Table 2. *Multiple logistic regression analysis of the association between risk factors and SCI on DWI*

Risk factors	OR	95% CI	*P* value
Age, years	1.0	0.96-1.06	.59
Male gender	2.1	0.7-6.2	.18
Diabetes mellitus	1.4	0.54-3.76	.45
Hypertension	0.8	0.25-2.15	.58
Hypercholesterolemia	1.5	0.55-4.13	.43
Cigarette smoking	0.6	0.27-1.41	.25
Potential cardiac sources	1.3	0.46-3.91	.59
Carotid disease	4.4	1.7-11.42	.002
Coagulopathy	6.8	1.33-35.17	.022

OR and 95% CI of SCI vs no SCI related to each risk factor.

Discussion

According to the recent literature, multiple small lesions in the cortex detected by DWI are presumed to come from multiple emboli or the breakup of an embolus.[3] Our findings show an association between SCI and carotid disease and coagulopathy, but not potential cardiac sources. We can presume that the size of the embolism, depending on its own properties, is an important factor in SCIs. The size of the particle should be smaller in arterial sources of embolism compared with cardiac sources of embolism, so arterial sources of embolism produce more distal infarction compared with cardiac embolism.[9] This is because arterial emboli are due primarily to smaller white thrombi (platelet aggregates), whereas cardiac emboli are mostly from larger red thrombi (platelet and fibrin network). In addition, macroscopic studies have shown that the fibrin network's size is 30-1500 μm, compared with a platelet aggregate size of 10-35 μm.[10]

Carotid disease was found to be an independent risk factor for SCI. Studies of MES detected by TCD have suggested an association between SCI and emboli from carotid disease.[11-16] Kimura et al[6] reported that, spotty (<10 mm) lesions detected on DWI were more frequent in patients with MES detected by TCD and were associated with large vessel disease. Molloy et al[11] detected MES in 41% of patients with >60% carotid stenosis, particularly with ulcerated plaques. Another study found increased MES with increasing degree of stenosis.[12] Our finding that SCI with carotid disease is less closely associated with bilateral and territorial multiple circulation lesions is supported by a recent report that multiple lesions in the unilateral anterior circulation and small scattered lesions in one vascular territory are related to large-artery atherosclerosis.[17]

Controversy exists regarding the etiology of infarcts with carotid disease. We found no significant difference between localization of SCI and the mean degree of carotid disease (data not shown). Szabo et al[18] reported small lesions in hemodynamic risk zones in patients with high-grade (>70%) and subtotal stenosis. Another study found borderzone infarcts mainly in patients with 90%-99% stenosis of the internal carotid artery (ICA).[19] Numerous recent studies on borderzone infarcts have demonstrated that so-called "rosary-like" infarcts are the result of hemodynamic mechanisms due to extensive ICA stenosis.[20-27] On the other hand, one study reported no etiologic difference between borderzone and territorial infarcts with carotid disease.[28] Embolism and hypoperfusion have been proposed to play synergistic roles.[29,30] Small embolic material prone to becoming lodged in distal field arterioles due to a limitation of washout rate is more likely to result in cortical microinfarctions in the setting of chronic hypoperfusion.

Coagulopathy also was found to be an independent risk factor for SCI. Embolic sources linked to coagulopathy are generally small and can cause SCIs. Trousseau's syndrome, a paraneoplastic neurologic syndrome, is associated with a high frequency of embolic infarcts due to cancer-induced hypercoagulability.[31] One of the most important pathogenetic factors in embolic stroke in patients with Trousseau's syndrome is nonbacterial thrombotic endocarditis (NBTE). A recent study of stroke patterns in patients with NBTE detected by DWI found several small (<10 mm) lesions distributed in more than one arterial territory.[32] Another study reported that acute multiple infarcts in both anterior and posterior circulations were associated with malignancy and cardiac embolism.[33] These findings support our conclusions that SCI with coagulopathy is associated with bilateral lesions

Table 3. *Blood coagulation markers in patients with and without SCIs*

	Mean ± 2 SD		
	SCI (+)	SCI (−)	*P* value*
TAT (ng/mL)	12.5 ± 25.9	7.2 ± 11.3	NS
D-dimer (μg/mL)	19.3 ± 65.0	6.69 ± 25.6	NS
βTG (μg/mL)	148.0 ± 255	130.9 ± 292.7	NS
PF4 (ng/mL)	75.2 ± 180.5	45.9 ± 118.2	NS

Abbreviation: NS, not significant.
*Mann-Whitney *U* test.

Table 4. *Localization of SCI and risk factors*

Localization of SCI	n	Risk factors	n (%)
Bilateral	7	Carotid disease	1 (7.7)*
		Coagulopathy	3 (75.0)†
		Potential cardiac sources	3 (37.5)
		Others	1 (16.6)
Territorial single circulation	15	Carotid disease	8 (61.5)
		Coagulopathy	1 (25.0)
		Potential cardiac sources	5 (62.5)
		Others	3 (50)
Territorial multiple circulations	8	Carotid disease	2 (15.4)‡
		Coagulopathy	2 (50.0)
		Potential cardiac sources	3 (37.5)
		Others	1 (16.6)
Borderzone	6	Carotid disease	3 (23.1)
		Coagulopathy	1 (25.0)
		Potential cardiac sources	0 (0)
		Others	2 (33.3)

"Others" includes 1 patient with thoracic aortic aneurysm and 5 patients with undetermined mechanisms of infarction. Risk factors overlapped in 3 patients displaying the following pathology: carotid disease and potential cardiac sources, carotid disease and coagulopathy, and potential cardiac sources and coagulopathy. All comparisons were done using Fisher's exact test.

*Bilateral lesions were less associated with SCI with carotid disease ($P = .009$).

†Bilateral lesions were associated with SCI with coagulopathy ($P = .038$).

‡SCI with carotid disease was less associated with territorial multiple circulation lesions ($P = .037$).

and also tends to be associated with territorial multiple circulation lesions.

TAT and D-dimer are coagulation and fibrinolysis markers that increase substantially in the hypercoagulable states of Trousseau's syndrome accompanied by disseminated intravascular coagulation, as well as in cardiac embolism.[34-36] Plasma levels of these coagulation markers are not elevated in patients with antiphospholipid syndrome.[37] On the other hand, the markers βTG and PF4 reflect platelet activation and are increased in atherothrombotic infarcts.[34,35] We found no significant differences in coagulation markers between the patients with SCIs and those without SCIs. Whereas patients with SCIs caused by Trousseau's syndrome increased coagulation markers, coagulation markers were often increased in those patients without SCIs who had infarcts. That would be why there were no significant differences in coagulation markers between patients with and without SCIs.

A limitation of this study is our use of ultrasonography as the primary diagnostic tool for assessing ICA stenosis and occlusion. MRA has better discriminatory power than duplex ultrasonography in diagnosing stenosis;[38] however, recent reports suggest that the combination of power Doppler and color duplex ultrasonography may be able to compensate for the lack of specificity of MRA, especially in high-grade stenoses and pseudo-occlusions.[7] Another limitation is that we did not estimate vertebrobasilar atherosclerosis because of the difficulty in doing so by carotid ultrasonography. Kock et al[39] reported an association between vertebrobasilar occlusive disease and multiple brain infarcts in the posterior circulation and suggested arterial embolism as the mechanism of these infarcts. An embolic source of infarcts of the posterior cerebral artery territories is a matter of some dispute.[40-42] In addition, we did not assess the quality of match between volumes of DWI between MRI sequences. However, we used the same b-values, and deemed the difference of the image qualities between sequences to be small, because we assessed cortical lesions, which were less affected by artifacts. Furthermore, the small study population conferred a statistical limitation on demonstrating associations among localization, risk factors, degree of ICA stenosis, and coagulation markers in patients with SCI.

