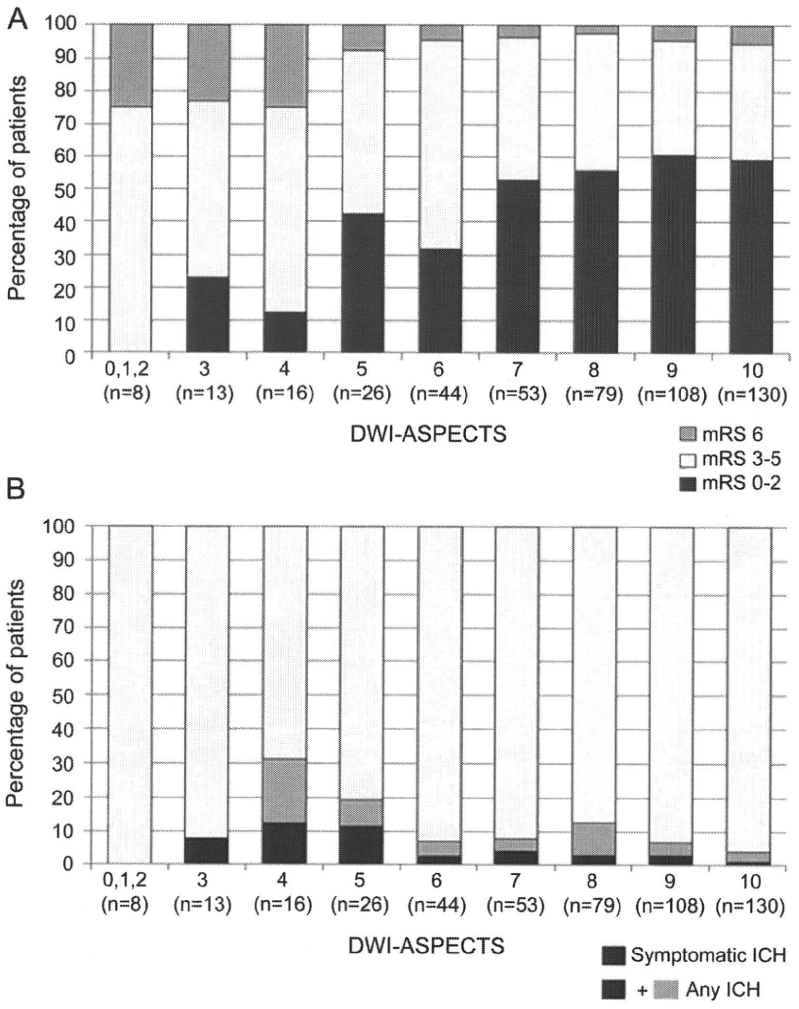
regression analysis, DWI-ASPECTS ≥9 was not an independent predictor of an mRS score of 0–1 (OR 1.40, 95% CI 0.87–2.24; $p = 0.160$).

Association of DWI-ASPECTS with mortality. DWI-ASPECTS was lower in patients who had died by 3 months (median 7, IQR 4–9.5) than in survivors (median 9, IQR 7–10; $p = 0.038$). Among patients with different DWI-ASPECTS, mortality was similar among patients with DWI-ASPECTS ≥7 and exceeded 20% when the score was ≤4 (figure 2A). The optimal cutoff DWI-ASPECTS to predict death at 3 months was ≤5, with a sensitivity of 38%, specificity of 88%, and an area under the ROC curve of 0.613. On multivariate regression analysis, DWI-ASPECTS ≤5 was not related to death at 3 months (OR 1.93, 95% CI 0.68–5.03; $p = 0.206$). When lowering the cutoff by 1 point, based on the findings in figure 2A, DWI-ASPECTS ≤4 was independently related to death (OR 3.61, 95% CI 1.23–9.91; $p = 0.021$) (table 2).

Association of DWI-ASPECTS with ICH. DWI-ASPECTS was lower in patients with sICH (median 7, IQR 5–9) than in those without (median 9, IQR 7–10; $p = 0.011$). The percentage of sICH was 4% or less among patients with DWI-ASPECTS ≥6, and exceeded 10% among patients with DWI-ASPECTS 4 and 5 (figure 2B). The optimal cutoff DWI-ASPECTS for predicting symptomatic ICH was ≤5, with a sensitivity of 40%, specificity of 87%, and an area under the ROC curve of 0.689. On multivariate regression analysis, DWI-ASPECTS ≤5 was an independent predictor of sICH (OR 4.74, 95% CI 1.54–13.64; $p = 0.008$) (table 2).

Analyses excluding patients with vertebrobasilar, anterior cerebral, and posterior cerebral arterial strokes. After excluding 44 patients with ischemia in the vertebrobasilar, anterior cerebral, and posterior cerebral artery systems, 433 patients (287 men, 71 ± 11 years old) were analyzed. The optimal cutoff DWI-ASPECTS to predict patients with mRS scores of 0–2 at 3 months was ≥7, with a sensitivity of 87%, specificity of 37%, and an area under the ROC curve of 0.637. On multivariate regression analysis, DWI-ASPECTS ≥7 was an independent predictor of an mRS score of 0–2 (OR 1.82, 95% CI 1.03–3.24; $p = 0.040$). Similarly, DWI-ASPECTS ≤4 was independently related to death (OR 3.96, 95% CI 1.31–11.19; $p = 0.016$), and DWI-ASPECTS ≤5 was an independent predictor of sICH (OR 4.76, 95% CI 1.52–14.20; $p = 0.009$).

Figure 2 **Modified Rankin Scale score (mRS) at 3 months (A) and parenchymal intracranial hemorrhage (ICH) within the initial 36 hours (B) in patients with each DWI-ASPECTS score**



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

DISCUSSION In this study, the associations between DWI-ASPECTS and clinical outcomes at 3 months after IV rt-PA therapy were assessed. The major new finding of this study was that pretreatment DWI-ASPECTS was associated with functional and vital outcomes at 3 months; DWI-ASPECTS ≥7 was predictive of an mRS score of 0–2, and DWI-ASPECTS ≤4 was predictive of death.

Extensive EIC over one-third of the MCA territory on CT has been reported to be predictive of poor functional outcome and symptomatic ICH after thrombolytic therapy.[1-3] ASPECTS ≥8 could exclude most patients with EIC over one-third of the MCA territory on CT,[17] and it had a prognostic value for favorable outcome among acute stroke patients treated with IV rt-PA.[10,18] In contrast, EIC on DWI is the earliest indicator of brain ischemic changes, and it is more sensitive and clearer to delineate the extension of brain ischemia than EIC on CT.[19] A coauthor of this study previously reported

that initial DWI-ASPECTS ≤5 was independently associated with NIHSS score ≥20 at 7 days after rt-PA therapy.[20] In our single-center study, initial DWI-ASPECTS ≥7 was independently associated with an mRS score of 0–1 at 3 months after rt-PA.[21] In this study, DWI-ASPECTS ≥7 was independently predictive of patients with a 3-month mRS score of 0–2.

Barber et al.[11] assessed ASPECTS for stroke patients within 6 hours of onset using both CT and DWI, and they found that DWI-ASPECTS was lower than ASPECTS on CT. The mean ASPECTS difference between the 2 modalities was 0.43. The superior ability of DWI over CT to detect the extension of EIC, as well as the time delay for DWI performance, appeared to cause the difference. Thus, the present cutoff of DWI-ASPECTS ≥7 to predict functional outcome appears to have a close relationship with the cutoff ASPECTS ≥8 on CT as a known prognostic variable for rt-PA-treated patients.[10,18]

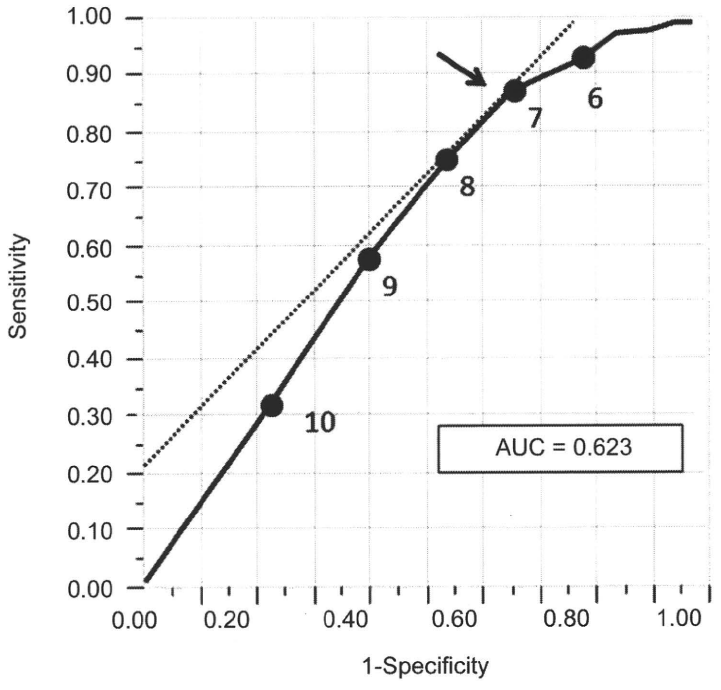
In the NINDS rt-PA Stroke Study, IV rt-PA for patients with baseline ASPECTS on CT <3 increased mortality compared with placebo treatment; 2 of the 5 deaths in the rt-PA therapy group were associated with symptomatic ICH compared with none in the placebo group.[22] DWI-ASPECTS was reported to predict unfavorable short-term outcome (NIHSS score ≥20 at 7 days)[20]; however, to our knowledge, the score has not been previously reported to affect mortality after rt-PA. In figure 2A, the marked increase in mortality is shown below DWI-ASPECTS ≤4, indicating the association of low DWI-ASPECTS and higher mortality rates. However, precise cutpoints were difficult to define. Of the 9 deaths in patients with DWI-ASPECTS ≤4, 3 resulted from symptomatic ICH, 5 from cerebral herniation due to massive stroke, and 1 from severe cardiac failure (data not shown).

