Effects of *Helicobacter pylori* Infection on Long-term Risk of Peptic Ulcer Bleeding in Low-Dose Aspirin Users

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BACKGROUND & AIMS: Current guidelines recommend testing for *Helicobacter pylori* infection among users of low-dose aspirin (ASA) who are at high risk for developing ulcers. However, it is not clear whether this strategy affects long-term risk of ulcer bleeding. We assessed the utility of testing ASA users with a high risk of ulcer bleeding for *H pylori* infection. METHODS: In a prospective study, we recruited 3 cohorts of ASA users (≤160 mg/day). The first group included *H pylori*-positive users of ASAs with bleeding ulcers in whom the infections were eradicated (n = 249). They resumed ASA after ulcer healing and *H pylori* eradication. The second group included *H pylori*-negative (past and present) users of ASA who developed bleeding ulcers (n = 118). They received enteric-coated ASA after ulcer healing. The average-risk cohort included new users of ASA without a history of ulcers (n = 537). None of the subjects received regular treatment with anti-ulcer drugs. The primary end point was ulcer bleeding with ASA use in 5048 patient-years of follow-up evaluation. RESULTS: The incidence of ulcer bleeding (per 100 patient-years) in the *H pylori*–eradicated cohort (0.97; 95% confidence interval [CI], 0.53–1.80) did not differ significantly from that of the average-risk cohort (0.66; 95% CI, 0.38–0.99). The *H pylori*-negative cohort had a high incidence of recurrent bleeding (5.22; 95% CI, 3.04–8.96) (incidence rate ratio, 8.52; 95% CI, 4.29–16.95 vs the average-risk cohort). CONCLUSIONS: The long-term incidence of recurrent ulcer bleeding with ASA use is low after *H pylori* infection is eradicated. ASA users without current or past *H pylori* infections who develop ulcer bleeding have a high risk of recurrent bleeding. Tests for *H pylori* infection can be used to assign high-risk ASA users to groups that require different gastroprotective strategies.

Keywords: Stomach; *H pylori*; Aspirin; Prediction; Ulcer Bleeding; Low-Dose Aspirin.

Low-dose aspirin (ASA) has emerged as the most important cause of peptic ulcer bleeding in Western countries. In Scotland, hospitalizations for ASA-associated peptic ulcer bleeding have increased from 15 of 100,000 in 1996 to 40 of 100,000 in 2005.1,2 Patients receiving ASA for cardiothrombotic diseases who develop peptic ulcer bleeding have markedly increased mortality.3 Recently, a secondary analysis of cardiovascular trials showed that daily use of ASA also reduces the risk of all cancers.4 With increasing use of ASA for cardiothrombotic diseases and cancer prevention, the global burden of ASA-associated peptic ulcer disease is expected to increase.

A number of risk factors are known to increase the risk of peptic ulcer bleeding with ASA use. These include a history of peptic ulcer or ulcer bleeding, old age, renal failure, concurrent use of ASA and clopidogrel, and *Helicobacter pylori* infection.5–7 Among these risk factors, a history of peptic ulcer bleeding is one of the most important predictors of ulcer bleeding with ASA use,7 whereas *H pylori* is the only treatable risk factor. Eradication of *H pylori* therefore offers a hope of reducing the risk of ulcer bleeding in ASA users.

Current European and US guidelines recommend test-and-treat *H pylori* infection in ASA users who are at risk of ulcer bleeding.8–10 Despite these guidelines, the long-term benefit of eradicating *H pylori* in high-risk ASA users is uncertain. In a 6-month randomized trial of ASA users with *H pylori* infection complicated by ulcer bleeding, we previously showed that the incidence of recurrent ulcer bleeding was comparable between the group receiving *H pylori* eradication alone (1.9%) and the group receiving a proton pump inhibitor (PPI) (0.9%).11 In another 12-month randomized trial, however, up to 15% of ASA users developed recurrent ulcer bleeding after eradication of *H pylori* alone.12 In light of these conflicting findings, current guidelines recommend that co-therapy with a PPI is still needed in high-risk ASA users after eradication of *H pylori*.8–10 Because PPIs are more effective in preventing ASA-associated ulcers in the presence of *H pylori* infection,13 the clinical relevance of testing for *H pylori* in high-risk ASA users becomes questionable. To date, the strategy of test-and-treat *H pylori* for ASA users is not popular among primary care doctors or specialists.

