Table 5 Information in Japanese package inserts regarding use of antiplatelet drugs in pregnant women

Drug	Guideline for use in pregnant women
Aspirin	up to week 28: may be used if risks outweigh the benefits, week 29 and later: do not use
Clopidogrel	may be used if risks outweigh the benefits
Ozagrel	may be used if risks outweigh the benefits
Cilostazol	do not use in pregnant women
Ticlopidine	do not use in pregnant women

informed consent are necessary for administration in the third trimester of pregnancy.

The Japanese package inserts for clopidogrel and ozagrel recommend use only when the benefits outweigh the risks (Table 5). Cilostazol and ticlopidine are contraindicated in pregnant women. On the other hand, aspirin and ozagrel are reported to be effective in preventing placental thrombosis in pregnant women with autoimmune disorders such as antiphospholipid syndrome.

Conclusion

In the present paper, the author, who is not a specialist in perinatal medicine, has discussed using antithrombotic drugs in pregnancy based on guidelines and package insert information. Searching the literature often found disagreement between information in FDA categories, Japanese guidelines, Japanese package inserts, and overseas package inserts, but this was not further pursued. Neurosurgeons and neurologists also commonly encounter pregnant women with thromboembolism, such as ischemic stroke. Up-to-date information and correct selection of drugs are necessary in consultation with specialists in perinatal care.

Conflicts of Interest Disclosure

The author declares that he has no conflict of interest.

References

1) Briggs GG, Freeman RK, Yaffe SJ: *Drugs in Pregnancy and Lactation, 8th ed.* Philadelphia, PA, Lippincott Williams & Wilkins, 2008
2) Furie KL, Kasner SE, Adams RJ, Albers GW, Bush RL, Fagan SC, Halperin JL, Johnston SC, Katzan I, Kernan WN, Mitchell PH, Ovbiagele B, Palesch YY, Sacco RL, Schwamm LH, Wassertheil-Smoller S, Turan TN, Wentworth D; American Heart Association Stroke Council, Council on Cardiovascular Nursing, Council on Clinical Cardiology, and Interdisciplinary Council on Quality of Care and Outcomes Research: Guidelines for the prevention of stroke in patients with stroke or transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 42: 227–276, 2011
3) JCS Joint Working Group: Guidelines for indication and management of pregnancy and delivery in women with heart disease (JCS 2010): digest version. *Circ J* 76: 240–260, 2012
4) JCS Joint Working Group: [Guidelines for management of anticoagulant and antiplatelet therapy in cardiovascular disease (JCS 2009)] (Japanese). Kyoto, the Japanese Circulation Society. Available at http://www.j-circ.or.jp/guideline/pdf/JCS2009 _ hori _ h.pdf. Accessed April 17, 2013
5) Uchiyama S, Ibayashi S, Matsumoto M, Nagao T, Nagata K, Nakagawara J, Tanahashi N, Tanaka K, Toyoda K, Yasaka M: Dabigatran and factor Xa inhibitors for stroke prevention in patients with nonvalvular atrial fibrillation. *J Stroke Cerebrovasc Dis* 21: 165–173, 2012

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NIHSS-time score easily predicts outcomes in rt-PA patients: The SAMURAI rt-PA registry

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ABSTRACT

Background: We aimed to devise a scale comprising a simple multiplication of initial National Institutes of Health Stroke Scale (NIHSS) score and onset-to-treatment time (OTT) as a scale for predicting outcomes after recombinant tissue plasminogen activator (rt-PA) therapy.

Methods: Data from rt-PA patients in 10 stroke centers in Japan were investigated. NIHSS-time score was calculated as initial NIHSS score × OTT.

Results: Subjects comprised 526 patients. Median NIHSS score was 12 (7–18), and median OTT was 2.42 h (2.00–2.75 h). Median NIHSS-time score was 27.7 (16.9–41.7). Good (modified Rankin Scale [mRS] 0–1) and poor (mRS 4–6) outcome rates at 3 months for patients with NIHSS-time scores ≤10 were 71.1% and 7.8%, compared to 54.7% and 16.5% for scores >10 and ≤20, 38.9% and 31.9% for scores >20 and ≤30, 25.0% and 44.6% for scores >30 and ≤40, and 17.4% and 61.8% for scores >40, respectively. Cut-off NIHSS-time scores to predict good and poor outcomes with 50% probability were defined as 20 and 40, respectively. Multivariate logistic regression analysis revealed NIHSS-time score as an independent predictor of good (odds ratio [OR], 0.587; 95% confidence interval [CI], 0.422–0.818, p = 0.002) and poor (OR, 1.756; 95%CI, 1.227–2.514, p = 0.002) outcomes after adjusting for age, sex, NIHSS score, OTT, Alberta Stroke Program Early CT Score, internal carotid artery occlusion, and glucose level.

Conclusions: NIHSS-time score predicts clinical outcomes in rt-PA patients.

1. Introduction

Intravenous administration of recombinant tissue plasminogen activator (rt-PA) can improve clinical outcomes in patients with acute ischemic stroke [1]. The frequencies of good outcomes (modified Rankin scale [mRS] score, 0–2) and poor outcomes (mRS score, 4–6) at 3 months after rt-PA therapy are approximately 50% and 40%, respectively [1,2]. Various factors are reportedly associated with outcomes, including age, sex, neurological deficits, onset-to-treatment time (OTT), glucose level on admission, early arterial recanalization, ischemic lesions on computed tomography (CT) or magnetic resonance imaging (MRI) before rt-PA infusion, M1 susceptibility vessel signs on T2*-weighted imaging, and internal carotid artery occlusion [3–14]. However, MRI studies are not always available for all hospitals, and assessing these factors requires specialized training and skill.

Neurological deficits and OTT can be determined for all patients with standard practice and attention. The initial National Institutes of Health Stroke Scale (NIHSS) score is known to be significantly related to clinical outcomes at 3 months after stroke [5], with a baseline NIHSS score ≥8 associated with unfavorable outcomes [15,16]. OTT is another important factor associated with patient outcomes [17]. The National Institutes of Neurological Disorders and Stroke (NINDS) rt-PA stroke study [18] reported that patients treated using rt-PA within 0–90 min after stroke onset showed an increased likelihood of improvement at 24 h and a

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favorable 3-month outcome compared to patients treated >90 min. In other words, early rt-PA treatment should improve patient outcomes. Furthermore, we have already reported that early recanalization depended on OTT [6].

Our hypothesis is that if NIHSS score and OTT parameters are combined, it may have much more clinical impact in acute stroke management. The present study aimed to devise a scale, "NIHSS-time score" using initial NIHSS score and OTT to predict patient outcomes after rt-PA therapy and assess whether this score can predict good and poor outcomes for patients.

2. Methods

This retrospective study was conducted using patient data obtained from the Stroke Acute Management with Urgent Risk-factor Assessment and Improvement (SAMURAI) rt-PA registry. The SAMURAI registry included acute ischemic stroke patients treated using rt-PA after admission to 10 stroke centers in Japan between October 2005 and July 2008. Details of this registry have been reported previously [19]. Based on this registry, only patients who were independent before stroke onset and showed a mRS score of 0–1 were enrolled. Administration of rt-PA therapy was performed based on Japanese guidelines for rt-PA therapy, which follow the inclusion and exclusion criteria used in the NINDS study and Japan Alteplase Clinical trial (J-ACT) [1,2,20]. A single alteplase dose of 0.6 mg/kg (to a maximum of 60 mg) was administered intravenously, with 10% given as a bolus within 3 h of stroke onset, followed by continuous infusion of the remainder over 1 h. Institutional review boards of the each participating stroke center approved the methods for retrospective data collection and submission to the SAMURAI registry for analysis.

The following clinical information was obtained from the registry: age; sex; OTT; neurological deficit (NIHSS score on admission); mRS score before and 3 months after stroke onset; vascular risk factors (hypertension, diabetes mellitus, dyslipidemia); atrial fibrillation; congestive heart failure; blood pressure before rt-PA infusion; stroke etiology; presence of arterial occlusion; and laboratory findings including levels of glucose, hemoglobin A1c, and creatinine before rt-PA therapy. Good and poor outcomes at 3 months after rt-PA therapy were defined as mRS scores of 0–1 and 4–6, respectively. Symptomatic intracerebral hemorrhage was defined according to the Safe Implementation of Thrombolysis in Stroke-Monitoring Study protocol as parenchymal hemorrhage type 2 on CT combined with an increase in NIHSS score of ≥4 from baseline [21]. In addition, we calculated the NIHSS-time score using this formula:

$$\text{NIHSS} - \text{time score} = \text{initial NIHSS score} \times \text{OTT(h)}.$$

For example, when a patient had initial NIHSS score of 9 and received rt-PA therapy 145 min after stroke onset, NIHSS-time score was calculated as follows:

First, 145 min was converted into 2.42 h.
Next, NIHSS score of 9 was multiplied by the 2.42 which equals 21.78.
Then, 21.78 was rounded to the nearest decimal place which is 21.8.
Therefore, the NIHSS-time score of the patients is 21.8.

Arterial occlusion was identified using magnetic resonance angiography (MRA), CT angiography (CTA), or duplex ultrasonography. The Alberta Stroke Program Early CT Score (ASPECTS) was calculated from CT data [9]. Stroke etiology was determined at hospital discharge using Trial of ORG 10172 in Acute Stroke Treatment criteria: 1) small-vessel occlusion; 2) large-artery atherosclerosis; 3) cardioembolism; or 4) other or undetermined etiology of stroke [22].

3. Statistical analysis

First, initial NIHSS score, OTT, and NIHSS-time score were compared among patients with mRS scores of 0–1, 2–3, and 4–6 at 3 months after onset. The association between OTT and mRS score 0–1 was investigated using logistic regression analysis adjusted for NIHSS score as well as univariate analysis, as previously reported [23]. Clinical characteristics of subgroups based on the NIHSS-time score were investigated. Second, we drew a scatter plot focused on mRS scores of 0–1, 2–3, and 4–6 using NIHSS score, and OTT parameters. Cut-off NIHSS-time scores to predict good and poor outcomes at 3 months with 50% probability were investigated. This level of accuracy was accepted as an appropriate to level to motivate physicians. Finally we conducted the multivariate logistic regression analysis to investigate the independence of the NIHSS-time score adjusted using age, sex, NIHSS score on admission, OTT, and other established variables comprising ASPECTS on CT, internal carotid artery occlusion, and blood glucose level. We used the Mann–Whitney *U* test to analyze differences in continuous variables and Fisher's exact test to analyze differences in categorical variables. Data are presented as median values (interquartile range [IQR]) or frequencies (%). All statistical analyses were performed using IBM SPSS Statistics for Windows version 19 software (Chicago, IL, USA). Results were considered significant for values of $p<0.05$.

4. Results

From October 2005 to July 2008, a total of 600 acute stroke patients treated with rt-PA were enrolled into the SAMURAI registry. Among these, a total of 74 patients were excluded from the present study: 68 patients with mRS score 2–5 before stroke onset; 1 patient with unknown OTT; and 5 patients with missing descriptions of mRS at 3 months after stroke onset. As a result, 526 patients (median age, 72 [64–78] years; 346 [65.8%] men) were enrolled into the present study. Median NIHSS score was 12 (7–18), median OTT was 2.42 h (2.00–2.75 h), and median NIHSS-time score was 27.7 (16.9–41.7).

Table 1 shows clinical characteristics among the 5 subgroups with NIHSS-time scores of ≤10, >10 and ≤20, >20 and ≤30, >30 and ≤40, and >40. Although a completely linear pattern was not seen, patients with a lower NIHSS-time score were younger than those with a higher NIHSS-time score. While diabetes mellitus was frequent in the lower NIHSS-time score subgroups, atrial fibrillation and congestive heart failure commonly appeared in the higher NIHSS-time score subgroups. ASPECTS was significantly lower in the high NIHSS-time score subgroups. Internal carotid artery and middle cerebral artery occlusions were more frequently seen in the high NIHSS-time score subgroups than the lower NIHSS-time score subgroups.

At 3 months after stroke onset, mRS score was 0–1 in 195 (37.1%) of the 526 patients, 2–3 in 139 (26.4%) and 4–6 in 192 (36.5%).

