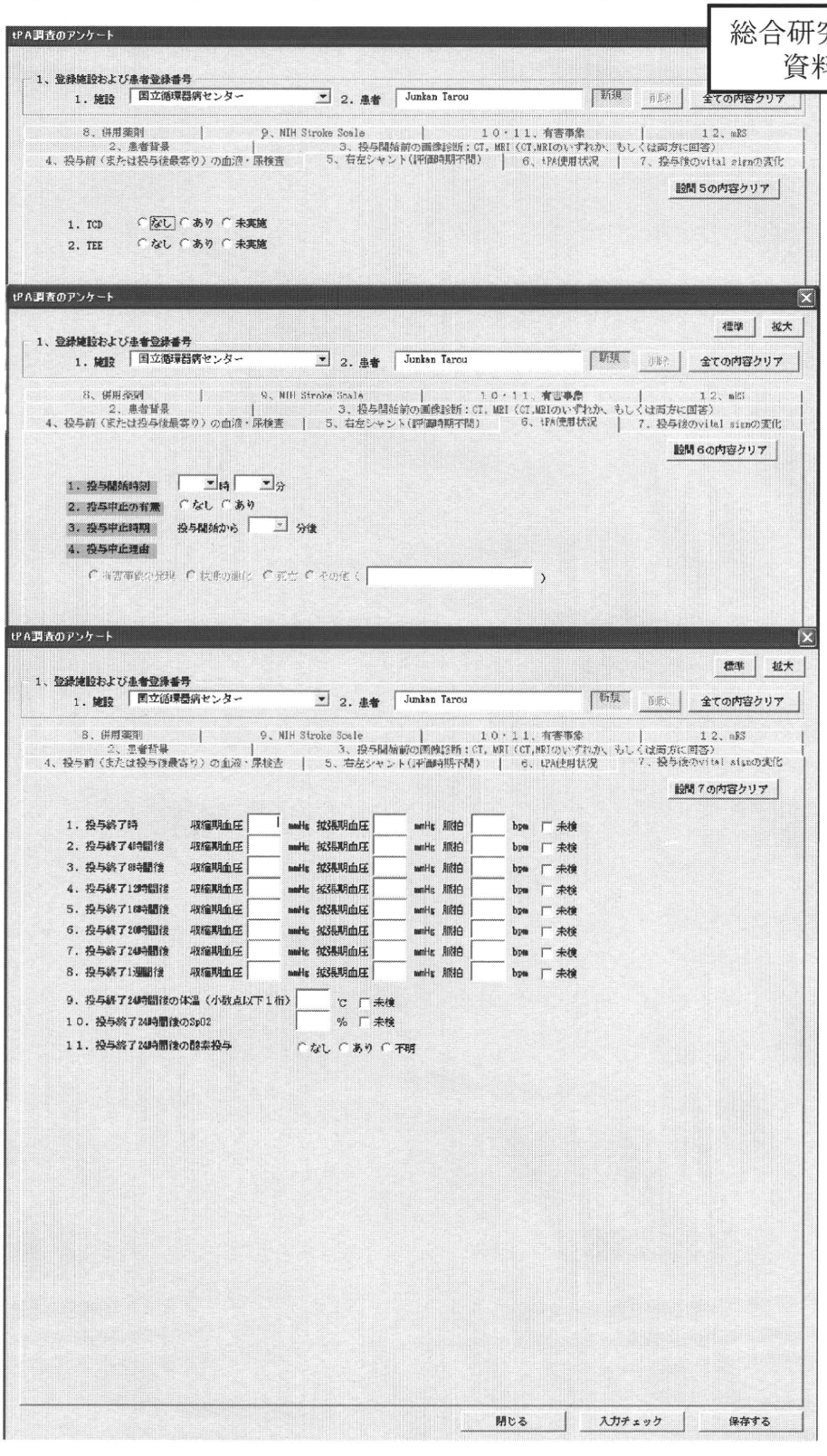
わが国における脳卒中再発予防のための急性期内科治療戦略の確立に関する研究

「多施設共同研究1：rt-PA患者登録研究」： 調査票 (3)

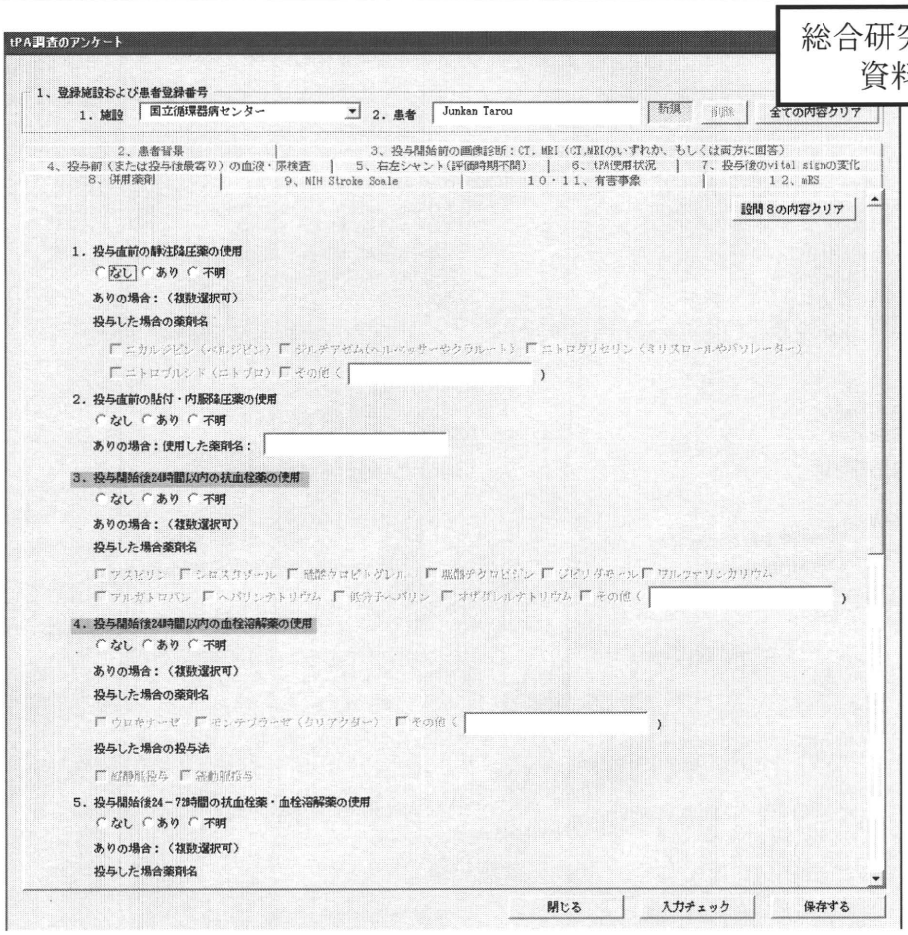
総合研究報告：
資料1-b

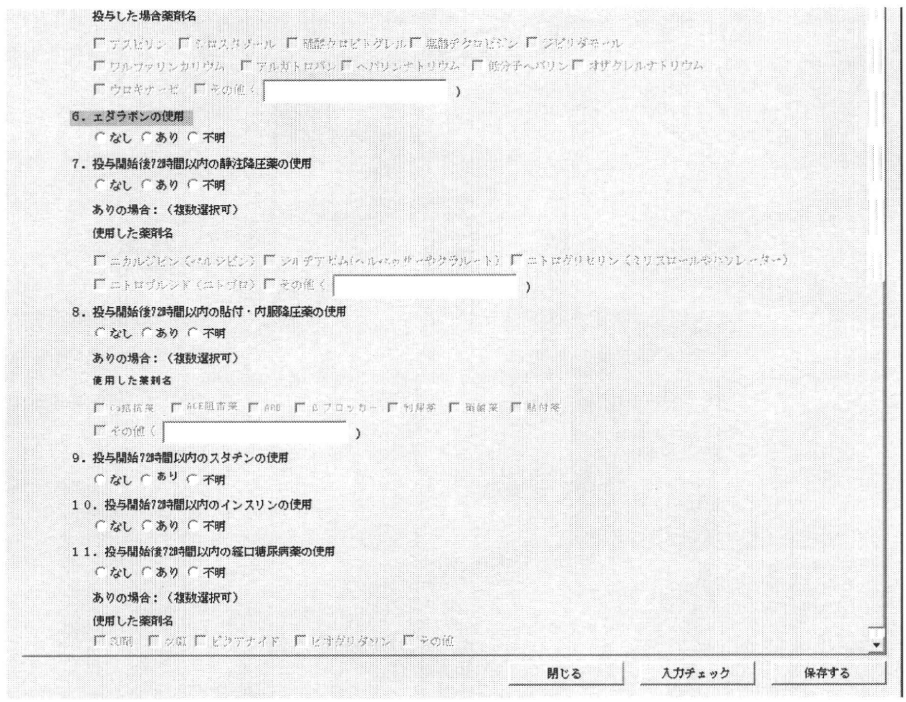


わが国における脳卒中再発予防のための急性期内科治療戦略の確立に関する研究

「多施設共同研究1：rt-PA患者登録研究」： 調査票 (4)