Abbreviations used in this paper: ASA, low-dose aspirin; CI, confidence interval; CV, cardiovascular; GI, gastrointestinal; IRR, incidence rate ratio; NSAID, nonsteroidal anti-inflammatory drug; PPI, proton pump inhibitor.

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Should we ignore *H pylori* testing and simply prescribe PPIs to all ASA users at increased risk of ulcer bleeding? Poor adherence to long-term gastroprotective co-therapy, which is common among the elderly, limits its effectiveness. Recently, European and US health authorities issued warnings about the safety of certain PPIs in patients receiving concomitant clopidogrel and the potential risk of fractures. If eradication of *H pylori* can reduce the long-term risk of ulcer bleeding with ASA use, there potentially may be hope of limiting PPI use to patients with very high ulcer risk.

Given the uncertain clinical utility of *H pylori* testing in ASA users, this 10-year prospective cohort study aimed to determine whether testing for *H pylori* would have any impact on the long-term incidence of ulcer bleeding in ASA users with high ulcer risk. We hypothesized that among ASA users with a history of ulcer bleeding, *H pylori* testing would influence the long-term incidence of recurrent ulcer bleeding with ASA use.

### Materials and Methods

**Screening of Study Population**

Consecutive users of ASA who presented with upper gastrointestinal bleeding to the Endoscopy Centre of the Prince of Wales Hospital were screened for eligibility. The Prince of Wales Hospital serves a local population of 1.5 million people in Hong Kong.

All patients underwent endoscopy within 24 hours of hospitalization to identify the source of bleeding, to secure hemostasis, and to determine their *H pylori* status. The inclusion criteria were endoscopically confirmed gastroduodenal ulcer bleeding and anticipated regular use of ASA for cardiothrombotic diseases. The exclusion criteria were uncontrolled bleeding requiring surgical intervention, previous gastric surgery except for a patch repair, the presence of gastrointestinal varices, gastric outlet obstruction, gastrosophageal reflux disease, renal failure (defined by a serum creatinine level of >200 μmol/L), moribund conditions, and active malignancy. Biopsy specimens were taken from the antrum and corpus for a rapid urease test and histology. *H pylori* was considered present if the bacteria were shown in histology. *H pylori* was absent if both the rapid urease test and histology were negative.

Patients infected with *H pylori* received 1 week of bismuth triple therapy (120 mg bismuth subcitrate, 400 mg metronidazole, 500 mg tetracycline all given 4 times/day) followed by 7 weeks of omeprazole 20 mg once daily. Those with negative tests for *H pylori* on initial endoscopy received 8 weeks of omeprazole 20 mg once daily. Follow-up endoscopy was arranged for all patients after stopping omeprazole for 2 weeks to check ulcer healing and *H pylori* status irrespective of the initial results. Biopsy specimens of the antrum and corpus were repeated for rapid urease test and histology. Patients with failed eradication received 1 week of PPI-triple therapy (20 mg omeprazole twice a day, 120 mg bismuth subcitrate 4 times/day, 400 mg metronidazole 4 times/day, 500 mg tetracycline 4 times/day). Eradication of *H pylori* was confirmed if all the tests were negative. Patients who failed re-treatment were excluded.

Patients with negative tests for *H pylori* on both initial and follow-up endoscopy underwent further evaluation to determine whether they had evidence of past *H pylori* infection. They were considered to have no evidence of past *H pylori* infection if they had a negative *H pylori* serology test and absence of intestinal metaplasia or atrophy in the antrum and corpus biopsy specimens. Patients with inconsistent results were classified as having indeterminate *H pylori* status. They were excluded from the cohort.

**Study Cohorts**

Three cohorts of ASA users were enrolled during the inception period between May 1995 and January 2000. The first cohort consisted of ASA users with ulcer bleeding and *H pylori* infection who had healed ulcers and successful eradication of *H pylori* on follow-up endoscopy (*H pylori*-eradicated cohort). They received plain ASA (<160 mg/day) without co-prescription of anti-ulcer drugs.

