Dual antiplatelet therapy (DAPT) with aspirin and oral P2Y12 inhibitors remains the cornerstone of therapy for patients with acute coronary syndrome (ACS). However, the administration of DAPT carries the significant risk of gastrointestinal bleeding. The 2016 American College of Cardiology/American Heart Association focused update on duration of DAPT in patients with coronary artery disease and the 2018 European Society of Cardiology/European Association for Cardio-Thoracic Surgery guideline on myocardial revascularization have recommended proton pump inhibitors (PPIs) among strategies to avoid bleeding complications in patients with ACS. However, the data are contrasting for the evidence as to whether PPIs have a protective effect on gastrointestinal bleeding in patients receiving antiplatelet therapy. Moayyedi et al, in their largest to date, double-blind, randomized trial investigating the effect of PPI therapy on prevention of gastrointestinal bleeding among patients with coronary artery disease receiving anticoagulation or aspirin therapy, reported that routine use of PPIs did not reduce upper gastrointestinal events, save bleedings from gastroduodenal lesions.

In this issue of Mayo Clinic Proceedings, Zhou et al report the results of Improving Care for Cardiovascular Disease in China–ACS and the American Heart Association and Chinese Society of Cardiology collaborative registry and quality improvement projects of association between PPI use and in-hospital gastrointestinal bleeding among 25,567 patients with ACS receiving DAPT and PPIs in 172 hospitals in China. The primary outcome of this study was gastrointestinal bleeding that occurred during hospitalization, diagnosed by physicians and recorded in medical records at the time of occurrence. The secondary outcome was all-type bleeding, either documented bleeding or defined as a decline in hemoglobin level of 4 g/dL or more during hospitalization. Patients taking PPIs were reported to have a higher rate of all-type bleeding (2.9% vs 1.8%; \(P<.001\)) in comparison to individuals not taking PPIs. After multivariable adjustment, PPI use was still associated with a 38% increased risk of all-type bleeding among all patients with ACS (odds ratio, 1.38; 95% CI, 1.15 to 1.66; \(P<.001\)). This study, which has obvious strengths, delivers results that are interesting but surprising. To reevaluate the association between PPI use and in-hospital outcomes (eg, variables of participating hospital, diabetes mellitus, coronary heart and cerebrovascular disease history, pre-hospital treatment with antiplatelet drugs, or in-hospital loading status of DAPT), the authors conducted propensity score–matched analysis, which revealed that the rates of gastrointestinal bleeding and all-type bleeding remained higher in patients taking PPIs (gastrointestinal bleeding: 0.8% vs 0.6% \(P=.04\); all-type bleeding: 2.6% vs 1.9% \(P=.002\); PPI vs no PPI, respectively). There are several limitations to this study that include the probability of observational and selection bias along with residual measured or unmeasured confounding factors (eg, relatively small odds ratios reported by the authors may result from lurking variables), the lack of examination to locate the source of gastrointestinal bleeding (especially the lack of the evaluation of the impact of PPI therapy on gastrointestinal bleeding in the small intestine), and the lack of reporting of some significant risk factors (eg *Helicobacter*...
