Original Article

Long-term efficacy and safety of rabeprazole in patients taking low-dose aspirin with a history of peptic ulcers: a phase 2/3, randomized, parallel-group, multicenter, extension clinical trial

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(Received 10 January, 2015; Accepted 26 January, 2015; Published online 8 April, 2015)

A 24-week, double-blind, clinical trial of rabeprazole for the prevention of recurrent peptic ulcers caused by low-dose aspirin (LDA) has been reported, but trials for longer than 24 weeks have not been reported. The aim of this study is to assess the long-term efficacy and safety of rabeprazole for preventing peptic ulcer recurrence on LDA therapy. Eligible patients had a history of peptic ulcers on long-term LDA (81 or 100 mg/day) therapy. Patients with no recurrence of peptic ulcers at the end of the 24-week double-blind phase with rabeprazole (10- or 5-mg once daily) or teprenone (50 mg three times daily) entered the extension phase. Rabeprazole doses were maintained for a maximum of 76 weeks, including the double-blind 24-week period and the extension phase period (long-term rabeprazole 10- and 5-mg groups). Teprenone was randomly switched to rabeprazole 10 or 5 mg for a maximum of 52 weeks in the extension phase (newly-initiated rabeprazole 10- and 5-mg groups). The full analysis set consisted of 151 and 150 subjects in the long-term rabeprazole 10- and 5-mg groups, respectively, and the cumulative recurrence rates of peptic ulcers were 2.2 and 3.7%, respectively. Recurrent peptic ulcers were not observed in the newly-initiated rabeprazole 10- and 5-mg groups. No bleeding ulcers were reported. No clinically significant safety findings, including cardiovascular events, emerged. The use of long-term rabeprazole 10- and 5-mg once daily prevents the recurrence of peptic ulcers in subjects on low-dose aspirin therapy, and both were well-tolerated.

***Key Words*:** **low-dose aspirin, peptic ulcer, bleeding ulcer, serious adverse events, rabeprazole**

Low-dose aspirin (LDA) use reduces cardiovascular events by about 25% in comparison to non-use, but increases gastrointestinal events two- to five-fold.[1–7] A recent large-scale observational study conducted in Japan found that 35.7% of patients using LDA to prevent the occurrence of ischemic cardiac and cerebrovascular disease had gastroduodenal mucosal injuries (6.5% ulcers and 29.2% erosions), and the risk of peptic ulcers was particularly high in smokers and patients with *Helicobacter pylori* (*H. pylori*) infections.[8] Other factors found to increase the risk of gastrointestinal events include age greater than 70 years, history of upper gastrointestinal bleeding, concomitant use of nonsteroidal anti-inflammatory drugs (NSAIDs), and antithrombotic agents used alone or in combination with other antithrombotic drugs.[9–11] LDA-induced gastroduodenal mucosal injuries must be vigilantly managed because they are often asymptomatic and carry the risk of undetected bleeding.[12] Histamine H_2 receptor antagonists and proton pump inhibitors (PPIs) can be used with LDA to reduce the occurrence of ulcers and erosions. PPIs, which potently suppress acid secretion, are superior in this respect to histamine H_2 receptor antagonists.[8,13] Several published guidelines and review articles contain statements recommending concomitant PPI use for secondary prevention of gastroduodenal mucosal injury associated with LDA therapy.[14,15]

Rabeprazole, a PPI developed by Eisai Co., Ltd., exerts a rapid and potent inhibitory effect on gastric acid secretion.[16] The drug is efficacious in gastro-esophageal reflux disease (GERD) and other acid-related diseases.[17–22] Long-term use of rabeprazole was confirmed to be safe in studies of two to five-year maintenance therapy for GERD.[21,23–25] Rabeprazole was recently found to reduce the incidence of esophageal and gastroduodenal mucosal injury due to LDA therapy in healthy volunteers.[26,27] Furthermore, rabeprazole affects CYP2C19 metabolic enzymes less than other PPIs,[28] and it minimally inhibit the antiplatelet effects of LDA and clopidogrel.[29,30]

Our recent 24-week, double-blind, comparative study (PLANETARIUM study) with a mucosal protective agent as the control showed that rabeprazole (10 and 5 mg) was effective

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doi: 10.3164/jcbn.15-1

and safe in the prevention of peptic ulcer recurrence in LDA users (the cumulative recurrence rate of peptic ulcers at 24 weeks was 1.4% in the rabeprazole 10-mg group, 2.8% in the rabeprazole 5-mg group and 21.7% in the teprenone group). [31] Long-term Japanese data over more than one year are available for the similar PPIs, lansoprazole and esomeprazole,[32,33] but the data for rabeprazole extended only to 24 weeks.[31,34] Therefore, an extension phase study following the 24-week double-blind phase was performed to address this deficit. In the extension phase, the subjects with no ulcer recurrence at week 24 of the double-blind phase were given rabeprazole for another 28 to 52 weeks (for a total of 52 to 76 weeks of treatment).

Materials and Methods

The study was a phase 2/3, randomized, parallel-group, multicenter, extension study conducted from December 2011 to December 2013 at 62 medical institutions throughout Japan (ClinicalTrials.gov Identifier: NCT01398410). The protocol of the extension study was reviewed and approved concurrently with that of the preceding 24-week, double-blind study by the institutional review boards of the participating medical institutions. The subjects gave written, informed consent again before participating in the extension study. The study was conducted in compliance with the ethical principles grounded in the Declaration of Helsinki, as well as the Good Clinical Practice guideline of Japan.

Study design. As shown in Fig. 1, the 24-week, double-blind phase contained three groups that received rabeprazole 10 mg once daily, rabeprazole 5 mg once daily, or teprenone 50 mg three times daily. The subjects allocated to the rabeprazole 10- and 5-mg groups in the double-blind phase were maintained on the same doses of rabeprazole in the 28 to 52-week extension phase, i.e., subjects were treated with rabeprazole for a 52 to 76-week period consisting of the 24-week, double-blind phase and the extension phase (long-term rabeprazole 10- and 5-mg groups). The subjects allocated to the teprenone group in the double-blind phase were randomized to take rabeprazole 10- or 5-mg at a ratio of 1:1 in the 28 to 52-week extension phase (newly-initiated rabeprazole 10- and 5-mg groups). The subjects not consenting to enter the extension phase were allowed to conclude treatment at the end of the double-blind phase. The extension phase was concluded for all subjects when the last subject in the extension phase completed week 28. This meant that the subjects in the extension phase completed the study at a variety of times from weeks 28 to 52. The key code was maintained double-blind in the long-term rabeprazole 10- and 5-mg groups until July 11, 2013, and from this day on, the key code was opened only for personnel of Eisai, the sponsor, but kept blinded to the investigators, sub-investigators, clinical research coordinators, subjects, and all others. The key code break was necessary for submission of the 24-week double-blind data to the Pharmaceuticals and Medical Devices Agency (PMDA), the Japanese authority, to obtain approval for a new indication for rabeprazole. On the other hand, the extension phase of the newly-initiated rabeprazole 10- and 5-mg groups concluded with double-blinding maintained.

