Supplemental Online Content

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

eAppendix 1: Recruitment by Site in ARAMIS Trial

NO.	Inclusion site	Number of patients recruited
1	Department of Neurology, Liaoning Health Industry Group Fukuang General Hospital	196
2	Department of Neurology, Tieling Central Hospital	68
3	Department of Neurology, General Hospital of Northern Theatre Command	55
4	Department of Neurology, Dandong Central Hospital	43
5	Department of Neurology, Tieling County Central Hospital	38
6	Department of Neurology, Fushun Second Hospital	36
7	Department of Neurology, The Fuqing Affiliated Hospital of Fujian Medical University	35
8	Department of Neurology, Tianjin Beichen Traditional Chinese Hospital	35
9	Department of Neurology, Panjin Central Hospital	31
10	Department of Neurology, Chaoyang Second Hospital	22
11	Department of Neurology, Donggang Central Hospital	18
12	Department of Neurology, The Second Affiliated Hospital of Dalian Medical University	17

13	Department of Neurology, Anyang People‘s Hospital	16
14	Department of Neurology, Suizhong Central Hospital	16
15	Department of Neurology, Chinese People’s Liberation Army 967 Hospital	14
16	Department of Neurology, Huludao Central Hospital	14
17	Department of Neurology, Zhoukou Central Hospital	12
18	Department of Neurology, Haicheng Traditional Chinese Medicine Hospital	10
19	Department of Neurology, The Dalinghe Affiliated Hospital of Jinzhou Medical University	10
20	Department of Neurology, Lvshunkou Traditional Chinese Medicine Hospital	9
21	Department of Neurology, Dawa District People‘s Hospital	9
22	Department of Neurology, Dandong First Hospital	8
23	Department of Neurology, The Zhongshan Affiliated Hospital of Dalian University	8
24	Department of Neurology, Army Hospital of Northern Theatre Command	7
25	Department of Neurology, Liaoyang Second People’s Hospital	5
26	Department of Neurology, Dalian Jiuzhou Shiji Hospital	4

27	Department of Neurology, Liaoning Health Industry Group Bengang General Hospital	4
28	Department of Neurology, Tonghua Cerebrovascular Hospital	3
29	Department of Neurology, The First Affiliated Hospital of Jinzhou Medical University	2
30	Department of Neurology, Shenyang 739 Hospital	2
31	Department of Neurology, Dengta Central Hospital	2
32	Department of Neurology, Dalian Liaoyu Hospital	2
33	Department of Neurology, Harbin First Hospital	2
34	Department of Neurology, Liaocheng Second People’s Hospital	2
35	Department of Neurology, The Third Affiliated Hospital of Jinzhou Medical University	2
36	Department of Neurology, Beipiao Central Hospital	1
37	Department of Neurology, Liaoyang County Stroke Hospital	1
38	Department of Neurology, The Affiliated Central Hospital of Shenyang Medical College	1

eAppendix 2: Committee Members

Steering Committee

1. Xun-Ming Ji (Chairman, Department of Neurosurgery, Xuanwu Hospital, Capital Medical University, Beijing, China)
2. Hui-Sheng Chen (Chief Investigator, Department of Neurology, General Hospital of Northern Theatre Command, Shenyang, China)
3. Yong-Zhong Lin (Local Principal Investigator, Department of Neurology, The Second Affiliated Hospital of Dalian Medical University, Dalian, China)
4. Hong Zhang (Local Principal Investigator, Department of Neurology, Liaoning Health Industry Group Fukuang General Hospital, Fushun, China)
5. Zhong-He Zhou (Senior Trials Manager, Department of Neurology, General Hospital of Northern Theatre Command, Shenyang, China)
6. Xin-Hong Wang (Trials Manager, Department of Neurology, General Hospital of Northern Theatre Command, Shenyang, China)
7. Duo-Lao Wang (Medical Statistician, Department of Clinical Sciences, Liverpool School of Tropical Medicine, Liverpool, UK)

Data Monitoring Committee

1. Yi-Long Wang (Chairman, Tiantan Hospital, Capital Medical University, Beijing, China)
2. Bo Song (Department of Neurology, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China)
3. Yan-Jiang Wang (Department of Neurology, Daping Hospital, Chongqing, China)
4. Yue-Song Pan (Medical Statistics, Tiantan Hospital, Capital Medical University,

Beijing, China)

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4. Long Liu (General Hospital of Northern Theatre Command, Shenyang, China)
5. Xiao-Zeng Wang (General Hospital of Northern Theatre Command, Shenyang, China)
6. Zhen-Dong Zheng (General Hospital of Northern Theatre Command, Shenyang, China)
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8. Dong Jiang (Liaoning Hehao Law Office, Shenyang, China)
9. Bin Lin (Shenyang Sport College, Shenyang, China)

Executive Committee

1. Hui-Sheng Chen (Department of Neurology, General Hospital of Northern Theatre Command, Shenyang, China)
2. Zhong-He Zhou (Senior Trials Manager, Department of Neurology, General Hospital of Northern Theatre Command, Shenyang, China)

3. Xin-Hong Wang (Trials Manager, Department of Neurology, General Hospital of Northern Theatre Command, Shenyang, China)
4. Hong Zhang (Department of Neurology, Liaoning Health Industry Group Fukuang General Hospital, Fushun, China)
5. Wei-Zhong Wang (Department of Neurology, Dandong Central Hospital, Dandong, China)
6. Er-Qiang Wang (Department of Neurology, The Fuqing Affiliated Hospital of Fujian Medical University, Fuqing, China)
7. Rui-Xian Wang (Department of Neurology, Tianjin Beichen Traditional Chinese Hospital, Tianjin, China)
8. Yu-Ling Dong (Department of Neurology, Chaoyang Second Hospital, Chaoyang, China)
9. Yong-Zhong Lin (Department of Neurology, The Second Affiliated Hospital of Dalian Medical University, Dalian, China)
10. Qing-Cheng Yang (Department of Neurology, Anyang People‘s Hospital, Anyang, China)
11. Jin Wang (Department of Neurology, Huludao Central Hospital, Huludao, China)
12. Lei Xia (Department of Neurology, Zhoukou Central Hospital, Zhoukou, China)
13. Guang-Bin Ma (Department of Neurology, Haicheng Traditional Chinese Medicine Hospital, Haicheng, China)
14. Jiang Lu (Department of Neurology, The Dalinghe Affiliated Hospital of Jinzhou Medical University, Jinzhou, China)
15. Zhuo Li (Department of Neurology, Panjin Central Hospital, Panjin, China)

