Table 3. Age- and multivariate risk-adjusted relative risk (RR) of recurrence or death in 1,466 stroke survivors within 3 years after the onset

	Age-adjusted			Multivariate risk-adjusted		
	RR	95% CI	p	RR	95% CI	p
Sex (female/male)	1.04	0.84–1.30	0.71	1.13	0.90–1.41	0.31
History of TIA (no/yes)	1.33	0.98–1.80	0.063	1.38	1.02–1.88	0.031
HT (no/yes)	1.12	0.89–1.41	0.34	1.20	0.94–1.53	0.15
DM (no/yes)	1.27	1.00–1.60	0.042	1.17	0.92–1.49	0.21
HLP (no/yes)	1.07	0.85–1.35	0.55	1.05	0.83–1.34	0.68
IHD (no/yes)	1.38	1.04–1.83	0.026	1.40	1.04–1.87	0.024
AF (no/yes)	1.60	1.26–2.01	0.0001	1.52	1.19–1.95	0.001
Rankin scale (good: 0–2/poor: 3–5)	2.73	2.15–3.47	<0.0001	2.64	2.07–3.37	<0.0001

Multivariate risk-adjusted = adjusted for all other risk factors; CI = confidence intervals.

The present study involves several limitations, such as concerns for data consistency or observation bias associated with data collection over a long period of time, as well as biases related to the selection of patients in a hospital-based study. The number of admitted male patients was about twice that of females in this study in contrast to other studies [6, 7], which should be taken into account in the interpretation of the results. We re-examined risk profiles as well as diagnoses of stroke subtypes in all the patients based on the criteria described above.

Changes in the distribution of stroke subtypes in the two age groups were similar to those in the two time periods, indicating that an increase in the elderly population influenced the alteration in the distribution of stroke subtypes in the recent decade. Although the frequency of ABI in the recent decade was comparable with that in the initial decade, the responsible lesions were changed by the time trends. The higher frequency of extracranial lesions in the recent decade, which is consistent with the findings in patients with ABI in Western countries, would be due to recent changes in risk profiles in Japan. The proportion of underlying cardiac diseases in CEI has changed during the study period. The most frequent cardiac source of emboli was nonvalvular AF, and 25% of patients with CEI had rheumatic heart disease, which decreased in prevalence in recent years. Treatment strategies have also changed during these 20 years. Thrombolytic therapy has not been approved by the government in Japan. More patients were given antithrombotic agents early after the stroke onset in the recent decade compared with the initial decade. Besides, therapeutic measures against HT and HLP have been improved during these 20 years. Although the recurrence-free survival rate within the initial year was not significantly different between the initial and recent decades, it was difficult to clarify the net effects of the changes in those variables on the long-term prognosis.

We analyzed the long-term prognosis within 3 years, and calculated the recurrence rate within 1 year after the index stroke by each stroke subtype in order to avoid an observation bias. Although a selection bias of patients may exist in hospital-based stroke registries, they allow us to obtain precise clinical data in consecutive stroke patients. Potential embolic sources were intensively investigated in patients with possible CEI, and vascular evaluations were performed in every patient. Laboratory data or blood pressure readings considered normal at the time of data collection might now be at levels where treatment options would also be considered.

The distribution of stroke subtypes in the present study was quite different from that in North America and Europe [8–11], while risk profiles by stroke subtypes were not so different from those in Western countries. LI was the most common subtype in this study, which is similar to other previous observations in Asia [12, 13]. The mean hospital stay was much longer than that reported from Western countries [6, 7, 10]. The longer hospital stay in Japan was also reported by Yoneda et al. [14], which may be attributed to a social security system including universal health insurance, and to differences in medical care or health care systems. An increase in the elderly population and a decrease in the number of children in recent years in Japan are driving forces in the need to establish well-organized medical care systems with a policy of early hospital

discharge. The outcome at discharge in this study was close to those reported in studies in stroke units in Europe at 3 months [6, 7].

One third of recurrent strokes during the observation period occurred within 1 year after the index stroke. The stroke recurrence rate within 1 year after the index stroke was 5–10%, depending on the stroke subtype, which was lower than that in other reports [8, 11, 15]. In patients with BH, 26 out of 350 patients recurred within 3 years after the index stroke; this annual recurrence rate of 2.5% is comparable with that in a recent study [16].

We identified a history of TIA, IHD, AF, and disability at discharge as significant risk factors for recurrence or death. IHD and AF were reported to be significant risk factors for recurrence-free survival [17]. Several studies have demonstrated that stroke patients with AF had higher mortality after the index stroke [18, 19], probably due to more severe initial neurological impairment [19], which was also ascertained as an independent predictor for recurrence or death in the present study. Heart disease, rather than stroke, caused death in stroke survivors in our study, although we could not distinguish patients who died of IHD from those who died of other cardiac causes.

In conclusion, the recurrence rate was different among stroke subtypes within 1 year after the index stroke. IHD, presence of AF, a history of TIA, and disability at discharge were important determinants for stroke recurrence and death within 3 years after the first-ever stroke.

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Aortic Arch Atherosclerotic Lesions and the Recurrence of Ischemic Stroke

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Background and Purpose—Aortic arch atherosclerotic lesions are often associated with embolic brain infarction. We investigated the relationship between stroke recurrence and the characteristics of aortic arch atherosclerotic lesions.

Methods—Among 487 stroke patients who underwent transesophageal echocardiography, 283 patients with brain embolism diagnosed without significant occlusive lesions (≥50%) in their cerebral arteries were included in this study. We measured the intima-media thickness (IMT) and evaluated the extension and mobility of the aortic arch atherosclerotic lesions. During a mean follow-up period of 3.4 years, we investigated the relationship between stroke recurrence and the various characteristics of the aortic arch atherosclerotic lesions.

Results—An IMT ≥4.0 mm was found in 67 patients (25.3%). In 51 of these patients, the aortic lesions extended to the origin of the branches of the arch. Recurrences of cerebral ischemic events were found in 32 patients (recurrence group) and not in the other 251 (nonrecurrence group). Aortic atheroma ≥4.0 mm (41% versus 22%), aortic atheroma extending to the branches (63% versus 39%), and both (38% versus 16%) were more frequently seen in the recurrence group than in the nonrecurrence group ($P<0.05$, $P<0.1$, $P<0.01$, respectively). After adjustment for age and the presence of hypertension, an aortic atheroma that was ≥4.0 mm as well as extending to the branches was found to be an independent predictor of ischemic stroke recurrence (hazard ratio=2.42, $P<0.05$).

Conclusions—Stroke recurrence is associated with the severity of the atheroma (IMT ≥4.0 mm) and plaque extension to the branches. (***Stroke*. 2004;35:1426-1429.**)

Key Words: aorta ■ stroke ■ recurrence ■ echocardiography

Several studies using transesophageal echocardiography (TEE) reported that severe atherosclerotic lesions are frequently observed in the aortic arch in patients with brain infarction of unknown cause.[1-9] In these studies, a wall thickness ≥3 to 5 mm, the presence of ulceration, or the presence of a mobile aortic arch plaque was found to be associated with embolic brain infarction. Amarenco et al[8] found that ulcerated plaques at the aortic arch are independently associated with brain infarction of unknown cause. They also reported that the association between aortic plaques and ischemic stroke is particularly strong when the plaques are ≥4 mm in thickness.[9] Moreover, a previous study demonstrated that atherosclerotic plaques ≥4 mm thick at the aortic arch are significant predictors of recurrent brain infarction and other vascular events.[10] Jones et al demonstrated that a complex aortic atheroma ≥5 mm or an atheroma with mobile elements is an independent risk factor for ischemic stroke.[11] However, no study has yet evaluated the relationship between the extent of aortic arch atherosclerotic lesions and the occurrence of brain infarction.

Several studies reported the characteristics of aortogenic brain embolism. Otsubo et al[12] suggested that the size of brain infarction in aortogenic brain embolism was smaller than that in cardiogenic brain embolism. Mentel et al[13] reported that aortogenic brain embolism tends to occur relatively more commonly in the vertebrobasilar system. However, in addition to their aortic atheroma, many patients with embolic brain infarction also have heart disease or an occlusive disease in their cerebral arteries that can be an embolic source for their brain infarction. Therefore, it is difficult to determine the actual role of an aortic atheroma on an embolic brain infarction, especially in patients with other potential sources of emboli.

The purpose of the present study was to evaluate the relationship between the characteristics of aortic arch atherosclerotic lesions and brain infarction in a longitudinal follow-up study in patients both with and without heart disease as possible sources of emboli.

Materials and Methods

TEE studies were performed in 487 ischemic stroke patients from January 1995 to December 1998. Based on 4 vessel cerebral angiography, magnetic resonance angiography, and duplex carotid ultrasonography, 283 patients with brain embolism diagnosed and

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without significant occlusive lesions (≥50%) in the cerebral arteries were included in this study. There were 194 men and 89 women, with a mean age of 63.2±25 (mean±SD) years. Of the 283 patients, 239 had a completed ischemic stroke and 40 had transient ischemic attacks. The remaining 4 patients were admitted to our hospital because of headache, vertigo, dizziness, or head injury, and computed tomography revealed a silent territorial cortical infarction in all of them. TEE studies were performed for an embolic source. In addition to the TEE studies, electrocardiography or transthoracic echocardiography, or both, were performed to evaluate the heart for possible embolic sources, such as atrial fibrillation, sick sinus syndrome, mitral valve stenosis, prosthetic valves, cardiomyopathy, old myocardial infarction, atrial septal defect, patent foramen ovale, pulmonary arteriovenous fistula, and infectious endocarditis. At least 1 such heart disease was observed in 162 patients; the remaining 121 patients had no heart disease. The following cerebrovascular risk factors were investigated: hypertension (systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg), diabetes mellitus (fasting plasma glucose ≥126 mg/dL or plasma glucose at any time ≥200 mg/dL), and hypercholesterolemia (plasma total cholesterol ≥220 mg/dL).

We used a commercially available real-time 2-dimensional echocardiography system (model SSD-2200; Aloka) equipped with a 5.0-MHz phased array biplane or omniplane transesophageal transducer. We observed the aortic arch with both transverse and sagittal views. Focal increases in intima-media thickness (IMT) ≥1.1 mm were regarded as atheromatous plaques. We evaluated the maximum IMT, extension of the aortic lesions, and presence of any mobile plaque at the arch. We observed the aortic arch from the distal to the proximal portion with a sagittal view and tried to identify the origin of the 3 branches. We carefully evaluated to which branches the atheroma reached. When all 3 branches were visible, they were labeled the left subclavian artery, left common carotid artery, and innominate artery, respectively, from the distal portion. When the atheromatous plaque of ≥1.1 mm extended to at least 1 origin of the branch, we defined it as an extending atheroma.

Patients were treated with antiplatelet therapy (114 patients), anticoagulant therapy (149 patients), or both (5 patients). In all 283 patients, we observed the recurrence of ischemic stroke and all death through the outpatient clinic until July 2000. The mean follow-up period was 3.4±1.4 (mean±SD) years and the minimum follow-up period was 1.4 years. When a patient could not go to our hospital regularly because of some circumstances such as removal, discontinuing visits to our outpatient clinic, and so on, we searched the status by phone. We investigated the relationship between the characteristics of the aortic arch atherosclerotic lesions and stroke recurrence.

We used 2-tailed t tests and χ^2 tests to compare proportions. A 2-tailed $P<0.05$ was considered to indicate statistical significance. The data were analyzed using Statview software. The incidence of stroke recurrence was expressed per 100 person-years of follow-up. We used the Kaplan–Meier method to evaluate the distribution of time to events. Kaplan–Meier curves were compared using the log-rank test to detect a trend. We also constructed a proportional hazards model, which included risk factors of cerebrovascular disease and the characteristics of the aortic atheroma. The characteristics of the aortic atheroma included: model 1, IMT ≥4 mm; model 2, extension to at least 1 branch (extending atheroma); and model 3, both of these.

Results

A wall thickness ≥4.0 mm was found in 67 (25.3%) of the 283 patients. In 51 of these 67 patients (76%), the aortic lesions were both ≥4.0 mm and extending to the origin of at least 1 branch. An aortic atheroma ≥4.0 mm was found to be statistically significantly more likely to extend to branches compared with an atheroma <4 mm ($P<0.01$). A mobile plaque was observed in 5 patients and all of them had an aortic atheroma that was both ≥4.0 mm and extending to at least 1 branch. The baseline characteristics according to the IMT are shown in Table 1. Patients with an aortic atheroma ≥4.0 mm were significantly older ($P<0.001$) and had hypertension more frequently ($P<0.0001$). There was no significant difference in follow-up period between patients with and without an aortic atheroma ≥4.0 mm.

TABLE 1. Baseline Characteristics of Patients According to the Thickness of the Aortic Atheroma

	Thickness of the Aortic Atheroma		
Characteristics	≥4 mm (n=67)	<4 mm (n=216)	P
Age (y)	65.5±9.5	61.9±11.8	<0.001
Males (%)	52 (78)	142 (66)	NS
Observation period (y)	3.17±1.58	3.50±1.41	NS
Hypertension (%)	59 (88)	128 (59)	<0.0001
Diabetes mellitus (%)	17 (25)	37 (17)	NS
Hypercholesterolemia (%)	29 (39)	52 (24)	NS
Heart disease (%)	34 (51)	128 (59)	NS
Treatment			
Antiplatelet (%)	33 (49)	81 (38)	NS
Anticoagulant (%)	30 (45)	119 (55)	NS
Follow-up period (y)	3.1±1.6	3.5±1.4	NS

NS indicates not significant.

Using TEE, we were able to identify all 3 branches of the aortic arch in 87 (31%) patients, 2 branches in 114 (40%), 1 branch in 78 (28%), and no branch was detected in 4 (1%) patients. Among the 87 patients in whom we were able to evaluate the origins of all 3 branches, heart disease as a possible embolic source was present in 48 patients. In the other 39 patients without heart disease, 14 (36%) patients had an aortic atheroma ≥4.0 mm. The initial ischemic lesions were shown to be in the vascular territories of the branch to whose origin the aortic atheroma extended in 10 (71%) of the 14 patients.

We observed 32 patients with stroke recurrence during the follow-up period. Of these 32 patients, 13 had an aortic atheroma ≥4.0 mm and 20 had an extending atheroma. In the 13 patients with an atheroma ≥4.0 mm and stroke recurrence, 12 patients had an extending atheroma and 2 of these patients also had a mobile plaque. Patients who had stroke recurrence had an aortic arch atheroma ≥4.0 mm or atheroma that was ≥4.0 mm as well as extending to at least 1 branch more frequently than those who had not ($P<0.05$, $P<0.01$, respectively). Patients with stroke recurrence were significantly older than those without stroke recurrence ($P<0.01$) (Table 2). No other significant differences in baseline characteristics were observed between these patients. Four patients died during the follow-up period, 1 because of stroke recurrence, 1 because of subarachnoid hemorrhage, and the other 2 because of heart attacks.

Of the 33 patients who had an atheroma ≥4.0 mm without any heart disease as a possible embolic source, 6 had a recurrent stroke and all of them were treated with antiplatelet therapy without anticoagulant therapy. The aortic arch atherosclerotic lesions in these 6 patients extended to at least 1 branch. In the 3 patients in whom we were able to evaluate all

TABLE 2. Comparison Between Patients With and Without Stroke Recurrence

Characteristics	Stroke Recurrence (+) (n=32)	(−) (n=251)	P
Age (y)	68.6±8.9	62.5±11.7	<0.01
Males (%)	22 (69)	172 (69)	NS
Hypertension (%)	26 (81)	161 (64)	<0.1
Diabetes mellitus (%)	7 (22)	47 (19)	NS
Hypercholesterolemia (%)	9 (28)	72 (29)	NS
Heart disease (%)	21 (66)	141 (56)	NS
Treatment			
Antiplatelet (%)	13 (41)	101 (40)	NS
Anticoagulant (%)	16 (50)	133 (53)	NS
Aortic atheroma (%)			
4≥4 mm (%)	13 (41)	54 (22)	<0.05
Extending atheroma (%)	20 (63)	98 (39)	<0.1
Both (%)	12 (38)	39 (16)	<0.01

the branches at the aortic arch by TEE, all the recurrent ischemic lesions occurred in the territory of the branch to whose origin the aortic atheroma extended. Five of the 6 recurrent ischemic lesions were observed in the same vascular territory as the initial lesion. One patient had a mobile plaque.

The incidence of stroke recurrence was 9.1% per person-year in patients with an aortic atheroma ≥4.0 mm in comparison with 2.3% per person-year in patients with an atheroma <4 mm. The incidence of stroke recurrence was 9.8% per person-year in patients with an aortic atheroma extending to at least 1 branch, compared with 2.9% per person-year in patients without an aortic atheroma extending to at least 1 branch.

Age and the presence of hypertension that showed $P<0.1$ in the univariate analysis for predicting stroke recurrence (Table 2) were included into the multivariate analysis with the characteristics of the aortic atheroma. After adjusting for age and hypertension, the multivariate analysis revealed that the presence of an aortic atheroma that was ≥4.0 mm or extending to at least 1 branch was not an independent predictor of stroke recurrence (models 1 and 2 in Table 3). However, the presence of an aortic atheroma that was both ≥4.0 mm and extending to at least 1 branch was an independent predictor of stroke recurrence (hazard ratio=2.42; 95% CI: 1.12 to 5.21; $P<0.05$) (model 3 in Table 3). Age was an independent predictor of stroke recurrence in all these multivariate analyses. Kaplan-Meier curve analysis revealed a significant difference in the recurrence-free survival between patients with an atheroma, both ≥4.0 mm and extending to at least 1 branch, and other patients ($P<0.001$ by log-rank test) (Figure). When we divided the 283 patients into 2 groups; patients with heart disease as a possible embolic source and those without heart disease as a possible embolic source, Kaplan–Meier curve analysis revealed a significant difference in the recurrence-free survival between patients with an atheroma ≥4.0 mm and patients with an atheroma <4 mm, both in patients with and without heart disease as a possible embolic source ($P<0.05$ by log-rank test in both).

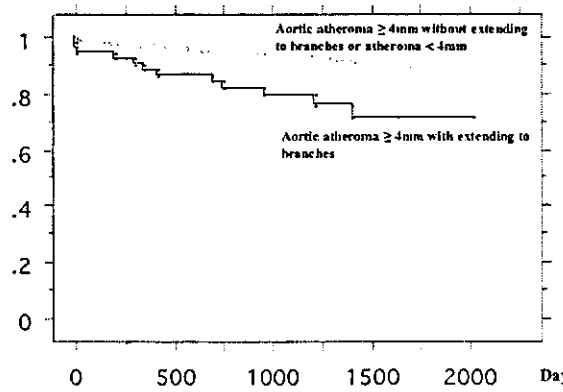
TABLE 3. Multivariate Analyses for Predicting Stroke Recurrence According to the Characteristics of Aortic Arch Atheroma

	Hazard Ratio	95% CI	P
Model 1			
Atheroma ≥4 mm	1.98	0.94–4.15	<0.1
Age	1.04	1.00–1.09	<0.05
Hypertension	1.44	0.57–3.68	NS
Model 2			
Atheroma extending to at least 1 branch	1.59	0.76–3.33	NS
Age	1.04	1.00–1.09	<0.05
Hypertension	1.53	0.60–3.85	NS
Model 3			
Aortic atheroma both ≥4 mm and extending to at least 1 branch	2.42	1.12–5.21	<0.05
Age	1.04	1.00–1.08	<0.05
Hypertension	1.37	0.53–3.52	NS.

Discussion

The present results show that an aortic atheroma ≥4.0 mm can be a significant predictor for recurrent ischemic stroke and are similar to those of The French Study of Aortic Plaques in Stroke Group. Our incidence of stroke recurrence was 9.1% per person-year in patients with an aortic atheroma ≥4.0 mm compared with 2.9% per person-year in patients with an atheroma <4.0 mm.

In univariate regression, an aortic atheroma ≥4.0 mm can be a significant predictor for recurrent ischemic stroke. We also evaluated the extension of the aortic atheroma using TEE. An association between the extension of the aortic atheroma to the branches and ischemic stroke has not previously been demonstrated. Our multiple regression analysis showed that an aortic atheroma ≥4.0 mm that also extended to at least 1 branch was a more significant predictor than an



Recurrence-free survival. Kaplan-Meier analysis of survival without stroke recurrence according to the thickness and extension of the aortic atheroma. A significant difference in recurrence-free survival was observed between patients with atheroma both ≥4.0 mm and extending to branches and those without ($P<0.001$ by log-rank test).

atheroma that did not extend to the branches. Kaplan-Meier curve analysis revealed a significant difference in the recurrence-free survival between patients with and without an atheroma both ≥4.0 mm and extending to at least 1 branch. We could observe all 3 branches at the aortic arch only in 31%, although at least 1 branch in 99%. This low value of 31% in detection rate of all 3 branches is a limitation of our study, which may cause difficulty in analysis of relationship between the extending atheroma and vascular territory of recurrence. However, it seems that our results showed some relationship between the extending atheroma and vascular territory of recurrence. Our 33 patients who had an atheroma ≥4.0 mm without any heart disease as a possible embolic source were diagnosed clinically as having a definite aortogenic brain embolism. Of these patients, 6 had a recurrent stroke. In these 6 patients, their aortic atheroma extended to at least 1 branch, and in 5 of these 6 patients, a recurrent stroke was observed in the same vascular territory as the initial stroke. Furthermore, in the 3 patients in whom we could evaluate all branches at the aortic arch with TEE, all the recurrent ischemic lesions were in the territory of the branch to whose origin the aortic atheroma extended. The vascular territory of aortogenic brain embolism could be related to which branch the aortic atheroma extended. Our results suggest that extension of the aortic atheroma to the branches is an important factor for stroke occurrence.

In the present study, no significant difference in the type of medical treatment (antiplatelet agents or anticoagulant agents) was observed between patients with and without stroke recurrence (Table 2). However, the incidence of stroke recurrence was 9.1% per person-year in patients with an aortic atheroma ≥4.0 mm and this incidence rate was lower than that found by The French Study of Aortic Plaques in Stroke Group (11.9% per person-year).[10] Our study included more patients that were being treated with anticoagulant agents (45% versus 20%). In fact, 30 of the 67 patients with aortic atheroma ≥4.0 mm were treated with anticoagulant agents. This difference was likely caused by the fact that more patients with heart disease as a possible embolic source were included in the present study than in The French Study of Aortic Plaques in Stroke Group. These factors could effectively explain the difference in the rate of stroke recurrence. The difference in the use of anticoagulants between the studies is interesting, but our study was not designed as a therapeutic trial.

Even in patients with heart disease as a possible embolic source, the presence of an aortic atheroma ≥4.0 mm was a significant predictor of stroke recurrence. Otsubo et al[14] suggested that an atherosclerotic lesion in the aortic arch is associated with a hypercoagulable state and that this might play an important role in the development and pathophysiology of thromboembolism. Thus, although an aortic atheroma itself is a possible embolic source, it might further increase the risk of intracardiac thrombus formation caused by the hypercoagulable state with which it is associated.

The present study revealed that a severe aortic atheroma has a significant association with ischemic stroke in patients with or without heart disease. Both the thickness and the extension of the aortic atheroma were found to be important factors for the occurrence of ischemic stroke. The optimal medical therapy (antiplatelet agents or anticoagulant agents) for patients with severe aortic atheroma remains to be determined by randomized trials.

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Analysis of 16,922 Patients with Acute Ischemic Stroke and Transient Ischemic Attack in Japan

A Hospital-Based Prospective Registration Study

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Key Words
Brain infarction · Transient ischemic attack · Prospective study · Stroke, acute · Stroke management

Abstract
Objective: The purpose of the present study was to clarify the present status of stroke medicine in Japan using a hospital-based, prospective registration study of 156 hospitals from all over Japan. ***Methods:*** Consecutive patients with acute ischemic stroke and transient ischemic attack (TIA) who presented to hospital within 7 days of onset from May 1999 to April 2000 were enrolled in this study. A common protocol was applied in every participating hospital. ***Results:*** A total of 16,922 patients (TIA, 6.4%) with a mean age of 70.6 ± 11.5 years (median 71 years, range 18–107 years) were enrolled in the study. Lacunar stroke was the most frequent stroke subtype (38.8%), followed by atherothrombotic (33.3%), cardioembolic (21.8%) and other stroke (6.1%). NIH stroke scale score on admission was 8.0 ± 7.9 (median 5; 25th to 75th percentile, 2–11). 36.8% arrived at hospital within 3 h of symptom onset, and 49.5% within 6 h. The ambulance was used for 70.2% of patients arriving within 3 h after onset, but in only 29.9% of patients visiting the hospital later than 3 h after onset ($p < 0.0001$). 60.8% displayed good outcome (modified Rankin Scale score of 0–2 at discharge), while 32.3% displayed poor outcome (score 3–5), and mortality rate was 6.9%. ***Conclusions:*** More than half of the acute stroke patients arrived at hospital later than 6 h after onset. Establishment of ideal emergency systems is needed for better management of stroke and for improvement of patient outcome, in particular, in the future after approval of intravenous recombinant tissue plasminogen activator for acute ischemic stroke by the Japanese government.

Although stroke mortality has gradually but markedly decreased during the last three decades in Japan [1], about 140,000 people died from stroke in 1999 [2]. The proportion of deaths from stroke was about 14.2% of the total national deaths, representing the third leading cause of death after total neoplasms and heart diseases [2]. Morikawa et al. [3] investigated secular trend in stroke incidence between 1977 and 1991 in Japanese rural areas, and reported that the proportion of brain hemorrhages among stroke decreased from 23.6 to 16.4%, whereas brain infarction increased from 64.1 to 73.6%. Kodama

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[4] also reported that the incidence of brain hemorrhage has decreased, while that of brain infarction has not. The number of patients with disability due to brain infarction may therefore have increased in recent decades.

Total medical expenses in Japan have been increasing annually reaching about 30.9 trillion yen (USD 350 billion) in 1999 [5]. Approximately 10% of these costs are attributable to stroke [6]. Stroke is the second most costly of all the diseases, and is the most costly in elderly people (≥65-year-olds) [6]. Medical expenses for stroke seem likely to continue increasing, leading to significant social problems including impacts on the health insurance system. To prevent and improve such circumstances, a clear understanding of the present status of stroke medicine is required, allowing analysis of the data for reconstruction of sociomedical systems. Therefore, we conducted a large prospective hospital-based registration study to make a database for acute ischemic stroke and transient ischemic attack (TIA) in 156 hospitals selected from approximately 5,000 hospitals throughout Japan.

Subjects and Methods

All the consecutive patients with acute ischemic stroke and TIA who were admitted within 7 days of onset to 1 of the 156 participating hospitals were registered to the central office, using the standardized common protocol and data sheets, for the 12-month period from May 1999 to April 2000. Thirteen collaborating members were selected from 7 districts according to juridical regions defined by the Ministry of Health, Labor and Welfare, Japan. About 20 hospitals, in which more than 50 acute ischemic stroke patients were treated between April 1997 and March 1998 were selected depending on population in each district: Hokkaido (20 hospitals); Tohoku (20 hospitals); Kanto (42 hospitals); Chubu (19 hospitals); Kinki (18 hospitals), Chugoku-Shikoku (18 hospitals), and Kyushu (19 hospitals). The involved departments in the participating hospitals comprised 82 neurosurgery, 54 neurology, 17 internal medicine, and 3 emergency departments. Among the 156 participating hospitals, there were 16 (10.3%) and 70 (44.9%) equipped specialized stroke care unit (SCU) and intensive care unit (ICU) services, respectively.

Diagnosis of acute brain infarction or TIA (≤7 days after onset) was made by a neurologist or neurosurgeon, and confirmed by computed tomography and/or magnetic resonance imaging in all registered patients. The following data were assessed prospectively in interviews of all patients or family members by doctors in each participating hospital during patient hospitalization and at the time of patient discharge, using common data sheets prepared by the protocol committee: (1) age and gender; (2) activity at onset (resting, working, sleeping, and unknown), and time and place of onset (home, office, outdoor, hospital, and other); (3) history of stroke; (4) stroke subtype [clinical categories of ischemic stroke [7]: lacunar, atherothrombotic (presence of arterial stenosis or occlusion caused by atherosclerosis), cardioembolic, and other]; (5) method of transportation to hospital (ambulance, unaided, assisted by family, already hospitalized, or other); (6) clinical symptoms at onset and NIH stroke scale (NIHSS) score [8] on admission; (7) time from onset to arrival at hospital; (8) use of thrombolytic agent and therapy within 7 days after onset; (9) cardiovascular risk factors [hypertension (HT), diabetes mellitus (DM), hyperlipidemia (HL), atrial fibrillation (AF) and current smoking]; (10) ward (SCU, ICU or general ward); (11) outcome at discharge, and (12) length of hospital stay.

The doctor in charge of each participating hospital reported the number of stroke and TIA admissions to the central office by fax at the end of every month. Documented data sheets were mailed to the central office within 1 month after patient discharge. If the central office judged the data as 'incomplete' due to insufficient description, the data sheets were mailed back to and revised by the doctor in charge, then remailed to the central office.

The patients' self-report of having HT, the use of antihypertensive agents, or a systolic blood pressure ≥160 mm Hg or diastolic blood pressure ≥95 mm Hg before onset were defined as HT. DM was defined according to the patients' self-report of DM, the use of oral hypoglycemic agents or insulin, fasting blood glucose levels ≥126 mg/dl, or glycosylated hemoglobin (HbA_{1c}) level ≥6.4% after acute stage. HL was defined according to the use of antihyperlipidemic agents or serum cholesterol level ≥220 mg/dl and/or triglyceride ≥150 mg/dl. The current smoking status was determined by patient report, and AF was diagnosed by electrocardiographic findings.

Information of clinical symptoms at stroke onset was obtained from patients, patients' family or ambulance staffs and was assessed as follows: reduced consciousness level, speech disturbance, headache, nausea/vomiting, vertigo/dizziness, visual, motor weakness, sensory and gait disturbances, and convulsion.

We investigated the application of thrombolytic agents [intravenous or intra-arterial urokinase (UK) and recombinant tissue plasminogen activator (rt-PA)], and medical (heparin, aspirin, ticlopidine, and warfarin) and surgical (decompression craniotomy, carotid endarterectomy, stenting, and percutaneous transluminal angioplasty) treatment within 7 days of stroke onset.

Patient outcome at discharge was evaluated by attending physicians from the participating hospital using the modified Rankin scale (mRs) [9]. Death was assigned an mRs score of 6.

Statistical analyses were performed using the commercially available Stat-View software version 4.5 (ASA Institute, Cary, N.C., USA). The Mann-Whitney U test or Kruskal-Wallis test were applied to detect differences in age, NIHSS score and length of hospital stay among subgroups. All other findings were assessed using the χ^2 test. Multivariate logistic regression models were utilized to identify factors associated with early hospital arrival, defined as arrival at hospital within 3 h of symptom onset. The following variables were chosen for inclusion as independent variables: age, sex, history of stroke, use of ambulance and clinical symptoms at onset. Furthermore, mRs scores of 0–2 and 3–6 at discharge were identified as good and poor outcome, respectively. Multivariate logistic regression models for poor outcome were created for all patients except for those with TIA. The following variables which were thought to be related to the patient's outcome at discharge were chosen for inclusion as independent variables: age (continuous), sex, HT, DM, HL, AF, history of stroke, nonlacunar stroke, admission ward, thrombolytic therapy, anticoagulants and antiplatelets within 7 days of stroke onset, and NIHSS score >6. Differences were considered statistically significant at the level of $p < 0.05$.

Table 1. Baseline characteristics of stroke and TIA patients

Characteristics		Stroke (n = 15,831)	TIA (n = 1,091)
Mean (median) age, years		70.7 (71)	69.5 (70)
Age groups, %	<45	1.9	2.9
	45–54	7.6	9.3
	55–64	19.5	19.7
	65–74	33.2	34.5
	75–84	28.2	24.3
	>84	9.8	9.3
Male sex, %		61.3	61.3
History of stroke, %		31.2	32.2
Patients' activity at onset, %	Moving	42.7	56.8
	Rest	34.0	31.8
	Sleep	13.4	8.0
	Unknown	9.9	3.4
Place of onset, %	Home	79.5	71.3
	Office	4.0	6.2
	Outside	9.2	14.5
	Hospital	4.4	5.6
	Others	2.9	2.4
Hospital arrival time, %	<3 h	35.4	56.3
	3–6 h	12.6	13.5
	6–12 h	10.4	7.5
	12–24 h	13.3	8.7
	>24 h	28.3	14.0
Use of ambulance, %		43.8	38.2
Risk factors, %	Hypertension	61.2	56.2
	Diabetes mellitus	24.7	18.7
	Hyperlipidemia	16.6	19.2
	Atrial fibrillation	21.1	17.0
	Smoking	17.3	20.1
Clinical symptoms at onset, %	Reduced consciousness level	25.2	18.5
	Speech disturbance	46.3	36.4
	Headache	3.5	2.2
	Nausea/vomiting	6.8	8.2
	Vertigo/dizziness	8.4	11.9
	Visual disturbance	4.3	5.0
	Motor weakness	70.9	64.7
	Sensory disturbance	15.3	23.8
	Gait disturbances	37.5	13.9
	Convulsion	0.7	0.6
Mean (median) NIHSS score at admission		8.3 (5)	2.9 (1)
NIHSS scores, %	0–6	57.4	86.6
	7–10	15.4	6
	11–15	9.9	4.5
	16–40	17.2	2.9
Stroke subtype, %	Lacunar stroke	38.8	**
	Atherothrombotic	33.3	**
	Cardioembolic	21.8	**
	Other	6.1	**
mRs score at discharge, %	mRs 0	14.4	78.8
	mRs 1	30.1	11.2
	mRs 2	14.1	2.9
	mRs 3	8.8	2.3
	mRs 4	15.1	3.4
	mRs 5	10.1	1.1
Case fatality rates, %	Death within 7 days	3.0	0
	Death within 28 days	5.1	0.1
Length of hospital stay; mean, SD, median		35, 34, 25	14, 12, 11

Results

During the study period, a total of 17,728 stroke or TIA patients were registered. We excluded 806 patients due to protocol violations such as double registration (n = 446), no accurate documentation of date and time of onset (n = 237), nonstroke patients (n = 2), visit later than 7 days of onset (n = 16), age under 15 years old (n = 8), and stroke onset after the study period (n = 97). Thus, 16,922 patients [10,370 men (61.3%), 6,552 women (38.7%)] were enrolled in the study. Patients were managed by neurosurgeons (49.4%), neurologists (43.5%), internists (9.3%) and emergency doctors (0.5%). The mean number of patients ± standard deviation (SD) for the participating hospitals was 111.3 ± 74.5 (median 102; range 1–490; 25th to 75th percentile, 61–142).

15,831 patients (93.6%) were diagnosed as having stroke, and 1,091 (6.4%) patients as having TIA, respectively. Table 1 shows baseline characteristics, including age, sex, history of stroke, activity at onset, place where event occurred, time from onset to hospital arrival, use of ambulance, risk factors, clinical symptoms, NIHSS score on admission, stroke subtype, mRs score at discharge, mortality at 7 and 28 days, and length of hospital stay.

Age

Mean age of the patients ± SD was 70.6 ± 11.5 years (median 71, range 18–107). Women were significantly older than men (mean age 73.6 ± 11.7, median 75, range 18–100 vs. mean age 68.7 ± 11.0, median 69, range 18–107; $p < 0.0001$). In 11,321 patients with first-ever stroke or TIA, the mean age of the patients ± SD was 69.6 ± 12.1 years (median 70, range 18–107). Again women were significantly older than men (mean age 72.8 ± 12.2, median 74, range 29–100, n = 4,492 vs. mean age 67.4 ± 11.5, median 67, range 18–102, n = 6,829; $p < 0.0001$).

Stroke Subtype

Lacunar stroke was the most frequent stroke subtype (38.8%), followed by atherothrombotic (33.3%), cardioembolic (21.8%) and other stroke (6.1%). Table 2 shows characteristics by stroke subtype.

Use of Ambulance

With regard to arrival at the hospital, 43.3% of patients were transferred by an ambulance, 17.0% arrived unaided using public transport or a private car, and 36.9% presented with assistance from family members. Excluding the 354 patients who developed stroke or TIA during hospitalization, the ambulance was used for 70.2% of patients

Table 2. Characteristics by stroke subtypes

Characteristics	Lacunar (n = 6,146)	Atherothrombotic (n = 5,267)	Cardioembolic (n = 3,451)	Other (n = 967)	p
Mean (median) age, years	69.6 (70)	70.8 (71)	73.5 (74)	66.0 (68)	<0.0001
Male sex, %	62.0	63.1	58.1	57.9	<0.0001
Hospital arrival within 3 h of stroke onset, %	22.2	33.0	61.5	40.0	<0.0001
Mean (median) NIHSS score at admission	4.5 (4)	8.7 (6)	14.7 (14)	8.2 (5)	<0.0001
History of stroke, %	31.1	31.7	31.8	27.2	0.405
Thrombolytic therapy, %	0.1	1.4	10.8	2.5	<0.0001
Admission ward, %					<0.0001
Stroke care unit	2.6	5.2	10.6	13.9	
Intensive care unit	6.0	14.1	25.3	13.4	
General ward	90.4	80.7	64.2	72.7	
mRs score at discharge, %					<0.0001
mRs 0–2	76.3	51.7	36.7	60.9	
mRs 3–5	22.6	41.4	44.8	29.8	
Mortality, %	1.1	6.9	18.6	10.3	<0.0001
Risk factors, %					
Hypertension	67.4	65.9	45.1	53.7	<0.0001
Diabetes mellitus	26.0	30.0	16.1	17.4	<0.0001
Hyperlipidemia	19.2	18.6	9.1	15.4	<0.0001
Atrial fibrillation	4.0	7.3	75.7	9.4	<0.0001
Smoking	20.0	19.3	10.0	15.4	<0.0001
Mean (median) day of length of hospital stay	29.0 (20)	40.0 (29)	40.5 (29)	31.4 (22)	<0.0001

χ^2 test used except for age, NIHSS score and length of hospital stay, for which the Kruskal-Wallis U test was used.

arriving within 3 h after onset, but in only 29.9% of patients visiting the hospital later than 3 h after onset ($p < 0.0001$).

NIHSS on Admission

The mean NIHSS score ± SD was 8.0 ± 7.9 (median 5; 25th to 75th percentile, 2–11). In the 5,607 stroke patients admitted within 3 h of onset, the mean NIHSS score ± SD was 11.9 ± 9 (median 10; 25th to 75th percentile, 4–8). Figure 1 shows the distribution of NIHSS scores for each stroke subtype. Median (25th to 75th percentile) NIHSS score was 4 (2–6) in lacunar stroke, 6 (3–12) in atherothrombotic, 14 (6–22) in cardioembolic, and 5 (2–11) in other stroke ($p < 0.0001$), respectively.

Time from Onset to Hospital Arrival

Patients admitted within 3 h of onset comprised 36.8%. Cumulative frequency was 49.5% within 6 h, 59.7% within 12 h, 72.7% within 24 h, 84.2% within 48 h, and 91.3% within 72 h. Frequency of early hospital admission <3 h after onset by stroke subtype was highest in cardioembolism ($p < 0.0001$). Mean NIHSS score ± SD was higher in patients arriving within 3 h of onset than in those arriving after 3 h (11.1 ± 9.3 vs. 6.2 ± 6.2; $p < 0.0001$). Multivariate logistic regression models demonstrated that the use of an ambulance (OR 3.4; 95% CI, 3.2–3.7), history of stroke (OR 1.1; 95% CI, 1.0–1.2), reduced consciousness level (OR 2.5; 95% CI, 2.3–2.7), speech disturbance (OR 1.1; 95% CI, 1.0–1.2), nausea/vomiting (OR 1.2; 95% CI, 1.0–1.4), motor weakness (OR 1.3; 95% CI, 1.2–1.4) and convulsion (OR 1.6; 95% CI, 1.1–2.5) were associated with early arrival at hospital.

Therapy within 12 h of Stroke Onset

477 patients (3.0%) were treated with thrombolytic agents in the preset survey, i.e. with intravenous rt-PA and UK (exceeding 200,000 IU) administration in 50 and 276, and with intra-arterial rt-PA and UK administration

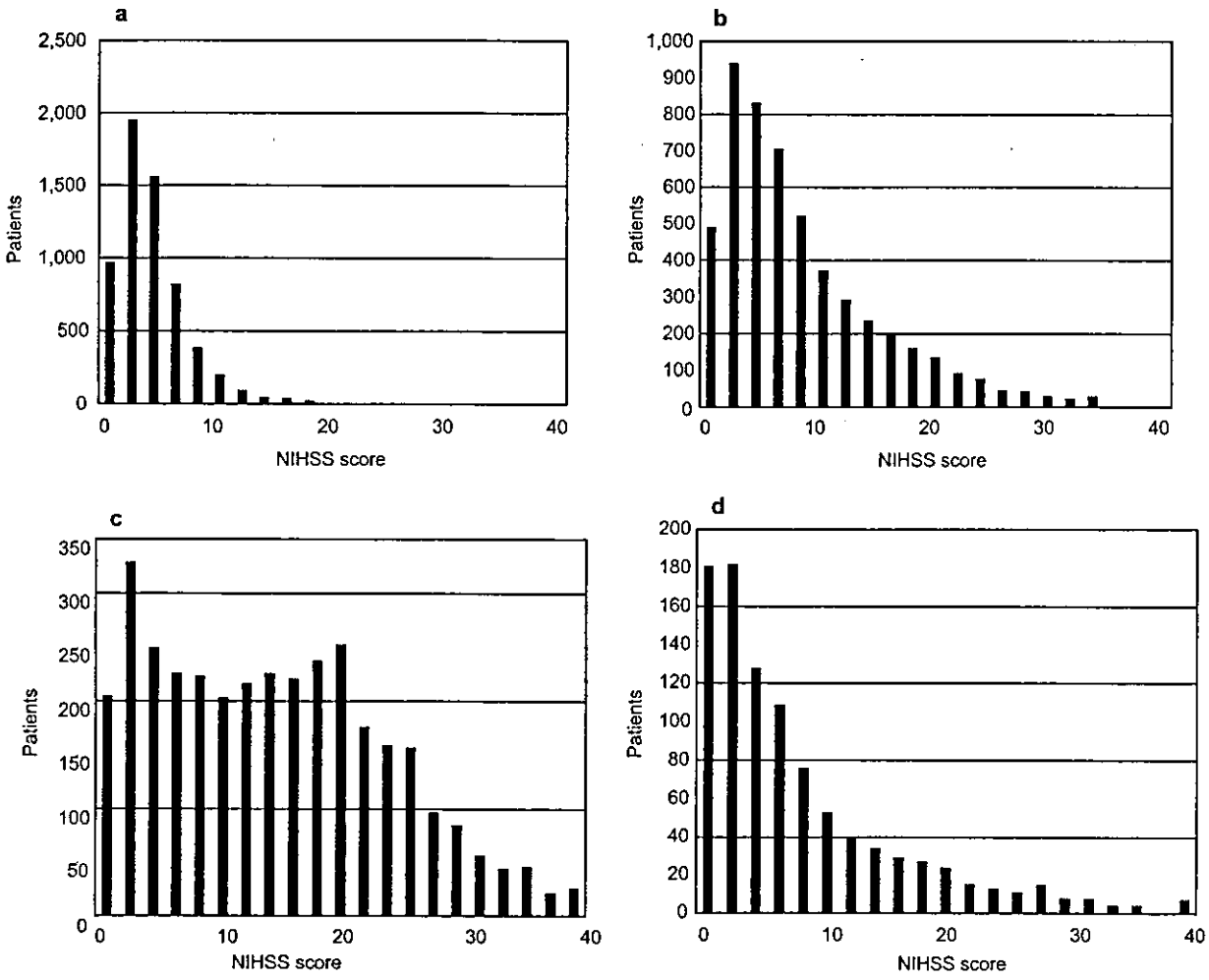

Fig. 1. Distribution of NIHSS scores for each stroke subtype. **a** Lacunar stroke. **b** Atherothrombotic stroke. **c** Cardioembolic stroke. **d** Other.

in 88 and 63, respectively. Of 5,607 acute stroke patients treated within 3 h of stroke onset, 415 (7.4%) were treated using thrombolytic therapy. Mean age ± SD of the patients treated with thrombolytic agents was 68.4 ± 10.7 years (median 69, range 20–107) and mean NIHSS score ± SD was 18.7 ± 8 (median 18, 25th to 75th percentile;12–24). Analyses by different thrombolytic agent (UK/rt-PA) and route of application (i.v./i.a.) were not performed because of a small number of patients in each category.

Therapy within 7 Days of Stroke Onset

Heparin (16.3%) was the most commonly used, followed by ticlopidine (14.1%), and aspirin (10.3%). Surgical treatment was performed in 262 patients (1.6%), with decompression craniotomy in 106 patients, percutaneous transluminal angioplasty in 54, carotid endarterectomy in 41, carotid stenting in 13 and miscellaneous surgical procedures in 69.

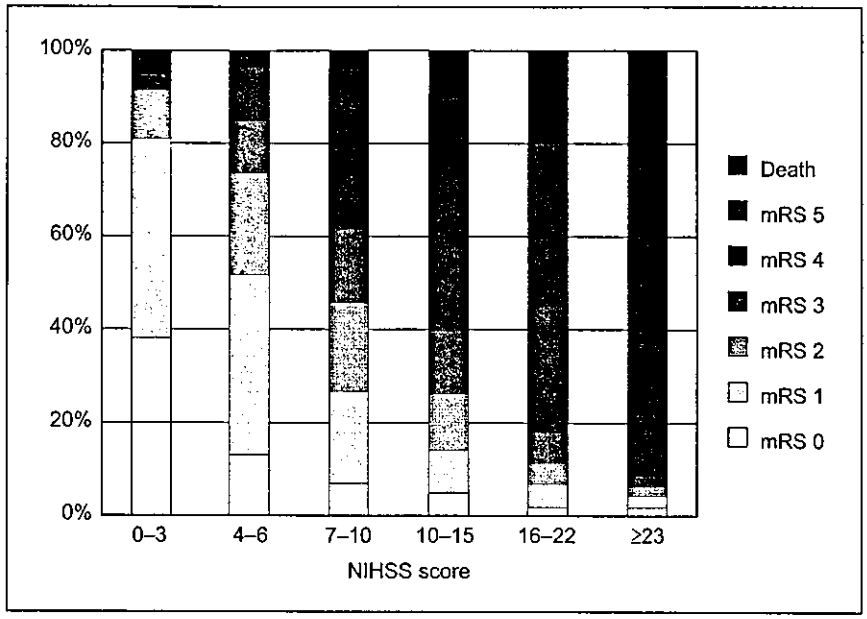

Fig. 2. NIHSS score at admission and mRs score at discharge.

Admission Ward

Patients were most commonly admitted to general wards (81.3%), followed by ICUs (12.9%) and SCUs (5.8%). No significant difference in age was observed among the three groups (SCU: 70.5 ± 11.6 years; ICU: 71.2 ± 11.8 years; general ward: 70.6 ± 11.4 years; p = 0.4819). However, NIHSS scores for general ward admission (mean ± SD; 7.2 ± 7.3, 25th to 75th percentile; 2–9) were significantly lower than those for SCU (10.9 ± 8.4, 4–16) or ICU (14.6 ± 9.8, 6–22) admission ($p < 0.0001$).

Outcome at Hospital Discharge

The distribution of mRs scores at discharge was as follows: 18.5% scoring 0, 28.9% scoring 1, 13.4% scoring 2, 8.4% scoring 3, 14.4% scoring 4, 9.6% scoring 5, and 6.9% scoring 6 (i.e., dead). Good outcomes (mRs 0–2) were attained for 58.6% of stroke patients. Frequency of good outcome at discharge was highest for lacunar stroke (76.3%), followed by other (60.9%), atherothrombotic (51.7%), and cardioembolic stroke (36.6%) ($p < 0.0001$). Figure 2 shows the relationship between NIHSS score on admission and mRs score at discharge. In stroke patients excluding TIA, multivariate logistic regression models demonstrated that female, increased age, DM, history of stroke, nonlacunar stroke, NIHSS score >6, and ICU admission represented independent factors associated with poor outcome at discharge (table 3).

Discussion

In the present study, lacunar stroke was the most frequent stroke subtype, followed by atherothrombosis and cardioembolism. In a community-based epidemiological study in Hisayama, Japan, stroke-free subjects (n = 1,621) were followed for 32 years from 1961. A total of 298 ischemic stroke patients were identified, with lacunar stroke diagnosed in 56%, atherothrombosis stroke in 21%, and cardioembolism in 19% [10]. The proportion of lacunar stroke in Japan exceeds that reported in Western countries [11–14]. Japanese people are considered to be at higher risk for arteriosclerosis of intracranial small arteries compared with Caucasians [15]. However, although the present study was hospital based, the proportion of lacunar stroke among all ischemic stroke cases was somewhat lower, while the proportion of atherothrombosis was higher compared to the results of the Hisayama study [10]. This may indicate that the incidence of lacunar stroke has been decreasing, or that atherothrombosis has been increasing, or both. Another Hisayama study [16] reported that the proportion of hypertensive patients in the population of Hisayama town had not changed since 1960, although pharmacotherapies had resulted in a reduced level of HT from severe to mild. HT represents the most important risk factor for ischemic stroke, and for lacunar stroke in particular [17]. We assume that lifestyle including dietary habits has been changed or westernized

Table 3. Univariate analysis and multivariate logistic regression analysis models for probability of good outcome (mRs of 0–2), and poor outcome (mRs of 3–5 and death)

Variable	Univariate analysis[1]			Multivariate logistic regression for poor outcome		
	good	poor	p	OR	95% CI	p
Female sex	34.0%	45.5%	<0.0001	1.35	1.238–1.477	<0.0001
Mean (SD) age, years	67.9 (11.1)	74.6 (10.8)	<0.0001	1.05	1.044–1.053	<0.0001
Hypertension	62.6%	59.2%	<0.0001	0.94	0.894–1.062	0.556
Diabetes mellitus	24.9%	24.4%	0.435	1.29	1.167–1.415	<0.0001
Hyperlipidemia	19.1%	13.1%	<0.0001	0.80	0.714–0.899	0.0002
Atrial fibrillation	14.2%	30.8%	<0.0001	0.91	0.815–1.018	0.0987
Current smoking	20.8%	12.5%	<0.0001	0.91	0.805–1.020	0.1017
History of stroke	26.7%	37.7%	<0.0001	1.48	1.358–1.621	<0.0001
Nonlacunar stroke	47.3%	52.7%	<0.0001	1.67	1.518–1.837	<0.0001
NIHSS score >6	25.6%	74.4%	<0.0001	10.38	9.512–11.336	<0.0001
Admission						
Stroke care unit	4.6%	7.6%	<0.0001	1.11	0.937–1.322	0.223
Intensive care unit	8.0%	21.0%	<0.0001	1.75	1.545–1.983	<0.0001
Thrombolytic therapy	5.6%	9.0%	<0.0001	0.76	0.611–0.950	0.0157
Heparin	13.1%	21.0%	<0.0001	1.07	0.954–1.204	0.2436
Antiplatelet (aspirin or ticlopidine)	24.7%	15.1%	<0.0001	0.65	0.583–0.720	<0.0001

[1] Mann-Whitney U test was used for age. χ^2 test was applied for the remainder.

in recent years, and improved medical management of HT may have reduced the proportion of lacunar stroke among ischemic stroke in Japan.

The efficacy of thrombolytic therapy, intravenous rt-PA in particular, in acute ischemic stroke has been proven in recent trials [18–20]. Although we could not make analyses by different thrombolytic agent (UK/rt-PA) and route of application (i.v./i.a.) because of a small number of patients in each category, the present study also suggests that the use of thrombolytic agents is associated with good outcome. However, rt-PA administration has not yet been approved for acute ischemic stroke by the Ministry of Health, Labor and Welfare in Japan, and rt-PA therefore cannot officially be used for acute ischemic stroke. Intra-arterial UK mainly within 6 h thus remains the standard thrombolytic therapy for acute ischemic stroke patients.

Barber et al. [21] reported that 27% of 1,168 ischemic stroke patients were admitted within 3 h of symptom onset, and of these, 26.7% received rt-PA. Overall, only 7.1% of ischemic stroke patients in their hospital received rt-PA. Chiu et al. [22] also stated that only a small percentage of acute stroke patients received this therapy. The major reason for these results on thrombolytic therapy is the short therapeutic time window. In the present study, 1,043 stroke patients (6.6%) arrived at hospital from 3 to 6 h of stroke onset without using an ambulance. They may have been excluded from intravenous rt-PA administration according to the guidelines for thrombolytic therapy outlined by the American Heart Association [23] because of delayed hospital arrival. If the use of an ambulance can reduce the time to hospital arrival, some of these patients could be treated using thrombolytic therapy in the future after approval of intravenous rt-PA for ischemic stroke by the Japanese government.

Several studies have shown better outcomes for patients treated in an SCU rather than in a general ward, [24–26] and managements in SCUs have been strongly recommended in Europe. In the present study, ICU admission was associated with relatively poor outcome under multivariate regression analysis. In hospitals with an ICU but not SCU, stroke patients with severe complications such as pneumonia and cardiac failure were probably managed in the ICU. Thus, the higher proportion of poor outcomes and mortality in the ICU admission might be caused by a higher proportion of severely and critically ill patients admitted to ICU.

AF represents the most powerful and treatable cardiac precursor of ischemic stroke. In this study, 21% of patients displayed AF, a higher proportion than reported in previous hospital-based reports from Western and Asian countries [27–29]. Lin et al. [30] demonstrated that the

1-year survival rate was lower in patients with AF compared to those without AF. Primary and secondary prevention of embolic events are thus one of the most important issues for AF patients.

Some limitations are present in this study. A total of 156 hospitals with relatively large numbers of acute stroke admissions were selected from approximately 5,000 hospitals throughout Japan. Some selection bias may therefore exist in the study. Furthermore, nonhospitalized stroke and TIA patients were not evaluated, although the number of such patients is very small because of the well-organized health insurance system (universal medical care system) in Japan. Thus, our results cannot completely be considered representative of the total Japanese stroke population. Secondly, the patients' outcome was assessed at discharge. Therefore, there may be the potential bias introduced by different time periods.

In conclusion, this study demonstrated that more than half of the acute stroke patients arrived at hospital later than 6 h after onset. Establishment of ideal emergency systems is needed for better management of stroke and for improvement of patient outcome, in particular, after approval of intravenous rt-PA for ischemic stroke patients by the Japanese government.

