Continuation of Low-Dose Aspirin Therapy in Peptic Ulcer Bleeding

A Randomized Trial

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Background: It is uncertain whether aspirin therapy should be continued after endoscopic hemostatic therapy in patients who develop peptic ulcer bleeding while receiving low-dose aspirin.

Objective: To test that continuing aspirin therapy with proton-pump inhibitors after endoscopic control of ulcer bleeding was not inferior to stopping aspirin therapy, in terms of recurrent ulcer bleeding in adults with cardiovascular or cerebrovascular diseases.

Design: A parallel randomized, placebo-controlled noninferiority trial, in which both patients and clinicians were blinded to treatment assignment, was conducted from 2003 to 2006 by using computer-generated numbers in concealed envelopes. (ClinicalTrials.gov registration number: NCT00153725)

Setting: A tertiary endoscopy center.

Patients: Low-dose aspirin recipients with peptic ulcer bleeding.

Intervention: 78 patients received aspirin, 80 mg, and 78 received placebo for 8 weeks immediately after endoscopic therapy. All patients received a 72-hour infusion of pantoprazole followed by oral pantoprazole. All patients completed follow-up.

Measurements: The primary end point was recurrent ulcer bleeding within 30 days confirmed by endoscopy. Secondary end points were all-cause and specific-cause mortality in 8 weeks.

Results: 156 patients were included in an intention-to-treat analysis. Three patients withdrew from the trial before finishing follow-up. Recurrent ulcer bleeding within 30 days was 10.3% in the aspirin group and 5.4% in the placebo group (difference, 4.9 percentage points [95% CI, −3.6 to 13.4 percentage points]). Patients who received aspirin had lower all-cause mortality rates than patients who received placebo (1.3% vs. 12.9%; difference, 11.6 percentage points [CI, 3.7 to 19.5 percentage points]). Patients in the aspirin group had lower mortality rates attributable to cardiovascular, cerebrovascular, or gastrointestinal complications than patients in the placebo group (1.3% vs. 10.3%; difference, 9 percentage points [CI, 1.7 to 16.3 percentage points]).

Limitations: The sample size is relatively small, and only low-dose aspirin, 80 mg, was used. Two patients with recurrent bleeding in the placebo group did not have further endoscopy.

Conclusion: Among low-dose aspirin recipients who had peptic ulcer bleeding, continuous aspirin therapy may increase the risk for recurrent bleeding but potentially reduces mortality rates. Larger trials are needed to confirm these findings.

Primary Funding Source: Institute of Digestive Disease, Chinese University of Hong Kong.


When patients present with peptic ulcer bleeding, the usual protocol is to treat the active bleeding with an endoscopic device, offer antisecretory therapy, and discontinue aspirin or other antiplatelet agents until the ulcer heals. However, there is a risk for cardiovascular and cerebrovascular events and death when antiplatelet agents are discontinued. The balance of risk and benefit for prescribing antiplatelet agents under these situations is an estimation of the chance of developing recurrent upper gastrointestinal bleeding against the chance of vascular thrombotic events in the cardiac and neurologic systems (11). We previously showed that intravenous infusion of proton-pump inhibitors

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Context
What happens if patients who take aspirin to prevent cardiovascular disease continue to take it after an acute gastrointestinal bleeding event?

Contribution
This trial included 156 adults with cardiovascular disease, history of aspirin use, and acute peptic ulcer bleeding. Immediately after successful endoscopic treatment, they were randomly assigned to receive low-dose aspirin (80 mg/d) or placebo for 8 weeks. All patients also received pantoprazole. More aspirin recipients than placebo recipients (10% vs. 5%) had recurrent ulcer bleeding within 30 days, although fewer aspirin recipients died (1% vs. 13%).

Caution
The study was small. Some deaths in the placebo group were from causes not normally prevented by aspirin.

—The Editors

tors reduced the incidence of recurrent ulcer bleeding in patients with non–aspirin-related peptic ulcer bleeding (12). Would the acid-suppressive effects of intravenous and oral proton-pump inhibitors confer sufficient protection to allow early resumption of aspirin therapy after successful endoscopic hemostasis?

