

## ORIGINAL ARTICLE

# Clopidogrel versus Aspirin and Esomeprazole to Prevent Recurrent Ulcer Bleeding

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## ABSTRACT

**BACKGROUND**

Concurrent therapy with a proton-pump inhibitor is a standard treatment for patients receiving aspirin who are at risk for ulcer. Current U.S. guidelines also recommend clopidogrel for patients who have major gastrointestinal intolerance of aspirin. We compared clopidogrel with aspirin plus esomeprazole for the prevention of recurrent bleeding from ulcers in high-risk patients.

**METHODS**

We studied patients who took aspirin to prevent vascular diseases and who presented with ulcer bleeding. After the ulcers had healed, we randomly assigned patients who were negative for *Helicobacter pylori* to receive either 75 mg of clopidogrel daily plus esomeprazole placebo twice daily or 80 mg of aspirin daily plus 20 mg of esomeprazole twice daily for 12 months. The end point was recurrent ulcer bleeding.

**RESULTS**

We enrolled 320 patients (161 patients assigned to receive clopidogrel and 159 to receive aspirin plus esomeprazole). Recurrent ulcer bleeding occurred in 13 patients receiving clopidogrel and 1 receiving aspirin plus esomeprazole. The cumulative incidence of recurrent bleeding during the 12-month period was 8.6 percent (95 percent confidence interval, 4.1 to 13.1 percent) among patients who received clopidogrel and 0.7 percent (95 percent confidence interval, 0 to 2.0 percent) among those who received aspirin plus esomeprazole (difference, 7.9 percentage points; 95 percent confidence interval for the difference, 3.4 to 12.4;  $P=0.001$ ).

**CONCLUSIONS**

Among patients with a history of aspirin-induced ulcer bleeding whose ulcers had healed before they received the study treatment, aspirin plus esomeprazole was superior to clopidogrel in the prevention of recurrent ulcer bleeding. Our finding does not support the current recommendation that patients with major gastrointestinal intolerance of aspirin be given clopidogrel.

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IT IS ESTIMATED THAT DURING THE PAST two decades 50 million Americans have started taking aspirin for the prevention of heart attack and stroke.<sup>1</sup> However, aspirin doubles the risk of upper gastrointestinal bleeding even at doses as low as 75 mg daily.<sup>2</sup> A history of upper gastrointestinal bleeding from an ulcer is the most important risk factor for subsequent upper gastrointestinal bleeding in patients taking aspirin.<sup>3,4</sup> Up to 15 percent of those taking aspirin who have a history of bleeding from ulcers had recurrent bleeding within one year.<sup>5</sup>

Proton-pump inhibitors reduce the risk of aspirin-induced ulcer bleeding,<sup>5-7</sup> and combination therapy with proton-pump inhibitors has been advocated for patients at high risk for ulcer bleeding who are taking aspirin.<sup>8,9</sup> However, compliance with the drug regimen may limit the usefulness of the combination therapy, especially among patients who are already receiving multiple drugs.

An alternative strategy is to replace aspirin with another antiplatelet drug that does not induce ulcer. Clopidogrel, which inhibits the platelet adenosine diphosphate receptor, has been shown to prevent ischemic events.<sup>10-13</sup> The Food and Drug Administration has approved clopidogrel for the treatment of vascular diseases.<sup>14</sup> In healthy volunteers, clopidogrel did not induce gastric damage.<sup>15</sup> It was reported to be more efficacious and to induce fewer episodes of gastrointestinal bleeding than aspirin.<sup>10</sup> Although the combination of clopidogrel and aspirin increases the overall risk of bleeding,<sup>11</sup> a recent analysis indicated that the excess risk of bleeding was attributed to the dose-dependent ulcerogenic effect of aspirin.<sup>16</sup>

The American College of Cardiology–American Heart Association guidelines recommend the use of clopidogrel for hospitalized patients with a coronary syndrome who are unable to take aspirin because of major gastrointestinal intolerance (class IA recommendation).<sup>17,18</sup> However, there has been no prospective trial to assess whether clopidogrel is an alternative to aspirin plus a proton-pump inhibitor for patients at risk for ulcer.

