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

Authors

Masatoshi Koga, MD1; Haruko Yamamoto, MD2; Manabu Inoue, MD1; Koko Asakura, PhD3; Junya Aoki, MD6; Yoshimitsu Hamasaki, PhD3; Takao Kanazawa, MD7; Rei Kondo, MD8; Masafumi Ohtaki, MD9; Ryo Itabashi, MD10; Kenji Kamiyama, MD11; Toru Iwama, MD12; Taizen Nakase, MD13; Yusuke Yakashiji, MD14; Shuichi Igarashi, MD15; Yoshinari Nagakane, MD16; Shunya Takizawa, MD17; Yasushi Okada, MD18; Ryosuke Doijiri, MD19; Akira Tsujino, MD20; Yasuhiro Ito21, MD; Hideyuki Ohnishi, MD22; Takeshi Inoue, MD23; Yasushi Takagi, MD24; Yasuhiro Hasegawa, MD25; Yoshiaki Shiokawa, MD26; Nobuyuki Sakai, MD27; Masato Osaki, MD28; Yoshikazu Uesaka, MD29; Shinichi Yoshimura, MD30; Takao Urabe, MD31; Toshihiro Ueda, MD32; Masafumi Ihara, MD3; Takanari Kitazono, MD33; Makoto Sasaki, MD34; Akira Oita, BS5; Sohei Yoshimura, MD1; Mayumi Fukuda-Doi, MD1,3; Kaori Miwa, MD1; Kazumi Kimura, MD6; Kazuo Minematsu, MD1,35; Kazunori Toyoda, MD1; for the THAWS trial investigators

Affiliations:

1. Department of Cerebrovascular Medicine and 2. Center for Advancing Clinical and Translational Sciences, 3. Departments of Data Science, 4. Neurology, and 5. Pharmacy, National Cerebral and Cardiovascular Center, Suita, Japan
6. Department of Neurology, Graduate School of Medicine, Nippon Medical School, Tokyo, Japan
7. Department of Stroke Medicine, Institute of Brain and Blood Vessels, Mihara Memorial Hospital, Isesaki, Japan
8. Department of Neurosurgery, Yamagata City Hospital Saiseikan, Yamagata, Japan
9. Department of Neurosurgery, Obihiro Kosei Hospital, Obihiro, Japan
10. Department of Stroke Neurology, Kohnan Hospital, Sendai, Japan
11. Department of Neurosurgery, Nakamura Memorial Hospital, Sapporo, Japan
12. Department of Neurosurgery, Gifu University School of Medicine, Gifu Japan
13. Department of Stroke Science, Research Institute for Brain and Blood Vessels, Akita, Japan
   (Department of Neurosurgery, Akita University, Akita, Japan)
14. Division of Neurology, Department of Internal Medicine, Saga University Faculty of Medicine, Saga, Japan
15. Department of Neurology, Niigata City General Hospital, Niigata, Japan
16. Department of Neurology, Kyoto Second Red Cross Hospital, Kyoto, Japan
17. Division of Neurology, Department of Internal Medicine, Tokai University School of Medicine, Isehara, Japan
18. Department of Cerebrovascular Medicine and Neurology, Cerebrovascular Center, National Hospital Organization Kyushu Medical Center, Fukuoka, Japan
19. Department of Neurology, Iwate Prefectural Central Hospital, Morioka, Japan
20. Department of Neurology and Strokology, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan
21. Department of Neurology, TOYOTA Memorial Hospital, Toyota, Japan
22. Department of Neurosurgery, Ohnishi Neurological Center, Akashi, Japan
23. Department of Stroke Medicine, Kawasaki Medical School General Medical Center, Okayama, Japan
24. Department of Neurosurgery, Tokushima University, Tokushima, Japan
25. Department of Neurology, St. Marianna University School of Medicine, Kawasaki, Japan
26. Department of Neurosurgery, Kyorin University School of Medicine, Mitaka, Japan
27. Department of Neurosurgery, Kobe City Medical Center General Hospital, Kobe, Japan
28. Department of Cerebrovascular Medicine, Stroke Center, Steel Memorial Yawata Hospital, Kitakyushu, Japan
29. Department of Neurology, Toranomon Hospital, Tokyo, Japan
30. Department of Neurosurgery, Hyogo College of Medicine, Nishinomiya, Japan
31. Department of Neurology, Juntendo University Urayasu Hospital, Urayasu, Japan
32. Department of Strokology, Stroke Center, St. Marianna University Toyoko Hospital, Kawasaki, Japan
33. Department of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan
34. Institute for Biomedical Sciences, Iwate Medical University, Yahaba, Japan
35. Headquarters of the Iseikai Medical Corporation, Osaka, Japan

