Table 1: Baseline characteristics of patients

	Group A	Group B	Group C	Group D	*P*
Patients, *n* (M/F)	39 (22/17)	52 (34/18)	133 (85/48)	42 (26/16)	.8219
Age, y (SD)	74.7 (9.0)	70.5 (10.1)	64.3 (11.4)	65.4 (11.3)	.0001
Stroke types, *n* (ischemic/hemorrhagic)	39 (33/6)	52 (33/19)	133 (97/36)	42 (20.22)	.0018
Antiplatelet therapy, *n* (%)	32 (82.1)	31 (59.6)	96 (72.2)	16 (38.1)	.0001
Hypertension, *n* (%)	26 (66.7)	44 (84.6)	81 (60.9)	36 (85.7)	.0013
Diabetes mellitus, *n* (%)	10 (25.6)	10 (19.2)	42 (31.6)	8 (19.0)	.2214
Hypercholesterolemia, *n* (%)	17 (43.6)	14 (26.9)	31 (23.3)	9 (21.4)	.0698

Note:—Group A, patients with advanced white matter hyperintensity (WMH) but without microbleeds; group B, patients with coexistence of microbleeds and advanced WMH; group C, patients without either microbleeds or advanced WMH; group D, patients with microbleeds but without advanced WMH.

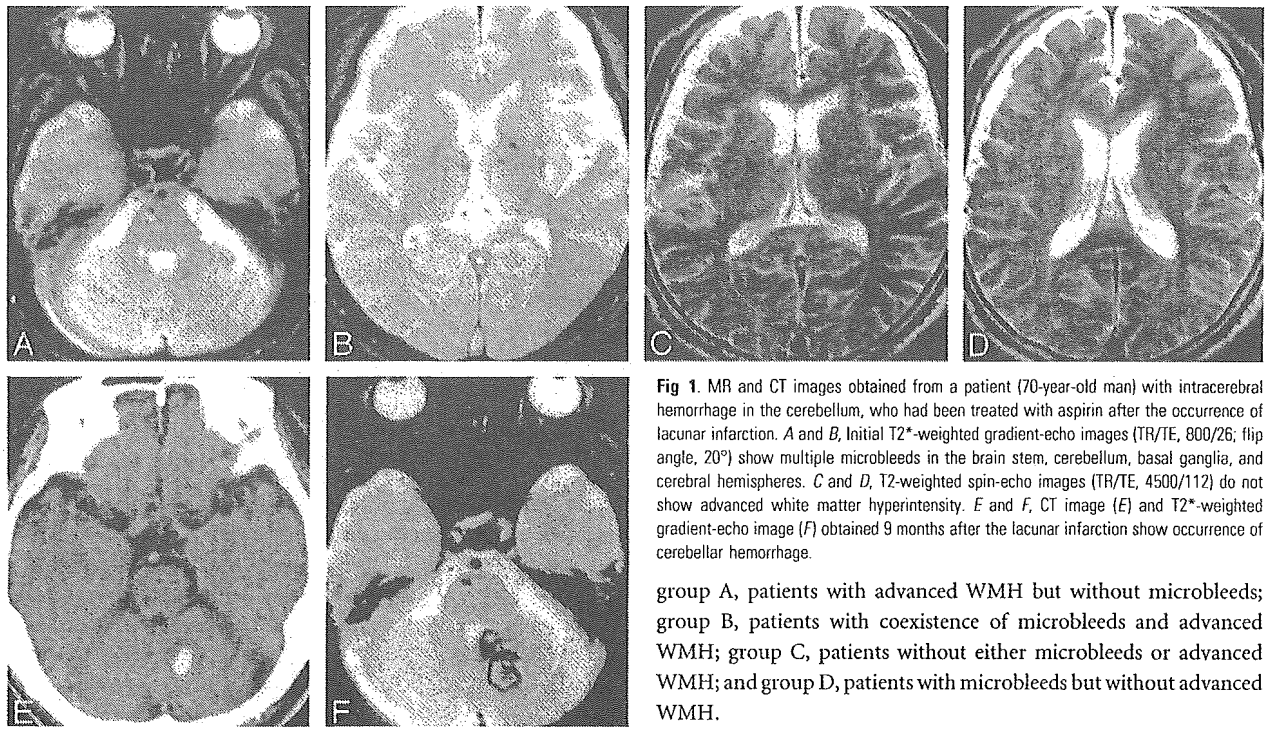

Fig 1. MR and CT images obtained from a patient (70-year-old man) with intracerebral hemorrhage in the cerebellum, who had been treated with aspirin after the occurrence of lacunar infarction. *A* and *B*, Initial T2*-weighted gradient-echo images (TR/TE, 800/26; flip angle, 20°) show multiple microbleeds in the brain stem, cerebellum, basal ganglia, and cerebral hemispheres. *C* and *D*, T2-weighted spin-echo images (TR/TE, 4500/112) do not show advanced white matter hyperintensity. *E* and *F*, CT image (*E*) and T2*-weighted gradient-echo image (*F*) obtained 9 months after the lacunar infarction show occurrence of cerebellar hemorrhage.

of ≥220 mg/dL and included patients currently undergoing cholesterol-lowering therapy.

All of the patients were examined by a 1T clinical MR unit (Siemens, Magneton Harmony, Siemens Medical Solutions, Malvern, Pa), and the whole brain was scanned with a section thickness of 5 mm and a 1.5-mm intersection gap. The imaging protocol consisted of axial T2-weighted spin-echo sequences (TR/TE, 4500/112; field of view, 201 × 230; matrix, 225 × 512) and axial T2*-weighted gradient-echo sequences (TR/TE, 800/26; flip angle, 20°; field of view, 230 × 230; matrix, 192 × 256). Microbleeds were defined as homogeneous round signal-intensity loss lesions on T2*-weighted MR images excluding lesions in the globus pallidus and in the subarachnoid space, which are likely to represent calcification and adjacent pial blood vessels, respectively. Intracerebral lesions with a hemorrhagic component were also excluded. The severity of WMH on T2-weighted images was graded by using the scoring system of Fazekas et al[22] into 4 grades: grade 0, absent; 1, punctate; 2, early confluent; and 3, confluent. WMH of grade 2 or 3 was regarded as advanced WMH. MR images were evaluated by 2 of the authors (H.N., E.N.) separately without knowledge of the patients' clinical profiles, and the number of microbleeds and the grading scores of WMH were determined by consensus. Patients were divided into 4 groups by the presence or absence of cerebral microbleeds and advanced WMH as follows: group A, patients with advanced WMH but without microbleeds; group B, patients with coexistence of microbleeds and advanced WMH; group C, patients without either microbleeds or advanced WMH; and group D, patients with microbleeds but without advanced WMH.

Follow-up of the patients started from the dates of their respective MR imaging studies. Patients were followed up until the recurrence of stroke or until March 2005. Intracerebral hemorrhage was diagnosed by CT. Acute ischemic stroke was confirmed by diffusion-weighted imaging and apparent diffusion coefficient maps. Whether the patients had received antiplatelet therapy after the ischemic stroke was recorded.

All values are expressed as means ± standard deviations. Among the 4 groups, the χ^2 test for independence was used for comparison of sex ratio, stroke type ratio, antiplatelet therapy, hypertension, diabetes mellitus, and hypercholesterolemia, and 1-factor analysis of variance for age was also used. The Kaplan-Meier method was used to estimate the rates of recurrent stroke. Cox proportional hazards regression analysis was used to assess the relationships of subsequent intracerebral hemorrhage or ischemic stroke with the following variables: age, sex, stroke type, days from stroke onset to registration, hypertension, diabetes mellitus, hypercholesterolemia, antiplatelet therapy, advanced WMH, and microbleeds.

Results

The population in this study consisted of 266 patients (67.2 ± 11.5 years of age, 167 men and 99 women) with a history of stroke. The number of the patients in each group was as follows: 39 patients in group A, 52 patients in group B, 133 pa-

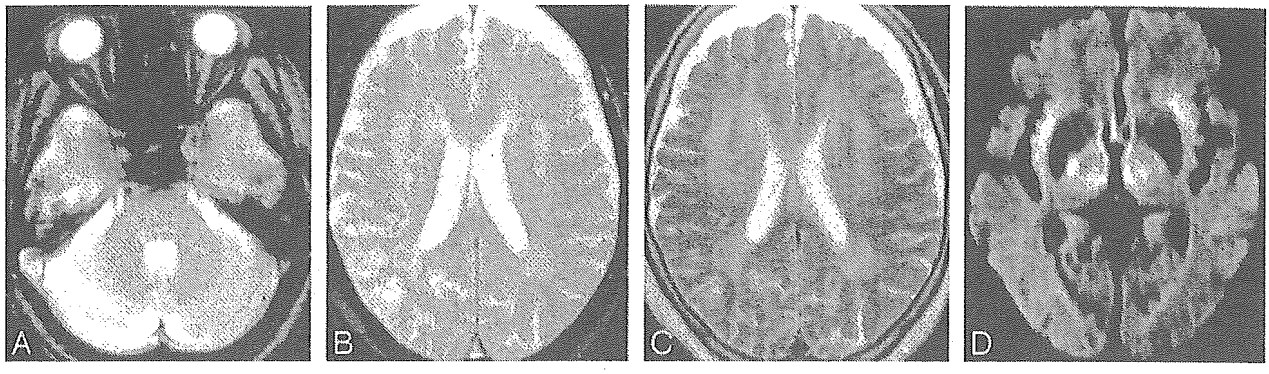

Fig 2. MR images obtained from a patient (85-year-old woman) with lacunar infarction in the right internal capsule after the occurrence of lacunar infarction in the right corona radiata. *A* and *B*, Initial T2*-weighted gradient-echo images (TR/TE, 800/26; flip angle, 20°) show no microbleeds. *C*, T2-weighted spin-echo image (TR/TE, 4500/112) shows advanced white matter hyperintensity. *D*, Diffusion-weighted image (single-shot echo-planar spin-echo sequence; TR/TE, 5300/135; b = 1000 mm^2/s) obtained 23 months after the lacunar infarction shows a hyperintense lesion in the right internal capsule, consistent with acute infarction.

Table 2: Frequency of development of recurrent stroke

	Recurrent Stroke, *n* (%)	Recurrence Rate by Kaplan-Meier Method	
		1 y	2 y
Group A (*n* = 39)	6 (15.4)	10.5	17.4
Group B (*n* = 52)	6 (11.5)	9.6	14.9
Group C (*n* = 133)	6 (4.5)	1.5	5.8
Group D (*n* = 42)	8 (19.0)	14.3	21.2

Note:—Group A, patients with advanced white matter hyperintensity (WMH) but without microbleeds; group B, patients with coexistence of microbleeds and advanced WMH; group C, patients without either microbleeds or advanced WMH; group D, patients with microbleeds but without advanced WMH.

