Supplementary Materials

Supplement to: Koga M, Yamamoto H, Inoue M, et al. Thrombolysis with alteplase at 0·6 mg/kg for stroke with unknown time of onset: a randomized controlled trial

Supplementary Information

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2. Supplementary Methods

The trial protocol was approved by the Ministry of Health, Labour, and Welfare, Japan to perform a treatment not covered by the national health insurance system.

The trial was performed at 45 centers in Japan. Sites were selected among those experienced in performing acute stroke thrombolysis with alteplase. Investigators were certified by web-based examination on image interpretation based on the imaging guideline provided by the WAKE-UP group. Members of a central image reading board reviewed all images acquired for patient enrollment to evaluate the compliance of imaging inclusion and exclusion criteria, and feedback on disagreements on these matters was provided to local sites.

Trial drug (alteplase) was freely provided by Mitsubishi Tanabe Pharma Corporation (Osaka, Japan) and Kyowa Kirin Co., Ltd (Tokyo, Japan). Otherwise, there was no industry funding or involvement in any aspect of the trial.

Clinical and imaging assessment

Certified neurologists, neurosurgeons, nurses, or CRCs performed clinical assessments at baseline, at 22 to 36 h, at 7 to 14 days, or at hospital discharge (if earlier), and at 90 days after randomization. At 90 days, mRS and adverse events were blindly assessed without information on treatment assignment by an independent physician, nurse, or CRC. Each investigator completed a training and certification program for NIHSS regarding entry criteria and modified Rankin Scale regarding outcome assessment. Assessments included demographic characteristics, a medical history, laboratory tests, and scores on the NIHSS on admission, at 24 h and 7 days (or at discharge), mRS at 7 days (or at discharge) and 90 days, concomitant medications, and serious and any adverse events within 90 days. Brain MRI was performed at baseline, at 22 to 36 h to identify intracranial hemorrhage, and at 7 to 14 days to delineate final infarct volume. DWI ASPECTS, a semiquantitative score, was assessed for early detection of ischemic lesions and scoring, for which the territory of the middle cerebral artery was allotted 10 points with 1 point subtracted for each area of ischemic lesion for each of the defined regions.[1] Scorings were performed by local site. Occlusions in MRA findings were rated by each site and then verified by core lab members (SY and MFD). Volumetric analysis was performed to measure baseline ischemic lesion volume on baseline DWI and to measure final infarct volume basically using NIH-approved software (MIPAV, Center for Information Technology, National Institutes of Health, version 8·0·2) developed for quantitative analysis and visualization of medical images from multiple modalities. Initial lesion masks were created by outlining all DWI-positive regions consistent with the acute ischemia present at baseline with adequate windowing and then were converted into short masks for volumetric quantification. All FLAIR images were also measured by similar techniques. Segmentation results were visually checked by two raters (KM and MI) and additional quantifications were performed if

disagreement for more than 20% difference in volume occurred. The Central Image Reading board finally reviewed and approved segmented stroke lesions.

Major protocol violation included any of the following; 1. Patients who were found not to meet at least 1 inclusion criterion after the start of the study. 2. Those who were found to meet at least 1 exclusion criterion after the start of the study. 3. Those who received treatment different from the assigned one. 4. Those who were treated with prohibited concomitant drugs including platelet aggregation inhibitors: ticlopidine hydrochloride, cilostazol, ozagrel, PGE 1, PGI 2, ethyl icosapentate, sarpogrelate hydrochloride, dipyridamole, trapidil, dilacef hydrochloride, trimetazidine hydrochloride, etc.; anticoagulants: warfarin, dabigatran, rivaroxaban, apixaban, low molecular weight heparin, fondaparinux, gabexate mesylate, nafamostat mesylate, camostat mesylate, freeze-dried concentrated human antithrombin III, freeze dried concentrated human activated protein C etc.; thrombolytic drugs: urokinase etc. (except alteplase as a trial drugs in the intervention group, this kind of drugs are prohibited from the trial enrollment to the trial end or discontinuation). These drugs were not restricted after 24 hours from the end of administration of the trial drugs (after 25 hours from the enrollment of trial in the control group). 5. Those who received endovascular treatment within 24 hours after the end of the investigation drugs administration (within 25 hours after the enrollment of trial in the control group).