Outcome Committee

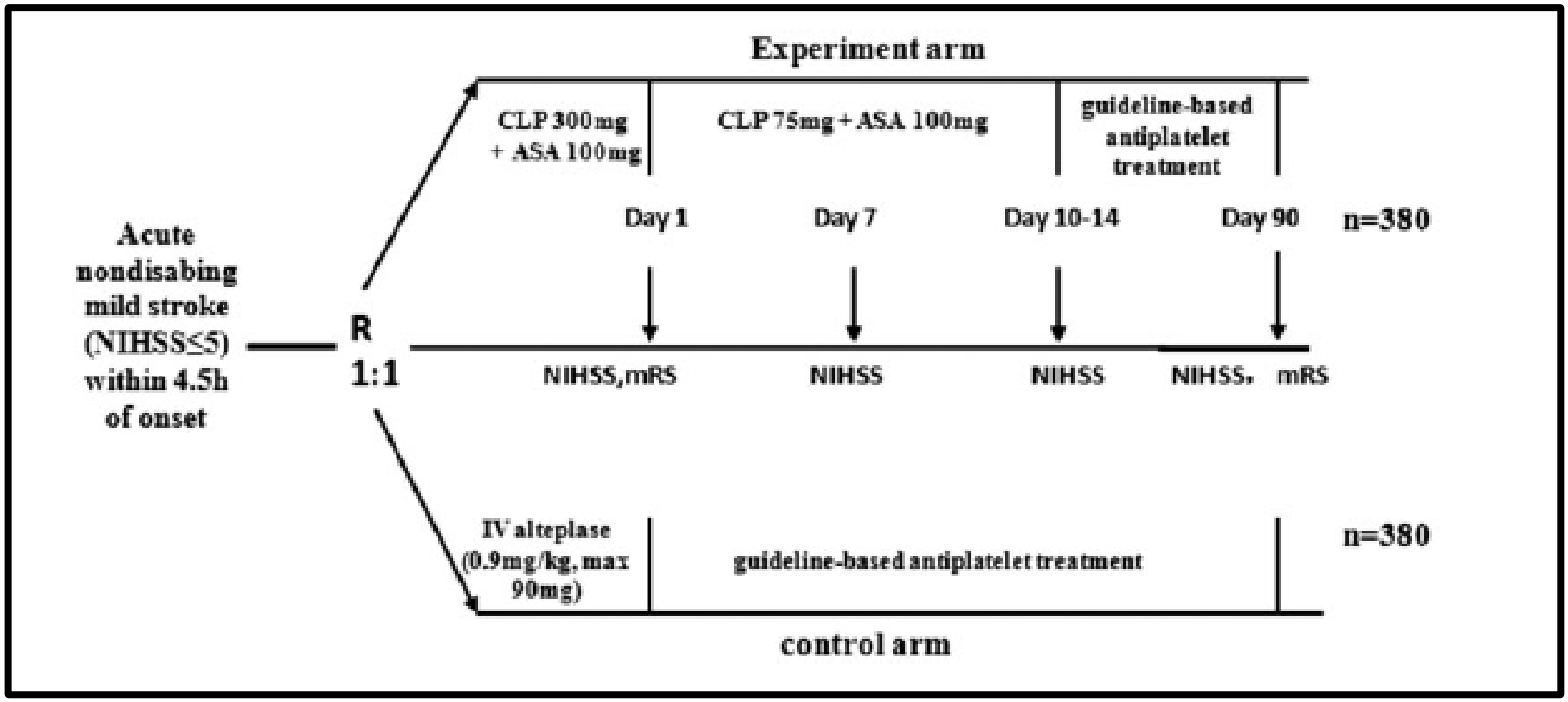
1. Yi Yang (Chairman, Department of Neurology, The First Affiliated Hospital of Jilin University, Changchun, China)
2. Xiu-Li Shang (Department of Neurology, The first affiliated Hospital of China Medical University, Shenyang, China)
3. Ding-Bo Tao (Department of Neurology, The First Affiliated Hospital of Dalian Medical University, Dalian, China)

Biostatisticians

1. Xiao-Wen Hou (Department of Health Statistics, Shenyang Medical College, Shenyang, China)
2. Yu Cui (Department of Neurology, General Hospital of Northern Theatre Command, Shenyang, China)

eMethods

1 Overview of Study Procedures:



Abbreviation: CLP = clopidogrel; ASA = aspirin; IV = intravenous; mRS = modified Rankin Scale; NIHSS = National Institutes of Health Stroke Scale.

2 Inclusion and Exclusion Criteria

Inclusion criteria:

1. Patient age≥ 18 years;
2. Study treatment can be started within 4.5 hours;
3. NIHSS score≤ 5, with≤ 1 on the NIHSS score in single item scores such as vision, language, neglect and single limb weakness and no score in consciousness item;
4. Ischemic stroke confirmed by head CT or MRI and clinical features;
5. Signed informed consent.

Exclusion criteria:

1. Serious neurological deficits before onset (mRS≥ 2);
2. Obvious head injuries or stroke within 3 months;
3. Subarachnoid hemorrhage;
4. History of intracranial hemorrhage;
5. Intracranial tumour, arteriovenous malformation or aneurysm;
6. Intracranial or spinal cord surgery within 3 months;
7. Arterial puncture at a noncompressible site within the previous seven days;
8. Gastrointestinal or urinary tract hemorrhage within the previous 21 days;
9. Major surgery within 1 month;
10. Systolic pressure ≥ 180 mmHg or diastolic pressure ≥ 110 mmHg;
11. Blood glucose <50 mg/dl (2.7 mmol/L);
12. Heparin therapy or oral anticoagulation therapy within 48 hours;
13. Platelet count of <100,000/mm^3 (This does not need to be verified prior to randomization if clinical abnormality is not suspected);

14. Oral warfarin is being taken and INR>1.6;
15. Abnormal APTT;
16. Pregnancy;
17. Neurological deficit after epileptic seizures;
18. Myocardial infarction within 3 months;
19. Cerebral infarction with definite anticoagulation indications, such as cerebral infarction caused by cardiogenic embolism;
20. Oral administration is not allowed due to dysphagia;
21. Allergy to study drugs;
22. Other serious illness that would confound the clinical outcome at 90 days;
23. Participating in other clinical trials within 3 months;
24. Patients not suitable for this clinical study considered by researcher.

3 Outcome assessment

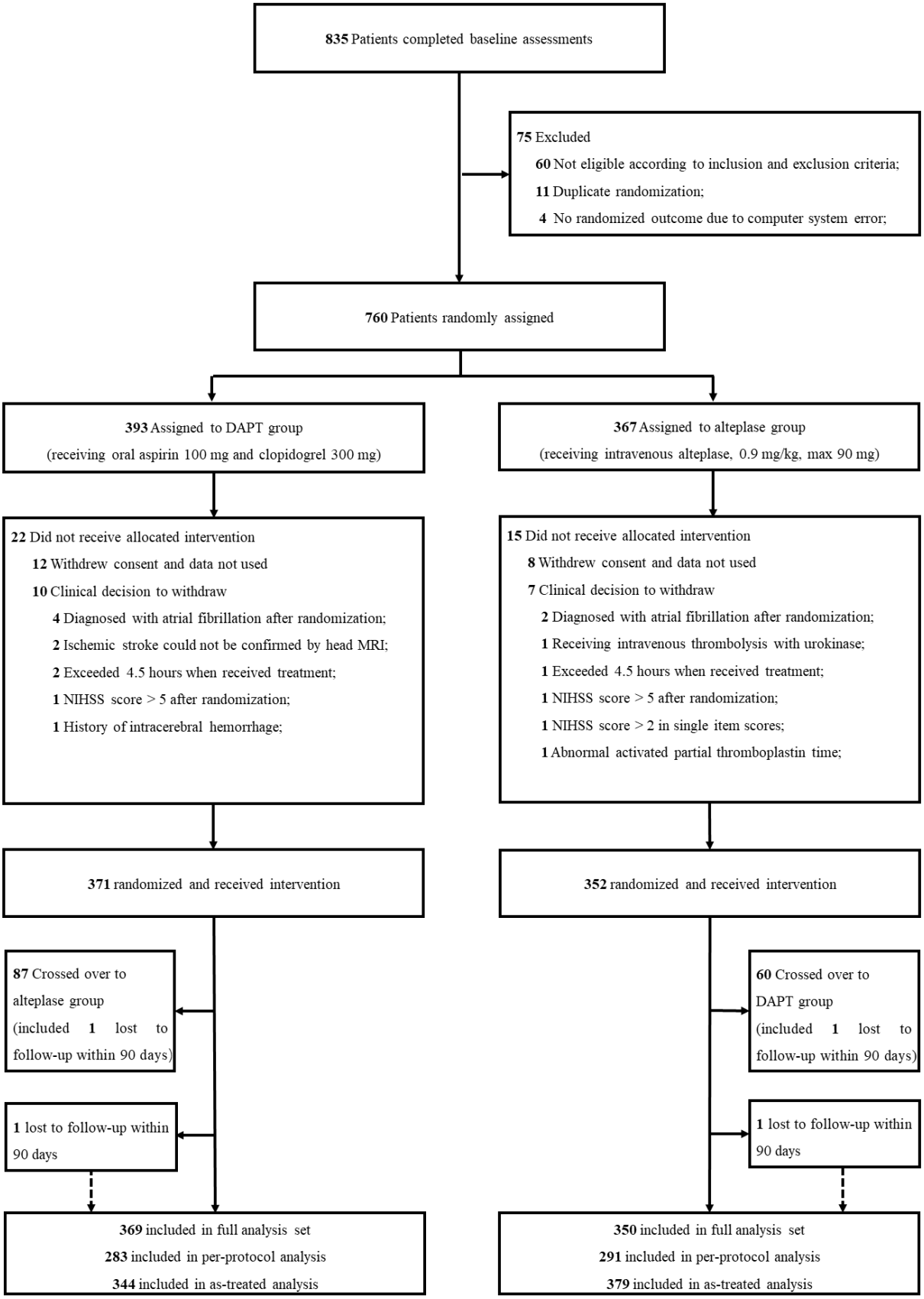
- **Structure interview for telephone assessment:** a structured telephone interview and interview algorithm was used as reported in a previous study.[1]
- **The training of modified Rankin Scale (mRS) assessment:** the blinded mRS assessors were trained uniformly on how to evaluate the mRS based on face to face or a structured telephone interview algorithm. After the training, 20 examples based on the neurological function description of patients were used to assess this score and assessors were certified when the intraclass correlation coefficient was ≥ 0.95.
- **Central adjudication of outcomes:** to enhance accuracy and masking of the efficacy outcome and safety outcome 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 the 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.

