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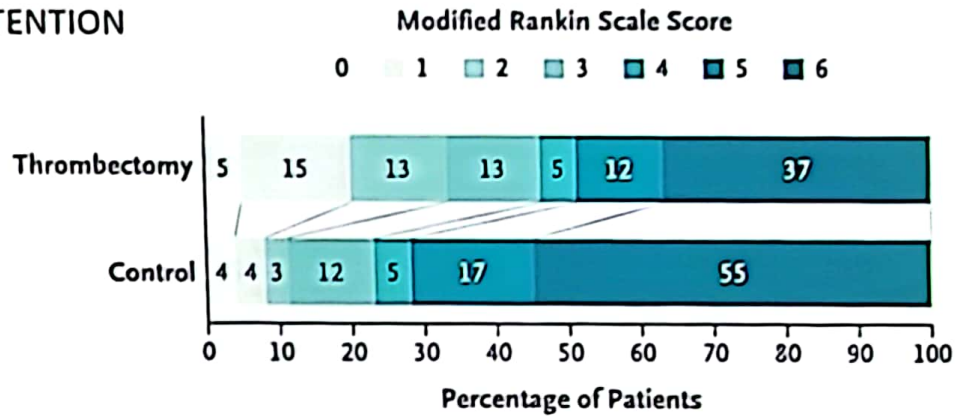
Intra-arterial Tenecteplase Following Successful Endovascular Reperfusion in Patients with Acute Posterior Circulation Arterial Occlusion: a Multicenter Randomized Controlled Trial (ATTENTION IA)

Wei Hu; Chunrong Tao; Li Wang; Zhongjun Chen; Adnan I. Qureshi; Thanh N. Nguyen; Jeffrey L. Saver; Paul G. Nogueira; Xinfeng Liu

Background

ATTENTION



N Engl J Med 2022 Vol. 387 Issue 15 Pages 1361-1372.

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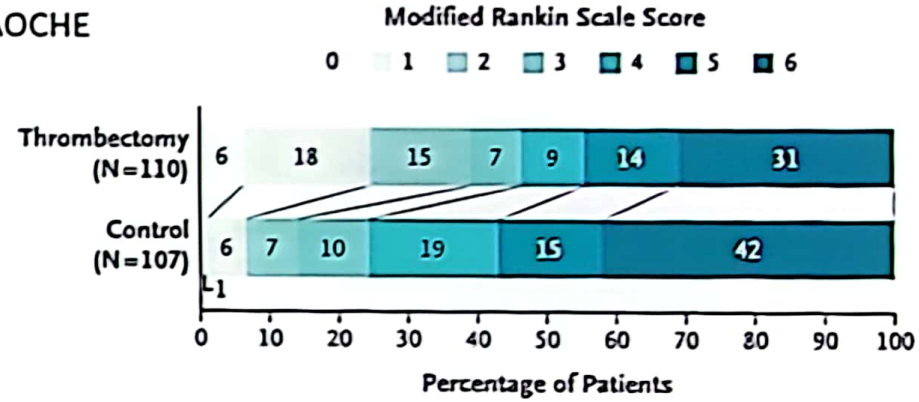

N Engl J Med 2022 Vol. 387 Issue 15 Pages 1373-1384

Background

- Endovascular thrombectomy (EVT) is an established treatment for patients with acute ischemic stroke caused by basilar artery occlusion.

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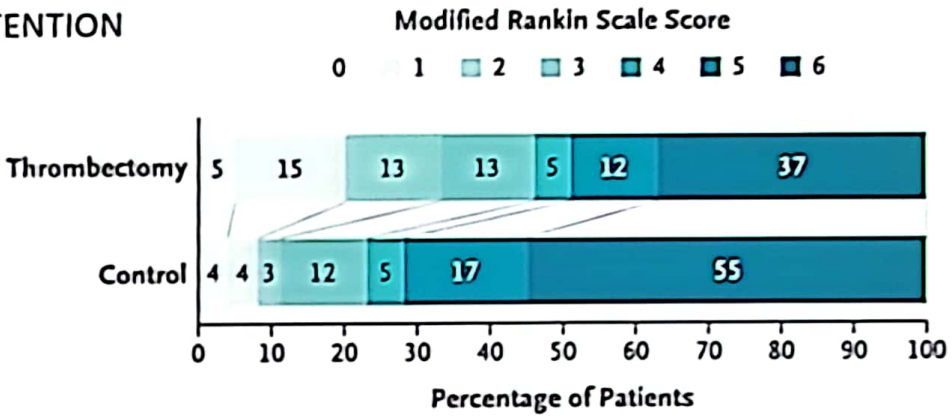