Pretreatment DWI volume has recently been recognized as an independent risk for sICH after thrombolysis.[4,23,24] Pretreatment DWI-ASPECTS ≤7 was advocated as a predictor of sICH after IV or intraarterial thrombolysis within 6 hours of onset.[12] In contrast, for our patients receiving IV thrombolysis within 3 hours, pretreatment DWI-ASPECTS ≤5 was an independent predictor of sICH.

MRI is currently not generally the primary imaging modality in acute stroke patients because of the possible time delay, its potentially inferior ability for detecting acute ICH, and its contraindications, which are mainly due to metal implants. Several studies have reported that MRI screening within 3 hours of onset did not delay IV rt-PA therapy or lead to worse outcomes relative to CT screening.[25,26] Regarding hyperacute ICH, MRI was reported to be as reliable as CT, because small amounts of deoxyhemoglobin are detectable within the first hours of ICH on T2*-weighted images.[27,28] Thus, MRI could be used as the modality for emergency imaging of acute stroke patients, whether ischemic or hemorrhagic.[29] In addition, MRI penumbral assessment with the mismatch between DWI and perfusion-weighted imaging (PWI) is promising to improve patient selection and outcome for IV rt-PA therapy.[30,31] Since planimetric PWI-DWI mismatch assessment is time-consuming, ASPECTS can be applied to assess PWI-DWI mismatch.[32]

This study has several limitations. First, DWI-ASPECTS is not useful for evaluating strength and size variations of high-intensity change within each allotted lesion on DWI. Because slight alterations in high intensity on DWI are believed to contain reversible ischemic tissues, DWI-ASPECTS may overestimate the extension of EIC.[33] Second, this was an observational study and patient eligibility for rt-PA was determined according to each patient's situation, though the determination was principally based on the Japanese guidelines.[8] In particular, eligibility of patients having large EIC on DWI depended on each physician's decision, and we did not assess how many patients with low DWI-ASPECTS and relatively high ASPECTS on CT were excluded from the

Figure 3 **Receiver operating characteristic curves of scoring of Alberta Stroke Programme Early CT Score using diffusion-weighted imaging for predicting modified Rankin Scale scores of 0-2**



The arrow indicates the optimal cutoff point. AUC = area under the receiver operating characteristic curve.

Table 2 **Characteristics associated with a modified Rankin Scale score of 0–2 and death at 3 months, and symptomatic intracerebral hemorrhage[a]**

	OR	95% CI	p
mRS 0–2			
Age, per 1-year increase	0.97	0.95–0.99	<0.001
Female	0.59	0.37–0.95	0.031
Hypertension	0.67	0.42–1.05	0.083
Baseline NIHSS, per 1-point increase	0.92	0.89–0.96	<0.001
DWI-ASPECTS ≥7	1.85	1.07–3.24	0.029
ICA occlusion	0.13	0.06–0.28	<0.001
Death			
Congestive heart failure	7.61	2.46–22.35	<0.001
DWI-ASPECTS ≤4	3.61	1.23–9.91	0.021
ICA occlusion	4.45	1.69–11.64	0.003
Symptomatic ICH			
DWI-ASPECTS ≤5	4.74	1.54–13.64	0.008

Abbreviations: ASPECTS = Alberta Stroke Programme Early CT Score; CI = confidence interval; DWI = diffusion-weighted imaging; ICA = internal carotid artery; ICH = intracerebral hemorrhage; mRS = modified Rankin Scale; NIHSS = NIH Stroke Scale; OR = odds ratio.
[a] Adjusted by characteristics selected by a backward selection procedure.

study. Third, 84 patients lacked MRI information, which may have caused selection bias. Fourth, all of the patients received 0.6 mg/kg alteplase, which is the recommended dose in Japan. Thus, the clinical value of DWI-ASPECTS in patients treated with the generally accepted standard dose of alteplase (0.9 mg/kg) outside of Japan was not ascertained. Fifth, we did not collect data for stroke patients who did not receive thrombolysis. Thus, we could not compare the present results with stroke outcome of patients who were excluded from the therapy because of extensive EIC. Finally, since DWI-ASPECTS for most of the patients was high (the lower 25% value was 7), the median DWI-ASPECTS did not differ much between patients with good outcomes and those without.

Pretreatment MRI with DWI provides valuable information for predicting clinical outcome after IV rt-PA therapy. Although clinical use of rt-PA should not be chosen solely using DWI-ASPECTS because it requires consideration of various underlying conditions, patients with DWI-ASPECTS of 4 or less do not seem to be good candidates for IV rt-PA since most patients with these scores have fatal or dependent outcomes. DWI-ASPECTS of 5 may be another warning sign for choosing rt-PA since more than 10% of patients with this score developed sICH. A confirmation of the present findings using patients treated with the regular dose of alteplase is needed.

DISCLOSURE

Dr. Nezu, Dr. Koga, Dr. Kimura, Dr. Shiokawa, Dr. Nakagawara, Dr. Furui, Dr. Yamagami, Dr. Okada, Dr. Hasegawa, Dr. Kario, Dr. Okuda, Dr. Nishiyama, and Dr. Naganuma report no disclosures. Dr. Minematsu serves on the editorial boards of *Cerebrovascular Diseases*, the *International Journal of Stroke*, and the *Journal of Stroke and Cerebrovascular Diseases* and receives research support from Asteras Pharma Inc., Takeda Pharmaceutical Company Limited, Sanofi-Aventis, Lundbeck Inc., Mitsubishi Tanabe Pharma Corporation, Kyowa Hakko Kirin Pharma, Inc., Hitachi Medical Corporation, MHLM, Japan, Research Grants for Cardiovascular Diseases, Grant-in-Aid, and the Foundation for Biomedical Research and Innovation. Dr. Toyoda receives research support from Grants-in-Aid from the Ministry of Health, Labour and Welfare, Japan.

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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」
サブ解析論文：要旨

Early ischemic change on CT versus DWI for stroke patients receiving intravenous rt-PA therapy: SAMURAI rt-PA Registry

Tomohisa Nezu, MD[1)], Masatoshi Koga, MD[2)], Jyoji Nakagawara, MD[3)], Yoshiaki Shiokawa, MD[4)], Hiroshi Yamagami, MD[5)], Eisuke Furui, MD[6)], Kazumi Kimura, MD[7)], Yasuhiro Hasegawa, MD[8)], Yasushi Okada, MD[9)], Satoshi Okuda, MD[10)], Kazuomi Kario, MD[11)], Masaki Naganuma, MD[1)], Koichiro Maeda, MD[1)], Kazuo Minematsu, MD[1)], and Kazunori Toyoda, MD[1)]

[1)]Department of Cerebrovascular Medicine, and [2)]Division of Stroke Care Unit, National Cerebral and Cardiovascular Center, Suita, Japan
[3)]Department of Neurosurgery and Stroke Center, Nakamura Memorial Hospital, Sapporo, Japan
[4)]Departments of Neurosurgery and Stroke Center, Kyorin University School of Medicine, Mitaka, Japan
[5)]Stroke Center, Kobe City Medical Center General Hospital, Kobe, Japan
[6)]Department of Stroke Neurology, Kohnan Hospital, Sendai, Japan
[7)]Department of Stroke Medicine, Kawasaki Medical School, Kurashiki, Japan
[8)]Department of Neurology, St Marianna University School of Medicine, Kawasaki, Japan
[9)]Department of Cerebrovascular Medicine, National Hospital Organization Kyushu Medical Center, Fukuoka, Japan
[10)]Department of Neurology, National Hospital Organization Nagoya Medical Center, Nagoya, Japan
[11)]Division of Cardiovascular Medicine, Department of Medicine, Jichi Medical University School of Medicine, Shimotsuke, Japan

Abstract

Background and Purpose: Alberta Stroke Programme Early CT Score (ASPECTS) is a quantitative topographic score to evaluate early ischemic change (EIC) in the middle cerebral arterial territory on CT as well as on diffusion-weighted imaging (DWI). The aim of the present study was to elucidate the relationship between CT-ASPECTS and DWI-ASPECTS for hyperacute stroke patients and their associations with outcomes after recombinant tissue-type plasminogen activator (rt-PA) therapy based on a multicenter registry.

Methods: ASPECTS was assessed on both CT and DWI before intravenous 0.6 mg/kg alteplase in 360 stroke patients (119 women, 71±11 years old). The outcomes were symptomatic intracerebral hemorrhage (sICH) within 36 h and independence at 3 months defined by a modified Rankin Scale (mRS) score of 0-2.

Results: DWI-ASPECTS was positively correlated with CT-ASPECTS (ρ= 0.511, $p<0.001$), and was lower than CT-ASPECTS (median 8 [interquartile range 6-9] vs. 9 [8-10], $P<0.001$). Higher baseline NIHSS score (standardized partial regression coefficient [β] 0.061, $p<0.001$) and cardioembolic stroke (β 0.35, $p<0.001$) were related to this discrepancy. The area under the ROC curve for predicting sICH (12 patients) using ASPECTS was 0.673 (95%CI 0.503-0.807) by CT and 0.764 (95%CI 0.635-0.858) by DWI (p=0.275). The curve for predicting independence at 3 months (192 patients) was 0.621 (0.564-0.674) by CT and 0.639 (0.580-0.694) by DWI (p=0.535).

Conclusion: For hyperacute stroke patients, DWI-ASPECTS scored about 1 point lower than CT-ASPECTS. Both CT-ASPECTS and DWI-ASPECTS were useful predictors of sICH and independence at 3 months after rt-PA.

