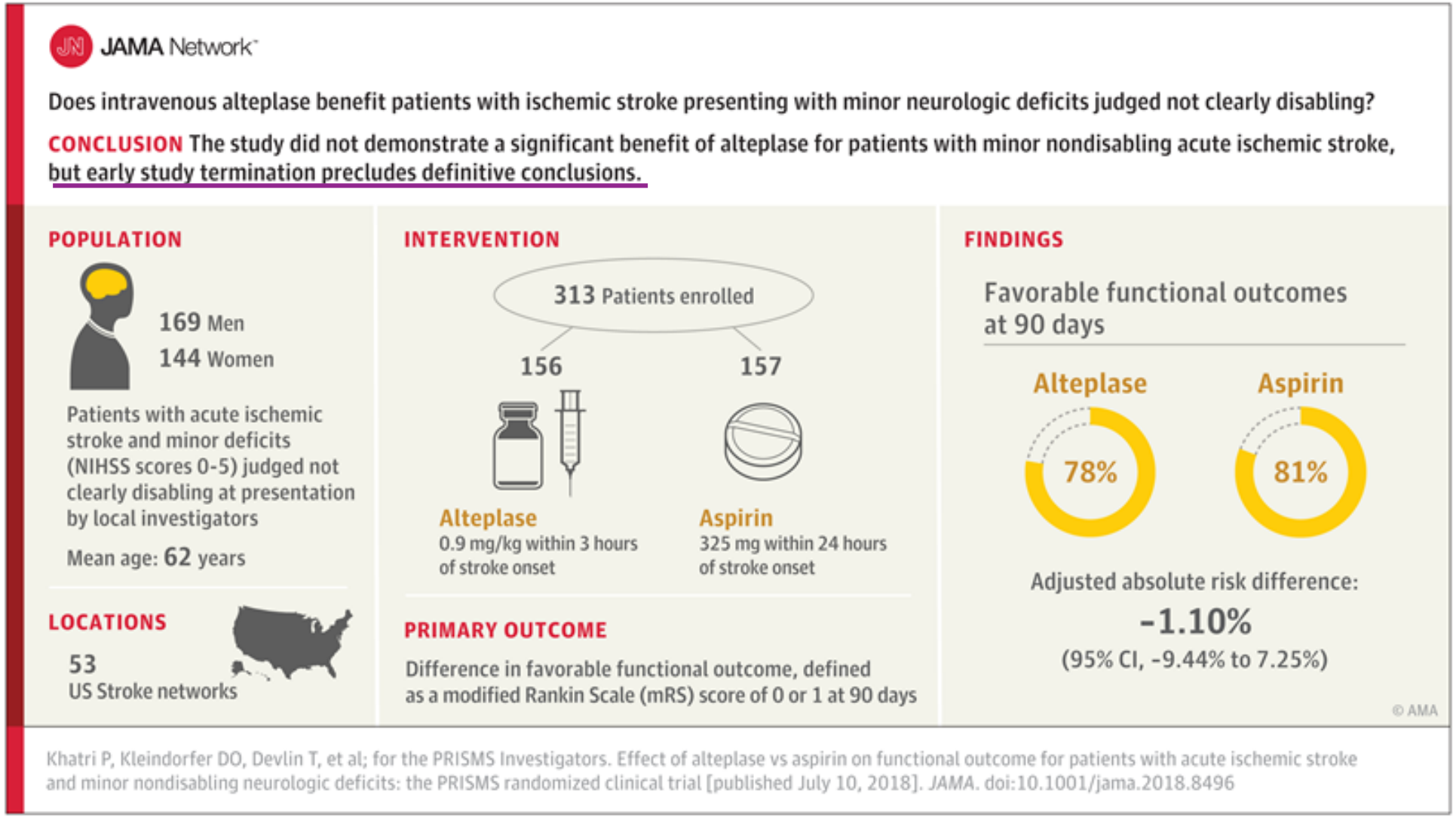
Duplice terapia antiaggregante vs Alteplase nei pazienti con ictus ischemico Minore: risultati del trial randomizzato ARAMIS