Subjects. Patients with the following conditions were eligible for the double-blind phase:[31] outpatients at least 20 years of age who were on LDA (81 or 100 mg/day) therapy for preventing thrombosis/embolization in cases of angina pectoris, myocardial infarction, an ischemic cerebrovascular disorder, or similar condition and who had a history of a gastric or duodenal ulcer but without a current acute gastroduodenal mucosal lesion, gastric ulcer, or duodenal ulcer, upper gastrointestinal hemorrhage, reflux esophagitis (modified Los Angeles Classification[35,36] Grade A or above), or Barrett's esophagus. Ulcer history was determined by an endoscopy central review panel.[31] Subjects with no ulcer recurrence at the final endoscopy of the double-blind phase (week 24) were entered into the extension phase if the underlying cardiovascular or cerebrovascular disease was stable and continued treatment with the same LDA dosage regimen was necessary.

Patients were eligible for study participation regardless of whether they were *H. pylori*-positive or -negative. Presence of *H. pylori* infection and CYP2C19 genotyping information were determined as previously described.[31]

Treatment. The study medications were prepared such that the active drugs were indistinguishable in appearance from their corresponding placebo. In the extension phase, following a double-dummy method, subjects in the rabeprazole 10-mg group received a rabeprazole 10 mg tablet and a rabeprazole 5 mg placebo tablet in the morning, while subjects in the rabeprazole 5-mg group received a rabeprazole 5 mg tablet and a rabeprazole 10 mg placebo tablet in the morning.

As in the double-blind phase, subjects in the extension phase

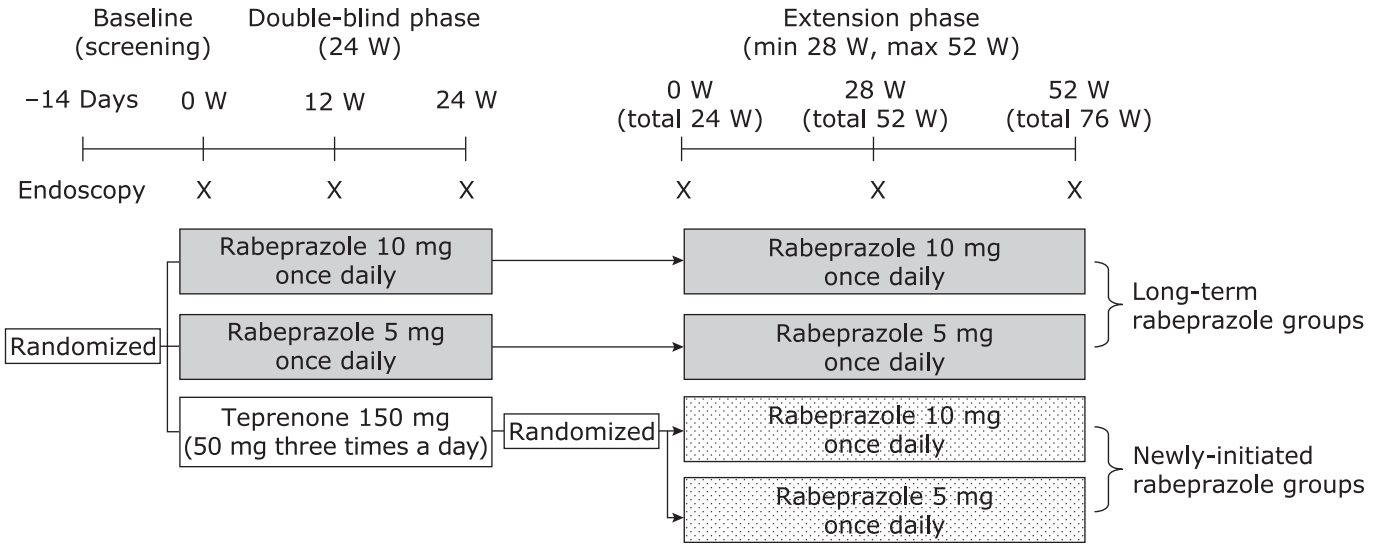

Fig. 1. Study design. The total number of weeks indicates the sum of the two treatment periods in the double-blind phase and the extension phase of the long-term rabeprazole groups. W indicates weeks.

were not allowed to take drugs indicated for improving ulcers or gastrointestinal symptoms (e.g., PPIs not used in the study, histamine H_2 receptor antagonists, prokinetics, mucosal protective agents, antacids, prostaglandin agents, traditional Chinese herbal medications) or atazanavir sulphate and rilpivirine hydrochloride, which are contraindicated for concomitant use with rabeprazole. The concomitant use of non-LDA anti-platelet drugs or anti-coagulants was permitted.

To maintain independence, the tasks of study medication allocation and key code retention were assigned to Bell Medical Solutions, Inc. (Tokyo, Japan), and the role of subject enrolment center was assigned to EPS Corporation (Tokyo, Japan).[31]

Assessments. The subjects in the extension phase made hospital visits every four weeks. Upper endoscopy was performed in the extension phase at week 28 and week 52 or at discontinuation. If there were findings suggestive of upper gastrointestinal hemorrhage or intolerable upper gastrointestinal symptoms, additional upper endoscopy was performed at the discretion of the investigator. If gastric or duodenal ulcers were observed, the case was treated as a recurrence, and study participation was terminated for that subject. Gastric and duodenal ulcers were rated based on the Sakita-Miwa classification as:[37] active stage (1, 2), healing stage (1, 2), or scar stage (1, 2). The Forrest classification[38] was used to assess the presence or absence of bleeding if an ulcer was observed: type I (a, b) and type II (a, b) indicating bleeding, and type III indicating no bleeding. Reflux esophagitis was assessed according to the modified Los Angeles Classification as: O (without mucosal breaks) and A to D (with mucosal breaks). The modified Lanza score was used to assess the severity of gastric or duodenal mucosal injury,[39,40] based on which gastric findings were rated from grade 0 (no erosion, no ecchymosis) to 5 (ulcer), and duodenal findings from grade 0 (no erosion, no ecchymosis) to 4 (ulcer). Laboratory tests were conducted and vital signs were measured every 4 weeks. At each visit, subjects were also surveyed for compliance with the study medications and LDA, the types of concomitant medications they were taking, and the occurrence of any adverse events.