In conclusion, carotid disease and coagulopathy are associated with SCI. Localization of SCI varies depending on the underlying disease and mechanisms of the infarcts. Early identification of SCI by DWI may help clarify the pathogenesis of stroke and guide therapeutic options in acute stroke patients.

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Risk Factor Profiles of Stroke, Myocardial Infarction, and Atrial Fibrillation: A Japanese Multicenter Cooperative Registry

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Objective: We sought to clarify risk factor profiles and current treatment of Japanese patients with stroke, myocardial infarction (MI), and nonvalvular atrial fibrillation (NVAF) using the database of the Japan Thrombosis Registry for Atrial Fibrillation, Coronary, or Cerebrovascular Events (J-TRACE). *Methods:* J-TRACE is a nationwide multicenter cooperative cohort of Japanese patients with MI, stroke, and NVAF. Baseline characteristics of 8087 Japanese patients (5804 male, average age 68.7 years) with history of stroke (n = 3554), MI (n = 2291), or NVAF (n = 2242) were analyzed. *Results:* History of stroke (14.7%) was more frequent than history of MI (2.6%) in patients with stroke, whereas history of stroke (6.6%) was less frequent than history of MI (7.6%) in patients with MI. In patients with NVAF, history of stroke (14.3%) was far more frequent than history of MI (3.4%). Hypertension was more frequent in stroke (74.4%) than MI (62.0%) or NVAF (57.7%), whereas hypercholesterolemia, diabetes mellitus, and cigarette smoking were more prevalent in patients with MI (56.1%, 35.1%, and 33.3%, respectively) than in those with stroke (35.7%, 22.4%, and 19.7%, respectively) or NVAF (26.9%, 17.2%, and 16.1%, respectively). Alcohol consumption (34.9%) and obesity (body mass index > 25) (32.8%) were most common in patients with NVAF. In all patients, nonmedication rates were higher in patients with hypercholesterolemia (29.8%) or diabetes (36.9%) than in those with hypertension (9.5%). Warfarin was used in 58.9% of patients with low-risk and 75.4% with high-risk NVAF. *Conclusion:* Risk factor profiles and their modification were not similar among patients in Japan with MI, stroke, and NVAF, although they share a high risk of thrombotic events. **Key Words:** Risk factor—stroke—myocardial infarction—atrial fibrillation—Registry.
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The Japan Thrombosis Registry for Atrial Fibrillation, Coronary, or Cerebrovascular Events (J-TRACE)[1] is a large nationwide multicenter cooperative registry for 3 major thromboembolic diseases that cause death or disability in Japan: stroke,[2] myocardial infarction (MI),[2] and nonvalvular atrial fibrillation (NVAF).[3] Atherothrombosis, including cerebrovascular disease, coronary artery disease, and peripheral artery disease, is the leading cause of death in the world.[4] This is true as well in the Japanese population. According to a report from the Japanese Ministry of Health, Labor, and Welfare, there were 159,625 cardiac deaths and 129,055 stroke deaths in 2005, making these the second and third most common causes of death in Japan, respectively.[5] NVAF is the leading cause of cardioembolic stroke and, according to the Japanese Multicenter Stroke Investigator's Collaboration, approximately 19% of 16,922 cases of acute ischemic stroke or transient ischemic attack were associated with NVAF.[6] It is thus of great importance to prevent vascular events in these patients at high risk.

The purpose of J-TRACE is to investigate risk factor profiles and current status of medications for risk factors and for the prevention of vascular events, and most importantly to determine vascular event rates in these patients at high risk. This type of large nationwide cohort study has never been previously conducted in Japan, and is expected to clarify the natural course of these major thromboembolic diseases and to provide important information for designing future randomized controlled trials. J-TRACE is, in addition, a unique registry with respect to its simultaneous registration of patients with atherothrombosis such as stroke and MI, and NVAF as those at high risk of thromboembolic events for the purpose of examination of the relationships between these conditions.

Methods

Patients Recruited

Recruitment was started in January 2005 and terminated in December 2006. The study protocol was reviewed by an institutional review board (IRB) at each site. A central IRB reviewed the study for those sites that did not have their own internal IRB. All patients gave informed consent after receiving a full explanation of the study from the investigators. Patients aged 20 to 90 years with history of stroke, MI, or NVAF were eligible to be enrolled in J-TRACE. Inclusion criteria for history of stroke, MI, or NVAF were ischemic or hemorrhagic stroke diagnosed by computed tomography or magnetic resonance imaging, MI diagnosed by electrocardiography (ST elevation or abnormal Q waves) and biochemical markers, and persistent or paroxysmal atrial fibrillation diagnosed by electrocardiography, respectively. Acute phase admitted patients with stroke or MI who were in unstable condition were excluded from this study.

Baseline Data Collected

Risk factors or comorbidities documented as baseline data were hypertension, diabetes mellitus, hypercholesterolemia, valvular heart diseases, congestive heart failure, cancer, cigarette smoking, and alcohol drinking. Antiplatelet agents, anticoagulants, lipid depressants, antihypertensives, and glucose-lowering drugs were also documented as baseline data. Body mass index (BMI) was calculated from body height and weight, which were documented as baseline data.

Study Organization and Sites

J-TRACE has a steering committee consisting of 5 members and 41 regional coordinators selected from 10 areas of Japan (Appendix). The majority of participants were cardiologists and neurologists, who accounted for 58.8% and 27.9% of participants, respectively.[7] Other participating physicians were neurosurgeons (7.0%), internists (3.3%), general practitioners (3.1%), and others. The steering committee members are responsible for study design, management of study progress, statistical analysis, and preparing publications. Regional coordinators consist of cardiologists, neurologists, internists, neurosurgeons, and stroke specialists. Their roles are to nominate study hospitals within their region and promote recruitment and communication among the study hospitals.

Data Management

We have developed a Website[1] for the J-TRACE study to collect all patient data through the Internet. For the security purposes, all investigators receive their own identification and password to access the Website after completing the process of study participation. Since all case report forms were automatically exposed to a logical check at the time of data entry, correctly completed case report forms were sent to the central secretariat only. The data management group of the secretariat performed appropriate quality assurance for the data on a regular basis.

Statistical Analysis

Continuous variables are shown as means and/or SD, and categorical variables in terms of frequency and percentage. Categorical variables were compared using Pearson Chi-square test and continuous variables using Student *t* test and analysis of variance. Variables exhibiting skewed distributions were compared using the Kruskal-Wallis test, and differences between groups were examined using the Mann-Whitney *U* test. Results were considered significant when the two-sided probability was less than .05. Statistical analysis was conducted using software (R Version 2.5.1, The R Foundation for Statistical Computing, Technische Universität at Wien, Vienna, Austria).

