8. Smith WS, Sung G, Saver J, et al, MERCI Trial Investigators. Mechanical thrombectomy for acute ischemic stroke: final results of the Multi MERCI trial. Stroke 2008; 39:1205-1212.
9. Penumbra Pivotal Stroke Trial Investigators. The penumbra pivotal stroke trial: safety and effectiveness of a new generation of mechanical devices for clot removal in intracranial large vessel occlusive disease. Stroke 2009; 40:2761-2768.
10. Yoshimura S, Egashira Y, Sakai N, et al, Recovery by Endovascular Salvage for Cerebral Ultra-acute Embolism-Japan Retrospective Survey Group. Retrospective nationwide survey of acute stroke due to large vessel occlusion in Japan: a review of 1,963 patients and the impact of endovascular treatment. Cerebrovasc Dis 2011;32:219-226.
11. Broderick JP, Palesch YY, Demchuk AM, et al, Interventional Management of Stroke (IMS) III Investigators. Endovascular therapy after intravenous t-PA versus t-PA alone for stroke. N Engl J Med 2013;368:893-903.
12. Ciccone A, Valvassori L, Nichelatti M, et al, SYNTHESIS Expansion Investigators. Endovascular treatment for acute ischemic stroke. N Engl J Med 2013;368:2433-2434.
13. Kidwell CS, Jahan R, Gornbein J, et al, MR RESCUE Investigators. A trial of imaging selection and endovascular treatment for ischemic stroke. N Engl J Med 2013;368:914-923.
14. Yamaguchi T, Mori E, Minematsu K, et al, Japan Alteplase Clinical Trial (J-ACT) Group. Alteplase at 0.6 mg/kg for acute ischemic stroke within 3 hours of onset: Japan Alteplase Clinical Trial (J-ACT). Stroke 2006;37: 1810-1815.
15. Tomsick T, Broderick J, Carrozella J, et al, Interventional Management of Stroke II Investigators. Revascularization results in the Interventional Management of Stroke II trial. AJNR Am J Neuroradiol 2008;29:582-587.
16. Mori E, Minematsu K, Nakagawara J, et al, Japan Alteplase Clinical Trial II Group. Effects of 0.6 mg/kg intravenous alteplase on vascular and clinical outcomes in middle cerebral artery occlusion: Japan Alteplase Clinical Trial II (J-ACT II). Stroke 2010;41:461-465.
17. Wahlgren N, Ahmed N, Dávalos A, et al, SITS-MOST investigators. Thrombolysis with alteplase for acute ischemic stroke in the Safe Implementation of Thrombolysis in Stroke-MOnitoring STudy (SITS-MOST): an observational study. Lancet 2007;369:275-282.

Review Article

Endovascular Treatment of Acute Ischemic Stroke: Honolulu Shock and Thereafter

Shinichi Yoshimura, MD, PhD, Manabu Shirakawa, MD, Kazutaka Uchida, MD, Yasue Tanaka, MD, and Seigo Shindo, MD

Recently, use of mechanical clot retrievers for acute stroke has gradually spread. However, 3 recent randomized controlled trials failed to show superiority of endovascular treatment compared to intravenous recombinant tissue plasminogen activator (IV rt-PA) alone or standard care. On the other hand, a Japanese nationwide survey demonstrated the efficacy of endovascular treatment in the IV rt-PA failed and ineligible patients, especially with the proximal artery occlusion such as the internal carotid artery. Earlier initiation and higher reperfusion of endovascular treatment seemed to be the main reason for the better result in this survey compared with the reported randomized studies. Because next-generation devices such as stent retrievers have been shown to provide better effects in terms of clinical outcomes compared with the Merci retriever, the efficacy of endovascular treatment is expected to be confirmed again by randomized controlled trials in the near future. **Key Words:** Acute stroke—clot retriever—tissue plasminogen activator—randomized trial.

Background

Despite the increasing use of intravenous recombinant tissue plasminogen activator (IV rt-PA), the large number of patients deemed ineligible for treatment because of time restrictions, or in whom treatment is ineffective because of cerebral large vessel occlusion, is now becoming recognized as problematic. Endovascular treatment has therefore been performed as rescue therapy in these patients.

From the Department of Neurosurgery, Hyogo College of Medicine, Nishinomiya, Hyogo, Japan.

Received October 20, 2013; revision received December 3, 2013; accepted December 21, 2013.

Address correspondence to Shinichi Yoshimura, Professor and Chairman, Department of Neurosurgery, Hyogo College of Medicine, 1-1 Mukogawa, Nishinomiya, Hyogo, Japan. E-mail: shinichiyoshimura@hotmail.com.

1052-3057/$ - see front matter

http://dx.doi.org/10.1016/j.jstrokecerebrovasdis.2013.12.039

Three randomized controlled trials were recently conducted to evaluate the efficacy of endovascular treatment in acute ischemic stroke,[1-3] but failed to show the superiority of endovascular treatment, a finding now called as the "Honolulu shock." This article analyzes the results of those randomized trials and discusses the future of treatment for these patients.

Problems with IV rt-PA

One problem with IV rt-PA is the large number of patients who are ineligible for treatment. Less than 5% of all patients with acute ischemic stroke are eligible for treatment with IV rt-PA. In the European Cooperative Acute Stroke Study III randomized trial of patients with a delayed time window for eligibility, IV rt-PA was effective even at 3-4.5 hours after stroke onset.[4] Those results led to a slight reduction in the number of ineligible patients, but major improvement of this issue has not yet been achieved.

Another problem is the low efficacy rate in patients with cerebral large vessel occlusion. In particular, favorable

Table 1. *Summary of 3 recent randomized controlled trials regarding endovascular treatment for acute stroke*

	IMS III			MR RESCUE			SYNTHESIS expansion		
	Endovascular treatment	IV t-PA only	*P*	Endovascular treatment penumbral	Standard care penumbral	*P*	Endovascular treatment	IV t-PA only	*P*
Number of patients	434	222		34	34		181	181	
Favorable outcome*	40.8%	38.7%	.25	21.0%	26.0%	.48	30.4%	34.8%	.37
Mortality	19.1%	21.6%	.52	18.0%	21.0%	.75	14.4%	9.9%	.22
Symptomatic ICH	6.2%	5.9%	.83	9.0%	6.0%	.24	6%	6%	.99

Abbreviations: ICH, intracranial hemorrhage; IMS III, Interventional Management of Stroke III; IV t-PA, intravenous tissue plasminogen activator; MR RESCUE, Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy; SYNTHESIS, Local Versus Systemic Thrombolysis for Acute Ischemic Stroke.

*Modified Rankin scale 0-2 in IMS III and MR RESCUE; 0-1 in Synthesis expansion.

outcome rates of only 10%-20% have been reported with internal carotid artery occlusion. In all cases, this was due to a failure to recanalize the occluded vessel,[5] representing a limitation of treatment with IV rt-PA.

Endovascular Treatment

The Merci Retriever was the first thrombus retrieval device, which is indicated within 8 hours of stroke onset in patients with large vessel occlusion or in those ineligible for or in whom IV rt-PA has proven ineffective. In the Multi MERCI trial,[6] the successful recanalization rate (Thrombolysis In Myocardial Infarction score, 2-3) was 68%, and the favorable outcome rate (modified Rankin Scale [mRS], 0-2) after 90 days was 36%. On the other hand, the Penumbra System, which was subsequently approved, achieves recanalization by thrombus aspiration. In a prospective study, the recanalization rate (Thrombolysis In Myocardial Infarction score, 2-3) was 82%, and the favorable outcome rate (mRS 0-2) was 25%.[7] Favorable computed tomography findings at baseline and recanalization within 5 hours were reported as good prognostic factors.[8]

Results of Randomized Controlled Trials

The results of the 3 randomized controlled trials of endovascular treatment in acute ischemic stroke were announced at the 2013 International Stroke Conference held in Honolulu, Hawaii. These included the Interventional Management of Stroke III (IMS-III) study[1] evaluating the effectiveness of endovascular treatment in addition to IV rt-PA, the Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy (MR RESCUE) study[2] evaluating the effectiveness of endovascular treatment based on imaging diagnosis, and the Local Versus Systemic Thrombolysis for Acute Ischemic Stroke (SYNTHESIS) Expansion study[3] comparing IV rt-PA and endovascular treatment (Table 1).

IMS-III

IMS-III was a multicenter, randomized controlled trial evaluating the effectiveness of endovascular treatment in addition to IV rt-PA.[1] Patients were assigned in a 2:1 ratio to an additional endovascular treatment group and IV rt-PA alone group. The primary end point was the mRS 0-2 rate after 90 days.

The study was expected to enroll 900 patients, but was stopped early after no additional effectiveness was being shown in the results from 656 patients. The primary end point did not differ significantly between groups (additional endovascular treatment group, 40.8%; rt-PA alone group, 38.8%; 95% confidence interval [CI], −6.1 to 9.1). Even in a subgroup analysis comparing mild stroke (National Institutes of Health Stroke Scale score 8-19) and severe stroke (score ≥20), there was still no significant difference. Furthermore, no significant differences were identified in mortality after 90 days (P = .52) or the rate of symptomatic intracranial hemorrhage after 30 hours (P = .83).

However, the IMS-III study had the following problems: (1) large vessel occlusion was not confirmed in more than half of the enrolled patients; (2) the mean time from IV rt-PA to endovascular treatment was 127 minutes (Table 2); and (3) the recanalization rate (Thrombolysis in Cerebral Infarction [TICI] grade, 2B-3, which means perfusion of half or greater of the vascular distribution of the occluded artery) with endovascular treatment was low, at only about 40% (Table 2).

Based on these results, endovascular treatment should of course target large vessel occlusions, and shortening the time until recanalization and higher rate of recanalization are important to achieve higher recanalization rates.

MR RESCUE

In the MR RESCUE study, patients treated within 8 hours of stroke onset who had large vessel occlusion (anterior circulation only) were evaluated by magnetic resonance imaging perfusion imaging to demonstrate a penumbra region and randomly assigned to an endovascular treatment group or standard treatment group.[2] Outcome was assessed according to the 90-day mRS.

Table 2. *Comparison of time to puncture and reperfusion after endovascular treatment in IMS III, MR RESCUE, and RESCUE-Japan registry*

0	IMS III	MR RESCUE	RESCUE-Japan registry
Onset to puncture		370 minutes	210 minutes
IV t-PA to puncture	127 minutes		70 minutes
Reperfusion: TICI 2B-3*	ICA: 38%M1: 44%	Total: 27%	Total: 53%ICA: 56%M1: 60%

Abbreviations: ICA, internal carotid artery; IMS III, Interventional Management of Stroke III; IV t-PA, intravenous tissue plasminogen activator; M1, middle cerebral artery M1 portion; MR RESCUE, Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy; SYNTHESIS, Local Versus Systemic Thrombolysis for Acute Ischemic Stroke; TICI, thrombolysis in cerebral infarction.

*TICI 2B, perfusion of half or greater of the vascular distribution of the occluded artery, TICI 3, complete reperfusion.

Also evaluated was whether endovascular treatment was more effective in patients with a larger penumbra (penumbral pattern).

The results showed no difference in mean 90-day mRS score, which was 3.9 in both groups. Moreover, endovascular treatment was no more effective even in the group showing a penumbral pattern. However, this study had the following limitations: (1) the mean time from stroke onset to initiation of endovascular treatment was 370 minutes and (2) the recanalization rate (TICI 2B-3) with endovascular treatment was only 27% (Table 2).

