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Risks of Bleeding Recurrence and Cardiovascular Events With Continued Aspirin Use After Lower Gastrointestinal Hemorrhage

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BACKGROUND & AIMS: It is not clear whether use of low-dose aspirin should be resumed after an episode of lower gastrointestinal (GI) bleeding. We assessed the long-term risks of recurrent lower GI bleeding and serious cardiovascular outcomes after aspirin-associated lower GI bleeding. **METHODS:** We performed a retrospective study of patients diagnosed with lower GI bleeding (documented melena or hematochezia and absence of upper GI bleeding) from January 1, 2000 through December 31, 2007 at the Prince of Wales Hospital in Hong Kong. Using the hospital registry, we analyzed data from 295 patients on aspirin and determined their outcomes during a 5-year period. Outcomes included recurrent lower GI bleeding, serious cardiovascular events, and death from other causes, as determined by an independent, blinded adjudication committee. Outcomes were compared between patients assigned to the following groups based on cumulative duration of aspirin use: <20% of the follow-up period (121 nonusers) vs ≥50% of the observation period (174 aspirin users). **RESULTS:** Within 5 years, lower GI bleeding recurred in 18.9% of aspirin users (95% confidence interval [CI], 13.3%−25.3%) vs 6.9% of nonusers (95% CI, 3.2%−12.5%; $P = .007$). However, serious cardiovascular events occurred in 22.8% of aspirin users (95% CI, 16.6%−29.6%) vs 36.5% of nonusers (95% CI, 27.4%−45.6%; $P = .017$), and 8.2% of aspirin users died from other causes (95% CI, 4.6%−13.2%) vs 26.7% of nonusers (95% CI, 18.7%−35.4%; $P = .001$). Multivariable analysis showed that aspirin use was an independent predictor of rebleeding, but protected against cardiovascular events and death. **CONCLUSIONS:** Among aspirin users with a history of lower GI bleeding, continuation of aspirin is associated with an increased risk of recurrent lower GI bleeding, but reduced risk of serious cardiovascular events and death.

Keywords: Complication; Intestine; Aspirin.

Low-dose aspirin reduces the risk for coronary artery and cerebrovascular diseases.[1–4] Emerging data suggest that aspirin also reduces the risk of multiple cancers.[5,6] In the United States, it has been estimated that 50% of men older than the age of 40 years use prophylactic aspirin.[7] Despite the potential benefits of aspirin, gastrointestinal (GI) bleeding is a major factor limiting its widespread use.[8–10]

Although the upper GI toxicity of aspirin has been well described in the literature,[1–4] there are relatively few data on lower GI bleeding with aspirin use. A number of observational studies reported that aspirin also increases the risk of lower GI bleeding.[8,9] Although the risk for upper GI bleeding with aspirin can be reduced by concomitant use of proton pump inhibitors,[4] there is no effective therapy to lessen the risk for lower GI bleeding in aspirin users. Importantly, patients who were hospitalized for lower GI bleeding had a higher mortality and a longer hospital stay than those with upper GI bleeding.[11] With the increasing use of aspirin in the aging population, the incidence of lower GI bleeding is expected to increase.

Patients with underlying cardiovascular diseases often require lifelong aspirin use. When these patients recover from an episode of aspirin-associated lower GI bleeding, the risk and benefit of resuming or discontinuing aspirin are not clear. There is a lack of data on the risk for recurrent lower GI bleeding and/or serious cardiovascular events in patients who resume aspirin use. In this study, we aimed to determine the long-term risks and predictors of recurrent lower GI bleeding, serious cardiovascular events, and death in patients with a history of aspirin-associated lower GI bleeding.

Materials and Methods

Patient Population

This was a single-center, retrospective cohort study conducted at the Prince of Wales Hospital, which serves a local population of 1.5 million people in Hong Kong. We identified a cohort of patients diagnosed with aspirin-associated lower GI bleeding between January 1, 2000 and December 31, 2007 from a prospectively collected GI bleeding registry.[12–14] This GI bleeding registry included all patients admitted with hematemesis, melena, or hematochezia. Patients received upper GI

Abbreviations used in this paper: **ATT, Antithrombotic Trialists' Collaboration; CI, confidence interval; GI, gastrointestinal; SHR, subdistribution hazard ratio.**

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endoscopy within 24 hours. Lower GI investigations were arranged for patients without an upper GI source identified. After informed consent was obtained at admission, a designated team of research nurses and doctors entered patient data into the GI bleeding registry through patient interview and data extraction from a territory-wide electronic health care database that covers >90% of the Hong Kong population (Clinical Management System). This Clinical Management System has been assessed and deemed satisfactory in terms of both its completeness and accuracy after implementation of a structured data entry method.[15] We collected data including demographic profile, nature, and number of comorbid illnesses, current and prior medication use, blood transfusion, laboratory results, current and previous endoscopy findings, duration of hospitalization, date of discharge, and diagnosis.[12–14] To assess drug exposure, all patients were systematically screened for any recent use of aspirin, nonsteroidal anti-inflammatory drugs, or other concomitant drugs. The Clinical Management System was used to identify prescriptions before the onset of GI bleeding. We also captured the use of any over-the-counter drugs and prescriptions directly from interviews with patients, family members, and primary care physicians.[16,17]