The second cohort consisted of ASA users with ulcer bleeding but no evidence of current or past *H pylori* infection (*H pylori*-negative cohort). After ulcers had healed, the *H pylori*-negative cohort received enteric-coated ASA (<160 mg/day) without regular co-prescription of anti-ulcer drugs. Enteric-coated ASA was an acceptable alternative to plain ASA for patients with high ulcer risk when the study was commenced in 1995.

The third cohort consisted of ASA-naive patients without a history of ulcer who attended the general outpatient clinic. They required long-term ASA for established cardiothrombotic diseases (average-risk cohort). They received plain ASA (<160 mg/day) without co-prescription of anti-ulcer drugs. *H pylori* status was not determined in this average-risk asymptomatic cohort because *H pylori* testing was not clinically indicated and eradication of *H pylori* may have biased the study outcome. The local ethics committee approved the study and all patients provided written informed consent.

**End Point**

The primary end point was the cumulative incidence of recurrent gastroduodenal ulcer bleeding with ASA use in 10 years. Gastroduodenal ulcer bleeding was defined as hematemesis and/or melena with gastroduodenal ulcers, erosions with blood in the stomach confirmed by endoscopy, or a decrease in the hemoglobin level greater than 2 g/dL in the presence of endoscopically proven ulcers. An independent blinded adjudication committee determined whether the events met the predefined criteria and assessed their likely causes (ie, recurrent bleeding associated with ASA alone or other concomitant drugs).

**Follow-up Assessment**

The 3 cohorts were followed up prospectively every 3 to 6 months until gastroduodenal ulcer bleeding occurred or up to 10 years of follow-up evaluation if no bleeding occurred. During each visit, drug compliance, use of concomitant drugs that may alter the risk of ulcer bleeding, symptoms of gastrointestinal bleeding, and hemoglobin level were monitored. We provided a direct line for patients to report any serious adverse event or symptoms of gastrointestinal bleeding. Designated research staff called back patients who did not present for follow-up evaluation. Patients who developed symptoms of overt bleeding were admitted and endoscopy was performed within 24 hours unless contraindicated. Patients who had a significant decrease in hemoglobin level greater than 2 g/dL were called back for work-up, including endoscopy and other possible causes of anemia.

Concomitant drugs that may alter the risk of ulcer bleeding including anti-ulcer drugs and drugs that can cause gastroduo-
denal ulcer bleeding (ie, nonsteroidal anti-inflammatory drugs [NSAIDs], other antiplatelet drugs, anticoagulants, and corticosteroids) were monitored during the follow-up period. Anti-ulcer drugs included PPIs, histamine-2-receptor antagonists, misoprostol, and sucralfate. Other antiplatelet drugs included clopidogrel, ticlodipine, and dipyridamole. Anticoagulants included warfarin and heparin. Corticosteroids included a daily dose of prednisolone greater than 7.5 mg or its equivalent. The use of these drugs was considered a drug violation and the duration of use was documented at each visit.

**Statistical Analysis**

Baseline characteristics were presented as means (±standard deviation) for continuous variables and as a frequency (percentage) for all categoric variables. One-way analysis of variance with post hoc Bonferroni correction, Kruskal–Wallis, and chi-square tests were performed to determine significant differences among cohorts.

To avoid bias caused by under-reporting of concomitant prescriptions from other clinics, hospitalizations in other districts, or missing data from loss to follow-up evaluation, we used a territory-wide electronic health care database that covers more than 90% of the Hong Kong population to identify concomitant drug violation, comorbid medical conditions, dates of admission and discharge, International Classification of Diseases, 9th revision, diagnostic codes, and causes of death as previously described.17,18 We estimated the total duration of drug violation from the cumulative period of prescriptions. Current use was defined as the period between the filling of the prescription and the end of the days of drug supply. Any prescription that was issued 30 days or fewer after the previous prescription was considered to be continuous exposure. We systematically screened for any use of over-the-counter drugs at each visit using a validated approach as previously described.17,18

In the analysis of recurrent ulcer bleeding, we classified drug exposure according to the cumulative duration of ASA use with or without concomitant drug violation. All periods of current use were mutually exclusive and not overlapping. Multivariable Poisson regression models were used to estimate the adjusted rates per 100 patient-years, adjusted incidence rate ratios (IRRs), 95% confidence intervals (CIs), and P values for comparisons between cohorts and drug combinations (grouped as ASA alone, ASA plus anti-ulcer drugs, ASA plus drugs that can cause gastroduodenal bleeding, and ASA plus anti-ulcer drugs and drugs that can cause gastroduodenal bleeding) while controlling for age, sex, and comorbidity (as assessed by American Society of Anesthesiologists grading).

