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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.

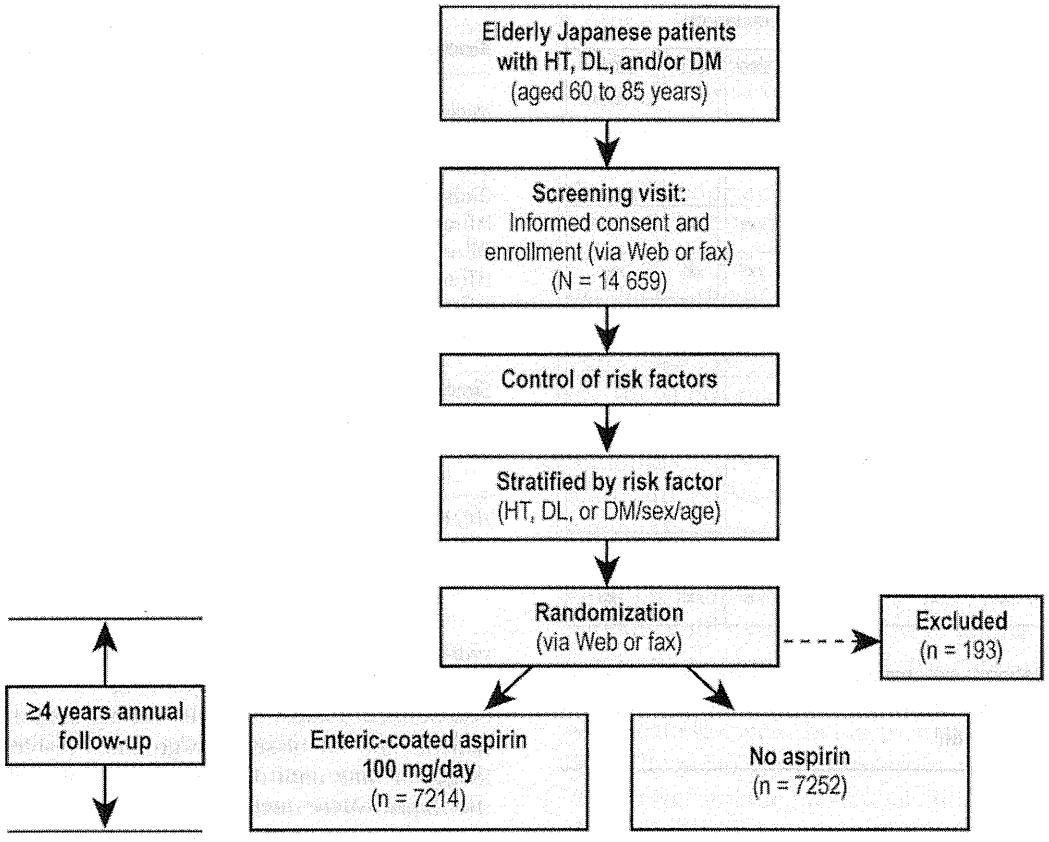
The JPPP is registered at www.clinicaltrials.gov with the trial identification number NCT00225849. The human rights and welfare of individual patients were duly respected and the scientific quality and reliability of the study were ensured as the study was conducted in accordance with the ethical principles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

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.

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.