Address correspondence to: Kazunori Toyoda, MD
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1. List of Investigators
THAWS trial investigators

Enrolling Centers (number of randomized patients)

- National Cerebral and Cardiovascular Center, Suita (29): Kazunori Toyoda (PI), Kazuo Minematsu, Masatoshi Koga, Masafumi Ihara, Manabu Inoue, Shoichiro Sato, Sohei Yoshimura, Mayumi Fukuda-Doi, Kaori Miwa, Hajime Ikenouchi, Takashi Okada, Toshihiro Ide, Kenta Seki
- Mihara Memorial Hospital, Isesaki (13); Ban Mihara (PI), Takao Kanzawa
- Yamagata City Hospital SAISEIKAN, Yamagata (11); Rei Kondo (PI), Wataru Mouri
- Obihiro-Kosei Hospital, Obihiro (9); Masafumi Ohtaki (PI)
- Nakamura Memorial Hospital, Sapporo (6); Kenji Kaminami (PI)
- Kohnan Hospital, Sendai (6); Ryo Itabashi (PI), Eisuke Furui
- Gifu University, Gifu (5); Toru Iwama (PI), Yukiko Enomoto, Yusuke Egashira
- Nippon Medical School, Tokyo (4); Kazumi Kimura (PI), Junya Aoki
- Saga University, Saga (4); Yusuke Yakushiji (PI)
- Research Institute for Brain and Blood Vessels, Akita (4); Taizen Nakase (PI) (currently working for Department of Neurosurgery, Akita University, Akita, Japan)
- Iwate Prefectural Central Hospital, Morioka (3); Ryosuke Dojiri (PI)
- Toyota Memorial Hospital, Toyota (3); Yasuhiro Ito (PI), Junichiro Suzuki
- Kyoto Second Red Cross Hospital, Kyoto (3); Yoshinari Nagakane (PI), Eijiro Tanaka
- National Hospital Organization Kyushu Medical Center, Fukuoka (3); Yasushi Okada (PI), Seiji Gotoh
- Niigata City General Hospital, Niigata (3); Shuichi Igarashi (PI)
- Ohnishi Neurological Center, Akashi (3); Hideyuki Ohnishi (PI), Hiroyuki Ohnishi
- Nagasaki University Hospital, Nagasaki (3); Akira Tsujino (PI), Yohei Tateishi
- Tokai University, Isehara (3); Shunya Takizawa (PI), Kazunari Homma
- Kyorin University, Mitaka (2); Yoshiaki Shiokawa (PI), Rieko Suzuki
- Kobe City Medical Center Central Hospital, Kobe (2); Nobuyuki Sakai (PI), Kenichi Todo, Nobuyuki Ohara
- St. Marianna University School of Medicine, Kawasaki (2); Yasuhiro Hasegawa (PI), Naoshi Sasaki
- Steel Memorial Yawata Hospital, Kitakyushu (2); Shuji Arakawa, Masato Osaki (PI)
- Kawasaki Medical School General Medical Center, Okayama (2); Tsuyoshi Inoue (PI)
- Tokushima University, Tokusima (2); Yasushi Takagi (PI), Yasuhisa Kanematsu
- Hyogo College of Medicine, Nishinomiya (1); Shinichi Yoshimura (PI)
- Toranomon Hospital, Tokyo (1); Yoshikazu Uesaka (PI)
• Juntendo University Urayasu Hospital, Urayasu (1); Takao Urabe (PI), Masao Watanabe
• St. Marianna University School of Medicine Toyoko Hospital (1); Toshihiro Ueda (PI)

