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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

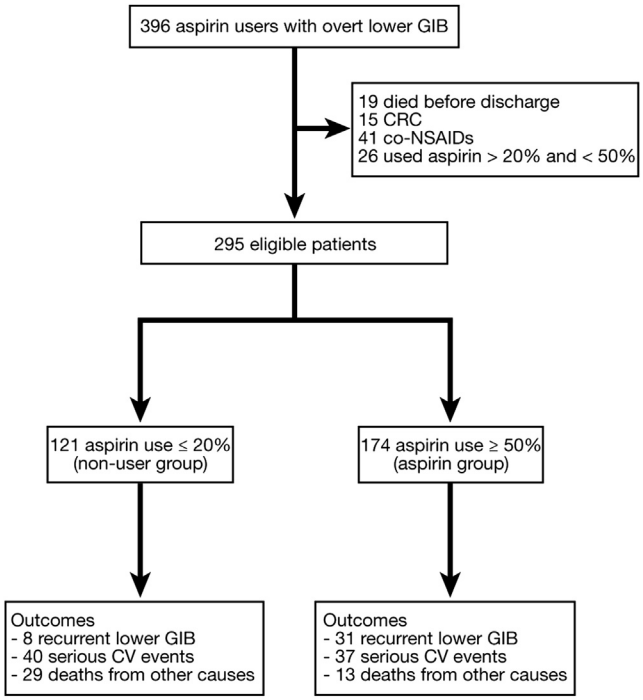

Figure 1. Disposition and outcomes of patients.

(upper or lower), blood transfusion, concomitant medication (anticoagulant, steroid, or nonaspirin antiplatelet drugs) within the past 30 days of index bleeding and cardiovascular risk (according to the APTC definition). Predictors achieving a $P < .2$ in univariable analysis were included in the initial multivariable model, to which backward stepwise approach was then applied. The estimated coefficients were presented as SHRs with their 95% confidence intervals (CIs). All analyses were repeated for secondary outcomes (serious cardiovascular events and death). The proportional subhazards assumption was assessed visually with Schoenfeld-type residual plots and interactions with time were tested. We did not detect any significant violations or any significant time by covariables interaction terms. A 2-sided value of $P < .05$ was chosen for statistical significance. All analyses were performed using SAS software, version 9.3 (SAS Institute Inc, Cary, NC) and the package cmprsk in R version 2.12.1 (www.r-project.org).

Results

We identified a total of 396 aspirin users with overt lower GI bleeding between January 2000 and December 2007. Among them, 295 patients were eligible for the study (121 in the nonuser group and 174 in the aspirin group). The disposition and outcomes of the patients are shown in Figure 1. In the nonuser group, 87% of the patients received aspirin during ≤10% of the observation period. In the aspirin group, 84% of patients received aspirin during ≥75% of the follow-up period. More than 88% of aspirin users took 80 mg aspirin daily. The remaining patients used 100 mg or 160 mg aspirin per day.

Compared with the aspirin group, nonusers were older (76.7 vs 73.1 years, $P = .003$), had a lower proportion of smokers (26.4% vs 42.0%; $P = .006$), and had a higher proportion of patients who had received blood transfusion ≥2 U at index bleeding (54.5% vs 39.7%; $P = .012$) (Table 1). Median follow-up was 1.7 years (interquartile range, 0.2−4.7 years) in the nonuser group and 2.7 years (interquartile range, 0.6−5.0 years) in the aspirin group.

The adjudication committee reviewed 76 cases of suspected recurrent lower GI bleeding (24 in the nonuser group and 52 in the aspirin group), and 39 cases were confirmed to have recurrent lower GI bleeding (8 in the nonuser group and 31 in the aspirin group). All patients with recurrent lower GI bleeding were hospitalized. Of the 8 patients with recurrent bleeding in the nonuser group, 3

Table 1. Baseline Characteristics of Patients

Characteristics	Nonuser group (n = 121)	Aspirin group (n = 174)	*P* value
Age, *y*, mean (SD)	76.7 (9.9)	73.1 (10.6)	.003
Age >70 y	88 (72.7)	112 (64.4)	.131
Male sex	61 (50.4)	91 (52.3)	.750
Drinkers (current or past)	19 (15.7)	41 (23.6)	.099
Smokers (current or past)	32 (26.4)	73 (42.0)	.006
Severity of comorbidity (>2)[a]	72 (59.5)	98 (56.3)	.586
History of GI bleeding	22 (18.2)	43 (24.7)	.183
Blood transfusion (≥2.0 U)	66 (54.5)	69 (39.7)	.012
Concomitant anticoagulant, steroid or non-aspirin antiplatelet drugs	16 (13.2)	22 (12.6)	.884
High cardiovascular risk[b]	111 (91.7)	166 (95.4)	.196

