Aspirin Withdrawal in Acute Peptic Ulcer Bleeding: Are We Harming Patients?

The management of sick patients is increasingly complex. Clinicians must weigh the benefits and harms attributable to a given therapeutic choice. This is certainly the case for patients who develop peptic ulcer bleeding while receiving antiplatelet therapy, such as low-dose aspirin (acetylsalicylic acid) or clopidogrel, anticoagulants, or a combination thereof, which is an increasingly common scenario (1–3). Clinicians face a dilemma: Should antiplatelet or anticoagulant therapy be stopped, and if so, for how long?

In this issue, Sung and colleagues (4) attempted to address this important clinical quandary by conducting a randomized trial. The research group from the Chinese University of Hong Kong has significantly shaped our knowledge of peptic ulcer bleeding over the past 2 decades. We should commend them for taking on this difficult trial in 156 patients who presented with acute peptic ulcer bleeding while receiving low-dose aspirin to prevent cardiovascular event recurrences. After endoscopic hemostasis and high-dose intravenous proton-pump inhibitors for treatment of high-risk endoscopic bleeding lesions, the patients were randomly assigned to receive low-dose aspirin, 80 mg/d, or placebo for 8 weeks. Both groups subsequently received a daily dose of an oral proton-pump inhibitor during follow-up.

The incidence of recurrent ulcer bleeding at 30 days, the primary outcome measure, was 10.3% in the low-dose aspirin group and 5.4% in the placebo group; the upper limit of the 95% CI of the difference exceeded the 10% noninferiority threshold set a priori (difference, 4.9 percentage points [95% CI, −3.6 to 13.4 percentage points]). This rejected the hypothesis that continued low-dose aspirin therapy was not inferior to placebo use. However, patients who received low-dose aspirin had lower all-cause 30-day mortality rates than those who received placebo (1.3% vs. 12.9%; difference, 11.6 percentage points [CI, 3.7 to 19.5 percentage points]). The low-dose aspirin group also had a lower mortality rate attributable to cardiovascular, cerebrovascular, or gastrointestinal complications (1.3% vs. 10.3%; difference, 9.0 percentage points [CI, 1.7 to 16.3 percentage points]). Kaplan–Meier estimates yielded hazard ratios of 1.9 (CI, 0.6 to 6.0) for 30-day recurrent bleeding, 0.2 (CI, 0.05 to 0.90) for mortality at 30 days, and 0.2 (CI, 0.05 to 0.70) for mortality attributable to complications.

The unusual choice of a noninferiority study design in this setting, with the selected upper noninferiority margin, led Sung and colleagues (4) to conclude that continuous aspirin therapy in patients with peptic ulcer bleeding was not equal to stopping aspirin therapy in risk for recurrent bleeding. The authors concluded this, despite choosing a wide noninferiority margin (10 percentage points), on the basis that recurrent ulcer bleeding is potentially treatable and interruption of low-dose aspirin therapy may lead to more serious cardiovascular outcomes. At first glance, on the basis of the primary outcome results of recurrent bleeding, low-dose aspirin administration seemed a less favorable option than stopping therapy for 8 weeks. However, of the 10 patients who did not meet the prespecified criteria for recurrent upper gastrointestinal bleeding, 2 probably did have recurrent bleeding (one with recurrent hematemesis who died before arriving at the hospital and another with recurrent melena who was too ill to have further endoscopic examination). Because both patients were in the placebo group, if they had been counted, the observed between-group difference in the recurrent bleeding rate would have been less.

We also need to assess the other facet of the risk–benefit equation. When taking into account nonfatal and fatal cardiovascular events, respective rates were 3.9% and 11.5% for the low-dose aspirin and placebo groups. Moreover, significantly more patients in the placebo group died during follow-up, whether from all causes or the combination of cardiovascular, cerebrovascular, or gastrointestinal complications. However, the trial was not originally powered for these secondary outcomes, and only 1 patient died in the low-dose aspirin group (compared with 10 in the placebo group). Of the 10 patients in the placebo group who died, 3 died of gastrointestinal complications and 2 died of pneumonia. The remaining 5 died of vascular complications (2 died of an acute coronary syndrome on days 1 and 7, 1 of recurrent stroke on day 12, and 2 of congestive heart failure on days 20 and 39).