In this study, large vessel occlusion was confirmed by magnetic resonance angiography before randomization, no effectiveness was demonstrated. The reason of failure seemed to be the long time until initiation of endovascular treatment and a low recanalization rate.

SYNTHESIS Expansion

The SYNTHESIS Expansion study randomized patients with acute ischemic stroke within 4.5 hours of onset to endovascular treatment or IV rt-PA.[3] The primary end point was defined as mRS 0-1 after 3 months (Table 2).

The results showed no significant difference between groups in the proportion of patients with a good outcome of mRS 0-1 ($P = .16$). The rate of symptomatic intracranial hemorrhage was 6% in both groups. Median time from onset until initiation of treatment was 3.75 hours in the endovascular treatment group and 2.75 hours in the IV rt-PA group ($P < .001$). Endovascular treatment was thus performed 1 hour later.

The major limitation in the SYNTHESIS study, as in the IMS-III study, was that large vessel occlusion was not confirmed before randomized assignment. Therefore, among the 181 patients in the endovascular treatment group, 165 actually received treatment. Among these, 109 received intra-arterial rt-PA and 56 underwent mechanical thrombolysis. In other words, about 10% of patients did not receive endovascular treatment after randomized assignment, and the modality in two thirds of those patients who did was intra-arterial rt-PA.

These study results, representing the so-called "Honolulu shock," were announced at the 2013 International Stroke Conference. However, all 3 studies had significant flaws in their designs and procedures. By addressing these faults, new directions for better treatment can come into view.

Rescue-Japan Registry

The Rescue-Japan Registry is the first nationwide, prospective registry of acute cerebral large vessel occlusion in Japan.[9] This study was performed to assess the impact of endovascular treatment on clinical outcome following approval of a mechanical clot retriever in Japan. The study demonstrated that endovascular treatment significantly improved clinical outcomes in IV t-PA-failed and -ineligible patients with proximal artery occlusion such as internal carotid artery.

In this registry, endovascular treatment was started much earlier (210 minutes after onset in RESCUE-Japan versus more than 360 minutes in MR RESCUE), and the reperfusion rate was higher than those of IMS III and MR RESCUE (TICI 2b-3: 52.5% in RESCUE-Japan versus 26% in MR RESCUE) (Table 2). The reason for the higher rate of reperfusion in the present study might be due to unlimited use of endovascular devices such as clot retrievers, intracranial/extracranial stents, balloons, thrombolytic agents, and their combinations, whereas a single device was allowed to use in IMS III. Another possible reason is that, in Japan, mechanical clot retrievers are allowed to be used by a board physician of the Japanese Society of NeuroEndovascular Therapy, which requires 100 or more neuroendovascular experience and passing the board examination. These differences should be considered when designing future comparative studies.

New Devices

Currently, the most promising new devices are stent-like thrombus retrieval devices. Stent retrievers allow thrombectomy to be performed by pulling back the deployed stent into the guide catheter, whereby the struts of the stent engage the thrombotic material. The device is applicable repeatedly and can be used even in small peripheral vessel branches. In contrast with conventional stent systems, stent retrievers require no anticoagulation

or antiplatelet treatment because the stent is not deployed permanently.

The main devices are the stent retrievers such as Solitaire (ev3) and the Trevo (Concentric Medical). Multicenter, prospective, randomized controlled trials comparing Solitaire and Merci (SWIFT study)[10] and comparing Trevo and Merci (Trevo 2 study)[11] have already been conducted, and superiority to the Merci Retriever has been demonstrated. Because these new devices achieve higher recanalization rates than previous devices, and the procedure times are shorter, this type of treatment is expected to become mainstream in the future.

Conclusions

Three recent randomized controlled studies found no effectiveness of endovascular treatment in acute ischemic stroke. However, limitations in the 3 studies included that large vessel occlusion was not yet confirmed, initiation of treatment was delayed, and recanalization rates were low. We believe that with the advent of new devices, controlled studies with modified protocols will demonstrate the superior effectiveness of endovascular treatment, thus further advancing the treatment of acute ischemic stroke.

References

1. Broderick JP, Palesch YY, Demchuk AM, et al, Interventional Management of Stroke (IMS) III Investigators. Endovascular therapy after intravenous t-PA versus t-PA alone for stroke. N Engl J Med 2013;368:893-903.
2. Kidwell CS, Jahan R, Gornbein J, et al, MR RESCUE Investigators. A trial of imaging selection and endovascular treatment for ischemic stroke. N Engl J Med 2013; 368:914-923.
3. Ciccone A, Valvassori L, Nichelatti M, et al, SYNTHESIS Expansion Investigators. Endovascular treatment for acute ischemic stroke. N Engl J Med 2013;368: 2433-2434.
4. Hacke W, Kaste M, Bluhmki E, et al, ECASS Investigators. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. N Engl J Med 2008; 359:1317-1329.
5. Hirano T, Sasaki M, Mori E, et al, Japan Alteplase Clinical Trial II Group. Residual vessel length on magnetic resonance angiography identifies poor responders to alteplase in acute middle cerebral artery occlusion patients: exploratory analysis of the Japan Alteplase Clinical Trial II. Stroke 2010;41:2828-2833.
6. Smith WS, Sung G, Saver J, et al, Multi MERCI Investigators. Mechanical thrombectomy for acute ischemic stroke: final results of the Multi MERCI trial. Stroke 2008;39: 1205-1212.
7. Penumbra Pivotal Stroke Trial Investigators. The penumbra pivotal stroke trial: safety and effectiveness of a new generation of mechanical devices for clot removal in intracranial large vessel occlusive disease. Stroke 2009; 40:2761-2768.
8. Goyal M, Menon BK, Coutts SB, et al, Penumbra Pivotal Stroke Trial Investigators, Calgary Stroke Program, and the Seaman MR Research Center. Effect of baseline CT scan appearance and time to recanalization on clinical outcomes in endovascular thrombectomy of acute ischemic strokes. Stroke 2011;42:93-97.
9. Yoshimura S, Sakai N, Okada Y, et al. RESCUE-Japan Registry Investigators. Efficacy of endovascular treatment for acute cerebral large vessel occlusion: analysis of nationwide prospective registry. J Stroke Cerebrovasc Dis 2014;23:1183-1190. http://dx.doi.org/10.1016/j.jstrokecerebrovasdis.2013.10.014.
10. Saver JL, Jahan R, Levy EI, et al, SWIFT Trialists. Solitaire flow restoration device versus the Merci Retriever in patients with acute ischaemic stroke (SWIFT): a randomised, parallel-group, non-inferiority trial. Lancet 2012; 380:1241-1249.
11. Nogueira RG, Lutsep HL, Gupta R, et al, TREVO 2 Trialists. Trevo versus Merci retrievers for thrombectomy revascularisation of large vessel occlusions in acute ischaemic stroke (TREVO 2): a randomised trial. Lancet 2012;380:1231-1240.

Long-term Magnetic Resonance Angiography Follow-up for Recanalized Vessels after Mechanical Thrombectomy

Yukiko Enomoto, MD, PhD,* Shinichi Yoshimura, MD, PhD,†
Yusuke Egashira, MD, PhD,* Toshinori Takagi, MD,* Masanori Tsujimoto, MD,*
and Toru Iwama, MD, PhD*

Background: Mechanical thrombectomy is an effective revascularization therapy for acute intracranial large vessel occlusion. We retrospectively evaluated magnetic resonance angiography (MRA) follow-up data to assess the long-term patency of recanalized vessels after mechanical thrombectomy. *Methods:* We retrospectively reviewed medical records of consecutive patients who had undergone mechanical thrombectomy for intravenous tissue plasminogen activator-failed/ineligible acute intracranial major vessel occlusion between October 2010 and April 2013 at our institution. MRA follow-up was performed at baseline and at 24 ± 6 hours and 3 months after mechanical thrombectomy. *Results:* Forty-nine patients underwent mechanical thrombectomy for acute intracranial major vessel occlusion. Mean age was 69.7 ± 11.5 years, and baseline median National Institute of Health Stroke Scale score was 15 (range, 8-24). Occlusion was found in the internal carotid artery in 18 patients (36.7%), middle cerebral artery in 26 patients (53%), and vertebral-basilar arteries in 5 patients (10.2%). Successful recanalization, as defined by a thrombolysis in cerebral infarction flow grade of 2b or 3, was achieved in 40 patients (81.6%). MRA follow-up at 24 hours after the treatment revealed that reocclusion of recanalized vessels was observed in 3 of 38 patients (7.9%). Long-term MRA follow-up showed that 2 of 27 patients (8.3%) developed diffuse severe stenosis of treated vessels. Both the patients had undergone treatment for middle cerebral artery occlusion with the Merci retriever and had been administered only anticoagulants, but not any antiplatelets. *Conclusions:* Reocclusion or late stenosis of successfully recanalized vessels was observed in 16.2% of patients. Long-term MRA follow-up of recanalized vessels will be useful, in particular, for the patient with middle cerebral artery occlusion who undergoes mechanical thrombectomy. **Key Words:** Acute ischemic stroke—mechanical thrombectomy—MRA—restenosis.

Introduction

Intravenous tissue plasminogen activator (IVtPA) improves clinical outcomes in patients experiencing acute ischemic stroke. However, it has a low frequency of recanalization of large occluded vessels, such as the internal carotid artery.[1-3]

Endovascular treatment provides a therapeutic option for acute ischemic stroke patients who are ineligible for or unresponsive to IVtPA. Mechanical clot extraction devices such as the Merci retriever (Concentric Medical, Mountain View, CA), the Penumbra system (Penumbra, Alameda, CA), and stent retrievers (Solitaire; Covidien/ev3, Dublin, Ireland or Trevo; Concentric Medical,

From the *Department of Neurosurgery, Graduate School of Medicine, Gifu University, Gifu; and †Department of Neurosurgery, Graduate School of Medicine, Hyogo Collage of Medicine, Hyogo, Japan.
Received May 22, 2014; revision received June 27, 2014; accepted July 8, 2014.
Address correspondence to Yukiko Enomoto, MD, PhD, Department of Neurosurgery, Gifu University Graduate School of Medicine, 1-1 Yanagido, Gifu 501-1194, Japan. E-mail: enomoto@gifu-u.ac.jp.
1052-3057/$ - see front matter

http://dx.doi.org/10.1016/j.jstrokecerebrovasdis.2014.07.011

Mountain View, CA) achieve vessel patency and yield higher recanalization rates.[4-8]

A meta-analysis of acute recanalization therapies revealed an overall recanalization rate of 83.6% for mechanical thrombectomy, which was the highest rate compared with 46.2% for IVtPA and 63.2% for intra-arterial thrombolysis.[1] In addition, recanalization was significantly associated with satisfactory outcomes and low mortality.[1]

Although the efficacy of mechanical thrombectomy is well known, procedural complications remain an issue after treatment.[4-8] Yuki et al[9] reported that mechanical thrombectomy induced structural changes and acute inflammatory reactions in treated vessels in swine model. Little is known about the long-term patency of recanalized vessel. Therefore, we retrospectively evaluated magnetic resonance angiography (MRA) data to assess the patency of recanalized vessels after mechanical thrombectomy.

