表2 SAMURAI-ICH研究，ATACH II試験への国内参加施設

| SAMURAI-ICHへの参加 | ATACH IIへの参加 | 施設名 | 研究者名 |
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～140mmHg，140～110 mmHgの3群に設定し，最も厳しく降圧した収縮期血圧110～140mmHgの群においても症状増悪や死亡率が想定される範囲内に収まった[11]．これに後続する本試験となるATACH II[7]は，米国National Institutes of Health (NIH)の助成による脳出血急性期の適切な降圧目標確立のための第III相国際試験で(ClinicalTrials.gov number, NCT01176565)，国内からも表2に示した17施設が参加している(UMIN000006526)．本試験は多施設共同，無作為化，同時対照比較，並行群間試験である．「脳出血発症後4.5時間以内にニカルジピン静注を開始してその後24時間にわたって静注を継続する積極降圧療法を行えば，標準降圧療法と比べて，90日後に死亡および機能障害に至る割合(mRS 4～6)が絶対値で10%以上，あるいは相対値で17%以上低下する」という作業仮説に基づき，発症後4.5時間以内で治療が開始された脳出血患者における90日後の死亡および機能障害の割合を，積極降圧療法群(収縮期血圧140mmHg以下)と標準降圧療法群(180mmHg以下)で比較検討することを主目的とする．登録患者の主な選択基準は，①非外傷性天幕上出血，②年齢18歳以上，③発症から4.5時間以内に無作為化を終了し，ニカルジピン投与を開始できる，④脳卒中患者の意識水準を示すGlasgow coma scaleが5点以上，⑤CTにおける血腫量が60ml未満，⑥治療前の収縮期血圧が180mmHgを超えることであり，全体で1,280例の登録を目指す．

本試験に国内多施設が参加するに至った経緯は他誌にも記載されており[10][12]，ここでは簡潔に紹介する．筆者らは2008年に，ATACH IIを主宰するMinnesota大学のQureshi教授，South Carolina大学のPalesch教授より，わが国から多施設を集めた試験参加依頼を受けた．すでにSAMURAI研究班などで急性期脳出血の至適降圧法を探求しており，国内脳出血患者への適切な治療法を確立するために必要と判断し，国内多施設での参加を決意し，2012年より症例登録を開始した．脳血管障害を含めた循環器領域で，NIH助成の研究者主導型国際試験に国内多施設が参加することは前例に乏しく，試験開始までの行程は決して容易ではなかった．最大の問題点は，研究者主導型国際試験参加のための研究支援組織基盤が未整備な点にある[13]．筆者らは今回の参加にあたって，まず研究体制の基盤整備を主題とした研究で厚生労働科学研究費や循環器病研究開発費を獲得し，米国側や国内多施設との交渉と連携から臨床研究賠償責任保険に至るまでの参加

前準備を充実させた．

臨床脳血管障害研究論文に関する最近の調査で，「日本，韓国，中国からの論文発表数は多いが，多国籍研究に共著者として加わることは少ない」と指摘された[19]．ATACH IIは症例登録完了までまだ4年を要する長距離レースであるが，国際的脳血管障害研究へのわが国の停滞を打破するために，その第一号の取り組みとして試験成功に向けて頑張りたい．

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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

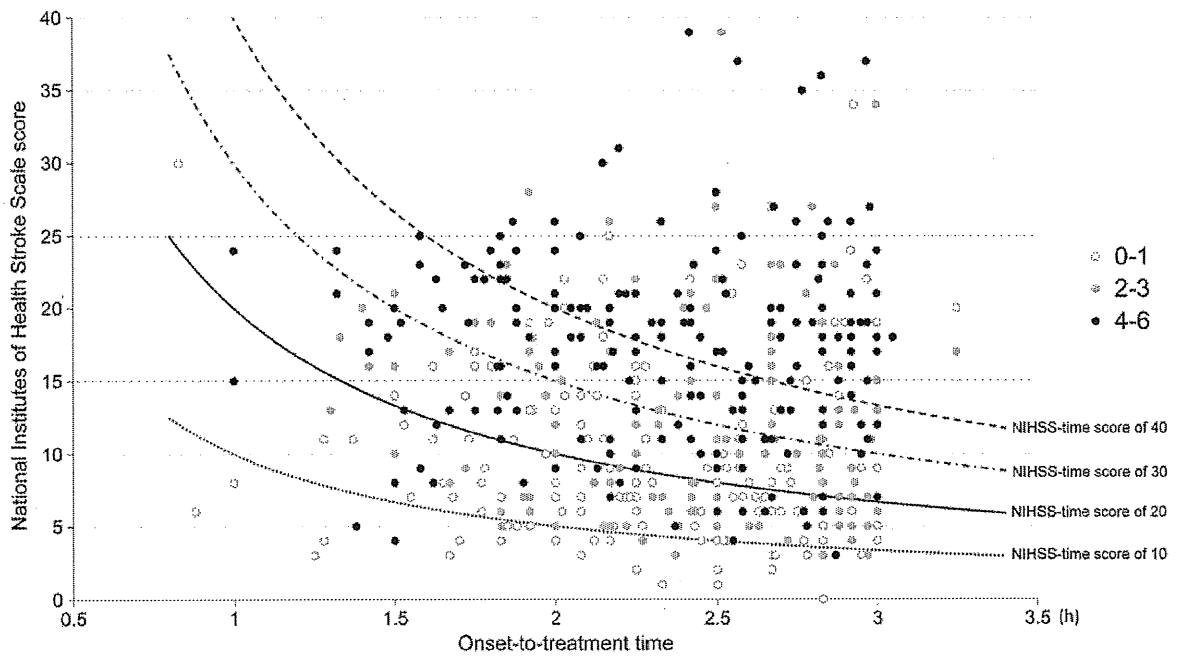


**Fig. 1.** Scatter plots of patients with modified Rankin scale score of 0–1 (white circle) and 2–6 (gray circle), and 4–6 and 0–3 (black circle) at 3 months after onset based on NIHSS scores and onset-to-treatment time. Curves are drawn based on the NIHSS-time scores of 10, 20, 30, and 40.