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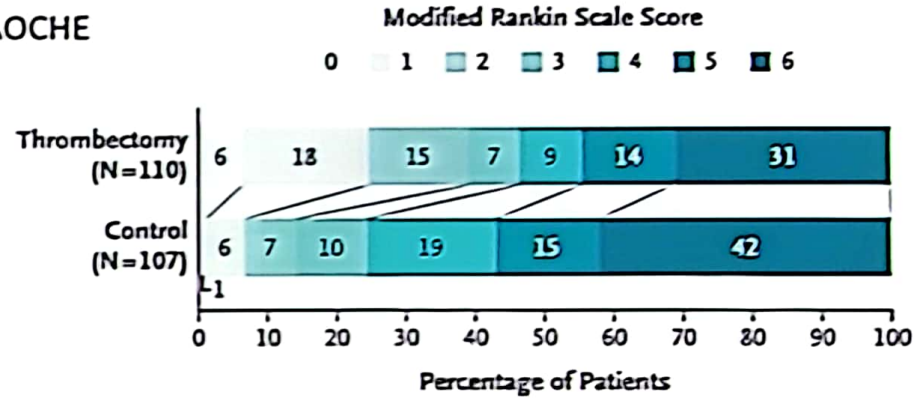

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Background

- Endovascular thrombectomy (EVT) is an established treatment for patients with acute ischemic stroke caused by basilar artery occlusion.
- However, excellent outcomes remain infrequent with EVT.

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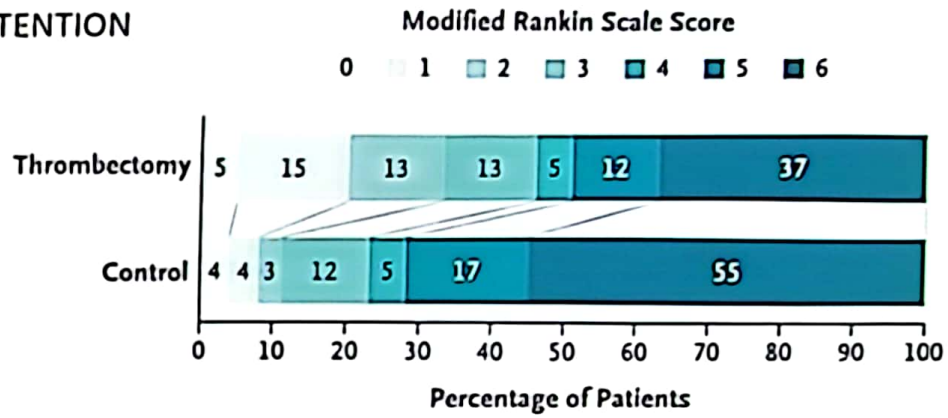

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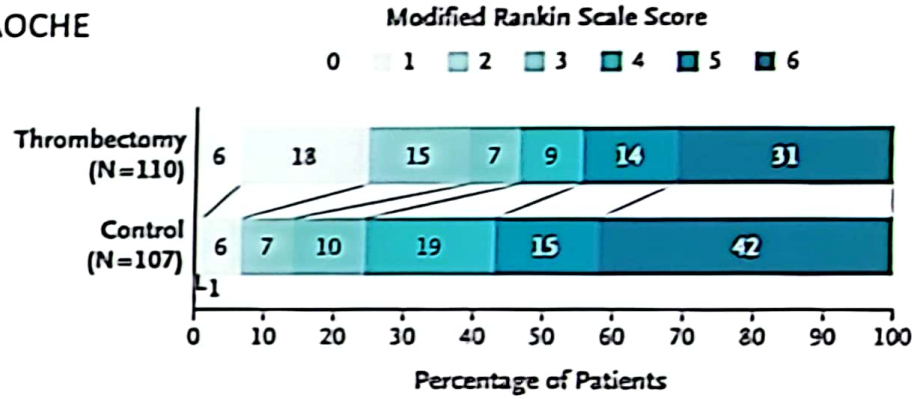