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.

4 Clinicaltrials.gov registration

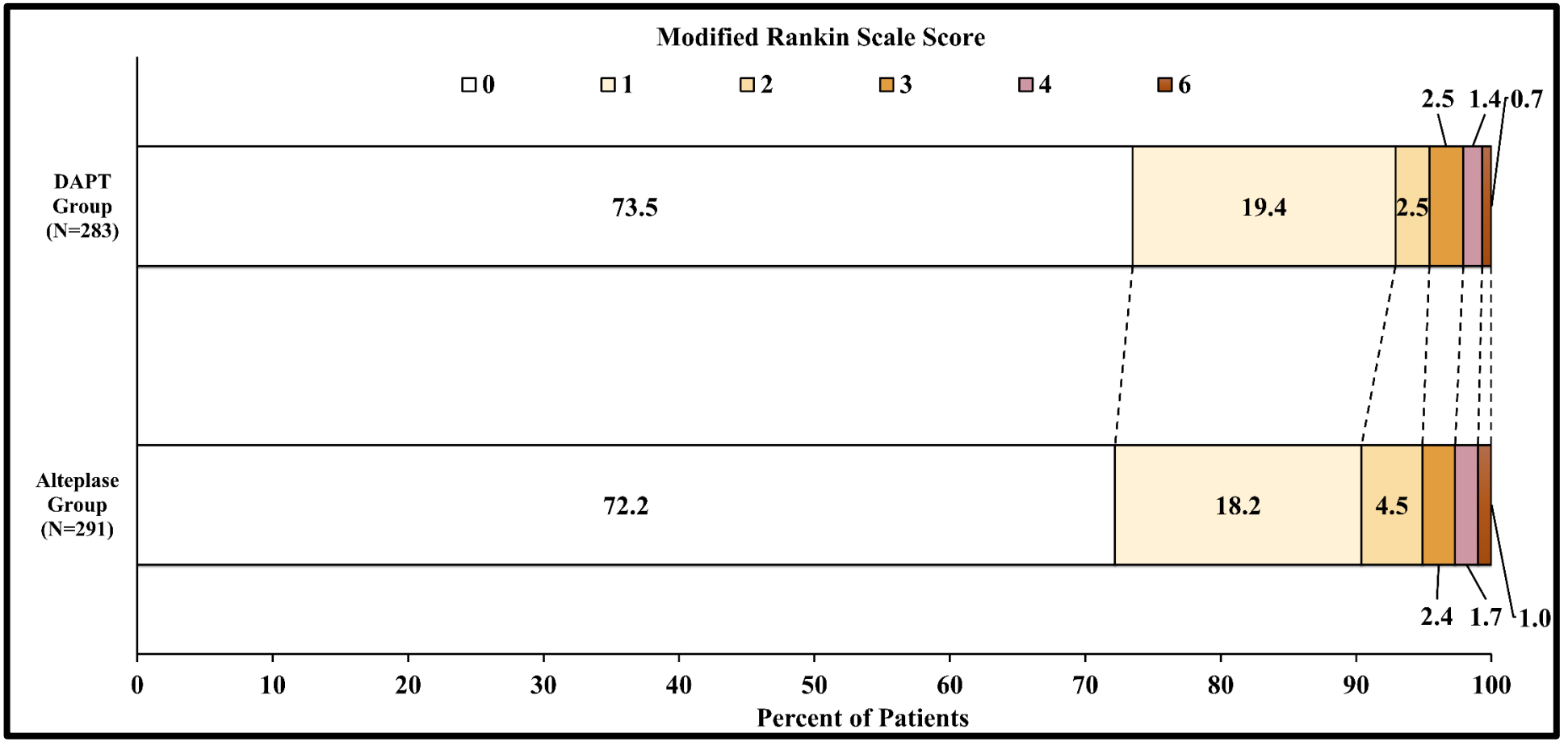
The ARAMIS trial is a multicenter, randomized, open-label, blinded-endpoint and noninferiority study, which was registered at clinicaltrials.gov on September 7th 2018 (NCT03661411). The trial was initially set-up on October 1, 2018 and recruited their first patient on October 26, 2018. The last patient was recruited on April 18, 2022 and finished on July 11, 2022. The recruitment status was changed as completed on April 18, 2022 and the study status was changed as completed on August 3rd, 2022.