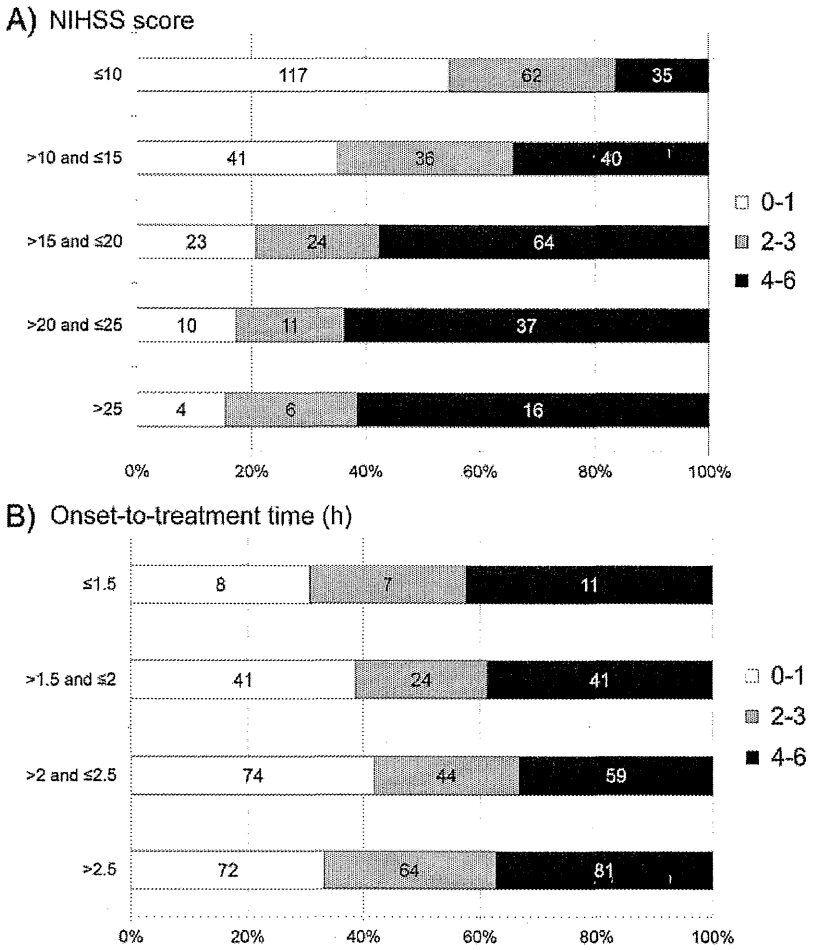


**Fig. 2.** Modified Rankin scale score at 3 months after stroke onset based on: A) initial NIHSS score; and B) onset-to-treatment time. Total numbers are given in the bars.

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).

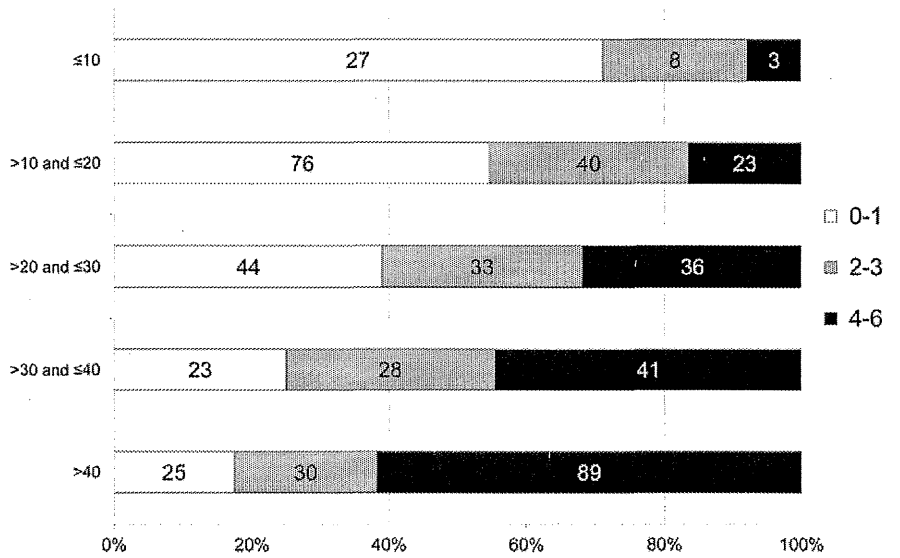


**Fig. 3.** Modified Rankin scale score at 3 months after stroke onset, based on NIHSS-time score. Total numbers are given in the bars.

**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

Y. Shiokawa receives research support from Daiichi Sankyo Company, Limited. K. Toyoda receives research support from Grants-in-Aid from the Ministry of Health, Labour and Welfare, Japan.

