acute gastroduodenal mucosal lesion, gastric ulcer or duodenal ulcer, upper gastrointestinal haemorrhage, reflux oesophagitis (the modified Los Angeles Classification[29, 30] Grade A or above) or Barrett's oesophagus (columnar-lined epithelium ≥3 cm). Other exclusion criteria included: patients with a history of upper gastrointestinal surgery, patients continuously using NSAIDs or adrenocortical steroids, patients with serious diseases of the heart, brain, blood, kidneys or liver, patients with malignant tumours, and patients with a history or presence of aspirin-sensitive asthma.

Patients were eligible for study participation regardless of whether they were *H. pylori*-positive or -negative. Presence of *H. pylori* infection was determined by enzyme immunoassay using an antibody determination kit (E-Plate Eiken *H. pylori* antibody) (Eiken Chemical Co., Ltd., Tokyo, Japan). The relative sensitivity, specificity and accuracy rate between results obtained by E-Plate and those obtained by culture/histological examination/rapid urease test were 100%, 80.0% and 97.1% respectively.[31] *Helicobacter pylori* eradication therapy was prohibited during the study. At baseline, CYP2C19 genotyping information was obtained using fluorescence correlation spectroscopy [homo extensive metabolizer (EM), hetero EM, or poor metabolizer (PM)]. Anti-*H. pylori* IgG antibody and CYP2C19 genotype analyses were performed by SRL Medisearch (Tokyo, Japan).

There were no restrictions on medications used before the start of the study. During the study period, concomitant use of the following was prohibited: drugs indicated for improving ulcers or gastrointestinal symptoms (such as PPIs, except those that were used in this study, histamine H_2 receptor antagonists, prokinetics, mucosal protective agents, antacids, prostaglandin agents; or traditional Chinese herbal medications, etc.), and atazanavir sulphate and rilpivirine hydrochloride, which are contraindicated for concomitant use with rabeprazole. The concomitant use of anti-platelet drugs or anticoagulants other than LDA was permitted.

Treatment

Subjects in this 24-week clinical trial were divided into three treatment groups: the rabeprazole 10-mg (once daily) group, the rabeprazole 5-mg (once daily) group and the teprenone 150-mg (50 mg three times a day) group. Subjects who met the inclusion criteria were randomly assigned in a 1:1:1 ratio to one of the three groups, using a dynamic allocation method where the following three baseline covariates were considered prognostic: age (under 70 years old or 70 years and older), concomitant use of anti-platelet or anticoagulant medication other than LDA (positive or negative), and institution. The study medications were prepared such that the active drugs were indistinguishable in appearance from their corresponding placebo. Following a triple-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, and a teprenone-placebo capsule in the morning, afternoon and evening; subjects in the rabeprazole 5-mg group received a rabeprazole 5-mg tablet and a rabeprazole 10-mg placebo tablet in the morning, and a teprenone-placebo capsule in the morning, afternoon and evening; while subjects in the teprenone group received 10-mg and 5-mg rabeprazole placebo tablets in the morning and a teprenone capsule in the morning, afternoon and evening. Bell Medical Solutions, Inc. (Tokyo, Japan) was contracted to allocate the study medication and safeguard the key codes. EPS Corporation (Tokyo, Japan) was contracted to administer the Subject Enrollment Center. Each of these organisations is a third party entity, which maintained independence from the institutions conducting the study and the sponsor (Eisai Co., Ltd.). By having the key code stored in Bell Medical Solutions, Inc., blinding of treatment groups from all personnel involved in the study was secured until code break.

Assessments

During the study period, subjects made hospital visits every 4 weeks. Upper endoscopy was performed at the start of the study, at week 12 and at week 24 or at discontinuation. If findings suggestive of upper gastrointestinal haemorrhage or intolerable upper gastrointestinal symptoms occurred, 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:[32] active stage (1, 2), healing stage (1, 2) or scar stage (1, 2). The Forrest classification[33] 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 oesophagitis was assessed according to the modified Los Angeles Classification[29, 30] as: O (without mucosal breaks) and A–D (with mucosal breaks). The modified Lanza score was used to assess the severity of gastric or duodenal mucosal injury,[34, 35] based on which gastric findings were rated from grade 0

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(no erosion, no ecchymosis) to 5 (ulcer), and duodenal findings from grade 0 (no erosion, no ecchymosis) to 4 (ulcer). Every 4 weeks, a physician interviewed the subject regarding any upper gastrointestinal symptoms (epigastric pain, stomach discomfort, feeling of abdominal fullness, heartburn and nausea/queasiness), and assessed these on a 4-grade scale (none, mild, moderate and severe). Laboratory tests were conducted and vital signs were measured every 4 weeks. Serum gastrin and thyroid function tests (TSH, F-T_3, F-T_4) were performed at the start of the study, at week 12 and at week 24 or at discontinuation. Data of serum gastrin levels were masked until code break. At each visit, subjects were also surveyed for compliance with the study drugs and LDA, as well as the types of concomitant medications they were taking and for the occurrence of any adverse events.

Endpoints

The primary endpoint was cumulative recurrence rate of gastric or duodenal ulcers at week 24 (Kaplan–Meier life-table estimates). Ulcer was defined as a mucosal break measuring ≥3 mm along its longest diameter with a white coating. The size definition of ≥3 mm was also used in recent studies from 10 countries (mostly European countries),[36] USA,[37] Taiwan,[38] and Japan, Korea, and Taiwan[39] where PPI and LDA were dosed. 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).

Secondary endpoints included cumulative incidence of bleeding ulcers at week 24 (Forrest Classification, type IIb or above), incidence of reflux oesophagitis at week 24 (Grade A or above based on the modified Los Angeles Classification), percentage of patients showing improvement/worsening of gastric and duodenal 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) and percentage of patients showing worsening of upper gastrointestinal symptoms (worsening was defined as an increase in severity of at least 1 grade at the final assessment compared to baseline).

Safety was evaluated based on adverse events, laboratory tests, vital signs, and the results of serum gastrin and thyroid function tests. Incidence rates were calculated for adverse events and drug-related adverse events in each treatment group.

Statistical analysis

Based on the results of studies on lansoprazole in patients with a history of ulcers,[40] it was postulated that the cumulative recurrence rate for gastric or duodenal ulcers at week 24 would be 4% in the rabeprazole 10-mg group and 17% in the teprenone group. A sample size of 122 subjects per group was estimated to be required, with a two-sided significance level of $\alpha = 0.05$ and a power of 90% (Fisher's exact test). In addition, in consideration of the quantity of data that would be lost due to ineligible subjects and early discontinuations, etc., the number of subjects required for randomisation was set at 150 per group, i.e. a total of 450 subjects in the three groups.

Efficacy analyses were primarily performed on the full analysis set (FAS), defined as all randomised subjects who received at least one dose of the study drug and showed no ulcers at baseline, and from whom the results of at least one endoscopic assessment was available. The primary endpoint was also analysed based on the per protocol set (PPS). All safety analyses were performed on the safety analysis set (SAS), defined as all randomised subjects who received at least one dose of the study drug.

For the cumulative recurrence rate of gastric or duodenal ulcers at week 24, the log-rank test was used to check superiority of each rabeprazole dose group as compared with the teprenone group. In this study, closed multiple testing procedures were used: the rabeprazole 10-mg group and teprenone group were compared in the first step, and only if a significant difference was observed, the rabeprazole 5-mg group and teprenone group were compared in the second step. The Kaplan–Meier method was used to estimate hazard ratios (+95% confidence intervals) for each rabeprazole dose group against the teprenone group. A secondary endpoint, the cumulative incidence of bleeding ulcers at week 24, was analysed in the same way. Fisher's exact test was used to compare the teprenone group and each rabeprazole dose group with respect to incidence rates of reflux oesophagitis, the percentage of subjects showing improvement/worsening of gastric and duodenal mucosal injury based on the modified Lanza score, and the percentage of subjects with worsening of upper gastrointestinal symptoms.

All statistical analyses were performed using SAS software, version 9.2 (SAS Institute., Cary, NC, USA).

P values of less than 0.05 were considered to indicate statistical significance.

RESULTS

Demographics

Four hundred and seventy-two subjects were randomised (Figure 1). There were 52 discontinuations (11%): 16 in the rabeprazole 10-mg group, 18 in the rabeprazole 5-mg group and 18 in the teprenone group. The main reasons for discontinuation were adverse events, subject choice and inadequate therapeutic effect. Four hundred and fifty-two subjects constituted the FAS for efficacy: 151 subjects in the rabeprazole 10-mg group, 150 in the rabeprazole 5-mg group and 151 in the teprenone group. The main reasons for exclusion from the FAS were lack of administration of the study drug, no evaluable endoscopic data and ineligibility to participate due to the presence of peptic ulcer at baseline. There were 431 subjects in the PPS (144, 144 and 143 subjects, respectively), and 471 subjects in the SAS (157, 156 and 158 subjects, respectively).

No major differences were observed among the treatment groups in terms of baseline characteristics (Table 1). The heterogeneities about previous drugs, the presence of *H. pylori* and eradication history were similar between the three groups. The mean compliance with study medication in each treatment group (SAS) was 99.5% in the rabeprazole 10-mg group, 99.1% in the rabeprazole 5-mg group and 96.9% in the teprenone group. There were two subjects in the rabeprazole 5-mg group and two subjects in the teprenone group with less than 75% compliance with the study medication.

