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

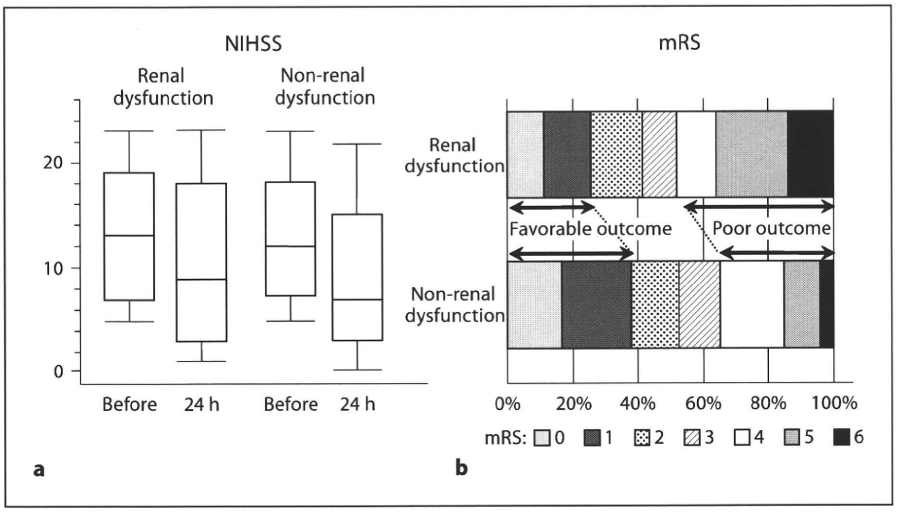

Fig. 1. Neurological deficits and outcome of patients with and without renal dysfunction. NIHSS score just before and 24 h after IV rt-PA therapy (**a**) and mRS score at 3 months (**b**) in patients with and without renal dysfunction. **a** Horizontal lines in boxes = Median NIHSS score; boxes = IQR;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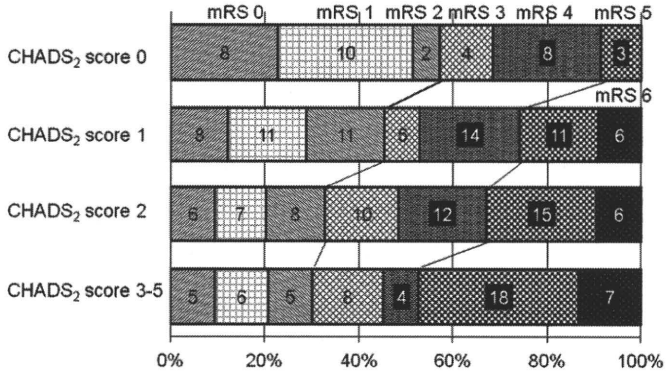

Fig. 1. $CHADS_2$ score and modified Rankin Scale at 3 months after stroke onset. The percentage of patients with mRS ≤2 gradually decreased as $CHADS_2$ score increased. In contrast, that of patients with mRS ≥5 gradually increased as $CHADS_2$ score increased.

$CHADS_2$ 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/d*l* vs. 115±34mg/d*l*，$p=0.050$）が低かったが，T-Chol（183±33mg/d*l* vs. 190±41mg/d*l*，$p=0.238$）や中性脂肪（129±99mg/d*l* vs. 114±74mg/d*l*，$p=0.137$），HDL-C（50±14mg/d*l* vs. 52±15mg/d*l*，$p=0.284$）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/d*l* vs. 187±40mg/d*l*，$p=0.003$），中性脂肪（150±87mg/d*l* vs. 112±75mg/d*l*，$p<0.001$），LDL-C（128±35mg/d*l* vs. 112±33mg/d*l*，$p=0.001$）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/d*l* vs. 141±47mg/d*l*，$p=0.033$），HDL-Cが高く（54±15mg/d*l* vs. 51±14mg/d*l*，$p=0.023$），ASPECTS7点以下の症例が

Table 1 Clinical characteristics.

