Supplemental Online Content

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This supplemental material has been provided by the authors to give readers additional information about their work.

eBox 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

eBox 2. Prespecified Outcome Measures in the SKIP Study

Primary efficacy endpoint
・Favorable outcome defined as mRS score 0-2 at 90 days after stroke onset
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 0-3 at 90 days after stroke onset
・Recanalization of TICI score 2b or 3 at the end of MT
・Recanalization of modified Mori grade 2 or 3 at 72 h after stroke onset
Adverse events
・Any ICH on CT or MRI within 36 h after stroke onset.
・symptomatic ICH on CT or MRI within 36 h after stroke onset as defined by the NINDS and SIT-MOST criteria.
・ Other 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

eTable. Primary and Secondary Efficacy Endpoints and Adverse Events

	MT alone	IVT + MT		Noninferiority analysis				Superiority analysis		
	n=101	n=103		Estimate of Difference (97.5% 1-sided CI)	Odds Ratio (97.5% 1-sided CI)[a]	P value[b]		Estimate of Difference (95% CI)	Odds Ratio (95% CI)	P value[b]
Primary outcome										
Modified Rankin Scale 0-2 at 90 days, no. (%)	60 (59.4%)	59 (57.3%)		2.1% (–11.4% to ∞)	1.09 (0.63 to ∞)	0.18				
Secondary outcomes										

Modified Rankin Scale reduction (shift analysis)					0.97 (0.60 to ∞)	0.27				
Mortality at 90 days, no. (%)	8 (7.9%)	9 (8.7%)						–0.8% (–9.5% to 7.8%)	0.90 (0.33 to 2.43)	1.00
TICI grade[c] ≥ 2B, no. (%)	91 (90.1%)	96 (93.2%)						–3.1% (–11.8% to 5.6%)	0.66 (0.24 to 1.82)	0.46
Modified Rankin Scale 0-1 at 90 days[d], no. (%)	41 (40.6)	46 (44.7)		-4.1% (-18.6 % to ∞)	0.85 (0.49 to ∞)	0.62				0.56
Modified Rankin Scale 0-3 at 90 days[d], no. (%)	74 (73.3%)	73 (70.9%)		2.4% (-11.7% to ∞)	1.13 (0.61 to ∞)	0.18				0.70

Modified Rankin Scale 5-6 at 90 days[d], no. (%)	16 (15.8%)	17 (16.5%)						-0.7% (-12.2% to 10.9%)	0.95 (0.45 to 2.01)	0.90
Modified MORI grade 2-3 at 72 hours[d,e], no. (%)	87/92 (94.6%)	97/101 (96.0%)						-2.4% (-9.0% to 4.1%)	0.54 (0.12 to 2.32)	0.41
Adverse events outcomes										
Any ICH at 36 h from onset, no. (%)	34 (33.7%)	52 (50.5%)						–16.8% (–32.1% to –1.6%)	0.50 (0.28 to 0.88)	0.02
Symptomatic ICH (NINDS criteria) at 36 h from onset[f], no. (%)	8 (7.9%)	12 (11.7%)						–3.7% (–13.0% to 5.6%)	0.65 (0.25 to 1.67)	0.48
Symptomatic ICH (SIT-MOST criteria) at 36 h from onset[g], no. (%)	6 (5.9%)	8 (7.8%)						–1.8% (–9.7% to 6.1%)	0.75 (0.25 to 2.24)	0.78