Table 3: Frequency of development of intracerebral hemorrhage

	Recurrent Stroke, *n* (%)	Recurrence Rate by Kaplan-Meier Method (%)	
		1 y	2 y
Group A (*n* = 39)	0 (0.0)	0	0
Group B (*n* = 52)	1 (1.9)	0	5.9
Group C (*n* = 133)	1 (0.8)	0	1.5
Group D (*n* = 42)	8 (19.0)	14.3	21.2

Note:—Group A, patients with advanced white matter hyperintensity (WMH) but without microbleeds; group B, patients with coexistence of microbleeds and advanced WMH; group C, patients without either microbleeds or advanced WMH; group D, patients with microbleeds but without advanced WMH.

Table 4: Frequency of development of ischemic stroke

	Recurrent Stroke, *n* (%)	Recurrence Rate by Kaplan-Meier Method (%)	
		1 y	2 y
Group A (*n* = 39)	6 (15.4)	10.5	17.4
Group B (*n* = 52)	5 (9.6)	9.6	9.6
Group C (*n* = 133)	5 (3.8)	1.5	4.4
Group D (*n* = 42)	0 (0.0)	0	0

Note:—Group A, patients with advanced white matter hyperintensity (WMH) but without microbleeds; group B, patients with coexistence of microbleeds and advanced WMH; group C, patients without either microbleeds or advanced WMH; group D, patients with microbleeds but without advanced WMH.

tients in group C, and 42 patients in group D. The baseline characteristics of the patients are summarized in Table 1. Cerebral microbleeds were found on T2*-weighted MR images in 94 (35.3%) of the patients.

The mean follow-up period was 564.8 ± 220.5 days. Three patients were lost to follow-up (2 patients in group C and 1 patient in group D), and 1 patient in group B died of a cause not related to stroke. During the follow-up period, 26 patients developed recurrent strokes, including 10 intracerebral hemorrhages and 16 ischemic strokes. Representative MR and CT images of patients with recurrent stroke are shown in Figs 1 and 2. Frequencies of the development of overall recurrent stroke, intracerebral hemorrhage, and ischemic stroke are shown in Table 2, Table 3, and Table 4, respectively. Development of intracerebral hemorrhage was the most frequently observed in patients of group D (19.0%). Analysis by the Kaplan-Meier method showed that the estimated recurrence rate of intracerebral hemorrhage was also the highest in patients in group D. The frequency of development of ischemic stroke was the highest in patients in group A (15.4%), followed by patients in group B (9.6%) and patients in group C (3.8%), whereas no patients in group D developed ischemic stroke. Patients in group A also showed the highest estimated recurrence rate of ischemic stroke in the 4 groups.

The detailed characteristics of the patients with recurrent stroke are summarized in Table 5. Only the development of ischemic stroke was observed in patients in group A. Development of ischemic stroke was observed in all except one of the recurrence patients in groups B and C. In contrast, patients in group D developed only intracerebral hemorrhage, and all of the 4 patients who developed intracerebral hemorrhage after ischemic stroke had been taking aspirin as an antiplatelet therapy.

The results of Cox proportional hazards regression analysis showed that the presence of microbleeds was significantly and independently associated with subsequent intracerebral hemorrhage (hazard ratio [HR], 85.626; 95% confidence interval [CI], 6.344–1155.649), whereas advanced WMH had a negative association with subsequent intracerebral hemorrhage (HR, 0.016; 95% CI, 0.001–0.258) (Table 6). Advanced WMH was associated with subsequent ischemic stroke (HR, 10.659; 95% CI, 2.601–43.678) (Table 7).

Discussion

Although both microbleeds and WMH are associated with small-artery disease, their features are different. The presence of microbleeds, which pathologically represent hemosiderin deposit,[1,2] is associated with the progression of bleeding-

Table 5: Detailed characteristics of patients with recurrent stroke

Group/Age (y)/Sex	Previous stroke	Microbleeds, *n*	WMH, Grade	Antiplatelet Therapy	Hyper-tension	Diabetes Mellitus	Hypercho-lesterolemia	Recurrent Stroke
A/84/F	Lacunar infarction	0	2	Cilostazol	(+)	(−)	(−)	Lacunar infarction
A/71/M	Lacunar infarction	0	2	Ticlopidine	(+)	(−)	(+)	Lacunar infarction
A/78/F	Atherothrombotic infarction	0	2	Ticlopidine	(−)	(−)	(+)	Atherothrombotic infarction
A/87/F	Lacunar infarction	0	2	Aspirin	(+)	(−)	(−)	Lacunar infarction
A/74/F	Lacunar infarction	0	2	Aspirin	(−)	(−)	(−)	Lacunar infarction
A/85/F	Lacunar infarction	0	3	Cilostrazol	(+)	(−)	(−)	Lacunar infarction
B/70/M	Atherothrombotic infarction	3	3	Ticlopidine	(+)	(−)	(+)	Atherothrombotic infarction
B/57/M	Intracerebral hemorrhage	19	2	(−)	(+)	(−)	(−)	Lacunar infarction
B/76/F	Lacunar infarction	2	2	Cilostazol	(+)	(−)	(+)	Lacunar infarction
B/66/M	Lacunar infarction	1	2	Aspirin	(+)	(+)	(+)	Lacunar infarction
B/55/M	Lacunar infarction	2	2	Cilostazol	(−)	(−)	(−)	Lacunar infarction
B/69/M	Lacunar infarction	13	3	Aspirin	(+)	(−)	(−)	Intracerebral hemorrhage
C/54/M	Lacunar infarction	0	1	Cilostazol	(+)	(+)	(−)	Lacunar infarction
C/61/F	Intracerebral hemorrhage	0	1	Aspirin + ticlopidine	(+)	(+)	(−)	Lacunar infarction
C/61/F	Atherothrombotic infarction	0	1	Aspirin + ticlopidine	(+)	(−)	(−)	Lacunar infarction
C/57/F	Lacunar infarction	0	0	Aspirin	(−)	(+)	(−)	Atherothrombotic infarction
C/54/M	Lacunar infarction	0	1	Aspirin	(−)	(+)	(−)	Lacunar infarction
C/74/M	Lacunar infarction	0	1	Aspirin	(−)	(+)	(−)	Intracerebral hemorrhage
D/77/M	Lacunar infarction	13	1	Aspirin	(−)	(−)	(−)	Intracerebral hemorrhage
D/70/M	Lacunar infarction	28	1	Aspirin	(+)	(−)	(+)	Intracerebral hemorrhage
D/73/M	Atherothrombotic infarction	1	1	Aspirin	(+)	(−)	(−)	Intracerebral hemorrhage
D/80/M	Atherothrombotic infarction	11	0	Aspirin	(+)	(−)	(−)	Intracerebral hemorrhage
D/82/M	Intracerebral hemorrhage	2	1	(−)	(−)	(−)	(−)	Intracerebral hemorrhage
D/51/M	Intracerebral hemorrhage	2	0	(−)	(+)	(−)	(−)	Intracerebral hemorrhage
D/53/F	Intracerebral hemorrhage	12	1	(−)	(+)	(−)	(−)	Intracerebral hemorrhage
D/55/M	Intracerebral hemorrhage	16	1	(−)	(+)	(−)	(−)	Intracerebral hemorrhage

Note:—Group A, patients with advanced white matter hyperintensity (WMH) but without microbleeds; group B, patients with coexistence of microbleeds and advanced WMH; group C, patients without either microbleeds or advanced WMH; group D, patients with microbleeds but without advanced WMH. Present is indicated by (+) and absent indicated by (−).

prone small-artery disease and with symptomatic intracerebral hemorrhage.[6-16] A recent cohort study showed that the presence of microbleeds is a risk factor for subsequent intracerebral hemorrhage in patients with ischemic stroke.[15] In contrast, the neuropathologic appearance corresponding to WMH (leukoaraiosis) is neuronal loss, ischemic demyelination, and gliosis,[17] and WMH has been reported to be a risk factor for ischemic stroke.[17-20] However, there have been no studies in which both microbeeds and WMH were evaluated as risk factors for subsequent stroke types in the same series of patients. The results of Cox proportional hazards regression analysis in the present study not only reconfirmed microbleeds as a risk factor for subsequent intracerebral hemorrhage and advanced WMH as a risk factor for subsequent ischemic stroke but also showed advanced WMH to be a negative risk factor for subsequent intracerebral hemorrhage.

Table 6: Cox proportional hazards regression analysis for predicting subsequent intracerebral hemorrhage

Variable	Hazards Regression	95% CI	P
Increased age	1.028	0.948–1.116	.5024
Male sex	16.476	1.448–187.467	.0239
Stroke type (intracerebral hemorrhage)	41.898	1.822–963.670	.0195
Microbleeds	85.626	6.344–1155.649	.0008
Advanced leukoaraiosis	0.016	0.001–0.258	.0035
Hypertension	0.163	0.026–1.044	.0555
Diabetes mellitus	0.83	0.092–7.461	.868
Hypercholesterolemia	0.333	0.030–3.667	.3689
Antiplatelet therapy	64.904	2.054–2050.683	.0178
Days from stroke onset to registration	1.009	1.003–1.015	.0017

Table 7: Cox proportional hazards regression analysis for predicting subsequent ischemic stroke

Variable	Hazards Regression	95% CI	P
Increased age	0.938	0.886–0.993	.0269
Male sex	0.297	0.094–0.936	.0381
Stroke type (ischemic stroke)	1.099	0.029–41.732	.9596
Microbleeds	0.609	0.174–2.132	.4378
Advanced leukoaraiosis	10.659	2.601–43.678	.001
Hypertension	1.129	0.367–3.474	.8327
Diabetes mellitus	0.821	0.277–2.434	.7225
Hypercholesterolemia	0.609	0.200–1.849	.381
Antiplatelet therapy	13.816	0.343–556.026	.1636
Days from stroke onset to registration	0.987	0.971–1.003	.106

No prospective studies have focused on combinations of microbleeds and advanced WMH as predictors for types of subsequent stroke. Kim et al[6] reported that microbleeds are a predictor of intracerebral hemorrhage in patients with no or mild leukoaraiosis but that they appear similarly both in ischemic stroke and hemorrhagic stroke in patients with advanced leukoaraiosis. We performed the first prospective study aimed at determining whether cerebral microbleeds and advanced WMH are risk factors for types of subsequent stroke, by focusing on combinations of the presence or absence of these 2 types of small-artery disease. The results indicated that the presence of microbleeds appears to be a risk factor for subsequent intracerebral hemorrhage when the patient does not have advanced WMH. Patients with microbleeds but without advanced WMH developed only intracerebral hemorrhage, and all of the patients who developed intracerebral hemorrhage after ischemic stroke had been taking aspirin as antiplatelet therapy. As Wong et al[9] reported, the presence of old silent microbleeds appears to be a risk factor for aspirin-associated intracerebral hemorrhage, and our results further suggest that the presence of cerebral microbleeds, but the absence of advanced WMH, might be a high risk for subsequent intracerebral hemorrhage.

