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Renin-Angiotensin System Blockade Safely Reduces Blood Pressure in Patients With Minor Ischemic Stroke During the Acute Phase

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The ACCESS (Acute Candesartan Cilexetil Therapy in Stroke Survivors) study found that administration of candesartan in the acute phase of stroke confers a long-term benefit in patients who have sustained acute ischemic stroke. This treatment did not significantly reduce blood pressure (BP) during the acute phase, however. We assessed the short-term safety of reducing BP with renin-angiotensin system blockade in hypertensive patients who sustained acute ischemic stroke. Our randomized study compared the effects of 14 days of oral candesartan (4 mg/day), perindopril (4 mg/day), or conventional therapy (topical nitrate only when systolic BP (SBP) was ≥220 mm Hg or diastolic BP (DBP) was ≥120 mm Hg) administered to hypertensive patients within 72 hours of the onset of minor ischemic stroke. We assessed neurologic symptoms using the National Institutes of Health Stroke Scale and the modified Rankin Scale within 72 hours of stroke onset before and after drug therapy. A total of 40 patients completed the protocol. Therapy with candesartan and perindopril reduced SBP/DBP values by 23/11 mm Hg (SBP, $P < .01$; DBP, $P = .07$) and 14/0 mm Hg (SBP, $P = .07$), respectively, compared with conventional treatment. Neurologic symptoms worsened in 2 patients who received perindopril, which has no statistical significance, despite the BP reduction in patients given candesartan or perindopril. Our findings indicate that low doses of candesartan or perindopril safely reduce SBP in hypertensive patients with acute ischemic stroke. **Key Words:** Acute ischemic stroke—antihypertensive treatment—candesartan—perindopril—neurologic symptoms.

Several observational studies have shown that elevated blood pressure (BP) values immediately after stroke are associated with poor clinical outcome or mortality.[1-3] However, the current general consensus[4] is that BP should not be lowered during the acute phase unless the patient has excessive hypertension (diastolic BP [DBP] > 120 mm Hg or systolic BP [SBP] > 220 mm Hg), requires urgent antihypertensive treatment (eg, aortic dissection), or requires preparation for thrombolytic therapy. Lowering BP during the acute phase of ischemic stroke might lead to neurologic worsening by reducing regional cerebral perfusion and expanding the irreversible ischemic area in the tissues surrounding the ischemic core (the so-called "penumbra"), because cerebrovascular autoregulation is transiently impaired in this area.[5-7]

Although aggressive BP reduction during the acute phase could be detrimental to cerebral perfusion, high BP values also might increase the risk of hemorrhagic transformation of the infarction, the development of brain edema, or further hypertensive organ damage.

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Theoretically, lowering BP from the early stage of stroke might prevent early recurrent stroke or forestall further vascular events; however, several small studies of aggressive antihypertensive treatment for acute ischemic stroke have reported neutral, adverse, and favorable outcomes.[8-13] A large randomized controlled trial (the ACCESS Study)[14] has shown that the early administration of the angiotensin II type 1 receptor blocker (ARB) candesartan cilexetil in acute ischemic stroke reduces long-term (1 year) cardiovascular morbidity and mortality. Nevertheless, the safety of using candesartan to lower BP during the acute phase remains unclear, because BP values did not significantly differ between the candesartan- and placebo-treated groups in the ACCESS Study. On the other hand, angiotensin-converting enzyme (ACE) inhibitors have been found to lower BP without decreasing cerebral blood flow in patients with hypertension,[15] ischemic stroke,[16,17] and carotid stenosis or occlusion.[18]

Why the early administration of candesartan after stroke did not decrease BP during the acute phase compared with placebo in the ACCESS Study remains unclear. However, oral administration of the ACE inhibitor lisinopril initiated within 24 hours of stroke onset significantly reduced BP even at low doses.[12] Consequently, we examined whether early oral administration of low doses of the ARB candesartan or the ACE inhibitor perindopril significantly decreased BP during the acute phase of stroke. We then evaluated the short-term safety of reducing BP with these drugs using neurologic and functional measures in hypertensive patients with acute ischemic stroke.

