Concurrent Lower Gastrointestinal Bleeding Risk and Myocardial Ischemic Risk: Resume Aspirin or Not?

See "Risks of bleeding recurrence and cardiovascular events with continued aspirin use after lower gastrointestinal hemorrhage," by Chan FKL, Leung Ki E-L, Wong GLH, et al, on page 271.

Teleologically, when there is bleeding, the natural response of the body is to promote clotting. This makes perfect sense if there is external injury that leads to bleeding and the response is also useful for some forms of internal "injury," such as gastrointestinal (GI) bleeding. However, in those prone to atherosclerosis, the prothrombotic stimulus of bleeding can provoke ischemic events leading to the paradox of patients who are bleeding also being at potentially high ischemic risk.[1] This mechanism is less likely to occur in a young healthy person, but in an older patient with established or silent atherosclerosis, myocardial ischemia may occur.[2] Furthermore, there is a linear risk of recurrent ischemic events in patients with a history of prior ischemic events, and the antiplatelet effect of aspirin reduces this risk substantially.[3,4] Withdrawal of aspirin, of course, removes this layer of antithrombotic protection. Hence, there is a rational biological basis to continue or quickly resume antiplatelet therapy in patients with recent GI bleeding, as counterintuitive as it may initially seem. In this issue of *Gastroenterology*, Chan et al[5] provide provocative retrospective data that support this hypothesis.

In an elegant analysis, Chan et al[5] examined, from a single center prospective registry, a total of 295 patients on aspirin with documented lower GI bleeding. Recurrent lower GI bleeding, serious cardiovascular (CV) events (nonfatal myocardial infarction, nonfatal stroke, or death from a vascular cause), and death from other causes were assessed by an independent, blinded adjudication committee. These outcomes were compared based on cumulative duration of aspirin use during the follow-up period. The aspirin users were defined as "use during $\geq$50% of the observation period" (n = 174), whereas nonusers were defined as "use $<$20% of the follow-up period" (n = 121). The primary endpoint was overt recurrent lower GI bleeding, which was defined as a significant bleeding episode (melena or hematochezia or a drop in hemoglobin $>$ 2 g/dL without an upper GI source or other non-GI cause of anemia being identified). Not surprisingly, over $\leq$5 years of follow-up, lower GI bleeding recurred in 18.9% of aspirin users versus 6.9% of nonusers (P = .007). However, serious CV events occurred in 22.8% of aspirin users versus 36.5% of nonusers (P = .017). Moreover, 8.2% of aspirin users died from other causes versus 26.7% of nonusers (P = .001). Importantly, in this observational study, multivariable analysis demonstrated that aspirin use was an independent predictor of rebleeding, although it protected against CV events and death.

A prior small clinical trial from the same group randomized 156 patients with upper GI bleeding from peptic ulcer treated with endoscopic intervention and proton pump inhibitors (PPIs) to continue aspirin or placebo.[6] The rate of confirmed recurrent ulcer bleeding within 30 days was 10.3% in the patients randomized to aspirin versus 5.4% in the patients receiving placebo. However, the patients randomized to aspirin had a significantly lower rate of all-cause mortality than patients who were randomized to placebo (1.3% vs 12.9%). Although that study focused on the risks in the immediate period after upper GI bleeding, the present nonrandomized study focused on the longer term risks following lower GI bleeding. Nevertheless, conceptually, the results of the 2 studies are concordant and complementary, supporting the resumption of antiplatelet therapy in patients with GI bleeding, once stabilized. Until and unless large multicenter randomized clinical trials are done on this topic, it seems reasonable to use these 2 studies to guide clinical care and, in general, continue or resume antiplatelet therapy in patients at high CV risk after either upper or lower GI bleeding, once the initial GI treatment is completed.

The strengths of this study include the use of a prospective registry and blinded outcome assessment. The statistical methodology was rigorous, including the application of competing-risks regression analysis. Baseline over-the-counter aspirin and non-steroidal anti-inflammatory drug use was documented; these variables have been frequently omitted from prior analyses.

An obvious limitation of the present analysis is its nonrandomized design. The observational nature may have resulted in unmeasured confounding. For example, patients with higher rebleeding risk may also have been at higher ischemic risk but had aspirin discontinued, and this higher risk may then have resulted in worse outcomes rather than discontinuation of aspirin per se. Moreover, the higher mortality rate owing to non-CV causes in the nonusers supports residual confounding. Aspirin use would be expected to reduce CV events, but there is no reason to think it should reduce deaths owing to sepsis, the predominant cause of non-CV death in this study, and any potential effects on cancer mortality remain speculative.[7] A further limitation is the relatively small sample size. It took 8 years to accrue a sufficient number of patients at this single site, and a future, multicenter randomized study would be ideal.