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# 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.

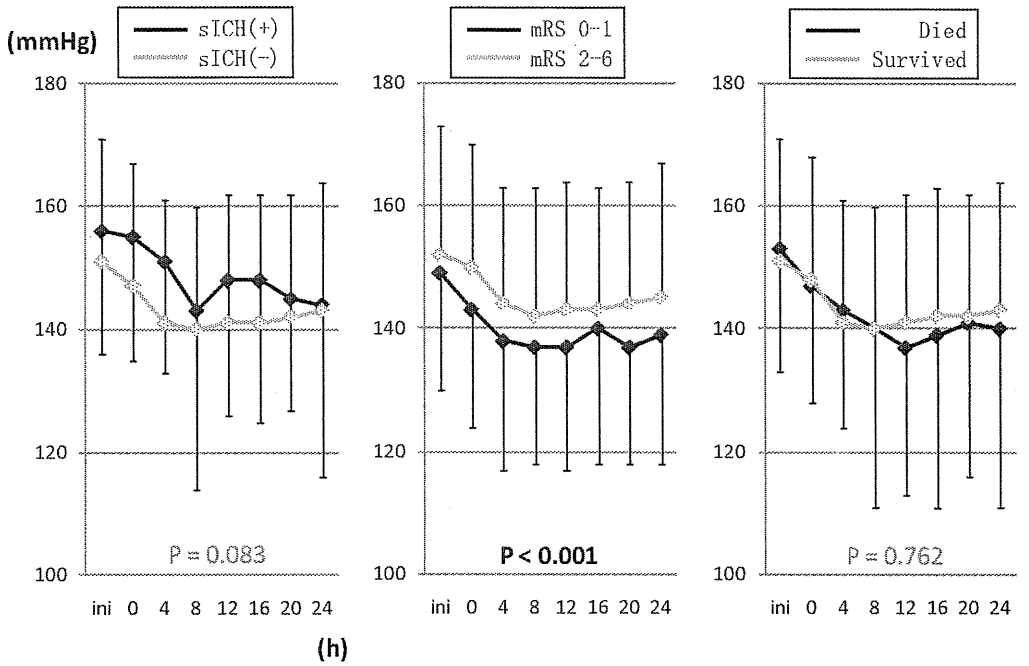


**Figure.** Comparisons of time course of systolic blood pressure according to symptomatic intracerebral hemorrhage (sICH), modified Rankin Scale (mRS) value, and mortality at 3 months. ini indicates initial.

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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# Early Neurological Deterioration within 24 Hours after Intravenous rt-PA Therapy for Stroke Patients: The Stroke Acute Management with Urgent Risk Factor Assessment and Improvement rt-PA Registry

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**Key Words**

Acute ischemic stroke · Diabetes mellitus · Hyperglycemia · Intracerebral hemorrhage · Thrombolysis · Tissue plasminogen activator

**Abstract**

***Background:*** The initial 24 h after thrombolysis are critical for patients' conditions, and continuous neurological assessment and blood pressure measurement are required during this time. The goal of this study was to identify the clinical factors associated with early neurological deterioration (END) within 24 h of stroke patients receiving intravenous recombinant tissue plasminogen activator (rt-PA) therapy and to clarify the effect of END on 3-month outcomes. ***Methods:*** A retrospective, multicenter, observational study was conducted in 10 stroke centers in Japan. A total of 566 consecutive stroke patients [211 women, 72 ± 12 years old, the median initial NIH Stroke Scale (NIHSS) score of 13] treated with intravenous rt-PA (0.6 mg/kg alteplase) was studied. END was defined as a 4-point or greater increase in the NIHSS score at 24 h from the NIHSS score just before thrombolysis. ***Results:*** END was present in 56 patients (9.9%, 18 women, 72 ± 10 years old) and was independently associated with higher blood glucose [odds ratio (OR) 1.17, 95% confidence intervals (CI) 1.07–1.28 per 1 mmol/l increase, $p < 0.001$], lower initial NIHSS score (OR 0.92, 95% CI 0.87–0.97 per 1-point increase, $p = 0.002$), and internal carotid artery (ICA) occlusion (OR 5.36, 95% CI 2.60–11.09, $p < 0.001$) on multivariate analysis. Symptomatic intracranial hemorrhage within the initial 36 h from thrombolysis was more common in patients with END than in the other patients (per NINDS/Cochrane

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protocol, OR 10.75, 95% CI 4.33–26.85, $p < 0.001$, and per SITS-MOST protocol, OR 12.90, 95% CI 2.76–67.41, $p = 0.002$). At 3 months, no patients with END had a modified Rankin Scale (mRS) score of 0–1. END was independently associated with death and dependency (mRS 3–6, OR 20.44, 95% CI 6.96–76.93, $p < 0.001$), as well as death (OR 19.43, 95% CI 7.75–51.44, $p < 0.001$), at 3 months. ***Conclusions:*** Hyperglycemia, lower baseline NIHSS score, and ICA occlusion were independently associated with END after rt-PA therapy. END was independently associated with poor 3-month stroke outcome after rt-PA therapy. 

## Introduction

Neurological deterioration within the initial couple of days affects stroke patients' long-term outcomes [1–11]. Neurological deterioration during acute stroke is associated with initial stroke severity [2], large vessel occlusion [3, 4], hypodensity >33% in the middle cerebral artery territory [5], the hyperdense middle cerebral artery sign on brain CT [5, 6], cerebral edema on early CT [5, 6], diabetes mellitus [4, 5, 7], hyperglycemia [6, 8, 9], high or low blood pressure [7, 8], early recurrent ischemic stroke [10], and symptomatic intracranial hemorrhage (sICH) [6, 11].