Patients and Methods

Patient Selection

Casual brachial artery BP was measured in patients admitted to our hospital (Itabashi Chuo Medical Center) with the onset of a motor deficit due to acute ischemic stroke within 36 hours. The inclusion criteria were similar to those described for the ACCESS Study.[14] Patients with mean values of at least 2 BP measurements of ≥200 mm Hg for SBP and/or ≥110 mm Hg for DBP at 6-24 hours after stroke onset, or ≥180 and/or ≥105 mm Hg at 24-36 hours after stroke onset, were invited to participate in the study. All patients underwent baseline 12-lead electrocardiography, biochemical and hematologic measurements, chest X-ray, magnetic resonance imaging, magnetic resonance angiography (MRA), and carotid ultrasonography at admission. Exclusion criteria were intracranial hemorrhage, age >85 years, moderate to severe neurologic symptoms (National Institutes of Health Stroke Scale [NIHSS] score >8), consciousness disorders that precluded oral drug administration, any occlusions or >70% stenoses of major vessels confirmed by carotid ultrasound and intracranial MRA, and other conditions explicitly requiring BP reduction, such as malignant hypertension, manifest cardiac failure, aortic dissection, and preparation for thrombolytic therapy. Patients who had received antihypertensive or vasoactive drugs at admission also were excluded from participating in the study. Patients were categorized by stroke subtype according to the TOAST classification system.[19] Our institution's Ethics Committee approved the study design. Written informed consent to participate was obtained from all patients, who were subsequently enrolled between February 2005 and May 2007.

Drug Administration

Patients were randomized to receive one of the following regimens: 4 mg candesartan cilexetil daily, 4 mg perindopril daily, or conventional antihypertensive treatment comprising topical nitrate only when SBP was ≥220 mm Hg or DBP was ≥120 mm Hg, according to current recommendations.[4] Patients were allocated to each group in order of the date of admission. Neurologic symptoms and severity were assessed using the NIHSS and the modified Rankin Scale (mRS). Drugs were administered within 72 hours of onset of stroke symptoms immediately after baseline evaluations. The same evaluations were repeated 14 days later, and the results were compared with baseline values. The NIHSS score was checked twice each day (morning and evening) up to day 14. Drug administration was discontinued when deterioration of the NIHSS score by 1 point or more coincided with a BP reduction of ≥15%.

BP Measurement

Nurses used a semiautomatic sphygmomanometer (model ES-H51; Terumo, Tokyo, Japan) to measure BP at least every 4 hours until 2 days after the baseline values were obtained and then 3 times daily (morning, daytime, and evening) for the next 12 days. After 5 minutes of supine rest, 3 brachial BP readings were obtained, and the middle value of these was taken as casual BP if the values differed by <10 mm Hg. The BP value of the day was defined as that obtained closest to 08:00 each day except for the baseline value, which was defined as that determined immediately before drug administration to the interventional groups.

Statistical Methods

Differences in baseline factors among the 3 groups were statistically compared using single-factor analysis of variance (ANOVA) for age, time to baseline assessment from stroke onset, BP values at admission and baseline, and NIHSS score. Differences in baseline and outcome parameters between groups were assessed using the χ^2 test where appropriate. Differences in daily BP values in the 3 groups were statistically analyzed using the Student *t*-test. Changes in neurologic severity assessed by the

NIHSS and mRS between baseline and day 14 among the 3 groups were compared using single-factor ANOVA. Statistical significance was taken at the level of 5% using StatView 5.0 (SAS Institute, Cary, NC) and a personal computer running Windows.

