Figure 2

Check items	Initial	Follow-up period					
		2006	2007	2008	2009	2010	2011 or end of follow-up
Background	xx						
Vascular events		xx	xx	xx	xx	xx	xx
Adverse events		xx	xx	xx	xx	xx	xx
Compliance with the treatment		x	x	x	x	x	x
Risk factors							
Blood pressure, serum lipids, blood glucose	xx	x*	x*	x*	x*	x*	x*
Body weight	xx	xx	xx	xx	xx	xx	xx
Smoking	xx	xx	xx	xx	xx	xx	xx

Schedule of examinations. xx, essential; x, to be reported wherever possible. Asterisk indicates examination results related to the disease under treatment are essential.

the study. Assuming that the maximum frequency of events in the aspirin and control groups was 0.786%, the number of required patients was recalculated without change in the relative rate of event reduction, which remained at 20%. The revised estimation indicated that approximately 14,960 patients for an expected number of events of 624 cases would be required to demonstrate a 20% reduction in the annual frequency of events from 0.874% to 0.698% by aspirin administration at a 2-sided $\alpha = .05$ and 80% statistical power during the enrollment period from the end of September 2006 until the end of June 2007. On the basis of this calculation, the enrollment target was reset at an estimated 14,960 patients to achieve 624 primary end point events, which is expected by the end of September 2011.

Statistical analysis

The primary goal of this study is to test the hypothesis that the time to the composite primary end point is significantly longer in patients treated with aspirin than in patients who were not given aspirin. The null hypothesis is that the time to onset of events does not differ between the 2 groups. The effect of treatment on the primary end point will be tested by the stratified log-rank test on all patients meeting inclusion criteria, with underlying disease (hypertension, dyslipidemia, and/or diabetes) used for stratification. End point analyses are planned for the stratified risk factor subgroups and for subgroups by sex and age. The statistical test will be performed in a 2-sided manner with a significance level set at .05. If aspirin is found to be inferior to no treatment, whether the difference is statistically significant is not of interest. To estimate the efficacy of aspirin therapy, the Cox proportional hazards model

Table I. Patient characteristics and underlying risk factors at baseline

Factor, n (%)	Aspirin (n = 7214)	No aspirin (n = 7252)	Total (N = 14 466)
Male	3046 (42.2%)	3061 (42.2%)	6107 (42.2%)
HT	6134 (85.0%)	6156 (84.9%)	12,290 (85.0%)
DL	5179 (71.8%)	5196 (71.6%)	10,375 (71.7%)
Diabetes	2442 (33.9%)	2461 (33.9%)	4903 (33.9%)
HT and DL	2821 (39.1%)	2824 (38.9%)	5645 (39.0%)
DL and DM	344 (4.8%)	354 (4.9%)	698 (4.8%)
HT and DM	492 (6.8%)	499 (6.9%)	991 (6.9%)
HT, DL, and DM	1442 (20.0%)	1442 (19.9%)	2884 (19.9%)
Obesity (BMI ≥ 25 kg/m^2)	2644 (36.7%)	2617 (36.1%)	5261 (36.4%)
Smoking	950 (13.2%)	936 (12.9%)	1886 (13.0%)
Family history	1967 (27.3%)	1986 (27.4%)	3953 (27.3%)
Low HDL-cholesterol (<40 mg/dL)	672 (9.3%)	663 (9.1%)	1335 (9.2%)

HT, Hypertension; *DL*, dyslipidemia; DM, diabetes mellitus; *BMI*, body mass index; *HDL*, high-density lipoprotein.

will be used to determine the intergroup hazard ratios for each end point and their corresponding 95% CIs. Corrections will also be incorporated for other factors used in the allocation of patients and for biased background variables as needed. The length of time until the onset of events will be estimated by the Kaplan-Meier method.

Interim analysis and data monitoring

The JPPP Steering Committee is overseeing the conduct of this study (see Appendix, available online). Case report form pages are entered into the study Web site or faxed to a central data center in Tokyo for input into the study database. An independent Data Monitoring Committee, composed of 4 academic members and an independent statistician, regularly monitors the results of the trial. Interim analyses have been planned at 1-year intervals beginning 6 months after the end of patient enrollment and continuing until final study analysis. After each interim analysis, the Data Monitoring Committee will advise whether the study should be continued and if the study protocol should be amended based on several factors including occurrence of unforeseen or serious adverse reactions, occurrence of adverse reactions at a higher incidence than expected, publication of new results from a similarly designed study, ethical issues generated by changes in the social environment, or if the interim analysis shows the clear superiority of aspirin over no treatment or no possibility of obtaining beneficial effects with aspirin relative to no treatment. To keep the α error for the study at 2.5% (1-sided), adjustment for multiple testing will be done using the Lan-Demets α consumption function; the α consumption function of the O'Brien-Fleming type will also be used.

Results

A total of 14,659 patients were enrolled at 1,000 study sites in 47 prefectures in Japan from March 28, 2005, to June 30, 2007, at which time patient recruitment was completed. Of these, baseline data were available for

Table II. Demographic and clinical characteristics at baseline

Parameter, mean (SD)	Aspirin (n = 7214)	No aspirin (n = 7252)	Total (N = 14 466)
Age (y)	70.6 (6.2)	70.5 (6.2)	70.6 (6.2)
Systolic blood pressure (mm Hg)	137.2 (15.8)	137.2 (15.8)	137.2 (15.7)
Diastolic blood pressure (mm Hg)	77.7 (10.4)	77.6 (10.3)	77.6 (10.3)
Total cholesterol (mg/dL)	202.8 (33.2)	203.6 (32.7)	203.2 (32.9)
Low-density-lipoprotein cholesterol (mg/dL)	118.7 (30.8)	119.3 (30.5)	119.0 (30.6)
High-density-lipoprotein cholesterol (mg/dL)	57.8 (16.0)	58.4 (16.0)	58.1 (16.0)
Triglycerides (mg/dL)*	115.5 (84-160)	114 (82-158)	115 (83-158)
Fasting blood glucose (mg/dL)†	107.8 (31.5)	107.8 (32.4)	107.8 (32.0)
Glycated hemoglobin (%)	5.7 (1.0)	5.7 (0.9)	5.7 (1.0)
Body mass index (kg/m^2)	24.2 (3.6)	24.2 (3.4)	24.2 (3.5)
Waist circumference (cm)‡	85.1 (9.9)	84.7 (10.3)	84.9 (10.1)

*Median (interquartile range).
†Values for diabetes mellitus (DM) and non-DM subjects; DM subjects had fasting blood glucose (mean [SD]) as follows: 132.9 (42), aspirin group; 133 (43.7), nonaspirin group; 132.9 (42.8), all; non-DM subjects had fasting blood glucose (mean [SD]) as follows: 95.0 (10.8), aspirin group; 94.8 (10.8), nonaspirin group; 94.9 (10.8), all.
‡Waist circumference data were available for 3950 patients, including 1967 patients in the aspirin group and 1983 patients in the no-aspirin group.