Appendix 1

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Early neurological deterioration represents recurrent attack in acute small non-lacunar stroke

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Abstract

The aim of this study was to identify the frequency and possible pathogenic mechanisms of early neurological deterioration in patients with acute small non-lacunar infarction. We studied 46 patients (35 men, 11 women; age, 70.3 ± 10.4 years) with acute small non-lacunar infarction. Small non-lacunar infarction was diagnosed using diffusion-weighted magnetic resonance imaging (DWI) as being <15 mm in diameter and located in the cortex and centrum ovale in the middle cerebral artery (MCA) territory. The patients were divided into two groups; Group D ($n=6$) had neurological deterioration within 7 days after symptom onset, while Group N ($n=40$) did not have any neurological deterioration. In Group D, the interval from symptom onset to clinical deterioration was 3.3 ± 1.5 days (range 2–6 days). Blood pressure on admission was higher in Group D than in Group N ($p<0.05$). In Group D, four of these five patients with follow-up DWI had new acute small ischemic lesions in addition to the initial lesions, indicating recurrent attacks of brain infarction. Neurological deterioration occurred within 7 days after symptom onset in 13% of patients. Neurological deterioration was frequently caused by recurrent infarction detected by DWI.

Keywords: Acute stroke; Small non-lacunar infraction; DWI; Neurological deterioration; Recurrent stroke

1. Introduction

Early neurological deterioration is a common event in acute stroke, being 20–40% in frequency [1]. In stroke patients with moderate-to-severe neurological deficits, European Cooperative Acute Stroke Study (ECASS) I reported that the incidence of early and late progressing stroke was 37.5% and 20.3% [2]. The cause of the progressing stroke is often explained by the development of brain edema associated with an brain infarct [2]. In lacunar infarction with mild neurological deficits, the incidence of a progressive course during the acute phase of stroke is also observed in 24–36% of patients [3–5]. The impairment of the microcirculation in penetrating artery may play a major role in this phenomenon. However, there is still no precise knowledge of the cause of progression and we are unable to predict patients at risk. Therefore, it is important to advance the search for the underlying pathogenic mechanisms of neurological deterioration in acute stroke patients.

Recently, we reported that symptomatic small non-lacunar infarcts (small centrum semiovale infarcts and cortical infarcts) were more frequently associated with large vessel disease and cardioembolism than lacunar infarcts [6,7]. We concluded that the mechanism of stroke in this form of infarction was often embolic from artery or heart, and should be differentiated from lacunar infarction, which is a small vessel disease.

Recurrent infarction must be considered as one potential cause of neurological deterioration following stroke. However, it is often difficult to distinguish progressing stroke from a recurrent attack. Neuroimaging may help the diag-

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nosis of a recurrent attack. If neuroimaging can display new lesions separately to the initial lesions, we can diagnose the patient as having a recurrent attack.

Diffusion-weighted imaging (DWI) is a powerful tool for detecting recent small ischemic lesions, particularly in the centrum ovale or cortex [6,8]. We experienced a patient with neurological deterioration in small non-lacunar infarcts, whose follow-up DWI study revealed new small infarcts in addition to the initial infarcts, indicating recurrent attacks. Therefore, we hypothesized that neurological deterioration during the acute phase in patients with small non-lacunar infarcts might be caused by recurrent attacks.

To the best of our knowledge, the frequency and mechanisms of neurological deterioration in patients with small non-lacunar infarcts remain unclear. We studied consecutive patients with small non-lacunar infarcts to solve the above-mentioned problems using DWI.

2. Materials and methods

The aim of this study was firstly to examine the frequency of neurological deterioration within 7 days after symptom onset in patients with small non-lacunar infarcts. Second, we compared clinical characteristics between patients with and without neurological deterioration. Furthermore, in patients with neurological deterioration, we performed a follow-up DWI study to detect new small ischemic lesions in addition to the initial lesions after deterioration.

We enrolled consecutive patients with small non-lacunar infarction admitted to our division of National Cardiovascular Center within 7 days of symptom onset between January 2000 and February 2002 into the present study. DWI was performed within 7 days of symptom onset to detect acute ischemic lesions.

Small non-lacunar infarcts were defined as follows: (1) lesions on DWI were acute; (2) diameter of the lesions was smaller than 15 mm; and (3) lesions were located in the cortex or centrum ovale [9]. An infarct situated in the corona radiata, putamen, globus pallidus, and internal capsule, which are supplied by the deep perforating arteries of the middle cerebral artery (MCA), were excluded from this study [9,10].

We assessed the neurological severity on admission using National Institutes of Health Stroke Scale (NIHSS) score [11] and handicap at discharge using modified Rankin scale (mRS) [12]. Neurological deterioration was diagnosed when NIHSS score increased ≥ 2 points from the baseline NIHSS score during the 7 days after symptom onset. The mode of deterioration was classified into four subgroups; abrupt, stepwise, fluctuating and linear slope-like. Patients were classified into two groups; patients displaying neurological deterioration (Group D), and those without any neurological deterioration (Group N).

MR imaging studies were conducted for all patients within 7 days after symptom onset. When patients had neurological deterioration, a follow-up DWI study was conducted. MR imaging was performed using a Siemens MAGNETOM Vision 1.5-T MR unit with echo-planar capability. DWI was performed simultaneously using a multislice, single-shot, spin echo planar imaging sequence in all patients within 7 days of symptom onset. Diffusion gradients were applied in each of the x-, y-, and z-axes with two b values (0 and 1000 s/mm^2). Fluid-attenuated inversion recovery (FLAIR, TR/TE, 9000/105) images was carried out simultaneously with DWI. The criterion for the diagnosis of acute infarcts on DWI was focal hyperintensity, judged not attributable to normal anisotropic diffusion or magnetic susceptibility artifacts.

Vascular risk factors were identified as follows: (1) use of antihypertensive agents, or systolic blood pressure >160 mm Hg or diastolic blood pressure >95 mm Hg on admission for hypertension; (2) use of oral hypoglycemic agents or insulin, or glycosylated hemoglobin (HbA1C) >6.4% for diabetes mellitus; (3) use of antihyperlipidemic agents or serum cholesterol level >220 mg/dl for hypercholesterolemia.

We carried out color-flow duplex carotid ultrasonography, conventional cerebral angiography, and magnetic resonance angiography (MRA) to evaluate arterial diseases in the carotid system. Color-flow duplex carotid ultrasonography (Toshiba SSA 270A, Toshiba Inc., Tokyo, Japan, or Ultramark 9 HDI, ATL, Bothel, WA) was performed in all patients as a routine test. The grade of arterial stenosis was determined according to the criteria used in the North American Symptomatic Carotid Endarterectomy Trial (NASCET) [13]. Arterial diseases were considered significant when stenosis >70%, occlusion, or ulceration were evident in the ipsilateral carotid system. In addition, the peak systolic blood flow velocity in the internal carotid artery (ICA) greater than 200 cm/s on ultrasonography was considered equivalent to ICA stenosis >70% for the NASCET criteria [14].

To detect an emboligenic cardiac disease, all patients were examined using 12-lead electrocardiography (ECG), 24-h ECG monitoring, and transthoracic echocardiography (TTE). Additionally, we conducted transesophageal echocardiography (TEE) to evaluate patent foramen ovale (PFO) and atherosclerosis of the aortic arch (aortic complicated plaque). Emboligenic cardiac diseases included non-valvular atrial fibrillation (NVAF), mitral stenosis, left ventricular aneurysm, prosthetic cardiac valves, dilated cardiomyopathy, and PFO. An aortic complicated plaque was considered significant as a plaque ≥ 4 mm or mobile plaque in the aortic arch visualized on TEE [15].

Statistical analysis was performed using a commercially available software package (Stat-View, version 5.0; SAS Institute, Cary, NC). Univariate analyses were performed by the Fisher exact test or Chi square test and the Mann–

Table 1
Demographic and clinical feature of patients of Group D

Age/Sex	Day of deterioration	Mode of deterioration	NIHSS score			Site of lesion (distribution, number)		Potential embolic source
			On admission	Before deterioration	After deterioration	Initial DWI	Follow-up DWI (after deterioration)	
						Initial lesion	Additional lesion	
77/M	2	abrupt	7	7	9	Lt MCA (cortex and subcortex), multiple	no change	Lt ICA 50% stenosis with ulceraion, Ao.
57/M	6	abrupt	7	7	13	Rt MCA (subcortex), Lt MCA (cortex), multiple	Rt MCA (subcoetex), single	Ao.
66/M	2	stepwise	5	5	9	Rt MCA (subcortex), Lt MCA (cortex, subcortex), multiple	Lt MCA (subcoetex), single	Bilateral ICA 70% stenosis, Ao.
78/M	3	stepwise	6	4	9	Rt MCA (cortex and subcortex), multiple	Rt MCA (cortex and subcortex), multiple	Rt.ICA 90% stenosis
81/F	3	stepwise	2	2	6	Lt MCA (subcortex), multiple	NA	NVAF, Ao.
74/M	4	fluctuating	6	6	8	Lt MCA (subcortex), multiple	Lt MCA (subcortex), single	>50% MCA stenosis

Ao.: aortic complicated plaque, NVAF: non valvular atrial fibrillation, NA: not available.

Whitney U-test between the two groups. Values of $p < 0.05$ were considered statistically significant.

