cluding the 1 with a poor outcome, had relatively mild early ischemic changes.

Since thrombolysis for ESRD patients has been understudied, one often hesitates to use rt-PA for ESRD patients with hyperacute stroke. Furthermore, one might wonder if HD within 24 h of rt-PA is safe or not. The strength of this study is to report that IV rt-PA is a feasible strategy for ESRD patients for the first time as far as we know.

This study's limitations included its retrospective, observational design, the small number of ESRD patients, and the lack of data on patients who did not receive thrombolysis for stroke. Another limitation was that the present results, which were based on low-dose alteplase, may not be applicable to the regular-dose therapy (0.9 mg/kg).

Appendix

Stroke Acute Management with Urgent Risk-Factor Assessment and Improvement (SAMURAI) Study Investigators:

Chief Investigator: K. Toyoda, National Cerebral and Cardiovascular Center.

Central Study Office: M. Koga, M. Naganuma, and H. Kanai, National Cerebral and Cardiovascular Center.

Investigators and Institutions: K. Kario, Jichi Medical University School of Medicine; J. Nakagawara, Nakamura Memorial Hospital; E. Furui, Kohnan Hospital; Y. Shiokawa, K. Nishiyama, Kyorin University School of Medicine; Y. Hasegawa, St Marianna University School of Medicine; S. Okuda, National Hospital Organization Nagoya Medical Center; H. Yamagami, Kobe City Medical Center General Hospital; K. Kimura, Kawasaki Medical School; Y. Okada, National Hospital Organization Kyushu Medical Center.

Acknowledgements

This study was supported in part by grants-in-aid (H20-Junkanki-Ippan-019 and H23-Junkanki-Ippan-010, chief investigator: K. Toyoda) from the Ministry of Health, Labour and Welfare, Japan.

Disclosure Statement

There are no conflicts of interest to disclose.

References

1 Iseki K, Fukiyama K, Okinawa Dialysis Study Group: Clinical demographics and long-term prognosis after stroke in patients on chronic haemodialysis. Nephrol Dial Transplant 2000;15:1808–1813.

2 Toyoda K, Fujii K, Fujimi S, Kumai Y, Tsuchimochi H, Ibayashi S, Iida M: Stroke in patients on maintenance hemodialysis: a 22-year single-center study. Am J Kidney Dis. 2005;45:1058–1066.

3 Lyrer PA, Fluri F, Gisler D, Papa S, Hatz F, Engelter ST: Renal function and outcome among stroke patients treated with IV thrombolysis. Neurology 2008;71:1548–1550.

4 Naganuma M, Koga M, Shiokawa Y, Nakagawara J, Furui E, Kimura K, Yamagami H, Okada Y, Hasegawa Y, Kario K, Okuda S, Nishiyama K, Minematsu K, Toyoda K: Reduced estimated glomerular filtration rate is associated with stroke outcomes after intravenous rt-PA: the Stroke Acute Management with Urgent Risk-Factor Assessment and Improvement (SAMURAI) rt-PA Registry. Cerebrovasc Dis 2011;31:123–129.

5 Toyoda K, Koga M, Naganuma M, Shiokawa Y, Nakagawara J, Furui E, Kimura K, Yamagami H, Okada Y, Hasegawa Y, Kario K, Okuda S, Nishiyama K, Minematsu K; Stroke Acute Management with Urgent Risk-Factor Assessment and Improvement Study Investigators: Routine use of intravenous low-dose recombinant tissue plasminogen activator in Japanese patients: general outcomes and prognostic factors from the SAMURAI register. Stroke 2009;40:3591–3595.

6 Nezu T, Koga M, Kimura K, Shiokawa Y, Nakagawara J, Furui E, Yamagami H, Okada Y, Hasegawa Y, Kario K, Okuda S, Nishiyama K, Naganuma M, Minematsu K, Toyoda K: Pre-treatment ASPECTS on DWI predicts 3-month outcome following rt-PA: SAMURAI rt-PA Registry. Neurology 2010;75:555–561.

7 Wahlgren N, Ahmed N, Eriksson N, Aichner F, Bluhmki E, Dávalos A, Erilä T, Ford GA, Grond M, Hacke W, Hennerici MG, Kaste M, Köhrmann M, Larrue V, Lees KR, Machnig T, Roine RO, Toni D, Vanhooren G; Safe Implementation of Thrombolysis in Stroke-MOnitoring STudy Investigators: Multivariable analysis of outcome predictors and adjustment of main outcome results to baseline data profile in randomized controlled trials: Safe Implementation of Thrombolysis in Stroke-MOnitoring STudy (SITS-MOST). Stroke 2008;39:3316–3322.

8 Aggarwal A, Kabbani SS, Rimmer JM, Gennari FJ, Taatjes DJ, Sobel BE, Schneider DJ: Biphasic effects of hemodialysis on platelet reactivity in patients with end-stage renal disease: a potential contributor to cardiovascular risk. Am J Kidney Dis 2002;40:315–322.

9 Horl MP, Horl WH: Hemodialysis-associated hypertension: pathophysiology and therapy. Am J Kidney Dis 2002;39:227–244.

10 Rodriguez-Yanez M, Castellanos M, Blanco M, Millan M, Nombela F, Sobrino T, Lizasoain I, Leira R, Serena J, Davalos A, Castillo J: Micro- and macroalbuminuria predict hemorrhagic transformation in acute ischemic stroke. Neurology 2006;67:1172–1177.

11 Yokoyama S, Hirano H, Uomizu K, Kajiya Y, Tajitsu K, Kusumoto K: High incidence of microbleeds in hemodialysis patients detected by T_2*-weighted gradient-echo magnetic resonance imaging. Neurol Med Chir 2005; 45:556–560.

12 Watanabe A: Cerebral microbleeds and intracerebral hemorrhages in patients on maintenance hemodialysis. J Stroke Cerebrovasc Dis 2007;16:30–33.

13 Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, Jones DW, Materson BJ, Oparil S, Wright JT Jr, Roccella EJ: National Heart, Lung, Blood Institute Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: The JNC 7 Report. JAMA 2003;289:2560–2572.

Journal of the Neurological Sciences 306 (2011) 49–53

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

$CHADS_2$ 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*

ARTICLE INFO

Article history:
Received 1 December 2010
Received in revised form 29 March 2011
Accepted 30 March 2011
Available online 14 April 2011

Keywords:
Acute stroke
$CHADS_2$ score
Atrial fibrillation
rt-PA
Thrombolysis
Cardiovascular events
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).

0022-510X/$ – see front matter © 2011 Elsevier B.V. All rights reserved.
doi: 10.1016/j.jns.2011.03.046

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.

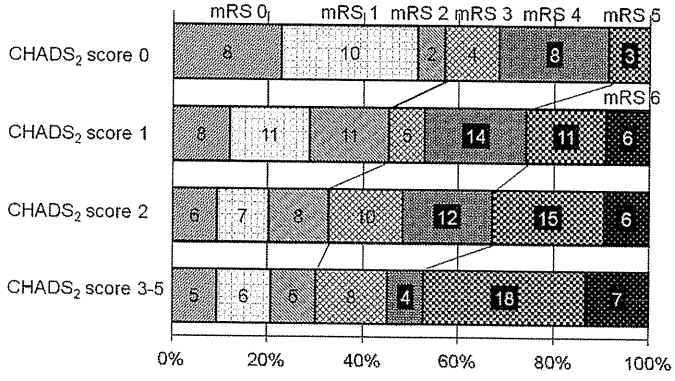


Fig. 1. $CHADS_2$ score and modified Rankin Scale at 3 months after stroke onset. The percentage of patients with mRS ≤2 gradually decreased as $CHADS_2$ score increased. In contrast, that of patients with mRS ≥5 gradually increased as $CHADS_2$ score increased.

$CHADS_2$ 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.
* $p<0.05$, † $p<0.01$, ‡ $p<0.005$, § $p<0.001$.

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.

Sources of funding

This study was supported in part by Grants-in-Aid (H20-Junkanki-Ippan-019 and H23-Junkanki-Ippan-010, chief investigator: Kazunori Toyoda) from the Ministry of Health, Labour and Welfare, Japan, and a Grant from the Japan Cardiovascular Research Foundation (the Bayer Scholarship for Cardiovascular Research).