Background

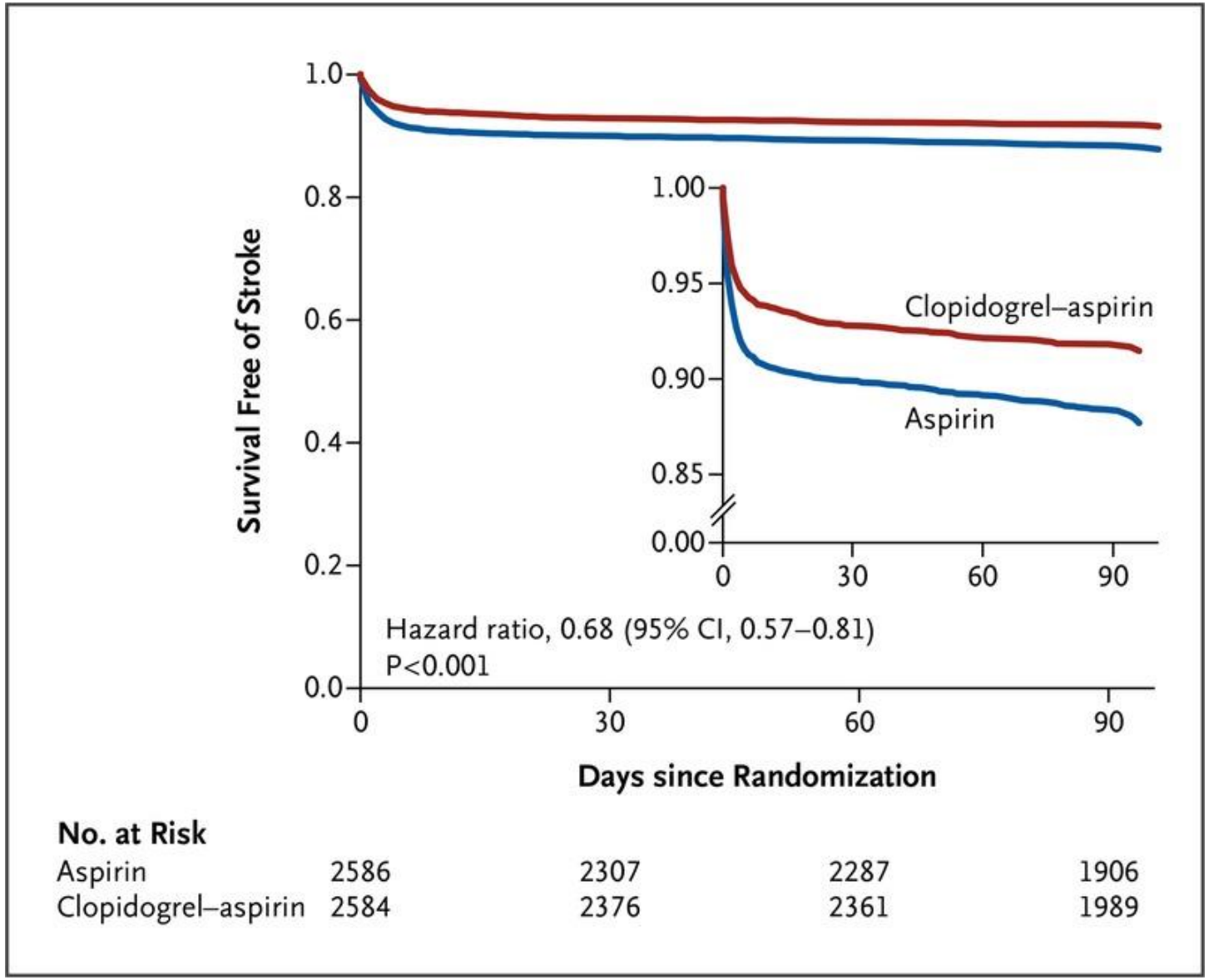
- Current guidelines recommend intravenous alteplase for patients with acute ischemic stroke (AIS) presenting within 4.5 hours of symptom onset.
- Minor stroke, defined as a National Institutes of Health Stroke Scale (NIHSS) score less than or equal to 5, accounted for approximately half of patients with AIS in 2016 (50.0%) and in 2019 (46.9%), but the evidence in support of intravenous thrombolysis for these patients has remained inconclusive.