Interim analysis and data monitoring

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

Results

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

Table II. Demographic and clinical characteristics at baseline

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

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

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

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

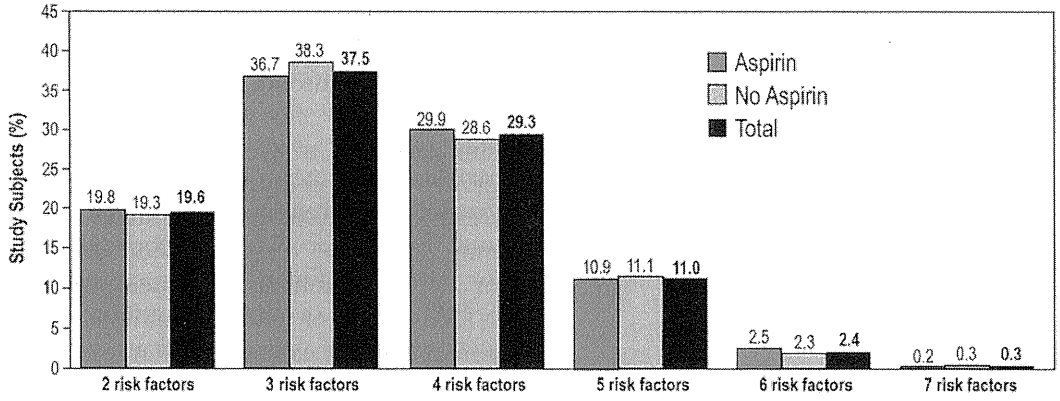
The most commonly used concomitant medications at randomization are shown in Table III. More than 90% of patients with hypertension were taking antihypertensive medication. About 60% of patients with dyslipidemia received lipid-modifying therapy, and 70% of patients with diabetes were being treated with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

Discussion

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

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

Figure 3



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

Table III. Medication use according to underlying disease

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

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

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

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

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

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

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ORIGINAL COMMUNICATION

Posterior circulation ASPECTS on diffusion-weighted MRI can be a powerful marker for predicting functional outcome

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Abstract There are few studies regarding functional outcome and lesion extent on diffusion-weighted MRI (DWI) in patients with posterior circulation (PC) infarction. The aim of our study was to assess whether a newly proposed posterior circulation Alberta Stroke Program Early CT Score (pc-ASPECTS) on DWI is useful for predicting functional outcome in PC patients. One hundred thirty-two patients with first-ever ischemic stroke in the posterior circulation within 24 h of onset who were admitted to our hospital were enrolled in the study. We compared background characteristics, vital signs, laboratory data, and MRI findings between favorable (F) and unfavorable (U) outcome groups at 3 months, according to the modified Rankin Scale (mRS). The F and U groups were defined as having a mRS of 0–2 and 3–6, respectively. pc-ASPECTS was scored by DWI obtained 12–36 h after onset. Ninety-eight patients (74.2%) were classified into the F group and 34 patients (25.8%) into the U group. On univariate analysis, F group patients were younger, had lower National Institutes of Health Stroke Scale (NIHSS) score at entry, and a lower rate of early neurological deterioration (END) and cardioembolic stroke than U group patients. On MRI, F group patients had lower leukoaraiosis and medial temporal atrophy score and higher pc-ASPECTS score on DWI compared to U group patients. Multiple logistic regression analysis revealed NIHSS ($p < 0.001$), END ($p = 0.0057$), pc-ASPECTS ($p < 0.001$), and leukoaraiosis ($p = 0.0091$) as independent predictors of functional outcome. pc-ASPECTS appears to be a powerful marker for predicting functional outcome, along with clinical severity and END. Leukoaraiosis may also be an independent predictor of functional outcome.

Keywords Posterior circulation infarction · Outcome assessment after stroke · Diffusion-weighted · MRI · ASPECTS

Introduction

Prediction of acute ischemic stroke outcome is essential for treatment planning, guidance of patient and relatives, and in the search for new therapeutic strategies [30]. Recent studies have identified many important factors helpful for predicting outcome, even within the early period after onset of ischemic stroke. Among them, stroke severity and age have been regarded as the most powerful indicators [1, 18]. Following the development of diffusion-weighted MRI (DWI), regional extent on DWI has been studied as another predictor of functional outcome, although the results remain controversial [4, 9, 13, 14, 23, 33, 36].

Previous examinations have focused on anterior circulation infarction (AC) [4, 13, 14, 23, 33, 36], with few studies examining DWI data and functional outcome in posterior circulation infarction (PC) [9]. Because the anatomical architecture of the posterior circulation has a high density of motor and sensory pathways and nuclei compared to the supratentorial hemisphere, lesion location rather than lesion volume may be critical for functional outcome in PC [9].