Statistical Analysis

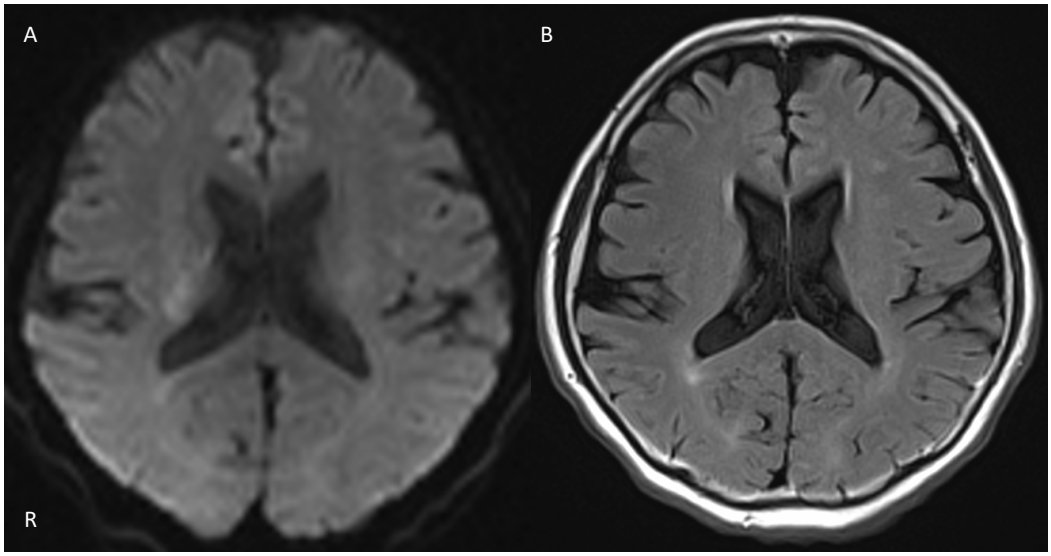
Missing data for mRS score at 90 days (n=8) and NIHSS score at 7 days (n=3) were replaced by mRS at 7 days or the time of discharge and NIHSS score at 24 h, respectively (last observation carried forward). We assessed the robustness and sensitivity of the conclusion with other methods to handle missing data (a marginal model with linearization based method and multiple imputation method). The proportion of patients with mRS 0-1 at 90 days between the alteplase and control groups (primary endpoint) was analyzed using the chi-square test. Relative risk (RR) for the primary outcome was calculated with the corresponding 95% confidence interval (CI). Category shifts for the modified Rankin scale at 90 days were analyzed by fitting a proportional-odds model to calculate the common odds ratio as a measure of the likelihood that intravenous alteplase would lead to lower scores on the mRS than would standard treatment (shift analysis), and NIHSS shift from baseline to 22-36 h or 7 days was analyzed by analysis of covariance, where the model included treatment group as a factor and NIHSS at baseline as a covariate. No multiplicity adjustment for secondary endpoints was applied. Safety data were analyzed descriptively for the treated set (safety analysis set), which consists of all randomized patients.

As a sensitivity analysis, the primary endpoint was evaluated including the mRS scores assessed by unblinded assessors. Prespecified and additional subgroup analyses for the primary endpoint were

conducted to investigate whether any differences in effects of intravenous alteplase were apparent between subgroups.

3. Supplementary Figure

Supplementary Figure I.



Diffusion-weighted imaging (right panel) shows a high-intensity signal on the right corona radiata, but fluid-attenuation inversion recovery does not show apparent signal change in the corresponding region.