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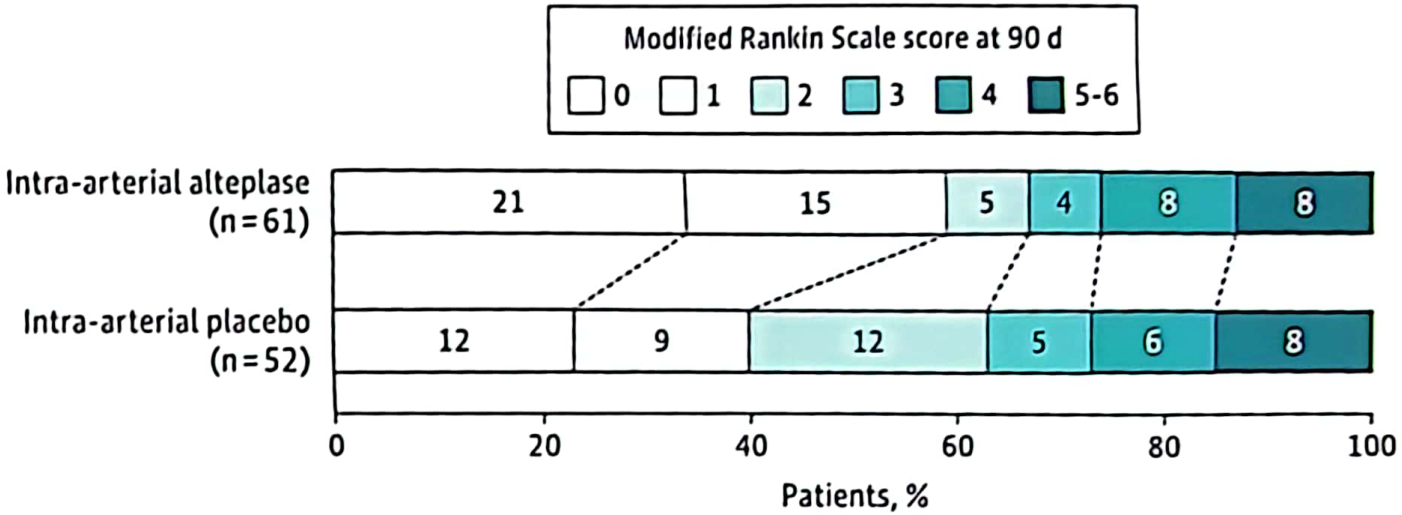
Background: The CHOICE Trial



Intra-arterial rt-PA following EVT in anterior circulation was safe and likely beneficial