Methods

Patients

We retrospectively reviewed medical records of consecutive patients who had undergone mechanical thrombectomy using Merci retriever and/or Penumbra system for IVtPA-failed/ineligible acute intracranial major vessel occlusion between October 2010 and April 2013 at our institution. Intracranial major vessels included the internal carotid artery (ICA), M1 or M2 segment of the middle cerebral artery (MCA), and vertebral-basilar arteries. This study was approved by the institutional investigational review board.

Procedure and Instruments

All patients underwent conventional cerebral angiography with the transfemoral approach to define the site and length of the occluded vessel. Once the occluded intracranial major vessel was identified, a femoral sheath was exchanged from 4Fr to 9Fr, and a 5000-U bolus of heparin was administered intravenously. In general, a mechanical extraction device was used via a balloon guiding catheter (9Fr OPTIMO; Tokai Medical Products, Aichi, Japan). Patients received adjunctive therapy (IVtPA, intra-arterial thrombolysis with tPA or urokinase, stenting, or balloon angioplasty), as needed, without any limitation. Antiplatelet and anticoagulant agents were also administered as necessary even in the perioperative period. Especially when stenting is required, patients received an oral administration of aspirin (200 mg) and clopidogrel loading doses (300-600 mg) through a nasogastric tube before stenting and continued with dual antiplatelet therapy of maintenance dose. For the prevention of second stroke, the patients had continued to take antiplatelet agents or anticoagulants, which depend on stroke etiology. As for the maintenance antithrombotic therapy at the time of discharge, 29 patients were only on antiplatelets, and 18 patients were only on anticoagulants.

Successful recanalization was defined as a thrombolysis in cerebral infarction flow grade of 2b or 3 in all treatable vessels,[10] confirmed by post-treatment digital subtraction angiography. Symptomatic hemorrhage was defined as any intracranial hemorrhage with a worsening of National Institute of Health Stroke Scale (NIHSS) score by 4 points or more within 24 hours. NIHSS and modified Rankin scores were obtained at baseline and after 3 months.

Computed tomography brain imaging was performed at baseline, just after the procedure, and any time when there was a decline in neurologic state. Magnetic resonance imaging (MRI) examinations were performed with a 1.5-T MRI unit (GE Medical Systems, Milwaukee, WI or Philips Medical Systems, Best, the Netherlands) using a standard head coil at baseline and at 24 ± 6 hours and 3 months after treatment. The MRI protocol consisted of diffusion-weighted image, fluid-attenuated inversion recovery, T1- and T2-weighted images, and 3-dimensional MRA of the circle of Willis.

Statistical Analysis

We examined baseline characteristics including demographics, medical history, risk factors, baseline NIHSS score, time to treatment, etiology subtype according to the Trial of ORG 10172 in Acute Stroke Treatment classification, and pre- or post-treatment antiplatelet agents or anticoagulants. All data were expressed as mean ± standard deviation. Differences between patients with and without patent target vessels at 3 months were analyzed using the chi-square test for continuous variables and the Fisher exact test for categorical variables. A P value of less than .05 was considered statistically significant. All statistical analyses were performed using a commercially available software (SPSS version 21.0; SPSS Inc, Chicago, IL).

Results

A total of 49 patients (18 women and 31 men) underwent mechanical thrombectomy. Mean age was 69.7 ± 11.5 years, and baseline median NIHSS score was 15 (range, 8-24). Prior IVtPA was performed in 30 patients (61.2%). The onset-to-admission time was 200.6 ± 158 minutes. Occlusion was found in the ICA in 18 patients (36.7%), MCA in 26 patients (53%), and vertebral-basilar arteries in 5 patients (10.2%). The final diagnosis of stroke etiology was cardiac embolism in 39 patients (79.6%), large artery atherosclerosis in 6 patients (12.2%), and other in 4 patients (8.2%). Past medical history included hypertension in 28 patients, diabetes mellitus in 12 patients, and dyslipidemia in 5 patients. Seven patients were previously treated with antiplatelet therapy.

The most common adjunctive treatment following mechanical thrombectomy was intra-arterial thrombolysis using urokinase or tPA (27 patients, 77.1%). Procedural complications occurred in 4 patients (8.1%; 1 vessel perforation, 1 major distal embolism, 1 dissection, and 1 symptomatic hemorrhage). Successful recanalization was

Table 1. *Clinical and radiological features with re-occlusion or late restenosis*

Number	Age/sex	Location	Etiology	Onset to administration (min)	NIHSS	IVtPA	Revascularization therapy	ICH	TICI	mRS (after 3m)	Antithrombotic therapy	Possible cause
Reocclusion cases												
1	72/M	rt.ICA + M1p	LAA	70	14	Failed	Merci, carotid stenting	-	3	1	Aspirin 200 mg, clopidogrel 300 mg, cilostazol 200 mg, argatroban (div)	Stent thrombosis
2	62/F	lt.M1d	CE	180	11	Failed	Penumbra, IAT (UK)	-	3	4	Heparin 10,000 U/24 h (div)	Re-embolism
3	49/F	lt.M1p	CE	180	22	Failed	Merci, Penumbra, IAT (UK)	-	2b	4	Aspirin 200 mg, heparin 10,000 U/24 h (div)	Dissection
Late restenosis cases												
4	78/M	lt.M1p	CE	300	15	-	Merci, PTA, IAT (UK)	aSAH	2b	3	-	Intimal hyperplasia
5	79/M	rt.M1p	CE	120	21	Failed	Merci, Penumbra, IAT (UK)	aSAH	3	4	-	

Abbreviations: aSAH, asymptomatic subarachnoid hemorrhage; CE, cardiac embolism; F, female; IAT, intra-arterial thrombolysis; ICA, internal carotid artery; ICH, intracranial hemorrhage; IVtPA, intravenous tissue plasminogen activator; LAA, large-artery atherosclerosis; lt., left; M1d, distal segment of M1; M1p, proximal segment of M1; M, male; mRS, modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale; PTA, percutaneous transluminal angioplasty; rt., right; TICI, thrombolysis in cerebral infarction; UK, urokinase.

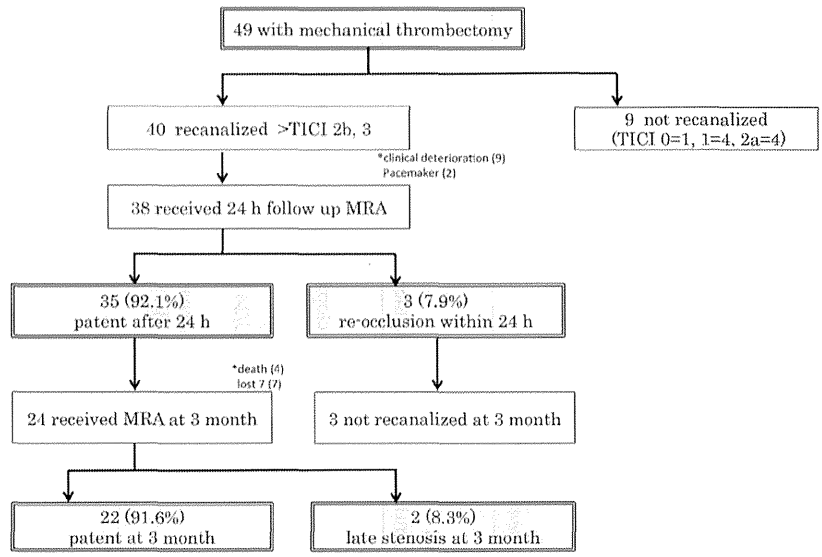

Figure 1. *Patient profile and flow chart of magnetic resonance angiography (MRA) follow-up. Abbreviation: TICI, thrombolysis in cerebral infarction.*

achieved in 40 patients (81.6%). Modified Rankin scores of 0 and 1 at 3 months were obtained in 15 patients (30.6%).

Thirty-eight patients were available for 24-hour MRA follow-up, excluding 11 who were unable to undergo MRI because of severe clinical deterioration (n = 9) or pacemaker use (n = 2). The patency of treated vessels was maintained in 35 of 38 patients (92.1%); however, reocclusion of treated vessels was observed in 3 patients (7.9%; Fig 1). Possible causes of reocclusion included in-stent thrombosis, re-embolism, and dissection (Table 1; Fig 2).

Long-term MRA follow-up was performed in 27 patients; 4 patients died and 7 patients were lost to follow-up. The patency of treated vessels was maintained in all patients at 3 months after treatment, except for 3 patients who had reocclusion at 24 hours and did not achieve natural recanalization before long-term follow-up. However, 2 patients (8.3%) developed diffuse severe stenosis of treated vessels. These patients had undergone treatment for MCA occlusion with the Merci retriever (Concentric Medical). Both patients were asymptomatic, and gradual improvement of stenosis was observed at the 1-year MRA follow-up (Fig 3). Statistical analysis revealed no significant difference between related factors and reocclusion or late stenosis. Because their etiology of stroke was diagnosed as cardioembolism, both patients had taken only anticoagulants and not any antiplatelets.

Discussion

In this study, reocclusion of treated vessels was observed within 24 hours in 7.9% of patients who had undergone endovascular therapy for acute stroke. Long-term MRA follow-up revealed that no patient developed reocclusion of treated vessels, but 8.3% developed late stenosis.

Our data suggest that, following endovascular therapy, recanalized vessels may be susceptible to acute reocclusion or late stenosis in the chronic stage.

Mechanical thrombectomy allows for rapid recanalization of large occluded arteries at a higher rate of success compared with IVtPA in patients with acute ischemic stroke and is thus used widely in the treatment of patients with large occluded intracranial arteries. However, there is a potential risk of arterial wall damage due to device use. Major clinical trials on mechanical thrombectomy have shown that symptomatic cerebral hemorrhage occurs at a rate of 2%-11.2% and procedural adverse events at 3%-17%.[4-8] The development of intraprocedural vessel perforation or postprocedural intracranial hemorrhage delays the initiation of postoperative antithrombotic therapy, and it may trigger subacute reocclusion of recanalized vessels.