Our study was a 12-month, prospective, randomized, double-blind trial that compared clopidogrel with aspirin plus esomeprazole for patients who had previous aspirin-induced ulcer bleeding. We hypothesized that after the ulcers had healed, clopidogrel would not be inferior to aspirin plus esomeprazole in the prevention of recurrent ulcer bleeding among these high-risk patients.

## METHODS

### STUDY POPULATION

The study was conducted at the Prince of Wales Hospital in Hong Kong. We screened consecutive users of low-dose aspirin (325 mg or less per day) who presented with upper gastrointestinal bleeding. The patients underwent endoscopy within 24 hours after presentation to identify the site of the bleeding. During endoscopy, three biopsy specimens were obtained from the antrum and two from the body of the stomach for a rapid urease test (CLO, Delta West) and for histologic examination for *Helicobacter pylori* with the use of hematoxylin and eosin stain and Warthin–Starry stain, if necessary. Patients with *H. pylori* infection were treated for one week with a triple-drug regimen that included a proton-pump inhibitor. Aspirin was withheld during this period. All patients received proton-pump inhibitors to promote the healing of ulcers. Follow-up endoscopy was performed eight weeks after eradication therapy, while the patients were not taking acid-suppressing drugs. *H. pylori* was considered to be present if any portion of the specimen was positive; it was considered to be absent or eradicated when all above-noted test results were negative.

Patients were considered eligible for inclusion if they had endoscopically confirmed ulcer healing, negative results on the test for *H. pylori* or successful eradication of *H. pylori* and anticipated regular use of antiplatelet therapy for the duration of the trial. The exclusion criteria were concomitant use of nonsteroidal antiinflammatory drugs (NSAIDs), cyclooxygenase-2 inhibitors, anticoagulant agents, other antiplatelet drugs, or corticosteroids; a history of gastric surgery other than a patch repair; allergy to aspirin or clopidogrel; and the presence of erosive esophagitis, gastric-outlet obstruction, renal failure requiring dialysis, terminal illness, or cancer.

### TREATMENT

Eligible patients were randomly assigned to receive either 75 mg of clopidogrel (Plavix, Sanofi-Synthelabo) daily plus esomeprazole placebo twice daily or 80 mg of aspirin daily plus 20 mg of esomeprazole (Nexium, AstraZeneca) twice daily for 12 months. Randomization was carried out with the use of a computer-generated list of random numbers. An independent staff member assigned the treatments according to consecutive numbers that were kept in sealed envelopes. We purchased the drugs and

repackaged them so that clopidogrel and aspirin appeared as identical blue capsules and esomeprazole and its placebo appeared as identical red capsules, according to the International Good Manufacturing Practice Guidelines for Pharmaceuticals. Consecutively numbered, sealed bottles of the study drugs were dispensed by a research nurse. Anticoagulant agents, NSAIDs, cyclooxygenase-2 inhibitors, over-the-counter analgesics (including herbal products), corticosteroids, misoprostol, histamine H<sub>2</sub>-receptor antagonists, sucralfate, antiplatelet drugs other than the study drugs, and proton-pump inhibitors were prohibited.

#### ASSESSMENT

After random assignment, the patients returned at month 1, month 3, and every three months thereafter until the end of the study. At each visit, hemoglobin levels and serum biochemical values were measured, and drug compliance, the use of other medications including over-the-counter drugs, and safety were assessed. Drug compliance was assessed with the use of pill counts. We also used a territory-wide electronic prescription database that captured all prescriptions written within the public health sector; and we retrieved over-the-counter drugs and prescriptions from the patients, their families, and their primary care doctors in order to identify any concomitant therapy with NSAIDs or aspirin. The assessment of safety was based on physical examination, laboratory tests, and observed or reported adverse events. A direct telephone line was provided for patients and physicians to use to report adverse events that occurred between the scheduled visits with the study physicians. Patients who discontinued the study drugs prematurely were followed until the end of the study, to determine whether gastrointestinal events had occurred.

The local ethics committee approved the protocol of the study and monitored the patients' safety data. All patients gave written informed consent. An independent, blinded adjudication committee reviewed the data to determine which patients had reached the study end points according to the prespecified criteria.