eFigure 1 Trial Profile



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

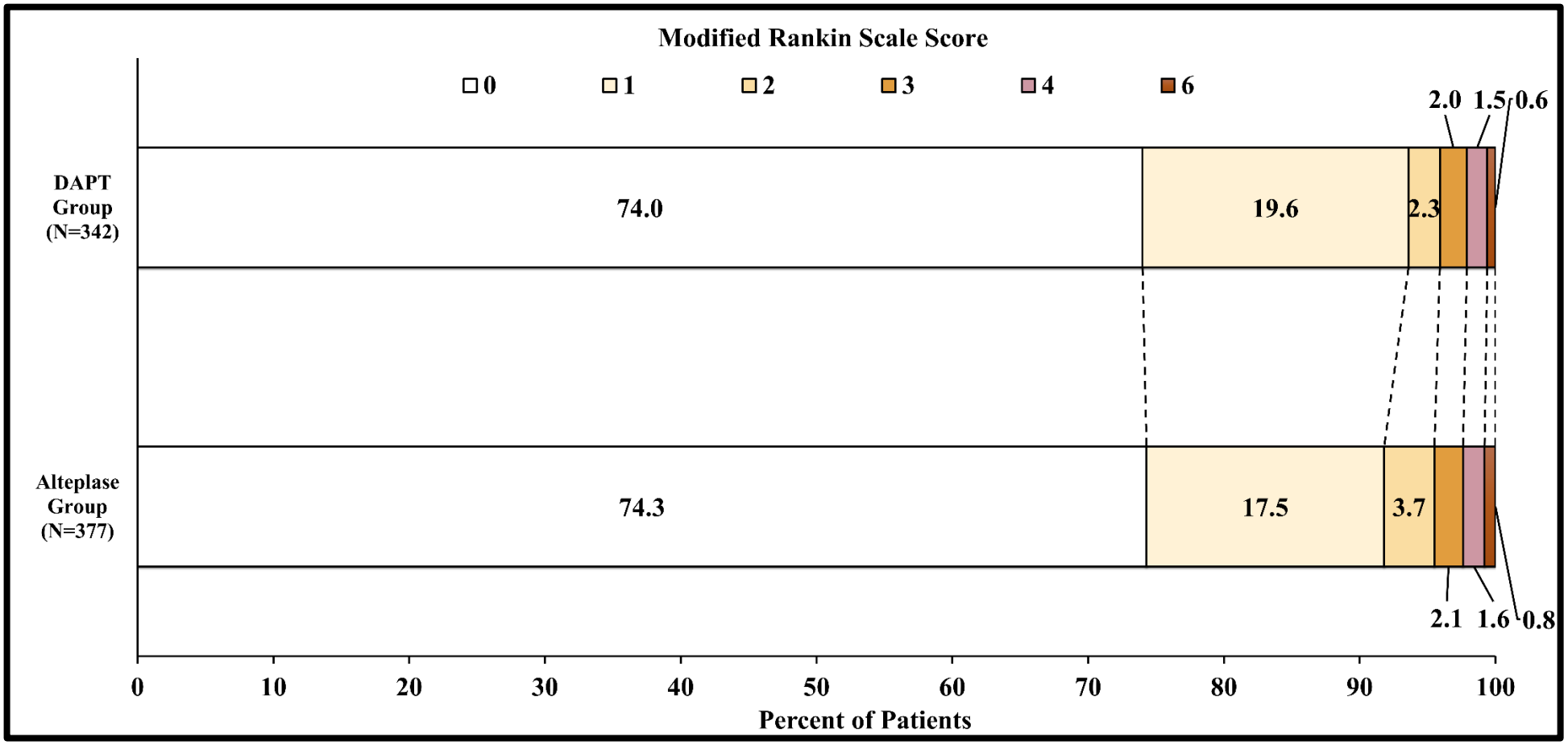
eFigure 2 Distribution of Modified Rankin Scale Scores at 90 Days in the Per-Protocol Analysis



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.

DAPT = dual antiplatelet treatment.

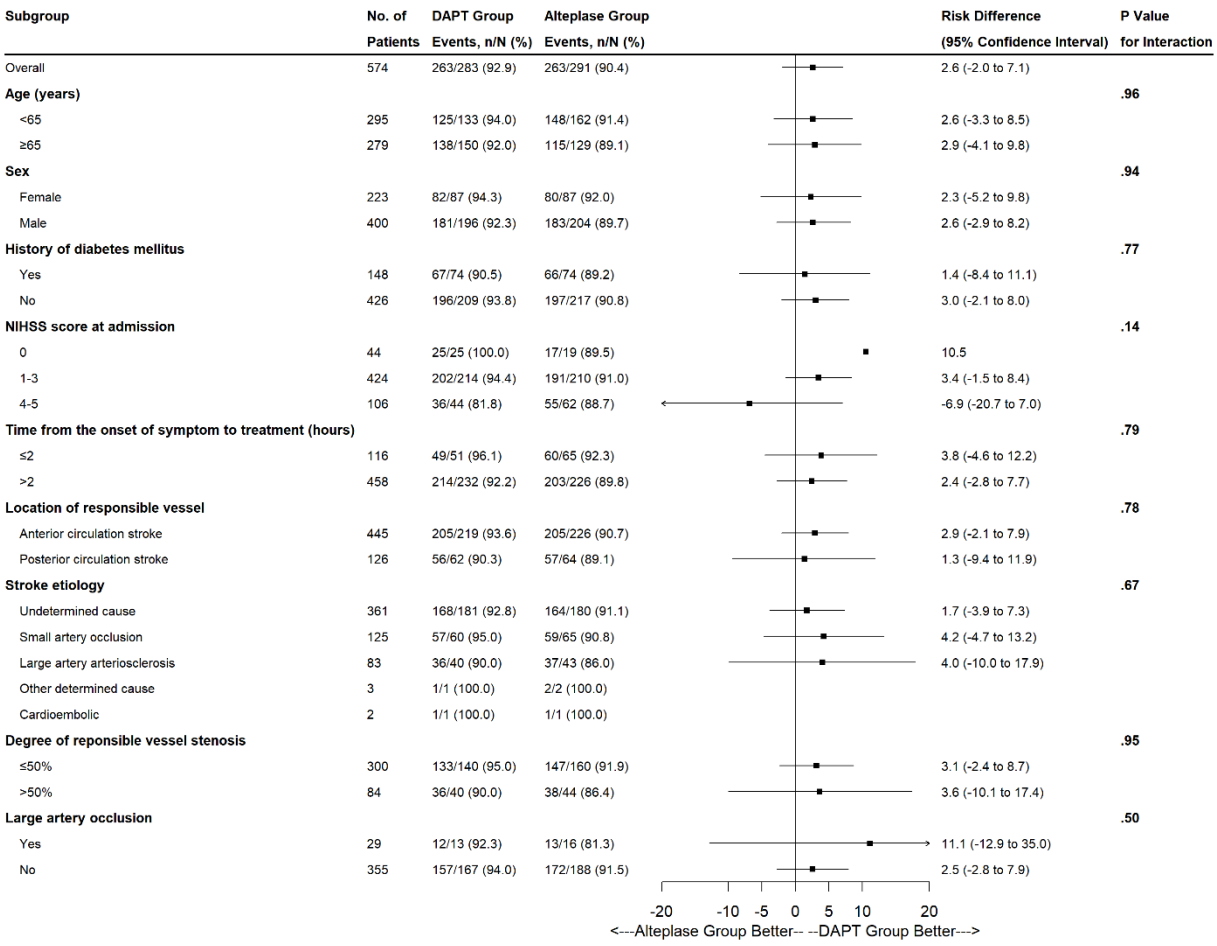
eFigure 3 Distribution of Modified Rankin Scale Scores at 90 Days in the As-Treated Analysis



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.

DAPT = dual antiplatelet treatment.