In this study, we hypothesized that after successful endoscopic control of ulcer bleeding, continuous aspirin therapy would not be not inferior to stopping aspirin therapy in terms of risk for recurrent bleeding in the presence of proton-pump inhibitors.

Methods
Design
We conducted a parallel randomized, placebo-controlled study in which both patients and clinicians were blinded to the treatment assignment. The clinical research ethics committee (institutional review board) of the Faculty of Medicine at the Chinese University of Hong Kong approved the study protocol. All patients or their legal representatives provided written, informed consent for participation in the trial, and the study complied with the Declaration of Helsinki, International Conference on Harmonisation of Technical requirements for registration of pharmaceuticals for human use Good Clinical Practice guidelines, and local regulations. We recruited and followed patients from February 2003 to October 2006. We vouch for the completeness and veracity of the data and data analysis.

Setting and Participants
We conducted this single-center study at a university medical center. Members of the gastroenterology team at the Endoscopy Center of Prince of Wales Hospital (Sha Tin, New Territories, Hong Kong) evaluated consecutive patients who presented with overt signs of upper gastrointestinal bleed-
recurrent gastrointestinal bleeding by endoscopy. We did not permit antiplatelet coprescription during follow-up.

**Follow-up Procedures and Monitoring**

After randomization, a designated team of physicians and surgeons who were unaware of treatment assignment managed the patients. During hospitalization, 1 investigator and 1 research nurse assessed the patients twice daily for any self-reported adverse events. We assessed the intensity of adverse events as mild (easily tolerated), moderate (interfered with normal activities), or severe (incapacitating) and determined the potential causality as unlikely, possible, or probable. A serious adverse event was any event that threatened a patient’s life, required prolonged hospitalization or rehospitalization, or resulted in persistent disability or death. After discharge, we provided 2 telephone hotlines for urgent inquiries and reporting of adverse events. Patients returned for follow-up 30 and 56 days after discharge. We assessed drug compliance by pill counts. We kept participants’ information anonymous and identified participants by their study numbers and initials. The study coordinator entered the data in the case report forms into the electronic database within 48 hours. Only the principal investigator and the study coordinator could access the data, and only the principal investigator could make changes to the electronic database. The database was locked after independent verification and was backed up once every 2 weeks by the server in our center.

**Outcomes**

Our primary end point was recurrent peptic ulcer bleeding within 30 days of endoscopic treatment. Patients received another endoscopic examination if they had recurrent hematemesis with vomiting of fresh blood; melena after a normal stool; a decrease in hemoglobin level greater than 2 g/dL within 24 hours, despite 2 or more units of blood transfused; or unstable hemodynamic status (systolic blood pressure ≤90 mm Hg or pulse ≥110 beats/min) after achieving stabilization. Recurrent ulcer bleeding was the presence of 1 or more of these clinical features and confirmed by endoscopic evidence, which included arterial spurring, nonbleeding visible vessel, adherent clot, or fresh blood in the stomach.

Secondary end points occurring during the 8-week study period included all-cause mortality; death attributed to cardiovascular, cerebrovascular, or gastrointestinal complications; requirement of blood transfusion; duration of hospital stay (measured from day of recruitment); requirement of surgery; and recurrence of acute ischemic events (the acute coronary syndrome and cerebrovascular accident). We diagnosed the acute coronary syndrome according to the American College of Cardiology guidelines, which included unstable angina, myocardial infarction without ST-segment elevation, and myocardial infarction with ST-segment elevation (13). We diagnosed cerebrovascular accident according to the World Health Organization criteria (14). An independent, blinded adjudication committee ascertained whether recurrent ulcer bleeding and atherothrombotic events had occurred according to the prespecified criteria and verified the causality of deaths. We included only events that were confirmed by an independent, blinded adjudication committee in the analysis.

