Supplement 2

※Initial SAP

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

Version 1.0

May 2nd, 2016

Statistical Analysis plan

UMIN 000021488

Principal Investigator: Kazumi Kimura, Department of Neurology,

Nippon Medical School

113-8603

1-1-5, Sendagi, Bunkyo-ku, Tokyo

Tel: 03-3822-2131 (extension 4050)

Fax: 03-3822-4865

E-mail: kentarow@nms.ac.jp

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Statistical analysis committee

Toshiaki Otsuka, M.D., Ph.D., Department of Hygiene and Public Health, Nippon Medical School, Tokyo, Japan

・Methods

Patient population

Intravenous tissue plasminogen activator-eligible acute ischemic stroke patients with occlusion of the internal cerebral artery or horizontal part of the middle cerebral artery were enrolled into the SKIP study. The occluded vessel was evaluated by magnetic resonance angiography (MRA) or computed tomographic angiography (CTA). Inclusion and exclusion criteria are listed in Table 1.

Randomization

Patients were randomly assigned in a 1:1 ratio to one of two treatment groups using a web-based data management system: the direct MT group or the bridging therapy group. Using a minimization algorithm, we balanced the number of patients into the two treatment groups of each hospital.

Clinical assessments at 90 days

A physician or clinical research coordinator who is blinded to treatment assignment assesses modified Rankin Scale (mRS) at 90 days after onset by telephone interview at 90 days.

Outcome measures

Efficacy and safety end-points in the initial protocol are listed in Supplemental Table 2.

The primary outcome measure is the rate of poor outcome defined as mRS 5,6 at 90 days. The secondary outcome measures are shift analysis of the mRS at 90 days after onset, per protocol (PP) analysis of mRS 5,6 at 90 days, and recanalization rate of the occluded arteries. Successful recanalization is defined as an extended modified Thrombolysis in Cerebral Infarction (eTICI) score[1] ≥ 2b according to angiographic findings after MT therapy. The safety outcomes are symptomatic ICH defined by the National Institute of Neurological Disorders and Stroke (NINDS) [2] and Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SIT-MOST[3]) criteria at 36 hours from onset and any ICH, including asymptomatic and symptomatic ICH.

Sample size calculation

A previous observational study[4] showed that poor outcome at 90 days for ischemic stroke was observed in 25% and 47.5% of patients who had

received direct MT and bridging therapy,respectively. According to those results, we estimated that 134 patients (67 patients in either group) would need to be enrolled to detect the superiority of direct MT to the combination of IVT and MT, based on a 2-sided α level of 0.05 and a power of 0.80. Accounting for possible treatment failures, protocol violations, and dropouts, we decided to enroll 200 patients.

Statistical analysis

The primary study outcome measure is superiority of the favorable outcome at 90 days. We will first use unadjusted logistic regression to test whether direct MT therapy will be superior to bridging therapy.

The secondary efficacy analyses include the comparison of ordinal scores on the modified Rankin scale to test for the superiority 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, and other MT parameters were compared between the two groups using unadjusted logistic regression analysis. The P-values are two-sided. JMP version 11 software (SAS Institute, Cari, NC) was used the analysis.

Study organization

The SKIP study was organized by a central coordinating center located at Nippon Medical School, and conducted in approximately 22 centers in Japan. The SKIP study receives no funding support.

Supplementary Tables.

Table 1. Inclusion and exclusion criteria of the SKIP study

Inclusion criteria
・Age ≥18 and <86 years at the time of informed consent
・Clinical diagnosis of acute ischemic stroke with clinical symptoms
・Modified Rankin scale score ≤2
・ICA or M1 occlusion on MRA or CTA
・Initial NIHSS ≥6
・ASPECTS on initial DWI ≥5 or on initial CT ≥6
・Onset to randomization within 4 h from onset.
・Written informed consent by patient or next of kin.
Exclusion criteria
・Contraindication for contrast agent or endovascular therapy
・Contraindication for IVT
・Presence of severe renal disorder (patients undergoing dialysis can be included)
・Pregnancy or possibility of pregnancy
・Unlikely to complete the study, such as due to progressive malignant tumor
・Judged incompatible with the study by the investigators

