CLINICAL—ALIMENTARY TRACT

Esomeprazole With Clopidogrel Reduces Peptic Ulcer Recurrence, Compared With Clopidogrel Alone, in Patients With Atherosclerosis

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BACKGROUND & AIMS: We performed a prospective, randomized, controlled study to compare the combination of esomeprazole and clopidogrel vs clopidogrel alone in preventing recurrent peptic ulcers in patients with atherosclerosis and a history of peptic ulcers. We also investigated the effects of esomeprazole on the antiplatelet action of clopidogrel. **METHODS:** From January 2008 to January 2010, long-term clopidogrel users with histories of peptic ulcers who did not have peptic ulcers at an initial endoscopy examination were assigned randomly to receive the combination of esomeprazole (20 mg/day, before breakfast) and clopidogrel (75 mg/day, at bedtime), or clopidogrel alone for 6 months. A follow-up endoscopy examination was performed at the end of the sixth month and whenever severe symptoms occurred. Platelet aggregation tests were performed on days 1 and 28 for 42 consecutive patients who participated in the pharmacodynamic study. **RESULTS:** The cumulative incidence of recurrent peptic ulcer during the 6-month period was 1.2% among patients given the combination of esomeprazole and clopidogrel (n = 83) and 11.0% among patients given clopidogrel alone (n = 82) (difference, 9.8%; 95% confidence interval, 2.6%–17.0%; $P = .009$). In the group given the combination therapy, there were no differences in the percentages of aggregated platelets on days 1 and 28 (31.0% ± 20.5% vs 30.1% ± 16.5%). **CONCLUSIONS: Among patients with atherosclerosis and a history of peptic ulcers, the combination of esomeprazole and clopidogrel reduced recurrence of peptic ulcers, compared with clopidogrel alone. Esomeprazole does not influence the action of clopidogrel on platelet aggregation.**

Keywords: Proton-Pump Inhibitor; Plavix; *CYP2C19*; Drug Interactions.

Platelet activation and aggregation play an important role in the pathogenesis of arterial thrombosis and lead to ischemic events. Clopidogrel is a thienopyridine derivative that inhibits platelet function by selectively and irreversibly blocking the adenosine diphosphate (ADP) receptor on platelets, thereby affecting ADP-dependent activation of the GpIIb-IIIa complex, the major receptors for fibrinogen present on the platelet surface.[1] Alone or in association with aspirin, clopidogrel successfully has been proven to be beneficial in the treatment of acute coronary syndrome[2] and to prevent ischemic events in patients with atherosclerotic diseases.[3]

The Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events study showed that long-term administration of clopidogrel to patients with atherosclerotic vascular disease is more effective than aspirin in reducing the combined risk of ischemic events.[4] In addition, clopidogrel induced fewer episodes of gastrointestinal bleeding than aspirin.[4] The American College of Cardiology–American Heart Association guidelines therefore recommend clopidogrel as an alternative to aspirin for patients with unstable angina or non–ST-segment elevation myocardial infarction who have an aspirin intolerance.[5]

However, a recent study showed that 12% of patients with a history of ulcer who took clopidogrel had ulcer bleeding within 1 year.[6] Furthermore, the cumulative incidence of recurrent bleeding in clopidogrel users who had ulcer bleeding history (subjects with high gastrointestinal risk) was higher than that in patients who took aspirin plus a proton pump inhibitor (PPI).[7] The mechanisms leading to recurrent ulcer bleeding among patients receiving clopidogrel are unclear. Nonetheless, an

Abbreviations used in this paper: hetEM, heterogeneous extensive metabolizer; homEM, homogeneous extensive metabolizer; ITT, intention to treat; NSAID, nonsteroidal anti-inflammatory drug; PM, poor metabolizer; PPA, percentage of platelet aggregation; PPI, proton pump inhibitor.

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animal study revealed that platelet ADP-receptor antagonists impair the healing of gastric ulcers by suppressing the release of platelet-derived growth factors.[8] We therefore speculate that clopidogrel also may hinder ulcer healing and/or precipitate ulcer formation in human beings.

Currently, there has been no prospective trial to assess whether PPI effectively can prevent recurrent peptic ulcer or ulcer complications in patients at risk of ischemic events. In addition, a potential interaction between clopidogrel and PPI recently has drawn much attention. We therefore conducted a 6-month, prospective, randomized, controlled trial to compare esomeprazole plus clopidogrel with clopidogrel alone for the prevention of recurrent peptic ulcer in atherosclerotic patients with a history of peptic ulcer, and to investigate the effect of esomeprazole on the antiplatelet action of clopidogrel.

Methods

Study Population

This open-labeled trial was conducted at the Kaohsiung Veterans General Hospital in Taiwan in accordance with the principles of good clinical practice from the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of the Kaohsiung Veterans General Hospital. All patients gave written informed consent before participating in the study. This trial is registered as a standard randomized Clinical Trial (ClinicalTrials.gov.identifier: NCT01138969).

