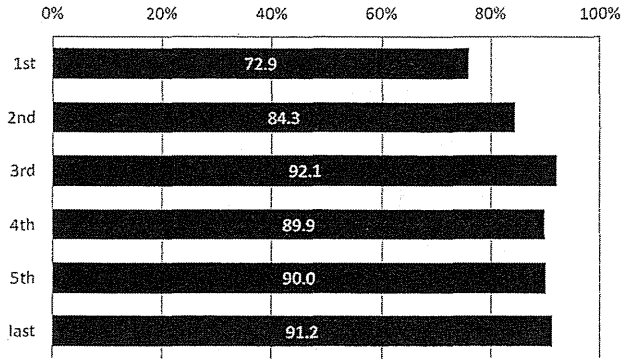

Fig. 1 Annual transition of the rate that magnetic resonance imaging (MRI) was performed (%). The rate that MRI was performed significantly increased from 72.9% in the first period to 92.1% in the third period (p = 0.005 comparing the first and second periods; p = 0.013 comparing the second and third periods), and was subsequently as high as around 90%.

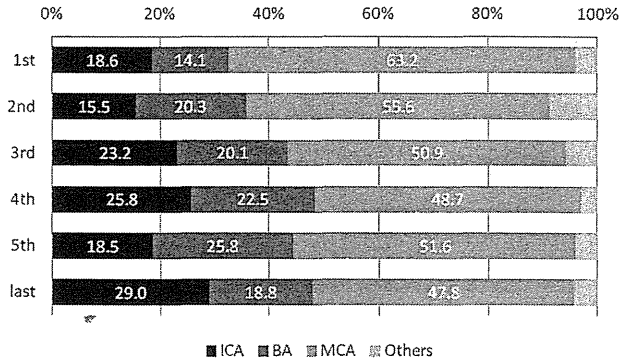

Fig. 3 Annual transition of the proportion of culprit occluded arteries (%). The incidence of ICA or BA occlusion tended to increase after approval of IV t-PA in contrast with MCA occlusion (ICA, p = 0.031; BA, p = 0.053; MCA, p = 0.026). BA: basilar artery, ICA: internal carotid artery, IV t-PA: intravenous thrombolysis using tissue plasminogen activator, MCA: middle cerebral artery.

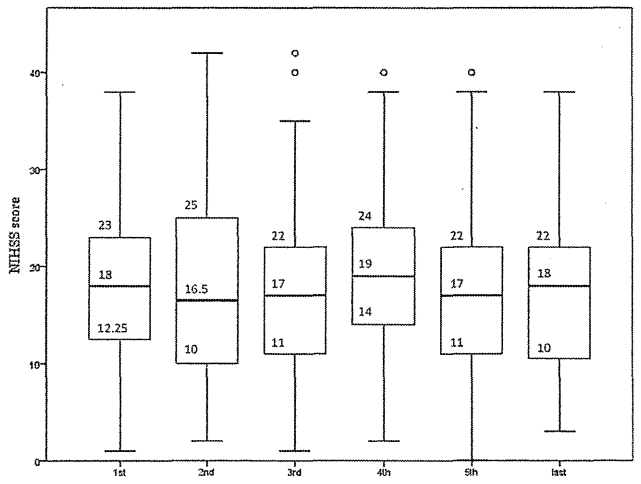

Fig. 2 Annual transition of stroke severity. Stroke severity did not change annually throughout the study period (p = 0.352). NIHSS: National Institutes of Health Stroke Scale.

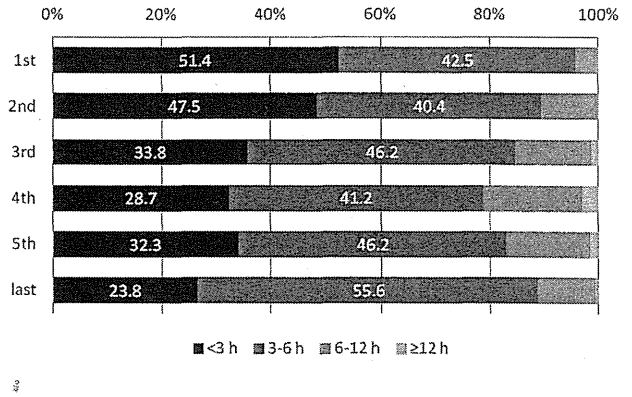

Fig. 4 Annual transition of the onset-to-treatment time (%). The proportion of patients with onset-to-treatment time within 3 hours significantly decreased from 51.4% in the first period to 23.8% in the last period (p < 0.001).

Fig. 3). The proportion of patients with OTT within 3 hours significantly decreased from 51.4% in the first period to 23.8% in the last period (p < 0.001, Fig. 4).

The proportion of patients receiving IV t-PA showed an annual increase from 1.5% in the second period just after the approval of IV t-PA to 16.0% in the fifth period (p = 0.015 comparing the third and fourth periods; p = 0.015 comparing the fourth and fifth periods; Fig. 5). In contrast, the frequency of EVT procedures including IAT abruptly dropped from 87.7% in the first period to 54.4% in the last period (p < 0.001, Fig. 6).

Despite the lack of a significant annual change in mortality or the proportion of patients with poor outcome, the proportion of patients with a favorable outcome decreased from 41.0% to 29.0% throughout the study period (p = 0.025 comparing the first and fifth periods; Fig. 7). The procedural complication rate showed no significant change throughout the study period, but there was a significant decrease in rate of all complications (p = 0.033); there was an insignificant trend for a decrease in the rate of intracranial hemorrhage

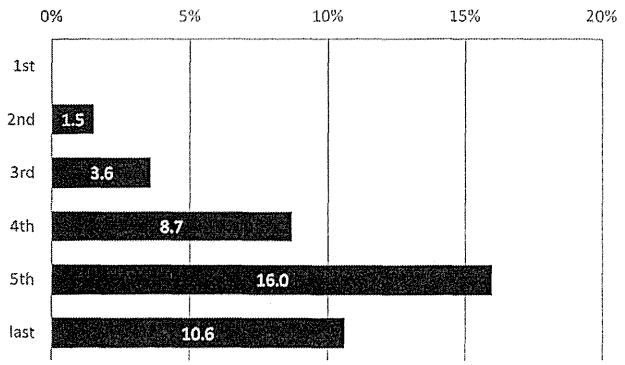

Fig. 5 Annual transition of the proportion of the patients receiving IV t-PA (%). The proportion of patients receiving IV t-PA showed an annual increase from 1.5% in the second period just after the approval of IV t-PA to 16.0% in the fifth period (p = 0.015 comparing the third and fourth periods; p = 0.015 comparing the fourth and fifth periods). IV t-PA: intravenous thrombolysis using tissue plasminogen activator.

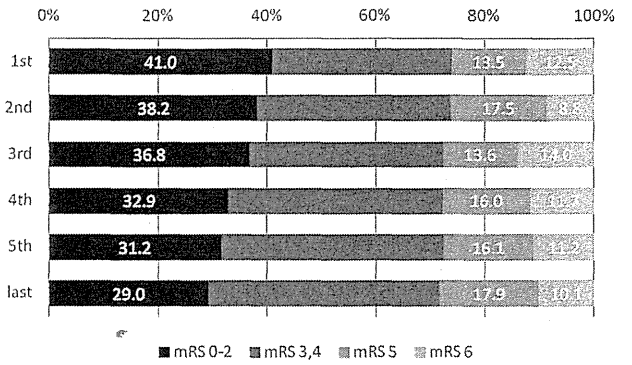

Fig. 7 Annual transition of the proportion clinical outcomes at 30 days after onset (%). The proportion of patients with a favorable outcome decreased from 41.0% to 29.0% throughout the study period (p = 0.025 comparing the first and fifth periods) despite the lack of a significant annual change in mortality or the proportion of patients with poor outcome. mRS: modified Rankin scale.