Table 1. *Baseline demographics in disease categorized at enrollment*

Risk factor	Disease categorized at enrollment		
	Stroke (n = 3554)	MI (n = 2291)	NVAF (n = 2242)
Age, years, mean (SD)	68.2 (10.1)	67.9 (10.5)	70.0 (9.5)
Male, %	69.3	78.5	68.8
Hypertension, %	74.4	62.0	57.7
Diabetes, %	22.4	35.1	17.2
Hypercholesterolemia, %	35.7	56.1	26.9
Cigarette smoking, %	19.7	33.3	16.1
Obesity (BMI > 25), %	28.5	34.5	32.8
Alcohol consumption, %	30.2	21.9	34.9
Heart failure, %	2.8	10.7	21.8

Results

A total of 8087 patients were recruited into the J-TRACE from 201 sites. They included 3554 patients with history of stroke, 2291 patients with history of MI, and 2242 patients with history of NVAF. Table 1 shows the baseline characteristics of the recruited patients by disease category. Mean age was youngest for patients with MI and oldest for patients with NVAF. Male percentage was more than approximately 10% higher for MI than for stroke and NVAF. Prevalence of risk factors exhibited distinct differences among the disease categories. Prevalence of hypertension was highest in patients with stroke, whereas the prevalence of diabetes, hypercholesterolemia, cigarette smoking, and obesity were highest in patients with MI, and alcohol consumption was most frequent in patients with NVAF. Heart failure was most frequent in patients with NVAF and most infrequent in patients with stroke. Mean number of risk factors per patient was significantly larger for MI (2.6 ± 1.2) than for stroke (2.1 ± 1.1) and NVAF (2.2 ± 1.3) ($P < .001$).

Table 2 shows history of stroke, MI, and NVAF in each disease category. History of stroke was much more frequent in patients with stroke (14.7%) than MI (6.6%), whereas history of MI (7.6%) was slightly more frequent than history of stroke (6.6%) in patients with MI. In patients with NVAF, history of stroke (14.3%) was much more frequent than history of MI (3.4%).

Fig 1 shows overlap in history of stroke, MI, and NVAF. Double histories of stroke and MI, stroke and NVAF, and MI and NVAF were noted in 2.7%, 10.2%, and 2.0% of patients, respectively. Triple history of stroke, MI, and NVAF was noted in 0.6% of patients.

Table 2. *History of stroke, myocardial infarction (MI), and non-valvular atrial fibrillation (NVAF) in disease categorized at enrollment*

Past history	Disease categorized at enrollment		
	Stroke (n = 3554)	MI (n = 2291)	NVAF (n = 2242)
Stroke	14.7%	6.6%	14.3%
MI	2.6%	7.6%	3.4%
NVAF	15.1%	4.8%	-

The use of medications for management of risk factors or for secondary prevention of vascular events is shown in Table 3. Calcium antagonists and angiotensin type 2 receptor blockers were the most and next most frequently prescribed antihypertensives in each disease category. Statins were more frequently prescribed for patients with MI than stroke or NVAF. Aspirin was more frequently prescribed for patients with MI than stroke or NVAF. Ticlopidine was also more frequently prescribed for patients with MI than stroke or NVAF. Use of clopidogrel was not documented because it had not been approved in Japan at the beginning of patient enrollment. Use of dipyridamole was quite rare in each disease category, probably because this agent has not been officially approved for the prevention of vascular events in these disease categories. Cilostazol was more frequently prescribed for stroke than for MI or NVAF. As expected, warfarin was much more frequently prescribed for NVAF than for stroke or MI. In all disease categories, nonmedication rates were higher in patients with diabetes

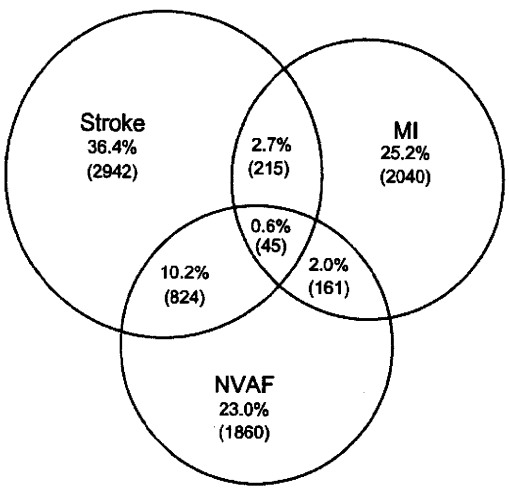

Figure 1. *Overlap in history of stroke, MI, and NVAF in J-TRACE population.*

Table 3. *Medication use in disease categorized at enrollment*

Medication	Disease categorized at enrollment		
	Stroke (n = 3554)	MI (n = 2291)	NVAF (n = 2242)
Hypertensive patients,	2644	1420	1293
Calcium antagonists	60.3	44.7	58.8
Angiotensin II receptor blockers	41.1	37.8	47.3
ACE inhibitors	18.9	29.1	21.4
β-blockers	9.7	29.0	25.5
Diuretics	7.9	17.2	29.2
α-blockers	6.4	3.2	4.9
Others	0.8	1.8	1.9
No medication	12.9	12.2	3.4
Diabetic patients,	796	804	386
Oral glucose lowering drugs	56.5	48.5	46.4
Insulin	10.7	13.8	8.5
Others	6.0	6.3	7.5
No medication	31.5	37.3	42.0
Hypercholesterolemic patients,	1268	1286	604
Statins	61.0	75.1	56.4
Others	9.8	6.4	7.5
No medication	30.9	21.0	37.4
Antithrombotics			
Aspirin	46.5	83.1	31.0
Ticlopidine	18.8	38.2	4.1
Cilostazol	10.2	5.6	1.7
Dipyridamole	0.7	0.9	0.7
Warfarin	20.1	11.0	70.1

(31.6%-42.0%) or hypercholesterolemia (21.0%-37.4%) than in those with hypertension (3.4%-12.9%).

Table 4 shows the relationship between $CHADS_2$ score and antithrombotic therapy in patients with NVAF. Warfarin was used in 58.9% of patients with NVAF and $CHADS_2$ score 0 (low risk), whereas it was used in 75.4% of patients with $CHADS_2$ score 2 or more (high risk).

Discussion

J-TRACE, a large nationwide multicenter cooperative registry, is unique in simultaneous recruitment of not only patients with stroke and MI but also those with NVAF, which are 3 major thromboembolic diseases that cause death or disability in the Japanese population, in order to prospectively investigate vascular event rates during a 3-year follow-up period. In this study, we examined baseline data to clarify risk factor profiles and present status of risk factor management and antithrombotic therapy for the prevention of vascular events in patients enrolled in J-TRACE.

There were distinct differences in risk factor profiles among patients with stroke, MI, and NVAF. History of stroke was much more frequent than history of MI in patients with stroke, whereas history of MI was only slightly more frequent than history of stroke in patients with MI. Previous epidemiologic studies showed that the incidence of stroke is more than double that of MI in the Japanese population,[5,8-11] unlike the opposite of findings for the North American population.[9-12] According to recent 1-year follow-up data from the REACH registry, a large international multicenter cooperative cohort study of atherothrombosis, the annual incidence of nonfatal stroke was 1.80%, and more than twice that of nonfatal MI (0.80%) in Japan, whereas nonfatal MI was more frequent (1.29%) than nonfatal stroke (1.18%) in North America.[13]

Table 4. *$CHADS_2$ score and antithrombotic therapy in patients with* NAVF

$CHADS_2$	Number of patients	Antiplatelet agent alone	Warfarin alone or with Antiplatelet agent
0	411	27.5%	58.9%
≧2	1070	18.6%	75.4%

$CHADS_2$; score congestive heart failure, hypertension, age ≥75 years, diabetes (each 1 point), and history of stroke or transient ischemic attack (2 points).