We screened for eligible patients who had a past history of gastroduodenal ulcer (a mucosal break ≥5 mm in diameter) documented by a previous endoscopic examination and who underwent endoscopy for dyspeptic symptoms or routine screening while receiving clopidogrel therapy to prevent ischemic events. We enrolled patients in the study if they met the following criteria: endoscopic examination revealed normal appearance or erythematous patches only (without subepithelial hemorrhages, erosions, or ulcers); they had received clopidogrel (75 mg or 37.5 mg/day) for at least 2 weeks; they had an atherosclerotic disease such as ischemic heart disease or stroke; they required long-term antiplatelet therapy; and they were adult patients age 18 years and older. Patients were excluded if they had a history of gastric or duodenal surgery other than oversewing of a perforation; if they were allergic to the study drugs; if they required long-term treatment with nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, aspirin, or anticoagulant agents; if they were pregnant; if they had active cancer, acute serious medical illness, or terminal illness; if they had gastroesophageal reflux disease; or if they received a PPI or antibiotic therapy within 2 weeks before endoscopy.

Study Protocol

Randomization and treatment. Eligible patients were assigned randomly to receive the following: (1) 20 mg/day of esomeprazole (Nexium; AstraZeneca, Sodertalje, Sweden) (before breakfast) plus 75 mg/d of clopidogrel (Plavix; Sanofi-Synthelabo, New York, NY) (at bedtime), or (2) 75 mg of clopidogrel (at bedtime) for 6 months. Randomization was performed 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. Patients were instructed to take esomeprazole 30 minutes before breakfast and clopidogrel at bedtime. Anticoagulants, cyclo-oxygenase-2 inhibitors, conventional NSAIDs, over-the-counter analgesics, corticosteroids, misoprostol, histamine H_2-receptor antagonists, and sucralfate were prohibited. The administration of an antacid (Iwell, Everest, Taiwan) was permitted for the control of dyspeptic symptoms. Compliance with the regimen was assessed by counting the pills that were returned.

If *Helicobacter pylori* infection was documented on recruitment, a 7-day course of anti–*H pylori* therapy consisting of 20 mg of esomeprazole, 1 g of amoxicillin, and 500 mg of clarithromycin given twice daily was administered. Urea breath test was performed at 4 weeks after the end of anti–*H pylori* therapy. Patients in whom *H pylori* infection was not eradicated, as indicated by positive results of urea breath tests, received a 10-day course of quadruple therapy consisting of esomeprazole 40 mg twice a day, bismuth subcitrate 120 mg 4 times per day, tetracycline 500 mg 4 times per day, and metronidazole 250 mg 4 times per day. An additional ^{13}C urea breath test was conducted to assess the final *H pylori* status 2 weeks after the 6-month trial for all the patients who had *H pylori* infection at recruitment. Esomeprazole and any other PPIs were on hold for 2 weeks before the final ^{13}C urea breath tests. Eradication was defined as a negative result of the final urea breath test.

Blood sampling for genotyping of *CYP2C19* was performed on day 1 for the subjects who provided informed consents for genetic study. The *CYP2C19* genotype was determined using the polymerase chain reaction–restriction fragment length polymorphism according to previous studies.[9] Genotypes were classified into 3 groups: homogeneous extensive metabolizer (homEM; *CYP2C19**1/*CYP2C19**1); heterogeneous extensive metabolizer (hetEM; *CYP2C19**1/*CYP2C19**2 and *CYP2C19**1/*CYP2C19**3); and poor metabolizer (PM; *CYP2C19**2/*CYP2C19**2, *CYP2C19**2/*CYP2C19**3, and *CYP2C19**3/*CYP2C19**3).

Detection of H pylori *on Recruitment*

On initial endoscopy, a biopsy specimen was obtained from the greater curvature within 5 cm of the pylorus for rapid urease test (CLO test; Delta West, Bentley, Australia). A negative CLO test was defined by the

absence of a change in color after 24 hours. In addition, one specimen taken from the greater curvature within 5 cm of the pylorus and another taken from the greater curvature of the middle body were subjected to microscopic examination for *H pylori* with the use of H&E stain and Warthin–Starry stain if necessary. *H pylori* was considered to be present if either of the 2 tests was positive; it was considered to be absent when both tests were negative.

Follow-up Evaluation

Patients were followed up as outpatients with visits every month. Upper gastrointestinal and cardiovascular symptoms were assessed at each visit. They were asked to return to the outpatient clinic if they had persistent dyspeptic symptoms (epigastric pain, fullness, nausea, or vomiting) and to report to the emergency room if they had evidence of gastrointestinal bleeding (hematemesis, melena, or sudden onset of severe epigastric pain), cardiovascular events (chest pain, syncope, or sudden onset of severe palpitation), or cerebrovascular accidents (conscious disturbance, hemiparesis, or dysphagia). Follow-up endoscopy with biopsy for urease test was performed whenever persistent dyspepsia, severe epigastric pain, hematemesis, or melena occurred, and at the end of the sixth month. The endoscopists who performed the follow-up endoscopy were unaware of the treatment group assignments. The events of acute coronary syndrome and cerebral vascular accidents during the study period were carefully monitored and assessed by physicians.