Results

Among 372 consecutive patients who were admitted to our hospital due to acute ischemic stroke, 44 who were eligible for the present study were randomly allocated to groups and administered with candesartan (4 mg/day), perindopril (4 mg/day), or conventional therapy. Four patients were withdrawn for reasons unrelated to treatment (Fig 1). Baseline data were finally obtained from 40 patients (Table 1). All of these patients were treated with intravenous sodium ozagrel or argatroban as antithrombotic therapy during the acute phase, but the proportion of use of these drugs did not differ among the 3 groups. During the study period, no patients in either the candesartan- or perindopril-treated group reported any mediation side effects, such as dizziness or dry cough.

Figure 2 shows the time course of the BP values. The mean BP at admission in all groups was 201/109 mm Hg, and this was spontaneously reduced by 20/9 mm Hg at the time of the baseline assessment. These changes in mean BP did not differ significantly among the 3 groups. The mean duration from stroke onset to the baseline assessment was 41 hours for the conventionally treated group, 48 hours for the candesartan-treated group, and 41 hours for the perindopril-treated group (not significantly different; $P = .63$). The mean SBP and DBP values in the conventionally treated group decreased spontaneously and gradually until day 14, and only 1 patient required topical nitrate for excessive hypertension. The mean SBP in the candesartan- and perindopril-treated groups also declined until day 14 and decreased significantly at days 1, 2, 3, and 5-14 in the candesartan-treated group and at days 3 and 13 in perindopril-treated group compared with the conventionally treated group. On the other hand, the mean DBP in the candesartan-treated group decreased significantly compared with the conventionally treated group at days 2 and 13, and mean DBP in the perindopril-treated group did not differ statistically from that in the conventionally treated group during the observational period. At day 14, the changes in SBP/DBP from baseline were −21/−10 mm Hg in the conventionally treated group, −39/−26 mm Hg in the candesartan-treated group, and −35/−11 mm Hg in the perindopril-treated group. At day 14, SBP was reduced significantly (by 23 mm Hg) in the candesartan-treated group compared with the conventionally treated group ($P < .01$), whereas that in the perindopril-treated group was reduced by 14 mm Hg, but the difference did not reach statistical significance ($P = .07$). At day 14, DBP was reduced by 11 mm Hg in the candesartan-treated group compared with the conventionally treated group, but the difference did not reach statistical significance ($P = .07$), and DBP values were similar in the perindopril-treated and conventionally treated groups.

Figure 3 shows individual changes in NIHSS and mRS scores. Neurologic symptoms worsened in 2 patients in the perindopril-treated group (open circles) on days 3 and 5. These patients continued receiving daily perindopril (4 mg) after the neurologic deterioration due to persistent high BP. Neurologic symptoms remained stable in all other patients during the observational period;