PRISMS trial



CHANCE trial

- 5170 patients within 24h after the onset of minor stroke or high-risk TIA
- clopidogrel at an initial dose of 300 mg, followed by 75 mg per day for 90 days, plus aspirin at a dose of 75 mg per day for the first 21 days) or to placebo plus aspirin (75 mg per day for 90 days

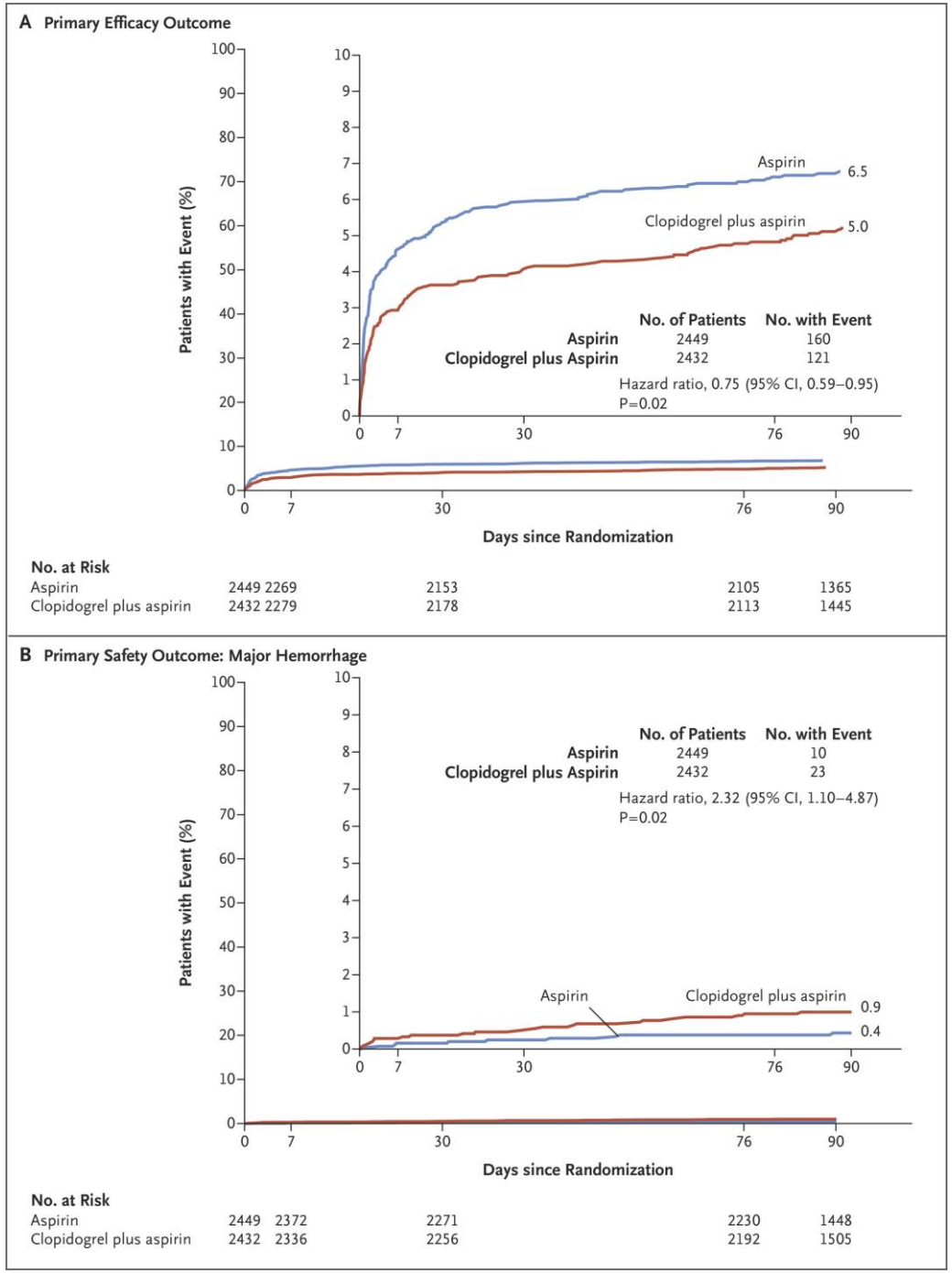


N Engl J Med 2013; 369:11-19

POINT trial

- 4881 patients with minor ischemic stroke or high-risk TIA