In patients with NVAF, history of stroke was far more frequent than history of MI. This finding was consistent with the fact that systemic embolism can occur in any organ of patients with NVAF, although cardiogenic embolism preferentially occurs in the brain in the majority of patients with NVAF.[14-16]

Hypertension was more frequent in stroke than in MI, whereas hypercholesterolemia, diabetes mellitus, cigarette smoking, and obesity were more frequent in MI than in stroke. These findings suggest that the impact of risk factors on the vascular beds differs between the brain and coronary arteries. Many epidemiologic studies have suggested that the magnitudes of these risk factors differ between cerebrovascular and cardiovascular events.[17-29]

Obesity (BMI > 25) was more frequent in not only patients with MI, but also patients with NVAF, than in patients with stroke. Many recent reports have suggested that obesity is a risk factor for atrial fibrillation.[30-32] According to the Framingham Heart Study, adjusted hazard ratios for NVAF associated with obesity were 1.52 (95% confidence interval, 109-2.13; $P = .02$) and 1.46 (95% confidence interval, 1.03-2.07; $P = .03$) for men and women, respectively, compared with individuals with normal BMI.[33] In this study, after adjustment for echocardiographic left atrial diameter in addition to clinical risk factors, BMI was no longer associated with NVAF risk, suggesting that the excess risk of NVAF associated with obesity is a result of left atrial dilatation. These findings raise the possibility that interventions to promote normal weight may reduce the population at risk for NVAF.

It is also of interest that alcohol consumption was most frequent in patients with NVAF. Findings regarding the relationship between alcohol consumption and risk of NVAF have been inconsistent in previous studies. The Framingham Study revealed little association between long-term moderate alcohol consumption and risk of NVAF, but a significantly increased risk of NVAF among subjects consuming more than 36 g/day.[34] Consumption of alcohol was associated with an increased risk of NVAF in men among 47,949 participants in the Danish Diet, Cancer, and Health Study.[35] The Copenhagen City Heart Study showed that heavy alcohol consumption is associated with a higher risk of atrial fibrillation, at least among men, which does not appear to be related to the adverse effects of heavy drinking on coronary heart disease or blood pressure.[36] The Cardiovascular Health Study, a population-based cohort of 5609 adults aged 65 years and older, has reported that current moderate alcohol consumption is not associated with risk of NVAF, but that former drinking identifies individuals at higher risk.[37]

In the group of all patients, nonmedication rate was much higher in patients with diabetes and hypercholesterolemia than in patients with hypertension. These findings indicated that patients with diabetes and hypercholesterolemia are not well treated despite recent increases in the number of patients affected by them. Promotion of awareness and management of these risk factors is needed to reduce vascular events.

It is surprising that warfarin was used even in 59% of patients with NVAF at low risk of stroke ($CHADS_2$ score 0), in whom aspirin but not warfarin is recommended by guidelines.[38] Many previous reports have indicated underuse of warfarin even in patients with high-risk NVAF. For example, only 53% of ideal patients with NVAF and no risk factors for hemorrhage received warfarin therapy as indicated by medical records for residents of 21 long-term care facilities in Connecticut.[39] According to data retrospectively collected from medical records at 38 US hospitals, only 54.7% of patients with NVAF at high risk for stroke received warfarin.[40] The discrepancy in use of warfarin in patients with NVAF between J-TRACE and previous reports appears to be related to differences in specialties of participating physicians. As in these previous reports, our previous nationwide survey of 1784 randomly selected Japanese physicians showed that aspirin is used in 68% but warfarin is used in only 59% of patients with high-risk NVAF, for whom warfarin is recommended for stroke prevention by guidelines.[41] The majority of participating physicians in J-TRACE were specialists such as cardiologists and neurologists in university and general hospitals, who are more likely to adhere to the guidelines. In addition, many specialists may not believe that aspirin can really prevent serious cardioembolic stroke in patients with NVAF even when they are at low risk. This belief might have been because of the results of the Japan Atrial Fibrillation and Stroke Trial (JAST), an open-label, prospective, randomized, controlled trial in 871 patients with low-risk NVAF.[42] In JAST, stroke rate was equal in the aspirin and no-aspirin groups.

In an analysis of electronic data from 1 million registered patients annually in the United Kingdom, only 56.5% of patients with NVAF at very high risk of stroke were taking anticoagulants in 2003, whereas 38.2% of patients at low risk received anticoagulants.[43] At baseline in J-TRACE, warfarin was used in 75.4% of patients with NVAF at high risk and 58.9% of those at low risk. The frequency of warfarin use was higher among patients with NVAF at both high and low risk in J-TRACE than that reported in the United Kingdom. It remains uncertain whether aspirin or warfarin should be used for stroke prevention in patients with low-risk NVAF, although this issue may be clarified by follow-up data of J-TRACE or future randomized controlled trials.

Design and preparation of this manuscript were exclusively performed by the J-TRACE Steering Committee.

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Blood Pressure Levels and Bleeding Events During Antithrombotic Therapy

The Bleeding With Antithrombotic Therapy (BAT) Study

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Background and Purpose—A prospective, multicenter, observational cohort study was conducted to clarify the association between major bleeding events and blood pressure (BP) levels during follow-up before development of bleeding events in antithrombotic users.

Methods—A total of 4009 patients taking oral antithrombotic agents for cardiovascular or cerebrovascular diseases (2728 men, 69±10 years old) were followed. Changes in systolic and diastolic BPs between entry and the last clinic visit before intracranial hemorrhage (ICH) or extracranial hemorrhage were assessed.

Results—Over a median follow-up of 19 months, ICH developed in 31 patients and extracranial hemorrhage developed in 77. Entry BP levels were similar among patients with ICH, those with extracranial hemorrhage, and those without hemorrhagic events. Both systolic BP and diastolic BP were relatively high during follow-up as compared with the levels at entry in patients with ICH, whereas they showed plateaus in patients with extracranial hemorrhage and patients without hemorrhagic events. Average systolic BP levels between 1 and 6 months (hazard ratio, 1.45; 95% CI, 1.08 to 1.92 per 10-mm Hg increase) and between 7 and 12 months (hazard ratio, 1.47; 95% CI, 1.05 to 2.01) as well as average diastolic BP levels between 7 and 12 months (hazard ratio, 2.05; 95% CI, 1.15 to 3.62) were independently associated with development of ICH after adjustment for established ICH predictors. The optimal cutoff BP level to predict impending risk of ICH was ≥130/81 mm Hg using receiver operating characteristic curve analysis.

Conclusions—An increase in BP levels during antithrombotic medication was positively associated with development of ICH, suggesting the importance of adequate BP control for avoiding ICH. BP levels did not appear to be associated with extracranial hemorrhage. (***Stroke.* 2010;41:1440-1444.)**

Key Words: anticoagulation ■ antiplatelet therapy ■ hypertension ■ intracerebral hemorrhage ■ stroke

Antithrombotic therapy is regarded as an essential primary and secondary preventive strategy for cardiovascular diseases and stroke.[1,2] However, bleeding events are inevitable complications of this therapy; in particular, intracranial hemorrhage (ICH) is a typical life-threatening event.[3] Carefully regulated warfarin therapy to international normalized ratios between 2 and 3 doubles the risk of ICH, and aspirin increases the risk by approximately 40%.[4]

Hypertension is a firmly established risk factor for ICH in the general population[5] as well as in warfarin users.[4] In the Perindopril Protection Against Recurrent Stroke Study (PROGRESS), in which 72% of enrolled patients with stroke were receiving antiplatelets and 10% were receiving anticoagulants, ICH was reduced by half after mean blood pressure (BP) -lowering by 9/4 mm Hg.[6] Thus, adequate antihypertensive therapy seems to prevent ICH during antithrombotic therapy. This raises an essential issue: whether antithrombotic users who finally developed ICH and other bleeding events had high BP levels throughout follow-up as well as how such patients' BP levels changed during follow-up.