We assessed whether the association of cohorts and the outcome was modified by concomitant drug violation, age, sex, and comorbidity, including their pair-wise product terms (ie, cohorts × age, cohorts × sex, cohorts × comorbidity, and cohorts × drug combinations) in addition to the individual variables in a Poisson regression model. We used negative binomial regression (a generalization of Poisson regression) if there was evidence in the data of overdispersion (variance of outcome greater than the mean). Overdispersion was tested by using the likelihood-ratio test.19 An independent blinded committee reviewed all the death records and adjudicated the causes of death (cardiovascular diseases, gastrointestinal bleeding, or other conditions). All statistical tests were 2-sided. A significance level of .05 was used. All analyses were performed using Intercooled STATA version 8 (Stata Corp, College Station, TX).

Sample size calculation was based on the assumption that the incidence of gastroduodenal ulcer bleeding was 0.5 events per 100 patient-years in average-risk ASA users20 and 1.75 events per 100 patient-years in ASA users with a history of ulcer bleeding.7 By using Poisson regression,21 a sample size of 3786 patient-years of follow-up evaluation would be needed (2524 patient-years in the average-risk cohort vs 1262 patient-years in the Hp-eradicated cohort) to show a rate ratio of 3.5 with 80% power and a 95% confidence level. Assuming a mean follow-up period of 5 years owing to early drop-out, the enrollment was planned for 505 and 253 patients in the average-risk cohort and the H pylori–eradicated cohort, respectively.

**Results**

Between May 1995 and January 2000, we screened 499 aspirin users admitted for peptic ulcer bleeding and 2614 cardiovascular patients without a history of ulcer who attended outpatient clinics. Of 499 aspirin users with ulcer bleeding, 15 with indeterminate H pylori status were excluded. A total of 367 patients were enrolled (249 in the H pylori–eradicated cohort and 118 in the H pylori–negative cohort). Of 2614 cardiovascular patients without ulcer history, 537 first-time aspirin users were recruited in the average-risk cohort (Figure 1). In November 1996, there were new observational data suggesting that enteric-coated ASA was associated with an increased risk of upper gastrointestinal bleeding.22 The local ethics committee did not recommend early termination of the H pylori–negative cohort because the available data at that time were not sufficient to confirm the gastrointestinal toxicity of enteric-coated ASA.

There were a total of 5048 patient-years of follow-up evaluation: 1349 patient-years in the H pylori–eradicated cohort, 454 patient-years in the H pylori–negative cohort, and 3245 patient-years in the average-risk cohort (Table 1). Between 6.8% and 11.7% of patients had defaulted on follow-up evaluation, we monitored these patients by telephone interview and assessed their outcome by a territory-wide electronic health care database (Figure 1). The H pylori–negative cohort was 3–4 years older and had more comorbidities (American Society of Anesthesiologists grade, ≥3) compared with the other 2 cohorts (Table 1). In the H pylori–eradicated cohort, patients were exposed to ASA alone during more than 75% of the follow-up period (1027 of 1349 patient-years). In contrast, concomitant drug violation with an anti-ulcer drug was common in the H pylori–negative cohort (204 of 454 patient-years) (Table 2). After being reviewed by the adjudication committee, the death rates as a result of cardiovascular (CV) diseases and gastrointestinal (GI) bleeding were 8.0%, 8.5%, 7.8%, and 0%, 0%, 0.2% in the H pylori–eradicated cohort, H pylori–negative cohort, and average-risk cohort, respectively. There was no significant difference in mortality as a result of CV events or GI bleeding among the 3 cohorts (P = .14). In the H pylori–eradicated group, there was a significant increase in mortality from other causes compared with the other 2 cohorts (P = .02).
By using Poisson regression to adjust for age, sex, and severity of comorbidity, the incidence rates and IRRs of gastroduodenal ulcer bleeding according to ASA use with or without concomitant drug violation are summarized in Table 3. Compared with patients younger than the age of 70, the adjusted incidence rate of gastroduodenal ulcer bleeding was significantly higher in patients older than age 70 years irrespective of study cohorts (IRR, 2.39; 95% CI, 1.50–3.81). In contrast, sex and severity of comorbidity were not significant risk factors.