14,466 patients (98.7%). With regard to the other patients, 88 (0.6%) did not meet eligibility criteria, 11 (0.1%) withdrew consent, 52 (0.4%) stopped attending study visits, and 42 (0.3%) were withdrawn by their enrolling physicians.

Baseline characteristics of patients in the aspirin and control groups were similar (Tables I and II). Overall, the mean (SD) age of the study cohort was 70.6 (6.2) years; 6,107 (42.2%) were men and 8,359 (57.8%) were women. Hypertension was the most common underlying disease found in 85.0% of the study cohort, with dyslipidemia and diabetes seen in 71.7% and 33.9%, respectively. Hypertension was comorbid with both dyslipidemia and diabetes in 19.9%, with only dyslipidemia in 39.0% and only diabetes in 6.9%. Among other risk factors, current smoking was reported by 13.0% of the study cohort overall (25.2% of men and 4.1% of women), family history of premature CV disease by 27.3%, and a body mass index ≥25 kg/m^2 by 36.4% of patients. Overall, 80.4% of the study cohort—80.2% in the aspirin group and 80.6% in the no aspirin group—had ≥3 risk factors (Figure 3). Waist circumference, measured in 3,950 patients (27.3% of the study cohort), averaged 84.9 cm. In this subset of patients, 44% of men and 21.7% of women met the criteria for metabolic syndrome established by the Japanese Committee for the Diagnostic Criteria of Metabolic Syndrome (waist circumference ≥85 cm in men, or ≥90 cm in women, and presence of ≥2 abnormalities: triglycerides ≥150 mg/dL and/or high-density-lipoprotein cholesterol <40 mg/dL or under treatment of dyslipidemia, systolic blood pressure ≥130 mm Hg and/or diastolic blood pressure ≥85 mm Hg or under treatment of hypertension, fasting glucose ≥110 mg/dL or under treatment of diabetes).[27] The percentages of patients with at least 3 risk determinants for the metabolic syndrome, according to the criteria established by the Adult Treatment Panel III of the National Cholesterol Education Program, were 44.3% of men and 60.5% of women, and 54.1% and 53.8% of patients in the aspirin and no aspirin groups, respectively.

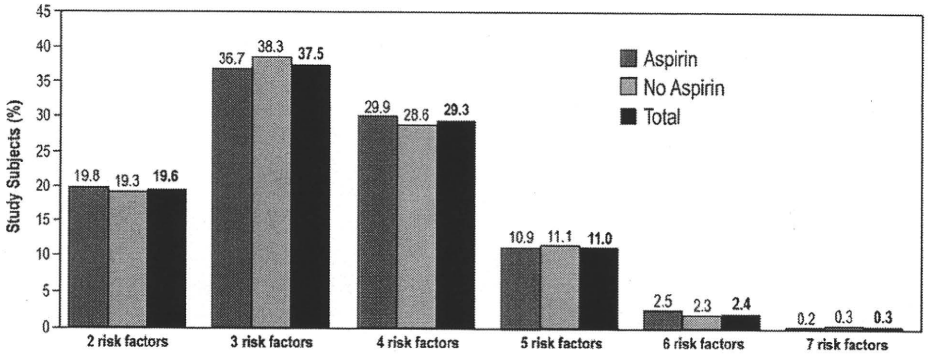
The most commonly used concomitant medications at randomization are shown in Table III. More than 90% of patients with hypertension were taking antihypertensive medication. About 60% of patients with dyslipidemia received lipid-modifying therapy, and 70% of patients with diabetes were being treated with diabetes medication. The mean blood pressure at randomization was 137/78 mm Hg, and the mean total cholesterol was 203 mg/dL (Table II).

Discussion

The JPPP is designed to evaluate the benefit-risk relationship of primary prevention of CV disease with low-dose, enteric-coated aspirin in the Japanese population, which has a lower CV risk compared with Western populations.[28] The JPPP was planned to enroll moderate- or higher risk Japanese patients, who had ≥2 risk factors, namely elderly patients with underlying hypertension, dyslipidemia, or diabetes. However, the results of the first general data examination showed that the incidence of end point events was lower than that estimated before the start of the study, and patient accrual was increased from the initially planned 10,000 patients to nearly 15,000 patients. The results of this initial data examination showed that CV event risk in the study population was lower than was initially estimated for elderly Japanese patients with ≥2 risk factors.

The lower CV event rate found in the JPPP study population might be explained by risk factors that were well controlled. Patients screened for the study were initiated on medication to control their risk factors. The percentage of patients in the JPPP at baseline who were at their control goals specified in guidelines was 38% for blood pressure, 59% for dyslipidemia (total cholesterol), and 40% for diabetes (blood glucose), similar to the control rates in recent surveys of Japanese patients with CV risk factors.[29-31] More than 90% of

Figure 3



Distribution of patients according to number of risk factors at baseline. Risk factors included hypertension, dyslipidemia, diabetes, smoking, family history, high-density-lipoprotein cholesterol <40 mg/dL, and age.

Table III. Medication use according to underlying disease

Disease medication, n (%)	Aspirin		No aspirin		Total	
Hypertension	n = 6134		n = 6156		N = 12 290	
Calcium blocker	3949	64.4%	4016	65.2%	7965	64.8%
β-Blocker	675	11.0%	688	11.2%	1363	11.1%
α-Blocker	385	6.3%	411	6.7%	796	6.5%
ACE inhibitor	846	13.8%	857	13.9%	1703	13.9%
ARB	2779	45.3%	2780	45.2%	5559	45.2%
Diuretic	506	8.2%	518	8.4%	1024	8.3%
Others	42	0.7%	37	0.6%	79	0.6%
No medication	414	6.7%	407	6.6%	821	6.7%
Dyslipidemia	n = 5179		n = 5196		N = 10 375	
Statin	2639	51.0%	2649	51.0%	5288	51.0%
Cholestyramine	29	0.6%	22	0.4%	51	0.5%
Fibrate	363	7.0%	356	6.9%	719	6.9%
Probucol	59	1.1%	50	1.0%	109	1.1%
Others	26	0.5%	22	0.4%	48	0.5%
No treatment	2114	40.8%	2150	41.4%	4264	41.1%
Diabetes	n = 2442		n = 2461		N = 4903	
Insulin	179	7.3%	154	6.3%	333	6.8%
Sulfonylurea	976	40.0%	930	37.8%	1906	38.9%
α-Glucosidase inhibitor	657	26.9%	639	26.0%	1296	26.4%
Biguanide	283	11.6%	248	10.1%	531	10.8%
Thiazolidinedione	333	13.6%	370	15.0%	703	14.3%
Nateglinide	207	8.5%	184	7.5%	391	8.0%
Others	0	0.0%	0	0.0%	0	0.0%
No medications	711	29.1%	795	32.3%	1506	30.7%

ACE, Angiotensin-converting enzyme; *ARB*, angiotensin receptor blocker.

patients with hypertension were taking antihypertensive medication. Approximately 40% of patients with dyslipidemia and 30% of patients with diabetes were not receiving medication for those conditions, suggesting that among individuals poorly responding to diet therapy or exercise therapy or those receiving routine examinations there seem to be cases where intensification of treatment of dyslipidemia or diabetes is overlooked, possibly due to infrequent blood tests. When the patients in this study are observed for 4 years, we may be able to obtain data that endorse the importance of early detection and monitoring with medication initiation.