The present study concerns the resumption of antiplatelet therapy after presumed lower GI bleeding, where overall management remains controversial because of a relative lack of evidence and small numbers. Moreover, it is

not always possible to differentiate confidently between upper and lower GI bleeding, and in this study almost one-half of the aspirin group bleeding was occult. Certainly, early colonoscopy within 24 hours reveals more lesions, but endoscopic intervention does not decrease mortality or rebleeding. However, it does decrease the duration of hospital stay, perhaps because of reassurance from a more accurate diagnosis, leading to earlier hospital discharge with less worrisome lesions.[8] Furthermore, endoscopic treatments in the colon are much less evaluated, and the diverse nature and anatomic locations of lower GI lesions, as exemplified by this study, make their investigation and endoscopic treatment particularly challenging. Techniques, such as glue, clips, electrocautery, and laser, are all reported but none is established, and the choice of intervention is likely to vary depending on the lesion. Hemostatic powders or granules sprayed at endoscopy promise some progress for arresting colonic bleeding but there are no pharmacologic agents such as the PPIs, which provide healing and prevention of rebleeding in the upper GI tract. Thus, the paradigm for managing ulcer bleeding cannot be reproduced for lower GI bleeding, and each case of lower GI bleeding should be managed individually. The question of antiplatelet therapy before colonoscopy or routine colonoscopic interventions such as polypectomy is covered by guidelines, and aspirin should not be stopped before such procedures.[8] In a United States survey of aspirin use before colonoscopy procedures, only 43% of 317 endoscopy units recommended continuing aspirin, 32% recommended stopping aspirin, and 24% advised asking the referring physician; only 20% of endoscopy units had formal established policies.[9,10]

In general, the dose of aspirin for chronic cardiac indications should be $\leq$100 mg; higher doses seem to increase the risk of GI bleeding without any clear cardiac benefit. In the present study by Chan et al, all patients were on $\leq$160 mg of aspirin. Nevertheless, in countries such as the United States, use of higher doses of aspirin for chronic cardiac indications persists, representing a potential opportunity to decrease GI bleeding risk.[11]

There remains complexity to the decision regarding stopping or resuming antithrombotic therapy, because it depends in part on the strength of the indication for treatment. For example, in a patient on aspirin for primary prevention, where there remains uncertainty regarding the value, it may be reasonable to withhold aspirin. In a stented patient with a recent acute coronary syndrome, it may be more prudent to continue dual antiplatelet therapy or consider bridging strategies with intravenous antiplatelet agents (although largely untested). In a patient in atrial fibrillation at high risk for a stroke or with a recent pulmonary embolus, it is unknown whether to interrupt or to continue the anticoagulant. Thus, there are several considerations—the exact antithrombotic regimen, the strength of the antithrombotic indication, the necessity of the endoscopic procedure, and the precise timing of any procedure. More randomized clinical trials to address these areas of uncertainty would be welcome, although none could address every possible clinical scenario. Perhaps no area of medicine is as ripe for collaboration between cardiologists and gastroenterologists to help navigate these common and vexing clinical conundrums.

The ongoing Rivaroxaban for the Prevention of Major Cardiovascular Events in Coronary or Peripheral Artery Disease (COMPASS) trial will provide considerable insight into GI bleeding in patients on antiplatelet and anticoagulant therapies, as well as a randomized assessment of the effect of long-term PPIs on upper GI bleeding in this setting.[12] Hopefully, these results will build upon data from the Clopidogrel and the Optimization of Gastrointestinal Events (COGENT) trial which demonstrated that prophylactic PPIs decreased upper GI bleeding in patients with recent acute coronary syndromes or stenting on dual antiplatelet therapy.[13–15] However, it is important to emphasize that PPIs are not effective beyond the duodenum, and recurrent bleeding may occur anywhere in the GI tract. There is currently no drug that protects the lower bowel (Table 1), although misoprostol might be studied for this purpose.

With respect to lower GI bleeding, much further work is needed. Randomized clinical trials evidence comparing the novel oral anticoagulants, including dabigatran versus warfarin, confirm they may be associated with both upper

Table 1. Strategies to Decrease GI Bleeding in Patients at High Cardiovascular Risk Who Require Antithrombotic Therapy

Increase risk of upper GI bleeding
Aspirin
Bisphosphonates
Corticosteroids (hospitalized patients only)
NSAIDs
Oral anticoagulants
Rivaroxaban vs warfarin
SSRIs
Decrease risk of upper GI bleeding
Antisecretory therapy (PPIs superior to H_2-RAs)
Clopidogrel 75 mg vs aspirin 325 mg
Coxibs versus NSAIDs
Low-dose versus high-dose aspirin
Misoprostol
Endoscopic techniques (banding, clipping, electrocautery, embolization, injection, laser coagulation)
Increase risk of lower GI bleeding
Aspirin
Bisphosphonates
Dabigatran (higher dose) vs warfarin
NSAIDs
Oral anticoagulants
Rivaroxaban vs warfarin
SSRI
Decrease risk of lower GI bleeding
? Misoprostol
Endoscopic techniques (banding, clipping, electrocautery, embolization, injection, laser coagulation)

Although strategies exist to decrease upper GI bleeding, none seems to be effective to reduce lower GI bleeding risk. The question mark sign (?) indicates uncertainty.
Coxibs, cyclooxygenase inhibitors; GI, gastrointestinal; H_2-RAs, histamine H_2-receptor antagonists; NSAIDs, nonsteroidal anti-inflammatory drugs; PPIs, proton pump inhibitors; SSRIs, selective serotonin reuptake inhibitors.