Efficacy

Ulcer recurrence. The primary endpoint, the cumulative recurrence rate (number) for gastric and duodenal ulcers at week 24, was 1.4% (two subjects) in the rabeprazole 10-mg group, 2.8% (four subjects) in the rabeprazole 5-mg group and 21.7% (32 subjects) in the teprenone group (Kaplan–Meier estimates, FAS). Thus, both the rabeprazole groups demonstrated a significantly better preventive effect than the teprenone group ($P < 0.001$ for both rabeprazole groups vs. the teprenone group, log-rank test) (Figure 2). In addition, the hazard ratio with respect to the teprenone group was 0.05 in the rabeprazole 10-mg group, and 0.11 in the rabeprazole 5-mg group, indicating a risk reduction of ulcer recurrence of 95% and 89% respectively. The cumulative recurrence rate (number) for gastric or duodenal ulcers at week 24 in the PPS was 1.4% (two subjects) in the rabeprazole 10-mg group, 2.8% (four subjects) in the rabeprazole 5-mg group and 22.0% (31 subjects) in the teprenone group ($P < 0.001$ for both rabeprazole groups vs. the teprenone group, log-rank test). Thus, both FAS and PPS analyses showed that the rabeprazole groups experienced a significantly better preventive effect than the teprenone group. The ulcer conditions (site, stage classification, size, number, ulcer with or without upper gastrointestinal symptoms) at the time of recurrence are shown in Table 2.

Figure 2 shows that cumulative ulcer recurrence rates at week 12 were 0% in the rabeprazole 10-mg group, 1.3% in the rabeprazole 5-mg group and 16.6% in the teprenone group (Kaplan–Meier estimates, FAS), indicating that rabeprazole at doses of both 10 and 5 mg are significantly efficacious at week 12 compared with the teprenone group.

Cumulative incidence of bleeding ulcers. Table 2 shows Kaplan–Meier estimates of the cumulative incidence of bleeding ulcers at week 24. No cases of bleeding ulcer were seen in the rabeprazole 10- or 5-mg groups, and a significantly better preventive effect was seen in the groups receiving rabeprazole compared to the teprenone group ($P = 0.001$ for both rabeprazole groups vs. the teprenone group, log-rank test). Bleeding ulcers were observed in seven subjects in the teprenone group (Forrest classification type Ib, three subjects and type IIb, four subjects).

Erosive oesophagitis. Incidence rates of reflux oesophagitis at the end of treatment are shown in Table 2. The rabeprazole 10-mg (zero subjects) and 5-mg groups (grade A, three subjects) both demonstrated a significantly greater preventive effect compared to the teprenone group (grade A, seven subjects; grade B, six subjects). ($P < 0.001$, $P = 0.018$, for each rabeprazole group vs. the teprenone group, respectively, Fisher's exact test).

Severity scores of gastroduodenal damage. The percentage of subjects with improvement/worsening of gastric mucosal injury and duodenal mucosal injury based on the modified Lanza scores are shown in Figure 3(a). Both the rabeprazole groups demonstrated significantly greater preventive effects on worsening compared to the teprenone group ($P < 0.001$ for both rabeprazole groups vs. the teprenone group, Fisher's exact test). In addition, for gastric mucosal injury, the rabeprazole 10-mg group

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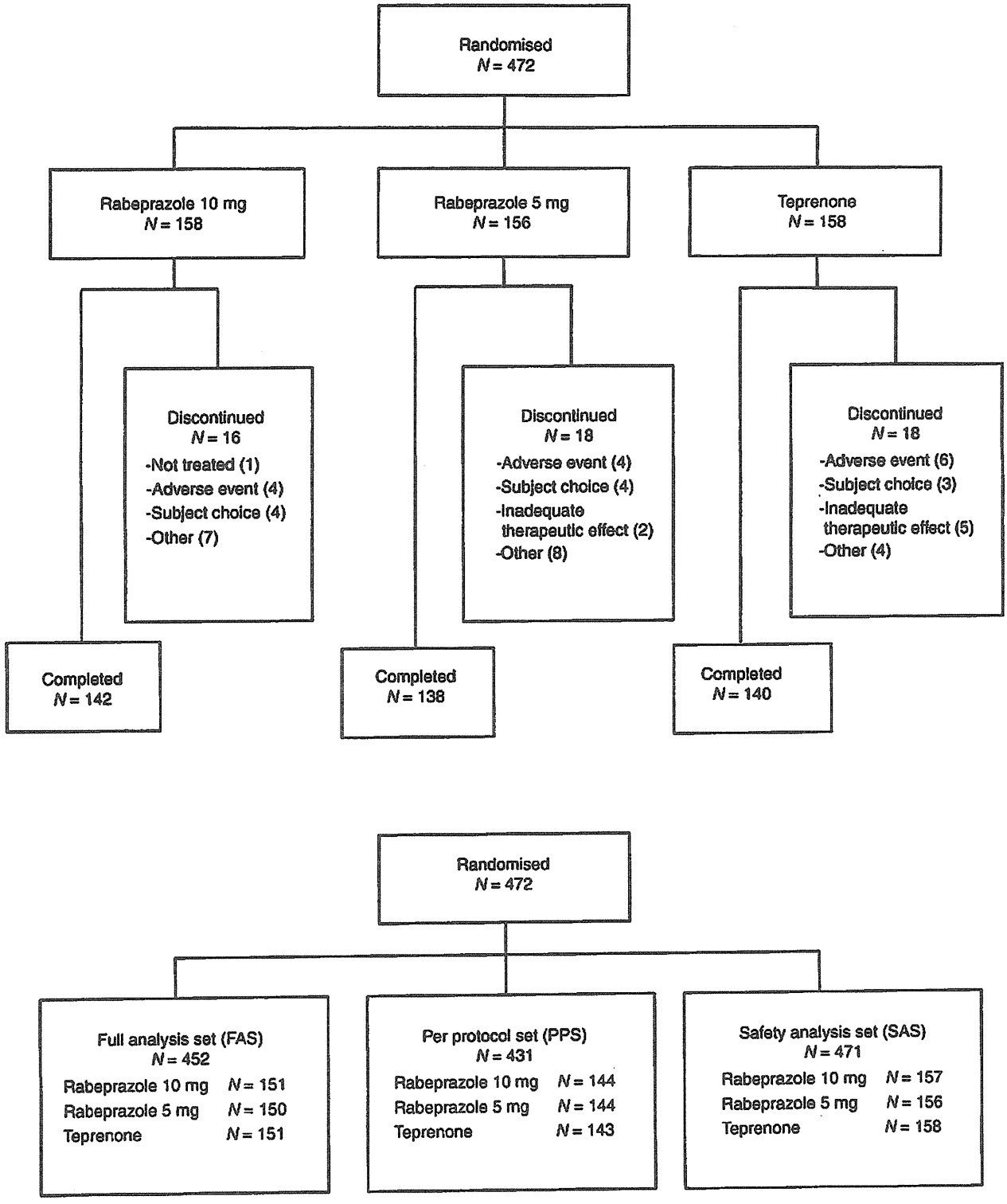

Figure 1 | Subject disposition and analysis set.

demonstrated a significantly greater improvement than the teprenone group (P = 0.040, Fisher's exact test). At end of treatment, the percentage of subjects with gastric mucosal injury of ≥grade 3 [presence of lesions (erosion, ecchymosis) in ≥2 regions or presence of ≥6 lesions] was 2.0% in the rabeprazole 10-mg group, 10.0% in the

Table 1 | Demographic and clinical characteristics (full analysis set)

	Rabeprazole 10 mg (n = 151)	Rabeprazole 5 mg (n = 150)	Teprenone (n = 151)
Male sex, *n* (%)	118 (78.1)	118 (78.7)	112 (74.2)
Mean age ± s.d. (years)	69.7 ± 9.6	69.2 ± 9.0	69.3 ± 7.9
Ischaemic condition*, *n* (%)			
Angina	62 (41.1)	67 (44.7)	65 (43.0)
Myocardial infarction	30 (19.9)	26 (17.3)	32 (21.2)
Ischaemic cerebrovascular disease	72 (47.7)	76 (50.7)	72 (47.7)
CABG or PTCA	49 (32.5)	51 (34.0)	46 (30.5)
Other	10 (6.6)	6 (4.0)	9 (6.0)
Aspirin dose (mg)			
81	14 (9.3)	12 (8.0)	16 (10.6)
100	137 (90.7)	138 (92.0)	135 (89.4)
Duration of aspirin use, *n* (%)			
<2 years	40 (26.5)	36 (24.0)	35 (23.2)
≥2 years	111 (73.5)	114 (76.0)	116 (76.8)
Concomitant use of anti-thrombotic drug except aspirin, *n* (%)	33 (21.9)	30 (20.0)	34 (22.5)
Helicobacter pylori status, *n* (%) (anti-*H. pylori* IgG antibodies)			
Positive	66 (43.7)	68 (45.3)	75 (49.7)
Negative (with history of eradication)	50 (33.1)	44 (29.3)	43 (28.5)
Negative (without history of eradication)	35 (23.2)	38 (25.3)	33 (21.9)
History of ulcers, *n* (%)			
Gastric	94 (62.3)	105 (70.0)	94 (62.3)
Duodenal	57 (37.7)	45 (30.0)	57 (37.7)
History of bleeding ulcers, *N* (%)			
Gastric	7 (4.6)	7 (4.7)	11 (7.3)
Duodenal	7 (4.6)	4 (2.7)	6 (4.0)
History of erosive oesophagitis, *n* (%)	18 (11.9)	26 (17.3)	22 (14.6)
Modified Lanza score ≥grade 1, *n* (%)			
Gastric	38 (25.2)	32 (21.3)	39 (25.8)
Duodenal	4 (2.6)	0 (0.0)	4 (2.6)
Pre-treatment drug for prevention of ulcer, *n* (%)			
PPIs	74 (49.0)	76 (50.7)	71 (47.0)
H_2 receptor antagonists	34 (22.5)	41 (27.3)	32 (21.2)
Mucosal protective agents	20 (13.2)	27 (18.0)	37 (24.5)
CYP2C19 genotypes, *n* (%)			
Homo EM	60 (39.7)	51 (34.0)	46 (30.5)
Hetero EM	65 (43.0)	76 (50.7)	77 (51.0)
PM	26 (17.2)	23 (15.3)	28 (18.5)
Current smoking, *n* (%)	26 (17.2)	23 (15.3)	22 (14.6)
Current alcohol consumption, *n* (%)	94 (62.3)	82 (54.7)	81 (53.6)

CABG, coronary artery bypass grafting; PTCA, percutaneous transluminal coronary angioplasty; CYP2C19, cytochrome P450 isoenzyme; EM, extensive metabolizer; PM, poor metabolizer.