In the *H pylori*–eradicated cohort, the adjusted incidence rate of recurrent ulcer bleeding (per 100 patient-years) was low among patients using ASA alone (0.97; 95% CI, 0.53–1.80). The incidence rates of ulcer bleeding were not significantly different between the *H pylori*–eradicated cohort and the average-risk cohort (0.66; 95% CI, 0.43–1.00).

**Table 1.** Baseline Characteristics of Patients Between Cohorts

<table>
<thead>
<tr>
<th></th>
<th><em>H pylori</em>–eradicated cohort (n = 249)</th>
<th><em>H pylori</em>–negative cohort (n = 118)</th>
<th>Average-risk cohort (n = 537)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (SD), y</td>
<td>67.9 (9.8)</td>
<td>72.3 (10.0)</td>
<td>68.7 (8.9)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Age &gt;70 y, n (%)</td>
<td>111 (44.6)</td>
<td>68 (57.6)</td>
<td>240 (44.7)</td>
<td>.031</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>174 (69.9)</td>
<td>67 (56.8)</td>
<td>273 (50.8)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>American Society of Anesthesiologists grade ≥3, n (%)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>157 (63.1)</td>
<td>96 (84.1)</td>
<td>384 (71.5)</td>
<td>.001</td>
</tr>
<tr>
<td>Follow-up period, patient-years</td>
<td>1349</td>
<td>454</td>
<td>3245</td>
<td></td>
</tr>
<tr>
<td>Median follow-up period, y (range)</td>
<td>8.71 (0.06–10)</td>
<td>6.29 (0.15–10)</td>
<td>10 (0.33–10)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

<sup>a</sup>American Society of Anesthesiologists grades were as follows: grade 1, normal healthy patients; grade 2, mild systemic illness; grade 3, severe but incapacitating systemic illness; and grade 4, life-threatening illness.
In the \textit{H pylori}–negative cohort, the incidence of ulcer bleeding with ASA alone (5.22; 95% CI, 3.04–8.96) was 5 times higher than that in the \textit{H pylori}–eradicated cohort and 8 times higher than that in the average-risk cohort (IRR, 7.91; 95% CI, 4.29–16.95) (Table 3).

There was a significant interaction between patient cohorts and concomitant drug violation (test for interaction, $P = .03$). Concomitant use of ASA and drugs that can cause gastroduodenal bleeding (ie, NSAIDs, anticoagulants, corticosteroids, or other antiplatelet drugs) markedly increased the risk of ulcer bleeding in all 3 cohorts. In the average-risk cohort, concomitant use of these drugs increased the incidence of ulcer bleeding by 4.8 times (5.10; 95% CI, 2.06–12.65). In the \textit{H pylori}–eradicated and \textit{H pylori}–negative cohorts, use of concomitant drugs increased the incidence rates of ulcer bleeding by more than 48 times (35.80; 95% CI, 17.50–73.25) and 143 times (123.67; 95% CI, 62.90–243.18), respectively. Co-therapy with anti-ulcer drugs significantly reduced but did not eliminate the excess risk of ulcer bleeding associated with concomitant drugs in the \textit{H pylori}–eradicated cohort.

\begin{table}[h]
\centering
\caption{Patient-Years and Events in the Three Cohorts During the Study Period According to ASA Use With or Without Concomitant Drug Violation.}
\begin{tabular}{lll}
\hline
& Patient-years & Bleeding ulcers, n \\
\hline
\textit{H pylori}–eradicated cohort (n = 249) & & \\
ASA & 1027 & 11 \\
ASA + anti-ulcer drugs & 264 & 2 \\
ASA + drugs that can cause gastroduodenal bleeding & 22 & 8 \\
ASA + anti-ulcer drugs + drugs that can cause gastroduodenal bleeding & 36 & 3 \\
Total & 1349 & 24 \\
\hline
\textit{H pylori}–negative cohort (n = 118) & & \\
ASA & 242 & 15 \\
ASA + anti-ulcer drugs & 192 & 2 \\
ASA + drugs that can cause gastroduodenal bleeding & 8 & 9 \\
ASA + anti-ulcer drugs + drugs that can cause gastroduodenal bleeding & 12 & 1 \\
Total & 454 & 27 \\
\hline
Average-risk cohort (n = 537) & & \\
ASA & 2724 & 18 \\
ASA + anti-ulcer drugs & 341 & 4 \\
ASA + drugs that can cause gastroduodenal bleeding & 98 & 5 \\
ASA + anti-ulcer drugs + drugs that can cause gastroduodenal bleeding & 82 & 1 \\
Total & 3245 & 28 \\
\hline
\end{tabular}
\end{table}