- Clopidogrel at a loading dose of 600 mg on day 1, followed by 75 mg per day from day 2 to day 90, plus aspirin (at a dose of 50 to 325 mg per day) vs. the same range of doses of aspirin alone.

N Engl J Med 2018; 379:215-225



JAMA | Original Investigation

Dual Antiplatelet Therapy vs Alteplase for Patients With Minor Nondisabling Acute Ischemic Stroke
The ARAMIS Randomized Clinical Trial

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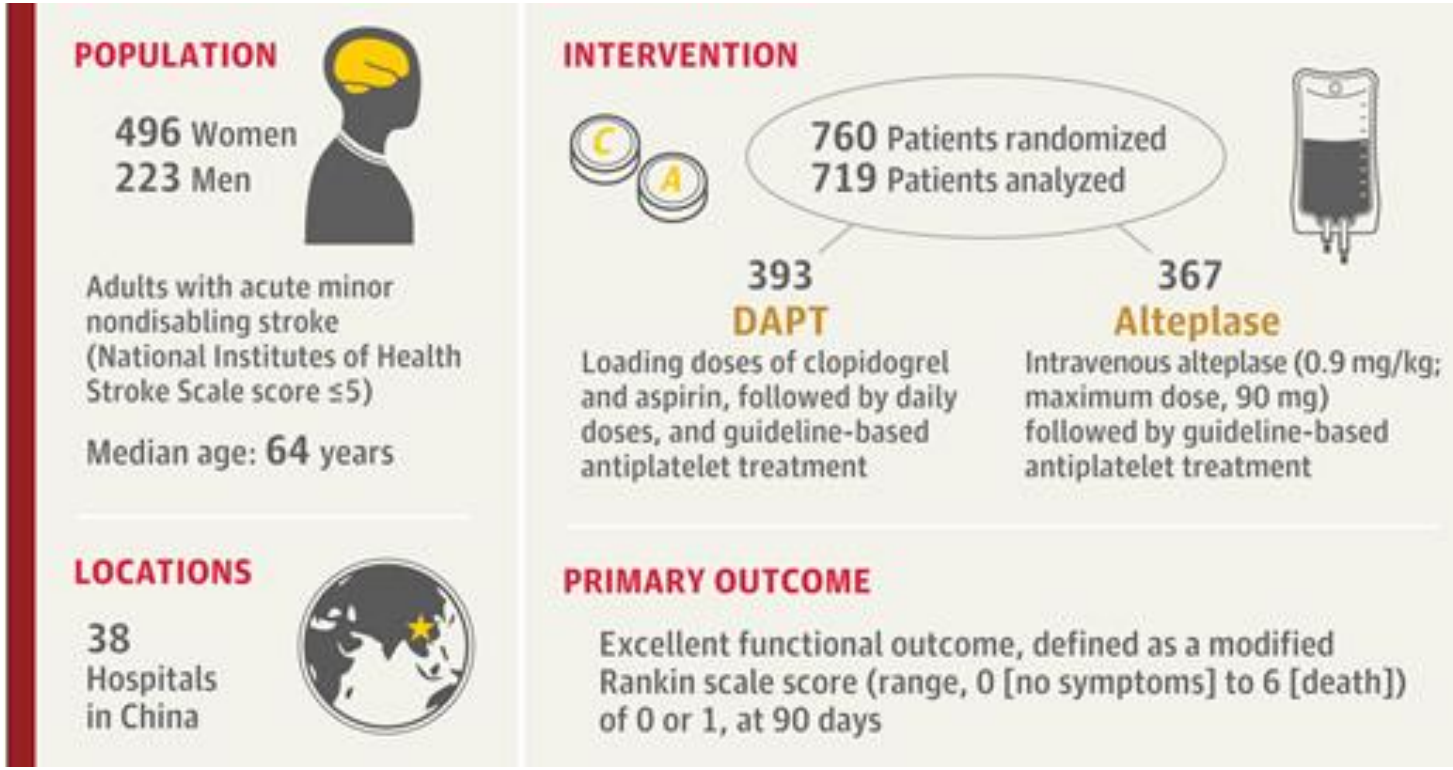
Methods

