Rapid Communication doi: 10.2176/nmc.rc.2021-0311

Neurol Med Chir (Tokyo) 62, 156–164, 2022 Online December 24, 2021

Randomized Clinical Trial of Endovascular Therapy for Acute Large Vessel Occlusion with Large Ischemic Core (RESCUE-Japan LIMIT): Rationale and Study Protocol

Shinichi Yoshimura,[1] Kazutaka Uchida,[1,2] Nobuyuki Sakai,[3] Hiroshi Yamagami,[4] Manabu Inoue,[5] Kazunori Toyoda,[5] Yuji Matsumaru,[6] Yasushi Matsumoto,[7] Kazumi Kimura,[8] Reiichi Ishikura,[9] and Takeshi Morimoto[2]

[1]*Department of Neurosurgery, Hyogo College of Medicine, Nishinomiya, Hyogo, Japan*
[2]*Department of Clinical Epidemiology, Hyogo College of Medicine, Nishinomiya, Hyogo, Japan*
[3]*Department of Neurosurgery, Kobe City Medical Center General Hospital, Kobe, Hyogo, Japan*
[4]*Department of Stroke Neurology, National Hospital Organization Osaka National Hospital, Osaka, Osaka, Japan*
[5]*Department of Cerebrovascular Medicine, National Cerebral and Cardiovascular Center, Suita, Osaka, Japan*
[6]*Division of Stroke Prevention and Treatment, Department of Neurosurgery, Faculty of Medicine, University of Tsukuba, Tsukuba, Ibaraki, Japan*
[7]*Department of Neuroendovascular Therapy, Kohnan Hospital, Sendai, Miyagi, Japan*
[8]*Department of Neurology, Graduate School of Medicine, Nippon Medical School, Tokyo, Japan*
[9]*Department of Radiology, Hyogo College of Medicine, Nishinomiya, Hyogo, Japan*

Abstract

Endovascular therapy is strongly recommended for acute cerebral large vessel occlusion (LVO) with an Alberta stroke program early computed tomography score (ASPECTS) ≥6 due to occlusion of the internal carotid artery or M1 segment of the middle cerebral artery. However, the effect of endovascular therapy for patients with a large ischemic core with an ASPECTS ≤5 (0–5) was not established. A multicenter, randomized, open-label, parallel-group trial was conducted to investigate the superiority of endovascular therapy over medical therapy without endovascular therapy for a large ischemic core with ASPECTS (3–5). Patients were randomly assigned to receive endovascular therapy or without endovascular therapy at a ratio of 1:1. The primary outcome was a moderate functional outcome, defined as a modified Rankin scale (mRS; scores ranging from 0 [no symptoms] to 6 [death]) ≤3 after 90 days. The secondary outcomes were defined as ordinal mRS, good functional outcome (mRS ≤2), excellent functional outcome (mRS ≤1), mRS shift analysis after 90 days, and early improvement of neurological findings at 48 hours. A total sample size of 200 was estimated to provide a power of 0.9 with a two-sided alpha of 0.05, for the primary outcome, considering a 15% dropout rate. This randomized clinical trial reported the applicability of endovascular therapy in patients with acute cerebral LVO with a large ischemic core.

Keywords: randomized clinical trial, acute ischemic stroke, large vessel occlusion, large ischemic core, endovascular therapy

Received September 28, 2021; Accepted November 19, 2021

Introduction

Endovascular therapy is strongly recommended for acute cerebral large vessel occlusion (LVO) with an

Alberta stroke program early computed tomography score (ASPECTS)[1] ≥6 due to occlusion of the internal carotid artery or M1 segment of the middle cerebral artery (M1) within 6 h of onset, and patients meeting the DAWN and DEFUSE criteria at 6–16 hours after onset.[2,3] However, the efficacy of endovascular therapy for patients with ASPECTS ≤5 has not been proven, and we believe that reperfusion therapy for patients with a large ischemic core might increase the risk of intracranial hemorrhage (ICH).[4]

