# Supplement 1

※Initial protocol

# Direct mechanical thrombectomy in acute LVO stroke (SKIP study): a randomized controlled trial

Research Plan

UMIN 000021488

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Planned Study period: From November 1st, 2016 to October 30th, 2019

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# 1. Study Organization

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4) Protocol Manager

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5) Allocation Manager

   Kentaro Suzuki; Department of Neurology, Nippon Medical School

6) Data Manager

   Hiroshi Nagayama; Department of Neurology, Nippon Medical School

7) Data monitoring and safety board

   Akio Morita; Department of Neurosurgery, Nippon Medical School

8) Statistical Manager

   Toshiaki Otsuka; Department of Public Health, Nippon Medical School

9) Event evaluation committee

   Hiroyuki Yokota; Department of Critical Care Medicine, Nippon Medical School

10) Radiological Judgement committees

   Teruyuki Hirano; Department of Stroke Medicine, Kyorin University

   Shigeru Fujimoto; Department of Neurology, Jichi University

## 2. Introduction and Rationale

Recombinant tissue-plasminogen activator (rt-PA) was approved by the authority in 2005 in Japan and widely used as a standard treatment for patients with acute ischemic stroke. However, it is also known that rt-PA has limited effect for patients with large vessel occlusion (LVO); previous studies showed the recanalization rate was as low as 5.9% in patients with internal carotid artery (ICA) and 16.7% in those with proximal middle cerebral artery horizontal segment (MCA M1) occlusion.[1, 2]

As the progress in devises, the reperfusion therapy for patients with LVO with mechanical thrombectomy (MT) can dramatically improve the recanalization rate. Randomized controlled trials (RCTs) presented around 2015 showed that adding MT could improve recanalization rate and outcome, compared with rt-PA treatment.[3-7]

In these RCT, onset-to-reperfusion time played a critical role and shorter onset-reperfusion time lead better outcome.[8] Indeed, 59% of the recanalized patients within 300 min achieved good functional outcome, it declined to 32% when recanalization was attained after 300 min from symptom onset. Shorter onset-to-groin puncture time was reported to be also associated with better outcome,[9] so reducing onset-to-puncture and -reperfusion time is needed in managing acute stroke patients with LVO.

Under the current guidelines, MT should be conducted in conjunction with rt-PA, when patients have indications for rt-PA. Therefore, there is no RCTs investigating the effectiveness of MT without rt-PA. One retrospective study revealed that MT without rt-PA, compared with MT plus rt-PA, reduced hemorrhagic complications and mortality.[10]

To skip rt-PA can reduce hemorrhagic complications and achieve better outcome. Therefore, we conduct prospective, multicentre RCT to elucidate the efficacy of MT without rt-PA for hyperacute ischemic stroke patients with LVO.

## 3. Purpose of the study

The aims of the present study is to elucidate the difference in clinical outcome, hemorrhagic complications, onset-to-reperfusion time, and the rate of effective recanalization between MT with and without rt-PA in acute stroke patients with LVO.

## 4. Study period

From November 1st, 2016 through October 30th, 2019 (study entry ends July 31st, 2019).

## 5. Study site

Department of Neurology, Nippon Medical School hospital

## 6. Sample size

Poor outcome (modified Rankin scale [mRS] 5 or 6, 3 months after stroke onset) was assumed to be 47.5% in the MT without rt-PA group and 25% in the MT with rt-PA group, the required number of patients is calculated to be 67 patients in each group, for a total of 134 patients. Assuming a dropout rate, 200 patients (100 patients in each group) has been set.

## 7. Drugs and devices used in the study

1) Information about drugs and devices

   Drug: alteplace (Activacin® [Kyowa Hakko Kirin] and Grtpa® [Tanabe Mitsubishi Pharmacy])

   Devices: Devices used for revascularization, such as: Penumbra® (Medico's Hirata), Trevo® (Stryker), Solitaire® (Medtronic), Revive® (Johnson & Johnson), Gateway® PTA Catheter, Wangspan® stent, Precice®, Carotid Wall® stent, and PROTÉGÉ®.

2) Expected adverse effect of the drugs or malfunction of the devices

   Hemorrhagic complications are known as adverse effects of these drugs and devices. When severe hemorrhagic complication occurs, every treatment is based on taking the highest priority on participants' safety.

## 8. Patient population

1) Patient condition

   Ischemic stroke

2) Inclusion criteria

| Inclusion criteria |
|---|

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|---|
| 1. Age ≥18 and <86 years at the time of informed consent |
| 2. Clinical diagnosis of acute ischemic stroke with clinical symptoms |
| 3. Modified Rankin scale score ≤2 |
| 4. ICA or M1 occlusion on MRA or CTA |
| 5. Initial NIHSS ≥6 |
| 6. ASPECTS on initial DWI ≥5 or on initial CT ≥6 |
| 7.Onset to randomization within 4 h from onset. (Recomendation topuncture within 30 min from randomization) |
| 8. Written informed consent by patient or next of kin. |

Reasons for inclusion

1. Effectiveness of endovascular treatment for children has not been established, and in many elderly patients it is difficult to perform endovascular treatment due to meandering of blood vessels.
2. Since some cases show rapid improvement due to spontaneous recanalization, we targeted cases where the symptoms persisted.
3. To fairly assess outcomes 90 days after symptom onset.
4. The efficacy of endovascular therapy has been proven in patients with ICA or M1 occlusion.
5. The above items with sufficient evidence to benefit from reperfusion were targeted, based on past reports.
6. The above items with sufficient evidence to benefit from reperfusion were targeted, based on past reports.
7. When assigned to the EVT without rt-PA group but the EVT is difficult to perform (e.g., running of the blood vessel), there will be clear disadvantage to the patients allocated to the EVT without rt-PA group. To prevent this, we included it in the selection criteria so that intravenous rt-PA therapy could be performed in cases where EVT was difficult.
8. As in previous reports, we include patients with the consent.

3) Exclusion criteria

| Exclusion criteria |
|---|

1. Contraindication for contrast agent or endovascular therapy
2. Contraindication for IVT.
3. Presence of severe renal disorder (patients undergoing dialysis can be included)
4. Pregnancy or possibility of pregnancy
5. Unlikely to complete the study, such as due to progressive malignant tumor
6. Judged incompatible with the study by the investigators

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Reason for exclusion

1. 2. 3. 4.

Since it is considered that angiography is not recommended in such situation. In the present study, only cases where both rt-PA intravenous therapy and EVT can be performed are included.

5.In order to fairly evaluate the outcome 90 days after onset.

6.In order to ensure the safety of the study subjects and appropriately carry out the study.

## 9. Informed consent

Before enrollment, physicians in charge must explain about this study with written and verbal explanation to all potential patients and/or their close relatives, using materials approved by institutional review board (IRB) in Nippon Medical School. Physicians guarantee potential patients and/or their close relatives chances to ask questions and sufficient time to decide whether they attend the study or not. Physicians in charge obtain informed consent from the potential patients after confirming their understanding and free will.