#### END POINTS

The primary end point was recurrent ulcer bleeding as defined according to prespecified criteria — namely, hematemesis or melena documented by the admitting physician, with ulcers or bleeding erosions confirmed on endoscopy, or a decrease in the

hemoglobin level of at least 2 g per deciliter in the presence of endoscopically documented ulcers or bleeding erosions. An ulcer was defined as a circumscribed mucosal break at least 0.5 cm in diameter and with a perceptible depth; a bleeding erosion was defined as a flat mucosal break of any size that occurred in the presence of blood in the stomach. Endoscopy was performed in a treatment-blinded fashion. Only events that were confirmed by the adjudication committee and that occurred during treatment or within 28 days after the discontinuation of treatment were included in the analysis.

The secondary end point was lower gastrointestinal bleeding, which was defined by either melena or rectal bleeding requiring hospitalization or transfusion, with negative results on upper endoscopy, or by a decrease in the hemoglobin level of at least 2 g per deciliter in association with a positive fecal occult blood test and negative results on upper endoscopy. Eligible patients underwent colonoscopy to locate the source of bleeding; those with a negative result were considered to have gastrointestinal bleeding of an obscure origin. Extragastrintestinal bleeding included intracranial hemorrhage and other bleeding disorders such as hematuria leading to hospitalization, hypotension, the need for transfusion, or the need to discontinue the study medication.

#### STATISTICAL ANALYSIS

We determined the size of the sample on the assumptions that about 1.5 percent of patients receiving aspirin plus esomeprazole would have recurrent ulcer bleeding within 12 months<sup>9</sup> and that clopidogrel would not be inferior to aspirin plus esomeprazole if the upper limit of the 95 percent confidence interval for the difference in the rates of recurrent ulcer bleeding did not exceed 4 percentage points. Accordingly, a sample size of 145 patients in each of the two treatment groups was necessary to give the study a power of 80 percent and a 5 percent level of significance with the use of a one-sided equivalence test of proportions.<sup>19</sup> Assuming that 10 percent of patients did not complete follow-up, a total sample of 319 patients would be required. No interim analysis was performed. The data analysis was carried out exclusively by the data review committee.

We used the Kaplan–Meier method to estimate the likelihood of reaching the end points in the intention-to-treat population,<sup>20</sup> which was defined as all patients who had taken at least one dose of

the study medication. The log-rank test was used to compare time-to-event curves for the two groups (SPSS software, version 10.0). Failure to take at least 80 percent of the study drugs or the use of prohibited drugs was considered a violation of the protocol. All P values and 95 percent confidence intervals were two-sided.

## RESULTS

### PATIENTS

Between September 2001 and June 2003, we screened 492 consecutive patients who were taking low-dose aspirin and who presented with hematemesis, melena, or both, and we enrolled a total of 320 of these patients. The reasons for exclusion were terminal illness (in 66 patients), cancer (43), end-stage renal failure (17), lower gastrointestinal bleeding (4), previous gastric surgery (2), gastric-outlet obstruction (1), erosive esophagitis (1), aspirin allergy (1), and concomitant treatment with anticoagulant agents (8), NSAIDs (3), or other antiplatelet drugs (1); in addition, 25 patients declined participation. The intention-to-treat analysis included all 320 patients: 161 patients were randomly assigned to receive clopidogrel, and 159 patients to receive aspirin plus esomeprazole (Table 1). The median follow-up was 12 months (range, 0.3 to 12) in both groups. All of the patients in the clopidogrel group and all but three patients in the aspirin-plus-esomeprazole group completed follow-up.

Ninety-four percent of the patients in each group took at least 80 percent of the assigned study drugs. The rates of discontinuation, excluding patients who reached the primary end point, were similar in the two groups — 11.8 percent in the clopidogrel group (4.3 percent because of adverse events, 1.9 percent because of recurrent ischemic events, 0.6 percent owing to withdrawal of consent, and 5.0 percent for other reasons) and 8.8 percent in the aspirin-plus-esomeprazole group (1.9 percent because of adverse events, 3.8 percent owing to withdrawal of consent, and 3.1 percent for other reasons). No patient who discontinued medications early had recurrent ulcer bleeding or anemia within the study period.