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Reduced Estimated Glomerular Filtration Rate Is Associated with Stroke Outcome after Intravenous rt-PA: The Stroke Acute Management with Urgent Risk-Factor Assessment and Improvement (SAMURAI) rt-PA Registry

Masaki Naganuma[a] Masatoshi Koga[a] Yoshiaki Shiokawa[b] Jyoji Nakagawara[d] Eisuke Furui[e] Kazumi Kimura[f] Hiroshi Yamagami[g] Yasushi Okada[h] Yasuhiro Hasegawa[i] Kazuomi Kario[j] Satoshi Okuda[k] Kazutoshi Nishiyama[c] Kazuo Minematsu[a] Kazunori Toyoda[a]

[a]Department of Cerebrovascular Medicine, National Cerebral and Cardiovascular Center, Suita, Departments of [b]Neurosurgery and [c]Neurology, Stroke Center, Kyorin University School of Medicine, Mitaka, [d]Department of Neurosurgery and Stroke Center, Nakamura Memorial Hospital, Sapporo, [e]Department of Stroke Neurology, Kohnan Hospital, Sendai, [f]Department of Stroke Medicine, Kawasaki Medical School, Kurashiki, [g]Stroke Center, Kobe City Medical Center General Hospital, Kobe, [h]Department of Cerebrovascular Diseases, National Hospital Organization, Kyushu Medical Center, Fukuoka, [i]Department of Neurology, St. Marianna University School of Medicine, Kawasaki, [j]Division of Cardiovascular Medicine, Department of Medicine, Jichi Medical University School of Medicine, Shimotsuke, and [k]Department of Neurology, National Hospital Organization, Nagoya Medical Center, Nagoya, Japan

Key Words

Infarction · Intracerebral hemorrhage · Renal dysfunction · rt-PA · SAMURAI

Abstract

Background: The aim of this study was to determine whether renal dysfunction affects the outcome of stroke patients treated with recombinant tissue plasminogen activator (rt-PA). ***Methods:*** A retrospective, multicenter, observational study was conducted to identify the effects of underlying risk factors on intravenous rt-PA therapy using 0.6 mg/kg alteplase in 10 stroke centers in Japan. Consecutive stroke patients with a premorbid modified Rankin Scale (mRS) score ≤3 who received rt-PA were studied. Renal dysfunction was defined as estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m^2 on admission. The outcome measures were any intracerebral hemorrhage (ICH) and symptomatic ICH within the initial 36 h; favorable (mRS 0–1) outcome, poor outcome (mRS 4–6) and mortality at 3 months. ***Results:*** Of a total of 578 patients (372 men; 64.4%, 71.4 ± 11.7 years old), renal dysfunction was present in 186 patients (32.2%). These patients were older and more commonly had hypertension, atrial fibrillation, prior ischemic heart disease and prior use of antithrombotic agents than patients without renal dysfunction. ICH (27.4 vs. 16.6%) and symptomatic ICH (8.1 vs. 2.6%) was more common in patients with renal dysfunction than in those without. At 3 months, patients with renal dysfunction had higher median mRS scores than those without (3 vs. 2). After multivariate adjustment for established outcome predictors, renal dysfunction was related to any ICH (odds ratio 1.81, 95% confidence interval 1.16–2.84), symp-

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Kazunori Toyoda, MD
Department of Cerebrovascular Medicine
National Cerebral and Cardiovascular Center
Fujishirodai 5-7-1, Suita, Osaka 565-8565 (Japan)
Tel. +81 6 6833 5012, Fax +81 6 6872 7486, E-Mail toyoda@hsp.ncvc.go.jp

tomatic ICH (2.64, 1.10–6.56), poor outcome (1.55, 1.01–2.38), and mortality (2.94, 1.38–6.42). ***Conclusions:*** Reduced eGFR was associated with early ICH and 3-month unfavorable outcome in stroke patients receiving intravenous rt-PA.

Introduction

Renal dysfunction is increasingly noted as a risk factor for stroke in the general population [1, 2], as well as in high-risk patients having diabetes mellitus [3], essential hypertension [4], and preexisting atherothrombotic disease [5, 6]. In a large cohort of patients with acute stroke, renal dysfunction was an independent predictor for long-term mortality and poor outcome [7–9].

Though intravenous (IV) thrombolysis is a standard therapy for acute stroke patients, the effect of renal dysfunction on vital and functional outcome measures following therapy is inconclusive. As far as we know, only one study (involving 196 stroke patients) reported that a high admission serum creatinine level was independently predictive of a modified Rankin scale (mRS) score ≥3 at 3 months after IV recombinant tissue plasminogen activator (rt-PA) [10]. This study also reported that an impaired estimated glomerular filtration rate (eGFR), defined as <90 ml/min/1.73 m^2, tended to be associated with symptomatic intracerebral hemorrhage (ICH). Since renal dysfunction appears to be an important predictor for stroke outcome, its significance for rt-PA-treated patients should be ascertained in a larger cohort using a multicenter design.

To identify adequate risk factor control in acute stroke patients treated with thrombolysis, a multicenter study group [Stroke Acute Management with Urgent Risk-Factor Assessment and Improvement (SAMURAI) Study Group] was formed. Here, we determined the association of renal dysfunction based on admission eGFR with stroke outcome after IV rt-PA using the database of this study group.

Patients and Methods

The SAMURAI rt-PA Registry Trial had a multicenter, hospital-based, retrospective, observational, cohort design [11]. Details of this study have been described previously [11, 12]. In brief, this study involved 600 consecutive patients with acute ischemic stroke receiving IV rt-PA from October 2005 to July 2008. Of these, 22 patients were ineligible for analysis; 17 patients had dependent activity of daily living before onset, corresponding to an mRS score ≥4, and 5 patients had incomplete 3-month mRS score data. Thus, the remaining 578 patients were included in the present study. Each local ethics committee approved the research protocol. Each patient received a single IV alteplase dose of 0.6 mg/kg, with 10% given as a bolus within 3 h of stroke onset, followed by a continuous IV infusion of the remainder over 1 h [13].

From the database of the SAMURAI rt-PA registers, the data listed in table 1 were extracted for this study. Neurological deficits were assessed using the National Institutes of Health Stroke Scale (NIHSS) score just before and 24 h after rt-PA. Ischemic stroke subtype according to the TOAST categories was elucidated based on information of non-contrast computed tomography (CT), diffusion-weighted magnetic resonance imaging (MRI), magnetic resonance angiography, CT angiography, cervical/transcranial ultrasound, transthoracic or transesophageal echocardiography, and 24-hour Holter monitoring in addition to neurological findings [14].

Kidney function was evaluated based on the eGFR using a revised equation for the Japanese population [15]; eGFR (ml/min/1.73 m^2) = 194 × (serum creatinine)$^{-1.094}$ × (age)$^{-0.287}$ × 0.739 (for women). To calculate eGFR, admission serum creatinine was used. According to the Kidney Disease Outcomes Quality Initiative guidelines of the National Kidney Foundation [16], renal dysfunction was defined as a reduced eGFR (<60 ml/min/1.73 m^2). The stage of renal dysfunction was classified as follows: stage 3 (eGFR 30–59 ml/min/1.73 m^2), stage 4 (15–29 ml/min/1.73 m^2), and stage 5 (<15 ml/min/1.73 m^2 or dialysis).

The major outcome measures were: any ICH defined as CT or MRI evidence of new ICH within the initial 36 h; symptomatic ICH with neurological deterioration corresponding to an increase of ≥1 point from the baseline NIHSS score (Cochrane/National Institute of Neurological Disorders and Stroke definition); favorable and poor outcome at 3 months, and mortality at 3 months. To assess favorable and poor outcome, definitions in the subanalyses of the National Institute of Neurological Disorders and Stroke rt-PA Trial (an mRS of 0–1 and 4–6, respectively) were used [17–20].

Statistical Analysis

Statistical test results were considered significant if $p < 0.05$. All analyses were performed using JMP statistical software (version 7.0.1; SAS Institute, Cary, N.C., USA). Baseline clinical characteristics and stroke features were compared using Student's unpaired t test for parametric continuous variables, Mann-Whitney's U test for nonparametric variables, and Fisher's exact test and the χ^2 test for categorical variables. To identify independent predictors of ICH within 36 h and stroke outcome at 3 months, multivariate logistic regression analysis was performed. For each outcome, sex, age, and renal dysfunction were initially entered, and the other variables listed in table 1 were chosen by a backward selection procedure using $p > 0.10$ in the likelihood ratio test for exclusion.

Results

A total of 578 patients (372 men, 71.4 ± 11.7 years old) were studied. Of these, 186 (32.2%) patients had renal dysfunction with eGFR <60 ml/min/1.73 m^2; 163 (28.2%)

Table 1. Baseline clinical characteristics

Baseline characteristics	Renal dysfunction (eGFR <60 ml/min/1.73 m^2) (n = 186)	No renal dysfunction (eGFR ≥60 ml/min/1.73 m^2) (n = 392)	p value
Male patients	113 (60.8)	259 (66.1)	0.227
Age, years	76.0 ± 9.8	69.2 ± 12.0	<0.001
Body mass index	22.7 ± 3.2	23.0 ± 3.4	0.397
Hypertension	137 (73.7)	219 (55.9)	<0.001
Diabetes mellitus	37 (19.9)	70 (17.9)	0.568
Dyslipidemia	35 (18.8)	89 (22.7)	0.329
Atrial fibrillation	97 (52.2)	148 (37.8)	0.001
Liver disease	8 (4.3)	9 (2.3)	0.194
Prior ischemic heart disease	37 (19.9)	37 (9.4)	<0.001
Prior ischemic stroke	39 (21.0)	62 (15.8)	0.129
Prior use of antithrombotic agents	92 (49.5)	125 (31.9)	<0.001
Systolic blood pressure, mm Hg	150 ± 20	151 ± 20	0.613
Diastolic blood pressure, mm Hg	80 ± 16	83 ± 15	0.077
Stroke subtype			
Large-artery atherosclerosis	24 (12.9)	65 (16.6)	0.141
Cardioembolism	128 (68.8)	236 (60.2)	
Lacune	5 (2.7)	23 (5.9)	
Other	29 (15.6)	68 (17.4)	
Internal carotid artery occlusion	29 (15.6)	59 (15.2)	0.902
Blood glucose, mmol/l	7.68 ± 2.77	7.61 ± 2.61	0.787
Hemoglobin A1c, %	5.8 ± 1.0	5.8 ± 1.1	0.995
Total cholesterol, mmol/l	4.68 ± 1.07	5.01 ± 1.01	<0.001
Triglyceride, mmol/l	1.30 ± 0.72	1.32 ± 0.95	0.809
HDL cholesterol, mmol/l	1.27 ± 0.36	1.38 ± 0.40	0.003
LDL cholesterol, mmol/l	2.83 ± 0.88	3.01 ± 0.87	0.043
Time to treatment onset, min	145 (121–167)	146 (122–166)	0.991
Admission NIHSS score	13 (7–19)	12 (7.25–18)	0.423

Numbers of patients (%) are shown except otherwise indicated; data are means ± SD or medians (IQR).

patients belonged to stage 3, 15 (2.6%) to stage 4, and 8 (1.4%) to stage 5. Four patients with stage 5 were on maintenance hemodialysis.