End Points

The primary end point was the occurrence of gastric and/or duodenal ulcers, as determined by endoscopy, during the 6-month study period. An ulcer was defined as a circumscribed mucosal break 5 mm or more in diameter, with a well-defined ulcer crater, whereas smaller lesions (<5 mm in diameter) were classified as erosions. The size of ulceration was measured by opening a pair of biopsy forceps of known span in front of the ulcer.[10] Only events that were confirmed by the adjudication committee and that occurred during treatment were included in the analysis. Patients who did not have follow-up endoscopic examination were assumed to have had normal findings. The secondary end points were as follows: (1) the occurrence of ulcer or erosion 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/dL in the presence of endoscopically documented ulcers or erosions[7]; (2) the occurrence of unstable angina defined as rest angina (angina occurring at rest and prolonged >20 min), new-onset angina (of at least Canadian Cardiovascular Society Class III severity), and increasing angina (angina occurring more frequently, longer in duration) with ischemic changes shown on the electrocardiogram[11]; (3) acute myocardial infarction defined as at least 2 positive results of typical chest pain, evolutionary electrocardiogram changes, and evolutionary cardiac enzyme changes; (4) the occurrence of ischemic stroke defined as sudden onset of neurologic deficit owing to cerebral ischemia documented by computed tomography; and (5) vascular death defined as death as a result of cardiovascular diseases or cerebrovascular accidents. Only events that were confirmed by the cardiovascular events review board were included in the analysis.

Platelet Aggregation Study

To investigate the pharmacodynamic effect of esomeprazole on clopidogrel users, all the patients enrolled in the aforementioned clinical trial were invited to participate in the platelet aggregation study until the number of eligible patients agreeing to join the trial reached 42 (see sample size calculation in the Statistical Analysis section). All patients had been on clopidogrel (75 mg/day) at bedtime for at least 4 weeks at the time of inclusion. Exclusion criteria were taking clopidogrel at a time of day other than bedtime, concomitant use of aspirin or anticoagulant, history of thrombocytopenia (<150,000 platelets/mL) or bleeding disorder, cirrhosis, uremia, *H pylori* infection, and pregnancy. The last dose of clopidogrel (75 mg) was taken at bedtime in the previous day before randomization. After written informed consent was obtained, the patients were randomized to either the esomeprazole-plus-clopidogrel group or the clopidogrel group as previously described. Blood samples for the platelet aggregation test were collected in the morning on day 1 before taking study medications, and in the morning on day 28 in both groups. Laboratory physicians were blinded to the treatment group and to whether the sample was from day 1 or day 28. A study nurse was in charge of the recruitment of patients and the termination of the pharmacodynamic study when sufficient cases were enrolled.

The ADP-induced platelet aggregation test was conducted to evaluate platelet function using a commercially available kit (ADP; Bio/Data Corp, Horsham, PA).[12] Aggregation response was expressed as the percentage of platelet aggregation (PPA) at 5 minutes. The method of the ADP-induced platelet aggregation test is shown in the Supplementary Materials and Methods section.

Statistical Analysis

When we started the study, there were no data available about the rate of recurrence of peptic ulcers in clopidogrel users with a history of peptic ulcer. We estimated that at the end of 6 months, the primary end point (relapse of peptic ulcer) after eradication of *H pylori* infection would occur in 20% of patients in the clopido-

Table 1. Baseline Characteristics of the Patients

Variable	Esomeprazole-plus-clopidogrel group (n = 83)	Clopidogrel group (n = 82)	*P* value
Age, *y* (mean ± standard deviation)	70.6 ± 11.5	73.3 ± 10.7	.129
Male sex, n (%)	65 (78.3)	59 (72.0)	.372
Smoking, n (%)	10 (12.0)	5 (6.1)	.184
Alcohol use, n (%)	4 (4.8)	3 (3.7)	1.000
Ingestion of coffee, n (%)	11 (13.3)	6 (7.3)	.210
Ingestion of tea, n (%)	18 (21.7)	17 (20.7)	.881
Medical history n (%)			
Cerebrovascular accident	33 (40.0)	27 (32.9)	.38
Ischemic heart diseases	59 (71.1)	54 (65.9)	.470
Hypertension	56 (67.5)	57 (69.5)	.778
Diabetes mellitus	35 (42.2)	23 (28.0)	.058
History of ulcer bleeding	30 (36.1)	25 (30.5)	.441
H pylori infection, n (%)			
Previous history	27 (32.5)	26 (31.7)	.910
Current infection	4 (4.8)	8 (9.8)	.473
Doses of clopidogrel on recruitment, n (%)			.367
37.5 mg/day	1 (1.2)	3 (3.7)	
75.0 mg/day	82 (98.8)	79 (96.3)	
CYP2C19 genotype			.807
No. of patients with data	61	64	
HomEM	27 (44.3)	32 (50.0)	
HetEM	27 (44.3)	25 (39.1)	
PM	7 (11.5)	7 (10.9)	

grel group and that the addition of esomeprazole would reduce the rate of relapse to 5%. It was estimated that we required a minimum of 76 patients in each treatment group to show an absolute difference of 15% with a type I error of 0.05 and a type II error of 0.2 in 2-sided tests. The homogeneity of the treatment groups at baseline and the major outcomes were analyzed by the chi-square test with Yates correction or the Fisher exact test for categoric data and the Student *t* test for continuous variables.

Analysis was by intention-to-treat (ITT) and per protocol. The ITT population included all randomized patients who received at least one dose of study drugs (clopidogrel or esomeprazole). Patients who did not have the final endoscopic examination were assumed to have had normal findings. The per-protocol population included all those in the ITT population who took more than 80% of the study drugs, did not take NSAIDs or other anti-ulcer drugs (with the exception of antacids and anti–*H pylori* therapy), and who underwent the final endoscopic examination.