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To determine the incidence and severity of bleeding complications in patients with cardiovascular diseases and stroke treated with oral antithrombotic therapy in Japan, a prospective, multicenter, observational study (the Bleeding with Antithrombotic Therapy [BAT] Study) was conducted. In its initial report of the overall results, adding antiplatelets to warfarin or single antiplatelet therapy doubled the risk of life-threatening or major bleeding events.[7] Here, the association between these patients' BP levels during follow-up and development of bleeding events was determined.

Patients and Methods

The BAT Study was a prospective, multicenter, observational cohort study on the incidence and severity of bleeding complications in antithrombotic users. A total of 4009 patients (2728 men, 69±10 years [mean±SD]) who were taking oral antiplatelet agents or warfarin for cardiovascular or cerebrovascular diseases were consecutively enrolled from 19 stroke and cardiovascular centers that were balanced regionally in Japan and observed for 2 to 30 months between October 2003 and March 2006. The study protocol, inclusion/exclusion criteria, and general results were published previously.[7] The medical ethics review boards of the participating institutes approved the study protocol, and all patients provided written informed consent.

Based on bleeding events during follow-up, the patients were divided into 3 groups: an "ICH group" for the patients developing any symptomatic ICH; an "extracranial hemorrhage (ECH) group" for those developing a life-threatening or major bleeding event other than ICH; and a "non-H group" for those without any life-threatening or major bleeding event. Bleeding events were classified according to the definition by the Management of ATherothrombosis with Clopidogrel in High-risk patients with recent transient ischemic attack or ischemic stroke study (MATCH).[8] Briefly, life-threatening bleeding was defined as: any fatal bleeding event; a drop in hemoglobin of ≥50 g/L; hemorrhagic shock; symptomatic ICH; or transfusion of ≥4 U of red blood cells. Major bleeding was defined as significantly disabling, severe intraocular bleeding, or transfusion of ≤3 U of red blood cells. Secondary hemorrhagic transformation of an ischemic stroke was not regarded as a bleeding event. When the patients developed a life-threatening or major bleeding event, observation was discontinued.

Comorbidities (ischemic and hemorrhagic stroke, heart disease, neoplasms, and liver cirrhosis) and cardiovascular risk factors (hypertension, diabetes mellitus, hypercholesterolemia, hypocholesterolemia [serum total cholesterol <130 mg/dL on enrollment], current or previous smoking habit, and alcohol consumption ≥2 drinks per day) listed in this study were the same as those in the previous study.[7] Follow-up evaluations were normally performed every month; each time, BP was measured using a mercury sphygmomanometer.

Statistical Methods

All analyses were performed using JMP 7 statistical software (SAS Institute Inc, Cary, NC). Average levels of systolic and diastolic BPs (SBP and DBP, respectively) between 1 and 6 months, between 7 and 12 months, and after 13 months as well as the levels at entry were assessed for the Cox proportional hazards regression analysis. BP levels at the last clinic visit of the observation period (the last visit before bleeding events for the ICH and ECH groups) and the average BP levels of all the follow-up measurements except for the levels at entry and at the last visit were assessed for the annual incidence and 95% CIs of ICH and the receiver operating characteristic (ROC) curves analysis. To compare baseline clinical characteristics and BP levels among the ICH, ECH, and Non-H groups, 1-way factorial analysis of variance with post hoc comparison by Dunnett test (with Non-H patients as control subjects) was used for continuous variables, and the χ^2 test was used for categorical variables. To examine the associations of BP levels and their changes with the development of ICH, a Cox proportional hazards regression analysis was performed using a forced entry method of established ICH predictors, including sex, age, hypertension, diabetes mellitus, current or previous smoking habit, alcohol consumption, prior cerebrovascular disease, and use of warfarin. Goodness of fit of the statistical model was tested using the likelihood ratio in the Whole Model Test and Akaike information criterion. Finally, the optimal cutoff BP levels to predict impending development of ICH (in other words, to predict the last clinic visit before ICH) were determined using ROC curves based on all the BP measurements during follow-up. A probability value <0.05 was considered statistically significant.

Results

Of 4009 enrolled patients, 1891 (47.2%) were taking single antiplatelet agents, 349 (8.7%) were taking dual antiplatelet agents, 1298 (32.4%) were taking warfarin, and 471 (11.7%) were taking warfarin plus antiplatelet agents. The main antiplatelet agents used in the enrolled patients were described previously.[7] Briefly, aspirin monotherapy, ticlopidine monotherapy, and aspirin plus ticlopidine were the major choice for both antiplatelet users (1340, 394, and 220 patients, respectively) and warfarin plus antiplatelets users (336, 69, and 49 patients, respectively). At entry, the median international normalized ratio was 1.97 (interquartile range, 1.69 to 2.33) in warfarin users (taking warfarin alone or warfarin plus antiplatelets).

During the median observation period of 19 months (interquartile range, 13 to 23 months), 108 life-threatening or major bleeding events, including 31 ICH and 77 ECH, occurred. In warfarin users, the median international normalized ratio at entry was 2.06 (interquartile range, 1.95 to 2.30) in the ICH group, 2.06 (1.65 to 2.46) in the ECH group, and 1.96 (1.69 to 2.33) in the Non-H group (P=0.149); and the median international normalized ratio at the last visit before bleeding events or on the day of the event was 2.28 (1.74 to 2.68) in the ICH group and 2.24 (1.75 to 3.06) in the ECH group (P=0.993). Among the 3 groups, observation period (P<0.001), age (P=0.003), use of warfarin (P=0.002), and neoplasm (P=0.013) were significantly different (Table 1).

Figure 1 shows the time courses of the BP levels. Both SBP and DBP levels at entry were similar among the 3 groups (Table 1). During follow-up, both SBP and DBP were relatively high as compared with the levels at entry in the ICH group, and they plateaued in the ECH and Non-H groups. BP levels were not significantly different among the 3 groups in any BP measurements.

The association of BP with the development of ICH was determined after adjustment for sex, age, hypertension, diabetes mellitus, current or previous smoking habit, alcohol consumption, prior cerebrovascular disease, and use of warfarin (Table 2). Average SBP levels between 1 and 6 months (hazard ratio [HR], 1.45; 95% CI, 1.08 to 1.92 per 10-mm Hg increase) and between 7 and 12 months (HR, 1.47; 95% CI, 1.05 to 2.01) as well as average DBP levels between 7 and 12 months (HR, 2.05; 95% CI, 1.15 to 3.62) were independently associated with ICH. The probability value of likelihood ratio in the Whole Model Test after multivariate adjustment was 0.055 for SBP at entry, 0.007 for average SBP between 1 and 6 months, 0.014 for average SBP between 7 and 12 months, 0.114 for average SBP after 13 months, 0.066 for DBP at entry, 0.046 for average DBP between 1 and 6 months, 0.010

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Table 1. Patients' Baseline Clinical Characteristics