4. Supplementary Tables

Supplementary Table I. Inclusion and exclusion criteria

Clinical inclusion criteria

- Clinical diagnosis of acute ischemic stroke with unknown symptom onset (e.g., acute wake-up ischemic stroke and acute ischemic stroke with unknown time of symptom onset)
- Age 20 years or older
- Last-known-well period without neurological symptoms >4.5 h*
- Treatment can be started within 4.5 h of symptom recognition (e.g., awakening)
- Initial NIHSS ≥2 and ≤25†
- Written informed consent by patient or next of kin

Imaging inclusion criteria

- Acute stroke MRI completed, including DWI and FLAIR
- ASPECTS on initial DWI ≥5
- Pretreatment MRI showing a pattern of "negative FLAIR," that is, acute ischemic lesion visible (or normally visible) on DWI, but no marked parenchymal hyperintensity visible on FLAIR indicative of acute ischemic lesion ≤4.5 h of age

Clinical exclusion criteria

- Pre-stroke mRS >1 (patients who have inability to carry out all daily activities and require some help or supervision)
- Contraindications in the Japanese guidelines for the intravenous application of recombinant tissue-type plasminogen activator (alteplase)
  - ✓ History of nontraumatic intracranial hemorrhage
  - ✓ History of stroke within the last 1 month (excluding transient ischemic attack)
  - ✓ History of significant head/spinal injury or surgery within the last 3 months
  - ✓ History of gastrointestinal or urinary tract bleeding within the last 21 days
  - ✓ History of major surgery or significant trauma other than head injury within the last 14 days
  - ✓ Hypersensitivity to alteplase or any of the excipients
  - ✓ Suspected subarachnoid hemorrhage
  - ✓ Concurrent acute aortic dissection
  - ✓ Concurrent hemorrhage (e.g., intracranial, gastrointestinal, urinary tract, or retroperitoneal)
  - ✓ Systolic blood pressure ≥185 mmHg despite antihypertensive therapy

- ✓ Diastolic blood pressure ≥110 mmHg despite antihypertensive therapy
- ✓ Significant hepatic disorder
- ✓ Acute pancreatitis
- ✓ Blood glucose <50 or >400 mg/dL (<2·8 or >22.2 mmol/L)
- ✓ Platelet count ≤100,000/mm^3
- ✓ PT-INR >1.7 or prolonged aPTT (>1.5 times baseline value [>approximately 40 s only as a guide]) for patients on anticoagulation therapy or those with abnormal coagulation. Any contraindication to MRI (e.g., cardiac pacemaker)

- Planned or anticipated treatment with surgery or endovascular reperfusion strategies (e.g., intra-arterial thrombolysis, mechanical recanalization techniques)
- Pregnant, lactating, or potentially pregnant
- Life expectancy 6 months or less by judgment of the investigator
- Inappropriate for study enrollment by judgment of the investigator

Imaging exclusion criteria

- Poor MRI quality precluding interpretation according to the study protocol
- Large DWI lesion volume >50% of the anterior cerebral artery or posterior cerebral artery territory (visual inspection)
- Large DWI lesion in brainstem or cerebellum (e.g., more than half of brainstem or more than half of unilateral cerebellar hemisphere)
- Any sign of intracranial hemorrhage on baseline MRI
- FLAIR showing marked parenchymal hyperintensity corresponding to the acute DWI lesion indicative of an acute ischemic lesion with a high likelihood of being >4·5 h old ("positive FLAIR")
- Any MRI findings indicative of a high risk of symptomatic intracranial hemorrhage related to potential intravenous alteplase treatment in the judgment of the investigator

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

*Revised from "Last-known-well period without neurological symptoms >4.5 h and <12 h of treatment initiation" in May 2015.

†Revised from "Initial NIHSS ≥5 and ≤25" in May 2015.