Regarding late-stage stenotic changes, mechanical thrombectomy could induce structural changes or acute inflammatory reactions in treated vessels.[9] Endothelial injury caused by balloon angioplasty or stenting is known to promote smooth muscle cell proliferation in the intima, resulting in a neointima over the injured site. Exuberant healing responses lead to narrowing of the vessel lumen (ie, intimal hyperplasia). Intimal hyperplasia typically occurs over the course of a few months and more often with stenting than with balloon angioplasty.[11] Late stenosis of treated vessels in our cases had developed in the same duration. Therefore, it was speculated that these late-stage stenotic change would be intimal hyperplasia triggered by vessel damage due to mechanical thrombectomy. Intimal hyperplasia requires additional intervention in 30%-40% of coronary arteries after balloon angioplasty and in over 60% of aortocoronary saphenous vein bypass grafts after surgery within several years.[11] The drug-eluting stent has been developed to prevent

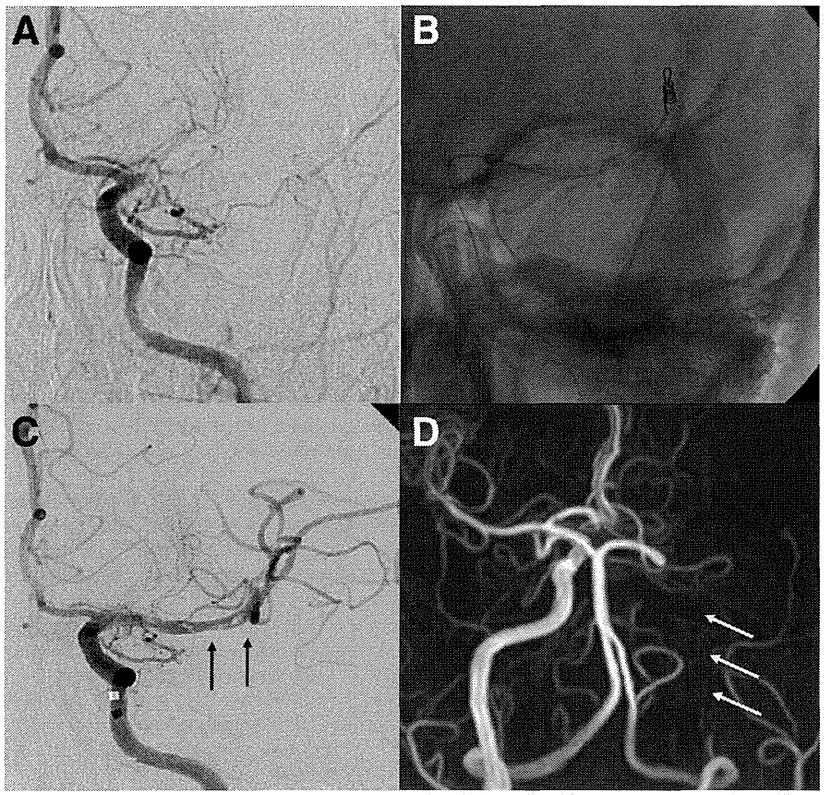

Figure 2. *Reocclusion of target vessel in a 49-year-old woman with left middle cerebral artery occlusion (A). The Merci retriever was used to achieve thrombolysis in cerebral infarction 2b recanalization. Final angiogram shows an intimal flap in the middle cerebral artery (black arrows) (C). Although repeat angiography was continued for 30 minutes to confirm whether it progress to occlusion, the patency was maintained. Magnetic resonance angiography at 24 hours after treatment shows occlusion of the internal carotid artery from the origin (white arrows) (D). The suspected cause is dissection due to procedural complications.*

restenosis by intimal hyperplasia. Recently, studies have shown that antiplatelets have inhibitory effect on restenosis due to intimal hyperplasia after stenting.[12,13] Our 2 patients who developed late restenosis had not taken any antiplatelets, so that we cannot deny that it had an influence on the developing of late restenosis.

In addition, a number of clinical trials using the Wingspan stent (Boston Scientific, Natick, MA) have been performed, demonstrating that the rate of in-stent restenosis ranges from 25% to 32.3% at a mean follow-up of 4.8-8.5 months.[14-17] Albuquerque et al[15] reported that MCA was associated with a higher rate of in-stent restenosis

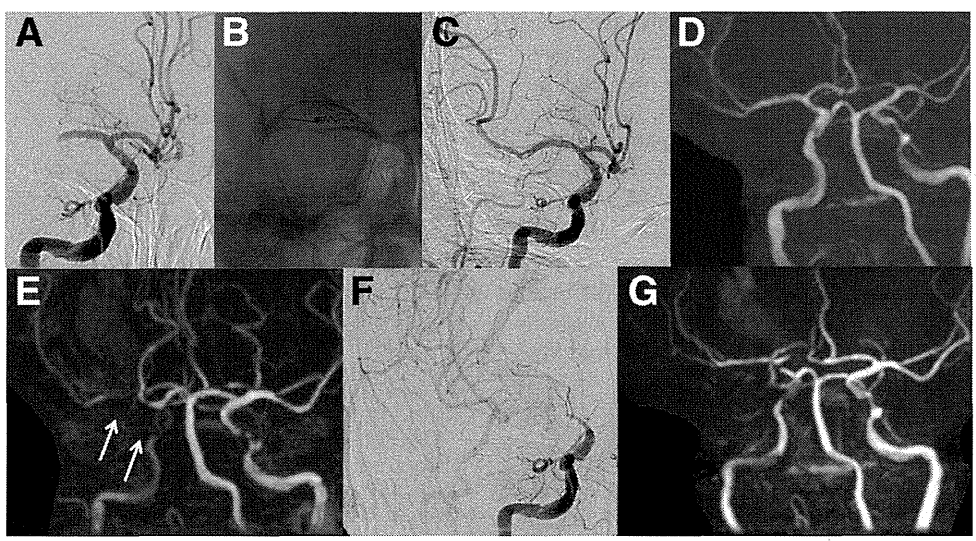

Figure 3. *Late restenosis in a 78-year-old man with right middle cerebral artery occlusion (A). Merci retriever (B) and Penumbra system were used to achieve thrombolysis in cerebral infarction 2b recanalization. Magnetic resonance angiography at 24 hours after treatment shows maintained patency of treated vessels (D). However, magnetic resonance angiography (E) and angiography (F) at 3 months shows diffuse stenosis (arrows) from the internal carotid artery to the right middle cerebral artery. Additional treatment was not performed, as the stenosis was clinically silent. magnetic resonance angiography at 1 year shows improved stenosis of these vessels (G).*

compared with the overall rate of restenosis for all sites (69.2% vs. 32.2%). Yu et al[18] reported that symptomatic in-stent restenosis was only observed in the MCA (3.3%). These findings suggest that the MCA is sensitive and more susceptible to restenosis compared with other vessels. MCA occlusion is known to more likely achieve recanalization by only thrombolytic therapy than ICA occlusion.[19] Therefore, there is a possibility that mechanical thrombectomy device is not suitable in MCA occlusion, unlike ICA occlusion.[20] Development of late stenosis by intimal hyperplasia after mechanical thrombectomy for acute ischemic stroke has not been previously reported.

The limitation of this study lies in its nonrandomized, single-center, retrospective design, and the number of analyzed patients was relatively small. Although stent retrievers had not been used in this study period, stent retrievers would also have potential risk of same phenomenon because it resembles Merci retriever (Concentric Medical) in structure and retrieval mechanism.

No previous clinical studies on mechanical thrombectomy for acute stroke have provided sufficient follow-up angiographic data regarding treated vessels, and whether poor clinical outcomes are related to reocclusion of recanalized vessels remains unknown. Thus, our results will be useful in providing a necessary framework to design a prospective study to address appropriate management of treated vessels. Our findings suggest that long-term follow-up is necessary, even for patients who achieved significant recanalization, as they may require retreatment for reocclusion or restenosis of treated vessels.

Conclusions

We retrospectively evaluated MRA data to assess the long-term patency of recanalized vessels after mechanical thrombectomy. At 24 hours after treatment, reocclusion of successfully recanalized vessels was observed in 3 patients (7.9%). At 3 months after treatment, late stenosis of recanalized vessels was observed in 2 patients (8.3%) who had undergone treatment for MCA occlusion with the Merci retriever (Concentric Medical).

Although mechanical thrombectomy can recanalize large occluded arteries more frequently and rapidly compared with other procedures, it has a potential risk of arterial wall damage due to device use. Long-term follow-up will be useful for monitoring recanalized vessels, in particular, for MCA occlusion.

References

1. Rha J, Saver JL. The impact of recanalization on ischemic stroke outcome: a meta-analysis. Stroke 2007;38:967-973.
2. Saqqur M, Uchino K, Demchuk AM, et al, CLOTBUST Investigators. Site of arterial occlusion identified by transcranial Doppler predicts the response to intravenous thrombolysis for stroke. Stroke 2007;38:948-954.
3. Wolpert SM, Bruckmann H, Greenlee R, et al. Neuroradiologic evaluation of patients with acute stroke treated with recombinant tissue plasminogen activator. The rt-PA Acute Stroke Study Group. AJNR Am J Neuroradiol 1993;14:3-13.
4. Gobin YP, Starkman S, Duckwiler GR, et al. MERCI 1: a phase 1 study of mechanical embolus removal in cerebral ischemia. Stroke 2004;35:2848-2854.
5. Smith WS, Sung G, Saver J, et al. Mechanical thrombectomy for acute ischemic stroke: final results of the Multi MERCI Trial. Stroke 2008;39:1205-1212.
6. The Penumbra Pivotal Stroke Trial Investigators. The Penumbra Pivotal Stroke Trial: safety and effectiveness of a new generation of mechanical devices for clot removal in intracranial large vessel occlusive disease. Stroke 2009;40:2761-2768.
7. Saver JL, Jahan R, Levy EI, et al, SWIFT Trialists. Solitaire flow restoration device versus the Merci Retriever in patients with acute ischaemic stroke (SWIFT): a randomised, parallel-group, non-inferiority trial. Lancet 2012; 380:1241-1249.
8. Nogueira RG, Lutsep HL, Gupta R, et al, TREVO 2 Trialists. Trevo versus Merci retrievers for thrombectomy revascularisation of large vessel occlusions in acute ischaemic stroke (TREVO 2): a randomised trial. Lancet 2012;380:1231-1240.
9. Yuki I, Kan I, Golshan A, et al. A swine model to analyze arterial structural changes induced by mechanical thrombectomy. AJNR Am J Neuroradiol 2014;34:E87-E90.
10. Tomsick T, Broderick J, Carrozella J, et al, Interventional Management of Stroke II Investigators. Revascularization results in the Interventional Management of Stroke II trial. AJNR Am J Neuroradiol 2008;29:582-587.
11. Rogers C, Karnovsky MJ, Edelman ER. Inhibition of experimental neointimal hyperplasia and thrombosis depends on the type of vascular injury and the site of drug administration. Circulation 1993;88:1215-1221.
12. Takigawa T, Matsumaru Y, Hayakawa M, et al. Cilostazol reduces restenosis after carotid stenting. J Vasc Surg 2010; 51:51-56.
13. Jennings DL, Kalus JS. Addition of cilostazol to aspirin and a thienopyridine for prevention of restenosis after coronary artery stenting: a meta-analysis. J Clin Pharmacol 2010;50:415-421.
14. Levy EI, Turk AS, Albuquerque FC, et al. Wingspan in-stent restenosis and thrombosis: incidence, clinical presentation, and management. Neurosurgery 2007;61:644-650.
15. Albuquerque FC, Levy EI, Turk AS, et al. Angiographic patterns of Wingspan in-stent restenosis. Neurosurgery 2008;63:23-27.
16. Turk AS, Levy EI, Albuquerque FC, et al. Influence of patient age and stenosis location on Wingspan in-stent restenosis. AJNR Am J Neuroradiol 2008;29:23-27.
17. Zaidat OO, Klucznik R, Alexander MJ, et al, NIH Multi-Center Wingspan Intracranial Stent Registry Study Group. The NIH registry on use of the Wingspan stent for symptomatic 70-99% intracranial arterial stenosis. Neurology 2008;70:1518-1524.
18. Yu SC, Leung TW, Lee KT, et al. Angioplasty and stenting of atherosclerotic middle cerebral arteries with Wingspan: evaluation of clinical outcome, restenosis, and procedure outcome. AJNR Am J Neuroradiol 2011;32:753-758.
19. Cho KH, Lee DH, Kwon SU, et al. Factors and outcomes associated with recanalization timing after thrombolysis. Cerebrovasc Dis 2012;33:255-261.
20. Pagola J, Rubiera M, Flores A, et al. Selecting endovascular treatment strategy according to the location of intracranial occlusion in acute stroke. Cerebrovasc Dis 2013; 35:502-506.