総合研究報告：
資料1-b

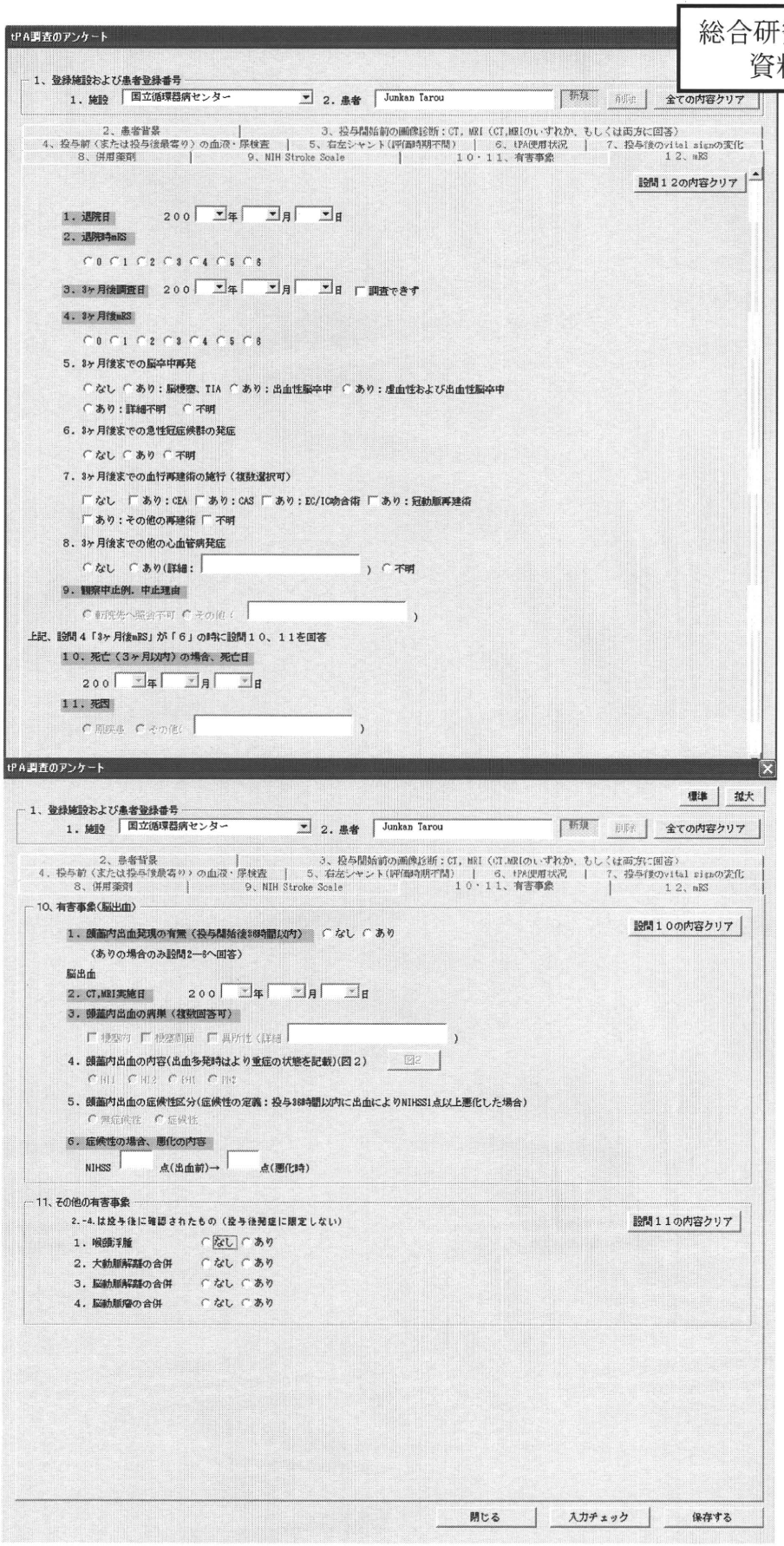




わが国における脳卒中再発予防のための急性期内科治療戦略の確立に関する研究

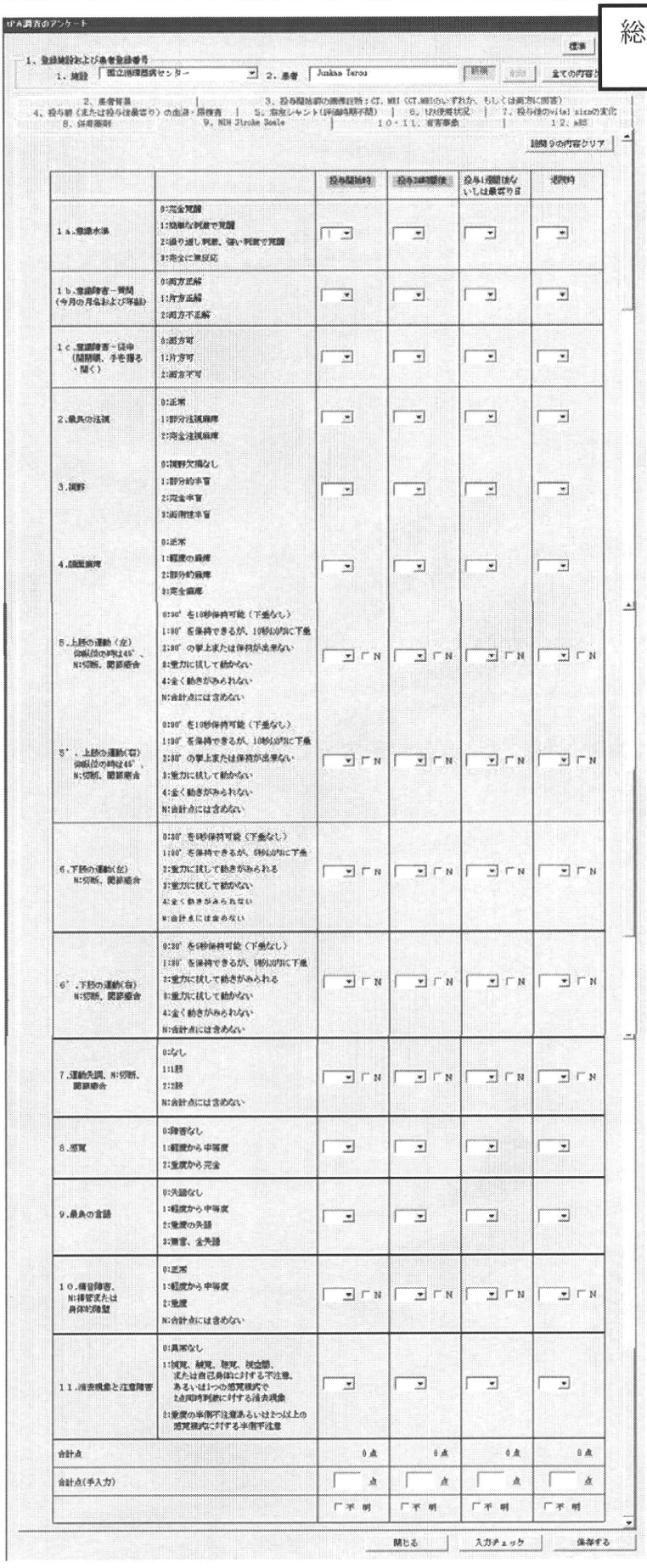
「多施設共同研究1：rt-PA患者登録研究」： 調査票 (5)

総合研究報告：
資料1-b



わが国における脳卒中再発予防のための急性期内科治療戦略の確立に関する研究
「多施設共同研究1：rt-PA患者登録研究」： 調査票 （6）

総合研究報告：
資料1-b



tPA調査のアンケート

標準

1、登録施設および患者登録番号
1．施設 国立循環器病センター　2．患者 Junkaa Taroo　新規　削除　全ての内容を

2、患者背景 | 3、投与開始前の画像診断：CT、MRI（CT,MRIのいずれか、もしくは両方に関与）
4、投与前（または投与後最寄り）の血液・尿検査 | 5、冠危レシント（評価時期不問） | 6、12誘導状況 | 7、投与後のvital signの変化
8、併用薬剤 | 9、NIH Stroke Scale | 10・11、有害事象 | 12、mRS

設問9の内容クリア

		投与開始時	投与24時間後	投与1時間後ないしは最寄り	退院時
1a.意識水準	0:完全覚醒 1:簡単な刺激で覚醒 2:繰り返し刺激、強い刺激で覚醒 3:完全に無反応	[1]			
1b.意識障害－質問（今月の月名および年齢）	0:両方正解 1:片方正解 2:両方不正解				
1c.意識障害－従命（閉眼開、手を握る・開く）	0:両方可 1:片方可 2:両方不可				
2.最良の注視	0:正常 1:部分注視麻痺 2:完全注視麻痺				
3.視野	0:視野欠損なし 1:部分的半盲 2:完全半盲 3:両側性半盲				
4.顔面麻痺	0:正常 1:軽度の麻痺 2:部分的麻痺 3:完全麻痺				
5.上肢の運動（左）仰臥位の時は45°、N:切断、関節癒合	0:90°を10秒保持可能（下垂なし） 1:90°を保持できるが、10秒以内に下垂 2:90°の挙上または保持が出来ない 3:重力に抗して動かない 4:全く動きがみられない N:合計点には含めない	N	N	N	N
5'.上肢の運動（右）仰臥位の時は45°、N:切断、関節癒合	0:90°を10秒保持可能（下垂なし） 1:90°を保持できるが、10秒以内に下垂 2:90°の挙上または保持が出来ない 3:重力に抗して動かない 4:全く動きがみられない N:合計点には含めない	N	N	N	N
6.下肢の運動（左）N:切断、関節癒合	0:30°を5秒保持可能（下垂なし） 1:30°を保持できるが、5秒以内に下垂 2:重力に抗して動きがみられる 3:重力に抗して動かない 4:全く動きがみられない N:合計点には含めない	N	N	N	N
6'.下肢の運動（右）N:切断、関節癒合	0:30°を5秒保持可能（下垂なし） 1:30°を保持できるが、5秒以内に下垂 2:重力に抗して動きがみられる 3:重力に抗して動かない 4:全く動きがみられない N:合計点には含めない	N	N	N	N
7.運動失調、N:切断、関節癒合	0:なし 1:1肢 2:2肢 N:合計点には含めない	N	N	N	N
8.感覚	0:障害なし 1:軽度から中等度 2:重度から完全				
9.最良の言語	0:失語なし 1:軽度から中等度 2:重度の失語 3:無言、全失語				
10.構音障害、N:挿管または身体的障壁	0:正常 1:軽度から中等度 2:重度 N:合計点には含めない	N	N	N	N
11.消去現象と注意障害	0:異常なし 1:視覚、触覚、聴覚、視空間、または自己身体に対する不注意、あるいは1つの感覚様式で2点同時刺激に対する消去現象 2:重度の半側不注意あるいは2つ以上の感覚様式に対する半側不注意				
合計点		0点	0点	0点	0点
合計点(手入力)		点	点	点	点
		不明	不明	不明	不明

閉じる　入力チェック　保存する

Arterial occlusion sites on magnetic resonance angiography influence the efficacy of intravenous low-dose (0·6 mg/kg) alteplase therapy for ischaemic stroke

T. Nakashima, K. Toyoda*, M. Koga, H. Matsuoka, K. Nagatsuka, T. Takada, H. Naritomi, and K. Minematsu

Aims **To determine the predictors of efficacy, including magnetic resonance imaging information, for low-dose intravenous alteplase therapy for stroke patients.**

Methods **Seventy-eight patients were prospectively enrolled in a single stroke centre receiving alteplase at a dose of 0·6 mg/kg during the initial 27 months after its approval in Japan. Ischaemic changes and vascular lesions were identified using computed tomography, diffusion-weighted magnetic resonance imaging, and magnetic resonance angiography. Early ischaemic signs were assessed using the Alberta Stroke Program Early CT Score.**