Baseline NIHSS score was 9 (6–14) in patients with mRS score of 0–1 at 3 months, 11 (7–17) with mRS score 2–3, and 18 (12–21) with mRS score 4–6 ($p<0.001$). Although univariate analysis did not show any significant correlation between OTT and clinical outcome, OTT was significantly related to favorable outcome after adjusting for baseline NIHSS score (odds ratio (OR), 0.675; 95% confidence interval [CI], 0.433–0.996, $p=0.048$).

NIHSS-time score was 19.5 (14.5–29.9) in patients with mRS score of 0–1, 27.5 (16.9–38.1) with mRS score 2–3, and 38.6 (26.6–50.5) with mRS score 4–6 ($p<0.001$). A scatter plot of NIHSS score and OTT is presented in Fig. 1. Curves are drawn based on NIHSS-time scores of 10, 20, 30, and 40. Fig. 2 shows the associations of mRS at 3 months after stroke onset with initial NIHSS score and OTT. The incidence of good outcome in patients with NIHSS score ≤10 was 54.7%, and this rate was markedly decreased in those patients with NIHSS score >10.

Frequencies of good and poor outcomes based on the NIHSS-time score are shown in Fig. 3. Patients with good and poor outcomes amounted to 71.1% and 7.8% of patients with NIHSS-time score ≤10,

Table 1
Clinical characteristics of subgroups based on the NIHSS-time score.

		NIHSS-time score					p value
	Total	≤10	>10 and ≤20	>20 and ≤30	>30 and ≤40	>40	
	n=526	n=38	n=139	n=113	n=92	n=144	
Baseline NIHSS score	12 (7–18)	4 (3–4)	7 (6–8)	11 (9–13)	15 (13–18)	21 (18–24)	
Onset to treatment time, hour	2.42 (2.00–2.75)	2.15 (1.80–2.67)	2.33 (2.00–2.65)	2.25 (1.83–2.59)	2.33 (2.00–2.72)	2.67 (2.31–2.88)	
NIHSS-time score	27.7 (16.9–41.7)	8.0 (5.3–8.9)	15.5 (13.2–17.5)	25.0 (22.7–27.6)	34.9 (33.2–37.1)	52.0 (45.2–61.1)	
Age	72 (64–78)	71 (60–79)	70 (62–75)	74 (65–79)	73 (64–79)	76 (67–80)	<0.001
Male	346 (65.8)	29 (76.3)	96 (69.1)	75 (66.4)	61 (66.3)	85 (59.0)	0.241
Hypertension	322 (61.2)	21 (55.3)	80 (57.6)	75 (66.4)	59 (64.1)	87 (60.4)	0.560
Diabetes mellitus	96 (18.3)	9 (23.7)	32 (23.0)	27 (23.9)	11 (12.0)	17 (11.8)	0.019
Dyslipidemia	112 (21.3)	9 (23.7)	37 (26.6)	23 (20.4)	20 (21.7)	23 (16.0)	0.289
Atrial fibrillation	215 (40.9)	11 (28.9)	40 (28.8)	46 (40.7)	40 (43.5)	78 (54.2)	<0.001
Congestive heart failure	37 (7.0)	1 (2.6)	7 (5.0)	6 (5.3)	3 (3.3)	20 (13.9)	0.005
Stroke subtype							
Cardioembolism	326 (62.0)	15 (39.5)	65 (46.8)	75 (66.4)	63 (68.5)	108 (75.0)	<0.001
ASPECTS	9 (8–10)	10 (9–10)	10 (9–10)	9 (8–10)	9 (7–10)	9 (7–10)	<0.001
Arterial occlusion site							
Internal carotid artery	77 (14.6)	2 (5.3)	9 (6.5)	7 (6.2)	17 (18.5)	42 (29.2)	<0.001
Middle cerebral artery	232 (44.1)	14 (36.8)	43 (30.9)	58 (51.3)	48 (52.2)	69 (47.9)	
Others	47 (8.9)	3 (7.9)	13 (9.4)	10 (8.8)	9 (9.8)	12 (8.3)	
Pretreatment systolic blood pressure	154 (138–164)	144 (136–164)	157 (140–166)	150 (136–161)	154 (138–163)	155 (136–165)	0.401
Pretreatment diastolic blood pressure	81 (71–91)	76 (70–90)	84 (72–92)	80 (76–90)	82 (70–97)	80 (70–90)	0.443
Symptomatic ICH	8 (1.5)	0 (0)	2 (1.4)	1 (0.9)	0 (0)	5 (3.5)	0.201
Laboratory findings							
Glucose, mg/dl	125 (106–151)	129 (112–170)	125 (109–158)	122 (103–157)	126 (107–156)	130 (110–156)	0.664
Hemoglobin A1c, %	5.9 (5.6–6.3)	5.9 (5.5–6.1)	5.9 (5.6–6.5)	6.0 (5.7–6.4)	5.8 (5.6–6.3)	5.9 (5.6–6.2)	0.494
Creatinine	0.80 (0.65–0.95)	0.84 (0.66–1.00)	0.79 (0.68–0.92)	0.75 (0.62–0.90)	0.84 (0.69–1.00)	0.78 (0.61–0.98)	0.499

Data are no. of patients (%) and median (interquartile range) for discontinuous variables. NIHSS indicates National Institutes of Health Stroke Scale; ASPECTS, Alberta Stroke Program Early CT Score; and ICH, intracerebral hemorrhage.

54.7% and 16.5% of patients with NIHSS-time score >10 and ≤20, 38.9% and 31.9% of patients with NIHSS-time score >20 and ≤30, 25.0% and 44.6% of patients with NIHSS-time score >30 and ≤40, and 17.4% and 61.8% of patients with NIHSS-time score >40, respectively. The frequency of good outcomes thus gradually decreased in parallel with increasing NIHSS-time scores. Conversely, the frequency of poor outcomes gradually increased in parallel with increments in the NIHSS-time score. The cut-off NIHSS-time scores to predict good and poor outcomes with 50% probability were determined to be ≤20 and >40, respectively.

Finally, multivariate logistic regression analysis was conducted to investigate factors independently associated with stroke outcomes after

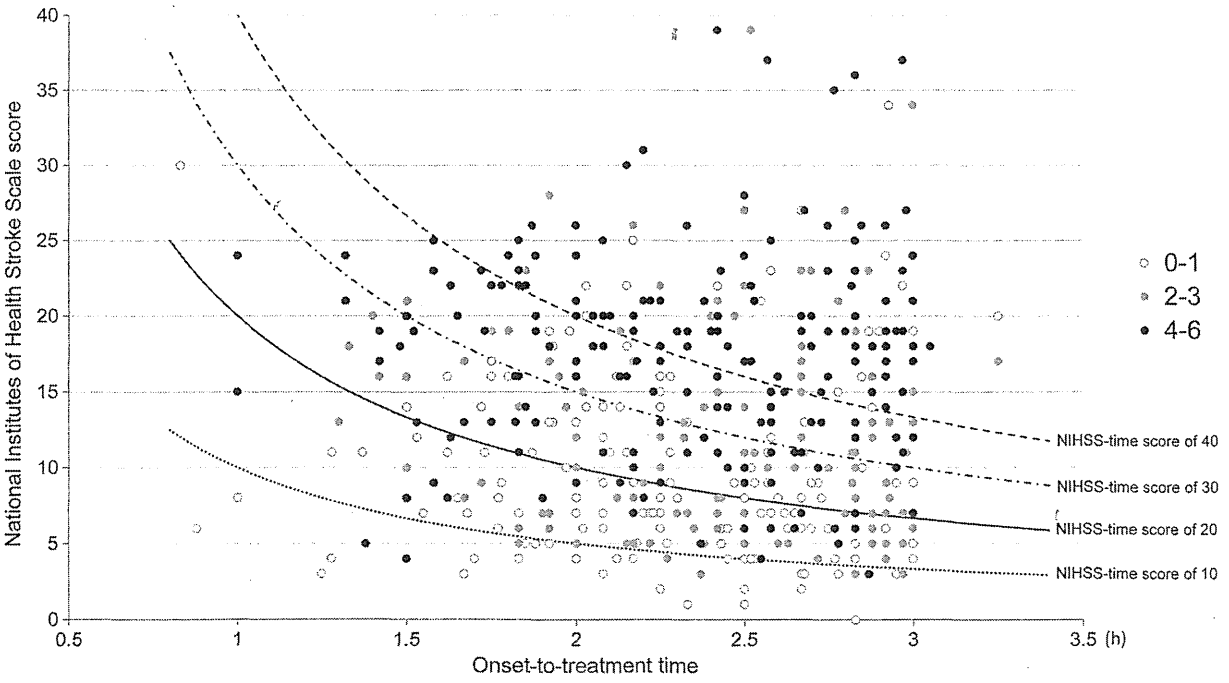

Fig. 1. Scatter plots of patients with modified Rankin scale score of 0–1 (white circle) and 2–6 (gray circle), and 4–6 and 0–3 (black circle) at 3 months after onset based on NIHSS scores and onset-to-treatment time. Curves are drawn based on the NIHSS-time scores of 10, 20, 30, and 40.

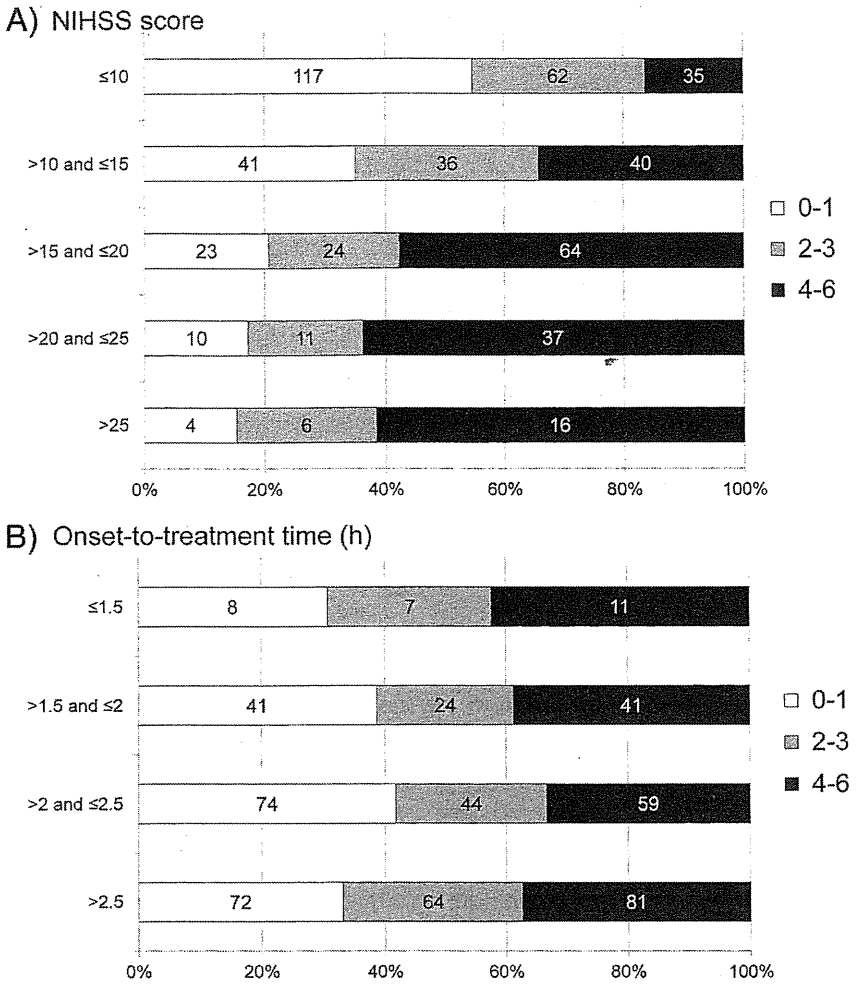

Fig. 2. Modified Rankin scale score at 3 months after stroke onset based on: A) initial NIHSS score; and B) onset-to-treatment time. Total numbers are given in the bars.

rt-PA therapy using variables of age, sex, NIHSS score on admission, OTT, NIHSS-time score, ASPECTS on CT, internal carotid artery occlusion, and blood glucose level. Multivariate logistic regression analysis revealed NIHSS-time score as an independent predictor of both good outcome (OR, 0.587; 95%CI, 0.422–0.818; $p = 0.002$) and poor outcome (OR, 1.756; 95%CI, 1.227–2.514; $p = 0.002$) (Table 2).

