

Intravenous Thrombolysis for Ischemic Stroke and more

Deviyani Mehta, MD

Content

- I have no financial disclosures



The NEW ENGLAND JOURNAL *of* MEDICINE

ESTABLISHED IN 1812

APRIL 6, 2023

VOL. 388 NO. 14

Trial of Endovascular Thrombectomy for Large Ischemic Strokes

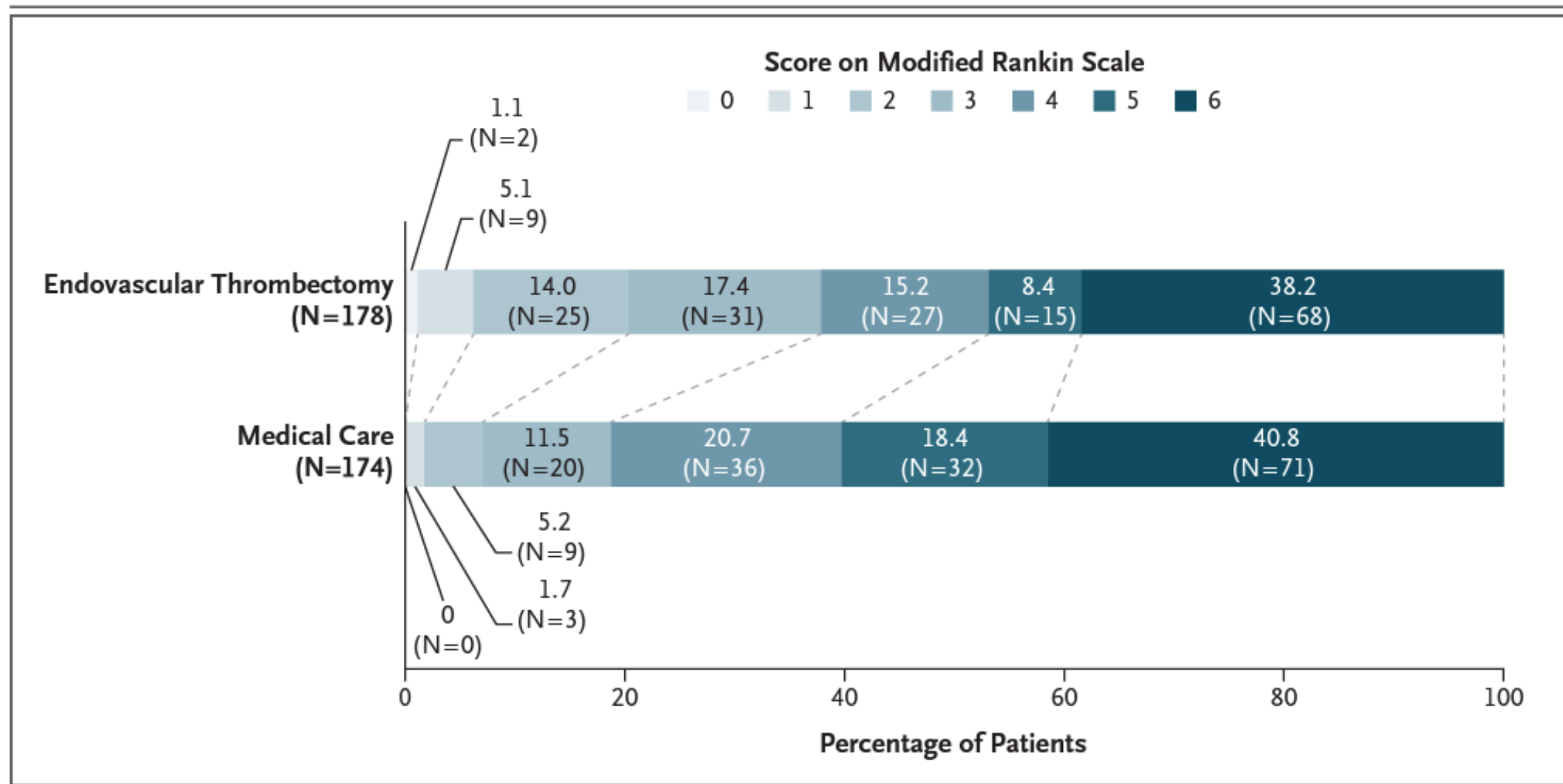
- **SELECT 2**
 - prospective, randomized, open-label, adaptive, international trial involving patients with stroke due to occlusion of the internal carotid artery or the first segment of the middle cerebral artery to assess endovascular thrombectomy within 24 hours after onset.
 - Patients had a large ischemic-core volume, defined as an ASPECT Score of 3 to 5 (range, 0 to 10, with lower scores indicating larger infarction) or a core volume of at least 50 ml on CTP or DWI sequence on MRI.
 - The primary outcome was the modified Rankin scale score at 90 days
 - Functional independence was a secondary outcome (mRS 0-2).