THrombolysis for Acute Wake-up and unclear-onset Strokes with alteplase at 0·6 mg/kg (THAWS) Trial

Masatoshi Koga[1]*, Kazunori Toyoda[2], Kazumi Kimura[3], Haruko Yamamoto[4], Makoto Sasaki[5], Toshimitsu Hamasaki[6], Takanari Kitazono[7], Junya Aoki[3], Kenta Seki[2], Kazunari Homma[2], Shoichiro Sato[2], and Kazuo Minematsu[2], on behalf of the THAWS investigators

Rationale **Because of lack of information regarding timing of stroke, patients who suffer stroke during sleep are generally ineligible for intravenous thrombolysis, although many of these patients could potentially recover with this treatment. Magnetic resonance image findings with positive diffusion-weighted imaging and no marked parenchymal hyperintensity on fluid-attenuated inversion recovery (negative pattern) can identify acute ischemic stroke patients within 4·5 h from symptom onset.**

Aims **The THrombolysis for Acute Wake-up and unclear-onset Strokes with alteplase at 0·6 mg/kg trial aims to determine the efficacy and safety of intravenous thrombolysis with alteplase at 0·6 mg/kg body weight, the approved dose for Japanese stroke patients, using magnetic resonance image-based selection in ischemic stroke patients with unclear time of symptom onset, and compare findings with standard treatment.**

Design **This is an investigator-initiated, multicenter, prospective, randomized, open-treatment, blinded-end-point clinical trial. The design is similar to the Efficacy and Safety of MRI-based Thrombolysis in Wake-up Stroke trial. Patients with unclear-onset time of stroke symptoms beyond 4·5 h and within 12 h after the time of the last-known-well period and within 4·5 h after symptom recognition, who showed a negative fluid-attenuated inversion recovery pattern, are randomized to either intravenous thrombolysis or standard treatment.**

Study outcomes **The primary efficacy end-point is modified Rankin Scale 0–1 at 90 days. The safety outcome measures are symptomatic intracranial hemorrhage at 22–36 h, and major bleeding and mortality at 90 days.**

Discussion **This trial may help determine if low-dose alteplase at 0·6 mg/kg should be recommended as a routine clinical strategy for ischemic stroke patients with unclear-onset time.**

Key words: acute ischemic stroke, clinical trials, diffusion-weighted imaging, fluid-attenuated inversion recovery imaging, thrombolysis, unclear-onset time

Correspondence: Masatoshi Koga*, Division of Stroke Care Unit, National Cerebral and Cardiovascular Center, 5-7-1 Fujishiro-dai, Suita, Osaka 565-8565, Japan.
E-mail: koga@ncvc.go.jp
[1]Division of Stroke Care Unit, National Cerebral and Cardiovascular Center, Suita, Japan
[2]Department of Cerebrovascular Medicine, National Cerebral and Cardiovascular Center, Suita, Japan
[3]Department of Stroke Medicine, Kawasaki Medical School, Kurashiki, Japan
[4]Department of Advanced Medical Technology Development, National Cerebral and Cardiovascular Center, Suita, Japan
[5]Advanced Medical Research Center, Iwate Medical University, Morioka, Japan
[6]Department of Biomedical Statistics, Osaka University Graduate School of Medicine, Suita, Japan
[7]Department of Clinical Science and Medicine, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan

Received: 6 February 2014; Accepted: 10 June 2014; Published online 4 August 2014

Conflict of interest: K. Toyoda: research support from Mitsubishi Tanabe Pharma Cooperation, honoraria from Mitsubishi Tanabe Pharma Cooperation; T. Kitazono: research support from Mitsubishi Tanabe Pharma Corporation, honoraria from Mitsubishi Tanabe Pharma Cooperation; K. Minematsu: research supports from Mitsubishi Tanabe Pharma Corporation, Kyowa Hakko Kirin Pharma, Inc., and Lundbeck, and honoraria from Mitsubishi Tanabe Pharma Cooperation and Kyowa Hakko Kirin Pharma, Inc.

Funding: Mihara Cerebrovascular Disorder Research Promotion Fund, and Intramural Research Fund for Cardiovascular Diseases of National Cerebral and Cardiovascular Center (H23-4-3; maintenance of the administration infrastructure for international multicenter studies of clinical stroke; P. I., K. Toyoda).

ClinicalTrials.gov identifier: NCT02002325

DOI: 10.1111/ijs.12360

Introduction and rationale

Currently, intravenous (i.v.) thrombolysis with recombinant tissue-type plasminogen activator (rt-PA) is the only evidence-based effective treatment for acute ischemic stroke within 4·5 h after symptom onset (1,2). Because the therapeutic time range for effective i.v. rt-PA therapy is limited, onset-to-treatment time is vital. Delayed thrombolysis may cause a life-threatening condition such as symptomatic intracranial hemorrhage (sICH). Because accurate onset-to-treatment time is not determined for patients with unclear-onset time of stroke symptoms or those who wake up with stroke symptoms, i.v. rt-PA therapy is usually contraindicated for these patients.

According to previous reports, about one-fourth of acute stroke patients suffer from stroke symptoms with unclear-onset time or onset during sleep (3–5). These patients were reported to have similar early ischemic findings on initial computed tomography (CT) or magnetic resonance imaging (MRI) compared with those presenting within three-hours (6) or six-hours of symptom recognition (7). Because onset of all subtypes of stroke has an early morning peak (8), a large number of patients who wake up with stroke symptoms may still be within the time window for i.v. thrombolysis when they arrive at the hospital.

Recently, stroke MRI findings with positive diffusion-weighted imaging (DWI) and no marked parenchymal hyperintensity on fluid-attenuated inversion recovery (FLAIR) (negative FLAIR pattern) was proposed to act as a 'brain clock' that indicates the stroke occurred within 3–4·5 h from stroke symptom onset (9–11). DWI depicts a reduced apparent diffusion coefficient indicating cytotoxic edema caused by ischemia within minutes of stroke (12). FLAIR is characterized by strong T2 weighting

together with suppression of cerebrospinal fluid signal and is often positive 3–4·5 h after stroke onset (9–11,13).

There are several reports of nonrandomized patients on thrombolysis based on CT or MRI findings in acute stroke patients with unclear-onset time. Most reports had retrospective study designs and suggested the safety and feasibility of thrombolysis for this subgroup of stroke patients (14–19). In Japan, a single-center, nonrandomized, prospective study involving 20 patients with unclear-onset time and negative FLAIR pattern on initial MRI showed no occurrence of sICH after i.v. rt-PA at 0·6 mg/kg alteplase; at 90 days, 47% of patients showed modified Rankin Scale (mRS) scores of 0–2 (15). However, there is no established data from randomized, controlled trials of i.v. rt-PA in patients with unclear-onset time. To our knowledge, there are six ongoing clinical trials to test the safety and efficacy of thrombolysis in acute stroke patients with unclear-onset time worldwide: the Safety of Intravenous Thrombolytics in Stroke on Awakening (SAIL-ON) (ClinicalTrials.gov Identifier NCT01643902), the Safety of Intravenous Thrombolysis for Wake-up Stroke (Wake-Up Stroke) (ClinicalTrials.gov Identifier NCT01183533), the Efficacy and Safety of MRI-based Thrombolysis in Wake-up Stroke (WAKE-UP) (ClinicalTrials.gov Identifier NCT01525290) (20), the Wake up Symptomatic Stroke in Acute Brain Ischemia (WASSABI) Trial (ClinicalTrials.gov Identifier NCT01455935), and WUS-rTPA (EudraCT no. 2010–019359-23). All of the trials use alteplase at 0·9 mg/kg. We hypothesized that stroke patients with unclear-onset time and a negative FLAIR pattern on MRI will improve more by i.v. thrombolysis than by standard treatment using alteplase at 0·6 mg/kg, a dose that is unique to Japanese patients. Thus, we planned a multicenter trial to test this hypothesis.

Methods

Design

The THrombolysis for Acute Wake-up and unclear-onset Strokes with alteplase at 0·6 mg/kg (THAWS) Trial is an investigator-initiated, multicenter, prospective, randomized, open-treatment, blinded-end-point clinical trial comparing i.v. rt-PA (alteplase) and standard treatment in unclear-onset stroke. This trial is registered with the ClinicalTrials.gov (Clinical Trials.gov Identifier NCT02002325) and the UMIN clinical trial (ID: UMIN000011630). Figure 1 shows a flowchart of the trial design. Table 1 shows a schedule of the trial. The design is similar to the WAKE-UP trial (20).

Patient population

Patients with acute ischemic stroke whose onset time of stroke symptoms cannot be determined represent the target population for the THAWS. Inclusion and exclusion criteria are listed in Table 2. As clinical inclusion criteria for timing of treatment initiation, time from last-known-well period without neurological symptoms to treatment initiation should be between 4·5 and 12 h, and time from symptom recognition to treatment initiation should be within 4·5 h. Patients with posterior circulation stroke including brain stem stroke are not excluded because they are reported to potentially have a longer therapeutic time window than those with anterior stroke (21). The negative FLAIR pattern as an acute ischemic lesion visible on DWI, but no marked parenchymal hyperintensity visible on FLAIR is a vital imaging inclusion (Fig. 2). Exclusion criteria mainly follow the prescribing information for alteplase in Japan. A detailed imaging guidebook kindly provided by the WAKE-UP steering committee will confer extensive examples illustrating inclusion and exclusion criteria on MRI (20).

MRI sequence and baseline assessment

DWI (spin-echo echo planar imaging), FLAIR (fast spin echo), T2* and magnetic resonance angiography (MRA) sequences are mandatory acquired. Perfusion imaging with dynamic susceptibility contrast is optionally added for baseline imaging. The details of DWI and FLAIR parameters are as follows: DWI with field of view (FOV) of 240 mm, acquisition matrix of 128 × 128, slice thickness of ≈5 mm, gap of 0–1 mm, repetition time (TR) of ≈8000 ms, and echo time (TE) of ≤100 ms; FLAIR on 1·5 Tesla MRI with FOV of 240 mm, acquisition matrix of 256 × 256, slice thickness of ≈5 mm, gap of 0–1 mm, TR of ≥8000 ms, TE of 100–140 ms, and inversion time (TI) of ≈2300 ms; and FLAIR on 3 Tesla MRI with FOV of 240 mm, acquisition matrix of 256 × 256, slice thickness of ≈5 mm, gap of 0–1 mm, TR of ≥10000 ms, TE of 95–125 ms, and TI of ≈2600 ms.

Basically, DWI and FLAIR lesions are visually assessed according to the WAKE-UP imaging guidebook. For DWI assessment, apparent diffusion coefficient map can be used to exclude a T2 shine through effect. If DWI lesion is extensively overlapping with a previous stroke lesion or extensive white matter change, such patient needs to be excluded. The guidebook optionally provides the objective guidance to include patients with relative signal intensity of <1·2 on FLAIR lesion corresponding to acute DWI lesion as compared with contralateral normal signal intensity.

Randomization and data management

Eligible patients are randomized 1:1 to either i.v. rt-PA (alteplase, the rt-PA group) or standard treatment (the control group). Both patients and investigators are open to treatment allocation. However, primary and secondary outcomes are assessed without information regarding treatment allocation by independent neurologists, neurosurgeons, or nurses. The Research Electronic Data Capture (REDCap) system is used for data entering and management.