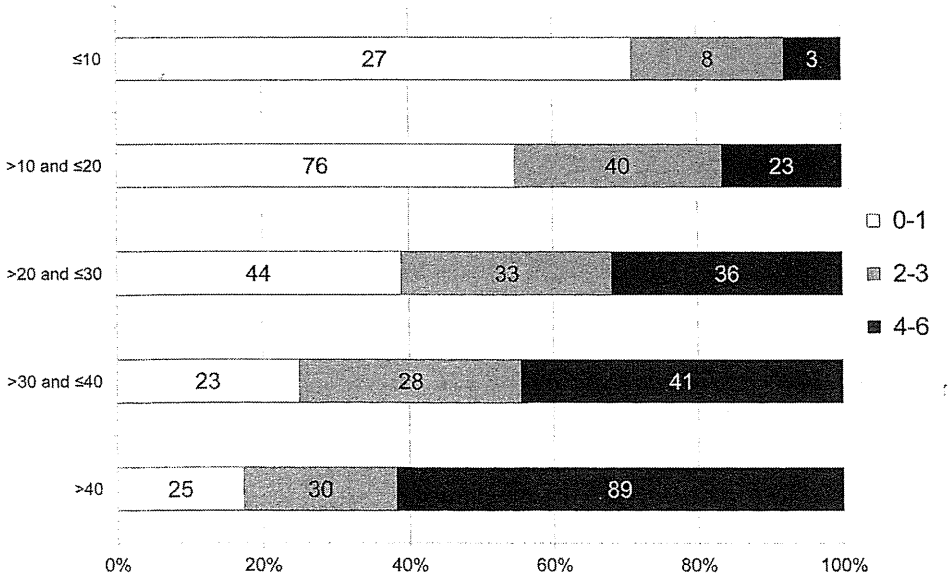

Fig. 3. Modified Rankin scale score at 3 months after stroke onset, based on NIHSS-time score. Total numbers are given in the bars.

Table 2
Multivariate logistic regression analysis of predictors for good and poor outcomes.

Parameters	Odds ratio	95% Confidence interval	p value
mRS score of 0–1			
Age, per 1-year increase	0.970	0.952–0.987	<0.001
Male	1.100	0.710–1.703	0.671
NIHSS score on admission, per 1-category increase	1.070	0.750–1.526	0.709
Onset to treatment time, per 1-category increase	1.113	0.860–1.440	0.416
NIHSS-time score, per 1-category increase	0.587	0.422–0.818	0.002
ASPECTS, per 1-point increase	1.165	1.003–1.353	0.045
Internal carotid artery occlusion	0.252	0.109–0.582	0.001
Glucose, per 1-mg/dl increase	0.045	0.991–1.000	0.045
mRS score of 4–6			
Age, per 1-year increase	1.045	1.022–1.069	<0.001
Male	0.895	0.567–1.414	0.635
NIHSS score on admission, per 1-category increase	1.033	0.730–1.462	0.855
Onset to treatment time, per 1-category increase	0.746	0.563–0.990	0.042
NIHSS-time score, per 1-category increase	1.756	1.227–2.514	0.002
ASPECTS, per 1-point increase	0.804	0.701–0.923	0.002
Internal carotid artery occlusion	4.945	2.630–9.299	<0.001
Glucose, per 1-mg/dl increase	1.004	0.999–1.008	0.095

NIHSS indicates National Institutes of Health Stroke Scale; mRS, modified Rankin scale; and ASPECTS, Alberta Stroke Program Early CT Score.
NIHSS score was categorized as ≤10, >10 and ≤15, >15 and ≤20, >20 and ≤25, and >25.
Onset to treatment time was categorized as ≤1, >1 and ≤1.5, >1.5 and ≤2, >2 and ≤2.5, and >2.5.
NIHSS-time score was categorized as ≤10, >10 and ≤20, >20 and ≤30, >30 and ≤40, and >40.

5. Discussion

The present study demonstrated the utility of the NIHSS-time score as a predictor of clinical outcomes after rt-PA therapy. To the best of our knowledge, this represents the first study to indicate the utility of a scale combining initial NIHSS score and OTT. The NIHSS-time score is determined as the simple product of initial NIHSS score and OTT, and is easily adaptable to clinical practice. Immediately on admission of an acute stroke patient to hospital, outcomes can be predicted using this NIHSS-time score.

NIHSS score was found to be significantly associated with clinical outcomes, supporting the findings from sub-analysis of the NINDS rt-PA trial [5]. The proportion of patients with an mRS score of 0–1 at 3 months was 76.4% among patients with an NIHSS score of 1–7, 45.6% with 8–14, and 23.3% with ≥15. Regarding OTT, meta-analysis identified serial linear relationships between delayed OTT and mRS scores of 0–1 at 3 months after onset. The OR for treatment within 1.5 h was 2.55 compared to the placebo group, compared to 1.64 for within 1.5–3 h, and 1.34 for within 3–4.5 h [23]. As initial NIHSS score and OTT were each independent predictors of patient outcome after rt-PA therapy, the simple product of these factors should offer a valuable score.

The advantage of the NINSS-time score over NIHSS score and OTT is that it enables calculation of the time left for good and poor stroke outcomes by dividing each cut-off score by the initial NIHSS score. Although the likelihood of independence has been widely accepted as affected by OTT [24], the temporal concept has remained rather abstract and has not been used to clearly delineate the time remaining to achieve the benefits of rt-PA in each candidate. Time calculated by NIHSS-time score should serve as a benchmark to modify management before rt-PA. Furthermore, frequencies of both good and poor outcomes clearly paralleled decrements and increments of NIHSS-time score. Conversely, changes in NIHSS score were not equal to the rate of change for good and poor clinical outcomes. Multivariate logistic regression analysis revealed the superiority of NIHSS-time score compared to NIHSS score and OTT. We are certain that the NIHSS-time score will allow dynamic improvements in acute stroke management.

An NIHSS-time score of 20 served as a cut-off to predict good outcomes with 50% probability after rt-PA therapy. As patients with severe deficits show shorter time constraints to obtain good outcomes, rt-PA should be given to patients with severe neurological deficits as soon as possible. Several modalities including CTA, MRI, MRA, and ultrasound examinations are available in stroke centers. However, a high priority should be placed on NIHSS-time score and examinations must be performed without affecting the NIHSS-time score.

Furthermore, both community education and pre-hospital triage are essential along with in-hospital care to minimize the OTT. Miyamatsu et al. [25] recently reported that a mass-media educational campaign using television increased knowledge about early symptoms of stroke. Acute stroke patients should be transferred to stroke center as soon as possible to reduce the OTT. Using an ambulance system has been proven to shorten the OTT compared to first seeking medical contact with a personal physician [26]. In Japan, the Kurashiki Prehospital Stroke Scale (KPSS), with a maximum score of 13, is widely used by paramedics to assess stroke severity [27]. Iguchi et al. [28] reported that KPSS ≥4 represents a good score to indicate prospective rt-PA patients. To reduce the NIHSS-time score, physicians should administer rt-PA therapy to acute stroke patients as soon as possible.

Three-fifths of patients with an NIHSS-time score >40 showed poor outcomes even with administration of rt-PA. This finding indicates the limitations of rt-PA therapy. Merci retriever and Penumbra aspiration systems have now become available [29,30], so combination therapy using rt-PA and endovascular therapy might be useful to improve outcomes in patients with NIHSS-time score >40. We recently reported that administration of edaravone, a free radical scavenger, during rt-PA infusion might enhance early recanalization in acute stroke patients [31]. We expect the development of pharmacotherapies to enhance early recanalization in rt-PA patients.

Several limitations must be considered in the interpretation of this study. First, the present registry investigation was an observational study. Second, the dose of rt-PA (0.6 mg/kg, the approved dose in Japan) used was lower than the internationally approved dosage of 0.9 mg/kg. Third, we simply made NIHSS-time score by multiplying NIHSS score by OTT, statistically described as interaction term. However, age has been another significant factor related to the clinical outcome. We did not include age as factors of NIHSS-time score to simplify this score more. In addition, we have to apply this score to another cohort to confirm the utility of the NIHSS-time score. Further large randomized study is needed to confirm our study results.

In conclusion, NIHSS-time score allows prediction of stroke outcomes in acute rt-PA stroke patients. This score is simple and readily

adaptable in clinical practice. To reduce the NIHSS-time score, physicians should administrate rt-PA to acute stroke patients as soon as possible.

Conflicts of interest

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References

[1] Tissue plasminogen activator for acute ischemic stroke. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. N Engl J Med Dec 14 1995;333(24):1581–7.
[2] Yamaguchi T, Mori E, Minematsu K, Nakagawara J, Hashi K, Saito I, et al. Alteplase at 0.6 mg/kg for acute ischemic stroke within 3 hours of onset: Japan Alteplase Clinical Trial (J-ACT). Stroke Jul 2006;37(7):1810–5.
[3] Heuschmann PU, Kolominsky-Rabas PL, Roether J, Misselwitz B, Lowitzsch K, Heidrich J, et al. Predictors of in-hospital mortality in patients with acute ischemic stroke treated with thrombolytic therapy. JAMA Oct 20 2004;292(15):1831–8.
[4] Kent DM, Price LL, Ringleb P, Hill MD, Selker HP. Sex-based differences in response to recombinant tissue plasminogen activator in acute ischemic stroke: a pooled analysis of randomized clinical trials. Stroke Jan 2005;36(1):62–5.
[5] Saver JL, Yafeh B. Confirmation of tPA treatment effect by baseline severity-adjusted end point reanalysis of the NINDS-tPA stroke trials. Stroke Feb 2007;38(2):414–6.
[6] Kimura K, Iguchi Y, Shibazaki K, Aoki J, Watanabe M, Matsumoto N, et al. Early stroke treatment with IV t-PA associated with early recanalization. J Neurol Sci Aug 15 2010;295(1–2):53–7.
[7] Alvarez-Sabin J, Molina CA, Montaner J, Arenillas JF, Huertas R, Ribo M, et al. Effects of admission hyperglycemia on stroke outcome in reperfused tissue plasminogen activator-treated patients. Stroke May 2003;34(5):1235–41.
[8] del Zoppo GJ, Poeck K, Pessin MS, Wolpert SM, Furlan AJ, Ferbert A, et al. Recombinant tissue plasminogen activator in acute thrombotic and embolic stroke. Ann Neurol Jul 1992;32(1):78–86.
[9] Barber PA, Demchuk AM, Zhang J, Buchan AM. Validity and reliability of a quantitative computed tomography score in predicting outcome of hyperacute stroke before thrombolytic therapy. ASPECTS Study Group. Alberta Stroke Programme Early CT Score. Lancet May 13 2000;355(9216):1670–4.
[10] Puetz V, Dzialowski I, Hill MD, Steffenhagen N, Coutts SB, O'Reilly C, et al. Malignant profile detected by CT angiographic information predicts poor prognosis despite thrombolysis within three hours from symptom onset. Cerebrovasc Dis 2010;29(6):584–91 [Research Support, Non-U.S. Gov't].
[11] Kimura K, Iguchi Y, Shibazaki K, Terasawa Y, Inoue T, Uemura J, et al. Large ischemic lesions on diffusion-weighted imaging done before intravenous tissue plasminogen activator thrombolysis predicts a poor outcome in patients with acute stroke. Stroke Aug 2008;39(8):2388–91.
[12] Nezu T, Koga M, Kimura K, Shiokawa Y, Nakagawara J, Furui E, et al. Pretreatment ASPECTS on DWI predicts 3-month outcome following rt-PA: SAMURAI rt-PA Registry. Neurology Aug 10 2010;75(6):555–61.
[13] Kimura K, Iguchi Y, Shibazaki K, Watanabe M, Iwanaga T, Aoki J. M1 susceptibility vessel sign on T2* as a strong predictor for no early recanalization after IV-t-PA in acute ischemic stroke. Stroke Sep 2009;40(9):3130–2.
[14] Rubiera M, Ribo M, Delgado-Mederos R, Santamarina E, Delgado P, Montaner J, et al. Tandem internal carotid artery/middle cerebral artery occlusion: an independent predictor of poor outcome after systemic thrombolysis. Stroke Sep 2006;37(9):2301–5.
[15] The NINDS t-PA Stroke Study Group. Intracerebral hemorrhage after intravenous t-PA therapy for ischemic stroke. Stroke Nov 1997;28(11):2109–18.
[16] DeGraba TJ, Hallenbeck JM, Pettigrew KD, Dutka AJ, Kelly BJ. Progression in acute stroke: value of the initial NIH stroke scale score on patient stratification in future trials. Stroke Jun 1999;30(6):1208–12.
[17] Saver JL. Time is brain-quantified. Stroke Jan 2006;37(1):263–6.
[18] Marler JR, Tilley BC, Lu M, Brott TG, Lyden PC, Grotta JC, et al. Early stroke treatment associated with better outcome: the NINDS rt-PA stroke study. Neurology Dec 12 2000;55(11):1649–55.
[19] Toyoda K, Koga M, Naganuma M, Shiokawa Y, Nakagawara J, Furui E, et al. Routine use of intravenous low-dose recombinant tissue plasminogen activator in Japanese patients: general outcomes and prognostic factors from the SAMURAI register. Stroke Nov 2009;40(11):3591–5.
[20] Shinohara Y, Yamaguchi T. Outline of the Japanese Guidelines for the Management of Stroke 2004 and subsequent revision. Int J Stroke Feb 2008;3(1):55–62.
[21] Wahlgren N, Ahmed N, Davalos A, Ford GA, Grond M, Hacke W, et al. Thrombolysis with alteplase for acute ischaemic stroke in the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST): an observational study. Lancet Jan 27 2007;369(9558):275–82.
[22] Adams Jr HP, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. Stroke Jan 1993;24(1):35–41.
[23] Lees KR, Bluhmki E, von Kummer R, Brott TG, Toni D, Grotta JC, et al. Time to treatment with intravenous alteplase and outcome in stroke: an updated pooled analysis of ECASS, ATLANTIS, NINDS, and EPITHET trials. Lancet May 15 2010;375(9727):1695–703.
[24] Lansberg MG, Schrooten M, Bluhmki E, Thijs VN, Saver JL. Treatment time-specific number needed to treat estimates for tissue plasminogen activator therapy in acute stroke based on shifts over the entire range of the modified Rankin Scale. Stroke Jun 2009;40(6):2079–84.
[25] Miyamatsu N, Kimura K, Okamura T, Iguchi Y, Nakayama H, Toyota A, et al. Effects of public education by television on knowledge of early stroke symptoms among a Japanese population aged 40 to 74 years: a controlled study. Stroke Feb 2012;43(2):545–9.
[26] Barsan WG, Brott TG, Broderick JP, Haley EC, Levy DE, Marler JR. Time of hospital presentation in patients with acute stroke. Arch Intern Med Nov 22 1993;153(22):2558–61.
[27] Kimura K, Inoue T, Iguchi Y, Shibazaki K. Kurashiki prehospital stroke scale. Cerebrovasc Dis 2008;25(1–2):189–91.
[28] Iguchi Y, Kimura K, Watanabe M, Shibazaki K, Aoki J. Utility of the kurashiki prehospital stroke scale for hyperacute stroke. Cerebrovasc Dis 2011;31(1):51–6.
[29] Smith WS, Sung G, Starkman S, Saver JL, Kidwell CS, Gobin YP, et al. Safety and efficacy of mechanical embolectomy in acute ischemic stroke: results of the MERCI trial. Stroke Jul 2005;36(7):1432–8.
[30] Bose A, Henkes H, Alfke K, Reith W, Mayer TE, Berlis A, et al. The Penumbra System: a mechanical device for the treatment of acute stroke due to thromboembolism. AJNR Am J Neuroradiol Aug 2008;29(7):1409–13.
[31] Kimura K, Aoki J, Sakamoto Y, Kobayashi K, Sakai K, Inoue T, et al. Administration of edaravone, a free radical scavenger, during t-PA infusion can enhance early recanalization in acute stroke patients — a preliminary study. J Neurol Sci Feb 15 2012;313(1–2):132–6.