SELECT 2

Table 1. Baseline Characteristics of the Patients (Intention-to-Treat Population).^{a,b}

Characteristic	Endovascular Thrombectomy (N = 178)	Medical Care (N = 174)
Median age (IQR) — yr	66 (58–75)	67 (58–75)
Female sex — no. (%)	71 (39.9)	74 (42.5)
Race or ethnic group — no. (%) [†]		
American Indian or Alaska Native	0	1 (0.6)
Asian	5 (2.8)	3 (1.7)
Black	26 (14.6)	24 (13.8)
White	132 (74.2)	130 (74.7)
Native Hawaiian or Pacific Islander	2 (1.1)	0
Other or unknown	13 (7.3)	16 (9.2)
Previous ischemic stroke — no. (%)	19 (10.7)	13 (7.5)
Right hemisphere affected — no. (%)	98 (55.1)	98 (56.3)
Occlusion location — no. (%) [‡]		
Internal carotid artery	80 (44.9)	66 (37.9)
M1 segment	91 (51.1)	100 (57.5)
M2 segment	7 (3.9)	8 (4.6)
Tandem occlusions — no. of patients (%)	56 (31.5)	44 (25.3)
Transfer to center with endovascular thrombectomy capabilities — no. (%)	106 (59.6)	105 (60.3)
Intravenous thrombolysis — no./total no. (%)	37/178 (20.8)	30/173 (17.3)
Median NIHSS score at hospital arrival (IQR) [§]	19 (15–23)	19 (15–22)
General anesthesia performed — no. (%)	104/177 (58.8)	—
Median interval between time that patient was last known to be well and randomization (IQR) — hr	9.07 (5.27–15.33)	9.79 (5.82–15.32)
Median interval between hospital arrival and imaging (IQR) — min		
CT	16 (9–27)	15 (7–24)
CT perfusion or MRI	26 (17–41)	25 (13–36)
Median interval between hospital arrival and arterial puncture (IQR) — min	109 (76–138)	—
Median interval between arterial puncture and reperfusion or end of procedure (IQR) — min	38 (25–61)	—
Median ASPECTS value on baseline CT imaging (IQR) [¶]	4 (3–5)	4 (4–5)
Imaging method used to estimate ischemic-core volume — no./total no. (%)		
CT perfusion	174/177 (98.3)	169/174 (97.1)
Diffusion-weighted MRI	3/177 (1.7)	5/174 (2.9)
Median estimated ischemic-core volume (IQR) — ml		
Overall	81.5 (57–118)	79 (62–111)
CT perfusion	81.5 (59–119)	79 (62–111)
Diffusion-weighted MRI	82 (56–89)	86 (84–104)
Median volume of critically hypoperfused lesion (IQR) — ml**	171 (127–226)	169 (127–216)
Median volume of tissue with Tmax of >10 sec (IQR) — ml	107 (70.5–152.5)	111 (67–147)

SELECT 2



SELECT 2

Table 2. Clinical Outcomes (Intention-to-Treat Population).*

Variable	Endovascular Thrombectomy (N = 178)	Medical Care (N = 174)	Effect Size (95% CI)
Primary outcome			
Median score on modified Rankin scale at 90 days (IQR) [†]	4 (3–6)	5 (4–6)	1.51 (1.20 to 1.89) [‡]
Secondary clinical outcomes			
Functional independence at 90 days — no./total no. (%) [§]	36/177 (20.3)	12/171 (7.0)	2.97 (1.60 to 5.51) [¶]
Independent ambulation at 90 days — no./total no. (%)	67/177 (37.9)	32/171 (18.7)	2.06 (1.43 to 2.96) [¶]
Successful reperfusion — no. (%) ^{**}	142 (79.8)	—	
Discharge location — no. (%)			
Home	19 (10.7)	10 (5.7)	
Acute care facility	11 (6.2)	16 (9.2)	
Inpatient rehabilitation facility	72 (40.4)	65 (37.4)	
Skilled nursing facility	23 (12.9)	20 (11.5)	
Hospice or home hospice	11 (6.2)	19 (10.9)	
In-hospital death	42 (23.6)	44 (25.3)	
Early neurologic improvement — no./total no. (%) ^{††}	20/174 (11.5)	13/172 (7.6)	1.47 (0.76 to 2.87) [¶]
Median quality-of-life scores (IQR) ^{‡‡}			
Mobility domain	35.2 (23.9 to 43.9)	25.1 (16.5 to 33.0)	10.10 (5.02 to 15.18) ^{§§}
Depression domain	47.9 (43.1 to 54.3)	53.6 (46.8 to 57.4)	–5.70 (–8.83 to –2.57)
Social domain	37.1 (32.7 to 42.0)	33.5 (27.7 to 37.8)	3.60 (1.11 to 6.09)
Cognitive domain	41.9 (35.0 to 49.6)	37.9 (30.9 to 42.9)	4.00 (0.51 to 7.49)

SELECT 2

Table 3. Safety Outcomes and Procedural Complications (Intention-to-Treat Population).*

Outcome	Endovascular Thrombectomy (N = 178)	Medical Care (N = 174)	Relative Risk (95% CI)
Symptomatic intracranial hemorrhage within 24 hr — no. (%)†	1 (0.6)	2 (1.1)	0.49 (0.04 to 5.36)
Early neurologic worsening — no. (%)‡	44 (24.7)	27 (15.5)	1.59 (1.03 to 2.45)
Death from any cause within 90 days — no./total no. (%)	68/177 (38.4)	71/171 (41.5)	0.91 (0.71 to 1.18)
Arterial access-site complications — no. (%)			
Occlusion	3 (1.7)	—	
Hematoma	1 (0.6)	—	
Infection	1 (0.6)	—	
Vascular injury — no. (%)			
Dissection	10 (5.6)	—	
Perforation	7 (3.9)	—	
Vasospasm	11 (6.2)	—	
Other	2 (1.1)	—	

SELECT 2

- Study stopped early (with 300 patients enrolled) due to efficacy having reached (after positive results from RESCUE-Japan LIMIT trial)
- Better outcomes were seen with thrombectomy and medical management rather than medical management alone within 24 hours of LSN.
- Incidence of symptomatic intracranial hemorrhage was low in both groups.
- 18% of pts. Had complications associated with procedure.