### GASTROINTESTINAL EVENTS

Thirty-four cases of suspected serious gastrointestinal events were evaluated by the adjudication committee. The committee identified 14 cases of

recurrent ulcer bleeding, 13 in the clopidogrel group (6 gastric ulcers, 5 duodenal ulcers, 2 both gastric and duodenal ulcers) and 1 (duodenal ulcer) in the aspirin-plus-esomeprazole group. All the patients with recurrent bleeding had presented with recurrent melena, hematemesis, or both, requiring hospitalization. The median diameter of the recurrent ulcers was 0.5 cm (range, 0.5 to 3.0 cm). Five patients required endoscopic control of active bleeding, and eight required transfusion (median, 3.5 units; range, 1 to 9). In 10 of the 14 patients with recurrent bleeding (71.4 percent), the ulcers recurred at their previous locations. None of the 14 patients had recurrent *H. pylori* infection. Two patients with recurrent ulcer bleeding in the clopidogrel group used concomitant NSAIDs.

The cumulative incidence of recurrent ulcer bleeding during the 12-month study period was 8.6 percent (95 percent confidence interval, 4.1 to 13.1 percent) among patients who received clopidogrel and 0.7 percent (95 percent confidence interval, 0 to 2.0 percent) among those who received aspirin plus esomeprazole (difference, 7.9 percentage points; 95 percent confidence interval for the difference, 3.4 to 12.4;  $P=0.001$ ) (Table 2 and Fig. 1). A per-protocol analysis of 293 patients showed that the cumulative incidence of recurrent bleeding was 7.5 percent (95 percent confidence interval, 3.0 to 11.9 percent) in the clopidogrel group and 0.7 percent (95 percent confidence interval, 0 to 2.2 percent) in the aspirin-plus-esomeprazole group (difference, 6.8 percentage points; 95 percent confidence interval for the difference, 2.3 to 11.3;  $P=0.005$ ).

Of the 20 patients who were found on adjudication not to have recurrent ulcer bleeding, 4 were found to have gastrointestinal cancer (3 had colon cancer and 1 had cholangiocarcinoma), and 2 had anemia that was not due to gastrointestinal blood loss. Of 14 patients who met the prespecified criteria for lower gastrointestinal bleeding, 7 received clopidogrel (6 had gastrointestinal bleeding of obscure origin and 1 had a bleeding rectal ulcer) and 7 received aspirin plus esomeprazole (5 had gastrointestinal bleeding of obscure origin, 1 had hemorrhoidal bleeding, and 1 had angiodysplasia). The cumulative incidence of lower gastrointestinal bleeding was 4.6 percent (95 percent confidence interval, 1.3 to 7.9 percent) in the clopidogrel group and 4.6 percent (95 percent confidence interval, 1.3 to 8.0 percent) in the aspirin-plus-esomeprazole group ( $P=0.98$ ).

**Table 1. Baseline Characteristics of the 320 Patients.\***

Characteristic	Clopidogrel (N=161)	Aspirin plus Esomeprazole (N=159)
Male sex — no. (%)	108 (67.1)	103 (64.8)
Age — yr	72.1±10.2	72.9±9.5
Current smoking — no. (%)	21 (13.0)	13 (8.2)
Current alcohol consumption — no. (%)	13 (8.1)	8 (5.0)
Source of bleeding — no. (%)		
Gastric ulcer	94 (58.4)	74 (46.5)
Duodenal ulcer	48 (29.8)	61 (38.4)
Gastric and duodenal ulcers	9 (5.6)	18 (11.3)
Gastric erosions	8 (5.0)	6 (3.8)
Duodenal erosions	2 (1.2)	0
Multiple episodes of ulcer bleeding — no. (%)	28 (17.4)	33 (20.8)
Diameter of ulcer — cm	1.3±3.1	1.3±3.3
Diameter ≥2 cm — no. (%)	20 (12.4)	21 (13.2)
Ulcer with active bleeding or nonbleeding visible vessels — no. (%)	45 (28.0)	54 (34.0)
Transfusion required — no. (%)	78 (48.4)	89 (56.0)
Ischemic condition — no. (%)		
Coronary heart disease	88 (54.7)	78 (49.1)
Cerebrovascular insufficiency	55 (34.2)	66 (41.5)
Peripheral vascular disease	8 (5.0)	6 (3.8)
Multiple ischemic conditions — no. (%)	10 (6.2)	9 (5.7)
Serum creatinine >1.2 mg/dl — no. (%)†	49 (30.4)	47 (29.6)
Previous <i>H. pylori</i> infection — no. (%)	74 (46.0)	74 (46.5)

\* Plus-minus values are means ±SD.