- Is dual antiplatelet therapy noninferior to intravenous thrombolysis in patients with minor nondisabling acute ischemic stroke?



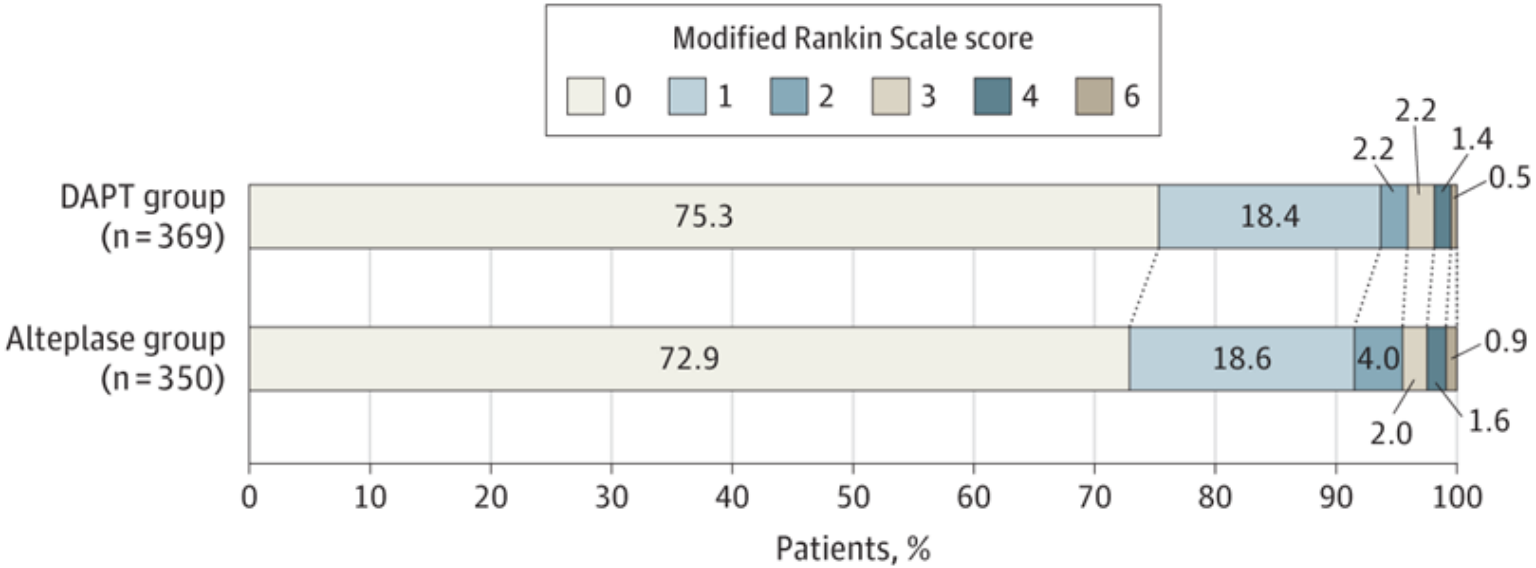
Baseline characteristics

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)

