方，Neuroform^{TM}を用いた臨床治験では，6.6%において血栓性合併症が生じたものの，morbid-mortalityは2.9%であり，3年間のフォローアップにおいて瘤内血栓化の促進と，コイルの安定性が確認されている[18]．一方，ステント内の狭窄は5.8%に認められ[19]，長期フォローアップの重要性が強調されている．

ステント，VRDにおいて最も心配な点は，ストラットによる分枝の閉塞であるが，実験的にも[20]，また臨床的にも[21,22]開存が保たれ，ほとんど問題ないとされている．また，ステント留置後の血管壁の変化については，4ヵ月で十分なステント上の内皮化が認められた[23]との報告がある．治療において両者とも従来法よりも抗血小板剤による血栓形成の確実な予防が必須であるが，瘤の根治的治療を実現する上で安全かつ有用なデバイスであると考えられる．

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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

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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.

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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.

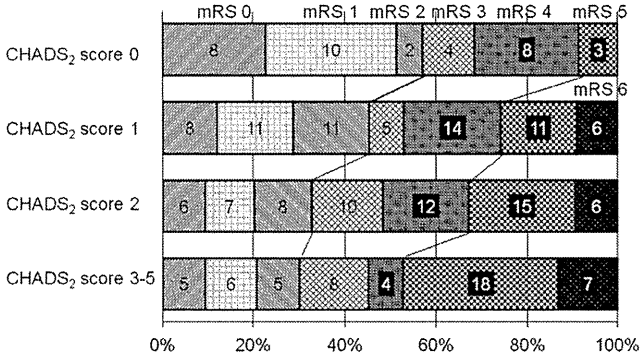

Fig. 1. $CHADS_2$ score and modified Rankin Scale at 3 months after stroke onset. The percentage of patients with mRS ≤ 2 gradually decreased as $CHADS_2$ score increased. In contrast, that of patients with mRS ≥ 5 gradually increased as $CHADS_2$ score increased.

$CHADS_2$ 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.

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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.

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Carotid Duplex Ultrasonography Can Predict Outcome of Intravenous Alteplase Therapy for Hyperacute Stroke

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We evaluated whether carotid duplex ultrasonography (US) can help predict the safety and efficacy of treating hyperacute stroke with intravenous (IV) tissue plasminogen activator (alteplase) therapy. Consecutive patients with stroke were assigned to the carotid artery occlusion (CO) group or the other (non-CO) group according to US findings before or immediately after receiving IV alteplase. Effectiveness and safety outcomes included early neurologic improvement, defined as a reduction in a National Institutes of Health Stroke Scale (NIHSS) score of ≥4 points within the initial 24 hours after stroke onset; completely independent routine activity, defined as a modified Rankin Scale score of ≤1 at day 90 after stroke onset; symptomatic intracranial hemorrhage (ICH) occurring within 36 hours after stroke onset; and any ICH. We enrolled 127 patients (27 in the CO group and 100 in the non-CO group) with a median baseline NIHSS score of 13 (range, 4-30). The CO group had a higher baseline NIHSS score (median, 18 vs 12; $P = .005$). After multivariate adjustment, the CO group was inversely associated with early improvement (odds ratio [OR] = 0.26; 95% confidence interval [CI] = 0.09-0.72) and independence at day 90 (OR = 0.23; 95% CI = 0.05-0.73) and positively associated with any ICH (OR = 3.11; 95% CI = 1.23-8.48). Our findings indicate that CO identified by US in the emergency clinical setting is an independent predictor of unfavorable outcome and ICH following IV alteplase therapy. **Key Words:** Alteplase—internal carotid artery occlusion—intracranial hemorrhage—ultrasonography—outcome.

Occlusion of the internal carotid artery (ICA) often provokes severe hypoperfusion of cerebral blood flow in the affected territory. Patients who sustain acute ICA occlusion tend to have poor clinical outcomes.[1] Mortality is high in patients with malignant middle cerebral artery (MCA) infarction, resulting principally from distal ICA occlusion. The fates of patients with and without a major arterial occlusive lesion might differ after intravenous (IV) tissue plasminogen activator (alteplase) therapy, because resistance to clot lysis and the fragility of infarcted brain tissue may depend on the patency of the ICA. Rapid evaluation of arterial status in the emergency clinical setting may help predict outcome after alteplase therapy.

Magnetic resonance angiography (MRA) and computed tomographic angiography (CTA) can detect occlusions or severe stenoses of the cervicocephalic arteries supplying the infarcted area in patients with acute stroke,[2,3] as well as intracranial abnormalities with greater sensitivity and specificity, than conventional cerebral angiography.[3,4] Large ischemic lesions on diffusion magnetic resonance

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imaging (MRI) before IV alteplase therapy predict poor outcome in patients with acute ischemic stroke,[5] and diffusion–perfusion mismatch can select patients with remaining salvageable tissue.[6] But MRI takes at least 15 minutes, including equipment arrangement and patient transfer, to generate information, and CTA carries a risk of renal failure and anaphylaxis.

Carotid duplex ultrasonography (US) is another noninvasive tool that can detect major extracranial carotid arterial disease.[7-10] Compared with conventional cerebral angiography, US is not associated with such invasive complications as cerebral and systemic embolism, contrast agent anaphylaxis, acute renal dysfunction, and arterial dissection.[11] Morever, with bedside US, it takes only a few minutes to detect significant occlusive lesions of carotid arteries. US findings can help identify the mechanism and type of ischemic stroke.

We tested the hypothesis that carotid duplex US findings can help predict the outcome and safety of IV alteplase therapy for patients with hyperacute ischemic stroke.

Materials and Methods

We prospectively enrolled all patients with stroke who were admitted to our emergency stroke care unit and received IV alteplase therapy between October 2005 (when this therapy was approved in Japan) and July 2008. Our institution's Ethics Committee approved the research protocol. Patients or their representatives (eg, family members) provided written informed consent for the treatment.

Patient eligibility for IV alteplase therapy was based principally on the inclusion and exclusion criteria applied in the National Institute of Neurological Disorders and Stroke (NINDS) study[12] and in the Japan Alteplase Clinical Trial (J-ACT).[13] Each patient received a single IV dose of 0.6 mg/kg (not exceeding 60 mg) of alteplase, with 10% given as a bolus, followed by a continuous IV infusion of the remainder over 1 hour, in accordance with the Japanese guidelines for IV alteplase therapy based on the J-ACT results.[13,14] As in the NINDS study,[12] the use of antithrombotic agents were prohibited for 24 hours after onset, blood pressure was maintained at <180/105 mm Hg, and neurologic symptoms were monitored.