Currently, there is no good clinical evidence that determines whether there is a benefit to aspirin use in Japanese individuals with multiple CV risk factors, especially if their risk factors, as has been observed in this study, are well controlled. Furthermore, the pattern of atherosclerotic events is different in Japanese than

in Western patients; stroke mortality is higher than IHD mortality in Japan, whereas the opposite occurs in Western populations.[21] The meta-analysis of Western studies showed a benefit on serious vascular events due to reduction in coronary events, a trend benefiting ischemic stroke, but an increase in gastrointestinal and extracranial bleeding.[17] Aspirin has also been reported to be associated with gastrointestinal bleeding in Japanese patients.[32,33] These differences emphasize the need to develop valid strategies for preventing atherosclerotic events in Japan based on national studies such as this one or on joint studies among multiple Asian countries rather than on Western studies.

In summary, the JPPP is the first and largest trial designed to evaluate whether the benefit of low-dose aspirin in elderly Japanese patients with CV risk factors for the primary prevention of atherosclerotic events outweighs any bleeding risk for a mean follow-up of 4 years. The results should be applicable to the lower risk Japanese populations and may affect guidelines and clinical practice.

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ORIGINAL ARTICLE
Arrhythmia/Electrophysiology

Sex-Related Differences in the Risk Factor Profile and Medications of Patients With Atrial Fibrillation Recruited in J-TRACE

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Background: Clinical characteristics, including risk factors for thromboembolism, and medications differ between men and women with atrial fibrillation (AF) in Western countries. Whether such a difference exists for Japanese patients with AF is unclear, so data from J-TRACE were used to investigate this issue.

Methods and Results: A total of 2,892 patients (2,028 men, 864 women; 70.3 years old) with AF were analyzed for the respective prevalences of risk factors and medications. CHADS2 score was calculated to determine thromboembolic risk level. Women were older (P<0.001), and more frequently had heart failure (P<0.001), and hypertension (P=0.051) than men. The proportion of subjects aged 75 years or older was higher among women than among men (P<0.001). CHADS2 score was therefore significantly higher in women than in men (2.05±1.29 vs 1.88±1.33, P<0.001). Sex-related differences were not observed for the prevalence of diabetes mellitus, myocardial infarction or ischemic stroke, nor did warfarin usage differ between men and women.

Conclusions: Sex-related differences were observed in the risk factor profile and medications of Japanese patients with AF. CHADS2 score was higher in women than in men. (*Circ J* 2010; **74:** 650–654)

Key Words: Atrial fibrillation; CHADS2 score; Clinical characteristics; Medications; Sex differences

Atrial fibrillation (AF) is a common cardiac arrhythmia seen in general practice as well as in the cardiology clinic. The prevalence of AF differs between men and women in Western countries,[1–3] and also in Japan.[4,5] Several studies have reported that there are sex-related differences in the clinical characteristics and medications of patients with AF.[6–10] A prospective, cohort study indicated that the effects of AF on the risk of stroke were greater in women than in men after adjustment for age and comorbidity.[9] Other studies also showed that AF is associated with an increase in cardiovascular events, including mortality and stroke, especially in women.[7,11,12] Some risk stratification schemes consider women to be at high risk for ischemic stroke,[13,14] while others do not.[15,16] However, because the sex-related differences in risk factors for cardiovascular diseases and medications of Japanese patients with AF have yet to be clarified, registry data for a large, nation-wide, multicenter, cooperative study, J-TRACE (The Japan Thrombosis Registry for Atrial Fibrillation, Coronary or Cerebrovascular Events),[17,18] were analyzed to address this issue in the present study.

Methods

The details of J-TRACE have been reported elsewhere.[17,18] Briefly, J-TRACE has a steering committee of 5 members and 41 regional coordinators selected from 10 regions of Japan (Appendix 1). Recruitment of patients to investigate risk factor profiles and current status of medications for risk factors and for prevention of cardiovascular events in patients with

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Table 1. Clinical Characteristics of Japanese Patients With AF

	Men (n=2,028)	Women (n=864)	P value
Age (years)	69.4±9.4	72.6±8.5	<0.001
≥75 years (%)	32.0	44.5	<0.001
Chronic AF* (%)	68.8 (1,062/1,543)	66.1 (462/699)	0.199
BMI (kg/m²)	23.8±3.2	23.4±4.1	<0.001
CHF (%)	17.0	27.1	<0.001
Hypertension (%)	57.2	61.1	0.051
DM (%)	19.1	16.7	0.125
Ischemic stroke (%)	29.4	26.3	0.089
VHD (%)	10.1	21.1	<0.001
MI (%)	7.6	5.9	0.096
HC (%)	25.1	35.5	<0.001
Drinker (%)	46.3	5.2	<0.001
Smoker (%)	21.2	4.3	<0.001
CHADS2 score	1.88±1.33	2.05±1.29	<0.001

Data are mean±SD or % of patients.
*In the myocardial infarction and stroke categories; subtypes of AF were not specifically determined.
AF, atrial fibrillation; BMI, body mass index; CHF, congestive heart failure; DM, diabetes mellitus; MI, myocardial infarction; VHD, valvular heart diseases including valve replacement; HC, hypercholesterolemia.

Table 2. Distribution of CHADS2 Scores

CHADS2 score	Men	Women
0	15.9	11.1
1	28.4	25.0
2	23.5	29.6
3	19.2	20.6
4	10.5	10.0
5	2.2	3.4
6	0.3	0.3

Figures are % of patients.
P<0.001 between men and women.

Table 3. Age and CHADS2 Score

	Age			P value
	<65 years	65–74 years	≥75 years	
Men	1.24±1.12 (n=572)	1.63±1.22 (n=808)	2.74±1.17 (n=648)	<0.001
Women	1.38±1.16 (n=153)	1.57±1.14 (n=326)	2.72±1.12 (n=385)	<0.001

Data are mean±SD.

prior stroke, myocardial infarction (MI) or AF began in January 2005 and ceased in December 2006.

Study Population

Patients aged 20–90 years were eligible for enrollment if they had at least 1 of the 3 cardiovascular diseases (stroke, MI or AF). The study protocol was approved by an Institutional Review Board at each participating site and all patients gave informed consent. Those in the AF category, and those in the stroke and MI categories who also had AF, comprised the study subjects for this subanalysis of J-TRACE. Those in the recovery phase of acute MI or acute stroke were not eligible for enrollment in J-TRACE.