Results **The median baseline National Institutes of Health Stroke Scale score of 78 patients was 12. In 19 patients (24%), the National Institutes of Health Stroke Scale score improved by ≥8 points at 24 h. After multivariate adjustment, occlusion at the internal carotid artery (odds ratio 11·82, 95% confidence interval 1·73–142·74), Alberta Stroke Program Early CT Score on diffusion-weighted imaging ≤6 (15·23, 1·88–351·50), and a lower National Institutes of Health Stroke Scale score (1·24, 1·08–1·47, per 1-point decrease) were inversely correlated with early improvement. Four patients (5%) had symptomatic intracranial haemorrhage. At 3 months, 76 patients (98%) survived, and 36 of 78 patients (46%) overall, but only two of 19 patients (11%) with internal carotid artery occlusion, had a favourable functional outcome, corresponding to a modified Rankin scale score ≤1. After multivariate adjustment, internal carotid artery occlusion (odds ratio 15·84, 95% confidence interval 3·12–128·69) and Alberta Stroke Program Early CT Score on diffusion-weighted imaging ≤6 (15·62, 1·78–410·12) were independent predictors of poor outcome.**

Conclusions **Intravenous alteplase therapy at a dose of 0·6 mg/kg resulted in a relatively good overall outcome when compared with outcomes reported by western studies using an alteplase dose of 0·9 mg/kg. However, patients with occlusion at the internal carotid artery did not respond to this low-dose alteplase therapy.**

Key words: carotid artery occlusion, cerebral infarction, stroke outcome, thrombolysis, tissue plasminogen activator

Introduction

Intravenous (i.v.) alteplase therapy at a dose of 0·9 mg/kg has been approved internationally for the treatment of hyperacute ischaemic stroke (1–4). However, a large population study indicated that Asian patients had a 2·3-fold higher risk of in-hospital mortality after thrombolysis compared with Caucasian patients (5). Because Asian ethnic origin is an important risk factor for haemorrhagic stroke (6), a smaller dose of alteplase may be appropriate for Asian stroke patients. After a dose comparison study using duteplase (7) and a multicentre study using a single dose of alteplase [Japan Alteplase Clinical Trial (J-ACT)] (8), i.v. alteplase therapy with a dose of 0·6 mg/kg was approved in Japan in 2005 (9), although there has never been a head-to-head comparison of the alteplase dose of 0·9 vs. 0·6 mg/kg. Immediately after approval, the Japan Stroke Society published the Japanese guidelines for this low-dose

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Conflict of interest: None.

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i.v. alteplase therapy (10), and arranged for educational lectures in every prefecture throughout Japan (11). However, the efficacy of this low-dose therapy in routine clinical practice has not yet been clarified.

Magnetic resonance imaging (MRI)-based thrombolysis up to 6 h after stroke onset might be safer than standard computed tomography (CT)-based thrombolysis (12, 13). To introduce i.v. alteplase therapy into our institute, MRI was considered better for understanding the stroke profile for two reasons: diffusion-weighted imaging (DWI) would allow assessment of the early ischaemic change, and MR angiography (MRA) would allow accurate identification of the site of arterial occlusion. The Alberta Stroke Program Early CT Score (ASPECTS) was a quantitative scoring method of the early ischaemic signs for CT (14, 15), and the scoring of ASPECTS using DWI has been reported to be similarly available with the scoring using CT (16). Sites of arterial occlusion may be critical for the outcome of thrombolysis. Occlusions at the terminal internal carotid artery (ICA) and at the tandem lesion of the ICA and middle cerebral artery (MCA) detected on transcranial Doppler (TCD) have been shown to be predictive of a poor outcome after i.v. alteplase (17, 18). Because Japanese patients do not often have a sufficient cranial window for TCD (19), TCD is not appropriate for routine use in thrombolysis; MRA may be a promising alternative.

The goal of this study was to identify the clinical and radiological (including DWI and MRA) predictors of clinical efficacy for low-dose i.v. alteplase given at a dose of 0·6 mg/kg to stroke patients.

Methods

We prospectively enrolled 333 consecutive patients who were admitted within 3 h after the onset of ischaemic stroke or transient ischaemic attack to the stroke care unit in the National Cardiovascular Center between October 2005 (when i.v. alteplase therapy was approved in Japan) and December 2007. Patient eligibility for alteplase therapy was determined principally based on the inclusion and exclusion criteria used in the National Institute of Neurological Disorders and Stroke (NINDS) study and J-ACT (1, 8). Patients with CT evidence of extensive early ischaemic change (affecting more than one-third of the MCA territory) were excluded from the study in principle according to the J-ACT. Those with the similar DWI evidence were also excluded. The local Ethics Committee approved the research protocol. Either patients or their representatives gave their written informed consent.

Each patient received a single alteplase dose of 0·6 mg/kg (not exceeding 60 mg) intravenously, with 10% given as a bolus, followed by a continuous i.v. infusion of the remainder over 1 h. As in the NINDS study (1), use of antithrombotic agents was prohibited for 24 h after onset, blood pressure was maintained at $<180/105$ mmHg, and neurological symptoms were frequently monitored. Unless contraindicated (as in renal insufficiency), all patients were given a free radical scavenger, edaravone, intravenously in the hyperacute stage (20). The neurological deficits on admission were evaluated using the National Institutes of Health stroke scale (NIHSS) score just before and right after the 1-h alteplase infusion, 1 h later, 24 h later, and 3 weeks later. 'Early improvement' was defined as a decrease in the score ≥ 8 points or the score of 0 at 24 h posttherapy compared with the initial score (21, 22). Activities of daily living (ADL) 3 months poststroke were assessed using the modified Rankin scale (mRS) score. A score ≤ 1 at 3 months poststroke was defined as a 'favourable chronic outcome' and a score ≥ 2 or death was defined as an 'unfavourable chronic outcome'.

Before alteplase therapy, all patients underwent brain non-contrast CT, as well as DWI and intracranial MRA (unless contraindicated). The ASPECTS was calculated on both CT and DWI by 2 or more vascular neurologists (14, 15). The patients were divided into four groups according to the arterial occlusion sites ipsilateral to ischaemia: (1) those with the ICA occlusion; (2) those with the MCA trunk (M1) occlusion; (3) those with the MCA branch (M2) occlusion; and (4) those with occlusion at other sites, including the anterior and posterior cerebral arteries and vertebrobasilar arteries, or those without documented occlusion on MRA. CT scans were repeated 24–36 h posttherapy. Symptomatic intracerebral haemorrhage (ICH) was defined as CT evidence of new ICH within the initial 36 h with neurological deterioration corresponding to an increase of ≥ 4 point from the baseline NIHSS score.

The patients' risk factors included sex, age, hypertension (systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg before stroke or a history of antihypertensive medication), diabetes mellitus (fasting blood glucose $\geq 7{\cdot}0$ mmol/l, a positive 75 g oral glucose tolerance test, or a history of antidiabetic medication), hypercholesterolaemia (serum total cholesterol $\geq 5{\cdot}7$ mmol/l or a history of antihypercholesterolaemic medication), atrial fibrillation, current smoking habit, current alcohol consumption, a history of ischaemic stroke, and use of antithrombotic agents before stroke. On admission, blood pressure and the blood parameters listed in Table 1 and its footnote were measured. Based on neurological, radiological, cardiological, and haematological profiles, the stroke subtype was determined during hospitalisation by a consensus of vascular neurologists according to the TOAST subtype classification system (23): cardioembolism, large-artery atherosclerosis (atherothrombosis), small-artery arteriosclerosis (lacune), and stroke of other determined or undetermined aetiology.

Statistics

Of the patients who were treated with i.v. alteplase, those with a premorbid mRS score ≥ 2 and those who were contraindicated to MRI were excluded from analyses. Baseline clinical characteristics and stroke features were compared between patients with and without early improvement, and between patients with favourable and unfavourable chronic outcomes, using the

Table 1 Underlying risk factors

		Improvement at 24 h		Outcome at 3 months	
	Total	Improved	Nonimproved	Favourable	Unfavourble
Number	78	19	59	36	42
Age	71±9	71±9	71±9	70±7	72±9
Male	59 (76)	14 (74)	45 (76)	28 (78)	31 (74)
Hypertension	60 (77)	17 (89)	43 (73)	23 (64)	37 (88)*
Diabetes mellitus	16 (21)	3 (16)	13 (22)	9 (21)	7 (19)
Hypercholesterolaemia	31 (40)	6 (32)	25 (42)	15 (42)	16 (38)
Atrial fibrillation	34 (44)	9 (47)	25 (42)	13 (36)	21 (50)
Current smoking	25 (32)	2 (11)	23 (39)*	8 (22)	17 (40)†
Current drinking	36 (46)	9 (47)	27 (46)	18 (50)	18 (43)
Previous ischaemic stroke	13 (17)	3 (16)	10 (17)	7 (17)	6 (17)
Antithrombotic use	30 (38)	10 (53)	20 (34)	17 (47)	13 (31)

Data are mean±SD for age and number of patients (%) for others. *$P<0.05$. †$P<0.1$ vs. 'improved' or 'favourable'.

χ^2-test, unpaired Student's *t*-test, or Mann–Whitney's *U*-test, as appropriate. To evaluate the correlation between ASPECTS on CT and ASPECTS on DWI, linear regression analysis and the Pearson correlation coefficient were used. Optimal cutoff ASPECTS for predicting early improvement and chronic outcome were determined using receiver operating characteristic (ROC) curves. To identify the independent risk factors related to early improvement and chronic outcome, sex, age, and the baseline variables that were automatically selected in a stepwise selection method were included in the multivariate analysis. A *P* value <0.05 was considered to be significant and a *P* value <0.1 was considered to be marginally significant. All calculations were performed using jmp 7 software (SAS Institute Inc., Cary, NC).

Results

Of the 333 patients who visited our stroke centre within 3 h after the onset of ischaemic stroke, 94 (28%) were treated with i.v. alteplase. They accounted for 10% of the 948 inpatients with acute ischaemic stroke in our centre during the same period. Of these 94 patients, five patients with the premorbid mRS score ≥ 2 and 11 patients who were contraindicated to MRI were excluded, which left 78 patients in the study. The underlying clinical characteristics of the 78 patients are summarised in Table 1, and stroke features and data on admission are summarised in Table 2. The ASPECTS on the admission CT and those on the admission DWI were well correlated ($R^2 = 0.326$, $P<0.001$, Fig. 1).

