Table 2 Factors associated with risk of gastroduodenal ulcer

Factor	Unadjusted OR	*p* value	Adjusted OR	*p* value
Age ≥65 years	0.58 (0.38–0.88)	0.0109	0.60 (0.39–0.94)	0.0246
Men	1.94 (1.14–3.55)	0.0212	1.45 (0.81–2.74)	0.2261
Current tobacco smoking	2.20 (1.24–3.71)	0.0047	1.87 (1.03–3.25)	0.0321
Alcohol use	1.44 (0.94–2.20)	0.0891	1.18 (0.75–1.86)	0.4736
Diabetes mellitus	1.25 (0.79–1.94)	0.3331	1.12 (0.52–2.22)	0.7526
H. pylori antibody positive	1.87 (1.21–2.91)	0.0050	1.83 (1.18–2.88)	0.0082
History of peptic ulcer	1.48 (0.91–2.34)	0.1063	1.52 (0.91–2.47)	0.0988
Enteric-coated aspirin	0.53 (0.31–0.97)	0.0285	0.57 (0.32–1.05)	0.0569
Proton pump inhibitor	0.37 (0.17–0.74)	0.0091	0.34 (0.15–0.68)	0.0050
H2-receptor antagonist	0.80 (0.45–1.35)	0.4251	0.62 (0.34–1.06)	0.0967
Cytoprotective drug	0.93 (0.51–1.61)	0.8158	0.84 (0.45–1.48)	0.5703
Angiotensin II receptor blocker	0.95 (0.62–1.46)	0.8211	0.87 (0.55–1.34)	0.5214
HMG-Co A reductase inhibitor	1.36 (0.90–2.09)	0.1489	1.38 (0.90–2.14)	0.1450
Antidiabetic drug	1.25 (0.74–2.04)	0.3801	1.20 (0.55–2.78)	0.6527

Factors associated with gastroduodenal injuries suggestive in Table 1, with significant difference and established for gastroduodenal injuries according to previous studies, were examined for risk of gastroduodenal ulcer using data of 1423 participants excluding those without *H. pylori* information. Risk of gastroduodenal ulcer was estimated by the odds ratio with 95 % confidential interval using a monovariate ("Unadjusted") or multivariate ("Adjusted", which adjusted by all listed variables) logistic regression model

Table 3 Factors associated with risk of gastroduodenal erosion

Factor	Unadjusted OR	*p* value	Adjusted OR	*p* value
Age ≥65 years	0.82 (0.64–1.05)	0.1210	0.83 (0.64–1.09)	0.1768
Men	1.23 (0.94–1.61)	0.1290	1.25 (0.93–1.70)	0.1413
Current tobacco smoking	0.69 (0.45–1.04)	0.0857	0.65 (0.41–1.01)	0.0597
Alcohol use	1.19 (0.94–1.50)	0.1497	1.14 (0.87–1.48)	0.3447
Diabetes mellitus	1.30 (1.00–1.67)	0.0465	1.06 (0.69–1.60)	0.7917
H. pylori antibody positive	0.38 (0.29–0.48)	<0.0001	0.34 (0.26–0.44)	<0.0001
History of peptic ulcer	0.94 (0.70–1.25)	0.6599	1.05 (0.77–1.43)	0.7597
Enteric-coated aspirin	0.47 (0.33–0.67)	<0.0001	0.47 (0.32–0.70)	0.0002
Proton pump inhibitor	0.44 (0.32–0.61)	<0.0001	0.32 (0.22–0.46)	<0.0001
H2-receptor antagonist	0.60 (0.44–0.81)	0.0010	0.49 (0.36–0.68)	<0.0001
Cytoprotective antiulcer drug	1.12 (0.82–1.51)	0.4776	1.01 (0.72–1.39)	0.9592
Angiotensin II receptor blocker	1.12 (0.88–1.42)	0.3496	1.21 (0.94–1.56)	0.1339
HMG-Co A reductase inhibitor	1.03 (0.81–1.30)	0.8159	1.05 (0.82–1.35)	0.6838
Antidiabetic drug	1.34 (1.00–1.78)	0.0484	1.27 (0.79–2.05)	0.3289

Factors associated with gastroduodenal injuries suggestive in Table 1, with significant difference and established for gastroduodenal injuries according to previous studies, were examined for risk of gastroduodenal erosion using data of 1330 participants excluding those without *H. pylori* information and with ulcer. Risk of gastroduodenal erosion was estimated by the odds ratio with 95 % confidential interval using a monovariate ("Unadjusted") or multivariate ("Adjusted", which adjusted by all listed variables) logistic regression model

Antiulcer drug therapy

Anti-ulcer drugs were prescribed for gastroprotection in 52.5 %. PPI, H2RA, and cytoprotective antiulcer drugs or their combination were used with similar rates, whereas use of PGA or its combination was much lower. Use of PPI alone was lower in the erosion group (10.1 %) and in the ulcer group (7.4 %) than in the AMB group (20.6 %) ($p < 0.0001$, $p = 0.0014$, respectively). However, the difference in use of H2RA was detected only in the erosion group. Moreover, use of cytoprotective antiulcer drugs was higher in the erosion group ($p = 0.0364$). In analyses, risks of both ulcer and erosion were significantly reduced with PPI therapy (OR = 0.34, 0.15–0.68, $p = 0.0050$ and OR = 0.32, 0.22–0.46, $p < 0.0001$, respectively). However, in the H2RA therapy group the risk of erosion but not of ulcer was reduced (OR = 0.49, 0.36–0.68, $p < 0.0001$). No relation was found between therapy with cytoprotective drugs and those risks (Tables 2, 3, 4).

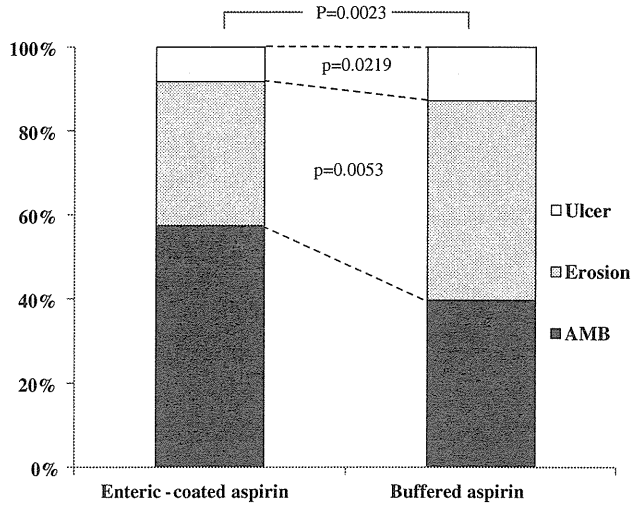

Fig. 2 Use of aspirin formulations and prevalence of gastroduodenal ulcer and erosion in patients not treated with antiulcer drugs. In 690 participants who were not treated with antiulcer drugs, prevalence of gastroduodenal erosion and ulcer were compared between patients receiving enteric-coated (88.7 %) and buffered aspirin (11.3 %). *AMB* absence of mucosal break

Upper GI cancer

Among 1,492 participants who received endoscopy, 37 participants (2.5 %, 95 % CI 1.75–3.40) had upper GI cancer, 4 patients (0.27 %, 0.07–0.68) had esophageal cancer, and 33 patients (2.21 %, 95 % CI 1.53–3.09) had gastric cancer. Additionally, colon cancer was found in one patient.

Discussion

Our study demonstrated that endoscopic gastroduodenal injuries were prevalent (35.7 %) among low-dose aspirin users in Japan, similar to Western countries. However, significant differences were found between the two regions in the methods aspirin was prescribed and the risk factors and drug treatment for gastroduodenal injuries. Use of other NSAIDs (6.5 %) with aspirin was rare in the present study, while it is frequent in Western countries. In spite of the recommendations in the AHA consensus and Japanese guidelines [12, 13], the use of PPI treatment was relatively low (19 %) and was similar to the use of H2RA or cytoprotective antiulcer agents. Cytoprotective agents are not generally used in Western countries. The recent approval (2010) of PPI for the prevention of mucosal injury in Japan may be contributing to the low PPI use.