Impact of Early Blood Pressure Variability on Stroke Outcomes After Thrombolysis

The SAMURAI rt-PA Registry

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Background and Purpose—The present study determines associations between early blood pressure (BP) variability and stroke outcomes after intravenous thrombolysis.

Methods—In 527 stroke patients receiving intravenous alteplase (0.6 mg/kg), BP was measured 8 times within the first 25 hours. BP variability was determined as ΔBP (maximum-minimum), standard deviation (SD), coefficient of variation, and successive variation.

Results—The systolic BP course was lower among patients with modified Rankin Scale (mRS) 0 to 1 than those without (P<0.001). Most of systolic BP variability profiles were significantly associated with outcomes. Adjusted odds ratios (95% confidence interval) per 10 mm Hg (or 10% for coefficient of variation) on symptomatic intracerebral hemorrhage were as follows: ΔBP, 1.33 (1.08–1.66); SD, 2.52 (1.26–5.12); coefficient of variation, 3.15 (1.12–8.84); and successive variation, 1.82 (1.04–3.10). The respective values were 0.88 (0.77–0.99), 0.73 (0.48–1.09), 0.77 (0.43–1.34), and 0.76 (0.56–1.03) for 3-month mRS 0 to 1; and 1.40 (1.14–1.75), 2.85 (1.47–5.65), 4.67 (1.78–12.6), and 1.99 (1.20–3.25) for death. Initial BP values before thrombolysis were not associated with any outcomes.

Conclusions—Early systolic BP variability was positively associated with symptomatic intracerebral hemorrhage and death after intravenous thrombolysis. (***Stroke.* 2013;44:816-818.**)

Key Words: acute stroke ■ blood pressure variability ■ hypertension ■ tissue plasminogen activator

Blood pressure (BP) is often elevated in patients with acute ischemic stroke, but value of lowering BP for such patients is controversial, particularly for those receiving intravenous (IV) recombinant tissue plasminogen activator (rt-PA). Several observational studies have identified a linear or U-shaped association between high systolic BP (SBP) on admission or within the first 24 hours with symptomatic intracerebral hemorrhage (sICH), mortality, and poor functional outcomes.[1-3] BP variability is an important trigger of vascular events,[4] and visit-to-visit SBP variability is a powerful predictor of stroke, independently of mean SBP.[5] Similarly, hour-to-hour BP variability during acute stroke also seems to predict stroke outcomes.[6] The present substudy of the Stroke Acute Management with Urgent Risk-factor Assessment and Improvement (SAMURAI) rt-PA Registry investigates associations between early BP variability during this period and outcomes of thrombolysis.

Patients and Methods

The SAMURAI rt-PA registry was created using a multicenter hospital-based retrospective observational design.[7] Six-hundred consecutive patients with acute ischemic stroke who received IV rt-PA (0.6 mg/kg, recommended dosage by the Japanese guidelines)[8] were registered.

Supine BP was measured just before starting IV rt-PA (initial) and at 0, 4, 8, 12, 16, 20, and 24 hours after completing the administration. Use of antihypertensives, such as IV nicardipine, was permitted if needed according to the guidelines.[8,9] The maximum (max), minimum (min), and average (mean) of these 8 BP values were calculated. We also calculated the following variability profiles: the difference between max and min (ΔBP), SD ($SD: \sqrt{(1/(n-1)\sum_{(i=1)}^{(n-1)}(BP_i - BP_{mean})^2}$), coefficient of variation (CV [%]: $SD/BP_{mean} \times 100$), and successive variation as the square root of the average difference in BP between each of the 8 successive measurements was calculated using the following equation: $\sqrt{(1/(n-1)\sum_{i=1}^{n-1}(BP_{i+1} - BP_i)^2}$[10]

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Outcomes included sICH (computed tomography evidence of new type I or type II parenchymal hemorrhage[11] with ≥1-point increase from the baseline National Institutes of Health Stroke Scale score) within the first 36 hours and modified Rankin Scale (mRS) score of 0 to 1 and death at 3 months. Associations between each BP profile and outcomes were determined using binominal logistic regression models adjusted by the known baseline characteristics (see detailed patient information and Statistical Methods in the online-only Data Supplement).[12]

Results

Among registered patients, 65 with premorbid mRS score 2 to 5, 7 with incomplete BP values, and 1 who died within 24 hours were excluded. Thus, data from 527 patients (182 women, 70.8±11.6 years old; Online Table I shows baseline characteristics) were eligible for analysis. Twenty-three patients (4.4%) had development sICH, 197 (37.4%) had mRS 0 to 1, and 29 (5.5%) died.

The SBP course tended to be higher among patients with sICH than those without (P=0.083), and it was significantly lower among patients with mRS 0 to 1 than those without (P<0.001; Figure). BP variability profiles were larger in patients receiving antihypertensives just before thrombolysis than the others (online Table II).

Larger variations in all SBP variability profiles were associated with sICH and death (Table). Smaller ΔBP was significantly associated with (P=0.043) and smaller successive variation was marginally significantly associated (P=0.081) with mRS 0 to 1. Although larger variations in all diastolic BP variability profiles were associated with sICH and death, no diastolic BP profiles were associated with mRS 0 to 1 (online Figure I and online Table III).

Discussion

The first major finding of this study was a positive association between all SBP and diastolic BP variability profiles and sICH and death. The second major finding was that SBP levels were lower throughout the first 25 hours after starting rt-PA in patients who had mRS score 0 to 1 than in those who did not. Furthermore, systolic ΔBP was inversely associated with mRS score 0 to 1. Finally, initial BP levels, as well as most of BP values at each time point, did not predict any outcomes.

In a substudy of the Second European-Australasian Acute Stroke Study (ECASS-II),[12] max, mean, and successive variation of 24-hour SBPs predicted hemorrhagic transformation and 3-month outcomes after thrombolysis. In that study, 80% of the patients received thrombolytic therapy within 3 to 6 hours after onset.[11] In our single-center study of IV rt-PA, max, mean, and min of SBPs were inversely associated with 3-month mRS score 0 to 2.[3] A recent single-center study showed that successive variation of SBP higher than the median value is associated with 3-month mRS score 0 to 2, but not with mortality or sICH.[13] Different contributions of BP variability to outcomes among investigations including the present study might be attributable to difference in indicators, measures of variability, or timing of BP measurements.

Contrary to the ECASS-II substudy,[12] initial BP values did not predict any outcomes in the present study. One explanation might be that we documented BP values immediately before starting thrombolysis and, accordingly, some very high BP values would have been modified by antihypertensive drugs. In addition, mental stress, bladder tonus, and other transient stimuli also modulate BP values and, therefore, measuring during the first few hours might not accurately reflect stroke conditions. These findings suggest that BP values determined during the first 24 hours of admission confer an advantage as a predictor of prognosis.

The present study stresses the impact of variability in BP as a predictor of stroke outcomes. These findings indicate that the therapeutic effects of modulating acute BP variability

Table. Associations Between Systolic Blood Pressure Profiles and Outcomes

	sICH		mRS 0–1		Death	
Initial	1.08	0.86–1.35	0.96	0.86–1.06	1.03	0.83–1.27
0 h	1.28	0.99–1.66	**0.87**	**0.78–0.97**	0.98	0.79–1.23
4 h	1.24	0.99–1.57	**0.89**	**0.80–0.99**	1.05	0.86–1.30
8 h	1.02	0.82–1.27	0.92	0.83–1.02	1.05	0.85–1.29
12 h	1.16	0.93–1.46	0.91	0.82–1.005	0.90	0.74–1.11
16 h	1.14	0.92–1.41	1.02	0.92–1.13	0.93	0.76–1.14
20 h	1.05	0.84–1.32	0.90	0.81–1.001	0.93	0.76–1.14
24 h	0.98	0.80–1.21	0.93	0.84–1.03	0.93	0.77–1.12
Max	**1.36**	**1.07–1.73**	**0.82**	**0.73–0.93**	1.19	0.93–1.50
Min	0.91	0.69–1.18	0.92	0.81–1.04	**0.74**	**0.57–0.94**
Mean	1.24	0.89–1.75	**0.86**	**0.74–0.99**	0.94	0.70–1.27
ΔBP	**1.33**	**1.08–1.66**	**0.88**	**0.77–0.99**	**1.40**	**1.14–1.75**
SD	**2.52**	**1.26–5.12**	0.73	0.48–1.09	**2.85**	**1.47–5.65**
CV	**3.15**	**1.12–8.84**	0.77	0.43–1.34	**4.67**	**1.78–12.6**
SV	**1.82**	**1.04–3.10**	0.76	0.56–1.03	**1.99**	**1.20–3.25**

BP indicates blood pressure; CV, coefficient of variation; Max, maximum; Min, minimum; mRS, modified Rankin Scale; SBP, systolic BP; sICH, symptomatic intracerebral hemorrhage; SD, standard deviation; and SV, successive variation.