A sample size calculation for pharmacodynamic study was based on the observed mean ± standard deviation (33% ± 20%) of the PPA under clopidogrel treatment (pretest of 30 long-term clopidogrel users in our outpatient clinic). We calculated that we needed to include 21 patients in each group to be able to detect a 20% difference in PPA with a power of 90% and a 2-sided α value of .05. The Student *t* test was used to compare the PPA between groups, and the paired *t* test was used to compare the PPA on days 1 and 28 in each group.

SPSS software (version 10.1; Chicago, IL) was used for all statistical calculations. A *P* value of less than .05 was considered statistically significant. All *P* values were 2-sided.

Results

Patients

From January 2008 to January 2010, we screened 253 consecutive patients who had a past history of gastroduodenal ulcer and underwent endoscopy with dyspeptic symptoms while receiving clopidogrel 75 or 37.5 mg/day, and a total of 165 of these patients were enrolled. Eighty-eight patients were excluded. Supplementary Figure 1 shows the trial profile.

All 165 randomized patients received at least one dose and were included in the ITT analysis (esomeprazole plus clopidogrel, n = 83; clopidogrel, n = 82). The 2 groups of patients had comparable age; sex; history of smoking; alcohol, coffee, and tea consumption; comorbid illnesses; status of *H pylori* infection; frequency of half-dose (37.5 mg/day) of clopidogrel use on enrollment; and genotypes of *CYP2C19* (Table 1).

Follow-up Evaluation

The median duration of follow-up evaluation was 6 months in both treatment groups (range, 2–6 mo). Ninety-six percent of the patients in each group took at least 80% of the assigned study drugs. The rates of loss to follow-up evaluation or drug intolerance were similar between groups: 4.8% in the esomeprazole-plus-clopidogrel group (2.4% because of loss of follow-up evaluation and 2.4% because of intolerance of the study medications) and 5.1% in the clopidogrel group (2.4% because of loss of follow-up evaluation and 3.7% because of intolerance of the study medications).

Gastrointestinal Events

All randomized patients received at least one dose of study drugs and were included in the ITT population. Dyspeptic symptoms occurred in 22.9% and 28.0% of the patients in the esomeprazole-plus-clopidogrel group and the clopidogrel group, respectively (Table 2; $P = .447$). The consumption of antacids was comparable between groups (51.3 ± 102.4 vs 65.6 ± 119.3 tablets, respectively; $P = .410$). The total numbers of follow-up endoscopies in the esomeprazole-plus-clopidogrel group and clopidogrel group were 68 and 69, respectively (mean number of follow-up endoscopies, 0.82 ± 0.42 vs 0.84 ± 0.43, respectively; $P = .737$). Thirty-one patients (esomeprazole-plus-clopidogrel, n = 16; clopidogrel, n = 15) did not have follow-up endoscopy and were assumed to have had normal findings. During the study period, 12 cases of suspected recurrence of gastroduodenal ulcers were eval-

Table 2. Gastrointestinal Events in Clopidogrel Users With or Without Esomeprazole Prophylaxis

Variable	Esomeprazole-plus-clopidogrel group (n = 83)	Clopidogrel group (n = 82)	*P* value
Dyspeptic symptoms, n (%)			
Total	19 (22.9)	23 (28.0)	.447
Severe dyspepsia	5 (6.0)	6 (7.5)	.707
Follow-up endoscopy, n (%)			
Total	68 (81.9)	69 (84.1)	
Indication of endoscopy			
Dyspepsia, n	2	4	
Gastrointestinal bleeding, n	0	1	
End-of-study endoscopy, n	66	64	
Recurrent peptic ulcer, n (%)			
Total	1 (1.2)	9 (11.0)	.009
Gastric ulcer	1 (1.2)	5 (6.1)	.117
Duodenal ulcer	0 (0.0)	4 (4.9)	.059
Peptic ulcer/erosion bleeding, n (%)			
Total	0 (0.0)	1 (1.2)	.497
Gastric ulcer/erosion	0 (0.0)	1 (1.2)	.497
Duodenal ulcer/erosion	0 (0.0)	0 (0.0)	—

uated by the adjudication committee. The committee identified 10 cases of recurrent peptic ulcer, 1 in the esomeprazole-plus-clopidogrel group (1 gastric ulcer) and 9 in the clopidogrel group (5 gastric ulcers, 4 duodenal ulcers). Of the 2 patients who were found on adjudication not to have recurrent peptic ulcer, 1 was found to have gastric erosions only (in the esomeprazole-plus-clopidogrel group), and 1 had duodenal erosions (in the clopidogrel group). The revisions to the endoscopic diagnosis in both cases were based on the size of mucosal breaks less than 5 mm.

In the esomeprazole-plus-clopidogrel group, the patient developing recurrent peptic ulcer was diagnosed by for-cause endoscopy. In the clopidogrel group, 3 recurrent peptic ulcers were identified by for-cause endoscopy, and 6 were identified at end-of-study endoscopy. The cumulative incidence of recurrent peptic ulcer during the 6-month study period was 1.2% (95% confidence interval, −1.1% to 3.5%) among patients who received esomeprazole plus clopidogrel and 11.0% (95% confidence interval, 4.2%–17.8%) among patients who received clopidogrel alone. The former was less than the latter (difference, 9.8%; 95% confidence interval, 2.6%–17.0%; $P = .009$) (Table 2).