The overall median NIHSS score declined from 12 at baseline to 9 immediately after the 1-h alteplase infusion, 9 at 1 h later, 7·5 at 24 h, and 3 at 3 weeks. Changes in the median NIHSS score by the different sites of occlusion are plotted in Fig. 2, which shows a plateau in patients with ICA occlusion, and a gradual decrease in the other patients. At 24 h, the NIHSS score of 19 patients (24%) improved by ≥ 8 points. Cutoff ASPECTS on CT based on ROC curves was ≤ 7 and cutoff ASPECTS on DWI was ≤ 6 for early improvement at 24 h. Current smoking ($P = 0.021$) and the initial NIHSS score ($P = 0.030$) were significantly different between patients with and without early improvement (Tables 1 and 2). After adjustment for age, sex, and selected variables using the stepwise selection method, ICA occlusion (odds ratio 11·82, 95% CI 1·73–142·74), ASPECTS on DWI ≤ 6 (15·23, 1·88–351·50), and a lower NIHSS score (1·24, 1·08–1·47, per 1-point decrease) were inversely correlated with early improvement (Table 3).

Four patients (5%) had symptomatic ICH within the initial 36 h; the initial occlusion site was the ICA in 1 (ASPECTS on DWI: 9), the M1 in 2 (ASPECTS on DWI: 4 for both), and the M2 in another (ASPECTS on DWI: 5). Of these, a patient with the ICA occlusion died in the acute stage, two patients with the M1 occlusion received surgical evacuation for severe brain oedema, and a patient with the M2 occlusion had a 3-month mRS score of 3.

At 3 months, two (2%) patients were dead; both of them had ICA occlusion. Of 78 patients overall, 36 (46%) recovered to a favourable functional outcome at 3 months. However, only two of 19 patients (11%) with ICA occlusion had a favourable outcome (Fig. 3). Cutoff ASPECTS on CT based on ROC curves was ≤ 9 and cutoff ASPECTS on DWI was ≤ 6 for chronic outcome. The sites of occlusion were significantly different between patients with favourable outcomes and those with unfavourable outcomes at 3 months ($P = 0.001$, Table 2). Compared with patients with favourable outcomes, those with unfavourable outcomes were more hypertensive ($P = 0.011$), more frequently showed ASPECTS on DWI ≤ 6 ($P = 0.008$), had higher NIHSS scores ($P = 0.002$), tended to more frequently have a smoking habit ($P = 0.085$), and tended to have higher initial diastolic blood pressures ($P = 0.066$, Tables 1 and 2). After multivariate adjustment, ICA occlusion (odds ratio 15·84, 95% CI 3·12–128·69) and ASPECTS on DWI ≤ 6 (15·62, 1·78–410·12) were independent predictors of an unfavourable outcome (Table 4).

Table 2 Stroke features and physiological data on admission

		Improvement at 24 h		Outcome at 3 months	
	Total	Improved	Nonimproved	Favourable	Unfavourble
Number	78	19	59	36	42
Onset-to-needle time (min)	136±27	126±33	139±25	134±29	137±26
Subtypes					
Cardioembolic	40 (51)	11 (58)	29 (49)	19 (53)	21 (50)
Atherothrombotic	16 (21)	2 (11)	14 (24)	7 (19)	9 (21)
Lacunar	2 (3)	0	2 (3)	0	2 (5)
Other	20 (26)	6 (31)	14 (24)	10 (28)	10 (24)
Site of occlusion on MRA					
ICA	19 (24)	2 (11)	17 (29)	2 (6)	17 (40)*
M1	20 (26)	7 (37)	13 (22)	9 (25)	11 (26)
M2	12 (15)	4 (21)	8 (14)	9 (25)	3 (7)
Others/no occlusion	27 (35)	6 (32)	21 (36)	16 (44)	11 (26)
Vertebrobasilar infarcts	6 (8)	3 (16)	3 (5)	4 (11)	2 (5)
ASPECTS on CT	9 (8–10)	10 (8–10)	9 (8–10)	10 (8–10)	9 (8–10)
ASPECTS on CT≤7‡	9 (12)	1 (5)	8 (14)	–	–
ASPECTS on CT≤9‡	27 (35)	–	–	9 (25)	18 (43)
ASPECTS on DWI	9 (8–10)	9 (8–10)	9 (7–10)	9 (8–10)	8·5 (7–10)†
ASPECTS on DWI≤6‡	11 (14)	1 (5)	10 (17)	1 (3)	10 (24)*
Initial NIHSS score	12 (8–18)	13 (12–20)	12 (7–18)*	11·5 (7–13)	14·5 (10–20)*
Data on admission					
Systolic blood pressure (mmHg)	161±35	154±39	163±33	155±31	166±37
Diastolic blood pressure (mmHg)	86±19	83±23	87±17	82±19	89±18†
Blood glucose (mmol/l)	7·5±3·0	7·5±2·1	7·5±3·2	7·7±3·1	7·3±2·8

Data are number of patients (%), mean±SD for continuous variables, and median (interquartile range) for discontinuous variables. Among blood tests, white blood cell count, haemoglobin, platelet count, highly sensitive C-reactive protein, total protein, albumin, blood urea nitrogen, creatinine, uric acid, aspartate/alanine aminotransferase, total/direct bilirubin, low/high-density lipoprotein, and triglyceride, as well as glucose were not different ($P>0·1$) between patients with and without improvement at 24 h or between patients with favourable and unfavourable outcome at 3 months. *$P<0·05$. †$P<0·1$ vs. 'improved' or 'favourable'. ‡Cutoff ASPECTS on CT based on ROC curves is ≤7 for early improvement and ≤9 for chronic outcome. Cutoff ASPECTS on DWI is ≤6 for both early improvement and chronic outcome. ASPECTS, Alberta Stroke Program Early CT Score; CT, computed tomography; DWI, diffusion-weighted imaging; ICA, internal carotid artery; MRA, MR angiography; NIHSS, National Institutes of Health Stroke Scale.

Discussion

The present study determined the efficacy and safety of low dose, i.v. alteplase therapy at a dose of 0·6 mg/kg for stroke patients, which is a therapeutic strategy that has only been approved in Japan (10, 11). The first major finding was that 24% of patients receiving therapy showed improvement of the NIHSS score ≥8 points within the initial 24 h, and 46% of the patients recovered completely independent ADL (corresponding to an mRS ≤1) at 3 months, while 5% had symptomatic ICH within the initial 36 h, and 2% were dead at 3 months. The second major finding was that occlusion at the ICA documented on MRA was associated with a several fold increased risk of failure to show early improvement and that of an unfavourable chronic outcome compared with other occlusion locations. This finding indicates an obvious limitation of this low-dose alteplase therapy. The third major finding was that ASPECTS on DWI ≤6 was another independent predictor for failure to show early improvement and an unfavourable chronic outcome.

Major neurological improvement of the NIHSS score ≥8 points is recommended as a useful marker of thrombolytic activity (21, 22). Relatively few patients showed a major improvement in the present study compared with those in the NINDS trial (32%) (22). In contrast, the 3-month outcome in our patients (46% of the patients had an mRS ≤1) was relatively good compared with those reported from western countries using alteplase at a dose of 0·9 mg/kg, including the NINDS trial (39%) (1), SITS-MOST (39%) (4), and the pooled results of the randomised trials (42%) (24). Our institute has extensive experience in stroke thrombolysis, participating in several clinical trials as a core institute (7, 8) and performing i.v. thrombolysis for 10% of acute ischaemic stroke patients. Thus, the present success may be institute specific.

Before the NINDS study (1), several trials reported that ICA occlusion documented on conventional angiogram responds poorly to i.v. thrombolysis (25–27). ICA occlusion or tandem ICA/MCA occlusion has been shown to be resistant to i.v. alteplase at a dose of 0·9 mg/kg, as documented on MRA or CT angiogram (28) and on TCD (17, 18). The present study confirmed these previous results and highlighted the strong influence of ICA occlusion on poor outcome in Japanese patients after i.v. alteplase at a lower dose than other countries, even after adjustment for other known confounders. Although

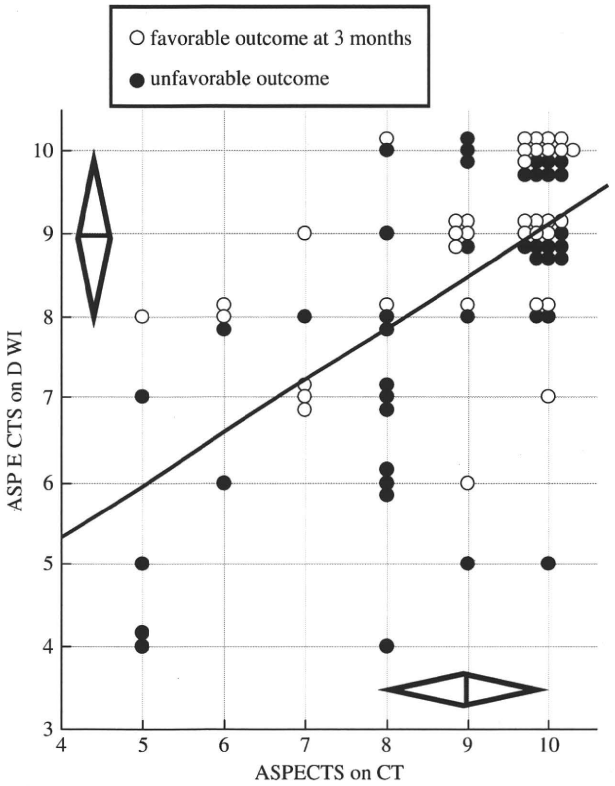

Fig. 1 Correlation between ASPECTS on CT and ASPECTS on diffusion-weighted imaging (DWI) $R^2 = 0{\cdot}326$, $P<0{\cdot}001$. Diamonds show the median value (9) and interquartile range (8–10) of Alberta Stroke Program Early CT Score (ASPECTS) on computed tomography and ASPECTS on DWI.

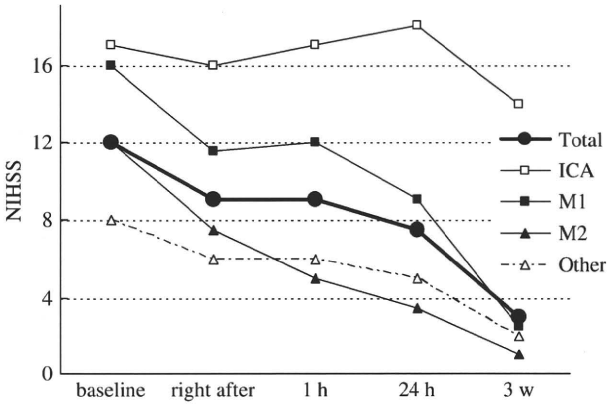

Fig. 2 Changes in the median National Institutes of Health Stroke Scale score by different sites of occlusion.