Treatment

Alteplase is supplied in glass vials. Labeling and packaging of study medication are conducted according to good manufacturing practice, good clinical practice, and local and national regulatory requirements. Patients randomized to the rt-PA group receive alteplase 0·6 mg/kg body weight i.v. up to a maximum of 60 mg, 10% as bolus, and 90% as continuous infusion over one-hour. Patients randomized to the control group do not receive i.v. rt-PA but are treated with one to three antithrombotic drugs, including aspirin (160–300 mg/day), clopidogrel (75 mg/day), argatroban, and unfractionated heparin, except for the combination of argatroban and heparin according to attending physician's decisions. Such antithrombotics are prohibited for use in the rt-PA group within the initial 25 h. Treatment has to be initiated

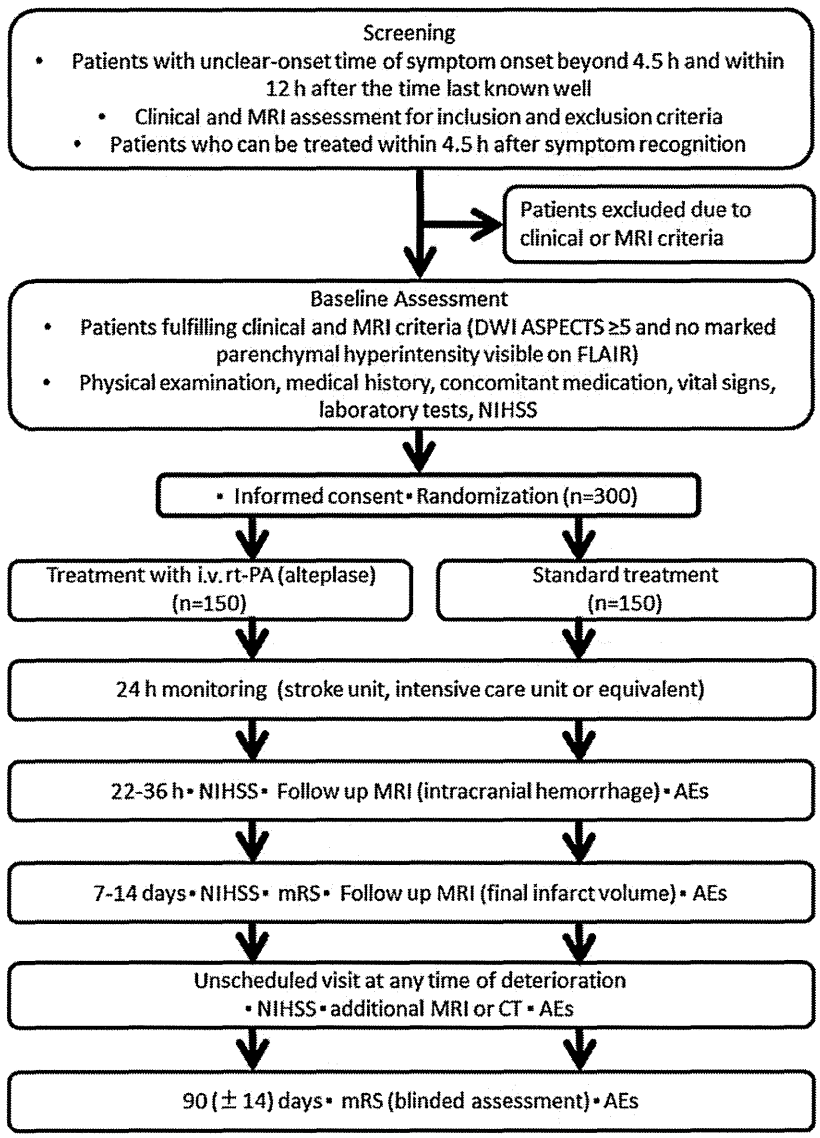

Fig. 1 Thrombolysis for Acute Wake-up and unclear-onset Strokes with alteplase at 0·6 mg/kg (THAWS) trial flow chart. AEs, adverse events; ASPECTS, the Alberta Stroke Program Early CT Score; CT, computed tomography; DWI, diffusion-weighted imaging; FLAIR, fluid-attenuated inversion recovery; i.v., intravenous; MRI, magnetic resonance imaging; NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale; rt-PA, recombinant tissue-type plasminogen activator.

as soon as possible within 60 min of the end of the MRI examination. In addition, i.v. edaravone (free radical scavenger) is routinely given before or soon after trial enrollment for both groups, for a maximum of 14 days, unless contraindicated or inappropriate. Other antiplatelets (e.g., cilostazol) and anticoagulants (e.g., warfarin) are prohibited within the initial 25 h, and thrombolytic agents such as urokinase and monteplase are prohibited during the 90-day study period in both groups.

Clinical and radiological assessments

Trained neurologists, neurosurgeons, or nurses will perform clinical assessment at baseline, at 22–36 h, at 7–14 days or at hospital discharge, and at 90 days after stroke onset. Neurological severity is evaluated using the National Institutes of Health Stroke Scale (NIHSS). At 90 days, a physician, nurse, or clinical research coordinator who is not aware of treatment assignment assesses mRS and adverse events at the clinic or by telephone interview. Investigators are recommended to complete a training and certification program for NIHSS and mRS.

In addition to the initial MRI prior to randomization, follow-up MRI is performed after 22–36 h to identify ICH, and after 7–14 days to delineate final infarct volume. All images are judged at the MRI examination scanner or the display for reading or viewing purposes by the local investigators. All investigators are recommended to pass a standardized training program for image judgment provided by the WAKE-UP committee. A central image reading board continuously monitors the fulfillment of the prespecified MRI standards in each participating center and the

Table 1 Schedule of assessments for THAWS trial

	Baseline	Administration of treatment	Observational period		
Timing	Enrollment	0 h	24 h* ± 3 h	Day 7 or discharge ± 1 day†	Day 90 ± 14 days
Consent	○				
Demographics/Baseline information/Medical history/Prior medication	○				
Screening/Eligibility	○				
Randomization	○				
Physical examination					
NIHSS	○		○	○	
mRS	Premorbid			○	○
Height/Weight	○				
Blood pressure/Pulse rate	○	○	○		
Body temperature	○				
Laboratory tests/Imaging					
Blood test	○		○		
Urine test	○				
Electrocardiogrphy	○				
MRI	○		○*	○†	
Adverse events		○	○	○	○
Alteplase administration		○			

*Follow-up MRI at 24 h is allowed to be obtained between 22 and 36 h after the treatment administration.
†Follow-up MRI at day 7 is allowed to be obtained between 7 and 14 days after the treatment administration or at discharge (whichever is first).
MRI, magnetic resonance imaging; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale.

compliance of patients randomized with the imaging inclusion and exclusion criteria.

Primary and secondary outcomes

Efficacy and safety end-points are listed in Table 3. Primary efficacy end-point is favorable outcome defined by mRS score 0–1 at 90 days after stroke onset. The safety end-points are sICH at 22–36 h and major bleeding (22), and death due to any cause at 90 days.

Data monitoring body

Data monitoring is centrally conducted by the members of Department of Advanced Medical Technology Development, National Cerebral and Cardiovascular Center. According to the order from the steering committee, the members occasionally visit collaborating hospitals to review source materials, including related medical records and documents for consent forms. Responsible authorities, related ethics committees, or directors of collaborating hospitals have the right to review source material if necessary.

Data and safety monitoring board

An independent data and safety monitoring board (DSMB) oversees the conduct of the trial. The occurrence of any safety end-point is immediately reported to the DSMB by the responsible physician via the central office, along with the accumulated number of safety end-points and total patient enrollment numbers. All safety end-points are mandatorily analyzed after inclusion of 150 and 300 patients. The proportion of sICH in the i.v. rt-PA group is compared with those of previous reports (23–27), and the proportions of major bleeding and death in the i.v. rt-PA group are compared with those in the control group. In any case of concern about the safety of participants, the DSMB makes a recommendation to the steering committee about continuing, stopping, or modifying the trial.

Sample size calculation

A total of 278 patients (139 per group) is required to ensure $1 - \beta = 90\%$ probability to demonstrate that the relative effect of i.v. rt-PA to standard treatment for ischemic stroke patients is more than a fraction of 0·5 of the combined relative effect of i.v. rt-PA across the stroke thrombolysis studies (15–17,28), by using one-sided chi-square test of significant level of 2·5%, where the effects of i.v. rt-PA and standard treatment are assumed 30% and 20% commonly for Japanese patients and comparable combined studies. Accounting for possible treatment failures, protocol violations, and dropouts, a total of 300 patients (150 per treatment group) will be recruited.

Statistical analysis

Analyses will be done according to an intention-to-treat (ITT) principle. A secondary per-protocol sensitivity analysis will be done to assess the robustness of conclusion from ITT basis analysis. Patient demographic data will be analyzed descriptively; categorical variables will be assessed with the chi-square test or Fisher's exact test, whereas continuous variables will be assessed with the Student's t-test or the Wilcoxon rank-sum test, as appropriate. The primary outcome is the proportion of patients with mRS 0–1 (i.e., primary end-point) at 90 days between the i.v. rt-PA and control groups, analyzed by the chi-square test. Relative risk (RR) for the primary outcome will be calculated with the corresponding 95% confidence interval. The secondary outcome is the change in NIHSS from baseline to at 24 h or 7 days, analyzed by analysis of covariance (ANCOVA), where the model includes

Table 2 Inclusion and exclusion criteria

Clinical inclusion criteria
• Clinical diagnosis of acute ischemic stroke with unknown symptom onset (e.g., acute wake-up ischemic stroke and acute ischemic stroke with unknown time of symptom onset)
• Age 20 years or older
• Last-known-well period without neurological symptoms > 4·5 h and <12 h of treatment initiation
• Treatment can be started within 4·5 h of symptom recognition (e.g., awakening)
• Initial NIHSS ≥ 5 and ≤25
• Written informed consent by patient or next of kin
Imaging inclusion criteria
• Acute stroke MRI including DWI and FLAIR completed
• ASPECTS on initial DWI ≥ 5
• Pretreatment MRI showing a pattern of 'negative FLAIR', that is, acute ischemic lesion visible (or normally visible) on DWI but no marked parenchymal hyperintensity visible on FLAIR indicative of an acute ischemic lesion ≤ 4·5 h of age
Clinical exclusion criteria
• Prestroke mRS > 1 (patients who have inability to carry out all daily activities and require some help or supervision)
• Contraindications in the Japanese guidelines for the intravenous application of recombinant tissue-type plasminogen activator (alteplase)
√ History of nontraumatic intracranial hemorrhage
√ History of stroke within the last one-month (excluding transient ischemic attack)
√ History of significant head/spinal injury or surgery within the last three-months
√ History of gastrointestinal or urinary tract bleeding within the last 21 days
√ History of major surgery or significant trauma other than head injury within the last 14 days
√ Hypersensitivity to alteplase or any of the excipients
√ Suspected subarachnoid hemorrhage
√ Concurrent acute aortic dissection
√ Concurrent hemorrhage (e.g., intracranial, gastrointestinal, urinary tract, or retroperitoneal)
√ Systolic blood pressure ≥ 185 mmHg despite antihypertensive therapy
√ Diastolic blood pressure ≥ 110 mmHg despite antihypertensive therapy
√ Significant hepatic disorder
√ Acute pancreatitis
√ Blood glucose < 50 or >400 mg/dL (<2·8 or >22·2 mmol/L)
√ Platelet count ≤ 100 000/mm^3
√ PT-INR > 1·7 or prolonged aPTT [>1·5 times the baseline value (> approximately 40 s only as a guide)] for patients on anticoagulation therapy or those with abnormal coagulation
• Any contraindication to MRI (e.g., cardiac pacemaker)
• Planned or anticipated treatment with surgery or endovascular reperfusion strategies (e.g., intra-arterial thrombolysis, mechanical recanalization techniques)
• Pregnant, lactating, or potentially pregnant
• Life expectancy six-months or less by judgment of the investigator
• Inappropriate for study enrollment by judgment of the investigator
Imaging exclusion criteria
• Poor MRI quality precluding interpretation according to the study protocol
• Large DWI lesion volume > 50% of the anterior cerebral artery or posterior cerebral artery territory (visual inspection)
• Large DWI lesion in brain stem or cerebellum (e.g., more than half of brain stem or more than half of unilateral cerebellar hemisphere)
• Any sign of intracranial hemorrhage on baseline MRI
• FLAIR showing marked parenchymal hyperintensity corresponding to the acute DWI lesion indicative of an acute ischemic lesion with a high likelihood of being >4·5 h old ('positive FLAIR')
• Any MRI findings indicative of a high risk of symptomatic intracranial hemorrhage related to potential intravenous alteplase treatment in the judgment of the investigator

aPTT, activated partial thromboplastin time; ASPECTS, Alberta Stroke Program Early CT score; DWI, diffusion weighted imaging; FLAIR, fluid attenuated inversion recovery; MRI, magnetic resonance imaging; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; PT-INR, prothrombin time international normalized ratio.

