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

本研究成果の国際学会発表一覧、演題抄録

4th Korean-Japanese Joint Stroke Conference, Fukuoka, 2008/11/21-23

1. Koga M, Toyoda K, Naganuma M, et al: Nationwide survey for hyperacute blood pressure lowering in patients with intracerebral hemorrhage in Japan.

18th European Stroke Conference, Stockholm, Sweden, 2009/5/26-29

2. Koga M, Toyoda K, Naganuma M, et al: Expert opinions on hyperacute blood pressure lowering in patients with intracerebral hemorrhage.
3. Toyoda K, Naganuma M, Koga M, et al: Stroke features and outcome of 600 patients receiving intravenous low-dose rt-PA for ischemic stroke: a Japanese multicenter observational study.

International Stroke Conference 2010, San Antonio, USA, 2010/2/24-26

4. Koga M, Kimura K, Shibasaki K, et al: Lower CHADS2 score is associated with favorable clinical outcome after intravenous rt-PA therapy in stroke patients with AF.
5. Koga M, Naganuma M, Shiokawa Y, et al: Low-dose intravenous rt-PA therapy for stroke patients out of the indications by the European licence: the SAMURAI study.
6. Mori M, Naganuma M, Okada Y, et al: Predictors of acute clinical deterioration in stroke patients receiving intravenous low-dose rt-PA: a multicenter observational study.
7. Naganuma M, Koga M, Shiokawa Y, et al: Reduced estimated glomerular filtration rate is associated with stroke outcomes after intravenous low-dose rt-PA: the Stroke Acute Management with Urgent Risk-factor Assessment and Improvement (SAMURAI) Study.
8. Nezu T, Koga M, Kimura K, et al: Pre-treatment DWI-ASPECTS has a relation with functional outcome at 3 months following intravenous rt-PA therapy.
9. Nezu T, Koga M, Kimura K, et al: Pre-treatment DWI-ASPECTS is superior to ct-aspects in detecting excellent to fairly good outcome after intravenous rt-PA therapy.
10. Yamagami H, Koga M, Shiokawa Y, et al: Impact of antiplatelet pre-treatment on intracranial hemorrhage and stroke outcome after intravenous thrombolysis: the Stroke Acute Management with Urgent Risk-factor Assessment and Improvement (SAMURAI) Study.

19th European Stroke Conference, Barcelona, Spain, 2010/5/25-28

11. Nishiyama M, Shiokawa Y, Yamada S, et al: Hemorrhagic transformation associated with intravenous low-dose recombinant tissue plasminogen activator therapy in Japanese patients from the SAMURAI rt-PA Registry.
12. Toyoda K: Acute stroke management in Japan: insights from the SAMURAI study. (Invited symposium)

10th Tiantan International Stroke Conference 2010, Beijing, China 2010/6/25-27

13. Toyoda K: Intravenous low-dose rt-PA for ischemic stroke: messages from SAMURAI rt-PA Registry. (Invited symposium)

7th World Stroke Congress, Seoul, Korea 2010/10/13-16

14. Endo K, Koga M, Sakai N, et al: Etiology, clinical profiles, treatment, and outcomes of acute ischemic stroke with major cerebral artery occlusion in Japan.
15. Kato T, Akiyama H, Hasegawa Y, et al: "Weekend effect" in thrombolytic therapy for acute ischemic stroke patients in a collaborative study of stroke centers in Japan.
16. Koga M, Endo K, Sakai N, et al: Characteristics of acute stroke patients with major artery occlusion who did not receive recanalization therapy.
17. Miyagi T, Koga M, Shiokawa Y, et al: Low-dose intravenous rt-PA therapy for acute stroke patients with the basilar artery occlusion.
18. Toyoda K: Intravenous low-dose rt-PA for ischemic stroke: SAMURAI rt-PA Registry. (Invited)
19. Yamagami H, Sakai N, Endo K, et al: Associations between treatment and outcomes in acute ischemic stroke with major cerebral artery occlusion.

International Stroke Conference 2011, Los Angeles, USA, 2011/2/9-11

20. Maeda K, Koga M, Okada Y, et al: Nationwide survey of expert opinions to restart anticoagulant therapy after intracerebral hemorrhage for patients with nonvalvular atrial fibrillation.
21. Makihara N, Okada Y, Koga M, et al: High-density lipoprotein cholesterol level is a predictor of outcome after intravenous recombinant tissue plasminogen activator therapy for acute stroke: the Stroke Acute Management with Urgent Risk-factor Assessment and Improvement (SAMURAI) rt-PA Registry.
22. Miyagi T, Koga M, Nakagawara J, et al: Intravenous rt-PA therapy for stroke patients without cerebral artery occlusion: SAMURAI Stroke Registry.
23. Nezu T, Koga M, Shiokawa Y, et al: Female sex is associated with unfavorable outcomes following low-dose intravenous rt-PA therapy: the SAMURAI rt-PA Registry.
24. Sakai N, Toyoda K, et al: Mechanical thrombectomy by the penumbra system has the potential to improve neurological and functional outcomes in japanese patient with acute ischemic stroke.

20th European Stroke Conference, Hamburg, Germany, 2010/5/25-28

25. Endo K, Kario K, Namekawa M, et al: Early Systolic Blood Pressure Variability is Associated with Stroke Outcome after Intravenous rt-PA: Stroke Acute Management with Urgent Risk-factor Assessment and Improvement (SAMURAI) rt-PA Registry.
26. Koga M, Yamagami H, Okada Y, et al: Moderately aggressive blood pressure lowering using intravenous nicardipine for acute intracerebral hemorrhage: an interim report of a multicenter, prospective, observational study.
27. Noda T, Okuda S, Koga M, et al : Edaravone usage in Japanese stroke patients treated with intravenous low-dose recombinant tissue plasminogen activator: the SAMURAI rt-PA Registry

≪抄録集≫

4th Korean-Japanese Joint Stroke Conference, Fukuoka, 2008/11/21-23

1. **Koga M, Toyoda K, Naganuma M, et al: Nationwide survey for hyperacute blood pressure lowering in patients with intracerebral hemorrhage in Japan.**

Purpose: Although acute hypertension is a major determinant of hematoma enlargement and poor clinical outcome in patients with intracerebral hemorrhage (ICH), there is no established strategy for the control of blood pressure (BP) during the acute phase. We conducted a nation-wide survey to reveal the expert opinions on the hyperacute antihypertensive treatment (AHT) in ICH patients.
Methods: The questionnaires in terms of the AHT strategies were sent to the responsible neurosurgeons/neurologists for stroke management in 1424 hospitals authorized by the Japan Neurosurgical Society, Societas Neurologica Japonica, and Japan Stroke Society. We report the interim results.
Results: Of 403 responders, 376 (93%) belonged to the hospital where acute ICH patients were managed. Of them, 374 responders (99.5%) agreed with AHT within 24 hours, and 315 (84%) started AHT immediately after the initial imaging. The threshold of systolic BP (SBP) for the initiation of AHT and the goal of SBP lowering were 160 and 150 mmHg in median, respectively. The most commonly used IV drug was nicardipine (59%), followed by diltiazem (33%); though a label of nicardipine in Japan does not recommend its usage for hyperacute ICH. As a second choice, 26% more responders chose nicardipine. Most responders who chose nicardipine (95%) reported that the drug has advantage in the power of BP reduction.
Conclusions: The expert opinions in Japan indicated that practical strategies for hyperacute BP reduction in ICH patients, including the target BP and the choice for antihypertensive agents, were different from the recommendations by the AHA and Japanese guidelines.