Upper gastrointestinal bleeding occurred in 1 patient in the clopidogrel group (1.2%; 95% confidence interval, −1.1% to 3.5%). Bleeding erosions were confirmed on endoscopy in this case. None of the patients in the esomeprazole-plus-clopidogrel group (0%) had peptic ulcer or erosion bleeding. The cumulative incidences of peptic ulcer bleeding in the 2 study groups were not significantly different (difference, 1.2%; 95% confidence interval, 0.5%–1.9%; $P = .497$).

A per-protocol analysis of 129 patients (esomeprazole-plus-clopidogrel, n = 64; clopidogrel, n = 65) showed that the cumulative incidences of recurrent peptic ulcer were 1.6% (95% confidence interval, −1.5% to 4.7%) among the patients treated by esomeprazole plus clopidogrel and 12.3% (95% confidence interval, 4.3%–20.3%) among the patients treated by clopidogrel alone (difference, 10.7%; 95% confidence interval, 2.1%–19.3%; $P = .033$). The cumulative incidences of peptic ulcer bleeding in the 2 study groups were not significantly different (difference, 1.5%; 95% confidence interval, −1.5% to 4.5%; $P = 1.000$).

Among the patients with ulcers (1 in the esomeprazole-plus-clopidogrel group and 9 in the clopidogrel group), only 1 (in the clopidogrel group) used NSAIDs within 1 month before follow-up endoscopy. *H pylori* infection was eradicated in all 4 infected patients in the esomeprazole-plus-clopidogrel group and in 7 of 8 patients in the clopidogrel group. The patient with eradication failure did not develop peptic ulcer or ulcer bleeding during the follow-up period.

Follow-up endoscopy at the end of the study revealed that *H pylori* infection during the study period occurred in 1 of the patients in the clopidogrel group who developed an uncomplicated duodenal ulcer at the end of 6 months. None of the patients in the esomeprazole-plus-clopidogrel group were infected by *H pylori* during the study period.

Cardiocerebral Events and Mortality

Unstable angina developed in 1 patient in the esomeprazole-plus-clopidogrel group and 1 patient in the clopidogrel group. Acute myocardial infarction occurred in 2 patients in the esomeprazole-plus-clopidogrel group and 2 patients in the clopidogrel group. None in the clopidogrel group developed a cerebral ischemic event, but 1 of the patients in the esomeprazole-plus-clopidogrel group had an ischemic stroke. Overall, there were no differences in the combined risk of unstable angina, acute myocardial infarction, and ischemic stroke between groups (4.8% vs 3.7%, respectively; difference, 1.1%; 95% confidence interval for the difference, −0.5% to 7.3%; $P = 1.000$; Table 3). During the study period, none of the patients in the esomeprazole-plus-clopidogrel group or the clopidogrel group died of ischemic events or a nonvascular death. The mortality rates in both groups were 0%.

In the esomeprazole-plus-clopidogrel group, *CYP2C19* genotypes were available in 61 patients providing informed consent for genetic study. Cardiocerebral events occurred in 1 of 27 hetEMs (3.7%) and 1 of 7 PMs (14.3%). None of 27 homEMs (0.0%) developed cardiocerebral events. In the clopidogrel group, *CYP2C19* genotypes were available in 64 patients. Cardiocerebral events occurred in 2 of 25 hetEMs (8.0%) and 1 of 7 PMs

Table 3. Ischemic Events in Clopidogrel Users With or Without Esomeprazole Prophylaxis

Variable	Esomeprazole-plus clopidogrel group (n = 83)	Clopidogrel group (n = 82)	*P* value
Cardiac thrombotic events, n (%)			
Unstable angina	1 (1.2)	1 (1.2)	1.000
Acute myocardial infarct	2 (2.4)	2 (2.4)	1.000
Cerebral thrombotic events, n (%)			
Ischemic stroke	1 (1.2)	0 (0.0)	1.000
Total thrombotic events, n (%)	4 (4.8)	3 (3.7)	1.000
Death, n (%)	0 (0.0)	0 (0.0)	—

(14.3%). None of 32 homEMs (0%) developed ischemic events.

Among all the study patients, none of the 60 homEMs developed cardiocerebral events (0%; 0 of 60). Cardiocerebral events occurred in 5.7% (3 of 53) and 14.3% (2 of 14) of hetEMs and PMs, respectively. The patients with reduced-function alleles of *CYP2C19* (PMs and hetEMs) had a higher combined cardiocerebral risk than the patients with full-function alleles (homEMs) (7.5% vs 0.0%; difference, 7.5%; 95% confidence interval for the difference, 5.9%–9.1%; $P = .032$).

Platelet Aggregation Test

Forty-two patients were included and randomized, 21 in the esomeprazole-plus-clopidogrel group and 21 in the clopidogrel group. In the esomeprazole-plus-clopidogrel group, there were no differences between the PPAs on days 1 and 28 (31.0% ± 20.5% vs 30.1% ± 16.5%; 95% confidence interval, −9.5 to 11.4; $P = .851$). In the clopidogrel group, the PPAs on days 1 and 28 were not significantly different (32.8% ± 23.9% vs 35.0% ± 23.9%; 95% confidence interval, −13.2 to 8.7; $P = .675$). In addition, there were no differences in the mean PPA between the 2 groups of patients on either day 1 (95% confidence interval, −16.1 to 12.6; $P = .805$) or day 28 (95% confidence interval, −18.2 to 8.3; $P = .456$) (Figure 1).