Of course, it is possible that because patients with microbleeds but without advanced WMH had a high frequency of intracerebral hemorrhage as the initial stroke and hypertension, they showed a higher prevalence of intracerebral hemorrhage as the subtype of recurrent stroke. In fact, previous studies have shown that intracerebral hemorrhage or uncontrolled hypertension predict future intracerebral hemorrhage. However, the results of Cox proportional hazards regression analysis revealed that microbleeds were associated with intracerebral hemorrhage as the subtype of recurrent stroke independent of initial stroke type (intracerebral hemorrhage) or the presence of hypertension. The results of the present study also indicate that patients with advanced WMH, but without microbleeds, might be prone to the development of ischemic stroke, and even patients with coexistence of microbleeds and advanced WMH might be at higher risk for the development of ischemic stroke than for the development of intracerebral hemorrhage. Investigation of combinations of the presence or absence of cerebral microbleeds and advanced WMH might enable identification of patients who are at high risk for development of subsequent intracerebral hemorrhage or ischemic stroke, which would contribute to therapeutic strategies including antiplatelet therapy.

Of course, our study had some limitations. Because the baseline backgrounds of the patients in the 4 groups were not necessarily the same and because the number of patients in each group was small, the results may be controversial and may not be confirmed in studies with a larger number of patients. In addition, the present study was an observational study and causality has yet to be established because bias and confounding could not be eliminated in an observational study. Furthermore, the severity of hypertension and its control were not recorded in the present study. It remains to be determined whether the presence of microbleeds increases the risk of future intracerebral hemorrhage in patients with intracerebral hemorrhage whose hypertension is uncontrolled. We expect that our results will be confirmed by multicenter studies with large numbers of patients.

Conclusion

Combinations of the presence or absence of microbleeds and advanced WMH appear to enable identification of patients who are at high risk for the development of subsequent intracerebral hemorrhage or ischemic stroke, which would contribute to therapeutic strategies including antiplatelet therapy.

Acknowledgments

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Low-Dose Aspirin for Prevention of Stroke in Low-Risk Patients With Atrial Fibrillation

Japan Atrial Fibrillation Stroke Trial

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Background and Purpose—Although the efficacy of anticoagulant therapy for primary prevention of stroke in patients with nonvalvular atrial fibrillation (NVAF) has been established, efficacy of antiplatelet therapy for low-risk patients is disputable in Japanese patients because of the frequent hemorrhagic complications. We examined the efficacy and safety of aspirin therapy in Japanese patients with NVAF in a prospective randomized multicenter trial.

Methods—Patients with NVAF were randomized to an aspirin group (aspirin at 150 to 200 mg per day) or a control group without antiplatelet or anticoagulant therapy. Primary end points included cardiovascular death, symptomatic brain infarction, or transient ischemic attack.

Results—A total of 426 patients were randomized to aspirin group and 445 to no treatment. The trial was stopped earlier because there were 27 primary end point events (3.1% per year; 95% CI, 2.1% to 4.6% per year) in the aspirin group versus 23 (2.4% per year; 95% CI, 1.5% to 3.5% per year) in the control group, suggesting a low possibility of superiority of the aspirin treatment for prevention of the primary end point. In addition, treatment with aspirin caused a marginally increased risk of major bleeding (7 patients; 1.6%) compared with the control group (2 patients; 0.4%; Fisher exact test $P=0.101$).

Conclusions—For prevention of stroke in patients with NVAF, aspirin at 150 to 200 mg per day does not seem to be either effective or safe. Further prospective studies are needed to determine the best preventive therapy for cerebrovascular events in Japanese patients with NVAF. (***Stroke.* 2006;37:447-451.**)

Key Words: aspirin ■ stroke ■ thrombosis

The efficacy of anticoagulant therapy has long been established for the primary prevention of stroke and transient ischemic attacks (TIAs) in patients with nonvalvular atrial fibrillation (NVAF).[1–4] Despite conclusive evidence of efficacy, several studies have shown that use of warfarin in patients with atrial fibrillation (AF) is suboptimal.[5] Indeed, antithrombotic therapy is not commonly given to Japanese NVAF patients (8%), probably because of the risk of critical bleeding during treatment.[6] Instead, antiplatelet therapy (45%) or nontreatment (47%) are often selected to manage patients with NVAF,[6] although little information is available about benefits and risks of aspirin treatment. Furthermore,

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despite the fact that a high dose of aspirin (325 mg per day) but not a low dose (75 mg per day) has been shown to be effective for prevention of stroke,[7,8] the majority of Japanese patients with NVAF are administered a low dose of aspirin (81 mg per day).[9] The rationale for use of low-dose aspirin in Japanese patients is based on the risk of gastrointestinal intolerance and the dose-dependent risk of bleeding.[10] In the present study, we aimed to examine the efficacy of low-dose aspirin for improving the prognosis of low-risk NVAF patients in a prospective randomized multicenter trial.

Methods

Patients

The Japan Atrial Fibrillation Stroke Trial (JAST) was performed at 13 centers and 76 affiliated hospitals in Japan. The protocol was approved by the institutional review board or ethics committee at each participating center or hospital, and written informed consent was given by each patient. Patients with chronic or intermittent AF documented by ECG at least twice within 12 months were candidates for this trial. Patients were excluded from the study if they met the following criteria: prosthetic heart valve, rheumatic heart disease, mitral valve disease, uncontrolled hypertension, hyperthyroidism, severe heart failure (New York Heart Association class IV), and a past history of symptomatic thromboembolic disease within a year, previous intracranial bleeding, or gastrointestinal hemorrhage within 6 months. Patients with other indications for anticoagulant therapy or antiplatelet agents were also excluded (ie, coronary artery disease, pulmonary embolization, venous thrombosis, and other diseases that the attending physician considered to be treated with these medicines). Furthermore, patients whose attending physicians considered it inappropriate for them to join the study were excluded. Patients with a history of stroke or TIA>1 year previously were exceptionally eligible if both the patient and physician agreed.

Design

The patients were randomly divided into 2 groups (ie, an aspirin group that received aspirin therapy [150 to 200 mg per day], and a control group that was not prescribed aspirin. Randomization was performed at 13 centers following instruction sheets sent from the executive office in Osaka University, and the randomized sequence was blocked from previewing by the investigators and the attending physician. The dose of aspirin was selected by the attending physician and also depending on the aspirin formulation available at each hospital. Patients were instructed to take aspirin every morning after breakfast. Treatment with 330 mg of aspirin on alternative days was also permitted. If patients taking anticoagulant or antiplatelet medicine were permitted to attend the study, they were required to discontinue their treatment for ≥2 weeks before randomization. Medication compliance was examined by physician's questioning at every visit to clinic. Compliance was defined as good when patients took aspirin more than two thirds of prescribed aspirin. Sporadic use of aspirin and nonsteroidal anti-inflammatory agents was discouraged. Other medications were not prohibited during this trial.

Primary end points included cardiovascular death, symptomatic brain infarction, or TIA, whereas the secondary end points included noncardiovascular death, intracranial hemorrhage, major bleeding, and peripheral embolization. The criteria for cerebrovascular events were confirmed clinical signs of an acute-onset neurological deficit of presumed vascular origin. A TIA was defined as focal symptoms lasting for <24 hours. Patients with stroke events were evaluated by expert physicians (stroke specialists) at the periodical meetings of the event monitoring committee and the end points were assessed by investigators who had no knowledge of each patient's treatment. Stroke, TIA, and intracranial bleeding were confirmed by computed tomography scanning or MRI in addition to the clinical data collected by the event monitoring committee. Subtypes of the cerebral infarction were also diagnosed by the committee according to the popularly used definitions.[11,12] The final diagnosis of the subtypes of stroke was made by consensus. Major bleeding was defined as fatal bleeding, bleeding needed for hospital admission for treatment, blood transfusion, or a decrease of hemoglobin concentration >4 g/dL. Initially, a sample size of 754 per group was estimated to be necessary on the basis of an anticipated event rate for the primary end points of 3% per year in the control group and 1.5% per year in the aspirin group, with an 80% power of test and a 2-sided significance of $P<0.05$. However, because the number of patients registered was smaller than expected, the sample size was reduced to 492 per group, and instead, the mean follow-up period was extended from 2 to 3 years at the steering committee meeting, held September 13, 2000.

To ensure the safety of the trial, informal interim analyses of the event rate for both primary and secondary end points were performed every 6 months by a data and safety monitoring committee after ≥75% of the target number of patients had been registered. The data and safety monitoring committee was established to recommend early termination of the trial if it observed a clinically important treatment effect, unpredictable side effects, or a futile data for continuation. No formal rules for stopping the trial were adopted before the initiation of enrollment.

Laboratory Methods

Routine blood examination was performed before, 3 months, and every year after the entry. Plasma thrombin–antithrombin complex (TAT) levels were determined using the enzyme immunoassay TAT[S] (SRL, Inc), and D-dimer levels were determined using a latex agglutination test (COBAS reagent D-dimer; Roche Diagnostics K.K.). These assays allowed measurement of plasma TAT and D-dimer levels to a minimum of 1.0 ng/mL and 0.10 μg/mL (100 ng/mL), respectively. Plasma fibrinogen levels were assayed by the Clauss methods with a Sysmex CA-7000 coagulometer and the appropriate reagents and standards. The lower detection limit of this test was 20 mg/dL. Laboratory analyses were done in a blinded fashion. After determination of the baseline concentrations of TAT, D-dimer, and fibrinogen, the study population was divided into quartiles with an equal number of patients (TAT: first quartile <1.20 ng/mL; second quartile from 1.20 to 1.90 ng/mL; third quartile from 1.90 to 2.70 ng/mL; and fourth quartile ≥2.70 ng/mL; D-dimer: first quartile <170 ng/mL; second quartile from 170 to 400 ng/mL; third quartile from 400 to 600 ng/mL; and fourth quartile ≥600 ng/mL; fibrinogen: first quartile <244 mg/dL; second quartile from 244 to 282 mg/dL; third quartile from 282 to 328 mg/dL; and fourth quartile ≥328 mg/dL).