**Statistical Analysis**

We previously showed that among patients with peptic ulcer bleeding who did not receive aspirin, 6.7% had recurrent ulcer bleeding within the 30 days after endoscopic therapy followed by high-dose proton-pump inhibitor therapy (12). Sample size estimation was based on the assumption that 6.7% of aspirin recipients who stopped aspirin therapy would develop recurrent bleeding in 30 days and that continuous aspirin therapy would not be inferior to stopping aspirin therapy if the upper limit of the 95% CI of the difference in recurrent bleeding did not exceed 10 percentage points. A sample size of 75 patients per group would give the study a power of 80% at a 5% level of significance with use of a 1-sided equivalence test of proportions (PASS software, version 2008, NCSS, Kaysville, Utah). We allowed a wide non-inferiority margin of 10 percentage points because recurrent ulcer bleeding is potentially treatable, whereas interruption of aspirin therapy may lead to more serious cardiovascular outcomes. Our previous study showed that the 30-day recurrent bleeding rate was up to 22.5% after endoscopic therapy without high-dose proton-pump inhibitors (12). An independent data safety and monitoring committee did 1 planned interim analysis of the primary and secondary end points in November 2005 to compare the safety of the 2 treatments. If 1 treatment was markedly inferior to the other (in terms of significant increase in recurrent bleeding), we used a predefined early stopping rule that specified termination of the trial if the analysis reached a level of significance of 0.025. The result of the interim analysis did not lead to protocol amendment or early termination of the trial.

We used the Kaplan–Meier method to estimate the likelihood of reaching the end point of recurrent upper gastrointestinal bleeding within 30 days according to the intention-to-treat population (all patients who had received at least 1 dose of study medication). We also used the Kaplan–Meier method to compare the 2 groups for all-cause mortality and combined cardiovascular, cerebrovascular, and gastrointestinal mortality within 8 weeks. Statistical tests for demographic data and secondary end points included the t test, Mann–Whitney U test, chi-square test, and Fisher exact test where appropriate. We did all analyses by using SPSS, version 14 (SPSS, Hong Kong).

**Role of the Funding Source**

An independent educational grant from the Institute of Digestive Disease, Chinese University of Hong Kong, supported our study. Altana Pharma, Hong Kong, provided the pantoprazole that we used in our study. We received no financial support from industry, and Altana Pharma had no role in the design of the study, collection of data, statistical analysis, manuscript preparation or interpretation, or decision to submit the manuscript for publication.
RESULTS
From February 2003 to September 2006, 3412 consecutive patients received a diagnosis of upper gastrointestinal bleeding. Among them, 267 patients had aspirin-related bleeding events. We enrolled 156 patients in the study: 78 in the aspirin group and 78 in the placebo group (Figure 1). Patients in each group did not receive crossover intervention during the trial. The 2 groups were similar

Figure 1. Study flow diagram.

Patients who presented with upper gastrointestinal bleeding (from February 2003 to September 2006) 
(n = 3412)

Confirmed peptic ulcer bleeding with high-risk stigmata of recent hemorrhage 
(n = 705)*

Peptic ulcer bleeding with stigmata and achieved successful endoscopic hemostasis 
(n = 664)

Nonaspirin or NSAID recipient 
(n = 230)
NSAID or OTC NSAID recipient (n = 167)

Bleeding due to aspirin-induced ulcer 
(n = 267)

Randomly assigned patients (n = 156)

Aspirin 
(n = 78)

Suspected clinical recurrent bleeding within 30 d  
(n = 13)

Confirmed recurrent bleeding within 30 d  
(n = 8)

Died 
(n = 1)

Early termination:  
Needed double antiplatelet therapy (n = 1) 
Needed warfarin (n = 1)

Placebo 
(n = 78)

Suspected clinical recurrent bleeding within 30 d  
(n = 9)

Confirmed recurrent bleeding within 30 d  
(n = 4)

Died 
(n = 10)

Excluded patients (n = 111)  
Allergic to aspirin: 1  
Intestinal obstruction: 1  
Needed double antiplatelet therapy: 1  
Ulcer perforation: 1  
Previous gastric surgery: 4  
Concomitant use of anticoagulant drugs: 7  
Terminal cancer: 11  
Moribund conditions: 34  
Unable to or declined consent: 45  
Miscellaneous: 6