Clinical data included age and sex; time from symptom onset (or time when the patient last appeared to be normal) to the initiation of IV alteplase therapy; carotid artery US findings before or immediately after the initiation of alteplase therapy; National Institute of Health Stroke Scale (NIHSS) score immediately before (baseline) and 24 hours after alteplase therapy; concomitant diseases; current smoking and drinking habits; imaging data, including hemorrhagic transformation detected by computed tomography (CT) or MRI during hospitalization; stroke subtype according to Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria;[15] and modified Rankin Scale (mRS) score at day 90. Among concomitant diseases, hypertension was defined as systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg before stroke onset or the use of antihypertensive medication. Diabetes was defined as preceding fasting blood glucose ≥126 mg/dL or the use of oral antidiabetic agents or insulin. Hypercholesterolemia was defined as total plasma cholesterol level ≥220 mg/dL or the use of antihypercholesterolemic medication.

Patients underwent US after hospitalization while awaiting the results of blood tests or immediately after starting alteplase therapy. US was performed with a bedside unit (Sonos 5500; Philips Medical Systems, Tokyo, Japan) with a 3- to 11-MHz linear transducer. On US, absent color flow signals on the ICA indicates the occlusion at or proximal to the artery, and absent end-diastolic flow velocity of the ICA indicates intracranial ICA occlusion.[16] Thus, carotid artery occlusion was defined as either of these US findings (Fig 1). Based on the US findings, the patients were divided into 2 groups: those with carotid artery occlusion (designated the CO group) and those without carotid artery occlusion (designated the non-CO group).

Before alteplase therapy, all patients underwent intracranial MRA to serve as the gold standard reference of carotid US findings, unless contraindicated. MRA was performed using the 3-dimensional time-of-flight technique (repetition time/echo time, 35/7.2 msec; 20-degree flip angle) with a 1.5 T system (Magnetom Vision; Siemens, Germany).

Outcomes included early neurologic improvement, defined as a ≥4-point reduction in NIHSS score within the initial 24 hours, and complete independence in activities of daily living (ADL), defined as an mRS score of 0 or 1, at 90 days. To assess long-term independence, patients with a mRS score of ≥2 before stroke onset were excluded. Safety outcomes included any intracranial hemorrhage (ICH) confirmed by head CT or MRI during hospitalization, and symptomatic ICH defined as early ICH with neurologic deterioration corresponding to a ≥1-point increase in the NIHSS score within 36 hours after alteplase therapy.

Statistical Analysis

Sensitivity, specificity, positive predictive value, and negative predictive value for detectng patients with carotid artery occlusion by carotid US were calculated when intracranial MRA findings were used as gold standard. Continuous and categorized variables were compared using the Student *t*-test and the χ^2 test, respectively. Nonparametric independent group comparisons were done using the Mann-Whitney *U*-test. To determine independent clinical variables to predict outcomes, significant variables were analyzed in a logistic regression model, with multivariate adjustments for age, sex, and confounders with an association of $P < .05$ with each outcome in univariate analysis. Statistical significance was established at $P < .05$.

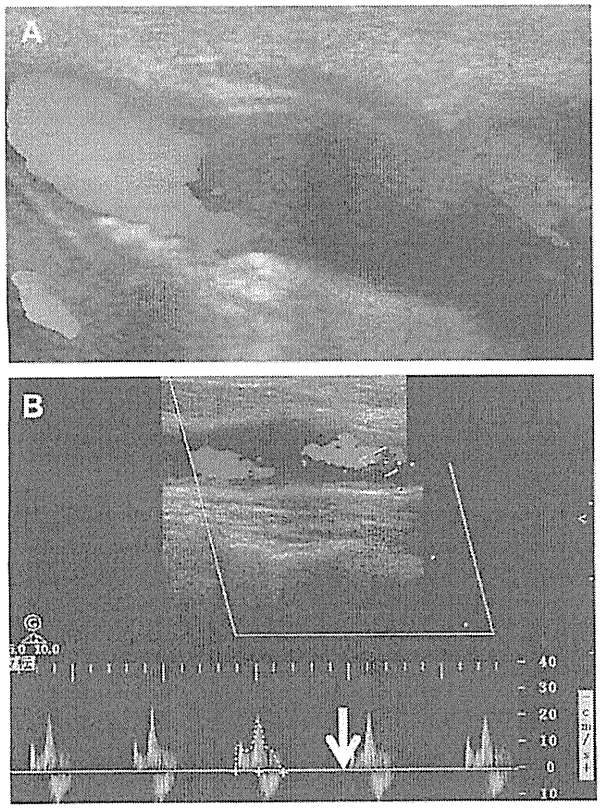

Figure 1. *Typical carotid US findings in ICA occlusion. (A) Absent flow of color in the affected ICA origin in a patient with atherothrombotic extracranial ICA occlusion. (B) Absent end-diastolic flow velocity of affected ICA (arrow) detected by pulsed Doppler US in a patient with distal ICA occlusion.*

Results

A total of 127 patients (89 men, mean age, 73 ± 9 years) were enrolled in the study. In 27 patients, carotid artery occlusion was detected by carotid US before or immediately after alteplase therapy. A total of 110 patients (87%) underwent MRA; 23 were found to have ICA occlusion. Sensitivity, specificity, positive predictive value, and negative predictive value for detect carotid artery occlusion by carotid US were 96%, 97%, 88%, and 99%, respectively. Table 1 summarizes the baseline characteristics and clinical outcomes of the study population. The median baseline NIHSS score was 13 (range, 4-30) and was higher in the CO group than in the non-CO group ($P = .005$). The median duration from symptom onset to IV alteplase therapy was 135 min (range, 50-180 min). US found no evidence of common carotid artery dissection possibly extending from the aortic arch in any patient. This finding, in combination with later examinations, ruled out aortic dissection in all patients.

Cardioembolism was the leading stroke subtype (57%). Atrial fibrillation was more common in the CO group than in the non-CO group. Early neurologic improvement and independence at day 90 were apparently less frequent in the CO group, whereas any ICH was more frequent in the CO group. Two patients in the CO group (7.4%) died within 90 days, one of symptomatic ICH and the other (who had asymptomatic ICH) of severe cerebral herniation due to massive stroke.

We used univariate analysis to test associations of the characteristic variables listed in Table 1 with outcomes (Table 2). Baseline NIHSS ($P = .042$), diabetes mellitus ($P = .049$), and carotid artery occlusion ($P = .039$) were inversely associated with early neurologic improvement. High pretreatment NIHSS score ($P = .015$) and carotid artery occlusion ($P = .002$) were inversely associated with independence at day 90. High baseline NIHSS score ($P = .047$) and carotid artery occlusion ($P = .009$) were associated with any ICH. No variables were significantly associated with symptomatic ICH.