Further analysis showed that the PPAs in the homEMs (n = 8), hetEMs (n = 7), and PMs (n = 3) treated by esomeprazole plus clopidogrel were 22.0% ± 16.0%, 34.6% ± 14.6%, and 38.0% ± 26.1%, respectively, on day 1. The PPAs in the 3 subgroups were 27.5% ± 14.0%, 34.3% ± 17.3%, and 40.3% ± 10.7%, respectively, on day 28. There were no significant differences between the PPAs on day 1 and day 28 in each subgroup ($P = .229$, .965, and .817, respectively). In the clopidogrel group, the PPAs in the homEMs (n = 12), hetEMs (n = 6), and PMs (n = 2) were 24.9% ± 19.7%, 31.5% ± 23.9%, and 63.0% ± 1.4%, respectively, on day 1. On day 28, the PPAs in the 3 subgroups were 26.0% ± 19.3%, 40.2% ± 25.3%, and 57.0% ± 13.1%, respectively. There were also no differences between the PPAs on days 1 and 28 in each subgroup ($P = .871$, .512, and .838, respectively).

Discussion

The current study showed 11.0% of the patients with a peptic ulcer history who took clopidogrel for the prevention of ischemic events had recurrent peptic ulcer during a 6-month follow-up period.

The data indicate that a significant number of atherosclerotic patients who have a past history of peptic ulcers develop recurrent peptic ulcers during clopidogrel use. Two prospective randomized trials showed that the cumulative incidence of recurrent bleeding or ulcer complications during a 12-month period ranged from 8.6% to 13.6% among patients who had an ulcer bleeding history and received clopidogrel.[7,13] In this study, we tested the hypothesis that esomeprazole plus clopidogrel would be superior to clopidogrel alone in the prevention of recurrent ulcer in high-risk patients. The data showed that only 1 of the 83 patients (1.2%) in the esomeprazole-plus-clopidogrel group developed a peptic ulcer. In addition, none of them had peptic ulcer/erosion bleeding. The data confirm our hypothesis that esomeprazole can effectively prevent recurrent ulcer in clopidogrel users who have a peptic ulcer history.

A recent study by Fork et al[14] showed that short-term use of clopidogrel did not induce gastric damage in healthy subjects. However, the current study revealed that 11% of the patients with peptic ulcer history developed recurrent ulcers after long-term use of clopidogrel. Currently, the specific causes leading to recurrent peptic ulcer among most patients receiving clopidogrel were unclear. In our study, only 1 patient with recurrent peptic ulcer concomitantly took NSAIDs within 1 month before follow-up endoscopy,

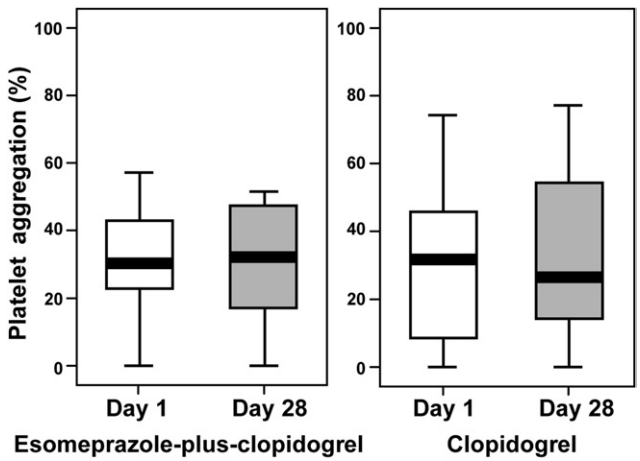

Figure 1. Mean ADP-induced platelet aggregation on days 1 and 28. In the esomeprazole-plus-clopidogrel group, there were no differences between the PPAs on day 1 and day 28 (31.0% vs 30.1%; $P = .851$). In the clopidogrel group, the PPAs on days 1 and 28 also were similar (32.8% vs 35.0%; 95% confidence interval, −13.2 to 8.7; $P = .675$). In addition, there were no differences in the mean PPA between the 2 groups of patients on either day 1 or day 28.

and another patient had *H pylori* infection. The other 9 patients with recurrent ulcers or ulcer complications in this study had no definite causes leading to ulcer formation. Nonetheless, it should be noted that most of our patients had advanced age and comorbid diseases. Chan et al[15] have shown that patients who have major comorbid illness have a predisposition to the development of ulcers even in the absence of *H pylori* infection or the use of NSAIDs.

The present results may be taken to indirectly suggest that clopidogrel may be associated with an increase in ulcers in a higher-risk population (those with prior ulcers). However, patients with prior ulcer have an increased risk of recurrent ulcers. An alternative hypothesis is that a significant number of the patients with high gastrointestinal risk would develop peptic ulcers (because of unreported surreptitious NSAID use or some unknown causes) whether or not they took clopidogrel. PPIs would be expected to decrease recurrent ulcers, even if the ulcers are unrelated to clopidogrel. The relatively high rates of recurrent ulcer bleeding in a high-risk population on clopidogrel in 2 Hong Kong studies[7,15] also could be owing to ulcers recurring in patients with prior ulcers and then the antiplatelet effect of clopidogrel causing these ulcers to bleed.