Baseline characteristics	No. (%)	
	Dual antiplatelet therapy (n = 369)	Alteplase (n = 350)
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)

Baseline characteristics	No. (%)	
	Dual antiplatelet therapy (n = 369)	Alteplase (n = 350)
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)
Degree of responsible vessel stenosis[f]		
Mild (<50%)	191/246 (77.6)	185/232 (79.7)
Moderate (50%-69%)	21/246 (8.5)	15/232 (6.5)
Severe (70%-99%)	14/246 (5.7)	16/232 (6.9)
Occlusion (100%)	20/246 (8.1)	16/232 (6.9)

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



- The raw distribution of scores is shown. Modified Rankin Scale scores ranged from 0 to 6, with 0 indicating 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 indicates dual antiplatelet therapy.

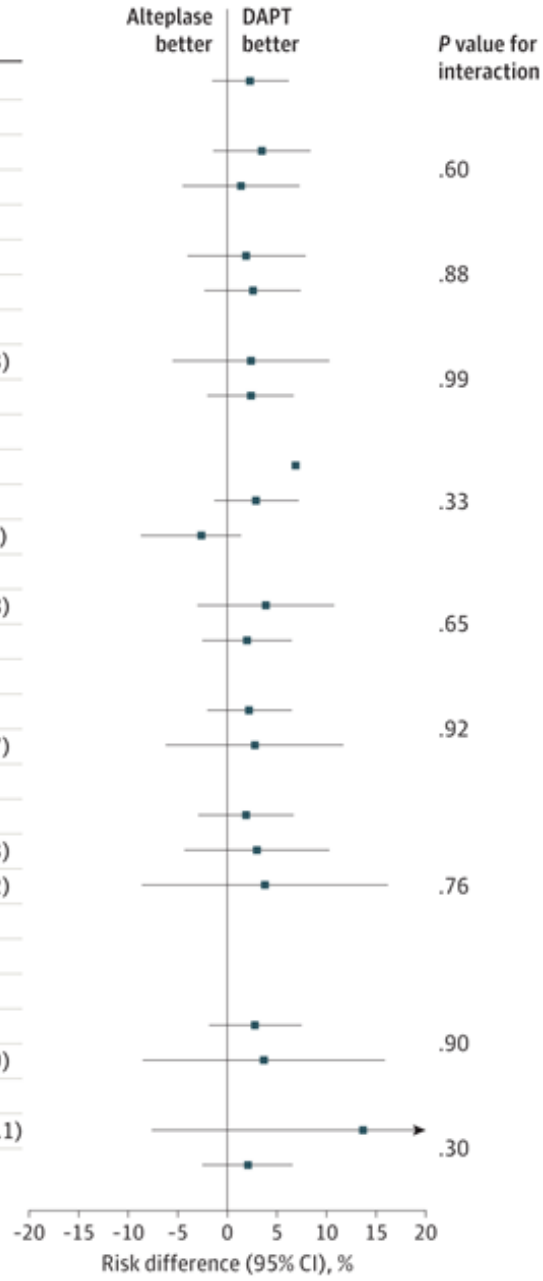
Trial Outcomes in the Full Analysis Set and Safety Population

- Early neurological improvement: decrease in NIHSS score ≥ 2.
- Early neurological deterioration: increase in NIHSS score of ≥ 2, but not as a result of ICH