The patients with renal dysfunction were older ($p < 0.001$) and more commonly had hypertension ($p < 0.001$), atrial fibrillation ($p = 0.001$), prior ischemic heart disease ($p < 0.001$), and prior use of antithrombotic agents ($p < 0.001$) than patients without renal dysfunction (table 1). Serum total cholesterol ($p < 0.001$), HDL cholesterol ($p = 0.003$), and LDL cholesterol ($p = 0.043$) levels were lower in patients with renal dysfunction than in those without. NIHSS scores were not significantly different between patients with renal dysfunction and those without immediately before [median (interquartile range, IQR); 13 (7–19) vs. 12 (7.25–18), $p = 0.423$] and 24 h after IV rt-PA [9 (3–18) vs. 7 (3–15), $p = 0.070$; fig. 1a].

Any ICH [51 (27.4%) vs. 65 patients (16.6%), $p = 0.004$] as well as symptomatic ICH within 36 h from IV rt-PA therapy [15 (8.1%) vs. 10 patients (2.6%), $p = 0.004$], was more common in the patients with renal dysfunction than in those without. After multivariate logistic regression analysis, renal dysfunction was significantly related to both any ICH (odds ratio, OR, 1.81, 95% confidence interval, CI, 1.16–2.84, $p = 0.009$) and symptomatic ICH (2.64, 1.10–6.56, $p = 0.031$; table 2). When the value of eGFR (a continuous variable) was used instead of eGFR <60 ml/min/1.73 m^2 (a categorical variable) as an indicator of renal dysfunction, it was related to any ICH (OR 0.89, 95% CI 0.80–0.99 per 10-ml/min/1.73 m^2 increase, $p = 0.029$) but not symptomatic ICH (0.89, 0.73–1.08, $p = 0.231$).

At 3 months, the patients with renal dysfunction had higher mRS scores than those without [median (IQR); 3

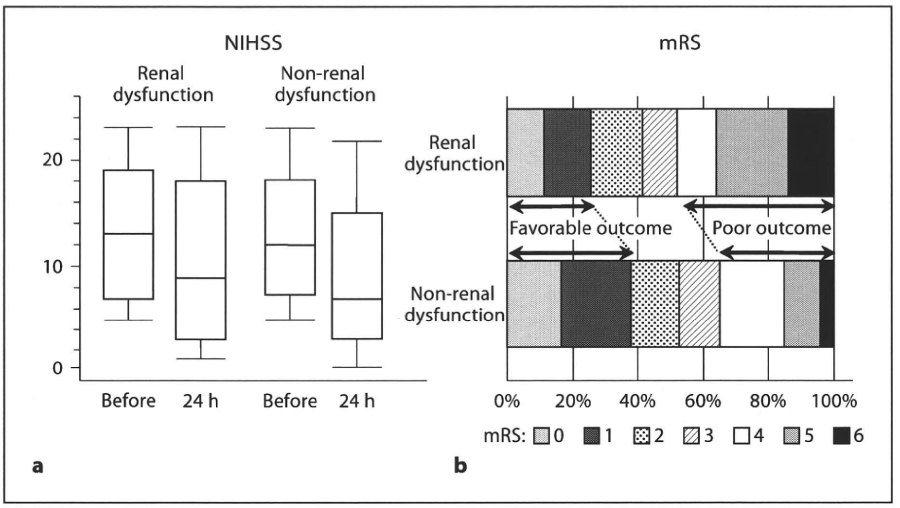

Fig. 1. Neurological deficits and outcome of patients with and without renal dysfunction. NIHSS score just before and 24 h after IV rt-PA therapy (**a**) and mRS score at 3 months (**b**) in patients with and without renal dysfunction. **a** Horizontal lines in boxes = Median NIHSS score; boxes = IQR; whiskers = upper and lower 90% ranges.

Table 2. Characteristics associated with ICH within 36 h

Characteristics	Any ICH			Symptomatic ICH		
	OR	95% CI	p value	OR	95% CI	p value
Male	1.12	0.71–1.78	0.638	1.99	0.74–6.32	0.201
Age (per year)	0.99	0.97–1.01	0.423	1.00	0.96–1.04	0.868
Renal dysfunction (eGFR <60 ml/min/1.73 m^2)	1.81	1.16–2.84	0.009	2.64	1.10–6.56	0.031
Atrial fibrillation	1.93	1.24–3.01	0.004	–	–	–
Liver disease	1.53	0.40–4.79	0.488	–	–	–
Prior use of antithrombotic agents	–	–	–	4.31	1.72–12.06	0.003
Blood glucose (per mmol/l)	1.06	0.98–1.14	0.153	1.11	0.96–1.26	0.126
Triglyceride (per mmol/l)	–	–	–	1.00	0.99–1.01	0.174
Admission NIHSS score (per point)	1.03	0.99–1.06	0.069	–	–	–

– = The variable was not included after the backward selection procedure.

Table 3. Characteristics associated with outcome at 3 months

Characteristics	Favorable outcome (mRS 0–1)			Poor outcome (mRS 4–6)			Death		
	OR	95% CI	p value	OR	95% CI	p value	OR	95% CI	p value
Male	1.14	0.74–1.76	0.545	0.84	0.55–1.29	0.430	0.68	0.32–1.48	0.331
Age (per year)	0.97	0.96–0.99	0.005	1.04	1.02–1.06	<0.001	1.01	0.97–1.05	0.718
Renal dysfunction (eGFR <60 ml/min/1.73 m^2)	0.70	0.44–1.09	0.114	1.55	1.01–2.38	0.046	2.94	1.38–6.42	0.006
Prior ischemic heart disease	–	–	–	–	–	–	4.33	1.84–10.05	<0.001
Internal carotid artery occlusion	0.24	0.10–0.51	<0.001	6.07	3.38–11.39	<0.001	4.32	2.00–9.36	<0.001
Blood glucose (per mmol/l)	0.91	0.84–0.99	0.024	1.08	1.01–1.17	0.033	1.17	1.04–1.31	0.007
Admission NIHSS score (per point)	0.91	0.88–0.94	<0.001	1.11	1.08–1.15	<0.001	1.09	1.04–1.15	<0.001

– = The variable was not included after the backward selection procedure. For favorable outcome analysis, patients with premorbid mRS score 2–3 were excluded.

(1–5) vs. 2 (1–4), $p < 0.001$; fig. 1b]. Twenty-five patients (13.4%) with renal dysfunction had died; of these, 5 died of stroke, 6 of heart disease (4 heart failure, 1 myocardial infarction, and 1 infectious endocarditis), 6 of severe infection (3 sepsis and 3 pneumonia), and 8 of unknown causes. In contrast, 15 patients (3.8%, $p < 0.001$) without renal dysfunction had died; of these, 9 died of stroke, 2 of pneumonia, and 4 of unknown causes. Similarly, favorable outcome was less common [48 (25.8%) vs. 149 patients (38.0%), $p = 0.004$], and poor outcome was more common [89 (47.9%) vs. 136 patients (34.7%), $p = 0.003$] in patients with renal dysfunction than in those without. After multivariate logistic regression analysis, renal dysfunction was significantly related to poor outcome (OR 1.55, 95% CI 1.01–2.38, $p = 0.046$) and mortality (OR 2.94, 95% CI 1.38–6.42, $p = 0.006$), although it was not related to favorable outcome (OR 0.70, 95% CI 0.44–1.09, $p = 0.114$; table 3). When the value of eGFR was used instead, it was significantly related to mortality (OR 0.81, 95% CI 0.67–0.96 per 10-ml/min/1.73 m^2 increase, $p = 0.020$), but not to favorable outcome (OR 1.09, 95% CI 0.99–1.20, $p = 0.081$) or poor outcome (OR 0.95, 95% CI 0.86–1.04, $p = 0.268$).

Discussion

In this observational study, we determined the influence of renal dysfunction on early ICH and the long-term outcome of ischemic stroke patients receiving IV rt-PA therapy. The major finding was that renal dysfunction, defined as reduced eGFR (<60 ml/min/1.73 m^2), which was calculated using the admission creatinine level, was related to any ICH and symptomatic ICH within 36 h, as well as poor outcome (mRS 4–6) and death at 3 months, although it was not related to favorable outcome (mRS 0–1).

According to the result of the largest postmarketing surveillance on rt-PA, the Safe Implementation of Thrombolysis in Stroke-Monitoring Study [21], advanced age, body weight, atrial fibrillation, high systolic blood pressure, hyperglycemia, admission NIHSS score, and current infarction on baseline imaging scans were associated with symptomatic ICH. In addition, advanced age, male sex, use of antiplatelet agents other than aspirin, congestive heart failure, higher diastolic blood pressure, hyperglycemia, higher NIHSS score, current infarction, and premorbid dependency were related to death at 3 months. Similar results have been reported in several other studies [22–26]. However, these studies did not assess renal dysfunction as a potential factor affecting stroke outcome. The present study is unique in that renal dysfunction was included as a potential factor and was proven to be associated with patient outcome after rt-PA.

Alteplase is metabolized by the liver, and liver function affects the half-life of alteplase [27]. In this study, liver disease was not associated with stroke outcome. In contrast, renal dysfunction might not prolong the half-life of alteplase. For example, the plasma concentration-time profile of alteplase was not altered after bilateral nephrectomy in rat models [28].