Recently, the interaction of PPIs and clopidogrel has drawn much attention,[16,17] and raises the concern for the safety of combination use of a PPI and clopidogrel. Clopidogrel is a prodrug that must be absorbed in the gastrointestinal tract and metabolized in the liver to generate active metabolites and acquire its antiplatelet properties. The metabolism of clopidogrel involves CYP2C19 isoenzymes. The CYP2C19 isoform is also the key enzyme for the metabolism of most PPIs. This has led to the assumption that some PPIs may potentially inhibit the CYP2C19 pathway and interfere with the conversion of clopidogrel to its active form. Three large retrospective observation studies also reported that patients prescribed clopidogrel who also took PPIs had significant increases in cardiovascular events.[18–20] Therefore, both the US Food and Drug Administration and the European Medicines Agency have posted safety warnings and discourage the use of PPIs with clopidogrel unless absolutely necessary.

It is important to note that the findings in observational studies[18–20] could be owing to channeling bias (eg, more frequent PPI use in sicker patients).[16] In this trial, the cumulative combined risk of ischemic events in the esomeprazole-plus-clopidogrel group and the clopidogrel group were 4.8% and 3.7%, respectively. There were also no differences in the incidence of ischemic events (unstable angina, acute myocardial infarct, and ischemic stroke) between clopidogrel users with or without esomeprazole therapy. However, this randomized controlled study was underpowered to make conclusions about the impact of PPI on the incidence of cardiovascular events in clopidogrel users. Recently, Bhatt et al[21] conducted a double-blind, prospective, randomized trial to investigate the effect of omeprazole in patients receiving both aspirin and clopidogrel. The data showed that there were no significant differences in cardiovascular events between the omeprazole and placebo groups. This large-scaled randomized controlled trial did not document a significant interaction of PPIs with clopidogrel with respect to cardiovascular events.

In the pharmacodynamic study of our randomized controlled trial, there were no differences in the ADP-induced platelet aggregation in clopidogrel users before and 28 days after use of esomeprazole. In addition, there were no differences in platelet aggregation between the esomeprazole-plus-clopidogrel group and the clopidogrel group on either day 1 or day 28. Our findings were consistent with a previous study[22] showing that ADP-induced platelet aggregation was significantly higher in patients on omeprazole but not significantly different in patients taking esomeprazole or pantoprazole when compared with those not prescribed a PPI.

It is important to note that we widely separated the administration of esomeprazole and clopidogrel in this study. The patients were instructed to take esomeprazole before breakfast and clopidogrel at bedtime. The half-lives of PPIs (and clopidogrel) are very short so this approximately 14- to 16-hour separation likely would minimize any potential interaction. Therefore, this study cannot completely exclude the potential interactions between esomeprazole and clopidogrel if they are given closer together. Nonetheless, our data indicate that there is no evidence of interaction when esomeprazole is given before breakfast and clopidogrel is administered at bedtime. The important finding does support current practice recommended by some investigators[16] and provides physicians a useful way to administer PPIs and clopidogrel in atherosclerotic patients who have high gastrointestinal risks.

In the current study, all the patients who underwent genetic polymorphism study and developed ischemic cardiocerebral events in this study were hetEMs or PMs. None of the 27 homEMs in the esomeprazole-plus-clopidogrel group and none of the 32 homEMs in the clopidogrel group developed cardiocerebral events. The patients with reduced-function alleles of *CYP2C19* (PMs and hetEMs) had a higher combined cardiocerebral risk than the patients with full-function alleles (homEMs) (7.5% vs 0.0%). The data supported previous studies[23] revealing that *CYP2C19* genotype is a key factor determining the response to clopidogrel in atherosclerotic patients.

Our study had several limitations. First, some of the patients did not receive follow-up endoscopy. The patients without symptoms who refused follow-up endoscopy were regarded as having no recurrent ulcers. Because peptic ulcer may be asymptomatic, the cumulative number of recurrent peptic ulcer by ITT analysis might be underestimated in both groups. Second, our findings relate only to clopidogrel monotherapy and this is not generalizable to most patients taking clopidogrel who are on dual antiplatelet therapy (low-dose aspirin and clopidogrel). Furthermore, the number of patients in this study was too small to make a robust

conclusion for the clinical impact of esomeprazole on cardiovascular events in clopidogrel users. Nonetheless, we showed that there were no differences in platelet aggregation before and 28 days after use of esomeprazole. This study was a randomized controlled trial investigating the effect of PPIs on the prevention of peptic ulcer in patients receiving clopidogrel monotherapy for atherosclerotic diseases.

In conclusion, esomeprazole plus clopidogrel is superior to clopidogrel alone in the prevention of recurrent peptic ulcer in atherosclerotic patients with a history of peptic ulcer. Esomeprazole does not influence the action of clopidogrel on platelet aggregation, at least when doses are widely separated.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at doi: 10.1053/j.gastro.2010.11.056.

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Reprint requests

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The registration number for this study is NCT01138969.

The statistical analysis of the entire data sets pertaining to efficacy (specifically primary and major secondary efficacy end points) and safety (specifically serious adverse events as defined in federal guidelines) have been confirmed independently by a biostatistician who is not employed by the corporate entity. The corresponding author had full access to all of the data and takes full responsibility for the veracity of the data and analysis.

Conflicts of interest

The authors disclose no conflicts.

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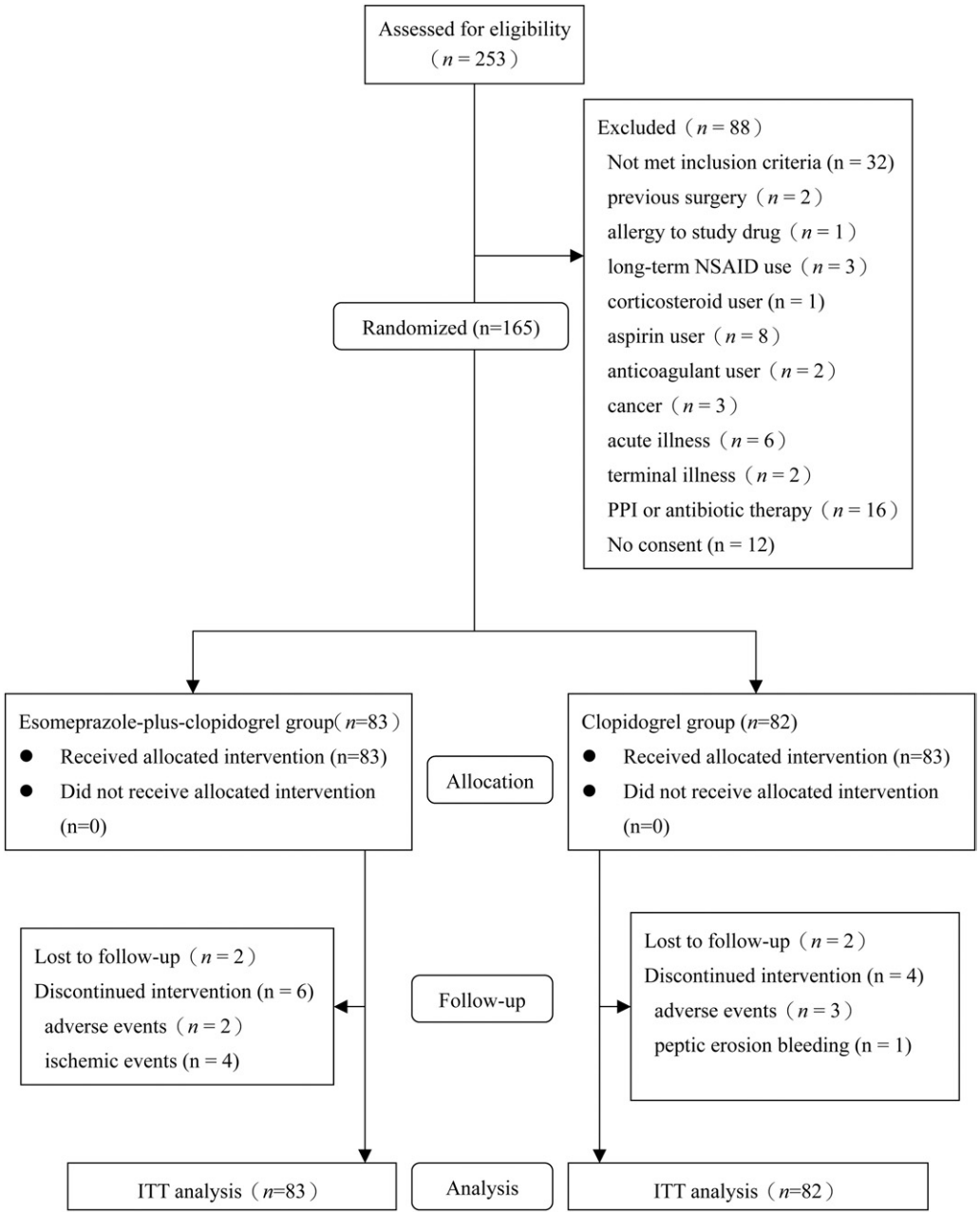
Supplementary Materials and Methods

ADP-induced platelet aggregation test was conducted to evaluate platelet function using a commercially available kit (ADP; Bio/Data Corp, Horsham, PA).[12] Room-temperature blood samples were processed within 2 hours of blood collection. Whole-blood specimens were centrifuged for 10 minutes at 200*g* to obtain platelet-rich plasma. Platelet-poor plasma was obtained on the remaining specimen by re-centrifugation at 2000*g* for 15 minutes. A platelet count was measured on the platelet-rich plasma and was adjusted to between $200 \times 10^3/\mu L$ and $300 \times 10^3/\mu L$ with platelet-poor plasma. Aggregation was performed in a PAP-4 Platelet Aggregometer (Bio/Data, Horsham, PA), which was first calibrated using platelet-rich plasma (0% aggregation) and platelet-poor plasma (100% aggregation). Aggregation was performed at 37°C in 0.2 mL of platelet-rich plasma in microvolume tubes and was initiated by adding ADP (stock 200 mmol/L) to final concentrations of up to 20 mmol/L. Aggregation response was expressed as a PPA at 5 minutes.[17]



Supplementary Figure 1. Disposition of patients.