\begin{table}[h]
\centering
\caption{Multivariable Poisson Regression Model Analysis.}
\begin{tabular}{llll}
\hline
& IRR (95% CI) & $P$ value \\
\hline
\textbf{Age y} & & & \\
$\leq$70 & 1.00 & & \\
$>$70 & 2.39 (1.50–3.81) & <.001 & \\
\hline
\textbf{Sex} & & & \\
Female & 1.00 & & \\
Male & 1.32 (0.81–2.15) & .262 & \\
\hline
\textbf{American Society of Anesthesiologists grade$^a$} & & & \\
$<3$ & 1.00 & & \\
$\geq3$ & 1.27 (0.75–2.14) & .372 & \\
\hline
\textbf{Drug} & & & \\
ASA & & & \\
ASA + anti-ulcer drugs & & & \\
ASA + drugs that can cause gastroduodenal bleeding & & & \\
ASA + anti-ulcer drugs + drugs that can cause gastroduodenal bleeding & & & \\
\hline
\end{tabular}
\end{table}

$^a$American Society of Anesthesiologists grades were as follows: grade 1, normal healthy patients; grade 2, mild systemic illness; grade 3, severe but incapacitating systemic illness; and grade 4, life-threatening illness.
were 8.0%, 8.5%, 7.8%, and 0%, 0%, 0.2% in the resulting from cardiovascular diseases and GI bleeding reviewed by the adjudication committee, the death rates among the 3 cohorts (Table 4). Apart from the interaction between patient cohort and concomitant drug violation, there was no other significant interaction in the adjusted incidence rates of ulcer bleeding.

The cumulative death rates were 34.5% in the *H pylori*–eradicated cohort, 29.7% in the *H pylori*–negative cohort, and 25.9% in the average-risk cohort before the occurrence of gastroduodenal ulcer bleeding (*P* = .04). After being reviewed by the adjudication committee, the death rates resulting from cardiovascular diseases and GI bleeding were 8.0%, 8.5%, 7.8%, and 0%, 0%, 0.2% in the *H pylori*–eradicated cohort, *H pylori*–negative cohort, and average-risk cohort, respectively. There was no significant difference in mortality caused by CV events or GI bleeding among the 3 cohorts (*P* = .14). In the *H pylori*–eradicated group, there was a significant increase in mortality from other causes compared with the other 2 cohorts (*P* = .02) (Table 4).

### Discussion

In this 10-year prospective cohort study, we set out to determine whether testing for *H pylori* status in ASA users with a high ulcer risk would have an impact on the long-term incidence of ulcer bleeding. All of these ASA users had a history of confirmed ulcer bleeding. They were divided into 2 cohorts, namely, ASA users with *H pylori* infection at the time of ulcer bleeding who subsequently received eradication therapy (*H pylori*–eradicated cohort) and ASA users who had no evidence of past or current *H pylori* infection at the time of ulcer bleeding (*H pylori*–negative cohort). We found that among *H pylori*–positive ASA users with a history of ulcer bleeding who received eradication therapy alone, the long-term incidence of recurrent ulcer bleeding with ASA was low. The incidence rates were not significantly different between the *H pylori*–eradicated cohort and the average-risk cohort. In contrast, ASA users without past or current *H pylori* infection who developed ulcer bleeding had an 8-fold increased incidence rate of recurrent ulcer bleeding compared with the average-risk cohort.