Most deaths due to upper gastrointestinal bleeding were not attributed to direct complications of recurrent bleeding, as is most often the case (5), and the authors further speculated that gastrointestinal bleeding may have led to a higher mortality rate in the placebo group because these patients were more vulnerable to atherothrombosis while not receiving low-dose aspirin therapy, thus tolerating bleeding poorly. Nonetheless, these data also suggest the possibility of a type I error due to chance alone.

When thinking of applying these results to our individual practices, we must also consider the external validity or generalizability of the results in light of the dose of aspirin (and oral proton-pump inhibitors) chosen, the high level of endoscopic expertise of the investigative team in treating ulcers, and the reported geographic differences in pharmacogenomics and physiologic responses to proton-pump inhibitors (6, 7).

What is a clinician to do on the basis of this information? First, additional trials may not be completed anytime...
soon because of the difficulty in studying such patients in this setting. Second, although we must question the interpretation of these data as methodologists, we have little difficulty in accepting them as practicing clinicians because of the respective prognoses of bleeding ulcers compared with cardiovascular complications—even more so, because the delay to thrombotic events is short (generally reported to be 7 to 30 days) and events often occur 7 to 10 days after low-dose aspirin withdrawal (8–11). The duration of low-dose aspirin therapy discontinuation is critical and should be studied further; however, adopting a strategy to reintroduce aspirin before 8 weeks seems warranted.

Perhaps of most importance, this trial forces us to reconsider the all-too-common acute focus on the gut in patients with upper gastrointestinal bleeding (even if this represents a vexing reality check for gastrointestinal endoscopists). The benefits of low-dose aspirin therapy must be weighed against its attendant risks in patients who develop peptic ulcer bleeding. Patients who receive antithrombotic therapy for primary prophylaxis should discontinue low-dose aspirin therapy unless the vascular risk profile worsens (1, 12). On the basis of all available data, international consensus recommendations (that included the results from Sung and colleagues [4]) concluded that patients with upper gastrointestinal bleeding who require secondary cardiovascular prophylaxis should resume low-dose aspirin therapy as soon as the cardiovascular risks outweigh the gastrointestinal risks (usually within 7 days) (13). We must also not forget to tend to the long-term management of patients who have had gastrointestinal bleeding while receiving low-dose aspirin. In this case, the data are convincing that the combination of low-dose aspirin and proton-pump inhibitors results in less recurrent bleeding than a switch to clopidogrel alone during the following 12 months (14, 15).

Until additional data become available to better guide management, clinicians will need to rely on limited evidence and appropriate use of common sense that considers the patient as a whole without focusing on one specific organ system to the detriment of another.

Alan N. Barkun, MD, CM, MSc
McGill University
Montreal, Quebec H3G 1A4, Canada

Marc Bardou, MD, PhD
Centre Hospitalier Universitaire de Dijon
Dijon Cedex, France

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Requests for Single Reprints: Alan N. Barkun, MD, CM, MSc, Division of Gastroenterology, Montreal General Hospital Site, McGill University Health Centre, 1650 Cedar Avenue, Room D7.148, Montreal, Quebec H3G 1A4, Canada; e-mail, alan.barkun@muhc.mcgill.ca.

Current author addresses are available at www.annals.org. This article was published at www.annals.org on 1 December 2009.


References
Current Author Addresses: Dr. Barkun: Division of Gastroenterology, Montreal General Hospital Site, McGill University Health Centre, 1650 Cedar Avenue, Room D7.148, Montreal, Quebec H3G 1A4, Canada.

Dr. Bardou: INSERM CIC-P 803, Centre Hospitalier Universitaire de Dijon, 2 Boulevard de Lattre de Tassigny, BP1542, 21079 Dijon Cedex, France.