Efficacy evaluations. Efficacy was evaluated according to the following measures. The cumulative recurrence rate of gastric or duodenal ulcers at the final evaluation (Kaplan-Meier life-table estimates) was included in the main analysis of efficacy. An ulcer was defined as a mucosal break measuring ≥3 mm along its longest diameter with a white coating.[31] The presence or absence of ulcer recurrence was determined by the endoscopy central review panel (panel of three endoscopy specialists: KH, MK, and MF) who were blinded to the investigators' assessments, based on endoscopy photos submitted by each of the institutions. In cases of ulcer recurrence, the stage classification was assessed (healing stage 2 or above). The following measures were included in the sub-analysis of efficacy: cumulative incidence of bleeding ulcers at final evaluation (Forrest Classification, type IIb or above), incidence of reflux esophagitis at final evaluation (Grade A or above based on the modified Los Angeles Classification), and percentage of subjects showing improvement/worsening of gastric mucosal injury based on modified Lanza scores (improvement was defined as a decrease of at least 1 grade and worsening as an increase of at least 1 grade at the final assessment compared to baseline).

Safety evaluations. Safety was evaluated based on adverse events, laboratory tests, and vital signs. The incidences of treatment-emergent adverse events (TEAEs), serious adverse events, and treatment-related adverse events were calculated in each treatment group. TEAEs were defined as any untoward or unintended signs, symptoms or diseases, and/or laboratory abnormalities that occurred after administration of a study drug. Serious adverse events were defined as follows: deaths, life-threatening events, hospitalization or prolongation of hospitalization for treatment, permanent or marked disorder/dysfunction, congenital disease or abnormality, other events of medical importance. Treatment-related adverse events were defined as any adverse events which were judged to be related to the study drug. The incidences of TEAEs were evaluated by age and by whether a non-LDA anti-platelet drug or anticoagulant was used. Serious adverse events related to cardiovascular events (according to whether clopidogrel was used), hemorrhage-related serious adverse events, adverse events related to bone fractures, and adverse events related to pneumonia were evaluated as significant adverse events in the context of combination therapy of LDA with PPI.

Statistical analysis. The number of subjects required for randomization in the double-blind phase was 150 per group or 450 totals in the three groups.[31] The sample sizes of the extension phase were set at 110 in each of the long-term rabeprazole 10- and 5-mg groups (2 groups, 220 subjects) and 40 each in the newly-initiated rabeprazole 10- and 5-mg groups (2 groups, 80 subjects) to account for subjects developing a recurrent ulcer or discontinuing the double-blind phase and subjects not consenting to participate in the extension phase.

Efficacy analyses were performed on the full analysis set. The full analysis set was defined as all subjects who received at least one dose of rabeprazole, had results of at least one post-initiation endoscopic assessment available, and showed no ulcers on baseline endoscopy. Efficacy was evaluated separately in the long-term groups and newly-initiated groups because of expected differences in the likelihood of these groups developing ulcer recurrence. The safety analysis set was defined as all subjects who received at least one dose of rabeprazole. Safety data of the long-term rabeprazole 10- and 5-mg groups were combined with those of the newly-initiated rabeprazole 10- and 5-mg groups to allow evaluation by dose for the safety analyses.

Kaplan-Meier estimates were used to calculate the cumulative recurrence rates of gastric or duodenal ulcers, and 95% confidence intervals were also calculated. The cumulative incidence of bleeding ulcers was similarly analyzed. The frequencies and summary statistics of the other efficacy and safety endpoints were calculated according to the type and scale of the particular measure. TEAEs were tabulated using ver. 15.1 of the Medical Dictionary for Regulatory Activities (MedDRA). Ischemic heart disease, cardiac failure, and cerebrovascular disorders in the standardized MedDRA queries (SMQs) were included in "cardiovascular-related adverse events". Similarly, hemorrhages in SMQs were included in "hemorrhage-related adverse events". All kinds of fractures were included in "fracture-related adverse events". Finally, aspiration pneumonia often caused by an incompetent swallowing mechanism was excluded from tabulations of pneumonia. All statistical analyses were performed using SAS software, ver. 9.2 (SAS Institute, NC). Additionally, the following post-hoc analyses were performed; for the cumulative recurrence rate of gastric or duodenal ulcers, the log-rank test was used to check superiority of the rabeprazole 10-mg group as compared with the rabeprazole 5-mg group. Stratified analysis of modified Lanza scores by baseline (grade 0, grade ≥1) was added. Fisher's exact test was used to compare the rabeprazole 10- and 5-mg groups in the safety analysis. *P* values of less than 0.05 were considered significant.

Results

Demographics. The demographic and clinical characteristics of the safety analysis set are shown in Table 1. No characteristics differed between the rabeprazole 10- and 5-mg groups. The heterogeneities in the history of drugs for ulcer prevention, the presence of *H. pylori*, and eradication history were similar between the groups.

The long-term rabeprazole 10- and 5-mg groups contained 158 and 156 subjects, respectively, at the start of the double-blind phase, and 16 and 18 of these subjects, respectively, were dis-

doi: 10.3164/jcbn.15-1

Table 1. Demographic and clinical characteristics (safety analysis set)

	Rabeprazole 10 mg (*n* = 204)	Rabeprazole 5 mg (*n* = 201)
Male, *n* (%)	152 (74.5)	153 (76.1)
Mean age ± SD (min–max), years	70.1 ± 9.3 (40–86)	69.4 ± 8.5 (35–90)
Ischemic conditions,[a] *n* (%)		
Angina	81 (39.7)	88 (43.8)
Myocardial infarction	42 (20.6)	36 (17.9)
Ischemic cerebrovascular disease	98 (48.0)	99 (49.3)
CABG or PTCA	67 (32.8)	65 (32.3)
Other	14 (6.9)	9 (4.5)
Aspirin dose		
81 mg	19 (9.3)	16 (8.0)
100 mg	185 (90.7)	185 (92.0)
Duration of Aspirin use, *n* (%)		
<2 years	49 (24.0)	50 (24.9)
≥2 years	155 (76.0)	151 (75.1)
Concomitant use of antithrombotic drug other than aspirin, *n* (%)	48 (23.5)	42 (20.9)
Helicobacter pylori status, *n* (%) (Anti-*H. pylori* IgG antibodies)		
Positive	90 (44.1)	92 (45.8)
Negative (with history of eradication)	71 (34.8)	57 (28.4)
Negative (without history of eradication)	43 (21.1)	52 (25.9)
History of ulcers, *n* (%)		
Gastric	123 (60.9)	140 (69.7)
Duodenal	79 (39.1)	61 (30.3)
None	2	0
History of bleeding ulcers, *n* (%)		
Gastric	10 (4.9)	12 (6.0)
Duodenal	8 (3.9)	7 (3.5)
History of erosive esophagitis, *n* (%)	25 (12.3)	35 (17.4)
Mucosal injury at baseline with Modified Lanza score ≥grade 1, *n* (%)		
Gastric	56 (27.5)	51 (25.4)
Duodenal	7 (3.4)	2 (1.0)
History of drug for prevention of ulcer, *n* (%)		
PPIs	94 (46.1)	99 (49.3)
H_2 receptor antagonists	49 (24.0)	54 (26.9)
Mucosal protective agents	30 (14.7)	38 (18.9)
CYP2C19 genotypes, *n* (%)		
Homo EM	79 (38.7)	65 (32.3)
Hetero EM	90 (44.1)	104 (51.7)
PM	35 (17.2)	32 (15.9)
Current smoking, *n* (%)	29 (14.2)	32 (15.9)
Current alcohol consumption, *n* (%)	116 (56.9)	107 (53.2)