The current study extends beyond the finding of our previous 6-month randomized trial, in that the long-term risk of recurrent ulcer bleeding with ASA use is low after eradication of *H pylori* alone. In addition, we found that concomitant use of drugs including NSAIDs, other antiplatelet drugs, anticoagulants, and corticosteroids predicted recurrent ulcer bleeding after eradication of *H pylori*. Our results therefore explained the discrepant finding reported by another randomized trial, in which the high rate of recurrent ulcer bleeding after receiving eradication therapy mostly occurred in ASA users who had failed eradication or received concomitant NSAIDs.

Our findings indicate that testing for *H pylori* status in ASA users with high ulcer risk can modify their long-term risk of ulcer bleeding and guide selective use of PPI co-therapy. A history of ulcer bleeding alone is no longer a good predictor of recurrent bleeding in *H pylori*–positive ASA users provided that *H pylori* has been eradicated successfully. Because the long-term incidence of recurrent ulcer bleeding with ASA use is low after successful eradication of *H pylori*, strict adherence to PPI co-therapy is probably not essential. This finding is highly relevant to clinical practice because many patients have poor adherence to long-term gastroprotective co-therapy. On the other hand, PPI co-therapy should be given selectively to *H pylori*–eradicated ASA users who use concomitant NSAIDs, anticoagulants, corticosteroids, or other antiplatelet drugs. Recently, famotidine was shown to reduce the gastric toxicity of ASA. Although the in vitro interaction between certain PPIs and clopidogrel remains a concern among clinicians and regulatory authorities, co-therapy with famotidine may be a potential alternative to PPIs in *H pylori*–eradicated ASA users receiving concomitant clopidogrel.

Interestingly, we also found that *H pylori*–eradicated patients are not equivalent to those who never had *H pylori* infection in terms of their risk of recurrent ulcer bleeding with ASA use. Our findings suggest that these 2 cohorts of ASA users developed ulcer bleeding through different mechanisms. We postulate that most of the ulcers in *H pylori*–positive ASA users were *H pylori*–induced ulcers. ASA probably provoked bleeding from pre-existing *H pylori* ulcers. Eradication of *H pylori* restored mucosal integrity such that resumption of ASA was not ulcerogenic enough to induce recurrent ulceration and bleeding. In contrast, the *H pylori*–negative cohort represented a group of patients who were susceptible to the GI toxicity of low-dose aspirin (ie, they had genuine ASA-induced ulcers). Old age and comorbidity probably ac-

### Table 4. Causes of death

<table>
<thead>
<tr>
<th></th>
<th><em>H pylori</em>–eradicated cohort</th>
<th><em>H pylori</em>–negative cohort</th>
<th>Average-risk cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV (%)</td>
<td>20 (8.0)</td>
<td>10 (8.5)</td>
<td>42 (7.8)</td>
</tr>
<tr>
<td>GI bleeding (%)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Others* (%)</td>
<td>66 (26.5)</td>
<td>25 (21.2)</td>
<td>96 (17.9)</td>
</tr>
</tbody>
</table>

*S* Other causes of death (*P* = .02).

(7.39; 95% CI, 2.35–23.24) and in the *H pylori*–negative cohort (8.66; 95% CI, 1.20–62.39) (Table 3). Concomitant use of anti-ulcer drugs had a significant protective effect in the *H pylori*–negative cohort, reducing the incidence of ulcer bleeding by 6 times (0.86; 95% CI, 0.21–3.50 among patients receiving ASA plus anti-ulcer drugs). The incidence of ulcer bleeding in the *H pylori*–negative cohort was not significantly higher than that of the average-risk cohort in the presence of anti-ulcer drugs (IRR, 0.81 95% CI, 0.15–4.44). In contrast, concomitant use of ASA and anti-ulcer drugs did not significantly reduce the risk of ulcer bleeding in the *H pylori*–eradicated and average-risk cohorts (Table 3). Apart from the interaction between patient cohort and concomitant drug violation, there was no other significant interaction in the adjusted incidence rates of ulcer bleeding.

