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

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.

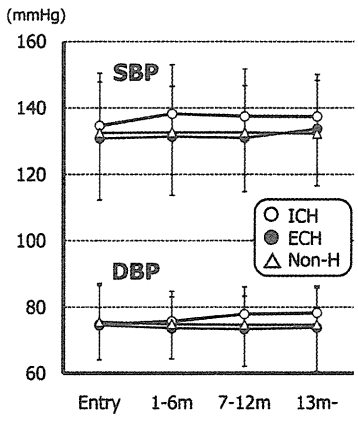

Figure 1. Time courses of BP. Average levels of SBP and DBP between 1 and 6 months, between 7 and 12 months, and after 13 months as well as the levels at entry are plotted. ICH indicates patients developing any symptomatic ICH; ECH, patients developing a life-threatening or major bleeding event other 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

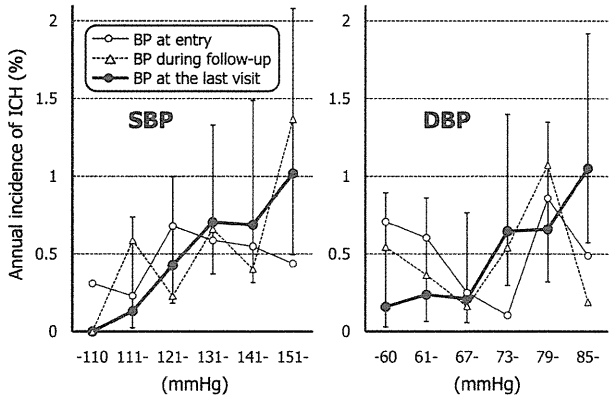

Figure 2. Annual incidence of ICH according to SBP and DBP levels. Bars indicate 95% CI for BP at the last clinic visit. "BP during follow-up" means average BP levels of all the follow-up measurements except for the levels at entry and at the last visit.

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.

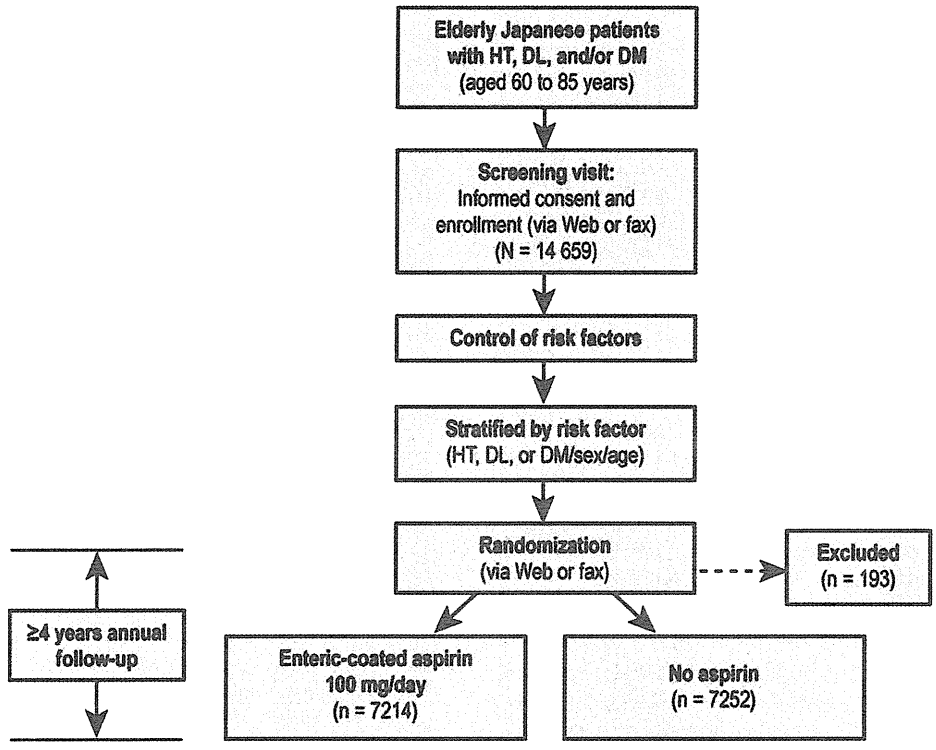
The JPPP is registered at www.clinicaltrials.gov with the trial identification number NCT00225849. The human rights and welfare of individual patients were duly respected and the scientific quality and reliability of the study were ensured as the study was conducted in accordance with the ethical principles 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.

The JPPP study is funded by the Japanese Ministry of Health, Labour and Welfare (Tokyo, Japan) and the Waksman Foundation of Japan Inc (Tokyo, Japan). Enteric-coated aspirin, 100 mg, tablets are provided at no charge by Bayer Yakuhin Ltd (Osaka, Japan).

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

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 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.

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.

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.

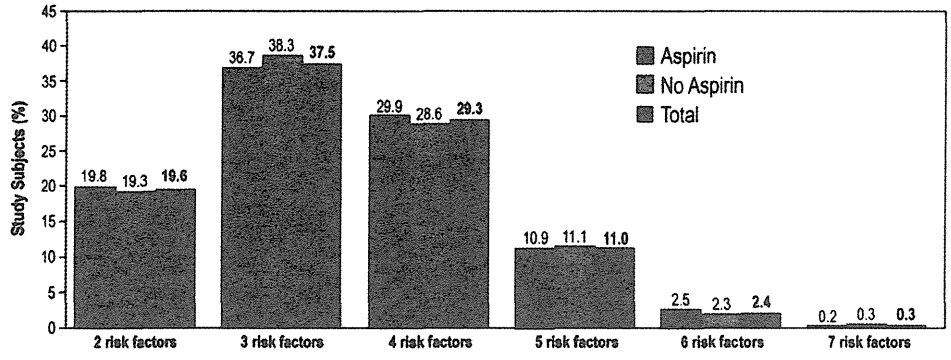
The most commonly used concomitant medications at randomization are shown in Table III. More than 90% of patients with hypertension were taking antihypertensive medication. About 60% of patients with dyslipidemia received lipid-modifying therapy, and 70% of patients with diabetes were being treated with 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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Appendix. Study Organization

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Data Management

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