* Multiple choice allowed.

rabeprazole 5-mg group and 29.1% in the teprenone group, indicating a significant difference between the rabeprazole 10-mg and 5-mg groups (P = 0.003, Fisher's exact test).

Upper gastrointestinal symptoms. Figure 3(b) shows the percentages of subjects with worsening of upper gastrointestinal symptoms. In terms of epigastric pain, stomach discomfort and heartburn, both the rabeprazole groups demonstrated a significantly greater preventive effect on worsening than the teprenone group (epigastric pain, P = 0.009 for both rabeprazole groups vs. the teprenone group; stomach discomfort, P = 0.006 and P = 0.018 for each rabeprazole group vs. the teprenone group, respectively; heartburn, P < 0.001 for both rabeprazole groups vs. the teprenone group, Fisher's exact method).

Subgroup analysis

Subgroup analyses were performed for the primary endpoint, cumulative recurrence rates of peptic ulcers at

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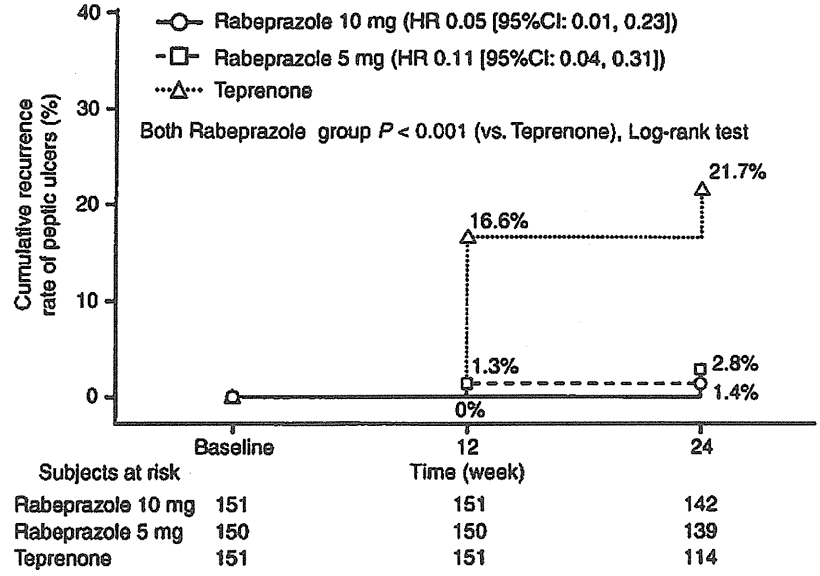

Figure 2 | Cumulative recurrence rates of peptic ulcers over 24 weeks (Kaplan–Meier estimates, FAS).

Table 2 | Endoscopic results (full analysis set)

Parameter	Rabeprazole 10 mg (n = 151)	Rabeprazole 5 mg (n = 150)	Teprenone (n = 151)	P value 10 mg vs. Teprenone 5 mg vs. Teprenone
Recurrent gastric and duodenal ulcers over 24 weeks, n	2	4	32	–
Site of ulcer, n				
Gastric	2	4	24	–
Duodenal	0	0	8	–
Grade of ulcer, n				
Healing stage	2	1	13	–
Active stage	0	3	19	–
Size of ulcer, n (mm)				
3≤ <5	1	1	17	–
5≤ <15	1	2	13	–
15≤	0	1	2	–
Number of ulcer, n				
Single	1	2	17	–
Multiple	1	2	15	–
Ulcer with or without upper gastrointestinal symptoms, n*				
With	0	0	15	–
Without	2	4	16	–
Bleeding ulcer, n (%; cumulative occurrence rate at week 24)	0 (0.0)	0 (0.0)	7 (4.6)	P = 0.001† P = 0.001†
Erosive oesophagitis, n (%; occurrence rate at end of treatment)	0 (0.0)	3 (2.0)	13 (8.6)	P < 0.001‡ P = 0.018‡

* One subject in the teprenone group did not give data of upper gastrointestinal symptoms at the time of ulcer recurrence.

† Log-rank test, significance level α = 0.05 (two sides).

‡ Fisher's exact test, significance level α = 0.05 (two sides).

week 24, based on Kaplan–Meier estimates of the FAS (Table 3). For each of the patient background factors (sex, age, LDA dose, concomitant use of anti-platelet or anticoagulant drugs except LDA, *H. pylori* infection, history of bleeding ulcers, CYP2C19 genotypes, current smoking and alcohol consumption habits), the hazard ratio for the rabeprazole groups vs. the teprenone group was either <1 or no ulcer recurrence was observed in the

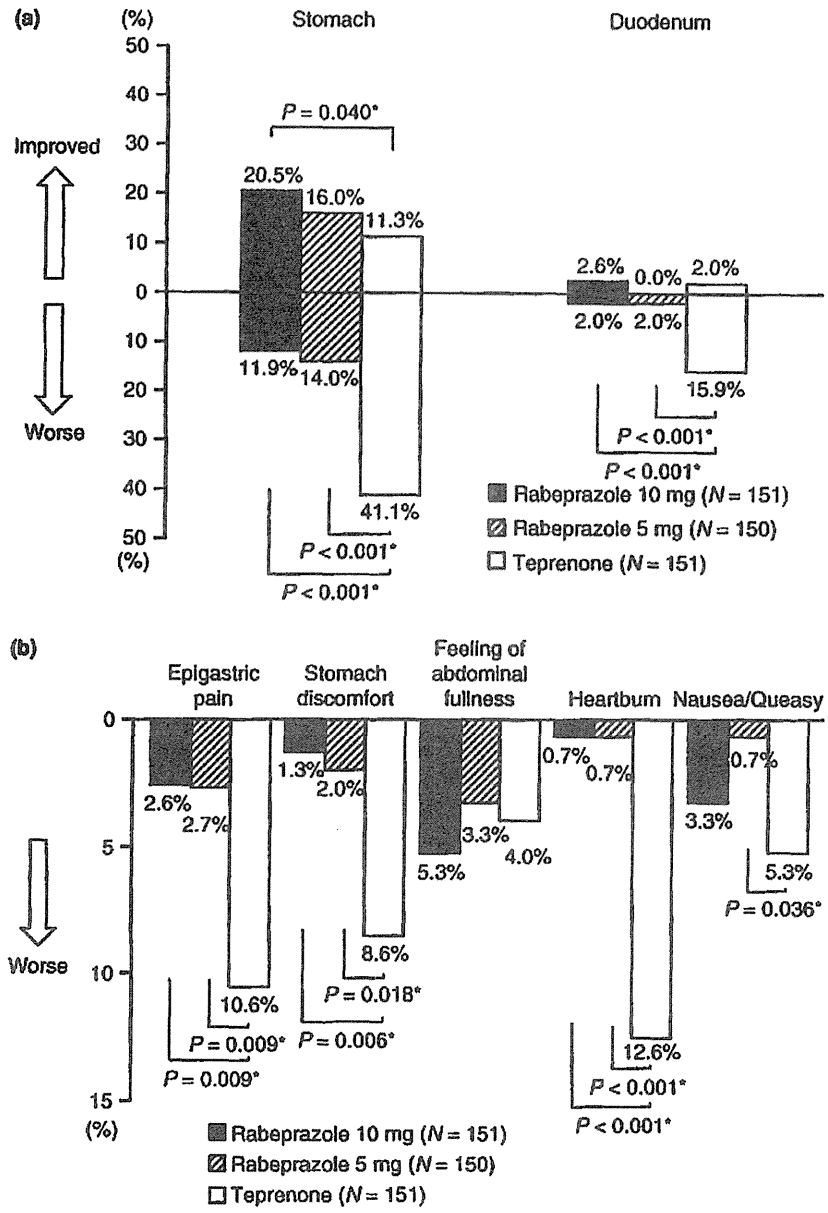

Figure 3 | Gastroduodenal damage and upper gastrointestinal symptoms (FAS). (a) Percentage of subjects with improvement/worsening of gastric mucosal injury and duodenal mucosal injury based on the modified Lanza scores at the final assessment compared to baseline. (b) Percentage of subjects with worsening of upper gastrointestinal symptoms at the final assessment compared to baseline.

rabeprazole group (in the latter case, hazard ratio was indicated as 'Not calculated'). Background factors had little impact on the superiority of the efficacy of the rabeprazole group compared with the teprenone group.

Safety

Table 4 shows a summary of the adverse events. Incidence rates of adverse events were 58.0% in the rabeprazole 10-mg group, 54.5% in the rabeprazole 5-mg group and 59.5% in the teprenone group. Incidence rates of drug-related adverse events were 8.9% in the rabeprazole 10-mg group, 4.5% in the rabeprazole 5-mg group and 10.1% in the teprenone group, indicating no clear differences among the three groups with respect to adverse events and drug-related adverse events. The most commonly occurring adverse event was nasopharyngitis in all groups.