Baseline Characteristics

All subtypes of AF were included. AF was diagnosed electrocardiographically using standard diagnostic criteria. Risk factors and comorbidities were collected from the medical record as baseline data. Among them were hypertension, diabetes mellitus, hypercholesterolemia, valvular diseases, MI, ischemic stroke, congestive heart failure, smoking, and drinking. Regular use of medications, including anticoagulants, antiplatelet agents, and drugs for hypercholesterolemia, hypertension, and diabetes mellitus, was also determined from the medical record. Each patient's CHADS2 score[15] was calculated to determine the level of cardioembolic risk: 1 point was given for advanced age (≥75 years), hypertension, congestive heart failure, or diabetes mellitus, and 2 points for prior stroke or transient ischemic attack.

Statistical Analysis

Continuous variables are shown as the mean±SD, and categorical variables as percentages. Continuous variables were compared by analysis of variance or Student's t-test, and categorical variables with the chi-square test, with P<0.05 considered significant.

Results

Risk Factor Profile

A total of 2,892 patients (2,028 men, 864 women; mean age, 70.3 years) with AF comprised the study group. Numbers of patients and their mean age in the 3 categories were as follows: AF category, 1,543 men (68.9±9.6 years old) and 699 women (72.4±8.5); stroke category, 399 men (70.6±8.4) and 141 women (73.0±8.3); MI category, 86 men (71.7±8.1) and 24 women (75.3±8.0). Their clinical characteristics are summarized in **Table 1**. Some of the characteristics exhibited differences by sex. Women were older (P<0.001), and more frequently had congestive heart failure (P<0.001), hypertension (P=0.051), valvular diseases or valve replacement (P<0.001), and hypercholesterolemia (P<0.001) than the men, but drank (P<0.001) and smoked (P<0.001) less frequently than men. The proportion of subjects aged 75 years or older was higher and body mass index was slightly but significantly lower in women than in men (P<0.001, each case). The prevalences of chronic AF, diabetes mellitus, MI, and ischemic stroke did not differ between men and women.

The CHADS2 score was slightly but significantly higher in women than in men (**Table 1**, P<0.001) because of their higher prevalence of older age (≥75 years), hypertension, and congestive heart failure. The distribution of CHADS2 scores differed significantly between men and women (**Table 2**, P<0.001). It increased with age for both men and women, but did not differ between men and women in any age group (**Table 3**).

Medications

Medications are summarized in **Table 4**. Use of warfarin and antiplatelet agents did not differ between men and women. Reflecting the differences in prevalence of hypertension and hypercholesterolemia between men and women, drugs for the treatment of these diseases were used more frequently in women than in men (P<0.001, each case). In contrast, use of antidiabetic drugs was similar in men and women.

There were no apparent sex-related differences in the rate of use of warfarin or aspirin at any CHADS2 score (**Table 5**).

Table 4. Medications at Baseline

	Men	Women	P value
Warfarin	73.1	72.7	0.807
Antiplatelet agents	37.9	36.0	0.328
Aspirin	32.1	30.8	0.504
Ticlopidine	5.0	5.0	0.316
Cilostazol	2.0	1.3	0.191
Antihypertensives	71.8	78.8	<0.001
ACEI	17.4	14.8	0.087
ARB	28.4	32.2	0.039
β-blockers	21.4	21.3	0.927
Calcium antagonists	36.4	42.5	0.002
Diuretics	18.6	33.4	<0.001
Lipid-lowering drugs	16.7	26.4	<0.001
Statins	14.9	23.7	<0.001
Antidiabetic drugs	10.6	10.9	0.825
Oral	8.7	8.6	0.921
Insulin	1.4	2.2	0.111

Data are % of patients.
Only major drugs for treatment of comorbidities and prevention of thromboembolism are listed (see Uchiyama et al[18] for more detailed information on medications in J-TRACE).
ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin II receptor blockers.

Table 5. Use of Warfarin and Aspirin at Each CHADS2 Score

CHADS2 score	Warfarin use (%)		Aspirin use (%)	
	Men	Women	Men	Women
0	57.9	61.4	32.3	28.1
1	68.9	66.2	33.9	31.4
2	74.8	73.8	30.6	32.0
3	84.9	77.0	26.9	30.3
4	81.1	87.2	34.4	29.1
5	77.3	79.3	31.3	27.6
6	83.3	66.7	83.3	66.7
P value	<0.001	0.001	0.008	0.852

Warfarin usage differed significantly among CHADS2 scores in both men (P<0.001) and women (P=0.001). It increased gradually from approximately 60% to 80% as the score increased from 0 to 3 for both men and women; thereafter it reached a plateau, except in the case of women with a score of 6. Aspirin usage also differed significantly among CHADS2 scores in men (P=0.008), but not in women (P=0.852). It did not show any apparent score-dependent increase as observed in the case of warfarin usage.

Discussion

The major findings of the present study are as follows. First, there were sex-related differences in the risk factor profile and medications of patients with AF recruited in J-TRACE. Women were older and more frequently had hypertension, valvular diseases, congestive heart failure, and hypercholesterolemia than men. The prevalence of diabetes mellitus, ischemic stroke, and MI did not differ between men and women. Second, CHADS2 score was consequently slightly but significantly higher in women than in men with AF. This sex-related difference could be largely related to the higher proportion of women aged 75 years or older. Third, no sex-related differences in the use of warfarin or aspirin were observed at any CHADS2 score.

Risk Factor Profile of Patients With AF

Reports from Western countries[6–10] suggest that sex-related differences could exist in the risk factors for cardiovascular diseases of patients with AF. In the present study, mean age was higher and the prevalence of hypertension also tended to be higher in women than in men, consistent with the previous reports;[6–9] however, the prevalence of congestive heart failure was also higher in women than in men in the present study, a finding that is inconsistent with those reports from Western countries.[6–9] Notably, the prevalence of diabetes mellitus and of a prior history of ischemic stroke were not consistent.[6–9]

Cohort studies of the general population in Japan have indicated that the prevalences of hypertension and diabetes mellitus are higher in men than in women.[19–21] The prevalence of cardiac diseases was not higher in women than in men with AF,[4,5] so the higher prevalences of hypertension and congestive heart failure in women with AF found in the present study do not simply reflect the prevalence of these diseases in the general population of Japan. Valvular disease is a well-known risk factor for AF,[22] especially for Japanese women.[23] Drinking and smoking could promote the development of AF,[22–25] and were present more frequently in men than in women in the present study, as in the general population of Japan.[4,5,19–21] The electrophysiological properties of the atria differ between men and women,[26] so greater comorbidity and age might be required for AF to develop in women than in men.