NOTE. Data are presented as n (%) unless otherwise noted.
[a]Severity of comorbidity was classified according to the American Society of Anesthesiology: grade 1, normal healthy patients; grade 2, mild systemic illness; grade 3, severe but incapacitating systemic illness; grade 4, life-threatening illness.
[b]High cardiovascular risk: we used Antithrombotic Trialists's Collaboration to include previous/current myocardial infarction, previous/current ischemic stroke, and other high-risk group (coronary heart disease, peripheral artery disease, hemodialysis, carotid disease, and diabetes).

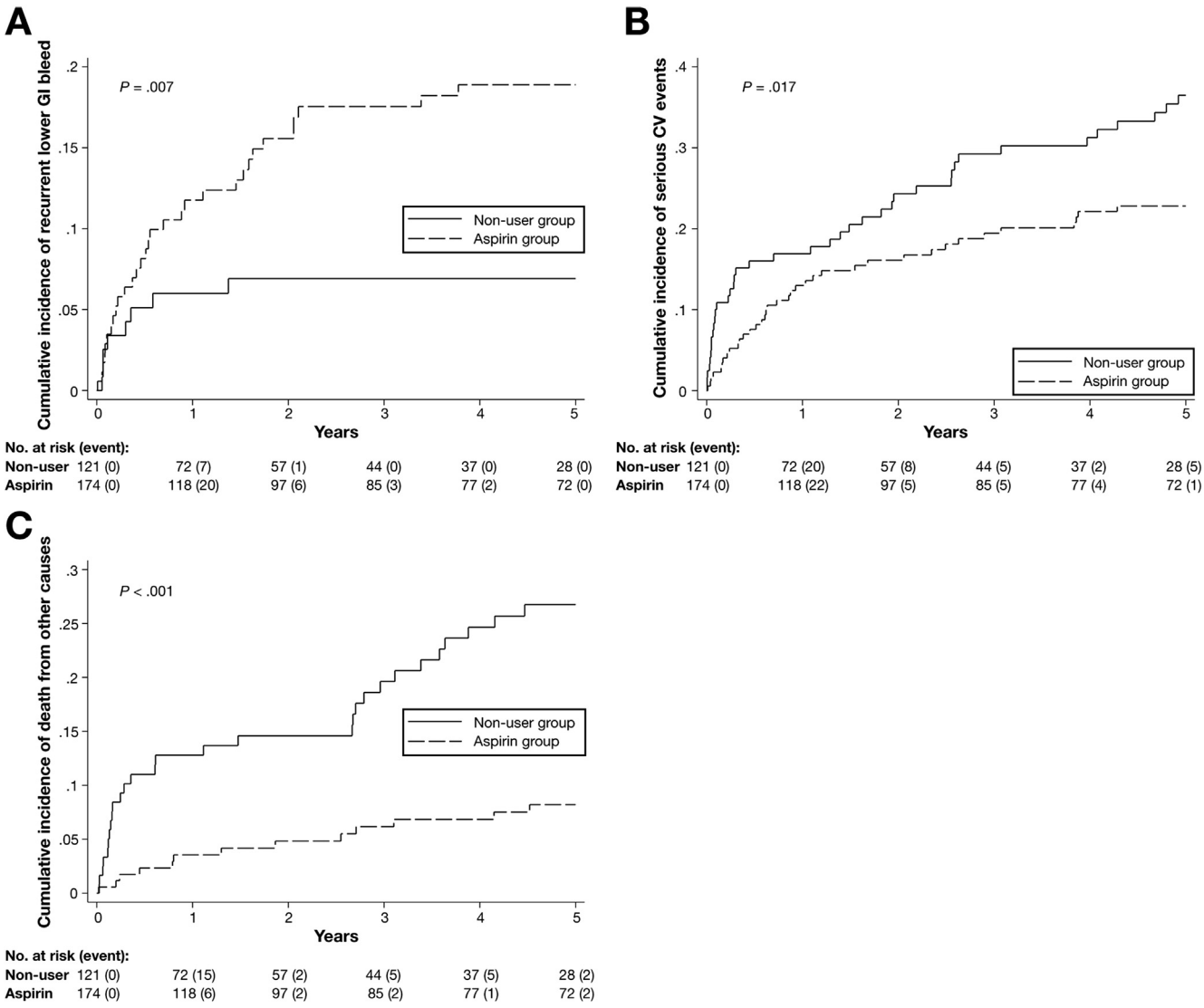

Figure 2. Cumulative incidence of (*A*) recurrent lower GI bleeding, (*B*) serious CV events, and (*C*) death from other causes at 5 years in nonuser group and aspirin group.