Adjusted risk difference of mRS 0-1: 18.24%

JAMA 2022 Vol. 327 Issue 9 Pages 826-835

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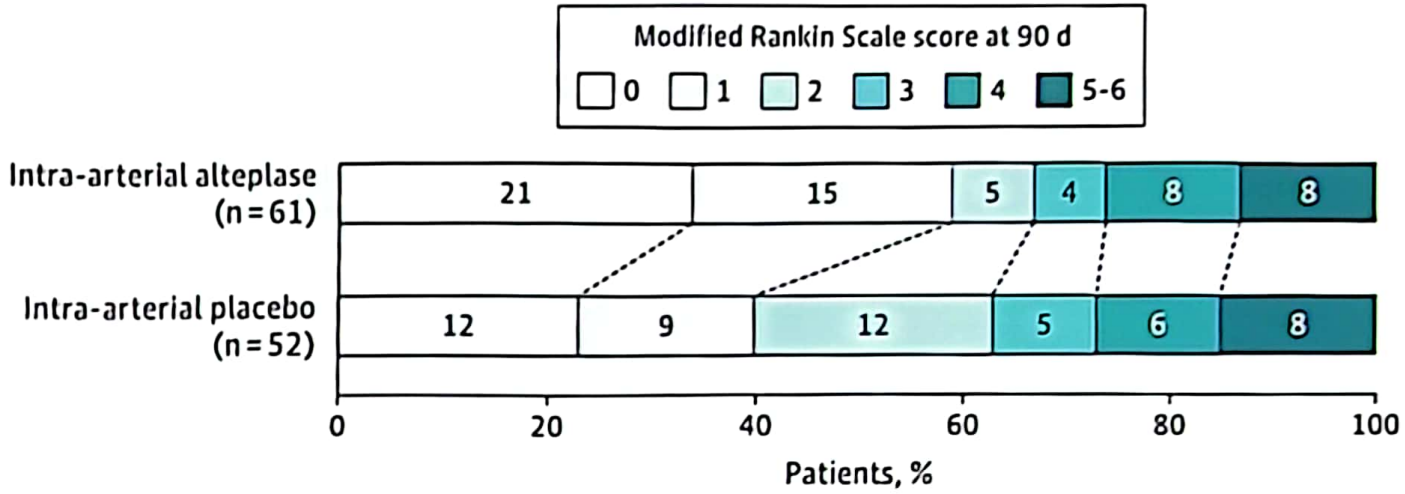

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Study Protocol

Study Design	Multi-center, prospective, randomized, open, blinded endpoint (PROBE), controlled trial
Patient Population	AIS patients with occlusion of the intracranial VA, BA, or the P1 segment of the PCA.
Sites	31 Comprehensive Stroke Centers in China
Sample Size	208 subjects ▪ Assumption 90-day mRS 0–1: 20% in standard medical care vs. 38% in IA TNK, yielding an absolute risk reduction of 18% ▪ Two-sided, normal approximation test, alpha = 0.05, 1:1 randomization, 80% power, 5% attrition
Follow-up	24-72 hours, 5-7 days or Discharge, and Day 90

Key Eligibility Criteria

INCLUSION

- Occlusion: vertebral, basilar, P1 segments
- EVT leading to **eTICI 2b50/3**
- Age ≥ 18 years
- NIHSS on admission ≥ 6
- pc-ASPECTS ≥ 6
- Estimated time of posterior circulation artery occlusion to randomization < 24 hours

EXCLUSION

- Premorbid mRS >1
- Contraindication to IVT (except time to therapy)
- Complete clinical recovery by end of the EVT procedure

Treatment Intervention

TNK group	IA tenecteplase (0.0625 mg/kg, max dose 6.25 mg) through a distal access catheter or microcatheter located proximal to the residual thrombus (if still present) or distal to the origin of the main pontine perforator branches over 15 s
Control group	terminated the procedure without additional IA therapy.