Conflict of interest/disclosures

Koga receives research support from the Japan Cardiovascular Research Foundation (the Bayer Scholarship for Cardiovascular Research). Kimura, Shibazaki, Shiokawa, Nakagawara, Furui, Yamagami, Okada, Hasegawa, Kario, Okuda, Nishiyama, Naganuma, Nezu and Maeda have no disclosures. Minematsu receives research support from Astellas Pharma Inc., Takeda Pharmaceutical Company Limited, Sanofi-Aventis, Lundbeck Inc., Mitsubishi Tanabe Pharma Corporation, Kyowa Hakko Kirin Pharma, Inc., Hitachi Medical Corporation, Research Grants for Cardiovascular Diseases and Grants-in-Aid from the Ministry of Health, Labour and Welfare, Japan, and the Foundation for Biomedical Research and Innovation. Kazunori Toyoda receives research support from Grants-in-Aid from the Ministry of Health, Labour and Welfare, Japan.

References

[1] Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. JAMA 2001;285:2864–70.
[2] Gage BF, van Walraven C, Pearce L, Hart RG, Koudstaal PJ, Boode BS, et al. Selecting patients with atrial fibrillation for anticoagulation: stroke risk stratification in patients taking aspirin. Circulation 2004;110:2287–92.
[3] Healey JS, Hart RG, Pogue J, Pfeffer MA, Hohnloser SH, De Caterina R, et al. Risks and benefits of oral anticoagulation compared with clopidogrel plus aspirin in patients with atrial fibrillation according to stroke risk: the atrial fibrillation clopidogrel trial with irbesartan for prevention of vascular events (ACTIVE-W). Stroke 2008;39:1482–6.
[4] Poli D, Antonucci E, Grifoni E, Abbate R, Gensini GF, Prisco D. Stroke risk in atrial fibrillation patients on warfarin. Predictive ability of risk stratification schemes for primary and secondary prevention. Thromb Haemost 2009;101:367–72.
[5] Hylek EM, Evans-Molina C, Shea C, Henault LE, Regan S. Major hemorrhage and tolerability of warfarin in the first year of therapy among elderly patients with atrial fibrillation. Circulation 2007;115:2689–96.
[6] Henriksson KM, Farahmand B, Johansson S, Asberg S, Terent A, Edvardsson N. Survival after stroke–the impact of CHADS2 score and atrial fibrillation. Int J Cardiol 2009;141:18–23.
[7] Nakashima T, Toyoda K, Koga M, Matsuoka H, Nagatsuka K, Takada T, et al. Arterial occlusion sites on magnetic resonance angiography influence the efficacy of intravenous low-dose (0.6 mg/kg) alteplase therapy for ischaemic stroke. Int J Stroke 2009;4:425–31.
[8] Wahlgren N, Ahmed N, Eriksson N, Aichner F, Bluhmki E, Davalos A, et al. Multivariable analysis of outcome predictors and adjustment of main outcome results to baseline data profile in randomized controlled trials: Safe Implementation of Thrombolysis in Stroke-MOnitoring STudy (SITS-MOST). Stroke 2008;39:3316–22.
[9] Kimura K, Iguchi Y, Shibazaki K, Terasawa Y, Inoue T, Uemura J, et al. Large ischemic lesions on diffusion-weighted imaging done before intravenous tissue plasminogen activator thrombolysis predicts a poor outcome in patients with acute stroke. Stroke 2008;39:2388–91.
[10] Toyoda K, Koga M, Naganuma M, Shiokawa Y, Nakagawara J, Furui E, et al. Routine use of intravenous low-dose recombinant tissue plasminogen activator in Japanese patients: general outcomes and prognostic factors from the SAMURAI register. Stroke 2009;40:3591–5.
[11] Nezu T, Koga M, Kimura K, Shiokawa Y, Nakagawara J, Furui E, et al. Pretreatment ASPECTS on DWI predicts 3-month outcome following rt-PA: SAMURAI rt-PA Registry. Neurology 2010;75:555–61.
[12] Shinohara Y, Yamaguchi T. Outline of the Japanese Guidelines for the Management of Stroke 2004 and subsequent revision. Int J Stroke 2008;3:55–62.
[13] Tissue plasminogen activator for acute ischemic stroke. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. N Engl J Med 1995;333:1581–7.
[14] Yamaguchi T, Mori E, Minematsu K, Nakagawara J, Hashi K, Saito I, et al. Alteplase at 0.6 mg/kg for acute ischemic stroke within 3 hours of onset: Japan Alteplase Clinical Trial (J-ACT). Stroke 2006;37:1810–5.
[15] Mori E, Minematsu K, Nakagawara J, Yamaguchi T, Sasaki M, Hirano T. Effects of 0.6 mg/kg intravenous alteplase on vascular and clinical outcomes in middle cerebral artery occlusion: Japan Alteplase Clinical Trial II (J-ACT II). Stroke 2010;41:461–5.
[16] Nakagawara J, Minematsu K, Okada Y, Tanahashi N, Nagahiro S, Mori E, et al. Thrombolysis With 0.6 mg/kg intravenous alteplase for acute ischemic stroke in routine clinical practice: the Japan post-Marketing Alteplase Registration Study (J-MARS). Stroke 2010;41:1984–9.
[17] Davalos A, Cendra E, Teruel J, Martinez M, Genis D. Deteriorating ischemic stroke: risk factors and prognosis. Neurology 1990;40:1865–9.
[18] Jorgensen HS, Nakayama H, Raaschou HO, Olsen TS. Effect of blood pressure and diabetes on stroke in progression. Lancet 1994;344:156–9.
[19] Weimar C, Ziegler A, Konig IR, Diener HC. Predicting functional outcome and survival after acute ischemic stroke. J Neurol 2002;249:888–95.
[20] Henon H, Godefroy O, Leys D, Mounier-Vehier F, Lucas C, Rondepierre P, et al. Early predictors of death and disability after acute cerebral ischemic event. Stroke 1995;26:392–8.
[21] Johnston KC, Connors Jr AF, Wagner DP, Knaus WA, Wang X, Haley Jr EC. A predictive risk model for outcomes of ischemic stroke. Stroke 2000;31:448–55.
[22] Thorvaldsen P, Asplund K, Kuulasmaa K, Rajakangas AM, Schroll M. Stroke incidence, case fatality, and mortality in the WHO MONICA project. World Health Organization Monitoring Trends and Determinants in Cardiovascular Disease. Stroke 1995;26:361–7.
[23] Longstreth Jr WT, Bernick C, Fitzpatrick A, Cushman M, Knepper L, Lima J, et al. Frequency and predictors of stroke death in 5,888 participants in the Cardiovascular Health Study. Neurology 2001;56:368–75.
[24] Moroney JT, Bagiella E, Paik MC, Sacco RL, Desmond DW. Risk factors for early recurrence after ischemic stroke: the role of stroke syndrome and subtype. Stroke 1998;29:2118–24.
[25] Adams Jr HP, Davis PH, Leira EC, Chang KC, Bendixen BH, Clarke WR, et al. Baseline NIH Stroke Scale score strongly predicts outcome after stroke: A report of the Trial of Org 10172 in Acute Stroke Treatment (TOAST). Neurology 1999;53:126–31.
[26] Leonardi-Bee J, Bath PM, Phillips SJ, Sandercock PA. Blood pressure and clinical outcomes in the International Stroke Trial. Stroke 2002;33:1315–20.
[27] Loor HI, Groenier KH, Limburg M, Schuling J, Meyboom-de Jong B. Risks and causes of death in a community-based stroke population: 1 month and 3 years after stroke. Neuroepidemiology 1999;18:75–84.
[28] Sacco RL, Shi T, Zamanillo MC, Kargman DE. Predictors of mortality and recurrence after hospitalized cerebral infarction in an urban community: the Northern Manhattan Stroke Study. Neurology 1994;44:626–34.
[29] Sellars C, Bowie L, Bagg J, Sweeney MP, Miller H, Tilston J, et al. Risk factors for chest infection in acute stroke: a prospective cohort study. Stroke 2007;38:2284–91.
[30] Ding R, Logemann JA. Pneumonia in stroke patients: a retrospective study. Dysphagia 2000;15:51–7.
[31] Wahlgren N, Ahmed N, Davalos A, Ford GA, Grond M, Hacke W, et al. Thrombolysis with alteplase for acute ischaemic stroke in the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST): an observational study. Lancet 2007;369:275–82.