Statistical Analysis

All analyses were performed on an intent-to-treat basis. Differences of continuous variables between the 2 treatment groups were determined by the t test. Categorical variables were compared by the χ^2 test. In the case of low cell count (<5), Fisher exact test was used instead of the χ^2 test. In the interim analyses, the binomial probability was computed to examine the possibility of overturning a trend shown by the interim analysis. CIs for event rates were computed using a Poisson distribution. Survival curves were constructed by the Kaplan–Meier method, and differences in survival were assessed using the log-rank test. Multivariate logistic regression analysis was used to determine factors associated with primary end points. Aspirin treatment, age ≥75 years, gender, paroxysmal AF, systemic hypertension, hyperlipidemia, heart failure, smoking status, diabetes mellitus, previous cerebrovascular disease, D-dimer highest quartile, TAT highest quartile, and fibrinogen highest quartile were included as parameters. For all analyses, significance was defined as $P<0.05$ (2-sided).

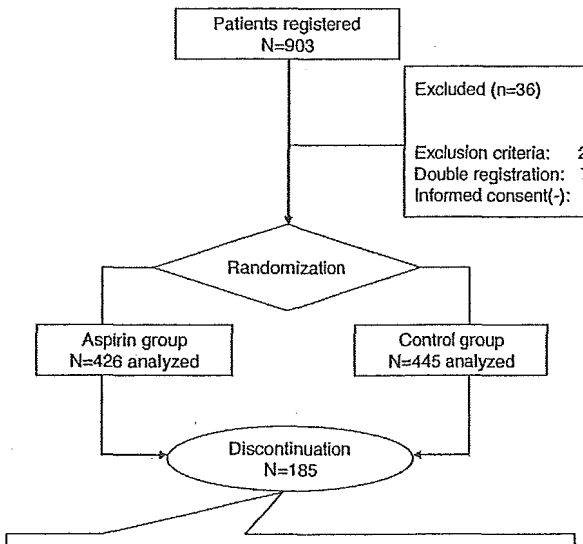
Results

Randomization was started on September 1, 1998, and the study was stopped early based on the recommendation of the data and safety monitoring committee on May 31, 2002. This decision was made because of the following results of interim

analysis: (1) treatment with aspirin caused a marginally higher risk of major bleeding, and (2) aspirin therapy was unlikely (0.015%) to be superior to no treatment for prevention of both the primary and secondary end points. At the time of early termination, 907 patients had been entered into the study. Among them, 36 patients were excluded because of failure to fulfill the enrollment criteria or other administrative reasons. Accordingly, 871 patients were randomized to the open-label treatment, including 426 in the aspirin group and 445 in the group without treatment (Figure 1). During follow-up, 96 patients in the aspirin group and 89 patients in the control group were withdrawn from the study. However, the period before withdrawal was included in the analysis. Consequently, the mean follow-up period was 768±403 days (median 810 days; range 15 to 1365 days). The baseline characteristics of the 2 groups were similar (Table 1), with little difference of important prognostic variables such as age, hypertension, heart failure, and previous history of warfarin treatment.

Effect of Aspirin on the End Points

Eighty-four percent of the patients in the aspirin group took aspirin regularly. When the study was terminated, there had been 27 primary end point events (3.1% per year; 95% CI, 2.1% to 4.6% per year) in the aspirin group versus 23 (2.4% per year, 95% CI, 1.5% to 3.5% per year) in the control group according to the intention-to-treat analysis, and this represents a 50% increase in the risk of primary end points (95% CI, 0.85% to 2.70%; $P=0.175$) in patients assigned to aspirin



Discontinuation

	Aspirin (n=426)	Control(n=445)	p value
Total discontinuation	96	89	0.360
Side effects	21	0	<0.001
Gastrointestinal	10	0	0.001
Minor bleeding	4	0	0.114*
Cardiac diseases	12	20	0.188
Ischemic heart disease	4	12	<0.001
Other diseases	4	7	0.001*
Personal reason	56	62	0.734
Unknown	3	0	0.249*
Days to discontinuation	365±344	439±344	0.148

* indicates Fisher's test.

Figure 1. Patient flow chart.

TABLE 1. Patient Characteristics

Characteristic	Aspirin (n=426)	Control (n=445)	*P* Value
Mean age, y	65.5	64.8	0.338
Men	71.1%	69.7%	0.636
Paroxysmal AF	44.6%	45.2%	0.866
Hypertension	36.6%	40.4%	0.264
Hyperlipidemia*	23.9%	21.2%	0.349
Current smoker	27.9%	32.8%	0.115
Diabetes mellitus	12.7%	15.3%	0.262
Previous cerebrovascular disease	2.6%	2.5%	0.917
Heart failure	8.3%	10.1%	0.355
High risk**	42.0%	47.7%	0.094
History of warfarin	7.0%	8.5%	0.410
TAT, ng/mL	3.2±5.1	3.3±5.6	0.726
D-dimer, ng/mL	1.1±6.1	1.0±5.3	0.747
Fibrinogen, mg/dL	289±66	292±72	0.559

*Defined as a documented fasting total cholesterol concentration >220 mg/dL, fasting triglyceride concentration >150 mg/dL, or antilipidemic therapy; **defined as patients with hypertension, previous cerebrovascular disease, or heart failure.

after adjusting for age, gender, paroxysmal AF, hypertension, hyperlipidemia, diabetes mellitus, smoking, previous cerebrovascular disease, heart failure, high TAT, high D-dimer, and high fibrinogen. Kaplan–Meier curves for the primary event-free rates in patients with or without aspirin treatment showed that this difference was not significant ($P=0.310$; Figure 2a), and the frequency of each individual primary end point was not significantly different between the 2 groups (Table 2). Also combined end points of stroke and TIA did not differ between the groups.

Secondary end point events were observed in 14 patients from the aspirin group and 9 patients from the control group. The frequency of each individual end point was not significantly different (Table 2). However, treatment with aspirin caused a marginally higher risk of major bleeding (7 patients; 1.6%) compared with the control group (2 patients; 0.4%), although Fisher's exact test did not show any statistical significance ($P=0.101$). Figure 2b shows the Kaplan–Meier curves for the event-free rate for combined primary and secondary end points in the aspirin group versus the control group ($P<0.109$). Treatment with aspirin led to a 42% increase in the risk of a combined end point events (95% CI, 0.85% to 2.40%; $P=0.185$) after adjusting for age, gender, paroxysmal AF, hypertension, hyperlipidemia, diabetes mellitus, smoking, previous cerebrovascular disease, heart failure, high TAT, high D-dimer, and high fibrinogen.

Multivariate logistic regression analysis revealed that an age of ≥75 years, diabetes mellitus, and the highest TAT quartile were independent predictors of the primary end points (Table 3). In contrast, heart failure and hypertension were not independently associated with the primary end points.

Five of the 7 patients with major bleeding were elderly, but their mean age of 66.4±9.0 years was not different from that of the other 862 patients (65.1±10.8 years). Intracranial

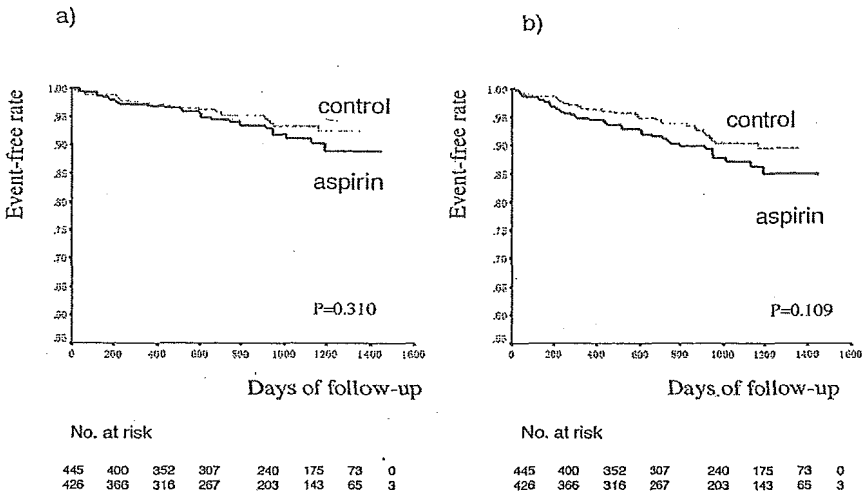


Figure 2. Kaplan–Meier survival curves for primary end points (a) and for primary plus secondary end points (b). Treatment with aspirin was not superior to treatment without aspirin for primary end points (log-rank; $P=0.310$) and secondary end points (log-rank; $P=0.109$)

bleeding was observed in 4 patients from the aspirin group (0.94%) and 2 patients from the control group (0.45%).

Discussion

The present study indicated that treatment with aspirin at 150 to 200 mg per day did not improve the prognosis of Japanese patients with NVAF. It was considered reasonable to terminate this study after the detection of observations indicating a very low possibility of aspirin being superior for prevention of the primary end point and a slightly higher risk of major bleeding in the aspirin group. The probability of the trial being able to show the superiority of aspirin treatment was extremely low, even if we assumed that the frequency of events was twice as high in the control group. Moreover, the risk of major bleeding in patients on aspirin treatment was higher than in the control. In fact, 1 more event in the aspirin group would have led to a significant difference.

In the present study, dividing the number of strokes and TIA with mean follow-up period, annual incidence of ischemic brain events was calculated as 2.8% in the aspirin group and 2.1% in the control group. These rates are low compared with previous trials[7,8] and are equivalent to those in the ATRIA study.[13] The relatively low rate of events in the participants might have masked a favorable antithrombotic effect of aspirin. Also, patient selection bias may have reduced the preventive effect of aspirin because relatively high-risk patients were included in this study. Patients with hypertension, heart failure, or previous cerebrovascular events, who are recommended to receive anticoagulant therapy in the American Heart Association (AHA)/The American College of Cardiology (ACC) guidelines,[3] were not excluded from the study. Although these risk factors were not independent predictors of clinical events in this study, the ineffectiveness of aspirin in high-risk patients may possibly have masked its benefit for others. Third, the aspirin dosage used in this study was lower than that recommended in the AHA/ACC guidelines.[3] Finally, a high prevalence of cardioembolic stroke in this study may have influenced the effect of aspirin (Table 2). Meta-analysis of the Stroke Prevention in Atrial Fibrillation (SPAF) I to III clinical trials showed that 52% of the ischemic strokes observed during these trials were classified as cardioembolic, and that aspirin appears to primarily reduce noncardioembolic stroke in AF patients.[14]

TABLE 2. Primary and Secondary End Points

	Aspirin (n=426)	Control (n=445)	*P* Value
Primary end points	27	23	0.458
Cardiovascular death	3	3	1.000*
Stroke	17	18	0.967
Cardiogenic embolism	14	12	0.609
Thrombotic infarction	3	2	0.959*
Lacunar infarction	0	4	0.135*
TIA	7	2	0.101*
Secondary end points	14	9	0.254
Noncardiovascular death	7	6	0.720
Peripheral emboli	0	1	1.000*
Major bleeding	7†	2‡	0.101*

*Fisher test; †includes 2 subdural bleedings, thalamic bleeding, subarachnoidal bleeding, urinary tract bleeding, gastric bleeding, and respiratory bleeding; ‡include subarachnoidal bleeding and thalamic bleeding.