Effect of Alteplase vs Aspirin on Functional Outcome for Patients With Acute Ischemic Stroke and Minor Nondisabling Neurologic Deficits

The PRISMS Randomized Clinical Trial

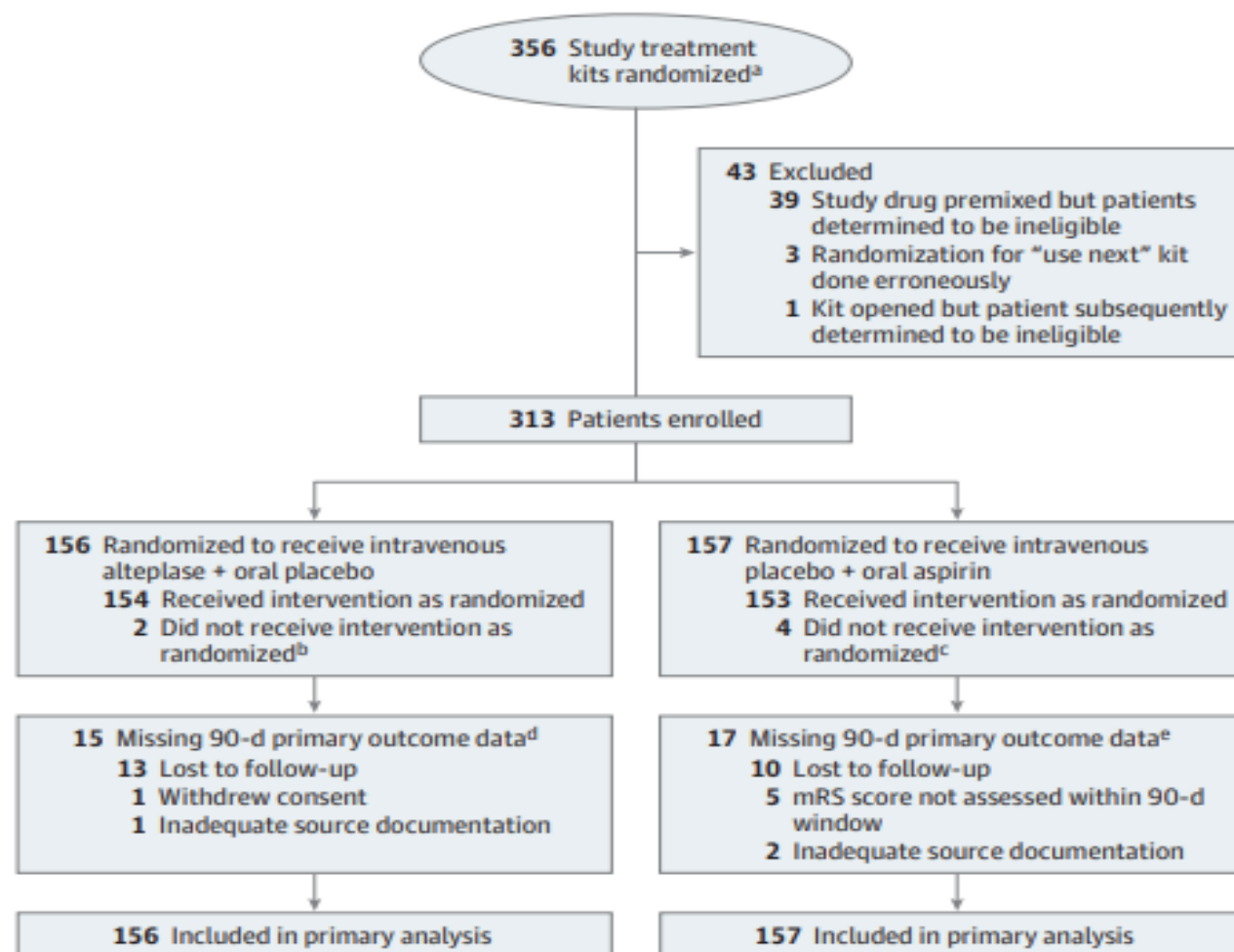
- Phase 3b, randomized, double-blind clinical trial testing the safety and efficacy of intravenous alteplase administered within 3 hours of symptom onset
- Inclusion criteria
 - clinical diagnosis of acute ischemic stroke,
 - age 18 years or older,
 - NIHSS score of 0 to 5, and deficits judged to not be clearly disabling at presentation.
- Randomized to receive IV tPA+ placebo ASA versus ASA 325mg with placebo IV tPA.

PRISMS

- Primary outcomes was mRS 0/1 at 90 days.
- Secondary Outcome consisted of global favorable recovery including mRS, Barthrel Index and NIHSS scores.
- Safety end point was symptomatic ICH within 36 hours with neurological decline attributed to ICH as well as all cause mortality within 90 days.
- Trial was terminated early because of enrollment below target.

