dose aspirin despite this significant GI risk. de Jong et al. (7) reported on data from 120 Dutch primary care centers looking at patients 18 years and older who were regularly prescribed low-dose ASA. They found that 26% of patients on low-dose aspirin (3,213 of 12,343) were considered at increased risk of GI complications but that the concomitant use of PPIs was only in 46% of these patients. In the low-dose aspirin group of the COGENT, omeprazole therapy was associated with 1.9% absolute risk reduction in primary upper GI events at 180 days (1.2% vs. 3.1%), which was comparable to the 1.7% absolute risk reduction for the high-dose aspirin-treated patients (p for interaction 0.80). This confirms similar findings from a recent meta-analysis of randomized trials of PPI therapy with low-dose aspirin (8). It is important to note that although older patients, those who were treated conservatively, and those outside the United States were more likely to be prescribed low-dose aspirin, they clearly enjoyed a benefit with concomitant PPI therapy. When compared with other efficacious therapies used in cardiovascular medicine, the number needed to treat of about 50 to prevent an upper GI event with the use PPIs in patients treated with DAPT and low-dose aspirin appears quite cost-effective.

This report from the COGENT must be placed in proper context. The median follow-up was only 110 days. Kaplan-Meier estimates in this trial are presented and low-dose aspirin appears quite cost-effective.

WHERE DO WE GO FROM HERE?

PPIs in patients on low-dose aspirin receiving DAPT are underutilized, and this needs to be evaluated as a quality metric in patients undergoing PCI with stenting. The real question becomes whether all patients on low-dose ASA should receive PPI in the long term versus only those at high risk of upper GI bleeding. As stated earlier, the current guidelines recommend PPI use in those who have a prior history of GI bleeding and in those with multiple risk factors for GI bleeding who require antiplatelet therapy, including advanced age, the use of nonsteroidal drugs, anticoagulant agents, and steroids, and the documentation of H. pylori infection. With the confirmation of the GI protective effects of PPIs without any excess of cardiovascular events in the COGENT, it appears that a practice change is in order when prescribing low-dose aspirin. The COGENT investigators should be commended for bringing this important GI safety issue to the forefront because it has been long overshadowed by both the concern about a PPI-clopidogrel interaction and by the false sense of security in the belief that low-dose aspirin, as opposed to high-dose aspirin, does not warrant a GI protective strategy.

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