(38%) received a median of 2 U (range, 2−3 U) transfusion. The source of recurrent bleeding included diverticular disease (n = 2), proctitis (n = 1), and bleeding of presumed small bowel origin (n = 5). Of the 31 patients with recurrent bleeding in the aspirin group, 20 (65%) received a median of 2 U transfusion (range, 1−6 U). The source of recurrent bleeding included diverticular disease (n = 7), large bowel angiodysplasia (n = 2), small bowel angiodysplasia (n = 1), small bowel erosions (n = 1), colitis (n = 1), ileal ulcer (n = 1), small bowel diverticulum (n = 1), and bleeding of presumed small bowel origin (n = 17). Four of the 7 patients with diverticular bleeding in the aspirin group presented with recurrent diverticular bleeding. The cumulative incidence of recurrent lower GI bleeding at 5 years was 6.9% (95% CI, 3.2%−12.5%) in the nonuser group and 18.9% (95% CI, 13.3%−25.3%) in the aspirin group (P = .007) (Figure 2*A*). Among the 37 patients who did not have recurrent lower GI bleeding (16 in the nonuser group and 21 in the aspirin group), 25 had upper GI bleeding (13 in the nonuser group and 12 in the aspirin group) and 12 patients had a drop in hemoglobin due to non-GI causes (3 in the nonuser group and 9 in the aspirin group).

The adjudication committee confirmed 77 serious cardiovascular events and 42 deaths from other causes during the observation period (Table 2). Of the 77 patients with serious cardiovascular events (40 in the nonuser group and 37 in the aspirin group), 30 had nonfatal myocardial infarction, 22 had nonfatal stroke, 10 died from vascular causes, and 15 died from uncertain causes. The cumulative incidence of serious cardiovascular events at 5 years was 36.5% (95% CI, 27.4%−45.6%) in the nonuser group and 22.8% (95% CI, 16.6%−29.6%) in the aspirin group (P = .017) (Figure 2*B*). A total of 42 patients died from other causes (29 in the nonuser group and 13 in the aspirin group), including sepsis (n = 22), cancer (n = 10), renal failure (n = 6), and miscellaneous (n = 4). The cumulative incidence of death from other causes at 5 years was 26.7% (95% CI, 18.7%−35.4%) in the nonuser group and 8.2%

Table 2. Causes of Primary and Secondary Outcomes

Event	Nonuser group (n = 121)	Aspirin group (n = 174)
Recurrent lower GI bleeding	8 (6.6)	31 (17.8)
Overt bleeding	6 (5.0)	19 (10.9)
Occult bleeding	2 (1.7)	12 (6.9)
Serious CV events[a]	40 (33.1)	37 (21.3)
Nonfatal MI	16 (13.2)	14 (8.0)
Nonfatal stoke	9 (7.4)	13 (7.5)
Death from a vascular causes	5 (4.1)	5 (2.9)
Death from an unknown cause in high-risk CV patients[b]	10 (8.3)	5 (2.9)
Death from other causes	29 (24.0)	13 (7.5)
Sepsis	16 (13.2)	6 (3.4)
Malignancy	6 (5.0)	4 (2.3)
Renal failure	4 (3.3)	2 (1.1)
Others	3 (2.5)	1 (0.6)

NOTE. Data are n (%) of patients.
CV, cardiovascular; MI, myocardial infarction.
[a]Serious CV events as defined by Antiplatelet Trialists' Collaboration: nonfatal MI, nonfatal stroke, or death from a vascular cause and including any death from an unknown cause because most deaths in high-risk CV patients are likely to be due to vascular causes.
[b]High-risk CV patients according to the criteria of Antithrombotic Trialists Collaboration.

(95% CI, 4.6%−13.2%) in the aspirin group ($P < .001$) (Figure 2*C*).