For the newly-initiated rabeprazole group, data of age, aspirin dose, concomitant use of antithrombotic drug, modified Lanza score, current smoking and current alcohol consumption were taken at the start of the extension phase. [a]Multiple choices allowed. CABG, coronary artery bypass grafting; PTCA, percutaneous transluminal coronary angioplasty; CYP2C19, cytochrome P450 isoenzyme; EM, extensive metabolizer; PM, poor metabolizer.

continued (Fig. 2a). A total of 125 and 111 of these subjects, respectively, entered the extension phase, and 20 and 8 of these subjects, respectively, were discontinued (Fig. 2a). The newly-initiated rabeprazole 10- and 5-mg groups consisted of 47 and 45 subjects, respectively, who received teprenone in the double-blind phase and were randomized to 10 or 5 mg of rabeprazole in the extension phase, and 4 and 5 of these subjects, respectively, were discontinued (Fig. 2a). In both the double-blind and extension phases, subjects were discontinued primarily for adverse events or subject's choice.

Analysis sets are shown in Fig. 2b. Subjects were excluded from the full analysis set primarily for not having received the study medications, lacking any evaluable endoscopy data after the start of rabeprazole treatment, and for being ineligible due to having an ulcer at baseline.

In the safety analysis set, the duration of study drug exposure (mean ± SD, min–max) was 383.8 ± 152.0 days (2–533 days) in the rabeprazole 10-mg group and 372.7 ± 163.2 days (4–538 days) in the rabeprazole 5-mg group. The mean compliance with study medication was 99.4 and 99.2% in the 10- and 5-mg rabeprazole groups, respectively. There were two subjects in the rabeprazole 5-mg group with less than 75% compliance with the study medication.

Efficacy

Ulcer recurrence and incidence of bleeding ulcers. Fig. 3 shows the Kaplan-Meier curves of the cumulative recurrence rates of peptic ulcers in the long-term rabeprazole 10- and 5-mg groups. At total week 76, the cumulative recurrence rates (%, 95% CI range, number of subjects) in the long-term groups were 2.2% (0.72–6.75, three subjects) in the 10-mg group and 3.7% (1.53–8.64,

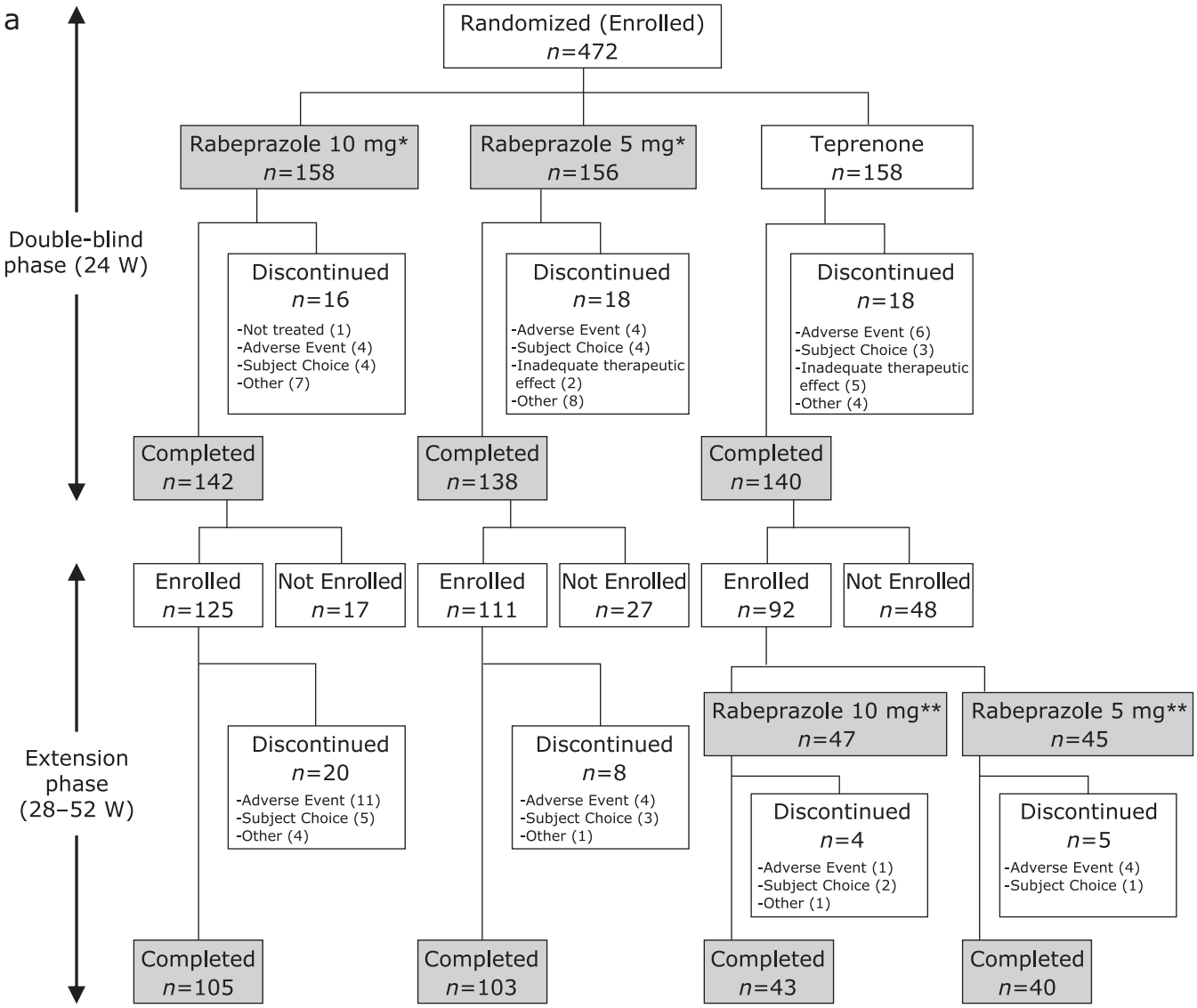

Fig. 2. Subject disposition (a) and analysis sets (b). *Long-term rebeprazole groups, **newly-initiated rebeprazole groups.