####

18th European Stroke Conference, Stockholm, Sweden, 2009/5/26-29

2. **Koga M, Toyoda K, Naganuma M, et al: Expert opinions on hyperacute blood pressure lowering in patients with intracerebral hemorrhage.**

Background: Acute hypertension is a major determinant of hematoma enlargement and poor clinical outcome in patients with intracerebral hemorrhage (ICH). It remains unknown, however, how to control blood pressure (BP) during the acute phase of ICH. We conducted a nationwide web questionnaire survey to reveal expert opinions on this issue in Japan. Methods: We sent the questionnaires to neurosurgeons, neurologists and others responsible for ICH management in 1424 hospitals authorized by the Japan Stroke Society, Japan Neurosurgical Society, and Societas Neurologica Japonica in July, 2008.
Results: Of 600 responders, 92% belonged to hospital where they managed acute ICH patients. Of them, 99.6% agreed with starting antihypertensive treatment within 24 hours after ICH onset, and 85% started it at an emergency room or CT/MRI room immediately after the diagnosis of ICH was made. Most of them answered that the threshold of SBP for the initiation of antihypertensive treatment was at 180 mmHg (36%) or 160 mmHg (31%), being significantly

different between neurosurgeons (median 160 mmHg, n=456) and neurologists/others (180 mmHg, n=92; p<0.001). The goal of SBP lowering was also biphasic, ≤ 160 mmHg (29%) and ≤ 140 mmHg (30%), being also different between neurosurgeons (median ≤ 150 mmHg) and neurologists/others (≤ 160 mmHg, p<0.001). Nicardipine was the first choice intravenous drug for 57% and the second choice for 27% of the responders. Twenty six percent answered, however, that nicardipine use is inappropriate mainly because of the Japanese official label contraindicating the use of nicardipine for hyperacute ICH patients while active intracranial bleeding continues. Conclusions: Japanese expert opinions especially by neurosurgeons recommended more aggressive BP lowering than indicated by the EUSI and AHA/ASA recommendations for acute ICH patients. Nicardipine was the most frequently used antihypertensive agent, but this was in conflict with the Japanese official label.

####

18th European Stroke Conference, Stockholm, Sweden, 2009/5/26-29

3. **Toyoda K, Naganuma M, Koga M, et al: Stroke features and outcome of 600 patients receiving intravenous low-dose rt-PA for ischemic stroke: a Japanese multicenter observational study.**

Background: For patients with acute ischemic stroke, IV rt-PA therapy using 0.6 mg/kg alteplase was approved in Japan in 2005. We conducted an observational study to clarify the actual conditions of this low-dose rt-PA therapy in major stroke centers.
Methods: Consecutive stroke patients treated with rt-PA from October 2005 (time of the approval) through July 2008 were registered from 10 Japanese stroke centers located without regional imbalance.
Results: A total of 600 stroke patients (377 men, 72±12 years in age) were studied, which occupied ≈4.4% of overall rt-PA-treated patients in Japan. Median baseline ASPECTS (perfect score of 10) was 10 on baseline CT (IQR 8 – 10, for 503 patients) and 9 on DWI (7 – 10, for 498 patients). The internal carotid artery was occluded in 16.5%, M1 in 28.4%, and M2 in 19.4% for 546 patients evaluated mainly using MRA. IV antihypertensive drugs were used just before rt-PA for 27.6% of patients, and IV edaravone, a free radical scavenger, was used in the hyperacute stage for 83.7%. Mean NIHSS scores decreased from 13 (IQR 7 – 19) before rt-PA to 8 (3 – 16) 24 h later. Any intracranial hemorrhage (ICH) developed in 19.8% of patients (PH1 5.0%, PH2 3.5%); symptomatic ICH with ≥1-point increase in NIHSS within 36 h developed in 3.7%. The leading stroke subtype at the final diagnosis was cardioembolism (63.3%). At 3 months, 37 patients (6.2%) were dead. For 469 patients (39.2%) with a premorbid mRS score ≤ 1 and without dropout for follow-up, 184 (39.2%) had a mRS score ≤ 1 at 3 months; when patients with ≥81 years or those with the baseline NIHSS score ≥25 were excluded from the analysis according to the criteria by SITS-MOST, 43.1% had the score ≤ 1.
Conclusions: In our multicenter survey, 3-month outcome of patients receiving low-dose IV rt-PA therapy using 0.6 mg/kg alteplase was similar to or better than those from Western trials and post-approval surveys using a dose of 0.9 mg/kg and that from a Japanese nationwide post-approval survey (unpublished interim report).

####

International Stroke Conference 2010, San Antonio, USA, 2009/2/24-26

4. **Koga M, Kimura K, Shibasaki K, et al: Lower CHADS2 score is associated with favorable clinical outcome after intravenous rt-PA therapy in stroke patients with AF.**

Background: $CHADS_2$ score is useful to predict the risk of ischemic stroke in patients with atrial fibrillation (AF). This study aimed to test whether $CHADS_2$ score can predict clinical outcome following intravenous alteplase (rt-PA) therapy in patients with AF.
Methods: A retrospective, multicenter, observational study was conducted to clarify the actual conditions of IV rt-PA therapy in 10 major stroke centers in Japan. Studied were a total of 218 consecutive stroke patients with AF (126 men, 74±10 years old) who were independent in activities of daily living corresponding to a modified Rankin Scale (mRS) ≤2 before symptom onset , and treated with intravenous rt-PA from October 2005 through July 2008. $CHADS_2$ score was calculated from five risk factors as follows: 2 points for prior ischemic stroke and 1 point for each of patients aged ≥75 years, with hypertension, with diabetes mellitus and with congestive heart failure. The outcomes were: any intracerebral hemorrhage (ICH) defined as CT evidence of new ICH within the initial 36 hours; symptomatic ICH with an increase of ≥1 point from the baseline NIHSS score; chronic independency at 3 month corresponding to mRS ≤2; and cardiovascular events, including stroke recurrence, within 3 months after rt-PA therapy.
Results: The median $CHADS_2$ score was 2 (IQR 1-2). The distribution of patients with each $CHADS_2$ score was: score of 0, 16.0%; 1, 30.3%; 2, 29.4%; 3, 13.3%; 4, 8.7%; 5, 2.3%; and 6, 0%. The median (IQR) of initial NIHSS score was 14.5 (9-20) in total, and it was 12 (7-17) in patients with $CHADS_2$ score of 0, 15 (9-20) with the score of 1, 14.5 (9.25-20.75) with the score of 2 and 16 (10.5-20.5) with the scores of 3 to 5 (p=0.30). Any ICH (symptomatic ICH) was found in 20.0% (2.9%), 27.3% (4.6%), 39.1% (10.9%) and 26.4% (0%) of patients by each $CHADS_2$ category as above, respectively. Chronic independency assessed from 193 patients who had available information was found in 62.5%, 44.1%, 32.1% and 32.6%, respectively (p=0.023). Cardiovascular events occurred in 0%, 0%, 11.9% and 9.4%, respectively. After multivariate adjustment by sex and initial NIHSS score, $CHADS_2$ score was inversely associated with chronic independency at 3 months (per 1 point increase in numerical order; OR 0.76, 95% CI 0.58-0.98; p=0.040).
Conclusion: Lower $CHADS_2$ score was associated with chronic independency at 3 months after intravenous rt-PA therapy in stroke patients with AF.