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The Alberta Stroke Program Early CT Score (ASPECTS) is a 10-point scoring system of middle cerebral artery (MCA) early ischemic change in which a score of 10 indicates normal CT and a score of 0 indicates diffuse ischemia throughout the MCA territory [5]. ASPECTS has advantages over methods that assess lesion volume alone because lesion volume is only weakly correlated with neurological outcome [32]. ASPECTS has been shown to be reproducible at varying levels of observer expertise and to enable prediction of functional outcome and symptomatic intracerebral hemorrhage after thrombolysis [5, 6, 31]. DWI ASPECTS also has been used as a reliable marker of functional outcome in patients with AC who received t-PA therapy [15]. Puetz et al. [24] recently proposed a new grading system for posterior circulation ischemia: posterior circulation ASPECTS (pc-ASPECTS).

The aim of the present study is to assess the usefulness of pc-ASPECTS for predicting functional outcome in PC patients.

Methods

The subjects of the study were 1,000 patients with first-ever acute ischemic stroke who were admitted within 24 h from onset to the Department of Neurology, Toda Central General Hospital, Saitama Prefecture, Japan, from May 1994 to August 2008. Inclusion criteria were as follows: (1) first-ever acute stroke symptoms within 24 h from onset, (2) symptoms persisted at admission and MRI (including DWI) confirmed an acute ischemic lesion in the posterior circulation, and (3) complete clinical follow up, including laboratory examinations and outcome information obtained after 3 months. Exclusion criteria were as follows: (1) previous modified Rankin Scale score (mRS) $\geq$2, (2) ineligibility for MRI, and (3) patients with isolated medullary infarction.

All patients had cranial CT (within 24 h after onset) and MRI studies on admission (from 12–36 h after onset). MR images were obtained on a 1.5-T system (GE Yokokawa, Tokyo, Japan). The MRI protocol included DW and fluid-attenuated inversion recovery (FLAIR) imaging. DWI trace images were obtained using an isotropic, single shot echo planar imaging (EPI) sequence, with b_{max} = 1,000 s/mm^2 (TR 5,000 ms, TE 100 ms), with 7-mm slices, and a 96 × 128 matrix.

A single neurologist (H.T.) blinded to all clinical and patient information read each patient's CT and MRI, and assessed ASPECTS on DWI according to the method described by Puetz et al. [24] (pc-ASPECTS). pc-ASPECTS utilizes a 10-point scoring system to assess ischemic lesions in the posterior circulation. We applied DWI to this scoring system by subtracting 1 point for each high-intensity lesion observed in the left or right thalamus, cerebellum, or posterior cerebral artery on DWI, and 2 points for each high-intensity lesion observed in any part of the midbrain or pons (Fig. 1). A pc-ASPECTS score of 10 indicates the absence of visible posterior circulation ischemia, while a score of 0 indicates ischemic lesions in all pc-ASPECTS territories [24]. The representative DWI pc-ASPECTS scores are shown in Fig. 1. Patients with isolated medullary infarction were excluded because pc-ASPECTS does not cover this region [24]. Overall, 132 patients met the study criteria. pc-ASPECTS was scored by DWI obtained 12–36 h after stroke onset to avoid false-negative DWI findings that may occur within 12 h after stroke onset in the PC group [19].

The following variables were collected for all patients: background characteristics [age, gender, time from onset, National Institutes of Health Stroke Scale score (NIHSS) on admission, antithrombotic therapy before onset]; vital signs on admission (systolic blood pressure, diastolic blood pressure, body temperature); risk factors [hypertension (previous use of antihypertensive agents or blood pressure of >160/90 mmHg at least twice before stroke onset), diabetes mellitus (use of insulin or oral hypoglycemic agents, fasting blood glucose $\geq$140 mg/dL, or random blood glucose $\geq$200 mg/dL), current cigarette smoking, transient ischemic attack]; laboratory data (C-reactive protein, blood glucose, glycosylated hemoglobin, hematocrit, fibrinogen); MRI [leukoaraiosis score on FLAIR imaging from 0 to 4 (according to the method of van Swieten et al. [35]), silent brain infarctions [patchy, high-intensity areas on FLAIR imaging that are sharply demarcated from the surrounding tissue irrespective to the current symptoms [29] and medial temporal atrophy from 0 to 3 (0, no atrophy; 1, mild atrophy; 2, moderate atrophy; 3, severe atrophy [20])]. Ischemic stroke subtypes were classified according to the TOAST criteria after investigations [17]. Each patient was examined daily by the same neurologist and early neurological deterioration (END) was defined as an increase of $\geq$1 point in the mRS between admission and after 72 h [29]. Functional outcome was assessed at 3 months using mRS; favorable outcome was defined as an mRS score of 0–2, and unfavorable as 3–6 (6 = dead).