	Pre-stroke statin use			Post-stroke statin use		
	User (N=67)	Non-user (N=533)	p value	User (N=60)	Non-user (N=540)	p value
Age (years)	72±9	72±12	0.730	69±11	72±12	0.105
Women	23 (34.3%)	200 (37.5%)	0.610	22 (36.7%)	201 (37.2%)	0.933
Hypertension	53 (79.1%)	313 (58.7%)	0.001	44 (73.3%)	322 (59.6%)	0.039
Diabetes mellitus	22 (32.8%)	88 (16.5%)	0.001	22 (36.7%)	88 (16.3%)	<0.001
Dyslipidemia	47 (70.1%)	78 (14.6%)	<0.001	28 (46.7%)	97 (18.0%)	<0.001
Coronary artery disease	24 (35.8%)	53 (9.9%)	<0.001	13 (21.7%)	64 (11.9%)	0.031
Previous ischemic stroke	15 (22.4%)	94 (17.6%)	0.342	18 (30.0%)	91 (16.9%)	0.012
Pre-stroke medications						
Antithrombotics	43 (64.2%)	182 (34.1%)	<0.001	27 (45.0%)	198 (36.7%)	0.206
Antihypertensives	50 (74.6%)	215 (40.3%)	<0.001	31 (51.7%)	234 (43.3%)	0.218
Antidiabetics/insulin	14 (20.9%)	38 (7.1%)	<0.001	9 (15.0%)	43 (8.0%)	0.066
Edaravone	52 (77.6%)	450 (84.4%)	0.155	58 (96.7%)	444 (82.2%)	0.004
Baseline NIHSS *	12 (7-18)	13 (8-19)	0.414	10 (6-15)	13 (8-19)	0.003
Findings on admission						
sBP (mmHg)	150±22	150±20	0.762	153±20	150±20	0.262
dBP (mmHg)	80±16	82±15	0.455	82±16	81±15	0.879
Blood glucose (mg/dl)	135±43	137±48	0.764	145±59	136±46	0.151
HbA1c (%) *	5.7 (5.3-6.5)	5.4 (5.2-5.8)	0.005	5.8 (5.3-6.6)	5.4 (5.1-5.8)	<0.001
T-Chol (mg/dl)	183±33	190±41	0.238	204±40	187±40	0.003
Triglyceride (mg/dl)	129±99	114±74	0.137	150±87	112±75	<0.001
HDL-C (mg/dl)	50±14	52±15	0.284	50±14	52±15	0.275
LDL-C (mg/dl)	106±31	115±34	0.050	128±35	112±33	<0.001
ASPECTS ≤ 7 **	11 (18.0%)	86 (19.5%)	0.779	6 (12.0%)	91 (20.2%)	0.165

* Median (interquartile range)

** 501 patients whose ASPECTS were available were included, including 61 pre-stroke statin users and 50 post-stroke statin users.

NIHSS = National Institutes of Health Stroke Scale, sBP = systolic blood pressure, dBP = diastolic blood pressure, T-Chol = total cholesterol, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, ASPECTS = Alberta Stroke Programme Early CT Score.

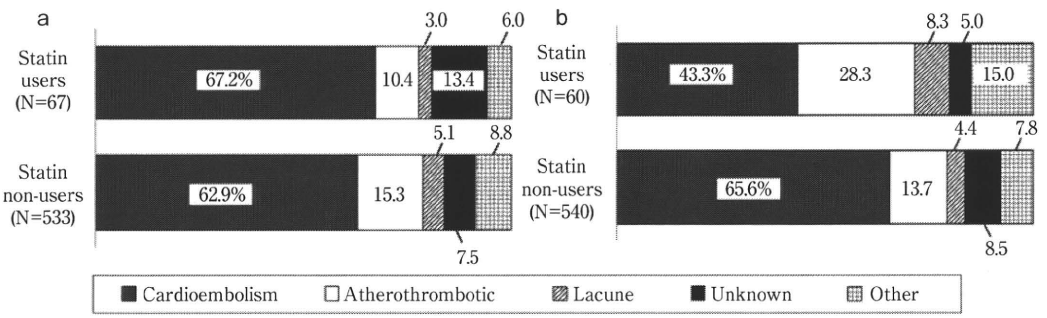

Fig. 1 Ischemic stroke subtype by pre- and post-stroke statin use.

a. Pre-stroke statin use.