PRISMS

Figure 1. Flow of Patients Through the PRISMS Trial



PRISMS

Table 1. Baseline Patient Characteristics

Characteristics	Intravenous Alteplase + Oral Placebo (n=156)	Intravenous Placebo + Oral Aspirin (n = 157)
Age, mean (SD), y	62 (14)	61 (13)
Male sex, No. (%)	77 (49)	92 (59)
Race, No. (%) ^a		
White	117 (75.0)	126 (80.3)
Black/African American	35 (22.4)	27 (17.2)
American Indian or Alaska Native	1 (0.6)	3 (1.9)
Asian	0	1 (0.6)
≥2 races	1 (0.6)	0
Unknown	2 (1.3)	0
Hispanic or Latino ethnicity, No. (%) ^a	14 (9.0)	18 (11.5)
Medical history, No. (%)		
Hypertension	126 (81.3)	124 (79.0)
Hyperlipidemia	114 (73.1)	114 (72.6)
Diabetes mellitus	57 (36.5)	44 (28.0)
Previous stroke	28 (17.9)	24 (15.3)
Atrial fibrillation	23 (14.7)	17 (10.8)
Medications prior to onset, No. (%)		
Antiplatelet agents	64 (41.0)	59 (37.6)
Anticoagulant agents	1 (0.6)	1 (0.6)
Time from symptom onset to intravenous study treatment bolus, h		
No. (%)		
0 to 2	25 (16.0)	36 (22.9)
>2 to 3	126 (80.8)	119 (75.8)
>3 ^b	5 (3.2)	2 (1.3)
Median (IQR)	2.7 (2.2-2.9)	2.6 (2.1-2.9)
Time from onset to oral study treatment, median (IQR), h	2.9 (2.5-3.1)	2.8 (2.4-3.1)
Baseline NIHSS score ^c		
No. (%)		
0	7 (4.5)	7 (4.5)
1	38 (24.4)	50 (31.8)
2	52 (33.3)	50 (31.8)
3	32 (20.5)	30 (19.1)
4	21 (13.5)	16 (10.2)
5	6 (3.8)	4 (2.5)
Mean (SD)	2.3 (1.2)	2.0 (1.2)
Glucose level, mean (SD), mg/dL	141.2 (72.9)	132.1 (61.8)
Systolic blood pressure >140 mm Hg, No. (%)	83 (53.2)	112 (71.3)
Diastolic blood pressure >90 mm Hg, No. (%)	31 (19.9)	44 (28.0)
Baseline international normalized ratio >1.1, No. (%)	42 (26.9)	52 (33.1)
Baseline ASPECTS, median (range) ^d	10 (7-10)	10 (7-10)

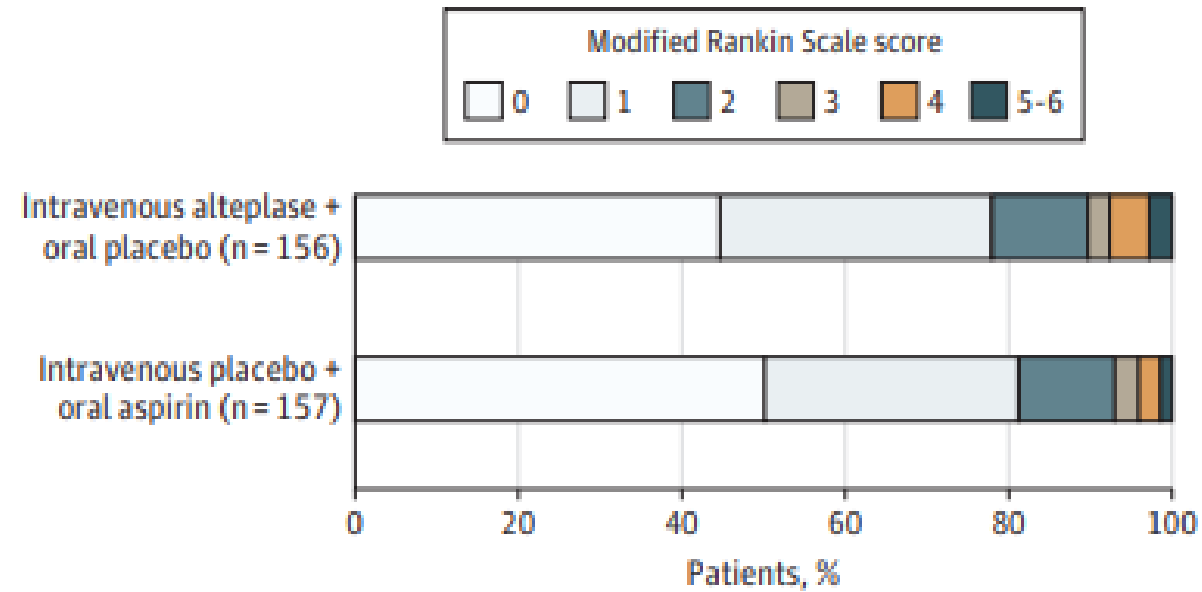
PRISMS

Table 2. Presenting Event Characteristics

Characteristics	No. (%)	
	Intravenous Alteplase + Oral Placebo (n = 156)	Intravenous Placebo + Oral Aspirin (n = 157)
Rapid improvement of symptoms prior to study treatment administration	8 (5.1)	7 (4.5)
Localization of presenting deficit ^a		
Right hemisphere	75 (48.1)	67 (42.7)
Left hemisphere	59 (37.8)	62 (39.5)
Unknown	19 (12.2)	21 (13.4)
Brainstem/cerebellum	9 (5.8)	18 (11.5)
Final diagnosis		
Acute cerebral ischemia	136 (88.3)	131 (85.6)
Neurovascular mimic ^b	18 (11.7)	22 (14.4)
Ischemic cerebral event etiology ^c	n=138	n=135
Small vessel disease	48 (34.8)	52 (38.5)
Undetermined etiology	40 (29.0)	46 (34.1)
Cardioembolism	20 (14.5)	17 (12.6)
Large artery atherosclerosis	20 (14.5)	10 (7.4)
Other determined etiology ^d	10 (7.2)	10 (7.4)

PRISMS

Figure 2. Modified Rankin Scale Score Distributions at 90 Days by Treatment Group



122 patients (78.2%) randomized to alteplase had favorable outcomes at 90 days compared with 128 patients (81.5%) randomized to aspirin

These distributions, which were used for the primary outcome analysis, included imputation for missing 90-day scores.