On univariable competing-risks regression analysis, aspirin use and smoking were significant predictors of recurrent lower GI bleeding (Table 3). On multivariable competing-risks regression analysis, only aspirin use remained significantly associated with an increased risk of recurrent lower GI bleeding (SHR, 2.76; 95% CI, 1.26−6.07; $P = .011$). Severity of comorbidity >2 was an independent predictor of serious cardiovascular events (SHR, 1.99; 95% CI, 1.23−3.23; $P = .005$), whereas aspirin use was protective (SHR, 0.59; 95% CI, 0.37−0.91; $P = .019$) for serious cardiovascular events. Old age was independently associated with increased risk of death from other causes (SHR, 1.06; 95% CI, 1.02−1.10; $P = .004$), whereas aspirin use was a protective factor (SHR, 0.33; 95% CI, 0.17−0.63; $P = .001$) (Table 3).

Discussion

We sought to determine the benefits and risks of resuming aspirin in patients with a history of lower GI bleeding. In this 5-year retrospective cohort study, patients who continued aspirin after an episode of lower GI bleeding had an almost 3-fold increased risk of recurrent lower GI bleeding compared with patients who discontinued aspirin. These episodes of recurrent bleeding were clinically significant because all patients required hospitalization and a substantial proportion of them received blood transfusion. Despite an increased risk of lower GI bleeding, continuation of aspirin was associated with a 1.6-fold reduced risk of serious cardiovascular events and a >3-fold reduced risk of dying from other conditions.

Our study places current guidelines in perspective. Recommendations to reduce the GI risk of antiplatelet therapy have focused largely on the upper GI tract.[4] Strategies for the prevention of aspirin-associated lower GI bleeding remain largely unknown. The decision on whether to resume aspirin after a severe episode of lower GI bleeding presents a management dilemma for physicians, patients, and their families, particularly in the absence of risk-mitigating therapies and a lack of data on the risks and benefits of resuming aspirin. To our knowledge, this is the first study to provide important information to assist in clinical decision making in such patients. The outcomes of this study indicate that the cardiovascular benefits of continuous aspirin therapy must be weighed against the risk of recurrent lower GI bleeding. Because there is substantial risk of recurrent bleeding, physicians should critically evaluate individual patients' cardiovascular risk before resuming aspirin therapy. Our findings also suggest a need for a composite end point to evaluate clinically significant events throughout the GI tract in patients receiving antiplatelet drugs.

The reduction in serious cardiovascular events in the aspirin cohort highlights the importance of continuous aspirin therapy in patients with high cardiovascular risk, despite an episode of lower GI bleeding. In a randomized controlled trial,[10] we previously showed that early resumption of aspirin after endoscopic treatment of upper GI bleeding reduced the short-term mortality associated with cardiovascular and cerebrovascular complications. The current study demonstrated the long-term cardiovascular benefits of aspirin therapy in patients with a history of lower GI bleeding.

The reduction in other causes of deaths in the aspirin cohort was an unexpected finding. A meta-analysis has shown that aspirin use not only reduces cardiovascular deaths, but also deaths from multiple cancers.[5] In our study, old age was found to be an independent predictor of nonvascular deaths, whereas aspirin was a protective factor. We believe that the reduction in other causes of death

