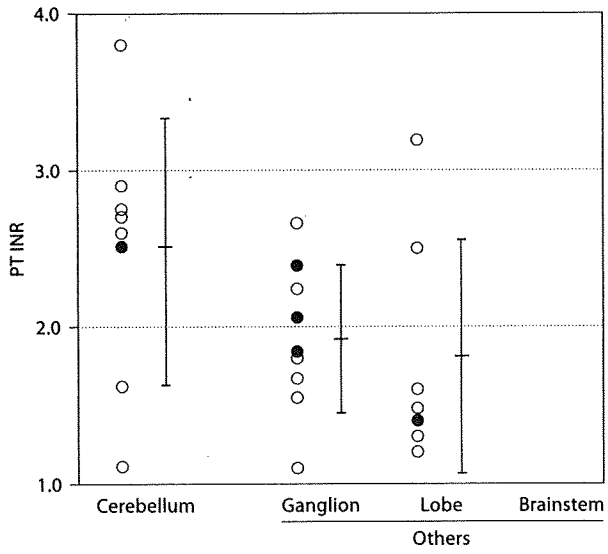
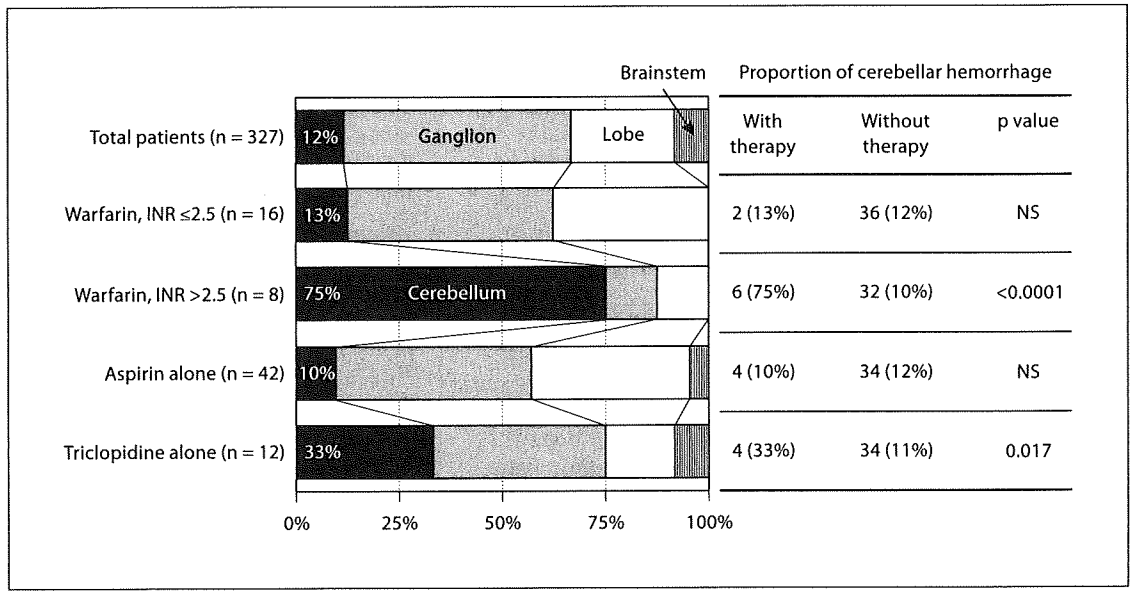


Fig. 1. Admission INR for prothrombin time (PT) for patients on warfarin therapy. Closed circles indicate patients who were also taking antiplatelets. Bars indicate means ± SD. The Mann-Whitney U test shows a significant difference in the INR between patients with CH and other hemorrhage.

patients with CH included cardioembolic stroke in 4 (all of whom received warfarin), other ischemic stroke in 11 (2 on warfarin therapy and 9 on antiplatelet agents), nonvalvular atrial fibrillation without previous stroke in 2 (all of whom received warfarin) and other peripheral vascular diseases in 1 patient (treated with aspirin). The proportion of CH to total ICH increased from 12% of the total patients to 75% of the patients on warfarin therapy with INR >2.5 ($p < 0.0001$) and to 33% of the patients on ticlopidine ($p = 0.017$, fig. 2).

On multivariate analysis using 'any antithrombotic therapy before stroke onset' and the items in table 1 that were statistically significantly or marginally significantly different between the 2 groups as variables, only high blood glucose on admission was independently related to CH (table 3, model 1). The results were similar when either warfarin or ticlopidine use was included instead of any antithrombotic therapy. On the other hand, when warfarin therapy with an INR >2.5 was included instead of any antithrombotic therapy, it was found to be an independent predictor of CH, as was high blood glucose (odds ratio 1.83, 95% confidence interval 1.10–3.06). The total number of major arteriosclerotic comorbidities and risk factors was also independently predictive of CH after



Proportion of cerebellar hemorrhage		
With therapy	Without therapy	p value
2 (13%)	36 (12%)	NS
6 (75%)	32 (10%)	<0.0001
4 (10%)	34 (12%)	NS
4 (33%)	34 (11%)	0.017

Fig. 2. Hematoma location in patients on various oral antithrombotic therapies at stroke onset. The table shows the proportion of CH to all ICH in patients with and without each type of antithrombotic therapy. Patients receiving both antiplatelet and warfarin therapy were included in the warfarin group. Data on treatment with cilostazol alone (n = 3) and multiple antiplatelets (n = 9) are not shown due to the small number of patients.

Table 3. Multivariate analysis of independent predictors of predilection for CH

Items	p value	OR	95% CI
Model 1			
Hypercholesterolemia	0.10	2.00	0.88–4.57
Symptomatic ischemic stroke	0.27	1.68	0.67–4.18
Heart diseases	0.12	1.99	0.83–4.78
Systolic BP >200 mm Hg	0.11	1.91	0.87–4.17
High blood glucose (by 100 mg/dl)	0.03	1.76	1.07–2.89
Platelet count (by 50,000/μl)	0.21	1.19	0.90–1.58
Preexisting antithrombotic therapy			
Any	0.63	1.26	0.50–3.19
Warfarin	0.08	2.95	0.86–10.1
Warfarin with an INR >2.5	0.001	19.5	3.32–114.9
Ticlopidine	0.24	2.28	0.58–8.96
Model 2			
Number of major comorbidities and risk factors	0.002	1.63	1.19–2.24
Warfarin with an INR >2.5	0.001	16.7	3.09–90.6

Adjusted by gender and age (by 10 years).

Model 1: analysis using each comorbidity and risk factor plus various types of preexisting antithrombotic therapy. Odds ratios (OR) and 95% confidence intervals (CI) of the first 6 items were determined in case of any antithrombotic therapy. Hypertension and diabetes mellitus were not included in the analysis although they showed marginally significant differences in table 1, because systolic BP >200 mm Hg and high blood glucose were used instead.

Model 2: using 'number of major comorbidities and risk factors' and 'warfarin with an INR >2.5'.

adjustment for gender, age and warfarin therapy with an INR >2.5 (table 3, model 2).

Ventricular bleeding on the initial CT was more frequent (p = 0.046), and severe initial neurological deficits (NIHSS ≥16) tended to be more frequent in patients with CH than in patients with other ICH (p = 0.063, table 4). Patients with CH on warfarin therapy had larger hematomas but did not have a higher NIHSS score than those receiving antiplatelet therapy or those not taking any antithrombotic therapy (fig. 3a, b). Patients with CH on ticlopidine did not have a statistically significantly different hematoma volume or NIHSS score compared to other patients (data not shown).

Three weeks after ICH onset, patients with CH tended to be less independent (p = 0.066) and more frequently required hematoma evacuation than those with other ICH (p = 0.035, table 4). The outcome did not differ among patients with a CH who were taking warfarin, antiplatelet agents or those who were not taking any antithrombotic therapy (fig. 3c).

Discussion

In this study, we focused on the important causal relationship between warfarin and CH during this period of widespread antithrombotic therapy. Our major new finding was that warfarin therapy with an INR >2.5 and the number of major arteriosclerotic comorbidities and risk factors were independently predictive of the more frequent occurrence of CH as compared to other ICH. Among antiplatelet agents, ticlopidine increased the proportion of CH to total ICH.

Kase et al. [13] studied the predilection for the cerebellum (9/24, 38%) as a bleeding location in patients on anticoagulant therapy based on their original data and prior small population studies. However, they did not offer a clear explanation for their findings. Our study confirmed their observations and highlighted the association of an INR >2.5 with an increase in CH compared to other ICH. However, we could not identify any causal pathological or pathophysiological characteristics. Cerebellar microbleeds were visualized in 29 of 98 Korean stroke patients (30%) who had microbleeds somewhere in

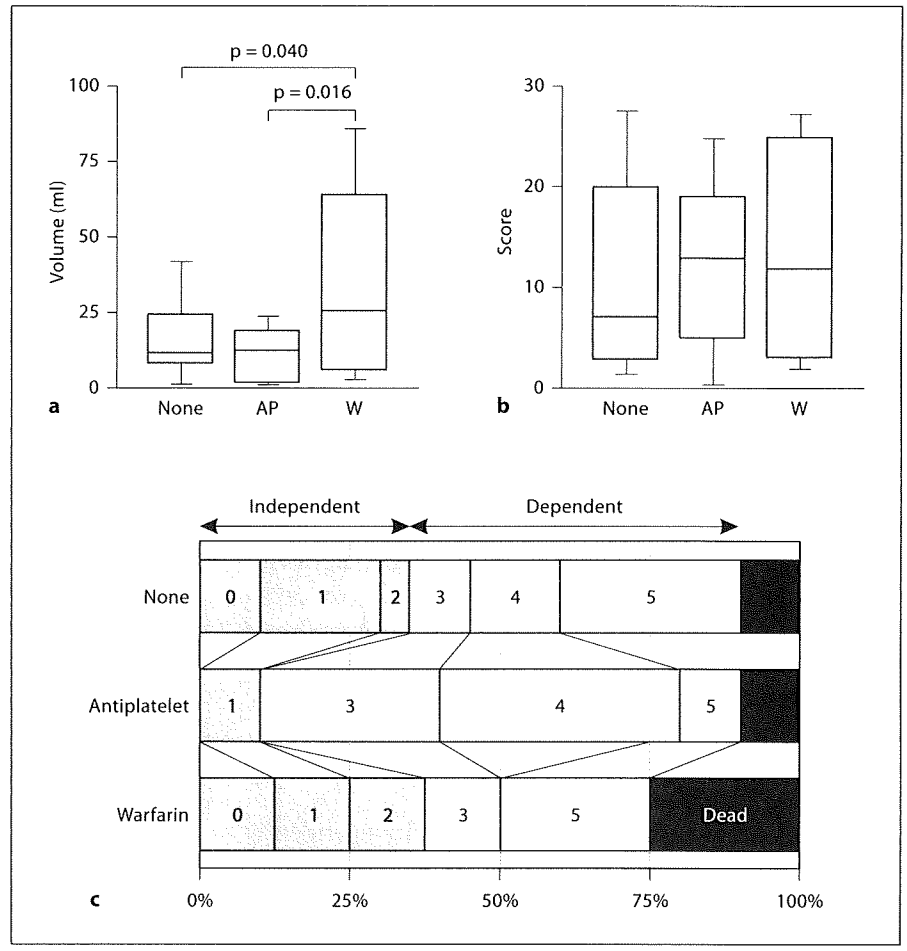


Fig. 3. Comparison of hematoma volume on admission (**a**), the NIHSS score on admission (**b**) and the modified Rankin Scale score, including acute death, at 3 weeks (**c**) among patients with a CH on antiplatelet (AP), warfarin (W) and no antithrombotic therapy (none). **a** Two-way factorial ANOVA shows a significant difference in hematoma volume among the 3 groups (p = 0.042) with post hoc differences shown.

Table 4. CT findings, neurological status and outcome of patients with ICH

	Cerebellar hemorrhage (n = 38)	Other hemorrhage (n = 289)	p value
CT findings			
Multiple hematoma	1 (3)	6 (2)	0.824
Volume of hematoma	19.8 ± 21.4	25.5 ± 38.5	0.373
Ventricular bleeding	18 (47)	90 (31)	0.046
ICH onset to CT <3 h	18 (49)	134 (46)	0.793
Neurological status			
mRS before ICH ≥ 3	4 (11)	14 (5)	0.149
NIHSS on admission ≥ 16	15 (39)	73 (25)	0.063
Outcome at 3 weeks			
Independent, mRS ≤ 2	11 (29)	129 (45)	0 066
Dependent, mRS ≥ 3	22 (58)	131 (45)	0.144
Dead	5 (13)	29 (10)	0.553
Required surgical evacuation	14 (37)	62 (21)	0.035

mRS = Modified Rankin Scale. Figures in parentheses indicate percentages.

the brain on T_2*-weighted gradient-echo MRI [21], which suggests a relatively high frequency of cerebellar microbleeds in the Asian population. Thus, chronic warfarin might cause subclinical cerebellar microbleeds to grow to symptomatic CH [18], thus explaining the increased prevalence of cerebellar involvement in warfarin-related ICH. A similar predilection for the cerebellum was not found in patients after coronary thrombolysis using tissue plasminogen activator or streptokinase; in these patients, the primary bleeding location was a hemispheric lobe [22–24]. After cerebrovascular thrombolysis using prourokinase, hemorrhages were found to occur primarily in the area of the preceding infarcts and not in the cerebellum [25]. Thus, different mechanisms may be operative in patients with postthrombolysis ICH compared to patients who have ICH during warfarin therapy.

Our study found that ticlopidine was associated with CH, although the result was based on data derived from a small number of patients. Aspirin was not associated with CH in this and in previous studies [26]. This difference between aspirin and ticlopidine might partly be due to a different intensity of treatment or a different mechanism of action with respect to antiplatelet function between these 2 agents.

High blood glucose on admission was independently associated with CH. This finding may be partly due to the high frequency of diabetic patients in the CH group. The prevalence of diabetes mellitus in patients with CH, as well as that of previous ischemic stroke, heart disease and hypercholesterolemia, would appear to be at least partly due to the use of antithrombotic therapy for these arteriosclerotic comorbidities. Interestingly, the proportion of CH increased with a greater number of comorbidities or risk factors. The existence of multiple comorbidities may complicate the acute management of these patients.

Although warfarin treatment appeared to contribute to greater initial hematoma size, this did not adversely affect the 3-week post-CH outcome. The effect of warfarin in patients with high INR values was primarily reversed using vitamin K or prothrombin complex concentrate including coagulation factors II, VII, IX and X [17, 27]. This strategy might have prevented hematoma growth and the associated poor outcome. The limitations of this analysis included the small patient sample and the fact that 3-week outcome might not be fully correlated with long-term outcome.

Despite these limitations, our study found that preexisting warfarin use increased the risk of CH. Recently, ultra-early use of recombinant activated factor VII after ICH has been reported to limit hematoma growth and improved the long-term outcome in patients without disorders of hemostasis [28]. This agent counteracts the effect of warfarin and may also be useful in patients on antiplatelet therapy, although currently there is no effective means to counteract the effects of antiplatelet therapy.

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Carotid Artery Calcification on Multislice Detector-Row Computed Tomography

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Key Words
Stroke · Brain infarction · Carotid artery plaque · Carotid stenosis · Renal failure

Abstract
Background: To determine the underlying conditions that affect the degree of calcification of carotid arterial plaques, measured quantitatively using multidetector row computed tomography (MDCT), and to study the association of carotid calcification with clinical symptomatology. ***Methods:*** We measured the calcification volume of stenotic lesions at the carotid bifurcation using MDCT in 84 consecutive patients who were scheduled to undergo carotid revascularization. These results were compared with the clinical and radiological characteristics of the patients. ***Results:*** On MDCT, calcification in the carotid plaques was present in 78 patients (93%). Compared to the other patients, patients in the highest quartile of calcification volume (quartile 4) had higher serum creatinine levels ($p < 0.001$) and tended to have fewer symptomatic ischemic events in the territory of the affected carotid artery in the preceding 6 months (29 vs. 49%, $p = 0.099$); in particular, there were fewer transient symptoms (5 vs. 27%, $p = 0.032$) and symptoms possibly occurring due to local embolism (14 vs. 37%, $p = 0.045$). On ultrasound, plaque ulceration was less prevalent in patients in quartile 4 than in the remaining patients (5 vs. 29%, $p = 0.026$), although the severity of carotid stenosis was similar among all the quartiles. ***Conclusions:*** Renal dysfunction was associated with enhanced carotid plaque calcification. Patients with severe carotid calcification were found to have a low risk of recent ischemic stroke, presumably due, in part, to a lower prevalence of emboligenic carotid ulceration. MDCT was valuable for the quantitative evaluation of carotid calcification.

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Introduction

Current preventive strategies for ischemic stroke patients with cervical internal carotid artery (ICA) stenosis are principally based on the severity of ICA stenosis [1, 2]. However, the pathological characteristics of the stenotic plaque also seem to be important for determining strategy. For example, severe circumferential calcification is a relative contraindication to carotid artery stenting (CAS) [3]. Carotid ultrasound has been found to be an available tool for the presurgical evaluation of carotid artery stenosis [4]. However, due to acoustic shadow, carotid ultrasound cannot provide detailed visualization of vascular calcification, which, on the other hand, computed tomography (CT) can. Multidetector row CT (MDCT) has been

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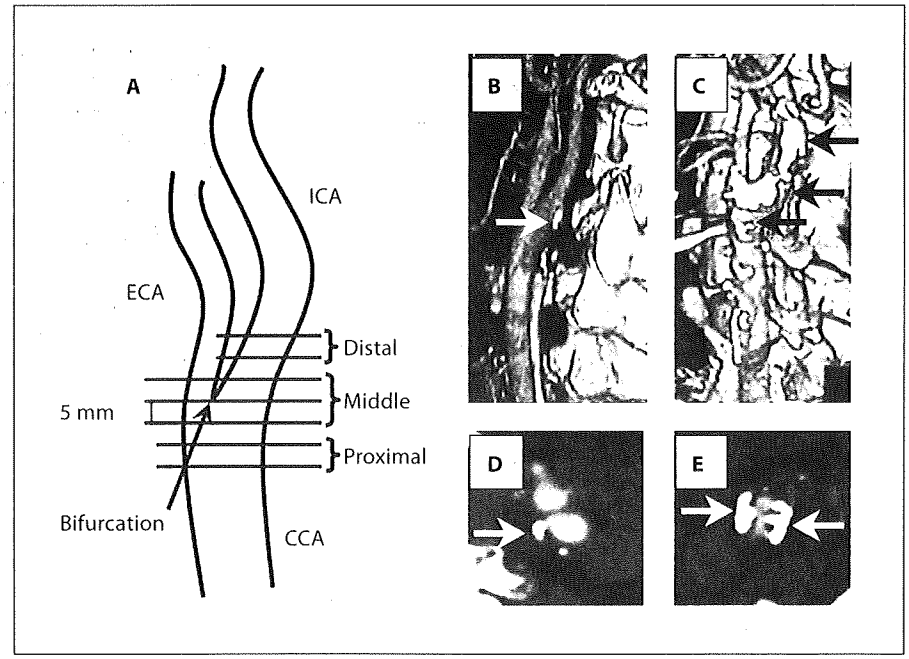

Fig. 1. Evaluation of calcification in the carotid plaque using MDCT. ECA = External carotid artery; CCA = common carotid artery. **A** Location of 7 slices around the carotid bifurcation. **B** Longitudinally localized calcification around the carotid bifurcation. **C** Longitudinally extended calcification primarily to the distal arterial wall. **D** Cross-sectionally localized calcification. **E** Cross-sectionally extended calcification.

reported to be superior to other conventional CT methods for quantifying vascular calcium [5–7].

We routinely assess the severity of stenosis and the tissue characteristics of carotid plaques using MDCT, duplex ultrasound, and conventional angiography. Patients with severe carotid stenosis are then assigned to carotid endarterectomy (CEA), CAS, or medical treatment, based on the results. The purpose of this study was to determine the underlying conditions that affect the degree of carotid calcification, that was measured quantitatively using MDCT, and to study the association of carotid calcification with patient symptomatology.

Methods

We studied 84 consecutive patients, 74 men and 10 women aged 50–84 years, who were scheduled to undergo CEA or CAS in our institute between 2003 and 2004 for stenotic lesions located at the carotid bifurcation. The inclusion criteria for CEA and CAS in our institute have previously been published [8, 9]. In all patients, carotid lesions were evaluated using MDCT, duplex ultrasound, and digital subtraction angiography (DSA), and cerebral hemodynamics were assessed using single photon emission computed tomography (SPECT).

Carotid CT imaging was done using a 16-row MDCT scanner (Multispeed Ultra 16x, GE Medical Systems, Milwaukee, Wisc., USA) with 13.4 mm/s table speed, 512 × 512 pixel matrix, 0.625-mm slice thickness, 0.6-mm reconstruction index, and 120 kV peak tube energy and autoregulation of tube currents. Contrast medium (Omnipaque 300 syringe, iohexol) was given by a power injector at a rate of 3.0 ml/s. To measure the volume of the carotid calcification, we multiplied the calcified area in the axial view of the CT film before construction. The calcified area was calculated for 7 axial 15-mm-thick slices around the bifurcation (fig. 1). The volume of calcification was determined by multiplying the calcified area by the slice thickness for 7 slices and then summing the results. We also evaluated the longitudinal and cross-sectional distributions of the calcification. The longitudinal distribution was classified into two groups: one with localized calcification that was present only in the middle 3 slices, and the other with extended calcification that expanded to proximal or distal slices. Cross-sectional distribution was also classified into two groups: one with localized calcification that was present only in the semicircle of the arterial wall at the slice with maximum calcification, and the other with extended calcification that expanded beyond the semicircle. The volume and distribution of calcification were assessed by a stroke specialist and a nonmedical researcher who were both blinded to the clinical history.

Conventional carotid duplex ultrasonography was performed using an HDI-5000 (Advanced Technology Laboratories, Bothell, Wash., USA) with a 12- to 5-MHz linear array transducer. The maximum area percent stenosis of the carotid artery was measured. A hyperechoic structure in the carotid arterial wall with an acoustic shadow was defined as plaque calcification. A crater ≥2 mm in depth on the plaque was defined as ulceration.

DSA was performed for clinical reasons and not just for study. On DSA, the degree of carotid stenosis was assessed with the method documented in the North American Symptomatic Carotid Endarterectomy Trial (NASCET) study [10].

SPECT was done at least 3 weeks after a stroke/transient ischemic attack (TIA) using the PRISM 2000X (two-head SPECT system, Picker, USA) and ^{99m}Tc-ethyl cysteinate dimer as the tracer

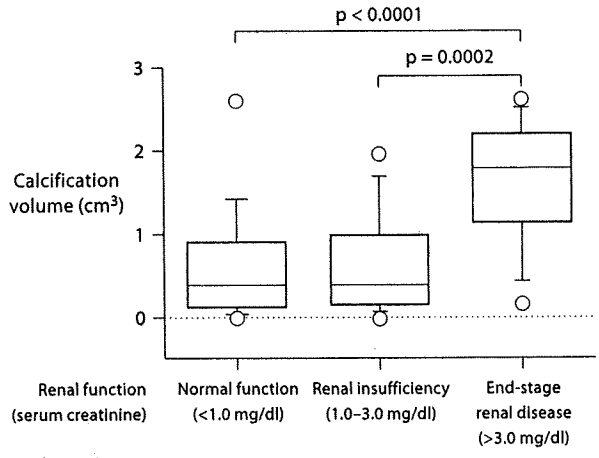

Fig. 2. Calcification volume in the carotid plaque according to renal function. Patients with end-stage renal disease had more calcification than the other two groups based on two-way factorial ANOVA with Bonferroni/Dunn post-hoc analysis.

according to a previously reported method [8]. Briefly, the regional cerebral blood flow (rCBF) values in the cortical area of the middle cerebral artery territory ipsilateral to the affected carotid artery were measured quantitatively using the Patlack plot method at rest and after the acetazolamide challenge test. Vascular reactivity was expressed using the following equation: reactivity (%) = [(post-acetazolamide CBF – resting rCBF)/resting rCBF] × 100. According to the criteria of the Japanese EC-IC bypass Trial [11], rCBF of the middle cerebral artery territory <40 ml/100 g/min (corresponding to 80% of the averaged value for control subjects) and vascular reactivity <10% on SPECT were regarded as indicating significant cerebral hemodynamic failure.

The following patient baseline characteristics were examined: gender, age, hypertension [systolic blood pressure (BP) ≥140/diastolic BP ≥90 mm Hg before stroke onset or history of antihypertensive medication], diabetes mellitus (fasting blood glucose ≥126 mg/dl, positive 75-gram oral glucose tolerance test, or history of antidiabetic medication), hyperlipidemia (serum total cholesterol ≥220 mg/dl, LDL cholesterol ≥140 mg/dl, or history of antihyperlipidemic medication), current or previous smoking habit, and alcohol drinking ≥2 drinks per day. On admission, the BP and body mass index were measured; blood tests included hemoglobin A_{1c}, total cholesterol, triglyceride, HDL cholesterol, LDL cholesterol, blood urea nitrogen (BUN), creatinine, calcium, and phosphate. Symptomatic ischemic stroke, TIA, and transient monocular blindness (TMB) in the territory of the affected carotid artery in the preceding 6 months were classified as a history of cerebral ischemia. These ischemic events were regarded as possibly caused by local embolism from the carotid plaque unless the culprit infarct was located only in the small-artery territory or the patient met the criteria for hemodynamic failure on SPECT.

Values are expressed as mean ± SD. Patients were divided into quartiles according to the volume of plaque calcification, and the physiological variables of the highest quartile of the calcification volume (quartile 4) were compared with each of the other quartiles using two-way factorial analysis of variance (ANOVA) with Bonferroni/Dunn post-hoc analysis. Serum creatinine levels among three patient groups with different renal function were also compared. The frequency of risk factors, stroke symptomatology, and ultrasound findings of the patients in quartile 4 were compared with the remaining patients using the chi-square test. For the analysis based on longitudinal and cross-sectional calcium distributions, chi-square and Mann-Whitney's U test were used as appropriate. A p value <0.05 was considered to be significant, and $0.05 \leq p < 0.1$ to be marginally significant.

Results

On MDCT, calcification in the carotid plaques was present in 78 patients (93%). The volume of calcification ranged from 0.03 to 2.62 cm^3. Longitudinally, calcification was localized in the middle slices in 32 patients, and extended only to the proximal slices in 6 patients, only to the distal slices in 24 patients, and to both slices in 16 patients. Cross-sectionally, calcification was localized within the semicircle of the arterial wall in 64 patients, mainly in the anterior wall in 15 patients and in the posterior wall in 49 patients, and extended beyond the semicircle in 14 patients.

On admission blood tests, BUN ($p = 0.020$) and creatinine ($p = 0.001$) levels were higher and calcium levels were lower ($p = 0.036$) in patients belonging to the highest quartile of calcification volume (quartile 4) as compared to the patients in the other quartiles (table 1). Calcification volume showed a stepwise increase with increasing renal dysfunction (fig. 2).

Episodes of symptomatic cerebral ischemia in the territory of the affected carotid artery in the preceding 6 months tended to be less frequent in quartile 4 patients than in the other patients ($p = 0.099$, table 2). In particular, transient ischemic events (TIA and TMB, $p = 0.032$) and ischemic events possibly caused by local embolism from the carotid plaque ($p = 0.045$) were less prevalent in quartile 4 patients.

On imaging examinations, the severity of the carotid stenosis seen on DSA or ultrasound did not differ among the quartiles (table 1). Ultrasound detected calcification with the acoustic shadow more frequently ($p < 0.0001$) and ulceration less frequently ($p = 0.026$) in the carotid plaque of quartile 4 patients than in the other patients (table 2). There was no significant difference in the resting rCBF or vascular reactivity found on SPECT among the four groups (table 1).

Table 1. Physiological variables by quartile of carotid calcification volume

	Quartile 1 (n = 21)	Quartile 2 (n = 21)	Quartile 3 (n = 21)	Quartile 4 (n = 21)	p value (ANOVA)
Calcification volume, median, cm^3	0.07***	0.26***	0.69***	1.63	<0.0001
Range	0 – 0.16	0.17 – 0.49	0.52 – 1.21	1.22 – 2.62	
Physiological status					
Age, years	68 ± 8	71 ± 6	72 ± 7	70 ± 6	0.257
Body mass index	23.6 ± 3.3	23.4 ± 2.6	23.5 ± 3.4	22.9 ± 2.6	0.847
Systolic BP, mm Hg	144 ± 17	140 ± 25	142 ± 25	148 ± 20	0.697
Diastolic BP, mm Hg	75 ± 10	77 ± 9	77 ± 11	79 ± 8	0.588
Blood test on admission					
Hemoglobin A_{1c}, %	6.6 ± 1.7	5.8 ± 0.8	6.2 ± 1.0	6.3 ± 1.6	0.259
Total cholesterol, mg/dl	195 ± 47	196 ± 42	195 ± 24	196 ± 33	0.999
LDL cholesterol, mg/dl	125 ± 44	128 ± 39	126 ± 27	125 ± 27	0.991
BUN, mg/dl	17.4 ± 13.0*	17.6 ± 5.2*	17.0 ± 8.1*	27.2 ± 18.3	0.020
Creatinine, mg/dl	1.2 ± 1.6**	0.9 ± 0.3**	1.3 ± 1.9*	3.7 ± 4.2	0.001
Calcium, mg/dl	9.5 ± 0.6	9.6 ± 0.4	9.7 ± 0.5*	9.2 ± 0.5	0.036
Phosphate, mg/dl	3.5 ± 1.3	3.4 ± 0.5	3.3 ± 0.4	4.1 ± 0.9	0.064
Calcium-phosphate product	33.6 ± 14.6	32.7 ± 4.3	32.3 ± 5.1	37.4 ± 8.0	0.354
Carotid artery stenosis					
On DSA (NASCET), %	82 ± 15	79 ± 12	83 ± 14	83 ± 13	0.721
On ultrasound (area), %	91 ± 6	91 ± 5	91 ± 6	91 ± 10	0.995
SPECT					
Resting rCBF, ml/100 g/min	40.5 ± 5.9	40.6 ± 5.2	44.5 ± 7.4	42.8 ± 7.0	0.130
Vascular reactivity, %	15.5 ± 19.0	18.8 ± 16.4	24.4 ± 19.1	18.9 ± 16.7	0.446

Six patients without MDCT-documented calcification belong to quartile 1.
* $p < 0.0083$, ** $p < 0.001$, *** $p < 0.0001$ vs. 'quartile 4' by two-way factorial ANOVA with Bonferroni/Dunn post-hoc analysis.

Compared to the 38 patients with localized or absent calcification, in the 46 patients with longitudinally extended calcification, calcification volume was larger ($p < 0.0001$), symptomatic cerebral ischemia ($p = 0.059$) and ischemic stroke ($p = 0.074$) tended to be less prevalent, ultrasound-documented calcification ($p < 0.0001$) of the plaque was more frequent, and ultrasound-documented ulceration ($p = 0.044$) of the plaque was less frequent (table 3). Similarly, compared to the 70 patients with localized or absent calcification, in the 14 patients with cross-sectionally extended calcification, calcification volume was larger ($p < 0.0001$), serum levels of BUN ($p = 0.053$), creatinine ($p = 0.087$), and phosphate ($p = 0.058$) tended to be higher, serum calcium levels were lower ($p = 0.036$), ultrasound-documented calcification ($p < 0.0001$) of the plaque was more frequent, and ultrasound-documented ulceration ($p = 0.031$) of the plaque was less frequent.

Discussion

In this study, we clarified the unique characteristics of patients with severe calcification of the carotid plaque. There were two major findings: (1) carotid calcification increased as renal dysfunction progressed, and (2) calcification was inversely related to the risk of recent symptomatic cerebral ischemia, presumably partly due to the lower prevalence of embolic carotid ulceration. MDCT was valuable for quantitatively evaluating carotid calcification.

Arterial disease in patients with chronic kidney disease is characterized by extensive calcification. Atherosclerotic plaques contain modified lipids, lipoproteins, and inflammatory cytokines, as well as minor key regulators, such as bone morphogenetic protein-2, osteopontin, matrix-carboxyglutamic acid protein, and osteoprotegerin, that regulate osteogenic differentiation of vascular

Table 2. Risk factors, stroke symptomatology, and ultrasound findings by quartile of carotid calcification volume

	Quartile 1 (n = 21)	Quartile 2 (n = 21)	Quartile 3 (n = 21)	Quartile 4 (n = 21)	p value[1]
Risk factors					
Male gender	21 (100%)	18 (86%)	17 (81%)	18 (86%)	0.697
Hypertension	17 (81%)	13 (62%)	14 (67%)	14 (67%)	0.785
Diabetes mellitus	8 (38%)	8 (38%)	12 (57%)	11 (52%)	0.528
Hyperlipidemia	8 (38%)	6 (29%)	8 (38%)	7 (33%)	0.895
Smoking habit	18 (86%)	13 (62%)	12 (57%)	15 (71%)	0.785
Drinking >2 cups/day	10 (48%)	5 (24%)	3 (14%)	6 (29%)	
Stroke symptomatology					
Symptomatic ischemia	15 (71%)	11 (52%)	5 (24%)	6 (29%)	0.099
Complete stroke	9 (43%)	5 (24%)	0	5 (24%)	0.880
TIA/TMB	6 (29%)	6 (29%)	5 (24%)	1 (5%)	0.032
Possible local embolism	10 (48%)	8 (38%)	5 (24%)	3 (14%)	0.045
Ultrasound					
Calcification	0	3 (14%)	8 (38%)	16 (76%)	<0.0001
Ulceration	7 (33%)	8 (38%)	7 (33%)	2 (10%)	0.026

Six patients without MDCT-documented calcification belong to quartile 1.
[1] Quartile 4 (n = 21) vs. other quartiles (n = 63) by chi-square test.

Table 3. Patient characteristics and distribution of carotid calcification

	Longitudinal			Cross-sectional		
	extended (n = 46)	localized (n = 38)	p value	extended (n = 14)	localized (n = 70)	p value
Calcification volume, cm^3	1.14 ± 0.65	0.20 ± 0.20	<0.0001	1.78 ± 0.58	0.50 ± 0.48	<0.0001
Blood test on admission						
BUN, mg/dl	21.8 ± 14.2	17.5 ± 10.4	0.162	28.4 ± 18.6	18.1 ± 10.6	0.053
Creatinine, mg/dl	2.3 ± 3.3	1.1 ± 1.2	0.293	4.1 ± 4.5	1.3 ± 1.8	0.087
Calcium, mg/dl	9.4 ± 0.6	9.5 ± 0.5	0.692	9.2 ± 0.5	9.5 ± 0.5	0.036
Phosphate, mg/dl	3.7 ± 0.8	3.5 ± 1.1	0.194	4.0 ± 0.9	3.5 ± 0.9	0.058
Stroke symptomatology						
Symptomatic ischemia	16 (35%)	21 (55%)	0.059	5 (36%)	32 (46%)	0.491
Complete stroke	7 (15%)	12 (32%)	0.074	3 (21%)	16 (23%)	0.907
TIA/TMB	9 (20%)	9 (24%)	0.647	2 (14%)	16 (23%)	0.476
Possible local embolism	12 (26%)	14 (37%)	0.289	4 (29%)	22 (31%)	0.833
Ultrasound						
Calcification	25 (54%)	2 (5%)	<0.0001	14 (100%)	13 (19%)	<0.0001
Ulceration	9 (20%)	15 (39%)	0.044	1 (7%)	23 (33%)	0.031

Six patients without MDCT-documented calcification belong to 'localized'.

cells and consequently impact on vascular calcification [12]. Additionally, in renal patients, elevated serum phosphate and calcium levels may stimulate sodium-dependent phosphate co-transport, creating osteoblast-like changes in cellular gene expression that lead to arterial calcification [13]. The patients with severe carotid calcification paradoxically showed low serum calcium levels, probably because some of them were on hemodialysis and took medications to reduce serum calcium. Nevertheless, these patients still had somewhat high levels of serum phosphate and calcium-phosphate product. Renal patients frequently have excessive coronary artery calcification [14] and increased intima-media thickness of carotid arteries [15]. However, the association of renal disease with carotid calcification has not been fully elucidated. The incidence of symptomatic and silent cerebrovascular diseases is much greater in renal patients than in the general population [16–18]. Therefore, in patients with chronic kidney disease, the characteristics of carotid artery lesions (including calcification) should be examined, as they are a potential cause of stroke.

Calcification is used as a clinical indicator of advanced atherosclerosis; it progresses nonlinearly with time, following a sigmoid-shaped curve [12]. However, the present results show that carotid calcification was inversely associated with the risk of recent symptomatic cerebral ischemia, especially transient symptoms and symptoms possibly caused by local embolism from the carotid plaque. Based on mechanical stress principles, the risk of plaque rupture caused by calcification might be biphasic [12]. On the one hand, the development of calcification in the plaque increases the interface area between the calcified and noncalcified regions where stress failure tends to occur and thus increases the risk of plaque rupture [19], while on the other hand, the coalescence of rigid plaques by excess calcification decreases the interface areas and the risk of rupture. The low frequency of ulceration in severely calcified carotid plaques seen in this study's patients tends to support this theory. A pathological study done using CEA specimens reported that symptomatic plaques contain less calcification and more macrophage infiltration [20]. Ultrasound studies have also reported that lipid and hemorrhage-rich echolucent carotid plaques, in contrast to hyperechoic plaques containing calcification and fibrous tissues, have been associated with neurological events [21]. Thus, calcification may indicate plaque stability against inflammation, disruption, and thrombosis.

CAS is an alternative to CEA [22]. However, circumferential calcification is an obstacle to successful revascularization by CAS [3], and calcification at the carotid bifurcation causes prolonged hypotension after CAS [23]. Thus, one should carefully determine the presence or absence of carotid calcification when choosing a therapeutic strategy for carotid stenosis. The approach highlighted in the present study for quantifying calcification should help when choosing between CAS and CEA. Furthermore, the evaluation of the carotid calcification using longitudinal and cross-sectional distributions, in contrast to quantitative evaluation, may be also valuable to some extent.

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Early Recurrence of Ischemic Stroke in Japanese Patients: The Japan Standard Stroke Registry Study

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Key Words
Stroke recurrence, risk factors · Stroke subtype · Cerebral infarction · Atherothrombotic stroke · Diabetes mellitus

Abstract
Background: To determine the factors that contribute to early ischemic stroke recurrence in Japanese patients. ***Methods:*** A multicenter stroke registration study based on a computerized database from 54 Japanese institutes, involving 8,036 patients with brain infarction who were hospitalized within 48 h after symptom onset between January 2000 and March 2004. ***Results:*** Within 30 days after the initial stroke, 395 patients (4.9%) developed a recurrent stroke. Recurrence most frequently occurred in atherothrombotic patients (6.6%), followed by cardioembolic patients (6.2%). Overall, hypertension (OR 1.348, 95% CI 1.071–1.696) and atrial fibrillation (OR 1.503, 95% CI 1.177–1.918), but not diabetes mellitus, were independently predictive of early recurrence. In atherothrombotic patients, diabetes mellitus (OR 1.485, 95% CI 1.058–2.085) and atrial fibrillation (OR 1.998, 95% CI 1.231–3.244) were independently related to early recurrence. At hospital discharge, the modified Rankin Scale score was higher in patients who had an early recurrence ($p < 0.0001$). ***Conclusions:*** This study was based on a large number of Japanese patients and confirmed that hypertension and atrial fibrillation contribute to early ischemic stroke recurrence. In addition, analysis by stroke subtype showed that diabetes mellitus was independently related to early recurrence in atherothrombotic patients.

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Introduction

Stroke recurrence continues to be a major risk for stroke survivors, despite advances in stroke prevention strategies and treatments [1]. Atherothrombotic ischemic stroke, atrial fibrillation, and both high and low admission blood pressures are known to be predictors of early stroke recurrence [1–3].

The incidence of stroke in Japan surpasses that of ischemic heart disease [4]. A high incidence of lacunar stroke and intracerebral hemorrhage [4, 5] has been documented; this is unique to Japan. To further clarify the characteristics of stroke in Japan, a large hospital-based registration study using a computerized database that included 16,280 patients from 54 institutes was conducted (the Japan Standard Stroke Registry Study: JSSRS) [6]. Using data from this database, we sought to identify the clinical features that were predictive of early ischemic stroke recurrence.

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Table 1. Baseline clinical characteristics

	All patients			Atherothrombotic stroke		
	recurrent	nonrecurrent	p value	recurrent	nonrecurrent	p value
Patients	395	7,641		174	2,471	
Age, years	72.0 ± 11.5 (395)	71.2 ± 11.9 (7,641)	0.1888	71.3 ± 10.8 (174)	71.7 ± 11.0 (2,471)	0.5825
Male gender, %	61.6 (393)	59.8 (7,633)	0.4815	66.5 (173)	63.0 (2,469)	0.3625
Previous ischemic stroke, %	35.2 (383)	29.8 (7,471)	0.0222	39.1 (169)	32.7 (2,422)	0.0876
Hypertension, %	66.6 (392)	60.6 (7,620)	0.0188	73.4 (173)	64.4 (2,466)	0.0167
Diabetes mellitus, %	25.7 (393)	24.5 (7,605)	0.5932	37.6 (173)	28.3 (2,466)	0.0090
Hyperlipidemia, %	22.5 (386)	22.6 (7,496)	0.9635	29.7 (172)	26.7 (2,419)	0.3999
Atrial fibrillation, %	33.4 (392)	24.8 (7,613)	0.0001	13.3 (173)	7.9 (2,463)	0.0122
Ischemic heart disease, %	13.3 (376)	11.8 (7,324)	0.3939	13.9 (166)	12.9 (2,372)	0.7112
Aortic aneurysm, %	1.6 (376)	1.0 (7,324)	0.3039	0.0 (166)	1.2 (2,372)	0.1592
Peripheral artery disease, %	0.8 (376)	0.3 (7,324)	0.1515	0.6 (166)	0.4 (2,372)	0.7317
Chronic kidney diseases, %	4.2 (334)	4.2 (6,440)	0.9786	4.2 (143)	4.3 (2,046)	0.9521
Hemodialysis, %	0.6 (334)	1.4 (6,440)	0.2002	1.4 (143)	1.4 (2,046)	0.9853
Alcohol consumption[1], %	9.7 (361)	9.4 (6,936)	0.8443	9.6 (157)	11.0 (2,183)	0.5646
Smoking habit[2], %	36.1 (352)	37.6 (6,770)	0.5564	41.6 (154)	39.7 (2,139)	0.6559
Prestroke medication						
Anticoagulants, %	10.1 (286)	7.3 (5,595)	0.0776	4.9 (142)	5.3 (1,892)	0.8547
Antiplatelets, %	24.1 (286)	17.6 (5,595)	0.0052	29.6 (142)	18.1 (1,892)	0.0007
Antihypertensives, %	55.1 (392)	47.0 (7,620)	0.0017	58.4 (173)	49.4 (2,466)	0.0229
Insulin, %	4.1 (393)	3.8 (7,605)	0.8054	6.4 (173)	4.5 (2,466)	0.2487
Prestroke mRS: 0–1, %	80.5 (220)	81.1 (4,318)	0.7975	84.7 (111)	80.7 (1,484)	0.3053

Numbers in parentheses indicate the number of patients whose data were available. [1] ≥2 drinks per day. [2] Current or previous.

Methods

Between January 2000 and March 2004, 10,261 patients with acute brain infarction were hospitalized within 48 h after stroke onset and were registered in the JSSRS. In 8,036 of these patients, there was appropriate documentation in the database to ascertain whether there was stroke recurrence within 30 days after the onset of the initial stroke; thus, these patients were eligible to be included in this study.

The subtype of the initial stroke was determined based on the patients' neurological, radiological, cardiological, and hematological profiles, principally according to the TOAST subtype classification system [7]: large-artery atherosclerosis (atherothrombotic), cardioembolism, small-artery occlusion (lacunar), and stroke of other determined or undetermined etiology. Patients were diagnosed as having a recurrent stroke based on the occurrence of additional neurological deficits or the progression of neurological deficits in conjunction with the appearance of a new infarct or hematoma that corresponded to the deficits; radiological confirmation was useful for differentiating stroke recurrence from progressing stroke. The patients' baseline characteristics and features of the initial stroke are listed in table 1. The severity of white matter lesions and periventricular hyperintensity was scored using scales developed in previous studies [8, 9]. Independent activity of daily living before the initial stroke corresponded to a modified Rankin Scale (mRS) score of 0 and 1. Patient outcome at discharge was evaluated using the mRS.

Values are expressed as mean ± SD. The baseline characteristics and stroke features were compared between patients with and without stroke recurrence using the χ^2-test, paired t test, and Mann-Whitney's U test, as appropriate. To identify the independent predictors of stroke recurrence, a multivariate logistic regression analysis was done using the baseline characteristics and stroke features that showed a statistically significant ($p < 0.05$) or a marginally significant ($0.05 \leq p < 0.15$) relationship with recurrence on univariate analyses as independent variables, with adjustments for age and gender. If >20% of patient data for a particular characteristic was missing on univariate analysis, then that characteristic was not used in the multivariate analysis. We also determined which stroke subtypes were independently related to recurrence.

Results

Of the 8,036 patients that were studied, 395 patients (4.9%) had a recurrent stroke within 30 days after the initial stroke. Recurrent strokes were most frequent in atherothrombotic stroke patients (174/2,645, 6.6%), followed by patients with cardioembolic stroke (143/2,318, 6.2%), stroke of other etiology (36/630, 5.7%), and lacunar stroke (42/2,443, 1.7%). Of the 254 patients in whom the day of

Cardioembolic stroke			Lacunar stroke			Stroke of other etiology		
recurrent	nonrecurrent	p value	recurrent	nonrecurrent	p value	recurrent	nonrecurrent	p value
143	2,175		42	2,401		36	594	
73.9 ± 11.8 (143)	73.9 ± 11.3 (2,175)	0.9873	71.2 ± 10.8 (42)	69.4 ± 11.5 (2,401)	0.3162	69.0 ± 13.6 (36)	66.4 ± 15.6 (594)	0.3191
58.5 (142)	55.0 (2,172)	0.4194	57.1 (42)	59.9 (2,398)	0.7195	55.6 (36)	63.6 (594)	0.3290
31.4 (137)	27.7 (2,119)	0.3451	39.0 (41)	29.7 (2,346)	0.1942	27.8 (36)	25.7 (584)	0.7806
61.0 (141)	52.5 (2,166)	0.0501	69.0 (42)	66.5 (2,398)	0.7259	52.8 (36)	51.0 (590)	0.8374
16.2 (142)	17.8 (2,160)	0.6325	23.8 (42)	28.5 (2,389)	0.5000	8.3 (36)	17.1 (590)	0.1692
14.0 (136)	14.4 (2,134)	0.8934	26.2 (42)	26.8 (2,355)	0.9302	16.7 (36)	19.2 (588)	0.7053
73.9 (142)	70.7 (2,170)	0.4150	4.9 (41)	5.3 (2,390)	0.9018	2.8 (36)	5.9 (590)	0.4300
14.8 (135)	14.6 (2,078)	0.9529	15.4 (39)	8.9 (2,295)	0.1635	2.8 (36)	9.2 (579)	0.1897
3.0 (135)	0.8 (2,078)	0.0091	2.6 (39)	0.9 (2,295)	0.2670	2.8 (36)	2.1 (579)	0.7753
1.5 (135)	0.4 (2,078)	0.0933	0.0 (39)	0.1 (2,295)	0.8213	0.0 (36)	0.5 (579)	0.6651
5.9 (119)	3.8 (1,880)	0.2500	2.6 (38)	4.2 (1,968)	0.6379	0.0 (34)	4.9 (546)	0.1842
0.0 (119)	1.3 (1,880)	0.2150	0.0 (38)	1.6 (1,968)	0.4281	0.0 (34)	1.5 (546)	0.4773
8.8 (133)	8.2 (2,005)	0.5503	16.2 (37)	9.0 (2,166)	0.1275	14.7 (34)	8.8 (582)	0.2413
27.3 (128)	30.6 (1,936)	0.4338	44.4 (36)	40.7 (2,128)	0.6450	35.3 (34)	42.0 (567)	0.4427
21.1 (95)	15.6 (1,427)	0.1561	0.0 (29)	3.7 (1,874)	0.2925	10.0 (20)	4.7 (402)	0.2898
20.0 (95)	16.5 (1,427)	0.3817	24.1 (29)	17.8 (1,874)	0.3789	5.0 (20)	18.4 (402)	0.1258
53.2 (141)	44.2 (2,166)	0.0371	57.1 (42)	48.7 (2,398)	0.2783	44.4 (36)	40.3 (590)	0.6263
1.4 (142)	2.4 (2,160)	0.4634	4.8 (42)	5.1 (2,389)	0.9292	2.8 (36)	1.5 (590)	0.5607
75.0 (76)	78.3 (1,081)	0.5068	75.0 (20)	84.3 (1,454)	0.2609	84.6 (13)	78.6 (299)	0.6029

stroke recurrence was documented, 162 patients (63.8%) developed a recurrence within the initial 7 days post onset (fig. 1). Of the 294 patients for whom the recurrent stroke type was documented, 280 patients (95.2%) had an ischemic stroke.

Baseline clinical characteristics and features of the initial stroke for all patients and by subtype are shown in tables 1 and 2. Overall, compared to patients who did not have a recurrent stroke, patients who had an early recurrence more frequently had: a previous ischemic stroke ($p = 0.0222$), hypertension ($p = 0.0188$), atrial fibrillation ($p = 0.0001$), antiplatelet ($p = 0.0052$) and antihypertensive ($p = 0.0017$) medication prior to the initial stroke, and progression of symptoms within 48 h ($p < 0.0001$).

Overall, on multivariate analysis, hypertension and atrial fibrillation were independently related to early stroke recurrence (table 3). In atherothrombotic stroke patients, diabetes mellitus and atrial fibrillation were independently related to recurrence. In cardioembolic stroke patients, hypertension and aortic aneurysm were independently related to recurrence. No independent predictors for early recurrence could be identified in patients with a lacunar stroke and in those with a stroke of other etiology.

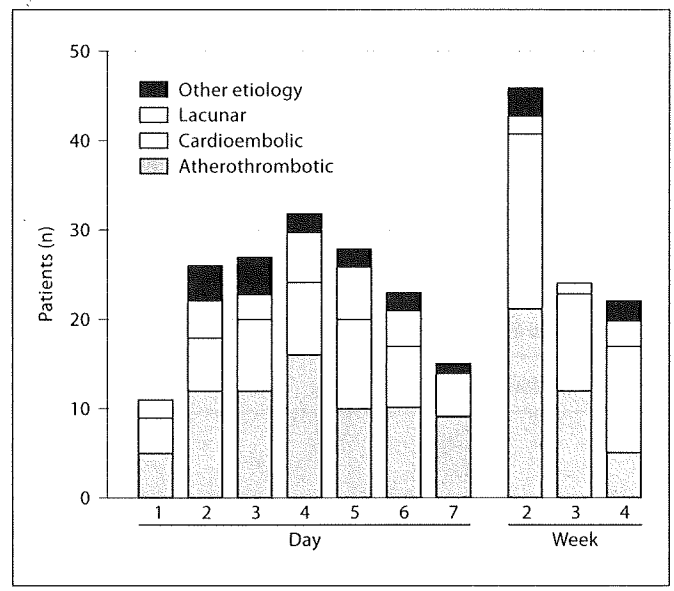

Fig. 1. Timing of stroke recurrence after stroke onset according to the initial stroke subtypes.

Table 2. Initial stroke features

	All patients			Atherothrombotic stroke		
	recurrent	nonrecurrent	p value	recurrent	nonrecurrent	p value
Patients	395	7,641		174	2,471	
Admission NIHSS	4 (0–36) (368)	4 (0–36) (7,155)	0.8779	4 (0–36) (164)	5 (0–36) (2,361)	0.0218
Admission NIHSS ≥8, %	38.0 (368)	33.7 (7,155)	0.0890	28.7 (164)	34.1 (2,361)	0.1514
Vertebrobasilar infarcts, %	20.3 (370)	19.6 (7,191)	0.7646	22.4 (161)	25.1 (2,367)	0.4308
White matter lesions, grade	0.96 ± 0.85 (273)	0.94 ± 0.87 (4,907)	0.8029	1.08 ± 0.89 (119)	1.04 ± 0.85 (1,561)	0.6814
Periventricular hyperintensity, grade	1.16 ± 1.00 (273)	1.11 ± 1.03 (4,878)	0.4416	1.32 ± 1.08 (120)	1.22 ± 1.00 (1,558)	0.2930
Admission systolic blood pressure, mm Hg	161.2 ± 29.1 (395)	160.1 ± 27.8 (7,641)	0.4264	163.7 ± 28.2 (169)	160.8 ± 27.0 (2,391)	0.1856
Admission diastolic blood pressure, mm Hg	86.5 ± 17.8 (395)	87.3 ± 16.5 (7,641)	0.3161	87.5 ± 16.2 (169)	86.7 ± 15.7 (2,391)	0.5431
Acute progression within 48 h after admission, %	31.8 (384)	18.1 (7,606)	<0.0001	30.8 (169)	23.9 (2,460)	0.0429

Numbers in parentheses indicate the number of patients whose data were available.

Table 3. Multivariate analysis of independent predictors for acute recurrence

Items	p value	OR	(95% CI)
Total (n = 8,036)			
Previous ischemic stroke	0.1089	1.205	(0.959–1.513)
Hypertension	0.0110	1.348	(1.071–1.696)
Atrial fibrillation	0.0011	1.503	(1.177–1.918)
Admission NIHSS ≥8	0.8162	1.029	(0.811–1.305)
Atherothrombotic (n = 2,645)			
Previous ischemic stroke	0.5258	1.117	(0.793–1.574)
Hypertension	0.0788	1.383	(0.963–1.984)
Diabetes mellitus	0.0222	1.485	(1.058–2.085)
Atrial fibrillation	0.0051	1.998	(1.231–3.244)
Admission NIHSS	0.0664	1.022	(0.999–1.046)
Cardioembolic (n = 2,318)			
Hypertension	0.0255	1.529	(1.053–2.218)
Aortic aneurysm	0.0147	4.070	(1.318–12.566)
Peripheral artery disease	0.0868	3.955	(0.820–19.092)
Vertebrobasilar infarcts	0.0749	1.579	(0.955–2.610)
Lacunar (n = 2,443)			
Alcohol consumption	0.0822	2.377	(0.895–6.313)
Admission SBP	0.2602	0.993	(0.981–1.005)
Admission NIHSS ≥8	0.2866	1.646	(0.658–4.116)

SBP = Systolic blood pressure.

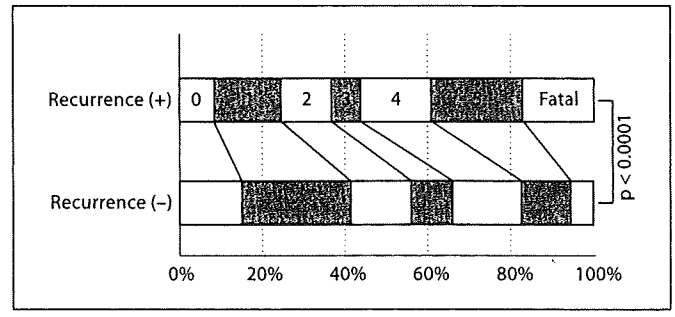

Fig. 2. Modified Rankin Scale score on discharge.

Among stroke subtypes, atherothrombotic stroke and stroke of other etiology were positive independent predictors for early recurrence after adjustment for age, gender, previous ischemic stroke, hypertension, atrial fibrillation, and a National Institute of Health Stroke Scale (NIHSS) score on admission ≥8; the last four characteristics showed a statistically significant ($p < 0.05$) or a marginally significant relationship ($p < 0.15$) with overall recurrence on univariate analyses (table 4). Lacunar stroke was a negative independent predictor for early recurrence. After adjustment, cardioembolic stroke was no longer positively related to recurrence, since, in this stroke subtype, atrial fibrillation has a strong association with recurrence.

At discharge, the median mRS score was higher in patients with recurrence than in those without a recurrence (3 vs. 2, $p < 0.0001$, fig. 2); for each stroke subtype, the median mRS score was also higher in patients with recurrence than in those without a recurrence (atherothrombotic stroke, 4 vs. 2, $p = 0.0021$; cardioembolic stroke, 5 vs. 3, $p < 0.0001$; lacunar stroke, 2 vs. 1, $p = 0.0286$; stroke of other etiology, 4 vs. 2, $p = 0.0064$).

Discussion

This study, which was based on a large sample of Japanese patients, confirmed the previous consensus that atherothrombotic stroke, hypertension, and atrial fibril-

Cardioembolic stroke			Lacunar stroke			Stroke of other etiology		
recurrent	nonrecurrent	p value	recurrent	nonrecurrent	p value	recurrent	nonrecurrent	p value
143	2,175		42	2,401		36	594	
9 (0–36) (132)	10 (0–36) (1,980)	0.9271	3 (0–13) (39)	3 (0–30) (2,279)	0.1028	4 (0–28) (33)	4 (0–35) (535)	0.4583
58.3 (132)	60.4 (1,980)	0.6378	20.5 (39)	11.7 (2,279)	0.0921	24.2 (33)	27.1 (535)	0.7192
15.9 (138)	10.7 (2,079)	0.0584	23.7 (38)	20.5 (2,249)	0.6247	24.2 (33)	27.0 (496)	0.7277
0.80 ± 0.81 (97)	0.84 ± 0.85 (1,415)	0.6727	0.89 ± 0.80 (27)	0.97 ± 0.90 (1,548)	0.6236	1.03 ± 0.81 (30)	0.78 ± 0.87 (383)	0.1260
0.99 ± 0.94 (96)	0.98 ± 0.99 (1,407)	0.8946	1.00 ± 0.83 (27)	1.18 ± 1.08 (1,533)	0.4009	1.20 ± 1.00 (30)	0.89 ± 1.04 (380)	0.1121
158.3 ± 29.7 (134)	157.6 ± 28.6 (2,061)	0.7619	170.0 ± 32.7 (40)	162.7 ± 27.4 (2,320)	0.0968	150.4 ± 23.1 (35)	154.9 ± 27.7 (552)	0.3455
85.3 ± 18.8 (134)	86.6 ± 17.3 (2,061)	0.4107	90.2 ± 21.5 (40)	89.1 ± 16.5 (2,320)	0.6704	81.8 ± 15.7 (35)	85.6 ± 16.1 (552)	0.1728
33.6 (140)	16.3 (2,163)	<0.0001	35.0 (40)	14.3 (2,391)	0.0003	25.7 (35)	15.5 (592)	0.1116

Table 4. Stroke subtypes as predictors for acute recurrence

Stroke subtype	Unadjusted (n = 8,036)		Adjusted 1 (n = 8,026)		Adjusted 2 (n = 7,318)	
	p value	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)
Atherothrombotic stroke	<0.0001	1.647 (1.343–2.021)	<0.0001	1.631 (1.328–2.003)	<0.0001	1.942 (1.537–2.453)
Cardioembolic stroke	0.0010	1.426 (1.155–1.761)	0.0018	1.407 (1.135–1.743)	0.2390	1.213 (0.879–1.674)
Lacunar stroke	<0.0001	0.260 (0.188–0.359)	<0.0001	0.263 (0.190–0.364)	<0.0001	0.246 (0.172–0.352)
Stroke of other etiology	0.3345	1.190 (0.836–1.693)	0.2440	1.235 (0.866–1.762)	0.0343	1.502 (1.030–2.190)

Adjusted 1 = Adjusted for age and gender; adjusted 2 = adjusted for age, gender, previous ischemic stroke, hypertension, atrial fibrillation, and admission NIHSS ≥8.

lation contribute to early ischemic stroke recurrence [1–3]. In addition, the analysis by each stroke subtype clarified that diabetes mellitus was independently related to early recurrence in patients with an atherothrombotic stroke.

It has been reported that within 30 days after the initial attack, stroke recurs in 1.5–6% of patients overall [1, 2, 10–12], and in up to 18.5% of atherothrombotic patients [2]. The wide variance in the risk of recurrent stroke might be partly due to differences in subjects' background characteristics, including ethnic differences, in the various studies. In this study, as well as in previous studies, recurrent stroke was found to be mostly ischemic and to occur mainly within the initial week [1, 11, 13].

The predictors of recurrent stroke may be time-specific and may differ between early and late recurrences [1]. In particular, diabetes mellitus is an established predictor of a late (>3 months after onset) recurrence [10, 11, 13]; however, its contribution to early recurrence has not been established. In this study, only among atherothrombotic stroke patients was diabetes mellitus more frequent in patients with a recurrent stroke than in patients without a recurrent stroke; in patients with the other three stroke subtypes, the prevalence of diabetes mellitus was equal or relatively less in patients with a recurrence than in patients without a recurrence. It would seem to be difficult to explain these apparently paradoxical results. However, diabetes increases intrinsic platelet activation, decreases endogenous inhibitors of platelet activity [14, 15], augments blood coagulability, and impairs fibrinolysis [16, 17]; these hemostatic abnormalities enhance local thrombus formation in the carotid and large cerebral arteries, which would appear to trigger the recurrence of atherothrombotic stroke. In addition, autonomic diabetic neuropathy is strongly related to stroke [18, 19]; patients with autonomic neuropathy appear to have a high risk of hemodynamic accidents, including orthostatic hypotension [20]. Thus, diabetes may enhance the risk of hemodynamic stroke recurrence in patients with large artery disease.

The contribution of an aortic aneurysm to cardioembolic stroke recurrence may be partly due to the statistical

limitation of this study, as there was only a small number of cardioembolic patients who had aortic aneurysms (only 20 of 2,318 patients).

A major limitation of this study was that around 20% of the acute stroke patients registered in the JSSRS were not included because their data regarding the presence of early stroke recurrence were incomplete. As well, for some patients included in this study, data on baseline characteristics and stroke features were missing, which affected the multivariate analyses. Another limitation was that some of the subanalyses related to recurrent stroke types (ischemic or hemorrhagic) were not done due to lack of information on the types for some of the patients. However, the present results primarily reflect the characteristics of ischemic recurrent strokes, since most (95.2%) of the 294 patients whose recurrent stroke type was documented had an ischemic stroke. Finally, in this study, we did not assess vascular lesions (extracranial or intracranial) or serological markers of hemostasis and infection, because the database did not require them, though early recurrence may be dependent on these conditions.

The management of risk factors during the acute stage of stroke may be essential for the prevention of stroke recurrence. In hypertensive patients, acute treatment with an angiotensin type 1 receptor blocker has been shown to decrease late (>12 months) recurrent stroke and cardiovascular events [21]. Likewise, acute blood glucose control may help prevent stroke recurrence. For example, the European Stroke Initiative Guidelines proposed that temporary insulin treatment may be necessary for acute ischemic stroke patients [22]. A randomized, controlled pilot study involving 25 patients indicated that rigorous glycemic control using sliding scale insulin is feasible and well tolerated after acute ischemic stroke [23]. Prospective studies are needed to establish the best acute management of the risk factors that are associated with early stroke recurrence.

Acknowledgments

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Case Report

Cerebrovascular Diseases

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Progressive Stroke Involving Bilateral Medial Medulla Expanding to Spinal Cord due to Vertebral Artery Dissection

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Pain and numbness around the right posterolateral part of the neck developed in a 38-year-old Japanese man without vascular risk factors 2 weeks after carrying a child on his shoulders. Two weeks thereafter, vertigo and nausea developed, accompanied by a sharp pain in the right side of the neck, and he was quickly taken to a local hospital.

On the following day (day 1), quadriplegia developed immediately after anteflexion of the neck and the patient was transferred to our hospital. Upon admission, he was alert and well oriented. He had conjugated deviation with horizontal nystagmus on both lateral gazes, mild dysarthria and dysphagia. His tongue was normal. Quadriplegia was predominant on the left side. Deep tendon reflexes were increased and the Babinski reflexes were bilaterally positive. Touch, pain, and temperature sensations were diminished with marked hyperesthesia on both sides of the face and extremities. Joint and vibratory sensation was preserved. No other physical findings were remarkable. An MRI examination demonstrated a high intensity area in the lower medulla oblongata expanding to the upper cervical cord and axial images showed that the lesion involved the ventral half of the bilateral medial medulla oblongata and upper cervical cord, with partial dorsal extension (fig. 1A–F). The right vertebral artery (VA) was indistinct according to MR angiography (MRA) (fig. 1G, H). Doppler sonography revealed absent diastolic flow in the right VA, indicating occlusion of the right VA before branching of the posterior inferior cerebellar artery.

Based on MR and Doppler findings, he was diagnosed as having the bilateral medial medullocervical infarction due to right VA occlusion possibly due to dissection. He was continuously perfused with intravenous sodium heparin (10,000 units/day) together with intravenous glycerol and edaravone, a free radical scavenger. Intravenous methylprednisolone was administered for 3 days (total 1,200 mg) to suppress local cellular edema and save the microcirculation. His symptoms rapidly improved, and only mild left hemiparesis persisted by day 3. Immediately after anteflexion of the neck on day 4, however, he fell into a deep coma with complete quadriplegia and ataxic respiration requiring mechanical ventilation. Repeated MRI revealed no additional infarcts. Cerebral angiography showed that the right VA tapered off and finally occluded at the level of the foramen magnum. The sudden progression of the arterial occlusion suggested that dissection was the etiology. The anterior spinal artery (ASA) could not be identified. Fat-suppressed T_1-weighted images showed a high crescent signal intensity surrounding the narrowed lumen of the right VA at the C1-C2 level (fig. 1F), suggesting an intraluminal hematoma due to dissection.

We immobilized his neck in a collar to prevent further progression of the arterial dissection by neck flexion. He regained consciousness and respiration recovered to normal on day 5. Quadriplegia and sensory deficits gradually improved and an MRA on day 29 showed that although stenotic and indistinct, the right VA was recanalized (fig. 1I, J). A Doppler sonogram on the same day showed that diastolic flow had recovered in the right VA. On day 77, he was discharged without need of living assistance, with the single residual effect being a neurogenic bladder.

Discussion

This patient was unique in two aspects. Firstly, unilateral VA dissection was the etiological mechanism of the bilateral medullocervical infarction. Secondly, anteflexion of the neck repeatedly triggered symptomatic deterioration probably by progressing the dissection.

Bilateral medial medullary infarction (MMI) might develop due to unilateral VA dissection from the point where an unpaired ASA branches off as an anatomical variation. However, systematic clinical studies have shown that of 12 patients with bilateral MMI among 126 with any MMI [1–7], only 1 patient developed stroke caused by unilateral VA dissection. The lower medulla that is usually supplied by the ASA was less the preferential site of MMI, and only 2 of the 12 patients with bilateral MMI described in previous reports had infarcts extending to the cervicomedullary junction, but not to the cervical cord [1, 5].

We applied anticoagulation to prevent the progression of brainstem ischemia under appropriate control of blood pressure and used radiological examinations to exclude aneurysmal changes in the cranial arteries. In addition, our experience revealed the importance of considering neck immobilization for acute stroke management due to VA dissection. Because the VA at the level of cervicomedullary junction is often compressed by neighboring structures [8], neck flexion and extension might mechanically stimulate a fragile artery in the absence of direct injury. Although the initial Doppler examination already indicated the VA occlusion, the neck anteflexion on day 4 might block the subtle anterograde flow via the narrow true lumen or the flow via the collat-

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