doi: 10.3164/jcbn.15-1

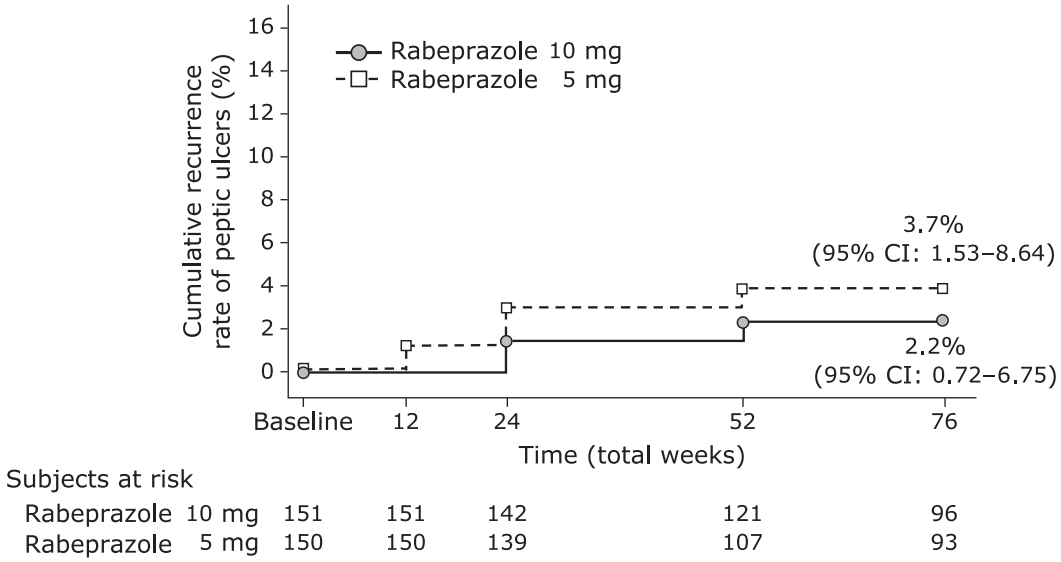

Fig. 3. Cumulative recurrence rates of peptic ulcers over 76 weeks in the long-term rabeprazole groups (Kaplan-Meier estimates, full analysis set).

Table 2. Details of subjects with ulcer recurrence in the long-term groups (full analysis set)

Long-term group	Age (years)/ Sex	LDA dose/ LDA duration	Ischemic condition	Other anti-thromboticdrugs/ *H. pylori* status	History of bleeding ulcers/ Erosive esophagitis	History of drug/ CYP2C19 genotype	Smoking/ Alcohol habit	Time (days)* of ulcer recurrence/ Ulcer site	Ulcer Grade/ Size/Number	Ulcer with bleeding/ Erosive esophagitis/ GI symptoms
Rabeprazole 10 mg	64 Male	81 mg 2–5 years	Angina	No Positive	No No	No Hetero EM	Yes Yes	161 Gastric	H2 stage 5–15 mm Multiple	No No No
Rabeprazole 10 mg	75 Male	100 mg ≥5 years	Angina PTCA	Yes (ticlopidine) Positive	No No	Famotidine Homo EM	No Yes	168 Gastric	H1 stage 3–5 mm Single	No No No
Rabeprazole 10 mg	64 Male	100 mg 2–5 years	Angina PTCA	Yes (warfarin, clopidogrel) Negative	No No	Rabeprazole Homo EM	No No	364 Gastric	H1 stage 3–5 mm Single	No No No
Rabeprazole 5 mg	55 Male	81 mg ≥5 years	Other	No Negative	No Yes	No Hetero EM	No Yes	78 Gastric	A1 stage 3–5 mm Multiple	No No No
Rabeprazole 5 mg	67 Male	100 mg ≥5 years	Ischemic cerebro-vascular disease	No Positive	No No	Rabeprazole PM	No Yes	91 Gastric	A2 stage ≥15 mm Multiple	No No No
Rabeprazole 5 mg	74 Female	81 mg ≥5 years	Ischemic cerebro-vascular disease	No Negative	No Yes	Ranitidine Hetero EM	No No	161 Gastric	H1 stage 5–15 mm Single	No No No
Rabeprazole 5 mg	70 Male	100 mg ≥5 years	Ischemic cerebro-vascular disease	No Negative	No No	Lansoprazole Hetero EM	No No	164 Gastric	A2 stage 5–15 mm Single	No No No
Rabeprazole 5 mg	59 Female	100 mg 2–5 years	Ischemic cerebro-vascular disease	Yes (warfarin) Negative	No No	Rabeprazole Hetero EM	No Yes	361 Gastric	H1 stage 3–5 mm Single	No No Yes (Stomach discomfort)

LDA, low-dose aspirin; A1/A2 stage, active 1/2 stage; H1/H2 stage, healing 1/2 stage. *Days were counted from the start of the 24-week double-blind phase.

five subjects) in the 5-mg group (Kaplan-Meier estimates, full analysis set). A significantly better preventive effect was not seen in the 10-mg group compared to the 5-mg group ($p = 0.440$). After entering the extension phase, one subject in each of the rabeprazole 10- and 5-mg groups developed ulcer recurrence. In each patient, recurrence occurred at total week 52. No bleeding ulcers were reported in either the long-term rabeprazole 10- or 5-mg group at any time throughout the double-blind and extension phases (i.e., to total week 76).

In the newly-initiated rabeprazole groups, no gastric or duodenal ulcers and no bleeding ulcers were reported in either the rabeprazole 10- or 5-mg group at any time during the extension phase (i.e., to week 52).

Details of subjects with ulcer recurrence in the long-term groups. Background information and endoscopic details about all subjects with ulcer recurrence are presented in Table 2. All subjects with a recurrent ulcer belonged to the long-term rabeprazole groups. No subject in the newly-initiated rabeprazole groups had a recurrent ulcer. The subjects with a recurrent ulcer had one or more previously-reported risk factors for LDA ulcers (i.e., age ≥70 years, *H. pylori*-positive, history of upper gastrointestinal tract bleeding, use of anticoagulants, smoking, alcohol consumption).

Erosive esophagitis. The incidences of reflux esophagitis (number of subjects, grade) in the long-term rabeprazole groups at the final evaluation were 0.7% (one subject, grade A) in the 10-mg group and 0% (zero subjects) in the 5-mg group.