The cumulative death rates were 34.5% in the *H pylori*–eradicated cohort, 29.7% in the *H pylori*–negative cohort, and 25.9% in the average-risk cohort before the occurrence of gastroduodenal ulcer bleeding (*P* = .04). After being reviewed by the adjudication committee, the death rates resulting from cardiovascular diseases and GI bleeding were 8.0%, 8.5%, 7.8%, and 0%, 0%, 0.2% in the *H pylori*–eradicated cohort, *H pylori*–negative cohort, and average-risk cohort, respectively. There was no significant difference in mortality caused by CV events or GI bleeding among the 3 cohorts (*P* = .14). In the *H pylori*–eradicated group, there was a significant increase in mortality from other causes compared with the other 2 cohorts (*P* = .02) (Table 4).
counted for their susceptibility. Thus, they were prone to recurrent ulceration and bleeding after resumption of ASA. Our prospective study also confirmed the observation of a previous retrospective case-control study that enteric-coated formulations cannot prevent ulcer bleeding in these high-risk ASA users.22

A modest but significant increase in overall mortality in the *H pylori*–eradicated cohort was unexpected. One should interpret this finding with caution because death was not a predefined end point in this study. In fact, post hoc adjudication of the causes of death revealed a significant increase in death caused by other unrelated conditions in the *H pylori*–eradicated cohort. We believe this finding occurred by chance. Our finding does not suggest a causal relationship between *H pylori* eradication and increased mortality in aspirin users.

Our findings have practical implications. First, testing for *H pylori* status in ASA users with a high ulcer risk will help stratify patients into distinct subgroups who require different gastroprotective strategies. Patients with a positive test for *H pylori* should receive anti-*H pylori* therapy followed by confirmation of eradication. Their need for long-term gastroprotective therapy depends on the success of *H pylori* eradication and concomitant use of drugs that can cause bleeding. We do not advocate substitution of PPIs by eradication therapy alone for high-risk ASA users. However, many patients have poor adherence to long-term gastroprotective co-therapy. Our finding suggests that we should emphasize the importance of successful *H pylori* eradication. Second, physicians should distinguish between *H pylori*–eradicated ASA users and those who are not infected by *H pylori*. The latter patients should receive adequate gastroprotective co-therapy if they have a history of ulcer because they are prone to ulcer bleeding with ASA use. Serology is probably a preferred test for identifying uninfected ASA users.

Our study had limitations. First, this was not a randomized trial. The absolute benefit of *H pylori* eradication cannot be quantified in the absence of a placebo group without receiving eradication therapy. However, it would be unethical to withhold eradication therapy in patients with a history of ulcer bleeding. Given the very low incidence rate of ulcer bleeding, a long-term prospective cohort study may provide the best alternative to a randomized trial to address this important clinical question. Second, the recruitment of new-onset, average-risk ASA users with established cardiothrombotic diseases may not be representative of ASA users in the general population. However, the incidence of ulcer bleeding in our average-risk cohort is consistent with that reported in another population-based observational study.20 Third, the lack of a significant reduction in recurrent ulcer bleeding among ASA users receiving concomitant anti-ulcer drugs in the *H pylori*–eradicated cohort could be a type II error. We want to re-emphasize that this study was not designed to assess the efficacy of gastroprotective therapies in preventing recurrent ulcer bleeding with ASA use after *H pylori* eradication. Ideally, all high-risk ASA users should receive prophylactic PPIs even after *H pylori* eradication. However, we found that the difference in the incidence of ulcer bleeding between patients receiving ASA alone and those receiving ASA plus anti-ulcer drugs was very small such that selective co-prescription of PPIs to ASA users with high residual ulcer risk after *H pylori* eradication may be a more rational approach. Most ASA users still would benefit from *H pylori* eradication alone despite a history of ulcer bleeding. Fourth, our study cohorts were all ethnic Chinese. Although the generalizability of our study results to other populations needs further evaluation, there is no evidence that ethnicity affects the role of *H pylori* as a risk factor for peptic ulcer bleeding.

In summary, testing for *H pylori* status stratifies ASA users into distinct subgroups requiring different gastroprotective strategies. The long-term incidence of ulcer bleeding with ASA use is low after *H pylori* eradication alone despite a history of ulcer bleeding. PPI co-therapy can be used selectively in those *H pylori*–eradicated ASA users who require concomitant NSAIDs, anticoagulants, corticosteroids, or other antiplatelet drugs. ASA users who developed ulcer bleeding without current or past *H pylori* infection are at high risk of recurrent bleeding and benefit most from PPI co-therapy. Our study provides novel data to guideline committees to refine their treatment recommendations for ASA users who are at risk of ulcer bleeding.

**References**