Odds ratio per 10 mm Hg with 95% confidence interval for each SBP profile adjusted for sex, age, baseline National Institutes of Health Stroke Scale score, onset-to-treatment interval, hypertension, diabetes mellitus, dyslipidemia, atrial fibrillation, intravenous antihypertensives just before recombinant tissue plasminogen activator, and ASPECTS on first computed tomography scan. Bold indicates, P<0.05.

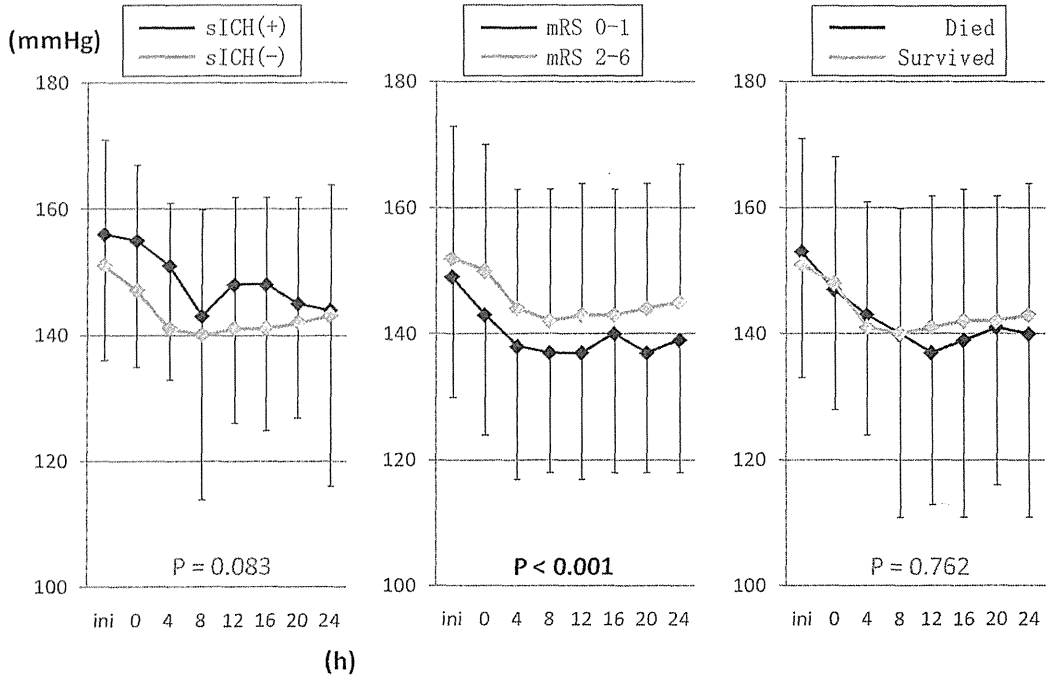

Figure. Comparisons of time course of systolic blood pressure according to symptomatic intracerebral hemorrhage (sICH), modified Rankin Scale (mRS) value, and mortality at 3 months. ini indicates initial.

should be investigated. An ongoing trial of early intensive BP-lowering in patients with thrombolysis, the Enhanced Control of Hypertension and Thrombolysis Stroke Study (ENCHANTED) (NCT01422616), would bring an answer for this problem.

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References

1. Wahlgren N, Ahmed N, Eriksson N, Aichner F, Bluhmki E, Dávalos A, et al; Safe Implementation of Thrombolysis in Stroke-MOnitoring STudy Investigators. Multivariable analysis of outcome predictors and adjustment of main outcome results to baseline data profile in randomized controlled trials: Safe Implementation of Thrombolysis in Stroke-MOnitoring STudy (SITS-MOST). *Stroke*. 2008;39:3316–3322.
2. Ahmed N, Wahlgren N, Brainin M, Castillo J, Ford GA, Kaste M, et al; SITS Investigators. Relationship of blood pressure, antihypertensive therapy, and outcome in ischemic stroke treated with intravenous thrombolysis: retrospective analysis from Safe Implementation of Thrombolysis in Stroke-International Stroke Thrombolysis Register (SITS-ISTR). *Stroke*. 2009;40:2442–2449.
3. Tomii Y, Toyoda K, Nakashima T, Nezu T, Koga M, Yokota C, et al. Effects of hyperacute blood pressure and heart rate on stroke outcomes after intravenous tissue plasminogen activator. *J Hypertens*. 2011;29:1980–1987.
4. Rothwell PM. Limitations of the usual blood-pressure hypothesis and importance of variability, instability, and episodic hypertension. *Lancet*. 2010;375:938–948.
5. Rothwell PM, Howard SC, Dolan E, O'Brien E, Dobson JE, Dahlöf B, et al. Prognostic significance of visit-to-visit variability, maximum systolic blood pressure, and episodic hypertension. *Lancet*. 2010;375:895–905.
6. Tomii Y, Toyoda K, Suzuki R, Naganuma M, Fujinami J, Yokota C, et al. Effects of 24-hour blood pressure and heart rate recorded with ambulatory blood pressure monitoring on recovery from acute ischemic stroke. *Stroke*. 2011;42:3511–3517.
7. Toyoda K, Koga M, Naganuma M, Shiokawa Y, Nakagawara J, Furui E, et al; Stroke Acute Management with Urgent Risk-factor Assessment and Improvement Study Investigators. Routine use of intravenous low-dose recombinant tissue plasminogen activator in Japanese patients: general outcomes and prognostic factors from the SAMURAI register. *Stroke*. 2009;40:3591–3595.
8. Shinohara Y, Yanagihara T, Abe K, Yoshimine T, Fujinaka T, Chuma T, et al. II. Cerebral infarction/transient ischemic attack (TIA). *J StrokeCerebrovasc Dis*. 2011;20(Suppl 4):S31–S73.
9. Adams HP Jr, del Zoppo G, Alberts MJ, Bhatt DL, Brass L, Furlan A, et al; American Heart Association; American Stroke Association Stroke Council; Clinical Cardiology Council; Cardiovascular Radiology and Intervention Council; Atherosclerotic Peripheral Vascular Disease and Quality of Care Outcomes in Research Interdisciplinary Working Groups. Guidelines for the early management of adults with ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council, Clinical Cardiology Council, Cardiovascular Radiology and Intervention Council, and the Atherosclerotic Peripheral Vascular Disease and Quality of Care Outcomes in Research Interdisciplinary Working Groups: the American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists. *Stroke*. 2007;38:1655–1711.
10. Schächinger H, Langewitz W, Schmieder RE, Rüddel H. Comparison of parameters for assessing blood pressure and heart rate variability from non-invasive twenty-four-hour blood pressure monitoring. *J Hypertens*. 1989;7(Suppl 3):81–84.
11. Hacke W, Kaste M, Fieschi C, von Kummer R, Davalos A, Meier D, et al. Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II). Second European-Australasian Acute Stroke Study Investigators. *Lancet*. 1998;352:1245–1251.
12. Yong M, Kaste M. Association of characteristics of blood pressure profiles and stroke outcomes in the ECASS-II trial. *Stroke*. 2008;39:366–372.
13. Kellert L, Sykora M, Gumbinger C, Herrmann O, Ringleb PA. Blood pressure variability after intravenous thrombolysis in acute stroke does not predict intracerebral hemorrhage but poor outcome. *Cerebrovasc Dis*. 2012;33:135–140.

Stroke Outcomes of Japanese Patients With Major Cerebral Artery Occlusion in the Post-Alteplase, Pre-MERCI Era

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This study examined outcomes of patients with acute ischemic stroke (AIS) with major cerebral artery occlusion after the approval of intravenous recombinant tissue-type plasminogen activator (IV rt-PA) but before approval of the MERCI retriever. We retrospectively enrolled 1170 consecutive patients with AIS and major cerebral artery occlusion (496 women; mean age, 73.9 ± 12.3 years) who were admitted within 24 hours after the onset of symptoms to 12 Japanese stroke centers between October 2005 and June 2009. Cardioembolism was a leading cause of AIS in this group (68.2%). The occlusion sites of the major cerebral arteries included the common carotid artery and internal carotid artery (ICA; 29.6%), middle cerebral artery (52.2%), and basilar artery (7.6%). Recanalization therapy (RT) was performed in 32.0% of patients (IV rt-PA, 20.0%; neuroendovascular therapy, 9.4%; combined, 2.5%). Symptomatic intracerebral hemorrhage within 36 hours with a ≥1-point increase in the National Institutes of Health Stroke Scale score occurred in 5.3% of the patients. At 3 months (or at hospital discharge), 29.3% of the patients had a favorable outcome (based on a modified Rankin scale score of 0-2), 23.8% were bedridden, and 15.6% died. After multivariate adjustment, RT was positively associated with a favorable outcome and negatively associated with death, whereas age, baseline National Institutes of Health Stroke Scale score, and ICA occlusion were negatively associated with a favorable outcome and positively associated with death. One-third of the patients with AIS and major cerebral artery occlusion were treated with RT, which was independently associated with favorable outcomes and death. However,

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40% of the patients became bedridden or died during the post-alteplase, pre-MERCI era in Japan. **Key Words:** Acute ischemic stroke—thrombolysis—t-PA—endovascular treatment.

Although the age-adjusted annual incidence of acute ischemic stroke (AIS) has gradually decreased,[1,2] the prognosis for many patients with AIS and major cerebral artery occlusion remains poor. Intravenous (IV) recombinant tissue-type plasminogen activator (rt-PA) can be administered within 3-4.5 hours of symptom onset, but is not very effective for patients with occlusion of the internal carotid artery (ICA)[3] or proximal middle cerebral artery (MCA).[4] Intra-arterial thrombolysis is another strategy for treating acute major cerebral artery occlusion, but its value is limited as well.[5,6] The effects of percutaneous transluminal angioplasty or intracranial stenting are unclear, given the lack of adequate clinical trials. New neuroendovascular devices to remove clots from occluded arteries, such as the MERCI retriever,[7,8] PENUMBRA System,[9] or Solitaire stent,[10] have been introduced worldwide; however, these have yet to be examined in randomized control trials. A concern surrounding the use of these devices is the possible high mortality rate if recanalization is not achieved.

In Japan, a council was established in 2009 to consider approval for such devices, and clinical data on patients with AIS and major cerebral artery occlusion who were not treated with these devices are required. In advance of the council, a joint research task force derived from the JR-NET2 (Japanese Registry of NeuroEndovascular Therapy 2) and SAMURAI (Stroke Acute Management with Urgent Risk Factor Assessment and Improvement) study groups on stroke medicine conducted a multicenter observational study to determine the current domestic status of AIS with major cerebral artery occlusion in the post-alteplase, pre-MERCI era.

Patients and Methods

We retrospectively registered 1170 consecutive patients (496 women; mean age, 73.9 ± 12.3 years) who were admitted within 24 hours of AIS onset with major cerebral artery occlusion to 12 stroke centers in Japan between October 2005 and June 2009. During the study period, a total of 5213 patients were admitted within 24 hours after the onset of any type of AIS to these stroke centers. The local Ethics Committees approved the retrospective collection of clinical information from databases and submission of the data to our central office. The major occluded cerebral arteries included the common carotid artery (CCA), ICA, anterior cerebral artery (ACA), MCA, posterior cerebral artery (PCA), basilar artery (BA), and vertebral artery (VA). Data from magnetic resonance angiography, computed tomography angiography, digital subtraction angiography, or carotid ultrasonography obtained on admission were examined to identify occlusion sites. Because most of the patients had occlusion of the ICA (including the CCA), MCA, and BA, subgroups comprising patients with occlusion of these 3 arteries were analyzed. Baseline data, including sex, age, onset-to-arrival time, and baseline neurologic deficits (based on National Institutes of Health Stroke Scale [NIHSS] score) were collected from medical records. Clinical stroke subtypes were determined by the consensus of vascular neurologists or neurosurgeons according to the TOAST subtype classification system.[11] Recanalization therapy (RT) initiated immediately after admission included IV rt-PA and/or neuroendovascular therapy, such as intra-arterial urokinase,[5,6] percutaneous transluminal angioplasty, and intracranial stenting. Mechanical thrombectomy devices were not yet approved for use in Japan during the study period.