Other hemorrhagic events[d,h], no. (%)	1 (1.0%)	4 (3.9%)						-2.9% (-7.7% to 1.9%)	0.25 (0.03 to 2.25)	0.22
All analyses were conducted using the primary analysis set.										
MT alone, mechanical thrombectomy alone; IVT + MT, intravenous thrombolysis plus mechanical thrombectomy; CI, confidence interval; TICI, Thrombolysis in Cerebral Infarction; ICH, intracerebral hemorrhage; NINDS, National Institute of Neurological Diseases and Stroke; SITS-MOST, Safe Implementation of Thrombolysis in Stroke-Monitoring Study; NIHSS, National Institutes of Health Stroke Scale; PP, per protocol										
[a]The non-inferiority margin was the odds ratio of 0.74 [b]P values refer to the comparison between MT alone and IVT + MT [c]The TICI grading system was based on the angiographic appearances of the treated occluded vessel and the distal branches: Scores on the TICI grade range from 0 to 3, with 0 indicating no perfusion, 1 indicating penetration with minimal perfusion, 2A indicating only partial filling (<50%) of the entire vascular territory, 2B indicating partial filling (≥50%), 2C indicating near complete perfusion with the exception of slow flow or a few distal cortical emboli, 3 indicating complete perfusion [d]Additional data from text [e]12 (5.8%) data for modified Mori grade were missing. We analyzed the recanalization rate of modified Mori grade except for missing data [f]Symptomatic ICH was also assessed according to NINDS trial criteria: any intracerebral hemorrhage with neurologic deterioration from baseline (increase of ≥1 in the NIHSS score) from baseline or death within 36 hours. [g]The main definition of symptomatic intracerebral hemorrhage was the definition from the SIT-MOST: a large local or remote parenchymal intracerebral hemorrhage (>30% of the infarcted area affected by hemorrhage with a mass effect or extension outside the infarct) in combination with neurologic deterioration from baseline (increase of ≥4 in the NIHSS score) or death within 36 hours [h]Five patients had other hemorrhagic events. One bleeding from fracture occurred in the mechanical thrombectomy alone group, whereas one gastrointestinal bleeding and three puncture site bleeding occurred in the combined group, respectively.										

eAppendix. SKIP study investigators

Nippon Medical School: Kazumi Kimura, MD, PhD, Kentaro Suzuki, MD, PhD, Yasuhiro Nishiyama, MD, PhD, Junya Aoki, MD, PhD, Chikako Nito, MD, PhD, Noriko Matsumoto, MD, PhD, Takuya Kanamaru, MD, PhD, Yuki Sakamoto, MD, PhD, Toshiaki Otsuka, MD, PhD, Akio Morita, MD, PhD, Hiroyuki Yokota, MD, PhD; ***University of Tsukuba Hospital***: Yuji Matsumaru, MD, PhD, Mikito Hayakawa, MD, Aiki Marushima, MD, PhD, Yoshiro Ito, MD, PhD, Masayuki Sato, MD, PhD, Shinya Minamimoto, MD, Tenyu Hino, MD, Taisuke Akimoto, MD, PhD; ***Seishou Hospital***: Masataka Takeuchi, MD; ***Yokohama Shintoshi Neurosurgical Hospital***: Masafumi Morimoto, MD, PhD, Mitsuhiro Iwasaki, MD, Chiyoe Hikita, MD, Yasufumi Inaka, MD, Hidekazu Yamazaki, MD, Shinya Fukuta, MD, Hiroaki Sato, MD; ***Nagareyama Central Hospital***: Ryuzaburo Kanazawa, MD, PhD, Tetsuhiro Higashida, MD, PhD, Takanori Uchida, MD, Yuichi Takahashi, MD, PhD, Tomoyuki Yoshihara, MD, PhD, Hidenori Ohbuchi, MD, PhD, Naoyuki Arai, MD; ***Akiyama Neurosurgical Hospital***: Yohei Takayama, MD, Takekazu Akiyama, MD, Takahito Yazaki, MD, PhD; ***Showa University Koto Toyosu Hospital***: Yuki Kamiya, MD, PhD, Ayako Kuriki, MD, PhD, Yoshifumi Miyauchi, MD, Keita Mizuma, MD, PhD, Hiroyasu Komuro, MD, Saori Fukuda, MD, Takashi Fujii MD, Yuta Kato, MD, Takahide Wada, MD; ***National Hospital Organization Disaster Medical Center***: Keigo Shigeta, MD, PhD, Hiroshi Yatsushige, MD, PhD, Masaya Enomoto MD, PhD, Kyoko Sumiyoshi, MD, PhD, Jiro Aoyama, MD,