When new information about efficacy and safety of rt-PA or MT, that may affect the participants' attendance to this study, written materials must be revised after IRB approval, and re-consent is obtained from the patients or their close relatives.

Because the potential patients for this study have stroke, consent from their close relatives is permitted due to difficulty in obtaining consent because of disturbance of consciousness, aphasia, or weakness. When the consent is obtained from patients' relatives, the closest relative should be selected. Moreover, explanation to the patient must not be omitted even if the informed consent is obtained from relatives.

We have prepared the written explanation with easy expression so as potential patients and their relatives can understand.

## 10 Study design

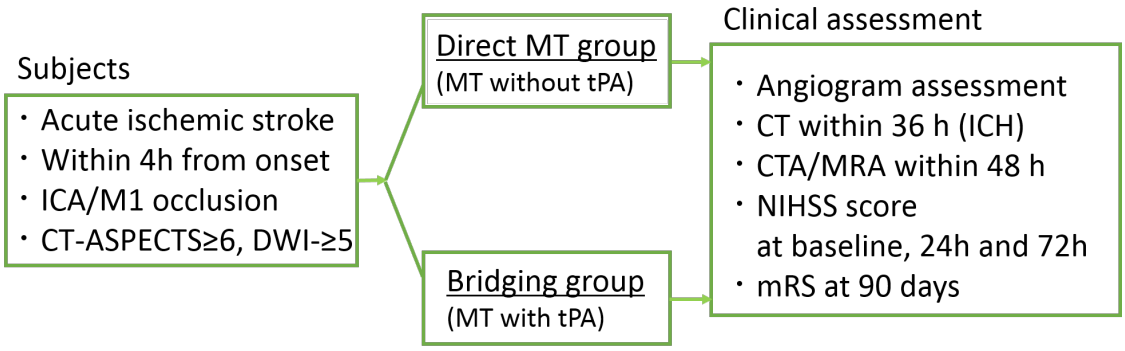
1) The kind of the study and study design

   The kind of the study: interventional

   Study design: multicentre, randomized, open-label study

2) Outline of the study

   To elucidate the efficacy of MT without rt-PA, compared with MT with rt-PA, randomized controlled study is conducted. Medical history taking and examinations are performed just before the informed consent and physicians ascertain the eligibility. When cessation of participation is applied from the patients or their relatives, patients are immediately removed from the study.




[MT without rt-PA group]

MT without rt-PA

Rt-PA therapy will be performed when MT is difficult to perform.

MT is regarded as difficult when time from groin puncture to guiding catheter placement exceeds 30 min.

[MT with rt-PA]

MT is performed after rt-PA therapy.

3) Rt-PA should be administered within 4.5 hours from symptom onset. The amount of 0.6mg/kg (maximum of 60 mg) is administered, 10% as bolus, and the rest of 90% as continuous infusion over one hour.

4) Concomitant treatment

   Below drugs must not concomitantly used within 24 hours after rt-PA therapy: warfarin, dabigatran, rivaroxaban, apixaban, and edoxaban.

5) Management and delivery of the drugs and the devices

The pharmaceutical and mechanical treatment performed in this study is approved as the treatment for stroke by the authority in Japan. Physicians use drugs or devices in the individual hospital.

6) Medication guidance

Not applicable

7) Case enrolment and random allocation

Physicians in charge should try to include all the patients who meet the inclusion criteria, and not to exclude from the study deliberately. Immediately after confirmation of LVO and obtaining consent from the patient, physicians allocated patients into specific group and avoiding treatment delay due to participation to this study.

The allocation is conducted with web-based system. After entering institutional ID and password, and completion of checklist, the system presents the results of allocation:

A) MT without rt-PA

B) MT with rt-PA

8) Patients eligibility

Physicians in charge must ascertain that the patients satisfy all the inclusion criteria and not correspond to none of the exclusion criteria (see p. 7-9).

9) Treatment after study participation

In this study, standard medical treatment is provided after hyperacute management, so standard medical treatment is continued to be provided for patients belonging to both groups.

10) Biological samples from study participants

In this study, biological sample from study participants is used only for study outcomes. All samples are discarded after anonymization. The storage period for case report forms ends the latter day of 5 years after announcement of study completion or 3 years after final result of the study is published.

## 11. Study outcome

Rationale for outcomes

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|---|
| Primary efficacy endpoint |
| ・Poor outcome defined as mRS score 5-6 at 90 days after stroke onset (superior) |
| Secondary efficacy endpoints |
| ・The mRS score at 90 days (shift analysis, non-inferior) |

- Favorable outcome defined as mRS score 0-1 at 90 days after stroke onset
- Favorable outcome defined as mRS score 0-2 at 90 days after stroke onset
- Favorable outcome defined as mRS score 0-3 at 90 days after stroke onset
- Favorable outcome defined as mRS score 0-1 at 90 days after stroke onset (non-inferior)
- Favorable outcome defined as mRS score 0-2 at 90 days after stroke onset (non-inferior)
- Favorable outcome defined as mRS score 0-3 at 90 days after stroke onset (non-inferior)
- Improvement of mRS score as of 90 days after stroke onset
- Reperfusion of TICI score 2b or 3 at the end of EVT
- Recanalization of modified Mori grade 2 or 3 at 72 h after stroke onset

Safety endpoints

- Any ICH on CT or MRI within 36 h after stroke onset.
- sICH as defined by NINDS and SITS-MOST criteria within 36 h after stroke onset.
- Major bleeding as defined by fatal bleeding, symptomatic bleeding in a critical area or organ, such as intraspinal, intraocular or bleeding causing a fall in hemoglobin ≥3 g/dL, or leading to transfusion of whole blood or red cells within 24 h after stroke onset

## 12. Observational items and examinations

1) Patients backgrounds

   Sex, Age, Height, Weight

   Vascular risk factors (Hypertension, Diabetes mellitus, Dyslipidemia, Atrial fiblliration, Chronic kidney disease, Heart failure, and smoking history)

   Past history of cerebrovascular diseases (Transient ischemic attack, Ischemic stroke, Intracerebral haemorrhage, and Subarachnoid haemorrhage)

   Past history of cardiovascular diseases (Myocardial infarction, Angina pectoris, peripheral artery disease)

2) Physical examinations, Imaging examinations

   Blood pressure and heart rate on admission

   NIHSS score: on admission, 24 h (±8 h) and 72 h (±8 h) after treatment, on discharge

   Premorbid mRS

Imaging: ASPECTS on CT or DWI-ASPECTS on DWI (as positive include small lesions)before treatment

Pre-treatment DWI and FLAIR more than 1 week after treatment

T2* on admission (presence of microbleeds and SVS)

Vascular imaging: Occluded vessel on CTA or MRA

TICI score just after EVT treatment

Presence of tandem lesion

State of recanalization (using modified Mori grade) on MRA or CTA 48 h (± 24h) after treatment

Time metrics: Onset-to-door, Door-to-groin puncture, Puncture-to-recanalization, Door-to-needle, and Door-to-randomization.