ICA, internal carotid artery; ASPECTS: Alberta Stroke Program Early CT Score; M1, first segment of middle cerebral artery; MRA, magnetic resonance angiography; CTA, computed tomographic angiography; DWI, diffusion-weighted imaging; IVT, intravenous thrombolysis

133 Table 2. Efficacy and safety assessment in the initial protocol

Primary efficacy endpoint
・Poor outcome defined as mRS score 5-6 at 90 days after stroke onset
Secondary efficacy endpoints
・The mRS score at 90 days (shift analysis)
・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
・Recanalization 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
・ICH on CT or MRI within 36 h after stroke onset.
・sICH as defined by an increase in NIHSS score of ≥4 from baseline on CT or MRI 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

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1. 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 2014;6:83-6.

2. Tissue plasminogen activator for acute ischemic stroke. N Engl J Med 1995;333:1581-7.

3. Wahlgren N, Ahmed N, Davalos 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 2007;369:275-82.

4. Broeg-Morvay A, Mordasini P, Bernasconi C, et al. Direct Mechanical Intervention Versus Combined Intravenous and Mechanical Intervention in Large Artery Anterior Circulation Stroke: A Matched-Pairs Analysis. Stroke 2016;47:1037-44.

※Final SAP

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

Version 2.0 (final protocol)

August 2nd, 2018

Statistical Analysis plan

UMIN 000021488

Principal Investigator: Kazumi Kimura, Department of Neurology,
Nippon Medical School

113-8603
1-1-5, Sendagi, Bunkyo-ku, Tokyo
Tel: 03-3822-2131 (extension 4050)
Fax: 03-3822-4865
E-mail: kentarow@nms.ac.jp

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・Methods

Patient population

Intravenous tissue plasminogen activator-eligible acute ischemic stroke patients with occlusion of the internal cerebral artery or horizontal part of the middle cerebral artery are enrolled into the SKIP study. The occluded vessel is evaluated by magnetic resonance angiography (MRA) or computed tomographic angiography (CTA). Inclusion and exclusion criteria are listed in Table 1.

Clinical assessments at 90 days

The mRS is assessed by physical examination or telephone interview at 90 days after onset by a third independent observer, who was also blinded.

Randomization

Patients were randomly assigned in a 1:1 ratio to one of two treatment groups using a web-based data management system: the direct MT group or the bridging therapy group. Using a minimization algorithm, we balanced the number of patients into the two treatment groups of each hospital.

Outcome measures

Efficacy and safety end-points in the initial protocol are listed in Supplemental Table 2. We changed the primary efficacy endpoint from superiority of the rate of poor outcome defined as mRS 5,6 to non-inferiority of the rate of favorable outcome defined as mRS 0-2 on 1 August 2018, because we fit the primary outcome to match other clinical trials of the same theme and change the theme to be useful to clinical practice. the SKIP investigators always requested IRB to use the mRS 0-2 for noninferiority as primary analysis. However the IRB required SKIP investigators to change from mRS 0-2 for noninferiority to mRS 5-6 for superiority as primary analysis prior to study start, because there were no confirm data to support the mRS 0-2 than mRS 5-6 approach. Then, when about half the patients had been enrolled in the trial, a group in Germany published an observational study that provided more data regarding the mRS 0-2 endpoint[4]. Therefore, IRB accepted to use mRS 0-2 for noninferiority as primary analysis.We show the end-points in the final protocol in Supplemental Table 3. The primary outcome measure is the rate of favorable outcome defined as modified Rankin scale score of 0-2 at 90 days (noninferiority). The secondary outcome measures are a shift analysis of the modified Rankin scale score at 90