	ICH	ECH	Non-H	P
Patient no.	31	77	3901	
Observation period, months	11 (5–14)	11 (6–14)	19 (14–23)	<0.001
Age, years	73±7	71±10	69±10	0.003
Male	81%	75%	69%	0.173
Use of warfarin*	61%	61%	44%	0.002
Comorbidities				
Ischemic stroke	68%	44%	55%	0.060
Hemorrhagic stroke	6%	1%	2%	0.122
Heart disease, arrhythmia	77%	74%	67%	0.217
Neoplasm	19%	12%	7%	0.013
Liver cirrhosis	6%	4%	2%	0.197
Risk factors				
Hypertension	65%	57%	61%	0.746
Diabetes mellitus	26%	34%	26%	0.296
Hypercholesterolemia	36%	32%	42%	0.173
Hypocholesterolemia	3%	1%	1%	0.152
Smoking habit, current	19%	10%	14%	0.269
Smoking habit, previous	29%	47%	36%	
Alcohol consumption	10%	6%	5%	0.413
SBP at entry, mm Hg	134.6±13.2	130.8±18.5	132.5±17.9	0.597
DBP at entry, mm Hg	74.8±12.3	74.5±10.4	75.6±11.0	0.672

Data are medians (interquartile range) for the observation period, means±SD for age and BP, and percent of patients for others.
*Taking warfarin alone or warfarin plus antiplatelets.

for average DBP between 7 and 12 months, and 0.117 for average DBP after 13 months. Thus, SBP between 1 and 6 months, SBP between 7 and 12 months, and DBP between 7 and 12 months showed relatively good fitness. Akaike information criterion was 446.4, 438.1, 326.4, and 204.4 for each SBP measurement and 447.0, 443.3, 325.6, and 204.5 for each DBP measurement, respectively. Based on Akaike information criterion, SBP and DBP after 13 months were better than other BP measurements in regard to goodness of fit.

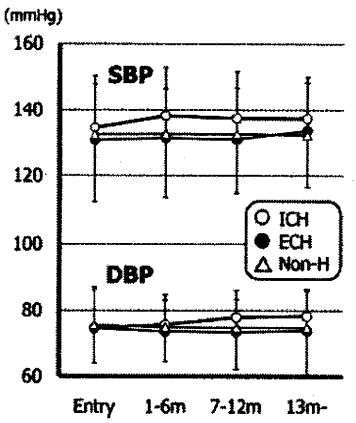

Figure 1. Time courses of BP. Average levels of SBP and DBP between 1 and 6 months, between 7 and 12 months, and after 13 months as well as the levels at entry are plotted. ICH indicates patients developing any symptomatic ICH; ECH, patients developing a life-threatening or major bleeding event other than ICH; Non-H, patients without any life-threatening or major bleeding event. All patients are included at entry and during 1 and 6 months; 21 patients with ICH, 53 patients with ECH, and 3293 Non-H patients are included during 7 and 12 months; and 13 patients with ICH, 30 patients with ECH, and 2936 Non-H patients are included after 13 months.

Table 2. Multivariate-Adjusted HR and 95% CI of BP Parameters for Development of ICH*

	HR	95% CI	P
SBP			
Level at entry	1.09	0.88–1.34	0.435
Mean level between 1 and 6 months	1.45	1.08–1.92	0.013
Mean level between 7 and 12 months	1.47	1.05–2.01	0.026
Mean level after 13 months	1.29	0.93–1.76	0.120
DBP			
Level at entry	0.97	0.68–1.39	0.880
Mean level between 1 and 6 months	1.28	0.78–2.13	0.337
Mean level between 7 and 12 months	2.05	1.15–3.62	0.016
Mean level after 13 months	1.50	0.89–2.53	0.126

*Per 10-mm Hg increase. Adjusted for sex, age, hypertension, diabetes mellitus, current or previous smoking habit, alcohol consumption, prior cerebrovascular disease, and use of warfarin.

Because the observation was discontinued within 6 months or within 12 months for many patients, especially for those with ICH and ECH, the following analyses were performed using BP levels at the last clinic visit and the average BP levels of all the follow-up measurements except for the levels at entry and at the last visit. At the last visit, both SBP and DBP were higher in the ICH group than in the Non-H group (141.7±13.6/81.3±10.3 mm Hg versus 132.4±17.8/74.7±10.9 mm Hg, $P=0.011$ for SBP and $P=0.003$ for DBP). Figure 2 shows annual incidence of ICH according to BP levels. ICH risk increased linearly as both SBP and DBP levels at the last clinic visit increased; the risk did not increase linearly as BP levels at entry or those during follow-up increased.

To predict the impending development of ICH, the optimal cutoff SBP level determined using ROC curves was ≥130 mm Hg with a sensitivity of 89.3%, specificity of

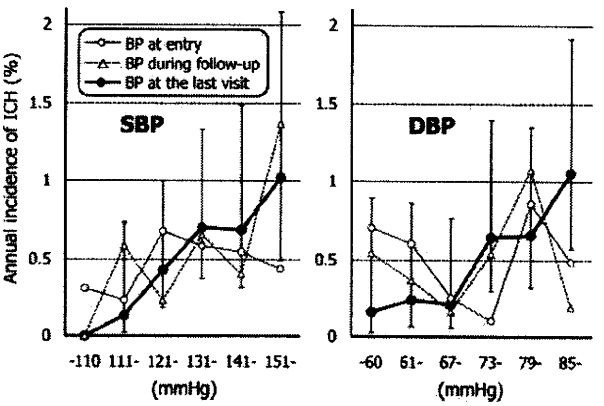

Figure 2. Annual incidence of ICH according to SBP and DBP levels. Bars indicate 95% CI for BP at the last clinic visit. "BP during follow-up" means average BP levels of all the follow-up measurements except for the levels at entry and at the last visit.

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41.8%, and an area under the ROC curve of 0.659; the optimal cutoff DBP level was ≥81 mm Hg with a sensitivity of 53.6%, specificity of 74.2%, and an area under the ROC curve of 0.676. Both SBP3 ≥130 mm Hg (OR, 6.23; 95% CI, 2.16 to 26.35; $P<0.001$) and DBP3 ≥81 mm Hg (OR, 3.49; 95% CI, 1.64 to 7.52; $P=0.001$) were independently associated with ICH after adjustment for the 8 established ICH predictors.

Discussion

A major new finding of the present observational study was that BP levels during the follow-up, but not the level at entry, were independently associated with the development of ICH. In particular, ICH risk increased linearly as BP levels at the last clinic visit increased. The estimated cutoff BP level to predict impending risk of ICH was ≥130/81 mm Hg. BP levels did not appear to be associated with major systemic (excluding intracranial) bleeding events.

Hypertension is an established modifiable risk factor for ICH during warfarin therapy along with intensity of anticoagulation, concomitant use of antiplatelets, and smoking and heavy drinking habits.[4] However, major trials involving anticoagulant users failed to show entry BP level as a predictor for major bleeding events.[9–11] To resolve the contradiction, we designed the present study, which assessed BP levels during follow-up. The present antithrombotic users developing ICH had approximately 2 to 4 mm Hg higher entry SBP than those without bleeding events, which was not statistically significant. However, their SBP and DBP increased by an average of approximately 4 mm Hg at the follow-up as compared with at entry, and this increase may trigger ICH. Such an increase might result from careless BP management or resistance to antihypertensive therapy. Regardless of the cause, avoidance of a BP increase would lessen the risk for ICH.