####

International Stroke Conference 2010, San Antonio, USA, 2009/2/24-26

5. **Koga M, Naganuma M, Shiokawa Y, et al: Low-dose intravenous rt-PA therapy for stroke patients out of the indications by the European licence: the SAMURAI study.**

Background: European regulatory agencies do not advocate intravenous recombinant tissue plasminogen activator (rt-PA) therapy in patients with severe stroke with NIH stroke scale

(NIHSS) score ≥25, age >80 years, and having prior stroke with concomitant diabetes, unlike the US and Japanese labelings. This study aimed to document clinical outcomes in patients treated with low-dose intravenous rt-PA (alteplase, 0.6 mg/kg) within 3 hours of stroke onset who met exclusion criteria of the above European licence.
Methods: A retrospective, multicenter, observational study was conducted to clarify the efficiency of intravenous low-dose rt-PA therapy in clinical practice in 10 major stroke centers in Japan. Studied were a total of 600 consecutive stroke patients (377 men, 72±12 years old) who were treated with rt-PA from October 2005 through July 2008. Of all the patients, 422 patients (292 men, 68±10 years old) satisfied inclusion criteria of the European licence (In-group) and 178 patients (85 men, 82±9 years old) did not (Ex-group). Baseline characteristics and clinical outcomes were compared between the two groups. Symptomatic intracerebral hemorrhage (ICH) was defined as CT evidence of new ICH within the initial 36 hours with an increase of '1 point from the baseline NIHSS score. Chronic favorable outcome was assessed by modified Rankin Scale (mRS) 0-2 at 3 months after rt-PA therapy; this outcome was evaluated only for patients who were independent (mRS 0-2) prior to stroke onset.
Results: Of 178 patients in Ex-group, 40 had severe stroke with NIHSS ≥25, 129 were >80 years old, and 25 had prior stroke and concomitant diabetes. Hypertension (68% vs. 59%, p=0.032), diabetes (24% vs. 16%, p=0.032), and atrial fibrillation (53% vs. 40%, p=0.004) were more common and hyperlipidemia (17% vs. 23%, p=0.108) was less common in Ex-group than In-group. Percentage ofpatients with premorbid mRS 0-2 was 83% in Ex-group and 98% in In-group (p=0.0001), and initial median NIHSS score was 16 and 11 (p<0.0001), respectively. As clinical outcomes, any ICH (symptomatic ICH) was observed in 15% (2%) of Ex-group and in 22% (5%) of In-group [p=0.037 (p=0.189)]. Chronic favorable outcome was found in 36% of Ex-group and 55% of In-group (p=0.0001) and mortality at 3 month was 13% and 5% (p<0.001), respectively.
Conclusion: Three-month functional and vital outcomes after low-dose rt-PA therapy in patients out of the indications by the European licence were less favorable compared with those in the others, although ICH was less common in the former than in the latter.

####

International Stroke Conference 2010, San Antonio, USA, 2009/2/24-26

6. **Mori M, Naganuma M, Okada Y, et al: Predictors of acute clinical deterioration in stroke patients receiving intravenous low-dose rt-PA: a multicenter observational study.**

Background and Purpose: The goal of this study was to determine clinical factors which contribute to acute neurological deterioration of stroke patients receiving intravenous (IV) low-dose recombinant tissue plasminogen activator (rt-PA) therapy.
Methods: A retrospective, multicenter, observational study was conducted to clarify the efficiency of IV rt-PA therapy using 0.6 mg/kg alteplase in clinical practice in 10 major stroke centers in Japan (Stroke Acute Management with Urgent Risk-factor Assessment and Improvement [SAMURAI] Study group). A total of 566 consecutive stroke patients (355 men, 72±12 years old) treated with IV rt-PA from October 2005 through July 2008 whose 24-hour

National Institute of Health Stroke Scale (NIHSS) score was available were studied. Acute deterioration was defined as 4 point or more increase in NIHSS score at 24 hour from the baseline NIHSS score.
Results: Acute deterioration was present in 56 patients (9.9 %, 38 men, 72±12 years old). Median baseline NIHSS score was 11 (IQR 7-16) in the patients with acute deterioration, and 13 (IQR 7-19) in those without (p=0.047). The patients with acute deterioration more commonly had diabetes mellitus (p=0.010), hyperlipidemia (p=0.035), internal carotid artery (ICA) occlusion (p<0.001), and prior use of oral hypoglycemic agents (p=0.028) and statin (p=0.022) than the patients without deterioration. After multivariate analysis, acute deterioration was independently related to baseline NIHSS score (OR 0.92, 95%CI 0.87-0.97 per 1-point increase, p=0.003), systolic blood pressure (1.19, 1.01-1.41 per 10-mmHg increase, p=0.040), diabetes mellitus (2.44, 1.18-4.92, p=0.014), ICA occlusion (6.96, 3.34-14.81, p<0.001). In the patients with acute deterioration, any intracranial hemorrhage (ICH, 42.9% vs. 17.5%, p<0.001) and symptomatic ICH (19.6% vs. 2.2%, p<0.001) within the initial 36 hours, as well as mortality at 3 months (25.0% vs. 4.3%, p<0.001) were more common, and independent activity of daily living, corresponding to modified Rankin Scale (mRS) ≤2, at 3 months was less common (8.7% vs. 58.5%, p<0.001) than those without deterioration.
Conclusions: Lower baseline NIHSS score, higher systolic blood pressure, diabetes mellitus, ICA occlusion were independent predictors of acute clinical deterioration in ischemic stroke patients receiving low-dose IV rt-PA therapy.

####

International Stroke Conference 2010, San Antonio, USA, 2009/2/24-26

7. **Naganuma M, Koga M, Shiokawa Y, et al: Reduced estimated glomerular filtration rate is associated with stroke outcomes after intravenous low-dose rt-PA: the Stroke Acute Management with Urgent Risk-factor Assessment and Improvement (SAMURAI) Study.**

Background: The goal of this study was to determine whether renal dysfunction affects the outcome of stroke patients treated with intravenous (IV) low-dose recombinant tissue plasminogen activator (rt-PA).
Methods: A retrospective, multicenter, observational study (the Stroke Acute Management with Urgent Risk-factor Assessment and Improvement [SAMURAI] Study) was conducted to identify effects of underlying risk factors on rt-PA therapy using 0.6 mg/kg alteplase in 10 major stroke centers in Japan. A total of 554 consecutive stroke patients (358 men, 71±12 years) with a premorbid modified Rankin Scale (mRS) ≤2 who received IV rt-PA from October 2005 through July 2008 were studied. Renal dysfunction was defined as reduced estimated glomerular filtration rate (eGFR) <60 ml/min/1.73m^2.
Results: Renal dysfunction was present in 173 patients (31.2 %). Patients with renal dysfunction were older (p<0.001), and more commonly had hypertension (p<0.001), atrial fibrillation (p=0.002), prior ischemic heart disease (p=0.004) and prior use of antithrombotic agents (p<0.001) than patients without renal dysfunction. In renal dysfunction patients, any intracranial hemorrhage (ICH, 28.3% vs 17.1%, p=0.003) and symptomatic ICH (8.1% vs 2.4%, p=0.004)

within the initial 36 hours, as well as mortality at 3 month (12.7% vs 3.9%, p<0.001) were more common, and chronic independency at 3 month corresponding to mRS ≤2 was less common (44.5% vs 54.1%, p=0.044) than patents without renal dysfunction. After multivariate adjustment, renal dysfunction was independently related to any ICH (OR 1.82, 95%CI 1.16-2.86, p=0.009), symptomatic ICH (OR 2.93, 95% CI 1.10-8.13, p=0.033), and chronic mortality (OR 2.93, 95%CI 1.33 - 6.62, p=0.008), though it was not related to chronic independency (OR 0.78, 95%CI 0.51 – 1.20, p=0.255).
Conclusions: Reduced eGFR was an independent predictor of ICH within 36 hours and mortality at 3 months in ischemic stroke patients receiving low-dose IV rt-PA therapy.

####

International Stroke Conference 2010, San Antonio, USA, 2009/2/24-26

8. Nezu T, Koga M, Kimura K, et al: Pre-treatment DWI-ASPECTS has a relation with functional outcome at 3 months following intravenous rt-PA therapy.