3) Treatment details

Blood pressure before treatment

IV rt-PA therapy: onset-to-needle time

EVT: Onset-to-reperfusion time (or time from symptom onset to final angiogram when no reperfusion is achieved), number of pass, methods (mechanical thrombectomy, angioplasty, or local fibrinolysis), devices (Penumbra, Trevo, Solitaire, Revive, balloons, and intracranial stents), intra-arterial drug infusion (urokinase or rt-PA)

Adverse events: Any intracerebral hemorrhage within 36 h and 7 days (±1 day) after treatment, Symptomatic intracerebral hemorrhage (SITS-MOST criteria and NINDS criteria), and other hemorrhagic complications.

4) Vital signs and laboratory data

Blood pressure (on admission, before treatment), Heart rate, Body temperature

Laboratory data: (WBC, Hemoglobin, Platelet count, Glucose, HbA1c, BNP, PT-INR, aPTT)

Anticoagulant drugs, Antiplatelets, or Statins before admission

5) Follow-up

mRS 90 days (±10 days) after onset (When mRS increase from pre-morbid mRS, denote whether the deterioration is due to stroke)

※a physician or clinical research coordinator who is blinded to treatment assignment assesses the mRS by telephone interview at 90 days.

Etiology (TOAST criteria)

Symptomatic recurrence during admission

Surgical intervention

6) Other adverse events

Other adverse events are defined as all unfavorable events such as abnormal laboratory values and adverse reactions, regardless of causal relationship with drugs or treatments. Describe the details of adverse effects, timing of onset / recover, degree, treatment, outcome, severity assessment, and relevance with the study drug or treatment in the medical chart and case report form. Follow up if necessary. The severity of adverse events is defined as (1) mild: the state that study participation can be continued without treatment, (2) moderate: the state that study participation can be continued with treatment, and (3) severe: the state that study participation should be suspended.

## 13. Study discontinuation

1) Study discontinuation criteria for each participant

Study participants who meet the below situation will be excluded from this study.

i. Offer to decline participation or withdrawal of consent from the patient or their representatives.
ii. Find out not to meet the inclusion criteria after study participation
iii. The study terminates early
iv. Difficult to study participation due to adverse events
v. The participant should be excluded from the study for other reasons than the above, judged by the attending physician

When the participant is excluded from this study, the date, reason, or situation of discontinuation will be recorded on their medical chart and case report form. Appropriate examinations will be performed on discontinuation to evaluate the efficacy and safety. When participants are excluded before treatment, patients will be informed about and treated with standard treatment. Physicians consider patients not to suffer disadvantages.

2) Study discontinuation criteria for this study

Principal investigator consider study termination when:

i. Obtaining serious information about safety or efficacy about the study
ii. Predicted risks seem to overwhelm the expected benefit
iii. Difficulty in recruiting participants and achieving the intended sample size
iv. Purpose of the study is achieved before study completion
v. Recommendation of termination is published from the institutional review board, or instructions to protocol change but difficult to accept the instruction

When terminating the study, principal investigator report study termination and its reason to the director of the institution, with written documents.

## 14. Adverse events

1) Management of adverse events

   Investigators must conduct appropriate treatment immediately when participants show unfavourable medical conditions (adverse events) such as hemorrhagic complications, and describe the adverse events on medical chart and case report form. When adverse events are decided to be severe, follow the instructions below 2) management of severe adverse events.

2) Management of severe adverse events

   When severe adverse events occur, principal investigator conduct appropriate treatment immediately, and promptly reports it to the director of the institution and institutional IRB. Principal investigator also reports it to investigator in other institutions. Severe adverse events include not only adverse events occurred within the study period, but also severe adverse events occurred after study completion and suspected to be associated with the study.

3) Definition of severe adverse events
   - i. Death, or events potentially lead death
   - ii. Hospital admission or extension of hospital stay due to treatment
   - iii. Disability or events potentially lead disability
   - iv. Severe status according to above criteria

4) Matters to be included about severe adverse events
   - i. Name of adverse event
   - ii. Time of occurrence
   - iii. Outcome (e.g., improve, unchanged, recovery, or death)
   - iv. Time course
   - v. Relevance to the study
     - a. No relevance
     - b. Probably no relevance
     - c. Probably relevant
     - d. Relevant

When severe adverse events are assessed no/probably no relevance to the study, presumed cause of the adverse events should be reported.

## 15. Statistical Analysis Plan

The primary study outcome measure was superiority of the poor outcome at 90 days. We first used unadjusted logistic regression to test whether direct MT therapy was superior to bridging therapy. The secondary efficacy analyses included the comparison of ordinal scores on the modified Rankin scale to test for the noninferiority of the direct MT vs bridging therapy with ordinal logistic regression (shift analysis), where the OR is calculated for each cut-point across the mRS (for example, 0 versus 1–6, then 0–1 versus 2–6, and so on), and then a summary OR is calculated from the individual ORs, under the assumption that the individual ORs are the same. We also performed secondary analyses of the primary outcome with adjustment for minimization and key prognostic covariates, as well as secondary analyses in the per-protocol population. Next, clinical characteristics, recanalization success rate, hemorrhagic event rate (Any ICH, symptomatic ICH and other hemorrhagic complication), and other MT parameters were compared between the two groups. For ease of interpretation, all reported P-values are multiplied by 2, so that an alpha of 0.05 can be used in analyses. The other P-values are two-sided. All P-values were pre-specified not to be adjusted. JMP version 11 software (SAS Institute, Cari, NC) was used the analysis.

## 16. Privacy policy

1) When treating raw data or consent forms, consider participants' privacy.
2) Identifying code is used in forms submitted to outside hospital, instead of names.
3) Correspondence table between participants' name and identifying code is strictly kept in the department of neurology.
4) When the results of the study are reported, no identifiable information is included.
5) Acquired data in the study is exclusively used for the study.

## 17. Consideration for safety or disadvantage

When adverse events are occurred, appropriate examination and treatment are performed promptly. Hemorrhagic complication can be occurred as a serious complication in this study. Prompt action is required for each sites and declared in this protocol (see Section 14. Adverse events).

## 18. Publish policy about the results of the study

Measurements or examinations required in this study is frequently tested in acute stroke management, and the results of examinations are reported to the patients or relatives. The results of this study is published promptly after completion of the study (see Section 24. Registration of research plan and publication of research results)

## 19. Cost burden for participants

Medical check-ups, measurements, examinations, and treatment in this study is totally under the public health insurance. No drugs or procedures beyond public health insurance is used or performed in this study. So, additional fee for participation to this study are not expected.