We analyzed the contributing factors to the efficacy and safety outcomes using multivariate adjustment (Table 3). The CO group was independently associated with the absence of early neurologic improvement (odds ratio [OR] = 3.79; 95% confidence interval [CI] = 1.39-11.42; $P = .008$), absence of complete independence at day 90 (mRS score of ≥2: OR = 4.44; 95% CI = 1.38-19.96; $P = .011$), and presence of ICH (OR = 3.11; 95% CI = 1.23-8.48; $P = .016$). Diabetes mellitus (OR = 2.77; 95% CI = 1.03-8.15; $P = .043$) and low NIHSS score (OR = 1.09; 95% CI = 1.02-1.18 per 1-point decrease; $P = .011$) were associated with the absence of early neurologic improvement.

Discussion

Our data indicate that the likelihood of a good outcome was decreased and the likelihood of ICH was increased in stroke patients with US-identified ICA occlusion after IV alteplase therapy. Rapid evaluation using US thus helped predict the effectiveness and safety of alteplase therapy.

Sites of arterial occlusion before alteplase therapy have frequently been identified using transcranial Doppler (TCD) sonography. Recanalization of the ICA after IV alteplase therapy documented on TCD or angiography is reportedly complete in 10% of patients, partial in 16%, and absent in 74%.[17] In addition, terminal ICA occlusion has the least likelihood of recanalization compared with the other types of occlusion (OR = 0.1).[18] Linfante et al[19] found that patients with ICA occlusion have higher NIHSS scores on days 1 and 3 and a lower proportion of recanalization defined by TCD or MRA compared with those with MCA occlusion after alteplase therapy. Consequently, occlusions at the terminal ICA and at a tandem lesion of the ICA and MCA are predictive of poor outcome after alteplase therapy.[18,20] On the other hand, whether carotid US can detect ICA occlusion in the clinical setting of alteplase therapy has not been unequivocally established.

We used carotid US to evaluate the major cerebral arteries because Asian patients with stroke generally do

Table 1. *Baseline characteristics and clinical outcomes*

		US findings	
	Total (n = 127)	CO group (n = 27)	Non-CO group (n = 100)
Characteristic variables			
Female sex	38 (30)	8 (30)	30 (30)
Age, years	73 ± 9	75 ± 8	73 ± 10
Baseline NIHSS score	13 (4-30)	18 (5-24)	12 (4-30)§
Onset to treatment, minutes	135 (50-180)	130 (79-180)	135.5 (50-180)
Hypertension	80 (64)	21 (78)	59 (59)
Diabetes mellitus	24 (19)	5 (19)	19 (19)
Hypercholesterolemia	34 (27)	7 (26)	27 (27)
Atrial fibrillation	58 (46)	17 (63)	41 (41)‡
Current smoking	31 (25)	8 (30)	23 (23)
Alcohol	59 (47)	14 (52)	45 (45)
Stroke subtype			
Large vessel	21 (17)	7 (26)	14 (14)
Cardioembolic	72 (57)	16 (59)	56 (56)
Small vessel	2 (2)	0 (0)	2 (2)
Other	32 (26)	4 (15)	28 (28)
Outcome variables			
Early neurologic improvement*	60 (47)	8 (30)	52 (52)‡
mRS score at 3 months	3 (0-6)	4 (0-6)	2 (0-6)§
Complete independence at 3 months†	44 (35)	3 (11)	41 (41)§
Any intracranial hemorrhage	61 (48)	19 (70)	42 (42)§
Symptomatic intracranial hemorrhage	5 (4)	1 (4)	4 (4)

Values are mean ± standard deviation in age, median (range) in baseline NIHSS score, interval between onset and treatment and mRS score at 3 months, or number (%) in the remaining variables.

*Reduction in NIHSS score of ≥4 points within the initial 24 hours.

†Defined as a mRS score of 0 or 1. Eleven patients with a score ≥2 before stroke onset were excluded.

‡$P < .05$.

§$P < .01$.

not have a sufficient bone window for TCD,[21,22] and obtaining information about arterial occlusion from TCD can be difficult. As an alternative, carotid US can detect intracranial ICA occlusion based on the absence of end-diastolic flow velocity.[16] The accuracy of the diagnosis of carotid occlusion by US is sufficiently high compared with MRA findings. B-mode, color Doppler, and pulsed-wave Doppler carotid US can identify an ICA occlusion in about 5 minutes. The American Heart and Stroke Association recommends completing the initial evaluation and starting medical therapy within 60 minutes of the patient's arrival at the emergency department.[23] Head CT and bedside carotid US imaging can be completed at the emergency department within the 20 minutes or so needed to generate the results of blood tests, including serum chemistry and hemostatic parameters, at our institute.

Another reason for the routine use of carotid US is to rule out aortic dissection extending to the CCA. Concomitant aortic dissection is a conspicuous cause of in-hospital death following IV alteplase therapy in Japan (Japan Stroke Society; http://www.jsts.gr.jp [in Japanese]).

The present study has some limitations. Carotid US cannot provide information about tandem lesions. The incidence of symptomatic ICH was too low to enable an assessment of its relationship with carotid US findings.

In summary, carotid US is a simple tool for detecting ICA occlusion within a few minutes in the emergency clinical setting of hyperacute stroke. Patients with ICA occlusion according to carotid US had worse outcomes and more ICH after IV alteplase therapy. Therefore, rapid non-invasive evaluation of the carotid artery using US might improve the selection of patients likely to benefit from IV alteplase therapy. Although ICA occlusion is a pessimistic sign for success in IV alteplase therapy, patients with such a lesion may still be candidates for this therapy until an alternative therapeutic strategy is established. In the near future, endovascular thrombus retrieval and