The outcomes were as follows: symptomatic intracerebral hemorrhage (sICH) within the initial 36 hours with neurologic deterioration corresponding to an increase of ≥1 point from the baseline NIHSS score, a favorable outcome corresponding to a modified Rankin scale (mRS) score of 0-2 at 3 months after stroke onset, death at 3 months, and an unfavorable outcome corresponding to an mRS score of 5-6 at 3 months. The mRS score at 3 months was investigated as thoroughly as possible from reviews of outpatient clinic medical records and from face-to-face or telephone interviews. The mRS score at hospital discharge was used when data from the 3-month assessment were unavailable.

Data were statistically analyzed with JMP Pro 9.0.2 statistical software (SAS Institute, Cary, NC). Clinical characteristics of the patients were compared using the Student t test, χ^2 test, and Mann-Whitney U test as appropriate. Factors that were independently associated with each outcome were determined using multivariate analyses with adjustment for sex, age, cardioembolism, onset-to-arrival time, ICA occlusion, baseline NIHSS score, and RT (forced-entry method). A P value $< .05$ was considered significant.

Results

Table 1 presents the baseline characteristics of the patients. Cardioembolism was the leading stroke subtype (68.2%), the MCA was the most frequently occluded artery (52.2%), and 32.0% of the patients underwent RT of some type.

Table 1. *Baseline characteristics of patients*

Characteristic	Value
Female sex, n (%)	496 (42.4)
Age, years, mean ± SD	73.9 ± 12.3
Stroke subtype, n (%)	
Cardioembolism	798 (68.2)
Large-artery atherosclerosis	243 (20.8)
Other	129 (11.0)
Occluded artery, n (%)	
CCA	17 (1.5)
ICA	346 (29.6)
ACA	6 (0.51)
MCA	611 (52.2)
PCA	45 (3.8)
BA	89 (7.6)
VA	56 (4.8)
RT, n (%)	374 (32.0)
IV rt-PA	235 (20.0)
Neuroendovascular	110 (9.4)
Combined	29 (2.5)

The time interval between onset of AIS and arrival at a hospital (ie, onset-to-arrival time) was 0-3 hours (the legal therapeutic time frame for IV rt-PA in Japan) for 638 patients (54.5%), 3-4.5 hours for 112 patients (9.6%), and 4.5-8 hours for 124 patients (10.6%) (Fig 1). The median onset-to-arrival time was 120 minutes (interquartile range [IQR], 60-360 min) overall, 75 minutes (IQR, 45-120 minutes) for the group who received RT therapy [RT(+)], and 200 minutes (IQR, 75-498 minutes) for the group who did not receive RT therapy [RT(−)] [$P < .001$ vs RT(+)]. Of the 638 patients who with an onset-to-arrival time of <3 hours, 253 (39.7%) received IV rt-PA therapy. Onset to arrival intervals did not differ significantly among patients with ICA, MCA, or BA occlusion ($P = .697$).

Median baseline NIHSS score was 16 (IQR, 8-21) overall, 16 (IQR, 11-21) for the RT(+) group, and 15 (IQR, 6-21) for the RT(−) group [$P < .001$ between the RT(+) and RT(−) groups] (Fig 2). Baseline NIHSS scores differed significantly ($P < .001$) among patients with ICA occlusion (median, 19; IQR, 13-24), MCA occlusion (median, 15; IQR, 9-20), and BA occlusion (median, 17; IQR, 7-32).

The clinical outcome was sICH in 62 patients overall (5.3%), and sICH was more common in the RT(+) group than in the RT(−) group (7.5% vs 4.3%; $P = .026$). The incidence rates of sICH did not differ significantly among patients with ICA, MCA, and BA occlusion ($P = .508$). mRS scores at 3 months were complete in 799 patients (68.3%), and mRS score at hospital discharge (mean hospital stay, 32.5 days) was used for the other patients (Fig 3). Outcomes were favorable in 343 patients overall (29.3%) and tended to be more frequent in the RT(+) group than in the RT(−) group (32.6% vs 27.8%; $P = .091$). The mortality rate was 15.6% (183 patients) overall and lower in the RT(+) group than in the RT(−) group (12.0% vs 17.3%; $P = .018$). Outcomes were unfavorable in 461 patients overall (39.4%); the rate of unfavorable outcomes was 36.1% in the RT(+) group and 41.0% in the RT(−) group ($P = .112$). Patients with ICA occlusion had lower rates of favorable outcomes (14.9%), higher mortality (28.1%), and higher rates of unfavorable outcomes (59.8%) compared with patients with BA occlusion (28.1%, 23.6%, and 44.9%, respectively) or MCA occlusion (32.6%, 8.8%, and 31.3%, respectively). Among groups with different onset-to-arrival times, the patients with an onset-to-arrival time of 3-4.5 hours had a lower rate of favorable outcomes (18.8%), and those with an onset-to-arrival time of 4.5-8 hours had higher mortality (26.6%) (Fig 4).

After multivariate adjustment (Table 2), a high baseline NIHSS score and cardioembolism were positively associated with sICH. Advanced age, high baseline NIHSS

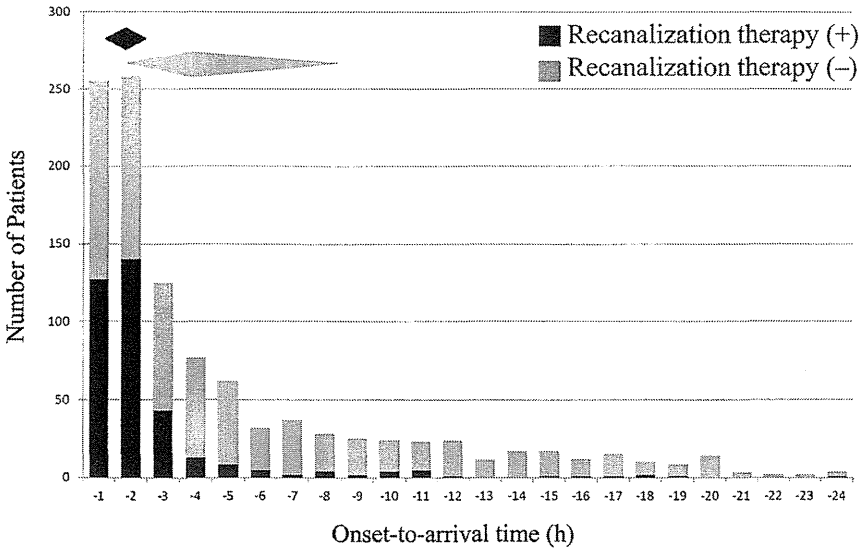

Figure 1. *Onset-to-arrival time at hospitals. Diamonds represent median values with IQR. Data were incomplete for 85 patients.*

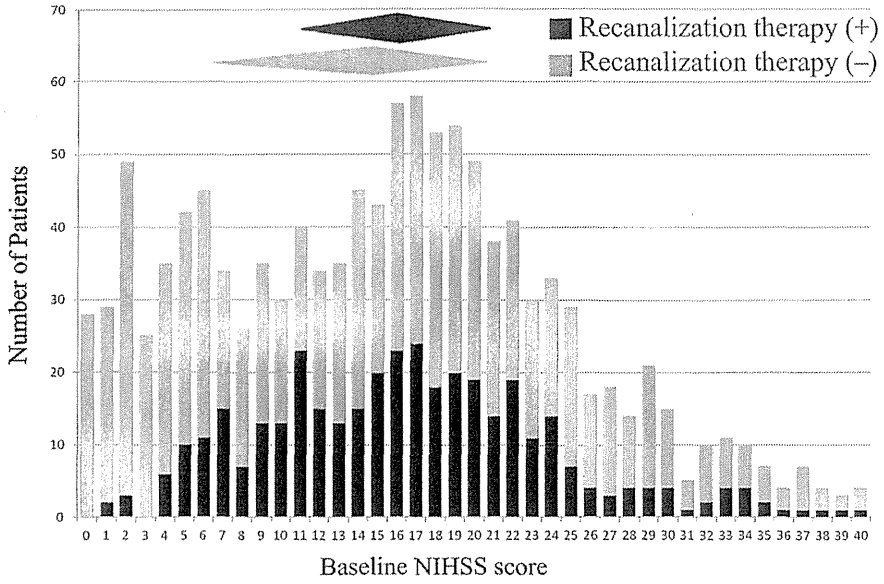

Figure 2. *Baseline NIHSS scores. Diamonds represent median values with IQR. Data were incomplete for 3 patients.*

score, and ICA occlusion were negatively associated with a favorable outcome and positively associated with death. RT was positively associated with a favorable outcome and negatively associated with death. In addition, age (per 10-year increment: odds ratio [OR], 1.71; 95% confidence interval [CI], 1.48-2.00; $P < .001$), baseline NIHSS score (per 1 point: OR, 1.14; 95% CI, 1.12-1.17; $P < .001$), and ICA occlusion (OR, 3.15; 95% CI, 2.27-4.39; $P < .001$) were positively associated with an unfavorable outcome.

Table 3 presents data on interactions between occluded arteries and RT for clinical outcomes. The frequency of sICH and death differed significantly between the RT(+) and RT(−) groups with ICA occlusion, and the frequency of a favorable outcome differed significantly between the 2 groups with MCA occlusion.

Discussion

This is the first large-population observational study in Japan to examine AIS with major cerebral artery occlusion, which is required to generate historical control data for comparison with stroke outcomes after the implementation of thrombectomy devices and other novel therapies. The major findings of this study can be summarized as follows. Cardioembolism was the etiologic mechanism for more than two-thirds of patients with AIS and major cerebral artery occlusion, 40% of patients were bedridden or dead at 3 months after onset of AIS, and RT was positively associated with favorable outcome and negatively associated with death after multivariate adjustment. After initial online presentation of the core results, official councils compared the core results with those of international trials of thrombectomy devices.[7-9] Their findings helped gain approval for the MERCI retriever and the PENUMBRA system for clinical use in Japan in 2010 and 2011, respectively, bypassing the need for domestic trials.

Two-thirds of Japanese candidates for IV rt-PA have cardioembolism,[12-15] a proportion far higher than that identified in trials and postmarketing surveys in other countries.[16,17] Thus, the high frequency of cardioembolism among patients with major cerebral artery occlusion in the present study was acceptable. Cardioembolism tends to

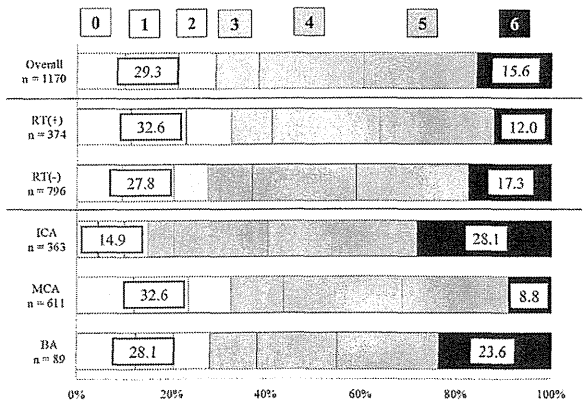

Figure 3. *mRS scores at 3 months. Left and right values are ratios (%) of patients with favorable outcomes and mortality, respectively.*

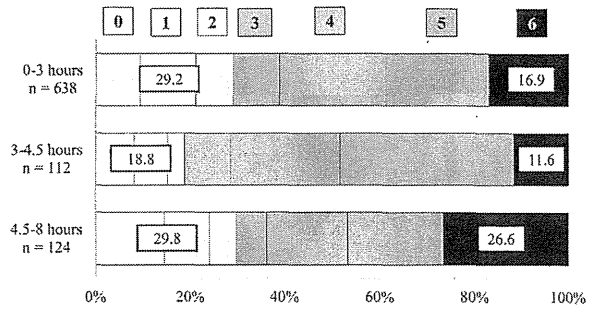

Figure 4. *Onset-to-arrival times (0-8 hours) and stroke outcomes. Left and right values are ratios (%) of patients with favorable outcomes and mortality, respectively.*

Table 2. *Multivariate analyses to identify factors associated with outcomes*

	SICH			Favorable outcome			Death		
	OR	95% CI	*P* value	OR	95% CI	*P* value	OR	95% CI	*P* value
Female sex	0.64	0.35-1.15	.141	0.85	0.60-1.21	.376	1.13	0.77-1.65	.525
Age, per 10-year increment	0.90	0.71-1.15	.382	**0.59**	**0.51-0.68**	**<.001**	**1.32**	**1.10-1.58**	**.002**
Onset to-arrival time, per minute	1.00	1.00-1.00	.117	1.00	1.00-1.00	.710	1.00	1.00-1.00	.126
Baseline NIHSS score	**1.05**	**1.01-1.08**	**.005**	0.84	**0.82-0.86**	**<.001**	**1.10**	**1.08-1.12**	**<.001**
ICA occlusion	1.49	0.83-2.63	.181	0.41	**0.27-0.62**	**<.001**	**2.94**	**2.05-4.22**	**<.001**
Cardioembolism	**3.75**	**1.67-10.0**	**.001**	1.16	0.80-1.69	.426	0.83	0.55-1.27	.391
RT	1.68	0.92-3.04	.089	2.09	**1.42-3.09**	**<.001**	**0.62**	**0.41-0.93**	**.020**

Force entry method adjusted for female sex, age, onset-to-arrival time, baseline NIHSS score, ICA occlusion, cardioembolism, and RT. Statistically significant associations are shown in bold type.

appear suddenly with severe symptoms, and thus patients with cardioembolism are often rushed to the hospital. Although cardioembolism per se was not a predictor of favorable or unfavorable outcomes at 3 months in this study, it was an independent predictor for sICH.