The following agents were administered during the first 3 days from entry: 86 patients (65.1%) were given anticoagulants (low-molecular-weight heparin, warfarin, unfractionated heparin, or argatroban, a direct thrombin inhibitor [29]), mainly to prevent deep vein thrombosis or pulmonary embolism, 29 (22.0%) were given antiplatelet agents (aspirin, ticlopidine, or ozagrel, a thromboxane A2 synthetase inhibitor [29]), and 69 (52.3%) were given edaravone, a free-radical scavenger [34]. No patients received thrombolytic therapy.

We compared favorable and unfavorable groups with respect to the above-mentioned variables. Continuous

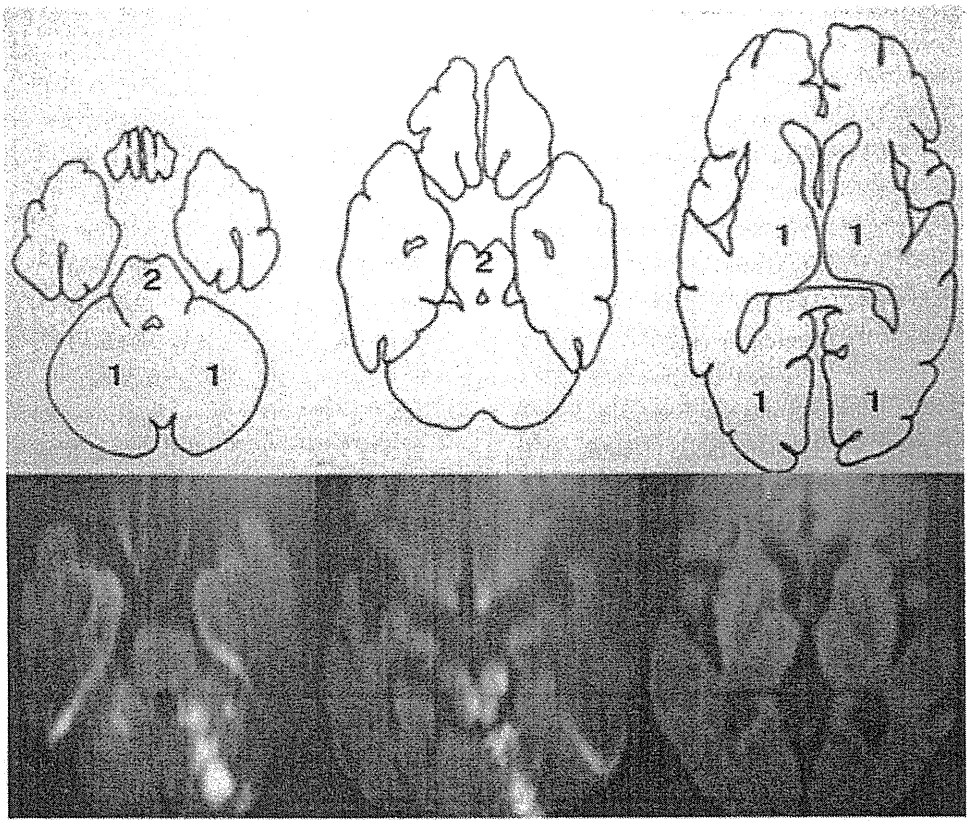

Fig. 1 *Top row* Posterior circulation ASPECTS (pc-ASPECTS) scoring system, as described by Puetz et al. [24] applied to DWI as a 10-point scoring system for evaluation of ischemic lesions in the posterior circulation. From an initial score of 10, we subtracted 1 point for each high-intensity lesion seen on DWI in the left or right thalamus, cerebellum, or posterior cerebral artery, and subtracted 2 points for each high-intensity lesion seen in any part of the midbrain or pons. A pc-ASPECTS score of 10 indicates the absence of visible posterior circulation ischemia, and a score of 0 indicates ischemic lesions in all pc-ASPECTS territories. *Bottom row* Representative pc-ASPECTS images. A 75-year-old woman presented with dysarthria, internuclear ophthalmoplegia, facial palsy, and ataxia in four extremities. Her initial NIHSS score was 9, and diffusion-weighted MRI at 24 h after stroke onset revealed high-intensity lesions in the bilateral cerebellum and midbrain. pc-ASPECTS score was 6, and modified Rankin Scale after 3 months was 3