3. Results

A total of 404 patients with acute ischemic stroke or TIA were admitted to our division within 7 days after symptom onset, and 356 (88%) patients were performed DWI within 7 days after symptom onset. Out of them, 46 patients (35 men, 11 women) with a small non-lacunar infarct were enrolled into the present study. Age (mean ± S.D.) of the patients was 70.3 ± 10.4 years (median 72-years-old, range 38–87).

An initial DWI study showed a small ischemic lesion in 14 patients, and multiple lesions in 32 patients. In 14 patients with a single lesion, the lesion was located in the cortex in seven patients, and in the subcortex in the other seven patients. In the 32 patients with multiple lesions, the lesions were located only in the cortex in seven patients, only in the subcortex in seven patients, and in both the cortex and subcortex in the remaining 18 patients.

We performed conventional cerebral angiography in six patients (13%), MRA in 27 patients (59%), and both assessments in 12 patients (26%). Twenty-three patients (50%) had a significant arterial disease. The following arterial lesions were observed; MCA occlusion in one patient, more than 50% stenosis of the horizontal portion of the MCA in three, ICA occlusion in four, more than 70% ICA stenosis in 10, less than 70% ICA stenosis but with ulceration in two, more than 70% ICA stenosis and the anterior cerebral artery occlusion in one, and more than 70% stenosis of the ICA and horizontal portion of the MCA in two.

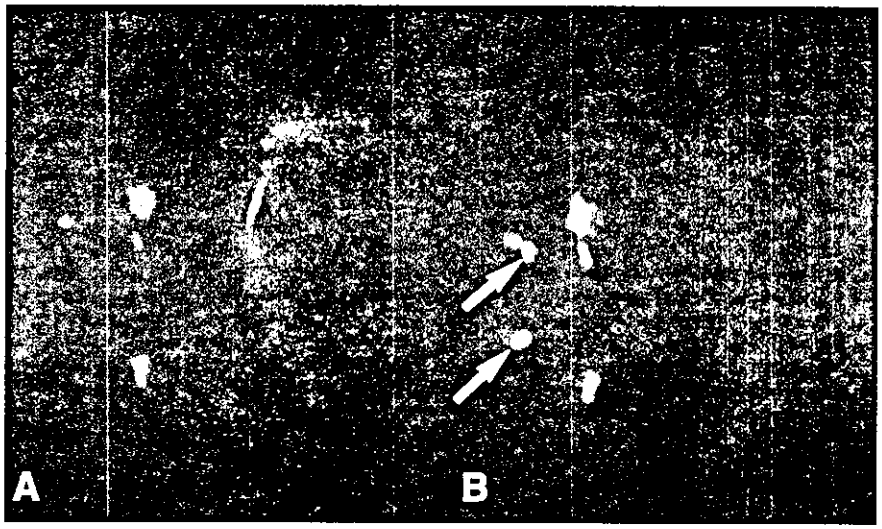

Fig. 1. A 78-year-old man presented with left hemiparesis and unilateral spatial neglect (USN). NIHSS score on admission was 6. Color-flow duplex carotid ultrasonography showed 90% stenosis in the right internal carotid artery. Diffusion-weighted imaging (DWI) on day 2 demonstrated acute small multiple ischemic lesions in the right hemisphere (A). He had stepwise deterioration with left sensory disturbance and hemiparesis from days 3 to 7. The NIHSS score increased from 4 (day 3) to 9 (day 7). Follow-up DWI on day 8 revealed additional acute ischemic lesions (B, arrows).

We conducted the TEE in 30 patients. Emboligenic cardiac diseases were detected in 22 (48%) patients; only NVAF in 10, only PFO in seven, left ventricular aneurysm with thrombus in two, both AF and a prosthetic mitral valve in one, and both NVAF and PFO in two. Aortic complicated plaques were detected in 17 patients. Overall, 41 patients (89%) had a potential embolic source.

Six patients (13%; Group D) had neurological deterioration, and 40 patients (87%; Group N) did not have any deterioration. The interval from symptom onset to neurological deterioration was 3.3 ± 1.5 days (range 2–6 days). No patients had neurological deterioration before the first MRI study. The mode was abrupt in two patients, fluctuating in one and stepwise in three. The demographic and clinical features of the six patients with neurological deterioration are summarized in Table 1. All patients had a potential embolic source. In the Group D, a follow-up MRI study was performed on all the patients except one, who declined an MRI test. Four of the five patients who underwent follow-up imaging had new acute ischemic lesions surrounding the initial lesions (Fig. 1). While the remaining one patient had no new lesions. In the Group N, a follow-up DWI study was performed in only one patient within 7 days of symptom onset. The patient did not have any new lesions except for initial lesions.

Table 2
Patient characteristics

	Group D $n=6$	Group N $n=40$	p
Age, years (mean ± S.D.)	72.2 ± 9.0	70.1 ± 10.7	0.65
Sex (M/F)	5/1	30/10	0.66
TIA within 7 days before symptom onset, *n* (%)	0	6(15)	0.58
Interval from symptom onset to admission, h (mean ± S.D.)	15.4 ± 13.4	17.9 ± 27.3	0.74
Interval from symptom onset to MRI study, h (mean ± S.D.)	32.7 ± 20.6	40.4 ± 42.4	0.76
NIHSS score on admission (median ± S.D.)	6 ± 2	3 ± 4	0.10
mRS at discharge (median ± S.D.)	2 ± 2	1 ± 1	0.73
Body temperature, °C	36.8 ± 0.6	36.3 ± 0.5	0.061
Systolic blood pressure, mm Hg	169.3 ± 22.1	146.4 ± 19.9	0.027
Diastolic blood pressure, mm Hg	90.7 ± 6.4	77.1 ± 10.0	0.0023
Laboratory parameters			
Serum glucose, mg/dl	109.0 ± 20.9	106.0 ± 21.1	0.74
Fibrinogen, mg/dl	384.2 ± 140.2	312.9 ± 70.7	0.22
Hematocrit, %	41.3 ± 6.9	40.3 ± 4.4	0.68
Blood-coagulation factors			
ATIII, %	91.0 ± 14.3	88.1 ± 13.6	0.55
D-Dimer, g/ml	3.0 ± 6.4	1.4 ± 1.7	0.29
TAT, mg/ml	2.9 ± 2.3	5.9 ± 11.0	0.94
Vascular risk factors, *n* (%)			
Hypertension	5(83.3)	33(82.5)	0.96
Diabetes mellitus	2(33.3)	14(35.0)	0.94
Hypercholesterolemia	2(33.3)	16(40.0)	0.76
Cigarette smoking	3(50.0)	17(42.5)	0.73
History of ischemic heart disease, *n* (%)	4(66.7)	13(32.5)	0.11
Peripheral arterial disease, *n* (%)	1(16.6)	2(5.0)	0.20
Emboligenic cardiac diseases, *n* (%)	1(16.6)	21(52.5)	0.10
Arterial diseases, *n* (%)	4(66.7)	19(47.5)	0.38
Aortic complicated plaque, *n*	4/5	13/25	0.25
Medication within 7 days of stroke onset			
Heparin, *n* (%)	5(83.3)	28(70)	0.50
Aspirin, *n* (%)	5(83.3)	25(62.5)	0.32

NIHSS: National Institutes of Health Stroke Scale, mRS: modified Rankin scale.
ATIII: antithrombin III, TAT: thrombin–antithrombin III complex.

Table 2 shows the clinical characteristics of the two groups. Systolic and diastolic blood pressures on admission were higher in Group D than in Group N. No statistically significant differences in age, sex, TIA within 7 days before symptom onset, the interval from symptom onset to admission, and to initial DWI study, NIHSS score on admission, body temperature on admission, laboratory parameters, blood-coagulation factors, vascular risk factors, history of ischemic heart disease, peripheral arterial disease, arterial and cardiac diseases, aortic complicated plaques and use of medication were observed between the two groups. An mRS score at discharge was not different.

4. Discussion

Our study demonstrated that the frequency of neurological deterioration in patients with small non-lacunar infarcts was 13% during 7 days of symptom onset. In lacunar stroke, frequency of neurological progression was 24–36% [3–5]. Nakamura et al. [4] reported that diabetes mellitus and the severity of motor deficits on admission might predict progression of motor deficits. Lodder et al. [5] showed that progression of symptom was associated with a large infarct volume. Lacunar infarction was caused by occlusion of deep perforators from the horizontal portion of MCA. On the other hand, small non-lacunar infarction was due to occlusion of the MCA branches and the medullary arteries originating from superficial branches of MCA. Furthermore, the frequency of arterial and cardiac disease was different between non-lacunar and lacunar infarction [6,7]. In fact, 89% of our patients had a potential embolic source. We suspect that a small non-lacunar infarct may be caused by embolism from a large artery and heart [6,7]. Therefore, the discrepancy in frequency of neurological deterioration between lacunar and small non-lacunar infarction was explained by the difference in the pathogenic mechanism of stroke.

High serum glucose levels, history of diabetes, stroke severity on admission, and early focal hypodensity and brain swelling on the initial CT scan have been associated with neurological deterioration in acute stroke [2,16–19]. Above-mentioned factors might result in insufficient collateral blood supply, expanding brain edema, or metabolic deterioration during acute phase of stroke. Infarct size in our patients was always too tiny for initial CT findings to represent an important factor. In the present study, no differences in serum glucose levels and history of diabetes were observed between