Table 3. Factors Associated With Risk of Different Outcomes

Variables	Univariable analysis		Multivariable analysis[a]	
	SHR (95% CI)	*P* value	Adjusted SHR (95% CI)	*P* value
Recurrent lower GI bleeding				
Age (per year increase)	1.01 (0.98–1.04)	.395		
Sex (male vs female)	1.08 (0.58–2.02)	.812		
Aspirin use (≥50% vs ≤20%)	2.76 (1.26–6.07)	.011	2.76 (1.26–6.07)	.011
Drinkers (current or past vs never)	1.16 (0.55–2.44)	.691		
Smokers (current or past vs never)	1.93 (1.03–3.60)	.040		
Severity of comorbidity (>2 vs ≤2)	1.54 (0.79–3.00)	.205		
History of GI bleeding (yes vs no)	1.46 (0.73–2.94)	.290		
Blood transfusion (≥2.0 U vs <2.0 U)	0.97 (0.52–1.83)	.927		
Concomitant anticoagulant, steroid, or non-aspirin antiplatelet drugs (yes vs no)	0.96 (0.38–2.46)	.935		
High CV risk (yes vs no)	0.51 (0.18–1.48)	.218		
Serious CV events				
Age (per year increase)	1.03 (1.01–1.05)	.006		
Sex (male vs female)	0.70 (0.44–1.09)	.114		
Aspirin use (≥50% vs ≤20%)	0.58 (0.37–0.91)	.017	0.59 (0.37–0.91)	.019
Drinkers (current or past vs never)	0.60 (0.31–1.13)	.114		
Smokers (current or past vs never)	0.54 (0.32–0.91)	.022		
Severity of comorbidity (>2 vs ≤2)[b]	2.00 (1.23–3.24)	.005	1.99 (1.23–3.23)	.005
History of GI bleeding (yes vs no)	1.14 (0.67–1.93)	.635		
Blood transfusion (≥2.0 U vs <2.0 U)	1.40 (0.90–2.19)	.135		
Concomitant anticoagulant, steroid, or non-aspirin antiplatelet drugs (yes vs no)	1.21 (0.66–2.23)	.534		
High CV risk (yes vs no)	1.29 (0.50–3.35)	.594		
Death from other causes				
Age (per year increase)	1.07 (1.03–1.11)	.001	1.06 (1.02–1.10)	.004
Sex (male vs female)	1.01 (0.55–1.84)	.985		
Aspirin use (≥50% vs ≤20%)	0.27 (0.14–0.53)	<.001	0.33 (0.17–0.63)	.001
Drinkers (current or past vs never)	1.18 (0.59–2.37)	.643		
Smokers (current or past vs never)	0.86 (0.45–1.63)	.645		
Severity of comorbidity (>2 vs ≤2)	2.01 (1.03–3.90)	.040		
History of GI bleeding (yes vs no)	0.58 (0.25–1.38)	.219		
Blood transfusion (≥2.0 U vs <2.0 U)	1.57 (0.85–2.87)	.147		
Concomitant anticoagulant, steroid, or non-aspirin antiplatelet drugs (yes vs no)	1.31 (0.58–2.94)	.517		
High CV risk (yes vs no)	0.81 (0.24–2.73)	.728		

CV, cardiovascular.
[a]All variables with $P < .2$ in the univariable analysis were entered into the multivariable analysis using a backward stepwise Fine and Gray's competing-risks regression model.
[b]High-risk CV patients according to the criteria of Antithrombotic Trialists's Collaboration.

among the aspirin users was partly related to the difference in age between the 2 cohorts, although a nonvascular protective effect of aspirin could not be excluded.

Our study has limitations. Firstly, there may be channeling bias, as clinicians tend to discontinue aspirin in patients who are older and who have severe bleeding. This can underestimate the cardiovascular benefit and bleeding risk of aspirin. Compared with the aspirin group, nonusers were older (76.7 vs 73.1 years) and had a higher rate of blood transfusion at index bleeding (54.5% vs 39.7%). The imbalance in baseline demographics, which is inherent to a retrospective study, did not undermine the importance of the current study. Secondly, the diagnosis of lower GI bleeding was largely by exclusion rather than by direct confirmation of the source of blood loss. However, any misclassification of recurrent lower GI bleeding should be equally distributed between aspirin users and nonusers with the use of blinded adjudication. Thirdly, we could not determine drug compliance in this retrospective study. We assessed drug exposure based on prescription pattern. In addition, there is a possibility that some patients may have used over-the-counter aspirin. Finally, we did not find concomitant use of anticoagulants, antiplatelets, and steroids as a predictor of recurrent lower GI bleeding. This may be due to the low percentage of concomitant drug use in both groups. Multicenter studies with large number of patients will be required to identify additional risk factors for recurrent lower GI bleeding with aspirin use.

In conclusion, resumption of aspirin after an episode of lower GI bleeding is associated with an increased risk of recurrent lower GI bleeding but a reduced risk of serious

cardiovascular events and death from other causes. The current study provides new clinical data to assist physicians in decision making through better understanding of the risks and benefits of resuming aspirin after an episode of lower GI bleeding.

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Conflicts of interest
These authors disclose the following: Francis Chan has served as a consultant to Pfizer, Eisai, Takeda, and Otsuka. He has received an independent research grant from Pfizer and has been paid lecture fees (including service on speakers' bureaus) by Pfizer, AstraZeneca, and Takeda. Justin Wu has received grant support from the National Institutes of Health. He has been paid lecture fees (including service on speakers' bureaus) by AstraZeneca. Siew C. Ng has been paid lecture fees by Takeda. The remaining authors disclose no conflicts.

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