variables are presented as mean ± SD, and non-continuous variables as percentages. Student's t test or the Mann–Whitney test was used in univariate analysis for continuous variables, and the χ^2 test was used for non-continuous variables. To identify independent predictors for functional outcome, multiple logistic regression analysis was performed. Variables selected for regression analysis were those found to be significant by univariate analysis. A level of $p < 0.05$ was regarded as statistically significant. Using receiver operating characteristic curve (ROC) analysis, we calculated cutoff points for ASPECTS and NIHSS that provided optimal sensitivities and specificities for predicting favorable outcome. Statistical analysis was performed using a commercial package (Esumi, Tokyo, Japan).

Results

A total of 132 patients (91 men, 41 women; mean ± SD age, 67.1 ± 10.5 years) were enrolled in the study. The number of patients who had a lesion detected in the following locations on DWI and the ASPECTS scores were: posterior cerebral artery territory, $n = 5$ (pc-ASPECTS 8, 9); thalamus, $n = 15$ (pc-ASPECTS 8, 9); cerebellum, $n = 20$ (pc-ASPECTS 8, 9); pons, $n = 51$ (pc-ASPECTS 8); midbrain, $n = 4$ (pc-ASPECTS 8); and multiple lesions, $n = 37$ (pc-ASPECTS 3–8).

Ninety-eight patients (74.2%) were classified into the F group and 34 patients (25.8%) into the U group. The F and U groups with respect to background characteristics, vital signs, and laboratory data are compared in Table 1. In the F group, patients were younger and had lower NIHSS score at entry than those in the U group. The F and U groups regarding MRI findings, stroke subtype, and outcome are compared in Table 2. F group patients had lower leukoaraiosis and medial temporal atrophy score on MRI, higher pc-ASPECTS score on DWI, and lower rate of cardioembolic stroke and END than did U group patients; other variables did not differ between the two groups. The predictors of functional outcome by multiple logistic regression analysis are listed in Table 3. NIHSS, END, pc-ASPECTS, and leukoaraiosis were independent predictors of functional outcome. The functional outcome according to the categorized pc-ASPECTS score on DWI is shown in Table 4. More than

Table 1 Comparison of background characteristics, vital signs, and laboratory data between the favorable and unfavorable outcome groups

	Favorable (n = 98)	Unfavorable (n = 34)	p value
Age	64.1 ± 10.9	70.3 ± 10.0	0.0025
Gender: male, n (%)	70 (71.4)	21 (61.8)	0.298
Time from onset	7.0 ± 6.4	6.8 ± 6.2	0.864
NIHSS at entry	4.7 ± 2.7	11.5 ± 7.6	<0.001
Prior antithrombotic therapy	23 (23.5)	6 (17.6)	0.51
Hypertension	69 (70.4)	24 (70.6)	0.982
Diabetes mellitus	26 (26.5)	12 (35.3)	0.329
Current smoker	48 (49.0)	13 (38.2)	0.276
Transient ischemic attack	9 (9.2)	3 (8.8)	0.944
Systolic blood pressure, mmHg	166.5 ± 32.3	166.3 ± 29.7	0.975
Diastolic blood pressure, mmHg	91.3 ± 19.2	93.8 ± 18.1	0.493
Body temperature, °C	36.4 ± 0.5	36.5 ± 0.6	0.144
C-reactive protein, mg/dL	0.47 ± 0.83	0.54 ± 1.39	0.770
Blood glucose, mg/dL	156.1 ± 64.9	156.3 ± 57.7	0.990
HbA_1c, %	5.9 ± 1.6	5.8 ± 1.4	0.707
Hematocrit, %	41.2 ± 4.9	42.2 ± 4.9	0.340
Fibrinogen, mg/dL	304.7 ± 75.8	318.9 ± 92.3	0.423

