Supplemental Online Content

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eAppendix
eMethods
eFigures
eTables

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

Supplementary 3

Table of Contents

eAppendix 1: Recruitment by Site in ARAIS Trial

Inclusion site	Number of patients recruited
Department of Neurology, Liaoning Health Industry Group Fukuang General Hospital	239
Department of Neurology, The Affiliated Nanshi Hospital of Henan University	89
Department of Neurology, Tieling County Central Hospital	75
Department of Neurology, Tonghua Vascular Disease Hospital	41
Department of Neurology, Lvshunkou Traditional Chinese Medicine Hospital	36
Department of Neurology, Haicheng Traditional Chinese Medicine Hospital	34
Department of Neurology, Anyang People‘s Hospital	34
Department of Neurology, Liaoning Health Industry Group Fuxinkuang General Hospital	34
Department of Neurology, Anshan Changda Hospital	30
Department of Neurology, General Hospital of Northern Theatre Command	25
Department of Neurology, Tianjin Beichen Traditional Chinese Hospital	18
Department of Neurology, Panjin Central Hospital	17
Department of Neurology, Nanyang Central Hospital	17
Department of Neurology, Fuqing Hospital	16
Department of Neurology, The Second Affiliated Hospital of Harbin Medical University	14
Department of Neurology, Huludao Second People‘s Hospital	10
Department of Neurology, Wafangdian Third Hospital	9
Department of Neurology, Liaocheng Brain Hospital	9
Department of Neurology, Guangxi Zhuang Autonomous Region People‘s Hospital	7
Department of Neurology, The First Affiliated Hospital of Anhui Medical University	7
Department of Neurology, The First Affiliated Hospital of Jinzhou Medical University	5
Department of Neurology, Nanning First People‘s Hospital	5
Department of Neurology, Tai'an County Enliang Hospital	5
Department of Neurology, Dawa District People‘s Hospital	5
Department of Neurology, Liaoyang County Stroke Hospital	5
Department of Neurology, Beipiao Central Hospital	4
Department of Neurology, Yunfu People‘s Hospital	3
Department of Neurology, Dandong Central Hospital	3
Department of Neurology, General Hospital of Tianjin Medical University	3
Department of Neurology, The Affiliated Hospital of Jiangnan University	2
Department of Neurology, Jiangmen People‘s Hospital	2
Department of Neurology, Beijing You'anmen Hospital	2
Department of Neurology, Department of Neurology, Xiuyan County Central People‘s Hospital	2
Department of Neurology, Tianjin First Central Hospital	2
Department of Neurology, Beijing Tiantan Hospital	2

Department of Neurology, Liaoyang Petrochemical General Hospital	2
Department of Neurology, Yongzhou Central Hospital	2
Department of Neurology, The Affiliated Central Hospital of Shenyang Medical College	1
Department of Neurology, Traditional Chinese Medicine Hospital of Jiangsu Provincial	1
Department of Neurology, Dalian Third People's Hospital	1
Department of Neurology, Ansteel Group General Hospital	1
Department of Neurology, Liaoyang Second People's Hospital	1
Department of Neurology, Tieli People's Hospital	1
Department of Neurology, The First Affiliated Hospital of Qiqihar Medical College	1
Department of Neurology, Datong Coal Mine Group General Hospital	1
Department of Neurology, Nei Monggo Autonomous Region People Hospital	1
Department of Neurology, Hainan Provincial People's Hospital	1
Department of Neurology, The Second Affiliated Hospital of Soochow University	1
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eMethods

Structured interview for telephone assessment: 90-day modified Rankin Scale scores were assessed by telephone interview using a modified version of the Structured Interview.[1] Item scoring was revised to be based upon functional limitations arising from both the pre-stroke period and the post-stroke period. While inter-rater reliability using this scoring method has not been validated, the approach aligns with that now generally taken in stroke trials.

Central adjudication of outcomes: to enhance accuracy and masking of the efficacy outcome and adverse events assessment, the 90-day modified Rankin Score was independently performed by two different assessors: a local assessor who performed the mRS interview in person or telephone, and another off-site central assessor who performed the mRS interview on telephone or through viewing a videotape of the mRS interview. If there was disagreement between local and the central assessors, a consensus was achieved by discussion. The local evaluator retained control of the final mRS score, following any discussion.