Table 2. *Univariate analysis of outcomes*

	Early neurologic improvement*		Complete independence at day 90†		Any ICH		Symptomatic intracranial hemorrhage	
	Present (n = 60)	Absent (n = 67)	Present (n = 44)	Absent (n = 83)	Present (n = 61)	Absent (n = 66)	Present (n = 5)	Absent (n = 122)
Females	19 (32)	19 (28)	11 (25)	27 (33)	20 (33)	18 (27)	2 (40)	36 (30)
Age, years	72 ± 9	75 ± 9	71 ± 8	74 ± 10	72 ± 9	74 ± 10	78 ± 8	73 ± 10
Baseline NIHSS score	13 (5-30)	11 (4-24)‡	11 (4-30)	13 (4-26)‡	14 (4-24)	11 (4-30)‡	15 (12-21)	12 (4-30)
Onset to treatment time	127.5 (50-180)	140 (78-178)	133.5 (50-180)	139 (78-180)	139 (79-180)	133.5 (50-180)	120 (105-143)	136.5 (50-180)
Hypertension	36 (61)	44 (67)	27 (61)	53 (65)	38 (62)	42 (64)	4 (80)	76 (63)
Diabetes mellitus	7 (12)	17 (25)‡	6 (14)	18 (22)	14 (23)	10 (15)	0 (0)	24 (20)
Hyperlipidemia	16 (27)	18 (27)	11 (25)	23 (28)	13 (21)	21 (32)	0 (0)	34 (28)
Atrial fibrillation	26 (44)	32 (48)	16 (36)	42 (51)	30 (49)	28 (42)	4 (80)	54 (45)
Current smoking	10 (17)	21 (31)	9 (21)	22 (27)	16 (26)	15 (23)	1 (20)	30 (25)
Alcohol consumption	30 (51)	29 (43)	22 (51)	37 (45)	28 (46)	31 (47)	1 (20)	58 (48)
Cardioembolic (subtype)	37 (62)	35 (52)	23 (52)	49 (59)	38 (62)	34 (52)	5 (100)	67 (55)
CO group	8 (13)	19 (28)‡	3 (7)	24 (29)§	19 (31)	8 (12)§	1 (20)	26 (21)

Values are mean ± standard deviation in age, median (range) in baseline NIHSS score, and interval between onset and treatment time, or number (%).
*Reduction in NIHSS score of ≥4 points within the initial 24 hours.
†Defined as mRS score of 0 or 1. Eleven patients with a score of ≥2 before stroke onset were excluded.
‡$P < .05$.
§$P < .01$.

Table 3. *Multivariate analysis of outcomes*

	Absence of early neurologic improvement*			mRS score ≥2 at day 90			Any ICH		
	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*
CO group	3.79	1.39-11.42	.008	4.44	1.38-19.96	.011	3.11	1.23-8.48	.016
Diabetes mellitus	2.77	1.03-8.15	.043	–	–	–	–	–	–
Baseline NIHSS score (per 1-point increase)	0.91	0.85-0.98	.011	1.05	0.98-1.13	.144	1.05	0.98-1.12	.165

Adjusted for age, sex, and confounders with an association of $P < .05$ with each outcome in univariate analysis.
Symptomatic intracranial hemorrhage was not tested due to the absence of significantly associated variables in univariate analysis.
*Increase, no change, or decrease in NIHSS score of <4 points within the initial 24 hours.

sonothrombolysis may improve the outcomes of patients with ICA occlusion, at which point this quick screening using US will work well.

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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

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Key Words
Acute ischemic stroke · Cerebral infarction · Chronic kidney disease · End-stage renal disease · Hemodialysis · Renal dysfunction · rt-PA · Thrombolysis

Abstract
Background: To examine the therapeutic effect of intravenous recombinant tissue plasminogen activator (rt-PA) therapy for stroke patients receiving maintenance hemodialysis (HD). ***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, 4 patients (3 men, 64–77 years old) on maintenance HD were studied. ***Results:*** The primary kidney disease requiring HD was glomerulonephritis in 2 patients, diabetic nephropathy in 1, and undetermined in 1. The duration of HD ranged between 1.2 and 28 years. Three patients developed stroke on the day of HD, including 1 during HD and another just after HD. All patients had stroke in the carotid arterial territory. Pretreatment NIH Stroke Scale scores ranged between 4 and 20, and decreased by 2–5 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 3 did not develop hemorrhagic complications. The modified Rankin Scale score at 3 months was 0 in 1 patient, 2 in 2 patients, and 4 in 1 patient. ***Conclusions:*** rt-PA therapy for stroke patients receiving maintenance HD might improve the stroke outcome. Ectopic hematoma was a unique complication in our case series.

Introduction

Patients receiving hemodialysis (HD) have a higher risk of stroke than the general population [1], and they often develop stroke during or just after HD while they remain in the clinic [2]. Thus, HD patients might have a high opportunity to receive urgent therapies for stroke, including intravenous (IV) recombinant tissue plasminogen activator (rt-PA). HD itself is not a contraindication to IV rt-PA in several guidelines, but heparinization is. In addition, severe renal damage appears to affect the outcome after rt-PA [3, 4].

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Table 1. Baseline characteristics and physiological and laboratory data on admission

	Patient 1 female	Patient 2 male	Patient 3 male	Patient 4 male
Age, years	74	77	68	64
Body mass index	17.6	21.1	20.3	27.9
Primary kidney disease	glomerulonephritis	undetermined	diabetic nephropathy	glomerulonephritis
Duration of hemodialysis, years	28	2	1.2	24
Stage of hypertension [13]	high normal	stage I	stage I	stage II
Other vascular risk factors	atrial fibrillation[1]	sick sinus syndrome	diabetes mellitus	–
Vascular comorbidities	MI, silent brain infarct	angina pectoris	MI	–
Other comorbidities	hepatitis C virus carrier, hyperparathyroidism	–	meningioma (resected)	gastric cancer (resected)
Premorbid modified Rankin Scale score	0	0	0	0
Prior medication				
Antithrombotics	aspirin	aspirin	none	none
Antihypertensives (vasodilator)	ISDN	torasemide, ISDN	none	nifedipine, limaprost
Antidiabetics	none	none	insulin	none
Physiological/laboratory data on admission				
Blood pressure, mm Hg	202/83	165/81	150/86	218/98
Platelet count, /μl	254,000	175,000	140,000	124,000
Hemoglobin, g/dl	12.1	12.9	10.6	10.6
Prothrombin time (INR)	1.13	0.89	1.10	0.90
Activated partial thromboplastin time, s	43.5	26	36.4	32
Blood urea nitrogen, mmol/l	3.9	22.8	12.1	11.8
Creatinine, μmol/l	230	919	327	415
Blood glucose, mmol/l	5.7	10.5	12.7	5.0
Hemoglobin A_{1c}, %	4.3	5.3	5.9	not measured
Total cholesterol, mmol/l	3.29	4.12	4.17	4.25
Triglyceride, mmol/l	0.59	1.24	1.50	0.64
HDL cholesterol, mmol/l	1.14	1.48	0.83	1.40
LDL cholesterol, mmol/l	1.89	2.07	2.64	2.41

INR = International normalized ratio; ISDN = isosorbide dinitrate; MI = myocardial infarction.
[1] Identified during acute hospitalization after stroke onset.