Table 3 Multivariate-adjusted odds ratios (OR) for failure in early improvement

	OR	95% CI	*P*-value
Age, per 10-year increase	0·94	0·34–2·48	0·901
Male	0·38	0·05–1·99	0·279
Hypertension	0·35	0·05–1·80	0·244
Current smoking	4·83	0·83–42·22	0·104
Antithrombotic use	0·26	0·06–1·09	0·075
ICA occlusion	11·82	1·73–142·74	0·025
ASPECTS on DWI ≤ 6	15·23	1·88–351·50	0·028
Initial NIHSS score, per 1-point decrease	1·24	1·08–1·47	0·005

Sex, age, and variables that were automatically selected in a stepwise selection method were used for the analysis. ASPECTS, Alberta Stroke Program Early CT Score; CI, confidence interval; DWI, diffusion-weighted imaging; ICA, internal carotid artery.

MRI is expensive and has some potential risks (29), it allows accurate identification of intracranial artery occlusion. In Japan, MRI equipment is widely available; thus, MRI-based thrombolysis appears to be acceptable.

Another advantage of MRI over CT for stroke diagnosis is easier identification of hyperacute ischaemia using DWI (30, 31). A positive relation between ASPECTS assessed on CT and on DWI was established (16). The ASPECTS on DWI ≤5 was recently reported to be a predictor for the NIHSS score ≥20 at 7 days after i.v. alteplase therapy (32). In the present study, ASPECTS on DWI, but not ASPECTS on CT, was predictive of both early improvement and chronic outcome after multivariate adjustment.

Other than the ICA occlusion and ASPECTS on DWI, a high initial NIHSS score was associated with a major early neurological improvement; this seems to be simply because high baseline points are needed for a marked decrease of ≥8 points.

The present study had several limitations. Because this was an observational study from a single stroke centre, our results could not be compared with those from other centres, with those of patients not receiving thrombolysis, and with those of Japanese patients treated with alteplase at a dose of 0·9 mg/kg. Second, the study also lacked data on recanalisation of the occluded artery after alteplase. Third, fewer lacunar patients were included than previous studies on i.v. alteplase therapy (1, 4). Because patients with minor damage corresponding to the NIHSS score ≤4 were not treated with alteplase in principle in our institute based on the criteria of J-ACT (8) and more than half the Japanese patients with lacunar stroke were reported to exhibit such minor deficits (33), and because cardioembolic patients generally visit hospitals much earlier than patients with other subtypes (33), the distribution of stroke subtypes appeared to be affected. In general, the efficacy of i.v. alteplase is thought to be similar among different stroke subtypes (1, 34).

In conclusion, i.v. alteplase therapy at 0·6 mg/kg resulted in a relatively good outcome for the present patients, although ICA occlusion and low ASPECTS on DWI were strong predictors of a poor outcome. For patients having ICA occlusion, alternatives may be required, including higher dose alteplase, combined i.v./intraarterial thrombolysis, or possibly mechanical thrombectomy using a thrombus-removal device (35). A randomised, multicentre trial (the Interventional Management of Stroke III Trial) is ongoing to determine the efficacy of the combined i.v./intraarterial

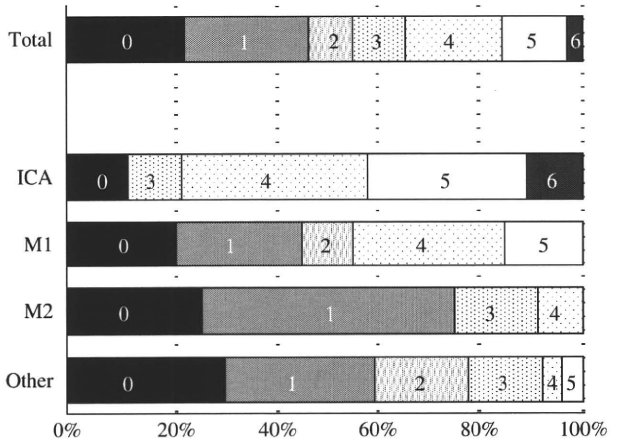

Fig. 3 Modified Rankin scale score at 3 months by different sites of occlusion.

Table 4 Multivariate-adjusted odds ratios (OR) for unfavorable chronic outcome

	OR	95% CI	*P*-value
Age, per 10-year increase	0·96	0·44–2·06	0·911
Male	0·59	0·12–2·73	0·496
Hypertension	3·99	1·02–18·56	0·058
Atrial fibrillation	2·41	0·69–9·17	0·175
Current smoking	4·03	0·98–19·27	0·063
Antithrombotic use	0·29	0·07–1·09	0·078
ICA occlusion	15·84	3·12–128·69	0·003
ASPECTS on DWI≤6	15·62	1·78–410·12	0·034

Sex, age, and variables that were automatically selected in a stepwise selection method were used for the analysis. ASPECTS, Alberta Stroke Program Early CT Score; CI, confidence interval; DWI, diffusion-weighted imaging; ICA, internal carotid artery.

approach to recanalisation using the thrombus-removal device, infusion of alteplase with low-energy ultrasound at the site of the thrombus, or infusion of alteplase via a standard microcatheter (36).

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Routine Use of Intravenous Low-Dose Recombinant Tissue Plasminogen Activator in Japanese Patients: General Outcomes and Prognostic Factors From the SAMURAI Register

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Routine Use of Intravenous Low-Dose Recombinant Tissue Plasminogen Activator in Japanese Patients

General Outcomes and Prognostic Factors From the SAMURAI Register

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Background and Purpose—A retrospective, multicenter, observational study was conducted to document clinical outcomes and to identify outcome predictors in patients treated with low-dose intravenous recombinant tissue plasminogen activator (0.6 mg/kg alteplase), which was approved in Japan in 2005, within 3 hours of stroke onset.

Methods—Consecutive patients with stroke treated with recombinant tissue plasminogen activator in 10 Japanese stroke centers were included.

Results—A total of 600 patients (377 men, 72±12 years old) were studied. Median National Institutes of Health Stroke Scale scores decreased from 13 before recombinant tissue plasminogen activator to 8 at 24 hours later. Symptomatic intracerebral hemorrhage within 36 hours with a ≥1-point increase from the baseline National Institutes of Health Stroke Scale score developed in 23 patients (3.8%; 95% CI, 2.6% to 5.7%). At 3 months, 43 patients had died (7.2%; 5.4% to 9.5%), and 199 patients (33.2%; 29.5% to 37.0%) had a modified Rankin Scale score ≤1. Analysis of 399 patients with a premorbid modified Rankin Scale score ≤1 who met the criteria of the European license (≤80 years old, an initial National Institutes of Health Stroke Scale score ≤24, etc) showed that 40.6% (35.9% to 45.5%) had a 3-month modified Rankin Scale score ≤1. After multivariate adjustment, younger age, lower initial National Institutes of Health Stroke Scale score, absence of internal carotid artery occlusion, higher Alberta Stroke Program Early CT Score on CT, and absence of intravenous antihypertensives just before recombinant tissue plasminogen activator were independently related to a 3-month modified Rankin Scale score ≤1. Congestive heart failure and hyperglycemia were independently related to mortality.

Conclusions—Three-month outcomes of patients receiving low-dose intravenous recombinant tissue plasminogen activator therapy in the present study were similar to those from postmarketing surveys using 0.9 mg/kg alteplase. **(*Stroke*. 2009;40:3591-3595.)**

Key Words: acute stroke ■ alteplase ■ cerebral infarction ■ recombinant tissue plasminogen activator ■ stroke outcome ■ thrombolysis

In 2005, intravenous (IV) alteplase therapy at a dose of 0.6 mg/kg was approved in Japan after a dose comparison study using duteplase[1] and a multicenter study using a single dose of alteplase (Japan Alteplase Clinical Trial [J-ACT]),[2] although a head-to-head comparison of the alteplase dose of 0.9 mg/kg versus 0.6 mg/kg has not been done. A postmarketing survey from our single stroke center found that 36 (46%) of 78 patients receiving low-dose recombinant tissue plasminogen activator (rtPA) therapy had a favorable 3-month outcome corresponding to a modified Rankin Scale (mRS) score ≤1.[3]

Based on the large population of patients included in Western randomized, controlled trials and postmarketing

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studies, several predictors of stroke outcome after rtPA have been identified, including advanced age, stroke severity, initial hyperglycemia, and high acute blood pressure.[4–7] Low-dose rtPA therapy may, in principle, share the same predictors. Because MRI is widely available in Japan, studies on low-dose rtPA were often based on MRI and MR angiography. In the above study from our center, occlusion of the internal carotid artery (ICA) and early ischemic signs on diffusion-weighted MRI (DWI), defined as an Alberta Stroke Program Early CT Score (ASPECTS) ≤6, were independently predictive of an mRS ≥2 at 3 months.[3] Kimura et al[8] reported that ASPECTS on DWI ≤5 was predictive of a National Institutes of Health Stroke Scale (NIHSS) score≥20 at 7 days. Chronic outcomes of low-dose rtPA therapy as well as the factors affecting the outcomes should be ascertained using a larger population with a multicenter design.

To determine appropriate risk factor control in acute stroke, a multicenter study group (Stroke Acute Management with Urgent Risk-factor Assessment and Improvement [SAMURAI] Study Group) was formed. A retrospective observational study was conducted to identify the effects of risk factors and other patient characteristics on the outcome of IV alteplase at a dose of 0.6 mg/kg. This article reports the overall general results.

Patients and Methods

The SAMURAI Study Group was composed of 10 Japanese stroke centers that were balanced regionally. In this study, all consecutive patients with ischemic stroke or transient ischemic attack who received IV rtPA therapy in these 10 centers between October 2005 (when IV alteplase therapy was approved in Japan) and July 2008 were registered. Patient eligibility for alteplase therapy was determined based primarily on Japanese guidelines for IV rtPA therapy,[9] which follow the inclusion and exclusion criteria used in the National Institute of Neurological Disorders and Stroke (NINDS) study and J-ACT.[2,10] Each local ethics committee approved the retrospective collection of clinical data from the database and submission of the data to our central office.