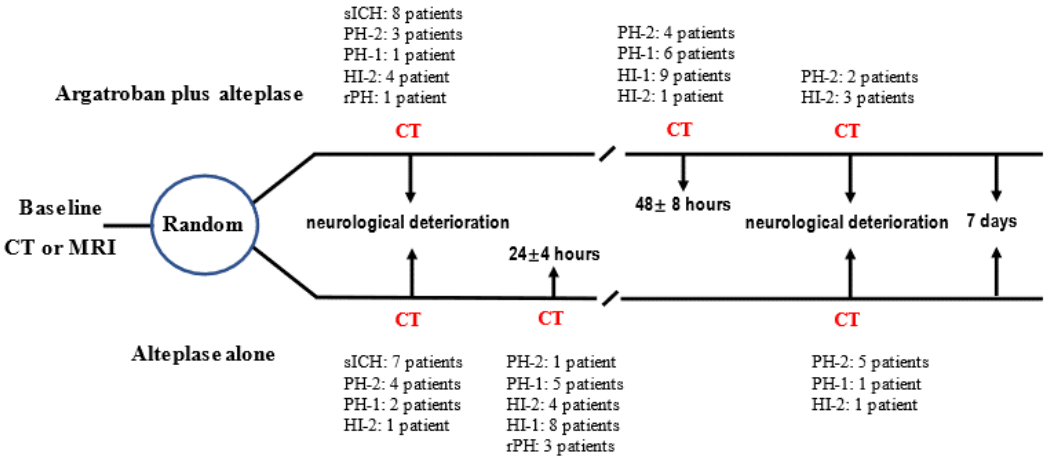
Definition of other vascular events: other vascular events include pulmonary embolism, peripheral vessel incident, and cardiovascular incident.

Clinicaltrials.gov registration

The ARAIS trial is a prospective, random, open-label, blinded endpoint and multi-center study, which is registered at clinicaltrials.gov on 12th Nov 2018 (NCT03740958). The trial was initially set-up on 21st Dec 2018 and recruited their first patient on 8th Jan 2019.

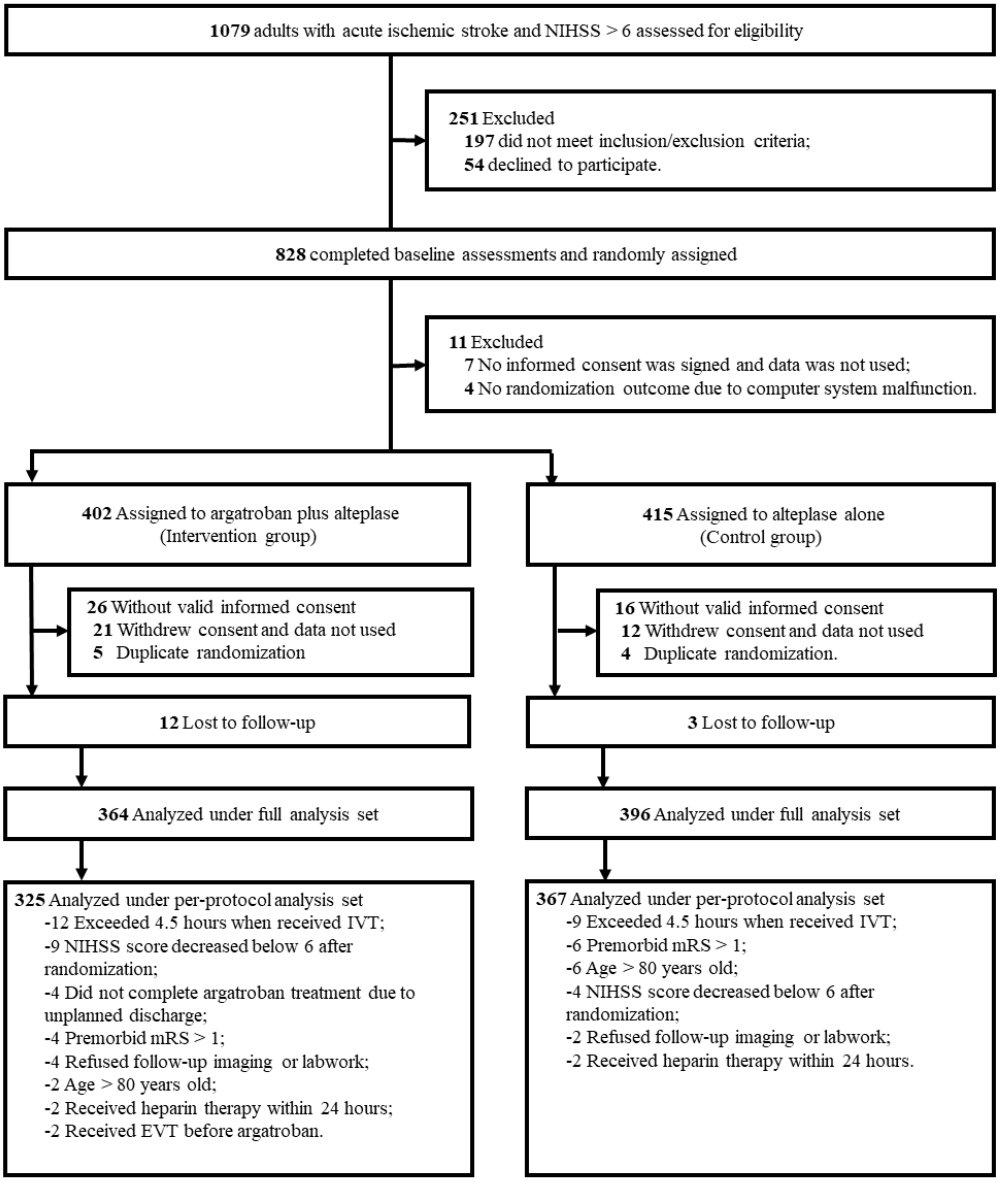
1. Wilson JT, Hareendran A, Grant M, et al. Improving the assessment of outcomes in stroke: use of a structured interview to assign grades on the modified Rankin Scale. *Stroke*. 2002; **33:**2243-6.

eFigure 1 Follow-up CT Scans in the Trial by Treatment Arm



Abbreviation: CT = computed tomography; MRI = magnetic resonance imaging; sICH = symptomatic intracranial hemorrhage; PH-2 = Parenchymal hematoma type 2; PH-1 = Parenchymal hematoma type 1; HI-2 = hemorrhagic infarction type 2; HI-1 = hemorrhagic infarction type 1; rPH = remote parenchymal hemorrhage

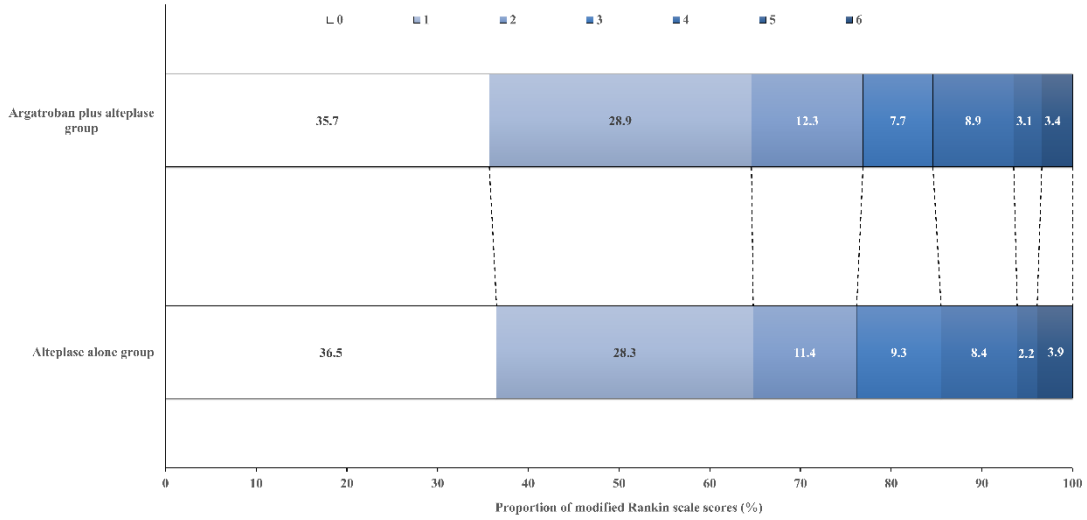
eFigure 2 Trial Profile



This figure shows the overall patient flow in the trial, including the full analysis set population and the per-protocol population.

Abbreviations: IVT = intravenous thrombolysis; EVT = endovascular treatment; mRS = modified Rankin Scale; NIHSS = National Institutes of Health Stroke Scale.

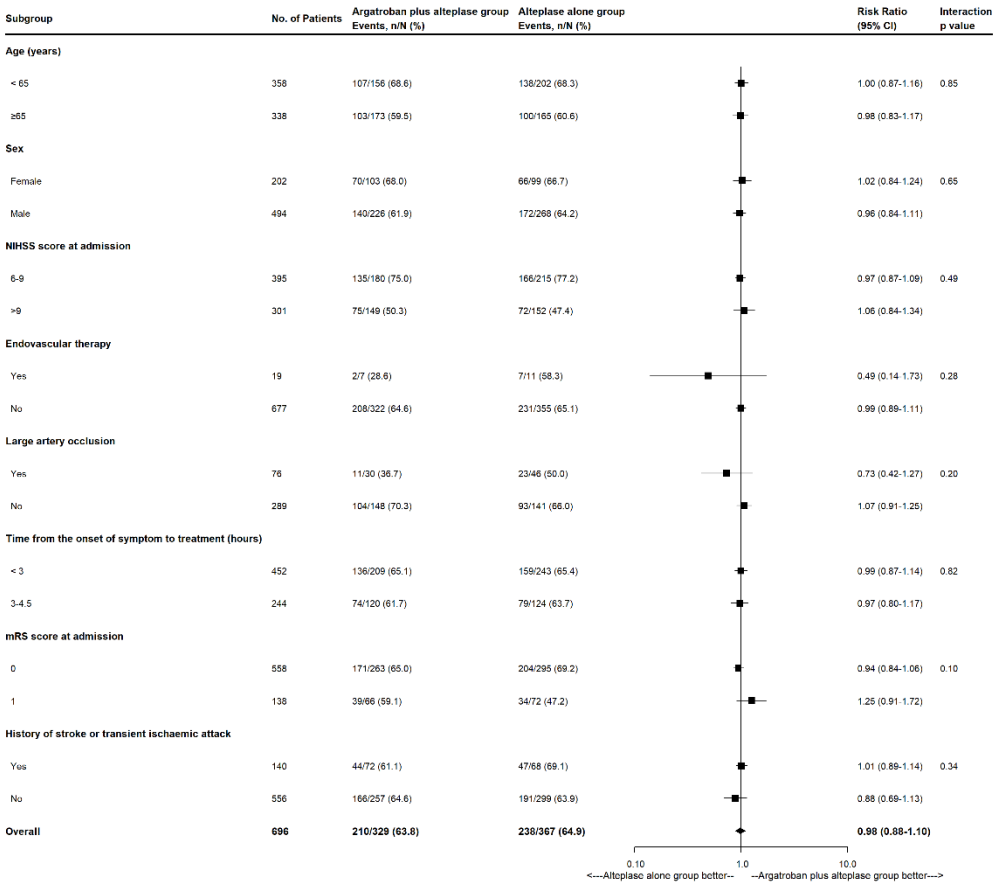
eFigure 3 Distribution of Modified Rankin Scale Scores at 90 Days in the Per-Protocol Analysis



The raw distribution of scores is shown. Scores ranged from 0 to 6. 0 = no symptoms, 1 = symptoms without clinically significant disability, 2 = slight disability, 3 = moderate disability, 4 = moderately severe disability, 5 = severe disability, and 6 = death.

Treatment with Argatroban + alteplase was not associated with an excellent functional outcome (a score of 0 or 1 on the modified Rankin Scale) at 90 days, with an adjusted risk difference of -0.4% (95% CI, -7.0%-6.3%; *P* value = .92). The difference between the Argatroban + alteplase group and alteplase group in the overall distribution of scores was not significantly significant in the ordinal logistic analysis. The odds ratio was 0.98 (95% CI 0.74-1.28), and the *P* value was .86; the adjusted odds ratio was 1.03 (0.56-1.88), and the adjusted *P* value was .93.

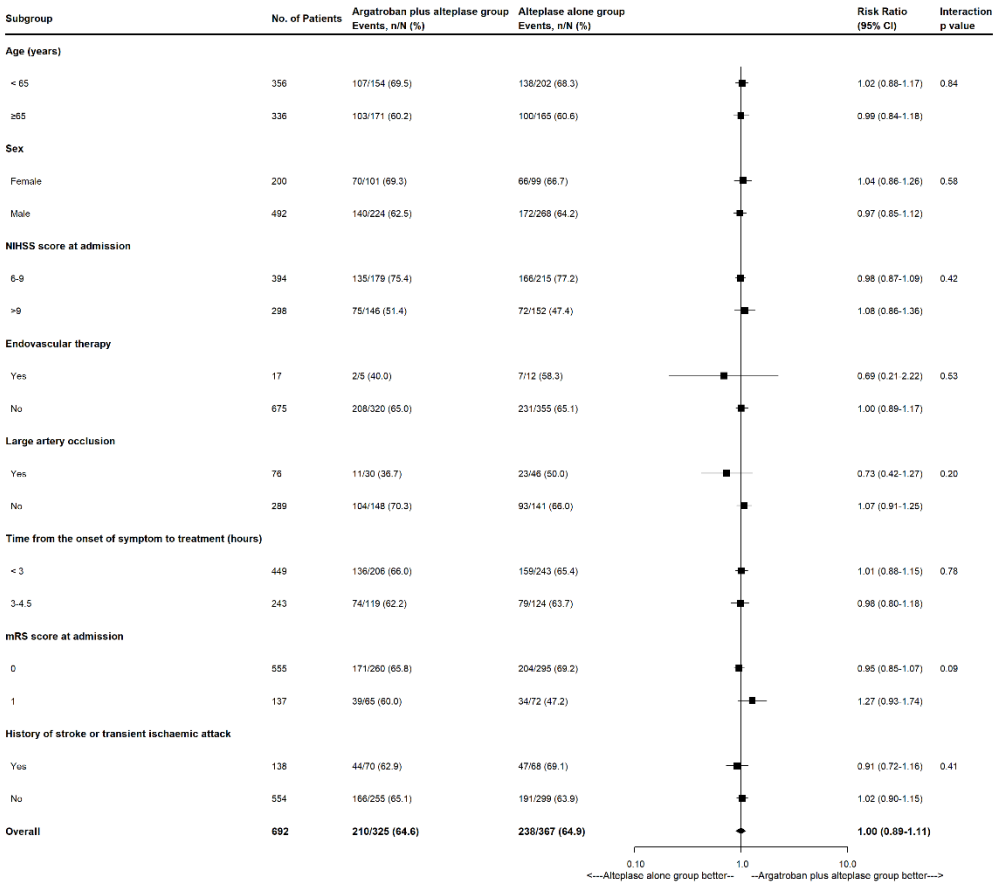
eFigure 4 Primary Outcome by Prespecified Subgroups in the Full Analysis Set



The primary outcome was a modified Rankin Scale score of 0–1 at 90 days. For subcategories, black squares represent point estimates (with the area of the square proportional to the number of events) and horizontal lines represent the 95% CI. NIHSS scores range from 0 to 42, with higher scores indicating more severe neurological deficits. For the NIHSS score, subgroups were dichotomised according to the median value.

Abbreviations: mRS = modified Rankin Scale; NIHSS = National Institutes of Health Stroke Scale.

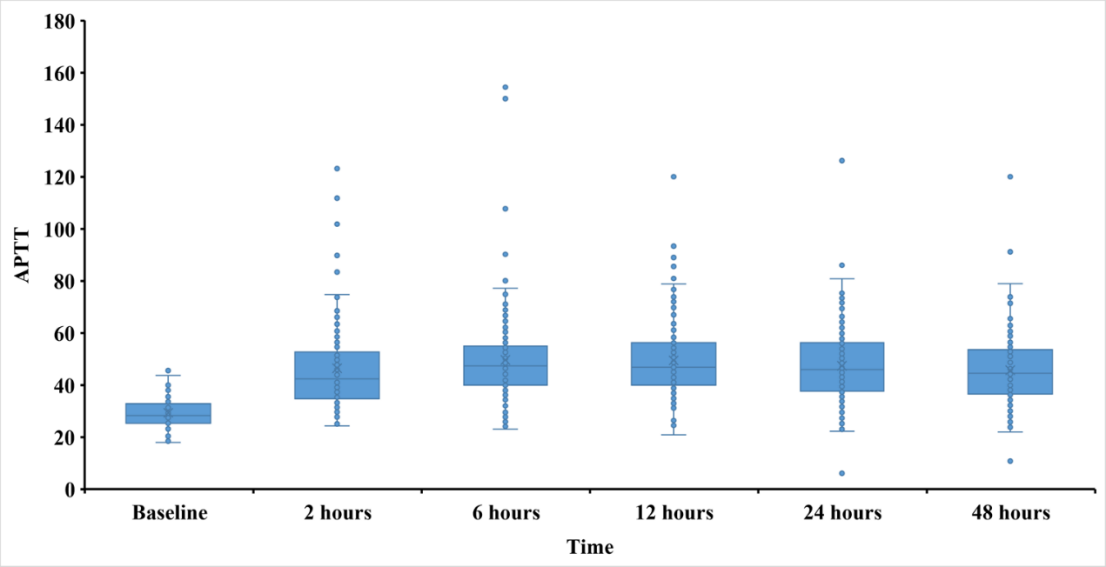
eFigure 5 Primary Outcome by Prespecified Subgroups in the Per-Protocol Analysis



The primary outcome was a modified Rankin Scale score of 0–1 at 90 days. For subcategories, black squares represent point estimates (with the area of the square proportional to the number of events) and horizontal lines represent the 95% CI. NIHSS scores range from 0 to 42, with higher scores indicating more severe neurological deficits. For the NIHSS score, subgroups were dichotomised according to the median value.

Abbreviations: mRS = modified Rankin Scale; NIHSS = National Institutes of Health Stroke Scale.

eFigure 6 The Activated Partial Thromboplastin Time (APTT) data: baseline, 2, 6, 12, 24 and 48 hours after randomization.



eTable 1. Baseline Characteristics of Population in the Per-Protocol Analysis

	Argatroban + alteplase group (n=325)	Alteplase alone group (n=367)
Age, median (IQR), y	66 (58-71)	63 (55-70)
Sex		
Male, No. (%)	224 (68.9%)	268 (73.0%)
Female, No. (%)	101 (31.1%)	99 (27.0%)
Current smoker, No. (%)	120 (36.9%)	137 (37.3%)
Current drinker, No. (%) [a]	65/315 (20.6%)	63/360 (17.5%)
Comorbidities, No. (%) [b]		
Hypertension	190 (58.5%)	208 (56.7%)
Diabetes	87 (26.8%)	73 (19.9%)
Previous ischemic or hemorrhagic stroke [c]	68 (20.9%)	64 (17.4%)
Atrial fibrillation	17/320 (5.3%)	21/362 (5.8%)
Hyperlipidemia	3 (0.9%)	3 (0.8%)
Previous transient ischaemic attack	3 (0.9%)	4 (1.1%)
Body-mass index, median (IQR), kg/m^2	23.7 (20.7-24.1)	23.9 (21.0-24.0)
Blood pressure at randomization		
Systolic blood pressure, median (IQR), mm Hg	157 (140-170)	150 (136-167)
Systolic blood pressure > 140 mm Hg, No. (%)	227 (69.8%)	238 (64.9%)
Diastolic blood pressure, median (IQR), mm Hg	90 (81-100)	88 (80-97)
Diastolic blood pressure > 90 mm Hg, No. (%)	138 (42.5%)	136 (37.1%)
Blood glucose, median (IQR), mg/dL	120.8 (102.6-171.4)	121.7 (102.2-161.6)
Blood glucose > 126 mg/dL, No. (%)	120/263 (45.6%)	135/301 (44.9%)
NIHSS score at randomization, median (IQR) [d]	9 (7-12)	8 (6-12)
GRAPHS score at randomization, median (IQR) [e]	75 (71-79)	74 (70-78)
ASPECTS score at randomization, median (IQR) [f]	9 (8-10)	9 (8-10)
Estimated premorbid function (mRS), No. (%) [g]		
No symptoms (score 0)	260 (80.0%)	295 (80.4%)
Symptoms without any disability (score 1)	65 (20.0%)	72 (19.6%)
Presumed stroke cause, No. (%) §		
Undetermined cause	213/325 (65.6%)	255/366 (69.6%)
Large-artery atherosclerosis	64/325 (19.7%)	69/366 (18.9%)
Small-artery occlusion	30/325 (9.2%)	26/366 (7.1%)
Cardioembolic	17/325 (5.2%)	15/366 (4.1%)
Other [h]	1/325 (0.3%)	1/366 (0.3%)
Location of responsible vessel, No. (%) [i]		
Anterior circulation stroke	141/178 (79.2%)	142/187 (75.9%)
Posterior circulation stroke	32/178 (18.0%)	41/187 (21.9%)
Anterior and posterior circulation stroke	5/178 (2.8%)	4/187 (2.2%)
Location of responsible artery (≥ 50% stenosis), No./total (%) [i]		
Internal carotid artery	17/71 (23.9%)	14/78 (17.9%)
Middle cerebral artery	41/71 (57.7%)	46/78 (59.0%)
Anterior cerebral artery	1/71 (1.4%)	4/78 (5.1%)

Posterior cerebral artery	4/71 (5.6%)	4/78 (5.1%)
Basilar artery	4/71 (5.6%)	6/78 (7.7%)
Vertebral artery	4/71 (5.6%)	4/78 (5.1%)
Time from the onset of symptom to intravenous thrombolysis, median (IQR), mins	155 (118-202)	154 (112-194)
Time to hospital discharge, median (IQR), days	10 (7-12)	9 (7-13)
Endovascular treatment, No. (%)	5/325 (1.5%)	12/367 (3.3%)

Abbreviations: IQR = interquartile range. NIHSS = National Institutes of Health Stroke Scale. mRS = modified Rankin Scale.

a Current drinkers consume alcohol at least once a week within one year before the onset of the disease and consume alcohol continuously for more than one year.

b The comorbidities were based on patients or family report.

c Prior ischemic stroke referred only to the patients with premorbid mRS ≤ 1.

d Scores on National Institutes of Health Scale (NIHSS) range from 0 to 42, with higher scores indicating more severe neurologic deficit; A mean NIHSS of 8-9 means moderate neurological deficit.

e GRASPS score ranged from 0 to 101, with higher scores indicating higher risk of symptomatic intracranial hemorrhage after intravenous alteplase.

f ASPECTS score ranged from 0 to 10, with higher scores indicating worse neurologic prognosis.

g Scores on the modified Rankin Scale (mRS) of functional disability range from 0 (no symptoms) to 6 (death).

h The presumed stroke cause was classified according to the "Trial of ORG 10172 in Acute Stroke Treatment (TOAST)" using clinical findings, brain imaging, and laboratory tests. Other causes included nonatherosclerotic vasculopathies, hypercoagulable states, and hematologic disorder.

i Definite conclusions based on vessel examination. The diagnosis was based on the clinician's interpretation of the clinical features and examination results at the time of discharge from the hospital.

eTable 2. Sensitive Analysis for Missing Primary Outcome in Dropout Subjects.

Methods	**Without primary outcome imputation**				**With primary outcome imputation**				
	Argatroban + alteplase group (329)	Alteplase alone group (367)	RR (95% CI)	P value	Argatroban + Alteplase group (402)	Alteplase alone group (415)	RR (95% CI)	P value	Imputation methods
mRS score 0-1 within 90 days, No. (%)	210/329 (63.8%)	238/367 (64.9%)	0.98 (0.88-1.10)	0.78	260/402 (64.7%)	267/415 (64.3%)	1.01 (0.84-1.21)	.92	Last observation carried forward
					210/402 (52.2%)	238/415 (57.3%)	0.89 (0.77-1.04)	.14	Worst-case scenario
					278/402 (70.4%)	282/415 (68.9%)	1.05 (0.85-1.29)	.65	Best-case scenario
					268/402 (66.7%)	275/415 (66.3%)	1.01 (0.91-1.11)	.92	Multiple imputation

Abbreviations: CI = confidence interval; mRS = modified Rankin Scale; RR = risk ratio.

eTable 3. Primary and Secondary Outcomes in the Per-Protocol Analysis.

	Group, No. (%)		Unadjusted			Adjusted [a]		
	Argatroban + alteplase group (n=325)	**Alteplase group (n=367)**	**Risk difference (95% CI)**	**Risk ratio (95% CI)**	***P* value**	**Risk difference (95% CI)**	**Risk ratio (95% CI)**	***P* value**
Primary outcome								
mRS score of 0 to 1 at 90 d [b, c]	210 (64.6)	238 (64.9)	-0.3 (-7.4 to 6.9)	1.00 (0.89 to 1.11)	.95	-0.4 (-7.0 to 6.3)	0.98 (0.89 to 1.08)	.65
Secondary outcomes								
mRS score of 0 to 2 within 90 d [c]	250 (76.9)	280 (76.3)	0.6 (-5.7 to 6.9)	1.01 (0.93 to 1.10)	.93	1.6 (-4.4 to 7.7)	1.02 (0.79 to 1.31)	.87
Early neurologic improvement within 48 h [c, d]	234 (72.0)	261 (71.1)	0.9 (-5.8 to 7.6)	1.01 (0.92 to 1.11)	.80	0.1 (-6.7 to 6.8)	1.00 (0.91 to 1.09)	.93
Early neurologic deterioration within 48 h [c, e]	10 (3.1)	18 (4.9)	-1.8 (-4.7 to 1.1)	0.63 (0.29 to 1.34)	.23	-1.9 (-4.9 to 1.0)	0.61 (0.29 to 1.31)	.21
Change in NIHSS score at day 14 from baseline, median (IQR) [f]	-0.37 (-0.70 to -0.14)	-0.37 (-0.85 to -0.12)	-0.01 (-0.07 to 0.05)		.75	-0.01 (-0.07 to 0.05)		.84
Stroke or other vascular events within 90 d [g]	1 (0.3)	1 (0.3)	1.13 (0.07-18.08)		.93	0.78 (0.04-15.18)		.87
mRS score distribution at 90 d [c, h]			0.98 (0.74-1.28)		.86	1.03 (0.56-1.88)		.93
0	116 (35.7)	134 (36.5)						
1	94 (28.9)	104 (28.3)						
2	40 (12.3)	42 (11.4)						
3	25 (7.7)	34 (9.3)						
4	29 (8.9)	31 (8.4)						
5	10 (3.1)	8 (2.2)						

6	11 (3.4)	14 (3.8)				

Abbreviations: CI = confidence interval; GMR = geometric mean ratio; mRS = modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; IQR = interquartile range.

[a] Adjusted for pre-specified prognostic variables (age, sex, NIHSS score at randomization, time from the onset of symptoms to thrombolysis, premorbid function [mRS score 0 or 1], and history of stroke or transient ischemic attack).

[b] mRS scores range from 0 to 6:0, no symptoms, 1 = symptoms without clinically significant disability, 2 = slight disability, 3 = moderate disability, 4 = moderately severe disability, 5 = severe disability; and 6 = death.

[c] Calculated using a generalized linear model.

[d] Early neurologic improvement was defined as a decrease between baseline and 48 score of ≥ 2 on the NIHSS score.

[e] Early neurologic deterioration was defined as an increase between baseline and 48 h of ≥ 4 on the NIHSS score, but not the result of cerebral hemorrhage.

[f] NIHSS scores range 0–42, with higher scores indicating greater stroke severity. The log (NIHSS+1) was analyzed using a generalized linear model. The treatment effect was presented as geometric mean ratio.

[g] Calculated using Cox regression model and presented by hazard ratio.

[h] This was used to describe a shift in measures of functioning according to the full range of scores on the mRS at 90 days and presented by odds ratio.

eTable 4. Baseline Characteristics in Patients with Missing Primary Outcome

	Argatroban + alteplase group (n=73)	Alteplase alone group (n=48)
Age, median (IQR), y	66 (58-74)	68 (60-76)
Sex		
Male, No. (%)	45/68 (66.2%)	31/44 (70.5%)
Female, No. (%)	23/68 (33.8%)	13/44 (29.5%)
Current smoker, No. (%)	21/67 (31.3%)	6/44 (13.6%)
Current drinker, No. (%) [a]	8/67 (11.9%)	6/44 (13.6%)
Comorbidities, No. (%) [b]		
Hypertension	22/68 (32.4%)	24/44 (54.5%)
Diabetes	11/68 (16.2%)	14/43 (32.6%)
Previous ischemic or hemorrhagic stroke [c]	12/68 (17.6%)	10/44 (22.7%)
Atrial fibrillation	2/41 (4.9%)	1/26 (3.8%)
Hyperlipidemia	0/68 (0.0%)	1/44 (2.3%)
Previous transient ischaemic attack	0/68 (0.0%)	1/44 (2.3%)
Body-mass index, median (IQR), kg/m^2	22.0 (20.1-22.8)	22.8 (20.8-24.0)
Blood pressure at randomization		
Systolic blood pressure, median (IQR), mm Hg	140 (135-156)	143 (135-160)
Systolic blood pressure > 140 mm Hg, No. (%)	28/68 (41.2%)	22/44 (50.0%)
Diastolic blood pressure, median (IQR), mm Hg	85 (80-90)	88 (80-90)
Diastolic blood pressure > 90 mm Hg, No. (%)	12/68 (17.6%)	9/44 (20.5%)
Blood glucose, median (IQR), mg/dL	118.3 (109.8-138.6)	123.7 (109.8-183.6)
Blood glucose > 126 mg/dL, No. (%)	23/55 (41.8%)	15/34 (44.1%)
NIHSS score at randomization, median (IQR) [d]	9 (6-12)	10 (6-14)
GRAPHS score at randomization, median (IQR) [e]	75 (68-79)	76 (71-83)
ASPECTS score at randomization, median (IQR) [f]	9 (7-10)	8 (7-10)
Estimated premorbid function (mRS), No. (%) [g]		
No symptoms (score 0)	55/68 (80.9%)	31/44 (70.5%)
Symptoms without any disability (score 1)	9/68 (13.2%)	7/44 (15.9%)
Mild disability (score 2)	4/68 (5.9%)	6/44 (13.6%)
Presumed stroke cause, No. (%)		
Undetermined cause	28/44 (63.6%)	21/35 (60.0%)
Large-artery atherosclerosis	7/44 (15.9%)	7/35 (20.0%)
Small-artery occlusion	4/44 (9.2%)	7/35 (20.0%)
Cardioembolic	3/44 (6.8%)	0/35 (0.0%)
Other [h]	2/44 (4.5%)	0/35 (0.0%)
Location of responsible vessel, No. (%) [i]		
Anterior circulation stroke	26/27 (96.3%)	20/22 (90.9%)
Posterior circulation stroke	1/27 (3.7%)	2/22 (9.1%)
Anterior and posterior circulation stroke	0/27 (0.0%)	0/22 (0.0%)
Location of responsible artery (≥ 50% stenosis), No./total (%) [i]		
Internal carotid artery	3/11 (27.3%)	2/10 (20.0%)
Middle cerebral artery	6/11 (54.5%)	6/10 (60.0%)

Anterior cerebral artery	1/11 (9.1%)	1/10 (10.0%)
Posterior cerebral artery	0/11 (0.0%)	1/10 (10.0%)
Basilar artery	1/11 (9.1%)	0/10 (0.0%)
Vertebral artery	0/11 (0.0%)	0/10 (0.0%)
Time from the onset of symptom to intravenous thrombolysis, median (IQR), mins	185 (126-238)	169 (121-225)
Time to hospital discharge, median (IQR), days	10 (7-12)	9 (7-13)
Endovascular treatment	2/68 (2.9%)	0/44 (0.0%)

Abbreviations: IQR = interquartile range. NIHSS = National Institutes of Health Stroke Scale. mRS = modified Rankin Scale.

[a] Current drinkers consume alcohol at least once a week within one year before the onset of the disease and consume alcohol continuously for more than one year.

[b] The comorbidities were based on patients or family report.

[c] Prior ischemic stroke referred only to the patients with premorbid mRS ≤ 1.

[d] Scores on National Institutes of Health Scale (NIHSS) range from 0 to 42, with higher scores indicating more severe neurologic deficit; A mean NIHSS of 8-9 means moderate neurological deficit.

[e] GRASPS score ranged from 0 to 101, with higher scores indicating higher risk of symptomatic intracranial hemorrhage after intravenous alteplase.

[f] ASPECTS score ranged from 0 to 10, with higher scores indicating worse neurologic prognosis.

[g] Scores on the modified Rankin Scale (mRS) of functional disability range from 0 (no symptoms) to 6 (death).

[h] The presumed stroke cause was classified according to the "Trial of ORG 10172 in Acute Stroke Treatment (TOAST)" using clinical findings, brain imaging, and laboratory tests. Other causes included nonatherosclerotic vasculopathies, hypercoagulable states, and hematologic disorder.

[i] Definite conclusions based on vessel examination. The diagnosis was based on the clinician's interpretation of the clinical features and examination results at the time of discharge from the hospital.

eTable 5. APTT and Argatroban Infusion in the Argatroban plus alteplase group.

Measurements, median (IQR)	Full analysis set	Per-protocol analysis set
Minutes from alteplase bolus to Argatroban bolus	46 (30-55)	47 (30-55)
Minutes of alteplase-Argatroban overlap	18 (8-31)	19 (8-31)
Hours to (or above) target APTT	5 (2-17)	5 (2-16)
Hours of Argatroban infusion	48 (48-48)	48 (48-48)
Hours at (or above) target APTT	14 (9-26)	14 (9-24)
No. Argatroban infusion adjustments	2 (1-3)	2 (1-3)
First APTT after Argatroban bolus (seconds)	39.0 (31.3-51.7)	38.7 (31.2-51.8)
Patients with target APTT at 2 hours	83 (22.8%)	75 (23.1%)

APTT indicates activated partial thromboplastin time; IQR, interquartile range.