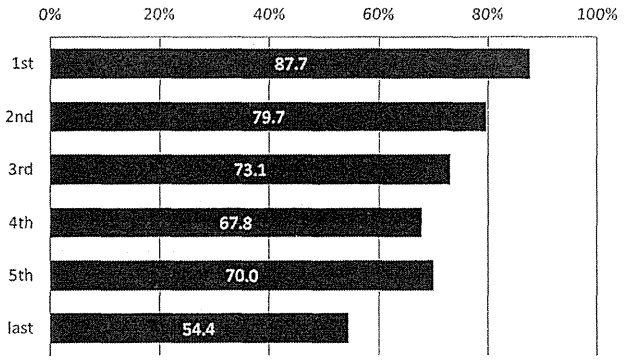

Fig. 6 Annual transition of the proportion of any endovascular procedural combinations including intraarterial thrombolysis (%). The frequency of EVT procedures including IAT abruptly dropped from 87.7% in the first period to 54.4% in the last period (p < 0.001). EVT: endovascular procedure, IAT: intra-arterial thrombolysis.

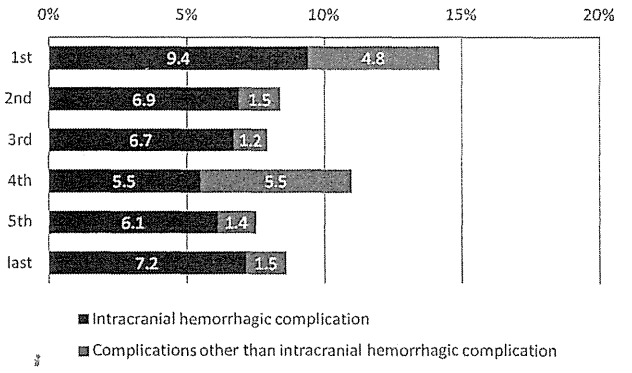

Fig. 8 Annual transition of the occurrence rate of procedural complications (%). The procedural complication rate showed no significant change throughout the study period, but there was a significant decrease in rate of all complications (p = 0.033); there was an insignificant trend for a decrease in the rate of intracranial hemorrhage between the first and second periods (p = 0.290).

between the first and second periods (p = 0.290, Fig. 8).

Discussion

This study is the first nationwide survey of endovascular revascularization treatment for acute stroke with major vessel occlusion, and provides important information about EVT status after the introduction of IV t-PA in Japan before the use of thrombectomy devices. We found that EVT for acute stroke with major vessel occlusion was mainly performed for MRI-evaluated severe stroke patients (median NIHSS score, 18) within 6 hours after onset, using mainly IAT and PTA/BCD.

The final recanalization rate of EVT in JR-NET 1 and 2 combined was 82.5%, and this is higher than that obtained by intra-arterial urokinase therapy for

MCA occlusion in the MCA Embolism Local Fibrinolytic Intervention Trial (MELT) in Japan (73.7%).[7] The 82.5% recanalization rate that we observed is also higher than that reported for IV t-PA for MCA occlusion in the Japan Alteplase Clinical Trial (J-ACT) II (51.7%)[8] and that obtained in the Japanese initial experience of 15 centers using the Merci Retriever (74.6%).[9] However, the interpretation of the results of these different studies requires caution, as complete recanalization was limited to 32.5% in our study and the recanalization grade that we used is not congruent with the generally accepted ordinal recanalization scale [Thrombolysis in Myocardial Infarction (TIMI)[10] or Thrombolysis in Cerebral Infarction (TICI)[11] grade evaluated by angiography, or the modified Mori grade by MRA[8]]. It has been reported that recanalization after PTA/BCD is better than stand-alone IAT,[12,13] and PTA/BCD enhances the thrombolytic effect of IAT.[14] The recanalization rate in our study reflects the final result of an EVT strategy that mainly consisted of IAT and PTA/BCD.

The proportion of patients with a favorable outcome was 35.8% in our study. This result is similar to or even better than the outcome results of some studies using thrombectomy devices (MERCI trial, 27.7%[5]; MultiMERCI trial, 36.0%[4]; Japanese initial experience using Merci Retriever, 28.2%[9]; Penumbra Pivotal Stroke trial, 25%[2]; The POST trial, 41.0%[6]). Since there were some differences in baseline characteristics, especially neurological severity (our study included patients with an NIHSS score < 8 in 11.7%), a simple comparison among studies is difficult. A subanalysis limited to patients with a significant neurological deficit (NIHSS score ≥ 8) is needed. The procedural complication rate in our study was 9.8%, including intracranial hemorrhagic complications in 7%. These complication rates are thought to be acceptable compared with other studies (MERCI trial, 7.1%[5]; Multi MERCI trial, 5.5%[4]; Penumbra Pivotal Stroke trial, 12.8%[2]; The POST trial, 5.7%[6]). However, we cannot draw any final conclusions about the safety of EVT in this study because the definition of procedural complications and the performance rate of IV t-PA were quite different among studies, and we lacked information on intracranial hemorrhage that was unrelated to EVT. Further study is needed to resolve this issue.

Although there were no significant differences in neurological severity, sex, age, or stroke subtypes between JR-NET 1 and 2, the incidence of a culprit lesion in the ICA or BA was higher in JR-NET 2, whereas the incidence of a culprit lesion in the MCA was lower, with a similar tendency in the annual transition. Furthermore, the OTT became significantly longer throughout the study period. Considering revascularization procedures, the rate that IV t-PA and PTA/BCD were performed increased throughout the study period, whereas the rate that IAT was performed decreased from JR-NET 1 to JR-NET 2, with a similar tendency in the annual transition.

The proportion of patients who received IV t-PA in the fifth period was only 16%, and lower than that of the Japanese initial experience with the Merci Retriever (42.0%).[9] This might suggest that interventionists had less enthusiasm for subsequent EVT after IV t-PA at that time for fear of hemorrhagic complications. Similarly, the changes in rate that EVT procedures were performed over time might reflect the fact that interventionists became more concerned about hemorrhagic complications due to proximal vessel occlusion such as ICA or BA with a prolonged OTT often causing a large infarct. In fact, the rate of procedural intracranial hemorrhagic complications in the first period was higher (9.4%) than those in the second to last periods after the approval of IV t-PA (5.5–7.2%).

Despite of lack of difference in the final recanalization rate between JR-NET 1 and 2, the proportion of patients who achieved a favorable outcome significantly decreased from 39% in JR-NET 1 to 32.2% in JR-NET 2 ($p = 0.027$), with a similar tendency in the annual transition. This provides additional evidence for shifting of the EVT indication to patients with higher risk factors such as ineligibility for IV t-PA, proximal vessel occlusion, and longer OTT.

This study has some limitations. This study was retrospective, and data were missing in some patients. The recanalization status and clinical outcomes were not evaluated by investigators who were blinded to the treatment strategy. In addition, the actual rate of TICI grade 2B + 3 as an index of substantial recanalization was not clear because of the ambiguous definition of recanalization status. Furthermore, the actual safety of EVT procedures could not be determined since we were not certain of the number of intracranial hemorrhages that were unrelated to EVT. Finally, no data on pre-EVT cerebral parenchymal imaging findings were collected.

The ongoing JR-NET 3 study is collecting recanalization status defined by TICI grade and information on the extent of the infarcted area defined by the Alberta Stroke Program Early CT Score (ASPECTS). This ongoing study is expected to give precise information on the general EVT status of acute stroke with major vessel occlusion in the post-thrombectomy device era in Japan.

Conclusion

EVT for acute stroke with major vessel occlusion was mainly performed with IAT and/or PTA/BCD and resulted in recanalization rate of up to 82.5%, and 35.8% of the patients had a favorable outcome at 30 days after onset before approval of mechanical thrombectomy devices in Japan. The results of this study may be used as baseline data for validation of the Merci Retriever (Concentric Medical, Mountain View, California, USA), Penumbra System (Penumbra Inc., Alameda, California, USA) or future novel EVT devices in Japan.

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Conflicts of Interest Disclosure

The authors declare that there are no conflicts of interest.