Tomoyuki Nakano, MD, Yukika Arai, MD; ***NTT Medical Center Tokyo***: Seiji Okubo, MD, PhD, Tomonari Saito, MD, PhD, Takehiro Katano, MD, Arata Abe, MD, PhD, Akihito Kutsuna, MD, Kazutaka Sawada, MD, Yuji Nishi, MD, Yuho Takeshi, MD; ***New Tokyo Hospital***: Norihiro Ishii, MD, PhD, Yoshinobu Sekihara MD, Yoshiyuki Takata, MD, PhD, Yuzo Saito, MD; ***Chiba Emergency Medical Center***: Yorio Koguchi, MD, PhD, Tosihiro Yamauchi, MD, PhD, Koji Suzuki, MD, PhD, Iichiro Matsuura, MD, Mitsuhiro Aikawa, MD; ***Dokkyo Medical University Saitama Medical Center***: Kensuke Suzuki, MD, PhD, Akio Hyodo, MD, PhD, Tomoji Takigawa, MD, PhD, Yosuke Kawamura, MD, Ryotaro Suzuki, MD, Ryuta Nakae, MD, PhD; ***National Center for Global Health and Medicine***: Masato Inoue, MD, PhD, Yuta Tamai, MD, Tetsuo Hara, MD, PhD; ***Funabashi Municipal Medical Center***: Hiromichi Naito, MD, Kazumi Hatayama, MD, PhD, Takuya Moriwaki, MD, PhD, Fumio Nemoto, MD, Jun Niimi, MD, Atsushi Tsuruoka, MD, PhD, Kenichiro Suyama, MD, Kenta Tasaka, MD, Kotaro Ueda, MD; ***Tokyo Metropolitan Tama Medical Center:*** Takahiro Ota, MD, PhD, Masayuki Ueda, MD, PhD; ***Kyorin University Hospital:*** Teruyuki Hirano, MD, PhD, Tatsuo Amano, MD, Hiroyuki Kawano, MD, PhD, Yoshiko Unno, MD, PhD, Yuko Honda, MD, PhD; ***National Hospital Organization, Mito Medical Center***: Noriyuki Kato, MD, PhD, Tomosato Yamazaki, MD, PhD, MD, Koji Hirata, MD; ***St. Marianna Toyoko Hospital***: Toshihiro Ueda, MD, PhD, Tatsuro Takada, MD, Noriko Usuki, MD, Satoshi Takaishi, MD, PhD, Tomohide Yoshie, MD, PhD, Kentaro Tatsuno, MD; ***The JIKEI University Hospital***: Yasuyuki Iguchi, MD, PhD,

Kenichiro Sakai, MD, PhD, Hiroki Takatsu, MD, Takahiro Maku, MD, Maki Takahashi, MD, Yuichi Murayama, MD, PhD, Toshihiro Ishibashi, MD, PhD, Shota Kakizaki, MD, Tatsuya Hirotsu, MD, Kazufumi Horiuchi, MD; ***Mihara Memorial Hospital***: Kazunori Akaji, MD, PhD, Hiroaki Kimura, MD, Yoshio Tanizaki, MD, PhD, Satoka Shidoh, MD, PhD, Ban Mihara, MD, PhD, Takao Kanzawa, MD, PhD, Youichi Mochizuki, MD; ***Toranomon Hospital***: Wataro Tsuruta, MD, PhD, Yoshikazu Uesaka, MD, PhD, Takayuki Hara, MD, PhD, Hisayuki Hosoo, MD, PhD, Masahiro Katsumata, MD, PhD; ***Tokyo Medical and Dental University***; Kazunori Miki, MD, PhD, Kazutaka Sumita, MD, PhD, Shigeru Nemoto, MD, PhD; ***Jichi Medical University***: Shigeru Fujimoto, MD, PhD, Ryota Tanaka, MD, PhD.