There were no deaths during the study treatment. A serious adverse event that occurred in two or more subjects was angina pectoris (two subjects in the teprenone group). Another serious adverse event for which a causal relationship with the study drug could not be ruled out was acute cholecystitis in one patient in the rabeprazole 10-mg group. Other serious adverse events, classified into ischaemic disease, cardiac failure and cerebrovascular disorders, were observed in two subjects in the rabeprazole 10-mg group (subdural haematoma and carotid artery stenosis, one patient each), one patient in the rabeprazole 5-mg group (angina pectoris in a patient

Table 3 | Cumulative recurrence rates of peptic ulcers over 24 weeks based on patient background (full analysis set)

Covariate classification	Events/*N* (%) Rabeprazole 10 mg (*n* = 151)	Rabeprazole 5 mg (*n* = 150)	Teprenone (*n* = 151)	Hazard ratio (95% CI) 10 mg vs. Teprenone 5 mg vs. Teprenone
Sex				
Men	2/118 (1.8)	3/118 (2.6)	28/112 (25.8)	0.06 (0.01, 0.24) 0.09 (0.03, 0.29)
Women	0/33 (0.0)	1/32 (3.3)	4/39 (10.3)	NC 0.29 (0.03, 2.59)
Age				
<70	1/72 (1.4)	2/73 (2.7)	18/72 (25.1)	0.05 (0.01, 0.37) 0.10 (0.02, 0.42)
≥70	1/79 (1.4)	2/77 (2.8)	14/79 (18.2)	0.06 (0.01, 0.48) 0.13 (0.03, 0.57)
Aspirin dose (mg)				
81	1/14 (7.1)	2/12 (16.7)	3/16 (19.8)	0.32 (0.03, 3.10) 0.80 (0.13, 4.80)
100	1/137 (0.8)	2/138 (1.5)	29/135 (21.9)	0.03 (0.00, 0.22) 0.06 (0.01, 0.25)
Concomitant use of anti-thrombotic drug except aspirin				
With	1/33 (3.2)	0/30 (0.0)	10/34 (30.1)	0.09 (0.01, 0.68) NC
Without	1/118 (0.9)	4/120 (3.4)	22/117 (19.2)	0.04 (0.01, 0.30) 0.16 (0.05, 0.46)
Helicobacter pylori status (Anti-*H. pylori* IgG antibodies)				
Positive	2/66 (3.1)	1/68 (1.5)	20/75 (27.3)	0.10 (0.02, 0.41) 0.05 (0.01, 0.36)
Negative	0/85 (0.0)	3/82 (3.8)	12/76 (15.8)	NC 0.21 (0.06, 0.75)
History of bleeding ulcers				
With	0/14 (0.0)	0/11 (0.0)	5/17 (29.9)	NC NC
Without	2/137 (1.6)	4/139 (3.0)	27/134 (20.6)	0.06 (0.02, 0.27) 0.13 (0.04, 0.36)
CYP2C19 genotypes				
Homo EM	1/60 (1.7)	0/51 (0.0)	14/46 (30.7)	0.05 (0.01, 0.35) NC
Hetero EM	1/65 (1.7)	3/76 (4.1)	15/77 (19.9)	0.07 (0.01, 0.52) 0.18 (0.05, 0.61)
PM	0/26 (0.0)	1/23 (4.3)	3/28 (11.0)	NC 0.40 (0.04, 3.86)
Current smoking				
With	1/26 (3.8)	0/23 (0.0)	8/22 (36.4)	0.09 (0.01, 0.69) NC
Without	1/125 (0.9)	4/127 (3.3)	24/129 (19.0)	0.04 (0.01, 0.28) 0.15 (0.05, 0.44)
Current alcohol consumption				
With	2/94 (2.2)	2/82 (2.4)	22/81 (27.7)	0.07 (0.02, 0.28) 0.08 (0.02, 0.33)
Without	0/57 (0.0)	2/68 (3.2)	10/70 (14.7)	NC 0.19 (0.04, 0.87)

NC, not calculated; CI, confidence interval.

concomitantly on clopidogrel), and three subjects in the teprenone group (angina pectoris in two subjects, one of whom was on concomitant clopidogrel, and embolic stroke in one subject). Cardiovascular adverse events did not trend disproportionately to the rabeprazole group compared to the teprenone group.

Table 4 | Adverse events (safety analysis set)

	Rabeprazole 10 mg (*n* = 157)	Rabeprazole 5 mg (*n* = 156)	Teprenone (*n* = 158)
Any adverse events, *n* (%)	91 (58.0)	85 (54.5)	94 (59.5)
Serious adverse events (SAEs), *n* (%)	6 (3.8)	10 (6.4)	10 (6.3)
Death	0 (0.0)	0 (0.0)	0 (0.0)
Other SAEs	6 (3.8)	10 (6.4)	10 (6.3)
Adverse events leading to study drug withdrawal, *n* (%)	5 (3.2)	7 (4.5)	5 (3.2)
Treatment-related adverse events, *n* (%)	14 (8.9)	7 (4.5)	16 (10.1)
≥2 events SAEs, *n* (%)			
Angina pectoris	0 (0.0)	1 (0.6)	2 (1.3)
≥2% adverse events, *n* (%)			
Constipation	5 (3.2)	1 (0.6)	6 (3.8)
Diarrhoea	6 (3.8)	4 (2.6)	2 (1.3)
Nasopharyngitis	22 (14.0)	25 (16.0)	25 (15.8)
Pharyngitis	1 (0.6)	6 (3.8)	2 (1.3)
Upper respiratory tract infection	3 (1.9)	5 (3.2)	2 (1.3)
Contusion	0 (0.0)	4 (2.6)	3 (1.9)
Diabetes mellitus	2 (1.3)	4 (2.6)	1 (0.6)
Epistaxis	1 (0.6)	0 (0.0)	4 (2.5)
Eczema	6 (3.8)	1 (0.6)	1 (0.6)
Hypertension	5 (3.2)	0 (0.0)	3 (1.9)

DISCUSSION

The use of LDA therapy to prevent the occurrence of arterial thrombotic disease is steadily increasing. On the other hand, ill effects of LDA therapy have also been pointed out, such as the occurrence of peptic ulcer and upper gastrointestinal haemorrhage.[3, 4, 8, 9] Acid-suppressive therapy with PPIs has already been recommended in a variety of guidelines and review articles on the prevention of upper gastrointestinal mucosal injury in patients taking LDA,[12, 41] and this practice is gradually spreading to the clinical setting. However, the efficacy of rabeprazole when combined with LDA has not yet been investigated sufficiently.

In previous studies, when investigations have been conducted in populations that included patients undergoing primary prevention for peptic ulcers, incidence rates for ulcers in the placebo group have ranged from 6.2% to 7.4%,[36, 37] suggesting that there were many patients taking LDA who did not necessarily need concomitant PPIs. Consequently, in this study, which is the first double-blind comparative study of rabeprazole, we targeted secondary prevention in a population with a history of ulcers, a higher risk group. In addition, from an ethical perspective as well as from the standpoint of feasibility, it was difficult to establish a placebo as the comparator in Japan, and hence, teprenone was selected instead.

The present study results have demonstrated that rabeprazole prevents ulcer recurrence in subjects taking LDA. Moreover, statistically significant effects in comparison with the teprenone group were confirmed not just in the rabeprazole 10-mg group (standard dose in Japan), but also in the 5-mg group. In the present 24-week study, ulcer recurrence rates were 1.4% in the rabeprazole 10-mg group and 2.8% in the rabeprazole 5-mg group. The present results with rabeprazole are comparable to those with other PPIs in subjects with a history of ulcers who were both negative and positive for *H. pylori*. That is, the recurrence rate with esomeprazole 20 mg plus gefarnate 100 mg at week 24 was 1.7% (98.3% nonrecurrence rate)[39] and those with lansoprazole 15 mg at day 181 was 2.1%.[40]

As shown in the present Table 2, several subjects showed ulcer with the size of ≥5 mm when recurrence occurred; that is, one subject in the rabeprazole 10-mg group, three subjects in the rabeprazole 5-mg group and 15 subjects in the teprenone group. Endoscopy confirmed no episodes of clinically significant bleeding ulcers in either the rabeprazole 10-mg or 5-mg groups. Furthermore, no subject in the rabeprazole 10-mg and 5-mg groups showed recurrence of ulcer that was accompanied by upper gastrointestinal symptoms, but 15 subjects in the teprenone group showed it.

The present recurrence rate was 21.7% in the teprenone group, while the previously reported rates were

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15.0% in the gefarnate plus placebo group[39] and 24.0% in the gefarnate group,[40] indicating that the present use of teprenone as the active control is valid.

In a previous LDA plus lansoprazole 30-mg study where the ulcer size definition of ≥5 mm was used and *H. pylori* was eradicated, the ulcer occurrence rate at month 12 was reported to be 1.6% in the lansoprazole group and 14.8% in the placebo group.[42] We consider that the larger size definition of ≥5 mm and *H. pylori* eradication would have contributed to the lower placebo value (14.8%) compared with active control values in the present and recent clinical studies (21.7%, 15.0% and 24.0%).

The improvement of secondary endpoints also demonstrated the efficacy of rabeprazole, namely, incidence rates of erosive oesophagitis, the severity scores of gastric and duodenal mucosal injury, and upper gastrointestinal symptom scores (epigastric pain, stomach discomfort and heartburn). These results are consistent with those of previous studies using rabeprazole in healthy individuals[43, 44] and those of an open-label study in patients with a history of ulcers.[21]

Overall, there were no major differences in most of the efficacy parameters between the rabeprazole 10-mg and 5-mg groups, except that the percentage of subjects with grade 3 or higher gastric mucosal injury based on Lanza scores at end of treatment was significantly lower in the 10-mg group than the 5-mg group, and the ulcer condition (grade and size), in the event of recurrence, was somewhat milder in the 10-mg group than the 5-mg group.