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Factors Associated with Early Recanalization Failure following Intravenous rt-PA Therapy for Ischemic Stroke

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Key Words
Acute ischemic stroke · Intravenous thrombolysis · Recanalization · High-density lipoprotein cholesterol · C-reactive protein

Abstract
Background: Although intravenous recombinant tissue-type plasminogen activator (rt-PA) therapy can be effective for ischemic stroke, a considerable percentage of patients do not receive any benefit as a result of early recanalization failure. We aimed to investigate the factors associated with early recanalization failure following intravenous rt-PA therapy. ***Methods:*** Patients with acute ischemic stroke and internal carotid artery (ICA) or middle cerebral artery occlusion on initial magnetic resonance angiography (MRA) who received intravenous rt-PA therapy within 3 h of stroke onset and underwent follow-up MRA within 8 h after treatment were enrolled. Baseline characteristics, stroke features, onset to treatment time, initial National Institutes of Health Stroke Scale (NIHSS) score, initial Alberta Stroke Programme Early CT Score on diffusion-weighted imaging-ASPECTS (Alberta Stroke Program Early Computed Tomography Score), the presence of ICA or M1 origin (the residual length <5 mm) (ICA/M1 origin occlusion), initial vital signs, and laboratory findings were recorded. Early recanalization on the follow-up MRA within 8 h was evaluated by modified Mori grade: grade 0, no reperfusion; grade 1, movement of thrombus; grade 2, partial recanalization, and grade 3, complete recanalization. ***Results:*** Seventy subjects (35 women, 77 ± 12 years) were enrolled. The median (interquartile range: IQR) NIHSS score was 18 (12.5–24), and the mean onset to treatment time was 141 ± 54 min. ICA was occluded in 29%, M1 origin in 17%, M1 middle in 13%, M1 distal in 26% and M2 in 15%. The median (IQR) pretreatment diffusion weighted imaging-ASPECTS was 8 (6–9), and follow-up time of MRA was 65 min (59–70) after rt-PA therapy. Thirty-two subjects (46%) showed modified Mori grade 0; 10 (14%), grade 1; 9 (13%), grade 2, and 19 (27%), grade 3. Multivariate analyses revealed ICA/M1 origin occlusion (OR 3.71, 95% CI 1.03–14.87, p = 0.044), and C-reactive protein (per 0.1-mg/dl increment, OR 1.19, 95% CI 1.03–1.44, p = 0.013) were independently associated with subjects with no recanalization (grade 0–1), whereas age (per years old, OR 0.93, 95% CI 0.86–0.99, p = 0.014) and high-density lipoprotein cholesterol (per 1-mg/dl increment, OR 0.94, 95% CI 0.89–0.98, p = 0.004) were inversely associated with those. ***Conclusion:*** ICA/M1 origin occlusion and C-reactive protein were positively and high-density lipoprotein cholesterol was negatively associated with early recanalization failure.

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Introduction

Intravenous recombinant tissue-type plasminogen activator (rt-PA) therapy was approved in 2005 in Japan, 9 years after it was approved in the US [1]. A nationwide postmarketing survey (J-MARS) [1] and our multicenter observational study (SAMURAI rt-PA registry) [2] revealed safety and efficacy similar to studies from the US [3], Canada [4] and the European Union [5]. About half of the patients treated with rt-PA followed by best medical management are dependent or dead at 3 months after stroke onset [1]. Internal carotid artery (ICA) occlusion is a strong indicator of unfavorable outcome following rt-PA therapy [2, 6, 7]. Additionally, M1 proximal occlusion (a residual length of <5 mm) was reported to be an indicator of poor response to rt-PA therapy [8]. Rha and Saver [9] reported a meta-analysis showing that early recanalization with or without any interventional therapy is related to neurological improvement and favorable outcome.

In 2004, the Merci retriever system was approved by the US Food and Drug Administration as the first mechanical thrombectomy device for removing clots in acute ischemic stroke patients. The Penumbra aspiration system followed, with approval in the US in 2008. These two devices were approved in Japan in 2010 and 2011, respectively. Such devices show a high recanalization rate and symptomatic intracerebral hemorrhage in about 10% of the patients [10–14], although the International Management of Stroke Trial 3 failed to show the superiority of mechanical thrombectomy or additional endovascular therapy to rt-PA therapy alone [15, 16]. Recently, retrievable stents showed more promising results [17, 18]. Patients who are refractory or ineligible for intravenous rt-PA therapy may be candidates for recently developing acute endovascular therapy. If we are able to discriminate those who are refractory to rt-PA therapy, we may be able to maximize our efforts to assemble neuro-interventionists, specialized nursing staffs, and X-ray technicians to more quickly get those patients catheterized and minimize unnecessary examinations. Thus, this study aimed to assess the factors associated with early recanalization failure following intravenous rt-PA therapy in patients with acute ischemic stroke.

Methods

This study was a retrospective analysis using the prospective National Cerebral and Cardiovascular Center stroke registry. We enrolled acute ischemic stroke patients with ICA or middle cerebral artery (MCA) occlusion on pretreatment magnetic resonance angiography (MRA) who were treated with intravenous rt-PA therapy within 3 h of onset and evaluated with a follow-up MRA within 8 h of onset from June 2010 through July 2013. Because the Japanese Government approved the Merci retriever in April 2010 and we needed information of early recanalization to choose rt-PA failure patients for the following endovascular therapy, the follow-up MRA was routinely done from June 2010 forward after our local ethical board's approval to conduct this study. Intravenous rt-PA therapy was performed using 0.6 mg/kg alteplase following Japanese guidelines. Inclusion and exclusion criteria were similar to those of the American Stroke Association/American Heart Association guideline [19]. The prospective National Cerebral and Cardiovascular Center stroke registry was used to collect patients' backgrounds including sex, age, stroke subtype, onset to treatment time, cardiovascular risk factors, comorbidities based on information prior to onset and additional information during hospitalization, vital signs, and imaging findings. Routine blood biochemistry and emergently available coagulation and fibrinolysis markers, such as activated partial thromboplastin time, prothrombin time, international normalized ratio, antithrombin III, fibrinogen, fibrin/fibrinogen degradation products, and D-dimer, were examined on admission. Brain natriuretic peptide was measured within 3 days after admission. Stroke severity was assessed using the National Institutes of Health Stroke Scale (NIHSS) score on admission. The Alberta Stroke Program Early Computed Tomography Score (ASPECTS) was assessed on the pretreatment diffusion-weighted imaging. The arterial occlusion site was assessed on the pretreatment MRA and dichotomized into ICA or M1 origin with the residual length of <5 mm occlusion and other occlusion (M1 middle, M1 distal and M2 occlusion). Recanalization status was evaluated on the follow-up MRA according to the modified Mori grade [20]: grade 0, no reperfusion; grade 1, movement of thrombus not associated with any flow improvement; grade 2, partial (branch) recanalization in <50% of the branches in the occluded arterial territory, and grade 3, nearly complete recanalization with reperfusion in ≥50% of the branches in the occluded-arterial territory.

Data are presented as mean ± SD or median (interquartile range). Factors relating recanalization failure (grade 0–1) were assessed using univariate and multivariate analyses. For the status of recanalization failure (grade 0–1), independent predictors were assessed from sex, age, and confounding factors ($p < 0.20$ by Student's t test, χ^2 test, Fisher's exact test or Wilcoxon's test) by backward stepwise-logistic regression analysis using $p > 0.10$ of the likelihood ratio test for exclusion. Confounding factors were selected from vascular risk factors, site of arterial occlusion, onset to treatment time, treatment to follow-up MRA time, initial levels of SBP, pulse rate, initial NIHSS and diffusion-weighted imaging-ASPECTS, and laboratory data on admission. Statistical significance was set at $p < 0.05$.