A multicenter randomized clinical trial of endovascular treatment for acute ischemic stroke in the Netherlands trial was the first randomized controlled trial that showed the effectiveness of endovascular therapy for acute ischemic stroke with LVO[5] and included patients with acute stroke with extracranial internal carotid and intracranial arterial occlusion demonstrated by computed tomography angiography (CTA), magnetic resonance angiography (MRA), or digital subtraction angiography, regardless of ASPECTS. The results did not show the effectiveness of endovascular therapy in patients with ASPECTS ≤4. Furthermore, the highly effective reperfusion evaluated in the Multiple Endovascular Stroke Trials study did not show the effectiveness of endovascular therapy for patients with computed tomography (CT)-ASPECTS ≤5 (or in some patients diffusion-weighted imaging [DWI]).[6] However, endovascular therapy for patients with ASPECTS on DWI ≤4 tended to be effective in the Thrombectomie des Artères Cerebrales trial.[7] On the other hand, only a few studies have reported the possibility that endovascular therapy is effective for patients with large ischemic cores in cohort studies. In addition, a pooled random-effect meta-analysis study of large core patients by either definition (ASPECTS <6, ischemic core volume ≥50 mL or both) demonstrated increased functional independence (modified Rankin scale [mRS] score 0–2) rates with endovascular therapy and decreased mortality.[8] We also reported the sub-analysis of the RESCUE-Japan Registry 2,[9] which suggests that endovascular therapy is effective even in patients with ASPECTS ≤5.[10]

Therefore, the aim of this study was to elucidate the efficacy of endovascular therapy for patients with a large ischemic core (ASPECTS 3–5).

Methods

Trial design

This is a multicenter, randomized, open-label, parallel-group trial to investigate the effectiveness of endovascular therapy for patients with acute cerebral LVO with a large ischemic core (ASPECTS 3–5). The eligibility criteria are presented in Table 1. In addition to patients within 6 h of onset, we include those at 6 to 24 h from the last known well time with no ischemic change on fluid-attenuated inversion recovery (FLAIR) images. It has been suggested that a large signal on head magnetic resonance imaging DWI but no large signal on FLAIR images (DWI–FLAIR mismatch) indicates that it is approximately 4.5 h after the time of onset. The WAKE-UP study demonstrated that intravenous alteplase improved functional outcomes in patients with DWI–FLAIR mismatch with an unknown time of onset.[11]

Table 1 Patient eligibility criteria

	Inclusion criteria
1	Acute ischemic stroke
2	Age ≥18
3	Baseline NIHSS ≥6 at the time of randomization
4	Pre-stroke mRS 0–1
5	Confirmed extra/intra-cranial ICA or M1 MCA occlusion on CTA or MRA
6	ASPECTS 3–5 on NCCT or DWI–MRI
7	Randomization can be finished within 6 hours from last known well time, or 6 to 24 hours from the last known well time without hyperintensity on FLAIR image in accordance with early ischemic change on NCCT or DWI
8	Endovascular treatment can be initiated within 60 minutes from randomization
9	Patient or legally authorized representative has signed the informed consent form
	Exclusion criteria
1	Significant mass effect with midline shift in CT or MRI
2	Known allergy (more severe than skin rash) to contrast agents
3	Evidence of acute ICH in CT or MRI
4	Pregnant or potentially pregnant
5	Clinical evidence of chronic occlusion
6	High risk of hemorrhage (platelet <40000/μl, APTT >50 seconds or PT-INR >3.0)
7	Participating in any other therapeutic investigational trial
8	Subjects who, in the judgment of the investigator, are likely to be non-compliant or uncooperative during the study

NIHSS: National Institutes of Health Stroke Scale, mRS: modified Rankin scale, ICA: internal carotid artery, MCA: middle cerebral artery, CTA: computed tomography angiography, MRA: magnetic resonance angiography, ASPECTS: Alberta stroke program early computed tomograph score, NCCT: non-contrast computed tomography, DWI: diffusion-weighted imaging, MRI: magnetic resonance imaging, FLAIR: fluid-attenuated inversion recovery, CT: computed tomography, ICH: intracranial hemorrhage, APTT: activated partial thromboplastin time, PT-INR: prothrombin time-international normalized ratio.

Registration, randomization, and data collection are performed using an electronic data capture (EDC) system. Randomization is performed centrally through the EDC system with a stochastic minimization algorithm to balance treatment assignment within institutions, age at the time of informed consent (<75 years or ≥75 years), time from onset of cerebral infarction or last known well to hospital arrival (<120 min or ≥120 min), National Institutes of Health Stroke Scale (NIHSS) at the time of obtaining informed consent (<21 or ≥21), and whether the patient was treated with intravenous alteplase after the onset of ischemic stroke.