Thromboembolic Risk

A sex difference in CHADS2 score was found in the present study, a finding consistent with the ATRIA study.[7] In the Euro Heart Survey the score might have been higher in women than in men, because mean age and the prevalences of hypertension, diabetes mellitus, and prior ischemic stroke were significantly higher in women than in men.[9] In some studies the levels of biomarkers of a prothrombotic state were higher in women with AF than in men with AF.[27,28] These findings could explain the inclusion of female sex as a risk factor in some schemes for predicting thromboembolic events in patients with AF.[13,14] In fact, among patients with acute stroke, embolic infarction is observed more frequently in women than in men.[29] It is difficult to determine the reasons for the sex-related difference in thromboembolic risk; however, some components of the CHADS2 score were observed more frequently in women in the ATRIA study,[7] Euro Heart Survey,[9] and in the present study.

Medications

Registry studies in Western countries have indicated that warfarin usage does not differ between men and women.[6,9] In the present study, the rate of warfarin usage did not differ between men and women as a whole nor did it differ between them at any CAHDS2 score (**Table 5**). Warfarin usage is at present not necessarily less frequent in women than in men, as reported in earlier registry[6] and community-based cohort[30] studies.

Use of aspirin and antidiabetic drugs was similar in men and women; however, drugs for hypertension and hypercholesterolemia were used more frequently by women than by men. The latter finding might reflect the sex-related differ-

ences in the prevalence of these diseases in the present study.

Study Limitations

First, enrollment of consecutive patients with stroke, MI, and AF was recommended, but may not necessarily have occurred at each participating site and this possible selection bias could have affected the present results. Second, data for subjects with AF were collected from 3 categories of J-TRACE,[17,18] possibly resulting in increased prevalences of ischemic stroke and MI. However, this might not necessarily have affected sex-related differences in the frequency of these diseases in the present study. Actually, when only patients of AF category were analyzed, the results did not differ in terms of sex-related differences in mean age, CHADS2 score, and prevalences of heart failure, hypertension, smoking, drinking habit and warfarin usage (data not shown). Third, the study design of the J-TRACE did not define the diagnostic criteria of comorbidities, including hypertension, hypercholesterolemia and others; however, data of comorbidities were collected from the medical record. If strict diagnostic criteria of comorbidities were used, the present results would not have changed greatly. Finally, the intensity of anticoagulation was not determined systematically, and follow-up data are not yet available.

Clinical Implications

Our findings indicate sex-related differences in the clinical risk factor profile of patients with AF, with the CHADS2 score slightly but significantly higher in women with AF than in men with AF in the clinical setting in Japan. Further follow-up studies are required to elucidate the effects of these sex-related differences on subsequent thromboembolic events.

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Disclosure

There is no conflict of interest to declare.

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Appendix 1

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Positional Relationship between Recurrent Intracerebral Hemorrhage/Lacunar Infarction and Previously Detected Microbleeds

BACKGROUND AND PURPOSE: Although MBs, ICH, and LI are secondary to cerebral microangiopathy, it remains unclear whether the location of subsequent ICH/LI corresponds to the previous location of MBs. We performed this study to clarify the positional relationship between recurrent ICH/LI and previously detected MBs.

MATERIALS AND METHODS: We evaluated patients with recurrent ICH/LI who had MBs, as shown on prior T2*-weighted MR imaging. We assessed retrospectively whether the location of recurrent ICH/LI corresponded to that of the prior MB. Patients with ICH were divided into the deep ICH group and the lobar ICH group, and the positional relationship between hematoma and previously detected MBs was evaluated.

RESULTS: A total of 55 patients, including 34 with recurrent ICH and 21 with recurrent LI were evaluated. Although the location of the LI corresponded to prior MBs in only 1 patient (4.8%), the location of ICH corresponded to prior locations of MBs in 21 patients (61.8%) (OR, 32.3; 95% CI, 3.86–270.3; $P < .001$). Among the patients with ICH, the correspondence ratio was higher in the deep ICH group (19 of 24 patients, 79.2%) than in the lobar ICH group (2 of 10 patients, 20%) (OR, 15.2; 95% CI, 2.42–95.3; $P < .002$).

CONCLUSIONS: The close positional association between recurrent ICH and prior MBs suggests that MBs represent hemorrhage-prone microangiopathy. In addition, different correspondence ratios between the deep ICH group and the lobar ICH group may be attributable to their different pathogenesis.

ABBREVIATIONS: ATBI = atherothrombotic brain infarction; CAA = cerebral amyloid angiopathy; CE = cardioembolic infarction; CI = confidence interval; DWI = diffusion-weighted imaging; ICH = intracerebral hemorrhage; LI = lacunar infarction; MB = microbleed; OR = odds ratio

MBs present as homogeneous round lesions with signal-intensity loss on gradient-echo T2*-weighted MR images. Pathologically, they represent hemosiderin deposits,[1,2] associated with small-vessel disease.

Previous studies have shown that MBs are observed more frequently in patients with ICH compared with patients with ischemic stroke.[3,4] Among patients with ischemic stroke, they are observed more frequently in patients with LI, which is based on small-vessel disease, compared with patients with ATBI or CE.[5,6] In addition, MBs are more prevalent among patients with recurrent stroke compared with patients with their first stroke.[4] Previous studies have also shown that the presence of MBs is an important risk factor for the occurrence of subsequent stroke, particularly hemorrhagic stroke.[7-9]

The topologic association, however, between the location of MBs and that of subsequent stroke is poorly understood. Although previous reports described the association between the hematoma and the distribution of MBs at the onset of ICH,[10,11] a few case reports[12,13] and several cases described in a prospective study that was performed for other purposes[7,14] have reported that the subsequent ICH occurred in the same lesion in which prior MBs were detected. Moreover, to our knowledge, topologic association in patients with LI has not been reported.

This retrospective study was designed to clarify the positional association between recurrent ICH/LI and previously detected MBs in a relatively large number of patients.

Materials and Methods

Study Design and Patients

We evaluated consecutive patients with acute recurrent ICH/LI who were admitted to our hospital from June 2003 to June 2008. Among them, the patients who had asymptomatic MBs identified on 1.5T gradient-echo T2*-weighted MR imaging, which was performed at the time of the prior stroke event, were included in the study. Patients with CE, ATBI, or undetermined classification were excluded. The diagnosis of acute stroke was made on the basis of neurologic and neuroradiologic examinations. Recurrent stroke was classified into ischemic stroke and ICH, and ischemic stroke was further subclassified as ATBI, CE, and LI, according to the diagnostic criteria based on the National Institute of Neurologic Disorders and Stroke Ad Hoc Committee Classification of Cerebrovascular Disease III.[15] Of the 55 patients included, 34 had recurrent ICH and 21 had recurrent LI.