Results

Of 207 subjects who were treated with intravenous rt-PA during the study period, 9 patients did not have pretreatment MRA mainly due to pacemaker implanta-

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tion, MRI unavailability or intracranial aneurysm clip and 122 subjects (58 women; 76 ± 14 years old) with ICA or MCA occlusion on pretreatment MRA. Of the 122 subjects, 74 (61%) underwent follow-up MRA within 8 h after stroke onset. Of these, 4 patients were excluded because of poor MRA quality to judge the Modified Mori grade. Thus, 70 patients (35 women, 77 ± 12 years old) were enrolled in our analyses (table 1). Cardioembolic stroke was the leading subtype (77%), followed by others (16%), and atherothrombotic infarction (7%). The median (interquartile range: IQR) NIHSS score was 18 (12.5–24), and the mean onset to treatment time was 141 ± 54 min. ICA was occluded in 29%, M1 origin in 17%, M1 middle in 13%, M1 distal in 26% and M2 in 15%. The median (IQR) pretreatment diffusion-weighted imaging-ASPECTS was 8 (6–9), and follow-up time of MRA was 65 min (59–70) after rt-PA therapy. Thirty-two subjects (46%) showed modified Mori grade 0; 10 (14%), grade 1; 9 (13%), grade 2, and the remaining 19 (27%), grade 3. Brain natriuretic peptide, fibrin/fibrinogen degradation products, and D-dimer all exceeded the normal range. Twenty-one patients (30%) were treated endovascularly with the Merci retriever or Penumbra system.

Univariate analysis results according to recanalization status are shown in table 2. Initial systolic blood pressure was lower in subjects with grade 0–1 than those with grade 2–3. Frequency of ICA/M1 occlusion was higher in subjects with grade 0–1 as compared with those with grade 2–3. Subjects with grade 0–1 had lower high-density lipoprotein (HDL) cholesterol levels and higher C-reactive protein levels than those with grade 2–3. Subjects with grade 0–1 tended to have lower hemoglobin levels and higher brain natriuretic peptide level.

After multivariate adjustment, ICA/M1 origin occlusion (OR 3.71, 95% CI 1.03–14.87, p = 0.044), and C-reactive protein (per 0.1-mg/dl increment, OR 1.19; 95% CI 1.03–1.44, p = 0.0013) were independently associated with subjects with no recanalization (grade 0–1) whereas advanced age (per year old, OR 0.93, 95% CI 0.86–0.99, p = 0.014) and HDL cholesterol (per 1-mg/dl increment, OR 0.94, 95% CI 0.89–0.98, p = 0.004) were inversely associated with those (table 3).

Discussion

We reported on the factors associated with recanalization failure on early follow-up MRA in subjects who were treated with intravenous rt-PA therapy. The first

Table 1. Subject characteristics

Number	70
Women, n (%)	35 (50)
Age, years	77±12
Onset to treatment time, min	141±54
Treatment to follow-up MRA time, min	65±15
Initial NIHSS, median (IQR)	18 (12.5–24)
Stroke subtype, n (%)	
Cardioembolic stroke	54 (77)
Atherothrombotic infarction	5 (7)
Others	11 (16)
Initial vital sign	
Systolic blood pressure, mm Hg	147±23
Diastolic blood pressure, mm Hg	82±17
Pulse rate, beats per min	83±20
Risk factors/comorbidities, n (%)	
Hypertension	53 (76)
Diabetes mellitus	17 (24)
Dyslipidemia	25 (36)
Atrial fibrillation	48 (69)
Ischemic heart disease	5 (7)
Congestive heart failure	17 (24)
Current smoking	9 (13)
Imaging findings on admission	
Arterial occlusion site, n (%)	
ICA	20 (29)
M1 origin (the residual length <5 mm)	12 (17)
M1 middle	9 (13)
M1 distal	18 (26)
M2	11 (15)
DWI-ASPECTS, median (IQR)	8 (6–9)
Laboratory data on admission	
White blood cell, $\times 10^3/\mu l$	6.7±2.5
Hemoglobin, g/dl	13.0±1.9
Platelet, $\times 10^3/\mu l$	189.7±58.3
Blood glucose, mg/dl	144.6±49.7
HbA1c, %	5.8±0.8
Total cholesterol, mg/dl	181.6±34.9
High density lipoprotein cholesterol, mg/dl	53.0±15.8
Low density lipoprotein cholesterol, mg/dl	102.1±27.1
Triglyceride, mg/dl	135.3±123.9
Creatinine, mg/dl	1.01±0.77
C-reactive protein, mg/dl	0.42±0.80
Brain natriuretic peptide, pg/ml, <18.4	289.7±395.2
Activated partial thromboplastin time, s	27.9±3.1
Prothrombin time-international normalized ratio	1.08±0.19
Fibrinogen, mg/dl	326.5±65.7
Antithrombin III, %	93.6±13.6
Fibrin/fibrinogen degradation products, μg/ml, <5.0	11.0±27.6
D-dimer, μg/ml, <1.0	3.3±7.2

Data are expressed as mean ± SD unless otherwise stated.

Table 2. Univariate analysis according to recanalization status

	Grade 0–1 (n = 42)	Grade 2–3 (n = 28)	p
Female, n (%)	24 (57)	11 (39)	0.143
Age, years	76±14	78±9	0.566
Onset to treatment time, min	137±52	147±56	0.446
Treatment to follow-up MRA time, min	66±15	64±15	0.492
Initial NIHSS, median (IQR)	18 (14–23.25)	16.5 (10.25–24)	0.648
Cardioembolic stroke, n (%)	32 (76)	22 (79)	0.816
Vital sign on admission			
Systolic blood pressure, mm Hg	142±21	154±25	0.040
Pulse rate, beats per min	82±19	84±20	0.592
Risk factors/comorbidities, n (%)			
Hypertension	30 (71)	23 (82)	0.306
Diabetes mellitus	10 (24)	7 (25)	0.909
Dyslipidemia, p = 0.1837	15 (36)	10 (36)	1.000
Atrial fibrillation	27 (64)	21 (75)	0.344
Ischemic heart disease	4 (10)	1 (4)	0.642
Congestive heart failure	10 (24)	7 (25)	0.909
Current smoking	5 (12)	4 (14)	0.771
Imaging findings on admission			
ICA/M1 origin occlusion	24 (57)	8 (29)	0.019
DWI-ASPECTS, median (IQR)	8 (6–8.25)	7.5 (6–9)	0.798
Laboratory data on admission			
White blood cell, $\times 10^3/\mu l$	6.4±2.7	7.1±2.1	0.297
Hemoglobin, g/dl	12.6±2.1	13.5±1.5	0.051
Platelet, $\times 10^3/\mu l$	189.0±61.9	190.9±53.5	0.894
Blood glucose, mg/dl	142.4±53.5	147.8±44.2	0.664
HbA1c, %	5.8±0.8	5.8±0.7	0.925
Total cholesterol, mg/dl	177.8±40.6	188.0±23.2	0.232
HDL cholesterol, mg/dl	49.0±15.7	56.0±14.2	0.009
LDL cholesterol, mg/dl	100.7±30.2	104.3±22.0	0.591
Triglyceride, mg/dl	148.2±147.2	115.9±75.4	0.288
Creatinine, mg/dl	1.09±0.96	0.88±0.26	0.282
C-reactive protein, mg/dl	0.57±0.99	0.20±0.26	0.021
Brain natriuretic peptide, pg/ml	360.4±488.8	186.1±143.8	0.072
Activated partial thromboplastin time, s	28.3±3.3	27.4±2.8	0.259
Prothrombin time-international normalized ratio	1.09±0.19	1.07±0.20	0.617
Fibrinogen, mg/dl	323.8±72.4	330.3±56.2	0.701
Antithrombin III, %	92.5±13.8	95.2±13.5	0.447
FDP (μg/ml), median (IQR)	13.0±34.2	8.0±11.9	0.489
D-dimer (μg/ml), median (IQR)	3.9±9.1	2.2±2.3	0.336

FDP = Fibrin/fibrinogen degradation products.

major finding was that early recanalization was identified within 8 h (median 65 min) in 40% of the subjects who had occlusion of a major intracranial artery on pretreatment MRA after rt-PA therapy. Next, an occlusion of a large major artery, such as ICA or M1 origin, was associated with failure of early recanalization and is an independent predictor of whether a subject will be refractory to intravenous rt-PA therapy. Third, a low level of HDL cholesterol was independently associated with a failure of early recanalization. Finally, elevated C-reactive protein level was also associated with a failure of early recanalization.