Background: ASPECTS is a score to evaluate the extent of early ischemic change (EIC) on CT as well as on diffusion-weighted MRI (DWI). The extent of EIC may have relation with functional outcome and symptomatic hemorrhagic transformation in patients with ischemic stroke after intravenous recombinant tissue plasminogen activator (rt-PA) therapy. DWI can more clearly delineate the extent of EIC within 3 hours after stroke onset as compared with CT. The aim of the present study was to evaluate whether a pre-treatment DWI-ASPECTS can predict functional outcome at 3 months following rt-PA therapy.
Methods: A retrospective, multicenter, observational study was conducted to clarify the practical conditions of IV rt-PA therapy using 0.6 mg/kg alteplase in 10 major stroke centers in Japan. Studied were a total of 498 consecutive stroke patients (328 men, 72±11 years) who were treated with intravenous rt-PA from October 2005 through July 2008, underwent MRI with DWI sequence before rt-PA therapy. Excluded were patients with fairly severe to severe disability, corresponding to a modified Rankin Scale (mRS) 4 and 5 before symptom onset. An ASPECTS (10 for no EIC and 0 for the largest EIC) was assessed on the initial DWI study. Primary outcome was mRS 0-3 at 3 months after stroke onset.
Results: Of 498 patients, 305 (61.2%) had excellent to fairly good outcome (mRS 0-3) at 3 months. They were younger (p<0.001), more frequently male (p=0.012), less hypertensive (p=0.021), and less commonly have atrial fibrillation (p<0.001) and internal carotid artery occlusion (p<0.001) than the other patients (mRS 4-6). Pre-treatment NIHSS score was lower (p<0.001) and DWI-ASPECTS was higher (p<0.001) in the patients with mRS 0-3 than in the others (mRS 4-6). The optimal cutoff score of DWI-ASPECTS to predict primary outcome was ≥7 with a sensitivity of 88% and specificity of 39%, and the area under the receiver-operating characteristic curve was 0.644. After multivariate logistic regression analysis with sex, age, pre-treatment NIHSS score, hypertension, atrial fibrillation and internal cerebral artery occlusion, the pre-treatment DWI-ASPECTS ≥7 was an independent predictor of mRS 0-3 at 3 months after rt-PA therapy (OR 2.88, 95% CI 1.68-5.00).
Conclusion: DWI-ASPECTS is useful to predict patients' chronic functional outcome following intravenous rt-PA therapy in this multicenter study.

####

International Stroke Conference 2010, San Antonio, USA, 2009/2/24-26

9. **Nezu T, Koga M, Kimura K, et al: Pre-treatment DWI-ASPECTS is superior to CT-ASPECTS in detecting excellent to fairly good outcome after intravenous rt-PA therapy.**

Background: ASPECTS is a quantitative topographic score to evaluate the extent of early ischemic change (EIC) in the middle cerebral arterial territory on CT as well as on diffusion-weighted MRI (DWI). DWI can more clearly delineate the extent of EIC within 3 hours after stroke onset as compared with CT. There were a few data regarding the comparison of ASPECTS between DWI and CT before rt-PA therapy in same patients so far. This study aimed at elucidating the relationship between DWI-ASPECTS and CT-ASPECTS before rt-PA therapy and their associations with chronic functional outcome.
Methods: A retrospective, multicenter, observational study was conducted to clarify the practical conditions of IV rt-PA therapy using 0.6 mg/kg alteplase in 10 major stroke centers in Japan. Studied were a total of 381 consecutive patients with anterior circulation ischemic stroke (249 men, 72±11 years) who were treated with intravenous rt-PA from October 2005 through July 2008, underwent both MRI with DWI sequence and CT before rt-PA therapy. Excluded were patients with fairly severe to severe disability, corresponding to a modified Rankin Scale (mRS) 4 and 5 before symptom onset. The MRI study was performed immediately after the CT study. An ASPECTS (10 for no EIC and 0 for the largest EIC) was assessed on the initial DWI and CT studies. Chronic functional outcome was assessed with mRS at 3 months after stroke onset.
Results: Of 381 patients, 230 (60.4%) had excellent to fairly good outcome (mRS 0-3) at 3 months. The pre-treatment DWI-ASPECTS (median 8, IQR 6-9) was lower than the pre-treatment CT-ASPECTS (9, 8-10) ($P<0.001$). DWI-ASPECTS was positively related with CT-ASPECTS ($r= 0.565$, $p<0.001$). The optimal cutoff score of DWI-ASPECTS to predict the patients with mRS 0-3 at 3 months was ≥ 7 with a sensitivity of 86% and specificity of 45%, and the area under the receiver-operating characteristic (ROC) curve was 0.681. On the other hand, the optimal cutoff score of CT-ASPECTS was ≥ 9 with a sensitivity of 76% and specificity of 48%, and the area under the ROC curve was 0.636.
Conclusion: DWI-ASPECTS had a positive relationship with CT-ASPECTS, but the former scored lower points than the latter. DWI-ASPECTS may be useful to predict excellent to fairly good outcome (mRS 0-3) at 3 months with higher sensitivity as compared with CT-ASPECTS.

####

International Stroke Conference 2010, San Antonio, USA, 2009/2/24-26

10. **Yamagami H, Koga M, Shiokawa Y, et al: Impact of antiplatelet pre-treatment on intracranial hemorrhage and stroke outcome after intravenous thrombolysis: the Stroke Acute Management with Urgent Risk-factor Assessment and Improvement (SAMURAI) Study.**

Background and Purpose: We sought to clarify the impact of antiplatelet (AP) pre-treatment on

intracranial hemorrhage (ICH) and 3-month outcome after intravenous recombinant tissue plasminogen activator (rt-PA) therapy in patients with ischemic stroke.
Methods: In a retrospective, multicenter, observational study, we studied data from consecutive patients treated with low-dose intravenous rt-PA (0.6 mg/kg alteplase) which was approved in Japan, within 3h after symptom onset. AP therapy previous to thrombolysis was obtained from clinical records. Any ICH was defined as CT evidence of new ICH within the initial 36 hours, and symptomatic ICH (sICH) with neurological deterioration corresponding to an increase of ≥1 point from the baseline NIHSS score. Favorable outcome reflecting independence was defined as a modified Rankin Scale score of 2 or less at 3 months.
Results: Of the 600 patients (377 men, 72 ± 12 years old) treated with rt-PA, 189 (31.5%) used AP drugs prior to thrombolysis; 159 (26.5%) used aspirin and 14 were pre-treated with dual AP drugs. Both ICH and sICH occurred more frequently in patients with AP pre-treatment than those not (ICH: 26.5% vs 16.8%, P = 0.008, sICH: 8.5% vs 1.7%, P < 0.001). Particularly, 8 of 14 patients (57.1%) who had received dual AP drugs developed ICH. In multivariate analysis, AP pre-treatment was an independent predictor of ICH (OR 1.69, 95% CI 1.05 – 2.71) and sICH (OR 6.06, 95% CI 2.22 – 16.5). Favorable outcome was fewer in patients with AP pre-treatment than those not (40.7% vs 50.4%, P=0.03), whereas it was not an independent predictor after multivariate analysis.
Conclusion: In Japanese patients, AP therapy previous to thrombolysis was associated with occurrence of ICH and sICH, and may lead to poor outcome, even though using low-dose rt-PA.

####

19th European Stroke Conference, Barcelona, Spain, 2010/5/25-28

11. Nishiyama M, Shiokawa Y, Yamada S, et al: Hemorrhagic transformation associated with intravenous low-dose recombinant tissue plasminogen activator therapy in Japanese patients from the SAMURAI rt-PA Registry.

Background: Routine use of low-dose (0.6mg/kg alteplase) intravenous (iv) recombinant tissue plasminogen activator (rt-PA) was approved in Japan in year 2005 for the patients suffering from cerebral ischemia within three hours of stroke onset. We investigated hemorrhagic transformation (HT) associated with low-dose iv rt-PA therapy using the SAMURAI rt-PA Registry, a retrospective, multicenter, observational study.
Methods: Consecutive stroke patients, who were treated with iv rt-PA therapy in 10 Japanese stroke centers, were included. Clinical data and information on HT within 36-hour after iv rt-PA therapy were collected. Severity of HT was determined according to neuroradiological findings.
Results: A total of 600 patients (377 men, 223 women; 72 ± 12 years old) were studied. HT was detected in 119 patients (19.8%) of entire cases (HI1 and HI2 in 10.8% and PH1 and PH2 in 8.5%). Symptomatic intracerebral hemorrhage within 36 hours after iv rt-PA therapy with a ≧1-point increase from the baseline National Institutes of Health Stroke Scale (NIHSS) score developed in 23 patients (3.8%). Cardiogenic embolism was related to any HT ($p<0.05$), while other types of ischemic stroke were not. Lower Alberta Stroke Program Early CT Score on MRI-DWI were related with any HT ($p<0.01$). After multivariate adjustment, presence of iv antihypertensive therapy immediately before iv rt-PA therapy (OR 2.1, 95% CI 1.3-3.4),

presence of heart diseases (OR 1.9, 95% CI 1.2-3.3), usage of more than two types of oral antiplatelet agents just before iv rt-PA therapy (OR 2.5, 95% CI 1.1-5.7) were also independently associated with any HT. Presence of any HT was related with poor functional outcome (NIHSS at 24-hour and modified Rankin Scale at 3-month) ($p<0.01$).
Conclusion: This retrospective multi-center observational study in Japan, investigating HT after iv rt-PA therapy in Japanese population, revealed various factors relating with HT after the low-dose iv rt-PA therapy.

####

19th European Stroke Conference, Barcelona, Spain, 2010/5/25-28

12. Toyoda K: Acute stroke management in Japan: insights from the SAMURAI study. (Invited symposium)

The SAMURAI (Stroke Acute Management with Urgent Risk-factor Assessment and Improvement) rt-PA Registry is a retrospective multicenter observational study by 10 stroke centers across Japan. Six hundred patients with ischemic stroke who received low-dose IV rt-PA using 0.6 mg/kg alteplase were registered. The results were differentiated from SITS-MOST and other studies, and published in *Stroke*. In SAMURAI, symptomatic ICH developed in 3.8% according to the NINDS/Cochrane definition, and 33% of overall patients had a modified Rankin scale (mRS) of 0-1 at 3 months. When the patients who met the European license were selected, 41% had a favorable outcome. The frequency of patients who died within 3 months was 7%. Thus, the general efficacy and safety of our low-dose rt-PA are similar to those of SITS-MOST and other surveys. Several substudies are ongoing. Nezu, et al clarified that Alberta Stroke Program Early CT Score (ASPECTS) on the diffusion-weighted image ≥7 was independently associated with mRS 0-1 at 3 months. A possible limitation is that the low-dose rt-PA may end in the incomplete recanalization. A recent Japanese trial, J-ACT 2, has an answer for this question. In 58 patients with the MCA occlusion on MRA and treated with alteplase at 0.6 mg/kg, ≈50% of the occluded MCAs were recanalized 6 hours after the onset, and 70% were recanalized 24 hours later. After multivariate analysis, recanalization at 6 hours as well as at 24 hours was independently associated with mRS 0-1 at 3 months. In conclusion, low-dose rt-PA for Japanese patients produced similar results as the post-marketing studies conducted in Western countries. DWI and MRA are available for predicting outcomes after rt-PA. The efficacy of the concomitant use of edaravone, a free radical scavenger which was available only in Japan, with rt-PA should be proven.

####

10th Tiantan International Stroke Conference 2010, Beijing, China 2010/6/25-27

13. Toyoda K: Intravenous low-dose rt-PA for ischemic stroke: messages from SAMURAI rt-PA Registry. (Invited symposium)

In 2005, intravenous alteplase therapy at a dose of 0.6 mg/kg was approved in Japan after a dose comparison study using duteplase and a multicenter study using a single dose of alteplase

(Japan Alteplase Clinical Trial [J-ACT]). To identify the effects of risk factors and other patient characteristics on the outcome of this low-dose rt-PA therapy, a multicenter observational study (the Stroke Acute Management with Urgent Risk-factor Assessment and Improvement [SAMURAI] rt-PA Registry) was performed (Toyoda K, et al: Stroke 2009;40:3591-3595). A total of 600 patients (377 men, 72 ± 12 years old, median NIH Stroke Scale [NIHSS] score 13) were studied. Symptomatic ICH within 36 hours developed in 23 patients (3.8%, 95% CI 2.6 – 5.7%). At 3 months, 43 patients had died (7.2%, 5.4 – 9.5%), and 199 patients (33.2%, 29.5 – 37.0%) had a modified Rankin Scale (mRS) score ≤1. Analysis of 399 patients with a premorbid mRS score ≤1 who met the criteria of the European license (≤80 years old, an initial NIHSS score ≤24, etc.) showed that 40.6% (35.9 – 45.5%) had a 3-month mRS ≤1. Several subanalyses for this registry were ongoing. For example, the pre-treatment Alberta Stroke Program Early CT Score (ASPECTS) assessed using diffusion-weighted imaging ≥7 was related to an mRS score of 0-2, ASPECTS ≤4 was related to death, and ASPECTS ≤5 was related to symptomatic ICH (Nezu T, et al: Neurology 2010). In this session, I introduce general outcomes and some subanalyses of the SAMURAI rt-PA Registry, as well as recent studies on rt-PA therapy in Japan.

####

7th World Stroke Congress, Seoul, Korea 2010/10/13-16

14. Endo K, Koga M, Sakai N, et al: Etiology, clinical profiles, treatment, and outcomes of acute ischemic stroke with major cerebral artery occlusion in Japan.

Aims: To investigate the etiology, clinical profiles, treatment, and outcomes of acute ischemic stroke (AIS) with major cerebral artery occlusion since the approval of intravenous rt-PA therapy in Japan.
Methods: We retrospectively enrolled consecutive AIS patients with common/internal carotid artery occlusion (ICAO), middle cerebral artery occlusion (MCAO) and basilar artery occlusion (BAO) admitted within 24-hour from onset between October, 2005 and June, 2009 in 12 stroke centers.
Results: A total of 1063 patients (600men, 74±12 years old) were studied. ICAO, MCAO and BAO were seen in 34%, 57% and 8% of all the patients, respectively. Cardioembolic stroke (CES), atherothrombotic infarction and the others were found in 71%, 19% and 10%, respectively. 60% of patients visited hospitals within 3-hour from onset. The median baseline NIHSS was 16. Recanalization therapy (intravenous rt-PA or neuroendovascular therapy) was performed in 33%. Symptomatic intracerebral hemorrhage (sICH) within 36-hour with a ≥1-point increase of NIHSS occurred in 6%. mRS 0-2 and 5-6 at 3-month after onset (or discharge) were seen in 26% and 42%, respectively. After multivariate adjustment, higher baseline NIHSS and CES were independently related to sICH; younger age, lower baseline NIHSS, absence of ICAO, and recanalization therapy were independently related to mRS 0-2; and older age, higher baseline NIHSS, ICAO, and delayed admission ≧3-hour were independently related to mRS 5-6.
Conclusions: Although recanalization therapy was performed in one-third of AIS with major cerebral artery occlusion, more than 40% had unfavorable outcome with current AIS

management strategy in Japan.

####

7th World Stroke Congress, Seoul, Korea 2010/10/13-16

15. Kato T, Akiyama H, Hasegawa Y, et al: "Weekend effect" in thrombolytic therapy for acute ischemic stroke patients in a collaborative study of stroke centers in Japan.

Aims: Several studies have demonstrated stroke outcomes are different between patients admitted weekend and weekday mainly due to the difference in staffing pattern. This effect has been termed the'weekend effect'. We investigated the effect of admission day on processes of care and outcomes of intravenous rt-PA therapy.
Methods: A total of 600 stroke patients (377 men, 72±12 years-old) underwent intravenous rt-PA therapy using 0.6 mg/kg alteplase were retrospectively registered from 10 major stroke centers in Japan. According to their admission day, patients were categorized to Weekday group (n = 403) and Weekend group (n = 197).
Results: There were no significant differences in patient's characteristics. No differences were observed in the quality assessment for the pretreatment evaluation including blood test and the frequency of neuroimaging such as MRI, MR angiography, carotid ultrasound examination, and 3D-CT angiography. There were no statistically significant differences in time from onset to treatment (141.1 ±30.1 vs. 141.1± 27.6 min), changes in NIHSS score at 24 h from baseline (-3.1 ±7.3 vs. -2.8±7.3 points), modified Rankin scale (mRS) at 3 months after treatment (34.6% vs. 35.2% in mRS < 2, and 9.0% vs. 6.3% in mRS = 6). Multiple logistic regression analysis revealed no significant effect of admission day on the neurological improvement nor mRS < 2 at 3 month after treatment.
Conclusion: Weekend effect was not observed in the rt-PA therapy in major stroke centers in Japan.

####

7th World Stroke Congress, Seoul, Korea 2010/10/13-16

16. Koga M, Endo K, Sakai N, et al: Characteristics of acute stroke patients with major artery occlusion who did not receive recanalization therapy.

Aims: To investigate factors relating to no recanalization therapy (intravenous rt-PA or neuroendovascular therapy) in acute ischemic stroke (AIS) patients with major artery occlusion presenting to hospital within 150 min from onset.
Methods: We retrospectively registered AIS patients with major artery occlusion admitted within 24-hour from onset between 2005 and 2009 in 12 stroke centers. 603 patients admitted within 150 min were selected and divided into two groups; 298 patients (49%) who received recanalization therapy (T-group) and 305 patients (51%) who did not (NonT-group).
Results: Patients in NonT-group were older (75±13 vs. 72±13 years, p=0.0024), were more frequently admitted ≥120 min from onset (20% vs. 10%, p=0.0011), more frequently had common/internal carotid artery occlusion (ICAO) (36% vs. 27%, p=0.0221), tended to less

frequently have cardioembolic stroke (71% vs. 77%, p=0.087), but scored similar NIHSS (median 17 vs. 16, p=0.83) as compared to those in T-group. After multivariate regression analysis, advanced age (per 1 year; OR 1.02, 95% CI 1.008-1.036), admission ≥120 min (2.17, 1.35-3.54) and ICAO (1.55, 1.07-2.23) were independently related to patients in NonT-group. mRS at discharge was ≤2 in 23% of NonT-group and 30% of T-group (p=0.056). In-hospital mortality rate was 21% and 10% (p=0.0004), respectively.
Conclusions: Advanced age, admission ≥120 min from stroke onset, and ICAO appeared to be major reasons why recanalization therapy was not chosen for AIS patients. Onset-to-door time should be shortened by education to citizens and paramedics and by improvement of the medical emergency system.

####

7th World Stroke Congress, Seoul, Korea 2010/10/13-16

17. Miyagi T, Koga M, Shiokawa Y, et al: Low-dose intravenous rt-PA therapy for acute stroke patients with the basilar artery occlusion.

Background and Aims: To determine baseline characteristics and outcomes in stroke patients with the basilar artery occlusion (BAO) treated with low-dose rt-PA.
Methods: A retrospective, multicenter, observational study involving 600 stroke patients treated with intravenous rt-PA (0.6 mg/kg, alteplase) was conducted in 10 stroke centers. Twenty-five patients with BAO (17 men, 32-92 years old) were assessed.
Results: Stroke subtypes included cardioembolic stroke in 15 patients and atherothrombotic infarction in 4. Median NIHSS scores were 16(IQR: 9-30.5) just before treatment, 11(4.25-21) at 24 hour, and 6(3-16.75) at discharge. Of 20 patients undergoing pre-treatment DWI, 16 had early ischemic change (EIC) in the brainstem, including 5 with isolated brainstem EIC. BA was recanalized during acute hospitalization in 18 patients. Patients with BAO had higher NIHSS score (median 16 vs 12, p<0.001), and more commonly showed neurological improvement within initial 24 hours (≥8 point-decrease in the NIHSS score, 56% vs 19%, p<0.0001) than the other 575 patients. Frequencies of neurological deterioration within initial 24 hours (≥4 point-increase in the NIHSS score, 16.0% vs 9.8%), symptomatic intracranial hemorrhage (sICH) within initial 36 hours (≥4 point-increase in the NIHSS score, 0% vs 3.8%), mRS ≤2 at 3 months (44.0% vs 47.5%), and motality at 3 months (4.0% vs 7.3%) were similar (p>0.1) between patients with BAO and others.
Conclusions: The rates of sICH and mortality in patients with BAO after low-dose rt-PA therapy were low as compared to those in BASICS and other previous reports. More than 40% of patients had favorable chronic outcome.

####

7th World Stroke Congress, Seoul, Korea 2010/10/13-16

18. Toyoda K: Intravenous low-dose rt-PA for ischemic stroke: SAMURAI rt-PA Registry. (Invited)

In 2005, intravenous alteplase therapy at a dose of 0.6 mg/kg was approved in Japan after a dose comparison study using duteplase and a multicenter study using a single dose of alteplase (Japan Alteplase Clinical Trial [J-ACT]). To identify the effects of risk factors and other patient characteristics on the outcome of this low-dose rt-PA therapy, a multicenter observational study (the Stroke Acute Management with Urgent Risk-factor Assessment and Improvement [SAMURAI] rt-PA Registry) was performed (Toyoda K, et al: Stroke 2009;40:3591-3595). A total of 600 patients (377 men, 72 ± 12 years old, median NIH Stroke Scale [NIHSS] score 13) were studied. Symptomatic ICH within 36 hours developed in 23 patients (3.8%, 95% CI 2.6 – 5.7%). At 3 months, 43 patients had died (7.2%, 5.4 – 9.5%), and 199 patients (33.2%, 29.5 – 37.0%) had a modified Rankin Scale (mRS) score ≤1. Analysis of 399 patients with a premorbid mRS score ≤1 who met the criteria of the European license (≤80 years old, an initial NIHSS score ≤24, etc.) showed that 40.6% (35.9 – 45.5%) had a 3-month mRS ≤1. Several subanalyses for this registry were ongoing. For example, the pre-treatment Alberta Stroke Program Early CT Score (ASPECTS) assessed using diffusion-weighted imaging ≥7 was related to an mRS score of 0-2 (OR 1.85, 95% CI 1.07 – 3.24), ASPECTS ≤4 was related to death (3.61, 1.23 – 9 .91), and ASPECTS ≤5 was related to symptomatic ICH (4.74, 1.54 – 13.64) (Nezu T, et al: Neurology 2010).

####

7th World Stroke Congress, Seoul, Korea 2010/10/13-16

19. Yamagami H, Sakai N, Endo K, et al: Associations between treatment and outcomes in acute ischemic stroke with major cerebral artery occlusion.

Aims: To investigate the associations between treatment and outcomes in acute ischemic stroke (AIS) with major artery occlusion in a retrospective observational study in Japan.
Methods: We retrospectively registered AIS patients with major artery occlusion admitted within 24-hour from onset between 2005 and 2009 in 12 stroke centers. 706 patients who had obtained modified Rankin scale (mRS) at 3 months were selected and categorized as three groups; 193 (27%) patients who treated with intravenous rt-PA (rt-PA group), 81 (11%) patients with neuro-endovascular treatment (NET group), and 432 (61%) patients with other medical treatment (medical group).
Results: Patients in NET group were younger than other groups (rt-PA group 74±11, NET group 68±14, medical group 75±13 years, P<0.005). Onset-to-admission time were faster in rt-PA group than other groups (rt-PA group 69±35, NET group 254±293, medical group 312±316 minutes, P<0.001). Cardioembolic stroke were fewer in medical group than other groups (rt-PA group 76%, NET group 74%, medical group 65%, P=0.012). Baseline NIHSS and incidence of carotid or basilar artery occlusion were similar in 3 groups. After multivariate regression analysis, IV rt-PA and NET were independently associated with favorable outcome (mRS at 3months ≦1) compared with medical treatment (rt-PA: OR 1.75, 95% CI 1.01-3.06, P=0.048,

NET: OR 2.12, 95%CI 1.03-4.36, P=0.041).
Conclusion: Although patients' background were quite difference, intravenous rt-PA and neuro-endovascular therapy appeared to be associated with favorable outcome in AIS patients with major cerebral artery occlusion.

####

International Stroke Conference 2011, Los Angeles, USA, 2011/2/9-11

20. Maeda K, Koga M, Okada Y, et al: Nationwide survey of expert opinions to restart anticoagulant therapy after intracerebral hemorrhage for patients with nonvalvular atrial fibrillation.

Background and Purpose: Warfarin-related intrecerebral hemorrhage (ICH) in patients with atrial fibrillation (AF) is associated with high incidence of subsequential hematoma enlargement and high mortality. Conversely, withholding of warfarin has a potential risk to develop thromboembolic complications such as embolic stroke. There is a considerable dilemma concerning when to restart anticoagulant therapy following ICH, because there is no established guideline for appropriate antithrombotic therapy in acute ICH patients with AF. We conducted a nationwide survey regarding ~~of~~ resumption of anticoagulant therapy in patients with acute ICH on warfarin with nonvalvular AF.
Methods: A questionnaire on standard therapeutic strategy for warfarin-related ICH in patients with nonvalvular AF was mailed to physicians responsible for ICH management at 416 institutes in October 2009.
Results: Of those mailed, 329 physicians (79%) responded with a filled-in questionnaire. On admission, all respondents stopped oral warfarin intake and 94% of them normalized prothrombin time (PT-INR) mainly by Vitamin K (63%), followed by fresh frozen plasma (20%), and prothrombin complex concentrations (10%). Regarding the further prevention of thromboembolism, 91% restarted anticoagulant, 3% used antiplatelets instead of warfarin, and 6% disagreed with restarting any antithrombotic therapy. Of those who restarted anticoagulation, the timing was within 4 days in 7%, 5 to 7 days in 21%, 8 to 14 days in 25%, 15 to 28 days in 28% and 29 days or later in 18%. The key findings on follow-up CT to restart anticoagulation were absorption tendency of hematoma in 47%, followed by discontinuation of hematoma growth in 28%, and complete absorption of hematoma in 17%. To restart anticoagulation, warfarin alone was used in 76% and unfractionated heparin alone or combined with warfarin in 20%. As a contraindication for restarting anticoagulation, recurrent ICH and poor functional status corresponding to the modified Rankin Scale score of 4 or 5 were two major reasons (170 respondents, 59.4% for each), followed by dementia or frequent falls (139, 48.6%), suspected cerebral amyloid angiopathy (107, 37.4%), multiple brain microbleeds on T2*-weighted MRI (85, 29.7%), advanced age (80 years old, 71, 24.8%), and so on.
Conclusions: For acute ICH patients with nonvalvular AF, a large majority of Japanese physicians stopped oral warfarin intake and normalized PT-INR on admission, and restarted anticoagulation several days to months later. However the strategies to normalize PT-INR and to restart anticoagulant therapy enormously varied and depended on physicians decisions.

####

International Stroke Conference 2011, Los Angeles, USA, 2011/2/9-11

21. Makihara N, Okada Y, Koga M, et al: High-density lipoprotein cholesterol level is a predictor of outcome after intravenous recombinant tissue plasminogen activator therapy for acute stroke: the Stroke Acute Management with Urgent Risk-factor Assessment and Improvement (SAMURAI) rt-PA Registry.

Background and Purpose: Recent studies showed that statin improved clinical outcome of ischemic stroke, but the effect of lipid levels on the outcome is controversial. We investigated whether baseline lipid levels were associated with clinical outcome at 3 months after IV recombinant tissue plasminogen activator (rt-PA) therapy for acute ischemic stroke.
Methods: Six-hundred consecutive patients who received IV rt-PA at ten stroke centers were registered in the SAMURAI rt-PA Registry. We assessed lipid levels on emergent visit; total cholesterol, triglyceride, high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol. The primary outcome was favorable outcome at 3 months corresponding to the modified Rankin scale ≤1. The secondary outcome was any intracranial hemorrhage (ICH) within the initial 36 hours. We examined whether each lipid profile was predictive of these outcomes.
Results: Of 600 patients, those with a premorbid modified Rankin scale ≥2 or those who had lack of any lipid profiles or initial MRI were excluded. Of 408 included patients (140 women, 70.9 ± 11.1 years old), 48 patients used statins prior to stroke. One-hundred and fifty-eight patients (38.7%) had favorable outcome. HDL-C level in patients with favorable outcome was higher than in those with unfavorable outcome (1.40 ± 0.40 mmol/l versus 1.32 ± 0.37 mmol/l, p=0.025), whereas other lipid levels or frequency of prior statin use were not different between two groups. The patients with favorable outcome were gradually increased with HDL-C levels divided into tertiles (32.1%, 39.1%, 44.9%). After multivariate analysis, HDL-C level was only independently related to favorable outcome among lipid profiles (OR 1.89; 95%CI 1.02-3.50 per 1-mmol/L, p=0.043). For 164 non-cardioembolic patients, HDL-C level was also independently related to favorable outcome (OR 2.95; 95%CI 1.11-7.83, p=0.030), although it was not for 244 cardioembolic patients. Any ICH occurred in 76 patients (18.6%). There were no significant associations between ICH and any lipid profiles.
Conclusions: Baseline HDL-C level was associated with favorable outcome at 3 months after IV rt-PA therapy for acute ischemic stroke.

####

International Stroke Conference 2011, Los Angeles, USA, 2011/2/9-11

22. Miyagi T, Koga M, Nakagawara J, et al: Intravenous rt-PA therapy for stroke patients without cerebral artery occlusion: SAMURAI Stroke Registry.

Background and Purpose: Information about cerebral artery occlusive lesions is not taken into account for the CT-based patient selection of intravenous rt-PA therapy. The safety and efficacy of intravenous rt-PA for patients without cerebral artery occlusion (CAO) have not been

elucidated. This study was aimed to clarify characteristics and outcomes in stroke patients without CAO who were treated with 0.6 mg/kg alteplase from the SAMURAI rt-PA registry, a retrospective, multicenter, observational study.
Methods: Studied were 416 patients with premorbid modified Rankin Scale (mRS) of 0-1 who underwent MRA to identify CAO before rt-PA therapy. Endpoint events were intracranial hemorrhage (ICH) within the initial 36 hours, and favorable (modified Rankin Scale [mRS] 0-1) and unfavorable (mRS 4-6) outcomes, and mortality at 3 months.
Results: CAO was documented in 327 patients (78.6%, 211 men, 71.9±11.3 years old), but not in 89 patients (21.4%, 65 men, 67.0±11.5 years old). As compared to patients with CAO, those without CAO were younger ($p<0.001$) and more frequently diabetic (27.0% vs. 16.8%, $p=0.031$), and had less commonly atrial fibrillation (13.5% vs. 48.3%, $p<0.001$), higher initial systolic (154.2±15.4 mmHg vs. 149.4±19.4 mmHg, $p=0.030$) and diastolic blood pressure values (85.7±13.4 mmHg vs. 81.0±14.7 mmHg, $p=0.006$), higher ASPECTS on DWI (median 9 vs. 8, $p<0.001$), lower initial NIHSS score (median 7 vs. 14, $p<0.001$), more commonly lacunar infarction (19.1% vs. 1.5%, $p<0.001$) but less frequently cardioembolic stroke (30.3% vs. 68.5%, $p=0.007$). With regards to endpoint events, patients without CAO had less frequently ICH within the initial 36 hours (11.2% vs. 22.9%, $p=0.015$), more frequently favorable outcome (56.2% vs. 33.6%, $p<0.001$), less commonly unfavorable outcome (16.9% vs. 43.3%, $p<0.001$), and no mortality at 3 months (vs. 7.7%, $p<0.001$) than those without CAO. After adjustment with various baseline features, absence of CAO was no longer associated with favorable outcome(OR 1.37, 95% CI 0.77-2.41), unfavorable outcome (0.58, 0.28-1.12), and ICH within the initial 36 hours (0.67, 0.30-1.37). Among patients without CAO, higher initial NIHSS score (OR 1.08, 95% CI 1.00-1.17 per 1-score increase, $p=0.048$) were associated with 3-month unfavorable outcome after multivariate adjustment with underlying features.
Conclusions: Although 3-month outcomes of stroke patients without CAO after rt-PA were better than those of patients with, these associations became insignificant after adjustment with baseline features. The initial neurological severity was associated with 3-months outcome in patients without CAO.