NSAID = nonsteroidal anti-inflammatory drug; OTC = over the counter.
* High-risk stigmata of hemorrhage included active spurting or oozing ulcer or ulcer showing protuberant vessel or adherent blood clot.
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Table 1. Participant Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Aspirin Recipients (n = 78)</th>
<th>Placebo Recipients (n = 78)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men, n (%)</td>
<td>48 (62)</td>
<td>49 (63)</td>
</tr>
<tr>
<td>Mean age (SD), y</td>
<td>74 (9)</td>
<td>74 (8)</td>
</tr>
<tr>
<td>Alcohol use, n (%)</td>
<td>6 (8)</td>
<td>6 (8)</td>
</tr>
<tr>
<td>Current smoker, n (%)</td>
<td>6 (8)</td>
<td>11 (14)</td>
</tr>
<tr>
<td>American Society of Anesthesiologists grade</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>43</td>
<td>50</td>
</tr>
<tr>
<td>3</td>
<td>34</td>
<td>26</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Indication for aspirin, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular diseases</td>
<td>40 (52)</td>
<td>47 (60)</td>
</tr>
<tr>
<td>Cerebrovascular diseases</td>
<td>30 (38)</td>
<td>23 (30)</td>
</tr>
<tr>
<td>Both</td>
<td>8 (10)</td>
<td>8 (10)</td>
</tr>
<tr>
<td>Previous NSAID use, n (%)</td>
<td>12 (15.4)</td>
<td>13 (16.7)</td>
</tr>
<tr>
<td>Helicobacter pylori positive, n (%)</td>
<td>31 (39.7)</td>
<td>33 (42.3)</td>
</tr>
<tr>
<td>Previous ulcer bleeding, n (%)</td>
<td>9 (12)</td>
<td>9 (12)</td>
</tr>
<tr>
<td>Mean baseline hemoglobin level (SD), g/dL</td>
<td>9.1 (2.4)</td>
<td>8.4 (2.2)</td>
</tr>
<tr>
<td>Bled during hospital stay, n (%)</td>
<td>12 (15.3)</td>
<td>11 (14.1)</td>
</tr>
<tr>
<td>Location of bleeding ulcer, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastric ulcer</td>
<td>43 (55)</td>
<td>41 (53)</td>
</tr>
<tr>
<td>Duodenal ulcer</td>
<td>34 (44)</td>
<td>35 (45)</td>
</tr>
<tr>
<td>Dieulafoy lesion</td>
<td>1 (1)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Endoscopic stigmata of bleeding, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Active bleeding</td>
<td>24 (31)</td>
<td>27 (35)</td>
</tr>
<tr>
<td>Visible vessel</td>
<td>35 (45)</td>
<td>32 (41)</td>
</tr>
<tr>
<td>Adherent clot</td>
<td>19 (24)</td>
<td>19 (24)</td>
</tr>
<tr>
<td>Mean size of ulcer (SD), cm</td>
<td>1.2 (0.8)</td>
<td>1.2 (0.6)</td>
</tr>
<tr>
<td>Ulcer ≥2 cm, n (%)</td>
<td>14 (18)</td>
<td>16 (21)</td>
</tr>
</tbody>
</table>

NSAID = nonsteroidal anti-inflammatory drug.
* Exposure to NSAID for >1 wk and ≥1 y before presenting with upper gastrointestinal bleeding.

with respect to demographic characteristics. More than 87% of patients had 90% or more drug compliance. About 15% of participants developed gastrointestinal bleeding during hospitalization for other medical conditions (Table 1). None of the patients we recruited received other antiplatelet agents, such as clopidogrel, additional proton-pump inhibitors, or antacid therapy. We did not give nonsteroidal anti-inflammatory drugs, warfarin, or corticosteroids to any patient throughout the study.

The adjudication committee evaluated 22 cases of suspected recurrent upper gastrointestinal bleeding. The committee identified 12 cases of confirmed recurrent bleeding: 8 in the aspirin group and 4 in the placebo group. Among patients with confirmed recurrent bleeding in the aspirin group, 1 case was from a gastric ulcer and 7 were from duodenal ulcers. All cases of confirmed recurrent bleeding in the placebo group were from duodenal ulcers (Table 2). The 30-day cumulative incidence of recurrent ulcer bleeding in the intention-to-treat population was 10.3% (CI, 3.4 to 17.2) in the aspirin group and 5.4% (CI, 0.3 to 10.5) in the placebo group (difference, 4.9 percentage points [CI, −3.6 to 13.4 percentage points]; hazard ratio, 1.9, [CI, 0.6 to 6.0]) (Figure 2). The site of recurrent bleeding was the same site as the original bleeding event. Three patients (4.7%) with recurrent bleeding ulcers and 61 patients (95.3%) who did not have recurrent bleeding tested positive for H. pylori.