215 days after onset, per protocol (PP) analysis of a modified Rankin scale score of
216 0-2 at 90 days, mortality at 90 days, and reperfusion rate of the occluded arteries.
217 Successful reperfusion is defined as an extended Thrombolysis in Cerebral
218 Infarction (eTICI) score [1] ≥2b (range, 0 [no reperfusion] to 3 [complete
219 reperfusion]) according to digital subtraction angiography findings after
220 mechanical thrombectomy therapy. The safety (adverse) events are
221 symptomatic intracerebral hemorrhage, as defined by the National Institute of
222 Neurological Disorders and Stroke (NINDS [2]) and Safe Implementation of
223 Thrombolysis in Stroke-Monitoring Study (SIT-MOST [3]) criteria, and any
224 intracerebral hemorrhage including asymptomatic and symptomatic intracerebral
225 hemorrhage at 36 hours from onset.
226
227 Sample size calculation
228 In the initial protocol, we estimated sample size of 134 patients (67
229 patients in either group) for the superiority analysis of poor outcome defined as
230 mRS 5,6 at 90 days. Then, we have changed the primary outcome and thus we
231 re-calculated sample size. A previous observational study[4] showed that
232 favorable outcome at 90 days for ischemic stroke was observed in 48.6% and

35.2% of patients who had received direct MT and bridging therapy, respectively. According to those results, we estimated that 178 patients (89 patients in either group) would need to be enrolled to detect the noninferiority of direct MT to the combination of IVT and MT, based on a 1-sided α level of 0.025 and a power of 0.80. Accounting for possible treatment failures, protocol violations, and dropouts, we decided to enroll 200 patients.

Definition of analysis sets

All patients who have been randomised to either cotrol or intervention arms will be included in the full analysis set irrespective of their protocol adherence and continued participation in the study. All analyses will be performed using the full analysis set. Noninderiority analyses of a modified Rankin scale score of 0-2 at 90 days will also be perfomed using the PP analysis set, which excludes patients whose modified Rankin scale at pre stroke is higher than 2 and a large volume infarct (Alberta Stroke Program Early CT Score of 0-5 or DWI- Alberta Stroke Program Early CT Score of 0-4) from full analysis set.

Statistical analysis

The primary study outcome measure is noninferiority of the favorable outcome at 90 days. We will first use unadjusted logistic regression to test whether direct MT therapy will be noninferior to bridging therapy. To satisfy the noninferiority hypothesis, the lower bound of the one-sided 97.5% confidence interval (CI) for the odds ratio (OR) of the primary outcome of the Direct MT group compared with the Bridging group needs to exceed 0.74. This noninferiority margin is derived from a previous meta-analysis of bridging therapy compared with the best medical treatment,[5] with the margin defined according to the upper bound of the 95% CI 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% CI of the estimated effect of the standard medical care and 1.0 (using bridging therapy with medical care and MT as a reference).

In a secondary efficacy analysis, the modified Rankin scale ordinal scores will be compared between groups to test for the non-inferiority of mechanical thrombectomy compared with combined intravenous thrombolysis plus mechanical thrombectomy, using ordinal logistic regression analysis (shift analysis), where the OR will be calculated for each cut-point across the mRS

scale score (for example, 0 versus 1–6, then 0–1 versus 2–6, and so on), and then a summary OR will be calculated from the individual ORs, under the assumption that the individual ORs are the same.. The proportional odds assumption will be validated by a Brant test. We will also performe secondary analyses of the primary outcome with adjustment for minimization and key prognostic covariates, as well as secondary analyses in the PP population. Thereafter, the clinical characteristics, successful reperfusion rate, hemorrhagic events rate, and other mechanical thrombectomy parameters will be compared between the two groups using unadjusted logistic regression analysis. As safety (adverse) events, any and symptomatic intracerebral hemorrhage will be assessed to superiority of mechanical thrombectomy alone compared with combined intravenous thrombolysis plus mechanical thrombectomy. Imputation for missing data will not be conducted becauase there were no missing data at the time of prespecified, interim safety analysis. Noninferiority analyses use a 1-sided 97.5% CI of the estimated effect whereas other analyses use a 2-sided 95% CI of the estimated effect for judgement of statistical significance. For point estimates, $p<0.05$ is considered statistically significant. All data analyses are performed with JMP version 11 software (SAS

Institute, Cari, NC) and Stata version 14 software (Stata Corp, College Station, TX).

Study organization

In the final protocol, the SKIP study was conducted at 23 stroke centers in Japan. And the SKIP study was funded by the Japanese Society for Neuroendovascular Therapy (JSNET).

Supplementary Tables.