There was no difference in ischemic stroke subtype between pre-stroke statin users and non-users (p=0.293).

b. Post-stroke statin use.

Cardioembolism was less common in statin users within 72 h after IV rt-PA than in non-users (p=0.001).

少なかった（11.3%vs. 23.2%，p=0.002）．年齢・性別，その他の因子を調整した多変量解析では，発症前および急性期のスタチン服用ともに転帰に関連する独立因子とはならなかったが（OR 1.05；95%CI 0.55～2.01, p=0.879），（OR 1.31；95%

Table 2 Predictors of intracranial hemorrhage and clinical outcome at 3 months (univariate analysis).

	ICH			Symptomatic ICH			Clinical outcome at 3 months		
	Presence (N=119)	Absence (N=481)	p value	Presence (N=23)	Absence (N=577)	p value	mRS ≤ 1 (N=199)	mRS ≥ 2 (N=336)	p value
Age (years)	72±10	72±12	0.579	72±8	72±12	0.961	67±13	73±10	<0.001
Women	42 (35.3%)	181 (37.6%)	0.637	6 (26.1%)	217 (37.6%)	0.262	61 (30.7%)	125 (37.2%)	0.121
Cardioembolism	88 (73.9%)	292 (60.7%)	0.007	17 (73.9%)	363 (62.9%)	0.283	115 (57.8%)	216 (64.3%)	0.135
Pre-stroke statins	19 (16.0%)	48 (10.0%)	0.063	5 (21.7%)	62 (10.7%)	0.164	23 (11.6%)	40 (11.9%)	0.904
Post-stroke statins							27 (13.6%)	29 (8.6%)	0.071
Baseline NIHSS *	16 (9-20)	12 (7-18)	0.005	15 (7-20)	13 (7.5-19)	0.465	9 (6-14)	15 (9-20)	<0.001
Findings on admission									
Blood glucose (mg/dl)	143±48	136±47	0.124	152±58	136±47	0.134	132±46	141±47	0.033
T-Chol (mg/dl)	187±38	189±40	0.683	188±44	189±40	0.923	190±38	189±42	0.821
Triglyceride (mg/dl)	115±99	116±71	0.928	131±164	115±72	0.645	124±86	113±73	0.128
HDL-C (mg/dl)	51±13	52±15	0.807	52±14	52±15	0.886	54±15	51±14	0.023
LDL-C (mg/dl)	111±32	115±34	0.269	112±42	114±34	0.813	112±33	115±35	0.367

* Median (interquartile range)

ICH = intracranial hemorrhage, NIHSS = National Institutes of Health Stroke Scale, T-Chol = total cholesterol, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol.

Table 3 Effects of pre-stroke statin use on intracranial hemorrhage (multivariate analysis).

		OR (95%CI)	p value
(Unadjusted)	Pre-stroke statins	1.71 (0.97-3.04)	0.063
(Adjusted) *	Pre-stroke statins	1.46 (0.76-2.81)	0.225
	Age (per 10 years increased)	1.00 (0.80-1.26)	0.998
	Women	0.69 (0.41-1.17)	0.167
	Cardioembolism	2.04 (1.19-3.51)	0.009
	Baseline NIHSS (per 1 point increased)	1.03 (0.99-1.07)	0.078
	Blood glucose (per 10 mg/dl increased)	1.05 (1.00-1.09)	0.046

* Adjustment for age, sex and the other factors chosen by a backward selection procedure using p>0.10 on the likelihood ratio test for exclusion.

OR = odds ratio, 95%CI = 95% confidence interval, NIHSS = National Institutes of Health Stroke Scale.

CI 0.66～2.59, p＝0.440)，脂質に関連する因子の中で高 HDL-C が転帰良好に関連した（OR 1.20；95%CI 1.01～1.42, p＝0.035)（Table 4)．

考　察

本研究は，rt-PA 静注療法を施行された急性期脳梗塞患者を対象に，スタチンが治療後の頭蓋内出血や転帰におよぼす影響を検討した，後ろ向き観察研究である．単変量解析の結果，発症前のスタチン服用が治療後の頭蓋内出血を増加，急性期のスタチン服用が3カ月後の転帰を改善する傾向がみられたが，年齢・性別，その他の因子を調整した多変量解析ではいずれも有意な関連はみられなかった．