Intravenous (IV) thrombolytic therapy with recombinant tissue plasminogen activator (rt-PA) has been shown to improve stroke outcomes [12, 13]. However, about half of the patients were not independent in their activities of daily living or died at 3 months despite IV rt-PA therapy [14]. Since the initial 24 h after thrombolysis are critical for patients' conditions, partly because of the frequent occurrence of intracranial hemorrhage (ICH), continuous neurological assessment and blood pressure measurement are required during this period of time [15]. Changes in the neurological status during this period may decisively affect outcomes after thrombolysis. The aims of this study were to identify the clinical factors that were associated with early neurological deterioration (END) within 24 h after IV rt-PA therapy and to clarify the effect of END on 3-month stroke outcomes.

## Patients and Methods

The Stroke Acute Management with Urgent Risk Factor Assessment and Improvement (SAMURAI) rt-PA Registry has a multicenter, hospital-based, retrospective, observational cohort design [16]. Details of this study have been described previously [16–18]. In brief, this study involved 600 consecutive patients with acute ischemic stroke receiving alteplase from October 2005 through July 2008. All of the patients treated during the study period were registered sequentially. Informed consent was obtained from all study participants. Of these, 34 patients whose 24-hour National Institutes of Health Stroke Scale (NIHSS) scores were not available were excluded from this study. The remaining 566 patients were included. 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 the Japanese guidelines and the approved labeling) intravenously, with 10% given as a bolus within 3 h of stroke onset, followed by a continuous IV infusion of the remainder over 1 h [19].

The data collected from the database of the SAMURAI rt-PA registers for the present study are listed in table 1. Neurological deficits were assessed using the NIHSS score just before and 24 h after rt-PA, and at discharge [median hospital stay 27 days, interquartile range (IQR) 18–44.5 days]. END was defined as a 4-point or greater increase in the NIHSS score at 24 h from the NIHSS score just before thrombolysis. The ischemic stroke subtype was defined according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) categories [20]. Early ischemic change on CT was quantitatively calculated using the Alberta Stroke Programme Early CT Score (ASPECTS) [21, 22]. To identify arterial occlusion sites, MR angiography, CT angiography, or ultrasound was performed [23].

The outcomes investigated were any ICH and sICH within the initial 24–36 h, NIHSS score at discharge, excellent functional outcome corresponding to modified Rankin Scale (mRS) score 0–1, death and dependency (mRS 3–6), and death at 3 months. Any ICH was defined as CT evidence of a new ICH [24]; it was assessed by at least two experienced vascular neurologists at each stroke center [16]. Symptomatic ICH was defined with neurological deterioration corresponding to an increase of $\geq 1$ point from the baseline NIHSS score according to the NINDS/Cochrane protocol [13]. Symptomatic ICH was also defined according to the Safe Implementation of Thrombosis in Stroke Monitoring Study (SITS-MOST) protocol as parenchymal hemorrhage type II combined with an increase of $\geq 4$ points from the baseline NIHSS score [14]. Outcomes at 3 months were assessed by clinical examination at a hospital clinic or by telephone survey for patients whose neurological deficits were too severe to visit the clinic. Mainly study assistance nurses carried out the follow-up survey by telephone. When the patients or their families could not be reached, they called repeatedly till they were successful. Five patients were lost to follow-up at 3 months and for these 5 patients the mRS scores at discharge were used as their 3-month follow-up status.

Statistical analysis was performed using JMP 9.0 statistical software (SAS Institute Inc., Cary, N.C., USA). Patients' baseline characteristics were compared between those with and without END using $\chi^2$ tests, unpaired t tests, and the Mann-Whitney U test, as appropriate. To identify the clinical factors associated with END, multivariate analyses were performed. Sex and age were initially entered, and the other variables listed in table 1 were chosen by a backward selection procedure using the Bayesian information criterion for exclusion. In addition, to identify the association between END and stroke outcomes, multivariate analyses with a backward selection procedure were performed. Statistical significance was established at $p < 0.05$.