treatment group as factor and NIHSS at baseline as a covariate. Safety data will be analyzed descriptively for the treated set, which consists of all randomized patients who receive at least one study treatment. The statistical analysis plan, which includes more technical and detailed elaboration of the principal features stated in the protocol, will separately be prepared and be finalized before breaking the blind.

Study organization and funding

The THAWS is organized by a central coordinating center located at the National Cerebral and Cardiovascular Center, and conducted in approximately 35 centers in Japan after the approval of Advanced Medical Technology Development authentication system by the Ministry of Health, Labour and Welfare. The steering committee manages the trial. The THAWS

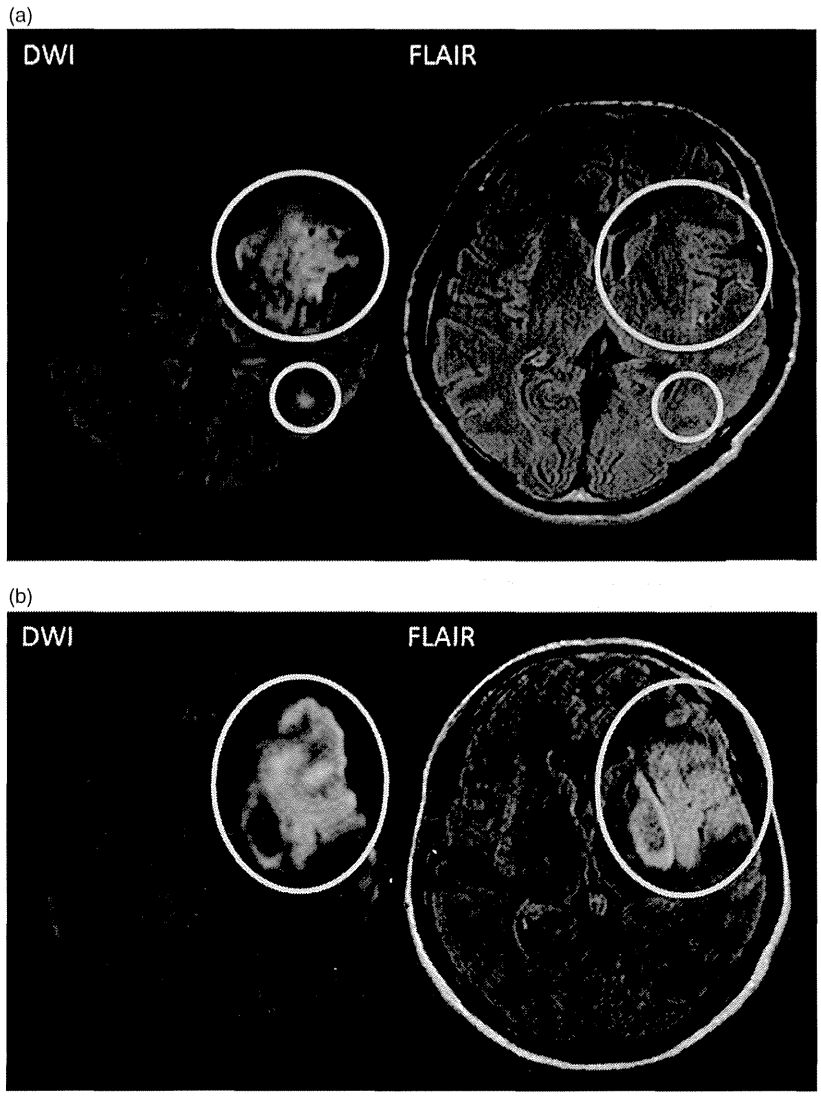

Fig. 2 Examples of magnetic resonance imaging (MRI) inclusion and exclusion criteria. (a) A negative fluid-attenuated inversion recovery (FLAIR) pattern shows an acute ischemic lesion clearly visible on diffusion-weighted imaging (DWI), but no marked parenchymal hyperintensity visible on fluid-attenuated inversion recovery (FLAIR) corresponding to the DWI lesion (yellow circles). (b) A positive FLAIR pattern shows an acute ischemic lesion clearly visible on DWI and clear parenchymal hyperintensity on FLAIR corresponding to the acute DWI lesion (yellow circle).

receives funding support from the Award from Charitable Trust Mihara Cerebrovascular Disorder Research Promotion Fund (to Minematsu) and the Intramural Research Fund for Cardiovascular Diseases of National Cerebral and Cardiovascular Center (H23-4-3).

Discussion and conclusion

The THAWS is a randomized, controlled trial of stroke thrombolysis with alteplase 0·6 mg/kg based on the presence of negative FLAIR pattern on initial MRI in patients with unclear-onset time of stroke symptom, that is, wake-up stroke. The negative FLAIR will ensure the enrollment of patients with ischemic lesions likely to be less than 4·5 h after stroke onset who are likely to benefit from thrombolysis. The THAWS may trigger approval of low-dose i.v. thrombolysis using MRI-based selection as a routine clinical practice for ischemic stroke patients with unclear-onset time. Furthermore, 0·6 mg/kg of alteplase is expected to have similar efficacy and higher safety than 0·9 mg/kg in Asian countries (29), and it is now investigated in the Enhanced Control of Hypertension and Thrombolysis Stroke Study (ENCHANTED) (Clinical Trials.gov Identifier NCT01422616).

Of several ongoing clinical trials on thrombolysis in acute stroke patients with unclear-onset time in worldwide, the WAKE-UP trial is the largest. We are in contact with the WAKE-UP group and they kindly provided us their detailed imaging guidebook and standardized training program for image judgment to share the same imaging inclusion criteria. We may conduct a meta-analysis with the ongoing trials for unclear-onset stroke, including the WAKE-UP trial.

Table 3 Efficacy and safety assessment

Primary efficacy end-point
• Favorable outcome defined by mRS score 0–1 at 90 days after stroke onset
Secondary efficacy end-points
• Categorical shift in NIHSS score at 24 h after the initiation of treatment • Categorical shift in NIHSS score at seven-days after the initiation of treatment • mRS score 0–2 at 90 days after stroke onset • Categorical shift in mRS score at 90 days after stroke onset • Recanalization of culprit artery on MRA 22–36 h after the initiation of treatment • Infarct volume on FLAIR 7–14 days after the initiation of treatment
Safety end-points
• sICH as defined by an increase of NIHSS score of ≥4 from baseline and parenchymal hematoma type II (PH-2) on MRI 22–36 h after the initiation of treatment • Major bleeding as defined by fatal bleeding, symptomatic bleeding in a critical area or organ, such as intraspinal, intraocular, retroperitoneal, intraarticular, or pericardial, or intramuscular with compartment syndrome, or bleeding causing a fall in hemoglobin level ≥ 2 g/dL, or leading to transfusion of ≥4·5 units (≈1125 mL) of whole blood or red cells according to the definition of the International Society on Thrombosis and Haemostasis (22) within 90 days after stroke onset • Death (mRS 6) due to any cause at 90 days after stroke onset

FLAIR, fluid attenuated inversion recovery; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; sICH, symptomatic intracerebral hemorrhage.

THAWS boards and institutions

Senior advisor: Kazuo Minematsu
Steering committee: Kazunori Toyoda (Chair), Kazumi Kimura (vice-chair), Haruko Yamamoto (data monitoring), Masatoshi Koga (central office)
Protocol committee: Junya Aoki, Toshimitsu Hamasaki, Kazumi Kimura, Masatoshi Koga, Shoichiro Sato, Kazunori Toyoda
Statistician: Toshimitsu Hamasaki
Independent safety monitoring board: Takanari Kitazono (Chair), Toshisuke Otsuki, Wataru Shimizu, Takashi Sozu
Central imaging reading board: Makoto Sasaki (Chair), Teruyuki Hirano, Kohsuke Kudo, Naomi Morita
Central pharmacy: Ken Kuwahara
Coordinating investigators: Sohei Yoshimura, Shoichiro Sato, Kazunari Homma, Kenta Seki
Secretariats: Haruka Kanai, Azusa Tokunaga

THAWS consortium

National Cerebral and Cardiovascular Center, Suita, Osaka – Kazunori Toyoda, Kazuyuki Nagatsuka, Haruko Yamamoto, Masatoshi Koga, Hiroshi Yamagami, Shoichiro Sato, Kazunari Homma, Kenta Seki
Kawasaki Medical School, Kurashiki – Kazumi Kimura, Junya Aoki
Hokkaido P.W.F.A.C. Obihiro-Kosei General Hospital, Obihiro – Masafumi Ohtaki
Nakamura Memorial Hospital, Sapporo – Kamiyama Kenji
Hirosaki Stroke and Rehabilitation Center, Hirosaki – Metoki Norifumi
Kohnan Hospital, Sendai – Eisuke Furui
Yamagata City Hospital SAISEIKAN, Yamagata – Rei Kondo
South Miyagi Medical Center, Shibata – Hiroshi Mochizuki
Niigata City General Hospital, Niigata – Shuichi Igarashi
Mihara Memorial Hospital, Isesaki – Ban Mihara
Jichi Medical University, Shimotsuke – Tomoaki Kameda
Saitama Medical University International Medical Center, Hidaka – Norio Tanahashi, Ichiro Deguchi
Juntendo University Urayasu Hospital, Urayasu – Takao Urabe
Juntendo University Hospital, Tokyo – Nobutaka Hattori
Jikei University School of Medicine, Tokyo – Yasuyuki Iguchi
Toranomon Hospital, Tokyo – Yoshikazu Uesaka
Kyorin University, Mitaka – Yoshiaki Shiokawa, Denbo Norihisa
St. Marianna University School of Medicine, Kawasaki – Yasuhiro Hasegawa
Tokai University, Isehara – Shunya Takizawa
Shizuoka Saiseikai General Hospital, Shizuoka – Jin Yoshii
Toyota Memorial Hospital, Toyota – Yasuhiro Ito
National Hospital Organization Nagoya Medical Center, Nagoya – Satoshi Okuda
Japanese Red Cross Kyoto Daini Hospital, Kyoto – Yoshinari Nagakane
Hyogo College of Medicine, Nishinomiya – Shinichi Yoshimura
Kobe City Medical Center Central Hospital, Kobe – Nobuyuki Sakai, Kenichi Todo.
Ohnishi Neurological Center, Akashi – Hideyuki Ohnishi
Kawasaki Hospital, Okayama – Tsuyoshi Inoue
Osaka Neurosurgical Hospital, Takamatsu – Hideo Ohyama
Kokura Memorial Hospital, Kokura – Ichiro Nakahara
Steel Memorial Yawata Hospital, Kitakyushu – Shigeru Fujimoto
Japanese Red Cross Fukuoka Hospital, Fukuoka – Kenichiro Fujii, Sohei Yoshimura
National Hospital Organization Kyushu Medical Center, Fukuoka – Yasushi Okada, Takeshi Uwatoko
Nagasaki University Hospital, Nagasaki – Akira Tsujino