TABLE 3. Multivariate Analyses of Factors Associated With Primary End Points

Characteristic	Hazard Ratio (95% CI)	*P* Value
Aspirin treatment	1.50 (0.84–2.70)	0.175
Age >75 years	2.06 (1.08–3.95)	0.028
Men	0.77 (0.37–1.67)	0.521
Paroxysmal AF	1.05 (0.56–1.84)	0.954
Systemic hypertension	0.82 (0.44–1.52)	0.524
Hyperlipidemia	1.37 (0.71–2.64)	0.353
Heart failure	0.45 (0.14–1.49)	0.191
Current smoker	1.45 (0.71–2.95)	0.310
Diabetes mellitus	2.46 (1.25–4.83)	0.009
Previous cerebrovascular disease	2.63 (0.89–8.09)	0.091
D-dimer highest quartile	1.01 (0.52–1.97)	0.968
TAT highest quartile	1.95 (1.06–3.56)	0.031
Fibrinogen highest quartile	1.16 (0.61–2.22)	0.644

Definitions as in Table 1.

The absolute risk of stroke varies widely according to age and the presence of coexistent disease. Factors associated with stroke among participants in the SPAF I to III trials who received placebo or aspirin therapy have been reported previously,[15] indicating that age, female sex, history of hypertension, systolic blood pressure, and previous stroke or TIA were independently associated with an increased risk of stroke. Multivariate analysis performed in this study showed that an age of >75 years, diabetes mellitus, and a TAT in the upper quartile were independently associated with an increase of primary end point events (Table 3).

A hypercoagulable state, including elevated levels of fibrinogen, D-dimer, and TAT, is often seen in patients with AF.[16,17] However, it has not been clearly determined whether these coagulation markers are predictors of ischemic stroke. This study revealed that patients with a high TAT level may possibly have a higher risk of primary end point events, although neither fibrinogen nor D-dimer was a predictor for unknown reasons.

Major bleeding complications, especially intracranial hemorrhage, are an important issue with respect to the prophylaxis of stroke in patients with NVAF. The incidence of major bleeding and intracranial hemorrhage was lower in the previous studies compared with the present study.[7,8,18] The incidence of intracerebral hemorrhage was reported to be higher in Japan than in Western countries,[19] so Japanese patients may be more prone to develop hemorrhagic events than Western patients.[11] Indeed, intracerebral microbleeding is frequently observed by MRI in Japanese.[20] To safely use aspirin for prophylaxis, further studies are needed to detect the Japanese patients with a high risk of major bleeding.

The present study has some potential limitations. Because the design of the trial was not double-blind, we were not able to exclude the existence several biases. Also, the trial was terminated prematurely because of the risk of hemorrhage and the lack of demonstrable superiority of aspirin treatment. Although interim analysis was designed to ensure the safety of the study, multiple interim analyses may have influenced the results. The high incidence of major bleeding may depend on racial or ethnic differences.

For prevention of stroke in patients with NVAF, aspirin at 150 to 200 mg per day does not seem to be either effective or safe. Further prospective studies are needed to determine the best preventive therapy for cerebrovascular events in Japanese patients with NVAF.

Acknowledgments

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Cilostazol in secondary prevention of stroke: Impact of the Cilostazol Stroke Prevention Study

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Abstract

According to recent epidemiological data in Japan, stroke affects roughly 5.3 males and 3.9 females per 1000 person-years and is the third leading cause of mortality. At present, management strategies for secondary prevention of stroke include aggressive treatment of cardiovascular risk factors (i.e., hypertension, smoking cessation, etc.). Antiplatelet drugs in Japan, namely aspirin and cilostazol, are utilized regularly for the prevention of secondary stroke. While aspirin is beneficial for a wide range of cardiovascular endpoints, including total and ischemic strokes, it is also associated with significantly increased risks for hemorrhagic infarction. Cilostazol, by contrast, has been shown to significantly reduce the risk of recurrent strokes without affecting the occurrence of intracranial hemorrhage. In the Cilostazol Stroke Prevention Study, a randomized double-blind, placebo-controlled trial involving more than 1000 Japanese patients, cilostazol was found to reduce the risk of secondary stroke by 41.7% compared with placebo, a statistically significant reduction ($P=0.015$). The greatest risk reduction (43.4% in cilostazol versus placebo, $P=0.0373$) was found in patients who initially had a lacunar infarction, suggesting that cilostazol has a specific effect against small-vessel disease. In addition, cilostazol achieved significant risk reductions on a number of combined endpoints (e.g., cerebral infarction, intracranial hemorrhage, myocardial infarction, or vascular death), and was associated with benefits in intent-to-treat analyses. These findings indicate that cilostazol may have a role as a vascular neuroprotectant, but the clinical implications are limited by the fact that patients were randomized to placebo instead of aspirin, which is the standard of care.

Keywords: Prevention of stroke; Antiplatelet; Cilostazol; Lacunar infarction; Intima-media thickness; Type II diabetes

1. Introduction

The burden of stroke is particularly high in Japan, with incidence rates generally exceeding those reported in the United States and other countries. According to data from the Hisayama [1] and Framingham [2] studies, stroke affects roughly 5.3 men and 3.9 women per 1000 person-years in Japan [1]; in contrast, the stroke rate in the United States is approximately 4.0 in men and 2.0 in women per 1000 person-years [2]. Interestingly, the relationship between stroke and coronary heart disease (CHD) also differs between the two countries. In the United States, the incidence of CHD (17.25 in men and 8.75 in women per 1000 person-years) [2] is markedly higher than that of stroke. In Japan, however, stroke occurs more often than CHD, which affects 3.5 men and 1.8 women per 1000 person-years [1].

Stroke is a greater cause of mortality in Japan than the United States as well. As demonstrated in an analysis of the World Health Organization database [3], the age-standardized, 5-year rates of stroke mortality per 1000 persons in Japan ranged from 0.79 to 10.01 in men and from 0.44 to 7.30 in women, depending on age. Corresponding rates in the United States were 0.42 to 5.26 in men and 0.33 to 4.36 in women.

In 2003, stroke was the third leading cause of death in Japan [4]. An estimated 16% of all Japanese deaths are considered to be stroke related [5]. Stroke is a leading cause of hospitalization in Japan as well; the preponderance of cerebral infarctions are lacunar (55.8–56.3%) followed by atherothrombotic (20.1–21.4%) and cardioembolic (16.2–21.5%) subtypes [6]. A hospital-based analysis found that the mean hospital stay for Japanese patients with acute

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ischemic stroke was 33 days, with an average hospital cost of US$ 6887 per patient [7]. Importantly, the incidence, mortality, and costs of stroke may all increase with the aging of the Japanese population [7].

In Japan, current management strategies for secondary prevention of stroke include aggressive control of cardiovascular risk factors including management of hypertension, lipid abnormalities, and smoking cessation. Antiplatelet therapy also plays a role, and in Japan, aspirin, ticlopidine, and cilostazol are utilized for secondary stroke prevention. A 1998 meta-analysis of 16 randomized, controlled trials evaluating aspirin for prevention of myocardial infarction (MI) and ischemic stroke involved a total of 55,462 participants [8]. In pooled analyses, aspirin (mean dose, 273 mg/day; mean duration, 37 months) was associated with significant absolute risk reductions in all-cause mortality (−120 per 10,000 persons; $P<0.001$), cardiovascular mortality (−97 per 10,000 persons; $P<0.001$), total MI (−137 per 10,000 persons; $P<0.001$), and fatal MI (−36 per 10,000 persons; $P<0.001$), as well as significant reductions in the absolute risks of total stroke (−31 per 10,000 persons; $P=0.02$) and ischemic stroke (−39 per 10,000 persons; $P<0.001$). Unfortunately, however, these benefits of aspirin were accompanied by an increase in the absolute risk of hemorrhagic stroke (+12 per 10,000 persons; $P<0.001$), which translated to a relative risk increase of 84% with aspirin therapy (Table 1) [8].

The authors of the pooled analysis concluded that the increased risk of hemorrhagic infarctions was not enough to outweigh the advantages of aspirin in most populations [8]. Nevertheless the potential for hemorrhagic adverse effects has important implications, particularly for Japanese individuals; according to the Hisayama Study, over 32% of all reported strokes in Japan are cerebral or subarachnoid hemorrhages [1].

As an alternative to aspirin therapy, cilostazol has been approved in Japan, but not the United States, for secondary prevention of cerebral infarction. Cilostazol, a type III phosphodiesterase inhibitor, has demonstrated a number of activities that may contribute to its efficacy in stroke prevention. Favorable characteristics of cilostazol include improvement of endothelial dysfunction, and decreasing of platelet aggregation [9]. Efficacy data, including that from the Cilostazol Stroke Prevention Study (CSPS) [9], support the use of cilostazol for protection against secondary cerebral infarctions. This report provides an overview of the CSPS trial, followed by a discussion of the role of cilostazol as preventive therapy in various populations at risk for secondary stroke.

2. The Cilostazol Stroke Prevention Study

2.1. Methodology

The CSPS trial assessed the efficacy of cilostazol for prevention of recurrent strokes, using a randomized, double-blind, and placebo-controlled protocol with an average follow-up period of about 2 years [9]. Patients aged <80 years with prior cerebral infarctions were recruited from 183 clinical institutes in Japan between April 1992 and March 1996. They were deemed eligible for the study if the onset of cerebral infarction occurred between 1 and 6 months before randomization, the cerebrovascular event had been confirmed by computed tomography or magnetic resonance imaging, and no serious complications (i.e., malignant tumors, liver cirrhosis, renal failure, or heart failure) were present. Patients with carotid and vertobrasilar system infarctions were included in the study. Patients with a history of intracranial hemorrhage were excluded from the trial, as were those with a possibility of past or future cardiogenic cerebral embolism or any of the following complications: mitral valve stenosis, prosthetic valve, endocarditis, MI within 6 weeks after onset, ventricular aneurysm, intraventricular or intra-atrial thrombosis, mitral valve prolapse (for patients aged <45 years without other causes of cerebral embolism induction), atrial fibrillation, sick sinus syndrome, and idiopathic cardiomyopathy. Additional exclusion criteria included severe cerebral deficits causing incapacitation; dependency or dementia; contraindications to cilostazol (i.e., hemostatic disorders, systemic

Table 1
Aspirin-associated risks of stroke, myocardial infarction, and death in 16 randomized, controlled trials

	No. of events/no. of participants[a]			*P*-value
	Aspirin group	Control group	AR (95% CI) per 10,000 persons[b]	
All-cause mortality	1883/28,570	2071/26,892	−120 (−77 to −162)	<0.001
Cardiovascular mortality	1476/28,570	1666/26,892	−97 (−59 to −135)	<0.001
Total myocardial infarction	827/27,830	1124/26,178	−137 (−107 to −167)	<0.001
Fatal myocardial infarction	360/27,090	415/25,426	−36 (−16 to −55)	<0.001
Total stroke[c]	703/28,570	742/26,892	−31 (−5 to −57)	0.02
Hemorrhagic	75	33	12 (5–20)	<0.001
Ischemic	480	576	−39 (−17 to −61)	<0.001
Fatal stroke	159/27,373	133/25,682	4 (−8 to 16)	0.5

Adapted from JAMA, "Aspirin and risk of hemorrhagic stroke: a meta-analysis of randomized controlled trials," He et al., Copyright 1998 [8]. AR: absolute risk.