**Table 1.** Baseline clinical characteristics

| | END (n = 56) | No END (n = 510) | p value |
|---|---|---|---|
| Females, n | 18 (32.1) | 193 (37.8) | 0.468 |
| Age, years | 71.5 ± 9.3 | 72.0 ± 11.9 | 0.733 |
| Risk factors and comorbidities, n | | | |
| Hypertension | 35 (62.5) | 312 (61.2) | 0.886 |
| Diabetes mellitus | 18 (32.1) | 85 (16.7) | 0.010 |
| Dyslipidemia | 18 (32.1) | 97 (19.0) | 0.034 |
| Atrial fibrillation | 29 (51.8) | 213 (41.8) | 0.157 |
| Prior ischemic stroke | 10 (17.9) | 93 (18.5) | 1.000 |
| Prior ischemic heart disease | 9 (16.8) | 62 (12.2) | 0.396 |
| Prior congestive heart failure | 2 (3.6) | 45 (8.8) | 0.300 |
| Prior use of antihypertensives | 28 (50.0 | 224 (43.9) | 0.399 |
| Prior use of hypoglycemic agents | 10 (17.9) | 36 (7.1) | 0.016 |
| Prior use of statins | 12 (21.4) | 51 (10.0) | 0.022 |
| Prior use of antithrombotic therapy | 25 (44.6) | 185 (36.3) | 0.244 |
| Physiological and laboratory data on admission | | | |
| Systolic BP, mm Hg | 158 ± 20 | 150 ± 20 | 0.005 |
| Diastolic BP, mm Hg | 84 ± 15 | 81 ± 15 | 0.216 |
| Blood glucose, mmol/l | 9 ± 3.5 | 7.4 ± 0.2 | <0.001 |
| Hemoglobin A1c, % | 6.1 ± 0.9 | 5.7 ± 1.0 | 0.021 |
| Initial NIHSS score | 11 (7–16) | 13 (7–19) | 0.076 |
| ASPECTS | 9 (8–10) | 10 (8–10) | 0.277 |
| ICA occlusion, n | 20 (35.7) | 67 (13.1) | <0.001 |
| Cardioembolism as stroke subtype, n | 32 (57.1) | 323 (63.3) | 0.384 |
| Onset-to-treatment time, min (IQR) | 141 (120–170) | 145 (121–166) | 0.894 |
| IV antihypertensives just before rt-PA, n | 18 (32.1) | 141 (27.7) | 0.531 |

Values in parentheses represent percentage or range. Total cholesterol (p = 0.997), HDL cholesterol (p = 0.379), LDL cholesterol (p = 0.538), triglycerides (p = 0.711), and creatinine (p = 0.366) were not significantly different between the two groups.

## Results

A total of 566 consecutive stroke patients (211 women, 72.0 ± 11.6 years old) were studied. Of these, 56 patients (9.9%, 18 women, 71.5 ± 9.3 years old) had END (fig. 1).

*Risk Factors Associated with END*

The baseline clinical characteristics of patients with and without END are presented in table 1. Patients with END more commonly had diabetes mellitus (p = 0.010), dyslipidemia (p = 0.034), prior use of hypoglycemic agents (p = 0.016), prior use of statins (p = 0.022), and internal carotid artery (ICA) occlusion (p < 0.001) than patients without END. Systolic blood pressure (p = 0.005), blood glucose (p < 0.001), and hemoglobin A1c levels (p = 0.021) were higher in patients with END than in those without. Initial NIHSS scores just before thrombolysis were not significantly different between the two groups (p = 0.076).

Multivariate regression analysis to identify the clinical factors associated with END showed that higher blood glucose [odds ratio (OR) 1.17, 95% confidence intervals (CI) 1.07–1.28 per 1 mmol/l increase, p < 0.001], lower initial NIHSS score (OR 0.92, 95% CI 0.87–0.97 per 1-point increase, p = 0.002), and ICA occlusion (OR 5.36, 95% CI 2.60–11.09, p < 0.001) were independently associated with END (table 2).

*Association of END with ICH within the Initial 36 Hours*

Of the 566 patients, 113 (20.0%) had some ICH, including 22 (3.9%) with sICH per NINDS/Cochrane and 7 (1.2%) with sICH per SITS-MOST. Compared to patients without END, patients with END more often had ICH (42.9 vs. 17.5%, p < 0.001), sICH per NINDS/Cochrane (19.6 vs. 2.2%, p < 0.001), and sICH per SITS-MOST (7.1 vs. 0.6%, p = 0.002). On multivariate regression analysis, END was independently associated with any ICH (OR