## 20. Compensation for health hazards

All treatments and examinations are conducted under the public health insurance. Health hazards attributable to this study are also treated under the public health insurance. Organisation, institutions, or individuals such as physician in charge involved in this study will not compensate the participants' self-pay burden, leave compensation, and additional hospital charge associated with extension of admission. Physicians in charge manage in-hospital resources to treat participants' health damage promptly and appropriately.

This study has clinical trial insurance for health hazards potentially attributable to this study. All the stuffs involved in this study are insured, and clinical trial insurance covers health damage (including death) to study participants from start of this study through one year after study completion. Clinical trial insurance covers:

(1) Economic burden of the insureds' legal liability for study participants (except from medical procedures).

(2) Economic burden of the insureds' liability for health hazards for study participants that is not clearly shown to have no relation to this study. This compensation is based on health damage compensation standard*, which is written in informed consent forms.

*Health damage compensation standard

In the event that death or physical disability corresponding to the first or second class of the sequelae according to the separate table of the Enforcement Order of the

Pharmaceuticals and Medical Devices Agency, The compensation will be paid with reference to the payment of the health damage relief business (hereinafter referred to as the “side effect damage relief system”) due to side effects or infection with biological products.

Investigators are mandatory required to purchase doctor liability insurance in preparation for liability. If a remedy for adverse drug reaction is available, investigators explain it to the study participants and work to ensure smooth claiming of benefits.

## 21. Monitoring and auditing

Described separately.

## 22. Response to ethical guidelines and the Declaration of Helsinki

This study will be conducted in compliance with the ethical guidelines for medical research on human health (Ministry of Health, Labor and Welfare, Japan, Dec. 2014) and the Helsinki Declaration.

## 23. Storage and disposal of samples and information

Samples and information related to this study (including copy of application documents, notification form, copy of various application forms and reports, study participants identification code list, consent form, copy of case report, and other data necessary to guarantee the reliability for data) are securely stored in Department of Neurology, Nippon Medical School, for a period of 5 years after the end of the study was reported, or 3 years from the date of reporting the final publication of the results of the study, whichever is later, and that information is not available outside this study.

After the storage period, discard the samples and information in an unidentified (anonymized) state.

## 24. Registration of research plan and publication of research results

The research plan of this study is registered in the University hospital Medical Information Network (UMIN). For assignment and data registration, use those created by ShibaSho Co., Ltd.

Regardless of the outcome, the results of this study will be submitted to the journal by the principal investigator or collaborator as soon as possible after the end of the study. The results obtained in this study will be jointly announced by the participating facilities.

## 25. Information on research funding sources and conflicts of interest

All the medical treatments in this study are performed under public health insurance. Insurance fee and miscellaneous expenses will be covered by research expenses from the Department of Neurology, Nippon Medical School. There are no conflicts of interest to report for this study.

## 26. Attribution of intellectual property rights

If intellectual property rights such as patent rights are found from the results of this study, they belong to the research institution or the researcher that conducts this study.

## 27. Content and method of reporting to the director of the institution

The principal investigator shall report the progress of the study to the director of the hospital and the IRB every year after the approval. In addition, reports will be made each time the study is stopped or completed.

The principal investigator shall promptly report to the director of the hospital and the IRB, when principal investigator acknowledges the occurrence of a serious adverse event, protocol deviation, needs to change or revise the protocol, and the protcol does not meet the current guidelines.

## 28. References and materials

References

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※Final protocol

# Direct mechanical thrombectomy in acute LVO stroke (SKIP study): a randomized controlled trial

Research Plan

UMIN 000021488

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Planned Study period: From November 1st, 2016 to October 30th, 2019

This research plan has created May 2nd, 2016

This research plan has accepted November 1st, 2016

This research plan has revised June 8th, 2018

## 1. Study Organization

1) Principal investigator

Kazumi Kimura, Department of Neurology, Nippon Medical School

Yuji Matsumaru, Department of Neurosurgery, Tsukuba University

2) Study site and investigators in charge

| Study site | Investigator | Title | Contact |
|---|---|---|---|
| Nippon Medical School | Kazumi Kimura<br>Kentaro Suzuki<br>Junya Aoki<br>Yasuhiro Nishiyama | Professor<br>Assistant Professor<br>Lecturer<br>Asssociate Professor | 03-3822-2131 |
| Tranomon Hospital | Wataro Tsuruta | Chief | 03-3588-1111 |
| Tokyo Metropolitan Tama Medical Center | Takahiro Ota<br>Masayuki Ueda | Chief<br>Chief | 042-323-5111 |
| The Jikei University | Yasuyuki Iguchi<br>Toshihiro Ishibashi | Professor<br>Asssociate Professor | 03-3433-1111 |
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| Showa University Koto Toyosu hospital | Yuki Kamiya | Associate Professor | 03-6204-6489 |
| Tokyo Medical and Dental University | Kazunori Miki | Assistant Professor | 03-3813-6111 |
| Yokohamashintoshi Neurosurgical Hospital | Masafumi Morimoto<br>Mitsuhiro Iwasaki | Director<br>Chief | 045-911-2011 |
| Mihara Memorial Hospital | Kazunori Akaji | Chief | 0270-24-3355 |
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| New Tokyo Hospital | Norihiro Ishii | Chief | 047-711-8700 |
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| | | | |
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| National Hospital Organization Disaster Medical Center | Keigo Shigeta | Chief | 042-536-5511 |
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| Nippon Medical School Public Health | Toshiaki Otsuka | Asssociate Professor | 03-3822-2131 |

3) Study Secretariat

   Department of Neurology, Nippon Medical School

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4) Protocol Manager

   Leader: Kazumi Kimura; Department of Neurology, Nippon Medical School

   Committee: Kentaro Suzuki; Department of Neurology, Nippon Medical School

5) Allocation Manager

   Kentaro Suzuki; Department of Neurology, Nippon Medical School

6) Data Manager

   Hiroshi Nagayama; Department of Neurology, Nippon Medical School

7) Data monitoring and safety board

   Akio Morita; Department of Neurosurgery, Nippon Medical School

8) Statistical Manager

   Toshiaki Otsuka; Department of Public Health, Nippon Medical School

9) Event evaluation committee

   Hiroyuki Yokota; Department of Critical Care Medicine, Nippon Medical School

10) Radiological Judgement committees

   Teruyuki Hirano; Department of Stroke Medicine, Kyorin University

Shigeru Fujimoto; Department of Neurology, Jichi University

## 2. Introduction and Rationale

Recombinant tissue-plasminogen activator (rt-PA) was approved by the authority in 2005 in Japan and widely used as a standard treatment for patients with acute ischemic stroke. However, it is also known that rt-PA has limited effect for patients with large vessel occlusion (LVO); previous studies showed the recanalization rate was as low as 5.9% in patients with internal carotid artery (ICA) and 16.7% in those with proximal middle cerebral artery horizontal segment (MCA M1) occlusion.[1, 2]

As the progress in devises, the reperfusion therapy for patients with LVO with mechanical thrombectomy (MT) can dramatically improve the recanalization rate. Randomized controlled trials (RCTs) presented around 2015 showed that adding MT could improve recanalization rate and outcome, compared with rt-PA treatment.[3-7]

In these RCT, onset-to-reperfusion time played a critical role and shorter onset-reperfusion time lead better outcome.[8] Indeed, 59% of the recanalized patients within 300 min achieved good functional outcome, it declined to 32% when recanalization was attained after 300 min from symptom onset. Shorter onset-to-groin puncture time was reported to be also associated with better outcome,[9] so reducing onset-to-puncture and -reperfusion time is needed in managing acute stroke patients with LVO.

Under the current guidelines, MT should be conducted in conjunction with rt-PA, when patients have indications for rt-PA. Therefore, there is no RCTs investigating the effectiveness of MT without rt-PA. One retrospective study revealed that MT without rt-PA, compared with MT plus rt-PA, reduced hemorrhagic complications and mortality.[10]

To skip rt-PA can reduce hemorrhagic complications and achieve better outcome. Therefore, we conduct prospective, multicentre RCT to elucidate the efficacy of MT without rt-PA for hyperacute ischemic stroke patients with LVO.

## 3. Purpose of the study

The aims of the present study is to elucidate the difference in clinical outcome, hemorrhagic complications, onset-to-reperfusion time, and the rate of effective recanalization between MT with and without rt-PA in acute stroke patients with LVO.

## 4. Study period

From November 1st, 2016 through October 30th, 2019 (study entry ends July 31st, 2019).

## 5. Study site

Department of Neurology, Nippon Medical School hospital

## 6. Sample size

Favorable outcome (modified Rankin scale [mRS] 0-2, 3 months after stroke onset) was assumed to be 48.6% in the MT without rt-PA group and 35.2% in the MT with rt-PA group,[11] the required number of patients is calculated to be 89 patients in each group, for a total of 178 patients. Assuming a dropout rate of 10%, 200 patients (100 patients in each group) has been set.

## 7. Drugs and devices used in the study

3) Information about drugs and devices

   Drug: alteplace (Activacin® [Kyowa Hakko Kirin] and Grtpa® [Tanabe Mitsubishi Pharmacy])

   Devices: Devices used for revascularization, such as: Penumbra® (Medico's Hirata), Trevo® (Stryker), Solitaire® (Medtronic), Revive® (Johnson & Johnson), Gateway® PTA Catheter, Wangspan® stent, Precice®, Carotid Wall® stent, and PROTÉGÉ®.

4) Expected adverse effect of the drugs or malfunction of the devices

   Hemorrhagic complications are known as adverse effects of these drugs and devices. When severe hemorrhagic complication occurs, every treatment is based on taking the highest priority on participants' safety.

## 8. Patient population

4) Patient condition

   Ischemic stroke

5) Inclusion criteria

Inclusion criteria

1. Age ≥18 and <86 years at the time of informed consent
2. Clinical diagnosis of acute ischemic stroke with clinical symptoms
3. Modified Rankin scale score ≤2
4. ICA or M1 occlusion on MRA or CTA
5. Initial NIHSS ≥6
6. ASPECTS on initial DWI ≥5 or on initial CT ≥6
7. Onset to randomization within 4 h from onset. (Recomendation topuncture within 30 min from randomization)
8. Written informed consent by patient or next of kin.

Reasons for inclusion

1. Effectiveness of endovascular treatment for children has not been established, and in many elderly patients it is difficult to perform endovascular treatment due to meandering of blood vessels.
2. Since some cases show rapid improvement due to spontaneous recanalization, we targeted cases where the symptoms persisted.
3. To fairly assess outcomes 90 days after symptom onset.
4. The efficacy of endovascular therapy has been proven in patients with ICA or M1 occlusion.
5. The above items with sufficient evidence to benefit from reperfusion were targeted, based on past reports.
6. The above items with sufficient evidence to benefit from reperfusion were targeted, based on past reports.
7. When assigned to the EVT without rt-PA group but the EVT is difficult to perform (e.g., running of the blood vessel), there will be clear disadvantage to the patients allocated to the EVT without rt-PA group. To prevent this, we included it in the selection criteria so that intravenous rt-PA therapy could be performed in cases where EVT was difficult.
8. As in previous reports, we include patients with the consent.

6) Exclusion criteria

Exclusion criteria

1. Contraindication for contrast agent or endovascular therapy
2. Contraindication for IVT.
3. Presence of severe renal disorder (patients undergoing dialysis can be included)
4. Pregnancy or possibility of pregnancy
5. Unlikely to complete the study, such as due to progressive malignant tumor
6. Judged incompatible with the study by the investigators

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Reason for exclusion

1. 2. 3. 4.

Since it is considered that angiography is not recommended in such situation. In the present study, only cases where both rt-PA intravenous therapy and EVT can be performed are included.

5.In order to fairly evaluate the outcome 90 days after onset.

6.In order to ensure the safety of the study subjects and appropriately carry out the study.

## 9. Informed consent

Before enrollment, physicians in charge must explain about this study with written and verbal explanation to all potential patients and/or their close relatives, using materials approved by institutional review board (IRB) in Nippon Medical School. Physicians guarantee potential patients and/or their close relatives chances to ask questions and sufficient time to decide whether they attend the study or not. Physicians in charge obtain informed consent from the potential patients after confirming their understanding and free will.

When new information about efficacy and safety of rt-PA or MT, that may affect the participants' attendance to this study, written materials must be revised after IRB approval, and re-consent is obtained from the patients or their close relatives.

Because the potential patients for this study have stroke, consent from their close relatives is permitted due to difficulty in obtaining consent because of disturbance of consciousness, aphasia, or weakness. When the consent is obtained from patients' relatives, the closest relative should be selected. Moreover, explanation to the patient must not be omitted even if the informed consent is obtained from relatives.

We have prepared the written explanation with easy expression so as potential patients and their relatives can understand.

## 10 Study design

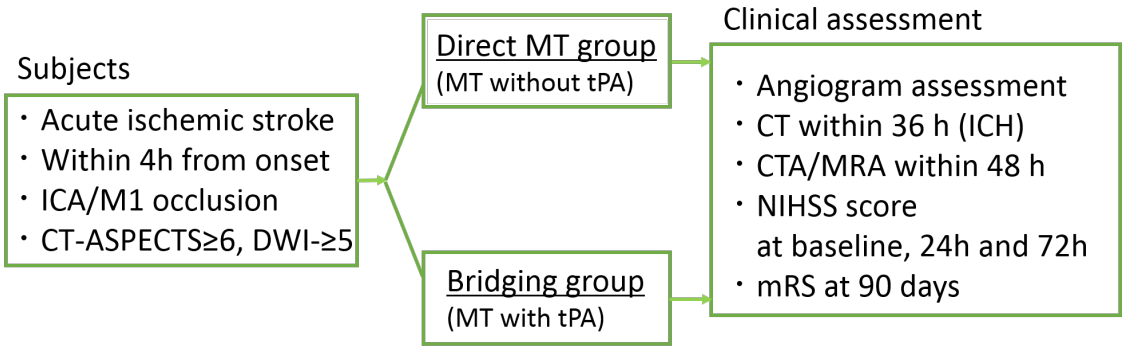
11) The kind of the study and study design

The kind of the study: interventional

Study design: multicentre, randomized, open-label study

12) Outline of the study

To elucidate the efficacy of MT without rt-PA, compared with MT with rt-PA, randomized controlled study is conducted. Medical history taking and examinations are performed just before the informed consent and physicians ascertain the eligibility. When cessation of participation is applied from the patients or their relatives, patients are immediately removed from the study.




[MT without rt-PA group]

MT without rt-PA

Rt-PA therapy will be performed when MT is difficult to perform.

MT is regarded as difficult when time from groin puncture to guiding catheter placement exceeds 30 min.

[MT with rt-PA]

MT is performed after rt-PA therapy.

13) Rt-PA should be administered within 4.5 hours from symptom onset. The amount of 0.6mg/kg (maximum of 60 mg) is administered, 10% as bolus, and the rest of 90% as continuous infusion over one hour.

14) Concomitant treatment

Below drugs must not concomitantly used within 24 hours after rt-PA therapy: warfarin, dabigatran, rivaroxaban, apixaban, and edoxaban.

15) Management and delivery of the drugs and the devices

The pharmaceutical and mechanical treatment performed in this study is approved as the treatment for stroke by the authority in Japan. Physicians use drugs or devices in the individual hospital.

16) Medication guidance

Not applicable

17) Case enrolment and random allocation

Physicians in charge should try to include all the patients who meet the inclusion criteria, and not to exclude from the study deliberately. Immediately after confirmation of LVO and obtaining consent from the patient, physicians allocated patients into specific group and avoiding treatment delay due to participation to this study.

The allocation is conducted with web-based system. After entering institutional ID and password, and completion of checklist, the system presents the results of allocation:

A) MT without rt-PA

B) MT with rt-PA

18) Patients eligibility

Physicians in charge must ascertain that the patients satisfy all the inclusion criteria and not correspond to none of the exclusion criteria (see p. 7-9).

19) Treatment after study participation

In this study, standard medical treatment is provided after hyperacute management, so standard medical treatment is continued to be provided for patients belonging to both groups.

20) Biological samples from study participants

In this study, biological sample from study participants is used only for study outcomes. All samples are discarded after anonymization. The storage period for case report forms ends the latter day of 5 years after announcement of study completion or 3 years after final result of the study is published.

## 11. Study outcome

| |
|---|
| Primary efficacy endpoint |
| ・Favorable outcome defined as mRS score 0-2 at 90 days after stroke onset (non-inferior)(intention to treat analysis) |
| Secondary efficacy endpoints |
| ・The mRS score at 90 days (shift analysis, non-inferior) |

・Poor outcome defined as mRS score 5-6 at 90 days after stroke onset

・Poor outcome defined as mortality at 90 days after stroke onset

・Favorable outcome defined as mRS score 0-1 at 90 days after stroke onset

・Favorable outcome defined as mRS score 0-2 at 90 days after stroke onset

・Favorable outcome defined as mRS score 0-3 at 90 days after stroke onset

・Favorable outcome defined as mRS score 0-1 at 90 days after stroke onset (non-inferior)

・Favorable outcome defined as mRS score 0-2 at 90 days after stroke onset (non-inferior)(per protocol analysis)

・Favorable outcome defined as mRS score 0-3 at 90 days after stroke onset (non-inferior)

・Improvement of mRS score as of 90 days after stroke onset

・Reperfusion of TICI score 2b or 3 at the end of EVT

・Recanalization of modified Mori grade 2 or 3 at 72 h after stroke onset

Safety endpoints

・Any ICH on CT or MRI within 36 h after stroke onset.

・sICH as defined by NINDS and SITS-MOST criteria within 36 h after stroke onset.

・ Major bleeding as defined by fatal bleeding, symptomatic bleeding in a critical area or organ, such as intraspinal, intraocular or bleeding causing a fall in hemoglobin ≥3 g/dL, or leading to transfusion of whole blood or red cells within 24 h after stroke onset

## 12. Observational items and examinations

1) Patients backgrounds
   Sex, Age, Height, Weight
   Vascular risk factors (Hypertension, Diabetes mellitus, Dyslipidemia, Atrial fiblliration, Chronic kidney disease, Heart failure, and smoking history)
   Past history of cerebrovascular diseases (Transient ischemic attack, Ischemic stroke, Intracerebral haemorrhage, and Subarachnoid haemorrhage)
   Past history of cardiovascular diseases (Myocardial infarction, Angina pectoris, peripheral artery disease)
2) Physical examinations, Imaging examinations
   Blood pressure and heart rate on admission

NIHSS score: on admission, 24 h (±8 h) and 72 h (±8 h) after treatment, on discharge
Premorbid mRS
Imaging: ASPECTS on CT or DWI-ASPECTS on DWI (as positive include small lesions) before treatment
Pre-treatment DWI and FLAIR more than 1 week after treatment
T2* on admission (presence of microbleeds and SVS)
Vascular imaging: Occluded vessel on CTA or MRA
TICI score just after EVT treatment
Presence of tandem lesion
State of recanalization (using modified Mori grade) on MRA or CTA 48 (± 24h) after treatment
Time metrics: Onset-to-door, Door-to-groin puncture, Puncture-to-recanalization, Door-to-needle, and Door-to-randomization.

3) Treatment details
Blood pressure before treatment
IV rt-PA therapy: onset-to-needle time
EVT: Onset-to-reperfusion time (or time from symptom onset to final angiogram when no reperfusion is achieved), number of pass, methods (mechanical thrombectomy, angioplasty, or local fibrinolysis), devices (Penumbra, Trevo, Solitaire, Revive, balloons, and intracranial stents), intra-arterial drug infusion (urokinase or rt-PA)
Adverse events: Any Intracerebral hemorrhage within 36 h and 7 days (±1 day) after treatment, Symptomatic intracerebral hemorrhage (SITS-MOST criteria and NINDS criteria), and other hemorrhagic complications.

4) Vital signs and laboratory data
Blood pressure (on admission, before treatment), Heart rate, Body temperature
Laboratory data: (WBC, Hemoglobin, Platelet count, Glucose, HbA1c, BNP, PT-INR, aPTT)
Anticoagulant drugs, Antiplatelets, or Statins before admission

5) Follow-up
mRS 90 days (±10 days) after onset (When mRS increase from pre-morbid mRS, denote whether the deterioration is due to stroke)
※the mRS was assessed by physical examination or telephone interview at 90 days after onset by a third independent observer, who was also blinded.
Etiology (TOAST criteria)

Symptomatic recurrence during admission

Surgical intervention

6) Other adverse events

Other adverse events are defined as all unfavorable events such as abnormal laboratory values and adverse reactions, regardless of causal relationship with drugs or treatments. Describe the details of adverse effects, timing of onset / recover, degree, treatment, outcome, severity assessment, and relevance with the study drug or treatment in the medical chart and case report form. Follow up if necessary. The severity of adverse events is defined as (1) mild: the state that study participation can be continued without treatment, (2) moderate: the state that study participation can be continued with treatment, and (3) severe: the state that study participation should be suspended.

## 13. Study discontinuation

3) Study discontinuation criteria for each participant

Study participants who meet the below situation will be excluded from this study.

vi. Offer to decline participation or withdrawal of consent from the patient or their representatives.

vii. Find out not to meet the inclusion criteria after study participation

viii. The study terminates early

ix. Difficult to study participation due to adverse events

x. The participant should be excluded from the study for other reasons than the above, judged by the attending physician

When the participant is excluded from this study, the date, reason, or situation of discontinuation will be recorded on their medical chart and case report form. Appropriate examinations will be performed on discontinuation to evaluate the efficacy and safety. When participants are excluded before treatment, patients will be informed about and treated with standard treatment. Physicians consider patients not to suffer disadvantages.

4) Study discontinuation criteria for this study

Principal investigator consider study termination when:

vi. Obtaining serious information about safety or efficacy about the study

vii. Predicted risks seem to overwhelm the expected benefit

viii. Difficulty in recruiting participants and achieving the intended sample size

ix. Purpose of the study is achieved before study completion

x. Recommendation of termination is published from the institutional review board, or instructions to protocol change but difficult to accept the instruction

When terminating the study, principal investigator report study termination and its reason to the director of the institution, with written documents.

## 14. Adverse events

5) Management of adverse events

Investigators must conduct appropriate treatment immediately when participants show unfavourable medical conditions (adverse events) such as hemorrhagic complications, and describe the adverse events on medical chart and case report form. When adverse events are decided to be severe, follow the instructions below 2) management of severe adverse events.

6) Management of severe adverse events

When severe adverse events occur, principal investigator conduct appropriate treatment immediately, and promptly reports it to the director of the institution and institutional IRB. Principal investigator also reports it to investigator in other institutions. Severe adverse events include not only adverse events occurred within the study period, but also severe adverse events occurred after study completion and suspected to be associated with the study.

7) Definition of severe adverse events

v. Death, or events potentially lead death
vi. Hospital admission or extension of hospital stay due to treatment
vii. Disability or events potentially lead disability
viii. Severe status according to above criteria

8) Matters to be included about severe adverse events

vi. Name of adverse event
vii. Time of occurrence
viii. Outcome (e.g., improve, unchanged, recovery, or death)
ix. Time course
x. Relevance to the study
   a. No relevance
   b. Probably no relevance
   c. Probably relevant

d. Relevant

When severe adverse events are assessed no/probably no relevance to the study, presumed cause of the adverse events should be reported.

## 15. Statistical Analysis Plan

The primary study outcome measure was noninferiority of the favorable outcome at 90 days. We first used unadjusted logistic regression to test whether direct MT therapy was noninferior to bridging therapy. To satisfy the noninferiority hypothesis, the lower bound of the one-sided 97.5% confidence interval for the odds ratio (OR) of the primary outcome of the Direct MT group compared with the Bridging group needed to exceed 0.74. This noninferiority margin was derived from a previous meta-analysis of bridging therapy compared with the best medical treatment,[12] with the margin defined according to the upper bound of the 95% confidence interval for the OR of the primary outcome with standard medical care versus the combination of medical care and MT. The margin of 0.74 represents the midpoint between the upper bound of the 95% confidence interval of the estimated effect of the standard medical care and 1.0 (using bridging therapy with medical care and MT as a reference). The secondary efficacy analyses included the comparison of ordinal scores on the modified Rankin scale to test for the noninferiority of the direct MT vs bridging therapy with ordinal logistic regression (shift analysis), where the OR is calculated for each cut-point across the mRS (for example, 0 versus 1–6, then 0–1 versus 2–6, and so on), and then a summary OR is calculated from the individual ORs, under the assumption that the individual ORs are the same. We also performed secondary analyses of the primary outcome with adjustment for minimization and key prognostic covariates, as well as secondary analyses in the per-protocol population. Next, clinical characteristics, recanalization success rate, hemorrhagic event rate (Any ICH, symptomatic ICH and other hemorrhagic complication), mortality and other MT parameters were compared between the two groups. For ease of interpretation, all reported P-values for noninferiority are multiplied by 2, so that an alpha of 0.05 can be used in analyses. The other P-values are two-sided. All P-values were pre-specified not to be adjusted. JMP version 11 software (SAS Institute, Cari, NC) was used the analysis.

## 16. Privacy policy

1) When treating raw data or consent forms, consider participants' privacy.
2) Identifying code is used in forms submitted to outside hospital, instead of names.

3) Correspondence table between participants' name and identifying code is strictly kept in the department of neurology.
4) When the results of the study are reported, no identifiable information is included.
5) Acquired data in the study is exclusively used for the study.

## 17. Consideration for safety or disadvantage

When adverse events are occurred, appropriate examination and treatment are performed promptly. Hemorrhagic complication can be occurred as a serious complication in this study. Prompt action is required for each sites and declared in this protocol (see Section 14. Adverse events).

## 18. Publish policy about the results of the study

Measurements or examinations required in this study is frequently tested in acute stroke management, and the results of examinations are reported to the patients or relatives. The results of this study is published promptly after completion of the study (see Section 24. Registration of research plan and publication of research results)

## 19. Cost burden for participants

Medical check-ups, measurements, examinations, and treatment in this study is totally under the public health insurance. No drugs or procedures beyond public health insurance is used or performed in this study. So, additional fee for participation to this study are not expected.

## 20. Compensation for health hazards

All treatments and examinations are conducted under the public health insurance. Health hazards attributable to this study are also treated under the public health insurance. Organisation, institutions, or individuals such as physician in charge involved in this study will not compensate the participants' self-pay burden, leave compensation, and additional hospital charge associated with extension of admission. Physicians in charge manage in-hospital resources to treat participants' health damage promptly and appropriately.

This study has clinical trial insurance for health hazards potentially attributable to this study. All the stuffs involved in this study are insured, and clinical trial insurance covers health damage (including death) to study participants from start of this study through one year after study completion. Clinical trial insurance covers:

(3) Economic burden of the insureds' legal liability for study participants (except from medical procedures).

(4) Economic burden of the insureds' liability for health hazards for study participants that is not clearly shown to have no relation to this study. This compensation is based on health damage compensation standard*, which is written in informed consent forms.

*Health damage compensation standard

In the event that death or physical disability corresponding to the first or second class of the sequelae according to the separate table of the Enforcement Order of the Pharmaceuticals and Medical Devices Agency, The compensation will be paid with reference to the payment of the health damage relief business (hereinafter referred to as the "side effect damage relief system") due to side effects or infection with biological products.

Investigators are mandatory required to purchase doctor liability insurance in preparation for liability. If a remedy for adverse drug reaction is available, investigators explain it to the study participants and work to ensure smooth claiming of benefits.

## 21. Monitoring and auditing

Described separately.

## 22. Response to ethical guidelines and the Declaration of Helsinki

This study will be conducted in compliance with the ethical guidelines for medical research on human health (Ministry of Health, Labor and Welfare, Japan, Dec. 2014) and the Helsinki Declaration.

## 23. Storage and disposal of samples and information

Samples and information related to this study (including copy of application documents, notification form, copy of various application forms and reports, study participants

identification code list, consent form, copy of case report, and other data necessary to guarantee the reliability for data) are securely stored in Department of Neurology, Nippon Medical School, for a period of 5 years after the end of the study was reported, or 3 years from the date of reporting the final publication of the results of the study, whichever is later, and that information is not available outside this study.

After the storage period, discard the samples and information in an unidentified (anonymized) state.

## 24. Registration of research plan and publication of research results

The research plan of this study is registered in the University hospital Medical Information Network (UMIN). For assignment and data registration, use those created by ShibaSho Co., Ltd.

Regardless of the outcome, the results of this study will be submitted to the journal by the principal investigator or collaborator as soon as possible after the end of the study. The results obtained in this study will be jointly announced by the participating facilities.

## 25. Information on research funding sources and conflicts of interest

All the medical treatments in this study are performed under public health insurance. Insurance fee and miscellaneous expenses will be covered by research expenses from the Department of Neurology, Nippon Medical School. There are no conflicts of interest to report for this study.

## 26. Attribution of intellectual property rights

If intellectual property rights such as patent rights are found from the results of this study, they belong to the research institution or the researcher that conducts this study.

## 27. Content and method of reporting to the director of the institution

The principal investigator shall report the progress of the study to the director of the hospital and the IRB every year after the approval. In addition, reports will be made each time the study is stopped or completed.

The principal investigator shall promptly report to the director of the hospital and the IRB, when principal investigator acknowledges the occurrence of a serious adverse event, protocol deviation, needs to change or revise the protocol, and the protcol does not meet the current guidelines.

## 28. References and materials

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## ※A summary of all protocol changes

| Dates of the change | Pre change | Post change |
|---|---|---|
| 6/8/2018 | 1.Study organization<br>・Add new member<br><br>・Change the hospital name | Nippon Medical School:<br>Yasuhiro Nishiyama<br><br>St. Marianna University Toyoko Hospital: Toshihiro Ueda |
| 6/8/2018 | 6.Sample size<br>Poor outcome (modified Rankin scale [mRS] 5 or 6, 3 months after stroke onset) was assumed to be 47.5% in the MT without rt-PA group and 25% in the MT with rt-PA group, the required number of patients is calculated to be 67 patients in each group, for a total of 134 patients. Assuming a dropout rate, 200 patients (100 patients in each group) has been set. | 6.Sample size<br>Favorable outcome (modified Rankin scale [mRS] 0-2, 3 months after stroke onset) was assumed to be 48.6% in the MT without rt-PA group and 35.2% in the MT with rt-PA group,[11] the required number of patients is calculated to be 89 patients in each group, for a total of 178 patients. Assuming a dropout rate of 10%, 200 patients (100 patients in each group) has been set. |
| 6/8/2018 | 11. Study outcomes<br>Primary efficacy endpoint:<br>superiority of the rate of poor outcome defined as mRS 5,6 | 11. Study outcomes<br>Primary efficacy endpoint:<br>noninferiority of the rate of favorable outcome defined as mRS 0-2 |
| | 11. Study outcomes<br>Secondary efficacy endpoint:<br>・The mRS score at 90 days<br>・noninferiority of the rate of favorable outcome defined as mRS 0-2 | 11. Study outcomes<br>Secondary efficacy endpoint:<br>・The mRS score at 90 days (shift analysis, non-inferior)<br>・Poor outcome defined as mRS score 5-6 at 90 days after stroke onset<br>・Poor outcome defined as mortality at 90 days after stroke onset |
| 6/8/2018 | 12.Observational items and examinations<br>a physician or clinical research coordinator who is blinded to treatment assignment assesses the mRS by telephone interview at 90 days. | 12.Observational items and examinations<br>the mRS was assessed by physical examination or telephone interview at 90 days after onset by a third independent observer, who was also blinded. |
| 6/8/2018 | 15.Statistical analysis plan<br>The primary study outcome measure was superiority of the poor outcome at 90 days. We first used unadjusted logistic regression to test whether direct MT therapy was superior to bridging therapy. | 15.Statistical analysis plan<br>The primary study outcome measure was noninferiority of the favorable outcome at 90 days. We first used unadjusted logistic regression to test whether direct MT therapy was noninferior to bridging therapy. To satisfy the noninferiority hypothesis, the lower bound of the one-sided 97.5% confidence interval for the odds ratio (OR) of the primary outcome of the Direct MT group compared with the Bridging group needed to exceed 0.74. This noninferiority margin was derived from a previous meta-analysis of bridging therapy compared with the best medical treatment,[12] with the margin defined according to the upper bound of the 95% confidence interval for the OR of the primary outcome with standard medical care versus the combination of medical care and MT. The margin of 0.74 represents the midpoint between the upper |

| | | |
|---|---|---|
| | | bound of the 95% confidence interval of the estimated effect of the standard medical care and 1.0 (using bridging therapy with medical care and MT as a reference). |
| 6/8/2018 | References: None | References<br>11.Weber R, Nordmeyer H, Hadisurya J, Heddier M, Stauder M, Stracke P, Berger K, Chapot R. Comparison of outcome and interventional complication rate in patients with acute stroke treated with mechanical thrombectomy with and without bridging thrombolysis. *J Neurointerv Surg*. 2017;9:229-233<br>12.Goyal M, Menon BK, van Zwam WH, Dippel DW, Mitchell PJ, Demchuk AM, Davalos A, Majoie CB, van der Lugt A, de Miquel MA, Donnan GA, Roos YB, Bonafe A, Jahan R, Diener HC, van den Berg LA, Levy EI, Berkhemer OA, Pereira VM, Rempel J, Millan M, Davis SM, Roy D, Thornton J, Roman LS, Ribo M, Beumer D, Stouch B, Brown S, Campbell BC, van Oostenbrugge RJ, Saver JL, Hill MD, Jovin TG. Endovascular thrombectomy after large-vessel ischaemic stroke: A meta-analysis of individual patient data from five randomised trials. *Lancet*. 2016;387:1723-1731 |