Based on differences in average BP levels at the last visit between the ICH group and the other 2 groups, we hypothesized that the cutoff SBP level to predict impending development of ICH was roughly between 132 and 142 mm Hg, and the cutoff DBP level was roughly between 75 and 81 mm Hg. After ROC curve analyses, 130/81 mm Hg appears to be the cutoff level. Although the statistical power judged from the area under the ROC curve is not strong, this cutoff level seems to be reasonable, because recent guidelines from the European Society of Hypertension and the European Society of Cardiology and those from the Japanese Society of Hypertension advocated <130/80 mm Hg as the target BP level in diabetics and in high- or very-high-risk patients.[12,13] Real target BP levels during antithrombotic therapy should be determined by systematic comparative trials.

Combination therapy with antithrombotics and antihypertensives appears to be preventive for ICH. In the interim report of the Secondary Prevention of Small Subcortical Strokes (www.sps3.org/), in which SBP was lowered to <149 mm Hg or <130 mm Hg, risk of ICH was less than expected in patients with stroke taking aspirin alone or aspirin plus clopidogrel (personal communication). Success in reducing ICH in PROGRESS, in which 82% of enrolled patients were receiving antithrombotics, was reviewed.[6] On the other hand, an angiotensin receptor blocker, telmisartan, did not reduce the risk of ICH for antiplatelet users who recently had ischemic stroke in the Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) study (HR, 0.81; 95% CI, 0.63 to 1.05)[14]; the relatively small number of patients developing ICH may be a reason for this failure to show an effect.

Major systemic (not intracranial) bleeding events developed under identical BP levels as those in our patients without major bleeding events. This indicates that hypertensive damage to gastrointestinal, dermal, and other systemic circulations is milder than the damage to cerebral circulation. Preventive strategies other than antihypertensives, including proton pump inhibitors and H2 receptor antagonists, appear to be promising for reducing gastrointestinal bleeding.[15,16]

The limitations of the present study include the relatively short duration of the observation period and the small numbers of bleeding events as a result, which may affect the statistical results and made it difficult to perform subanalyses for patients with different clinical backgrounds and different antithrombotic regimens. Second, information on patients' antihypertensive therapy was not given. Third, clopidogrel, a universal antiplatelet agent, was not used in our patients because the agent was approved for use in Japan in 2006, after the study was finished. Finally, data of many patients were not included in the analysis of the follow-up BP measurements during 7 and 12 months and after 13 months partly because of early discontinuance of the observation due to bleeding events. To overcome this limitation and to introduce a message that BP levels at the last clinic visit are important for ICH risk, we used the BP levels at the last visit for some analyses, including the ROC. However, it is not originally appropriate to use the last available measurement as a predictor of a bleeding event in a prospective study.

Because ischemic events are much more common than bleeding events, the use of antithrombotic agents has been increasing. The present study suggests that one should be careful to avoid BP elevations in antithrombotic users, and it is important to lower their BP adequately to avoid ICH.

Appendix

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Disclosures

None.

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Rationale, design, and baseline data of the Japanese Primary Prevention Project (JPPP)—A randomized, open-label, controlled trial of aspirin versus no aspirin in patients with multiple risk factors for vascular events

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Background Prevention of atherosclerotic disease has become an important public health priority in Japan due to the aging of the population and changes in diet and lifestyle factors.

Methods The Japanese Primary Prevention Project (JPPP) is a multicenter, open-label, randomized, parallel-group trial that is evaluating primary prevention with low-dose aspirin in Japanese patients aged 60 to 85 years with hypertension, dyslipidemia, or diabetes mellitus. The study cohort will be followed for a mean of 4 years. The primary end point is a composite of death from cardiovascular causes (including fatal myocardial infarction [MI], fatal stroke, and other cardiovascular death), nonfatal stroke (ischemic or hemorrhagic), and nonfatal MI. Key secondary end points include a composite of cardiovascular death, nonfatal stroke, nonfatal MI, transient ischemic attack, angina pectoris, or arteriosclerotic disease requiring surgery or intervention; each component of the primary end point; noncerebrovascular and noncardiovascular death; and extracranial hemorrhage requiring transfusion or hospitalization. End point assessment is done by a central adjudication committee that is blinded to treatment assignments.

Results Enrollment began in March 2005 and was completed in June 2007. A total of 14,466 patients were randomly allocated to receive enteric-coated aspirin, 100 mg/d, or no aspirin. At randomization, the study cohort had a mean (SD) age of 70.6 (6.2) years; 57.8% were women, 85.0% had hypertension, 71.7% had dyslipidemia, and 33.9% had diabetes. In the study cohort, 80.4% of patients had ≥3 risk factors.

Conclusion The JPPP is the largest primary prevention trial of aspirin in a Japanese population that is investigating whether the benefit of aspirin in reducing risk of vascular events outweighs any bleeding risk in elderly patients with multiple risk factors. (Am Heart J 2010;159:361-369.e4.)

By the year 2030, an estimated 1 of every 4 persons in Japan will be aged ≥60 years.[1] Together with the aging of the population, adoption of Western diets and lifestyles has contributed to the rising prevalence of lifestyle-related diseases, including hypertension, dyslipidemia, and diabetes mellitus. As a result, the prevention of atherosclerotic disease has become one of the most important public health issues in Japan.

It is well recognized that aspirin reduces the incidence of serious vascular events in high-risk patients with acute

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or established atherosclerotic disease. The meta-analysis conducted by the Antithrombotic Trialists' Collaboration involving >30 countries (including Japan) showed that aspirin at daily doses of ≥75 mg significantly reduced the risk of serious vascular events (ie, nonfatal myocardial infarction [MI] or stroke, or death due to a vascular cause) by 23% overall (19% to 32% when stratified by dose) compared with no aspirin use in the secondary prevention setting.[2] Recognizing this benefit, guidelines from Japan, as well as other countries, recommend the use of aspirin for secondary prevention of atherosclerotic disease.[3-10]

The Antithrombotic Trialists' Collaboration recently evaluated primary prevention with aspirin in a meta-analysis of the 6 large clinical studies in Europe and North America.[11-16] Aspirin was associated with a significant 12% proportional reduction in serious vascular events, due mainly to a reduction of about one fifth in major coronary events. There was a trend toward a reduction in ischemic stroke but an increase in hemorrhagic stroke.[17] Aspirin allocation was associated with an increase in major gastrointestinal and extracranial bleeds.

To date, no trials with aspirin for primary prevention of ischemic heart disease (IHD) have been reported in a general population of Japanese patients, and no epidemiological data for this population are available to allow selection of suitable candidates for aspirin therapy. Although a primary prevention trial of low-dose aspirin in Japanese patients with diabetes was recently reported, it lacked statistical power to demonstrate a significant reduction in atherosclerotic events.[18] In Japan, the use of aspirin for primary prevention of IHD has not been widespread in clinical practice. In the Reduction of Atherothrombosis for Continued Health (REACH) Registry, 14.4% of Japanese patients with ≥3 risk factors received aspirin, compared with 49.8% for the total population.[19,20]

Whereas the IHD mortality rate is higher than stroke mortality in the United States, Europe, and the Middle East, the situation is reversed in East Asia including Japan where the stroke mortality rate exceeds that of IHD.[21] Accordingly, the Japanese Primary Prevention Project (JPPP) was designed to test the clinical hypothesis that the benefit of primary prevention with low-dose, enteric-coated aspirin in reducing total atherosclerotic events (IHD and stroke) will outweigh risks of gastrointestinal or cerebrovascular bleeding in elderly Japanese patients with hypertension, hyperlipidemia, or diabetes.