Supplementary Table II. Acute treatments from randomization to 24 h

	Alteplase group (n=70)	Control group (n=61)
Any antithrombotic therapy	9 (12.9)	52 (85.3)
Antiplatelet therapy	6 (8.6)	30 (49.2)
Single antiplatelet therapy	4 (5.7)	16 (26.2)
Dual antiplatelet therapy	2 (2.9)	14 (23.0)
Anticoagulant therapy	4 (5.7)	40 (65.6)
Intravenous argatroban	2 (2.9)	15 (24.6)
Intravenous heparin	2 (2.9)	25 (41.0)
Intravenous edaravone	65 (92.9)	53 (86.9)
Antihypertensive medications	23 (32.9)	15 (24.6)
Intravenous antihypertensive medication	19 (27.1)	6 (9.8)
Oral antihypertensive medication	5 (7.1)	10 (16.4)

Supplementary Table III. Any and serious adverse events in the safety analysis set

Based on system organ class (MedDRA)	Alteplase group (n=71)		Control group (n=60)	
	Events	Patient n (%)	Events	Patient n (%)
Any adverse events, total	**59**	**35 (49.3)**	**38**	**24 (40.0)**
Nervous system disorders	**25**	**23 (32.4)**	**17**	**17 (28.3)**
Asymptomatic intracranial hemorrhage	13	12 (17.2)	10	10 (16.7)
Symptomatic intracranial hemorrhage	1	1 (1.4)	0	0 (0)
Neurological deterioration (NIHSS* ≥4) without intracranial hemorrhage	6	6 (8.6)	2	2 (3.3)
Recurrent ischemic stroke	3	2 (2.9)	3	3 (4.9)
Transient ischemic attack	1	1 (1.4)	0	0 (0)
Headache	1	1(1.4)	1	1 (1.6)
Symptomatic epilepsy	0	0 (0)	1	1 (1.6)
Respiratory, thoracic and mediastinal disorders	**7**	**6 (8.5)**	**2**	**2 (3.3)**
Exacerbation of chronic obstructive pulmonary disease	2	1 (1.4)	0	0 (0)
Pulmonary embolism	1	1 (1.4)	0	0 (0)
Aspiration pneumonia	4	4 (5.7)	2	2 (3.3)
Skin and subcutaneous tissue disorders	**7**	**7 (9.9)**	**1**	**1 (1.6)**
Cervical eruption	1	1 (1.4)	0	0 (0)
Subcutaneous bleeding	6	6 (8.5)	1	1 (1.6)
Infections and infestations	**4**	**4 (5.7)**	3	**3 (4.9)**
Urinary tract infection	2	2 (2.9)	1	1 (1.6)
Herpes zoster	1	1 (1.4)	0	1 (1.6)
Pneumonia	1	1 (1.4)	1	1 (1.6)
Cystitis	0	0 (0)	1	1 (1.6)
Gastrointestinal disorders	**4**	**4 (5.7)**	**2**	**2 (3.3)**
Lower gastrointestinal bleeding	0	0 (0)	1	1 (1.6)
Diarrhea	1	1 (1.4)	0	0 (0)
Oral bleeding	2	2 (2.9)	0	0 (0)
Vomit	1	1 (1.4)	1	1 (1.6)

Musculoskeletal and connective tissue disorders	**2**	**2 (2.9)**	**2**	**2 (3.3)**
Pseudogout	1	1 (1.4)	1	1 (1.6)
Muscular pain	0	0 (0)	1	1 (1.6)
Lumbago	1	1 (1.4)	0	0 (0)
Cardiac disorders	**1**	**1 (1.4)**	**2**	**2 (3.3)**
Acute coronary syndrome	0	0 (0)	1	1 (1.6)
Death due to heart failure	1	1 (1.4)	1	1 (1.6)
Psychiatric disorders	**0**	**0 (0)**	**3**	**3 (4.9)**
Post-stroke depression	0	0 (0)	1	1 (1.6)
Agitation	0	0 (0)	1	1 (1.6)
Delirium	0	0 (0)	1	1 (1.6)
Metabolism and nutrition disorders	**1**	**1 (1.4)**	**2**	**2 (3.3)**
Hyperkalemia	0	0 (0)	1	1 (1.6)
Hypokalemia	1	1(1.4)	1	1 (1.6)
Investigations	**3**	**3 (4.2)**	**0**	**0 (0)**
Urine occult blood	2	2 (2.9)	0	0 (0)
Abnormality of electroencephalogram	1	1 (1.4)	0	0 (0)
Surgical and medical procedures	**1**	**1 (1.4)**	**2**	**2 (3.3)**
Revascularization surgery for head or neck	1	1 (1.4)	1	1 (1.6)
Bladder fistula	0	0 (0)	1	1 (1.6)
General disorder and administration site conditions	**2**	**2 (2.9)**	**0**	**0 (0)**
Sudden death due to unknown cause	1	1 (1.4)	0	0 (0)
Pyrexia	1	1 (1.4)	0	0 (0)
Vascular disorders	**1**	**1 (1.4)**	**1**	**1 (1.6)**
Phlebitis	1	1 (1.4)	1	1 (1.6)
Renal and urinary disorders	**1**	**1 (1.4)**	**0**	**0 (0)**
Urinary retention	1	1 (1.4)	0	0 (0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**0**	**0 (0)**	**1**	**1 (1.6)**