Trial oversight

The principal investigator and members of the steering committee, event adjudication committee, and imaging evaluation committee designed and conducted this study in accordance with the ethical guidelines for medical and health research involving human subjects in Japan (Table 2). The protocol and consent forms were approved by the

Table 2 Study oversight

Role of study	Name	Institution
Principal investigator, Steering Committee, Chair	Shinichi Yoshimura, MD, PhD	Department of Neurosurgery, Hyogo College of Medicine Hospital
Principal investigator, Steering Committee	Nobuyuki Sakai, MD, PhD	Department of Neurosurgery, Kobe City Medical Center General Hospital
Principal investigator, Steering Committee	Hiroshi Yamagami, MD, PhD	Department of Stroke Neurology, National Hospital Organization Osaka National Hospital
Chief Trial Statistician Steering Committee	Takeshi Morimoto, MD, PhD, MPH	Department of Clinical Epidemiology, Hyogo College of Medicine
Steering Committee	Kazunori Toyoda, MD, PhD	Department of Cerebrovascular Medicine, National Cerebral and Cardiovascular Center
Steering Committee	Yuji Matsumaru, MD, PhD	Division of Stroke Prevention and Treatment, Department of Neurosurgery, Faculty of Medicine, University of Tsukuba
Steering Committee	Yasushi Matsumoto, MD	Department of Neuroendovascular Therapy, Kohnan Hospital
Steering Committee	Kazumi Kimura, MD, PhD	Department of Neurology, Nippon Medical School Hospital
Event Adjudication Committee, Chair	Fumihiro Sakakibara, MD	Department of Neurosurgery, Chibune General Hospital
Event Adjudication Committee	Norito Kinjo, MD	Department of Neurosurgery, Matsumoto Hospital
Event Adjudication Committee	Takuya Saito, MD	Department of Stroke Neurology, Kohnan Hospital
Independent Monitoring Committee	Kuniaki Ogasawara, MD, PhD	Department of Neurosurgery, Iwate Medical University
Independent Monitoring Committee	Naoya Kuwayama, MD, PhD	Department of Neurosurgery, University of Toyama
Independent Monitoring Committee	Teruyuki Hirano, MD, PhD	Department of Stroke and Cerebrovascular Medicine, Kyorin University
Imaging Evaluation Committee	Reiichi Ishikura, MD, PhD	Department of Radiology, Hyogo College of Medicine
Imaging Evaluation Committee	Manabu Inoue, MD, PhD	Department of Cerebrovascular Medicine, National Cerebral and Cardiovascular Center
Study Secretariat	Kazutaka Uchida, MD, PhD	Department of Neurosurgery, Hyogo College of Medicine Hospital
Study Secretariat	Mikiya Beppu, MD, PhD	Department of Neurosurgery, Hyogo College of Medicine Hospital
Data Center	Akito Uchio	Nexis Co., Ltd. Development Section 3

institutional review boards at the Hyogo College of Medicine (No. 3015), and each participating institute to which important protocol modification and safety information including serious adverse events in this trial are reported. All patients or their legally authorized representatives would provide written informed consent before randomization with the investigators. All institutes are regularly monitored by steering committee representatives, and the trial is monitored by a data center (Table 2). Auditing this trial would be conducted independently by the audit department of the Hyogo College of Medicine if the Independent Monitoring Committee or other oversight bodies requested with reasonable reasons. This trial was registered at Clinicaltrials.gov (NCT03702413).

Trial intervention

Patients randomly receive endovascular therapy with medical therapy or medical therapy alone at a ratio of 1:1 (Fig. 1). Treatment assignment is not concealed from the participants or treating physicians. Treatment should be performed according to randomization results. Eligible patients for intravenous thrombolysis were treated with alteplase (recombinant tissue-type plasminogen activator) at 0.6 mg/kg according to the guidelines in Japan.[12] Regarding the details of endovascular therapy, the most appropriate method of endovascular therapy should be selected by the physician in charge for each case. Approved devices to be used for endovascular therapy in Japan, including stent retriever, aspiration catheter, balloon angioplasty, intracranial stent, and carotid artery stent, were allowed as per demand from physicians in charge. However, devices that correspond to contraindications should not be used, and local intra-arterial fibrinolysis is not performed as endovascular recanalization therapy. The non-endovascular therapy group receives standard medical treatment according to the guidelines. There is no provision for other types of treatment (e.g., medication and rehabilitation). This study did not have any criteria or restrictions in the discontinuation of treatment. This study also did not have any restrictions on treatment options at recurrence.