Prevalence of gastroduodenal ulcer and erosion

The prevalence of endoscopic gastroduodenal ulcer associated with low-dose aspirin (6.5 %) was lower in our study than in previous studies. The prevalence of ulcer and erosion were 18 and 42 %, respectively, among 101 Japanese patients with ischemic heart disease in the study of Nema et al. [14], while that of upper GI ulcer was 12.4 % in 305 Japanese patients in the study of Shiotani et al. [15]. According to Yeomans et al., the point prevalence was 11 % for endoscopic gastroduodenal ulcer and 63 % for erosion in 187 patients taking aspirin for at least 24 days [4]. Factors contributing to the lower prevalence of

Table 4 Relationship between aspirin-associated gastroduodenal injuries and antiulcer drug treatment

	Total n = 1454	AMB n = 935 (64.3)	Erosion n = 425 (29.2)	p value[a]	Ulcer n = 94 (6.5)	p value[b]
No antiulcer drug (%)	690 (47.5)	390 (41.7)	242 (56.9)	<0.0001	58 (61.7)	0.0003
PPI alone (%)	243 (16.7)	193 (20.6)	43 (10.1)	<0.0001	7 (7.4)	0.0014
H2RA alone (%)	263 (18.1)	192 (20.5)	58 (13.6)	0.0025	13 (13.8)	0.1367
CAD alone (%)	171 (11.8)	98 (10.5)	62 (14.6)	0.0364	11 (11.7)	0.7246
PGA alone (%)	2 (0.1)	1 (0.1)	1 (0.2)	0.5275	0 (0.0)	1.0000
PPI + H2RA (%)	2 (0.1)	1 (0.1)	1 (0.2)	0.5275	0 (0.0)	1.0000
PPI + CAD (%)	33 (2.3)	26 (2.8)	7 (1.6)	0.2558	0 (0.0)	0.1606
PPI + PGA (%)	1 (0.1)	0 (0.0)	0 (0.0)	1.0000	1 (1.1)	0.0914
CAD + PGA (%)	1 (0.1)	0 (0.0)	1 (0.2)	0.3125	0 (0.0)	1.0000
H2RA + CAD (%)	47 (3.2)	34 (3.6)	9 (2.1)	0.1803	4 (4.3)	0.7716
PPI + H2RA + CAD (%)	1 (0.1)	0 (0.0)	1 (0.2)	0.3125	0 (0.0)	1.0000

Association of gastroduodenal injuries with concomitant use of antiulcer drug was analyzed using data of 1454 participants. The proportions of participants who received each category of antiulcer treatment were examined in the three groups of gastroduodenal conditions. Those in each treatment category were evaluated between the erosion group or the ulcer group versus the AMB group with Fisher's exact test

PPI proton pump inhibitor, *H2RA* histamine 2-receptor antagonist, *CAD* cytoprotective antiulcer drug, *PGA* prostaglandin analog

[a] p value between AMB and Erosion

[b] p value between AMB and Ulcer

ulcer or erosion in our study may be as follows: (1) a total of 41 % of the participants were treated with PPI or H2RA; (2) concomitant use of other NSAIDs was much lower; and (3) the criterion for mucosal ulcer was a mucosal break of 5 mm or greater in diameter with unequivocal depth. Nonetheless, by our estimation the prevalence of low-dose aspirin-induced endoscopic gastroduodenal ulcer in Japan is approximately 5–10 % in clinical practice.

Risk factors for gastroduodenal ulcer and erosion

Clinically important risk factors for aspirin-associated upper GI bleeding include aging, history of peptic ulcer or GI bleeding, concomitant use of anticoagulants or NSAIDs, and *H. pylori* infection in Western populations [16]. However, a limited number of studies endoscopically examined ulcer risk factors [15, 17]. In a study of Shiotani et al. [17] aging, history of peptic ulcer, and concomitant use of antithrombotic drugs and NSAIDs were associated with peptic ulcer, but regular alcohol drinking, smoking, and *H. pylori* infection were not in 425 low-dose aspirin users. In our study, a history of peptic ulcer, and the concomitant use of anticoagulants and NSAIDs had little association with endoscopic gastroduodenal ulcer and erosion. The reason may include (1) elderly patients with high risk for peptic ulcer such as those taking concomitant anticoagulants and NSAIDs might not be recruited, and (2) the number of concomitant NSAID use in this study was small, which may lead to an underestimation of the risk.

Aging was a risk factor for low-dose aspirin related gastroduodenal ulcer in many studies [4, 16, 17], whereas we observed that age >65 years old was associated a significant reduction in the risk of aspirin-associated ulcer. Furthermore in the analysis of 690 patients not treated with antiulcer drugs, the prevalence of ulcer was significantly lower in the elderly population (See the Supplementary table). The consensus of prior data is that risk of aspirin-associated ulcer increases with advancing age. This means that there may be a significant bias in our methodology or the Japanese may differ in gastric physiology from the rest of the world. In Japanese populations, the older generation has significantly reduced gastric acid secretion compared to younger generations due to atrophic gastritis [18]. Therefore, younger generations may have an inherently higher acid secretion and thus a higher risk of ulcers. However, the age-associated increase in atrophic gastritis is not specific gastritis is not a phenomenon which is specific to Japanese patients. Therefore, it is very likely to be a significant bias in our methodology that elderly patients with at high risk for peptic ulcer might not be recruited.

According to studies of Western populations, the presence of *H. pylori* infection is a significant risk for gastroduodenal ulcer [19]. Our study also demonstrated a twofold increase in ulcer risk in the presence versus the absence of *H. pylori* antibody. However, those results were conflicting with those of Shiotani et al. [15, 17] in Japanese populations where *H. pylori* infection was not associated with peptic ulcer in low-dose aspirin users. The findings may be affected by the study population and the definition of ulcer, which will be discussed in a separate section. In our study, the risk of erosion was significantly lower in the presence of *H. pylori* antibody. The cause and pathogenesis of aspirin-induced endoscopic gastroduodenal ulcer may be different from those of erosion in the presence of *H. pylori* infection.

Aspirin formulation

The prevalence of gastroduodenal injuries was significantly lower with enteric-coated aspirin than with buffered aspirin in our study. Others found that the risks of upper GI bleeding were similar among three forms of aspirin [20]. Although the prevalence of endoscopic gastroduodenal erosion was significantly lower with enteric-coated aspirin than with buffered aspirin, ulcer frequency was similar between the two formulations in the study of Nema et al. [21]. Dammann et al. [22] demonstrated that endoscopic gastroduodenal mucosal lesions were significantly less likely with enteric-coated aspirin (100 mg/day) than with plain aspirin, and the lesion score with coated aspirin was similar to that of placebo without aspirin. Further studies on the influence of aspirin formulation are needed in Japan.

Antiulcer drugs for prevention of gastroduodenal injury

Use of PPI was significantly less in the patients with ulcer or erosion, whereas use of H2RA was less in the patients with erosion, but not with ulcer. Use of cytoprotective drugs, which are widely prescribed in Japan, was higher in the patients with erosion. According to the risk analyses, only PPI presents reduced risks of both ulcer and erosion. The usefulness of PPI in the prevention of ulcers induced by low-dose aspirin is well established in Western countries and in Japan. In a comparative study by Yeomans et al. [23] the development of gastrointestinal ulcer was lower (1.6 %) with esomeprazole 20 mg/day than with placebo (5.4 %), demonstrating a reduction of 70 % in the 991 participants aged ≥60 years receiving low-dose aspirin for 26 weeks without preexisting endoscopic ulcers and without concomitant NSAIDs. Although their study design differed from ours, their findings support our study results. The effectiveness of PPI for the prevention of low-dose aspirin associated gastric or duodenal ulcers was demonstrated in a randomized comparative study by Sugano et al. [24] of a PPI, lansoprazole (15 mg/day), versus a cytoprotective antiulcer drug, gefarnate (100 mg/day), for

secondary prevention. The recurrence of ulcers was 90 % lower with lansoprazole than with gefarnate for an administration of 12 months or longer. According to Taha et al. [25] H2RA treatment with famotidine for 20 weeks reduced the risk of aspirin-induced peptic ulcer by 80 %. However, the risk of gastroduodenal erosion but not of ulcer was significantly lower with H2RA in our study. Study design and the ethnicity of the study populations may have contributed to the difference in results between the two studies.