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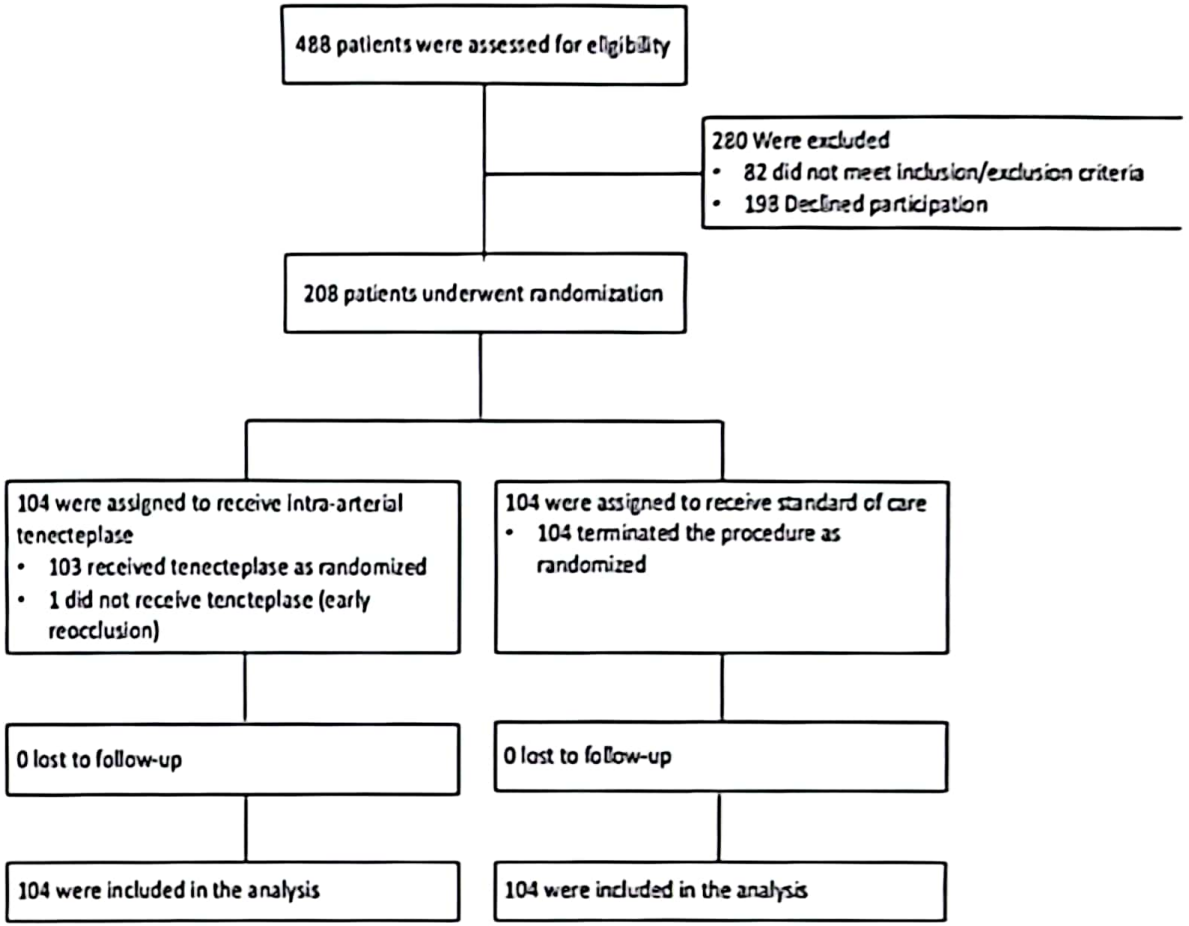
Study Endpoints

Primary Endpoint	Excellent outcome defined as mRS of 0–1 at day 90 (±14 days)
Secondary Endpoints	(1) Favorable outcome defined as mRS of 0–2 at day 90 (±14days); (2) Ordinal mRS Shift analysis at day 90 (±14days); (3) NIHSS at 24–72 h and at 5–7 days or discharge; (4) EQ5D-5L and Barthel index at 90 days (±14 days).
Safety Endpoints	Mortality at 90 day (±14days); Symptomatic ICH* rates within 36 hours Procedural related complications

* Symptomatic ICH was defined by the modified **Heidelberg definition** (local or remote parenchymal hemorrhage type 2, subarachnoid hemorrhage, and/ or intraventricular hemorrhage on the post-treatment imaging scan, combined with a neurological deterioration of 4 points or more on the NIHSS from baseline, or from the lowest NIHSS between baseline and 36 hours, or leading to death that the CEC judged causative of the deterioration).