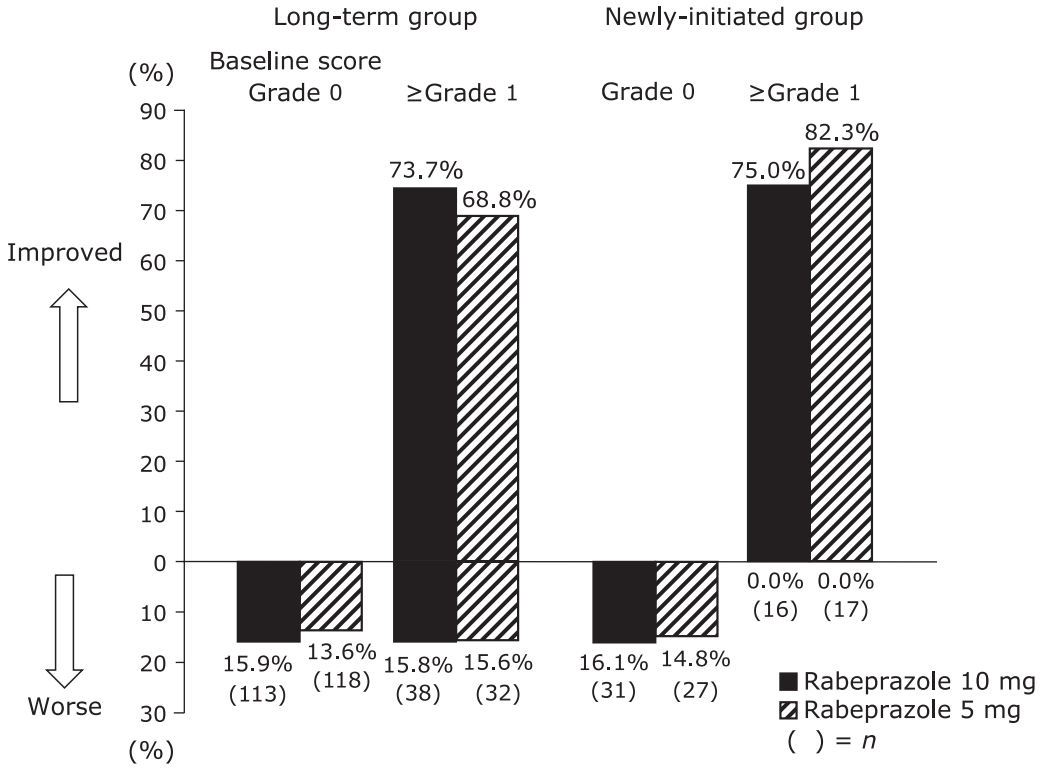

Fig. 4. Gastric mucosal damage (full analysis set). The percentages of subjects with improvement/worsening of gastric mucosal injury based on modified Lanza scores at the final assessment compared to baseline. Subjects in each of the rabeprazole 10- and 5-mg groups were separated in two sub-groups with grade 0 or grade ≥1 at baseline.

The incidences of reflux esophagitis in the newly-initiated rabeprazole groups at the final evaluation were 2.1% (one subject, grade A) in the 10-mg group and 0% (zero subjects) in the 5-mg group.

Severity scores of gastric damage. The percentages of subjects showing improvement/worsening of gastric mucosal injury based on modified Lanza scores are shown in Fig. 4, where subjects in each of rabeprazole 10- and 5-mg groups were separated in two sub-groups with grade 0 or grade ≥1 at baseline. As the figure shows, the percentages of subjects showing improvement/worsening were similar between the 10-mg group and the 5-mg group, in both the long-term and newly-initiated rabeprazole groups. On the other hand, the severity score of duodenal damage at baseline was grade 0 in most subjects.

Safety. In the safety evaluation, the data of the long-term groups and those of the newly-initiated groups were combined and analyzed by rabeprazole doses.

Treatment-emergent adverse events (TEAEs), treatment-related adverse events. TEAEs and treatment-related adverse events are summarized in Table 3.

The incidences of TEAEs were 83.8% in the rabeprazole 10-mg group and 77.1% in the rabeprazole 5-mg group ($p = 0.1031$). In decreasing order, the most common adverse events were nasopharyngitis, constipation, and diarrhoea in the rabeprazole 10-mg group and nasopharyngitis, back pain, and contusion in the rabeprazole 5-mg group.

The incidences of treatment-related adverse events were 13.7% in the rabeprazole 10-mg group and 8.0% in the rabeprazole 5-mg group ($p = 0.0785$). The treatment-related adverse events with an incidence of at least 2% were constipation only (2.5%) in the rabeprazole 10-mg group and none in the 5-mg group.

The incidences of adverse events by age (<70 years, ≥70 years) were 82.6% (76 of 92 subjects) and 84.8% (95 of 112 subjects), respectively, in the rabeprazole 10-mg group and 78.7% (74 of 94 subjects) and 75.7% (81 of 107 subjects), respectively, in the rabeprazole 5-mg group. The incidences did not differ substantially in these age categories. The incidences of adverse events by whether a non-LDA anti-platelet drug or anticoagulant was used (used, not used) were 81.3% (39 of 48 subjects) and 84.6% (132 of 156 subjects), respectively, in the rabeprazole 10-mg group and 83.3% (35 of 42 subjects) and 75.5% (120 of 159 subjects), respectively, in the rabeprazole 5-mg group. Incidences were not consistently higher in the subjects using non-LDA antithrombotics.

Serious adverse events. Serious adverse events are summarized in Table 3.

The incidences of serious adverse events were 14.7% in the rabeprazole 10-mg group and 16.4% in the rabeprazole 5-mg group ($p = 0.6819$). One death (completed suicide) was reported in the rabeprazole 5-mg group but was considered causally unrelated to the study medication. The serious adverse events reported in at least two subjects were gastric cancer (four subjects) in the rabeprazole 10-mg group and angina pectoris (three subjects), cataract (two subjects), and coronary artery restenosis (two subjects) in the rabeprazole 5-mg group. The treatment-related serious adverse events were acute cholecystitis (one subject) and gastrointestinal hemorrhage (one subject) in the rabeprazole 10-mg group.

Significant adverse events. The significant adverse events are summarized in Table 3. The incidences of cardiovascular-related serious adverse events in the safety analysis set were 2.0% (4/204) in the rabeprazole 10-mg group and 5.5% (11/201) in the rabeprazole 5-mg group ($p = 0.0697$). In detail, for the subjects who took concomitant clopidogrel, the incidences in the rabeprazole 10- and 5-mg groups were 0% (0/19) and 30.0% (6/20), respectively. For the subjects who did not take concomitant clopidogrel,

doi: 10.3164/jcbn.15-1

Table 3. Treatment-emergent adverse events (safety analysis set)