Each patient received a single alteplase dose of 0.6 mg/kg (not exceeding 60 mg) IV with 10% given as a bolus within 3 hours of stroke onset followed by a continuous IV infusion of the remainder over 1 hour. Like in the NINDS study,[10] use of antithrombotic agents was prohibited in principle for 24 hours after onset, blood pressure was maintained at <180/105 mm Hg, and neurological signs and symptoms were frequently monitored.

Before rtPA therapy, all patients underwent brain noncontrast CT or DWI. The ASPECTS was calculated on both CT and DWI; it is a 10-point quantitative topographical scoring method of the early ischemic signs, originally developed for CT, which divides the middle cerebral arterial territory into 10 regions of interest.[11,12] To identify arterial occlusion sites, MR angiography, CT angiography, or ultrasound was performed. The baseline characteristics listed in Tables 1 and 2 were studied.

The outcomes were: completely independent activity of daily living at 3 months corresponding to an mRS ≤1; death at 3 months; any intracerebral hemorrhage (ICH) defined as CT evidence of new ICH within the initial 36 hours; and symptomatic ICH with neurological deterioration corresponding to an increase of ≥1 point from the baseline NIHSS score. Symptomatic ICH was also defined according to the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST)[13] protocol as parenchymal hemorrhage Type II combined with an increase of ≥4 points from the baseline NIHSS score. Outcomes at 3 months were assessed by clinical examination at a hospital clinic (or by phone survey for patients whose neurological deficits were too severe to visit the clinic). The examiners at the clinics were familiar with patients' stroke features in some hospitals and not in others. For patients who were lost to follow-up at 3 months, mRS at hospital discharge was assessed instead.

Table 1. Baseline Characteristics and Physiological Data of 600 Patients

Demographics	
Male	377 (62.8%)
Age, years	72±12
Risk factors and comorbidities	
Hypertension	366 (61.0%)
Diabetes mellitus	110 (18.3%)
Dyslipidemia	125 (21.0%)
Atrial fibrillation	258 (43.4%)
Congestive heart failure (n=588)	51 (8.7%)
Prior ischemic stroke	109 (18.2%)
Premorbid mRS ≥2	65 (10.8%)
Prior ischemic heart disease	77 (13.1%)
Prior use of anticoagulants	53 (8.8%)
Prior use of antiplatelets	192 (32.0%)
Prior use of antihypertensives	265 (44.5%)
Prior use of statins	67 (11.2%)
Physiological data on admission	
Body weight, kg	58.7±11.9
Body height, cm (n=534)	160.1±8.9
Body mass index (n=534)	22.9±3.3
Systolic blood pressure, mm Hg	150.2±20.2
Diastolic blood pressure, mm Hg	81.4±15.4
Pulse rate, beats/min	79.7±19.4
Body temperature, °C	36.3±0.6
Blood glucose, mmol/L (n=585)	7.62±2.64
Total cholesterol, mmol/L (n=551)	4.88±1.03
Creatinine, mmol/L	81.0±66.8

Data are no. of patients (%) and means±SD for continuous variables.

Statistics

All calculations were performed using JMP 7 software (SAS Institute Inc). A probability value <0.05 was considered significant. The proportions and 95% CIs of patients with ICH and mRS ≤1 as well as mortality were calculated for all patients as well as for patients who met the criteria of the European license (patients ≤80 years old with an initial NIHSS score ≤24 and without any history of prior stroke and concomitant diabetes). Multivariate analyses were performed to find predictors for an mRS ≤1 and death at 3 months based on the characteristics in Tables 1 and 2. For each outcome, a backward selection procedure was performed using $P>0.10$ of the likelihood ratio test for exclusion. We assessed the main effects of each characteristic and did not assess bivariable interaction of characteristics. Multivariate analyses were also done simply with adjustment for sex, age, and initial NIHSS score.

Results

A total of 600 patients with stroke (377 men, 72±12 years old) were registered. During the same period, a domestic survey estimated that approximately 13 500 Japanese patients with stroke received IV rtPA therapy. Thus, the present patients accounted for approximately 4.4% of the rtPA-treated patients in Japan during that time period. Of these 600

Table 2. Stroke Features and Process Measures for the 600 Patients

Stroke Features	
Time of stroke onset	
6 AM to 2 PM	292 (48.7%)
2 PM to 10 PM	244 (40.7%)
10 PM to 6 AM	64 (10.6%)
Arterial occlusion site (n=546)	
Internal carotid artery	91 (16.7%)
Middle cerebral artery trunk (M1)	159 (29.1%)
Middle cerebral artery branch (M2)	108 (19.8%)
Anterior cerebral artery	7 (1.3%)
Posterior cerebral artery	18 (3.3%)
Vertebral artery	4 (0.7%)
Basilar artery	22 (4.0%)
Stroke subtype	
Cardioembolism	380 (63.3%)
Atherothrombotic stroke	91 (15.2%)
Lacune	29 (4.8%)
Other mechanisms	100 (16.7%)
ASPECTS on CT (n=501)	10 (8–10)
ASPECTS on DWI (n=520)	8 (7–10)
Initial NIHSS score	13 (7.3–19)
Process measure	
Onset-to-treatment time, minutes	145 (121–166)
Interruption of rtPA	6 (1.0%)
IV antihypertensives just before rtPA	164 (27.6%)
IV edaravone	502 (83.7%)

Data are no. of patients (%) and median (interquartile range) for discontinuous variables.

patients, 422 (70.3%) met the criteria of the European license (patients ≤80 years old with an initial NIHSS score ≤24 and without any history of prior stroke and concomitant diabetes).

The baseline characteristics of the 600 patients as well as their stroke features and process measures are listed in Tables 1 and 2. The leading risk factor was hypertension (61.0%) followed by atrial fibrillation (43.4%). MR angiography was performed in 479 patients, CT angiography was performed in 15, and ultrasound was performed in 369. The leading site of arterial occlusion was the trunk of the middle cerebral artery (29.1%) followed by its branch (19.8%). The leading stroke subtype was cardioembolism (63.3%).

The median NIHSS score decreased from 13 (interquartile range, 7.25 to 19) before rtPA to 8 (interquartile range, 3 to 16) 24 hours later. ICH developed in 119 patients (19.8%; 16.8% to 23.2%); of these, 30 showed parenchymal hemorrhage Type I (5.0%) and 21 showed parenchymal hemorrhage Type II (3.5%). Symptomatic ICH within 36 hours developed in 23 patients (3.8%; 2.6% to 5.7%). Symptomatic ICH within 36 hours per the SITS-MOST definition developed in 8 patients (1.3%; 0.7% to 2.6%); 7 of these met the criteria of the European license (7 of 422 [1.7%; 0.8% to 3.4%]).

Vital prognosis at 3 months was available for all 600 patients, but the mRS scores for 5 patients were not available. mRS scores at hospital discharge in these 5 patients were 2, 4, 4, 5, and 5, and their durations of hospitalization were 38, 30, 33, 18, and 37 days, respectively.

Of the total 600 patients, 199 patients (33.2%; 95% CI, 29.5% to 37.0%) had an mRS score ≤1 at 3 months, when the score at hospital discharge was used for 5 patients who were lost to follow-up at 3 months (Figure). When 65 patients with a premorbid mRS score ≥2 were excluded from the analysis, 199 (37.2%; 33.2% to 41.4%) of 535 patients had an mRS score ≤1. In addition, when patients who did not meet the criteria of the European license were excluded, 162 (40.6%; 35.9% to 45.5%) of 399 patients had a score ≤1.

At 3 months, 43 patients (7.2%; 95% CI, 5.4% to 9.5%) died, including 7 with symptomatic ICH. Nineteen patients died within the initial week of stroke. Fifteen patients died directly of stroke, 7 died of heart disease (5 heart failure, one heart rupture, and one infective endocarditis) and 6 died of pneumonia. Of 422 patients who met the criteria of the European license, 20 died (4.7%; 3.1% to 7.2%).

Multivariate regression analysis using a backward selection method indicated that younger age, lower initial NIHSS

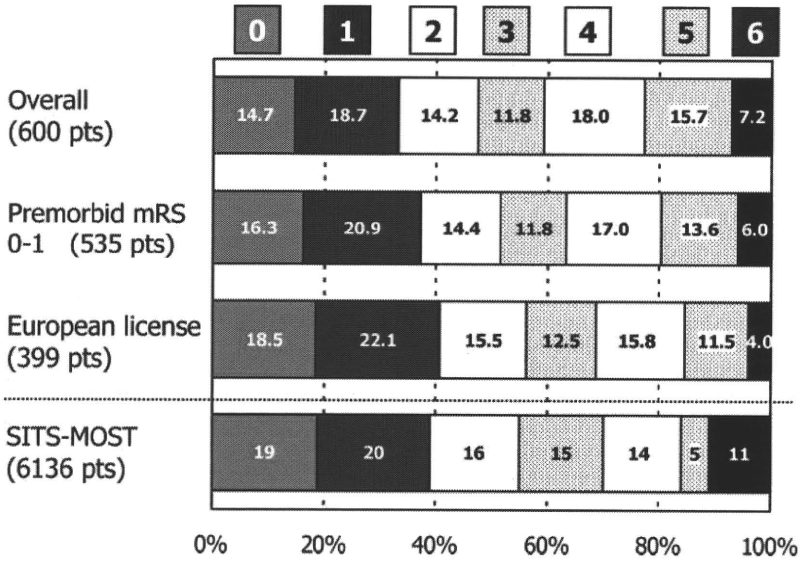

Figure. mRS score at 3 months in the present patients and those in SITS-MOST.

Table 3. Characteristics Associated With an mRS Score ≤1 and Death at 3 Months

Characteristic	OR	95% CI	*P* Value
mRS score ≤1			
Age, per 10-year increase	0.74	0.59–0.91	0.006
Initial NIHSS score, per 1-point increase	0.92	0.88–0.95	<0.001
Glucose, per 1-mmol/L increase	0.90	0.81–1.00	0.053
Internal carotid artery occlusion	0.27	0.11–0.61	0.003
ASPECTS on CT, per 1-point increase	1.25	1.06–1.51	0.013
IV antihypertensives just before rtPA	0.38	0.21–0.67	0.001
Death			
Congestive heart failure	5.90	2.74–12.27	<0.001
Prior use of statin	1.59	0.60–3.72	0.331
Glucose, per 1-mmol/L increase	1.14	1.03–1.26	0.015

Adjusted by characteristics selected by a backward selection procedure. "mRS score ≤1" was analyzed based on 535 patients with a premorbid mRS ≤1. "Death" was analyzed based on 600 patients.

score, absence of ICA occlusion, higher ASPECTS on CT, and absence of IV antihypertensives just before rtPA were independently related to an mRS ≤1 at 3 months (Table 3). In addition, hypertension (P=0.013), higher initial systolic blood pressure (P=0.046), and higher initial glucose level (P=0.034) were inversely related, and cardioembolism (P=0.034) was positively related to an mRS ≤1 after simple adjustment for sex, age, and the initial NIHSS score.