pylori infection status). Nevertheless, this report carries important clinical implications. In accordance with the current recommendations, DAPT is frequently prescribed with PPIs to minimize aspirin/P2Y12 antagonist–related adverse effects in the upper gastrointestinal tract. The clinical benefit of this coadministration is regarded as obvious and safe and has come to be viewed as standard medical practice. However, the data are mounting on the adverse and harmful effects of DAPT on the small intestine augmented by prescription of PPIs. The PPIs suppress gastric acid secretion, effectively reducing aspirin-related damage in the stomach and duodenum, but without any proven benefit in the prevention of aspirin-related damage in the lower gastrointestinal tract. Moreover, both aspirin and PPIs alter the small intestinal microbiome and gastrointestinal barrier integrity, which contributes to the injury of the small bowel mucosa and may be responsible for clinically significant complications. Zheng et al documented that long-term DAPT significantly increased the incidence of both ischemic and bleeding events after percutaneous coronary intervention. Their study indicated that DAPT is responsible for intestinal injury, followed by translocation of intestinal bacteria into the bloodstream, increasing the incidence of adverse events after percutaneous coronary intervention in patients with coronary artery disease. Metabolic endotoxemia has previously been associated with the development and progression of cardiovascular disease and atherosclerosis. Prospective data from the Bruneck study, conducted more than 2 decades ago, delivered early evidence linking the risk of atherosclerosis with bacterial endotoxemia. Antibiotic treatments in patients shortly after a first coronary event in the STAMINA (South Thames Trial of Antibiotics in Myocardial Infarction and Unstable Angina) and ROXIS (Roxithromycin in Ischemic Syndromes) trials were associated with overall risk reduction of secondary end points, counted as recurrent ischemia, myocardial infarction, or ischemic death. However, the data from more recent studies delivered contrasting results for the role of antibiotics in patients with ACS. Nevertheless, current evidence linking gut microbiome with mucosal injury and cardiovascular disease is mounting. As the pathogenesis of many chronic diseases revolves around microbiome and gut barrier alterations, the use of nonsteroidal anti-inflammatory drugs (NSAIDs) has been associated with increased rates of myocardial infarction, cardiovascular death, and stroke. Relevant are the insights from the China Acute Myocardial Infarction Registry in a study by Shi et al on the clinical impact of PPIs coadministered with DAPT in patients with ACS and low risk of bleeding. This study reported the prevalent use of PPIs in patients receiving DAPT and found no extragastrointestinal protective effect while revealing an increased risk of stroke observed during the 2-year follow-up. What are the conclusions and take-home message for medical practitioners taking care and involved in the management of patients with ACS? The results from meta-analysis of efficacy and safety of PPIs with DAPT for coronary artery disease are contrasting. Analysis restricted to randomized clinical trials found that PPIs reduce the risk of gastrointestinal bleeding (relative risk [RR], 0.32; \( p < .001; \ I^2 = 0 \)), which contrasts with data from observational studies, which show that PPIs significantly increase the risk of all-cause mortality (RR, 1.25; \( p < .001; \ I^2 = 82 \)), without reducing gastrointestinal bleeding risk (RR, 0.74; \( p = .24; \ I^2 = 79 \)). The data from recently published secondary analysis of the prospective COMPASS (The Cardiovascular Outcomes for People Using Anticoagulation Strategies) trial confirmed that use of PPIs during the period of 3 years was safe except for a possible increased risk for enteric infection. The quest for optimal gastrointestinal protection in patients with ACS is open and does not concern only PPI safety but also, and importantly so, their efficacy in the prevention of overall gastrointestinal bleeding. The latest 2021 American College of Cardiology/American Heart Association/Society for Cardiovascular
Angiography and Interventions guideline for coronary revascularization urges clinicians to weigh the risks of bleeding and recurrent ischemia when determining the choice and protocol of DAPT. In the recent randomized clinical trial OPT-PEACE (Optimal Antiplatelet Therapy for Prevention of Gastrointestinal Injury), which maintained DAPT for 6 months followed by single antiplatelet therapy with aspirin or clopidogrel from 6 to 12 months, resulted in less gastrointestinal mucosal injury and clinical bleeding compared with DAPT through 12 months. Physicians should aim for best possible stratification of patients at high risk of gastrointestinal bleeding (eg, patients with a past history of gastrointestinal bleeding). The PPIs are registered as drugs used for prevention of gastroduodenal ulcers induced by NSAIDs in patients at risk for continuous NSAID treatment. The quest is also about finding other agents capable of protecting the mucosa in the gastrointestinal tract in areas in addition to the stomach and duodenum and against harmful effects of DAPT. Beyond PPIs, other measures have to be implemented to protect small bowel tract mucosa. Microbiota modulation is one innovative and promising method of such holistic care. Several bacterial strains have already been tested in humans to try to reverse aspirin/NSAID-related enteropathy, to maintain the gut barrier, and to prevent mucosal damage in the small intestine. Based on available data, the question of full safety of both drugs (DAPT and PPIs) administered together is still incomplete. Future preclinical and clinical trials—including gastrointestinal microbiome and metabolome testing along with capsule endoscopy evaluation of small bowel mucosal injury—in patients taking DAPT and PPIs are essential in answering the most relevant questions of optimal care of patients with ACS.

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