Enrollment: January 24, 2023 to August 24, 2023



Demographics

Characteristic	Tenecteplase (N = 104)	Control (N = 104)
Mean age ± SD-yr	65.0 ± 11.3	67.3 ± 10.8
Male sex - no. (%)	84 (80.8)	73 (70.2)
mRS score 1 before stroke - no. (%)	10 (9.6)	11 (10.6)
Median NIHSS (IQR)	19.5 (12, 35)	23 (14, 35)
Median pc-ASPECTS (IQR)	9 (8, 10)	8 (8, 10)

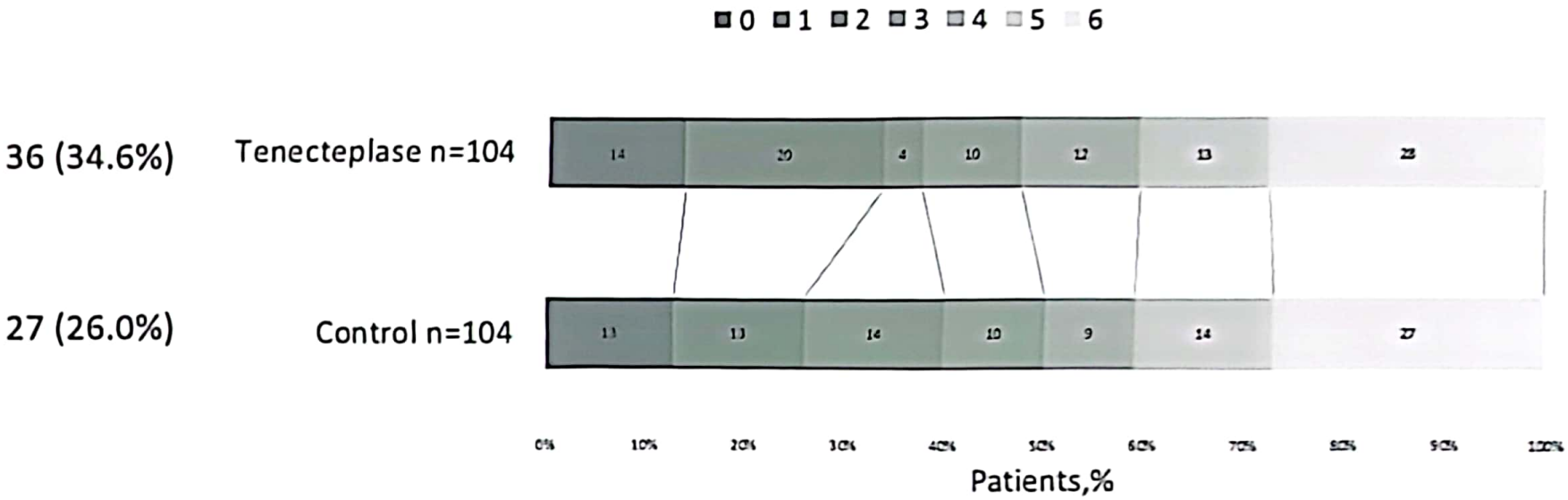
Treatment time in hours

Characteristic	Tenecteplase (N = 104)	Control (N = 104)
	Median hours (IQR)	
Onset to puncture	4.6 (3.1, 7.0)	5.9 (2.9, 7.8)
Onset to recanalization	5.8 (4.0, 8.4)	7.0 (3.8, 9.4)
Puncture to recanalization	1.0 (0.6, 1.4)	1.0 (0.7, 1.7)
Recanalization to randomization	0.2 (0.1, 0.4)	0.2 (0.1, 0.5)

Artery occlusion site

Characteristic	Tenecteplase (N = 104)	Control (N = 104)
Vertebral artery V4	26 (25.0)	28 (26.9)
Proximal Basilar artery	23 (22.1)	18 (17.3)
Middle Basilar artery	24 (23.1)	28 (26.9)
Distal Basilar artery	28 (26.9)	23 (22.1)
P1 segment	3 (2.9)	7 (6.7)

Primary Outcome: mRS 0-1 at 90 days



Measure of Effect	Adjusted Value (95% CI)	P value
Risk ratio	1.3 (0.9, 2.0)	0.15
Risk difference	7.6% (−4.3, 19.5)	0.21

Adjusted for age, pre-stroke mRS, time from onset to randomization, stroke severity (NIHSS) .
The 95% CI not adjusted for multiple comparisons.