PRISMS

Table 4. Adverse Event Results (As-Treated Analysis)

Adverse Events	No. (%)		Risk Difference, % (95% CI)
	Intravenous Alteplase + Oral Placebo (n = 156)	Intravenous Placebo + Oral Aspirin (n = 157)	
Primary Adverse Event Assessment			
Symptomatic intracranial hemorrhage within 36 h	5 (3.2)	0	3.3 (0.8 to 7.4)
Secondary Adverse Event Assessments			
Symptomatic intracranial hemorrhage within 36 h, SITS-MOST definition ^a	2 (1.3)	0	1.3 (−1.2 to 4.6)
Any radiologic intracranial hemorrhage within 36 h by central reader	11 (7.1)	5 (3.3)	3.9 (−1.2 to 9.5)
By radiological subtype ^b			
Hemorrhagic infarction type 1	2	3	
Hemorrhagic infarction type 2	2	1	
Parenchymal hematoma type 1	1	0	
Parenchymal hematoma type 2	4	0	
Remote parenchymal hematoma type 1	2	0	
Intraventricular hemorrhage	2 ^c	0	
Subarachnoid hemorrhage	3 ^c	1	
Mortality within 90 d	1 (0.6)	0	
Stroke-related and neurologic deaths within 90 d	0	0	
Patients with serious adverse events ^d	40 (26.0)	20 (13.1)	12.9 (4.1 to 21.7) ^e
Patients with any adverse events	119 (77.3)	104 (68.0)	

PRISMS

- Patients with minor, nondisabling acute ischemic stroke, treatment with alteplase compared with aspirin did not increase the likelihood of favorable functional outcome at 90 days.
- Treatment benefit with alteplase was also not demonstrated for secondary and exploratory end points at 90 days.
- The study results raise the hypothesis that even a 6% treatment effect might be unlikely. However, the very early study termination precludes any definitive conclusions.

Dual Antiplatelet Therapy vs Alteplase for Patients With Minor Nondisabling Acute Ischemic Stroke

The ARAMIS Randomized Clinical Trial

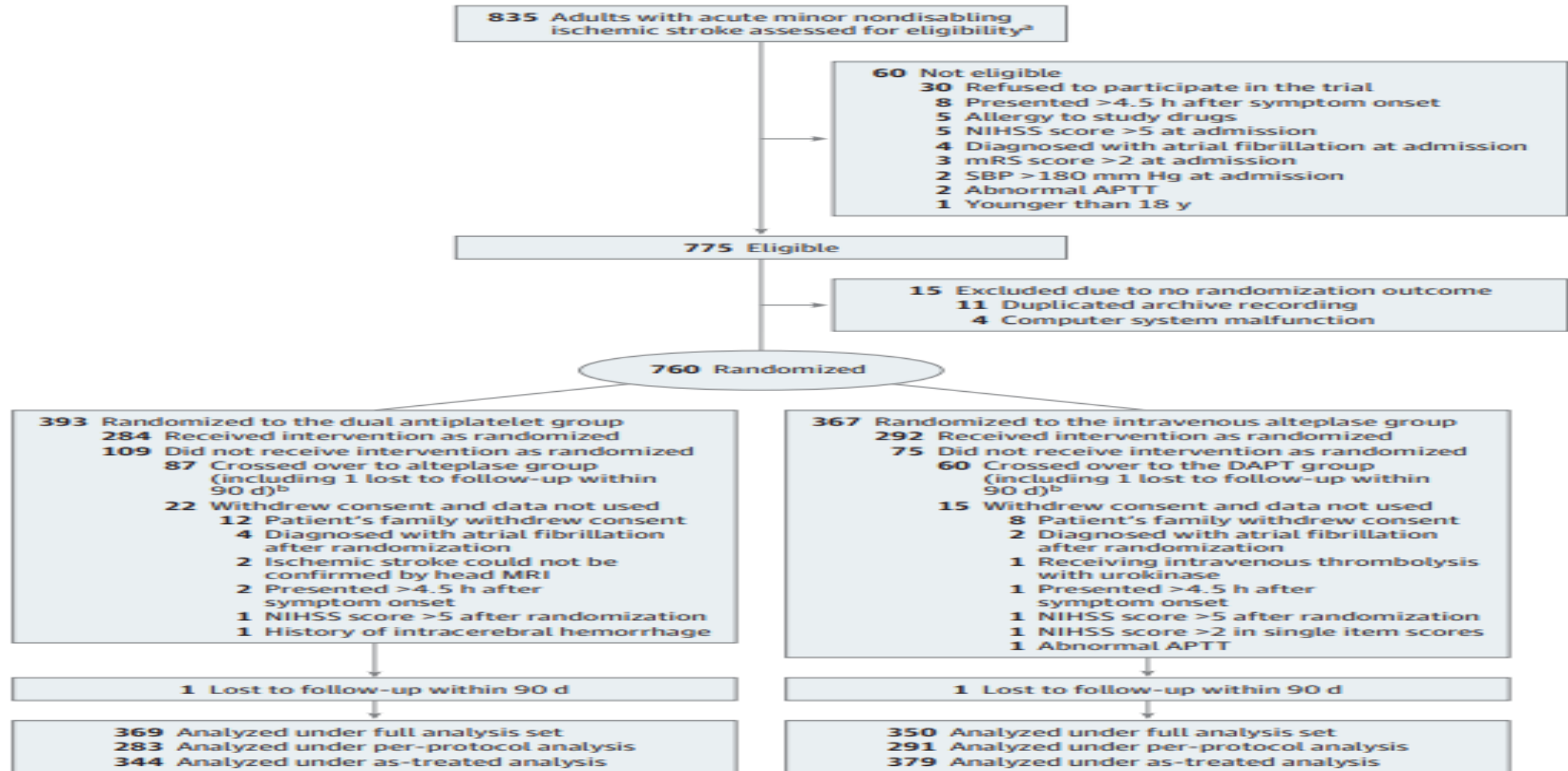
- A multicenter, randomized, open-label, blinded end point assessment, noninferiority trial to assess the efficacy and safety of DAPT compared with intravenous alteplase in patients presenting with minor stroke and nondisabling deficits within 4.5 hours of symptom onset.
- Inclusion criteria
 - 18 years or older
 - had an acute ischemic stroke with an NIHSS score less than or equal to 5
 - less than or equal to 1 point on single-item scores, such as vision, language, neglect, or single limb weakness, and a score of 0 in the consciousness item at the time of randomization
 - had CT or MRI performed on admission to identify ischemic stroke
 - could start receiving study treatment within 4.5 hours of stroke symptoms.
- Exclusion criteria
 - Prestroke disability (modified Rankin Scale [mRS] score ≥ 2 ;
 - history of intracerebral hemorrhage, or definite indication for anticoagulation.

ARAMIS

- Patient received Alteplase or DAPT (load of Clopidogrel 300mg on Day1 followed by 75 mg, ASA 100 mg daily) for 12 ± 2 days then single agent or DAPT based on guidelines for 90 days.
- Primary outcome is mRS of 0-1.
- Secondary Outcome is favorable mRS, early neurological improvement or deterioration, new stroke or other vascular events at 90 days, all cause mortality.
- Safety outcome is sICH

ARAMIS

Figure 1. Patient Flow in the ARAMIS Randomized Clinical Trial



ARAMIS

Table 1. Baseline Characteristics in the Full Analysis Set

Baseline characteristics	No. (%) Dual antiplatelet therapy (n = 369)	Alteplase (n = 350)
Age, median (IQR), y	65 (57-71)	64 (56-71)
Sex		
Men	256 (69.5)	240 (68.6)
Women	113 (30.6)	110 (31.4)
Current smoking ^a	122 (33.1)	118 (33.7)
Current drinking ^a	59 (16.0)	56 (16.0)
Medical history		
Hypertension	211 (57.2)	169 (48.3)
Diabetes	101 (27.4)	86 (24.6)
Prior ischemic stroke ^b	82 (22.2)	77 (22.0)
Prior transient ischemic attack	4 (1.1)	2 (0.6)
Time from onset of symptoms to receipt of assigned treatment, median (IQR), min	182 (134-230)	180 (127-225)
Time from onset of symptoms to hospital discharge, median (IQR), d	8 (6-11)	8 (6-10)
INR at randomization, median (IQR)	1.00 (0.94-1.05)	0.98 (0.93-1.04)
INR >1.2 at randomization	5/358 (1.4)	4/344 (1.2)
APTT at randomization, median (IQR), s	31.8 (27.2-36.3)	31.9 (27.4-35.7)
Median APTT >43.5 s at randomization	15 (4.1)	13 (3.7)
Systolic blood pressure at randomization, median (IQR), mm Hg	150 (137-166)	151 (139-162)
Median systolic blood pressure >140 mm Hg at randomization	245 (66.4)	242 (69.1)
Diastolic blood pressure at randomization, median (IQR), mm Hg	88 (81-95)	88 (80-95)
Median (IQR) diastolic blood pressure >90 mm Hg at randomization	142 (38.5)	132 (37.7)
Blood glucose level at randomization, median (IQR), mmol/L	6.3 (5.4-8.3)	6.4 (5.4-8.1)
Blood glucose level >7.0 mmol/L at randomization	112/316 (35.4)	121/314 (38.5)
NIHSS score at randomization, median (IQR) ^c	2 (1-3)	2 (1-3)
NIHSS score of 0 at randomization	27 (7)	29 (8)
Estimated prestroke function (mRS score)		
No symptoms (score of 0)	275 (74.5)	256 (73.1)
Symptoms without any disability (score of 1)	94 (25.5)	94 (26.9)
Presumed stroke cause ^d		
Undetermined cause	225 (61.0)	221 (63.1)
Small artery occlusion	87 (23.6)	79 (22.6)
Large artery atherosclerosis	54 (14.6)	46 (13.1)
Other determined cause	2 (0.5)	3 (0.9)
Cardioembolic	1 (0.3)	1 (0.3)
Location of responsible vessel ^e		
Anterior circulation	283 (76.7)	279 (79.7)
Posterior circulation	83 (22.5)	70 (20.0)
Anterior and posterior circulation	3 (0.8)	1 (0.3)

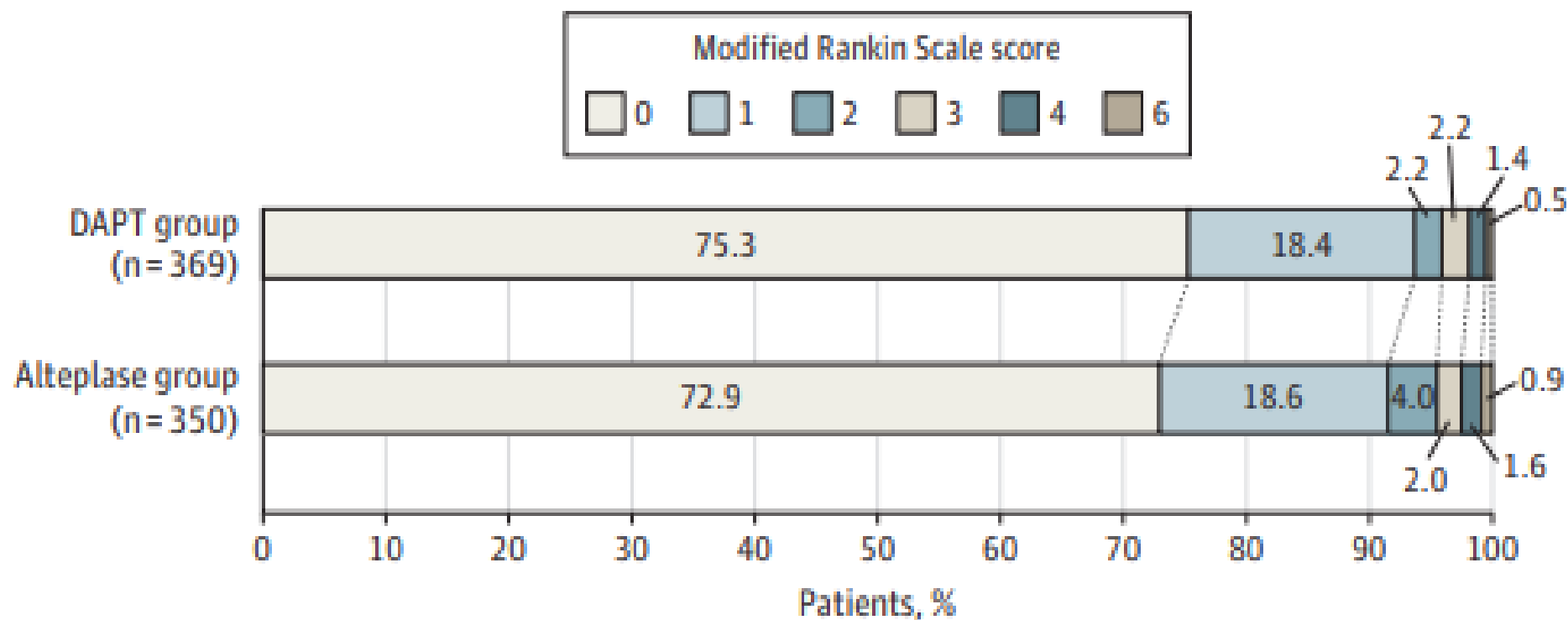
ARAMIS

Table 2. Trial Outcomes in the Full Analysis Set and Safety Population

Outcome	No. (%)		Treatment effect metric	Unadjusted		Adjusted ^a	
	Dual antiplatelet treatment (n = 369)	Alteplase (n = 350)		Treatment difference (95% CI)	P value	Treatment difference (95% CI)	P value
Primary outcome (full analysis set)							
mRS score 0-1 within 90 d ^b	346 (93.8)	320 (91.4)	Risk difference ^{c,d}	2.3% (−1.5% to 6.2%)	<.001	2.3% (−1.6% to 6.1%)	<.001
			Risk ratio ^c	1.38 (0.81 to 2.32)	.23	1.36 (0.80 to 2.30)	.22
Secondary outcomes (full analysis set)							
mRS score 0-2 within 90 d ^b	354 (95.9)	334 (95.4)	Risk difference ^c	0.5% (−2.5% to 3.5%)	.74	0.5% (−3.5% to 2.5%)	.83
			Risk ratio ^c	1.12 (0.56 to 2.24)	.74	1.12 (0.56 to 2.25)	.64
mRS score distribution within 90 d ^b			Odds ratio ^c	1.16 (0.83 to 1.61)	.39	1.11 (0.80 to 1.55)	.51
Early neurological improvement within 24 h ^e	62 (16.8)	74 (21.1)	Risk difference ^c	−4.1% (−9.8% to 1.7%)	.16	−3.1% (−8.7% to 2.4%)	.27
			Risk ratio ^c	0.95 (0.89 to 1.02)	.17	0.84 (0.62 to 1.14)	.27
Early neurological deterioration within 24 h ^f	17 (4.6)	32 (9.1)	Risk difference ^c	−4.5% (−8.2% to −0.8%)	.02	−4.6% (−8.3% to −0.9%)	.02
			Risk ratio ^c	0.50 (0.29 to 0.89)	.02	0.50 (0.28 to 0.89)	.02
Median change in NIHSS score at 24 h from baseline ^g	0 (−0.41 to 0)	0 (−0.69 to 0)	Geometric mean ratio ^c	0.03 (−0.05 to 0.11)	.51	0.01 (−0.07 to 0.09)	.68
Stroke or other vascular events within 90 d	1 (0.3)	2 (0.6)	Hazard ratio ^h	0.47 (0.04 to 5.20)	.54	0.46 (0.04 to 5.17)	.45
Death at 90 d	2 (0.5)	3 (0.9)	Risk difference ^c	−0.3% (−1.5% to 0.9%)	.61	−0.3% (−1.5% to 0.9%)	.49
			Risk ratio ^c	0.63 (0.11 to 3.76)	.61	0.58 (0.10 to 3.51)	.49
Safety outcomes (safety population)							
Symptomatic intracerebral hemorrhage ⁱ	1/371 (0.3)	3/352 (0.9)	Risk difference ^c	−0.6% (−1.7% to 0.5%)	.30	−2.4% (−12.1% to 7.3%)	.63
			Risk ratio ^c	0.32 (0.03 to 3.02)	.32	0.31 (0.03 to 2.99)	.36
Any bleeding events ^j	6/371 (1.6)	19/352 (5.4)	Risk difference ^c	−3.8% (−6.5% to −1.1%)	.006	−3.6% (−6.4% to −0.7%)	.01
			Risk ratio ^c	0.30 (0.12 to 0.74)	.009	0.31 (0.12 to 0.76)	.01

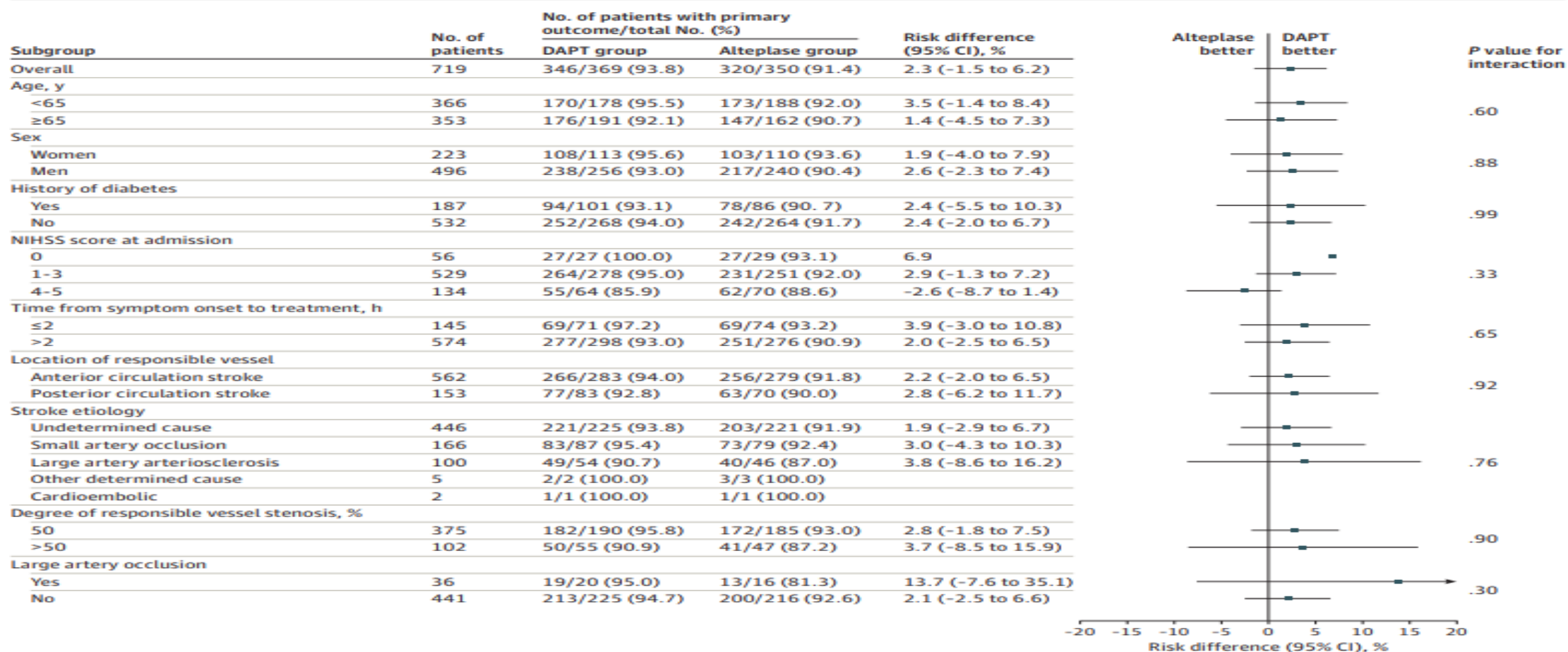
ARAMIS

Figure 2. Distribution of Modified Rankin Scale Scores at 90 Days in the Full Analysis Set



ARAMIS

Figure 3. Primary Outcome by Prespecified Subgroups in the Full Analysis Set



ARAMIS

- Patients with nondisabling minor acute ischemic stroke, DAPT was noninferior to intravenous alteplase when administered within 4.5 hours of stroke onset for the primary outcome of excellent functional outcome at 90 days.
- This trial demonstrated that short-term DAPT (12 [\pm 2] days) initiated in patients presenting within 4.5 hours of a nondisabling minor stroke had noninferior efficacy to intravenous alteplase on 90-day functional outcome with less bleeding risk.

ARAMIS

- Limitations: high cross over rate between 2 groups
- Study conducted in Asian population only.
- Imaging done prior to enrollment to confirm stroke.

Thank you!