The results of subgroup analyses showed that in the teprenone group, there were many subjects with ulcer recurrence among populations positive for *H. pylori*, and with concomitant use of an anti-thrombotic drug and with a history of bleeding ulcers, which are reported to be general risk factors for LDA-associated ulcers,[40, 45] while ulcer recurrence in each of these population subtypes was not observed in the rabeprazole groups. Multivariate analysis showed that teprenone administration was the only risk factor for ulcer development in this study (data not shown).

Under conditions of routine clinical care, LDAs are administered for extended periods, often in patients with multiple risk factors. Further, LDA users without current or past *H. pylori* infections who develop ulcer bleeding were reported to have a very high risk of recurrent bleeding in a long-term study.[46] In routine clinical care, it is difficult to thoroughly investigate whether the patient has a history of ulcers or upper gastrointestinal haemorrhage, and the existence and type of any concomitant medication. Taking these into consideration, we believe that rabeprazole 10 mg may exert a reliable and stable prophylactic effect in all types of patients because there were only two subjects in the rabeprazole groups with ulcer recurrence in this study, and the pharmacodynamic effect (as seen with 24-h gastric pH monitoring) was better in the rabeprazole 10-mg group than the 5-mg group.[47] In fact, subgroup analyses in this study among *H. pylori*-negative subjects who require more potent inhibition of acid secretion showed that ulcer recurrence was experienced by three subjects in the rabeprazole 5-mg group, but none of the subjects in the 10-mg group.

Appropriate selection of the concomitant PPI is an important issue in elderly LDA users. Rabeprazole is less affected by CYP2C19 genotype,[15–17] and has little interaction with clopidogrel, which is often used together with LDA.[20, 48–50] It is also reported to be safe even if used concomitantly with warfarin after open-heart surgery, as it is unlikely to produce haemorrhagic complications.[51] In the present study, 20% of subjects had concomitant administration of anti-platelet agents or anticoagulants, and serious adverse events, such as ischaemic disease, cardiac failure or cerebrovascular disorders occurred in two subjects (1.3%) in the rabeprazole 10-mg group, one subject (0.6%) in the rabeprazole 5-mg group and three subjects (1.9%) in the teprenone group, indicating that use of rabeprazole did not increase the frequency or type of serious cardiovascular adverse events. There were also no deaths among the study population.

This study has the following limitations. First is the problem of the duration of treatment. In this study, to confirm the efficacy of rabeprazole vs. teprenone, the duration of treatment was set at 24 weeks. However, once LDA treatment is begun as routine clinical care, treatment may continue on a semi-permanent basis. This study did not adequately investigate if the efficacy and safety of rabeprazole can be sustained over a longer time frame. To overcome this limitation, a long-term study is currently ongoing for subjects who had not experienced ulcer recurrence at week 24, extending the duration of treatment by an additional 52 weeks (maximum duration of treatment of 76 weeks) (ClinicalTrials.gov Identifier: NCT01398410). The results of this long-term study will certainly provide additional key information. The second limitation is the problem of the subjects included. A procedure that would require *H. pylori* eradication in all *H. pylori*--

positive subjects should be considered to eliminate the effect of *H. pylori* infection on ulcer recurrence. However, because the objective was to cover all scenarios that could potentially be encountered in routine clinical care, it was decided to treat *H. pylori* infection status as irrelevant. Third, is the problem of the number of subjects. In this study, the focus was on ulcer recurrence rates, and the sample size was determined based on evidence from similarly designed studies involving other PPIs. Therefore, for evaluating efficacy in subgroup analyses and safety in terms of adverse events related to haemorrhage, etc., the power may be inadequate. Future, larger studies are needed to address these problems.

In conclusion, both rabeprazole 5 and 10 mg are efficacious in preventing ulcer recurrence in subjects with a history of ulcers currently taking LDA for cardiovascular protection. The drug is well tolerated at both these doses.

AUTHORSHIP

Guarantor of the article: Kazuma Fujimoto.

Author contributions: Ryuichi Iwakiri was involved in protocol planning, patient recruitment, data interpretation, and writing and editing the original paper. Kazuhide Higuchi, Mototsugu Kato and Mitsuhiro Fujishiro, as endoscopy specialists, were involved in protocol planning and data interpretation, and were members of the endoscopy central review panel. 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. Masao Yamauchi, Makoto Sanomura and Hidemitsu Nakagawa contributed to patient recruitment 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.

ACKNOWLEDGEMENTS

The authors thank all contributing members (listed in the Appendix) 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 in the study monitoring.

Declaration of personal interests: 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. Mitsuhiro Fujishiro has served in speaking and teaching commitments for Eisai Co., Ltd and has received from scholarship grants from Dainippon Sumitomo Pharma Co., Ltd. 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 from research grants from Eisai Co., Ltd. Masao Yamauchi has received from research grants from AstraZeneca K.K. 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 membership 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. The following authors have nothing to declare: Ryuichi Iwakiri, Toshihisa Takeuchi, Makoto Sanomura, Hidemitsu Nakagawa and Yasushi Okada.

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

REFERENCES

1. Huang JQ, Sridhar S, Hunt RH. Role of *Helicobacter pylori* infection and non-steroidal anti-inflammatory drugs in peptic-ulcer disease: a meta-analysis. *Lancet* 2002; 359: 14–22.
2. Ootani H, Iwakiri R, Shimoda R, *et al.* Role of *Helicobacter pylori* infection and nonsteroidal anti-inflammatory drug use in bleeding peptic ulcers in Japan. *J Gastroenterol* 2006; 41: 41–6.
3. Nakayama M, Iwakiri R, Hara M, *et al.* Low-dose aspirin is a prominent cause of bleeding ulcers in patients who underwent emergency endoscopy. *J Gastroenterol* 2009; 44: 912–8.
4. Taha AS, Angerson WJ, Knill-Jones RP, Blatchford O. Upper gastrointestinal haemorrhage associated with low-dose aspirin and anti-thrombotic drugs – a 6-year analysis and comparison with non-steroidal anti-inflammatory drugs. *Aliment Pharmacol Ther* 2005; 22: 285–9.
5. Saini SD, Fendrick AM, Scheiman JM. Cost-effectiveness analysis: cardiovascular benefits of proton pump inhibitor co-therapy in patients using aspirin for secondary prevention. *Aliment Pharmacol Ther* 2011; 34: 243–51.
6. Smith SC Jr, Benjamin EJ, Bonow RO, *et al.* AHA/ACCF secondary prevention and risk reduction therapy for patients with coronary and other atherosclerotic vascular disease: 2011 update: a guideline from the American Heart Association and American College of Cardiology Foundation. *Circulation* 2011; 124: 2458–73.
7. Ogawa H, Nakayama M, Morimoto T, *et al.*; Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes (JPAD) Trial Investigators. Low-dose aspirin for primary prevention of atherosclerotic events in patients with type 2 diabetes: a randomized controlled trial. *JAMA* 2008; 300: 2134–41. Erratum in: JAMA 2009; 301: 1882.
8. Yeomans ND, Lanas AI, Talley NJ, *et al.* Prevalence and incidence of gastroduodenal ulcers during treatment with vascular protective doses of aspirin. *Aliment Pharmacol Ther* 2005; 22: 795–801.
9. Nema H, Kato M, Katsurada T, *et al.* Endoscopic survey of low-dose-aspirin-induced gastroduodenal mucosal injuries in patients with ischemic heart disease. *J Gastroenterol Hepatol* 2008; 23: S234–6.
10. Derry S, Loke YK. Risk of gastrointestinal hemorrhage with long term use of aspirin: meta-analysis. *BMJ* 2000; 321: 1183–7.
11. Weisman SM, Graham DY. Evaluation of the benefits and risks of low-dose aspirin in the secondary prevention of cardiovascular and cerebrovascular events. *Arch Intern Med* 2002; 162: 2197–202.
12. Abraham NS, Hlatky MA, Antman EM, *et al.*; ACCF/ACG/AHA. ACCF/ACG/AHA 2010 expert consensus document on the concomitant use of proton pump inhibitors and thienopyridines: a focused update of the ACCF/ACG/AHA 2008 expert consensus document on reducing the gastrointestinal risks of antiplatelet therapy and NSAID use. *Am J Gastroenterol* 2010; 105: 2533–49.
13. Kinoshita Y, Ashida K, Hongo M; Japan Rabeprazole Study Group for NERD. Randomised clinical trial: a multicentre, double-blind, placebo-controlled study on the efficacy and safety of rabeprazole 5 mg or 10 mg once daily in patients with non-erosive reflux disease. *Aliment Pharmacol Ther* 2011; 33: 213–24.
14. Kinoshita Y, Hongo M; Japan TWICE Study Group. Efficacy of twice-daily rabeprazole for reflux esophagitis patients refractory to standard once-daily administration of PPI: the Japan-based TWICE study. *Am J Gastroenterol* 2012; 107: 522–30.
15. Kodaira C, Uchida S, Yamade M, *et al.* Influence of different proton pump inhibitors on activity of cytochrome P450 assessed by [(13)C]-aminopyrine breath test. *J Clin Pharmacol* 2012; 52: 432–9.
16. Furuta T, Shirai N, Sugimoto M, Ohashi K, Ishizaki T. Pharmacogenomics of proton pump inhibitors. *Pharmacogenomics* 2004; 5: 181–202.
17. Ohbuchi M, Noguchi K, Kawamura A, Usui T. Different effects of proton pump inhibitors and famotidine on the clopidogrel metabolic activation by recombinant CYP2B6, CYP2C19 and CYP3A4. *Xenobiotica* 2012; 42: 633–40.
18. Hosohata K, Masuda S, Yonezawa A, *et al.* Absence of influence of concomitant administration of rabeprazole on the pharmacokinetics of tacrolimus in adult living-donor liver transplant patients: a case-control study. *Drug Metab Pharmacokinet* 2009; 24: 458–63.
19. Takahashi K, Motohashi H, Yonezawa A, *et al.* Lansoprazole-tacrolimus interaction in Japanese transplant recipient with CYP2C19 polymorphism. *Ann Pharmacother* 2004; 38: 791–4.
20. Yamane K, Kato Y, Tazaki J, *et al.* Effects of PPIs and an H_2 blocker on the antiplatelet function of clopidogrel in Japanese patients under dual antiplatelet therapy. *J Atheroscler Thromb* 2012; 19: 559–69.
21. Sanuki T, Fujita T, Kutsumi H, *et al.* Rabeprazole reduces the recurrence risk of peptic ulcers associated with low-dose aspirin in patients with cardiovascular or cerebrovascular disease: a prospective randomized active-controlled trial. *J Gastroenterol* 2012; 47: 1186–97.
22. Shirakabe H, Takemoto T, Kobayashi K, *et al.* Clinical evaluation of teprenone, a mucosal protective agent, in the treatment of patients with gastric ulcers: a nationwide, multicenter clinical study. *Clin Ther* 1995; 17: 924–35.
23. Sakamoto C, Ogoshi K, Saigenji K, *et al.* Comparison of the effectiveness of geranylgeranylacetone with cimetidine in gastritis patients with dyspeptic symptoms and gastric lesions: a randomized, double-blind trial in Japan. *Digestion* 2007; 75: 215–24.
24. Miyake K, Tsukui T, Shinji Y, *et al.* Teprenone, but not H_2-receptor blocker or sucralfate, suppresses corpus *Helicobacter pylori* colonization and gastritis in humans: teprenone inhibition of *H. pylori*-induced interleukin-8 in MKN28 gastric epithelial cell lines. *Helicobacter* 2004; 9: 130–7.
25. Yanagawa A, Endo T. Prophylactic effect of teprenone against gastroduodenal lesions caused by non-steroidal anti-inflammatory drugs (NSAIDs): controlled trail using the envelope method and placebo-controlled double-blind trial. *J Rheumatol* 2000; 3: 191–7.
26. Umegaki E, Kuramoto T, Kojima Y, *et al.* Geranylgeranylacetone, a gastromucoprotective drug, protects against NSAID-induced esophageal, gastroduodenal and small intestinal mucosal injury in healthy subjects: a prospective randomized study involving a comparison with famotidine. *Intern Med* 2014; 53: 283–90.
27. Hirakawa T, Rokutan K, Nikawa T, Kishi K. Geranylgeranylacetone induces heat shock proteins in cultured guinea pig gastric mucosal cells and rat gastric mucosa. *Gastroenterology* 1996; 111: 345–57.