Renal dysfunction is a bystander of stroke, since it is associated with traditional vascular risk factors, including aging, hypertension, diabetes mellitus, dyslipidemia, and smoking [29]. In addition, renal dysfunction is now known to be an independent predictor for stroke [1, 2, 5, 30, 31], partly via nontraditional vascular risk factors, e.g. inflammatory factors, and homocysteinemia. However, the effect of these nontraditional risk factors on stroke outcome has not been clarified, in particular after rt-PA. In patients with acute stroke not receiving IV rt-PA, albuminuria was independently associated with hemorrhagic transformation [32]. Since ICH is a major cause of poor outcome for thrombolysed patients, renal dysfunction may affect chronic outcome after rt-PA via increasing ICH risk. Moreover, renal dysfunction might impair endothelial release of t-PA [33], and increase plasminogen activator inhibitor-1 activity [34] and plasma levels of lipoprotein(a) [35]; these abnormalities might obstruct the reperfusion phenomenon and worsen stroke outcome after IV rt-PA.

An interesting finding regarding the patients who died was that indirect death other than stroke was common as the cause of death for patients with renal dysfunction, though direct stroke death accounted for most of the causes of death for patients without renal dysfunction. This finding suggests that patients with renal dysfunction often had heart problems and susceptibility to infection, developed dependency and died due to non-stroke complications.

Certain limitations need to be considered prior to interpretation of the present results. First, patients who did not receive IV rt-PA were not included in this study. Thus, the influence of renal dysfunction on stroke outcome could not be compared between patients who were treated with rt-PA and those who were not. Second, renal dysfunction was correlated with older age, hypertension, atrial fibrillation, prior ischemic heart disease, and prior use of antithrombotic agents, and this multicolineality may inflate the variances of the parameter estimates. Thus, the present association of renal dysfunction with outcome measures after multivariate analyses may be

overestimated to some extent. Third, eGFR was not measured prior to stroke onset, and therefore eGFR may have been affected by stroke. Fourth, eGFR was calculated using admission creatinine levels, which may have been impaired by acute stroke effects. Repeated assessment in the chronic stroke stage is needed to ascertain that the present patients with reduced eGFR have chronic kidney disease. Fifth, urinary albumin was not measured. Generally, urinary albumin increases during acute ischemic stroke [36]. 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).

In conclusion, reduced eGFR based on the admission creatinine level was predictive of an unfavorable outcome after IV rt-PA in acute stroke patients. In patients with renal dysfunction, additional therapeutic strategies to improve the efficacy of rt-PA are needed.

Disclosure Statement

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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」
サブ解析論文：要旨

Intravenous recombinant tissue plasminogen activator therapy for stroke patients receiving maintenance hemodialysis: the Stroke Acute Management with Urgent Risk-factor Assessment and Improvement (SAMURAI) rt-PA Registry

Masaki Naganuma, MD [1)], Mayumi Mori, MD[3)], Tomohisa Nezu, MD[1)], Noriko Makihara, MD [3)], Masatoshi Koga, MD [2)], Yasushi Okada, MD [3)], Kazuo Minematsu, MD [1)], Kazunori Toyoda, MD [1)]
on behalf of the Stroke Acute Management with Urgent Risk-factor Assessment and Improvement (SAMURAI) Study Investigators

[1)]Department of Cerebrovascular Medicine, and [2)]Division of Stroke Care Unit, National Cerebral and Cardiovascular Center, Suita, Japan
[3)]Department of Cerebrovascular Medicine, National Hospital Organization Kyushu Medical Center, Fukuoka, Japan

Abstract
Background: To examine the therapeutic effect of intravenous recombinant tissue plasminogen activator (rt-PA) therapy for stroke patients receiving maintenance hemodialysis.
Methods: Of 600 stroke patients receiving intravenous rt-PA using 0.6 mg/kg alteplase who were enrolled in a multicenter observational study in Japan, four patients (3 men, 64 to 77 years) on maintenance hemodialysis were studied.
Results: The primary kidney disease requiring hemodialysis was glomerulonephritis in two patients, diabetic nephropathy in one, and undetermined in one. The duration of hemodialysis ranged between 1.2 and 28 years. Three patients developed stroke on the day of hemodialysis, including one during hemodialysis and another just after hemodialysis. All patients had stroke in the carotid arterial territory. Pretreatment NIH Stroke Scale scores ranged between 4 and 20, and decreased by 2 to 5 points at 7 days. One patient needed intravenous antihypertensive therapy before rt-PA; he developed an ectopic cortical hematoma and intraventricular hemorrhage after rt-PA. The other three did not develop hemorrhagic complications. The modified Rankin Scale score at 3 months was 0 in one patient, 2 in two, and 4 in one.
Conclusion: Rt-PA therapy for stroke patients receiving maintenance hemodialysis might improve the stroke outcome. Ectopic hematoma was a unique complication in our case series.

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$CHADS_2$ score is associated with 3-month clinical outcomes after intravenous rt-PA therapy in stroke patients with atrial fibrillation: SAMURAI rt-PA Registry

Masatoshi Koga [a], Kazumi Kimura [c], Kensaku Shibazaki [c], Yoshiaki Shiokawa [d], Jyoji Nakagawara [e], Eisuke Furui [f], Hiroshi Yamagami [g], Yasushi Okada [h], Yasuhiro Hasegawa [i], Kazuomi Kario [j], Satoshi Okuda [k], Masaki Naganuma [b], Tomohisa Nezu [b], Koichiro Maeda [b], Kazuo Minematsu [b], Kazunori Toyoda [b,*]

[a] Division of Stroke Care Unit, National Cerebral and Cardiovascular Center, Suita, Japan
[b] Department of Cerebrovascular Medicine, National Cerebral and Cardiovascular Center, Suita, Japan
[c] Department of Stroke Medicine, Kawasaki Medical School, Kurashiki, Japan
[d] Department of Neurosurgery, and Stroke Center, Kyorin University School of Medicine, Mitaka, Japan
[e] Department of Neurosurgery and Stroke Center, Nakamura Memorial Hospital, Sapporo, Japan
[f] Department of Stroke Neurology, Kohnan Hospital, Sendai, Japan
[g] Stroke Center, Kobe City Medical Center General Hospital, Kobe, Japan
[h] Department of Cerebrovascular Disease, National Hospital Organization Kyushu Medical Center, Fukuoka, Japan
[i] Department of Neurology, St Marianna University School of Medicine, Kawasaki, Japan
[j] Division of Cardiovascular Medicine, Department of Medicine, Jichi Medical University School of Medicine, Shimotsuke, Japan
[k] Department of Neurology, National Hospital Organization Nagoya Medical Center, Nagoya, Japan

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Outcomes

ABSTRACT

Purpose: The aim of this study was to examine whether $CHADS_2$ score is associated with clinical outcomes following recombinant tissue type plasminogen activator (rt-PA) therapy in stroke patients with atrial fibrillation (AF).

Methods: We studied 218 consecutive stroke patients with AF [126 men, mean age 74.2 (SD 9.6) years] who received intravenous rt-PA therapy. $CHADS_2$ score was calculated as follows: 2 points for prior ischemic stroke and 1 point for each of the following: age ≥ 75 years, hypertension, diabetes, and congestive heart failure.

Results: Congestive heart failure was documented in 23 patients, hypertension in 138, age ≥ 75 years in 116, diabetes in 35, and prior stroke in 35. The distribution of each $CHADS_2$ score was: score of 0, 16.1% of patients; 1, 30.3%; 2, 29.4%; and 3 to 5, 24.3%. The median initial NIHSS score for each $CHADS_2$ category was 12 (IQR 8–17), 16 (10–20), 14.5 (10–20.75), and 16 (11–21), respectively ($p = 0.168$). Symptomatic ICH within the initial 36 h was found in 2.9%, 4.6%, 6.3%, and 0% of patients with each $CHADS_2$ category, respectively. Cardiovascular events within 3 months occurred in 0%, 0%, 7.8% and 5.7%, respectively. Percentage of patients with chronic independence at 3 months corresponding to modified Rankin Scale ≤ 2 was 57.1%, 45.5%, 31.3%, and 28.3%, respectively. Adjusted $CHADS_2$ score was inversely associated with chronic independence (OR 0.72, 95% CI 0.55–0.93).

Conclusion: Lower $CHADS_2$ score was associated with chronic independence at 3 months after intravenous rt-PA therapy in stroke patients with AF.

1. Introduction

Atrial fibrillation (AF) is a major cause of ischemic stroke and systemic thromboembolism. Several risk stratification schemes have been developed to quantify the risk of stroke in patients with AF. The $CHADS_2$ score is an easy-to-use classification scheme that estimates the risk of ischemic stroke in patients with AF. It is well-validated and derived from pooled individual data from a large number of multicenter trial participants who had nonvalvular AF and were prescribed aspirin. [1,2] High-risk patients with $CHADS_2$ scores ≥ 3 are reported to benefit from warfarin therapy. [2] Physicians can use the $CHADS_2$ score to make decisions about antithrombotic therapy based on patient-specific risk of stroke, and the score is also applied to predict hemorrhagic events in high-risk patients for stroke treated with anticoagulation. [3–5] Regarding stroke outcomes, one study reported a positive association between $CHADS_2$ score and all-cause mortality after stroke. [6] However, the association between the score and functional outcomes after stroke has not yet been elucidated.

* Corresponding author at: Department of Cerebrovascular Medicine, National Cerebral and Cardiovascular Center, 5-7-1 Fujishiro-dai, Suita, Osaka 565-8565, Japan. Tel.: +81 6 6833 5012; fax: +81 6 6872 7486.
E-mail address: toyoda@hsp.ncvc.go.jp (K. Toyoda).

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Table 1
Baseline characteristics of patients according to $CHADS_2$ score.