####

International Stroke Conference 2011, Los Angeles, USA, 2011/2/9-11

23. Nezu T, Koga M, Shiokawa Y, et al: Female sex is associated with unfavorable outcomes following low-dose intravenous rt-PA therapy: the SAMURAI rt-PA Registry.

Background: Sex differences in the effect of intravenous (IV) rt-PA therapy for ischemic stroke are controversial. The aim of this study was to elucidate the sex differences in the stroke outcome after low-dose IV rt-PA (0.6mg/kg alteplase) therapy.
Methods: A retrospective, multicenter, observational study was conducted to clarify the practical conditions of low-dose IV rt-PA therapy in 10 stroke centers in Japan (SAMURAI rt-PA Registry: Stroke 2009;40:3591-3595). Studied were consecutive patients with a premorbid modified Rankin Scale (mRS) ≤ 2 who were treated with IV rt-PA from October 2005 through July 2008. We assessed baseline data, including sex, age, comorbidities (hypertension, diabetes,

hyperlipidemia, and atrial fibrillation), time from onset to treatment, NIH stroke scale (NIHSS) score, Alberta Stroke Programme Early CT score (ASPECTS), and presence of internal carotid artery (ICA) occlusion identified on MR angiography or carotid ultrasound. Outcomes were a favorable outcome defined as an mRS score 0-2 and death at 3 months, as well as symptomatic intracerebral hemorrhage (sICH) within 36 hours: i.e. a parenchymal ICH associated with neurological deterioration corresponding to an increase of ≥4 point from the baseline NIHSS score.
Results: Of 554 patients (358 men, 71±11 years) who were studied, 282 (50.9%) had a favorable outcome and 35 (6.3%) died at 3 months. Symptomatic ICH was identified in 16 patients (2.9%). Women were older (mean age 75±11 vs. 69±12 years, p<0.001), more frequently had atrial fibrillation (50.8 vs. 37.5%, p=0.004), and had higher median initial NIH Stroke Scale score (13 vs. 12, p=0.009) than men. There were no significant sex differences in hypertension, diabetes, hyperlipidemia, time from onset to treatment, ASPECTS, and ICA occlusion. Women had less favorable outcome (41.3% vs. 56.2%, p=0.001) than men. There were no significant sex differences in mortality (8.7% vs. 5.0%, p=0.102) and sICH (3.1% vs. 2.8%, p=0.999). After multivariate analysis using the stepwise backward selection procedure with age and other baseline data, women were inversely related to favorable functional outcome at 3 months (odds ratio 0.63, 95%CI 0.40-0.99, p=0.044).
Conclusion: Initial stroke symptoms were severer in female patients who were scheduled to receive intravenous rt-PA therapy than in male ones. After adjustment for the initial severity and other baseline features, women were independently related to unfavorable stroke outcome 3 months after rt-PA.

####

International Stroke Conference 2011, Los Angeles, USA, 2011/2/9-11

24. Sakai N, Toyoda K, et al: Mechanical thrombectomy by the penumbra system has the potential to improve neurological and functional outcomes in japanese patient with acute ischemic stroke.

Introduction: Mortality from acute ischemic stroke in Japan is known to be much lower than that reported in the West. In Japan, IV rt-PA therapy has been approved since 2005, and endovascular intervention is indicated in patients who are either contraindicated to, or failed IV rt-PA therapy. However, mechanical thrombectomy devices, such as the Merci Retriever or Penumbra System are not approved, and it remains controversial if mechanical thrombectomy has a role for acute stroke intervention in Japan.
Methods: This study was a retrospective review of 1176 acute stroke patients from 13 hospitals in the JR-NET2 and SAMURAI registry group. The goal was to select those who would qualify for mechanical thrombectomy therapy but were never treated. These patients (N=334) had large vessel occlusions who presented within 8 hours from symptom onset with a NIHSS score of at least 8 and not eligible for IV rt-PA therapy. Their outcomes were then compared with matched patients pooled from the Penumbra Pivotal and POST trials* who were treated by the Penumbra System (N=143). The primary endpoints were all cause mortality, poor functional outcome as defined by a modified Rankin Scale (mRS) score of >5 and good

functional outcome as defined by a mRS score of ≤2 at 90 day post-procedure.

Results:

	JAPANESE PATIENTS (N=334)	POOLED PENUMBRA PATIENTS* (N=143)
Age (mean)(years)	77	64
Female	48%	46%
Baseline NIHSS (median)	20	17
Mortality at 90 Days	36.2%	30.1%
mRS 5 + mRS 6 at 90 Days	62.3%	39.2% #
mRS ≤ 2 at 90 Days	12.0%	31.5% #

** Stroke 2009;40:2761-2768. JNIS 2010;In Press.*

 # P <0.01 from a 2-tailed Fisher's Exact Test.

Conclusion: These results suggest that patients with large vessel occlusion, eligible for mechanical thrombectomy in Japan, who present within 8 hours from symptom onset and with a NIHSS score of at least 8 could potentially get benefits from treatment by the Penumbra System.

####

20th European Stroke Conference, Hamburg, Germany, 2010/5/25-28

25. Endo K, Kario K, Namekawa M, et al: Early Systolic Blood Pressure Variability is Associated with Stroke Outcome after Intravenous rt-PA: Stroke Acute Management with Urgent Risk-factor Assessment and Improvement (SAMURAI) rt-PA Registry.

Background: Early systolic blood pressure (SBP) profiles were reported to be independent predictors for long-term stroke outcome in ECASS-II trial. The aim of this study was to elucidate the association of early SBP variability with the outcomes of stroke patients treated with low-dose recombinant tissue plasminogen activator (rt-PA).

Methods: A retrospective, multicenter, observational study was conducted to identify the effects of underlying risk factors on intravenous (IV) rt-PA therapy using 0.6 mg/kg alteplase in 10 stroke centers in Japan (the SAMURAI rt-PA Registry). Consecutive stroke patients with a premorbid modified Rankin Scale (mRS) score <=1 who received rt-PA were studied. BP was measured at 0 (just before IV rt-PA), 1, 4, 8, 12, 16, 20 and 24hours and standard deviation (SD), successive variation (SV) and difference between max and min (max-min) were used to represent SBP variability. Stroke outcomes were assessed with symptomatic intracerebral hemorrhage (sICH) within 36 hours with a >=1-point increase from the baseline National Institutes of Health Stroke Scale (NIHSS) score, 3-month favorable outcome (mRS 0-1) and death within 3 months.

Results: Of a total of 535 patients (women 35%, 71+-12 years old), mean SD, SV and max-min were 14+-6, 17+-7 and 42+-18mmHg, respectively. High SD and max-min were associated with an increased risk of sICH [adjusted OR (/10mmHg) 2.97, 95% CI 1.61-5.63; 1.42, 1.16-1.76; respectively], although SV was not [1.61, 0.93-2.71]. High SD, SV and max-min were inversely associated with 3-month favorable outcome [0.66, 0.45-0.95; 0.68, 0.50-0.91; 0.84, 0.74-0.95;