28. Suemasu S, Tanaka K, Namba T, *et al.* A role for HSP70 in protecting against indomethacin-induced gastric lesions. *J Biol Chem* 2009; 284: 19705–15.
29. Hoshihara Y. Endoscopic findings of GERD. *Nippon Rinsho* (in Japanese) 2004; 62: 1459–64.
30. Hongo M. Minimal changes in reflux esophagitis: red ones and white ones. *J Gastroenterol* 2006; 41: 95–9.
31. Fujioka T, Tokieda M. Validity of serum anti-*Helicobacter pylori* antibody using immunoassay for the diagnosis in eradication of *Helicobacter pylori* (in Japanese). *Jpn J Med Pharm Sci* 2000; 43: 573–9.
32. Kaneko E, Hoshihara Y, Sakaki N, *et al.* Peptic ulcer recurrence during maintenance therapy with H_2-receptor antagonist following first-line therapy with proton pump inhibitor. *J Gastroenterol* 2000; 35: 824–31.
33. Heldwein W, Schreiner J, Pedrazzoli J, Lehnert P. Is the forrest classification a useful tool for planning endoscopic therapy of bleeding peptic ulcers? *Endoscopy* 1989; 21: 258–62.
34. Lanza FL, Royer GL Jr, Nelson RS, Chen TT, Seckman CE, Rack MF. A comparative endoscopic evaluation of the damaging effects of nonsteroidal anti-inflammatory agents on the gastric and duodenal mucosa. *Am J Gastroenterol* 1981; 75: 17–21.
35. Lanza F, Peace K, Gustitus L, Rack MF, Dickson B. A blinded endoscopic comparative study of misoprostol versus sucralfate and placebo in the prevention of aspirin-induced gastric and duodenal ulceration. *Am J Gastroenterol* 1988; 83: 143–6.
36. Yeomans N, Lanas A, Labenz J, *et al.* Efficacy of esomeprazole (20 mg once daily) for reducing the risk of gastroduodenal ulcers associated with continuous use of low-dose aspirin. *Am J Gastroenterol* 2008; 103: 2465–73.
37. Scheiman JM, Devereaux PJ, Herlitz J, *et al.* Prevention of peptic ulcers with esomeprazole in patients at risk of ulcer development treated with low-dose acetylsalicylic acid: a randomised, controlled trial (OBERON). *Heart* 2011; 97: 797–802.
38. Luo JC, Huang KW, Leu HB, *et al.* Randomised clinical trial: rabeprazole plus aspirin is not inferior to rabeprazole plus clopidogrel for the healing of aspirin-related peptic ulcer. *Aliment Pharmacol Ther* 2011; 34: 519–25.
39. Sugano K, Choi MG, Lin JT, *et al.*; LAVENDER Study Group. Multinational, double-blind, randomised, placebo-controlled, prospective study of esomeprazole in the prevention of recurrent peptic ulcer in low-dose acetylsalicylic acid users: the LAVENDER study. *Gut* 2014; 63: 1061–8.
40. Sugano K, Matsumoto Y, Itabashi T, *et al.* Lansoprazole for secondary prevention of gastric or duodenal ulcers associated with long-term low-dose aspirin therapy: results of a prospective, multicenter, double-blind, randomized, double-dummy, active-controlled trial. *J Gastroenterol* 2011; 46: 724–35.
41. Laine L, Jensen DM. Management of patients with ulcer bleeding. *Am J Gastroenterol* 2012; 107: 345–60.
42. Lai KC, Lam SK, Chu KM, *et al.* Lansoprazole for the prevention of recurrences of ulcer complications from long-term low-dose aspirin use. *N Engl J Med* 2002; 346: 2033–8.
43. Nishino M, Sugimoto M, Kodaira C, *et al.* Relationship between low-dose aspirin-induced gastric mucosal injury and intragastric pH in healthy volunteers. *Dig Dis Sci* 2010; 55: 1627–36.
44. Sugimoto M, Nishino M, Kodaira C, *et al.* Esophageal mucosal injury with low-dose aspirin and its prevention by rabeprazole. *J Clin Pharmacol* 2010; 50: 320–30.
45. Lanas A, Scheiman J. Low-dose aspirin and upper gastrointestinal damage: epidemiology, prevention and treatment. *Curr Med Res Opin* 2007; 23: 163–73.
46. Chan FK, Ching JY, Suen BY, Tse YK, Wu JC, Sung JJ. Effects of *Helicobacter pylori* infection on long-term risk of peptic ulcer bleeding in low-dose aspirin users. *Gastroenterology* 2013; 144: 528–35.
47. Hayato S, Hasegawa S, Hojo S, *et al.* Dose-response relationships of rabeprazole 5, 10, 20, and 40 mg once daily on suppression of gastric acid secretion through the night in healthy Japanese individuals with different CYP2C19 genotypes. *Eur J Clin Pharmacol* 2012; 68: 579–88.
48. Funck-Brentano C, Szymezak J, Steichen O, *et al.* Effects of rabeprazole on the antiplatelet effects and pharmacokinetics of clopidogrel in healthy volunteers. *Arch Cardiovasc Dis* 2013; 106: 661–71.
49. Uotani T, Sugimoto M, Nishino M, *et al.* Ability of rabeprazole to prevent gastric mucosal damage from clopidogrel and low doses of aspirin depends on CYP2C19 genotype. *Clin Gastroenterol Hepatol* 2012; 10: 879–85.
50. Hokimoto S, Mizobe M, Akasaka T, *et al.* Impact of CYP2C19 polymorphism and proton pump inhibitors on platelet reactivity to clopidogrel and clinical outcomes following stent implantation. *Thromb Res* 2014; 133: 599–605.
51. Hata M, Hayasaka M, Sezai A, *et al.* Proton pump inhibitors may increase the risk of delayed bleeding complications after open heart surgery if used concomitantly with warfarin. *Thorac Cardiovasc Surg* 2008; 56: 274–7.