	Total	$CHADS_2$ 0	$CHADS_2$ 1	$CHADS_2$ 2	$CHADS_2$ 3–5	p
Patients, n (%)	218	35 (16.1)	66 (30.3)	64 (29.4)	53 (24.3)	NA
Men, n (%)	126 (57.8)	22 (62.9)	43 (65.2)	36 (56.3)	25 (47.2)	0.226
Age, mean ± SD	74.2 ± 9.6	67.2 ± 5.1	71.0 ± 8.5	76.9 ± 11.1	79.3 ± 6.9	<0.001
Congestive heart failure, n (%)	23 (10.6)	0 (0)	2 (3.0)	3 (4.7)	18 (34.0)	<0.001
Hypertension, n (%)	138 (63.3)	0 (0)	39 (59.1)	53 (82.8)	46 (86.8)	<0.001
Age ≥ 75 years, n (%)	116 (53.2)	0 (0)	22 (33.3)	50 (78.1)	44 (83.0)	<0.001
Diabetes, n (%)	35 (16.1)	0 (0)	3 (4.6)	14 (21.9)	18 (34.0)	<0.001
Prior stroke, n (%)	35 (16.1)	0 (0)	0 (0)	4 (6.3)	31 (58.5)	<0.001
ASPECTS on initial CT (n = 215), median (IQR)	9 (7–10)	9 (8–10)	8 (7–10)	9 (8–10)	9 (8–10)	0.319
Internal carotid artery occlusion (n = 217), n (%)	41 (18.9)	7 (20.0)	9 (13.9)	14 (21.9)	11 (20.8)	0.660
Initial NIHSS, median (IQR)	15 (9.75–20)	12 (8–17)	16 (10–20)	14.5 (10–20.75)	16 (11–21)	0.168

NA: not applicable.

Intravenous (IV) recombinant tissue plasminogen activator (rt-PA) therapy is a standard treatment for acute stroke. Several clinical characteristics including higher National Institutes of Health Stroke Scale (NIHSS) score, advanced age, large infarct volume, high blood pressure, and internal carotid artery occlusion were reported to be associated with poor clinical outcome following IV rt-PA therapy for acute stroke. [7–10] However, there is no risk stratification scheme to detect early cardiovascular events and clinical outcomes after IV rt-PA therapy. This study aimed to investigate the ability of $CHADS_2$ score to predict clinical outcomes at 3 months after IV rt-PA therapy using our multicenter registry. [10,11]

2. Subjects and methods

Patients were derived from the Stroke Acute Management with Urgent Risk-factor Assessment and Improvement (SAMURAI) rt-PA Registry. [10] The details of this study have been described previously. [10] In brief, this study involved 600 consecutive stroke patients treated with IV rt-PA from October 2005 (when the therapy was approved in Japan) through July 2008 in 10 stroke centers in Japan. Patient eligibility for alteplase (rt-PA) therapy was determined based on the Japanese guideline for IV rt-PA therapy, [12] 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 (J-ACT). [13,14] Patients on warfarin therapy were included only when the pretreatment prothrombin time international normalized ratio (PT-INR) was <1.7. 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) intravenously, with 10% given as a bolus within 3 h of stroke onset, followed by a continuous IV infusion of the remainder over 1 hour. Safety and efficacy of 0.6 mg/kg alteplase therapy was confirmed by a post-marketing multicenter study (the Japan Alteplase Clinical Trial 2: J-ACT 2) [15] and a post-marketing nationwide survey (the Japan post-Marketing Alteplase Registration Study: J-MARS). [16] We collected baseline data including sex, age, comorbidities (clinical congestive heart failure, hypertension, diabetes mellitus, and atrial fibrillation), oral warfarin intake,and initial neurologic deficits using the National Institutes of Health Stroke Scale (NIHSS), extension of early ischemic change on pretreatment CT as assessed by the Alberta Stroke Program Early CT Score (ASPECTS), and internal carotid artery occlusion on MRA or carotid ultrasound.

$CHADS_2$ score was derived from the individual stroke risk factors: congestive heart failure (C), hypertension (H), age ≥ 75 years (A), diabetes mellitus (D), and prior stroke (S). Two points were given for prior stroke, and 1 point was assigned for each of the other factors. [1,2]

The clinical outcomes were as follows: any and symptomatic intracerebral hemorrhage (ICH) within the initial 36 h; cardiovascular events within 3 months; and independence and unfavorable outcome at 3 months. ICH was defined as CT evidence of new hemorrhage, and symptomatic ICH was defined as that associated with neurological deterioration corresponding to an increase of ≥4 points from the baseline NIHSS score. A cardiovascular event was defined as any ischemic or hemorrhagic stroke, acute coronary syndrome, aortic dissection, peripheral arterial embolism, or deterioration of congestive heart failure. Independence corresponded to a modified Rankin Scale (mRS) score of 0–2, and unfavorable outcome to an mRS of 5 or 6.

Statistical analysis was performed using JMP 7.0 statistical software (SAS Institute Inc., Cary, NC, USA). Results are expressed as mean ± standard deviation other than when specified. Baseline characteristics were compared between patients with each $CHADS_2$ score component using χ^2 tests, unpaired *t*-tests, and the Mann–Whitney *U* test, as appropriate. The prevalence of each clinical outcome in patients with each

Table 2
Clinical outcomes of patients according to $CHADS_2$ score.

	$CHADS_2$ category				Model 1			Model 2		
	$CHADS_2$ 0	$CHADS_2$ 1	$CHADS_2$ 2	$CHADS_2$ 3–5	Odds ratio[a]	95% CI	p	Odds ratio[a]	95% CI	p
Intracerebral hemorrhage (ICH), n (%)	7 (20.0)	18 (27.3)	25 (39.1)	14 (26.4)	1.06	0.84–1.34	0.617	1.07	0.84–1.35	0.601
Symptomatic ICH, n (%)	1 (2.9)	3 (4.6)	4 (6.3)	0 (0)	0.74	0.37–1.34	0.340	0.73	0.36–1.35	0.370
Cardiovascular event, n (%)	0 (0)	0 (0)	5 (7.8)	3 (5.7)	1.59	0.92–2.75	0.092	1.60	0.91–2.86	0.101
Recurrent ischemic stroke, n (%)	0 (0)	0 (0)	3 (4.7)	1 (1.9)	1.40	0.65–2.89	0.358	1.61	0.63–4.06	0.290
mRS ≤ 2 at 3 months, n (%)	20 (57.1)	30 (45.5)	20 (31.3)	15 (28.3)	0.74	0.57–0.94	0.015	0.72	0.55–0.93	0.015
mRS ≥ 5 at 3 months, n (%)	3 (8.6)	17 (25.8)	21 (32.8)	25 (47.2)	1.53	1.19–1.99	0.001	1.58	1.21–2.11	0.001

Model 1: adjusted by sex and initial NIHSS score.
Model 2: adjusted by sex, initial NIHSS score, ASPECTS, and presence of internal carotid artery occlusion.
[a] Per 1 point increase of $CHADS_2$ score.

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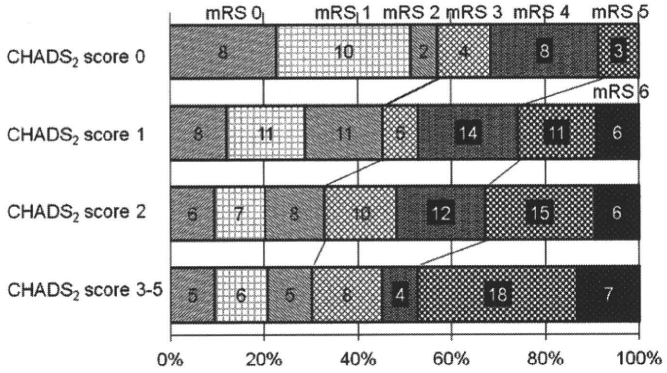

Fig. 1. $CHADS_2$ score and modified Rankin Scale at 3 months after stroke onset. The percentage of patients with mRS ≤ 2 gradually decreased as $CHADS_2$ score increased. In contrast, that of patients with mRS ≥ 5 gradually increased as $CHADS_2$ score increased.

$CHADS_2$ score group was calculated. Multivariate adjustment with sex and initial NIHSS (model 1) and that with sex, initial NIHSS, ASPECTS, and presence of internal carotid occlusion (model 2) were performed for clinical outcomes. All statistical tests were 2 sided, and probability values <0.05 were considered significant.

3. Results

Of a total 600 consecutive patients in the SAMURAI rt-PA Registry, 258 [146 men, mean age 75.1 (SD 10.0) years] had atrial fibrillation. Of these, 14 patients for whom no information on congestive heart failure, hypertension, diabetes, or prior stroke was available and 26 patients with prior disability corresponding to an mRS ≥ 3 were ineligible for the study. Thus, 218 patients [126 men, mean age 74.2 (SD 9.6) years] were studied.

Of these 218 patients, 29 (13.3%) took warfarin orally and PT-INR was less than 1.7 in all these patients on admission. Congestive heart failure was documented in 23 patients (10.6%), hypertension in 138 (63.3%), age ≥ 75 years in 116 (53.2%), diabetes in 35 (16.1%), and prior stroke in 35 (16.1%). The median $CHADS_2$ score was 2, the lower quartile was 1, and the higher quartile was 2. The distributions of each $CHADS_2$ score were: 35 patients with a $CHADS_2$ score of 0, 66 with 1, 64 with 2, 29 with 3, 19 with 4, 5 with 5, and none with 6. Because of the small number of patients with $CHADS_2$ score ≥ 3, patients were categorized into 4 groups as follows: $CHADS_2$ 0, $CHADS_2$ 1, $CHADS_2$ 2 and $CHADS_2$ 3 to 5. Patients with $CHADS_2$ score ≥ 3 are regarded as having high risk for stroke in the original study. [2]

Table 1 shows baseline characteristics in the 4 groups. ASPECTS, initial NIHSS score, and frequency of internal carotid artery occlusion did not differ among the 4 groups. Clinical outcomes in each group are shown in Table 2. There were no significant associations between any or symptomatic ICH and $CHADS_2$ groups. More than 5% of patients with $CHADS_2$ scores of 2 to 5, but none of those with $CHADS_2$ scores of 0 and 1, had cardiovascular events within 3 months after stroke onset. After adjustment for sex and initial NIHSS score, $CHADS_2$ score tended to be positively related to cardiovascular events within 3 months ($p = 0.092$). Of a total 8 patients with cardiovascular events, 4 had recurrent ischemic stroke. Three of them had a $CHADS_2$ score of 2 and one had a score of 3. Two of them developed stroke before recommencing anticoagulation (2.8% of 71 patients without recommencement), and two developed stroke after recommencing anticoagulation (1.4% of 147 patients with recommencement).