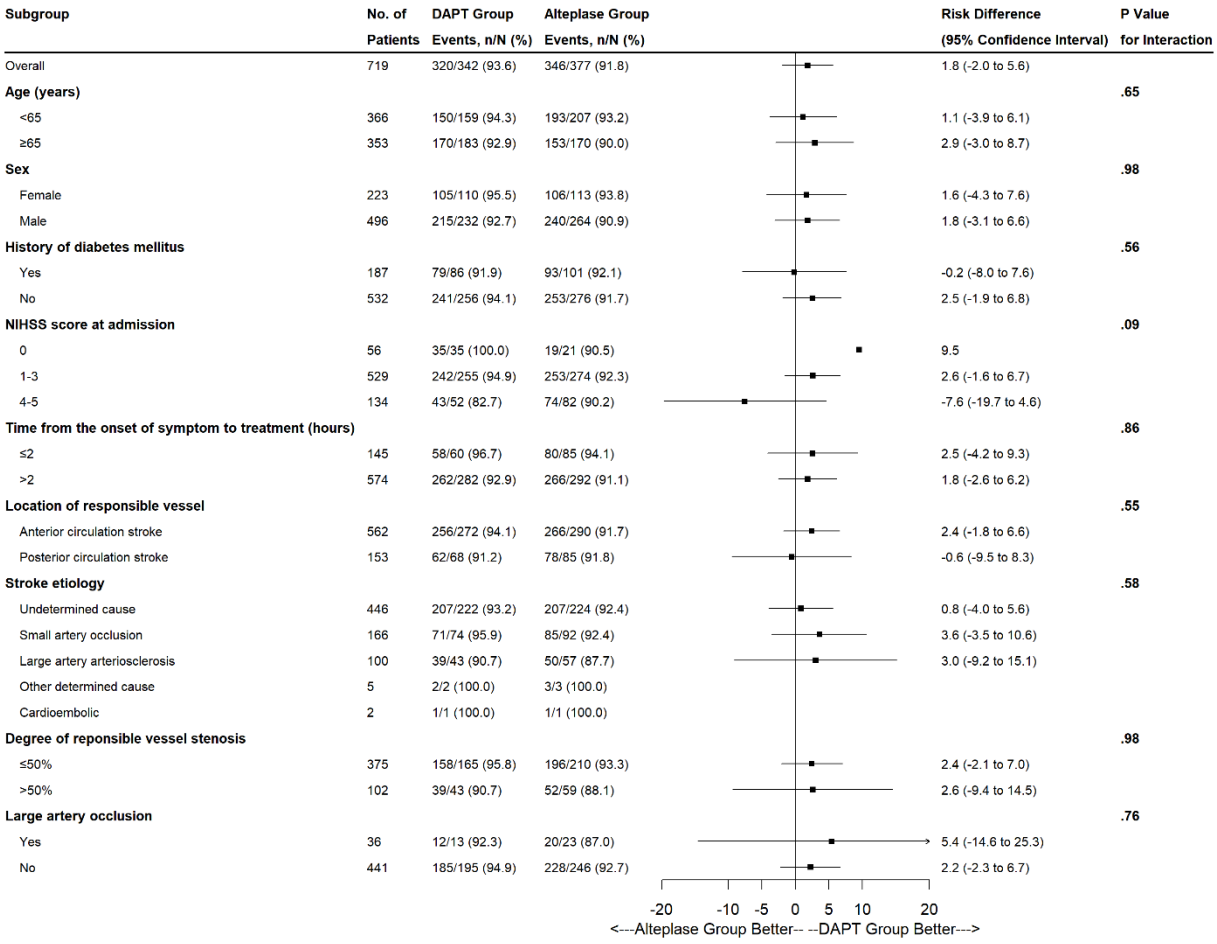
eFigure 4 Primary Outcome by Prespecified Subgroups in the Per-Protocol Analysis



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.

mRS = modified Rankin Scale; NIHSS = National Institutes of Health Stroke Scale. DAPT = dual antiplatelet treatment.

eFigure 5 Primary Outcome by Prespecified Subgroups in the As-Treated 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.

mRS = modified Rankin Scale; NIHSS = National Institutes of Health Stroke Scale. DAPT = dual antiplatelet treatment.

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

Baseline characteristics	**DAPT Group (N=283)**	**Alteplase Group (N=291)**
Age, years	65 (58-72)	63 (56-70)
Sex		
Male	196 (69.3%)	204 (70.1%)
Female	87 (30.7%)	87 (29.9%)
Current smoker [a]	85 (30.0%)	105 (36.1%)
Current drinker	45 (15.9%)	52 (17.9%)
Medical history		
History of hypertension	163 (57.6%)	136 (46.7%)
History of diabetes mellitus	74 (26.1%)	74 (25.4%)
Prior ischemic hemorrhagic stroke [b]	67 (23.7%)	60 (20.6%)
Prior transient ischemic attack	4 (1.4%)	2 (0.7%)
Median time from onset of symptom to assigned treatment, min	187 (135-235)	171 (125-218)
Median time from onset to hospital discharge, day	8 (6-11)	8 (6-10)
Median INR at randomisation	1.00 (0.94-1.05) [n =275]	0.99 (0.94-1.04) [n =290]
Median systolic blood pressure at randomisation, mm Hg	148 (135-161)	152 (139-163)
Median diastolic blood pressure at randomisation, mm Hg	87 (81-95)	88 (80-95)
Median blood glucose level at randomisation, mmol/litre	6.2 (5.4-7.9) [n = 244]	6.4 (5.4-8.2) [n = 260]

Baseline characteristics	DAPT Group (N=283)	Alteplase Group (N=291)
Median NIHSS score at randomisation [c]	2 (1-3)	2 (1-3)
NIHSS scores 0 at randomization	25 (8.8%)	19 (6.5%)
Estimated pre-stroke function (mRS)		
No symptoms (score 0)	202 (71.4%)	213 (73.2%)
Symptoms without any disability (score 1)	81 (28.6%)	78 (26.8%)
Presumed stroke cause [d]		
Undetermined cause	181 (64.0%)	180 (61.9%)
Small-artery occlusion	60 (21.2%)	65 (22.3%)
Large-artery atherosclerosis	40 (14.1%)	43 (14.8%)
Other determined cause	1 (0.4%)	2 (0.7%)
Cardioembolic	1 (0.4%)	1 (0.3%)
Location of responsible vessel [e]		
Anterior circulation	219 (77.4%)	226 (77.7%)
Posterior circulation	62 (21.9%)	64 (22.0%)
Anterior and posterior circulation	2 (0.7%)	1 (0.3%)
Degree of responsible vessel stenosis [f]		
Mild (< 50%)	118/180 (65.6%)	140/204 (68.6%)
Moderate (50%-69%)	19/180 (10.6%)	13/204 (6.4%)
Severe (70%-99%)	13/180 (7.2%)	19/204 (9.3%)
Occlusion (100%)	30/180 (16.7%)	32/204 (15.7%)

Data are n/N (%) or median (IQR). DAPT = dual antiplatelet treatment. INR = international normalized ratio. 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] Referring only to the patients with premorbid mRS ≤ 1.

[c] Patients with NIHSS scores less than or equal to 5 were eligible for this study; NIHSS scores range from 0 to 42, with higher scores indicating more severe neurological deficit.

[d] The presumed stroke cause was classified according to the "Trial of Org 10172 in the Acute Stroke Treatment (TOAST)" classification system.

[e] The classification was defined according to the anatomical location of responsible vessel based on the patient's clinical presentation and neuroimaging, which refers to the clinical features of the "Oxfordshire Community Stroke Project (OCSP)" classification system.

[f] The degree of stenosis was determined by cerebral vessel examination. The diagnosis was based on the clinician's interpretation of the clinical presentation and results of the investigations at the time of hospital discharge.

eTable 2. Baseline Characteristics of the Population in the As-Treated Analysis

Baseline characteristics	DAPT Group (N=344)	Alteplase Group (N=379)
Age, years	65 (58-73)	63 (56-70)
Sex		
Male	233 (67.7%)	266 (70.2%)
Female	111 (32.3%)	113 (29.8%)
Current smoker [a]	99 (28.8%)	143 (37.7%)
Current drinker	50 (14.5%)	66 (17.4%)
Medical history		
History of hypertension	196 (57.0%)	185 (48.8%)
History of diabetes mellitus	86 (25.0%)	101 (26.6%)
Prior ischemic stroke [b]	84 (24.4%)	76 (20.0%)
Prior transient ischemic attack	4 (1.2%)	2 (0.5%)
Median time from onset of symptom to assigned treatment, min	190 (138-236)	169 (125-215)
Median time from onset to hospital discharge, day	8 (6-10)	8 (6-10)
Median INR at randomisation	1.00 (0.94-1.05) [n =331]	0.99 (0.93-1.04) [n = 375]
Median systolic blood pressure at randomisation, mm Hg	149 (136-161)	153 (140-166)
Median diastolic blood pressure at randomisation, mm Hg	88 (81-94)	88 (80-96)
Median blood glucose level at randomisation, mmol/litre	6.2 (5.4-7.8) [n = 299]	6.4 (5.4-8.2) [n = 333]

Baseline characteristics	DAPT Group (N=344)	Alteplase Group (N=379)
Median NIHSS score at randomisation [c]	2 (1-3)	2 (1-3)
NIHSS scores 0 at randomization	35 (10.2%)	21 (5.5%)
Estimated pre-stroke function (mRS)		
No symptoms (score 0)	246 (71.5%)	288 (76.0%)
Symptoms without any disability (score 1)	98 (28.5%)	91 (24.0%)
Presumed stroke cause [d]		
Undetermined cause	223 (64.8%)	225/378 (59.5%)
Small-artery occlusion	74 (21.5%)	92/378 (24.3%)
Large-artery atherosclerosis	44 (12.8%)	57/378 (15.1%)
Other determined cause	2 (0.6%)	3/378 (0.8%)
Cardioembolic	1 (0.3%)	1/378 (0.3%)
Location of responsible vessel [e]		
Anterior circulation	274 (79.7%)	292 (77.0%)
Posterior circulation	68 (19.8%)	85 (22.5%)
Anterior and posterior circulation	2 (0.6%)	2 (0.5%)
Degree of responsible vessel stenosis [f]		
Mild (< 50%)	138/209 (66.0%)	183/270 (67.8%)
Moderate (50%-69%)	21/209 (10.0%)	17/270 (6.3%)
Severe (70%-99%)	17/209 (8.1%)	26/270 (9.6%)
Occlusion (100%)	33/209 (15.8%)	44/270 (16.3%)

Data are n/N (%) or median (IQR). DAPT = dual antiplatelet treatment. INR = international normalized ratio. 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] Referring only to the patients with premorbid mRS ≤ 1.

[c] Patients with NIHSS scores less than or equal to 5 were eligible for this study; NIHSS scores range from 0 to 42, with higher scores indicating more severe neurological deficit.

[d] The presumed stroke cause was classified according to the "Trial of Org 10172 in the Acute Stroke Treatment (TOAST)" classification system.

[e] The classification was defined according to the anatomical location of responsible vessel based on the patient's clinical presentation and neuroimaging, which refers to the clinical features of the "Oxfordshire Community Stroke Project (OCSP)" classification system.

[f] The degree of stenosis was determined by cerebral vessel examination. The diagnosis was based on the clinician's interpretation of the clinical presentation and results of the investigations at the time of hospital discharge.

eTable 3. Antiplatelet Treatment from Hospital Discharge to 90 day Follow-up.

	DAPT Group (N=369)	Alteplase Group (N=350)
Aspirin plus Clopidogrel	34 (9.2%)	32 (9.1%)
Aspirin alone	332 (90.0%)	307 (87.7%)
Clopidogrel alone	3 (0.8%)	11 (3.2%)

eTable 4. Trial Outcomes in the Per-Protocol Analysis.

Outcome	DAPT Group (N=283)	Alteplase Group (N=291)	Treatment Effect Metric	Unadjusted		Adjusted [a]	
				Treatment Difference (95% CI)	P Value	Treatment Difference (95% CI)	P Value
Primary outcome							
mRS [b] score 0-1 within 90 days	263 (92.9%)	263 (90.4%)	RD [c,d]	2.6% (-2.0% to 7.1%)	<0.001	2.2% (-2.2% to 6.7%)	<0.001
			RR [c]	1.36 (0.79 to 2.36)	0.27	1.29 (0.74 to 2.25)	0.33
Secondary outcomes							
mRS [b] score 0-2 within 90 days	270 (95.4%)	276 (94.8%)	RD [c]	0.6% (-3.0% to 4.1%)	0.76	0.7% (-2.8% to 4.2%)	0.68
			RR [c]	1.12 (0.54 to 2.32)	0.76	1.00 (0.48 to 2.09)	0.88
mRS [b] score distribution within 90 days			OR [c]	1.10 (0.76 to 1.58)	0.62	0.98 (0.68 to 1.43)	0.93

Outcome	DAPT Group (N=283)	Alteplase Group (N=291)	Treatment Effect Metric	Unadjusted		Adjusted [a]	
				Treatment Difference (95% CI)	P Value	Treatment Difference (95% CI)	P Value
Early neurological improvement within 24 hours [e]	41 (14.5)	68 (23.4)	RD [c]	-8.9% (-15.2% to -2.5%)	0.006	-5.7% (-12.0% to 0.5%)	0.07
			RR [c]	0.62 (0.44 to 0.88)	0.008	0.70 (0.50 to 0.99)	0.04
Early neurological deterioration within 24 hours [f]	14 (4.9)	29 (10.0)	RD [c]	-5.0% (-9.3% to -0.7%)	0.02	-4.5% (-9.0% to 0.0%)	0.05
			RR [c]	0.50 (0.27 to 0.92)	0.03	0.52 (0.28 to 0.97)	0.04
Median change in NIHSS score at 24 hours from baseline [g]	0 (-0.41 to 0)	0 (-0.69 to 0)	GMR [c]	0.08 (-0.01 to 0.16)	0.09	0.04 (-0.05 to 0.13)	0.20
Stroke or other vascular events within 90 days	1 (0.4)	2 (0.7)	HR [h]	0.51 (0.05 to 5.63)	0.58	0.51 (0.05 to 5.76)	0.46
Death at 90 days	2 (0.7)	3 (1.0)	RD [c]	-0.3% (-1.8% to 1.2%)	0.68	-0.3% (-1.8% to 1.2%)	0.74
			RR [c]	0.69 (0.12 to 4.07)	0.68	0.64 (0.10 to 3.88)	0.61

Data are n/N (%) or median (IQR). CI = confidence interval; DAPT = dual antiplatelet treatment; GMR = geometric mean ratio; RR = risk ratio; RD = risk difference; OR = odds ratio; HR= hazard ratio; mRS = modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; IQR = interquartile range.

[a] Adjusted for pre-specified prognostic variables (age, sex, history of diabetes mellitus, NIHSS score at randomization, time from symptom onset to receive assigned treatment, location of responsible vessel, and stroke etiology). The degree of vascular stenosis was planned in the covariate adjusted analyses but was excluded due to a large proportion of missing values (see the Supplement 2).

[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] Noninferiority will be claimed if the lower limit of one-sided 97.5% (two-sided 95%) confidence interval for the risk difference is above -4·5%. P values for noninferiority of crude and adjusted analysis were presented, respectively.

[e] Early neurological improvement was defined as a decrease between baseline and 24 hours score of ≥ 2 on the NIHSS.

[f] Early neurological deterioration was defined as an increase between baseline and 24 hours of ≥ 2 on the NIHSS, but not as a result of cerebral hemorrhage.

[g] NIHSS scores range 0–42, with higher scores indicating greater stroke severity. The log (NIHSS+1) was analyzed using a generalized linear model.

[h] Calculated using Cox regression model. No violation of hazard proportionality assumption was found and P value for the interaction was 0.86.

eTable 5. Trial Outcomes in the As-Treated Analysis.

Outcome	DAPT Group (N=344)	Alteplase Group (N=379)	Treatment Effect Metric	Unadjusted		Adjusted [a]	
				Treatment Difference (95% CI)	P Value	Treatment Difference (95% CI)	P Value
Primary outcome							
mRS [b] score 0-1 within 90 days	320/342 (93.6%)	346/377 (91.8%)	RD [c]	1.8% (-2.0% to 5.6%)	<0.001	1.4% (-2.3% to 5.1%)	<0.001
			RR [c]	1.28 (0.76 to 2.16)	0.36	1.16 (0.68 to 1.99)	0.52
Secondary outcomes							
mRS [b] score 0-2 within 90 days	328/342 (95.9%)	360/377 (95.5%)	RD [c]	0.4% (-2.6% to 3.4%)	0.78	0.4% (-2.6% to 3.3%)	0.81
			RR [c]	1.10 (0.55 to 2.20)	0.78	1.05 (0.52 to 2.15)	0.98
mRS [b] score distribution within 90 days			OR [c]	1.01 (0.72 to 1.40)	0.96	0.90 (0.64 to 1.26)	0.69
Outcome			**Treatment**	**Unadjusted**		**Adjusted [a]**	

	DAPT Group (N=344)	Alteplase Group (N=379)	Effect Metric	Treatment Difference (95% CI)	P Value	Treatment Difference (95% CI)	P Value
Early neurological improvement within 24 hours [f]	47 (13.7%)	89 (23.5%)	RD [c]	-9.9% (-15.5% to -4.3%)	0.001	-7.6% (-13.2% to -2.0%)	0.008
			RR [c]	0.58 (0.42 to 0.80)	0.001	0.66 (0.48 to 0.92)	0.01
Early neurological deterioration within 24 hours [f]	17 (4.9%)	32 (8.4%)	RD [c]	-3.5% (-7.1% to 0.1%)	0.06	-2.7% (-6.6% to 1.2%)	0.17
			RR [c]	0.59 (0.33 to 1.04)	0.06	0.62 (0.35 to 1.11)	0.11
Median change in NIHSS score at 24 hours from baseline [g]	0 (-0.41 to 0)	0 (-0.69 to 0)	GMR [c]	0.09 (0.02 to 0.17)	0.02	0.06 (-0.02 to 0.14)	0.06
Stroke or other vascular events within 90 days	1/342 (0.3%)	2/377 (0.5%)	HR [h]	0.55 (0.05 to 6.05)	0.62	0.55 (0.05 to 6.30)	0.49
Death at 90 days	2/342 (0.6%)	3/377 (0.8%)	RD [c]	-0.2% (-1.4% to 1.0%)	0.73	-0.2% (-1.4% to 1.0%)	0.74
			RR [c]	0.73 (0.12 to 4.37)	0.74	0.69 (0.11 to 4.28)	0.71

Data are n/N (%) or median (IQR). CI = confidence interval; DAPT = dual antiplatelet treatment; GMR = geometric mean ratio; RR = risk ratio; RD = risk

difference; OR = odds ratio; HR= hazard ratio; mRS = modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; IQR = interquartile range.

[a] Adjusted for pre-specified prognostic variables (age, sex, history of diabetes mellitus, NIHSS score at randomization, time from symptom onset to receive assigned treatment, location of responsible vessel, and stroke etiology). The degree of vascular stenosis was planned in the covariate adjusted analyses but was excluded due to a large proportion of missing values (see the Supplement 2).

[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] Noninferiority will be claimed if the lower limit of one-sided 97.5% (two-sided 95%) confidence interval for the risk difference is above -4·5%. P values for noninferiority of crude and adjusted analysis were presented, respectively.

[e] Early neurological improvement was defined as a decrease between baseline and 24 hours score of ≥ 2 on the NIHSS.

[f] Early neurological deterioration was defined as an increase between baseline and 24 hours of ≥ 2 on the NIHSS, but not as a result of cerebral hemorrhage.

[g] NIHSS scores range 0–42, with higher scores indicating greater stroke severity. The log (NIHSS+1) was analyzed using a generalized linear model.

[h] Calculated using Cox regression model. No violation of hazard proportionality assumption was found and P value for the interaction was 0.85.

eTable 6. Sensitivity Analysis for Missing Primary Outcome in Dropout Subjects in the Full Analysis Set.

Methods	**Without primary outcome imputation**				**With primary outcome imputation**				
	DAPT group (N=369)	Alteplase group (N=350)	Risk difference (95% CI)	P value for noninferiority	DAPT group (N=393)	Alteplase group (N=367)	Risk difference (95% CI)	P value for noninferiority	Imputation methods
mRS score 0-1 within 90 days	346 (93.8%)	320 (91.4%)	2.3% (-1.5% to 6.2%)	0.0002	366 (93.1%)	331 (90.2%)	2.9% (-1.0% to 6.9%)	< .001	Last observation carried forward
					346 (88.0%)	320 (87.2%)	0.8% (-3.8% to 5.5%)	0.01	Worst-case scenario
					370 (94.1%)	337 (91.8%)	2.3% (-1.3% to 6.0%)	< .001	Best-case scenario

Data are n (%). CI = confidence interval; DAPT = dual antiplatelet.

eTable 7. Validation of Statistical Results for the Primary Outcome Analyses.

Analysis Population	Analysis	Risk Difference	Two-sided 95% Confidence Interval		P Value for Noninferiority
			Lower	Upper	
Full analysis set	Crude analysis	2.3%	-1.5%	6.2%	< .001
	Adjusted analysis using propensity score	2.3%	-1.6%	6.1%	< .001
	Adjusted analysis using inverse probability weighting	2.4%	-0.3%	5.1%	< .001
Per-protocol	Crude analysis	2.6%	-2.0%	7.1%	0.001
	Adjusted analysis using propensity score	2.2%	-2.2%	6.7%	0.002
	Adjusted analysis using inverse probability weighting	3.1%	0.1%	6.2%	< .001
As-treated	Crude analysis	1.8%	-2.0%	5.6%	< .001
	Adjusted analysis using propensity score	1.4%	-2.3%	5.1%	< .001
	Adjusted analysis using inverse probability weighting	2.7%	0.2%	5.7%	< .001

eTable 8. Sensitivity Analysis for the Effect of Crossover on Primary Outcome in the Full Analysis Set.

Outcome	DAPT Group (N=369)	Alteplase Group (N=350)	Treatment Effect Metric	Unadjusted		Adjusted [a]	
				Treatment Difference (95% CI)	P Value	Treatment Difference (95% CI)	P Value
mRS [b] score 0-1 within 90 days	346 (94%)	320 (91%)	**Original analysis of primary outcome**				
			RD [c,d]	2.3% (-1.5% to 6.2%)	< .001	2.3% (-1.6% to 6.1%)	< .001
			RR [c]	1.38 (0.81 to 2.32)	0.23	1.36 (0.80 to 2.30)	0.22
			Sensitivity analysis of primary outcome				
			RD [c,d]	1.7% (-2.1% to 5.5%)	< .001	1.8% (-2.0% to 5.6%)	< .001
			RR [c]	1.32 (0.78 to 2.23)	0.30	1.34 (0.79 to 2.26)	0.28

Data are n/N (%). CI = confidence interval; DAPT = dual antiplatelet treatment; RR = risk ratio; RD = risk difference; mRS = modified Rankin Scale; [a] Adjusted for pre-specified prognostic variables (age, sex, history of diabetes mellitus, NIHSS score at randomisation, time from symptom onset to receive assigned treatment, location of responsible vessel, and stroke aetiology) in the original analysis and adjusted for the above specified prognostic variables plus crossover variable (1=Yes and 0=No) in the sensitive analysis. The degree of vascular stenosis was planned in the covariate adjusted analyses but was excluded due to a large proportion of missing values (see the appendix 3). [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 binomial-identity model. Non-inferiority will be claimed if the lower limit of one-sided 97.5% (two-sided 95%) confidence interval for the risk difference is above -4·5%. *P* values for noninferiority of crude and adjusted analysis were presented, respectively. [d] Calculated using a binomial-log regression model.

eTable 9. Occurrence of Symptomatic Intracerebral Hemorrhage According to Different Definitions.

	DAPT Group (N=371)	Alteplase Group (N=352)
Symptomatic intracerebral hemorrhage		
ECASS-II [a]	1 (0.3%)	3 (0.9%)
SITS-MOST [b]	1 (0.3%)	3 (0.9%)
NINDS [c]	1 (0.3%)	4 (1.1%)
HBC [d]	1 (0.3%)	3 (0.9%)
Radiologic hemorrhage type		
Parenchymal hematoma		
Type 2 [e]	0 (0.0%)	1 (0.3%)
Type 1 [f]	0 (0.0%)	0 (0.0%)
Hemorrhagic infarction		
Type 2 [g]	0 (0.0%)	0 (0.0%)
Type 1 [h]	1 (0.3%)	1 (0.3%)
Remote parenchymal hemorrhage [i]	0 (0.0%)	2 (0.6%)

[a] ECASS indicates European Cooperative Acute Stroke Study. Symptomatic intracranial hemorrhage was defined as any evidence of bleeding on the head CT scan associated with clinically significant neurologic deterioration (NIHSS score ⩾ 4 points increase) in the opinion of the clinical investigator or independent safety monitor. [b] SITS-MOST indicates the Safe Implementation of Thrombolysis in Stroke Monitoring Study. Symptomatic intracranial hemorrhage was defined as local or remote parenchymal hemorrhage type 2 on the 22–36 h post-treatment imaging scan, combined with a neurological deterioration of 4 points or more on the NIHSS from baseline, or

from the lowest NIHSS value between baseline and 24 h, or leading to death.

[c] NINDS indicates the National Institute of Neurological Disorders and Stroke rt-PA Stroke Study. Symptomatic intracranial hemorrhage was defined as any hemorrhage plus any neurological deterioration [NIHSS score ⩾1] or that leads to death within 7 days.

[d] HBC indicates Heidelberg Bleeding Classification. Symptomatic intracranial hemorrhage was defined as new intracranial hemorrhage detected by brain imaging associated with any of the item below: (1) ≥4 points total NIHSS at the time of diagnosis compared to immediately before worsening. Note that a 4 points change is not compared with the baseline admission NIHSS score but instead to the immediate predeterioration neurological status. (2) ≥2 point in one NIHSS category. (3) Leading to intubation/hemicraniectomy/EVD placement or other major medical/surgical intervention. (4) Absence of alternative explanation for deterioration.

[e] Parenchymal hematoma type 2 was defined as confluent bleeding occupying more than 30% of the infarct volume and causing significant mass effect.

[f] Parenchymal hematoma type 1 was defined as confluent bleeding occupying less than 30% of the infarct volume with some slight mass effect.

[g] Hemorrhagic infarction type 2 was defined as confluent petechiae within the infarcted area but no space-occupying effect.

[h] Hemorrhagic infarction type 1 was defined as small petechiae along the margins of the infarct.

[i] Remote parenchymal hemorrhage was defined as intracranial hemorrhage outside the infarcted brain tissue.

eTable 10. Baseline Characteristics of Patients with Crossover

Baseline characteristics	Randomized to DAPT Group (N=87)	Randomized to Alteplase Group (N=60)
Age, years	64 (56-70)	66 (58-76)
Sex		
Male	61 (70.1%)	36 (60.0%)
Female	26 (29.9%)	24 (40.0%)
Current smoker [a]	38 (43.7%)	13 (21.7%)
Current drinker	14 (16.1%)	4 (6.7%)
Medical history		
History of hypertension	49 (56.3%)	33 (55.0%)
History of diabetes mellitus	27 (31.0%)	12 (20.0%)
Prior ischemic stroke [b]	16 (18.4%)	17 (28.3%)
Prior transient ischemic attack	0 (0.0%)	0 (0.0%)
Median time from onset of symptom to assigned treatment, min	168 (124-202)	200 (157-240)
Median time from onset to hospital discharge, day	8 (6-11)	8 (6-10)
Median INR at randomisation	0.99 (0.91-1.05) [n = 84]	0.97 (0.93-1.04) [n = 55]
Median systolic blood pressure at randomization, mm Hg	160 (141-170)	150 (138-160)
Median diastolic blood pressure at randomization, mm Hg	90 (81-97)	90 (81-94)
Median blood glucose level at randomization, mmol/litre	6.6 (5.4-9.2) [n = 72]	6.5 (5.4-7.8) [n = 54]

Baseline characteristics	**Randomized to DAPT Group (N=87)**	**Randomized to Alteplase Group (N=60)**
Median NIHSS score at randomization [c]	2 (1-3)	2 (1-3)
NIHSS scores 0 at randomization	2 (3.3%)	20 (16.7%)
Estimated pre-stroke function (mRS)		
No symptoms (score 0)	74 (85.1%)	44 (73.3%)
Symptoms without any disability (score 1)	13 (14.9%)	16 (26.7%)
Presumed stroke cause [d]		
Undetermined cause	45 (51.7%)	41 (68.3%)
Small-artery occlusion	27 (31.0%)	14 (23.3%)
Large-artery atherosclerosis	14 (16.1%)	4 (6.7%)
Other determined cause	1 (1.1%)	1 (1.7%)
Cardioembolic	0 (0.0%)	0 (0.0%)
Location of responsible vessel [e]		
Anterior circulation	65 (74.7%)	54 (90.0%)
Posterior circulation	21 (24.1%)	6 (10.0%)
Anterior and posterior circulation	1 (1.1%)	0 (0.0%)
Degree of responsible vessel stenosis [f]		
Mild (< 50%)	51/66 (77.3%)	25/29 (86.2%)
Moderate (50%-69%)	4/66 (6.1%)	2/29 (6.9%)
Severe (70%-99%)	4/66 (6.1%)	2/29 (6.9%)
Occlusion (100%)	7/66 (10.6%)	0/29 (0.0%)

Data are n/N (%) or median (IQR). DAPT = dual antiplatelet treatment. INR = international normalized ratio. 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] Referring only to the patients with premorbid mRS ≤ 1.

[c] Patients with NIHSS scores less than or equal to 5 were eligible for this study; NIHSS scores range from 0 to 42, with higher scores indicating more severe neurological deficit.

[d] The presumed stroke cause was classified according to the "Trial of Org 10172 in the Acute Stroke Treatment (TOAST)" classification system.

[e] The classification was defined according to the anatomical location of responsible vessel based on the patient's clinical presentation and neuroimaging, which refers to the clinical features of the "Oxfordshire Community Stroke Project (OCSP)" classification system.

[f] The degree of stenosis was determined by cerebral vessel examination. The diagnosis was based on the clinician's interpretation of the clinical presentation and results of the investigations at the time of hospital discharge.