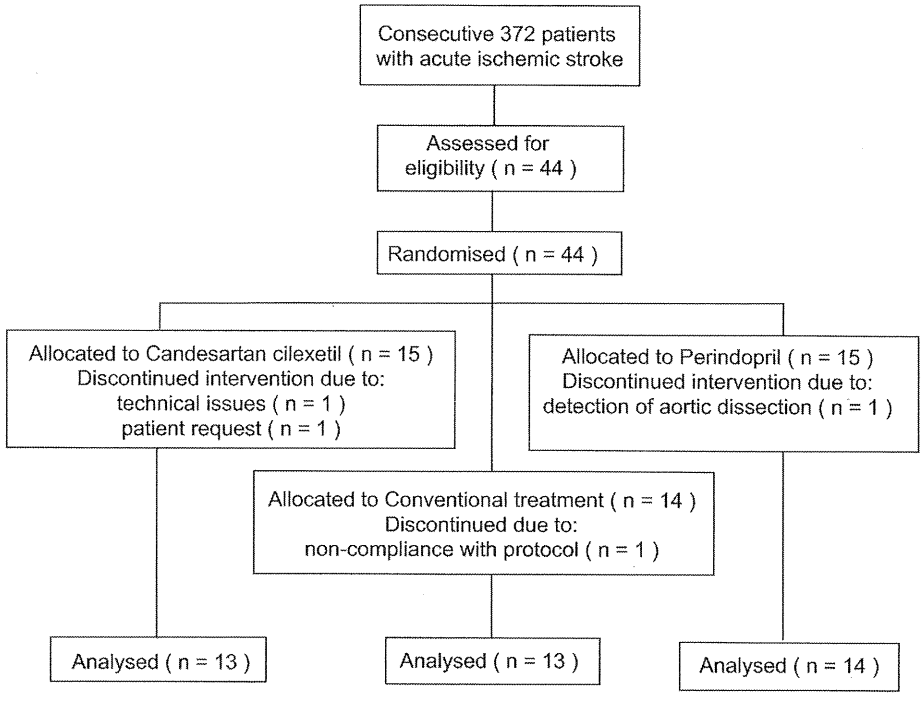

Figure 1. *Flow diagram of the patients recruited to the study.*

Table 1. *Baseline data of study participants*

Drug allocation	Conventional treatment	Candesartan cilexetil	Perindopril	*P*
Number of patients	13	13	14	
Age, years	81 ± 8	61 ± 12	62 ± 6	.02
Male gender	11	11	11	.89
TOAST classification	8 SVO, 5 UD	9 SVO, 1 CE, 3 UD	10 SVO, 4 UD	
Time to baseline from stroke onset, hours	41 ± 25	48 ± 23	41 ± 12	.63
BP at admission, mm Hg				
SBP	201 ± 12	199 ± 13	204 ± 12	.52
DBP	107 ± 20	110 ± 10	111 ± 21	.73
BP at baseline, mm Hg				
SBP	183 ± 15	178 ± 19	182 ± 16	.71
DBP	98 ± 14	104 ± 11	101 ± 10	.50
NHSS score at baseline	3.8 ± 1.8	3.6 ± 2.0	3.1 ± 1.3	.48
Medical history				
Hypertension	13 (100)	13 (100)	14 (100)	NA
Diabetes mellitus	2 (15)	3 (23)	4 (29)	.71
Hyperlipidemia	1 (8)	3 (23)	2 (14)	.54
Smoking habit	6 (46)	4 (31)	7 (50)	.57
Previous stroke or transient ischemic attack	1 (8)	0 (0)	0 (0)	NA
Atrial fibrillation	1 (8)	1 (8)	0 (0)	NA

Data are given as number of patients (%) or as mean ± standard deviation.
CE, cardioembolism; SVO, small-vessel occlusion; UD, stroke of undetermined etiology; NA, not analyzed.

however, the proportions of patients with neurologic deterioration did not differ statistically between perindopril and candesartan or conventional treatment (candesartan or conventional treatment, 0%; perindopril, 14%; χ^2 test, both $P = .48$). Between baseline and day 14, the changes in mean NIHSS score were −1.5 in the conventionally treated group, −1.5 in the candesartan-treated group, and −1.1 in the perindopril-treated group, and changes in mean mRS score were −1.0, −0.8, and −0.9, respectively. The changes in mean NIHSS and mRS scores between baseline and day 14 did not differ significantly among the 3 groups ($P = .51$ and .70, respectively).

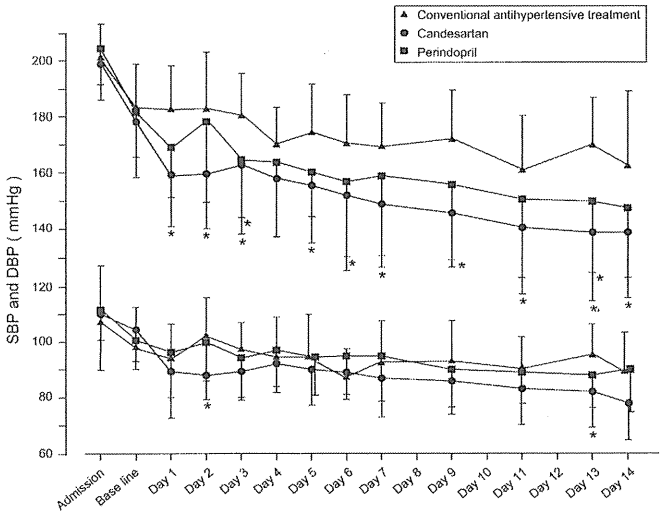

Figure 2. *Course of SBP and DBP from admission to day 14. Data are presented as mean ± standard deviation (bars). *Statistically significant BP reduction after candesartan or perindopril administration compared with conventional antihypertensive treatment for SBP and DBP (P < .05).*

Discussion

We have shown that the early administration of a low dose of candesartan cilexetil or perindopril decreased BP in hypertensive patients with acute ischemic stroke. Candesartan significantly reduced SBP compared with conventional treatment, as did perindopril, but to a lesser extent. The usual dosages of these drugs in Japan are 4-8 mg/day (maximum, 12 mg) for candesartan and 2-4 mg/day (maximum 8 mg) for perindopril. Candesartan reportedly reduces BP more effectively than ACE inhibitors at the standard dosages of either drug in patients with mild to moderate hypertension.[20] Considering this, we predicted that candesartan or perindopril at 4 mg/day would equally reduce BP. The dose of either drug might have been too low to affect highly elevated BP, but we established 4 mg/day specifically to avoid an excessive reduction. This dose of both candesartan and perindopril indeed reduced mean BP compared with conventional treatment. A previous study found that the ACE inhibitor lisinopril significantly reduces BP levels during the acute phase of ischemic stroke even at low doses.[12] Therefore, low doses of ARBs or ACE inhibitors should be a safe and effective antihypertensive treatment for patients with acute ischemic stroke.

During the study period, neurologic symptoms worsened in 2 patients in the perindopril-treated group at days 3 and 5. Both of these patients had small-vessel

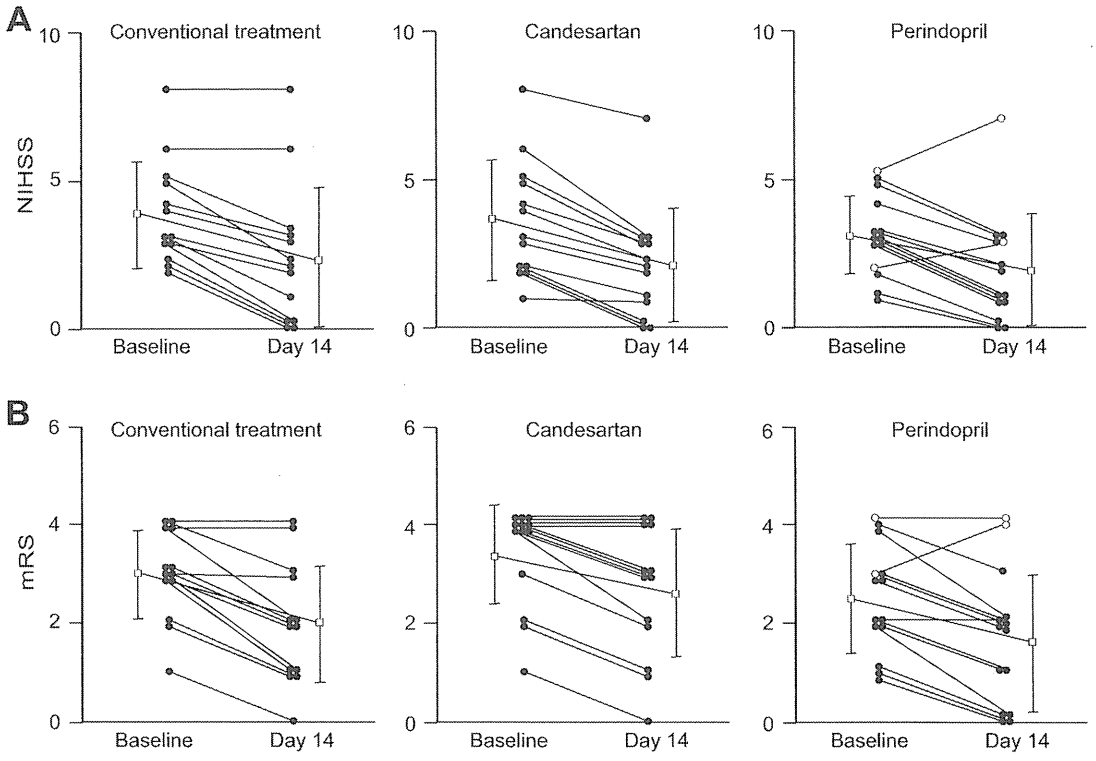

Figure 3. *Individual changes in NIHSS (A) and mRS (B) scores. Open circles (○) in the perindopril-treated group indicate patients with deteriorated NIHSS score during the observational period. Open squares (□) represent mean NIHSS or mRS score. Data are presented as mean ± standard deviation.*

occlusion (lacunar infarction), and the neurologic deterioration was not accompanied by an excessive reduction in BP. The neurologic deterioration that occasionally develops during the first few days in patients with lacunar infarction is not necessarily associated with a reduction in BP.[21] The reason why the neurologic symptoms worsened in these 2 patients is unknown, but the degree of deterioration was mild. In contrast, no patients in the candesartan-treated group exhibited worsened neurologic symptoms during the observational period despite significant BP reductions. The ACCESS Study also found no worsening of neurologic symptoms in patients given candesartan starting in the acute phase, although BP did not differ from those given placebo.[14] Although the population of the present study was too small to determine statistical differences in the proportion of patients with neurologic deterioration who received candesartan and perindopril, candesartan might have exerted some unique, BP-independent neuroprotective effects, as several experimental studies have already shown.[22-24]

Current guidelines[4] recommend antihypertensive treatment during the acute phase of stroke only for excessive hypertension or a few specific indications, although no definite evidence supports this recommendation. Several small studies have applied aggressive antihypertensive treatment from the early phase of stroke using various agents. Theoretically, calcium channel antagonists exert cerebroprotective effects by limiting postischemic intracellular calcium influx and by preferentially dilating cerebral blood vessels. The randomized Intravenous Nimodipine West European Trial (INWEST) evaluated whether the calcium channel antagonist nimodipine delivered intravenously within 24 hours of stroke is neuroprotective and improves neurologic and functional outcomes in acute stroke.[9] The results showed that unfavorable outcomes among patients treated with nimodipine were associated with decreased BP, although reanalysis of some of the data demonstrated that favorable outcomes were associated with higher BP among treated patients with mild to moderate stroke.[25] The β-blockers should limit catecholamine-induced cardiac and neurologic damage and reduce the metabolic demands of the ischemic brain. However, trials of β-blockers in monotherapy or in combination have identified a nonsignificant increase in mortality and worsened neurologic and functional outcomes after 6 months compared with a placebo, despite a significant drop in BP.[8] Although thiazide diuretics have proven benefits in the primary and secondary prevention of stroke, bendrofluazide administered within 96 hours after stroke does not decrease BP;[10] therefore, bendrofluazide is unsuitable if BP reduction is required during the immediate poststroke phase. A more recent study found that the oral ACE inhibitor lisinopril administered within 24 hours of stroke onset significantly reduced BP and did not affect neurologic and functional measures, although 1 patient developed fluctuating dysarthria and withdrew from the study.[12] Furthermore, the CHHIPS (Controlling Hypertension and Hypotension Immediately Post-Stroke) trial found that lisinopril or labetalol significantly reduced BP without increasing serious events in acute stroke.[13] The ACCESS Study confirmed the long-term benefit of early candesartan administration in acute ischemic stroke;[14]

however, the short-term safety in case of reducing BP during the acute phase was unclear, because early candesartan administration did not significantly reduce BP. Therefore, the present study provides new insight into the safety of reducing BP with candesartan during the acute phase.

In conclusion, our findings demonstrate that even a low dose of candesartan safely and significantly reduced BP in hypertensive patients with acute ischemic stroke without worsening neurologic symptoms. Perindopril also reduced BP in these patients, but to a lesser extent than candesartan. The ACCESS Study has already demonstrated that early candesartan administration confers long-term benefits via BP-independent mechanisms;[14] therefore, the early use of candesartan in acute stroke not only should be safe when the need for BP reduction is urgent, but also should protect against further vascular events. Our findings should be interpreted with caution, however, because of the small number of patients in this study. Further, larger-scale studies are needed. Several studies to assess antihypertensive therapy in acute ischemic stroke, including COSSACS (Continue Or Stop post-Stroke Antihypertensives Collaborative Study), are currently underway.

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Blood Pressure Levels and Bleeding Events During Antithrombotic Therapy

The Bleeding With Antithrombotic Therapy (BAT) Study

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

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

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

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

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

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

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

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

Patients and Methods

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

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

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

Statistical Methods

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

Results

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

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

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

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

Table 1. Patients' Baseline Clinical Characteristics

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

Data are medians (interquartile range) for the observation period, means±SD for age and BP, and percent of patients for others.

*Taking warfarin alone or warfarin plus antiplatelets.

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

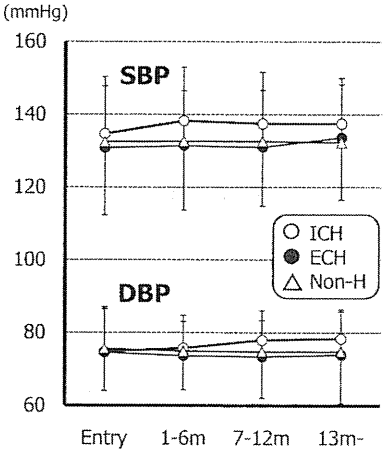

Figure 1. Time courses of BP. Average levels of SBP and DBP between 1 and 6 months, between 7 and 12 months, and after 13 months as well as the levels at entry are plotted. ICH indicates patients developing any symptomatic ICH; ECH, patients developing a life-threatening or major bleeding event other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

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

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

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

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

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

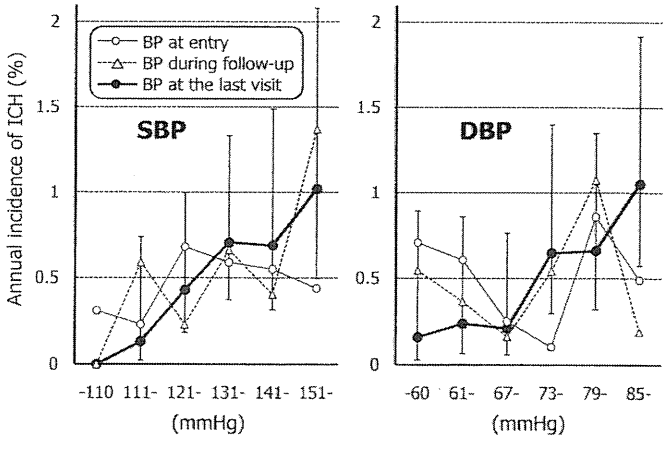

Figure 2. Annual incidence of ICH according to SBP and DBP levels. Bars indicate 95% CI for BP at the last clinic visit. "BP during follow-up" means average BP levels of all the follow-up measurements except for the levels at entry and at the last visit.

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

Discussion

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

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

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

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

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

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

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

Appendix

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Disclosures

None.