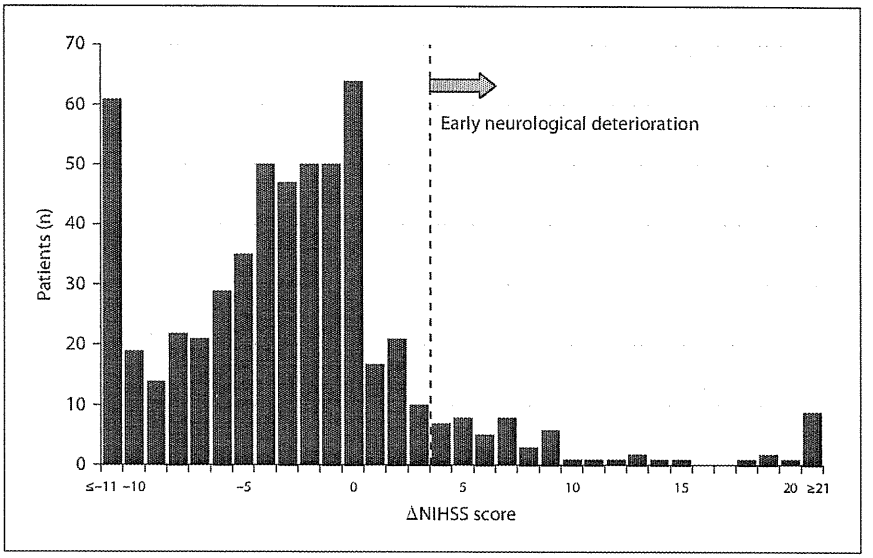


**Fig. 1.** Change in NIHSS score between baseline score before thrombolysis and 24 h after it.

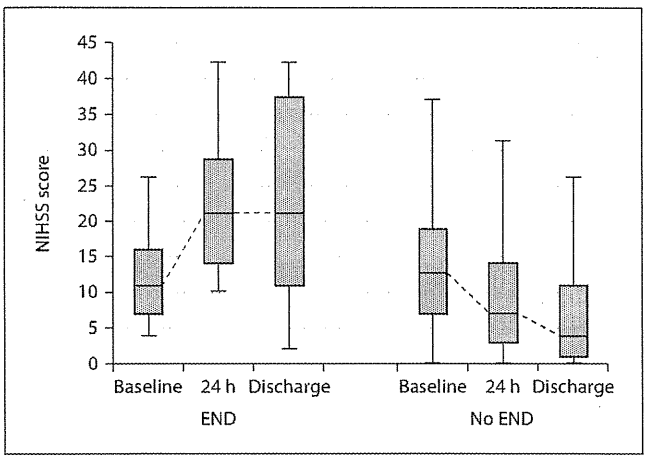


**Fig. 2.** Course of the NIHSS score during hospitalization. The horizontal line in the box is the median, the bottom and top of the box are the 25th and 75th percentile, respectively, and the ends of the whiskers are the minimum and maximum values.

**Table 2.** Multivariate logistic regression analysis for END

| | Adjusted OR | 95% CI | p value |
|---|---|---|---|
| Female | 0.81 | 0.41–1.55 | 0.529 |
| Age (per 10 years) | 1.02 | 0.78–1.35 | 0.911 |
| Blood glucose (per 1 mmol/l) | 1.17 | 1.07–1.28 | <0.001 |
| Initial NIHSS score (per 1 point) | 0.92 | 0.87–0.97 | 0.002 |
| ICA occlusion | 5.36 | 2.60–11.09 | <0.001 |

These variables were chosen by a backward selection procedure using the Bayesian information criterion for exclusion.

3.38, 95% CI 1.87–6.06, $p < 0.001$), sICH per NINDS/Cochrane (OR 10.75, 95% CI 4.33–26.85, $p < 0.001$), and sICH per SITS-MOST (OR 12.90, 95% CI 2.76–67.41, $p = 0.002$).

*Association of END with 3-Month Outcomes*

The median NIHSS score at discharge of the 566 patients was 4 (IQR 1–13). The discharge NIHSS score of patients with END was different from that of patients without END [21 (IQR 11–37.5) vs. 3 (1–11), $p < 0.001$] (fig. 2).

Five patients were lost to follow-up at 3 months, and their mRS score at discharge was used as the 3-month mRS score. None of these 5 patients showed END; at hospital discharge, 1 had mRS of 2, 2 had mRS of 4, and 2 had mRS of 5. Of the 566 patients, 190 (33.6%) had an excellent functional outcome (mRS 0–1), 295 (52.1%) had death and dependency (mRS 3–6), and 38 (6.7%) had died by 3 months. No patients with END were independent while 37.3% of patients without END were independent ($p < 0.001$, fig. 3). Patients with END had poorer stroke outcomes than those without END at 3 months (death and dependency: 91.1 vs. 47.8%, $p < 0.001$; death: 25.0 vs. 4.7%, $p < 0.001$).

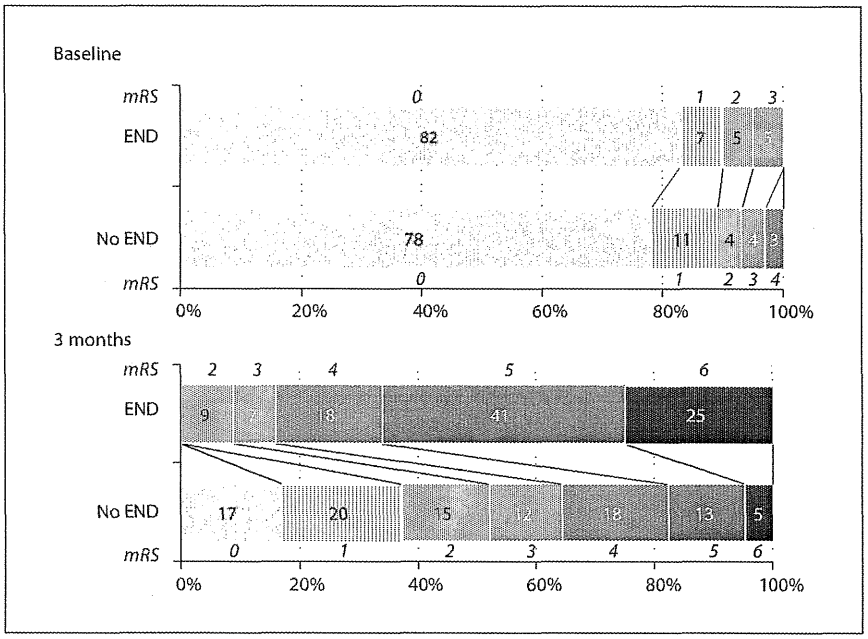


**Fig. 3.** mRS score at baseline and at 3 months.

**Table 3.** Association of END with each outcome parameter

| | OR | 95% CI | p value |
|---|---|---|---|
| Any ICH | 3.38 | 1.87–6.06 | <0.001 |
| sICH (NINDS/Cochrane protocol) | 10.75 | 4.33–26.85 | <0.001 |
| sICH (SITS-MOST protocol) | 12.90 | 2.76–67.41 | 0.002 |
| Death and dependency at 3 months (mRS score 3–6) | 20.44 | 6.96–76.93 | <0.001 |
| Death at 3 months | 19.43 | 7.75–51.44 | <0.001 |

These variables were chosen by a backward selection procedure using the Bayesian information criterion for exclusion.