Although advanced age was significantly associated with early recanalization after multivariate adjustment,

Table 3. Independent factors associated with recanalization failure

Factors associated with grade 0–1	OR	95% CI	p
Age, per 10 years old	0.93	0.86–0.99	0.014
Female sex	3.68	0.97–16.73	0.057
ICA/M1 origin occlusion	3.71	1.03–14.87	0.044
HDL cholesterol, per 1-mg/dl increment	0.94	0.89–0.98	0.004
C-reactive protein, per 0.1-mg/dl increment	1.19	1.03–1.44	0.013
Hemoglobin, per 1-g/dl increment	0.71	0.46–1.05	0.088

the absolute difference in the mean age between patients with grade 0–1 and those with grade 2–3 was 2 years and most of both patients were septuagenarians. Therefore, age does not seem to be a useful measure to discriminate refractory patients to intravenous rt-PA therapy. Interestingly, female sex tended to be an indicator of refractory patients to intravenous rt-PA therapy in this study. Generally speaking, female sex is associated with poor stroke outcomes [21, 22]. However, women are reported to have similar clinical outcomes as men following intravenous rt-PA therapy [23, 24].

The Japan Alteplase Clinical Trial (J-ACT) 2 showed early recanalization rates of 51.7 and 69.0% on 6- and 24-hour follow-up MRAs, respectively, after rt-PA therapy in patients with M1 or M2 occlusion on pretreatment MRA [20]. Mendonça et al. [25] reported that the early recanalization rate was 42.2% in patients with proximal MCA occlusion and 29.9% in those with distal MCA occlusion on follow-up transcranial Doppler at 1 h after rt-PA therapy. Although our subjects included those with ICA occlusion (29%), the early recanalization rate was comparable to that reported by Mendonça et al. [25]. The remaining more than half of the patients did not achieve early recanalization. Currently, the options for patients who are refractory to rt-PA therapy are mechanical thrombectomy and possibly new-generation thrombolytic agents such as desmoteplase and tenecteplase, and sonothrombolysis. Earlier detection of recanalization is key to adding newly developing treatment.

An ICA occlusion is resistant to intravenous rt-PA therapy and the recanalization rate was 4.4–25% with rt-PA therapy alone from previous studies [8, 26–28]. Our single-center studies [6, 7], the SAMURAI rt-PA registry [2], and a large multicenter registry which enrolled patients with major artery occlusion [29] showed that ICA occlusion was independently associated with poor clinical outcomes at 3 months after stroke onset in the era of rt-PA, but prior to MERCI and Penumbra. M1 origin occlusion was reported to be independently associated with early recanalization failure and unfavorable outcome [8]. Our data reconfirmed that ICA/M1 origin occlusion is an independent indicator of early recanalization failure following rt-PA therapy alone. Large major artery occlusion appears to reflect a large thrombus volume; larger volumes would be more difficult to dissolve with any treatment.

A low HDL cholesterol level was associated with refractory patients to rt-PA therapy in this study. HDL cholesterol is known as a potent protective factor for cardiovascular diseases and stroke. In addition to the direct role against atherosclerosis to remove free cholesterol from macrophages in the arterial wall, it also inhibits prothrombotic and proinflammatory phenomena [30, 31], and promotes endothelial nitric oxide synthesis, and increases vasodilatation [30, 32]. HDL cholesterol also has a potential to improve fibrinolytic activity derived from vascular endothelial cell [33]. We previously reported that the admission HDL cholesterol level was associated with favorable outcome 3 months after intravenous rt-PA therapy [34]. HDL cholesterol may play an important role to improve thrombolysis in patients treated with rt-PA.

C-reactive protein is a well-known inflammation biomarker, which plays a central role in the pathogenesis of atherosclerosis [35]. Increased plasma C-reactive protein level is associated with an increased risk of ischemic stroke [36]. t-PA converts plasminogen to plasmin which degrades fibrin clots. Plasminogen activator inhibitor-1, the main physiological inhibitor of t-PA, is present in plasma, platelets, endothelial cells, vascular smooth muscle cells, and extracellular matrix. C-reactive protein inhibits release of intrinsic t-PA and stimulates release of plasminogen activator inhibitor-1 from vascular endothelial cells [37, 38]. Therefore, the presence of high plasma level of C-reactive protein may decrease the fibrinolytic activity of endothelial cells.

This study has some limitations that need to be addressed. First, the sample size was small. This could lead to selection bias. Second, because we perform intravenous rt-PA therapy with 0.6 mg/kg of alteplase, our results may not be directly applicable to those with 0.9 mg/kg. Finally, other markers of coagulation and fibrinolysis were not evaluated although most of them are not assessable in an acute clinical setting.

It is important to improve acute stroke treatment for those who are refractory to intravenous rt-PA therapy. To

adequately explore rescue therapies, and to minimize unnecessary efforts, stroke teams need information on the site of the arterial occlusion, and perhaps laboratory findings such as HDL cholesterol level and C-reactive protein level. In the rapidly advancing field of acute stroke treatment, acute assessment of patients' background, imaging, and laboratory tests would also help to develop stroke-treatment strategies further. Our findings need to be confirmed by further investigations in a large number of patients.

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Disclosure Statement

Nothing to disclose.

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Effects of Sex Difference on Clinical Features of Acute Ischemic Stroke in Japan

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Background: Sex differences in stroke characteristics and outcomes have been inconsistent. The goal of this study was to determine the influence of sex on underlying patient characteristics, stroke subtypes and conditions, and outcomes after ischemic stroke from a nationwide registration study. *Methods:* A total of 33,953 patients with acute ischemic stroke, including 13,323 women, were registered in a multicenter, hospital-based registration study based on a computerized database from 162 Japanese institutes (the Japan Standard Stroke Registry Study) between January 2000 and November 2007. *Results:* Women were significantly older than men at stroke onset (75.0 ± 11.7 *v* 69.3 ± 11.4 years; $P < .0001$). After age adjustment, women more frequently had cardioembolic events (odds ratio [OR] 1.090; 95% confidence interval [95% CI] 1.036-1.146; $P = .0009$) and other strokes (OR 1.177; 95% CI 1.079-1.284; $P = .0003$) and were more hypertensive (OR 1.056; 95% CI 1.006-1.108; $P = .0267$) and more dyslipidemic (OR 1.301; 95% CI 1.234-1.373; $P < .0001$) than men. After multivariate adjustment, onset-to-arrival time was longer ($\beta = 0.0554$; $P = .026$), the initial National Institutes of Health Stroke Scale score was higher ($\beta = 0.1565$; $P < .001$), and the duration of hospitalization was longer ($\beta = 0.035$; $P = .010$) in women than in men. At hospital discharge, women less commonly had a modified Rankin Scale (mRS) score of 0 to 1 (OR 0.802; 95% CI 0.741-0.868; $P < .0001$) and more commonly had a mRS score of 4 to 6 (OR 1.410; 95% CI 1.293-1.537; $P < .0001$) than men. *Conclusions:* Women developed more severe strokes than men in Japan. After multivariate adjustment for initial severity and other characteristics, acute care hospital stays were longer and stroke outcomes at discharge were worse in women than in men. **Key Words:** Asian ethnic—brain infarction—gender—sex difference—stroke.

Patient sex may be an important determinant for stroke conditions and outcomes. Several studies have shown an advanced age distribution,[1-7] a predominance of cardioembolic mechanisms,[2,8,9] the frequent coexistence of atrial fibrillation,[1,3-5,10,11] and hypertension[1-5,10,11] in female stroke patients compared to male stroke patients. In contrast, the influence of sex on stroke severity and outcomes seems to be inconsistent,[2-5,7,10-14] especially in patients of Asian ethnicity. Stroke is the third most common cause of death and the leading cause of dependency in Japan; among stroke types, subarachnoid hemorrhage is known to predominantly occur in women.[15] However, little evidence of sex differences in subtype, severity, and outcome has been reported for ischemic stroke patients.

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A multicenter stroke registration study (the Japan Standard Stroke Registry Study [JSSRS]) was conducted to clarify characteristics of Japanese stroke patients.[16,17] Using data from the JSSRS, the present study aimed to clarify the contribution of sex to stroke subtypes, underlying risk factors, initial conditions at onset, and outcomes of ischemic stroke patients. As another essential demographic factor, contribution of age to these issues was also sought.