Definition of ulcer and erosion as surrogate marker

Endoscopic gastroduodenal ulcer has been suggested to be a useful surrogate marker for potentially serious aspirin adverse event such as GI bleeding [26]. However, as described by Graham [27], ulcers are often defined by a mucosal defect of "3 mm or more" or "5 mm or more" in diameter in clinical studies, but aspirin-induced ulcer is often difficult to distinguish from erosion. No internationally recognized clear definition of "ulcer" or "a method of measuring ulcer size" has been established. Our definition of endoscopic ulcer was a mucosal defect 5 mm or more in diameter. However, when an ulcer with a 10 mm or larger diameter is defined as a "large ulcer," 25 % or more of ulcers were large ulcers in patients receiving H2RA or a cytoprotective antiulcer drug, but none of the ulcers were large ulcers in those receiving PPI in the present study (data not shown). Thus, the size of ulcers must be carefully defined for assessing effectiveness of antiulcer drugs in clinical studies that use endoscopically defined ulcers as the primary endpoint. A large cohort study is needed to clarify the risk factors of serious adverse events such as GI bleeding, and to verify endoscopically defined ulcer as a useful surrogate marker of GI bleeding in low-dose aspirin users.

Gastric cancer

This is the first study reporting the prevalence of gastric cancer diagnosed by endoscopy among aspirin users. Among 1,492 patients who received endoscopy, 37 patients had gastric cancer (2.5 %). Reports on the possible prevention of gastric cancer with aspirin have been published [28, 29], but it seems that more studies are necessary in the regions with a high prevalence of gastric cancer, such as Japan.

Limitation

We did not conduct the systematic screening in each hospital for patient recruitment. Our registry recruited patients taking preventive aspirin for high risk CV in clinical practice and gave informed consent to this study. Inclusion bias may be a potential limitation of this study.

Conclusion

Gastroduodenal ulcer and erosion are common among patients receiving low-dose aspirin for prophylaxis of CV disease in the Japanese population (35.7 %). Factors that increase risks of mucosal injuries are current tobacco smoking and the presence of *H. pylori* infection. The use of PPI is helpful to reduce the risk of ulcer and erosion. Furthermore, the association between endoscopic ulcer and serious complications such as GI bleeding should be clarified in the future.

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Conflict of interest SG received research grants from Sanofi-Aventis, Eisai, Boehringer Ingelheim, Otsuka, and Daiichi-Sankyo, and received honorarium for sitting on advisory panels from Eisai, Sanofi-Aventis, Otsuka, Bayer, Novartis, AstraZeneca, Astellas, Pfizer, Medtronics-Japan, Mitsubishi Tanabe, Takeda, Daiichi-Sankyo, Mochida, and MSD. KS received grants from AstraZeneca, Takeda, Astellas and Daiichi-Sankyo and also sat on advisory panels for AstraZeneca, and Takeda. YI received honorarium for lecturing from Sanofi-Aventis, Daiichi-Sankyo and Bayer, and sat on advisory panels for AstraZeneca, Daiichi-Sankyo, and Sanofi-Aventis. All other authors declare that they have no conflicts of interest.

Appendix

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INTERNAL MEDICINE

□ CASE REPORT □

Recombinant Tissue-type Plasminogen Activator (rt-PA) Therapy in an Acute Stroke Patient Taking Dabigatran Etexilate: A Case Report and Literature Review

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Abstract

Whether recombinant tissue-type plasminogen activator (rt-PA) therapy can be administered in acute stroke patients treated with dabigatran remains controversial. We administered rt-PA (0.6 mg/kg) in an acute stroke patient treated with dabigatran (110 mg bid) whose activated partial thromboplastin time (APTT) was 37.1 seconds 113 minutes after onset, 10 hours after the last dose of dabigatran. His symptoms improved from the National Institute of Health Stroke Scale score of 10 to 1 after treatment without hemorrhagic complications. The administration of rt-PA therapy is feasible in acute stroke patients on dabigatran when taking into account the APTT and time from the last dose.

Key words: recombinant tissue-type plasminogen activator (rt-PA) therapy, dabigatran, activated partial thromboplastin time (APTT)

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Introduction

A prothrombin time international normalized ratio (PT-INR) of 1.7 or below and an activated partial thromboplastin time (APTT) of 40 seconds or below are widely known standards for the administration of recombinant tissue-type plasminogen activator (rt-PA) in acute stroke patients treated with warfarin or heparin, respectively. However, it remains controversial whether rt-PA therapy can be administered in acute stroke patients on dabigatran therapy.

Case Report

A 79-year-old Japanese man with non-valvular atrial fibrillation (NVAF), hypertension, diabetes mellitus and dyslipidemia developed acute brain infarction with the sudden onset of right hemiparesis and dysarthria. He had changed anticoagulants from warfarin to dabigatran after dabigatran became available in Japan. He also had taken antihypertensive and antihyperlipidemic agents. He had been treated with low-dose dabigatran etexilate (110 mg bid) due to a past history of stomach ulcers. He was transported to our hospital 30 minutes after onset. On admission, he was 166 cm tall, with a body weight of 80 kg and a BMI of 29. The National Institutes of Health Stroke Scale (NIHSS) score was 10, and the APTT was 37.1 seconds (Table 1). A non-contrast computed tomography (CT) scan revealed no

Table 1. Blood Chemistry Analysis

Hematological analysis		Blood chemistry	
WBC	8,700/μL	TP	7.3 g/dL
RBC	551 × 10^4/μL	Alb	4.4 g/dL
Hb	16.4 g/dL	AST	24 IU/L
Ht	44.7%	ALT	22 IU/L
Plt	170 × 10^3/μL	LDH	247 mg/dL
		BUN	10 mg/dL
Coagulation tests		Cr	0.9 mg/dL
PT sec	17.0 sec	Glu	126 mg/dL
PT-INR	1.26	T-cho	142 mg/dL
APTT sec	37.1 sec	TG	125 mg/dL
Fib	277 mg/dL	HDL-chol	29 mg/dL
DD dimar	0.6 /μL	LDL-chol	102 mg/dL
		NT-proBNP	543 pg/dL

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Table 2. Recent Reports of Dabigatran-treated Patients Undergoing rt-PA Therapy

Reference	Country	Age (years)	Sex	Dabigatran dose (mg)	Last dose (hours)	APTT (sec)	rt-PA time from onset (min)	NIHSS score before rt-PA	NIHSS score after rt-PA	Outcome
(1)	America	51	M	150 mg BID	9.8	26.4	120	14	?	improved
(2)	Brazil	73	M	110 mg BID	7	38	153	6	?	improved
(3)	America	64	M	150 mg BID	10	37.6	205	8	?	improved
(4)	Spain	62	M	110 mg BID	3	37.1	190	18	?	died (with hemorrhage)
(5)	Belgium	42	F	?	7	34.8	270	19	12	improved
(6)	Spain	76	F	220 mg	15	30.6	120	4	0	improved
(7)	Japan	78	F	110 mg BID	10	39.1	105	9	8	improved
(8)	Japan	72	M	110 mg BID	7	39.1	160	11	0	improved
Present study	Japan	79	M	110 mg BID	10	37.1	113	10	1	improved

evidence of early ischemia (ASPECTS; CT Alberta Stroke Program Early CT Score was 10). Meanwhile, axial diffusion-weighted imaging and magnetic resonance angiography (MRA) demonstrated hyperintense signals in the left frontoparietal cerebral cortex without intracranial stenotic lesions. A carotid ultrasonographic examination revealed stenosis of the bifurcation of the left common carotid artery. The patient was diagnosed as having an acute unclassified stroke with NVAF and moderate stenosis (NASCET 50% stenosis on CT angiography) of the left CCA bifurcation. Treatment with rt-PA (0.6 mg/kg) was started 113 minutes after onset and 10 hours after the last dose of dabigatran. Soon after starting the rt-PA therapy, his symptoms improved, with the NIHSS score decreasing from 10 to 1, leaving only a unilateral sensory disturbance. However, 20 hours after the administration of rt-PA, the patient developed recurrence of ischemic stroke without a hemorrhagic stroke in the left frontal lobe. He had moderate carotid stenosis with an ulcer on carotid CT angiography; we believed that the stenotic lesion was a cause of the recurrent ischemic stroke on the same side. Transthoracic echocardiography did not demonstrate any intracardiac thrombi. Therefore, the patient underwent carotid endarterectomy on day 29 after the initial stroke. He was discharged from the hospital on day 46 with an NIHSS score of one and a residual sensory disturbance on the right side.