Ten patients did not meet the prespecified criteria for recurrent upper gastrointestinal bleeding (5 patients in the aspirin group and 5 in the placebo group). Among them, 8 patients had no endoscopic evidence of recurrent bleeding and 2 (in the placebo group) did not have endoscopy (1 patient had recurrent hematemesis and died before arriving at the hospital, and 1 patient developed recurrent melena but was too ill to have further endoscopic examination).

Table 2. Primary and Secondary End Points

<table>
<thead>
<tr>
<th>End Point</th>
<th>Aspirin Recipients (n = 78)</th>
<th>Placebo Recipients (n = 78)</th>
<th>Difference (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suspected recurrent bleeding in 30 d, n (%)</td>
<td>13 (16.8)</td>
<td>9 (12.0)</td>
<td>–</td>
</tr>
<tr>
<td>Confirmed recurrent bleeding in 30 d, n (%)</td>
<td>8 (10.3)</td>
<td>4 (5.4)</td>
<td>4.9 (−3.6 to 13.4)†</td>
</tr>
<tr>
<td>Gastric ulcer/duodenal ulcer, n/ (%)</td>
<td></td>
<td></td>
<td>0/4</td>
</tr>
<tr>
<td>Stigmata of recent hemorrhage, n</td>
<td></td>
<td></td>
<td>–</td>
</tr>
<tr>
<td>Active bleeding</td>
<td>3</td>
<td>3</td>
<td>–</td>
</tr>
<tr>
<td>Visible vessel</td>
<td>2</td>
<td>1</td>
<td>–</td>
</tr>
<tr>
<td>Adherent clot</td>
<td>3</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td>Median units of blood transfused (range), n</td>
<td>2 (0 to 10)</td>
<td>3 (0 to 9)</td>
<td>0 (−1.0 to 0.0)‡</td>
</tr>
<tr>
<td>Surgery, n (%)</td>
<td>0 (0)</td>
<td>1 (1.3)</td>
<td>1.3 (−6.5 to 12.1)</td>
</tr>
<tr>
<td>Median hospital stay (range), d</td>
<td>5 (3 to 25)</td>
<td>4.5 (1 to 45)</td>
<td>1 (0.0 to 1.0)†</td>
</tr>
<tr>
<td>Death, n (%)</td>
<td></td>
<td></td>
<td>–</td>
</tr>
<tr>
<td>30 d</td>
<td>1 (1.3)</td>
<td>7 (9)</td>
<td>11.6 (3.7 to 19.5)†</td>
</tr>
<tr>
<td>56 d</td>
<td>1 (1.3)</td>
<td>10 (12.9)</td>
<td>11.6 (3.7 to 19.5)†</td>
</tr>
<tr>
<td>Cause of death, n</td>
<td></td>
<td></td>
<td>–</td>
</tr>
<tr>
<td>Cardiovascular complications</td>
<td>1</td>
<td>5</td>
<td>–</td>
</tr>
<tr>
<td>Gastrointestinal complications</td>
<td>0</td>
<td>3</td>
<td>–</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>0</td>
<td>2</td>
<td>–</td>
</tr>
</tbody>
</table>

* When the difference is between 2 percentages, it is expressed as percentage points.
† 95% CIs are Kaplan–Meier estimates.
‡ Difference in medians (95% CI of the difference).
The total number of units of blood transfused was similar between the 2 treatment groups (Table 2). Only 1 patient in the placebo group required surgery because of a perforated ulcer. The duration of hospital stay was also similar between the 2 groups (Table 2).