APPENDIX 1: MEMBERS OF THE PLANETARIUM STUDY GROUP: PLANETARIUM (PREVENTION OF RECURRENT GASTRIC OR DUODENAL ULCERS CAUSED BY LOW-DOSE ASPIRIN WITH RABEPRAZOLE TREATMENT -A MULTICENTRE, RANDOMISED, PARALLEL-GROUP, DOUBLE-BLIND, COMPARATIVE TRIAL-)

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特集 抗血栓療法と出血性合併症

抗凝固療法と頭蓋内出血

Anticoagulant Therapy and Intracranial Hemorrhage

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KEY WORDS

ワルファリン
新規経口抗凝固薬
第Ⅸ因子複合体
組織因子
第Ⅶ因子活性

SUMMARY

新規経口抗凝固薬（novel oral anticoagulants：NOAC）における頭蓋内出血発症率はワルファリンと比較して大幅に低い．その理由として，脳に組織因子が多いことやNOACが第Ⅶ因子の血漿濃度に影響せず，外因系凝固カスケードが発動しやすいことなどがあげられる．抗凝固療法中に頭蓋内出血が発生した場合の緊急是正として，ワルファリン療法中は第Ⅸ因子複合体とビタミンK投与が最も効果的である．NOACの場合は胃洗浄や活性炭投与，第Ⅸ因子複合体の投与などを考慮する．

はじめに

心原性脳塞栓症における抗凝固療法は，再発予防に有効である一方で大出血や頭蓋内出血の発症率を上昇させる．本稿では抗凝固療法中の頭蓋内出血の頻度，特徴，急性期の対応と予防方法についてワルファリンおよび新規経口抗凝固薬（novel oral anticoagulants：NOAC）を対比しながら概説する．

抗凝固療法中の頭蓋内出血の頻度

日本を含むアジア人は，欧米人と比較して頭蓋内出血の発症率が高いことが疫学調査から明らかにされているが，ワルファリン療法中の頭蓋内出血発症率もアジア人は白人よりも高いことが報告されている[1)2)]．日本人におけるワルファリン療法中の大出血発現率は2.1～3.6%/年，頭蓋内出血は0.6%～1.0%/年と報告されている[3)]．NOACのダビガトラン，リバーロキサバン，アピキサバン，およびエドキサバンのグローバ

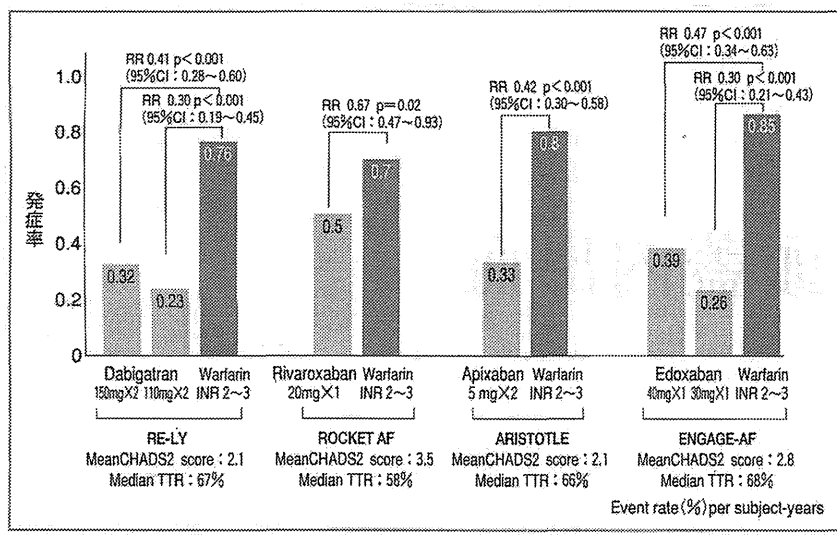

図1 第Ⅲ相試験におけるワルファリン群と新規経口抗凝固薬群の頭蓋内出血発現率

RELY 試験，ROCKET AF 試験，ARISTOTLE 試験および ENGAGE-AF 試験における頭蓋内出血発現率．いずれの試験でもワルファリン群と比較し新規経口抗凝固薬各群で大幅に低い．

（文献 4～8 より作成）

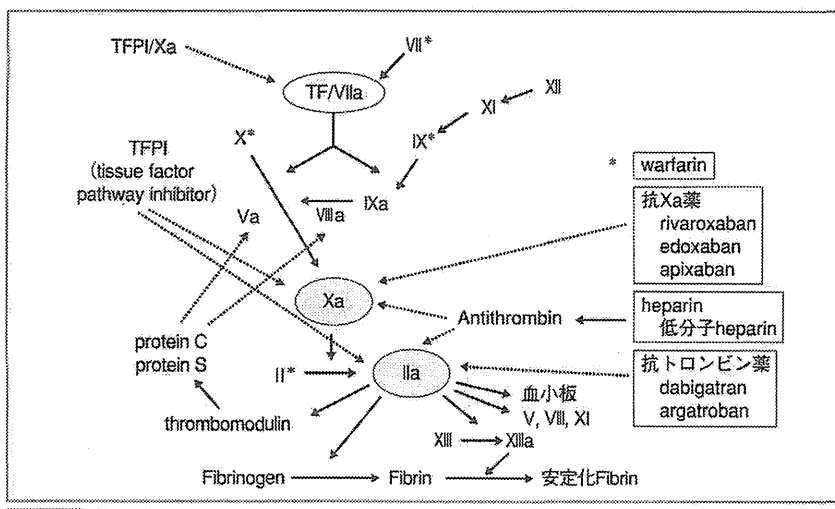

図2 凝固カスケード

ル第Ⅲ相試験によると，頭蓋内出血の発現率はワルファリン群が0.7～0.85%/年に対して，NOAC は0.23～0.5%/年と低値を示している（図1）[4)-8)]．

新規経口抗凝固薬で頭蓋内出血が少ない理由

凝固カスケードを図2に示す．ワルファリンはプロトロンビン（Ⅱ），第Ⅶ，Ⅸ，X因子と4つの凝固因子の産生を抑制するが，ダビガトラン，リバーロキサバン，アピキサバン，およびエドキサバンはトロンビン（Ⅱa）か第Xa因子の1ヵ所のみを阻害する．このように，NOAC は凝固抑制ポイントの数が少ないためワルファリンよりも頭蓋内出血が少ないものと考えられる．また，NOAC で頭蓋内出血が少ない理由として，脳には組織因子が多いことや血漿中第Ⅷ因子濃度に影響を及ぼさないことが関係する[9)]．脳に損傷が起こると，組織因子と第Ⅶ因子が複合体を形成することによって，外因系凝固カスケードが発動する．ワルファリン療法中は第Ⅶ因子の産生が強く抑制されており，組織因子との複合体が形成されにくいため外因系凝固カスケードが発動し難い．しかし，NOAC 療法中は第Ⅶ因子を抑制しないため凝固カスケードは容易に発動する．NOAC はワルファリンと比べ，凝固カスケード開始の反応が起こりやすいために頭蓋内出血が少ないと考えられる．さらに NOAC とワルファリンでは安全域に差がある．抗凝固薬の血中濃度を上昇させると抗凝固作用を示し，さらに上昇させると出血が起こりはじめる．前者の血中濃度を A，後者の血中濃度を B とすると，B/A が大きければ安全域は広く，小さければ安全域は狭いことになる．ワルファリンでは B/A が1に近く，NOAC では大きい値を示す[10)]．また，薬物血中濃度の日内変動も頭蓋内出血の頻度の差に関与していると推定される．ワルファリンは薬剤効果の日内変動が極めて小さく，強い凝固作用が持続する．一方，NOAC 療法では血中濃度にピークとトラフが存在

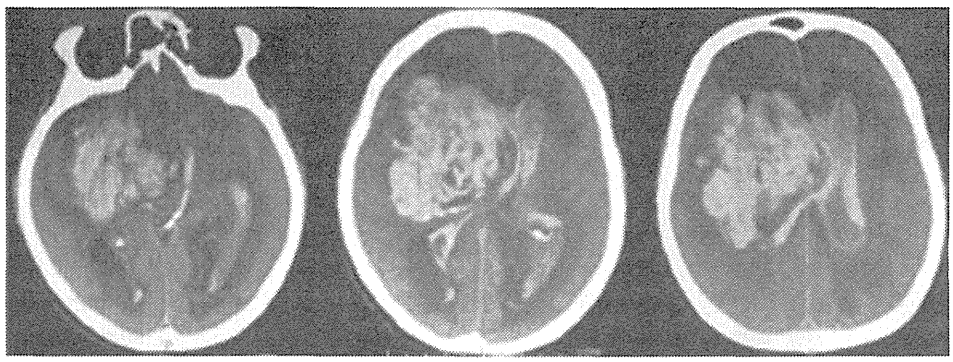

図3　ワルファリン療法中に発症した脳内出血例の頭部CT写真

82歳男性．心房細動にてワルファリン内服中に発症した脳内出血．発症2時間後の頭部CT画像．来院時に呼吸は停止し，対光反射なし．PT-INRは9.4と上昇しており，来院1時間後に死亡された．

する．NOAC療法中はワルファリンと異なり，プロテインCやプロテインSなどの生理的凝固阻止因子の産生を抑制しないので，ピークのみならず，トラフにおいても生理的凝固阻止因子が十分に作用を発揮して，病的血栓の形成を抑制していると考えられる[4]．しかし生理的凝固阻止因子は出血を助長しないので，トラフにおいては生理的止血への抑制作用は弱く，頭蓋内出血が少なくなるものと考えられる．

ワルファリン療法中の頭蓋内出血の特徴と対応

ワルファリン療法中の頭蓋内出血の特徴は，血腫が大きいことや，PT-INRが高いと増大しやすく，転帰が不良であることである（図3）[11][12]．ワルファリン投与中に頭蓋内出血が起こった時，まずは休薬し止血処置を行うことや十分な降圧が重要である．しかし急速にPT-INRの補正を必要とする場合は，第Ⅸ因子複合体の投与が有用である．われわれは，頭蓋内出血時のPT-INRが2.0以上5.0未満では第Ⅸ因子複合体を500単位投与し，PT-INRが5.0以上の場合には1,000単位を投与している．いずれの場合も投与10分後にPT-INRを再検し追加投与の必要性を検討する[13]．第Ⅸ因子複合体の単独投与を行うと，24時間後にPT-INRの再上昇がみられるが，ビタミンKを同時に投与するとPT-INRの再上昇は起こらない（図4）[14]．