Fig. 1 shows the association between $CHADS_2$ score and mRS at 3 months. $CHADS_2$ score was negatively related to chronic independence (mRS ≤ 2) and positively related to unfavorable outcome (mRS ≥ 5). Frequency of chronic independence decreased by 26% (95% CI 6–43%, $p = 0.015$) and that of unfavorable outcome increased by 53% (95% CI 19–99%, $p = 0.001$) for each 1-point increase in the $CHADS_2$ score after adjustment for sex and initial NIHSS score (model 1). Those associations were still significant after adding radiological profiles (ASPECTS and internal carotid artery occlusion) to the multivariate adjustment (model 2). After adjustment for sex and $CHADS_2$ score, initial NIHSS score was negatively associated with chronic independence (per 1 point increase, OR 0.86, 95% CI 0.81–0.90, $p < 0.0001$) and positively associated with unfavorable outcome (per 1 point increase, OR 1.16, 95% CI 1.07–1.19, $p < 0.0001$). After adjustment for $CHADS_2$ score and initial NIHSS score, female sex tended to be negatively related to chronic independence (OR 0.56, 95% CI 0.30–1.06, $p = 0.077$) and were not associated with unfavorable outcome (OR 1.28, 95% CI 0.67–2.44, $p = 0.456$).

Associations among each component of the $CHADS_2$ score are shown in Table 3. Advanced age was related to other $CHADS_2$ components apart from diabetes. Clinical outcomes of patients with and without each $CHADS_2$ component are shown in Table 4. Congestive heart failure, hypertension, and prior stroke were not related to any clinical outcomes. Advanced age was related to unfavorable outcome (mRS ≥ 5) at 3 months ($p = 0.002$), and diabetes was inversely related to chronic independence (mRS ≤ 2) at 3 months ($p = 0.029$).

4. Discussion

This study showed significant associations between $CHADS_2$ score and clinical outcomes following IV rt-PA therapy in acute stroke patients with AF. The major findings of this study were as follows. First, $CHADS_2$ score tended to be positively related to cardiovascular events within 3 months. The rate of cardiovascular events at 3 months after onset was more than 5% in patients with a $CHADS_2$ score of 2 or more. Second, the proportion of independent patients at 3 months decreased significantly as $CHADS_2$ score increased. $CHADS_2$ score was inversely related to independence (mRS ≤ 2) and positively related to unfavorable outcome (mRS ≥ 5) at 3 months.

Several established risk factors for stroke, including advanced age, high systolic blood pressure, hyperglycemia on admission, and diabetes

Table 3
Baseline characteristics of patients with and without each component of $CHADS_2$ score.

	Congestive heart failure		Hypertension		Age ≥ 75 years		Diabetes		Prior stroke	
	Y (n=23)	N (n=195)	Y (n=138)	N (n=80)	Y (n=116)	N (n=102)	Y (n=35)	N (n=183)	Y (n=35)	N (n=183)
Age	79.6 ± 9.7 *	74.4 ± 10.0	74.7 ± 10.3	73.2 ± 8.3	81.1 ± 4.7 §	66.3 ± 7.5	72.1 ± 13.1	74.6 ± 8.8	77.6 ± 7.8 ‡	73.5 ± 9.8
Male	12 (47.8)	114 (58.5)	80 (58.0)	46 (57.5)	52 (44.8) §	74 (72.6)	22 (62.9)	104 (56.8)	20 (57.1)	106 (57.9)
Congestive heart failure			16 (11.6)	7 (8.8)	19 (16.4) ‡	4 (3.9)	4 (11.4)	19 (10.4)	3 (8.6)	20 (10.9)
Hypertension	16 (69.6)	122 (62.6)			81 (69.8) *	57 (55.9)	26 (74.3)	112 (61.2)	25 (71.4)	113 (61.8)
Age ≥ 75 years	19 (82.6) ‡	97 (49.7)	81 (58.7) *	35 (43.8)			16 (45.7)	100 (54.6)	24 (68.6) *	92 (50.3)
Diabetes	4 (17.4)	31 (15.9)	26 (18.8)	9 (11.3)	16 (13.8)	19 (18.6)			7 (20.0)	28 (15.3)
Prior stroke	3 (13.0)	32 (16.4)	25 (18.1)	10 (12.5)	24 (20.7) *	11 (10.8)	7 (20.0)	28 (15.3)		
Initial NIHSS	20 (14–25) †	14 (9–19)	15 (10–20)	15 (9–20)	16 (11–21) *	14 (8–18.25)	10 (7–16) ‡	16 (11–20)	15 (11–21)	15 (9–20)

NIHSS: National Institutes of Health Stroke Scale.
* $p < 0.05$, † $p < 0.01$, ‡ $p < 0.005$, § $p < 0.001$.

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Table 4
Clinical outcomes of patients with and without each component of $CHADS_2$ score.

	Congestive heart failure		Hypertension		Age ≥ 75 years		Diabetes		Prior stroke	
	Y/N (n = 23/195)	OR* (95% CI)	Y/N (n = 138/80)	OR* (95% CI)	Y/N (n = 116/102)	OR* (95% CI)	Y/N (n = 35/183)	OR* (95% CI)	Y/N (n = 35/183)	OR* (95% CI)
Intracerebral hemorrhage (ICH)	6/58	0.69 (0.23–1.85)	46/18	1.70 (0.90–3.30)	36/28	1.30 (0.68–2.50)	12/52	1.35 (0.59–2.96)	8/56	0.59 (0.23–1.35)
Cardiovascular events within 3 months	3/5	4.18 (0.72–21.25)	7/1	3.59 (0.60–68.68)	6/2	2.28 (0.40–18.19)	2/6	1.98 (0.26–10.83)	1/7	0.65 (0.03–4.15)
mRS ≤ 2 at 3 months	3/82	0.30 (0.06–1.10)	47/38	0.58 (0.29–1.13)	36/49	0.75 (0.38–1.49)	11/74	0.37 (0.14–0.88)†	13/72	1.24 (0.52–2.30)
mRS ≥ 5 at 3 months	14/52	2.37 (0.86–6.67)	47/19	1.49 (0.74–3.09)	50/16	3.13 (1.53–6.65)†	11/55	1.84 (0.74–4.48)	12/54	1.02 (0.43–2.34)

mRS: modified Rankin Scale.
*Adjusted by sex, initial National Institutes of Health Stroke Scale (NIHSS) and other $CHADS_2$ components.
† $p < 0.05$.
Symptomatic ICH was omitted from the analysis because of the small number of patients.

are also known to be predictive of neurological deterioration and poor vital and functional outcome in acute stroke. [17,18] Thus, a cumulative assessment of the risk factors could be a better predictor for stroke outcome than individual factors. Some components of the $CHADS_2$ score that were reported to be definite or potential outcome predictors following acute ischemic stroke [13,19–28] were not related to any outcomes after IV rt-PA therapy in the present patients, probably due to the small sample size. However, $CHADS_2$ score itself had a strong association with both favorable and unfavorable outcomes.

$CHADS_2$ score was originally associated with risk for embolic events, and tended to be related to cardiovascular events involving stroke recurrence within 3 months in the present patients. Thus, these cardiovascular complications appeared to have some effect on mRS at 3 months. The initial neurological severity was similar among patients with different $CHADS_2$ scores, and therefore does not seem to explain the poor outcome in patients with high $CHADS_2$ score. Since advanced age and diabetes are associated with pneumonia and other febrile diseases during acute stroke, [29,30] such complications in patients with high $CHADS_2$ score may affect outcomes at 3 months.

Frequency of major hemorrhage is high in AF patients on anticoagulation with $CHADS_2$ score of >1 or >2. [3,5] However, this study did not show significant increases in ICH associated with higher $CHADS_2$ scores after rt-PA therapy. Thus, early ICH after rt-PA also does not explain the poor outcome in patients with high $CHADS_2$ scores. Patients with PT-INR ≥ 1.7 were not included according to the guideline, [12] and this might explain the present lack of association between $CHADS_2$ score and ICH, which contrasts with findings from previous reports. In addition, exclusion of patients with an initial blood pressure of >185/110 mmHg and strict blood pressure management during the initial days according to the guidelines might also decrease ICH risk and mask the contribution of $CHADS_2$ score to ICH.

The present study has some limitations which need to be discussed. First, this was a retrospective observational study with a relatively small population, which might affect the statistical findings. Second, the last component of $CHADS_2$ score was originally "prior stroke and transient ischemic attack"; however, our data on prior transient ischemic attack were incomplete, and accordingly $CHADS_2$ score in some patients might have been underestimated. Third, each component of $CHADS_2$ influenced the selection of eligible patients for rt-PA therapy; e.g., patients with advanced age and those with severe hypertension were not recognized as appropriate candidates for treatment. Thus, there were fewer patients with high $CHADS_2$ score than low $CHADS_2$ score. Although patients >80 years old and those with diabetes concomitant with prior stroke are not recommended to receive rt-PA in European countries, [31] they are eligible in the Japanese guideline. [12]

The present study indicates that risk stratification for AF patients using the $CHADS_2$ scheme is a useful predictor not only for risk of ischemic stroke but also for chronic independence following IV rt-PA therapy, regardless of anticoagulation status. Careful observation and preventive therapy for early clinical deterioration and complications may be required in such patients during the acute to subacute stage of stroke. However, the efficacy of acute intensive management of treatable $CHADS_2$ components, including acute blood pressure lowering and blood glucose normalization, for improvement of stroke outcome remains to be determined.