特集

脳卒中の登録・観察研究

SAMURAI 研究と SUMO 研究：脳卒中急性期の治療手段，治療の場

上原敏志，豊田一則
UEHARA Toshiyuki, TOYODA Kazunori
国立循環器病研究センター脳血管内科

脳卒中急性期診療に関する二つの厚生労働科学研究の成果を紹介する．SUMO（Stroke Unit Multicenter Observational）研究では，stroke unit での脳卒中急性期治療が 3 ヵ月後の転帰を改善することが示され，脳卒中診療施設の structure よりも，そこでおこなわれている process がより重要であることが明らかとなった．SAMURAI（Stroke Acute Management with Urgent Risk-factor Assessment and Improvement）研究では，わが国独自の用量（0.6 mg/kg）を用いた遺伝子組み換え組織型プラスミノーゲン・アクチベータ（recombinant tissue-type plasminogen activator：rt-PA）静注療法が，海外における 0.9 mg/kg と同等の有効性を示し得ること，全国アンケートにて国内多数施設が急性期脳出血患者に対して，ニカルジピン静注を用いた収縮期血圧 140～160 mmHg ないしそれ以下への降圧治療をおこなっていることなどが示された．

Key Words
急性期脳卒中，脳卒中専門病棟（stroke unit），rt-PA 静注療法，脳出血急性期降圧

はじめに

脳卒中はわが国の代表的な国民病であり，厚生医療政策における主要な標的疾患である．これまで脳卒中征圧を目的とした多くの多施設共同研究が，厚生労働科学研究費補助金の助成を得て施行されてきた．このうち平成 16,17 年度厚生労働科学研究「わが国における Stroke Unit の有効性に関する多施設共同前向き研究」（SUMO 研究，主任研究者：峰松一夫，現国立循環器病研究センター副院長）と平成 20～22 年度厚生労働科学研究「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」（SAMURAI 研究，主任研究者：豊田一則）を紹介する．ともにわが国の伝統美を研究名に当てて，わが国発の情報発信を強く意識した臨床研究である．

1 Stroke Unit Multicenter Observational（SUMO）研究の契機

脳卒中の初期治療を脳卒中専門病棟（stroke unit：SU）でおこなえば，死亡率の低下，自宅復帰率の上昇，在院日数の短縮効果が得られる事実が 1990 年以降，欧州を中心に報告された．SU の有効性を証明した Stroke Unit Trialists' Collaboration のメタ解析では，脳卒中急性期の診療体制を表❶のように分類している[1)2)]．SU は，「多職

表❶ 脳卒中急性期患者の診療体制

1．Stroke unit（SU）型 他疾患と明確に分離された「脳卒中専門病棟（病床）」があり，多職種からなる専属の「脳卒中チーム」が治療する．以下の三つに細分される． ① 急性期集中治療型 数日以内の急性期のみ診療し，通常 7 日以内に退出する． ② 急性期＋安定期リハビリ型 急性期診療に加えてリハビリテーションもおこなう．数週間入院し，必要なら数ヵ月入院する場合もある． ③ 安定期リハビリ型 病状の安定した（おおむね発症 7 日以降）患者のリハビリテーションを含む診断・治療をおこなう．数週間入院し，必要なら数ヵ月入院する場合もある．
2．Mixed assessment 型 脳卒中患者のみに限定せず，障害をもつ疾患の診療とリハビリテーションをおこなっている専用病棟（病床）． 例：神経内科病棟が脳卒中患者を受け入れ，他の神経疾患に混じって脳卒中患者の治療をおこなう場合など．
3．Mobile stroke team 型 脳卒中患者専用の病棟（病床）は用意されていない．院内で明確に認知されている「脳卒中治療チーム」が，各病棟に出向いて脳卒中患者の診断と治療にあたる．
4．一般病棟型 急性期脳卒中患者専用の特定の病棟（病床）は用意せず，脳卒中治療チームも組織していない．

(Stroke Unit Trialist Collaboration, 1997[1][2]より作成)

種からなる専属の脳卒中チームが配属され，他疾患と明確に区分された脳卒中患者専用の病棟（病床）」と定義され，acute (intensive) stroke unit（急性期集中治療型），combined acute/rehabilitation unit（急性期＋安定期リハビリ型），rehabilitation unit（安定期リハビリ型）の三つの形態に細分されている．メタ解析の結果，SU での治療は，一般病棟での治療にくらべて，死亡を 3%減少（絶対リスク低下率）させ，施設入所率を 3%減少させ，自立患者を 6%増加させることが明らかとなった．この解析結果を受けて，欧州各地に SU が設置されるようになった[3]．さらにその後の研究により，SU での治療は，5～10 年後の生命予後・機能予後の改善のみならず activities of daily life（ADL）や quality of life（QOL）までも改善することが示された[4][5]．

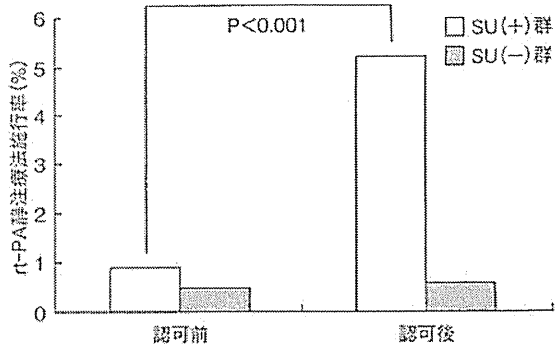
米国では，2000 年にブレインアタック連合が，遺伝子組み換え組織型プラスミノーゲン・アクチベータ (recombinant tissue-type plasminogen activator：rt-PA) 静注療法をおこなうための専門施設である一次脳卒中センター (primary stroke center：PSC) にとって SU は必須のものと位置づけ，SU の施設要件を示してその普及と質の向上がはかられた[6]．わが国でも，2004 年に発表された「脳卒中治療ガイドライン[7]」のなかで，SU での脳卒中治療がグレード A（おこなうよう強く求められる）に位置づけられた．しかしながら，これは欧米の医療体制下における一般病棟治療との比較により導かれた結論であり，医療体制の異なるわが国における有用性を推測するに足るデータはなかった．そこでわが国の医療体制に則した有効な SU の定義や具備すべき条件を明らかにし，SU により提供される医療の質を評価可能なものにすることを目的として，SUMO 研究班が結成された[8]．

2 SUMO 研究の成果

1．脳卒中診療体制に関する全国アンケート調査

本研究班では，まず表❶の Stroke Unit Trialists' Collaboration の分類・定義を明確に示したうえで，全国 9,102 病院中，精神，結核，ハンセン，歯科，社会福祉付属病院の 5 種を除く 7,835 病院に対して脳卒中診療体制に関するアンケート調査をおこなった．2,617 病院から回答を得た（回答率 33.4%）．その結果によると，脳卒中診療施設のなかで SU を設置していたのは 8.3%（急性期集中治療型 SU：0.9%，急性期治療＋リハビリ型

SU：7.4%）であった．63.8%の施設が一般病棟で急性期治療をおこない，脳卒中チームをもたない一般病棟混在型の体制をとっていた．夜間，休日も脳卒中専門医が初期対応をしている施設は21.6%のみであった．SU型の体制をとる施設は，大規模病院（ベッド数中央値440床）に多く，一般病棟混在型は小規模病院（ベッド数中央値145床）に多かった．本アンケート調査により，わが国の脳卒中診療をになっている大多数の施設は，ブレイン・アタック連合が示したPSCの必須条件を満たしていないことが明らかとなった[9]．



図❶ rt-PA静注療法認可前後での本療法施行率の変化（Stroke Unitの有無での比較）
（Sato S *et al*, 2009[10]より引用）

●2．SUの有効性に関する多施設共同前向き観察研究（SUMO研究）

わが国の医療体制に則した有効なSUのあり方（定義，具備すべき条件）を明らかにすることを目的として，多施設共同前向き観察研究がおこなわれた．対象は，発症3日以内に入院した完成型脳卒中（クモ膜下出血を除く，初発，再発は問わない）であった．登録期間は2004年12月1日～2005年12月31日で，3ヵ月後の追跡調査は2006年3月31日で終了した．共通の調査票により，性別，年齢，脳卒中発症日時および入院日時，既往歴，脳卒中専門科による初期診療の有無，急性期の診断検査・治療内容，入院時および第7日目の神経症状重症度（National Institutes of Health Stroke Scale：NIHSS），脳卒中再発増悪の有無，リハビリ施行日数，多職種によるカンファレンス実施の有無，クリニカルパス使用の有無，第28日目の日常生活自立度（modified Rankin Scale：mRS，Barthel Index）などを調査した．3ヵ月後の追跡調査ではmRSやおもな生活場所（自宅，リハビリテーション専門病院，老健施設など）を調査した．研究参加施設はSUをもつ中核5施設（国立循環器病センター，秋田県立脳血管研究センター，横浜市立脳血管医療センター，国立病院機構九州医療センター，中国労災病院勤労者リハビリテーションセンター）に加え，全国112施設の参加を得て，診療形態も地域背景も異なる合計117施設で開始された．参加施設の脳卒中診療体制を詳細に調査し，診療形態を，SU（急性期）型，SU（急性期＋リハビリ）型，Mixed assessment型，Mobile team型，一般病棟型の五つに分類した．