The location of recurrent ICH was assessed by using CT, and the location of recurrent LI was assessed by DWI and apparent diffusion

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Table 1: Characteristics of patients with ICH and LI

Characteristic	ICH (n = 34)	LI (n = 21)	P Value[a]
Demographic data			
Median age, (yr) (range)	69.5 (51–84)	72 (57–89)	.020
Male sex, No. (%)	25 (73.5)	13 (61.9)	.365
Vascular risk factors			
Hypertension (%)	97.0	100	1.000
Diabetes mellitus (%)	24.2	31.6	.746
Hyperlipidemia (%)	45.2	52.6	.608
Antithrombotic therapy (%)	56.3	78.9	.135
Prior stroke subtype, No. (%)			
ICH	13 (38.2)	2 (9.5)	.029
LI	12 (35.3)	18 (85.7)	.005
ATBI	4 (11.8)	1 (5.9)	.639
CE	5 (14.7)	0 (0)	.144
No. of MBs, median (range)	12.5 (1–73)	6 (1–83)	.070
Time from prior stroke, median day (range)	247.5 (14–1873)	179 (3–860)	.188
Correspondence to MBs, No. (%)	21 (61.8)	1 (4.8)	<.001

[a] χ^2 test, Fisher exact test, Student t test, or Mann-Whitney U test were used.

coefficient maps. We assessed, retrospectively, whether the location of recurrent ICH/LI corresponded to that of the previously detected MBs. Furthermore, patients with ICH were divided into the deep ICH group (hematoma present in the thalamus, the putamen, the pons, and the cerebellum) and the lobar ICH group (hematoma in a subcortical location), and the positional relationship between the hematoma and previously detected MBs was evaluated. There were no patients with a recurrent caudate hemorrhage in the present study. Previous antithrombotic therapy, the number of previously detected MBs, and the duration from the prior stroke to the recurrence were also evaluated in each patient. In patients with recurrent ICH, the hemorrhage volume was also evaluated. The study protocol for the chart review was approved by our institutional review board.

Vascular Risk Factors

We assessed vascular risk factors such as history of previous stroke and the presence of hypertension, diabetes mellitus, or hyperlipidemia. "Hypertension" was defined as systolic blood pressure of ≥140 mm Hg or diastolic blood pressure of ≥90 mm Hg, which were measured with an automated cuff-oscillometric device at least 2 times in the outpatient department before recurrence of stroke, or current medical treatment for hypertension. "Diabetes mellitus" was defined as a glycosylated hemoglobin A_{1c} concentration of ≥6.5% or current use of hypoglycemic agents. "Hyperlipidemia" was defined as a low-attenuation lipoprotein cholesterol level of ≥140 mg/dL or current cholesterol-lowering therapy. We also recorded the prevalence of antithrombotic therapy before occurrence of the recurrent stroke in each patient.

Neuroradiologic Examinations

All patients were examined by using a 1.5T clinical MR imaging unit (Magnetom Symphony; Siemens, Erlangen, Germany) with a section thickness of 5 mm and a 1.5-mm gap between sections. We used axial T2*-weighted gradient-echo sequences (TR/TE, 800/26 ms; flip angle, 20°; FOV, 230 × 230; matrix, 192 × 256) to detect MBs at the onset of the prior stroke. In addition, at the onset of the recurrent stroke, we also performed axial DWI with single-shot echo-planar spin-echo sequences (TR/TE, 5300/135 ms; FOV, 196 × 261; matrix, 80 × 128; b-values, 0 and 1000/mm^2) to evaluate the location of recurrent LI, and we performed axial head CT to evaluate the location and the volume of recurrent ICH. MBs were defined as homogeneous round lesions with a diameter of ≤5 mm characterized by signal-intensity loss on T2*-weighted MR images. Signal-intensity-loss lesions in the globus pallidum (which likely represented calcification) and the subarachnoid space (which likely represented adjacent pial vessels) were excluded. Intracerebral lesions were also excluded if they had a hemorrhagic component associated with tumor, arteriovenous malformation, cavernous hemangioma, or trauma.

"Corresponding" or "correspondence" was used if the location of MBs detected on prior T2*-weighted MR imaging was involved in the ICH detected on CT or the LI detected on DWI at the onset of recurrent stroke. Two of the authors (Y.S., H.N.) without detailed knowledge of the patients' clinical profiles retrospectively compared the same section of each film and determined the correspondence of MBs with subsequent stroke. In addition, we calculated the hemorrhage volume with the ABC/2 method, in which A is the greatest diameter on the largest hemorrhage section, B is the diameter perpendicular to A, and C is the approximate number of axial sections with hemorrhage multiplied by the section thickness.[16]

Statistical Analysis

For the cases of recurrent ICH versus LI and deep brain versus lobar ICH, the χ^2 test or Fisher exact test for independence was used for comparison of sex ratio, hypertension, diabetes mellitus, hyperlipidemia, antithrombotic therapy, and correspondence between prior MBs and recurrent stroke for each group. The Student t test was used for comparison of age at the time of recurrent stroke. The Mann-Whitney U test was used for comparison of the hemorrhage volume, the number of previously detected MBs, and the time from prior stroke to the recurrence in each ICH group. $P < .05$ was considered significant. The Statistical Package for the Social Sciences, Version 16.0 for Windows (SPSS, Chicago, Illinois) was used for statistical analysis.

Results

Baseline Data

Of the 55 patients included in this study, 34 had recurrent ICH (25 men and 9 women) and 21 patients had recurrent LI (13 men and 8 women). The patients with ICH (median age, 69.5 years; range, 51–84 years) were younger compared with the patients with LI (median age, 72 years; range, 57–89 years;