We have reported the effects of IV rt-PA given to stroke patients with renal dysfunction using the Stroke Acute Management with Urgent Risk-factor Assessment and Improvement (SAMURAI) rt-PA Registry [4]. Reduced estimated glomerular filtration rate <60 ml/min/1.73 m^2 on admission was independently associated with intracerebral hemorrhage (ICH) within 36 h after rt-PA and unfavorable functional outcome or death at 3 months. The results suggest that end-stage renal disease (ESRD) is also associated with poor outcome after rt-PA, although, to the best of our knowledge, this issue has never been examined.

The aim of this study was to determine the effect of IV rt-PA therapy in stroke patients on maintenance HD using the same registry.

Patients and Methods

The SAMURAI rt-PA Registry had a multicenter, hospital-based, retrospective, observational, cohort design [4–6]. A total of 600 consecutive patients with acute ischemic stroke receiving alteplase at 0.6 mg/kg (the recommended dose in Japanese guidelines and the approved labeling) from October 2005 through July 2008 were registered. From the registry, ESRD patients receiving maintenance HD or peritoneal dialysis were studied. The local ethics committee approved the research protocol. Baseline characteristics, physiological and laboratory data on admission, stroke features, and outcomes were assessed for each patient. Diffusion-weighted MRI (DWI) and MRA were performed before rt-PA infusion in addition to head CT. Early ischemic change was assessed using the Alberta Stroke Program Early CT Score (ASPECTS) [6].

Results

Of the 600 patients, none were on peritoneal dialysis and 4 (0.7%, 3 men, 64–77 years old) were undergoing maintenance HD before IV rt-PA therapy. These 4 patients were studied.

Baseline characteristics and physiological and laboratory data on admission are listed in table 1. In brief, the primary kidney disease responsible for HD was glomeru-

Table 2. Stroke features and outcomes

	Patient 1	Patient 2	Patient 3	Patient 4
Timing of stroke onset	just after HD	non-HD day	2 h after HD	during HD
Major neurological signs	aphasia, unilateral spatial neglect, right hemiparesis	unilateral spatial neglect, left hemiparesis	aphasia, right facial palsy	aphasia
ASPECTS on CT	10	9	10	10
ASPECTS on DWI	9	8	9	10
Site of arterial occlusion	M2	ICA	undetectable	undetectable
Stroke territory	left carotid	right carotid	left carotid	left carotid
Stroke etiology	cardioembolism	cardioembolism	undetermined	undetermined
Onset to rt-PA time, min	130	139	150	166
Pre-rt-PA antihypertensives	none	none	none	IV nicardipine
Antithrombotic therapy after rt-PA	IV unfractionated heparin 24 h after rtPA followed by warfarin	IV argatroban 24 h after rtPA followed by warfarin	IV unfractionated heparin 24 h after rtPA followed by aspirin	IV unfractionated heparin 48 h after rtPA followed by aspirin
Timing of restarting HD after rt-PA	20 h later	20 h later	2 days later	22 h later
Intracerebral hemorrhage during acute stage	absent	absent	absent	present (see fig. 2)
NIH stroke scale score				
Baseline	20	13	11	4
24 h after rt-PA	18	11	5	5
7 days after rt-PA	18	9	6	2
Modified Rankin Scale score at 3 months	4	2	2	0

ICA = Internal carotid artery.

lonephritis in 2 patients, diabetic nephropathy in 1, and undetermined in 1. The duration of HD ranged between 1.2 and 28 years. All patients had hypertension, and 2 were taking aspirin prior to stroke. Stroke features and outcomes are listed in table 2. One patient developed stroke during HD and another just after HD. All patients had stroke in the carotid arterial territory; 2 were due to cardioembolism and 2 were of undetermined mechanisms. In the latter 2, emboligenic diseases were not identified using transesophageal echocardiography and Holter ECG. For patient 4, hemodialytic procedure by itself may be a possible cause of stroke since he developed stroke during HD. One patient needed IV antihypertensive therapy just before rt-PA. Pretreatment NIH Stroke Scale scores ranged between 4 and 20 and decreased by 2–5 points at 7 days. No patients showed neurological deterioration. The modified Rankin Scale score at 3 months was 0 in 1 patient, 2 in 2 patients, and 4 in 1 patient.

Early ischemic changes on baseline DWI are shown in figure 1. Early ischemic changes were found in the left insular and frontal cortices in patient 1, the right basal ganglia and corona radiata extending to the insular cortex in patient 2, and the left basal ganglia and corona radiata in patient 3. DWI-ASPECTS in these patients ranged between 8 and 9. In patient 4, ischemic changes were not identified on the baseline DWI, and they were later detected as tiny scattered infarcts in the left cortex. This patient developed transient headache and vomited once, 1 h after rt-PA; CT revealed an ectopic hematoma in the left temporal lobe with the left intraventricular hemorrhage. This patient had IV heparin 48 h after rt-PA, and the hematoma no longer grew after that. The other 3 patients did not develop any intracranial or systemic hemorrhagic complications.

Discussion

In this observational study, 4 stroke patients with HD receiving IV rt-PA were reported. The major finding was that 3 patients had functional independence (modified Rankin Scale score ≤ 2) at 3 months, although ICH with transient headache occurred in 1 of these 3.

Stroke patients with ESRD are at a disadvantage for IV rt-PA for several reasons [7–9]. First, advanced diabetes, which is known to be associated with poor outcome after IV rt-PA, is frequent in ESRD patients. Second, ESRD patients often have hypertension resistance to