最終的には，全国84施設より6,815例（男性4,062例，平均年齢71歳）が登録された．入院後24時間以内の診療プロセスと3ヵ月後の転帰良好（mRS 0～1）との関連についてロジスティック回帰分析をおこなった結果，動脈血ガス分析，嚥下機能評価の施行および，初診時医師が脳卒中に精通した医師であることが，転帰良好に関連していた．

また，SUMO研究の登録期間中である2005年10月にrt-PA静注療法が認可されたことから，脳梗塞4,620例を対象とした，rt-PA静注療法認可前後における脳梗塞診療プロセスおよびrt-PA静注療法施行率の変化に関する検討をおこなった[10]．その結果によると，rt-PA静注療法認可後，画像診断では，非侵襲的で時間を要さない検査（MRI/MRA，頸部超音波検査），臨床検査では，rt-PA静注療法を考慮する際に必須となる検査（血糖，凝固検査）の施行率が増加していた．また，SUを有する施設ではrt-PA静注療法施行率が認可後に有意に増加していた（0.9%→5.1%）のに対して，SUを有さない施設では有意な変化はなかった（0.5%→0.6%）（図❶）．

SUMO研究により，わが国においてもSU治療が脳卒中発症3ヵ月目の転帰を改善することが示され，脳卒中診療施設のstructureよりも，そこでおこなわれているprocessがより重要であることが明らかとなった．

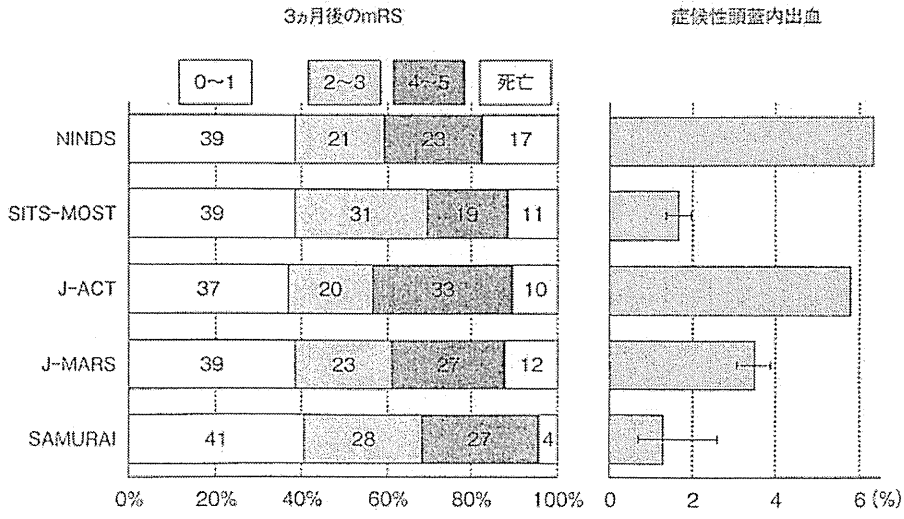
3 Stroke Acute Management with Urgent Risk-factor Assessment and Improvement (SAMURAI) rt-PA Registry

脳卒中の超急性期～急性期は，治療介入による転帰改

著効果が最も期待される時期である．SAMURAI 研究班は，SU あるいは stroke care unit（SCU）で実際におこなわれる脳卒中の適切な急性期治療を探求する目的で組まれた．脳梗塞，脳出血などを対象にいくつかの研究を並行しておこなっているが，現段階で成果発表が先行している rt-PA 静注療法の多施設共同観察研究から説明する．

国内での rt-PA 静注療法承認後 2008 年 7 月までの間に，研究班に所属する 10 施設でこの治療を受けた急性期脳梗塞患者 600 例（女性 223 例，72±12 歳）を，後ろ向きに連続登録した[11]．同じ期間に国内で約 13,500 例が rt-PA 静注療法を受けており，本研究での登録症例はその 4.4%にあたった．このうち 422 例（70.3%）が欧州での適応基準［換言すれば Safe Implementation of Thrombolysis in Stroke-MOnitoring Study（SITS-MOST[12]）］の登録基準：80 歳以下，治療前 NIHSS 25 未満，糖尿病と脳梗塞既往の合併例以外など）を満たした．治療後 36 時間以内に 119 例（19.8%，16.8～23.2%）に頭蓋内出血を認め，そのうち 30 例が PH（parenchymal hematoma）type Ⅰ，21 例が PH type Ⅱであった．症候性頭蓋内出血は，NIHSS 値で 1 点以上の進行を症候性とみなすと 23 例（3.8%，2.6～5.7%）に，SITS-MOST の定義に合わせて 4 点以上の進行を伴う PH type Ⅱと定義すると 8 例（1.3%，0.7～2.6%）に認めた．3 ヵ月後に 199 例（33.2%，95%CI 29.5～37.0%）が完全自立（mRS 0～1）した．発症前にすでに mRS が 2 以上であった 65 例を除くと，完全自立者は 37.2%（33.2～41.4%）に達した．さらに欧州の適応基準にしたがって患者を限定すると，399 例中 162 例（40.6%，35.9～45.5%）が完全自立した．また 600 例中 43 例が 3 ヵ月以内に死亡し，うち 7 例は症候性頭蓋内出血を起こした患者であった．この成績を米国 National Institute of Neurological Disorders and Stroke（NINDS）主導による多施設共同臨床試験[13]，欧州での市販後調査 SITS-MOST [12]，国内での第Ⅲ相試験 Japan Alteplase Clinical Trial（J-ACT）[14]，国内での市販後調査 Japan post-Marketing Alteplase Registration Study（J-MARS）[15]と比べる（図❷）．本研究や J-MARS の結果は，対象患者を欧州の適応基準に限定して求めている．また症候性頭蓋内出血は NIHSS 値で 4 点以上の進行を基準としたが，NINDS 試験のみは軽度の症状進行も含めている．rt-PA 静注療法によって約 4 割の患者が 3 ヵ月後に完全自立することを期待でき，また症候性頭蓋内出血はたかだか 6%程度であった．本研究では，出血発症率や死亡率が他研究よりも低かった．

本登録研究のいくつかのサブ研究が進行中である．2010 年末現在で 3 編が原著論文として掲載されており，要旨を簡潔に示す[16]～[18]．MRI 拡散強調画像（diffusion-weighted image：DWI）での早期虚血所見を Alberta Stroke Program Early CT Score（ASPECTS，10 点法）を



図❷ 国内外の臨床試験における 3 ヵ月後の mRS および，36 時間以内の症候性頭蓋内出血発症率
（Toyoda K *et al*, 2009[11]より引用）

用いて評価し[19]，3ヵ月後の転帰との関連を調べた研究においては，多変量解析でDWI-ASPECTS 7以上が機能的自立(mRS 0～2)との間に有意な関連を(オッズ比1.85，95%CI 1.07～3.24，P=0.029)，またDWI-ASPECTS 4以下が死亡との間に有意な関連を認めた(オッズ比3.61，95%CI 1.23～9.91，P=0.021)[16]．入院時の血中クレアチニン値を用いて推算糸球体濾過率を算出し，この値が60 mL/分/1.73 m^2未満の場合を腎機能障害ありと定義して，3ヵ月後の転帰との関連を調べた研究においては，多変量解析で腎機能障害が転帰不良(mRS 4～6：オッズ比1.55，95%CI 1.01～2.38，P=0.046)や死亡(オッズ比2.94，95%CI 1.38～6.42，P=0.006)との有意な関連を認めた[17]．スタチン服用と治療成績との関連を調べた研究においては，多変量解析でスタチンの発症前服用(オッズ比1.05，95%CI 0.55～2.01)，急性期服用(オッズ比1.31，95%CI 0.66～2.59)のいずれも3ヵ月後の完全自立(mRS 0～1)と関連しなかった[18]．