Discussion

Nine patients treated with rt-PA thrombolysis for acute stroke under dabigatran therapy were reviewed (Table 2). Eight of these patients had favorable outcomes. However, one patient with large ischemic lesions in the left middle cerebral arterial territory developed intracerebral hemorrhage following rt-PA administration three hours after the last dose of dabigatran (110 mg) and ultimately died. Common points associated with a favorable outcome among the eight patients with good outcomes were: 1. the APTT did not exceed 40 seconds and 2. the time from the last dose to injection was greater than seven hours (median: 9.8 h, range: 7 to 15 h). Because the time required to attain the maximum concentration of dabigatran ranges from 30 minutes to four hours, the APTT decreases gradually after four hours; however, it remains prolonged before that time. Therefore, it appears reasonable to avoid administering rt-PA within four hours after the last dose of dabigatran. Although measurements of APTT are not yet standardized, an APTT of less than 40 seconds may be a favorable marker for the administration of rt-PA. In order to establish criteria for safely administering rt-PA thrombolysis in patients with acute stoke under dabigatran treatment, more cases of patients receiving rt-PA for acute stroke during dabigatran therapy must be accumulated.

In conclusion, according to a literature review of nine cases, including the current case, the administration of rt-PA therapy is feasible in acute stroke patients on dabigatran if the APTT does not exceed 40 seconds and the time from the last dose to injection is greater than seven hours.

The authors state that they have no Conflict of Interest (COI).

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Which Should Be the Essential Components of Stroke Centers in Japan? A Survey by Questionnaires Sent to the Directors of Facilities Certified by the Japan Stroke Society

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Key Words
Stroke center · Acute stroke · Questionnaire

Abstract
Background: We conducted a survey by questionnaire to identify the essential components of stroke centers in Japan and compared our results with the European Expert Survey. ***Methods:*** In 2007, a questionnaire was mailed to the directors of 740 facilities certified by the Japan Stroke Society to ask their opinion on the essential components of comprehensive stroke centers (CSC), primary stroke centers (PSC) and any hospital ward (AHW) admitting acute stroke patients. The directors were asked to provide 1 of the following 6 possible answers regarding 112 components: 'irrelevant'; 'useful but not necessary'; 'desirable'; 'important but not absolutely necessary'; 'absolutely necessary', or 'question unclear or ambiguous'. The components considered 'absolutely necessary' by more than 75% of the respondents were compared between our survey and the European Expert Survey. In addition, we compared the rates of neurosurgeons and neurologists who answered 'absolutely necessary' with regard to each component. ***Results:*** Responses were obtained from 428 directors (57.8% response rate). Among these respondents, 298 (69.6%) were neurosurgeons. There was no component considered 'absolutely necessary' for AHW by more than 75% of the respondents, and this was similar to the results of the European Expert Survey. The following components were considered 'absolutely necessary' for PSC in our survey: brain CT scanning 24 h a day, 7 days a week (24/7); automated monitoring of the ECG, pulse oximetry, blood pressure and breathing, and respiratory support. In both our survey and the European Expert Survey, the essential components for CSC were as follows: physiotherapist; brain CT scanning 24/7; monitoring of the ECG, pulse oximetry and blood pressure; carotid surgery; angioplasty and stenting, and intravenous recombinant tissue plasminogen activator protocols. The components multidisciplinary stroke team, stroke-trained nurse, ultrasonography, collaboration with an outside rehabilitation center, stroke pathway and clinical research were deemed essential only in the European Expert Survey. However, MRI 24/7, MR angiography 24/7, conventional angiography 24/7, respiratory support as well as most neuroendovascular and neurosurgical treatments were considered necessary for CSC by more than 75% of the respondents in our survey. Analyzing the responses from only neurologists reduced the differences between our survey and the European Expert Survey. ***Conclu-***

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sions: The present study indicated the essential components expected for stroke centers in Japan. Our survey demonstrated that more emphasis was likely to be placed on installations than on a dedicated stroke team and the use of stroke care maps. In addition, the results of this study may reflect some characteristics of the stroke care environment in Japan, such as the predominance of neurosurgeons and widespread use of MRI.

Introduction

In 2000, the Brain Attack Coalition (BAC) discussed the concept of stroke centers and proposed two levels: (1) primary stroke centers (PSC) to stabilize and provide emergency care for patients with acute stroke and (2) comprehensive stroke centers (CSC) to diagnose and treat stroke patients who require a high intensity of medical and surgical care, specialized tests or interventional therapies [1]. The BAC developed recommendations with criteria for PSC in 2000 [2] and for CSC in 2005 [3].

A meta-analysis of available randomized controlled trials that compared stroke unit (SU) care with conventional care has shown that SU care reduced mortality, institutionalization and dependency [4–6]. In 2007, the European Stroke Initiative (EUSI) executive committee reported the result of the European Expert Survey conducted to identify, from expert opinions, what should be the major components of SU [7].

In Japan, intravenous recombinant tissue plasminogen activator (rt-PA) therapy was approved in October 2005. In 2007, we carried out a survey by questionnaire to identify what should be the essential components of stroke centers and compared our findings with those of the European Expert Survey [7].

Materials and Methods

Between October and December 2007, we mailed a questionnaire to the directors of 740 facilities certified by the Japan Stroke Society to ask their opinion on what should be the essential components of PSC, CSC and any hospital ward (AHW) admitting acute stroke patients. A PSC was defined as a center providing intravenous rt-PA therapy 24 h a day, 7 days a week (24/7), and a CSC as a center providing higher-level care than a PSC. For our questionnaire, we slightly modified the components derived from the European Expert Survey to suit the current medical trends in Japan. As shown in table 1, a total of 112 components were divided into the following 6 categories: personnel; diagnostic procedures; monitoring; invasive treatments provided; infrastructure, and protocols and procedures. The directors were asked to provide 1 of 6 possible answers regarding each component: 'irrelevant'; 'useful but not necessary'; 'desirable'; 'important but not absolutely necessary'; 'absolutely necessary', or 'question unclear or ambiguous'. The 6 possible responses were the same as those in the European Expert Survey [7]. The questionnaire was mailed a second time to those directors who did not respond within 2 months after the time the first survey had been sent.

In this study, components considered as 'absolutely necessary' by more than 75% of the respondents were extracted as 'essential components'. We excluded an item where a similar item considered an 'essential component' had a higher level of requirement. For example, if both 'CT scan 24/7' and 'CT scan' were extracted as 'essential components', 'brain CT scan' was excluded because a CT scan available 24/7 reflects a higher level of requirement than just a CT scan available in the hospital. The components considered as 'absolutely necessary' by more than 75% of the respondents were compared between our survey and the European Expert Survey. In addition, we compared the rates of neurosurgeons and neurologists (or stroke medicine physicians) who answered 'absolutely necessary' with regard to each component in our study, using Fisher's exact test or the χ^2 test. Statistical test results were considered significant if $p < 0.05$. The analyses were performed using JMP statistical software (version 10.0.2; SAS Institute, Cary, N.C., USA).

Results

We obtained responses from 428 directors (57.8% response rate). Among these respondents, 298 (69.6%) were neurosurgeons, 102 (23.8%) neurologists or stroke medicine physicians and 9 (2.1%) specialists in other fields; the specialty of 19 respondents (4.4%) was unknown.

Table 1 shows the rates of the respondents who answered 'absolutely necessary' with regard to stroke components for CSC, PSC and AWH. The results are classified according to the entire group of respondents, neurosurgeons and neurologists (or stroke medicine physicians). The components considered 'absolutely necessary' for CSC by more than 75% of the respondents in our survey and the European Expert Survey are listed in table 2.