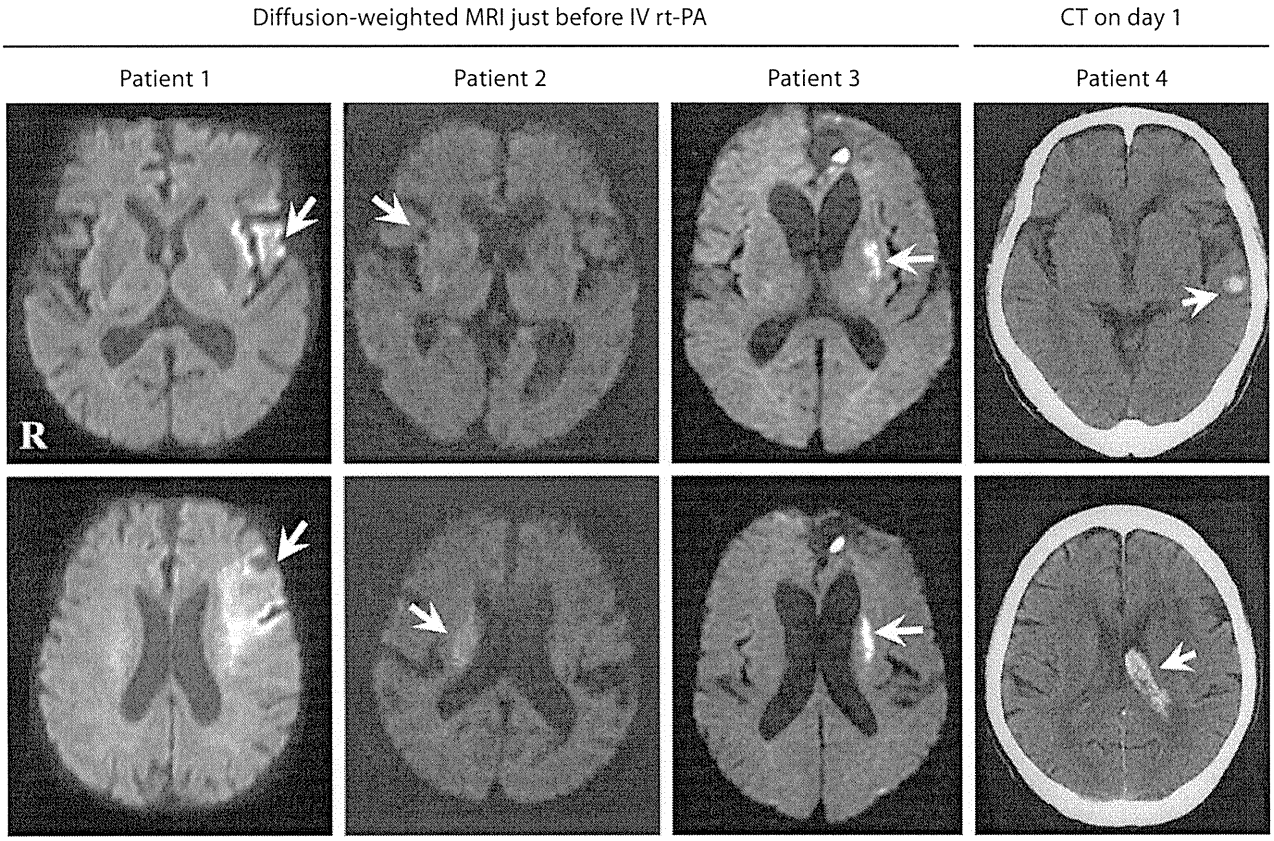

Fig. 1. DWI just before IV rt-PA therapy in patients 1–3, and CT on the day of thrombolysis in patient 4. Arrows show early ischemic changes or ectopic hemorrhage.

antihypertensives and other vascular risk factors and vascular comorbidities as predictors for a poor outcome. Third, blood surface interactions during HD lead to impairment of platelet function and a decrease in platelet number.

Another major disadvantage of ESRD patients is their high risk of ICH. Renal dysfunction is a predictor for hemorrhagic transformation in acute ischemic stroke with or without thrombolysis, presumably partly due to endothelial dysfunction related to renal dysfunction [4, 10]. Previous studies reported a relatively high percentage of ICH among total stroke in ESRD patients [1, 2]. In addition, HD is generally given three times per week using heparin as an anticoagulant, and the activated partial thromboplastin time often exceeds the normal range. A unique finding of the present study was the ectopic hematoma after rt-PA in patient 4. Since 19–35% of patients receiving HD had cerebral microbleeds documented on T_2*-weighted, gradient echo MRI [11, 12], such microbleeds might have grown to be an overt hematoma in this patient. Receiving rt-PA soon after stopping HD (although activated partial thromboplastin time returned to the normal range) and the high baseline blood pressure that required IV antihypertensive therapy may have triggered this ICH; the coexistence of such conditions may be a contraindication to rt-PA.

In spite of several disadvantages, 3 of the present 4 ESRD patients had functional independence 3 months after rt-PA. Since the study population was small, the efficacy and risk of IV rt-PA in ESRD patients could not be determined from this study alone. However, IV rt-PA does appear to be effective for some ESRD patients. A comparison between the patient having a poor outcome and the other patients suggests that initial neurological severity is a good predictor of outcome after rt-PA, as in general stroke patients. Moreover, these 4 patients, in-

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:

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Disclosure Statement

There are no conflicts of interest to disclose.

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Effects of hyperacute blood pressure and heart rate on stroke outcomes after intravenous tissue plasminogen activator

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Background and purpose The present study clarifies associations between stroke outcomes after intravenous tissue plasminogen activator (tPA) and blood pressure (BP) as well as heart rate (HR) profiles.

Methods We assessed 125 patients with stroke who received tPA within 3 h of onset. We obtained baseline, mean, maximum, minimum, and coefficient of variation values for BP and HR during the initial 24 h. The primary outcome was independence at 3 months corresponding to a modified Rankin Scale score of 2 or less. The secondary outcomes were early neurological improvement at 24 h and intracerebral hemorrhage (ICH) within 36 h.

Results Among the patients, 64 (51%) achieved independence, 66 (53%) early improvement, and 26 (21%) developed ICH. The 24-h time courses of SBP ($P=0.033$), pulse pressure (PP, $P=0.007$), and HR ($P<0.001$) were lower among patients who reached independence than among those who did not. After multivariate adjustment, 24-h mean levels of SBP (odds ratio 0.69, 95% confidence interval 0.48–0.97, per 10-mmHg increase), PP (0.63, 0.41–0.94), and HR (0.59, 0.42–0.80, per 10-bpm increase) were inversely associated with independence, as were their maximum and minimum values. In particular, mean SBP values were inversely associated with independence at 8–16 and 16–24 h (0.73, 0.54–0.97 and 0.66, 0.47–0.91, respectively), but not at 0–8 h (0.79, 0.57–1.07). Baseline and maximum SBP were inversely associated with early improvement. Maximum and coefficient of variation of SBP were associated with ICH.

Conclusion Lower SBP, PP, and HR values during the initial 24 h after tPA, especially at 8 h thereafter, were associated with independence at 3 months. *J Hypertens* 29:000–000 © 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Keywords: blood pressure, heart rate, hypertension, outcome, stroke, thrombolysis, tissue plasminogen activator

Abbreviations: ADL, activities of daily living; BP, blood pressure; HR, heart rate; ICH, intracerebral hemorrhage; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; tPA, tissue plasminogen activator

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Introduction

Intravenous (i.v.) thrombolytic therapy using tissue plasminogen activator (tPA) is currently the only evidence-based pharmacotherapy for treating hyperacute ischemic stroke [1–3]. High baseline blood pressure (BP) prior to tPA reportedly results in poor outcomes for some patients after tPA partly because of an increased risk of intracerebral hemorrhage (ICH) [4–6] and favorable outcomes for others [7]. Thus, high baseline BP might not be an ideal outcome predictor. Other studies have revealed a close association between the course of high BP during the initial 24 or 72 h after stroke and poor long-term outcomes [7–9]. Generally, avoidance of an obviously elevated BP is recommended both before and soon after thrombolysis [10]. As BP often fluctuates on the day of stroke occurrence, generally reaching a peak upon hospital admission and falling thereafter [11,12], it is important to clarify which characteristics of acute BP profiles affect outcomes after tPA.