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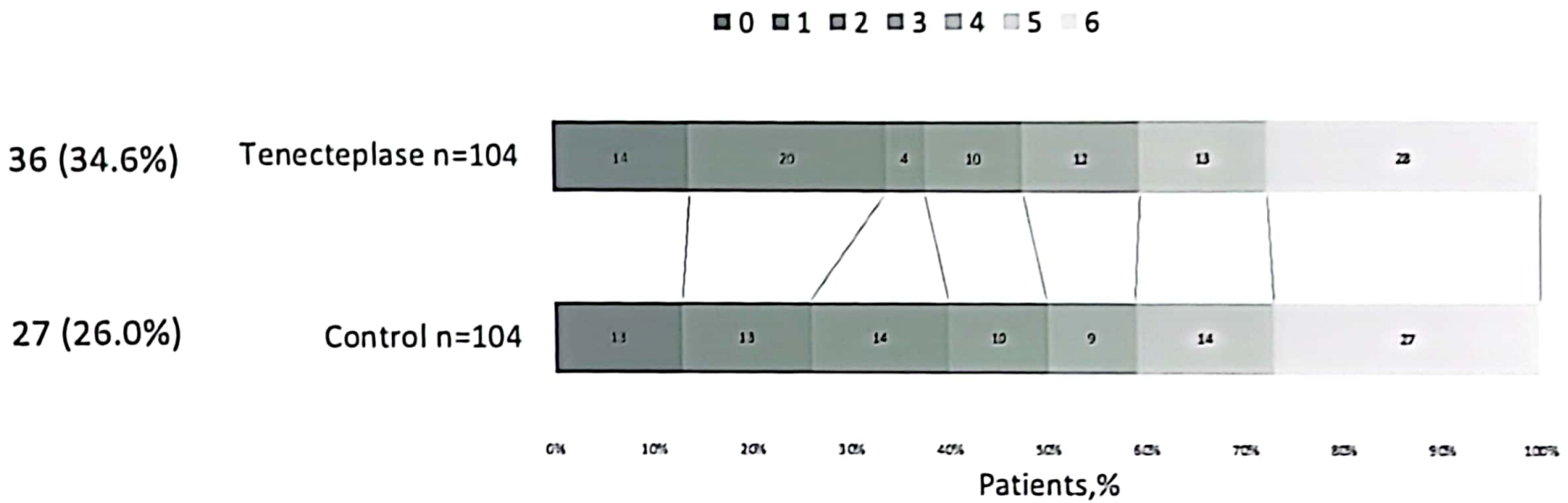