血栓溶解療法を施行された急性期脳梗塞患者に対する発症前のスタチン服用の影響についてしらべた近年の研究では，スタチン服用の割合は 17.7～25% と報告されている[6)9)10)]．本研究では 11.2% とやや少なく，これは本研究で，心原性脳塞栓症の割合が多いという病型分布の違いや，人種の違いなどが原因と考えられた．これまでの研究と同様に，本研究でも発症前にスタチンを服用している症例は，脂質異常症，虚血性心疾患のほかに高血圧や糖尿病といった複数の動脈硬化因子を合併しており，ハイリスク症例が多いことがわかった．また，急性期にスタチンの投与を受ける症例では，これらに加えて，脳梗塞再発例が多く，とくにアテローム血栓性脳梗塞やラクナ梗塞で，抗血栓薬以外の治療薬としてスタチンが認識，選択されていることが示唆された．

血栓溶解療法（経動脈性をふくむ）と頭蓋内出血の関連についての検討では，低 LDL-C[9)]が症候性頭蓋内出血の危険因子（OR 0.968；95%CI 0.941～0.955)，発症前のスタチン服用[10)]が頭蓋内出血の危険因子（OR 3.1；95%CI 1.53～6.39）との報告がある．しかし，rt-PA 静注療法症例を対象とした検討[6)]では，スタチンや脂質値と頭蓋内出血との有意な関連はみられなかった．ただし LDL-C85mg/dl 未満の割合（Bang ら[9)]33%，本研究 18%）や，スタチン服用群の高血圧合併率（Meier

Table 4 Effects of pre- and post-stroke statin use on clinical outcome at 3 months (multivariate analysis).

		OR (95%CI)	p value
(Unadjusted)	Pre-stroke statins	0.97 (0.56-1.67)	0.904
	Post-stroke statins	1.66 (0.95-2.90)	0.071
(Adjusted) *			
Model 1	Pre-stroke statins	1.05 (0.55-2.01)	0.879
	Age (per 10 years increased)	0.74 (0.60-0.91)	0.005
	Women	0.77 (0.47-1.27)	0.308
	Cardioembolism	1.53 (0.95-2.46)	0.078
	Baseline NIHSS (per 1 point increased)	0.91 (0.87-0.94)	<0.001
	Blood glucose (per 10 mg/dl increased)	0.95 (0.91-1.00)	0.070
	HDL-C (per 10 mg/dl increased)	1.20 (1.01-1.42)	0.035
	ASPECTS ≤ 7	0.59 (0.31-1.10)	0.096
Model 2	Post-stroke statins	1.31 (0.66-2.59)	0.440

Model 1) A logistic regression model was performed including pre-stroke statins.
Model 2) A logistic regression model was performed including post-stroke statins. Independent predictors identified by a backward selection procedure were the same as in model 1.
* Adjustment for age, sex and the other factors chosen by a backward selection procedure using p>0.10 on the likelihood ratio test for exclusion.
OR = odds ratio, 95%CI = 95% confidence interval, NIHSS = National Institutes of Health Stroke Scale, HDL-C = high-density lipoprotein cholesterol, ASPECTS = Alberta Stroke Programme Early CT Score.

ら[10]92.6%，Álvarez-Sabin ら[6]69.2%，本研究 79.1%）などの背景因子や治療法がそれぞれの研究でことなっていることから単純な比較はできない．

スタチンは出血性梗塞と相関する MMP-9（matrix metalloproteinase-9）の活性化を抑制することが動物実験で報告されている[11][12]．MMP-9 は，脳虚血によって活性が上昇し，血管内皮細胞を傷害して血液脳関門の破綻をひきおこすと考えられる．rt-PA の投与によってさらに MMP-9 活性が増強され，出血性変化が助長されるが，スタチンはこれを抑制することで，出血性梗塞に保護的に作用する可能性がある．一方で，スタチンは内因性 t-PA を上昇させ，PAI-1（plasminogen activator inhibitor-1）を抑制して抗凝固作用を示すことが報告されている[13]．観察研究では，スタチンが血栓溶解療法後の再開通率を上昇させるとの報告があり[14]，閉塞血管の再開通は，時期によっては頭蓋内出血の危険因子となる[15]．スタチンは頭蓋内出血に対して保護する作用，助長する作用の両面をもつ可能性があり，再開通の有無や時期などとの関連もふくめた検討が望まれる．