Methods

Study design

The JPPP is a multicenter, open-label, parallel-group, centrally randomized controlled trial. Patients were recruited by General Practitioners at 1,000 centers (clinics) in 47 prefectures in Japan. Patients underwent a screening examination, and if eligibility criteria were met, they were asked to participate. Those who consented to participate received treatments to control their risk factors at the screening examination and returned for baseline evaluation and randomization approximately 1 month later. Patients were randomized using a central computerized system to receive aspirin or no treatment (Figure 1). To ensure that both groups were well balanced, randomization was stratified by the patients' underlying diseases (hypertension, dyslipidemia, diabetes, or various combinations of each for 7 strata). It was assumed that sex and age (<70 vs ≥70 years) would be balanced by the minimization method in each stratum. Patients allocated to the aspirin group were treated with one 100-mg tablet of enteric-coated aspirin (Bayaspirin, 100-mg tablet, Bayer Yakuhin, Ltd., Osaka, Japan) per day. The observation period was defined as the day of randomization until the day of the patient's final visit for their final general examination. Patients in both groups continued to receive their ongoing medications throughout the study. The schedule of study visits and assessments is shown in Figure 2. The JPPP trial uses the Prospective Randomized Open Label Blinded End point (PROBE) design, whereby the adjudication of end points is done centrally by an event adjudication committee that is blinded to treatment assignments.[22] This is a limitation of the study because the PROBE design does not control for lack of ascertainment; however, the Japanese Pharmaceutical Affairs Law strictly limits the use of placebo in large physician-driven studies of approved products such as aspirin. Blinded placebo is permitted to be used only in some small preregistration studies in Japan.

The JPPP is registered at www.clinicaltrials.gov with the trial identification number NCT00225849. The human rights and welfare of individual patients were duly respected and the scientific quality and reliability of the study were ensured as the study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki and the Ethical Guidelines for Clinical Studies. Before enrollment of any patient, the protocol and consent form were approved by the institutional review board of each participating center. All patients provided written informed consent.

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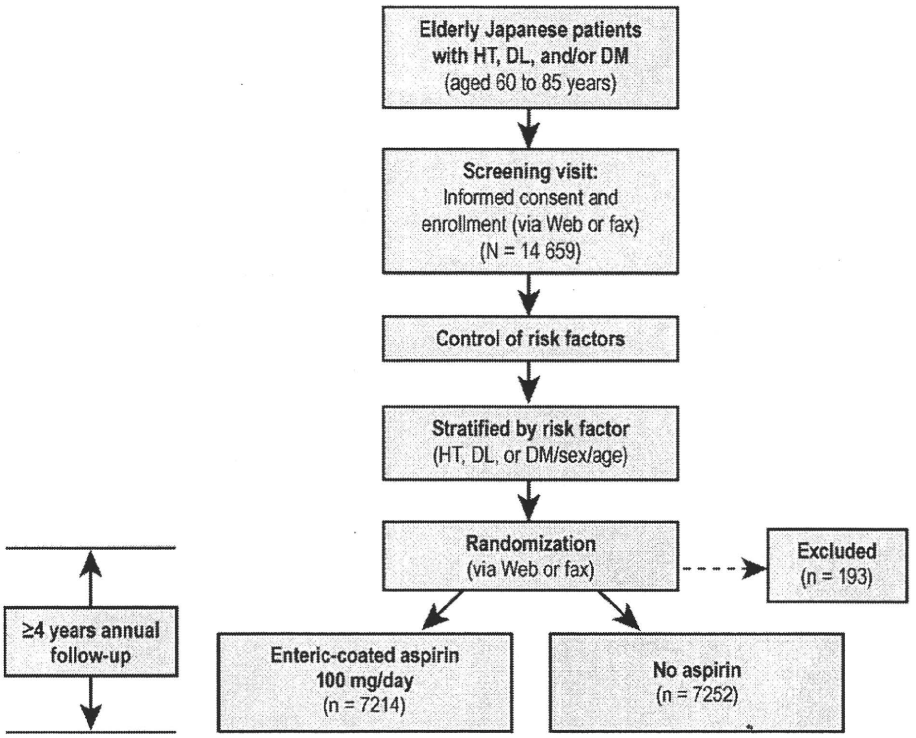
Study population

Patients aged 60 to 85 years who had not been previously diagnosed with any atherosclerotic disease were eligible if at the initial screening examination, they met the criteria for hypertension, dyslipidemia, or diabetes, or were receiving medication for one or more of these diseases. Hypertension was defined by a systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg; dyslipidemia was defined by any of the following: total cholesterol ≥220 mg/dL, low-density-lipoprotein cholesterol ≥140 mg/dL, high-density-lipoprotein cholesterol <40 mg/dL, or triglycerides ≥150 mg/dL; and diabetes by any of the following: fasting morning blood glucose ≥126 mg/dL, any blood glucose ≥200 mg/dL, 2-hour blood glucose ≥200 mg/dL in the 75-g glucose tolerance test, or glycated hemoglobin ≥6.5% in accordance with Japanese

Figure 1



Study design. *DL*, Dyslipidemia; *DM*, diabetes mellitus; *HT*, hypertension.

guidelines.[23-25] In principle, hypertension, dyslipidemia, and diabetes were to be controlled after the screening examination to respective target values in accordance with therapeutic guidelines proposed by academic societies in Japan.[23-25] We did not include patients aged >85 years in the study because in Japan, the clinical significance of aggressive treatment of patients aged >85 years for their cardiovascular (CV) risk factors is uncertain in accordance with the current CV prevention guidelines.

Patients were excluded if they had a history of coronary artery disease or cerebrovascular disease (including transient ischemic attack), atherosclerotic disease requiring surgery or intervention, atrial fibrillation, peptic ulcers, von Willebrand disease or other conditions associated with a tendency for bleeding, clotting factor deficiencies and other serious blood abnormalities, or aspirin-sensitive asthma. Patients receiving treatment with aspirin or other antiplatelet agents (eg, clopidogrel, ticlopidine, cilostazol, dipyridamole, and trapidil) or anticoagulants (warfarin) or long-term treatment with nonsteroidal antiinflammatory drugs were also excluded, as were those with a history of hypersensitivity to aspirin or salicylic acid.

End point definitions

The primary end point is a composite of death from CV causes (including fatal MI, fatal stroke, and other CV death), nonfatal stroke (ischemic or hemorrhagic), and nonfatal MI. The most important secondary end points are: (1) a composite of death from CV causes, nonfatal stroke (ischemic or hemorrhagic), nonfatal MI, transient ischemic attack, angina pectoris, and arteriosclerotic disease requiring surgery or intervention; (2) death from CV disease; (3) death from causes other than CV; (4) each end point event individually; and (5) serious extracranial hemorrhage requiring transfusion or hospitalization. Myocardial infarction was diagnosed according to the European Society of Cardiology/American College of Cardiology guidelines.[26] Ischemic stroke is defined as acute regional neurologic deficit maintained for 24 hours, with imaging evidence of cerebral infarction or intracerebral hemorrhage. In accordance with the PROBE methods, adjudication of end point events is done centrally twice a year by an independent event adjudication committee that is blinded to treatment assignments.

Sample size determination

The originally expected primary end point event rate in the control group was 1.5% to 2.0% per year. Assuming a mean follow-up of 4 years and a relative risk reduction of 20% with aspirin compared with no treatment, a sample size of 10,000 patients was originally considered to be sufficient to provide 80% power at a 2-sided $\alpha = .05$ level of significance. However, the first general examination, after the enrollment of 6,745 patients in July 2006 revealed 14 primary end point events (including unsettled ones) indicating that the incidence of events was lower than that estimated before the start of