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

Primary Outcome by Prespecified Subgroups in the Full Analysis Set

Subgroup	No. of patients	No. of patients with primary outcome/total No. (%)		Risk difference (95% CI), %	*P* value for interaction
		DAPT group	Alteplase group		
Overall	719	346/369 (93.8)	320/350 (91.4)	2.3 (-1.5 to 6.2)	
Age, y					
<65	366	170/178 (95.5)	173/188 (92.0)	3.5 (-1.4 to 8.4)	.60
≥65	353	176/191 (92.1)	147/162 (90.7)	1.4 (-4.5 to 7.3)	
Sex					
Women	223	108/113 (95.6)	103/110 (93.6)	1.9 (-4.0 to 7.9)	.88
Men	496	238/256 (93.0)	217/240 (90.4)	2.6 (-2.3 to 7.4)	
History of diabetes					
Yes	187	94/101 (93.1)	78/86 (90. 7)	2.4 (-5.5 to 10.3)	.99
No	532	252/268 (94.0)	242/264 (91.7)	2.4 (-2.0 to 6.7)	
NIHSS score at admission					
0	56	27/27 (100.0)	27/29 (93.1)	6.9	
1-3	529	264/278 (95.0)	231/251 (92.0)	2.9 (-1.3 to 7.2)	.33
4-5	134	55/64 (85.9)	62/70 (88.6)	-2.6 (-8.7 to 1.4)	
Time from symptom onset to treatment, h					
≤2	145	69/71 (97.2)	69/74 (93.2)	3.9 (-3.0 to 10.8)	.65
>2	574	277/298 (93.0)	251/276 (90.9)	2.0 (-2.5 to 6.5)	
Location of responsible vessel					
Anterior circulation stroke	562	266/283 (94.0)	256/279 (91.8)	2.2 (-2.0 to 6.5)	.92
Posterior circulation stroke	153	77/83 (92.8)	63/70 (90.0)	2.8 (-6.2 to 11.7)	
Stroke etiology					
Undetermined cause	446	221/225 (93.8)	203/221 (91.9)	1.9 (-2.9 to 6.7)	
Small artery occlusion	166	83/87 (95.4)	73/79 (92.4)	3.0 (-4.3 to 10.3)	
Large artery arteriosclerosis	100	49/54 (90.7)	40/46 (87.0)	3.8 (-8.6 to 16.2)	.76
Other determined cause	5	2/2 (100.0)	3/3 (100.0)		
Cardioembolic	2	1/1 (100.0)	1/1 (100.0)		
Degree of responsible vessel stenosis, %					
50	375	182/190 (95.8)	172/185 (93.0)	2.8 (-1.8 to 7.5)	.90
>50	102	50/55 (90.9)	41/47 (87.2)	3.7 (-8.5 to 15.9)	
Large artery occlusion					
Yes	36	19/20 (95.0)	13/16 (81.3)	13.7 (-7.6 to 35.1)	.30
No	441	213/225 (94.7)	200/216 (92.6)	2.1 (-2.5 to 6.6)	



Limitations

- The noninferiority design of the trial may be a main limitation due to DAPT as a standard treatment in this target population according to the current guidelines.
- High crossover rate (20.4%)
- The lack of vessel imaging data in some patients makes the subgroup analysis of etiology and large artery occlusion less powerful, because previous studies showed the possible benefit of alteplase or tenecteplase in patients with mild stroke with large artery atherosclerosis or large artery occlusion
- Open-label design; blinded end point evaluations were used to reduce bias in the assessment of the primary end point. For secondary end points, the neurologist who was unblinded to the treatment assessment conducted the early neurological assessment, which may have led to assessment bias for the early neurological outcomes.
- Patients with possible cardioembolism were excluded and a lower percentage of women were enrolled.
- High rates of the primary end point in the DAPT and alteplase groups may have created a ceiling effect.

Conclusions

- Among patients presenting with minor nondisabling acute ischemic stroke within 4.5 hours of symptom onset, dual antiplatelet treatment was noninferior to intravenous alteplase with regard to excellent functional outcome at 90 days.