One patient in the aspirin group died 30 days after randomization. The patient was a woman aged 78 years who had a history of ischemic heart disease and gangrene of the toes. She developed an aspirin-related bleeding duodenal ulcer and died of congestive heart failure despite successful endoscopic hemostasis. In the placebo group, 10 patients died (3 within 1 week, 4 between 1 week and 30 days, and 3 between 30 days and 8 weeks). These included 5 patients who died of vascular complications (2 died of the 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), 3 who died of gastrointestinal complications (2 died of perforated peptic ulcers on days 15 and 16 and 1 of uncontrolled bleeding on day 2), and 2 who died of pneumonia (1 on day 35 and 1 on day 56). We did not do co-intervention, such as percutaneous coronary angioplasty, before these patients died. The 30-day mortality rate was lower in the aspirin group than in the placebo group (1.3% [CI, 0% to 3.8%] vs. 9% [CI, 2.7% to 15.3%]; difference, 7.7 percentage points [CI, 0.9 to 14.5 percentage points]; hazard ratio, 0.2 [CI, 0.05 to 0.90]).

The Kaplan–Meier estimate of all-cause mortality at 8 weeks was lower in the aspirin group than the placebo group (1.3% [CI, 0% to 3.8%] vs. 12.9% [CI, 5.5 to 20.3%]; difference, 11.6 percentage points [CI, 3.7 to 19.5 percentage points]; hazard ratio, 0.2 [CI, 0.06 to 0.60]) (Figure 3, top). The mortality rate attributed to cardiovascular, cerebrovascular, or gastrointestinal complications was lower in the aspirin group than in the placebo group (1.3% [CI, 0% to 3.8%] vs. 10.3% [CI, 3.4% to 17.2%]; difference, 9 percentage points [CI, 1.7 to 16.3 percentage points]; hazard ratio, 0.2 [CI, 0.05 to 0.70]) (Figure 3, bottom). In the primary analysis of confirmed recurrent bleeding in 30 days, patients who died were censored at the time of death if they had not experienced recurrent bleeding beforehand; a sensitivity analysis was done considering death as a competing end point (Pepe and Mori test) (15). The adjusted cumulative incidence of recurrent upper gastrointestinal bleeding at 30 days was 10.3% for patients who received aspirin and 5.1% for patients who received placebo (Pepe and Mori test $P = 0.174$) (15).

Six nonfatal, recurrent acute ischemic events were reported (2 in the aspirin group and 4 in the placebo group): 3 patients had the acute coronary syndrome and 3 had acute stroke. A total of 14 patients in the aspirin group had other adverse events (1 had a vasovagal attack, 1 had type 2 respiratory failure, 1 had a seizure, 1 had gout, 2 had fever, 2 had dizziness, 1 had cough, 1 had chest infection, 1 had ankle edema, 1 had anemia, and 2 had nausea and vomiting). Three patients in the placebo group had adverse events (1 had a hallucination and 2 had chest infection).

**DISCUSSION**

We show that, in the presence of proton-pump inhibitors and endoscopic therapy, continuing aspirin therapy in patients with peptic ulcer bleeding was not equivalent to stopping aspirin therapy in terms of risk for recurrent ulcer bleeding. However, prolonged discontinuation of aspirin therapy in these patients led to higher mortality rates.

Aspirin and antiplatelet agents have been widely used in the secondary prevention of acute coronary syndrome and ischemic stroke, especially after interventional therapies. Searching MEDLINE for studies published in English for guideline recommendations until July 2009, the American Heart Association/American College of Cardiology and American Stroke Association updated guidelines recommend starting or continuing aspirin therapy, 75 to 162 mg, indefinitely unless contraindicated for myocardial infarction (16) and starting aspirin treatment at the initial dose of 325 mg within 24 to 48 hours after onset of ischemic stroke (17). In patients with increased risk for bleeding, the guidelines recommend using a lower dose of aspirin but did not mention whether aspirin therapy should be discontinued for some period. On the other hand, “a thorough review of any medications with special attention to the use of anticoagulants, antiplatelet agents, or medications associated with gastrointestinal hemorrhage should be performed” (18).
In high-risk patients with cardiovascular diseases, the timing of discontinuing antiplatelet treatment has often been problematic. A recent study found that patients in whom antiplatelet therapy was withheld before coronary artery bypass graft surgery had a higher incidence of cardiovascular complications than those who continued antiplatelet therapy (19). However, perioperative administration of aspirin or other antithrombotic therapy has been found to increase major bleeding complications (20, 21). Although the risk for bleeding complications needs to balance with the risk for thrombosis, we did not find guidelines on whether aspirin therapy should be continued in patients with peptic ulcer bleeding.