また，スタチンが脳梗塞の転帰を改善することは，多くの臨床研究で示されている[3]~[5]．実験的には，スタチンの投与によって，梗塞巣が縮小，脳血流量が増加し，神経症候が改善することが観察されており，eNOS（endothelial nitric oxide synthase）の発現増強を介した血管新生や神経形成の促進作用によるものと考えられている[16][17]．rt-PA 静注療法症例においても，スタチンは 3 カ月後の転帰を改善することが報告され[6]，多面的作用の効果が期待されたが，本研究では，発症前のスタチン服用と 3 カ月後の転帰に明らかな関連はみとめられなかった．急性期のスタチン服用においては，単変量解析で良好な転帰と関連する傾向がみられたが，多変量解析の結果，独立因子とはならず，急性期のスタチンが非心原性脳梗塞やより軽症例に多くもちいられていることが交絡因子であったと考えられた．また，発症前からのスタチン継続例（31%）が少ない点も，転帰との関連に影響を与えた可能性がある．本研究ではスタチン継続の有無については，症例数が少ないため検討をおこなっていないが，脳梗塞発症当日からのスタチン継続による転帰への好影響も報告されている[18]．

本研究の限界として，スタチン服用群と非服用群間で背景因子に差がある点が挙げられる．これについては多変量解析をおこなって他の因子の調整を試みたが，背景因子の偏りが結果に影響した可能性は否定できない．また，スタチン服用者の割合が少なく，統計学的検討に症例数が十分でない点やスタチンの種類の詳細についての情報がない点も本研究の限界であり，今後，スタチンの種類や継続もふくめ，大規模な前向き研究での更なる検討が期待される．

今回の多変量解析では，頭蓋内出血において心原性脳塞栓症と血糖が，転帰において年齢，入院時 NIHSS，HDL-C が関連因子となった．他の因子については，SAMURAI rt-PA Registry の全体成績ですでに報告されている[7]．今回脂質値を検討に加えた結果，HDL-C が転帰良好の規定因子となった点が，興味深い．Newman らは，脳梗塞患者一般において，HDL-C の低値が転帰不良と関連すると報告した[19]．今回の対象症例における治療成績と脂質諸値の関連については，別の論文で詳述する予定である．

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Abstract

Effects of statin use on intracranial hemorrhage and clinical outcome after intravenous rt-PA for acute ischemic stroke: SAMURAI rt-PA Registry

Noriko Makihara, M.D.[1], Yasushi Okada, M.D.[1], Masatoshi Koga, M.D.[2], Yoshiaki Shiokawa, M.D.[3], Jyoji Nakagawara, M.D.[4], Eisuke Furui, M.D.[5], Kazumi Kimura, M.D.[6], Hiroshi Yamagami, M.D.[7], Yasuhiro Hasegawa, M.D.[8], Kazuomi Kario, M.D.[9], Satoshi Okuda, M.D.[10], Masaki Naganuma, M.D.[2] and Kazunori Toyoda, M.D.[2]

[1]Department of Cerebrovascular Disease, Cerebrovascular Center and Clinical Research Center, National Hospital Organization Kyushu Medical Center
[2]Cerebrovascular Division, Department of Medicine, National Cardiovascular Center
[3]Department of Neurosurgery and Stroke Center, Kyorin University School of Medicine
[4]Department of Neurosurgery and Stroke Center, Nakamura Memorial Hospital
[5]Department of Stroke Neurology, Kohnan Hospital
[6]Department of Stroke Medicine, Kawasaki Medical School
[7]Department of Neurology, Stroke Center, Kobe City General Hospital
[8]Department of Neurology, St. Marianna University School of Medicine
[9]Division of Cardiovascular Medicine, Department of Medicine, Jichi Medical University School of Medicine
[10]Department of Neurology, National Hospital Organization Nagoya Medical Center

Purpose: We evaluated whether pre- and post-stroke statin use was associated with intracranial hemorrhage (ICH) and clinical outcome at 3 months after intravenous recombinant tissue plasminogen activator (IV rt-PA) for acute ischemic stroke.