Values in parentheses are percentages

NIHSS National Institutes of Health Stroke Scale, *HbA_1c* glycosylated hemoglobin

Table 2 Comparison of MRI findings, stroke subtype, and outcome between the favorable and unfavorable outcome groups

	Favorable (n = 98)	Unfavorable (n = 34)	p value
MRI			
Leukoaraiosis	0.8 ± 1.2	1.5 ± 1.4	0.0039
Silent infarction	27 (27.6)	13 (38.2)	0.247
Medial temporal atrophy	0.43 ± 0.81	1.06 ± 1.10	0.0022
ASPECTS	8.1 ± 1.1	6.5 ± 1.3	<0.001
Stroke subtype			
Cardioembolic	10 (10.2)	11 (32.4)	0.0023
Large-artery	33 (33.7)	7 (20.6)	0.152
Small-vessel	41 (41.8)	7 (20.6)	0.067
Other/undetermined	14 (14.3)	9 (26.5)	0.106
Neurological deterioration	7 (7.1)	9 (26.5)	0.0028
mRS at 3 months	1.2 ± 0.6	3.9 ± 1.2	<0.001

Values in parentheses are percentages

ASPECTS Alberta Stroke Program Early CT score on diffusion-weighted MRI, *mRS* modified Rankin Scale

Table 3 Predictors of unfavorable functional outcome as analyzed by multiple logistic regression analysis

	OR	95% CI	p
Age	1.03	0.96–1.10	0.372
NIHSS	1.42	1.16–1.76	<0.001
ASPECTS	0.40	0.23–0.67	<0.001
Leukoaraiosis	2.42	1.25–4.70	0.0091
Medial temporal atrophy	0.85	0.41–1.77	0.667
Neurological deterioration	14.24	21.68–93.53	0.0057
Cardioembolic stroke	2.34	0.40–13.81	0.348

OR odds ratio, *CI* confidence interval

80% of patients with pc-ASPECTS ≥8 had favorable outcome, while the frequency of favorable outcome for patients with pc-ASPECTS ≤5 was only 10%. According to the ROC analysis, the optimal cutoff score of predicting favorable outcome was pc-ASPECTS ≥7 (sensitivity 0.74, specificity 0.82, positive predictive value 0.41, negative predictive value 0.95) and NIHSS ≤5 (sensitivity 0.53, specificity 0.94, positive predictive value 0.85, negative predictive value 0.73). The combined analysis by pc-ASPECTS ≥7 and NIHSS ≤5 did not add meaningful information for predicting outcome (sensitivity 0.63, specificity 0.62, positive predictive value 0.22, negative predictive value 0.91).

Table 4 Functional outcome according to the categorized pc-ASPECTS score

pc-ASPECTS	*n*	Favorable	Unfavorable
3–5	10	1 (10%)	9 (90%)
6, 7	24	16 (66.7%)	8 (33.3%)
8, 9	98	81 (82.7%)	17 (17.3%)
Total	132	98	34

Discussion

Several studies have evaluated whether lesion volume on DWI can reliably predict functional outcome in acute ischemic stroke; however, the results are controversial [4, 9, 13, 14, 23, 33, 36]. In addition, most previous studies have focused on AC. There have been several studies of DWI in PC, but few studies examined the correlation between DWI and functional outcome in PC [9, 10]. Because the anatomical structure in posterior circulation has a higher density of motor and sensory pathways and nuclei than in the supratentorial hemisphere, lesion location rather than lesion volume may be critical for functional outcome [9]. Previous studies failed to detect a correlation between lesion volume on DWI and neurological scale at onset [22] or functional outcome [9] in PC patients. In 2008, Puetz et al. [24] proposed a new semi-quantitative grading system for PC (pc-ASPECTS) that is relatively simple and easy to apply, and is based on previous findings that the numbers of territories involved and involvement of the pons and midbrain have a critical bearing on functional outcome in PC [11]. This method applies pc-ASPECTS to CT angiography source images obtained within 24 h from onset, and enables prediction of functional outcome in patients with suspected vertebrobasilar ischemia or basilar artery occlusion.