Comparison between Our Survey and the European Expert Survey

In the overall results of our survey, there was no component considered 'absolutely necessary' for AHW by more than 75% of the respondents. The components considered 'absolutely necessary' for PSC by more than 75% of the respondents were as follows: brain CT scan 24/7 in the category of diagnostic procedures; automated monitoring of the ECG, pulse oximetry, blood pressure and breathing in the category of monitoring, and respiratory support in the category of invasive treatments provided. 'Multidisciplinary stroke team' and 'stroke-trained nurse',

Table 1. Rate of the respondents answering 'absolutely necessary' with regard to each component of the questionnaire

		CSC				PSC				AHW			
		overall	neurosurgeon	neurologist	p value	overall	neurosurgeon	neurologist	p value	overall	neurosurgeon	neurologist	p value
I. Personnel													
1-1	Physician certified by Japan Stroke Society (24/7)	36.6	33.5	46.0	0.0256	9.5	7.3	16.3	0.0092	1.0	1.5	0	0.2193
1-2	Physician certified by Japan Stroke Society on call	59.1	61.0	55.7	0.3617	32.7	35.3	28.9	0.2507	5.6	7.1	3.0	0.141
1-3	Physician certified by Japan Stroke Society on staff	63.3	63.0	66.0	0.5992	45.2	44.3	51.0	0.2578	8.5	8.7	9.3	0.8696
2-1	Physician with expertise in stroke medical care for ≥3 years (24/7)	65.4	61.7	74.0	0.0275	22.2	23	26.5	0.2835	3.3	3.0	3.0	0.991
2-2	Physician with expertise in stroke medical care for ≥3 years on call	72.5	72.2	72.2	0.9946	51.8	53.9	43.3	0.0738	9.1	9.7	6.1	0.2791
2-3	Physician with expertise in stroke medical care for ≥3 years on staff	70.0	70.3	71.1	0.8799	59.4	58.2	61.5	0.5724	20.6	21.5	17.4	0.3841
3-1	Neurologist (24/7)	39.9	33.6	55.0	0.0002	8.2	4.9	16.3	0.0003	0.5	0.4	1.0	0.473
3-2	Neurologist on call	54.0	50.4	63.5	0.0264	23.8	22.0	27.8	0.2426	4.0	4.1	4.0	0.9431
3-3	Neurologist on staff	59.2	53.3	72.9	0.0008	34.0	23.1	58.3	<0.0001	8.8	7.7	13.1	0.1101
4-1	Neurosurgeon (24/7)	47.1	43.5	55.0	0.0478	12.1	11.3	14.4	0.4222	1.8	2.7	0	0.1013
4-2	Neurosurgeon on call	74.5	74.6	**75.8**	0.8217	46.1	50.0	35.7	0.0147	7.7	10.1	3.1	0.0303
4-3	Neurosurgeon on staff	71.0	69.4	**76.0**	0.2186	53.0	51.7	56.6	0.6216	12.0	13.4	8.3	0.1797
5-1	Neurovascular interventional physician (24/7)	26.7	25.0	32.0	0.176	2.1	2.6	0	0.1105	0.5	0.4	1.0	0.4606
5-2	Neurovascular interventional physician on call	51.9	53.2	46.4	0.2517	14.5	15.9	10.3	0.1788	1.8	2.3	1.0	0.4466
5-3	Neurovascular interventional physician on staff	57.2	55.9	60.8	0.4062	16.2	17.9	10.5	0.0936	3.2	3.6	2.0	0.4398
6-1	Diagnostic radiologist (24/7)	13.2	9.7	22.0	0.0017	0.8	0.7	0	0.402	0	0	0	
6-2	Diagnostic radiologist on call	15.9	14.2	19.6	0.2139	3.3	2.9	4.2	0.5447	0.8	0.8	1.0	0.7967
6-3	Diagnostic radiologist on staff	33.0	27.7	46.4	0.0008	10.8	7.4	20.0	0.0007	2.5	1.8	5.2	0.0784
7	Cardiologist on staff	68.5	66.9	71.0	0.4509	32.4	31.9	29.9	0.7118	7.7	6.8	9.1	0.451
8	Internist on staff	55.4	54.8	55.0	0.9731	30.9	30.9	27.8	0.5764	15.8	14.6	17.2	0.548
9	Stroke medical director	70.5	68.4	**78.0**	0.0704	34.2	31.9	40.2	0.1371	3.7	3.6	4.0	0.8364
10	Multidisciplinary stroke team	72.7	69.0	**83.0**	0.0071	23.3	17.4	36.1	0.0001	2.2	2.5	1.0	0.3754
11	Physician with expertise in carotid surgery	55.5	52.5	65.0	0.0304	8.4	8.1	9.2	0.7452	0.7	1.1	0	0.3003
12	Stroke-trained nurse	64.9	59.6	**78.0**	0.0009	24.1	18.7	36.7	0.0003	2.5	2.5	0	0.1123
13	Emergency department staff	55.3	51.4	67.0	0.0071	14.8	11.7	23.5	0.0044	2.0	1.8	3.0	0.459
14	Physician expert in carotid ultrasonology	48.4	40.1	71.0	<0.0001	15.0	8.8	31.6	<0.0001	0.2	0.4	0	0.5516
15	Technician expert in carotid ultrasonology	55.6	50.9	70.1	0.001	17.5	15.7	24.2	0.0587	0.7	0.4	2.1	0.1052
16	Physician expert in TCD	30.4	23.3	50.5	<0.0001	4.8	3.2	9.5	0.0137	0	0	0	
17	Technician expert in TCD	26.7	22.6	38.1	0.0028	3.8	2.9	6.3	0.1244	0.3	0	1.0	0.0884
18	Physician expert in ECG	60.7	55.2	77.1	0.0001	22.3	15.7	37.2	<0.0001	2.3	2.5	2.1	0.821
19	Technician expert in ECG	49.1	43.4	67.0	<0.0001	17.8	13.2	27.4	0.0014	1.8	1.4	3.1	0.2933
20	Social worker	73.6	70.0	**82.5**	0.0168	50.1	44.6	62.8	0.0024	20.0	19.1	18.6	0.9124
21	Physician trained in rehabilitation	51.1	44.5	68.0	<0.0001	21.8	16.4	33.0	0.0006	6.0	4.3	6.3	0.441
22	Physician certified by Japanese Association of Rehabilitation Medicine	32.5	27.4	45.4	0.0011	8.3	5.3	16.0	0.001	1.5	1.4	0	0.2365
23	Physiotherapist	**81.2**	**79.8**	**85.6**	0.2082	59.3	55.5	68.1	0.0322	25.9	22.8	30.2	0.1487

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Table 1 (continued)