Death due to gastric cancer	0	0 (0)	1	1 (1.6)
Serious adverse events, total	**9**	**9 (12.7)**	**6**	**6 (10.0)**
Nervous system disorders				
Symptomatic intracranial hemorrhage	1	1 (1.4)	0	0 (0.0)
Neurological deterioration (NIHSS* ≥4) without intracranial hemorrhage	2	2 (2.8)	1	1 (1.7)
Asymptomatic hemorrhagic infarction	0	0 (0.0)	1	1 (1.7)
Recurrent ischemic stroke	1	1 (1.4)	1	1 (1.7)
Transient ischemic attack	1	1 (1.4)	0	0 (0.0)
Cardiac disorders				
Death due to heart failure	1	1 (1.4)	1	1 (1.6)
General disorder and administration site conditions				
Sudden death due to unknown cause	1	1 (1.4)	0	0 (0.0)
Respiratory, thoracic and mediastinal disorders				
Exacerbation of chronic obstructive pulmonary disease	1	1 (1.4)	0	0 (0.0)
Pulmonary embolism	1	1 (1.4)	0	0 (0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)				
Death due to gastric cancer	0	0 (0.0)	1	1 (1.7)
Surgical and medical procedures				
Revascularization surgery for head or neck	0	0 (0)	1	1 (1.7)

Sorted by descending frequency for system organ class in all patients.

Data are presented as number (%)

*NIHSS: National Institutes of Health Stroke Scale

5. CONSORT 2010 checklist

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	3, 4
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	5
	2b	Specific objectives or hypotheses	5
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	5-10
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	7
Participants	4a	Eligibility criteria for participants	7, 8
	4b	Settings and locations where the data were collected	6
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	8-10
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	10, 11
	6b	Any changes to trial outcomes after the trial commenced, with reasons	N/A

Sample size	7a	How sample size was determined	11, 12
	7b	When applicable, explanation of any interim analyses and stopping guidelines	6
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	8, 9
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	8, 9
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	8, 9
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	8, 9
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	9
	11b	If relevant, description of the similarity of interventions	N/A
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	11, 12
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	11, 12
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	Figure 1
	13b	For each group, losses and exclusions after randomisation, together with reasons	Figure 1
Recruitment	14a	Dates defining the periods of recruitment and follow-up	12
	14b	Why the trial ended or was stopped	12
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 1
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	Tables 2

Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	Tables 2
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	Tables 2
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	Figure 3
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	Supplementary Table 3
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	20
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	20
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	16-20
Other information			
Registration	23	Registration number and name of trial registry	5
Protocol	24	Where the full trial protocol can be accessed, if available	Upon request
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	22

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

6. Reference

1. Barber PA, Hill MD, Eliasziw M, Demchuk AM, Pexman JH, Hudon ME, et al. Imaging of the brain in acute ischaemic stroke: Comparison of computed tomography and magnetic resonance diffusion-weighted imaging. *J Neurol Neurosurg Psychiatry*. 2005;76:1528-1533