In our study, early resumption of aspirin therapy led to a 50% increased risk for recurrent bleeding within 1 month (from 5.4% in the placebo group to 10.3% in the aspirin group). Despite a higher risk for recurrent bleeding from the peptic ulcer, only 1 of 78 patients who resumed aspirin therapy early after endoscopic therapy died of causes not related to bleeding. In contrast, discontinuing aspirin therapy did not prevent ulcer mortality in 3 patients who received placebo therapy, despite use of a proton-pump inhibitor. The small number of deaths would restrict further interpretation of the results on mortality rates. Yet, the transfusion requirements between the 2 treatments were almost identical, which implies that recurrent bleeding was relatively mild and did not affect clinical outcome of these patients.

In contrast, mortality rates were higher when aspirin therapy was discontinued until ulcers healed. Most deaths were related to cardiovascular events. We speculate that gastrointestinal bleeding might lead to a higher mortality rate in the placebo group because these patients were more vulnerable to atherothrombosis and therefore could not tolerate bleeding well. The fact that none of the patients who received aspirin and only 3 who received placebo died of gastrointestinal complications could be a chance finding. The difference in mortality rates, however, remained significant even if we excluded death due to gastrointestinal complications. The protective effect of antiplatelet agents seems to outweigh their potential gastrointestinal toxicity.

Unlike most cases of death related to gastrointestinal bleeding that occurred usually within the first 3 to 5 days after index bleeding (9), death in the placebo group of happened throughout 8 weeks of follow-up. This phenomenon may be related to the fact that, despite rapid clearance of aspirin from the circulation, the antiplatelet effects of aspirin last for at least a few days because of the permanent inactivation of the platelets’ cyclooxygenase activity on prostaglandin synthase 1 and synthase 2 (11). One might infer that aspirin can be discontinued for 3 to 5 days after index bleeding and resumed after stabilization. This strategy, which in theory minimizes the bleeding risk and vascular ischemia risk, needs confirmation by a study designed to address the optimal time to restart antiplatelet therapy.

Our study has several limitations. First, the sample size of 156 patients is relatively small. The patients we targeted were older and often had several comorbid conditions, and many were unable or unwilling to give informed consent for the study. However, the 156 patients who we recruited represented this critically ill group, as indicated by their age and American Society of Anesthesiology grade. Although our results suggest that continued aspirin therapy may increase the risk for recurrent bleeding, prolonged discontinuation leads to adverse cardiovascular and cerebrovascular outcomes, which are more serious. Second, the study de-
sign did not allow us to compare the protective effects of proton-pump inhibitors with aspirin because both treatment groups received high-dose intravenous pantoprazole followed by oral pantoprazole. Given the published efficacy of proton-pump inhibitors, it would be unethical to study the effects of early resumption of aspirin in the absence of an effective protective agent. Yet, the low recurrent bleeding rate in both treatment groups compared with previous studies suggests that there were substantial protective effects (12). Third, we used low-dose aspirin (80 mg); whether our results can be extrapolated to a higher dose of 165 mg to 320 mg is uncertain. However, available evidence supports the use of a daily dose of aspirin in the range of 75 to 100 mg for the long-term prevention of serious vascular events in high-risk patients (16, 17). Prudent use of low-dose aspirin in patients with history of peptic ulcer bleeding is warranted. Finally, 2 patients in the placebo group had symptoms of recurrent bleeding but were not included in the primary analyses as having recurrent bleeding because they did not have endoscopy. Adding these 2 cases as recurrent bleeding will further reduce the difference between the 2 groups.

In conclusion, among patients with peptic ulcer bleeding who received low-dose aspirin, continuous aspirin therapy may increase the risk for recurrent bleeding. However, antiplatelet agents potentially reduce overall mortality. Early resumption of low-dose aspirin therapy with proton-pump inhibitors in patients with bleeding ulcers and cardiovascular diseases should be considered.

From the Institute of Digestive Disease, Chinese University of Hong Kong, Sha Tin, New Territories, Hong Kong.

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