SAMURAI rt-PA Registryの全体成績における完全自立患者の割合は，国内外の大規模市販後調査J-MARS，SITS-MOSTと変わらず，わが国でのみ採用されている0.6 mg/kgという投与量のアルテプラーゼが，海外における0.9 mg/kgと同等の有効性を示しうることが明らかにされた．早期虚血変化の広がりの程度は虚血の強さを示唆しており，治療成績への関与が強いことも示された．わが国ではMRIが広く普及しており，DWIでの早期虚血所見やMRAでの血管閉塞部位の情報をもとに，rt-PAの治療適応をより適切に判定することが期待できる．ただし画像精査に伴う治療開始の遅れを，最小限に食い止める必要がある．

4 SAMURAI研究における脳出血急性期降圧に関する知見

SAMURAI研究のもう一つの主柱は，急性期脳出血患者の適切な血圧管理法の探求である．脳出血急性期の血圧高値は，概して予後不良と関連する．国内外の指針は収縮期血圧180 mmHg以上または平均血圧130 mmHg以上を降圧開始の目安としている．また国際高血圧学会は，220/120 mmHgを超える患者に，血圧値で20%程度までの降圧を推奨している．降圧目標値として，米国の指針は平均血圧110 mmHgまたは血圧160/90 mmHgを例示している．近年発表されたIntensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial (INTERACT)パイロット試験[20]結果に基づき，米国の指針では収縮期血圧150～220 mmHgの患者に対する140 mmHgまでの急性期降圧が安全であることが，新たに推奨された．しかしながら，これらの推奨指針はいずれもエビデンスが十分といえず，真に適切な降圧法は解明されていない．また急性期に用いる静注用降圧薬として，米国の指針ではラベタロール(国内では静注薬未販売)やニカルジピンが推奨されるが，国内でのニカルジピンの添付文書には，頭蓋内出血で止血が完成していない患者や脳卒中急性期で頭蓋内圧亢進の患者には使用禁忌とされることが書かれている．しかしながら渉猟しうる範囲で，ニカルジピンが血腫増大や予後増悪に関連したことを示す基礎的・臨床的研究は無い．脳出血治療の国際的標準化をはかるうえでも，国内外の指針で同一薬の評価がまったく異なる矛盾を，早急に解決する必要がある．

本研究班が2008年におこなった国内アンケート調査では，降圧開始の目安とする収縮期血圧は180 mmHg以下，160 mmHg以下との回答が多く，到達目標値は140 mmHg以下，150 mmHg以下，160 mmHg以下との回答が84%を占めた[21]．静注降圧薬として，過半数の施設が急性期脳出血患者の静注降圧治療における第一選択薬にニカルジピンをあげ，ほとんどの回答者が選択理由としてすぐれた降圧効果をあげた反面，添付文書による使用制限を問題点として指摘している．現在，日本脳卒中学会を介して，添付文書改定意見を厚生労働省に提出中である．またアンケート調査で国内多数施設がおこなっていたニカルジピン静注を用いた収縮期血圧140～160 mmHgないしそれ以下への降圧の安全性・有効性を検討するため，研究参加10施設で前向き観察研究を始めた．また米国で本主題への多施設共同介入試験Antihypertensive Treatment of Acute Cerebral Hemorrhage 2 (ATACH2)を企画するミネソタ大学Qureshi教授らと連携を取り，日米共同でのATACH2試験参加を開始する予定である．

おわりに

SAMURAI研究とSUMO研究によって，欧米とは医療体制の異なるわが国における，脳卒中急性期治療の場と

しての SU，またそこで実際におこなわれる治療（とくに rt-PA 静注療法）の現状および有効性が示された．

●文　献●

1) Stroke Unit Trialists' Collaboration：Collaborative systematic review of the randomised trials of organised inpatient (stroke unit) care after stroke. *Br Mrd J* 314：1151-1159, 1997
2) Stroke Unit Trialists' Collaboration：How do stroke units improve patient outcomes? A collaborative systematic review of the randomized trials. *Stroke* 28：2139-2144, 1997
3) Brainin M *et al*：Organization of stroke care：education, referral, emergency management and imaging, stroke units and rehabilitation. European Stroke Initiative. *Cerebrovasc Dis* 17 (Suppl 2)：1-14, 2004
4) Jørgensen HS *et al*：Treatment and rehabilitation on a stroke unit improves 5-year survival. A community-based study. *Stroke* 30：930-933, 1999
5) Indredavik B *et al*：Stroke unit treatment improves long-term quality of life：a randomized controlled trial. *Stroke* 29：895-899, 1998
6) Alberts MJ *et al*：Recommendations for the establishment of primary stroke centers. Brain Attack Coalition. *JAMA* 283：3102-3109, 2000
7) 篠原幸人ほか編：脳卒中治療ガイドライン 2004，協和企画，東京，2004，p14
8) 峰松一夫：わが国における Stroke unit の有効性に関する多施設共同前向き研究．平成 16 年度厚生労働省科学研究費補助金による長寿科学総合研究事業報告書．
9) 長谷川泰弘ほか：Stroke Unit の現状と課題：急性期脳卒中診療体制に関する全国アンケート調査から．脳卒中 28：545-549，2006
10) Sato S *et al*：Impact of the approval of intravenous recombinant tissue plasminogen activator therapy on the processes of acute stroke management in Japan：the Stroke Unit Multicenter Observational (SUMO) Study. *Stroke* 40：30-34, 2009
11) Toyoda K *et al*：Routine use of intravenous low-dose recombinant tissue plasminogen activator in Japanese patients：general outcomes and prognostic factors from the SAMURAI register. *Stroke* 40：3591-3595, 2009
12) Wahlgren N *et al*：Thrombolysis with alteplase for acute ischaemic stroke in the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST)：an observational study. *Lancet* 369：275-282, 2007
13) The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group：Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med* 333：1581-1587, 1995
14) Yamaguchi T *et al*：Alteplase at 0.6 mg/kg for acute ischemic stroke within 3 hours of onset：Japan Alteplase Clinical Trial (J-ACT). *Stroke* 37：1810-1815, 2006
15) Nakagawara J *et al*：Thrombolysis with 0.6 mg/kg intravenous alteplase for acute ischemic stroke in routine clinical practice：the Japan post-Marketing Alteplase Registration Study (J-MARS). *Stroke* 41：1984-1989, 2010
16) Nezu T *et al*：Pretreatment ASPECTS on DWI predicts 3-month outcome following rt-PA：SAMURAI rt-PA Registry. *Neurology* 75：555-561, 2010
17) Naganuma M *et al*：Reduced estimated glomerular filtration rate is associated with stroke outcomes after intravenous rt-PA：the Stroke Acute Management with Urgent Risk-factor Assessment and Improvement (SAMURAI) rt-PA Registry. *Cerbrovasc Dis* 31：123-129, 2011
18) 牧原典子ほか：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及ぼす影響：Stroke Acute Management with Urgent Risk-factor Assessment and Improvement (SAMURAI) rt-PA Registry. 臨床神経学 40：225-231，2010
19) Barber PA *et al*：Validity and reliability of a quantitative computed tomography score in predicting outcome of hyperacute stroke before thrombolytic therapy. ASPECTS Study Group. Alberta Stroke Programme Early CT Score. *Lancet* 355：1670-1674, 2000
20) Anderson CS *et al*：Intensive blood pressure reduction in acute cerebral haemorrhage trial (INTERACT)：a randomised pilot trial. *Lancet Neurol* 7：391-399, 2008
21) Koga M *et al*：Nationwide survey of antihypertensive treatment for acute intracerebral hemorrhage in Japan. *Hypertens Res* 32：759-764, 2009

うえはら・としゆき

上原敏志　国立循環器病研究センター脳血管内科医長

1965 年，香川県生まれ．
1990 年，神戸大学医学部卒業，医学博士．専門は，脳卒中学．
趣味は，スポーツ観戦．

第36回日本脳卒中学会総会（2011/7 京都）
シンポジウム　「日本発の大規模観察研究」

1. 氏名：　豊田　一則　（Kazunori Toyoda）
2. 所属：　国立循環器病研究センター　脳血管内科
2’ 英文所属：
Department of Cerebrovascular Medicine, National Cerebral and Cardiovascular Center
3. 演題名：　SAMURAI (Stroke Acute Management with Urgent Risk-factor Assessment and Improvement)研究
3’ 英文演題名：　SAMURAI Study
4. 抄録本文

SAMURAI (Stroke Acute Management with Urgent Risk-factor Assessment and Improvement)研究は、厚生労働科学研究としての国内10施設による多施設共同研究で、複数の主題に沿って研究を遂行中である。主たる成果として、「rt-PA 患者登録研究」と「超急性期脳出血への降圧療法に関する研究」を紹介する。前者では、研究参加施設で登録されたrt-PA静注を受けた急性期脳梗塞600例の臨床データを解析し、その全体成績としてわが国独自の用量（アルテプラーゼ 0.6 mg/kg）によるrt-PA静注療法が国外の標準用量での治療と同等以上の治療成績を得ていることや、各危険因子と治療成績の関連を調べたサブ解析を報告し、海外からも評価を得た。また後者では、わが国の急性期脳出血患者に適した降圧手段や降圧目標を明らかにするため、全国アンケート調査による現状把握を行い、国内多数施設の意見であったニカルジピン静注を用いた収縮期血圧140～160 mmHgないしそれ以下への降圧の安全性・有効性を検討するため、前向き観察研究を行った。研究成果をもとに、本主題への日米共同の介入試験 Antihypertensive Treatment of Acute Cerebral Hemorrhage II (ATACH-II)を始める予定である。

研究参加施設：自治医科大学循環器内科、中村記念病院脳神経外科、広南病院脳血管内科、杏林大学脳卒中センター、聖マリアンナ医科大学神経内科、NHO名古屋医療センター神経内科、神戸市立医療センター中央市民病院脳卒中センター、川崎医科大学脳卒中医学教室、NHO九州医療センター、国立循環器病研究センター

ASPECTS on pretreatment diffusion weighted imaging for intravenous rt-PA therapy: SAMURAI rt-PA Registry

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

1)Division of Stroke Care Unit and 2)Department of Cerebrovascular Medicine, National Cerebral and Cardiovascular Center, Suita, Japan

3)Department of Stroke Medicine, Kawasaki Medical School, Kurashiki, Japan

4)Departments of Neurosurgery and Stroke Center, Kyorin University School of Medicine, Mitaka, Japan

5)Department of Neurosurgery and Stroke Center, Nakamura Memorial Hospital, Sapporo, Japan

6)Department of Stroke Neurology, Kohnan Hospital, Sendai, Japan; the Department of Stroke Medicine

7)Stroke Center, Kobe City Medical Center General Hospital, Kobe, Japan

8)Department of Cerebrovascular Medicine, National Hospital Organization Kyushu Medical Center, Fukuoka, Japan

9)Department of Neurology, St Marianna University School of Medicine, Kawasaki, Japan

10)Division of Cardiovascular Medicine, Department of Medicine, Jichi Medical University School of Medicine, Shimotsuke, Japan

11)Department of Neurology, National Hospital Organization Nagoya Medical Center, Nagoya, Japan

Abstract

Alberta Stroke Programme Early CT Score (ASPECTS) is a quantitative topographical score to evaluate early ischemic change in the middle cerebral arterial territory on CT as well as on diffusion-weighted imaging (DWI). DWI can detect ischemic change in hyperacute stroke rather than CT. We elucidated the relationship between CT-ASPECTS and DWI-ASPECTS and evaluated whether DWI-ASPECTS predicts 3-month stroke outcomes in patients treated with intravenous rt-PA therapy. From SAMURAI rt-PA registry, 360 patients with first-ever ischemic stroke in the MCA territory who underwent both pretreatment CT and DWI and received rt-PA (0.6 mg/kg alteplase) therapy in 10 stroke centers in Japan were retrospectively studied. ASPECTS was assessed on CT and DWI just prior to rt-PA injection. 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 to 9] versus 9 [8 to 10], P<0.001). Using receiver operating characteristic curves, the optimal cutoff DWI-ASPECTS to predict favorable outcome (an mRS score of 0-2) was ≥7. On multivariate regression analysis, DWI-ASPECTS ≥7 was related to favorable outcome (odds ratio [OR] 2.51; 95% confidence interval [CI] 1.33-4.80; p=0.005), DWI-ASPECTS ≤4 tended to be related to death (OR 3.08; 95% CI 0.89-10.04; p=0.067), and DWI-ASPECTS ≤5 was related to symptomatic intracerebral hemorrhage (sICH) (OR 7.90; 95% CI 2.29-28.44; p=0.001). DWI-ASPECTS was independently predictive of functional outcome at 3 months, as well as sICH within 36 hours, following rt-PA therapy for stroke patients.

Key words: early ischemic change, ASPECTS, DWI, CT, outcomes
236 words (250 words limitation)

国際学会参加報告書

Thrombolysis and Acute Stroke Treatment (TAST) in 2011: Preparing for the Next Decade
2011年12月1～3日、ニューヨークシティー、米国

急性期脳卒中の内科複合治療の確立に関する研究
分担研究者　古賀　政利　国立循環器病研究センター脳卒中集中治療科

□TAST2011の概要□

Thrombolysis and Acute Stroke Treatment (TAST) は、1990 年に Deutschland の Heidelberg で第 1 回会議が開催され、以降 2 年毎に世界各地の主要都市で開催されてきた。この会議では、特に急性期虚血性脳卒中の研究に第一線で従事している世界の専門家が一同に交いして、最先端の研究内容や治療法、今後の展望を議論してきた。今回は第 11 回目で、当初 2010 年に予定されていたが諸事情があり 2011 年末に New York Academy of Sciences (NYAS) 主催として、World Trading Center 跡地に隣接する NYAS ビルで開催された。学会の副題は、「Preparing Next Decade」であり、これからの 10 年の急性期脳卒中治療を見据え準備するための会議となった。日本からは、東北大学高次脳機能障害学　森悦朗教授、中村記念病院脳神経外科　中川原譲二脳卒中センター長、東京女子医大神経内科　長尾毅彦准教授と筆者が参加した。

□本研究班からの報告□

12 月 3 日の 3 日目の「Data Blitz Session 2 - Hot Topic/Updates」のセッションで、「ASPECTS on Pretreatment Diffusion Weighted Imaging for Intravenous Rt-PA Therapy: SAMURAI Rt-PA Registry」の演題で発表した。当初、一般演題はポスター演題のみの応募であったが、事務局から口演発表への変更依頼を受けた経緯があった。本研究班で 600 例を登録した SAMURAI rt-PA registry から rt-PA 療法前に CT と diffusion weighted MRI (DWI) の両方で評価した 360 例で各々の早期虚血病巣の拡がりを Alberta Stroke Programme Early CT Score (ASPECT) で評価した結果を報告した。DWI は発症早期からの虚血性変化検出能が高く、CT よりもそれを正確に評価出来る。DWI-ASPECTS は CT-ASPECTS と良く相関し、CT-ASPECTS よりも 1 点低かった。DWI-ASPECTS7 点以上は 3 ヶ月後の転帰良好 (modified Rankin Scale 0-2) と、5 以下は症候性頭蓋内出血と独立して関連していた。この結果は、rt-PA 対象例の転帰予測に重要なものと考える。

以下に、3 日間の主要な内容を纏める。

□1日目□

12 月 1 日の初日は、MRI や超音波などの画像を駆使した診断やモニタリングと血管内治療デバイスを用いた治療に関するサテライトシンポジウムが開催され、日進月歩で発展する診断技術と、新規治療デバイスの症例選択やテクニカルな問題など日常実地臨床における最先端の知見に触れることが出来た。その後、ワシントン大学内科教室 Gregory J. del Zoppo 教授らによる「開会挨拶」、オタワ大学神経化学教授 Antonie M Hakim 教授による最近 10 年の急性期脳卒中治療の変遷に関して「基調講演 1」と続いた。Antonie M Hakim 教授は Canadian Stroke Network の中心人物の一人で、rt-PA 静注療法を受けれる患者の割合を増やすためにネットワーク構築や発症時の対応などの患者教育、2 次予防などを含めた総合的なマネ

ージメントを行ってきた。今後、治療時間の延長や脳保護薬の併用で rt-PA 療法の対象が増える可能性がある。しかし、最も有効な方法は、Telestroke（インターネットを使用した遠隔での専門医による診断や治療方針決定方法）の拡大により更に多くの患者に治療薬を使用できる機会を増やしていくことであると話した。

□2 日目□

「Science of Acute Stroke Intervention」、「Data Blitz Session 1 - Hot Topic/Updates」、「How to Make Acute Intervention More Widely Available」、「Clinical Management of Medical Issues in The Acute Setting」、「基調講演 2」のセッションが行われた。

「Science of Acute Stroke Intervention」では、George Howard 教授が米国の今後 30 年の人口構成の変化を紹介し、今後脳卒中患者は倍増していくことが予想されることを報告した。また、米国の脳卒中危険因子は、高血圧の prevalence が下がり、糖尿病が上がるということが予測されているようである。これに関して、Werner Hacke 教授は、2011 年 9 月に World Health Organization（WHO）の new international agenda on non-communicable disease（NCDs）に関する国際会議が開催されたことをコメントした。これまで感染性疾患を中心に対策を講じてきたところを、今後は悪性疾患、心血管疾患、脳卒中、閉塞性呼吸器疾患、糖尿病が問題であり、こちらに軸足を移していくことが議決された。WHO は各国に NCDs に関するプログラムを要求する様になるだろう。Wolf-Dieter Heiss 教授は、以前よりペナンブラ（急性期の救済可能な脳虚血組織）の概念を発展させてきたが、虚血の中にペナンブラの核が複数存在して（mini core＆mini penumbra）、それらが合わさっていくという新しい考えを紹介した。

「Data Blitz Session 1 - Hot Topic/Updates」では、脳底動脈閉塞による急性期脳卒中の登録研究を行ってきた Helsinki 大学グループと、Basilar Artery International Cooperation Study (BASICS)グループからの報告が行われた。脳底動脈閉塞症では早期の再開通療法が重要であるが、現在までの観察研究では rt-PA 静注療法単独か rt-PA 静注療法＋血管内治療の何れが優れているかわからないので、BASICS グループはこれらの安全性と有効性を比較する無作為化試験を計画している。また、3rd International Stroke Trial からは、3035 例で 2011 年 7 月に登録を終了し登録患者の背景因子が報告された。この研究では、欧州の適応外である 80 歳越え症例の安全性と有効性が明らかになるであろう。

「Clinical Management of Medical Issues in The Acute Setting」では、Joseph P. Broderick 教授が International Management of Stroke Trial III の登録状況を報告した。この研究では主幹動脈閉塞による急性期脳卒中を rt-PA 単独と rt-PA＋血管内治療に無作為に 1：2 に割り付けており、目標 900 例中 600 例が登録された。順調に登録が進んでおり、結果がでるのが楽しみである。Geoffrey A. Donnan 教授は、rt-PA 療法の効果は限られたものであるが、この効果を最大限に引き出すための今後の治療戦略を紹介した。その中には、血管内治療との併用や、超音波血栓溶解促進療法（sonothrombolysis）、tenecteplase などの alteplase 以外の血栓溶解薬などがある。また、MRI などの画像診断による対象者を絞った治療時間の延長や、この画像診断により症候性頭蓋内出血リスクが高い、もしくはペナンブラがないために治療効果が期待出来ない患者の検出ができる可能性が高く、Extending the time for Thrombolysis in Emergency Neurological Deficit（EXTEND）試験で明らかにしていく。また、rt-PA の容量を下げる（例えば日本で使用している 0.6mg/kg の alteplase）と

症候性頭蓋内出血リスクが下がる可能性があり、豪州を中心に Enhanced Control of Hypertension and Thrombolysis Stroke Trial（ENCHANTED、主任研究者 Craig Anderson 教授）が開始された。発症から病院までの対応は改善の余地がかなり残されていることも議論した。

□3 日目□

「Evolution of Tissue Injury」、「基調講演 3」、「Data Blitz Session 2 - Hot Topic/Updates」、「Conditions of Agent Delivery and Its Optimization」のセッションが行われた。

「Evolution of Tissue Injury」で Maiken Nedergaard 教授は、脳保護研究ではグリア細胞の重要性があまり注目されてこなかったことを指摘した。グリア細胞は虚血後に新たなアストロサイトやオリゴデンドロサイトを生み出す能力がある。最近の研究では、グリア細胞の中には虚血に感受性の高い集団が存在することが指摘されている。今後は、グリア細胞にも注目していく必要があるだろう。また、p2Y12 レセプターのミクログリアの動きを駆動する役割が指摘された。この作用はクロピドグレル投与下では著明に抑制される。グリア細胞は血液脳関門を構成する一部にもなっており今後の研究の発展が期待される。J. Marc Simard 教授は、in vitro の研究で rt-PA に glibenclamide を併用すると matrix metalloproteinase（MMP）9 や MMP2 の産生が抑制され、死亡率や転帰が改善される可能性を示した。森悦朗教授は、日本で使用されている rt-PA 0.6mg の alteplase の安全性と有効性を示し、最適な容量（0.9mg/kg と 0.6mg/kg のどちらが安全で有効であるか）の問題は解決できていないことを提起した。Andrei V. Alexandrov 教授は、sonothrombolysis のための operator independent（施行者の技術によらず装着できる）の経頭蓋超音波装置を開発したことを報告し、2012 年にも無作為割付試験（CLOTBUST-ER）で rt-PA 単独と rt-PA＋超音波の比較試験を開始する。Werner Hacke 教授は、現在 4.5 時間まで有効性が示されている rt-PA 療法であるが、90 分を超えるとその効果はかなり小さいことを指摘した。90 分以降では画像診断により症例選択を検討することも重要かもしれない。また、ECASS4-extend として、Geoffrey A. Donnan 教授の EXTEND 試験と同じプロトコールで 2012 年から症例登録を開始する。

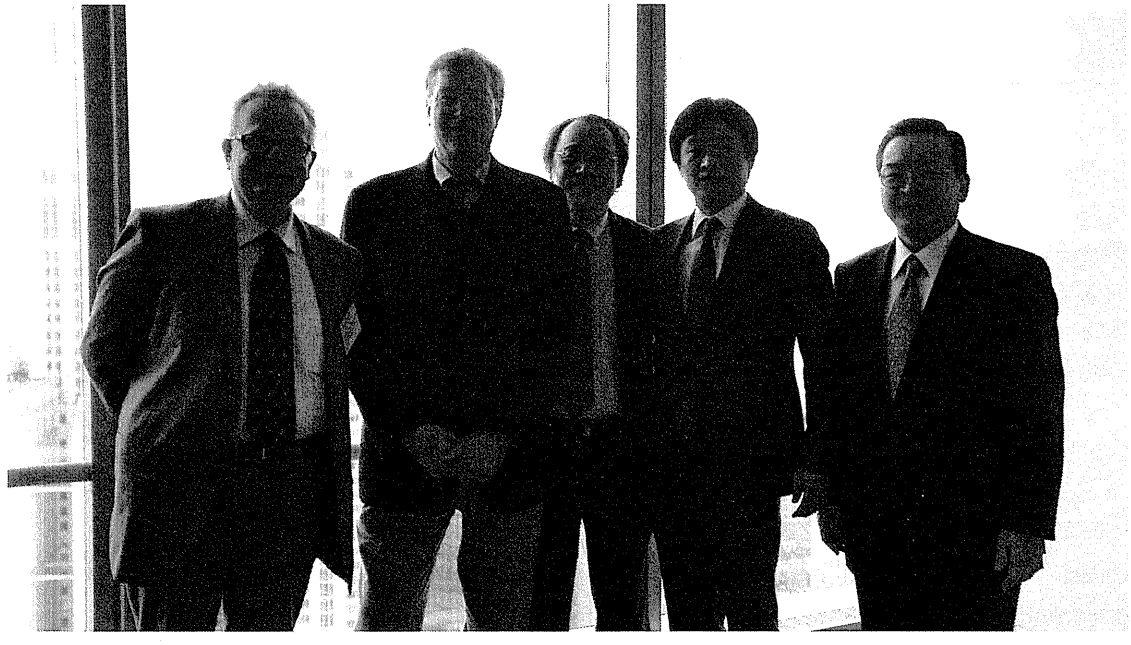
「基調講演 3」では、会長の Gregory J. del Zoppo 教授が、脳虚血では neurovascular unit の概念が重要であるが、加齢による neurovascular unit の integrity に対する影響はほとんどわかっていないことを指摘した。加齢変化した neurovascular unit の integrity のために、虚血下では抗血栓薬がこれらの毛細血管床に到達できにくい可能性もある。