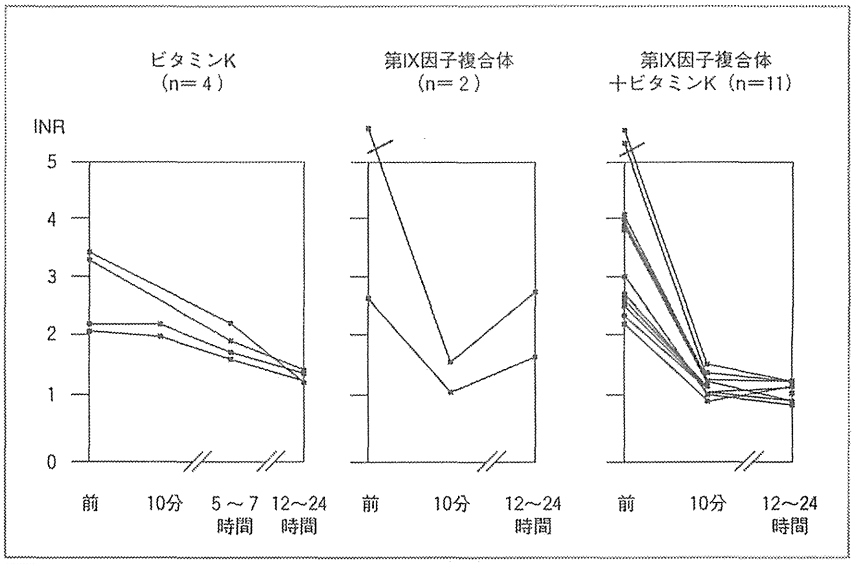

図4　第Ⅸ因子複合体投与とPT-INRの変化

ビタミンKのみ投与後（左），第Ⅸ因子複合体のみを投与後（中）および第Ⅸ因子複合体とビタミンK投与後（右）のINRの推移．ビタミンK単独投与ではINR是正に時間を要す．第Ⅸ因子複合体を単独で投与すると半減期に応じてINRは12～24時間後に再上昇するが，ビタミンKを同時に投与すると肝での合成が加わりINRの再上昇はみられない．

（文献14より引用）

新規抗凝固薬療法中の頭蓋内出血の特徴と対応

NOACの第Ⅲ相試験は，いずれのNOACもワルファリン群と比較し頭蓋内出血が大幅に少ないことを示

している．さらに古森らは，ダビガトラン療法中の頭蓋内血腫が小さいことや増大し難いことを報告している[15]．頭蓋内出血の頻度が低いことや血腫が増大し難い傾向は，前述のワルファリンとNOACの作用機転の差異から説明できる．アジア人と非アジア人を比較すると，アジア人での頭蓋内出血発症率はワルファリン群では高いが，NOACでは十分な抑制作用を示していることから，アジア人における抗凝固療法中の頭蓋内出血を抑えるという観点からNOACの選択はより一層望ましいといえる[16]．

NOAC投与中に大出血が起こった場合，まずはワルファリン投与中の出血と同じく，休薬，止血，補液，頭蓋内出血時の十分な降圧が重要となる．NOACに対する特異的な中和抗体や低分子化合物が開発中であるが，一般臨床ではまだ使うことができない．NOAC投与中の頭蓋内出血では最終内服時間の把握が大切である．内服後の最高血中濃度到達時間（Tmax）は約1～4時間であるため，内服から4時間以内の場合には胃洗浄や活性炭投与による吸収抑制を考慮する．ダビガトランは蛋白結合率が低いため透析での除去が期待されるが，リバーロキサバン，アピキサバンは蛋白結合率が高く，透析による除去は困難である．NOACの抗凝固作用の緊急是正には第Ⅸ因子複合体投与が有用である[16]．

抗凝固療法中の頭蓋内出血を避ける方法

頭蓋内出血の代表である脳内出血のリスクで管理可能なリスクである高血圧，高血糖，過度の飲酒，喫煙については徹底的な管理が基本である[8]．BAT研究によれば抗血栓療法中の頭蓋内出血発症例と非発症例の血圧のカットオフ値は130／81mmHgであったという[17]．この値未満に血圧を管理することが抗血栓療法中の血圧管理の1つの目安といえよう．

さらに抗血栓薬の併用は頭蓋内出血の大きなリスクであるので[1]，できるだけ抗血小板薬の併用を避けることも重要であろう．併用せざるを得ない場合は，日本人における頭蓋内出血発症率が低いシロスタゾールやクロピドグレルの投与を考慮すべきである．アスピリンは消化管出血に注意を払うとともに，欧米人と比較して日本人で頭蓋内出血や脳内出血発症率が高いことに注意する．

おわりに

抗凝固療法と頭蓋内出血について概説した．頭蓋内出血を避けるポイントは，脳内出血のリスク管理と頭蓋内出血発症率の低いNOACを投与禁忌事項や低用量選択基準に十分精通して選択することであり，ワルファリン療法中には厳格なPT-INR管理が重要である．NOAC療法中の頭蓋内出血発症時の対応は確立しておらず，さらなるデータの集積と解析が必要である．

文献

1）Shen AY, Yao JF, Brar SS, et al: Racial/ethnic differences in the risk of intracranial hemorrhage among patients with atrial fibrillation. J Am Coll Cardiol **50**: 309-315, 2007

2）Hori M, Connolly SJ, Zhu J, et al: Dabigatran versus warfarin: effects on ischemic and hemorrhagic strokes and bleeding in Asians and non-Asians with atrial fibrillation. Stroke **44**: 1891-1896, 2013

3）Toyoda K, Yasaka M, Iwade K, et al: Bleeding with Antithrombotic Therapy (BAT) Study group. Dual antithrombotic therapy increases severe bleeding events in patients with stroke and cardiovascular disease: a prospective, multicenter, observational study. Stroke **39**: 1740-1745, 2008

4）Connolly SJ, Ezekowitz MD, Yusuf S, et al: Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med **361**: 1139-1151：2009

5）Patel MR, Mahaffey KW, Garg J, et al: The ROCKET AF investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med **365**: 883-891, 2011

6）Granger CB, Alexander JH, McMurray JJ, et al: ARISTOTLE committees and investigators. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med **365**: 981-992, 2011

7）Giugliano RP, Ruff CT, Braunwald E, et al: Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med **369**: 2093-2104, 2013

8）Hart RG, Diener HC, Yang S, et al: Intracranial hemorrhage in atrial fibrillation patients during anticoagulation with warfarin or dabigatran: the RE-LY trial. Stroke **43**: 1511-1517, 2012

9）Drake TA, Morrissey JH, Edgington TS: Selective cellular expression of tissue factor in human tissues. Implications for disorders of hemostasis and thrombosis. Am J Pathol **134**: 1087, 1989

10) 大村剛史，池上幸三郎，堀　克彦，他：抗凝固薬ダビガトランエテキシラートのA-Vシャントモデルにおける抗血栓および出血に対する作用ならびに抗血栓作用に対するビタミンKの影響．Pharma Medica **29**：137-142，2011
11) 矢坂正弘，岡田　靖：新規経口抗凝固療法時代の脳出血止血治療．臨床神経 **52**：1113-1116，2012
12) Yasaka M, Minematsu K, Naritomi H, et al : Predisposing factors for enlargement of intracerebral hemorrhage in patients treated with warfarin. Thromb Haemost **89** : 278-283, 2003
13) Yasaka M, Sakata T, Naritomi H, et al : Optimal dose of prothrombin complex concentrate for acute reversal of oral anticoagulation. Thromb Res **115** : 455-459, 2005
14) Yasaka M, Sakata T, Minematsu K, et al : Correction of INR by prothrombin complex concentrate and vitamin K in patients with warfarin related hemorrhagic complication. Thromb Res **108** : 25-30, 2002
15) 古森元浩，國場和仁，矢坂正弘，他：ダビガトラン内服中に発症した頭蓋内出血3　症例，第201回神経学会九州地方会，福岡，2013
16) Kaatz S, Kouides PA, Garcia DA, et al : Guidance on the emergent reversal of oral thrombin and factor Xa inhibitors. Am J Hematol **87**(Suppl 1)：S141-S145, 2012
17) Toyoda K, Yasaka M, Uchiyama S, et al : Blood pressure levels and bleeding events during antithrombotic therapy : the Bleeding with Antithrombotic Therapy (BAT) Study. Stroke **41** : 1440-1444, 2010

EXPERT INTERVIEW

—研究と臨床のフロントラインから—

心原性脳塞栓症のチーム医療

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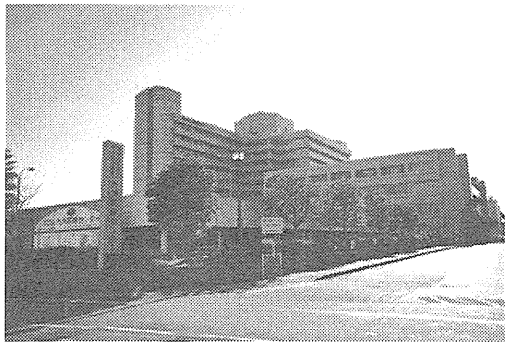

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Profile

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脳卒中急性期の内科治療，頸動脈狭窄症の臨床とともに「脳血管障害は全身血管病」をスローガンにトータルな診療を心がける。地域の脳卒中医療連携の推進，わかりやすい言葉や画像での市民啓発，若手脳卒中専門医の育成に力を注いでいる。