† To convert the value for creatinine to micromoles per liter, multiply by 88.4.

#### EXTRAGASTROINTESTINAL BLEEDING AND OTHER ADVERSE EVENTS

Three patients who received clopidogrel had extragastrointestinal bleeding: two patients had intracranial hemorrhage, and one had severe hematuria requiring hospitalization for transfusion. None of the patients who received aspirin plus esomeprazole had extragastrointestinal bleeding. Other adverse events occurred in 9.4 percent of the clopidogrel group (7.5 percent of patients had dyspepsia, and 1.9 percent had allergy) and in 4.4 percent of the aspirin-plus-esomeprazole group (2.5 percent of patients had dyspepsia and 1.9 percent had allergy). Recurrent ischemic events occurred in 9 patients in the clopidogrel group (1 patient had myocardial infarction, 6 had unstable angina, and 2 had cerebrovascular insufficiency) and in 11 patients in the aspirin-plus-esomeprazole group (1 had myo-

cardial infarction, 7 had unstable angina, and 3 had cerebrovascular insufficiency).

#### MORTALITY

Of 12 patients who died, 8 were in the clopidogrel group (1 patient died from myocardial infarction, 1 from an intracranial hemorrhage, 1 from heart failure, 3 from sepsis, and 2 from uncertain causes), and 4 were in the aspirin-plus-esomeprazole group (1 patient died from myocardial infarction, 1 from cerebrovascular insufficiency, 1 from renal failure, and 1 from uncertain causes).

#### DISCUSSION

We tested the hypothesis that clopidogrel would not be inferior to aspirin plus esomeprazole in the prevention of recurrent ulcer bleeding in high-risk patients. The patients enrolled in this study had multiple risk factors, including a recent history of aspirin-induced ulcer bleeding, advanced age, and coexisting conditions. We found that among these high-risk patients who received clopidogrel after their ulcers had healed, the incidence of recurrent ulcer bleeding was unacceptably high: 8.6 percent of the patients had recurrent bleeding during the 12-month period of the study, as compared with only 0.7 percent of the patients receiving aspirin plus esomeprazole. This finding is not consistent with the current American College of Cardiology–American Heart Association practice guidelines, which recommend the use of clopidogrel as an alternative antiplatelet agent for patients who have major gastrointestinal intolerance of aspirin.<sup>18</sup>

Current evidence regarding the gastrointestinal safety of clopidogrel was derived from a secondary analysis of studies that did not use prespecified criteria to report gastrointestinal complications.<sup>10,11</sup> Although one study found a lower incidence of gastrointestinal bleeding among patients receiving clopidogrel than among those receiving aspirin,<sup>10</sup> a relatively high dose of aspirin (325 mg daily) was used as the comparator.

Our results raise doubt about the gastrointestinal safety of clopidogrel even in the absence of active ulcers. Although all the patients had confirmed ulcer healing before undergoing randomization, those in whom upper gastrointestinal bleeding recurred actually had bleeding from recurrent ulcers. None had recurrent *H. pylori* infection. Only two patients with recurrent bleeding used concomitant NSAIDs. This finding was consistent with a retro-

spective study that reported that 12 percent of patients with a history of ulcer who took clopidogrel had ulcer bleeding within one year.<sup>21</sup>

The mechanisms leading to recurrent ulcer bleeding among patients receiving clopidogrel are unknown. Studies in animals have shown that platelet adenosine diphosphate-receptor antagonists impair the healing of gastric ulcers by suppressing the release of platelet-derived growth factors.<sup>22</sup> We speculate that clopidogrel may induce recurrent ulcers in the previously damaged gastric mucosal barrier, as suggested by the high rate of recurrence at the previous location (71.4 percent) in our study. Alternatively, patients who have major coexisting conditions may have a predisposition to the development of ulcers even in the absence of *H. pylori* infection or the use of NSAIDs.<sup>23</sup> Clopidogrel probably provoked bleeding from recurrent ulcers in these high-risk patients.