[a] Two studies did not report fatal stroke, two did not report myocardial infarction, and four did not report fatal myocardial infarction.

[b] Data are absolute risk differences and 95% confidence intervals from a fixed-effects model weighted by sample size.

[c] Unclassified stroke cases were also included.

bleeding, pregnancy, possible pregnancy, or breast-feeding); and diseases requiring nonstudy antiplatelet, anticoagulant, or fibrolytic medications [9].

In total, 1095 subjects were registered for the trial, with 1067 deemed eligible for intent-to-treat (ITT) analyses and 1052 comprising the final evaluable population, with 526 subjects in each arm. The treatment group received 100 mg of oral cilostazol twice daily. This was not an active comparator trial with standard of care aspirin but rather a comparison with placebo. As specified by the study protocol, subjects were evaluated at 12-week intervals from the time of treatment initiation until the conclusion of the trial. The mean duration of follow-up was 651.8 days in the cilostazol group and 569.7 days in the placebo group [9].

The primary outcome for the CSPS trial was the recurrence of cerebral infarction, which was classified using standardized criteria to insure diagnostic accuracy and consistency across all institutes. The Evaluation Committee, which consisted of blinded experts in stroke research and clinical practice, classified all endpoints using standardized criteria. Secondary endpoints included MI, intracranial hemorrhage (either cerebral or subarachnoid), transient ischemic attack (TIA), other thrombotic and embolic disorders (i.e., acute arterial thrombosis and embolism, angina pectoris, pulmonary embolism, and venous thrombosis), and death (i.e., vascular death, that occurring within 28 days following vascular events, and all-cause mortality). In addition, the following combinations of events were evaluated: (1) recurrence of cerebral infarction or MI; (2) recurrence of cerebral infarction, intracranial hemorrhage, or TIA; (3) recurrence of cerebral infarction, intracranial hemorrhage, MI, or vascular death; (4) all vascular events.

Table 2
Baseline characteristics of ITT patients in the Cilostazol Stroke Prevention Study

Variable	Cilostazol	Placebo
No. allocated	533	534
Age (years)[a]	65.2 ± 8.7	65.1 ± 8.8
Gender		
Male (%)	64.7	66.5
Mechanism of cerebral infarction (%)		
Cerebral thrombosis	89.5	88.6
Cerebral embolism	1.1	0.7
Undefined cerebral infarction	9.4	10.7
Time from cerebral infarction to randomization (%)		
≤60 days	51.4	50.0
61–120 days	27.8	31.1
≥121 days	20.6	18.9
Unknown	0.2	0
Clinical category of cerebral infarction (%)		
Lacunar	75.0	73.8
Atherothrombotic	14.1	13.1
Mixed	9.0	11.4
Others	1.1	1.5
Unknown	0.8	0.2
Involved arterial system (%)		
Internal carotid artery	15.4	16.1
Anterior cerebral artery	3.4	3.0
Middle cerebral artery	64.7	66.3
Posterior cerebral artery	7.7	8.2
Vertebrobasilar artery	19.5	21.3
Other	1.1	1.3
Unknown	0.4	0.2
Size of infarction (%)		
Small (diameter ≤ 1.5 cm)	75.2	73.6
Medium	23.1	24.3
Large (>1/2 of lobe)	1.5	1.7
Unknown	0.2	0.4
Blood pressure (mmHg)[a]		
Systolic	138.6 ± 18.1	140.2 ± 17.9
Diastolic	80.2 ± 10.9	81.3 ± 11.7
History (%)		
Hypertension	61.2	60.3
Ischemic heart disease	7.9	8.2
Diabetes mellitus	26.5	23.0
Hyperlipidemia	23.5	25.5
Duration of drug intake (days)[a]	632.2 ± 467.7	695.1 ± 456.3

Adapted from Journal of Stroke and Cerebrovascular Diseases, Volume 9, Gotoh et al., "Cilostazol Stroke Prevention Study: a placebo-controlled double-blind trial for secondary prevention of cerebral infarction," 147–57. Copyright 2000, with permission from National Stroke Association [9].

[a] Values are mean ± S.D.

2.2. *Baseline characteristics of the ITT population*

In general, the two treatment groups were well matched with regard to age, gender, and clinical profiles. As shown in

Table 3
Validated events in the evaluable patients ($n = 1052$) of Cilostazol Stroke Prevention Study

Event type	Cilostazol ($n = 526$)	Placebo ($n = 526$)	Total
Nonfatal events			
Cerebral infarction	30	54	84
Transient ischemic attack	3	5	8
Myocardial infarction	3	3	6
Intracranial hemorrhage[a]	4	6	10
Other vascular events	8	1	9
Subtotal	48	69	117
Fatal events			
Cerebral infarction	0	3	3
Transient ischemic attack	0	0	0
Myocardial infarction	0	0	0
Intracranial hemorrhage[a]	0	1	1
Other vascular events	0	0	0
Subtotal	0	4	4
Total	48	73	121

Adapted from Journal of Stroke and Cerebrovascular Diseases, Volume 9, Gotoh et al., "Cilostazol Stroke Prevention Study: a placebo-controlled double-blind trial for secondary prevention of cerebral infarction," 147–57. Copyright 2000, with permission from National Stroke Association [9]. Primary endpoint = recurrence of cerebral infarction (patients who had suffered a cerebral infarction at 1–6 months before randomization).

[a] Intracranial hemorrhage: cerebral hemorrhage and subarachnoid hemorrhage.

Table 2 [9], the distribution of stroke subtypes, size of cerebral infarctions, and histories of diabetes and cardiovascular disease did not differ between cilostazol- and placebo-treated patients. In both groups, the majority of patients suffered a stroke ensuing from cerebral thrombosis; most were lacunar infarctions characterized by small size (diameter of ≤1.5 cm), middle cerebral artery involvement, and an onset within 60 days before randomization. About two-thirds of patients in each group were male and had a history of hypertension. The mean duration of drug intake was 632.2 days in the cilostazol group and 695.1 days in the placebo group [9].

2.3. *Efficacy results*

The number of fatal and nonfatal validated events among cilostazol- and placebo-treated patients in the final evaluable population is depicted in Table 3 [9]. With respect to the primary outcome, recurrence of stroke, there were 30 cerebral infarctions (all nonfatal) in the cilostazol group versus 57 cerebral infarctions (54 nonfatal) in the placebo group, yielding annual event rates of 3.37% and 5.78%, respectively. The relative risk (RR) reduction in secondary stroke for cilostazol compared with placebo was 41.7% (95% CI, 9.2–62.5%), a statistically significant decline (log-rank test: $P = 0.0150$) [9].

In addition to the significant improvement in risk for secondary stroke, cilostazol was associated with a 39% reduction in the RR of cerebral infarction or MI (33 events versus 60 events; annual event rate 3.71% versus 6.09%; $P = 0.0202$), a composite outcome, although this difference is attributable to the reduction in cerebral infarctions rather than MI, which was the same in both groups. Cilostazol was also associated with a 40.9% reduction in the RR of the composite outcome cerebral infarction, intracranial hemorrhage, or TIA (37 events versus 69 events; annual event rate 4.17% versus 7.06%; $P = 0.009$), and a 38.8% reduction in the RR of cerebral infraction, intracranial hemorrhage, MI, or vascular death (37 events versus 67 events; annual event rate 4.16% versus 6.80%; $P = 0.0151$). The between-group differences in all vascular events, vascular deaths, and all-cause mortality, however, did not reach statistical significance (Table 4) [9]. Death from any cause during the trial period including the follow-up after termination of protocol treatment was reduced (RR = 43.8%, $P = .0415$) in the cilostazol group as compared with the placebo group.

When outcomes were stratified according to clinical category, patients whose initial stroke was classified as a lacunar infarction were found to have the greatest risk reduction with cilostazol compared with placebo [9]. In this sub-

Table 4
Occurrence of primary and secondary endpoints in evaluable patients of the Cilostazol Stroke Prevention Study

	Outcome events			Event rate per year (%)	RRR (%) (95% CI)	*P*-value[b]
	Nonfatal	Fatal	Total			
Cerebral infarction (primary endpoint)						
Cilostazol (nyr, 889.6[a])	30	0	30	3.37	41.7 (9.2–62.5)	0.0150
Placebo (nyr, 986.0)	54	3	57	5.78		
Secondary endpoint						
Cerebral infarction or myocardial infarction						
Cilostazol (nyr, 889.6[a])	33	0	33	3.71	39.0 (6.8–60.1)	0.0202
Placebo (nyr, 986.0)	57	3	60	6.09		
Cerebral infarction, intracranial hemorrhage, or TIA						
Cilostazol (nyr, 887.1[a])	37	0	37	4.17	40.9 (11.9–60.4)	0.0090
Placebo (nyr, 977.4)	65	4	69	7.06		
Cerebral infarction, intracranial hemorrhage, myocardial infarction, or vascular death						
Cilostazol (nyr, 889.6[a])	37	0	37	4.16	38.8 (8.6–59.0)	0.0151
Placebo (nyr, 986.0)	63	4	67	6.80		
All vascular events						
Cilostazol (nyr, 881.4[a])	48	0	48	5.45	27.1 (−5.0 to 49.4)	0.0858
Placebo (nyr, 977.3)	69	4	73	7.47		
Vascular death						
Cilostazol (nyr, 889.6[a])		0	0			0.0604
Placebo (nyr, 986.2)		4	4	0.41		
Death from any cause						
Cilostazol (nyr, 889.7[a])		9	9	1.01	0.2 (−145.5 to 59.5)	0.9791
Placebo (nyr, 986.3)		10	10	1.01		

Adapted from Journal of Stroke and Cerebrovascular Diseases, Volume 9, Gotoh et al., "Cilostazol Stroke Prevention Study: a placebo-controlled double-blind trial for secondary prevention of cerebral infarction," 147–57. Copyright 2000, with permission from National Stroke Association [9]. CI, confidence interval; nyr; number of patient-years; RRR, relative risk reduction. Number of patients who had suffered a cerebral infarction at 1–6 months before randomization = Cilostazol: 526, placebo: 526 patients. Primary endpoint = recurrence of cerebral infarction.