		CSC				PSC				AHW			
		overall	neurosurgeon	neurologist	p value	overall	neurosurgeon	neurologist	p value	overall	neurosurgeon	neurologist	p value
24	Occupational therapist	**78.0**	**75.5**	**83.5**	0.1044	51.3	48.4	57.5	0.1288	19.8	18.1	22.9	0.3051
25	Speech therapist	**76.0**	74.1	**80.4**	0.212	47.8	44.5	56.4	0.0455	16.6	14.9	18.8	0.3682
II. Diagnostic procedures													
1-1	CT scan 24/7	**98.5**	**98.2**	**99.0**	0.618	**94.5**	**94.0**	**95.7**	0.5124	56.3	53.9	60.4	0.2676
1-2	CT scan	**76.4**	74.6	**82.6**	**0.119**	**75.5**	72.3	**86.7**	0.006	59.6	55.3	71.0	0.008
2-1	Perfusion CT 24/7	28.8	28.5	31.0	0.6459	8.3	9.3	7.4	0.5626	2.0	2.2	2.1	0.9224
2-2	Perfusion CT	28.9	28.2	30.9	0.6325	9.5	10.0	9.6	0.9053	1.0	0.7	2.1	0.2716
3-1	MRI with T1-, T2-, T2*-weighted and FLAIR sequences 24/7	**82.4**	**80.8**	**86.6**	0.196	50.4	48.0	55.8	0.1917	9.9	10.0	10.3	0.9225
3-2	MRI with T1-, T2-, T2*-weighted and FLAIR sequences	**75.9**	73.9	**85.0**	0.0296	61.1	57.7	71.0	0.0243	19.5	18.5	22.7	0.3675
4-1	Diffusion-weighted MRI 24/7	**85.9**	**85.1**	**88.7**	0.3778	56.7	55.0	60.0	0.3922	11.1	10.3	14.4	0.2705
4-2	Diffusion-weighted MRI	74.1	73.6	**78.7**	0.3223	62.1	59.8	69.2	0.1071	17.7	17.2	18.8	0.7344
5-1	Perfusion MRI 24/7	41.5	40.3	49.5	0.1148	12.3	12.5	12.6	0.9733	1.3	1.1	2.1	0.4884
5-2	Perfusion MRI	41.2	39.9	46.2	0.2884	17.1	18.0	17.0	0.8346	2.8	2.6	3.1	0.7834
6-1	Carotid ultrasonography 24/7	50.5	45.0	68.0	<0.0001	17.8	12.1	33.7	<0.0001	1.5	1.5	2.1	0.6804
6-2	Carotid ultrasonography	67.2	64.7	77.7	0.0202	45.6	39.3	63.4	<0.0001	8.3	8.7	8.3	0.8848
7-1	TCD 24/7	23.4	20.1	30.6	0.033	3.1	2.2	5.2	0.1375	0.3	0	1	0.099
7-2	TCD	32.5	27.7	44.1	0.0035	6.9	6.7	6.4	0.924	0.3	0.4	0	0.5504
8-1	MR angiography 24/7	**83.7**	**83.3**	**85.7**	0.5811	52	52.4	49	0.5057	8.4	9.7	5.1	0.1617
8-2	MR angiography	**75.3**	74.9	**79.8**	0.3416	65.4	62.7	72.3	0.0933	17	16.9	18.8	0.674
9-1	CT angiography 24/7	64.2	65.6	61.2	0.4391	31.5	34.4	20.8	0.0131	4.8	6.7	1	0.0301
9-2	CT angiography	67.8	68.2	68.1	0.9812	47.6	51	39.1	0.0535	0.3	0.4	0	0.1649
10-1	Conventional angiography 24/7	**84.0**	**84.8**	**81.6**	0.4654	44.7	50.2	29.2	0.0004	6.7	9	1	0.0076
10-2	Conventional angiography	77.1	**75.9**	**83.0**	0.1563	57.2	60.4	48.9	0.054	12.1	13.9	7.3	0.0889
11-1	SPECT 24/7	23.2	22.3	25.5	0.5241	3.3	3.3	3.1	0.935	0.5	0.8	0	0.3894
11-2	SPECT	55.6	55.2	59.0	0.5255	23.5	24.2	20.2	0.4343	2.6	2.3	3.1	0.6352
12-1	Transthoracic echocardiography 24/7	52.8	49.1	63.3	0.0158	17.8	15.4	22.9	0.0936	1.5	1.5	2.0	0.708
12-2	Transthoracic echocardiography	66.9	62.6	**79.0**	0.0037	49.7	44.4	61.7	0.0039	12.3	11.2	16.7	0.1661
13-1	Transesophageal echocardiography 24/7	21.0	20.5	23.5	0.5397	2.5	1.5	4.2	0.118	0.3	0.4	0	0.5448
13-2	Transesophageal echocardiography	54.5	51.7	62.1	0.0806	24.1	20.6	31.9	0.0256	3.1	3.3	3.1	0.9216
14-1	Coagulation test 24/7	**84.1**	**81.8**	**90.8**	0.0165	64.1	59.5	75.0	0.0042	16.0	16.7	17.4	0.8888
14-2	Coagulation test	74.5	72.2	**83.0**	0.0385	66.3	61.8	78.7	0.003	33.1	30.6	39.6	0.1073
III. Monitoring													
1	Automated ECG monitoring at the bedside	**96.7**	**95.6**	**100**	0.0356	**93.5**	**92.0**	**97.9**	0.0431	68.8	66.3	71.4	0.3519
2	Automated monitoring of pulse oximetry	**94.7**	**93.5**	**98.9**	0.0892	**90.9**	**89.5**	**94.8**	0.1207	62.3	59.1	65.3	0.2821
3	Automated monitoring of blood pressure	**95.2**	**94.6**	**98.9**	0.3425	**90.2**	**89.1**	**92.7**	0.3085	64.8	65.0	59.2	0.3079
4	Automated monitoring of breathing	**90.5**	**90.6**	**89.8**	0.8292	**78.3**	**78.3**	**77.1**	0.8033	49.2	51.8	43.9	0.1769
5	Monitoring of temperature	72.4	72.0	**76.5**	0.3846	53.1	53.6	55.2	0.7884	31.7	34.7	26.5	0.1398
6	Automated electroencephalographic monitoring	32.8	34.3	30.0	0.4341	10.7	12.6	5.1	0.0387	2.5	2.6	2.0	0.7602

Table 1 (continued)

		CSC				PSC				AHW			
		overall	neurosurgeon	neurologist	p value	overall	neurosurgeon	neurologist	p value	overall	neurosurgeon	neurologist	p value
7	Automated TCD monitoring	24.9	24.6	26.0	0.7737	5.5	6.5	2.0	0.0915	0.5	0.7	0	0.3925
8	Automated evoked potentials	34.2	36.5	27.3	0.0977	11.8	13.0	7.1	0.118	1.7	2.2	0	0.1365
9	Automated intracranial pressure monitoring	39.2	37.7	40.0	0.6828	12.5	13.0	9.2	0.3233	1.5	1.5	1.0	0.7343
IV. Invasive treatments provided													
1	Intra-arterial thrombolysis	**86.3**	**88.1**	**82.0**	0.1271	37.4	41.0	27.6	0.018	5.5	6.5	2.2	0.0843
2	Carotid surgery	**83.1**	**84.8**	**79.8**	0.2633	29.4	32.4	22.5	0.0647	4.7	6.2	1.1	0.0384
3	Angioplasty and stenting	**80.1**	**80.9**	**79.8**	0.8509	19.0	19.8	17.4	0.598	2.7	3.3	1.1	0.2286
4	Intra-arterial thrombectomy	60.8	61.2	60.7	0.9675	17.8	19.9	12.2	0.091	2.2	3.3	0	0.0671
5	Surgery for aneurysms	**91.8**	**92.4**	**89.9**	0.4504	54.1	56.1	48	0.1636	10.8	12.4	6.7	0.141
6	Coiling for aneurysms	**82.3**	**83.8**	**79.8**	0.3942	27.9	30.2	21.4	0.0955	4.7	5.4	2.2	0.1567
7	Hemicraniectomy	**92.3**	**93.1**	**91.0**	0.484	63.6	67.6	54.1	0.0162	12.7	13.8	10.0	0.3333
8	Ventricular drainage	**94.0**	**94.6**	**92.1**	0.5622	67.1	72.3	53.1	0.0005	15.2	17.4	10.0	0.0796
9	Surgery for hematoma	**93.8**	**94.6**	**91.0**	0.3591	67.8	72.6	54.1	0.0008	13.8	15.3	8.9	0.1145
10	Induced hypothermia	32.6	35.0	27.0	0.0992	9.2	10.8	6.1	0.1768	1.0	1.1	1.1	0.944
11	Respiratory support	**96.0**	**95.7**	**97.8**	0.2904	**87.5**	**85.6**	**92.9**	0.0622	54.6	50.9	58.9	0.0567
V. Infrastructure													
1	Emergency department	59.7	56.3	70.8	0.0167	23.2	19.1	33.7	0.0031	6.0	3.3	14.4	0.0004
2	Stroke outpatient clinic	49.8	44.0	67.4	0.0002	17.2	14.4	26.5	0.0066	1.8	1.5	3.4	0.3212
3	SU	72.4	67.9	**82.0**	0.0072	27.3	23.0	36.1	0.012	3.0	2.6	4.4	0.4604
4	Intensive-care unit	**82.1**	**80.1**	**86.5**	0.1264	43.1	38.8	55.1	0.005	8.5	7.6	13.3	0.1872
5	Air ambulance	29.9	24.9	43.8	0.0024	3.8	2.9	5.1	0.3095	0.8	0.4	2.2	0.1167
6	Inpatient rehabilitation	69.2	67.2	74.2	0.1448	49.5	45.5	58.2	0.031	20.6	18.5	22.2	0.3299
7	Outpatient rehabilitation available	26.6	27.4	22.5	0.5046	19.2	19.1	22.0	0.471	8.5	8.3	7.8	0.9173
8	Collaboration with outside rehabilitation center	68.7	67.2	73.0	0.4784	53.1	48.9	62.2	0.0232	24.9	21.4	25.6	0.2514
9	Anticoagulation clinic	**82.3**	**79.4**	**88.8**	0.0177	71.3	65.1	**86.7**	**<0.0001**	38.3	33.3	46.7	0.0056
10	A direct-line system between emergency medical services	**76.4**	74.0	**85.0**	0.0253	44.6	41.7	54.1	0.0345	11.0	10.5	14.1	0.3302
VI. Protocols and procedures													
1	Stroke database	63.9	57.7	**81.0**	<0.0001	24.6	20.7	35.7	0.003	5.3	5.1	5.1	0.9932
2	Intravenous rt-PA protocols	**85.9**	**83.9**	**94.4**	0.0443	66.9	62.0	**79.6**	0.0015	15.3	13.8	19.2	0.2021
3	Community stroke awareness program	47.8	43	61.8	0.002	16.6	12.9	25.5	0.0034	3.7	3.3	4.4	0.7243
4	Prevention program	42.3	36.6	60.7	<0.0001	15.6	12.5	22.5	0.0178	5.3	4.0	6.1	0.3945
5	Stroke pathways	45.1	40.5	60.7	0.0008	23.8	19.3	38.8	0.0001	3.7	2.5	7.8	0.0426
6	Stroke research department	44.6	40.1	56.2	0.0062	10.7	8.9	13.4	0.2072	2.0	1.8	2.3	0.8919

Actual rates of 75% or more are shown in bold text. TCD = Transcranial Doppler.