	Rabeprazole 10 mg (*n* = 204)	Rabeprazole 5 mg (*n* = 201)
Any treatment-emergent adverse events (TEAEs), *n* (%)	171 (83.8)	155 (77.1)
≥5% TEAEs, *n* (%)		
Nasopharyngitis	57 (27.9)	64 (31.8)
Constipation	16 (7.8)	9 (4.5)
Diarrhoea	16 (7.8)	11 (5.5)
Back pain	13 (6.4)	14 (7.0)
Eczema	12 (5.9)	6 (3.0)
Upper respiratory tract infection	10 (4.9)	10 (5.0)
Contusion	7 (3.4)	14 (7.0)
Treatment-related adverse events, *n* (%)	28 (13.7)	16 (8.0)
≥2% Treatment-related adverse events, *n* (%)		
Constipation	5 (2.5)	0 (0.0)
Serious adverse events (SAEs), *n* (%)	30 (14.7)	33 (16.4)
Death	0 (0.0)	1 (0.5)
Other SAEs*	30 (14.7)	32 (15.9)
Hospitalization	28 (13.7)	26 (12.9)
Persistent or significant disability/incapacity	0 (0.0)	1 (0.5)
Other important medical events	6 (2.9)	10 (5.0)
≥2 serious adverse events, *n* (%)		
Gastric cancer	4 (2.0)	1 (0.5)
Angina pectoris	1 (0.5)	3 (1.5)
Cataract	1 (0.5)	2 (1.0)
Coronary artery restenosis	0 (0.0)	2 (1.0)
Treatment-related serious adverse events, *n* (%)	2 (1.0)	0 (0.0)
Acute cholecystitis	1 (0.5)	0 (0.0)
Gastrointestinal hemorrhage**	1 (0.5)	0 (0.0)
Significant adverse events, *n* (%)		
Cardiovascular-related serious adverse events	4 (2.0)	11 (5.5)
Hemorrhage-related serious adverse events	3 (1.5)	2 (1.0)
Fracture-related adverse events	6 (2.9)	7 (3.5)
Pneumonia-related adverse events	0 (0.0)	0 (0.0)

*Multiple choices allowed. **No gastric or duodenal ulcer recurrence was reported.

the incidences were 2.2% (4/185) and 2.8% (5/181), respectively. Thus, no relationship was identified between rabeprazole dose and clopidogrel use.

The incidences of hemorrhage-related serious adverse events were 1.5% (3/204) in the rabeprazole 10-mg group and 1.0% (2/201) in the rabeprazole 5-mg group ($p = 1.000$). Subdural hematoma (one subject in the rabeprazole 10-mg group) was the only cerebrovascular event.

A fracture-related adverse event occurred in six subjects (2.9%) in the rabeprazole 10-mg group and seven subjects (3.5%) in the rabeprazole 5-mg group ($p = 0.7858$). A fracture-related serious adverse event occurred in three subjects in the rabeprazole 10-mg group (spinal compression fracture, femoral neck fracture, lower limb fracture) and in two subjects in the rabeprazole 5-mg group (spinal compression fracture, femoral neck fracture). A thoracic vertebral fracture (one subject in the rabeprazole 10-mg group) was the only event assessed as treatment-related.

Pneumonia was not reported in either group.

Discussion

The prevention of peptic ulcer recurrence by rabeprazole in patients taking LDA had not previously been investigated in a long-term (more than 24 weeks), randomized, clinical trial. The present long-term administration trial evaluated the efficacy and safety of treatment with rabeprazole for up to 76 weeks (total weeks of the double-blind and extension phases) in subjects who showed no ulcer recurrence until the end of the 24-week double-blind phase.

The findings from this extension study were as follows: (1) once daily rabeprazole 10 and 5 mg were efficacious for preventing peptic ulcer recurrence for up to 76 weeks in LDA users with a history of ulcers; (2) No cases of bleeding ulcer were seen not just in the rabeprazole 10-mg group (standard dose in Japan), but also in the rabeprazole 5-mg group; and (3) the use of long-term rabeprazole and LDA posed no safety concerns even in subjects taking clopidogrel, warfarin, and multiple other antithrombotic drugs (who accounted for 23.5% of cases in the rabeprazole 10-mg group and 20.9% of cases in the rabeprazole 5-mg group).

Recently, long-term studies of LDA + PPI using lansoprazole 15 mg (study from Japan)[32] and esomeprazole 20 mg (study from Japan, Korea and Taiwan)[33] were reported (lansoprazole 15 mg is half dose and esomeprazole 20 mg is standard dose in Japan, respectively). The cumulative occurrence rates in these studies [3.7% for lansoprazole (361 days) and 1.7% for esomeprazole (48 weeks)] were similar to the present cumulative recurrence rates of 2.2% in the long-term rabeprazole 10-mg group and 3.7% in the long-term rabeprazole 5-mg group. This finding shows that the ulcer recurrence-preventing effect of rabeprazole is well-maintained for long periods. The eight subjects who developed ulcer recurrence in the present study had at least one previously-reported risk factor for LDA-induced ulcers,[8–11] but no common risk factor contributing to these recurrences was identified, possibly due to the small recurrence number of cases.

The incidence of TEAEs was about 80% in the rabeprazole 10- and 5-mg groups. In 52-week studies of rabeprazole for GERD maintenance therapy, the incidences of adverse events were also around 80%, with the commonly reported adverse events being diarrhoea, nausea, abdominal pain, rhinitis, pharyngitis, and headache,[41–43] which were similar to those in the present study. The incidences of serious adverse events (about 15%) in the present study were also comparable to those associated with GERD maintenance therapy. Hence, the types and frequencies of adverse events in the present study were comparable to those in previous clinical studies of rabeprazole without LDA therapy.

When taken together, clopidogrel and PPIs compete for CYP2C19, which reduces clopidogrel efficacy and consequently increases cardiovascular events.[44,45] However, in the prospective COGENT study of omeprazole, concomitant PPI and clopidogrel use reduced upper gastrointestinal bleeding without increasing cardiovascular events, leading to the conclusion that the two drugs can be used safely together.[46] A cross-over study of rabeprazole and omeprazole in Japanese patients receiving aspirin and clopidogrel therapy due to prior percutaneous coronary intervention showed that omeprazole significantly reduced the antiplatelet effect of clopidogrel, and this effect on clopidogrel was stronger than that of rabepazole.[30] Moreover, recent reports found that, in dual antiplatelet therapy with aspirin and clopidogrel, rabeprazole did not significantly affect the platelet aggregability of LDA and clopidogrel[29,47,48] or increase cardiovascular events.[49] In the present study, about 95% of all subjects used LDA for secondary prevention and 9.6% ($n = 39$) of all subjects had concomitant administration of clopidogrel. Although the present incidence of serious cardiovascular events in the subjects who used clopidogrel (15.4%, 6/39) was higher than that in the subjects not taking clopidogrel (2.5%, 9/366) in the combined rabeprazole groups (10 and 5 mg), no significant tendencies were identified that suggested an interaction between rabeprazole dose and clopidogrel use. The incidence of serious cardiovascular events (3.7%, 15 of 405 subjects) in the combined rabeprazole groups (10 and 5 mg) did not exceed the 6.7% (per year) incidence of serious cardiovascular events identified in a meta-analysis of aspirin in secondary prevention.[50]

Hemorrhagic events require special care in clinical practice. In addition to gastrointestinal bleeding, intracranial bleeding is a notable adverse drug reaction to LDA.[51] The 1.2% incidence (5 of 405 subjects) of serious hemorrhage-related adverse events in the combined rabeprazole groups (10 and 5 mg) did not differ greatly from the incidence of severe bleeding in LDA users overall (5.58 per 1,000 persons/year).[51] Subdural hematoma, one kind of intracranial bleeding, occurred in only one subject in the present study (incidence of 0.25% in the 10- and 5-mg groups combined). Therefore, there were no signs suggesting that rabeprazole plus LDA promoted hemorrhage.