Measurements

Clinical research coordinators or physicians in charge obtain information on patients, including institution name, name of patient identification, age, sex, time of onset (last known well time), time of arrival at the institution, allergy to contrast agent, mRS before onset, and intravenous alteplase after onset. In addition, imaging evaluation, past history, medication, blood tests, details of treatment, neurological assessment (NIHSS), vital signs, final diagnosis, mRS, and adverse events will be stored (Table 3).

Imaging evaluation

Before randomization, each institution has to determine ASPECTS 3–5 using non-contrast CT or DWI and diagnosed internal carotid artery (ICA) or M1 occlusion using CTA or MRA. Along with these images, computed tomography perfusion imaging (CTP) or DWI images are acquired to measure the core volume in the central review. Each institution should record the reperfusion degree by endovascular therapy with thrombolysis in cerebral infarction grading system[13] and the presence of ICH after treatment, which would be confirmed by an independent central core laboratory. For that reason, Digital Imaging and Communications in Medicine images will be submitted to the office for central core laboratory.

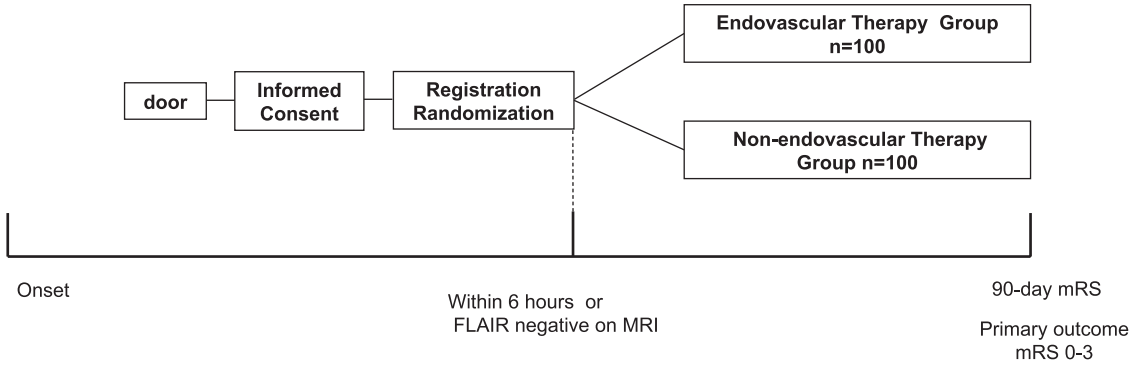

Fig. 1 Study design. After the eligible patients arrived at each institute and informed consent was obtained, they were randomly allocated to the endovascular therapy group who received thrombectomy or to the medical therapy group without endovascular therapy. FLAIR negative: without hyperintensity on fluid-attenuated inversion recovery, MRI: magnetic resonance imaging, mRS: modified Rankin scale.

Table 3 Summary of observation, tests, reporting items, and schedule

Schedule	At enrollment		Observation period			
	Before randomization	After randomization	Very Early	Early	Discharge	End
Implementation item/ implementation period	Within 6 hours from the time of last known well or within 6–24 hours from the time of last known well		Within 12 hours after randomization	Within 48 hours (± 24 hours) after randomization	either 7 days (± 2 day) after randomization or at discharge which is earlier	90 days (± 30 days) after randomization
Informed consent	○					
Confirmation of inclusion and exclusion criteria	○					
Basic data	○ Only randomization factors	○ Details				
Demographics and baseline characteristics data		○				
Vital sign		○	○	○	○	○
Laboratory data		○		○		
Chest x-ray, ECG test		○				
mRS		○ (Before onset)			○	○
NIHSS	○ Only scores	○ Details	○	○	○	
Imaging	○ (*1) CT/CTA/ CTP or MRI/ MRA			○ CT or MRI	○ CT/CTA or MRI/MRA	
ASPECTS		○				
Occclusion site		○				
Type of cerebral infarction		○			○	
Details of EVT and complications			○ Only EVT group			
Recanalization status (TICI grade)			○ Only EVT group			
Recanalization status (mMORI grade)					△	
Serious adverse events		⟷				
Clinically significant adverse events		⟷				
Decompressive craniectomy		⟷				

*1: Imaging (at enrollment). Within 6 hours from last known well time: CT/CTA/CTP or MRI/MRA. Within 6–24 hours from last known well time: MRI/MRA. ECG: Electrocardiogram, mRS: modified Rankin scale, NIHSS: National Institutes of Health Stroke Scale, CT: computed tomography, CTA: computed tomography angiography, MRA: magnetic resonance angiography, ASPECTS: Alberta stroke program early computed tomography score, EVT: Endovascular therapy, TICI: Thrombolysis In Cerebral Infarction, mMORI: modified Mori Grade.

Outcomes

The primary outcome is defined as a moderate functional outcome (mRS ≤3) after 90 days.[14] The secondary outcomes are good functional outcome (mRS ≤2), excellent functional outcome (mRS ≤1), mRS shift analysis after 90 days, and early improvement of neurological findings defined as NIHSS[15] improvement of ≥8 points at 48 hours. Assessments of mRS and NIHSS after 90 days will be conducted by personnel blinded to the initial treatment period. Safety outcomes are symptomatic ICH defined as any type of ICH with NIHSS worsening ≥4 points within 48 hours, any ICH within 48 hours,[16] death (mRS 6) within 90 days, recurrence of ischemic stroke within 90 days, and decompressive craniectomy within 7 days.

Data management

Data management, including data entry, query, coding, security, storage, and any related processes to promote data quality, is performed by the independent data center (Nexis Co., Ltd., Fukuoka, Japan).

Sample size and statistical analysis

A total of 200 patients (100 in the endovascular group and 100 in the medical group) were examined. We analyzed 338 patients with DWI-ASPECTS 3–5 in RESCUE-Japan Registry 2[9]; those were the eligible patients of this study. Twenty-four patients (12.5%) and 55 patients (37.7%) had an mRS of 0–3 at 90 days, which was the primary outcome in this study, among 192 patients in the non-endovascular group and 146 patients in the endovascular group, respectively.[10] The odds ratio (OR) adjusting for baseline characteristics was 3.42 for the endovascular group, since this was an observational study and its effect could be larger than clinical trials. Thus, we assumed the relative risk at 2.7 times (3.42 × 0.8 = 2.7) with a discount of 20% of efficacy in clinical practice. When the type I error level is set at two-sided 0.05 and the power of the test is 0.90, 81 patients in each cohort are required. Estimating the clinical dropout rate at 15%, the required sample size was calculated to be 191 patients in both groups. Considering the possible additional withdrawal of consent, we set the target sample size to 100 patients in each cohort and a total of 200 patients.

The analysis set was divided into an endovascular therapy group and a non-endovascular therapy group, and descriptive statistics were calculated on the demographics and baseline characteristics.

The primary outcome is shown as the number of subjects, percentages, ORs, and 95% confidence intervals (CIs) of patients with an mRS score of 0–3 at 90 days after the start of hospitalization calculated for the endovascular therapy and non-endovascular therapy groups, respectively. The results were subjected to test between the endovascular and non-endovascular therapy groups.

Secondary outcomes are shown as same as the primary outcome or as common ORs with a one-level lower shift analysis with mRS. Safety outcomes are also shown as the number of subjects, percentages, and ORs, and 95% CIs were calculated for each safety outcome in the same manner as above.

Subgroup analyses for primary outcomes are planned to estimate ORs and 95% CIs in each prespecified subgroup. The interactions between endovascular therapy group and each subgroup were tested.

The prespecified subgroup factors are as follows:

1) Age at the time of informed consent (<75 years or ≥75 years). Time from onset of cerebral infarction or last known well to hospital arrival (<120 min or ≥120 min).

2) Time from onset of cerebral infraction or last known well to hospital arrival (<120 min or ≥120 min).

3) Time from onset of cerebral infraction or last known well to hospital arrival (<120 min or ≥120 min). NIHSS score at the time of informed consent (<21 or ≥21).

4) Whether the patient was treated with intravenous alteplase after the onset of cerebral infraction.

Continuous variables are indicated by mean and standard deviation or median and quartiles, depending on the type of distribution, and the t-test or Wilcoxon rank-sum test was used. In addition, categorical variables were indicated by the sample size or percentages, and the chi-square test or Fisher's exact test was used. Differences were considered statistically significant at two-tailed $p < 0.05$.

All statistical analyses are performed by a chief trial statistician (Morimoto T) and a physician (Uchida K) using JMP 15.1 (SAS Institute Inc., Cary, NC, USA) and SAS 9.4 (SAS Institute Inc.) based on the statistical analysis plan. For baseline data, missing data are not imputed, and data with missing data are analyzed as they were. Because of the short enrollment and follow-up periods and the estimated low risk of adverse events, no interim analyses are planned.

Other exploratory analyses will be performed based on the recommendation from the Steering Committee.

Discussion

In the previous study, we showed the effectiveness of endovascular therapy for patients having ICA or M1 occlusion with ASPECTS ≤5 on non-contrast CT or DWIs were extracted from 2420 acute LVO patients admitted within 24 h after onset, who were

registered to the nationwide registry, RESCUE-Japan registry 2.[10] A small retrospective study also showed that in patients with acute LVO of anterior circulation with DWI-ASPECTS ≤5 (n = 108), the patients with mRS 0–2 at 90 days after onset were significantly more observed in the endovascular therapy group (n = 60) compared to non-endovascular therapy group (n = 48), and the mortality was significantly lower.[17] In addition, another small cohort study revealed that patients with DWI-ASPECTS ≤6 had less benefit from endovascular therapy than patients with DWI-ASPECTS ≥7, but outcomes (patients with mRS ≥3) were still better than those with medication alone (endovascular therapy 11 of 15 vs. medication alone 23 of 23; p = 0.019).[18]

A retrospective study based on a registry of patients with DWI-ASPECTS ≤5 treated by endovascular therapy suggested that DWI-ASPECTS 3–5 was one of the markers predictive of good prognosis.[19] In our previous study, in 369 patients with ASPECTS 3–5, good functional outcome was more observed in the endovascular therapy group than in the non-endovascular therapy group (20.4% vs. 6.6%; p <0.0001; adjusted OR 2.04 [0.96–4.37]). In contrast, in 135 patients with ASPECTS 0–2, good functional outcomes were obtained in 2 of 15 patients in the endovascular therapy group (13.3%), but not in the non-endovascular therapy group (0%). Adjusted OR could not be calculated because of an insufficient number of patients.[10]

The ASPECTS score is not only associated with the size of the infarct core and stroke severity but also highly dependent on the elapsed time from stroke onset, as evident by the significant difference in onset to door times between groups (110 min [50–195] vs. 270 min [110–656.3]).[10] Thus, the time from stroke onset seemed to be one of the most important factors for endovascular therapy in cases with a large ischemic core. Another interesting point was that a good functional outcome was significantly more observed in the endovascular therapy group with ICA occlusion but not with M1 occlusion. There has been a concern that hemorrhagic events are caused by endovascular therapy when patients have a large ischemic core,[5] but a previous study showed no increase in hemorrhage in the endovascular therapy group.[10]

Another pooled random-effect meta-analysis of 11 including 12 studies of large core patients by either definition (ASPECTS <6, ischemic core volume ≥50 mL or both) demonstrated increased functional independence (mRS 0–2) rates with endovascular therapy (25% vs. 7%; pooled OR: 4.39; 95% CI: 2.53–7.64) and decreased mortality (23% vs. 33%; pooled OR: 0.53; 95% CI: 0.40–0.71).[9]

We hope that this trial will have a great impact on the establishment of a novel strategy to demonstrate the applicability of endovascular therapy in patients with a large ischemic core.

Trial status

The first patient was recruited on November 29, 2018. The last patient is expected to be recruited on September 2021. The Hyogo College of Medicine provides central trial management and coordination.

Acknowledgement

We would like to thank all investigators for their efforts in conducting the RESCUE-Japan LIMIT.

Funding

This study was supported in part by the MIHARA cerebrovascular disorder research promotion fund of the Japanese Society for NeuroEndovascular Therapy. The funding sources did not participate in any part of the study, from conception to article preparation.

Authors' Contributions

All authors intellectually contributed to the study protocol development, including study design, trial intervention, inclusion and exclusion criteria of patients, and measurement of variables and outcomes. The statistical analysis plan was made by the chief trial statistician.

Ethics Approval and Consent to Participate

The protocol and consent forms were approved by the institutional review boards at the Hyogo College of Medicine (No. 3015) and each participating center. All patients or their legally authorized representatives provided written informed consent prior to randomization.

Access to Data

Access to the final trial dataset is rigidly restricted to investigators authorized by the steering committee, and any activity is recorded. There are contractual agreements that limit such access to investigators.

Confidentiality

Confidentiality in the collection of personal information is protected in accordance with the ethical

guidelines for medical and health research involving human subjects in Japan.

Compensation

Compensation to those who suffer from death or severe damage requiring hospitalization from trial participation is provided by the clinical trial insurance organized by the trial sponsor (Hyogo College of Medicine).

Dissemination Policy

The results of this trial are disseminated through publications and conference presentations to participants, healthcare professionals, and the public.

Conflicts of Interest Disclosure

Dr. Yoshimura reports research grants from Medico's Hirata, Medtronic, and Termo, and lecturer fees from Medtronic, Kaneka, and Stryker. Dr. Uchida reports lecturer's fees from Daiichi-Sankyo, Bristol-Myers Squibb, Stryker, and Medtronic. Dr. Sakai reports a research grant from Biomedical Solutions, Daiichi-Sankyo, and Termo; lecturer's fees from Asahi-Intec, Biomedical Solutions, Daiichi-Sankyo, and Medtronic; and membership on the advisory boards for Johnson & Johnson, Medtronic, and Terumo. Dr. Yamagami discloses research grants from Bristol-Myers Squibb; lecturer's fees from Stryker, Medtronic, Termo, Johnson & Johnson, Biomedical Solutions, and Medico's Hirata; and membership of the advisory boards for Daiichi-Sankyo. Dr. Inoue reports the lecturer's fees from Bayer Co., Ltd., Bristol-Myers Squibb Co., Ltd., Medico's Hirata Co., Ltd.; and manuscript fees from Gakken Medical Co., Ltd. and Hokuryukan Co., Ltd. Dr. Toyoda reports the lecturer's fees from Daiichi Sankyo, Takeda, Bayer Yakuhin, and Bristol-Myers Squibb. Dr. Matsumaru discloses lecturer fees from Medtronic, Stryker, Terumo, Johnson & Johnson, Kaneka, and Jimro. Dr. Mastumoto reports the lecturer's fees from Kaneka Medics, Medico's Hirata, Fuji systems, GE healthcare, Otuka Pharmaceutical Limited, Takeda Pharmaceutical Limited, Medtronic Japan, Century Medical, Terumo, Medtronic, and Stryker Japan. Dr. Kimura discloses research grants from CSL Behring K.K., EP-CRSU Co., Ltd., AABP K.K., Alexion Pharmaceuticals, Inc., Eisai Co., Ltd., Kyowa Kirin Co., Ltd., Daiichi-Sankyo Company, Ltd., Teijin Pharma Ltd., Medtronic Japan Co., Ltd., Bristol-Myers Squibb K.K., Bayer Yakuhin, Ltd., Boehringer-Ingelheim, and Helios Co., Ltd., and lecturer's fees from Daiichi-Sankyo Company, Ltd., Nippon Boehringer Ingelheim Co., Ltd., Bristol-Myers Squibb K.K., Bayer Yakuhin, Ltd., Takeda Pharmaceutical Co., Ltd., Medtronic Japan Co., Ltd., Otsuka Pharmaceutical Co., Ltd., FP Pharmaceutical Co., Ltd., Alexion Pharmaceuticals, Inc., Nippon Pharmaceutical Co., Ltd., Chugai Pharmaceutical Co., Ltd., Kyowa Kirin Co., Ltd., Abbott Medical Japan LLC, Shire PLC, Sanofi Genzyme K.K., CSL Behring K.K., Novartis Pharma K.K., Toa Eiyo Ltd., Medico's Hirata Inc., and Helios Co., Ltd. Dr. Morimoto reports lecturers' fees from Bristol-Myers Squibb, Daiichi Sankyo, Japan Lifeline, Kowa, Kyocera, Novartis, and Toray; manuscript fees from Bristol-Myers Squibb and Kowa; and advisory board for Sanofi. Dr. Ishikura has no conflicts of interest to report.