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Table 2. Components considered 'absolutely necessary' for CSC by more than 75% of the respondents

Our survey	European Expert Survey [7]
Personnel	
Physiotherapist[a]	**Multidisciplinary stroke team**
Occupational therapist[a]	**Stroke-trained nurse**
Speech therapist[a]	Physiotherapy start within 2 days[a]
Diagnostic procedures	
Brain CT scan 24/7	**Brain CT scan 24/7**
MRI (T1, T2, T2*, FLAIR) 24/7	**CT priority for stroke patients[a]**
Diffusion-weighted MRI 24/7	Extracranial Doppler sonography
MR angiography 24/7	Extracranial duplex sonography
Conventional angiography 24/7	Transthoracic echocardiography
Coagulation test 24/7[a]	
Monitoring	
ECG	**ECG**
Pulse oximetry	Pulse oximetry
Blood pressure	Blood pressure
Breathing	
Invasive treatments provided	
Intra-arterial thrombolysis	
Carotid surgery	Carotid surgery
Angioplasty and stenting	Angioplasty and stenting
Surgery for aneurysms	
Coiling for aneurysms	
Hemicraniectomy	
Ventricular drainage	
Surgery for hematoma	
Respiratory support	
Infrastructure	
Intensive care unit	**Emergency department**
Anticoagulation clinic	Collaboration with outside rehabilitation center
A direct-line system between emergency medical services[a]	
Protocols and procedures	
Intravenous rt-PA protocols	**Intravenous rt-PA protocols**
	Stroke faculty[a]
	Stroke pathway
	Clinical research

The components indicated in bold are those considered 'absolutely necessary' for PSC by more than 75% of the respondents. There was no component considered 'absolutely necessary' for AHW by more than 75% of the respondents in both surveys.

[a] Components that were not included in another survey.

which were considered 'absolutely necessary' for PSC by more than 75% of the respondents in the European Expert Survey, were considered 'absolutely necessary' for PSC by only 24% of our respondents.

In addition to the essential requirements listed above for PSC, our survey identified the following components required for CSC: rehabilitation therapists (physiotherapist, occupational therapist and speech therapist) in the category of personnel; MRI with diffusion, T1, T2, T2*-weighted and FLAIR MRI sequences 24/7, MR angiography 24/7, conventional angiography 24/7 and coagulation test 24/7 in the category of diagnostic procedures; intra-arterial thrombolysis, carotid surgery, angioplasty and stenting, surgery for aneurysms, coiling for aneurysms, hemicraniectomy, ventricular drainage and surgery for hematoma in the category of invasive treatments provided; intensive care unit , anticoagulation clinic and a direct-line system between emergency medical services in the category of infrastructure, and intravenous rt-PA protocols in the category of protocols and procedures.

The components for CSC required by more than 75% of the respondents in both our survey and the European Expert Survey were the following: physiotherapist; brain CT scan 24/7; automated monitoring of the ECG, pulse oximetry and blood pressure; carotid surgery as well as angioplasty and stenting, and intravenous rt-PA protocols. Multidisciplinary stroke team, stroke-trained nurse, carotid ultrasonography, transthoracic echocardiography, collaboration with outside rehabilitation center, stroke pathway and clinical research were requirements for CSC only in the European Expert Survey. However, MRI 24/7, MR angiography 24/7, conventional angiography 24/7, respiratory support as well as most neuroendovascular and neurosurgical treatments were required by more than 75% of the respondents only in our survey (table 2).

Comparison between Neurosurgeons and Neurologists (or Stroke Medicine Physicians) in Our Survey

If the response rate was compared between neurosurgeons and neurologists (or stroke medicine physicians) in our survey, the rates of respondents who answered 'absolutely necessary' with regard to all survey items were higher for the neurologists (or stroke medicine physicians) than for the neurosurgeons, except for the components neurosurgeon on call, CT angiography, conventional angiography as well as most neuroendovascular and neurosurgical treatments. For PSC, the components considered 'absolutely necessary' by more than 75% of the neurologists (or stroke medicine physicians), but by less than 75% of the neurosurgeons, were: coagulation test 24/7 (neurologists vs. neurosurgeons: 75.0 vs. 59.5%; $p = 0.0042$), anticoagulation clinic (86.7 vs. 65.1%; $p < 0.0001$) and intravenous rt-PA protocols (79.6 vs. 62.0%; $p = 0.0015$). For CSC, the components considered 'absolutely necessary' by more than 75% of the neurologists (or

stroke medicine physicians), but by less than 75% of the neurosurgeons, were: multidisciplinary stroke team (83.0 vs. 69.0%; p = 0.0071), stroke-trained nurse (78.0 vs. 59.6%; p = 0.0009), physician expert in echocardiography (77.1 vs. 55.2%; p = 0.0001), social worker (82.5 vs. 70.0%; p = 0.0168), carotid ultrasonography (77.7 vs. 64.7%; p = 0.0202), transthoracic echocardiography (79.0 vs. 62.6%; p = 0.0037), SU (82.0 vs. 67.9%; p = 0.0072), a direct-line system between emergency medical services and the hospital (85.0 vs. 74.0%; p = 0.0253) and stroke database (81.0 vs. 57.7%; p < 0.0001). There was no component considered 'absolutely necessary' by more than 75% of the neurosurgeons but by less than 75% of the neurologists.

Discussion

This study showed the components considered 'absolutely necessary' for CSC and PSC by more than 75% of the directors of facilities certified by the Japan Stroke Society. Compared with the European Expert Survey, the respondents to our questionnaire placed less emphasis on the components multidisciplinary stroke team, stroke-trained nurse, ultrasonography, stroke pathway and clinical research. However, MRI, MR angiography, conventional angiography as well as neuroendovascular and neurosurgical treatments received more emphasis in our survey.

Stroke care provided by an organized and dedicated team and the use of stroke care maps lead to shortened hospital stays, fewer complications and a better functional outcome [7]. Thus, the EUSI published recommendations for stroke care stating that stroke patients should be treated in SU [8]. The BAC recommends acute stroke teams, SU and written care protocols as criteria for PSC [2]. In our survey, however, only 24% of the respondents considered a multidisciplinary stroke team, stroke-trained nurse and stroke pathway as 'absolutely necessary' for PSC. On the other hand, respiratory support as well as automated monitoring of pulse oximetry, blood pressure and breathing were considered 'absolutely necessary' for PSC by almost 90% of the respondents. These results of our survey suggest that more emphasis was placed on installations than on a dedicated stroke team and the use of stroke care maps.

In 2009, we conducted a questionnaire survey of facilities certified by the Japan Stroke Society on the clinical management of transient ischemic attack (TIA) [9]. In that survey, physicians were asked about diagnostic examinations for TIA patients presenting within 24 h of onset. The rates of respondents who answered 'routinely performed during initial assessment' were 97.5% for brain MRI, 94.9% for MR angiography and 63.3% for carotid ultrasonography. In a similar survey conducted in Canada, the corresponding rate for brain MRI was 15.5%, for MR or CT angiography 23.4% and for carotid ultrasonography 88.7% [10]. These results suggest that MRI and MR angiography were more commonly used as examinations for stroke patients in Japan than in other countries. This could be one of the reasons why MRI and MR angiography were more likely to be emphasized as 'essential components' in the present survey compared with the European Expert Survey.

In Japan, neurosurgeons have played a central role in the clinical management of stroke. According to the results of our survey on the clinical management of TIA, 67% of the doctors performing an initial management for TIA patients were neurosurgeons [9]. Approximately 70% of the respondents were neurosurgeons in the present survey, whereas most of the European stroke experts were neurologists [7]. When we analyzed our survey data separately for neurosurgeons and neurologists, the components considered 'absolutely necessary' by more than 75% of the neurologists included multidisciplinary stroke team, stroke-trained nurse and ultrasonography. Analyzing the data from only the neurologists in our survey reduced the differences between our survey and the European Expert Survey. Given these results, the difference in results between our survey and the European Expert Survey could partly be explained by the different proportion of neurosurgeons and neurologists among the respondents.