Non-Enrolling Centers
• Osaka Neurosurgical Hospital, Takamatsu; Hideo Ohyama (PI)
• Fukuoka Red Cross Hospital, Fukuoka; Jiro Kitayama (PI), Yoshiki Sanbongi
• Kawasaki Medical School, Kurashiki; Yoshiki Yagita (PI)
• Saitama Medical University International Medical Center, Hidaka, Norio Tanahashi (PI)
• Jikei University School of Medicine, Tokyo; Yasuyuki Iguchi (PI)
• Juntendo University, Tokyo; Ryota Tanaka (PI)
• Toho University Omori Hospital; Ken Miura (PI)
• Showa University Fujigaoka Hospital, Yokohama; Tomoaki Terada (PI)
• Musashino Red Cross Hospital, Musashino; Masahiko Ichijyo (PI)
• Kitasato University, Sagamihara; Kazutoshi Nishiyama, Tsugio Akutsu (PI)
• Nagoya Second Red Cross Hospital, Nagoya; Keizo Yasui (PI)
• National Hospital Organization Kyoto Medical Center, Kyoto; Ryo Ohtani (PI)
• Sanin Rosai Hospital, Yonago; Masayoshi Kusumi (PI)
• Kokura Memorial Hospital, Kokura; Konosuke Furuta (PI), Shoji Matsumoto
• Saiseikai Kumamoto Hospital, Kumamoto; Toshiro Yonehara (PI)
• Kumamoto Red Cross Hospital, Kumamoto; Tadashi Terasaki (PI)
• Miyakonojo Medical Association Hospital, Mitazaki; Hajime Ohta (PI)
• National Hospital Organization Kagoshima Medical Center; Hideki Matsuoka (PI)

THAWS boards
Senior advisor: Kazuo Minematsu: National Cerebral and Cardiovascular Center, Suita, Japan

Steering committee: Kazunori Toyoda (chair): National Cerebral and Cardiovascular Center, Suita, Japan
Kazumi Kimura (vice-chair): Nippon Medical School, Tokyo, Japan
Haruko Yamamoto (data monitoring): National Cerebral and Cardiovascular Center, Suita, Japan
Masatoshi Koga (central office): National Cerebral and Cardiovascular Center, Suita, Japan

Protocol committee:
Junya Aoki: Nippon Medical School, Tokyo, Japan
Kazumi Kimura: Nippon Medical School, Tokyo, Japan
Masatoshi Koga: National Cerebral and Cardiovascular Center, Suita, Japan
Shoichiro Sato: National Cerebral and Cardiovascular Center, Suita, Japan
Toshimitsu Hamasaki: National Cerebral and Cardiovascular Center, Suita, Japan
Kazunori Toyoda: National Cerebral and Cardiovascular Center, Suita, Japan

**Statistician:** Toshimitsu Hamasaki, Koko Asakura: National Cerebral and Cardiovascular Center, Suita, Japan

**Data monitoring:** Haruko Yamamoto, Megimi Sakakibara: National Cerebral and Cardiovascular Center, Suita, Japan

**Independent Data and Safety Monitoring Board**
- Takanari Kitazono (chair); Kyushu University, Fukuoka, Japan
- Toshiho Ohtsuki; Kinki University, Osakasayama, Japan
- Wataru Shimizu; Nippon Medical School, Tokyo, Japan
- Takashi Sozu; Tokyo University of Science, Tokyo, Japan

**Central Imaging Reading Board**
- Makoto Sasaki (chair); Iwate Medical University, Morioka, Japan
- Teryuki Hirano; Kyorin University, Mitaka, Japan
- Kohsuke Kudo; Hokkaido University, Sapporo, Japan
- Naomi Morita; Iseikai Hospital, Osaka, Japan

**Central pharmacy:** Ken Kuwahara, Akira Oita: National Cerebral and Cardiovascular Center, Suita

**Coordinating investigators:** Manabu Inoue, Sohei Yoshimura, Shoichiro Sato, Takashi Okada, Hajime Ikenouchi, Kazunari Homma, Kenta Seki, Hiromi Ohara, Mihoko Uotani: National Cerebral and Cardiovascular Center, Suita, Japan

**Secretariats:** Kayo Murata, Shoko Kamiyoshi, Haruka Kanai, Azusa Tokunaga: National Cerebral and Cardiovascular Center, Suita, Japan
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.
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/mm³

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

| Treatment                              | 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) |
|-------------------------------------|------------------------|----------------------|
| **Any adverse events, total**       | 59                     | 38                   |
| **Events**                          | **Patient n (%)**      | **Events**           | **Patient n (%)** |
| Nervous system disorders            | 25                     | 24                   |
| **Events**                          | **Patient n (%)**      | **Events**           | **Patient n (%)** |
| Asymptomatic intracranial hemorrhage| 13                     | 10                   |
| Symptomatic intracranial hemorrhage | 1                      | 0                    |
| Neurological deterioration (NIHSS* ≥4) without intracranial hemorrhage | 6 | 2 | 6 (8.6) | 2 (3.3) |
| Recurrent ischemic stroke           | 3                      | 3                    |
| Transient ischemic attack           | 1                      | 0                    |
| Headache                            | 1                      | 1                    |
| Symptomatic epilepsy                | 0                      | 1                    |
| Respiratory, thoracic and mediastinal disorders | 7 | 2 | 7 (8.5) | 2 (3.3) |
| Exacerbation of chronic obstructive pulmonary disease | 2 | 0 | 2 (3.3) | 0 (0) |
| Pulmonary embolism                  | 1                      | 0                    |
| Aspiration pneumonia                | 4                      | 2                    |
| Skin and subcutaneous tissue disorders | 7 | 1 | 7 (9.9) | 1 (1.6) |
| Cervical eruption                   | 1                      | 0                    |
| Subcutaneous bleeding               | 6                      | 1                    |
| Infections and infestations         | 4                      | 3                    |
| Urinary tract infection             | 2                      | 1                    |
| Herpes zoster                       | 1                      | 0                    |
| Pneumonia                           | 1                      | 1                    |
| Cystitis                            | 0                      | 1                    |
| Gastrointestinal disorders          | 4                      | 2                    |
| Lower gastrointestinal bleeding     | 0                      | 1                    |
| Diarrhea                            | 1                      | 0                    |
| Oral bleeding                        | 2                      | 0                    |
| Vomit                               | 1                      | 1                    |
| Condition                                                                 | Count | Rate (%) | Count | Rate (%) |
|--------------------------------------------------------------------------|-------|----------|-------|----------|
| **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 (0.0) | 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, 1b  | Identification as a randomised trial in the title                            | 1                   |
|                     |         | Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts) | 3, 4                |
| Introduction        | 2a, 2b  | Scientific background and explanation of rationale                           | 5                   |
|                     |         | Specific objectives or hypotheses                                             | 5                   |
| Methods             | 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, 6b  | Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed | 10, 11              |
|                     |         | 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 | 8a | Method used to generate the random allocation sequence | 8, 9 |
| generation | 8b | Type of randomisation; details of any restriction (such as blocking and block size) | 8, 9 |
| Allocation | 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 | 13a | For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome | Figure 1 |
| (a diagram is strongly recommended) | 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

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**

For binary outcomes, presentation of both absolute and relative effect sizes is recommended

**Tables 2**

## Ancillary analyses

Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory

**Figure 3**

## Harms

All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)

**Supplementary Table 3**

## Discussion

### Limitations

Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses

20

### Generalisability

Generalisability (external validity, applicability) of the trial findings

20

### Interpretation

Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence

16-20

## Other information

### Registration

Registration number and name of trial registry

5

### Protocol

Where the full trial protocol can be accessed, if available

Upon request

### Funding

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](http://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