Methods

JSSRS is a multicenter stroke registration study based on a computerized database from 162 Japanese institutes. Between January 2000 and November 2007, a total of 47,782 acute stroke patients who were hospitalized within 7 days after stroke onset were registered. Among them, 33,953 patients with ischemic stroke were enrolled in the present study.

The subtype of the initial stroke was determined based on the patient's neurologic, radiologic, hematologic, and cardiologic profiles, principally according to the National Institute for Neurologic Disorders and Stroke (NINDS) Classification of Cerebrovascular Diseases III system: atherothrombotic, cardioembolic, lacunar, and stroke of other etiology. Underlying risk factors (listed in Table 1) were also assessed. As the initial condition, the time interval between symptom onset and hospital arrival and National Institutes of Health Stroke Scale (NIHSS) score on admission were evaluated. As stroke outcomes, length of hospital stay in days, the modified Rankin Scale (mRS) score at hospital discharge and in-hospital death were assessed. Favorable outcome was defined as a mRS score of 0 to 1, corresponding to minimal or no disability. Poor outcome was defined as a mRS score of 4 to 6, corresponding to severe disability or death.

Statistical Analysis

Univariate comparisons of characteristics between women and men and among different age distributions were performed with the Chi-square test for dichotomous variables and the t or Mann–Whitney tests for continuous variables. Multivariate logistic regression analyses or multiple linear regression analyses were performed to identify the independent influence of sex and age distribution on stroke conditions and outcome. For each condition and outcome, underlying characteristics which were appropriate for each analysis were entered for adjustment by a forced entry method. $P < .05$ was considered statistically significant. All statistical analyses were performed with the JMP package 8 (SAS Institute Inc, Cary, NC) for Windows.

Results

Of the 33,953 patients who were enrolled in the study, 13,323 (39.2%) were women. The age distribution of stroke patients registered in the study is shown in Figure 1. Women were older than men at stroke onset (75.0 ± 11.7 v 69.3 ± 11.4 years; $P < .0001$). Men were more common than women in the septuagenarians or younger, and women were more common in the octogenarians or older.

Stroke Subtypes and Risk Factors

Prevalence of stroke subtypes and risk factors for each sex are shown in Table 1. In both women and men,

Table 1. *Stroke subtypes and risk factors*

	Women (n = 13,323)	Men (n = 20,630)	OR for women	95% CI	OR by 10-year increase	95% CI
Stroke subtype, %						
Atherothrombotic	31.8	35.3	0.831	0.793-0.872*	1.048	1.027-1.068*
Cardioembolic	30.3	24.9	1.090	1.036-1.146*	1.390	1.358-1.422*
Lacunar	30.9	32.5	1.035	0.986-1.086	0.827	0.811-0.844*
Other/unknown	7.0	7.3	1.177	1.079-1.284*	0.687	0.665-0.710*
Risk factor, %						
Previous stroke (n = 32,418)	27.8	30.6	0.687	0.628-0.751*	1.232	1.186-1.280*
Hypertension (n = 32,698)	66.7	64.3	1.056	1.006-1.108†	1.093	1.071-1.114*
Diabetes mellitus (n = 32,891)	24.2	29.5	0.824	0.783-0.868*	0.866	0.848-0.884*
Dyslipidemia (n = 29,873)	29.7	27.0	1.301	1.234-1.373*	0.801	0.784-0.819*
Atrial fibrillation (n = 32,799)	26.1	22.3	0.947	0.897-1.001	1.592	1.552-1.634*
Heavy drinking‡ (n = 26,278)	0.9	14.2	0.066	0.053-0.080*	0.678	0.654-0.703*
Current smoking (n = 26,288)	7.7	40.6	0.142	0.131-0.154*	0.568	0.553-0.584*

Abbreviations: CI, confidence interval; OR, odds ratio.
OR for women is adjusted for age. OR by 10-year increase is adjusted for sex.
*P <.001.
†P <.05.
‡>46 g of alcohol/day.

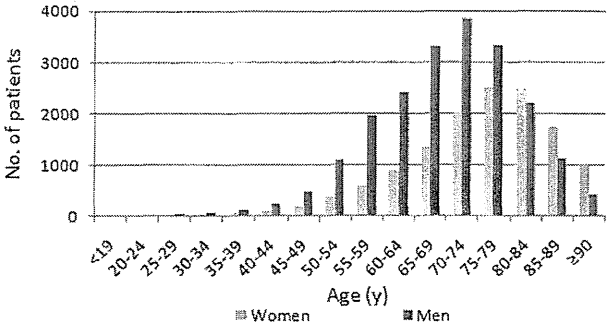

Figure 1. *Sex and age distribution.*

atherothrombotic stroke was most frequent. An analysis adjusting for age showed that cardioembolic stroke (odds ratio [OR] 1.090; 95% confidence interval [95% CI] 1.036-1.146; $P = .0009$) and other stroke (OR 1.177; 95% CI 1.079-1.284; $P = .0003$) were more common, and atherothrombotic stroke (OR 0.831; 95% CI 0.793-0.872; $P < .0001$) was less common in women than men. After adjustment for sex, atherothrombotic and cardioembolic strokes were more common and lacunar and other strokes were less common with advanced age ($P < .0001$ for all).

After adjustment for age, hypertension (OR 1.056; 95% CI 1.006-1.108; $P = .0267$) and dyslipidemia (OR 1.301; 95% CI 1.234-1.373; $P < .0001$) were more common, and previous history of stroke (OR 0.687; 95% CI 0.628-0.751; $P < .0001$), diabetes mellitus (OR 0.824; 95% CI 0.783-0.868; $P < .0001$), heavy drinking (OR 0.066; 95% CI 0.053-0.080; $P < .0001$), and current smoking (OR 0.142; 95% CI 0.131-0.154; $P < .0001$) were less common in women than in men. Although atrial fibrillation was more common in women than men in a univariate analysis ($P < .0001$), it tended to be less common in women after adjustment for age (OR 0.947; 95% CI 0.897-1.001; $P = .0523$).

Condition on Admission and Outcomes

Onset-to-arrival time, initial NIHSS score, and length of hospital stay in days are shown in Figure 2. Onset-to-arrival time was shorter ($P = .0004$), the initial NIHSS score was higher ($P < .0001$), and the duration of hospitalization was longer ($P < .0001$) in women than in men. After multivariate adjustment for age, stroke subtypes, risk factors, and stroke severity, onset-to-arrival time (standardized partial regression coefficient [β] = 0.0544; $P = .0261$) and hospitalization (β = 0.0355; $P = .0101$) was longer in women than men (Table 2). Female predominance of the higher NIHSS score (β = 0.1565; $P < .0001$) remained significant after adjustment for age, stroke subtypes, risk factors, and onset-to arrival time. In contrast, aging had a significant association only with the initial NIHSS score after multivariate adjustment for sex (β = 0.1151; $P < .0001$).

The plots in Figure 3 represent distributions of mRS grade of patients with different sex and age distributions. At hospital discharge, 33.0% of women and 45.4% of men obtained a favorable outcome (mRS 0-1; $P < .0001$). Meanwhile, 41.8% of women and 27.3% of men had a poor outcome (mRS 4-6; $P < .0001$), and 7.1% of women and 4.5% of men were dead ($P < .0001$). After adjustment for age, stroke subtype, risk factors, and the initial NIHSS score, women less commonly had a favorable outcome (OR 0.802; 95% CI 0.741-0.868; $P < .0001$) and more commonly had a poor outcome (OR 1.410; 95% CI 1.293-1.537; $P < .0001$) than men (Table 3). Mortality was not different between sexes (OR 0.938; 95% CI 0.802-1.097; $P = .4249$). After multivariate adjustment, aging was independently associated with favorable outcome (OR 0.659; 95% CI 0.637-0.681 by 10-year increase; $P < .0001$), poor outcome (OR 1.651; 95% CI 1.586-1.719; $P < .0001$), and death (OR 1.276; 95% CI 1.186-1.373; $P < .0001$).