The results of this survey helped to change current practice in Japan. After this survey, we became aware of the importance of multidisciplinary stroke teams. As an example, a system of certified stroke nurses was started in 2010.

In 2011, the American Heart Association/American Stroke Association published a scientific statement on metrics for measuring the quality of care in CSC [11]. The survey conducted by the Executive Committee of the European Stroke Initiative demonstrated that less than 10% of European hospitals admitting acute stroke patients have optimal facilities, and that even the minimum level was not available in 40% of them [12]. Recently, the European Stroke Organization (ESO) Stroke Unit Certification Committee published a special report titled 'European Stroke Organization recommendations to establish a stroke unit and stroke center' [13]. It may also be important for Japan to determine how many hospitals are

able to provide care covering 'essential components of stroke centers'.

The present study has some limitations. First, the rate of response to our questionnaire was not high. Second, the data for this study were collected in 2007 and thus may not reflect current trends in clinical practice such as the use of neurovascular devices like the Merci retriever and Penumbra System. Third, although not only components considered 'absolutely necessary' by more than 75% but also those considered as such by more than 50% of the respondents were extracted in the European Expert Survey, we only extracted components considered 'absolutely necessary' by more than 75% of the respondents as 'essential components'.

In conclusion, the present study indicated the components that stroke centers were expected to have in Japan. Our survey demonstrated that more emphasis was likely to be placed on installations than on a dedicated stroke team and the use of stroke care maps. In addition, the results of this study may reflect some characteristics of the stroke care environment in Japan, such as the predominance of neurosurgeons and widespread use of MRI.

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Disclosure Statement

None.

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AP&T Alimentary Pharmacology and Therapeutics

Randomised clinical trial: prevention of recurrence of peptic ulcers by rabeprazole in patients taking low-dose aspirin

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SUMMARY

Background
Few studies have evaluated the effects of rabeprazole on low-dose aspirin (LDA)-induced gastroduodenal injuries.

Aim
To conduct a randomised, double-blind, triple-dummy, active-controlled, multicentre trial, named the PLANETARIUM study, to assess the efficacy, dose–response relationship and safety of rabeprazole for peptic ulcer recurrence in Japanese patients on long-term LDA therapy.

Methods
Eligible patients had a history of endoscopically confirmed peptic ulcers and were receiving long-term LDA (81 or 100 mg/day) therapy for cardiovascular or cerebrovascular protection. Subjects were randomly segregated into three groups receiving rabeprazole 10 mg once daily (standard dose in Japan), rabeprazole 5 mg once daily, or teprenone (geranylgeranylacetone; mucosal protective agent commercially available in Japan) 50 mg three times per day as an active control. The primary endpoint was recurrence of peptic ulcers over 24 weeks.

Results
Among 472 randomised subjects, 452 subjects (n = 151, 150, 151, respectively) constituted the full analysis set. The cumulative recurrence rates of peptic ulcers over 24 weeks in the 10- and 5-mg rabeprazole groups were 1.4% and 2.8%, respectively, both of which were significantly lower than that in the teprenone group (21.7%). The cumulative occurrence rate of bleeding ulcers over 24 weeks in the teprenone group was 4.6%, while bleeding ulcers were not observed in the 10- or 5-mg rabeprazole groups. Rabeprazole was well tolerated at both doses.

Conclusion
Rabeprazole prevents the recurrence of peptic ulcers with no evidence of a major dose–response effect in subjects on low-dose aspirin therapy.

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INTRODUCTION

The two main causes of peptic ulcer are *Helicobacter pylori* infection and use of medications such as low-dose aspirin (LDA) and nonsteroidal anti-inflammatory drugs (NSAIDs).[1, 2] As *H. pylori*-positive populations are decreasing in the EU, USA, Japan, etc., the occurrence of ulcers attributable to *H. pylori* is also decreasing in these countries, while drug-induced ulcers are on the rise.[3, 4] The use of aspirin as one of the key anti-thrombotic drugs for ischaemic heart disease and cerebrovascular disease is rapidly increasing.[5–7] However, erosive lesions were previously reported in approximately 40–60%, peptic ulcers in approximately 10–20%[8, 9] and gastrointestinal bleeding in approximately 1–2%[10, 11] of patients on LDA therapy, with reports of cases in which haemorrhage and perforation resulted in death. To overcome LDA-induced adverse effects, the concomitant use of proton pump inhibitors (PPI) has been recommended as a measure to prevent upper gastrointestinal mucosal injury.[12] In Japan, combination therapy of LDA with lansoprazole or esomeprazole is available, although combination therapy with rabeprazole is not yet available.

Rabeprazole exerts a rapid and potent inhibitory effect on gastric acid secretion, and has been reported to be efficacious against various acid-related diseases, with an emphasis on GERD.[13, 14] Users of LDA are primarily elderly and often have multiple diseases and take concomitant medications. Under these circumstances, PPIs with fewer drug interactions would be preferred, because the drug interaction may induce adverse effects or decrease the efficacy of the concomitantly administered drug by increasing or decreasing its plasma concentration, respectively. A recent study of the effects of PPIs on cytochrome 450 (CYP) activity assessed by the [^{13}C]-aminopyrene breath test in healthy subjects showed that omeprazole and lansoprazole at the standard doses inhibit CYP activity, while rabeprazole does not.[15] This finding is consistent with the previously known fact that rabeprazole has relatively less effects on CYP2C19 and CYP3A4.[16, 17] Thus, for example, rabeprazole provides a clinically safe combination with tacrolimus, which is metabolised by CYP2C19 and CYP3A4,[18, 19] and with clopidogrel, which is activated by CYP2C19.[20]

Rabeprazole is a promising candidate PPI for use in combination with LDA. So far, only an open-label comparative study of the preventive effects of rabeprazole on ulcer recurrence in patients on LDA therapy has been reported[21]; there are no reports of double-blind comparative studies, which have the minimum bias, or reports investigating the preventive effects of 5-mg rabeprazole (in Japan, the standard dose of rabeprazole is 10 mg).

We conducted a Phase 2/3 double-blind comparative study (PLANETARIUM study) to confirm the efficacy and safety of 5- and 10-mg rabeprazole in preventing the recurrence of gastric and duodenal ulcers in patients with a history of peptic ulcer who were on long-term LDA therapy. As an active control, we used teprenone (geranylgeranylacetone). Teprenone was first commercialised by Eisai Co., Ltd. in Japan in 1984 for curing gastric ulcer and gastritis.[22, 23] Teprenone decreased *H. pylori* density in the corpus of gastritis patients.[24] The clinical mucoprotective efficacy of teprenone against NSAID-induced gastroduodenal injury was previously reported.[25, 26] Teprenone has shown to induce heat shock protein 70 (HSP70) resulting in protection against NSAID-induced gastric lesions.[27, 28]

MATERIALS AND METHODS

The PLANETARIUM study is a Phase 2/3, randomised, parallel-group, double-blind, triple-dummy, active-controlled, multicentre study, and was conducted between July 2011 and March 2013 at 63 institutions in Japan. This study was registered at http://clinicaltrials.gov (NCT01397448). Before the start of the study, the protocol was reviewed and approved by the individual Institutional Review Boards of each institution. Written informed consent was obtained from all subjects prior to enrolment. This study was conducted in compliance with the Good Clinical Practice guidelines and ethical principles based on the Declaration of Helsinki.

Subjects

Subjects were out-patients ≥20 years old, with a history of gastric or duodenal ulcer (ulcer scar at baseline endoscopy or ulcer scar/active ulcer at prior endoscopy), taking LDA (81 or 100 mg/day) for preventing thrombosis/embolisation in patients with angina pectoris, myocardial infarction or ischaemic cerebrovascular disorders. Eligibility was determined based on the subjects' history of ulcer or the presence of an ulcer scar at baseline endoscopy, as determined by the endoscopy central review panel (panel of three endoscopy specialists: KH, MK and MF), using endoscopy photos submitted by each institution. Other inclusion criteria included stable disease condition of the patient, with no pressing need to change the dosage and administration of aspirin. Patients with the following findings on baseline endoscopy performed within 14 days before randomisation were excluded: