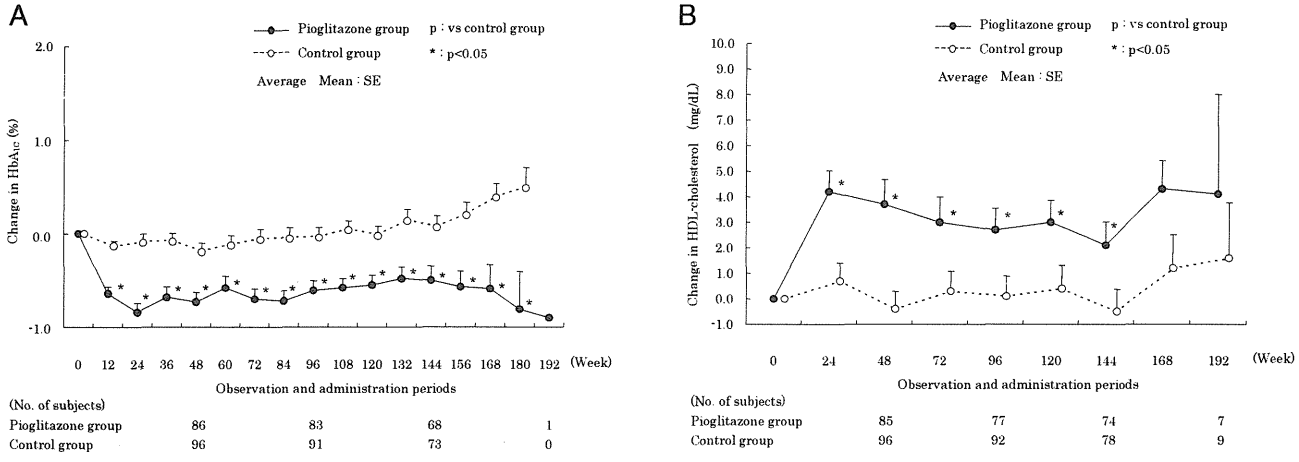

Fig. 2. Changes in HbA_{1c} and HDL-cholesterol during long-term treatment.

Error bars indicate SEM.
HbA_{1c} was significantly lower in the pioglitazone group from week 12 to week 180 ($p<0.05$).
HDL-cholesterol level was significantly higher in the pioglitazone group from week 24 to week 144 ($p<0.05$).

mm vs -0.031 ± 0.2327 mm, respectively; p=NS). Similarly, pioglitazone tended to induce greater regression of mean-IMT but the between-group difference again did not reach statistical significance (-0.058 ± 0.1718 mm vs -0.043 ± 0.1644 mm, respectively; p= NS) (**Fig. 1**). Similar results were obtained after stratification by baseline characteristics (presence or absence of previous CV events; 2 or ≥3 risk factors for macrovascular events; age ≤59 or ≥60 years; male or female). GEE analysis of the endpoint also produced similar results.

The number of patients given the average dose of pioglitazone less than 15 mg, 15–30 mg, and over 30 mg were 41, 47, and 1, respectively. The changes in max-IMT and mean-IMT showed no significant correlation with the averaged dose of pioglitazone (data not shown).

Metabolic Parameters

HbA_{1c} was significantly ($p<0.05$) lower in the pioglitazone group than in the control group from week 12 to week 180. The changes from the baseline HbA1c levels were −0.73% at week 48, −0.61% at week 96, and −0.50% at week 144 in the pioglitazone group, while −0.18%, −0.03%, and 0.08% in the control group (**Fig. 2A**).

HDL-cholesterol levels were significantly higher in the pioglitazone group from week 24 to week 144 ($p<0.05$). The increase from baseline HDL-cholesterol level was 3.7 mg/dL at week 48, 2.7 mg/dL at week 96, and 2.1 mg/dL at week 144 in the pioglitazone group, and −0.4 mg/dL, 0.1 mg/dL, and −0.5 mg/dL in the control group (**Fig. 2B**).

The increase in body weight (from baseline) was significantly greater in the pioglitazone group from week 8 to the end of the study ($p<0.05$) (mean value ranged from 0.7 to 3.5 kg) compared with the control group (mean value ranged from −1.2 to 0.0 kg). Regarding other metabolic parameters, there were no significant differences between the two treatment groups.

Discussion

Carotid ultrasound measurements of IMT are well-accepted predictors of CV events in subjects with and without type 2 diabetes[18, 19]. Changes in carotid IMT over time correlate with future CV event rates[20]. Diabetes, which confers an increased risk of CV disease, accelerates carotid IMT progression[21]. In a recent review of 11 carotid IMT intervention trials in diabetes, the mean carotid IMT progression rate in type 2 diabetic subjects without intervention was 0.034 mm/year (95% CI, 0.029 to 0.039; median SD, 0.054)[22]. Several studies have assessed the effect of various therapeutic agents on carotid IMT as a measure of atherosclerosis. Although pioglitazone was associated with reduced CV events in the PROactive study[13], few investigations have evaluated its effects on IMT. To date, trials have been confined to 6-month studies comparing pioglitazone with sulfonylurea oral anti-diabetic agents or diet alone[22, 23], and the more extensive CHICAGO study. This randomized double-blind trial was performed over a 72-week period in patients with type 2 diabetes in the

Chicago metropolitan area, and reported that pioglitazone significantly reduced carotid IMT compared with glimepiride[12]. Current studies have only been performed in European and American populations[11, 12] and no investigations have evaluated the efficacy of pioglitazone against CV events and IMT over a prolonged period of time in Asian patients. The present study was the first to assess the effects of long-term pioglitazone treatment on macrovascular outcomes[15] and the progression of carotid IMT in Japanese type 2 diabetic subjects without a recent history of macrovascular events.

We found that suppression of carotid IMT progression was more marked in the pioglitazone group than in the non-pioglitazone group, compared with baseline measurements, suggesting that pioglitazone may suppress the progression of atherosclerosis in this patient group; however, between-group differences did not achieve statistical significance.

When comparing the results of the current study to previous trials, it appears that the lack of significant differences between groups may be attributable to several factors. For example, we measured IMT at six centers whereas only one facility with a single ultrasonographer was utilized in the CHICAGO study. Whilst the stratified (dynamic) randomization of patients employed in our study should have minimized this source of variation, it is possible that the smaller groups per institution might have resulted in such an imbalance. A second factor is the smaller total sample size in our study: we assessed 186 cases compared with 361 in the CHICAGO study. The number of patients treated was based on the assumption of a change of −0.022 mm in the non-pioglitazone group, whereas the actual differences were −0.031 and −0.043 mm. This significant decrease even in the non-pioglitazone group possibly reflects the more frequent use of biguanides and α-glucosidase inhibitors in the non-pioglitazone group[24, 25]. Interestingly, the findings of this substudy mirror the results of the "parent" PROBE trial, which also found a non-significant trend towards improved macrovascular outcomes in the pioglitazone group versus the control group[15]. However, the improved outcomes were not as great as those reported in the PROactive study[13] and this was likely due to the type of patients included in the study (i.e. milder disease with no recent history of CV events) and the high use of concomitant anti-diabetic agents. Also, the minimized number of differences in the drop-out rate (15 in the pioglitazone group and 14 in the control group) may not account for the lack of treatment differences between the groups. These suggestions may help to explain the results obtained in this substudy investigating changes in IMT. To determine whether there is a clear clinical benefit of including pioglitazone in the treatment regimen for patients with type 2 diabetes and coexistent risk factors for cardiovascular disease, both in terms of macrovascular outcomes and carotid IMT, further well-controlled single-facility studies with larger subject numbers are required.

The mechanisms by which pioglitazone treatment significantly reduces carotid IMT are unclear, but several possibilities have been hypothesized. The reduction of carotid IMT may be related to the improvement of traditional risk factors. As shown in several previous investigations[7, 8, 12, 13], pioglitazone therapy decreases HbA1c levels and increases HDL-cholesterol levels, and similar changes were observed in the present study (**Fig. 2**). Although the difference in the number of metabolic risks or fasting insulin level did not affect the change in IMT in both groups (data not shown), the beneficial effect of pioglitazone on carotid IMT may be at least partially attributed to the modulation of hyperglycemia and/or dyslipidemia. Another possibility is that pioglitazone may have decreased carotid IMT by improving insulin sensitivity, since insulin resistance is reported to be a risk factor for carotid atherosclerosis[26]. In addition to these metabolic actions, pioglitazone has beneficial effects on endothelial cell function[27] and may have mediated the regression of carotid IMT by improving arterial vasodilator capacity, platelet aggregation, and intimal thickening. Indeed, pioglitazone has been shown to reduce neointimal thickening after endothelial injury in animal models of atherosclerosis[10]. Furthermore, pioglitazone can modify systemic inflammatory and coagulation markers[8, 9]. Recently, pioglitazone was found to modify the progression of carotid atherosclerosis induced by various genetic risk factors[28]. Taken together, the overall pattern of changes induced by pioglitazone suggests a general improvement in a number of different risk factors associated with atherosclerosis. In this study, endothelial function was not measured and metabolic level was not evaluated. Therefore, other studies are need to clarify the possibility that pioglitazone induces the regression of carotid atherosclerosis by improving endothelial function or the possibility that the metabolic level may affect the improvement of the carotid atherosclerosis by pioglitazone.

In conclusion, our study demonstrated that pioglitazone induced and maintained the regression of carotid IMT in Japanese patients with type 2 diabetes and coexisting risk factors for cardiovascular disease. Compared with a control group receiving oral anti-

diabetic therapy without a thiozolidinedione, pioglitazone produced greater improvements but did not achieve statistical significance. Larger, well-controlled studies are required to verify the current findings and to fully elucidate the clinical benefits of pioglitazone in this type of patient.

Acknowledgements

This clinical study was supported by a financial grant from Takeda Pharmaceutical Co., Ltd, Osaka, Japan. Editorial assistance was provided by Caroline McGown PhD, ContentEdNet. The authors would like to thank the members of the following committees for their assistance with the clinical trial:

The Independent Safety Data Monitoring Committee members; Toshiaki Hanafusa, First Department of Internal Medicine, Osaka Medical College; Minoru Kubota, Health care center, Kwansei Gakuin University; Kiyoshi Yoshida, Department of Cardiology, Kawasaki Medical School.

The Macrovascular Events Evaluation Committee members; Akira Yamashina, Second Department of Internal Medicine, Tokyo Medical University; Tsutomu Yamazaki, Department of Clinical Epidemiology & Systems, Graduate School of Medicine, University of Tokyo; Shin-ichi Momomura, Saitama Medical Center, Jichi Medical University; Takashi Iwase, Iwase Internal Medicine Cardiology Clinic.

References

1) Haffner SM, Lehto S, Rönnemaa T, Pyörälä K, Laakso M: Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. N Engl J Med, 1998; 339: 229-234
2) Stamler J, Vaccaro O, Neaton JD, Wentworth D: Diabetes, other risk factors, and 12-year cardiovascular mortality for men screened in the Multiple Risk Factor Interventional trial. Diabetes Care, 1993; 16: 434-444
3) Laakso M: Glycemic control and the risk for coronary heart disease in patients with non-insulin-dependent diabetes mellitus. The Finnish studies. Ann Intern Med, 1996; 124: 127-130
4) UK Prospective Diabetes Study (UKPDS) Group: Intensive blood-glucose control with sulfonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes. Lancet, 1998; 352: 837-853
5) UK Prospective Diabetes Study (UKPDS) Group: Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet, 1998; 352: 854-865
6) Bolen S, Feldman L, Vassy J, Wilson L, Yeh HC, Marinopoulos S, Wiley C, Selvin E, Wilson R, Bass EB, Brancati FL: Systematic review: comparative effectiveness and safety of oral medications for type 2 diabetes. Ann Int Med, 2007; 147: 386-399
7) Schoonjans K, Auwerx J: Thiazolidinediones: an update. Lancet, 2000; 355: 1008-1010
8) Szapary PO, Bloedon LT, Samaha FF, Duffy D, Wolfe ML, Soffer D, Reilly MP, Chittams J, Rader DJ: Effects of pioglitazone on lipoproteins, inflammatory markers, and adipokines in nondiabetic patients with metabolic syndrome. Arterioscler Thromb Vasc Biol, 2006; 26: 182-188
9) Miyazaki Y, Mahankali A, Wajcberg E, Bajaj M, Mandarino LJ, DeFronzo RA: Effect of pioglitazone on circulating adipocytokine levels and insulin sensitivity in type 2 diabetic patients. J Clin Endocrinol Metab, 2004; 89: 4312-4319
10) Yoshimoto T, Naruse M, Shizume H, Naruse K, Tanabe A, Tanaka M, Tago K, Irie K, Muraki T, Demura H, Zardi L: Vasculo-protective effects of insulin sensitizing agent pioglitazone in neointimal thickening and hypertensive vascular hypertrophy. Atherosclerosis, 1999; 145: 333-340
11) Nissen SE, Nicholls SJ, Wolski K, Nesto R, Kupfer S, Perez A, Jure H, De Larochelliere R, Staniloae CS, Mavromatis K, Saw J, Hu B, Lincoff AM, Tuzcu EM; PERISCOPE Investigators: Comparison of pioglitazone vs glimepiride on progression of coronary atherosclerosis in patients with type 2 diabetes. The PERISCOPE randomized controlled trial. JAMA, 2008; 299: 1561-1573
12) Mazzone T, Meyer PM, Feinstein SB, Davidson MH, Kondos GT, D'Agostino RB Sr, Perez A, Provost JC, Haffner SM: Effect of pioglitazone compared with glimepiride on carotid intima-media thickness in type 2 diabetes. A randomized trial. JAMA, 2006 296: 2572-2581
13) Dormandy JA, Charbonnel B, Eckland DJ, Massi-Benedetti M, Moules IK, Skene AM, Tan MH, Lefebvre PJ, Murray JD, Standl E, Wilcox RG, Wilhelmsen L, Betteridge J, Birkeland K, Golay A, Heine RJ, Koranyi L, Laakso M, Mokan M, Norkus A, Pirags V, Podar T, Scheen A, Scherbaum W, Schernthaner G, Schmitz O, Skrha J, Smith U, Taton J; PROactive Investigators: Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomized controlled trial, Lancet, 2005; 366: 1279-1289
14) Lincoff AM, Wolski K, Niholls SJ, Nissen SE: Pioglitazone and risk of cardiovascular events in patients with type 2 diabetes mellitus. JAMA, 2007; 298: 1180-1188
15) Kaku K, Daida H, Kashiwagi A, Yamashina A, Yamazaki T, Momomura S, Iwase T, Yamasaki Y, Nagatsuka K, Kitagawa K, Kawamori R. Long-term effects of pioglitazone in Japanese patients with type 2 diabetes without a recent history of macrovascualr morbidity. Curr Med Res Opin, 2009; 25: 2925-2932
16) Shima K, Endo J, Oimomi M, Oshima I, Omori Y, Katayama Y, Kanazawa Y, Kawai T, Kawamori R, Kanno T, Kiyose H, Kuwajima M, Nakashima K, Nagamine Y, Baba S, Hoshino T: Inter laboratory difference in GHb measurement in Japan-the fourth report of the GHb Standardization Committee, the Japan Diabetes Society, J

Jpn Diab Soc, 1997; 40: 321-326 (in Japanese)
17) Koshiyama H, Shimono D, Kuwamura N, Minamikawa J, Nakamura Y: Rapid communication: inhibitory effect of pioglitazone on carotid arterial wall thickness in type 2 diabetes. J Clin Endocrinol Metab, 2001; 86: 3452-3456
18) Bernard S, Sérusclat A, Targe F, Charriere S, Roth O, Beaune J, Berthezène F, Moulin P: Incremental predictive value of carotid ultrasonography in the assessment of coronary risk in a cohort of asymptomatic type 2 diabetic subjects. Diabetes Care, 2005; 28: 1158-1162
19) O'Leary DH, Polak JF, Kronmal RA, Manolio TA, Burke GL, Wolfson SK Jr: Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. Cardiovascular Health Study Collaborative Research Group. N Engl J Med, 1999; 340: 14-22
20) Hodis HN, Mack WJ, LaBree L, Selzer RH, Liu CR, Liu CH, Azen SP: The role of carotid arterial intima-media thickness in predicting clinical coronary events. Ann Intern Med, 1998; 128: 262-269
21) Wagenknecht LE, Zaccaro D, Espeland MA, Karter AJ, O' Leary DH, Haffner SM: Diabetes and progression of carotid atherosclerosis: the Insulin Resistance Atherosclerosis Study. Arterioscler Thromb Vasc Biol, 2003; 23: 1035-1041
22) Yokoyama H, Katakami N, Yamasaki Y: Recent advances of intervention to inhibit progression of carotid intima-media thickness in patients with type 2 diabetes mellitus. Stroke, 2006; 37: 2420-2427
23) Pfützner A, Marx N, Lubben G, Langenfeld M, Walcher D, Konrad T, Forst T: Improvement of cardiovascular risk markers by pioglitazone is independent from glycemic control: results from the pioneer study. J Am Coll Cardiol, 2005; 45: 1925-1931
24) Katakami N, Yamasaki Y, Hayaishi-Okano R, Ohtoshi K, Kaneto H, Matsuhisa M, Kosugi K, Hori M: Metformin or gliclazide, rather than glibenclamide, attenuate progression of carotid intima-media thickness in subjects with type 2 diabetes. Diabetologia, 2004; 47: 1906-1913
25) Yamasaki Y, Katakami N, Hayaishi-Okano R, Matsuhisa M, Kajimoto Y, Kosugi K, Hatano M, Hori M: alpha-Glucosidase inhibitor reduces the progression of carotid intima-media thickness. Diabetes Res Crin Pract, 2005; 67: 204-210
26) Park SW, Kim SK, Cho YW, Kim DJ, Song YD, Choi YJ, Huh BW, Choi SH, Jee SH, Cho MA, Lee EJ, Huh KB: Insulin resistance and carotid atherosclerosis in patients with type 2 diabetes. Atherosclerosis, 2009; 205: 309-313
27) Campia U, Matuskey LA, Panza JA: Peroxisome proliferator-activated receptor-gamma activation with pioglitazone improves endothelium-dependent dilation in nondiabetic patients with major cardiovascular risk factors. Circulation, 2006; 113: 867-875
28) Saitou M, Osonoi T, Kawamori R, Katakami N, Kaneto H, Matsuhisa M, Yamasaki Y: Genetic risk factors and the anti-atherosclerotic effect of pioglitazone on carotid atherosclerosis of subjects with type 2 diabetes -A retrospective study- J Atheroscler Thromb, 2010; 17: 386-394

Appendix 1

Listing of all investigational sites and investigators

Site	Investigator
Kurihara Diabetic Care Clinic	Yoshio Kurihara
Keijinkai Sasaki Diabetic Hospital	Takashi Sasaki
Toei Hospital	Ryo Sugiura
Kenichi Yamada Clinic	Kenichi Yamada
Okuguchi Clinic*	Fuminobu Okuguchi
Nakakinen Clinic*	Takeshi Osonoi
Minamiakatsuka Clinic	Hideo Takahashi
Kawai Clinic	Koichi Kawai
Arisaka Clinic	Tomoyuki Arisaka
Kobayashi Clinic of Internal Medicine and Gastroenterology	Izuru Kobayashi
Aiso Clinic*	Yoshitaka Aiso
Sugawara Medicine Clinic	Masahiro Sugawara
Kenkoukan Suzuki Clinic	Kazuo Suzuki
Matsuba Clinic	Ikuro Matsuba
Okada Clinic	Akira Okada
Abe Diabetes Clinic	Nobuyuki Abe
Jinnouchi Clinic Diabetes Center*	Hideaki Jinnouchi
Heiwadai Hospital*	Syuji Nakamura
Yano Clinic	Nobuki Yano
Tempozan Naika Clinic*	Jun Hashiguchi

*; Six centers where the carotid ultrasound protocol was performed.

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

Tomomi Nakamura, MD,*† Yukiko Tsutsumi, MD,* Yuko Shimizu, MD,* and Shinichiro Uchiyama, MD*

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.

From the *Department of Neurology, Tokyo Women's Medical University, Tokyo, Japan; and †Department of Neurology, Itabashi Chuo Medical Center, Tokyo, Japan.

Received January 27, 2009; revision received July 13, 2009; accepted August 15, 2009.

Address correspondence to Tomomi Nakamura, MD, Department of Neurology, Tokyo Women's Medical University, 8-1 Kawada-cho, Shinjuku-ku, Tokyo 162-8666, Japan. E-mail: tnakamur@nij.twmu.ac.jp.

1052-3057/$ - see front matter

doi:10.1016/j.jstrokecerebrovasdis.2009.08.006

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;

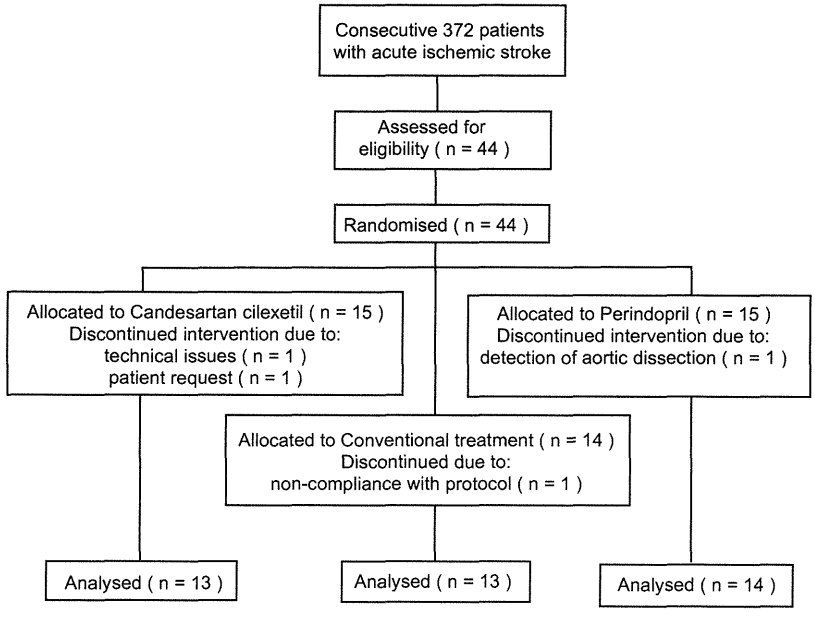

Figure 1. *Flow diagram of the patients recruited to the study.*

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).

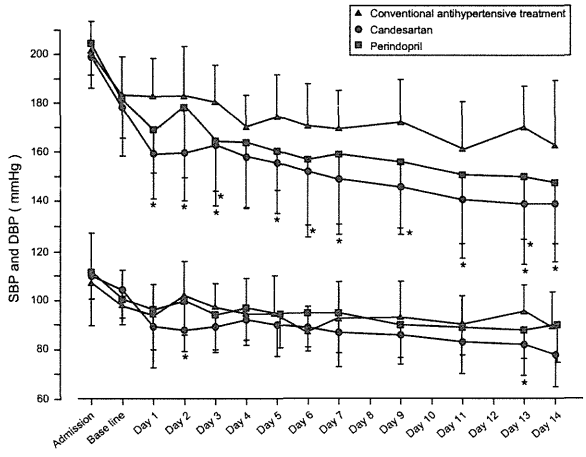

Figure 2. *Course of SBP and DBP from admission to day 14. Data are presented as mean ± standard deviation (bars). *Statistically significant BP reduction after candesartan or perindopril administration compared with conventional antihypertensive treatment for SBP and DBP (P < .05).*

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

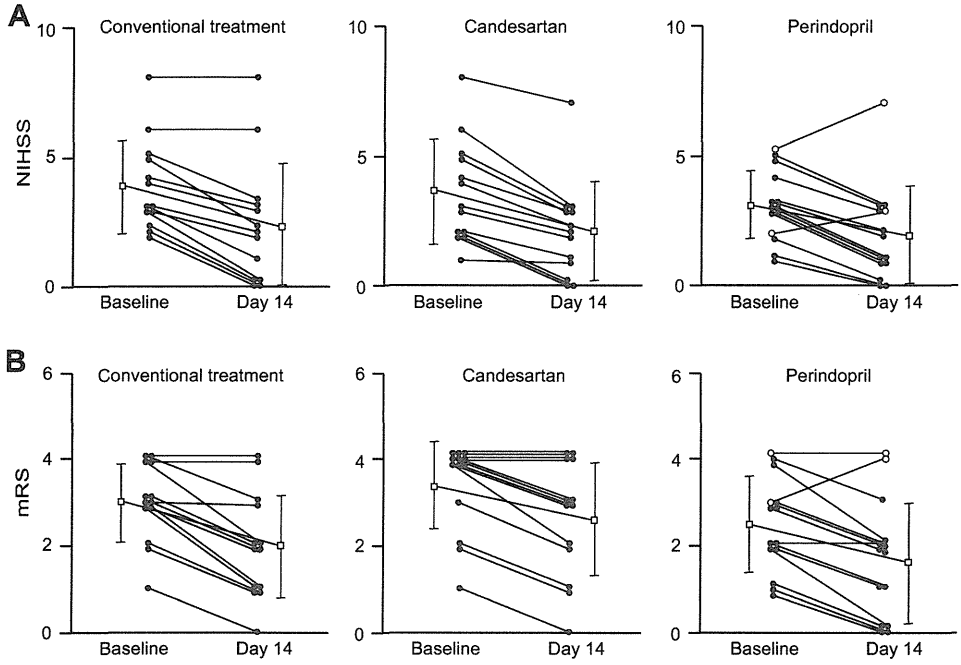

Figure 3. *Individual changes in NIHSS (A) and mRS (B) scores. Open circles (○) in the perindopril-treated group indicate patients with deteriorated NIHSS score during the observational period. Open squares (□) represent mean NIHSS or mRS score. Data are presented as mean ± standard deviation.*

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.

References

1. Robinson TG, Dawson SL, Ahmed U, et al. Twenty-four hour systolic blood pressure predicts long-term mortality following acute stroke. J Hypertens 2001;19:2127-2134.
2. Leonardi-Bee J, Bath PMW, Phillips SJ, et al, for the IST Collaborative Group. Blood pressure and clinical outcomes in the International Stroke Trial. Stroke 2002; 33:1315-1320.
3. Rodriguez-Garcia JL, Botia E, de La Sierra A, et al. Significance of elevated blood pressure and its management on the short-term outcome of patients with acute ischemic stroke. Am J Hypertens 2005;18:379-384.
4. Adams H, Adams R, Del Zoppo G, et al. Guidelines for the early management of patients with ischemic stroke: A scientific statement from the Stroke Council of the American Heart Association/American Stroke Association. Stroke 2005;36:916-921.
5. Graham DI, McGeorge A, Fitch W, et al. Ischemic brain damage induced by rapid lowering of arterial pressure in hypertension. J Hypertens 1984;2:297-304.
6. Vorstrup S, Paulson OB, Lassen NA. Cerebral blood flow in acute and chronic ischemic stroke using xenon-133 inhalation tomography. Acta Neurol Scand 1986;74:439-451.
7. Dawson SL, Blake MJ, Panerai RB, et al. Dynamic but not static cerebral autoregulation is impaired in acute ischemic stroke. Cerebrovasc Dis 2000;10:126-132.
8. Barer DH, Cruickshank JM, Ebrahim SB, et al. Low-dose β blockade in acute stroke (BEST Trial): An evaluation. Br Med J 1988;296:737-741.
9. Ahmed N, Nasman P, Wahlgren NG. Effect of intravenous nimodipine on blood pressure and outcome after acute stroke. Stroke 2000;31:1250-1255.
10. Eames PJ, Robinson TG, Panerai RB. The systemic haemodynamic and cerebral autoregulatory effects of bendrofluazide in the subacute post-stroke period. J Hypertens 2004;22:2017-2024.
11. Willmot M, Ghadami A, Whysall B, et al. Transdermal glyceryl trinitrate lowers blood pressure and maintains cerebral blood flow in recent stroke. Hypertenstion 2006;47:1209-1215.
12. Eveson DJ, Robinson TG, Potter JF. Lisinopril for the treatment of hypertension within the first 24 hours of acute ischemic stroke and follow-up. Am J Hypertens 2007;20:270-277.
13. Potter JF, Robinson TG, Ford GA, et al. Controlling hypertension and hypotension immediately post-stroke (CHHIPS): A randomized, placebo-controlled, double-blind pilot trial. Lancet Neurol 2009;8:48-56.
14. Schrader J, Luders S, Kulschewski A, et al. The ACCESS Study: Evaluation of acute candesartan cilexetil therapy in stroke survivors. Stroke 2003;34:1699-1703.
15. Minematsu K, Yamaguchi T, Tsuchiya M, et al. Effect of angiotensin-converting enzyme inhibitor (captopril) on cerebral blood flow in hypertensive patients without a history of stroke. Clin Exp Hypertens 1987;9:551-557.
16. Dyker AG, Grosset DG, Lees K. Perindopril reduces blood pressure but not cerebral blood flow in patients with recent cerebral ischemic stroke. Stroke 1997; 28:580-583.
17. Hatazawa J, Shimosegawa E, Osaki Y, et al. Long-term angiotensin-converting enzyme inhibitor perindopril therapy improves cerebral perfusion reserve in patients with previous minor stroke. Stroke 2004;35:2117-2122.
18. Walters MR, Bolster A, Dyker AG, et al. Effect of perindopril on cerebral and renal perfusion in stroke patients with carotid disease. Stroke 2001;32:473-478.
19. Adams HP, Bendixen BH, Kappelle LJ, et al. the TOAST Investigators. Classification of subtype of acute ischemic stroke: Definitions for use in a multicenter clinical trial. Stroke 1993;24:35-41.
20. Malmqvist K, Kahan T, Dahl M. Angiotensin II type 1 (AT_1) receptor blockade in hypertensive women: Benefits of candesartan cilexetil versus enalapril or hydrochlorothiazide. Am J Hypertens 2000;13:504-511.
21. Nakamura K, Saku Y, Ibayashi S, et al. Progressive motor deficits in lacunar infarction. Neurology 1999;52:29-33.
22. Nishimura Y, Ito T, Saavedra JM. Angiotensin II AT1 blockade normalizes cerebrovascular autoregulation and reduces cerebral ischemia in spontaneously hypertensive rats. Stroke 2000;31:2478-2486.
23. Iwai M, Liu HW, Chen R, et al. Possible inhibition of focal cerebral ischemia by angiotensin II type 2 receptor stimulation. Circulation 2004;110:843-848.
24. Fagan SC, Kozak A, Hill WD, et al. Hypertension after experimental cerebral ischemia: Candesartan provides neurovascular protection. J Hypertens 2006;24:535-539.
25. Fogelholm R, Palomaki H, Erila T, et al. Blood pressure, nimodipine, and outcome of ischemic stroke. Acta Neurol Scand 2004;109:200-204.

Risk Factors for Small Cortical Infarction on Diffusion-Weighted Magnetic Resonance Imaging in Patients With Acute Ischemic Stroke

Chisako Yano, MD, Makoto Iwata, MD, PhD, and Shinichiro Uchiyama, MD, PhD

Diffusion-weighted magnetic resonance imaging (MRI) is sensitive for detecting acute ischemic lesions. The present study evaluated risk factors associated with small cortical infarction (SCI) on diffusion-weighted MRI. We analyzed 123 patients with acute ischemic stroke retrospectively. We defined an SCI as a cortical lesions <1.5 cm in diameter detected by diffusion-weighted MRI. Risk factors and comorbidities included hypertension, hypercholesterolemia, diabetes mellitus, cigarette smoking, potential cardiac sources of embolism, carotid disease, and coagulopathy. Carotid disease was defined as >50% stenosis or occlusion in the internal carotid artery, detected by carotid ultrasonography. In addition, we analyzed plasma levels of coagulation and fibrinolysis markers. We also compared carotid disease, potential cardiac sources, and coagulopathy among localization of SCI. SCI was identified in 22.8% of patients with acute ischemic stroke. Carotid disease (odds ratio [OR] = 4.4; 95% confidence interval [CI] = 1.7-11.42; P = .002) and coagulopathy (OR = 6.8; 95% CI = 1.33-35.17; P = .02) were found to be independent risk factors for SCI. SCI with carotid disease was not associated with bilateral and multiple territorial lesions, whereas SCI with coagulopathy was associated with bilateral lesions. No borderzone lesions were found in SCI patients with cardiac sources. Our findings suggest that carotid disease and coagulopathy are independent risk factors for SCI. Localization of SCI varies depending on the underlying diseases. **Key Words:** Small cortical infarction—acute ischemic stroke—diffusion-weighted magnetic resonance imaging—carotid artery disease—coagulopathy.

The advent of diffusion-weighted magnetic resonance imaging (MRI), or DWI, greatly increased the ability to detect small cortical infarctions (SCIs). Some claim that DWI is superior to conventional T2-weighted or proton-density MRI for detecting previous minor strokes and transient ischemic attacks.[1,2] SCIs are easily confused with signals of cerebrospinal fluid on T2-weighted or proton-density MRI. Furthermore, small, disseminated satellite lesions are silent and may go unrecognized when <1 cm in diameter. The high signal-to noise ratio of DWI allows detection of disseminated small lesions on the cortical edge that might be missed on conventional T2-weighted imaging.[3] Recent studies have found that multiple small lesions visible on DWI are likely caused by emboli from a cardiac source or carotid occlusive disease.[3-5] Another study of microembolic signals (MES) detected by transcranial Doppler (TCD) found an association between MES and carotid occlusive disease and spotty lesions in the cortex.[6] These results lend support to the hypothesis that the predominant mechanism of SCI is mainly emboli from carotid disease.

Although numerous previous studies have explored carotid disease with small infarcts in the cortical area

From the Department of Neurology, Tokyo Women's Medical University School of Medicine, Tokyo, Japan.

Received June 3, 2009; revision received October 7, 2009; accepted November 7, 2009.

Address correspondence to Shinichiro Uchiyama, MD, PhD, Department of Neurology, Tokyo Women's Medical University School of Medicine, 8-1 Kawada-cho, Shinjuku-ku, Tokyo 162-8666, Japan. E-mail: suchiyam@nij.twmu.ac.jp.

1052-3057/$ - see front matter

doi:10.1016/j.jstrokecerebrovasdis.2009.11.003

and multiple infarcts, including cortical small lesions, the mechanisms of SCI have received little attention. In this study, we examined vascular risk factors and blood coagulation parameters in patients with and without SCIs and compared these risk factors with localization of the lesions to investigate the etiology of SCI.

Subjects and Methods

The study group comprised 123 patients (82 men and 41 women; mean age, 67.8 years) who were consecutively admitted with acute ischemic stroke to the Tokyo Women's Medical University Hospital and underwent DWI examination between September 2003 and January 2006. The following clinical data were investigated for all patients: blood chemistry studies, coagulation testing, urinalysis, chest radiography, electrocardiography, echocardiography, MRI, magnetic resonance angiography (MRA), 24-hour electrocardiographic monitoring, and carotid ultrasonography. MRI was performed using a 1.5 T system (Toshiba Excelart, Toshiba, Japan, Philips Intera, Philips, the Netherlands, GE Signa: GE medical systems, USA, or Shemens Vision: Shemens, Germany) equipped with single-shot ecoplanar imaging. Multimodal MRI included axial T1-weighted, T2-weighted, fluid-attenuated inversion recovery, MRA, and DWI sequences. The exact sequence parameters were as follows: TR/TE, 6000/130, 3014/78, 1000/100.7, or 4000/100; matrix size, 128 × 128, 256 × 256, 128 × 128, or 96 × 128; field of view, 270 × 300, 250 × 250, 220 × 220, or 220 × 220; slice thickness, 7 mm; b-values, 1000 s/mm^2. Diffusion gradients were applied in successive scans in each of the x, y, and z directions, and a DWI image was formed from the average of these values. SCI was defined as a cortical hyperintense lesion with diameter of <1.5 cm on DWI.

Differences in gender, age, risk factors for stroke, and plasma levels of coagulation markers between patients with SCI and without SCI were analyzed. The risk factors included hypertension (blood pressure >140/90 mm Hg or a history of hypertension requiring medical treatment), hypercholesterolemia (serum total cholesterol level >220 mg/dL or a history of hypercholesterolemia requiring medical treatment), diabetes mellitus (glycosylated hemoglobin level >6.5% or a history of treatment with an oral glucose depressant or insulin), regular cigarette smoking, and potential cardiac sources of embolism, including atrial fibrillation, patent foramen ovale, and thrombus in the left atrium. Duplex ultrasound and power Doppler ultrasound (Toshiba SSA-350A and SSA-550A) were used to detect carotid artery stenosis or occlusion.[7] European Carotid Surgery Trial (ECST) criteria were used to define carotid stenosis. To exclude carotid occlusion due to cardiac embolism in cardiac disease, cases with both carotid occlusion and potential cardiac sources were classified only as potential cardiac sources, not carotid disease. We also investigated a history of Trousseau's syndrome (ie, coagulopathy induced by cancer) and antiphospholipid syndrome (fulfilling the Sapporo criteria[8]), both of which were classified as coagulopathy. Coagulation markers included β-thromboglobulin (βTG), platelet factor 4 (PF4), thrombin-antithrombin III complex (TAT), and D-dimer. βTG and PF4 were measured using Asserachrom βTG kit and PF4 kits (Diagnostica Stago, Asnèires, France), TAT was measured using the TAT SRL kit (SRL, Tokyo, Japan), and D-dimer was measured using the Lpia-ace D-dimer kit (Mitsubishi Kagaku Iatron, Tokyo, Japan). Plasma levels of these hemostatic markers were quantified by enzyme-linked immunosorbent assay.

The localization of SCIs was classified as bilateral lesions, territorial single circulation (anterior or posterior circulation) lesions, territorial multiple circulation (bilateral or anterior and posterior circulation) lesions, or borderzone lesions (Fig 1). Borderzone lesions were defined as SCIs in superficial borderzone areas. Six of 7 SCI patients with bilateral lesions were categorized as having territorial multiple circulation lesions. One SCI patient with bilateral lesions who had a coagulopathy as a risk factor had lesions in bilateral borderzones, and was categorized as having borderzone lesions. Risk factors, including carotid disease, coagulopathy, and potential cardiac sources, were compared among the various SCI localization categories.

Statistical Analysis

All data were entered into SPSS version 7.5 for Windows (SPSS, Chicago, IL) for analysis. Differences in the prevalence of risk factors among patients with and without SCI were analyzed using the χ^2 test for the variables with 5 or more possible values. Fisher's exact test was used to analyze the prevalence of the lesion patterns of SCI for the nominal variables with fewer than 5 possible values. The Mann-Whitney *U* test was used to test the distribution of the continuous variables, such as age and plasma level of coagulation markers, between patients with and without SCI. These risk factors also were analyzed as independent determinants for SCI by multiple logistic regression analysis. The results are expressed as odds ratio (OR) of relative risk, with 95% confidence interval (CI). Statistical significance was established as $P < .05$.

Results

SCI was detected in 28 of 123 patients (22.8%). Carotid disease was significantly associated with SCI (Table 1), and all of the patients with SCI had the lesions on the same side with carotid disease. There were no significant differences in age, gender, or the prevalence of diabetes mellitus, hypertension, hypercholesterolemia, cigarette smoking, or potential cardiac sources between patients with and without SCI. Multiple logistic regression analysis

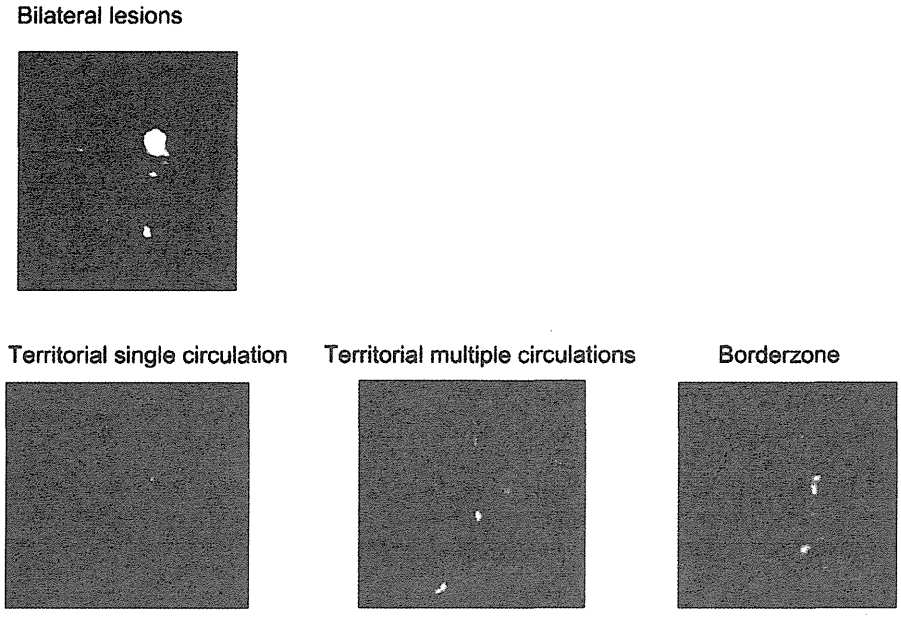

Figure 1. *We classified the localizations of SCI into bilateral lesions, territorial single circulation (anterior or posterior circulation), territorial multiple circulation (bilateral or anterior and posterior circulations), and borderzone lesions. Borderzone lesions were defined as SCI in superficial borderzone areas.*

found that carotid disease (OR = 3.9; 95% CI = 1.5-10.0; P = .004) and coagulopathy (OR = 6.7; 95% CI = 1.33-35.17; P = .02) were independent risk factors for SCI (Table 2). Analysis of plasma levels of coagulation parameters revealed no significant differences between patients with and without SCI (Table 3). Likewise, there were no significant differences in plasma levels of coagulation parameters between SCI patients with carotid disease and those with coagulopathy (data not shown).

Table 4 summarizes the localization of SCI and underlying diseases. Among the SCI patients, 13 had carotid disease, 8 had potential cardiac sources, 4 had coagulopathy, and 6 had unidentified sources of infarctions. Risk factors overlapped in 3 patients displaying the following pathology: carotid disease and potential cardiac sources, carotid disease and coagulopathy, and potential cardiac sources and coagulopathy. Bilateral lesions were less closely associated with carotid disease (P = .009); on the other hand, SCI with coagulopathy was associated with bilateral lesions (P = .038). Territorial multiple circulation lesions were less closely associated with carotid disease (P = .037) and more closely associated with coagulopathy (P = .058). No borderzone lesions were found in any SCI patient with potential cardiac sources.

Table 1. *Background characteristics of patients with and without small cortical infarcts (SCIs)*

Characteristic	SCI (+) (n = 28)	SCI (−) (n = 95)	P value*
Age, years, ± SD	69.8 ± 14.1	67.0 ± 13.4	.21†
Male gender (%)	21 (75.0%)	61 (64.2%)	.36
Diabetes mellitus	15 (53.6%)	42 (44.2%)	.40
Hypertension	18 (64.2%)	65 (68.4%)	.65
Hypercholesterolemia	12 (42.9%)	39 (41.1%)	1.00
Cigarette smoking	12 (42.9%)	44 (46.3%)	.55
Potential cardiac sources	8 (28.6%)	20 (21.1%)	.46
Atrial fibrillation	6	19	
Patent foramen ovale	1	1	
Thrombus in left atrium	1	0	
Carotid disease	13 (46.4%)	12 (12.6%)	.001
Occlusion	3	3	
Mean degree of stenosis	75.2 ± 21.4	70.0 ± 21.7	.56†
Coagulopathy	4 (14.3%)	5 (5.3%)	.21
Trousseau's syndrome	3	2	
Antiphospholipid syndrome	1	3	

*χ^2 test unless indicated otherwise.
†Mann-Whitney U test.

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

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

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

Discussion

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

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

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

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

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

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

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

Table 4. *Localization of SCI and risk factors*

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

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

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

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

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

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

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

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

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

References

1. Schulz UG, Briley D, Meagher T, et al. Diffusion-weighted MRI in 300 patients presenting late with subacute transient ischemic attack or minor stroke. Stroke 2004;35:2459-2465.
2. Wardlaw JM, Armitage P, Dennis MS, et al. The use of diffusion-weighted magnetic resonance imaging to

identify infarctions in patients with minor strokes. J Stroke Cerebrovasc Dis 2000;9:70-75.
3. Baird AE, Lovblad KO, Schlaug G, et al. Multiple acute stroke syndrome: Marker of embolic disease? Neurology 2000;54:674-678.
4. Koennecke HC, Bernarding J, Braun J, et al. Scattered brain infarct pattern on diffusion-weighted magnetic resonance imaging in patients with acute ischemic stroke. Cerebrovasc Dis 2001;11:157-163.
5. Takahashi K, Kobayashi S, Matui R, et al. The differences of clinical parameters between small multiple ischemic lesions and single lesion detected by diffusion-weighted MRI. Acta Neurol Scand 2002;106:24-29.
6. Kimura K, Minematsu K, Koga M, et al. Microembolic signals and diffusion-weighted MR imaging abnormalities in acute ischemic stroke. AJNR Am J Neuroradiol 2001;22:1037-1042.
7. Clevert DA, Johnson T, Michaely H, et al. High-grade stenoses of the internal carotid artery: Comparison of high-resolution contrast enhanced 3D MRA, duplex sonography and power Doppler imaging. Eur J Radiol 2006;60:379-386.
8. Wilson WA, Gharavi AE, Koike T, et al. International consensus statement on preliminary classification criteria for definite antiphospholipid syndrome: Report of an international workshop. Arthritis Rheum 1999; 42:1309-1311.
9. Timsit SG, Sacco RL, Mohr JP, et al. Brain infarction severity differs according to cardiac or arterial embolic source. Neurology 1993;43:728-733.
10. Gower DJ, Lewis JC, McWhorter JM, et al. Carotid plaque as a source of emboli in humans: A scanning electron microscopic study. Neurosurgery 1987;20:362-368.
11. Molloy J, Markus HS. Asymptomatic embolization predicts stroke and TIA risk in patients with carotid artery stenosis. Stroke 1999;30:1440-1443.
12. Droste DW, Dittrich R, Kemeny V, et al. Prevalence and frequency of microembolic signals in 105 patients with extracranial carotid artery occlusive disease. J Neurol Neurosurg Psychiatry 1999;67:525-528.
13. Golledge J, Greenhalgh RM, Davies AH. The symptomatic carotid plaque. Stroke 2000;31:774-781.
14. Sitzer M, Muller W, Siebler M, et al. Plaque ulceration and lumen thrombus are the main sources of cerebral microemboli in high-grade internal carotid artery stenosis. Stroke 1995;26:1231-1233.
15. Georgiadis D, Lindner A, Manz M, et al. Intracranial microembolic signals in 500 patients with potential cardiac or carotid embolic source and in normal controls. Stroke 1997;28:1203-1207.
16. Stork JL, Kimura K, Levi CR, et al. Source of microembolic signals in patients with high-grade carotid stenosis. Stroke 2002;33:2014-2018.
17. Kang DW, Chalela JA, Ezzeddine MA, et al. Association of ischemic lesion patterns on early diffusion-weighted imaging with TOAST stroke subtypes. Arch Neurol 2003;60:1730-1734.
18. Szabo K, Kern R, Gass A, et al. Acute stroke patterns in patients with internal carotid artery disease: A diffusion-weighted magnetic resonance imaging study. Stroke 2001;32:1323-1329.
19. Tsiskaridze A, Devuyst G, de Freitas GR, et al. Stroke with internal carotid artery stenosis. Arch Neurol 2001; 58:605-609.
20. Yong SW, Bang OY, Lee PH, et al. Internal and cortical border-zone infarction: Clinical and diffusion-weighted imaging features. Stroke 2006;37:841-846.
21. Chaves CJ, Silver B, Schlaug G, et al. Diffusion- and perfusion-weighted MRI patterns in border zone infarcts. Stroke 2000;31:1090-1096.
22. Momjian-Mayor I, Baron JC. The pathophysiology of watershed infarction in internal carotid artery disease: Review of cerebral perfusion studies. Stroke 2005;36:567-577.
23. Derdeyn CP, Khosla A, Videen TO, et al. Severe hemodynamic impairment and border zone region infarction. Radiology 2001;220:195-201.
24. Arakawa S, Minematsu K, Hirata T, et al. Topographic distribution of misery perfusion in relation to internal and superficial border zones. AJNR Am J Neuroradiol 2003;24:427-435.
25. Del Sette M, Eliasziw M, Streifler JY, et al, for the North American Symptomatic Carotid Endarterectomy (NASCET) Group. Internal border zone infarction: A marker for severe stenosis in patients with symptomatic internal carotid artery disease. Stroke 2000;31:631-636.
26. Lee PH, Bang OY, Oh SH, et al. Subcortical white matter infarcts: Comparison of superficial perforating artery and internal border-zone infarcts using diffusion-weighted magnetic resonance imaging. Stroke 2003;34:2630-2635.
27. Wong KS, Gao S, Chan YL, et al. Mechanisms of acute cerebral infarctions in patients with middle cerebral artery stenosis: A diffusion-weighted imaging and microemboli monitoring study. Ann Neurol 2002;52:74-81.
28. De Reuck J, Paemeleire K, Santens P, et al. Cobalt-55 positron emission tomography in symptomatic atherosclerotic carotid artery disease: Border zone versus territorial infarcts. Clin Neurol Neurosurg 2004; 106:77-81.
29. Caplan LR. Brain embolism, revisited. Neurology 1993; 43:1281-1287.
30. Caplan LR, Hennerici M. Impaired clearance of emboli (washout) is an important link between hypoperfusion, embolism, and ischemic stroke. Arch Neurol 1998; 55:1475-1482.
31. Cestari DM, Weine DM, Panageas KS, et al. Stroke in patients with cancer: Incidence and etiology. Neurology 2004;62:2025-2030.
32. Singhal AB, Topcuoglu MA, Buonanno FS. Acute ischemic stroke patterns in infective and nonbacterial thrombotic endocarditis: A diffusion-weighted magnetic resonance imaging study. Stroke 2002;33:1267-1273.
33. Roh JK, Kang DW, Lee SH, et al. Significance of acute multiple brain infarction on diffusion-weighted imaging. Stroke 2000;31:688-694.
34. Takano K, Yamaguchi T, Kato H, et al. Activation of coagulation in acute cardioembolic stroke. Stroke 1991; 22:12-16.
35. Yamazaki M, Uchiyama S, Maruyama S. Alterations of haemostatic markers in various subtypes and phases of stroke. Blood Coagul Fibrinolysis 1993;4:707-712.
36. Uchiyama S, Yamazaki M, Hara Y, et al. Alterations of platelet, coagulation, and fibrinolysis markers in patients with acute ischemic stroke. Semin Thromb Hemost 1997; 23:535-541.
37. Terashi H, Uchiyama S, Hashimoto S, et al. Clinical characteristics of stroke patients with antiphospholipid antibodies. Cerebrovasc Dis 2005;19:384-390.
38. Nederkoorn PJ, van der Graaf Y, Hunink MG. Duplex ultrasound and magnetic resonance angiography compared with digital subtraction angiography in carotid artery stenosis: A systematic review. Stroke 2003; 34:1324-1332.
39. Koch S, Amir M, Rabinstein AA, et al. Diffusion-weighted magnetic resonance imaging in symptomatic

vertebrobasilar atherosclerosis and dissection. Arch Neurol 2005;62:1228-1231.
40. Yamamoto Y, Georgiadis AL, Chang HM, et al. Posterior cerebral artery territory infarcts in the New England Medical Center Posterior Circulation Registry. Arch Neurol 1999;56:824-832.
41. Kumral E, Bayulkem G, Atac C, et al. Spectrum of superficial posterior cerebral artery territory infarcts. Eur J Neurol 2004;11:237-246.
42. Cals N, Devuyst G, Afsar N, et al. Pure superficial posterior cerebral artery territory infarction in the Lausanne Stroke Registry. J Neurol 2002;249:855-861.

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

Shinichiro Uchiyama, MD, PhD,* Yoshisato Shibata, MD, PhD,†
Takayuki Hirabayashi, MD, PhD,‡ Ban Mihara, MD, PhD,§
Naohisa Hamashige, MD, PhD,// Kazuo Kitagawa, MD, PhD,¶
Shinya Goto, MD, PhD,# Hideki Origasa, PhD,†† Kazuyuki Shimada, MD, PhD,‡‡
Hiroyuki Kobayashi, MD, PhD,** Mitsuhiro Isozaki, PhD,**
and Yasuo Ikeda, MD, PhD,§§ for the J-TRACE Investigators

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.

*From the Department of Neurology, Tokyo Women's Medical University, Tokyo, †Department of Cardiology, Miyazaki Medical Association Hospital, Miyazaki, ‡Department of Cardiology, Sunagawa City Medical Center, Sunagawa, §Department of Neurology, Institute of Brain and Vessel, Mihara Memorial Hospital, Isezaki, //Department of Cardiology, Chikamori Hospital, Kochi, ¶Department of Neurology, Osaka University School of Medicine, Osaka, #Departments of Internal Medicine, Tokai University School of Medicine, Isehara, ** Clinical Pharmacology, Tokai University School of Medicine, Isehara, ††Department of Biostatistics, Toyama University Graduate School, Toyama, ‡‡Department of Internal Medicine, Jichi Medical School, Shimono; and §§Department of Internal Medicine, Keio University School of Medicine, Tokyo, Japan.

Received January 23, 2009; revision received March 6, 2009; accepted March 13, 2009.

Supported by the Japan Heart Foundation.

Address correspondence to Shinichiro Uchiyama, MD, PhD, Department of Neurology, Tokyo Women's Medical University School of Medicine, 8-1 Kawada-cho, Shinjuku-ku, Tokyo 162-8666, Japan. E-mail: suchiyam@nij.twmu.ac.jp.

1052-3057/$—see front matter

doi:10.1016/j.jstrokecerebrovasdis.2009.04.004

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

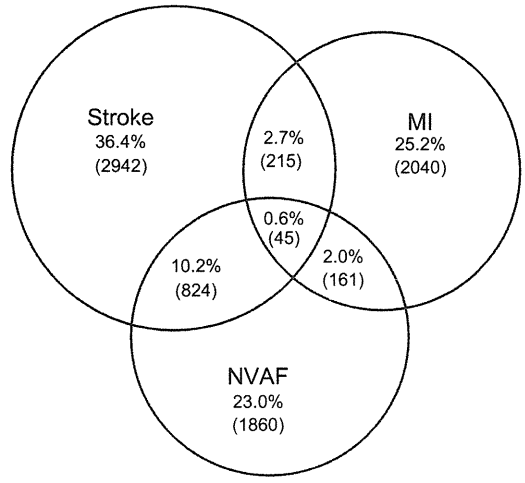

Figure 1. *Overlap in history of stroke, MI, and NVAF in J-TRACE population.*