Discussion

This is a nationwide multicenter hospital-based registration study on sex differences in characteristics and outcomes of Japanese patients with acute ischemic stroke. As previous studies have often reported, women were older at stroke onset, more commonly had cardioembolic and other strokes, and were more hypertensive and more dyslipidemic than men. In addition, this study shows major findings on the initial severity and outcomes; after multivariate adjustment, women had longer onset-to-arrival

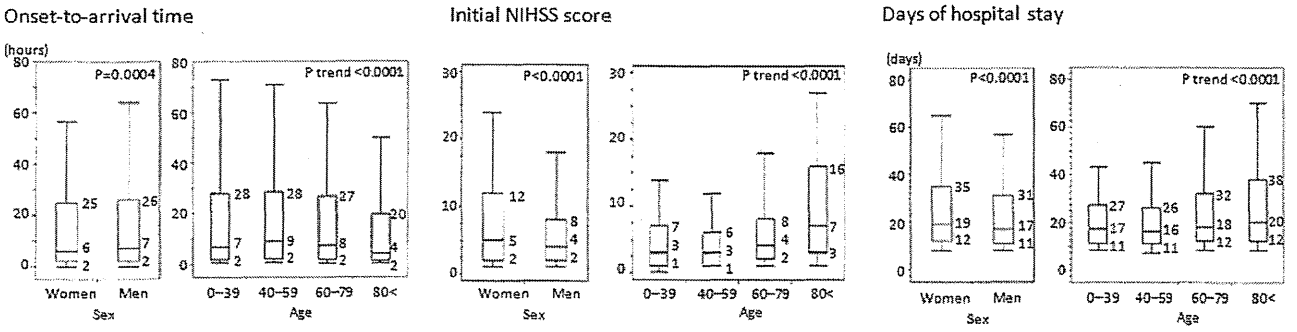

Figure 2. *Onset-to-arrival time, initial National Institutes of Health Stroke Scale score, and days of hospitalization. Box-and-whisker plots are shown. Boxes represent interquartile range. Lines across boxes indicate median values. Whiskers represent the 10th and 90th percentile values.*

Table 2. *Multiple analyses on onset-to-arrival time, initial National Institutes of Health Stroke Scale score, and days of hospitalization*

	Women		Age (by 10 years)	
	β coefficient*	*P* value	β coefficient*	*P* value
Onset-to-arrival time	0.0544	.0261	0.0080	.4356
Initial NIHSS score	0.1565	<.0001	0.1151	<.0001
Days of hospital stay	0.0355	.0101	0.0004	.9456

*β coefficient means standardized partial regression coefficient. The initial National Institutes of Health Stroke Scale score was log-transformed and adjusted for age (or sex), stroke subtype, risk factors, and onset-to-arrival time. Onset-to-arrival time and day of hospital stay were log-transformed and adjusted for age (or sex), stroke subtype, risk factors, and the initial National Institutes of Health Stroke Scale score.

time, higher initial NIHSS score, longer stay in an acute care hospital, and poorer outcomes at discharge.

Women, on average, were approximately 6 years older than men at stroke onset and women were more common than men in patients aged ≥80 years in the present study. The separation of age distribution was 65 years in the Oxford Vascular Study[18] and 85 years in the Framingham Heart Study.[6] Because estrogen has anti-inflammatory effects[19] and decreases cerebral vascular tone and increases cerebral blood flow by enhancing endothelial-derived nitric oxide and prostacyclin pathways,[20] a lifetime exposure to ovarian estrogens may protect middle-aged and autumnal women against ischemic stroke. Endogenous estradiol level has been reported to be an indicator of stroke risk in older postmenopausal women.[21] Cardioembolic stroke has been known to be common in women's stroke,[2,8,9] and is associated with a high prevalence of atrial fibrillation in women.[1,3-5,10,11] In the Framingham Heart Study, female sex was an independent risk factor for stroke in the population with new-onset atrial fibrillation.[22] In this study, the prevalence of atrial fibrillation in women disappeared after adjustment for age, suggesting a strong relationship between atrial fibrillation and age in women. Concerning other risk factors, women with strokes are reported to more commonly have hypertension[1-5,10,11] and less commonly have diabetes,[1,5,11] heavy drinking,[2-4] and tobacco use[2-5,11] than men; the present results generally agreed with previous ones.

When initial stroke severity was measured by the NIHSS, Scandinavian Stroke Scale, or Canadian Neurological Scale, some studies found that women had greater severity than men,[2,7,11,13] and the other studies did not find sex differences.[4,12,14] A higher prevalence of comatose state at stroke onset in women than in men has also been reported.[3,10] Sex differences in onset-to-arrival time varied widely among studies; in women, it was shorter,[23] longer,[24-26] or not significantly different from men.[4,27-30] In the present study, although women arrived to the hospital earlier without any adjustment, they arrived later after adjustment for initial stroke severity and other characteristics. Women live longer than men, and old women may be more likely to live alone than men; this may be a reason for prehospital delay in women.[27,29]

Functional outcomes were poorer in women than men, even after adjustment for initial severity, although mortality did not differ between men and women. Some previous studies have reported poorer outcomes in women,[5,7,10] although the reported sex differences in mortality has been inconsistent.[3,10,13,31,32] Women experience more depression than men after stroke,[5,33,34] and poststroke depression is known to hinder functional recovery[12,33] and increase mortality.[34] Genetic factors may be associated with sex differences in stroke severity and outcomes. XX cells and XY cells have been reported to respond differently to simulated ischemia and toxicity in vitro.[35,36] In animal studies, estrogen attenuated tissue damage after experimental stroke and improved stroke outcome.[37,38] Long after

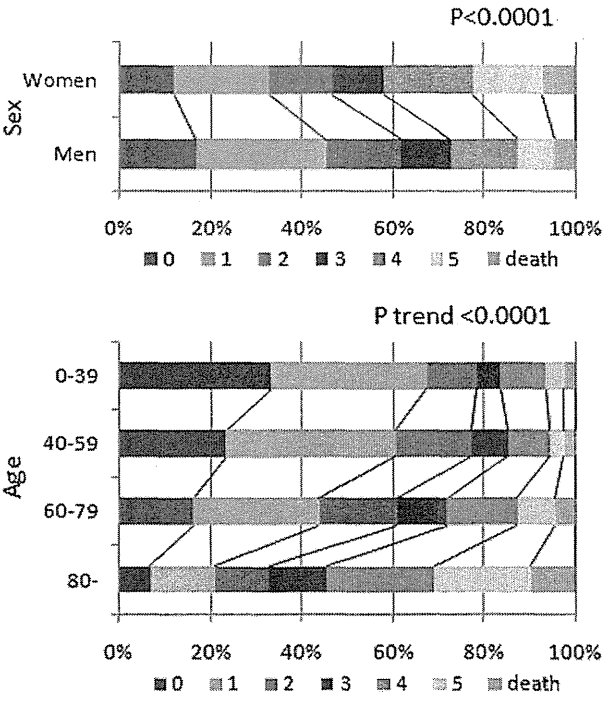

Figure 3. *Modified Rankin Scale score at discharge.*

Table 3. *Multiple analyses on outcomes at discharge**

	Women			Age (by 10 years)		
	OR	95% CI	*P* value	OR	95% CI	*P* value
Favorable outcome (mRS 0-1)	0.802	0.741-0.868	<.0001	0.659	0.637-0.681	<.0001
Poor outcome (mRS 4-6)	1.410	1.293-1.537	<.0001	1.651	1.586-1.719	<.0001
Death	0.938	0.802-1.097	.4249	1.276	1.186-1.373	<.0001

Abbreviations: CI, confidence interval; mRS, modified Rankin Scale; OR, odds ratio.
*Adjusted for age (or sex), stroke subtype, risk factors, and the initial National Institutes of Health Stroke Scale score.

menopause, such protective effects of estrogen might no longer be anticipated.

One strength of the present study is the large study population. To the best of our knowledge, this is the third largest study on sex differences in stroke[1,13] and the largest study of stroke patients of Asian descent. Because lifespans are longer in Asians—in particular in Asian women—the management of stroke in older women is an important problem. It is promising that intravenous tissue plasminogen activator is reported to work better for women than for men.[39,40] Limitations of the present study were that all the inpatients in the participating hospitals during the study period might not have been enrolled, and that stroke outcomes at 3 months were not available in this registry.