Multivariate regression analysis indicated that END was independently associated with death and dependency (OR 20.44, 95% CI 6.96–76.93, $p < 0.001$), as well as death (OR 19.43, 95% CI 7.75–51.44, $p < 0.001$, table 3), at 3 months.

## Discussion

In this observational study, the clinical factors associated with END within 24 h after IV rt-PA therapy and the effect of END on stroke outcomes were determined. The first major finding was that END was independently associated with higher blood glucose, lower baseline NIHSS score and ICA occlusion. The second major finding was that END was independently associated with early ICH after IV rt-PA. The third major finding was that none of the patients with END had an excellent outcome (mRS 0–1) at 3-month follow-up; they were more often dependent or had a fatal outcome (mRS 3–6) at 3 months after multivariate adjustment.

END was present in one tenth of the patients in our study. Previous studies indicated that END was present in 14–38% of patients after IV rt-PA [5, 6] and in 13–40% of patients who did not receive thrombolysis [2–4, 7, 8]. However, it is important to note that the definition of END differed among the studies. The time interval to assess deterioration differs greatly among studies, including the initial 24 h [5, 6, 9, 11], 36 h [7], 48–72 h [1, 2, 4, 8, 10], and 7 days after stroke onset [3]. As an indicator for

neurological deterioration, the Scandinavian Neurological Stroke scale [5, 7], the Canadian Neurological Scale [8], and different cutoff scores of the NIHSS (increase of more than 1 [4], 3 [2], and 4 points [1, 6, 9–11]) were used. Thus, a direct comparison of the results among these studies is difficult.

In the present study, higher blood glucose was associated with END. Hyperglycemia is known to be a risk factor for poor outcome of stroke patients even after early recanalization following thrombolysis [9, 25, 26]. Hyperglycemia is also known to be a risk factor for thrombolysis-associated sICH [27]. Possible mechanisms of hyperglycemia-associated neurological deterioration include endothelial damage, deteriorating tissue acidosis, and worsening of blood-brain barrier breakdown [9, 25, 26]. ICA occlusion was inversely correlated with early improvement (≥8-point decrease in the NIHSS score) 24 h after IV rt-PA in our single-center cohort [28]. The present results may be the reverse side of the same coin. A reduction in local cerebral perfusion pressure after ICA occlusion with poor leptomeningeal collaterals could be a reason for END [1]. It was paradoxical that the lower baseline NIHSS score was associated with END in the present study, the opposite of what was found in previous studies [2, 3, 5–7]. These unusual results may be due to a ceiling effect, preventing the high score from increasing further. Prior use of antithrombotic therapy and history of congestive heart failure may influence early neurological states after thrombolysis via growth of ICH [27, 29], although they were not associated with END in the present study.

Symptomatic ICH often occurs within several hours after thrombolysis and is the most common cause of END [6]. In our cohort, sICH was more than 10 times as frequent in END patients as in other patients. In addition, acute arterial reocclusion [6], acute recurrent stroke [10, 11], edema progression [1, 30], and noncerebral accidents including infections and cardiovascular events are less common causes of END, although these possible mechanisms of END were not assessed in the present study. Of these, large swelling edema and edema with ICH were reported to show a strong association with a poor 3-month outcome [30].

The clear messages from the present study are that END within 24 h excludes independence and is associated with a very high risk of death and dependency (OR 20.44) at 3 months. These findings are similar to those from previous trials on IV rt-PA [5, 6]. Thus, careful stroke care to avoid END could lead to better 3-month outcomes.

Certain limitations need to be considered prior to interpretation of the present results. First, patients who did not receive rt-PA were not included in this study. Second, early recanalization of the occluded cerebral artery, which greatly affects early neurological status, was not assessed. Third, END was evaluated at 24 h and sICH was assessed within the initial 24–36 h. Fourth, biochemical variables were modified by onset of stroke and they might not reflect patients' characteristics before stroke onset. Finally, the present results based on low-dose rt-PA therapy (0.6 mg/kg) may not be applicable to the regular dose therapy (0.9 mg/kg).

Hyperglycemia, lower baseline NIHSS score, and ICA occlusion were independently associated with END after rt-PA therapy. The present study clearly indicates that END within 24 h after thrombolysis has an important association with poor 3-month outcomes.


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# Intravenous Alteplase at 0.6 mg/kg for Acute Stroke Patients with Basilar Artery Occlusion: The Stroke Acute Management with Urgent Risk Factor Assessment and Improvement (SAMURAI) Recombinant Tissue Plasminogen Activator Registry

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*Background:* The therapeutic efficacy of low-dose intravenous alteplase (0.6 mg/kg) for basilar artery occlusion (BAO) remains unknown. *Methods:* BAO patients enrolled from the Japanese multicenter registry involving 600 stroke patients treated with the low-dose intravenous alteplase were studied. *Results:* Twenty-five patients had BAO (8 women ranging from 32-92 years of age; mean baseline National Institutes of Health Stroke Scale [NIHSS] score 16). The stroke subtype was cardioembolic in 15 patients and atherothrombotic in 4 patients. BAO was recanalized during hospitalization in 18 (78%) of 23 patients undergoing follow-up angiography. Within the initial 24 hours, 14 patients (56%) had a ≥8-point decrease in the NIHSS score, being more common than 267 patients with middle cerebral artery occlusion (MCO) from the same registry (odds ratio [OR] 2.50; 95% confidence interval [CI] 1.06-5.97) after adjustment by sex, age, and baseline NIHSS score. In addition, 4 patients (16%) had a ≥4-point increase in the score, being marginally more common than MCO patients (OR 3.13; 95% CI 0.81-10.25). Symptomatic intracranial hemorrhage within the initial 36 hours (8% *v* 5%), independence at 3 months (modified Rankin Scale score ≤2, 48% *v* 52%), and mortality at 3 months (4% *v* 6%) were similar when comparing BAO and MCO patients. When compared with previous studies of BAO, vital and functional outcomes at 3 months were relatively better in our study.