Methods: This study enrolled 600 consecutive patients (72 ± 12 years, woman 37.2%) who received IV rt-PA at ten stroke centers that participated in the SAMURAI rt-PA Registry from October 2005 to July 2008.

Results: Statins were used prior to stroke in 11.2% and within 72 h after IV rt-PA in 10.0% of patients. One hundred nineteen patients (19.8%) developed ICH. Pre-stroke statin use was not an independent factor associated with ICH (OR 1.46; 95%CI 0.76-2.81, p = 0.225). Of 535 patients with a premorbid mRS≤1, 199 (37.2%) had a favorable clinical outcome at 3 months (mRS≤1). Pre-stroke statin use (OR 1.05; 95%CI 0.55-2.01, p = 0.879), as well as post-stroke statin use (OR 1.31; 95%CI 0.66-2.59, p = 0.440), was not an independent predictor of outcome.

Conclusions: In patients who received IV rt-PA for acute ischemic stroke, statin use did not increase ICH after thrombolysis, nor was it associated with clinical outcome.

(Clin Neurol 2010;50:225-231)

Key words: brain infarction, thrombolysis, statin, dyslipidemia, intracranial hemorrhage

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

主任研究者　豊田　一則　　国立循環器病研究センター　脳血管内科　部長

「多施設共同研究 2：超急性期脳出血への降圧療法に関する研究」

課題名

「急性期脳出血症例に対する降圧療法の安全性と有効性に関する多施設共同研究」

古賀政利　（国立循環器病研究センター　脳卒中集中治療科　医長）

A. 研究目的

わが国において脳卒中は死因の第 3 位、要介護疾患の首位である。とくに脳出血は脳卒中の 17%～30%を占め、発症率が欧米諸国の数倍高い。高血圧は脳出血の最も重要な原因であり、発症時の血圧高値は血腫拡大、症候増悪、転帰不良、死亡の重要な決定因子である。したがって、米国心臓協会・米国脳卒中協会のガイドラインでは、収縮期血圧（systolic blood pressure: SBP）180mmHg もしくは平均血圧 130mmHg を超える場合に降圧を考慮することが推奨されている（Class IIb, Level of Evidence C）が、どの程度まで降圧するかの具体的目標値は確立されていない（Morgenstern J, et al. Stroke. 2010）。

INTERACTパイロット研究では、SBP 140mmHgを目標とした積極的な降圧療法が、血腫拡大を抑制することが報告された（Anderson CS, et al. Lancet Neurol. 2008）。米国ATACH研究では、ニカルジピンの経静脈投与によりSBPの目標値を200-170, 170-140, 140-110 mmHgの3群に設定し、積極的な降圧の実行可能性と安全性が報告された（Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH) investigators. Crit Care Med 2010）。本年よりSBP降圧目標値を180-140, 140-110 mmHgの2群に分け、治療成績を比べる第Ⅲ相試験ATACH2が開始され、その主任研究者（A Qureshi教授, Minnesota大学）から厚生労働科学研究「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（H20－循環器等（生習）－一般－019、主任研究者 豊田一則、以下厚労H20-019班）に共同参加を呼びかけられ、本年からの参加に向けた準備中である。ATACH 2への参加は厚労H20-019班の研究目的に合致し、わが国における急性期脳出血症例への降圧指針を確立するために重要である

ATACH2参加の前段階として、厚労H20-019班では2008年に全国WEBアンケート調査を行った。国内施設の82%がSBP 140～160 mmHgないしそれ以下を降圧目標値に定め、降圧薬としてニカルジピン静注が第一選択の57%、第二選択まで含めると84%を占めた（Koga M, et al. Hypertens Res 2009）。ニカルジピンの位置づけは国内外で多少異なり、欧米で脳出血患者への代表的推奨薬である一方、わが国の添付文書（資料6ページ）では一部の脳出血患者（止血が完成していないと推定される患者、頭蓋内圧が亢進している患者）に使用が制限され、かつ制限対象患者の判断基準が曖昧である。また、渉猟し得た範囲で、わが国の添付文書での使用制限に理論的根拠はない。日本高血圧学会による高血圧治療ガイドライン2009では、この制限に言及しつつ、ニカルジピンの微量点滴静注を推奨している。国内外の指針の乖離を是正すべく、現在日本脳卒中学会・日本脳神経外科学会・日本高血圧学会の三学会合同で、厚生労働省に添付文書改訂の要望書を提出している。アンケートから示された降圧目標値や降圧薬の日本人への安全性と有効性を、前向き観察研究で確かめるべきであろう。ATACH 2への参加を念頭に置き、同試験の治療手段（薬剤量、投与速度など）が日本人に適しているかも、検証を要す。