After multivariate regression analysis using a backward selection method, congestive heart failure and higher initial glucose level were independently related to death at 3 months (Table 3). In addition, older age (P=0.048), higher initial NIHSS score (P<0.001), ischemic heart disease (P<0.001), prior use of anticoagulants (P=0.047), prior use of antihypertensives (P=0.016), lower body weight (P=0.032), and ICA occlusion (P<0.001) were positively related, and use of the IV free radical scavenger, edaravone (which was approved for clinical use in Japan in 2001 after a multicenter randomized clinical trial),[14] was inversely related to death (P=0.002) after adjustment for sex, age, and the NIHSS score.

Discussion

The first major finding of this study was that 33.2% (95% CI, 29.5% to 37.0%) of patients with stroke in our cohort had an mRS ≤1 at 3 months after receiving low-dose (0.6 mg/kg) IV alteplase therapy, a therapeutic strategy that has only been approved in Japan. When patients who did not meet the criteria of the European license as well as those with a premorbid mRS score ≥2 were excluded, like in SITS-MOST,[13] 40.6% (35.9% to 45.5%) had a score ≤1. These percentages were similar to the percentage of patients with an mRS score ≤1 in J-ACT[2] (37%) and those in Western postmarketing surveys using 0.9 mg/kg alteplase (35% in Standard Treatment with Alteplase to Reverse Stroke [STARS]; 37% in Canadian Alteplase for Stroke Effectiveness Study [CASES]; 38.9%, 37.7 to 40.1% in SITS-MOST).[13,15,16] In addition, the frequency of symptomatic ICH in our study (3.8%; 2.6% to 5.7%) was relatively low compared with that in the NINDS study (6.4%)[10] and CASES (4.6%; 3.4% to 6.0%)[16] and similar to that in SITS-MOST (1.3%; 0.7% to 2.6% in ours versus 1.7%; 1.4% to 2.0% in SITS-MOST using the SITS-MOST definition).[13] Our definition for symptomatic ICH was similar to the others; accordingly, this low frequency suggests a true reduction in risk of ICH by low-dose rtPA. Our mortality rate at 3 months (4.7%; 3.1% to 7.2%, for patients meeting the criteria of the European license) was also lower than that in SITS-MOST (11.3%; 10.5% to 12.1%)[13] and CASES (22.3%; 20.0% to 25.0%).[16] Because our result was from experienced centers, it might be better than the overall results in Japan. At the very least, low-dose IV rtPA given to Japanese patients in experienced centers resulted in relatively good efficacy and safety compared with regular-dose therapy in Western patients.

The second major finding was that age, initial neurological severity, ICA occlusion, ASPECTS on CT, and IV antihypertensives just before rtPA were related to long-term independence, and congestive heart failure and initial glucose level were related to mortality after low-dose rtPA; some of these are known predictors.[4–6] Of these, admission hyperglycemia was reported to be associated with a poor recanalization rate of the occluded artery and increased risk of death, symptomatic ICH, and poor functional status.[6,17,18] High acute blood pressure is associated with poor outcome after rtPA.[4,6,7,19] In a multivariate analysis from Safe Implementation of Thrombolysis in Stroke–International Stroke Thrombolysis Register (SITS-ISTR) involving 11 080 patients, a high average systolic blood pressure at 2 to 24 hours was associated with high mortality, high rates of symptomatic ICH, and low rates of functional independence.[7] However, the effect of emergent IV antihypertensives on stroke outcome is being disputed; a recent study found no effect.[20] A major advance in our data set was that we had pretreatment MR angiography information. In addition to our MR angiography studies,[3] some studies using transcranial Doppler showed ICA occlusion to be resistant to IV rtPA.[21,22] We should note that our patients with ICA occlusion had much higher initial median NIHSS scores than those without ICA occlusion (18 versus 12, P<0.001), although the inverse association between ICA occlusion and long-term independence was significant after adjustment for the NIHSS score. An association of lower body weight with mortality after adjustment for sex, age, and the NIHSS score suggests that alteplase at a dose of 0.6 mg/kg was insufficient for lightweight patients, because a dose in proportional to body weight may be inadequate in such patients due to the plasma distribution and activation of alteplase.

The limitations of the present study include missing data of 3-month mRS scores for 5 patients as well as missing data for some baseline characteristics; these affected the data on chronic outcomes and limited the number of patients available for the multivariate analyses. Second, this was an observational study, and patient eligibility for rtPA was determined according to each patient's situation, although the determination was principally based on the Japanese guidelines.[9] We did not collect data for patients with stroke who visited our centers within 3 hours after onset and did not receive thrombolysis. Third, some continuous variables might

have been re-evaluated as categorized factors for proper statistical analyses. Our previous studies indicated that ASPECTS on DWI beyond threshold values was indicative of poor stroke outcome,[3,8] but the present study using ASPECTS as a continuous variable did not. Detailed analyses on outcome predictors should be explored in further subanalyses.

In conclusion, chronic outcomes and the factors affecting chronic outcomes were determined in Japanese patients with stroke receiving low-dose IV rtPA therapy. In future studies, we plan to determine the contribution of each risk factor and other patient characteristics to the outcomes.

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Disclosures

None.

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Pretreatment ASPECTS on DWI predicts 3-month outcome following rt-PA

SAMURAI rt-PA Registry

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ABSTRACT

Objective: To evaluate whether the pretreatment Alberta Stroke Programme Early CT Score (ASPECTS) assessed using diffusion-weighted imaging (DWI) predicts stroke outcomes at 3 months following IV recombinant tissue-type plasminogen activator (rt-PA) therapy.

Methods: Stroke patients treated with rt-PA (0.6 mg/kg alteplase) in 10 stroke centers in Japan were retrospectively studied. ASPECTS was assessed on DWI just prior to rt-PA injection. The primary outcome was a modified Rankin Scale (mRS) score of 0–2 at 3 months. Secondary outcomes included death at 3 months and symptomatic intracerebral hemorrhage (sICH) within 36 hours.

Results: For the 477 patients (316 men, 71 ± 11 years old) enrolled, the median NIH Stroke Scale score was 13 (interquartile range 7–18.5), the median ASPECTS on DWI was 8 (7–10), and sICH was identified in 15 patients (3.1%). At 3 months, 245 (51.4%) had an mRS score of 0–2, and 29 (6.1%) had died. Patients with an mRS score of 0–2 had higher median ASPECTS (9; interquartile range 8–10) than other patients (8; 6–9, $p < 0.001$). Using receiver operating characteristic curves, the optimal cutoff ASPECTS to predict an mRS score of 0–2 was ≥7. On multivariate regression analysis, ASPECTS ≥7 was related to an mRS score of 0–2 (odds ratio 1.85; 95% confidence interval 1.07–3.24), ASPECTS ≤4 was related to death (3.61; 1.23–9.91), and ASPECTS ≤5 was related to sICH (4.74; 1.54–13.64).

Conclusion: ASPECTS on DWI was independently predictive of functional and vital outcomes at 3 months, as well as sICH within 36 hours, following rt-PA therapy for stroke patients. ***Neurology*** **2010;75:555–561**

GLOSSARY

ASPECTS = Alberta Stroke Programme Early CT Score; **CI** = confidence interval; **DWI** = diffusion-weighted imaging; **EIC** = early ischemic change; **ICH** = intracerebral hemorrhage; **IQR** = interquartile range; **MRA** = magnetic resonance angiography; **mRS** = modified Rankin Scale; **NIHSS** = NIH Stroke Scale; **NINDS** = National Institute of Neurological Disorders and Stroke; **OR** = odds ratio; **PWI** = perfusion-weighted imaging; **ROC** = receiver operating characteristic; **rt-PA** = recombinant tissue-type plasminogen activator; **sICH** = symptomatic intracerebral hemorrhage; **SAMURAI** = Stroke Acute Management with Urgent Risk-factor Assessment and Improvement.

Early ischemic change (EIC) allows the prediction of subsequent infarct locations, and large EIC often results in clinically significant intracerebral hemorrhage (ICH) following thrombolysis.[1-4] Thus, for patients with large EIC on the initial CT, as assessed, for example, using the one-third of cerebral hemisphere rule, IV recombinant tissue-type plasminogen activator (rt-PA) is contraindicated according to several guidelines from the United States, Canada, Europe, and Japan.[5-8] However, visual assessment of the EIC volume depends on the reader's experience and skill, and the intrarater and interrater reliabilities in detecting EIC are not

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sufficiently high.[9] In addition, strict evaluation of the volume by computerized planimetry takes time to analyze. An alternative approach for grading EIC on CT is a quantitative topographic score, the Alberta Stroke Programme Early CT Score (ASPECTS).[10] For this score, the territory of the MCA is allotted 10 points, and 1 point is subtracted for each area of EIC for each of the defined regions.

Diffusion-weighted MRI (DWI) can quickly detect hyperacute ischemic brain tissue. The contrast between ischemic tissue and normal tissue can be clearer on DWI than on conventional MRI and CT. The scoring of ASPECTS using DWI (DWI-ASPECTS) has been reported to be similar to that using CT.[11] DWI-ASPECTS predicts the risk of symptomatic ICH (sICH) after thrombolysis.[12] However, the evidence for the association between DWI-ASPECTS and chronic outcome after rt-PA therapy has been inconclusive. The aim of the present study was to evaluate whether pretreatment DWI-ASPECTS predicts functional and vital outcomes 3 months after rt-PA therapy.