The optimal dose of proton-pump inhibitors for patients at high risk from the use of aspirin remains undefined. One study showed that among aspirin users with a history of ulcer bleeding who received lansoprazole at 30 mg once daily, the incidence of recurrent bleeding over 12 months was 1.6 percent. However, the upper limit of the 95 percent confidence interval was as high as 9.0 percent.<sup>5</sup> We used a twice-daily dose of a proton-pump inhibitor to provide better acid control than the once-daily dose.<sup>24,25</sup>

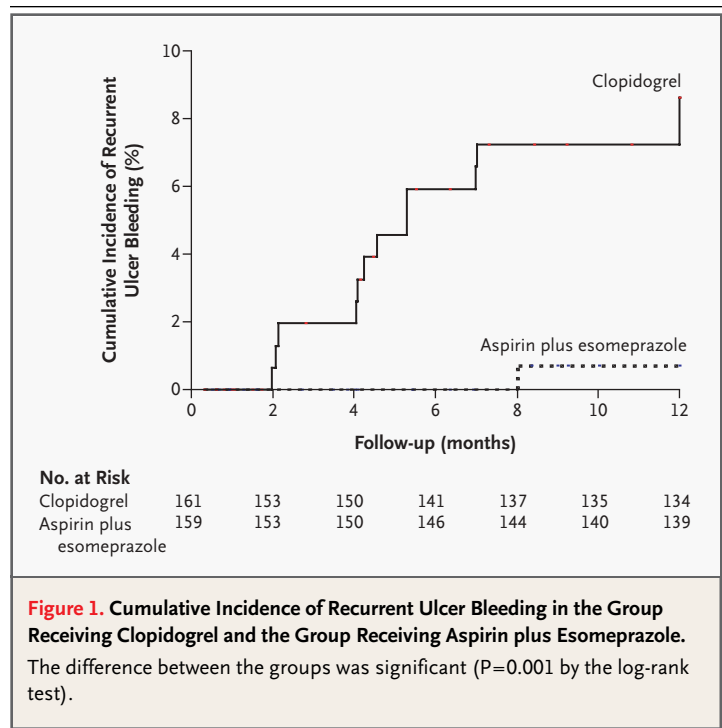
Our study has several limitations. First, the risk reduction achieved by clopidogrel or aspirin plus esomeprazole could not be determined, because we did not include a group of patients with a history of ulcer bleeding who used aspirin without prophylaxis. A previous study reported that about 15 percent of patients with a history of ulcer bleeding who used aspirin had recurrent bleeding within one year.<sup>5</sup> It would therefore be unethical to prescribe aspirin without prophylaxis for high-risk patients. Second, whether genetic variation in the metabolism of aspirin and proton-pump inhibitors among racial and ethnic groups has any effect on the risk of bleeding and the efficacy of treatment remains unknown. Third, because the study drugs were repackaged from the form available commercially, there may have been differences in uptake and absorption that changed the therapeutic efficacy of the drugs or had adverse effects.

In summary, among patients with a history of aspirin-induced ulcer bleeding, aspirin plus esomeprazole was superior to clopidogrel for the pre-

**Table 2. Kaplan–Meier Estimates of the Likelihood of Recurrent Ulcer Bleeding and Lower Gastrointestinal (GI) Bleeding at 12 Months.**

Type of Bleeding	Probability of Bleeding (95% CI)*		P Value	
	Clopidogrel	Aspirin plus Esomeprazole		
	<i>percent</i>		<i>Difference between the Groups</i>	
			<i>percentage points</i>	
Recurrent ulcer bleeding	8.6 (4.1 to 13.1)	0.7 (0 to 2.0)	7.9 (3.4 to 12.4)	0.001
Lower GI bleeding	4.6 (1.3 to 7.9)	4.6 (1.3 to 8.0)	0.0 (–4.6 to 4.6)	0.98

\* CI denotes confidence interval.



vention of recurrent bleeding. Our observations do not support the current recommendation that clopidogrel be used for patients who have major gastrointestinal intolerance of aspirin.

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