[a] Patient-years at risk for outcome.

[b] Log-rank test.

Table 5
Occurrence of secondary stroke in subgroups of evaluable patients stratified by cerebral infarction subtype in the Cilostazol Stroke Prevention Study

	Cerebral infarction	Event rate per year (%)	RRR (%)	*P*-value[b]
Lacunar infarction				
Cilostazol (nyr, 673.8[a])	20	2.97	43.4	0.0373
Placebo (nyr, 743.4)	39	5.25		
Atherothrombotic infarction				
Cilostazol (nyr, 109.8[a])	7	6.37	39.8	0.2620
Placebo (nyr, 104.0)	11	10.58		
Mixed-type infarction				
Cilostazol (nyr, 90.7[a])	3	3.31	44.5	0.4361
Placebo (nyr, 117.5)	7	5.96		

Adapted from Journal of Stroke and Cerebrovascular Diseases, Volume 9, Gotoh et al., "Cilostazol Stroke Prevention Study: a placebo-controlled double-blind trial for secondary prevention of cerebral infarction," 147–57. Copyright 2000, with permission from National Stroke Association [9]. nyr, number of patient years; RRR, relative risk reduction. Number of patients who had suffered a cerebral infarction at 1–6 months before randomization = Cilostazol: 526 patients, placebo: 526 patients. Primary endpoint = recurrence of cerebral infarction. Log-rank test.

[a] Patient-years at risk for outcome.

[b] Log-rank test.

group, cilostazol was associated with 20 recurrent strokes during follow-up, which corresponded to an event rate of 2.97% per year, in comparison to 39 stroke recurrences, or 5.25% per year, among placebo-treated patients. Thus, cilostazol reduced the RR of secondary cerebral infarctions in this subgroup by 43.4% ($P = 0.0373$). For patients with initial atherothrombotic or mixed-type infarctions, the risk reductions provided by cilostazol were comparable to those achieved in patients with initial lacunar infarctions, although they were not statistically significant (Table 5) [9], probably due to the small number of patient groups, and thus, a smaller number of events.

2.4. Safety and tolerability

Safety analyses showed significantly higher rates of headache with cilostazol (12.8%) than with placebo (3.2%; $P < 0.0001$). In addition, compared with placebo, cilostazol was associated with a significantly higher incidence of palpitations (5.3% versus 0.4%; $P < 0.0001$) and increase in pulse rate (19% versus 7.9%; $P < 0.0001$) during the trial. In total, 13.2% of cilostazol- and 6.2% of placebo-treated patients withdrew from the study due to nonvascular adverse events [9].

As the adverse events were, in general, mild to moderate and self-limiting, safety and tolerability findings were encouraging with respect to cilostazol. There was no evidence that cilostazol was associated with increased rates of gastrointestinal bleeding, dizziness, nausea, gastrointestinal pain, skin rash, or any bleeding disorders compared with placebo. Moreover, the percentages of patients with blood pressure increases and EKG abnormalities did not differ between groups. Patients treated with cilostazol were significantly more likely than those receiving placebo to show improvements in serum triglycerides (6.6% versus 2.9%; $P = 0.0097$) and high-density lipoprotein cholesterol (14.3% versus 5.2%; $P < 0.0001$) over the study period [9].

Perhaps most importantly, no increase in the occurrence of intracranial hemorrhage (cerebral hemorrhage or subarachnoid hemorrhage) was observed with cilostazol therapy. Overall, only four patients in the cilostazol group compared with seven in the placebo group had a cerebral or subarachnoid hemorrhage over the study period. Notably, none of the hemorrhagic events in the cilostazol group were fatal; in contrast, there was one fatal intracranial hemorrhage in the placebo group [9].

3. Discussion

The positive results of the CSPS trial, which showed a significant reduction in the risk of secondary cerebral infarction with cilostazol, have been supported and extended by findings from a subsequent study of this agent in a diabetic population. This controlled trial [10] showed that cilostazol prevented the progression of carotid intima-media thickness (IMT), an important surrogate measurement of cardiovascular risk, and decreased the risk of primary silent brain infarction in Japanese patients with diabetes mellitus having no symptoms and signs of vascular events. Taken together, these data support an expanded role for cilostazol in the secondary prevention of stroke. However, the findings are limited since the comparison was with placebo and not standard of care aspirin. Thus, it is not known if cilostazol would have been superior to aspirin had this been an active comparator trial.

Environmental and genetic variables act independently and in combination with vascular risk factors (e.g., hypertension, dyslipidemia, homocysteinemia, and diabetes) to produce subclinical disease carotid IMT increase, which can in turn lead to either MI or stroke, depending on the location of the thrombus. In addition to increasing the risk of MI [11,12] and intermittent claudication [13], increase in carotid IMT, as shown by ultrasonographic progression, has been established as an important risk factor for stroke [12,14,15]. According

to data from the Cardiovascular Health Study [12], which followed 5858 individuals aged 65 years and older for an average of 6.2 years, the risk of stroke increased by nearly 30% for each standard deviation (S.D.) increase in IMT of the common carotid artery (adjusted RR 1.28; $P<0.001$), with subjects in the highest quintile of carotid IMT showing an adjusted RR of 2.13 compared with the lowest IMT quintile.

Even greater risk increases were found in two case-control studies. In the GÉNIC (The Étude du Profil Génétique de l'Infarctus Cérébral) Study involving over 900 subjects [15], each S.D. increase in IMT of the common carotid artery increased the risk of stroke by 73% after adjustment for risk factors ($P<0.0001$). Similarly, analyses of the Rotterdam Study [14] showed a 34% increase in stroke risk for each S.D. carotid IMT increase in 7983 individuals aged ≥55 years. Taken together, these findings confirm observations from the Osaka Follow-up Study for Ultrasonographic Assessment of Carotid Atherosclerosis (OSACA) Study [16], which demonstrated a link between severe carotid atherosclerosis (defined as plaque score >10; lesions with a carotid IMT >1.1 mm were defined as plaques) and an increased incidence of recurrent stroke events among patients with a previous history of cerebrovascular disease. Notably, the association between carotid atherosclerosis and secondary stroke may be further influenced by levels of high sensitive C-reactive protein (hs-CRP), as atherosclerosis patients in the highest tertile of hs-CRP concentrations have been shown to experience greater changes in plaque scores and plaque numbers per year ($P<0.05$) compared with patients in lower hs-CRP tertiles [17].

For patients with diabetes mellitus, the prevention of secondary strokes may be especially challenging. Pathophysiologically, the metabolic abnormalities associated with diabetes (e.g., hyperglycemia, dyslipidemia, and insulin resistance) may render the arteries of diabetic patients more susceptible to vascular disease. In addition, diabetes impairs the function of endothelial cells, smooth muscle cells, and platelets, all of which may contribute to the extent of atherosclerosis in this population [18]. The end result of these diabetes-related dysfunctions is an increased risk of cardiovascular events, including recurrent strokes. As evidence, the European Stroke Prevention Study (ESPS) [19] found a significantly higher rate of secondary strokes in diabetic (20.4%) compared with nondiabetic (16.3%) subjects, even after treatment with antiplatelet medications (13.8% versus 8.8%). Importantly, data from both the ESPS trial and the Ticlodipine Aspirin Stroke Study [20] indicate that antiplatelets are less effective in diabetic patients than the general population for the prevention of secondary strokes.

In light of the reduced efficacy of antiplatelet medications among diabetic patients, the benefits demonstrated by cilostazol in the diabetic population are particularly encouraging. In the study mentioned above [10], Japanese patients with type II diabetes and no symptoms of vascular disease were randomized to cilostazol 100–200 mg/day ($n=46$) or no therapy ($n=43$) for the prevention of IMT progression and silent infarction events. During a mean follow-up of 3.2 years, patients receiving cilostazol showed almost no change in carotid IMT (0.00 ± 0.20 mm) from baseline, whereas patients in the control group had an increase of 0.17 ± 0.19 mm (Fig. 1) [10]. Notably, the between-group difference in IMT progression was statistically significant ($P<0.001$), as was the difference in the number of silent infarct-like lesions (2 out of 43 patients versus 16 out of 46 patients; $P<0.001$). The progression of silent infarctions was significantly related to both the change in IMT ($P=0.004$) and cilostazol administration ($P=0.009$) in a stepwise multivariate regression analysis (Fig. 2) [10]. Although larger studies will eventually be needed, these data indicate that cilostazol reduces carotid IMT progression in diabetic patients, a benefit that could translate into effective secondary stroke prevention for this population, but additional studies with clinical endpoints of stroke and death are needed. In addition, the data suggest that cilostazol may have further efficacy in preventing primary silent brain infarctions among patients

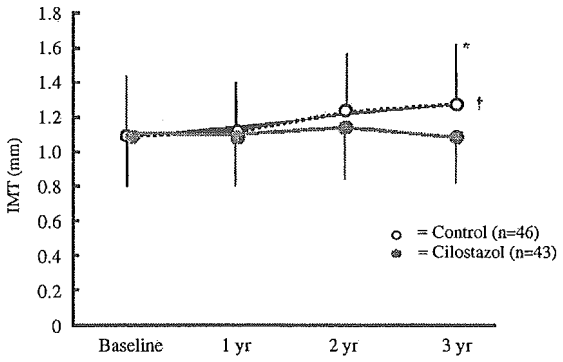

Fig. 1. Effect of cilostazol on IMT in patients with type II diabetes. *$P<0.01$ vs. control; †significant vs. baseline. Adapted with permission from Diabetologia, Shinoda-Tagawa et al., Copyright 2002 [10].

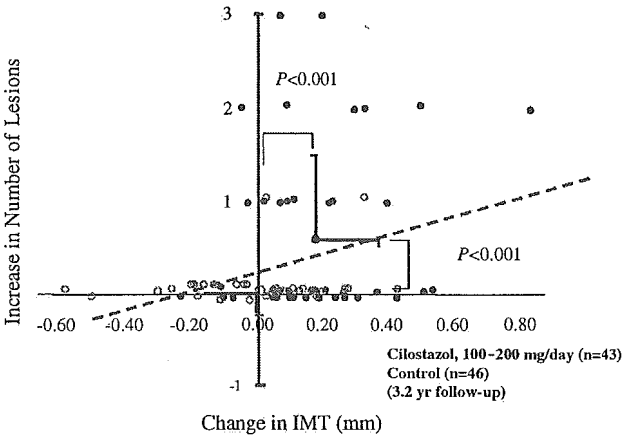

Fig. 2. Effects of cilostazol on IMT and silent infarctions in patients with type II diabetes. Relationship between the change in IMT and the increase in number of infarct-like lesions in diabetic subjects with (○) and without (●) cilostazol after the observation period. Average data were given with S.D. of IMT and S.D. of the number of lesions. Adapted with permission from Diabetologia, Shinoda-Tagawa et al., Copyright 2002 [10].

with diabetes. This latter effect may be of particular importance considering that the projected annual incidence of silent infarctions is high (over nine million in the United States in 1998) [21] and that the presence of silent infarct-like lesions may increase the risk of dementia in older persons by more than 100% (hazard ratio, 2.26) [22].