「Conditions of Agent Delivery and Its Optimization」では、Markku Kaste 教授が、Helsinki 大学中央病院では年間 300 例以上に rt-PA 療法を行っていることを紹介した。これは入院した脳梗塞の 31%で、94%は来院後 60 分以内に施行している。2011 年の来院から rt-PA 投与開始までの時間は中央値で 20 分（IQR14-32）であった。これらの成果は、救急隊への教育、来院前の診療する脳卒中医への電話連絡、来院前の家族や目撃者から、および州管理電子診療録からの情報収集、来院前採血および CT 発注、救急外来内 CT 設置、検査技師の救急外来への血液検体回収、簡易 PT INR 測定、来院前 CT 検査室確保、救急ストレッチャーから CT ベッドへの直接移動、CT ベッド上での神経所見評価・CT 画像評価、そして適応があれば事前に調合した rt-PA を投与することで達成できたことが紹介された。

次回は Brasilia で World Stroke Congress 2012 が予定されている 2012 年の 10 月頃に合わせて、Argentina での開催が検討され、会を終えた。

図 1. TAST2011 での発表風景

図 2. 会長 Gregory J. del Zoppo 教授（左から 2 人目）、森悦朗教授（中央）、中川原譲二先生（右端）、筆者（右から 2 人目）



Low-dose alteplase safe in patients outside European indications

Last Updated: 2011-11-25 10:40:25 -0400 (Reuters Health)

Journal

By Megan Brooks

NEW YORK (Reuters Health) - Low-dose intravenous alteplase can be safely administered to patients with acute ischemic stroke who are outside European indications, although outcomes are "less favorable."

That's according to observational data from Japan, reported by Dr. Masatoshi Koga from the National Cerebral and Cardiovascular Center in Osaka and colleagues in a paper online September 29 in Stroke.

They note that patients with severe stroke as indicated by a baseline National Institutes of Health Stroke Scale (NIHSS) score of 25, those older than 80 years and those with any history of prior stroke and concomitant diabetes were excluded from the European postmarketing monitoring study for recombinant tissue-type plasminogen activator (rtPA) "without sufficient rationale."

Currently, European regulatory agencies do not advocate rtPA therapy for patients with these exclusion criteria.

However, data from the Japanese multicenter registry suggest that it is safe and can be effective to use 0.6 mg/kg alteplase in patients with acute stroke outside the European indications as compared with those who meet inclusion criteria.

The analysis centered on 422 patients who met the inclusion criteria based on European guidelines (the "IN" group) and 178 who did not (the "OUT" group).

Compared to the IN group, the OUT group had a higher percentage of females and patients who were older, hypertensive, diabetic, and had higher NIHSS scores and internal carotid artery occlusion.

Of the 178 patients in the OUT group, 129 (72%) were older than age 80, 40 (22%) had severe stroke with an NIHSS score of 25 or higher, and 25 (14%) had prior stroke plus diabetes.

The researchers report that any intracerebral hemorrhage (ICH) was significantly less common in patients in the OUT group (15%) than the IN group (22%). The adjusted odds ratio was 0.50.

The frequency of symptomatic ICH did not differ significantly between the OUT (2%) and IN groups (3%), however, with an aOR of 0.53.

However, an unfavorable outcome -- defined as a modified Rankin Scale (mRS) score of 5 to 6 -- and death were significantly more likely in the OUT group than in the IN group (aOR, 2.48 and 2.04, respectively). Thirty-nine percent of the OUT patients had an unfavorable outcome compared with 16% of the IN patients; 13% of OUT patients died compared with 5% of the IN patients.

Unfavorable outcome and death were also more common in patients with more severe stroke (NIHSS score 25 or greater) and in those older than 80 years.

In Japan, more than 25% of ischemic strokes occur in patients aged 80 or older, the authors note. In an email to Reuters Health, Dr. Koga said, "We think that the safety of low-dose rtPA (0.6 mg/kg alteplase) therapy was demonstrated in Japanese patients with stroke outside European indications."

"We believe that patients with 'aged over 80 years' and those with NIHSS score of 25 or more may still be able to gain beneficial effect from rtPA therapy, because they often have unfavorable outcome," Dr. Koga added.

He said the effectiveness of treating outside the European indications is still a matter of debate, however.

"Our study is not a randomized comparison between those with rtPA and those without. Furthermore RCTs on rtPA did not include a sufficient number of patients aged over 80 years," Dr. Koga noted.

Stroke 2011.

Thrombolysis for Acute Stroke in Hemodialysis: International Survey of Expert Opinion

Santiago Palacio, Nicole R. Gonzales,† Navdeep S. Sangha,† Lee A. Birnbaum,* and Robert G. Hart**

Summary

Background and objectives Although data are absent, it has been stated that thrombolysis is probably not safe in the treatment of acute stroke in patients undergoing hemodialysis. The objective of this study was for stroke experts to define the range of management concerning thrombolytic treatment of acute stroke in hemodialysis.

Design, setting, participants, & measurements Sixty-five stroke experts in thrombolytic therapy of acute ischemic stroke were queried regarding their personal experience in the use of thrombolysis in hemodialysis patients. Hypothetical case scenarios were presented.

Results Of the 65 stroke experts who were queried, 40 (62%) responded. One-third of the responders had previously treated hemodialysis patients with recombinant tissue-type plasminogen activator (rt-PA). Most favored use of intravenous rt-PA for hemodialysis patients with acute ischemic stroke. When presented with a case of a patient who had recently undergone dialysis with a mildly prolonged activated partial thromboplastin time (aPTT), 50% favored immediate intravenous thrombolysis. Seventy-eight percent of the experts would have considered an intra-arterial approach and would have preferred mechanical clot retrieval to thrombolysis.

Conclusions Despite the acknowledged absence of data and prevalent concerns about bleeding risk, most surveyed experts favored its use. One-third reported treating hemodialysis patients with this therapy. Although these results do not substitute for data, they usefully define the range of current practice of stroke experts.

Clin J Am Soc Nephrol 6: 1089–1093, 2011. doi: 10.2215/CJN.10481110

*Department of Neurology, University of Texas Health Science Center, San Antonio, Texas; and †Department of Neurology, University of Texas Health Science Center, Houston, Texas

Correspondence: Dr. Santiago Palacio, Department of Neurology, University of Texas Health Science Center, 8300 Floyd Curl Drive MC# 7883, San Antonio, TX 78229-3900. Phone: 210-450-0530; Fax: 210-562-9371; E-mail: palacios0@uthscsa.edu

Introduction

An estimated 1.5 million patients with end-stage renal disease receive chronic hemodialysis worldwide (1). Hemodialysis serves as a multiplier for other vascular risk factors, and stroke rates are substantial, averaging approximately 4% per year with an estimated 60,000 acute ischemic strokes occurring annually among hemodialysis patients (2). Hemodialysis treatment is often complicated by relative hypotension, and although data are limited, a substantial fraction (approximately 30%) of strokes appear to occur during or immediately after hemodialysis (2,3). Most patients receive intravenous heparin at the onset of or during hemodialysis, typically carried out 3 times weekly, and consequently hemodialysis patients with acute stroke are more likely to present to the emergency department with elevated prothrombin times/partial thromboplastin times (4). Even between dialysis treatments, patients are predisposed to bleeding, suspected to be due to uremic platelet dysfunction (5). For these reasons, the benefit and particularly the risk of intravenous thrombolytic therapy given for acute ischemic stroke may hypothetically be different for patients undergoing chronic hemodialysis compared with other patients.

Should hemodialysis patients experiencing acute ischemic stroke be treated with thrombolytic therapy applying the same criteria as for patients without renal failure? Clinical trials testing intravenous recombinant tissue-type plasminogen activator (rt-PA) for acute ischemic stroke did not specifically exclude hemodialysis patients. However, there are no good published data addressing the safety or efficacy of thrombolysis for hemodialysis patients with acute ischemic stroke. A single case report of a hemodialysis patient given intravenous rt-PA reported a good outcome, albeit with asymptomatic hemorrhagic transformation (6). Major guidelines are silent on this issue. Relevant to rt-PA treatment of hemodialysis patients with acute ischemic stroke, major guidelines recommend that the activated partial thromboplastin time (aPTT) must be in the normal range if heparin has been given in the previous 48 hours (7–10). In the absence of better information, we solicited the experience and opinions of 64 experts in thrombolytic therapy of acute stroke.