We explored whether pc-ASPECTS on DWI can predict functional outcome in a relatively large number of patients, and found it to be an independent predictor of functional outcome after 3 months. The rate of patients with favorable outcome is much higher than that in the BASICS-Registry in which patients with basilar artery occlusion were analyzed [27], but a similar rate in the study by Puetz et al. [24] which included 130 patients with clinically suspected vertebrobasilar ischemia. Other investigators have recently studied PC patients using various radiological methods [8, 25, 26]. Cho et al. [8] examined 29 patients with acute basilar artery occlusion who were treated with endovascular procedures and found that brainstem DWI score (0–22) was the only independent baseline predictor of clinical outcome. Renard et al. [25] analyzed 16 patients with acute basilar artery occlusion who received intra-arterial thrombolysis. They measured lesions of PC structures on DWI using a 10-point semi-quantitative score, which is somewhat more complicated than pc-ASPECTS. They found that high lesion score was an additional predictor of poor outcome. Schaefer et al. [26] reported that pons and midbrain hypoattenuation on pretreatment CT angiography source imaging showed a strong correlation with clinical outcome in 16 patients with vertebrobasilar occlusion who were treated with intra-arterial thrombolysis.

These results and the present results suggest that in PC patients, lesion location (especially pons to midbrain) and involvement of multiple territories are more critical than lesion volume in determining functional outcome [11, 26, 28]; therefore, semi-quantitative measurement is desirable for predicting functional outcome in PC patients. Although DWI imaging is considered the diagnostic "Gold Standard" in patients with PC [24], and pc-ASPECTS on DWI appears to be a promising method for measuring ischemic extent in PC, more research is needed to investigate the most reliable scoring system for PC patients.

A remarkable finding of the present study was that leukoaraiosis (LA) was an independent predictor of functional outcome in PC patients. Some recent reports suggest a correlation between LA and functional outcome after ischemic stroke [2, 12, 16]. Arsava et al. [2] and Kissela et al. [16] demonstrated in a relatively large number of patients that LA or periventricular white matter disease is an independent predictor of functional outcome after ischemic stroke; however, the exact locations of the lesions for indexing ischemic stroke were not documented in these studies. Grips et al. [12] analyzed 34 patients with isolated cerebellar infarction and found that the presence and severity of supratentorial white matter lesions on MRI significantly determined functional outcome.

Several mechanisms may be related to LA and poor functional outcome. LA regions have reduced vascular density and cerebral blood flow, which may lead to infarct growth in the acute setting by preventing peripheral compensation [2, 3]. An intact system of intrahemispheric and interhemispheric connectivity is essential for favorable functional recovery after stroke, but neuropathological and functional neuroimaging studies have shown that neuronal connectivity is decreased in patients with LA. Moreover, LA is a well-known risk factor for developing post-stroke cognitive impairment and depression, which may adversely affect patients' compliance with treatment and recovery programs [2]. It can be speculated that reduced neural connectivity has a greater negative impact on functional outcome than does reduced focal cerebral blood flow. It has been suggested that in PC patients with LA, circulation from the frontal and parietal cortex to the basal ganglia via white matter tracts is disturbed, causing disturbance of gait, and that disconnection from the supplementary motor cortex prevents planning and initiation of locomotion from

the basal ganglia following multilocular diffuse network destruction [12].

Early neurological deterioration was an independent predictor of functional outcome. Many reports have indicated a relation between early neurological deterioration and poor clinical outcome [7, 29, 30]. Because several modifiable factors are included in this situation [7], future developments in acute management are expected.

There are several limitations in our study. First, patients with isolated medullary infarction were excluded primarily because these regions are not included in pc-ASPECTS; therefore, the present study does not cover all patients with PC. The main findings would have changed if patients with DWI lesions in the medulla would have not been excluded but given an ASPECTS score of 10. Second, the time window of this study (within 24 h) is very long in view of current thrombolytic therapy. While a wider therapeutic time window for thrombolytic therapy may be feasible, especially in patients with PC [21], further studies are required using a shorter time after onset.

In conclusion, we evaluated the usefulness of newly developed pc-ASPECTS on DWI in predicting functional outcome in acute posterior circulation ischemic stroke, and found that this appears be a powerful marker for predicting functional outcome. Leukoaraiosis may also be an independent predictor of functional outcome.

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Conflict of interest statement None.

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