In the CSPS trial, it is notable that the greatest effects of cilostazol therapy were seen in patients with lacunar-type infarctions. While the magnitude of these benefits is expected due to the lacunar-heavy distribution of the study population, the robust effects demonstrated by cilostazol in secondary stroke prevention for this subtype of patients may have important clinical implications. Just as antiplatelet agents are generally less effective in diabetic populations [19,20], they also appear to have limited efficacy in patients with lacunar-type infarctions [23,24]. The fact that lacunar strokes are more hypertensive and degenerative in nature than atheroembolic infarcts indicates that cilostazol may be working against a slightly different stroke etiology than other antiplatelet medications. However, further studies would be needed to determine if cilostazol was superior to aspirin or clopidogrel in preventing lacunar strokes using an active comparator design.

Thus far, cilostazol has demonstrated impressive effects; nevertheless, more studies are needed. To this end, the CSPS 2 trial is designed to determine whether cilostazol is more beneficial than aspirin in symptomatic stroke patients. This trial, like its predecessor, is not assessing the efficacy of cilostazol in the setting of typical background medications. Currently, the standard of care for patients with atherothrombotic disease includes antiplatelet treatment, and in some cases, dual antiplatelet therapy (e.g., clopidogrel plus aspirin). Most likely, this standard will soon be extended to stroke patients, who also benefit from statins and blood pressure-lowering medications. It is thus important to determine whether cilostazol is effective in preventing recurrences in stroke patients already receiving standard therapies. Appropriately designed trials should be conducted to address this issue.

4. Conclusion

Stroke represents a major health concern. Aggressive risk management should be sought for all patients, particularly those in regions where stroke incidence and mortality rates are comparatively high, such as Japan. As a strategy for recurrent stroke reduction, the phosphodiesterase inhibitor cilostazol has demonstrated several positive effects on atherosclerotic disease. These beneficial characteristics, combined with the robust efficacy data generated by the CSPS and a subsequent diabetes trial, indicate that cilostazol reduces risk for strokes with both a large-vessel and small-vessel etiology. Additional studies will be needed before a solid recommendation can be made for using cilostazol in the secondary prevention of stroke in the United States.

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特集　メタボリック症候群

脳血管病リスクとしてのメタボリック症候群*

松本昌泰**

Key Words：TIA, atherothrombotic infarction, large vessel disease, carotid ultrasonography, statin

はじめに

生活習慣の欧米化とともに，糖尿病，高脂血症，肥満症などの有病率が増加し，アテローム性動脈硬化疾患の危険因子として，いわゆるメタボリック症候群の意義が注目を集めている．一方，従来より本邦では動脈硬化性疾患に占める脳血管障害のウエートが大きいが，動脈硬化危険因子としてのメタボリック症候群の増加は脳血管障害の発症率やその臨床病型などにどのような影響を及ぼしつつあるのだろうか．

本稿では，まずはじめに脳血管の解剖学的特徴を紹介し，脳血管障害の臨床病型と動脈硬化病変の関わりについてまとめ，頸動脈超音波エコー法やMRI, MRAなどの各種臨床計測法の進歩を踏まえて，脳血管障害のリスクとしてのメタボリック症候群の意義を考察する．

脳血管の解剖学的特徴

脳血管疾患のリスクとしてのメタボリック症候群の関わりを論ずる上で，脳血管の構造上の特徴を認識しておくことが肝要である[1]．通常，脳血管は大動脈から総頸動脈，内頸動脈，椎骨動脈などの頭蓋外動脈から前，中，後大脳動脈，脳底動脈などの頭蓋内主幹動脈に至る比較的口径の大きな動脈(大血管；large vessel)と，脳主幹動脈から分枝して脳底部より脳実質内に穿通する深部穿通枝や大脳皮質より深部に達する白質髄質枝などの表在穿通枝からなる小口径動脈(小血管：small vessel)に分けられる．

また，総頸動脈や椎骨動脈が冠動脈同様に栄養血管(vasa vasorum)を有する弾性型動脈であるのに対し，内頸動脈，脳底動脈や脳主幹動脈は筋型動脈であり，栄養血管を有さず，中膜筋層は薄く，冠動脈や腎動脈と比較すると，外膜の発達がきわめて悪い．これらの特徴に加えて，頭蓋内血管には血液・脳関門(blood-brain barrier；BBB)が一部の特殊な脳領域を除けば，毛細血管に至るまで発達しており，物質の透過を妨げている．

このような，脳血管の解剖学的特徴は栄養血管が炎症の場となる大動脈炎症候群では脳動脈のうち，総頸動脈や椎骨動脈のみが犯される事実とも一致している．また，高血圧，糖尿病などの血管内皮細胞が傷害される病態がないかぎり，BBBのためにLDLなどの血漿蛋白の血管壁への侵入が起こりにくく，さらに外膜からの炎症細胞の集積や細胞増殖性反応が発生しにくいために，高コレステロール血症などによる頭蓋内脳動脈の粥状硬化の進展が他臓器の動脈に比

* Metabolic syndrome and cerebrovascular disease.

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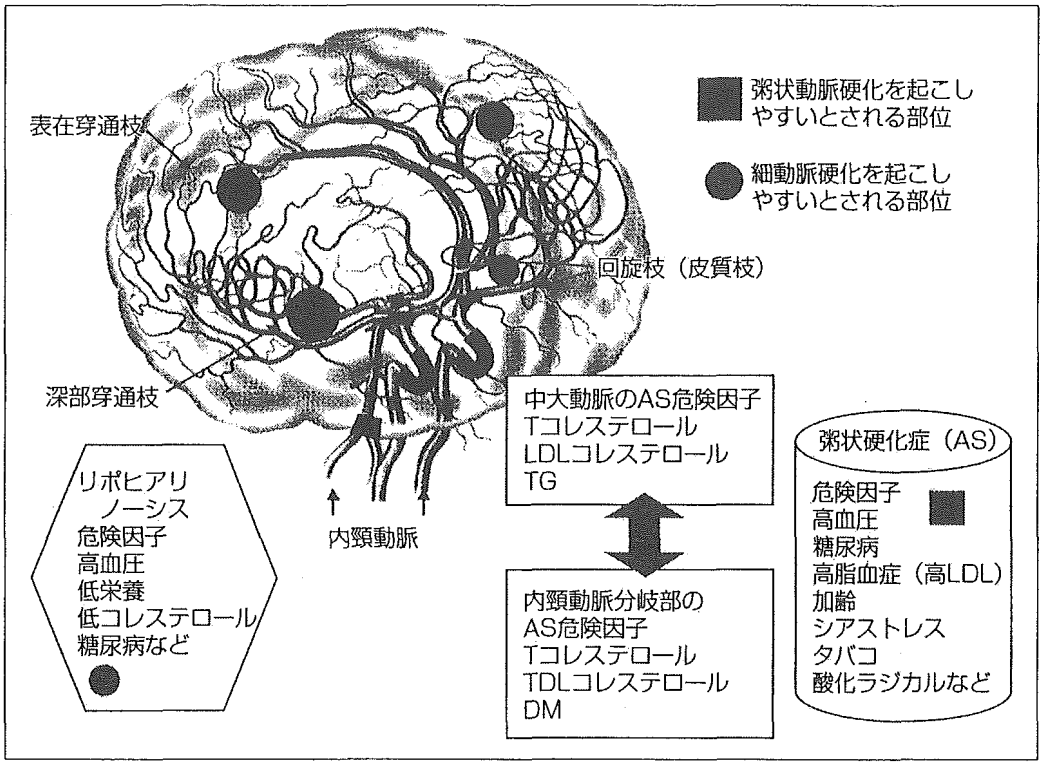

図1　脳血管とアテローム動脈硬化および細動脈硬化
アテローム動脈硬化ならびに細動脈硬化をきたしやすい部位と危険因子.（文献[1]より改変引用）

べて遅れることになる．したがって，脳血管障害発症の基盤を形成する動脈硬化病変の形成，進展にかかわる危険因子もこのような脳血管の解剖学的特徴を反映して，脳血管のレベルごとに異なることが知られている(図1)[1]．通常，高血圧や糖尿病を合併するメタボリック症候群ではBBBが障害されやすく，高脂血症の大血管や小血管への影響が出やすくなり，アテローム性動脈硬化や細小動脈硬化の進展が促進されるものと想定される．

脳血管障害の病型分類とメタボリック症候群

脳血管障害は多様な病態の総称であり，それぞれの臨床病型に応じて病態や成因も異なっている．脳血管障害の臨床病型分類として，現在国際的にもっとも広く用いられているのが1990年に発表されたNational Institute of Neurological Disorders and Stroke(NINDS)分類[2]であり，その臨床病型は①無症候性，②局所性脳機能障害，③血管性痴呆，④高血圧性脳症に大別されている．さらに，②は一過性脳虚血発作(TIA)と脳卒中に分けられ，後者には脳出血，くも膜下出血，動静脈奇形からの頭蓋内出血，脳梗塞の4病型がある．したがって，脳血管障害の病態や成因について論じる際には，これら8つの臨床病型に関して論じる必要があるが，ここではメタボリック症候群との関連が想定されるTIAおよび脳梗塞の臨床病型の概要についてまとめる．

1．TIA

臨床的に明らかな脳の局所神経症状が発現し，24時間以内に完全に消失するものと定義されている．ただし通常は，数分から数十分以内に症状が完全消失し，長くても1時間以内によくなる場合が大部分である．TIAはアテローム血栓性脳梗塞に前駆することが多く，その大部分は頸動脈分岐部のアテローム動脈硬化病変に形成された壁在性血栓が剥離して微小塞栓として脳動脈を一過性に閉塞し，発症する(微小塞栓機序)．また，高度の狭窄や閉塞による潜在的な脳血流不全状態がある時に，脱水や血圧低下などにより，一過性に血流不全状態が強くなり症状を発現することもある(血行力学機序)(図2)[3]．いずれにしても，原則的にlarge vessel diseaseに属す