References

1) Pexman JH, Barber PA, Hill MD, et al.: Use of the Alberta stroke program early CT score (ASPECTS) for assessing CT scans in patients with acute stroke. *AJNR Am J Neuroradiol* 22: 1534–1542, 2001
2) Powers WJ, Rabinstein AA, Ackerson T, et al.: Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 50: e344–e418, 2019
3) Yamagami H, Hayakawa M, Inoue M, et al.: Guidelines for mechanical thrombectomy in Japan, the Fourth Edition, March 2020: a guideline from the Japan Stroke Society, the Japan Neurosurgical Society, and the Japanese Society for Neuroendovascular Therapy. *Neurol Med Chir (Tokyo)* 61: 163–192, 2021
4) Cucchiara B, Kasner SE, Tanne D, et al.: Factors associated with intracerebral hemorrhage after thrombolytic therapy for ischemic stroke: pooled analysis of placebo data from the Stroke-Acute Ischemic NXY Treatment (SAINT) I and SAINT II Trials. *Stroke* 40: 3067–3072, 2009
5) Berkhemer OA, Fransen PS, Beumer D, et al.: A randomized trial of intraarterial treatment for acute ischemic stroke. *N Engl J Med* 372: 11–20, 2015
6) Goyal M, Menon BK, van Zwam WH, et al.: Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. *Lancet* 387: 1723–1731, 2016
7) Bracard S, Ducrocq X, Mas JL, et al.: Mechanical thrombectomy after intravenous alteplase versus alteplase alone after stroke (THRACE): a randomised controlled trial. *Lancet Neurol* 15: 1138–1147, 2016
8) Sarraj A, Grotta JC, Pujara DK, Shaker F, Tsivgoulis G: Triage imaging and outcome measures for large core stroke thrombectomy—a systematic review and meta-analysis. *J Neurointerv Surg* 12: 1172–1179, 2020
9) Yoshimura S, Sakai N, Uchida K, et al.: Endovascular therapy in ischemic stroke with acute large-vessel

occlusion: recovery by endovascular salvage for cerebral ultra-acute embolism Japan Registry 2. *J Am Heart Assoc* 7: e008796, 2018
10) Kakita H, Yoshimura S, Uchida K, et al.: Impact of endovascular therapy in patients with large ischemic core: subanalysis of recovery by endovascular salvage for cerebral ultra-acute embolism Japan Registry 2. *Stroke* 50: 901–908, 2019
11) Thomalla G, Simonsen CZ, Boutitie F, et al.: MRI-guided thrombolysis for stroke with unknown time of onset. *N Engl J Med* 379: 611–622, 2018
12) Toyoda K, Koga M, Iguchi Y, et al.: Guidelines for intravenous thrombolysis (recombinant tissue-type plasminogen activator), the Third Edition, March 2019: a guideline from the Japan Stroke Society. *Neurol Med Chir (Tokyo)* 59: 449–491, 2019
13) Goyal M, Fargen KM, Turk AS, et al.: 2C or not 2C: defining an improved revascularization grading scale and the need for standardization of angiography outcomes in stroke trials. *J Neurointerv Surg* 6: 83–86, 2014
14) van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J: Interobserver agreement for the assessment of handicap in stroke patients. *Stroke* 19: 604–607, 1988
15) Lyden P, Brott T, Tilley B, et al.: Improved reliability of the NIH Stroke Scale using video training. NINDS TPA Stroke Study Group. *Stroke* 25: 2220–2226, 1994
16) 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. *Lancet* 369: 275–282, 2007
17) Mourand I, Abergel E, Mantilla D, et al.: Favorable revascularization therapy in patients with ASPECTS ≤5 on DWI in anterior circulation stroke. *J Neurointerv Surg* 10: 5–9, 2018
18) Ohta T, Morimoto M, Okada K, et al.: Mechanical thrombectomy in anterior circulation occlusion could be more effective than medical management even in low DWI-ASPECTS patients. *Neurol Med Chir (Tokyo)* 58: 156–163, 2018
19) Manceau PF, Soize S, Gawlitza M, et al.: Is there a benefit of mechanical thrombectomy in patients with large stroke (DWI-ASPECTS ≤5)? *Eur J Neurol* 25: 105–110, 2018

Corresponding author: Shinichi Yoshimura, MD, PhD
Department of Neurosurgery, Hyogo College of Medicine, 1-1 Mukogawa, Nishinomiya, Hyogo 663-8501, Japan.
e-mail: hyogoneuro@yahoo.co.jp