The results of the Japan Alteplase Clinical Trial (J-ACT) led to i.v. thrombolysis with alteplase (0.6 mg/kg) within 3 h of stroke onset being approved in Japan during 2005 [13]. The efficacy of this low-dose tPA strategy was determined by a postmarketing, multicenter, observational study [14]. According to the guidelines published by the Japan Stroke Society (JSS) [15], the vital signs of all of our patients were frequently measured during the initial 24 h after i.v. tPA thrombolysis. Thus, we obtained complete data for consecutive tPA-treated patients to analyze the initial 24-h course of BP. We also postulated that the 24-h course of heart rate (HR), which is another essential, easily measurable and understudied sign, could predict outcomes. We, therefore, clarified the influence of 24-h BP and HR profiles on

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early and long-term outcomes of stroke patients after receiving i.v. low-dose tPA.

Patients and methods

Patient population

We registered 130 consecutive Japanese patients with stroke who were treated with i.v. tPA within 3 h of symptom onset and admitted to our stroke care unit between October 2005 and August 2008. Patient eligibility for i.v. tPA therapy was determined based principally on the JSS guidelines [15], which follow the inclusion and exclusion criteria applied in the National Institute of Neurological Disorders and Stroke (NINDS) tPA study [1] and J-ACT [13]. All patients received i.v. alteplase at a dose of 0.6 mg/kg with 10% administered as a bolus, followed by continuous i.v. infusion of the remainder over a period of 1 h. Of these, two patients who did not receive the full dose of tPA because of changes in their condition including vomiting during i.v. infusion and three who did not have independent activities of daily living (ADL) corresponding to a modified Rankin Scale (mRS) score of at least 3 before stroke onset were excluded, leaving 125 eligible patients (93 men, 72.7 ± 9.0 years).

Assessment of blood pressure and heart rate

BP was measured in the supine position by trained nurses using a standard mercury sphygmomanometer; the average of two consecutive measurements spaced by 1–2 min, and additional measurements if the first two were quite different, was used for analysis [16]. Baseline BP and HR values of the patients were recorded immediately upon arrival at the emergency room. i.v. tPA therapy was initiated at the stroke care unit, and patients remained there for at least 2 days. After starting tPA infusion, BP and HR were measured every 15 min during the first 2 h, every 30 min from 2 to 6 h, and then hourly from 6 to 24 h. To characterize BP and HR profiles, we calculated the mean, maximum, minimum, and coefficient of variation (coefficient of variation = standard standard deviation/mean value × 100%) values during the initial 24 h after i.v. tPA, as well as the mean values between 0 and 8 h, 8 and 16 h, and 16 and 24 h. According to the guidelines, antihypertensive agents were administered when SBP was at least 185 mmHg or DBP at least 110 mmHg just before i.v. tPA, and SBP more than 180 mmHg or DBP more than 105 mmHg during the initial 24 h after i.v. tPA [10,15]. i.v. nicardipine was the first choice agent.

Baseline characteristics

We determined the following baseline characteristics from the prospective database: sex, age, hypertension (BP ≥140/90 mmHg before stroke onset or taking regular antihypertensive agents), diabetes mellitus (fasting blood glucose ≥7.0 mmol/l, hemoglobin (Hb) A1c ≥6.5%, or taking antidiabetic agents), hyperlipidemia (total cholesterol ≥5.7 mmol/l, triglyceride ≥1.7 mmol/l, or taking antihyperlipidemic agents), atrial fibrillation (documented during hospitalization or a history of atrial fibrillation), previous symptomatic ischemic stroke, current smoking habit, and antihypertensive and antithrombotic use prior to onset. Stroke subtype was determined according to the TOAST subtype classification system [17].

On admission, blood tests included blood glucose and HbA1c. Kidney function was evaluated based on the estimated glomerular filtration rate (eGFR) using a revised equation for the Japanese population [18]; eGFR (ml/min/1.73 m^2) = 194 × (serum creatinine)$^{-1.094}$ × (age)$^{-0.287}$ × 0.739 (for women). To calculate eGFR, the admission serum creatinine was used.

Before i.v. tPA, all patients underwent brain noncontrast ~~CT~~, as well as intracranial magnetic resonance angiography (MRA, unless contraindicated). The Alberta Stroke Program Early CT score (ASPECTS) on CT, a 10-point quantitative topographic scoring method of early ischemic signs in the middle cerebral arterial (MCA) territory, as well as the arterial occlusion site ipsilateral to ischemia was assessed by at least two vascular neurologists [19]. AQ2

Outcomes

The primary outcome was independent ADL at 3 months corresponding to a mRS score of 2 or less. We researched the 3-month outcome by clinical examination at a hospital clinic (or by phone survey for patients whose neurological deficits were too severe to visit the clinic). The secondary outcomes consisted of early neurological improvement defined as a reduction of at least 4 points from the baseline National Institutes of Health Stroke Scale (NIHSS) score or a total NIHSS score of 0 or 1 at 24 h after i.v. tPA, and ICH defined as CT evidence of new ICH within 36 h after i.v. tPA regardless of additional symptoms.

Control of blood pressure and blood glucose

Control of BP and blood glucose after the initial 24 h was achieved principally according to the JSS guidelines 2004 [15]. During the initial weeks, the guidelines recommend to treat high BP only when BP exceeds 220/130 mmHg or patients have underlying severe cardiovascular diseases. However, we usually maintained BP levels in these weeks more strictly to less than 180/105 mmHg as we did during the initial 24 h. During the chronic stage, the guidelines recommend to lower BP to less than 170/95 mmHg as an example. The guidelines advocated that hyperglycemia should be corrected but did not specify absolute goals. We treated patients with antidiabetic agents principally when HbA1c exceeded 6.5%.

Statistical analysis

Data were statistically analyzed using JMP 7.0 software (SAS Institute Inc, Cary, North Carolina, USA). Statistical

significance for the two groups was assessed by Mann–Whitney *U*-tests for continuous variables and Pearson χ^2 tests for categorical variables. We compared the 24-h BP or HR time course between patients with and without each outcome using the two-way repeated measures analysis of variance (ANOVA). Predictors for each outcome were determined by multivariate analyses based on the baseline characteristics, blood tests on admission including eGFR, and 24-h BP and HR profiles of the patients. A backward selection procedure was performed for each outcome using *P* more than 0.10 of the likelihood ratio test for exclusion. A level of *P* less than 0.05 was considered statistically significant.