The frequency of death or becoming bedridden in the present study (39.4%) indicates the severity of AIS with major cerebral artery occlusion. This frequency is more than double the rate of 17.5% reported by the J-MUSIC study, a Japanese hospital-based registration study that included patients with stroke with and without cerebral artery occlusion.[18] Of interest, in our study population, the mortality rate (15.6%) was relatively lower than the rate of bedridden patients with an mRS score of 5 (23.8%). This tendency also has been recognized in other Japanese studies of ischemic stroke[3,4,6,12,15] and ICH,[19] and is presumably related to the Japanese philosophy of maintaining intensive therapy even for terminal patients (eg, to prevent gastrointestinal hemorrhage or aspiration pneumonia). Moreover, treatments that are common only in Japan, such as IV edaravone[20] or glycerol,[21] might lead to reduced mortality. Thus, comparisons of vital outcomes between Japanese studies and studies from other countries should be interpreted with discretion.

A meta-analysis of AIS confirmed that vessel recanalization within 24 hours is closely associated with improved functional outcomes and reduced mortality; in that analysis, the OR for mRS score 0-2 was 4.43, and that for mortality was 0.24.[22] Our multivariate data are consistent with those values. The effect of RT was limited in patients with MCA occlusion; however, our results were drawn not from patients with successful recanalization, but rather from those scheduled for RT. Thus, our results might indicate that the outcomes for AIS patients who can be candidates for RT tend to be favorable regardless of the success or failure of RT.

One limitation of the present study is that it was a retrospective observational analysis of data from a relatively small number of high-volume centers. Thus, the results do not reflect domestic conditions throughout Japan.

Table 3. *Interaction of occluded artery and RT for clinical outcomes*

		sICH		Favorable outcome		Death	
	N	n (%)	OR (95% CI)	n (%)	OR (95% CI)	n (%)	OR (95% CI)
ICA occlusion	363						
RT(−)	258	14 (5.4)	1	37 (14.3)	1	80 (31.0)	1
RT(+)	105	11 (10.5)	**2.66 (1.02-7.18)**	17 (16.2)	2.23 (0.86-6.05)	22 (21.0)	**0.47 (0.25-0.85)**
P value			**.046**		.100		**.013**
MCA occlusion	611						
RT(−)	398	17 (4.3)	1	114 (28.6)	1	39 (9.8)	1
RT(+)	213	14 (6.6)	1.20 (0.51-2.77)	85 (39.9)	**2.24 (1.40-3.60)**	15 (7.0)	0.87 (0.42-1.72)
P value			0.673		**.001**		.684
BA occlusion	89						
RT(−)	51	3 (5.9)	1	13 (25.5)	1	15 (29.4)	1
RT(+)	38	2 (5.3)	0.64 (0.07-4.71)	12 (31.6)	3.86 (0.80-22.0)	6 (15.8)	0.31 (0.09-1.01)
P value			.659		.259		.052

Adjusted for female sex, age, onset-to-arrival time, baseline NIHSS score, and cardioembolism. Statistically significant associations are shown in bold type.

Another limitation is that the RT(−) group was rather heterogeneous, including patients who were so severely affected that they were contraindicated for RT as well as those who were so mildly affected that such therapy was unnecessary. A third limitation is that because 3-month mRS score data were missing for 30% of the patients, mRS scores at hospital discharge were used instead. Because the average duration of hospitalization was 32.5 days, and at least one report has indicated that 1-month mRS reliably estimates final 3-month disability outcomes,[23] this limitation might not have significantly affected the results.

In conclusion, almost one-third of our patients with AIS due to major cerebral artery occlusion underwent RT, and this predicted favorable 3-month outcomes. However, 40% of patients with AIS still had unfavorable outcomes even after IV rt-PA had been approved in Japan. We hope that use of the newer endovascular devices will further improve outcomes in these patients.

References

1. Carandang R, Seshadri S, Beiser A, et al. Trends in incidence, lifetime risk, severity, and 30-day mortality of stroke over the past 50 years. JAMA 2006;296:2939-2946.
2. Kubo M, Hata J, Doi Y, et al. Secular trends in the incidence of and risk factors for ischemic stroke and its subtypes in Japanese population. Circulation 2008;118:2672-2678.
3. Nakashima T, Toyoda K, Koga M, et al. Arterial occlusion sites on magnetic resonance angiography influence the efficacy of intravenous low-dose (0.6 mg/kg) alteplase therapy for ischaemic stroke. Int J Stroke 2009;4:425-431.
4. Hirano T, Sasaki M, Mori E, et al. Residual vessel length on magnetic resonance angiography identifies poor responders to alteplase in acute middle cerebral artery occlusion patients: Exploratory analysis of the Japan Alteplase Clinical Trial II. Stroke 2010;41:2828-2833.
5. Furlan A, Higashida R, Wechsler L, et al, for the PROACT Investigators. Intra-arterial prourokinase for acute ischemic stroke. The PROACT II study: A randomized controlled trial. JAMA 1999;282:2003-2011.
6. Ogawa A, Mori E, Minematsu K, et al. Randomized trial of intraarterial infusion of urokinase within 6 hours of middle cerebral artery stroke: The Middle Cerebral Artery Embolism Local Fibrinolytic Intervention Trial (MELT) Japan. Stroke 2007;38:2633-2639.
7. Smith WS, Sung G, Starkman S, et al. Safety and efficacy of mechanical embolectomy in acute ischemic stroke: Results of the MERCI trial. Stroke 2005;36:1432-1438.
8. Smith WS, Sung G, Saver J, et al. Mechanical thrombectomy for acute ischemic stroke: Final results of the Multi MERCI trial. Stroke 2008;39:1205-1212.
9. Bose A, Henkes H, Alfke K, et al. The PENUMBRA system: A mechanical device for the treatment of acute stroke due to thromboembolism. AJNR Am J Neuroradiol 2008;29:1409-1413.
10. Castano C, Dorado L, Guerrero C, et al. Mechanical thrombectomy with the solitaire AB device in large artery occlusions of the anterior circulation: A pilot study. Stroke 2010;41:1836-1840.
11. Adams HP Jr, Bendixen BH, Kappelle LJ, et al. Classification of subtype of acute ischemic stroke: Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. Stroke 1993; 24:35-41.
12. Toyoda K, Koga M, Naganuma M, et al. Routine use of intravenous low-dose recombinant tissue plasminogen activator in Japanese patients: General outcomes and prognostic factors from the SAMURAI register. Stroke 2009;40:3591-3595.
13. Naganuma M, Koga M, Shiokawa Y, et al. Reduced estimated glomerular filtration rate is associated with stroke outcome after intravenous rt-PA: The Stroke Acute Management with Urgent Risk Factor Assessment and Improvement (SAMURAI) rt-PA Registry. Cerebrovasc Dis 2011;31:123-129.
14. Makihara N, Okada Y, Koga M, et al. The effect of serum lipid levels on stroke outcome after rt-PA therapy: SAMURAI rt-PA Registry. Cerebrovasc Dis 2012;33:240-247.
15. Nakagawara J, Minematsu K, Okada Y, et al. Thrombolysis with 0.6 mg/kg intravenous alteplase for acute ischemic stroke in routine clinical practice: The Japan Post-Marketing Alteplase Registration Study (J-MARS). Stroke 2010;41:1984-1989.
16. National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. N Engl J Med 1995; 333:1581-1587.
17. Wahlgren N, Ahmed N, Davalos A, et al. Thrombolysis with alteplase for acute ischaemic stroke in the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST): An observational study. Lancet 2007;369:275-282.
18. Kimura K, Kazui S, Minematsu K, et al. Analysis of 16,922 patients with acute ischemic stroke and transient ischemic attack in Japan: A hospital-based prospective registration study. Cerebrovasc Dis 2004;18:47-56.
19. van Asch CJ, Luitse MJ, Rinkel GJ, et al. Incidence, case fatality, and functional outcome of intracerebral haemorrhage over time, according to age, sex, and ethnic origin: A systematic review and meta-analysis. Lancet Neurol 2010;9:167-176.
20. Edaravone Acute Infarction Group. Effect of a novel free radical scavenger, edaravone (MCI-186), on acute brain infarction: Randomized, placebo-controlled, double-blind study at multicenters. Cerebrovasc Dis 2003; 15:222-229.
21. Bayer AJ, Pathy MS, Newcombe R. Double-blind randomised trial of intravenous glycerol in acute stroke. Lancet 1987;1:405-408.
22. Rha JH, Saver JL. The impact of recanalization on ischemic stroke outcome: A meta-analysis. Stroke 2007; 38:967-973.
23. Ovbiagele B, Lyden PD, Saver JL. Disability status at 1 month is a reliable proxy for final ischemic stroke outcome. Neurology 2010;75:688-692.

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Special Theme Topic: Japanese Surveillance of Neuroendovascular Therapy in JR-NET/JR-NET2—Part I

Endovascular Treatment of Acute Stroke with Major Vessel Occlusion before Approval of Mechanical Thrombectomy Devices in Japan: Japanese Registry of Neuroendovascular Therapy (JR-NET) and JR-NET 2

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Abstract

The aim of this study was to clarify the general status and historical transition of endovascular therapy (EVT) of acute stroke with major vessel occlusion before approval of mechanical thrombectomy devices in Japan from January 2005 to December 2009. We extracted 1,409 acute ischemic stroke patients receiving EVT (513 women, 69.8 ± 11.8 years) from two nationwide registry studies, the Japanese Registry of Neuroendovascular Therapy (JR-NET) and JR-NET 2. The median baseline National Institutes of Health Stroke Scale (NIHSS) score was 18, and 81.3% of the patients received EVT within 6 hours after symptom onset. The culprit occluded arteries were the internal carotid artery (ICA) in 21.2%, middle cerebral artery (MCA) in 53.0%, and basilar artery (BA) in 20.6%. Intravenous thrombolysis was administered to 6.7% of the patients, and EVT mainly consisted of intra-arterial thrombolysis and percutaneous balloon angioplasty/balloon clot disruption. The final recanalization rate was 82.5%, and the clinical outcome was favorable in 35.8% and fatal in 11.6% at 30 days after onset or at discharge. There was no significant change in neurological severity at baseline throughout the study period, but the onset-to-treatment time became longer and the proportion of ICA or BA occlusion increased annually. Although the final recanalization rate was similar throughout the study period, the incidence of a favorable outcome tended to decreased annually from 41.0% to 29.0%. These results could be considered as baseline data that can be used to validate the beneficial effects of novel EVT devices in Japan.