Table 1. Inclusion and exclusion criteria of the SKIP study

Inclusion criteria
・Age ≥18 and <86 years at the time of informed consent
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Exclusion criteria
・Contraindication for contrast agent or endovascular therapy
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・Presence of severe renal disorder (patients undergoing dialysis can be included)
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・Unlikely to complete the study, such as due to progressive malignant tumor
・Judged incompatible with the study by the investigators

ICA, internal carotid artery; ASPECTS: Alberta Stroke Program Early CT Score; M1, first segment of middle cerebral artery; MRA, magnetic resonance angiography; CTA, computed tomographic angiography; DWI, diffusion-weighted imaging; IVT, intravenous thrombolysis

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Secondary efficacy endpoints
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・Favorable outcome defined as mRS score 0-1 at 90 days after stroke onset (non-inferior)
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Safety endpoints
・ICH on CT or MRI within 36 h after stroke onset.
・sICH as defined by an increase in NIHSS score of ≥4 from baseline on CT or MRI 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

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302 Table 3. Efficacy and safety assessment in the final protocol

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)
・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
・Recanalization of TICI score 2b or 3 at the end of EVT
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Safety endpoints
・ICH on CT or MRI within 36 h after stroke onset.
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References

1. 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 2014;6:83-6.

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5. 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 2016;387:1723-31.

324 ※A summary of all SAP changes

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Dates of the change	Ver 1.0 change	Ver 2.0 change
8/2/2018	Clinical assessments at 90 days A physician or clinical research coordinator who is blinded to treatment assignment assesses modified Rankin Scale (mRS) at 90 days after onset by telephone interview at 90 days.	The modified Rankin scale (mRS) is assessed by physical examination or telephone interview at 90 days after onset by a third independent observer, who was also blinded.
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	(SIT-MOST[3]) criteria at 36 hours from onset and any ICH, including asymptomatic and symptomatic ICH.	scale score at 90 days after onset, per protocol (PP) analysis of a modified Rankin scale score of 0-2 at 90 days, mortality at 90 days, and reperfusion rate of the occluded arteries. Successful reperfusion is defined as an extended Thrombolysis in Cerebral Infarction (eTICI) score[1] ≥2b (range, 0 [no reperfusion] to 3 [complete reperfusion]) according to digital subtraction angiography findings after mechanical thrombectomy therapy. The adverse events are symptomatic intracerebral hemorrhage, as defined by the National Institute of Neurological Disorders and Stroke (NINDS[2]) and Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SIT-MOST[3]) criteria, and any intracerebral hemorrhage including asymptomatic and symptomatic intracerebral hemorrhage at 36 hours from onset.
8/2/2018	<u>Sample size calculation</u> A previous observational study[4] showed that poor outcome at 90 days for ischemic stroke was observed in 25% and 47.5% of patients who had received direct MT and bridging	<u>Sample size calculation</u> In the initial protocol, we estimated sample size of 134 patients (67 patients in either group) for the superiority analysis of poor outcome defined as mRS 5,6 at 90 days.

	therapy,respectively. According to those results, we estimated that 134 patients (67 patients in either group) would need to be enrolled to detect the superiority of direct MT to the combination of IVT and MT, based on a 2-sided α level of 0.05 and a power of 0.80. Accounting for possible treatment failures, protocol violations, and dropouts, we decided to enroll 200 patients.	Then, we have changed the primary outcome and thus we re-calculated sample size. A previous observational study[4] showed that favorable outcome at 90 days for ischemic stroke was observed in 48.6% and 35.2% of patients who had received direct MT and bridging therapy, respectively. According to those results, we estimated that 178 patients (89 patients in either group) would need to be enrolled to detect the noninferiority of direct MT to the combination of IVT and MT, based on a 1-sided α level of 0.025 and a power of 0.80. Accounting for possible treatment failures, protocol violations, and dropouts, we decided to enroll 200 patients.
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8/2/2018	Study organization	Study organization

	The SKIP study was organized by a central coordinating center located at Nippon Medical School, and conducted in approximately 22 centers in Japan. The SKIP study receives no funding support.	In the final protocol, the SKIP study was conducted at 23 stroke centers in Japan. And the SKIP study was funded by the Japanese Society for Neuroendovascular Therapy (JSNET).
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