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

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Objective: We sought to clarify risk factor profiles and current treatment of Japanese patients with stroke, myocardial infarction (MI), and nonvalvular atrial fibrillation (NVAF) using the database of the Japan Thrombosis Registry for Atrial Fibrillation, Coronary, or Cerebrovascular Events (J-TRACE). *Methods:* J-TRACE is a nationwide multicenter cooperative cohort of Japanese patients with MI, stroke, and NVAF. Baseline characteristics of 8087 Japanese patients (5804 male, average age 68.7 years) with history of stroke (n = 3554), MI (n = 2291), or NVAF (n = 2242) were analyzed. *Results:* History of stroke (14.7%) was more frequent than history of MI (2.6%) in patients with stroke, whereas history of stroke (6.6%) was less frequent than history of MI (7.6%) in patients with MI. In patients with NVAF, history of stroke (14.3%) was far more frequent than history of MI (3.4%). Hypertension was more frequent in stroke (74.4%) than MI (62.0%) or NVAF (57.7%), whereas hypercholesterolemia, diabetes mellitus, and cigarette smoking were more prevalent in patients with MI (56.1%, 35.1%, and 33.3%, respectively) than in those with stroke (35.7%, 22.4%, and 19.7%, respectively) or NVAF (26.9%, 17.2%, and 16.1%, respectively). Alcohol consumption (34.9%) and obesity (body mass index > 25) (32.8%) were most common in patients with NVAF. In all patients, nonmedication rates were higher in patients with hypercholesterolemia (29.8%) or diabetes (36.9%) than in those with hypertension (9.5%). Warfarin was used in 58.9% of patients with low-risk and 75.4% with high-risk NVAF. *Conclusion:* Risk factor profiles and their modification were not similar among patients in Japan with MI, stroke, and NVAF, although they share a high risk of thrombotic events. **Key Words:** Risk factor—stroke—myocardial infarction—atrial fibrillation—Registry.

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The Japan Thrombosis Registry for Atrial Fibrillation, Coronary, or Cerebrovascular Events (J-TRACE)[1] is a large nationwide multicenter cooperative registry for 3 major thromboembolic diseases that cause death or disability in Japan: stroke,[2] myocardial infarction (MI),[2] and nonvalvular atrial fibrillation (NVAF).[3] Atherothrombosis, including cerebrovascular disease, coronary artery disease, and peripheral artery disease, is the leading cause of death in the world.[4] This is true as well in the Japanese population. According to a report from the Japanese Ministry of Health, Labor, and Welfare, there were 159,625 cardiac deaths and 129,055 stroke deaths in 2005, making these the second and third most common causes of death in Japan, respectively.[5] NVAF is the leading cause of cardioembolic stroke and, according to the Japanese Multicenter Stroke Investigator's Collaboration, approximately 19% of 16,922 cases of acute ischemic stroke or transient ischemic attack were associated with NVAF.[6] It is thus of great importance to prevent vascular events in these patients at high risk.

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

Methods

Patients Recruited

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

Baseline Data Collected

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

Study Organization and Sites

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

Data Management

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

Statistical Analysis

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

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

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

Results

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

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

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

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

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

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

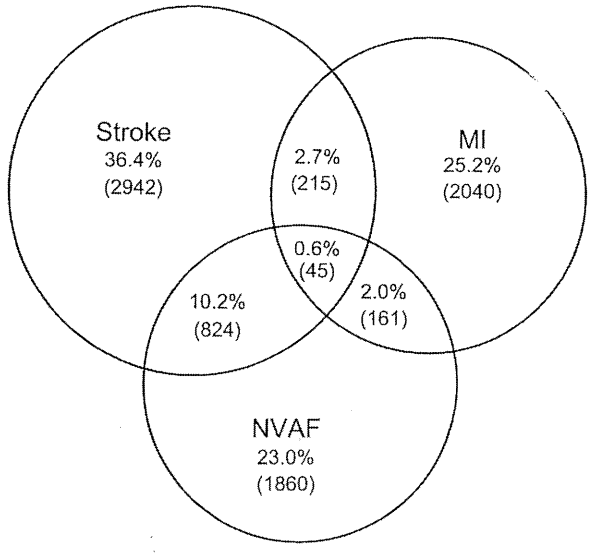

Figure 1. *Overlap in history of stroke, MI, and NVAF in J-TRACE population.*

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

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

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

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

Discussion

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

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

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

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

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

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

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

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

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

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

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

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

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

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