Key words: acute ischemic stroke, intracranial major vessel occlusion, endovascular treatment, nationwide survey, recanalization

Introduction

Acute stroke with major vessel occlusion is generally recognized as a serious disease. Immediate recanalization by intravenous (IV) thrombolysis using recombinant tissue plasminogen activator (t-PA) is not sufficiently achieved in such stroke patients. In recent years, endovascular therapy (EVT) using mechanical thrombectomy devices has been evaluated in stroke patients with major vessel occlusion. The results of several studies have shown immediate recanalization with better clinical outcomes than

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were obtained with thrombolytic therapy.[1–6]

The Japanese Registry of Neuroendovascular Therapy (JR-NET) 1 and JR-NET 2 were created to clarify the general status of neuroendovascular therapy performed by specialist physicians certified by the Japanese Society for Neuroendovascular Therapy (JSNET). Clinical and procedural data on a total of 32,000 neuroendovascular procedures were retrospectively collected from January 2005 to December 2006 (JR-NET 1) and from January 2007 to December 2009 (JR-NET 2). The two study periods encompassed the time form approval of IV t-PA (October 2005) in Japan until the approval of the Merci Retriever (Concentric Medical, Mountain View, California, USA, 2010) and Penumbra System (Penumbra Inc., Alameda, California, USA, 2011) thrombectomy devices.

The aim of this study was to clarify the general status of endovascular treatment of acute stroke with major vessel occlusion before approval of mechanical thrombectomy devices in Japan, and to determine if there were changes in stroke characteristics or treatment patterns throughout the periods encompassed by JR-NET 1 and 2.

Materials and Methods

Among all datasets of JR-NET 1 and 2, we extracted 1,409 patients (619 from JR-NET 1 and 790 from JR-NET 2; 513 women; mean age, 69.8 ± 11.9 years) who underwent endovascular revascularization therapy for acute stroke with major vessel occlusion. The Institutional Review Board at each center approved the use of retrospective data from the patients.

We compared the following baseline characteristics between JR-NET 1 and 2: age, sex, baseline National Institutes of Health Stroke Scale (NIHSS) score, stroke subtypes, and culprit occluded arteries. Furthermore, we compared the use of computed tomography (CT), magnetic resonance imaging (MRI), and the onset-to-treatment time (OTT) between the two studies. We also compared the two studies for the use of revascularization procedures such as endovascular treatment (EVT) with or without preceding IV t-PA, stand-alone intra-arterial thrombolysis (IAT), stand-alone percutaneous transluminal angioplasty (PTA)/balloon clot disruption (BCD), other single procedures including stenting, thromboaspiration or clot retrieval, the combination of IAT and PTA/BCD, and other procedural combinations. Moreover, we determined if there were differences between the two studies in the recanalization rate (complete, partial, or none), symptomatic procedural complications with any clinical deterioration within 24 hours of EVT (intracranial hemorrhage or ischemia, puncture site, and other systemic complications) and clinical outcomes. A favorable clinical outcome was defined as a modified Rankin scale (mRS) score of 0–2 and a poor outcome as a mRS score of 5–6 or death at 30 days after stroke onset. Finally, we analyzed the annual transition in baseline characteristics, the use of IV t-PA and EVT procedures, and the treatment results in the two studies. For the annual transition analysis, we divided the entire period encompassed by the two studies into six periods: the first period (pre-IV t-PA period, until September 2005), the second period (October 2005–September 2006), the third period (October 2006–September 2007), the fourth period (October 2007–September 2008), the fifth period (October 2008–September 2009), and the last period (October–December 2009).

The culprit occluded arteries were separated into the internal carotid artery [ICA, including simultaneous middle cerebral artery (MCA) and/or other vessel occlusion]; the MCA (isolated MCA occlusion); the basilar artery (BA), including simultaneous vertebral and/or posterior cerebral artery occlusion); and the other arteries.

IV t-PA was performed using 0.6 mg/kg of alteplase, and EVT procedures were done according to protocol at each center by a JSNET-certified specialist physician or operator.

The recanalization status was evaluated angiographically at the end of EVT by the attending physician at each center. Partial recanalization was defined as any degree of recanalization other than complete. The mRS score at hospital discharge was used as a substitute for outcome when 30-day outcome data were unavailable. Hemorrhagic events after severe stroke that were unrelated to any EVT procedure were not collected in this retrospective analysis.

Data were statistically analyzed with IBM SPSS Statistics 20 software (IBM SPSS, Chicago, Illinois, USA). We used a chi-square test, Fisher's exact test, Mann-Whitney U-test, or Kruskal-Wallis test, as appropriate. A p-value < 0.05 was considered significant.

Results

I. Patient characteristics

Table 1 shows the patients' baseline characteristics and diagnostic imaging modalities. The median baseline NIHSS score was 18 [interquartile range (IQR), 11–23], and 11.7% of the patients had a mild neurological deficit (NIHSS score < 8). Cardioembolic stroke was the most frequent stroke subtype (64.9%) and atherothrombotic stroke was

the second most frequent subtype (22.6%). The culprit occluded arteries were ICA in 21.2%, MCA in 53.0%, and BA in 20.6%. MRI was the most frequently used imaging modality (86.5%), and CT was used in 55.9%. The OTT was ≤ 3 hours in 37.4%, 3–6 hours in 43.9%, 6–12 hours in 11.6%,

Table 1 Patients' baseline characteristics and imaging modalities

	Total	JR-NET 1	JR-NET 2	p
n	1,409	619	790	
Age, mean ± SD (range)	69.8 ± 11.9 (6–96)	69.5 ± 11.4 (16–96)	70.0 ± 12.2 (6-93)	0.237
Male (%)	896/1,391 (64.4)	400/601 (66.6)	496/790 (62.8)	0.146
NIHSS	(n = 875)	(n = 293)	(n = 582)	
Baseline NIHSS, median (IQR)	18 (11–23)	17 (11–24)	18 (12–22)	0.969
NIHSS < 8 (%)	102 (11.7)	37 (12.6)	65 (11.2)	0.525
Stroke subtypes (%)	(n = 1,249)	(n = 471)	(n = 778)	0.660
Cardioembolic	811 (64.9)	305 (64.8)	506 (65.0)	
Atherothrombotic	282 (22.6)	103 (21.9)	179 (23.0)	
Iatrogenic	44 (3.5)	21 (4.5)	23 (3.0)	
Others	44 (3.5)	18 (3.8)	26 (3.3)	
Unknown	68 (5.4)	24 (5.1)	44(5.7)	
Culprit occluded artery (%)	(n = 1,248)	(n = 470)	(n = 778)	< 0.001
ICA	264 (21.2)	84 (17.9)	180 (23.1)	
MCA	661 (53.0)	269(57.2)	391 (50.3)	
BA	257 (20.6)	82 (17.4)	174 (22.4)	
Other arteries	68 (5.4)	35 (7.4)	33 (4.2)	
Imaging modalities (%)	(n = 1,212)	(n = 455)	(n = 757)	
CT	677 (55.9)	299 (65.7)	378 (49.9)	< 0.001
MRI	1,048 (86.5)	363 (79.8)	685 (90.5)	< 0.001
Onset-to-treatment time (%)	(n = 1,184)	(n = 453)	(n = 731)	< 0.001
< 3 h	443 (37.4)	221 (48.8)	222 (30.4)	
3–6 h	520 (43.9)	183 (40.4)	337 (46.1)	
6–12 h	137 (11.6)	34 (7.5)	103 (14.1)	
≥ 12 h	84 (7.1)	15 (3.3)	69 (9.4)	

BA: basilar artery, CT: computed tomography, ICA: internal carotid artery, IQR: interquartile range, JR-NET: Japanese Registry of Neuroendovascular Therapy, MCA: middle cerebral artery, MRI: magnetic resonance imaging, NIHSS: National Institutes of Health Stroke Scale.

Table 2 Revascularization procedures

	Total	JR-NET 1	JR-NET 2	p
n	1,409	619	790	
IV t-PA (%)	81/1,202 (6.7)	4/441 (0.9)	77/761 (10.1)	< 0.001
Endovascular procedures (%)	(n = 1,245)	(n = 471)	(n = 774)	< 0.001
Stand-alone IAT	466 (37.4)	223 (47.3)	243 (31.4)	
Stand-alone PTA/BCD	199 (16.0)	39 (8.3)	160 (20.7)	
Other single procedures	64 (5.1)	24 (5.1)	40 (5.2)	
IAT + PTA/BCD	341 (27.4)	135 (28.7)	206 (26.6)	
Other procedural combinations	175 (14.1)	50 (10.6)	125 (16.1)	
Any combination including IAT	917 (73.7)	388 (82.4)	529 (68.3)	< 0.001

BCD: balloon clot disruption, IAT: intra-arterial thrombolysis, IV t-PA: intravenous thrombolysis using tissue plasminogen activator, JR-NET: Japanese Registry of Neuroendovascular Therapy, Other single procedures: includes stenting, thromboaspiration, clot retrieval and others, PTA: percutaneous transluminal angioplasty, .

and > 12 hours in 7.3%.

II. Revascularization procedures

Table 2 shows information on the revascularization procedures. IV t-PA was administered in 6.7% of the patients prior to EVT. EVT mainly consisted of IAT and PTA/BCD using a PTA balloon. Stand-alone IAT was performed in 37.4%: IA urokinase (UK) was administered in 34.4%, IA t-PA in 2.2%, and IA UK + t-PA in 0.7%; the combination of IAT and PTA/BCD was used in 27.4% and stand-alone PTA/BCD in 16.0%. The frequency of the combination including IAT was 73.7%.

III. Treatment results and procedural complications

Table 3 shows the treatment results and procedural complications. Final recanalization was obtained in 82.5% of the patients (partial, 50.0%; complete, 32.5%). The clinical outcome was favorable in 35.8%, poor in 27.3% and fatal in 11.6% at 30 days after onset.

IV. Comparison of JR-NET 1 and 2

Tables 1, 2, and 3 present the clinical characteristics, treatment results, and statistical analysis of each registry study. There were no significant differences in age, sex, neurological severity, or stroke subtypes between JR-NET 1 and 2. However, there was a significantly higher rate of ICA occlusion and BA occlusion in JR-NET 2 than in JR-NET 1, whereas there was a significantly lower rate of MCA occlusion in JR-NET 2 than in JR-NET 1 ($p < 0.001$). CT was performed less frequently in JR-NET 2 than in JR-NET 1 ($p < 0.001$), whereas MRI was performed more frequently ($p < 0.001$). The OTT was significantly longer in JR-NET 2 than in JR-NET 1 ($p < 0.001$). IV t-PA and stand-alone PTA/BCD increased from JR-NET 1 to JR-NET 2, (both p-values < 0.001), whereas the rate of stand-alone IAT decreased from JR-NET 1 to JR-NET 2 ($p < 0.001$). Although the final recanalization and mortality rates were not significantly different, the proportion of patients with a favorable outcome significantly decreased from JR-NET 1 to JR-NET 2 ($p = 0.027$). The overall procedural complication rate, especially the rate of intracranial hemorrhage, tended to decrease from JR-NET 1 to JR-NET 2 ($p = 0.093$ and 0.086, respectively).

V. Annual transition analyses

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. 1). Although stroke severity did not change annually throughout the study period ($p = 0.352$, Fig. 2), 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, $p = 0.026$;

Table 3 Treatment results and procedural complications

	Total	JR-NET 1	JR-NET 2	p
n	1,409	619	790	
Final recanalization (%)	1,030/1,249 (82.5)	384/471 (81.5)	646/778 (83.0)	0.299
Partial	624 (50)	222 (47.1)	402 (51.7)	
Complete	406(32.5)	162 (34.4)	244 (31.4)	
Procedural complications (%)	136/1,386 (9.8)	68/599 (11.4)	68/787 (8.6)	0.093
Intracranial hemorrhagic complication	97 (7.0)	50 (8.3)	47 (6.0)	0.086
Intracranial ischemic complication	23 (1.7)	13 (2.2)	10 (1.3)	0.194
Puncture site complication	7 (0.5)	2 (0.3)	5 (0.6)	0.706
Other complications	10 (0.7)	4 (0.7)	6 (0.8)	1.00
Clinical outcome at 30 days (%)	(n = 1,376)	(n = 600)	(n = 776)	
Favorable outcome	492 (35.8)	234 (39.0)	258 (33.2)	0.027
Poor outcome	375 (27.3)	159 (26.5)	216 (27.8)	0.581
Death	159 (11.6)	66 (11.0)	93 (12.0)	0.571

JR-NET: Japanese Registry of Neuroendovascular Therapy.