Results

Of the 125 eligible patients, 89 (71%) had hypertension and 49 (39%) were treated with antihypertensive agents before stroke onset. The median baseline NIHSS score was 13 [interquartile range (IQR) 7–18]. With respect to outcomes, 64 (51%) achieved independent ADL at 3 months, 66 (53%) early neurological improvement, and 26 (21%) developed ICH. The baseline characteristics, stroke features, clinical status, and baseline BP and HR were summarized in Table 1. BP was less than 180/105 mmHg during the initial weeks and less than 170/95 mmHg during the following period for all patients.

Figure 1 shows the initial overall 24-h SBP, DBP, and HR courses for all patients. Both SBP and DBP decreased by about 10 mmHg from the baseline measurement to the initiation of i.v. tPA, decreased by about 2 mmHg 2 h after initiation, and reached a plateau thereafter. HR mildly decreased during this period.

Between patients with and without independence, two-way repeated measures ANOVA showed differences in the 24-h time courses of SBP ($P=0.033$), PP ($P=0.007$), and HR ($P<0.001$; Fig. 2). Levels of SBP and PP were similar within the initial hours between patients with and without independence and differed later. After multivariate adjustment, mean, maximum, and minimum levels of SBP ($P=0.035$, $P=0.013$, and $P=0.027$, respectively), PP ($P=0.029$, $P=0.018$, and $P=0.020$, respectively), and HR ($P=0.001$, $P=0.004$, and $P=0.010$, respectively) during the 24 h were inversely associated with independence (Table 2). When these physiological parameters were separately assessed at different intervals, mean SBP at 8–16 ($P=0.037$) and 16–24 h ($P=0.014$), mean PP at 8–16 ($P=0.046$) and 16–24 h ($P=0.023$), and mean HR at 0–8 ($P=0.007$), 8–16 ($P<0.001$), and 16–24 h ($P=0.002$) were inversely associated with independence.

Between patients with and without early improvement, the ANOVA showed differences in the 24-h time course of HR ($P=0.019$; Fig. 3), but not in those of SBP ($P=0.141$), DBP ($P=0.286$), or PP ($P=0.156$). After multivariate adjustment, baseline and maximum levels of SBP ($P=0.031$ and $P=0.023$, respectively) and baseline PP ($P=0.018$) during the 24 h were inversely associated with early improvement.

Between patients with and without ICH, the ANOVA did not identify differences in the 24-h time courses of SBP ($P=0.098$), PP ($P=0.052$; Fig. 3), DBP ($P=0.836$), or HR ($P=0.886$). After multivariate adjustment, maximum level and coefficient of variation of SBP ($P=0.028$ and $P=0.021$, respectively) and PP ($P=0.005$ and $P=0.013$, respectively) during the 24 h were positively associated with ICH.

Table 1 Baseline characteristics

	All patients ($n=125$)
Baseline characteristics	
Men	93 (74%)
Age, years	72.7 ± 9.0[§]
Hypertension	89 (71%)[§]
Diabetes mellitus	25 (20%)
Hyperlipidemia	58 (40%)[§]
Atrial fibrillation	61 (49%)[§]
Previous ischemic stroke	25 (20%)
Current smoking habit	31 (25%)[†]
Antihypertensive use prior to onset	49 (39%)
Antithrombotic use prior to onset	45 (36%)
Blood tests on admission	
Blood glucose, mmol/l	8.23 ± 2.91
HbA1c, %	5.74 ± 1.15
eGFR, ml/min/1.73 m^2	67.81 ± 24.01[§]
Stroke features and clinical status	
Subtypes[§]	
Cardioembolic	71 (57%)
Atherothrombotic	22 (18%)
Lacunar	0 (0%)
Other	32 (25%)
Site of occlusion on MRA[*,§]	
Internal carotid artery	21 (18%)
MCA trunk	28 (24%)
MCA branch	16 (14%)
Vertebral/basilar artery	2 (2%)
Other site/no occlusion	35 (42%)
ASPECTS on CT	9 (7–10)[‡]
Baseline NIHSS score	13 (7–18)[§]
NIHSS score at 24 h	8 (3–15)[‡]
Antihypertensive use within 24 h	28 (22%)
Baseline BP and HR	
SBP, mmHg	158.4 ± 33.0[†]
DBP, mmHg	88.1 ± 19.4
PP, mmHg	70.3 ± 23.4[†]
HR, bpm	77.9 ± 19.8

Data are expressed as mean ± SD, median (interquartile range), or *n* (%) as appropriate. ASPECTS, Alberta Stroke Program Early CT score; BP, blood pressure; eGFR, estimated glomerular filtration rate; HR, heart rate; MRA, magnetic resonance angiography; NIHSS, National Institutes of Health Stroke Scale; PP, pulse pressure. *22 patients contraindicated for MRA were excluded. [§]$P<0.05$ between patients with and without independent activities of daily living (ADL); age (70.4 ± 9.2 vs. 75.1 ± 8.2 years, $P=0.007$), hypertension (63 vs. 80%, $P=0.028$), hyperlipidemia (48 vs. 31%, $P=0.049$), atrial fibrillation (39 vs. 59%, $P=0.026$), eGFR (72.92 ± 27.01 vs. 62.44 ± 19.18 ml/min/1.73 m^2, $P=0.021$), stroke subtypes (cardioembolism, 53 vs. 61%; atherothrombotic, 11 vs. 25%; other, 36 vs. 15%; $P=0.011$), site of occlusion on MRA (internal carotid artery, 8 vs. 28%; MCA trunk, 16 vs. 32%; MCA branch, 13 vs. 14%; vertebral/basilar artery, 2 vs. 2%; other site or no occlusion, 61 vs. 24%; $P=0.002$), baseline NIHSS score [12 (7–15) vs. 16 (10–20), $P<0.001$], NIHSS score at 24 h [4 (1–7) vs. 16 (11–20), $P<0.001$]. [†]$P<0.05$ between patients with and without early neurological improvement; current smoking (17 vs. 34%, $P=0.026$), SBP (152.6 ± 32.9 vs. 164.7 ± 32.2 mmHg, $P=0.008$), PP (65.6 ± 23.1 vs. 75.6 ± 22.7 mmHg, $P=0.015$). [‡]$P<0.05$ between patients with and without ICH; NIHSS score at 24 h [14 (11–18) vs. 7 (2–14), $P<0.001$], ASPECTS on CT [8 (6–9) vs. 9 (8–10), $P=0.003$].