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*Conclusions:* The use of low-dose alteplase resulted in similar outcomes when comparing acute BAO and MCO patients. **Key Words:** Acute stroke—basilar artery occlusion—cardioembolic stroke—low-dose recombinant tissue plasminogen activator—thrombolysis—vertebrobasilar arteries.


Occlusion of the basilar artery (BA) often results in unfavorable clinical outcomes, such as death, locked-in state, and coma.[1] Outcomes of acute BA occlusion (BAO) are dependent on the clinical state at presentation, the length and location of the occlusion, the time to treatment, and the degree of recanalization.[2-9] A systematic analysis revealed that intra-arterial or intravenous (IV) thrombolysis resulted in a good clinical outcome in 38% of BAO patients with partial or complete recanalization, but only in 2% of patients who did not achieve recanalization.[10] Because BAO patients comprise only 5% of total stroke patients undergoing thrombolysis,[11,12] IV recombinant tissue plasminogen activator (rt-PA) therapy for BAO has been relatively understudied.

In our multicenter observational study (Stroke Acute Management with Urgent Risk Factor Assessment and Improvement [SAMURAI] rt-PA Registry)[13] and in a nationwide Japan post-Marketing Alteplase Registration Study (J-MARS),[14] IV rt-PA therapy using a unique dose (0.6 mg/kg alteplase) for Japanese patients found similar safety and efficacy when compared with therapy using a 0.9 mg/kg dose of alteplase that has been used in trials and postmarketing surveys in Western countries.[15,16] Because most of the patients enrolled in the SAMURAI rt-PA Registry and J-MARS had carotid territorial stroke, a separate substudy is required to determine the outcomes of vertebrobasilar territorial stroke patients treated with this unique dose of IV rt-PA. The purpose of this study was to document characteristics and outcomes of patients with BAO from the SAMURAI rt-PA Registry who underwent treatment with IV low-dose rt-PA therapy within 3 hours of symptom onset.[13]

## Subjects and Methods

Six hundred consecutive patients with acute ischemic stroke who received IV rt-PA therapy between October 2005 and July 2008 in 10 Japanese stroke centers were enrolled in the SAMURAI rt-PA Registry.[13,17-20] Of these, patients with BAO and acute symptoms or signs attributable to ischemia of the posterior circulation were studied. The methods and overall general results of this multicenter study have been reported.[13] Each local ethics committee approved the retrospective collection of clinical data from the database and submission of the data to our central office. Patient eligibility for alteplase therapy was determined based on the Japanese guidelines for IV rt-PA therapy[21]; each patient received a single alteplase dose of 0.6 mg/kg (the recommended dose in Japanese guidelines and within the approved labeling) intravenously, with 10% given as a bolus within 3 hours of stroke onset, followed by a continuous IV infusion of the remainder over the course of 1 hour.

Arterial occlusion sites were evaluated on admission before rt-PA infusion using time of flight (TOF) magnetic resonance angiography (MRA) on a 1.5-T machine, unless patients had contraindications, unsteadiness, or time limitations. Computed tomographic angiography (CTA) and carotid duplex ultrasonography were alternative choices. BAO was defined as the inability to detect patency of the entire or the distal portion of the BA on MRA or CTA or collapse of the bilateral vertebral arteries with no or slow flow signals (indicating distal occlusion) on ultrasound.[22,23] Recanalization of BAO after IV rt-PA therapy, either partial or complete, was estimated based on MRA, CTA, or digital subtraction angiography (DSA) during the acute hospitalization.

Acute ischemic lesions were evaluated before rt-PA infusion principally using diffusion-weighted MRI (DWI) on a 1.5-T machine. 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 1000 s/mm$^2$ and the low b-value was 0 s/mm$^2$ in all stroke centers. Ischemic lesions of BAO patients were assessed on pretreatment DWI, and its extension was semiquantitatively scored by the posterior circulation Acute Stroke Prognosis Early Computed Tomography Score (pc-ASPECTS) on pretreatment DWI, as proposed by Puetz et al.[24,25] pc-ASPECTS was originally based on computed tomography–derived data and allots the posterior circulation 10 points. One point each is subtracted for early ischemic changes in the left or right thalamus, cerebellum, or posterior lobe, respectively, and 2 points each are subtracted for early ischemic changes in any part of the midbrain or pons.[24,25] In this study, pc-ASPECTS was assessed using DWI data. Even when the signal change was subtle or patchy, it was regarded as a significant change. An example of scoring can be seen in Figure 1.

Baseline characteristics were also assessed, including sex, age, hypertension, diabetes mellitus, dyslipidemia, and history of ischemic stroke. Variables related to stroke included the National Institutes of Health Stroke Scale (NIHSS) score on admission, the NIHSS scores at 24 hours after IV rt-PA and at discharge, onset-to-treatment time, and stroke subtype classified according to Trial of