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Conflict of interest/disclosures

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原　著

rt-PA 静注療法施行症例におけるスタチンの頭蓋内出血および転帰におよぼす影響

—Stroke Acute Management with Urgent Risk-factor Assessment and Improvement (SAMURAI) rt-PA Registry—

牧原　典子[1)*]　岡田　靖[1)]　古賀　政利[2)]　塩川　芳昭[3)]　中川原譲二[4)]
古井　英介[5)]　木村　和美[6)]　山上　宏[7)]　長谷川泰弘[8)]　苅尾　七臣[9)]
奥田　聡[10)]　永沼　雅基[2)]　豊田　一則[2)]

要旨：目的：スタチンの発症前ないし急性期服用が，脳梗塞患者における rt-PA 静注療法後の頭蓋内出血や転帰に与える影響について検討した．方法：SAMURAI rt-PA Registry 参加 10 施設で，rt-PA 静注療法を受けた脳梗塞患者連続 600 例を対象に後ろ向きに調査した．結果：発症前に 67 例（11.2%）が，急性期に 60 例（10.0%）がスタチンを服用した．頭蓋内出血を 119 例（19.8%）に合併し，スタチンの発症前服用との関連はみられなかった（OR 1.46；95%CI 0.76〜2.81）．3 カ月後の完全自立患者（mRS≦1）は 199 例（発症前 mRS≦1 の 535 例中 37.2%）で，スタチンの発症前・急性期服用との関連はみられなかった（OR 1.05；95%CI 0.55〜2.01），（OR 1.31；95%CI 0.66〜2.59）．結論：rt-PA 静注療法施行症例でスタチンによる頭蓋内出血や転帰への影響はみとめられなかった．（臨床神経 2010;50:225-231）

Key words：脳梗塞，血栓溶解療法，スタチン，脂質異常症，頭蓋内出血

はじめに

急性期脳梗塞に対して 2005 年に遺伝子組み換え組織型プラスミノゲン・アクティベータ（recombinant tissue plasminogen activator：rt-PA）静注療法が適応認可され，神経症候の劇的な改善をもたらしうる治療として，現在，多くの症例に使用されている．血圧や抗血栓薬の使用については，適正使用指針で厳格な基準が示されているが，脳保護薬やスタチンなどその他の併用薬の使用状況やそれらが与える影響については明らかでない．

スタチンについては，脳卒中の再発予防への有用性[1)2)]や転帰改善効果[3)〜5)]が，多くの研究によって示され，その多面的作用に注目が集まっている．血栓溶解療法への影響についての報告も近年散見され，Álvarez-Sabin らは，rt-PA による血栓溶解療法が施行された中大脳動脈領域の脳梗塞症例について発症前のスタチン服用が 3 カ月後の良好な転帰に関連する因子であったと報告した[6)]．

しかし，その一方で，スタチンや LDL コレステロール（LDL-C）の低値が頭蓋内出血を増加させることも懸念されている．血栓溶解療法において，頭蓋内出血はとくに転帰に影響する重要な合併症であり，本研究では，rt-PA 静注療法施行症例について，スタチンの服用が頭蓋内出血および転帰に与える影響について検討した．

*Corresponding author: 国立病院機構九州医療センター脳血管内科脳血管センター臨床研究センター〔〒810-8563　福岡市中央区地行浜 1—8—1〕
[1)]国立病院機構九州医療センター脳血管内科脳血管センター臨床研究センター
[2)]国立循環器病センター内科脳血管部門
[3)]杏林大学脳神経外科
[4)]中村記念病院脳神経外科
[5)]広南病院脳血管内科
[6)]川崎医科大学脳卒中医学
[7)]神戸市立医療センター中央市民病院脳卒中センター
[8)]聖マリアンナ医科大学神経内科
[9)]自治医科大学循環器内科
[10)]国立病院機構名古屋医療センター神経内科
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対象と方法

「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」班（Stroke Acute Management with Urgent Risk-factor Assessment and Improvement [SAMURAI] Study Investigators）に参加する10施設で，2005年10月から2008年7月までにrt-PA静注療法を施行された脳梗塞連続症例を対象に後ろ向き調査をおこなった．この調査の全体成績は，すでに別報で報告されている[7]．本研究では，登録患者の発症前のスタチン服用の有無とrt-PA投与後72時間以内のスタチン服用の有無をしらべ，それぞれを発症前服用群/非服用群，急性期服用群/非服用群とし，使用頻度や臨床的特徴について調査した．

臨床的特徴として，年齢，性別，病型，合併症（高血圧，糖尿病，脂質異常症，虚血性心疾患，脳梗塞の既往），発症前投薬（抗凝固薬や抗血小板薬などの抗血栓薬，降圧薬，経口糖尿病薬またはインスリン），入院時重症度（National Institutes of Health Stroke Scale：NIHSS），投与前血圧，検査所見（随時血糖，HbA1c，総コレステロール[T-Chol]，中性脂肪，HDLコレステロール[HDL-C]，LDL-C），CT所見について検討をおこなった．CT所見については，ASPECTS（Alberta Stroke Programme Early CT Score）[8]にて評価し，7点以下と8点以上の2群に分けて検討した．

頭蓋内出血・症候性頭蓋内出血の有無について，rt-PA投与後36時間以内にCTまたはMRI（T_2*）にて評価し，発症前のスタチン服用および脂質値との関連を検討した．なお，症候性頭蓋内出血については，Cochrane/NINDS基準に基づいて，NIHSS1点以上の神経症候の悪化をともなうものとした[7)9)]．

また，3カ月後のmRS（modified Rankin Scale）が1以下を転帰良好群，2以上を転帰不良群とし，発症前およびrt-PA投与後72時間以内のスタチン服用との関連を検討し，また脂質値との関連についてもしらべた．なお，転帰の検討においては，発症前mRS2以上の症例を除外した．

統計解析については，統計解析ソフト（SPSS Statistics 17.0）を使用し，$\chi 2$検定，t検定およびMann-Whitney U検定をもちいて比較，$p<0.05$を有意差ありとした．多変量解析では，スタチンの関与について，頭蓋内出血の合併および3カ月後の転帰良好を従属変数として，年齢・性別を調整，その他の因子を変数減少法（尤度比検定法で$p>0.10$となる変数を除外）によるロジスティック回帰分析にて調整をおこなった．

結　果

対象症例は600例で，年齢72±12歳，女性223例（37.2%），発症前のスタチン服用群は67例（11.2%）であった（Table 1）．発症前服用群/非服用群間で，年齢，性別，病型分布（Fig. 1-a），入院時NIHSSに差はみられなかった．発症前服用群では，非服用群と比較して，高血圧（79.1% vs. 58.7%，$p=0.001$），糖尿病（32.8% vs. 16.5%，$p=0.001$），脂質異常症（70.1% vs. 14.6%，$p<0.001$），虚血性心疾患（35.8% vs. 9.9%，$p<0.001$）を合併していることが多く，発症前に抗血栓薬（64.2% vs. 34.1%，$p<0.001$），降圧薬（74.6% vs. 40.3%，$p<0.001$）を服用している例や，経口糖尿病薬あるいはインスリンでの糖尿病薬物治療（20.9% vs. 7.1%，$p<0.001$）を受けている例も有意に多かったが，脳梗塞の既往については，両群間に差はみとめなかった（22.4% vs. 17.6%，$p=0.342$）．検査所見では，服用群でHbA1cが高く（中央値：5.7% vs. 5.4%，$p=0.005$），LDL-C（106±31mg/dl vs. 115±34mg/dl，$p=0.050$）が低かったが，T-Chol（183±33mg/dl vs. 190±41mg/dl，$p=0.238$）や中性脂肪（129±99mg/dl vs. 114±74mg/dl，$p=0.137$），HDL-C（50±14mg/dl vs. 52±15mg/dl，$p=0.284$）には差はみとめなかった．

急性期のスタチン服用群は60例（10.0%）で，発症前からの継続症例は21例であった（Table 1）．急性期服用群/非服用群間では，発症前服用と同じく，年齢，性別に差はなかったが，病型分布（Fig. 1-b）では，非服用群とくらべて，服用群で心原性脳塞栓症が少なく（43.3% vs. 65.6%，$p=0.001$），入院時NIHSSは有意に低い結果であった（中央値：10点 vs. 13点，$p=0.003$）．合併症では，発症前服用と同様に，高血圧（73.3% vs. 59.6%，$p=0.039$），糖尿病（36.7% vs. 16.3%，$p<0.001$），脂質異常症（46.7% vs. 18.0%，$p<0.001$），虚血性心疾患（21.7% vs. 11.9%，$p=0.031$）の合併例が急性期服用群で有意に多く，加えて脳梗塞の既往がある症例（30.0% vs. 16.9%，$p=0.012$）も多かった．検査所見では，HbA1c（中央値：5.8% vs. 5.4%，$p<0.001$），T-Chol（204±40mg/dl vs. 187±40mg/dl，$p=0.003$），中性脂肪（150±87mg/dl vs. 112±75mg/dl，$p<0.001$），LDL-C（128±35mg/dl vs. 112±33mg/dl，$p=0.001$）が有意に高かった．

対象症例600例中，119例（19.8%）に頭蓋内出血がみとめられ，23例（3.8%）が症候性であった（Table 2）．頭蓋内出血合併例で，発症前のスタチン服用例が多い傾向にあったが（16.0% vs. 10.0%，$p=0.063$），脂質値との関連はみられなかった．年齢・性別，その他の因子を調整した多変量解析の結果では，発症前のスタチン服用は頭蓋内出血に関連する独立因子とはならなかった（OR 1.46；95%CI 0.76～2.81，$p=0.225$）（Table 3）．また，症候性頭蓋内出血においても関連はみられなかった（OR 1.27；95%CI 0.33～4.81，$p=0.728$）．

3カ月後の転帰に関しては，発症前のmRSが1以下であった535例について検討をおこなった．転帰良好群は199例（37.2%）で，発症前のスタチン服用との関連はみとめなかったが，急性期のスタチン服用例が転帰良好群で多い傾向があった（13.6% vs. 8.6%，$p=0.071$）（Table 2）．また，転帰不良群と比較して，転帰良好群は，年齢（67±13歳 vs. 73±10歳，$p<0.001$），入院時NIHSSが低く（中央値：9点 vs. 15点，$p<0.001$），高血圧の合併（51.8% vs. 65.8%，$p=0.001$）が少なかった．検査所見では，有意に血糖が低く（132±46mg/dl vs. 141±47mg/dl，$p=0.033$），HDL-Cが高く（54±15mg/dl vs. 51±14mg/dl，$p=0.023$），ASPECTS7点以下の症例が