本研究はATACH2を計画するためのパイロット研究である。本研究の目的は、全国WEB

アンケートで多数意見として示された急性期脳出血への降圧目標や降圧薬の妥当性、およびATACH2の降圧手段の日本人への安全性を証明することである。作業仮説は、「急性期脳出血症例に対して、ATACH2に準じたニカルジピンの持続静注で、国内施設の多くが定める降圧目標域に効率よく到達でき、ニカルジピンの副作用や血腫拡大などの出現を過去の報告から想定される範囲内に抑えて、安全に降圧治療を遂行できる」である。

B. 研究方法

研究デザイン：多施設共同前向き観察研究

対象：厚労H20-019班の研究参加10施設で症例登録期間内に入院する急性期脳出血200症例。

○選択基準

- ✓ 年齢 20 歳以上
- ✓ 天幕上脳出血
- ✓ Glasgow Coma Scale≧5
- ✓ 入院時に血圧を 5 分以上の間隔で 2 回測定して SBP＞180mmHg
- ✓ 発症 2.5 時間以内に頭部 CT で脳出血と診断
- ✓ 初回 CT で脳出血の血腫量≦60ml
- ✓ 発症 3 時間以内（CT 撮影後 30 分以内）にニカルジピン持続静注による降圧治療を開始

○除外基準

- ✓ 発症時刻不明
- ✓ 既知の脳腫瘍、動静脈奇形、動脈瘤
- ✓ 外傷による脳出血
- ✓ 天幕下出血（小脳出血と脳幹出血）
- ✓ 脳実質出血に伴う脳室内出血量が多い場合
- ✓ 脳外科手術対象と考えられる症例
- ✓ 妊娠、授乳中、30 日以内の出産
- ✓ 出血素因、凝固異常
- ✓ ワーファリン使用患者の場合、INR≧1.7
- ✓ 血小板数＜5 万/mm^3
- ✓ 本人もしくは家族等の代諾者から文書でのインフォームドコンセントが得られない場合
- ✓ 主治医もしくは担当医が不適当と判断した場合

【方法】

Stroke Care Unitなどの頻回のモニターが可能な病棟で、発症3時間以内にニカルジピン持続静脈投与で降圧を開始された症例を前向きに登録し、追跡する。目標SBPを120～160 mmHgに設定して24時間継続することが推奨される。24時間以降の降圧方法は、担当医の判断に任せる。

＜推奨される降圧手段＞

- ✓ シリンジポンプを用いたニカルジピン 5mg/h の持続静注で治療開始　（治療開始時のニカルジピン 1mg の急速投与可）
- ✓ 治療開始後の 2 時間は 15 分間隔で血圧測定
- ✓ 目標に達していない場合には 2.5mg/h ずつ増量　（最大 15mg/h）
- ✓ 目標域に達したらその時点のニカルジピン投与量を維持し、それ以降は目標 SBP 域を維持するように投与量を 1～2.5mg/h で増減
- ✓ 15mg/h を 30 分使用しても 160mmHg 以下に下がらない場合は他剤（ニトログリセリン、ジルチアゼムなど）を併用もしくはこれらへ変更
- ✓ 治療開始 2 時間以降で目標 SBP に達している場合は、以後は 60 分間隔で血圧測定

【登録項目】

- ● 患者背景
- ✓ 年齢および性別
- ✓ 危険因子（高血圧、糖尿病、高脂血症）
- ✓ 生活歴（飲酒、喫煙）
- ✓ 脳血管障害の既往（脳梗塞、一過性脳虚血発作、脳出血、クモ膜下出血）
- ✓ 発症前のmodified Rankin Scale (mRS)