Saiseikai Kumamoto Hospital, Kumamoto – Toshiro Yonehara
Japanese Red Cross Kumamoto Hospital, Kumamoto – Tadashi Terasaki

References

1 Hacke W, Kaste M, Bluhmki E *et al.* Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *N Engl J Med* 2008; **359:**1317–29.
2 Lees KR, Bluhmki E, von Kummer R *et al.* Time to treatment with intravenous alteplase and outcome in stroke: an updated pooled analysis of ECASS, ATLANTIS, NINDS, and EPITHET trials. *Lancet* 2010; **375:**1695–703.
3 Mackey J, Kleindorfer D, Sucharew H *et al.* Population-based study of wake-up strokes. *Neurology* 2011; **76:**1662–7.
4 Kang DW, Kwon JY, Kwon SU, Kim JS. Wake-up or unclear-onset strokes: are they waking up to the world of thrombolysis therapy? *Int J Stroke* 2012; **7:**311–20.
5 Koton S, Tanne D, Bornstein NM. Ischemic stroke on awakening: patients' characteristics, outcomes and potential for reperfusion therapy. *Neuroepidemiology* 2012; **39:**149–53.
6 Todo K, Moriwaki H, Saito K, Tanaka M, Oe H, Naritomi H. Early CT findings in unknown-onset and wake-up strokes. *Cerebrovasc Dis* 2006; **21:**367–71.
7 Serena J, Davalos A, Segura T, Mostacero E, Castillo J. Stroke on awakening: looking for a more rational management. *Cerebrovasc Dis* 2003; **16:**128–33.
8 Marsh EE 3rd, Biller J, Adams HP Jr *et al.* Circadian variation in onset of acute ischemic stroke. *Arch Neurol* 1990; **47:**1178–80.
9 Aoki J, Kimura K, Iguchi Y, Shibazaki K, Sakai K, Iwanaga T. FLAIR can estimate the onset time in acute ischemic stroke patients. *J Neurol Sci* 2010; **293:**39–44.
10 Thomalla G, Rossbach P, Rosenkranz M *et al.* Negative fluid-attenuated inversion recovery imaging identifies acute ischemic stroke at 3 hours or less. *Ann Neurol* 2009; **65:**724–32.
11 Petkova M, Rodrigo S, Lamy C *et al.* MR imaging helps predict time from symptom onset in patients with acute stroke: implications for patients with unknown onset time. *Radiology* 2010; **257:**782–92.
12 Minematsu K, Li L, Fisher M, Sotak CH, Davis MA, Fiandaca MS. Diffusion-weighted magnetic resonance imaging: rapid and quantitative detection of focal brain ischemia. *Neurology* 1992; **42:**235–40.
13 Ebinger M, Galinovic I, Rozanski M, Brunecker P, Endres M, Fiebach JB. Fluid-attenuated inversion recovery evolution within 12 hours from stroke onset: a reliable tissue clock? *Stroke* 2009; **41:**250–5.
14 Aoki J, Kimura K, Iguchi Y *et al.* Intravenous thrombolysis based on diffusion-weighted imaging and fluid-attenuated inversion recovery mismatch in acute stroke patients with unknown onset time. *Cerebrovasc Dis* 2011; **31:**435–41.
15 Aoki J, Kimura K, Shibazaki K, Sakamoto Y. Negative fluid-attenuated inversion recovery- based intravenous thrombolysis using recombinant tissue plasminogen activator in acute stroke patients with unknown onset time. *Cerebrovasc Dis Extra* 2013; **3:**35–45.
16 Barreto AD, Martin-Schild S, Hallevi H *et al.* Thrombolytic therapy for patients who wake-up with stroke. *Stroke* 2009; **40:**827–32.
17 Cho AH, Sohn S-I, Han M-K *et al.* Safety and efficacy of MRI-based thrombolysis in unclear-onset stroke. *Cerebrovasc Dis* 2008; **25:**572–9.
18 Breuer L, Schellinger PD, Huttner HB *et al.* Feasibility and safety of magnetic resonance imaging-based thrombolysis in patients with stroke on awakening: initial single-centre experience. *Int J Stroke* 2010; **5:**68–73.
19 Ebinger M, Scheitz JF, Kufner A, Endres M, Fiebach JB, Nolte CH. MRI-based intravenous thrombolysis in stroke patients with unknown time of symptom onset. *Eur J Neurol* 2012; **19:**348–50.
20 Thomalla G, Fiebach JB, Østergaard L *et al.* A multicenter, randomized, double-blind, placebo-controlled trial to test efficacy and safety of magnetic resonance imaging-based thrombolysis in wake-up stroke (WAKE-UP). *Int J Stroke* 2014; **9:**829–36.
21 Ostrem JL, Saver JL, Alger JR *et al.* Acute basilar artery occlusion: diffusion-perfusion MRI characterization of tissue salvage in patients receiving intra-arterial stroke therapies. *Stroke* 2004; **35:**e30–4.
22 Schulman S, Kearon C. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *J Thromb Haemost* 2005; **3:**692–4.
23 The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med* 1995; **333:**1581–7.
24 Saqqur M, Uchino K, Demchuk AM *et al.* Site of arterial occlusion identified by transcranial Doppler predicts the response to intravenous thrombolysis for stroke. *Stroke* 2007; **38:**948–54.
25 Wahlgren N, Ahmed N, Dávalos A *et al.* Thrombolysis with alteplase for acute ischaemic stroke in the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST): an observational study. *The Lancet* 2007; **369:**275–82.
26 Yamaguchi T, Mori E, Minematsu K *et al.* Alteplase at 0.6 mg/kg for acute ischemic stroke within 3 hours of onset: Japan Alteplase Clinical Trial (J-ACT). *Stroke* 2006; **37:**1810–5.
27 Toyoda K, Koga M, Naganuma M *et al.* Routine use of intravenous low-dose recombinant tissue plasminogen activator in Japanese patients: general outcomes and prognostic factors from the SAMURAI register. *Stroke* 2009; **40:**3591–5.
28 Kang DW, Sohn SI, Hong KS *et al.* Reperfusion therapy in unclear-onset stroke based on MRI evaluation (RESTORE): a prospective multicenter study. *Stroke* 2012; **43:**3278–83.
29 Chao AC, Hsu HY, Chung CP *et al.* Outcomes of thrombolytic therapy for acute ischemic stroke in Chinese patients: the Taiwan Thrombolytic Therapy for Acute Ischemic Stroke (TTT-AIS) study. *Stroke* 2010; **41:**885–90.

Relationship Between Magnetic Resonance Angiography–Diffusion-weighted Imaging Mismatch and Clinical Outcome in Endovascular Treatment for Acute Ischemic Stroke: Subgroup Analysis of the Recovery by Endovascular Salvage for Cerebral Ultra-acute Embolism–Japan Registry

Ichiro Deguchi, MD, PhD,* Tomohisa Dembo, MD, PhD,† Shinichi Yoshimura, MD, PhD,‡ Nobuyuki Sakai, MD, DMSc,§ Yasushi Okada, MD, PhD,‖ Kazuo Kitagawa, MD, PhD,¶ Kazumi Kimura, MD, PhD,# Toshio Hyogo, MD, PhD,** Hiroshi Yamagami, MD, PhD,†† Yusuke Egashira, MD, PhD,‡‡ and Norio Tanahashi, MD, PhD*

Background: The presence or absence of the penumbra area is important when performing reperfusion therapy in patients with acute ischemic stroke. As a predictor of this penumbra area, magnetic resonance angiography (MRA)–diffusion-weighted imaging (DWI) mismatch is attracting attention. The usefulness of MRA–DWI mismatch (MDM) using the DWI–Alberta Stroke Program Early Computed Tomography Score (ASPECTS) in endovascular treatment (EVT) of patients with cerebral large vessel occlusion was evaluated. *Methods:* Of 1442 patients registered in the Recovery by Endovascular Salvage for Cerebral Ultra-acute Embolism–Japan Registry between July 1, 2010 and June 30, 2011 who presented to the hospital within 24 hours of the onset of acute cerebral infarction because of cerebral large vessel occlusion, 188 patients who had internal carotid artery or middle cerebral artery occlusion and achieved recanalization with EVT were included. Of these, 71 patients underwent intracranial EVT because intravenous recombinant tissue plasminogen activator therapy was ineffective. The associations between the presence or absence of MDM (MDM-positive [MDM-P], DWI-ASPECTS ≥ 6; MDM-negative [MDM-N], DWI-ASPECTS < 6) and 90-day prognosis (modified Rankin Scale [mRS]) and symptomatic intracranial hemorrhage (sICH) were examined. *Results:* Of the 188 patients analyzed, the time from symptom onset to admission was within 3 hours in 143 patients, 3-8 hours in 36 patients, and 8 hours or more in 9 patients. The time from the onset was within 3 hours in 118 patients in the MDM-P and 25 patients in the MDM-N cases. Favorable outcomes (mRS score ≤2 at 90 days) were seen in 63 patients (53.4%) in the MDM-P group and 7 patients (28.0%) in the MDM-N group, showing a significantly more favorable clinical outcome in the MDM-P group

From the *Department of Neurology, Saitama Medical University International Medical Center, Saitama; †Department of Neurology, Kyorin University; ‡Department of Neurosurgery, Hyogo College of Medicine; §Department of Neurosurgery and Stroke Center, Kobe City Medical Center General Hospital; ‖Department of Cerebrovascular Medicine and Neurology, National Hospital Organization, Kyushu Medical Center; ¶Department of Neurology, Osaka University, Osaka; #Department of Stroke Medicine, Kawasaki Medical School; **Department of Neurosurgery, Nakamura Memorial Hospital; ††Department of Neurology, National Cerebral and Cardiovascular Center; and ‡‡Department of Neurosurgery, Gifu University, Japan.

Received November 1, 2013; revision received November 29, 2013; accepted December 7, 2013.

Address correspondence to Ichiro Deguchi, MD, PhD, Department of Neurology, Saitama Medical University International Medical Center, 1397-1 Yamane, Hidaka, Saitama 350-1298, Japan. E-mail: ideguchi@saitama-med.ac.jp.

1052-3057/$ - see front matter

http://dx.doi.org/10.1016/j.jstrokecerebrovasdis.2013.12.053