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Estimation of Stroke Etiology from Lesion Patterns on Diffusion-Weighted Magnetic Resonance Imaging in Patients with Carotid Artery Occlusive Disease

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Key Words
Acute stroke · Carotid artery disease · Diffusion-weighted imaging · Stroke classification

Abstract
Background: Various mechanisms can be considered in ischemic stroke with internal carotid artery (ICA) occlusive diseases. We clarified the etiologic mechanisms from lesion patterns on diffusion-weighted imaging (DWI). ***Methods:*** One hundred and twenty consecutive ischemic stroke patients with ipsilateral ICA occlusive diseases were enrolled and classified into 3 groups according to the size of DWI lesions: group A, massive; group B, moderate-to-large; and group C, small. Group C was divided into 3 subgroups according to the number of lesions: C1, 1–3; C2, 4–9; and C3, 10 or more. The relationship between the DWI findings and stroke subtypes according to the TOAST classification was investigated. ***Results:*** Cardioembolism was significantly more common in groups A and B than in group C, while large-artery atherosclerosis (LAA) was more frequent in group C than in groups A and B. In group A, cardioembolism accounted for 32%, while LAA was not observed. Statistical analyses showed trends toward a higher frequency of LAA in groups C2 and C3 than in group C1. ***Conclusions:*** Mechanisms of acute stroke in ICA diseases can be simply assessed from the lesion size and number, which may be useful in considering acute therapeutic strategies.

Introduction

In acute ischemic stroke patients with internal carotid artery (ICA) diseases, various lesion patterns can be observed on computed tomography or magnetic resonance (MR) imaging. In particular, diffusion-weighted imaging (DWI) is more useful for the detection of acute ischemic stroke [1, 2]. However, the variability of ischemic lesion patterns on DWI [3] makes the judgement of stroke etiology more difficult. For example, in cases of ICA occlusive lesion accompanied by atrial fibrillation, diagnostic interpretation of topographic features on DWI is often difficult. Some studies have shown that infarcts caused by cardioembolism are generally larger than those caused by artery-to-artery embolism; however, cardioembolic stroke also causes multiple scattered lesions [4–7]. In another study, it was reported that acute ischemic lesions in

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ICA occlusive disease without atrial fibrillation were mostly multiple on DWI [8]. However, Jung et al. [7] and Lodder et al. [9] suggested that the degree of ICA stenosis could contribute to infarct size. To the best of our knowledge, the etiology of acute stroke associated with ipsilateral ICA occlusive disease has not yet been precisely investigated from the viewpoints of lesion size and number on DWI in previous studies. In the daily clinical situation, the early diagnosis of ischemic stroke etiology is important since it is connected with the selection of acute stroke treatment which largely determines the long-term prognosis. The aim of the present study was to clarify whether the etiology can be estimated from DWI lesion patterns in acute stroke patients with ipsilateral ICA occlusive diseases.

Methods

Study Population

We retrospectively studied consecutive ischemic stroke patients with ipsilateral ICA occlusive diseases who were admitted to our department within 72 h after stroke onset during the period from January 1998 to July 2005. ICA occlusive lesions [≥50%; evaluated by the North American Symptomatic Carotid Endarterectomy Trial (NASCET) method [10]] were confirmed with carotid ultrasonography, MR angiography, or cerebral digital subtraction angiography within 24 h after admission, mostly within 3 h.

Magnetic Resonance Imaging

DWI was performed within 72 h of symptom onset using a 1.5T scanner with echo-planar imaging capability (Magnetom Vision, 1.5T; Siemens Medical Systems, Erlangen, Germany). Transaxial DWI was obtained using a single-shot spin-echo echo-planar imaging sequence with an effective TE of 100 ms, slice thickness of 4.0 mm, interslice gap of 2.0 mm, with 20 slices, a matrix size of 128, field-of-view of 23 cm, and 20 s of data acquisition time. Diffusion sensitive gradients were applied to each of the x, y, and z directions with $b = 1{,}000$ s/mm^2, and the trace image was calculated to obtain a standard isotropic DWI. Acute ischemic lesions were determined on the trace image as high signal regions by consensus reading between a neurologist (N.O.) and a neuroradiologist (N.Y.) blinded to the clinical findings.

Ischemic Lesion Patterns on DWI

Based on the volume of high-intensity lesions on DWI, patients were classified into 3 groups: group A, massive lesions in which the size of the largest infarction is larger than or equal to half of the cerebral hemisphere (corresponding to almost complete middle cerebral artery infarction); group B, moderate-to-large lesions in which the maximum diameter of at least one lesion is 30 mm or more and the size is smaller than half of the cerebral hemisphere; and group C, small lesions in which the diameter of all lesions is less than 30 mm. Group C was further divided into 3 subgroups according to the number of lesions: group C1, 1–3 lesions; group C2, 4–9 lesions; and group C3, 10 or more lesions.

Stroke Subtype Classification

Routine evaluations for cardiac disease, carotid artery disease, intracranial artery disease, and cerebral ischemic lesions were performed in all patients using chest radiography, 12-lead electrocardiography, continuous telemetric electrocardiographic monitoring, carotid ultrasonography within 24 h after admission, conventional MR imaging, DWI, and MR angiography. Transthoracic (n = 38) or transesophageal echocardiography including microbubble testing (n = 27) was also performed in patients younger than 50 years and those with suspected heart disease or no definite cause of stroke after initial evaluation. Cardiac diseases that create a risk of potential cardiac embolic sources include intracardiac thrombus, atrial fibrillation, recent myocardial infarction (<4 weeks), sick sinus syndrome, a patent foramen ovale with an atrial septum aneurysm, mitral valve stenosis, prosthetic valves, and endocarditis [11]. Transcranial Doppler ultrasonography with bubble contrast (n = 12) was performed to detect a right-to-left shunt and to assess microembolic signals, intracranial arterial diseases, collateral flow, and recanalization after occlusion. Carotid MR angiography (n = 7) and digital subtraction angiography (n = 68) were performed to evaluate arterial diseases, collateral circulation, and the potential for endovascular or surgical treatment.

Stroke subtype was determined on the basis of the TOAST classification (Trial of Org 10172 in Acute Stroke Treatment) [11] as follows: (1) large-artery atherosclerosis (LAA), (2) cardioembolism (CE), (3) small-vessel occlusion (SVO), (4) stroke of other determined etiology (O), (5) stroke of undetermined etiology (U) due to 2 or more identified causes (U-a), negative evaluation (U-b), or incomplete evaluation (U-c). Because all subjects had carotid occlusive diseases, diagnoses of stroke subtype were made as follows: if a patient with a cardioembolic and no other embolic source had ICA occlusion followed by significant recanalization, the patient was classified as 'CE'; if a patient had atherosclerotic [12] nonrecanalized ICA occlusion and no other cause of stroke, the patient was classified as 'LAA'; other patients with ICA occlusion were classified as 'O' or 'U'. In stroke subtype U, if a patient had ICA occlusion followed by significant recanalization and no cause of stroke was found despite extensive investigations, the patient was classified as 'U-b'. Patients with ICA stenosis (≥50% evaluated by the NASCET method) were classified as 'LAA', 'O', or 'U'. None of the patients with an ICA occlusive lesion was classified as 'SVO'. Because of the differential diagnosis of ICA occlusive diseases such as cardiogenic embolus, atherosclerotic thrombus, arteritis, and dissection, the results of carotid ultrasound imaging, MR imaging, MR angiography, and digital subtraction angiography were interpreted by 4 expert stroke neurologists (N.O., H.M., K.N., and H.N.), an expert neurosonographer (K.N.), and an expert neuroradiologist (N.Y.). Examples of each DWI lesion pattern and stroke subtype diagnosis are provided in figure 1.

Analysis of Stroke Subtype U

In stroke subtype U, to make the estimation of stroke etiology easier, we assessed the location of the ICA occlusion and determined whether there were any cases of ischemic lesions in vascular territories other than the ICA. In addition, we investigated the relationship between the presence of cardioembolic sources and DWI lesion patterns.