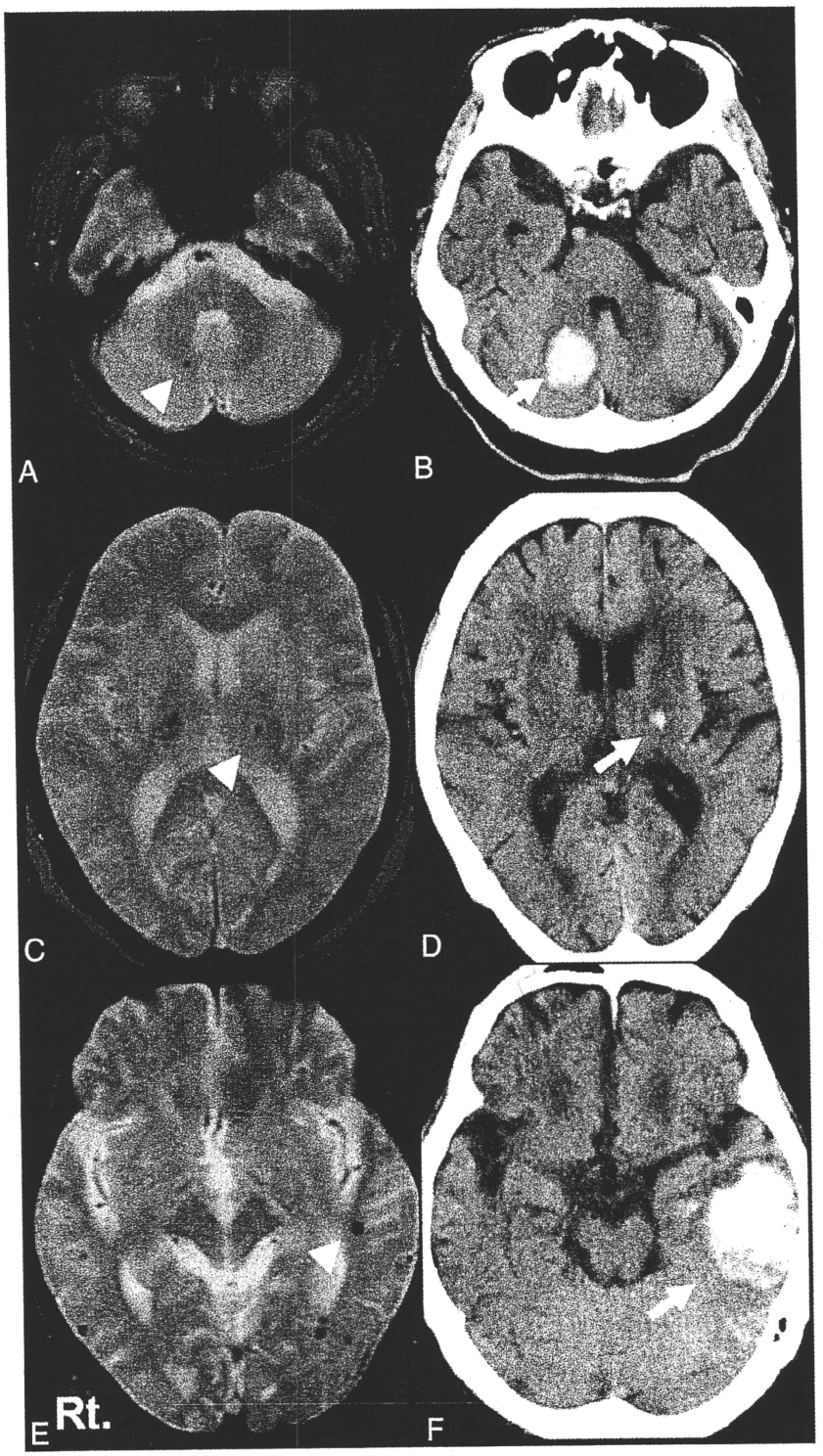

Fig 1. Representative cases. T2*-weighted MR image (*A*) and CT scan (*B*) in an 84-year-old patient. Recurrent right cerebellar hemorrhage (*arrow*) corresponds to the location of MBs detected 9 months before (*arrowhead*). T2*-weighted MR image (*C*) and CT scan (*D*) in an 80-year-old patient. Recurrent left thalamic hemorrhage (*arrow*) corresponds to the location of MBs detected 35 months before (*arrowhead*). T2*-weighted MR image (*E*) and CT scan (*F*) in an 85-year-old patient. Recurrent left lobar hemorrhage (*arrow*) corresponds to the location of MBs detected 3 months before (*arrowhead*).

$P = .020$). Other demographic and clinical data are shown in Table 1.

Positional Relationship between Recurrent ICH/LI and Previously Detected MBs. We evaluated the positional relationship between recurrent ICH/LI and previously detected MBs. In the recurrent ICH group, hematoma corresponded to the prior MBs in 21 of 34 patients (61.8%). Representative cases are shown in Fig 1. In contrast, LI corresponded to the

Table 2: Characteristics of corresponding and noncorresponding groups in patients with ICH

Characteristic	Corresponding (n = 21)	Noncorresponding (n = 13)	P Value[a]
Demographic data			
Median age, (yr) (range)	70 (51–84)	62 (55–78)	.188
Male sex, No. (%)	17 (81.0)	8 (61.5)	.151
Vascular risk factors			
Hypertension (%)	100	92.3	.934
Diabetes mellitus (%)	25.0	30.8	.681
Hypercholesterolemia (%)	26.3	61.5	.071
Antithrombotic therapy (%)	42.1	76.9	.075
Prior stroke subtype, No. (%)			
ICH	8 (38.1)	5 (35.7)	.886
LI	9 (42.9)	3 (21.4)	.282
ATBI	1 (4.8)	3 (21.4)	.279
CE	3 (14.3)	2 (14.3)	1.000
Hemorrhage volume, median (range) (cm^3)	15.1 (0.36–162)	3.43 (0.16–58.4)	.077
No. of MBs, median (range)	16 (4–73)	4 (1–49)	.014
Time from prior stroke, median day (range)	263 (58–1873)	150 (14–1407)	.748

[a] χ^2 test, Fisher exact test, Student t test, or Mann-Whitney U test were used.

prior MBs in only 1 of 21 patients (4.8%) in the recurrent LI group. The correspondence ratio was, therefore, higher in the recurrent ICH group than in the recurrent LI group (OR, 32.3; 95% CI, 3.86–270.3; $P < .001$). The number of MBs and the time from prior stroke to the recurrent stroke were equivalent between the recurrent ICH group and the recurrent LI group (Table 1).

Among the ICH group, the number of MBs was higher in the "corresponding" group (median, 16; range, 4–73) than in the "noncorresponding" group (median, 4; range, 1–49; P = .001). The hemorrhage volume and the time from prior stroke were equivalent between both groups. Vascular risk factors, antithrombotic therapy, and prior stroke subtype were also equivalent between both groups (Table 2).

We also evaluated the association between the initial stroke subtype and correspondence between MB and stroke in the patients with recurrent ICH. Of the 34 patients in the recurrent ICH group, 13 patients had prior ICH and 21 had prior ischemic stroke. Among them, hematoma corresponded to the prior MBs in 8 of 13 patients with prior ICH (61.5%) and 13 of 21 patients with prior ischemic stroke (61.9%). The corresponding ratio was equivalent between the patients with prior ICH and the patients with prior ischemic stroke (P = .98).

Positional Relationship between Recurrent ICH and Previously Detected MBs in the Deep ICH Group versus the Lobar ICH Group. We evaluated the positional relationship between recurrent ICH and previously detected MBs for each type of hematoma (deep ICH versus lobar ICH). In the deep ICH group, hematoma corresponded to the prior MBs in 19 of 24 cases (79.2%) including 10 of 11 cases (90.0%) of thalamic hemorrhage, 6 of 7 cases (85.7%) of putaminal hemorrhage, 2 of 4 cases (50.0%) of cerebellar hemorrhage, and 1 of 2 cases (50.0%) of pontine hemorrhage (Fig 2). In contrast, in the lobar ICH group, hematoma corresponded to the prior MBs in only 2 of 10 patients (20.0%) (Fig 2). Among the patients with ICH, the correspondence ratio was higher in the deep ICH group than in the lobar ICH group (OR, 15.2; 95% CI, 2.42–95.3; $P < .002$). The hemorrhage volume, number of MBs, and the time from prior stroke to the recurrent ICH were equivalent between both groups (Table 3).