Aspirin-associated lower GI bleeding was defined as use of aspirin (≤325 mg/d) within 1 week of the onset of bleeding; documented melena or rectal bleeding by the attending doctor; and exclusion of upper GI bleeding as confirmed by upper endoscopy. To avoid confounding conditions, we excluded patients who had hemorrhoidal bleeding confirmed by proctoscopy; colorectal cancer (confirmed ≤12 months after the index bleeding); or concomitant use of nonsteroidal anti-inflammatory drugs (used within 1 month of index bleeding). The study was approved by the local ethics committee.

Data Extraction

After identifying the study cohort from the GI bleeding registry, we extracted their demographic and clinical data, including age, sex, history of alcohol consumption or smoking, comorbidities (assessed by the American Society of Anesthesiologists grading), hemoglobin, blood transfusion, previous GI bleeding, and concomitant medications. Significant bleeding was defined as transfusion of ≥2 U red cells. Patients with high cardiovascular risk were defined according to the Antithrombotic Trialists' Collaboration (ATT) definition, which included subjects with a history of unstable angina, acute myocardial infarction, prior myocardial infarction, stroke, or transient ischemic attack. We used the Clinical Management System to identify readmissions to other hospitals, concomitant illnesses, prescriptions, and causes of death. The total duration of aspirin use was estimated from the cumulative period of prescription, which began from the resumption of aspirin after the index bleeding episode until recurrent lower GI bleeding, serious cardiovascular events as defined by APTC (nonfatal myocardial infarction, nonfatal stroke, or death from a vascular cause), or death from other causes, whichever came first. Patients were followed up for up to 5 years or until the end of the study period (December 31, 2012). Study subjects were allocated to 1 of 2 groups according to their cumulative duration of aspirin use: <20% of the follow-up period (nonuser group) vs ≥50% of the observation period (aspirin group).

Study Outcomes

The primary end point was recurrent lower GI bleeding, which was defined as recurrent overt bleeding (melena or hematochezia without an upper GI source) or a drop in hemoglobin >2 g/dL, without an upper GI source or other non-GI causes of anemia. We excluded hemorrhoidal bleeding and colorectal cancer as lower GI outcomes. Secondary end points were serious cardiovascular events as defined by APTC (nonfatal myocardial infarction, nonfatal stroke, or death from a vascular cause) and death from other causes. Each death was reviewed and was assigned an underlying cause based on all available medical information. Patients were censored if they had confirmed upper GI bleeding or a drop in hemoglobin >2 g/dL due to an unknown cause. An independent blinded adjudication committee confirmed these end points according to predefined criteria.

Sample Size Estimation

We have previously shown that among aspirin users with a history of upper GI bleeding, the annual incidence of lower GI bleeding was 4.6%.[18] Assuming that the risk of recurrent lower GI bleeding was 3 times lower in patients who discontinued aspirin than those who continued aspirin, the estimated annual incidence of recurrent lower GI bleeding after discontinuation of aspirin would be 1.5%. Using survival analysis, the 5-year cumulative incidence of recurrent lower GI bleeding in all patients would be about 15%, including both users and nonusers. In the same previous study, we also found that the annual incidence of serious cardiovascular events and death was 9.4% among aspirin users with a history of GI bleeding.[18] We therefore estimated that the overall 5-year cumulative incidence of serious cardiovascular events and death was about 45% for both groups in our cohort. In order to detect a subdistribution hazard ratio (SHR) of 3, a total sample size of 288 subjects would be required to achieve a statistical power of 80% at 5% level of significance (2-sided).[19] Assuming a mean accrual rate of 35 to 40 eligible patients per year, it would take about 8 years (January 2000 to December 2007) to achieve the target sample size.

Statistical Analysis

Continuous variables were expressed as mean ± SD or median and interquartile range where appropriate, and discrete variables as frequency (percentage). Characteristics of nonusers and aspirin users were compared using unpaired *t*-test or Mann-Whitney U-test for continuous variables and χ^2 or Fisher's exact test for categorical variables. As serious cardiovascular events and death were considered to be competing events when they occurred before recurrent lower GI bleeding, we calculated the cumulative incidence of recurrent lower GI bleeding in the presence of competing risk events.[20] Gray's test was used to compare cumulative incidence between the 2 groups.[21] Competing-risks regression based on the method described by Fine and Gray,[22] with serious cardiovascular events and death treated as competing risks, was performed to identify variables associated with recurrent lower GI bleeding. The following predefined covariables at baseline were extracted and included in the analysis: age, sex, alcohol consumption, smoking, severity of comorbidities (evaluated by American Society of Anesthesiologists grading), history of GI bleeding