Table 1 **Baseline characteristics**[a]

	Total (n = 477)	mRS 0-2 (n = 245)	mRS 3-6 (n = 232)
Age, y	71 ± 11	69.0 ± 11.8[b]	73.9 ± 9.5
Male	316 (66.2)	180 (73.5)[b]	136 (58.6)
Hypertension	301 (63.5)	143 (58.6)[c]	158 (68.7)
Diabetes mellitus	89 (18.7)	46 (18.9)	43 (18.5)
Dyslipidemia	102 (21.5)	55 (22.5)	47 (20.4)
Congestive heart failure	30 (6.5)	8 (3.4)[b]	22 (9.8)
Stroke subtype[c]			
Cardioembolism	293 (61.4)	146 (59.6)	147 (63.4)
Atherothrombotic stroke	77 (16.2)	31 (12.8)	46 (19.8)
Lacunar stroke	22 (4.6)	15 (6.9)	7 (3.0)
Other	85 (17.8)	53 (21.7)	32 (13.8)
Arterial occlusion site (n = 457)[b]			
Internal carotid artery	73 (16.0)	8 (3.2)	65 (28.0)
Middle cerebral artery trunk (M1)	135 (29.5)	67 (27.3)	68 (29.3)
Middle cerebral artery branch (M2)	93 (20.4)	55 (22.4)	38 (16.4)
Anterior cerebral artery	7 (1.5)	2 (0.8)	5 (2.2)
Posterior cerebral artery	16 (3.5)	9 (3.7)	7 (3.0)
Vertebrobasilar arteries	21 (4.6)	11 (4.5)	10 (4.3)
Not occluded	99 (21.7)	71 (29.0)	28 (12.1)
Onset to treatment time, min	141 ± 28	140.0 ± 26.9	141.9 ± 29.4
Pretreatment systolic blood pressure, mm Hg	151 ± 20	151.6 ± 18.2	150.1 ± 21.4
Pretreatment diastolic blood pressure, mm Hg	82 ± 15	82.9 ± 13.5	81.7 ± 16.5
Baseline NIH Stroke Scale score	13 (7-18.5)	9 (6-14)[b]	17 (11-20.75)
DWI-ASPECTS	8 (7-10)	9 (8-10)[b]	8 (6-9)

Abbreviations: ASPECTS = Alberta Stroke Programme Early CT Score; DWI = diffusion-weighted imaging; mRS = modified Rankin Scale.

[a] Data are mean ± SD for age, onset to treatment time, and blood pressure, median (interquartile range) for baseline NIH Stroke Scale score and DWI-ASPECTS, and number of patients (%) for others.

[b] $p < 0.01$ vs mRS 3-6 by t test, χ^2 test, or Mann-Whitney U test.

[c] $p < 0.05$.

METHODS Patients were derived from the Stroke Acute Management with Urgent Risk-factor Assessment and Improvement (SAMURAI) rt-PA Registry. The details of this study have been described previously.[13] In brief, this was a retrospective, observational study involving consecutive stroke patients treated with IV rt-PA from October 2005 through July 2008 in 10 stroke centers in Japan. Patient eligibility for alteplase therapy was determined based on the Japanese guideline for IV rt-PA therapy,[8] which followed the inclusion and exclusion criteria used in the National Institute of Neurological Disorders and Stroke (NINDS) study and the Japan Alteplase Clinical Trial.[14,15] According to the Japanese guideline, patients with CT-documented extensive EIC (size is not defined) were not eligible for the treatment. Since the guideline does not refer to EIC on DWI, the eligibility of patients having large EIC on DWI depended on each physician's decision. Each local ethics committee approved the retrospective collection of clinical data from the database and submission of the data to our central office. Each patient received a single alteplase dose of 0.6 mg/kg (the recommended dose in Japanese guidelines and the approved labeling) IV, with 10% given as a bolus within 3 hours of stroke onset, followed by a continuous IV infusion of the remainder over 1 hour.

Baseline data, including sex, age, comorbidities (hypertension, diabetes, hyperlipidemia, and congestive heart failure), blood pressure on admission, time from onset to treatment, neurologic deficits using the NIH Stroke Scale (NIHSS) score, and stroke subtype according to the TOAST categories,[16] were collected for all patients. Before rt-PA infusion, MRI studies, including DWI and magnetic resonance angiography (MRA), were performed on a 1.5-Tesla machine immediately before or after CT studies, principally within 10 minutes after CT. Administration of rt-PA was began around 10 minutes after CT and MRI. For the DWI sequence, high-b-value images corresponding to diffusion measurements in 3 gradient directions were acquired, in addition to a single, low-b-value image. The high b-value was 1,000 s/mm^2 and the low b-value was 0 s/mm^2 in all stroke centers. At least 2 experienced vascular neurologists in each stroke center evaluated the initial DWI and CT images to calculate quantitative EIC using ASPECTS later as a post hoc analysis. Arterial occlusion was assessed on the initial MRA. ICH was defined as CT evidence of new parenchymal hemorrhage type I or type II within the initial 36 hours[2]; it was also assessed by at least 2 experienced vascular neurologists of each stroke center. Symptomatic ICH was defined as a parenchymal ICH associated with neurologic deterioration corresponding to an increase of ≥4 points from the baseline NIHSS score.

The primary outcome was independence at 3 months, corresponding to a modified Rankin Scale (mRS) score of

0–2. Secondary outcomes were the mRS score of 0–1 at 3 months, death at 3 months, and sICH within the initial 36 hours.

Statistical analysis was performed using the JMP 7.0 statistical software (SAS Institute Inc., Cary, NC). Baseline characteristics were compared between patients with an mRS score of 0–2 and those with an mRS score of 3–6 using χ^2 tests, unpaired t tests, and the Mann-Whitney U test, as appropriate. To obtain the cutoff DWI-ASPECTS for discriminating between patients with and without each outcome, receiver operating characteristic (ROC) curves were constructed. Multivariate analyses were performed to identify predictors for primary and secondary outcomes. For each outcome, a backward selection procedure was performed using $p > 0.10$ of the likelihood ratio test as the exclusion criterion. These analyses were later repeated for patients who did not have culprit infarcts or culprit arterial occlusions in the vertebrobasilar arterial territory, the isolated anterior cerebral artery territory, or the isolated posterior cerebral artery territory. Statistical significance was established at $p < 0.05$.

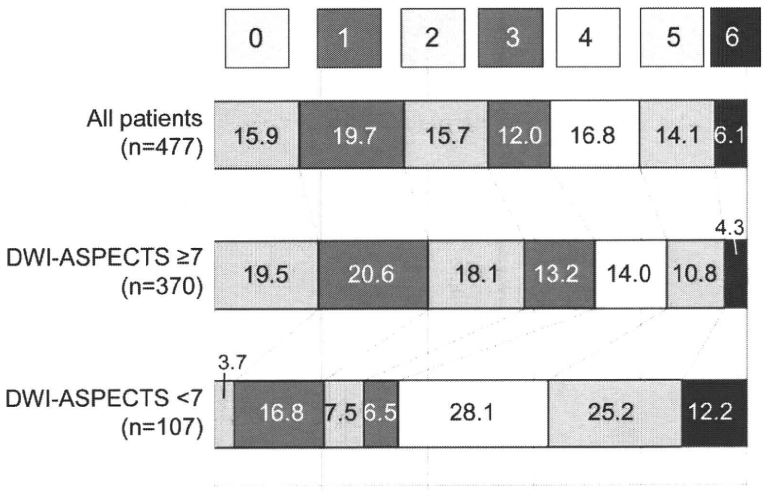
RESULTS A total of 600 consecutive patients were enrolled from the SAMURAI register. Of these, 70 patients could not undergo MRI prior to rt-PA mainly due to contraindications, unsteadiness, or time limitation, and 14 patients had inferior quality DWI images that were unsuitable for evaluating EIC. Of the remaining 516 patients who received pretreatment DWI, 35 were excluded from the analysis because their premorbid mRS score was 3 or more, and 4 were excluded because their 3-month mRS scores were not available. Finally, 477 patients (316 men, 71 ± 11 years old) were studied. The baseline clinical characteristics of these patients are presented in table 1. The median NIHSS score was 13 (interquartile range [IQR] 7–18.5). The median initial DWI-ASPECTS was 8 (IQR 7–10). DWI-ASPECTS was 6 or less in 107 patients (22.4%); of these, 37 patients had ASPECTS on the initial CT of 6 or less. ASPECTS on CT for most of these 37 patients was judged to be 7 or more at the time of the treatment decision, and was revised to be lower on the later reassessment.

Of these 477 patients, 245 (51.4%) were independent (mRS 0–2), and 29 (6.1%) had died by 3 months (figure 1). Within the initial 36 hours, 40 (8.4%) had parenchymal ICH, including 15 (3.1%) with sICH.

Association of DWI-ASPECTS with functional outcome. In table 1, the baseline characteristics are compared between patients with mRS scores of 0–2 and those with mRS scores of 3–6. The median initial DWI-ASPECTS was 9 (IQR 8–10) in patients with mRS scores of 0–2 and 8 (IQR 6–9) in those with mRS scores of 3–6 ($p < 0.001$). Patients with mRS scores of 0–2 were more frequently male ($p < 0.001$), younger ($p < 0.001$), less hypertensive ($p = 0.028$), less commonly had congestive heart failure ($p = 0.007$), and had lower baseline NIHSS scores ($p < 0.001$) than those with mRS scores of 3–6. Stroke subtype ($p = 0.030$) and arterial occlusion site ($p < 0.001$) differed between the groups; the internal carotid artery was relatively often occluded in patients with mRS scores of 3–6. Figure 2A shows the 3-month mRS scores in patients with different DWI-ASPECTS. The percentage of patients with mRS scores of 0–2 was similar among those with DWI-ASPECTS ≥7 and gradually decreased with the reduction in the DWI-ASPECTS when the score was ≤6. The optimal cutoff DWI-ASPECTS to predict patients with mRS scores of 0–2 at 3 months was ≥7, with a sensitivity of 88%, specificity of 33%, and an area under the ROC curve of 0.623 (figure 3). Overall, 215 (58.1%) of 370 patients with DWI-ASPECTS ≥7 and 30 (28.0%) of 107 patients with DWI-ASPECTS ≤6 had mRS scores of 0–2 ($p < 0.001$, figure 1). On multivariate regression analysis using backward selection, DWI-ASPECTS ≥7 was an independent predictor of an mRS score of 0–2 (odds ratio [OR] 1.85, 95% confidence interval [CI] 1.07–3.24; $p = 0.029$), along with younger age, male sex, lower NIHSS score, and absence of internal carotid artery occlusion (table 2).

For the analysis of the secondary outcome on mRS scores of 0–1 at 3 months, 26 patients with the premorbid mRS score of 2 were excluded. For the remaining 451 patients (304 men, 71 ± 11 years old), the optimal cutoff DWI-ASPECTS to predict patients with mRS scores of 0–1 was ≥9, with a sensitivity of 62%, specificity of 56%, and an area under the ROC curve of 0.627. On multivariate

Figure 1 **Modified Rankin Scale score at 3 months**



DWI-ASPECTS = scoring of Alberta Stroke Programme Early CT Score using diffusion-weighted imaging.