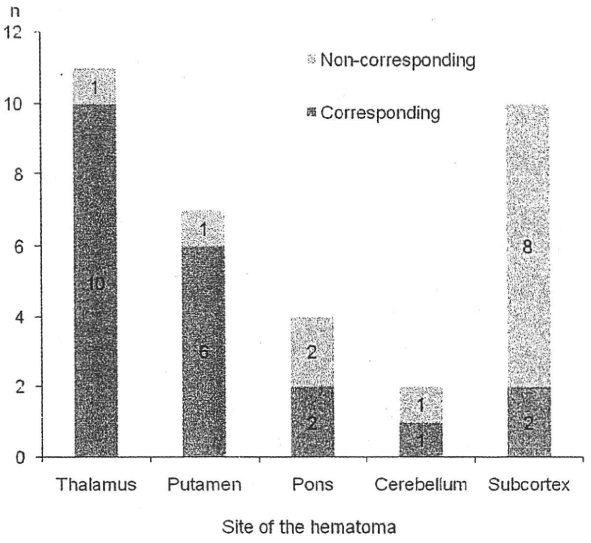

Fig 2. Correspondence of MBs in each part of the hematoma. The correspondence ratio was higher in the deep ICH group, particularly in thalamic and putaminal hemorrhage, than in the lobar ICH group.

Among the deep ICH group, the number of MBs in the whole brain and in the gray matter (thalamus, putamen, and caudate nucleus) was higher in the corresponding group (median, 16; range, 4–56; and median, 8; range, 3–28) than in the noncorresponding group (median, 4; range, 1–11; and median, 2; range, 1–8; P = .003 and P = .015). The time from prior stroke was equivalent between both groups. Vascular risk factors and prior stroke subtype were also equivalent between both groups. The rate of antithrombotic therapy was significantly higher in the noncorresponding group than in the corresponding group (Table 4).

Discussion

We found that the correspondence ratio was higher in patients with recurrent ICH than in patients with recurrent LI. In addition, among the patients with recurrent ICH, the correspondence ratio was higher in the deep ICH group, particularly in hemorrhage involving the putamen and thalamus, compared with the lobar ICH group.

Table 3: Characteristics of deep ICH and lobar ICH groups

Characteristic	Deep ICH (n = 24)	Lobar ICH (n = 10)	P Value[a]
Demographic data			
Median age (yr) (range)	69.5 (51–84)	66 (55–84)	.694
Male sex, No. (%)	17 (70.8)	8 (80.0)	.692
Vascular risk factors			
Hypertension (%)	100	90.0	.303
Diabetes mellitus (%)	26.1	20.0	1.000
Hyperlipidemia (%)	45.5	44.4	1.000
Antithrombotic therapy (%)	50.0	77.8	.237
Prior stroke subtype, No. (%)			
ICH	9 (37.5)	4 (40.0)	1.000
LI	11 (45.8)	1 (10.0)	.061
ATBI	1 (4.2)	3 (30.0)	.067
CE	3 (12.5)	2 (20.0)	.618
Hemorrhage volume, median (range) (cm^3)	6.92 (0.16–66.9)	30.3 (0.69–162)	.287
No. of MBs, median (range)	13 (1–56)	8 (1–73)	.304
Time from prior stroke, median day (range)	292.5 (14–1873)	187.5 (79–1033)	.696
Correspondence to MBs, No. (%)	19 (79.2)	2 (20.0)	.002

[a] χ^2 test, Fisher exact test, Student t test, or Mann-Whitney U test were used.

Table 4: Characteristics of the corresponding and noncorresponding groups in the deep ICH group

Characteristic	Corresponding (n = 19)	Noncorresponding (n = 5)	P Value[a]
Demographic data			
Median age, (yr) (range)	70 (51–84)	67 (60–78)	.996
Male sex, No. (%)	15 (78.9)	2 (40.0)	.126
Vascular risk factors			
Hypertension (%)	100	100	-
Diabetes mellitus (%)	16.7	60.0	.078
Hypercholesterolemia (%)	29.4	60.0	.309
Antithrombotic therapy (%)	35.3	100	.035
Prior stroke subtype, No. (%)			
ICH	7 (36.8)	2 (40.0)	1.000
LI	9 (47.4)	2 (40.0)	1.000
ATBI	0 (0)	1 (20.0)	.208
CE	3 (15.8)	0 (0)	1.000
No. of MBs, median (range)			
In the whole brain	16 (4–56)	4 (1–11)	<.001
In the deep gray matter	8 (3–28)	2 (1–8)	.015
Time from prior stroke, median day (range)	322 (58–1873)	99 (14–1407)	.746

[a] χ^2 test, Fisher exact test, Student t test, or Mann-Whitney U test were used.

Only a few case reports[12,13] and several cases described in prospective studies performed other purposes[7,14] found that the subsequent ICH occurred in the same lesion in which prior MBs were detected. The present study is the first report focusing on the positional relationship between the subsequent ICH and the prior detected MBs in a relatively large number of patients.

Pathologically, MBs represent hemosiderin deposits that result from the fragility of small vessels in conditions such as lipohyalinosis, CAA, or arteriosclerosis.[1,2] The presence of MBs is closely associated with small-vessel diseases such as ICH and LI,[5,6] and it has been reported to be an important risk factor for subsequent stroke, particularly hemorrhagic stroke.[7-9]

The difference in correspondence ratios between ICH and LI may result from the difference in topology among ICH, LI, and MBs. Previous studies showed that MBs tend to be frequently present at the site of hypertensive ICH.[17,18] In contrast, MBs are seldom detected in the posterior limb of the internal capsule or the corona radiata,[18] which are the frequent sites of LI. This topographic difference may explain the discrepancy of the correspondence ratios between ICH and LI. However, it remains unclear why MBs are seldom detected in the frequent sites of LI and, furthermore, why the locations of prior MBs and recurrent LI do not coincide in other brain regions, even though both MBs and LI are based on microangiopathy. The close topologic association between prior MBs and recurrent ICH but not recurrent LI indicates that MBs are a form of small-vessel disease that is bleeding-prone.

The present study also reveals that the correspondence ratio in the deep ICH group was higher than that in the lobar ICH group, though the hemorrhage volume and the number of MBs were equivalent between both groups. Our findings may support the results of the Rotterdam Scan Study that MBs in a deep or infratentorial location were associated with hypertensive or atherosclerotic microangiopathy, whereas lobar MBs were related to CAA.[19] In the deep ICH group, close topologic association of prior MBs with subsequent ICH, particularly in the putamen and thalamus, suggests that subsequent hemorrhage may result from rerupture of microangiopathic vessels, such as those with lipohyalinosis in the deep brain area, which had been detected as MBs. In addition, the