A prospective cohort study reported that chronic use of PPIs was associated with increased risk of hip fracture, particularly among women with a history of smoking.[52] A nested case-control study and a meta-analysis indicated that long-term PPI therapy increased the risk of hip fracture (adjusted odds ratio 1.44[53] and relative risk ratio 1.30,[54] respectively), but other studies did not find a causal relationship between the use of PPI and an increased risk of bone fracture.[55,56] The incidence of all types of fracture-related adverse events in the combined rabeprazole groups (10 and 5 mg) was 3.2% (13 of 405 subjects). The incidence of fractures in the present long-term study was not high in the study population, which had a mean age of 70 years (and a maximum age of 90 years), especially considering that the prevalence of osteoporosis, femoral neck fractures, and vertebral body fractures in Japan is much higher in people at least 60 years old.[57,58]

Patients beginning to take PPIs were found to be at increased risk of community-acquired pneumonia,[59] but no subject in the present study developed pneumonia.

This study has several limitations. First, no comparator was used. Although the use of the comparator teprenone in the 24-week double-blind phase facilitated strict comparison, it was not ethically possible to establish a placebo or placebo-like control group for the longer-term investigation. Second, blinding was compromised. Since the data of the double-blind phase were submitted to the PMDA (Japanese regulatory authority) before the completion of the extension phase, the key codes for the long-term rabeprazole groups were unmasked in the extension phase to personnel of the sponsor, Eisai, alone. However, blinding was maintained for the investigators and subjects in the long-term rabeprazole groups, and double-blinding was maintained for the newly-initiated rabeprazole groups throughout the study. These actions minimized bias and ensured data reliability.

In conclusion, the findings of this extension study indicate that long-term rabeprazole prevents ulcer recurrence very safely and efficaciously in LDA users.

Acknowledgments

The authors would like to thank all contributing members and the sponsor, Japan/Asia Clinical Research Product Creation Unit of Eisai Co., Ltd., Tokyo, Japan and the project members of Mediscience Planning Inc., Tokyo, Japan for their contribution to study monitoring.

This study was funded by Eisai Co., Ltd., Tokyo, Japan. Writing support was provided by Eisai. Data management and analyses were undertaken by Eisai.

Members of the PLANETARIUM (Prevention of recurrent gastric or duodenal ulcers caused by Low-dose AspiriN with rabeprazolE Treatment -A multicenter, RandomIzed, parallel-group, doUble-blind, coMparative trial-) study group[31]

Guarantor of the article: Kazuma Fujimoto.

Author contributions:

Mitsuhiro Fujishiro, as an endoscopy specialist, was a member of the endoscopy central review panel, and was involved in protocol planning, data interpretation, and writing and editing the original paper. Kazuhide Higuchi and Mototsugu Kato, as endoscopy specialists, were involved in protocol planning and data interpretation, and were members of the endoscopy central review panel. Ryuichi Iwakiri, Toshio Watanabe, and Toshihisa Takeuchi were involved in protocol planning, patient recruitment, and data interpretation. Tetsuo Arakawa and Yoshikazu Kinoshita, as specialists in gastroenterology, were involved in protocol planning, implementation and overall coordination of the study, and data interpretation. Yasushi Okada and Hisao Ogawa, as cerebrovascular and cardiovascular specialists, were involved in protocol planning, implementation and overall coordination of the study, and data interpretation. Nobuyuki Sugisaki was the sponsor's (Eisai Co., Ltd.) employee in charge of this study. Kazuma Fujimoto, as the principal investigator, had overall responsibility for the study. All authors reviewed this article and approved the final version of the manuscript.

The PLANETARIUM study group contributed to acquisition of data. All members introduced the patients to the experiments, received the agreements of all participating patients.

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doi: 10.3164/jcbn.15-1

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Abbreviations

CABG	coronary artery bypass grafting
CYP2C19	cytochrome P450 isoenzyme
EM	extensive metabolizer
LDA	low-dose aspirin
MedDRA	Medical Dictionary for Regulatory Activities
PM	poor metabolizer
PMDA	Pharmaceuticals and Medical Devices Agency
PTCA	percutaneous transluminal coronary angioplasty
PPI	proton pump inhibitor
SMQs	standardized MedDRA queries
TEAE	treatment-emergent adverse event

Conflict of Interest

Mitsuhiro Fujishiro has served in speaking and teaching commitments for Eisai Co., Ltd. Kazuhide Higuchi has served in speaking and teaching commitments for Eisai Co., Ltd. and Daiichi Sankyo Company, Ltd. and has received scholarship grants from Eisai Co., Ltd., and Daiichi Sankyo Company, Ltd. Mototsugu Kato has served in speaking and teaching commitments for Eisai Co., Ltd., Daiichi Sankyo Company, Ltd., Takeda Pharmaceutical Co., Ltd., Otsuka Pharmaceutical Co., Ltd., and AstraZeneca K.K. and has received scholarship grants from Eisai Co., Ltd., Takeda Pharmaceutical Co., Ltd., Daiichi Sankyo Company, Ltd., AstraZeneca K.K., and Astellas Pharma Inc. Yoshikazu Kinoshita has served in speaking and teaching commitments in Eisai Co., Ltd., Daiichi Sankyo Company, Ltd., Takeda Pharmaceutical Co., Ltd. and AstraZeneca K.K. and has received research grants and scholarship grants from Eisai Co., Ltd., Daiichi Sankyo Company, Ltd., Takeda Pharmaceutical Co., Ltd. and AstraZeneca K.K. Toshio Watanabe has received research grants from Eisai Co., Ltd. Nobuyuki Sugisaki is an employee of Eisai Co., Ltd. Hisao Ogawa has served on advisory committees and review panels for Eli Lilly Japan K.K, Novartis Pharma K.K., and Pfizer Japan Inc., has served as a board member of Takeda Pharmaceutical Co., Ltd., has received research grants from AstraZeneca K.K., Astellas Pharma Inc., Bayer Holding Ltd., Boehringer Ingelheim, Chugai Pharmaceutical Co., Ltd., Daiichi Sankyo Company, Ltd., Eisai Co., Ltd, Kowa Company, Ltd., Mitsubishi Tanabe Pharma Corporation, MSD K.K., Novartis Pharma K.K., Otsuka Pharmaceutical Co., Ltd., Shionogi & Co., Ltd., and Takeda Pharmaceutical Co., Ltd., and has served in speaking and teaching commitments for Pfizer Japan Inc. and Sanofi K.K. Tetsuo Arakawa has served on advisory committees and review panels for Eisai Co., Ltd, and Otsuka Pharmaceutical Co., Ltd. Kazuma Fujimoto has served on advisory committees and review panels for Eisai Co., Ltd.

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