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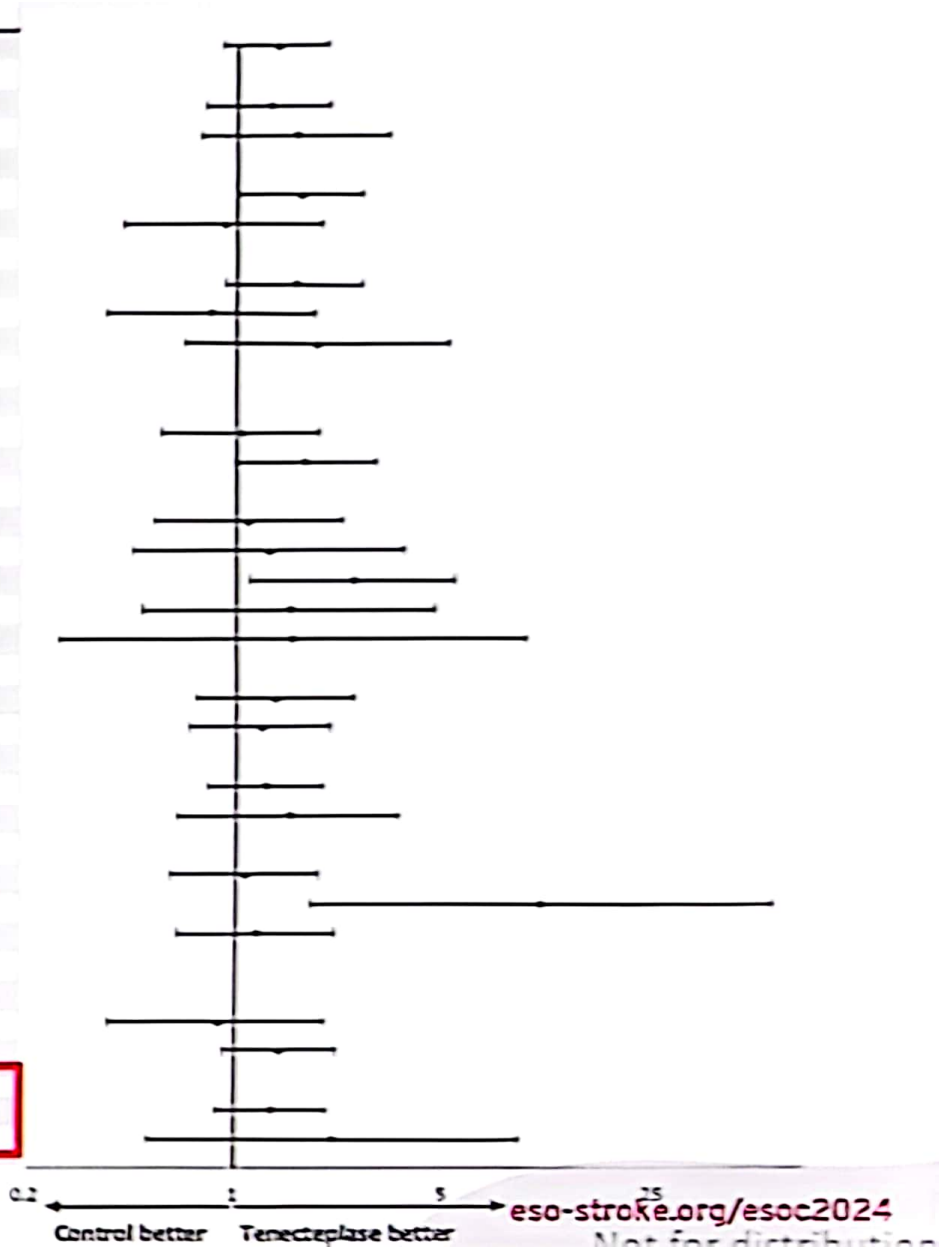
The 95% CI not adjusted for multiple comparisons.

Day 90 mRS 0-1 by Subgroup

Subgroup	No. of patients	Adjusted Risk Ratio (95%CI)
All patients	208	1.34 (0.90, 1.98)
Age		
<70 yr	117	1.27 (0.79, 2.03)
≥70 yr	91	1.56 (0.77, 3.17)
NIHSS score		
6-19	94	1.63 (1.02, 2.60)
≥20	114	0.91 (0.43, 1.93)
Cause of stroke		
Large-artery atherosclerosis	129	1.55 (0.92, 2.62)
Cardioembolism	52	0.82 (0.37, 1.82)
Undetermined or other cause	27	1.84 (0.67, 5.10)
Estimated time from posterior artery occlusion to randomization		
<6 hr	81	1.03 (0.56, 1.87)
≥6 hr	127	1.68 (0.98, 2.89)
Location of artery occlusion		
Vertebral artery V4	54	1.09 (0.53, 2.24)
Proximal Basilar artery	41	1.28 (0.45, 3.61)
Middle Basilar artery	52	2.45 (1.12, 5.35)
Distal Basilar artery	51	1.50 (0.49, 4.58)
P1 segment	10	1.54 (0.26, 9.29)
Baseline PC-ASPECTS		
≤8	102	1.35 (0.74, 2.46)
>8	106	1.21 (0.70, 2.08)
Intravenous thrombolysis		
No	155	1.26 (0.81, 1.96)
Yes	53	1.50 (0.64, 3.48)
First-line thrombectomy strategy		
Aspiration	80	1.07 (0.61, 1.89)
Stent retriever	36	10.44 (1.78, 61.17)
Aspiration and stent-retriever combination	78	1.17 (0.64, 2.12)
eTICI		
2b50-2b67	29	0.83 (0.38, 2.00)
[illegible]	178	1.41 (0.92, 2.19)
Immediate stenting		
No	165	1.32 (0.87, 2.02)
Yes	43	2.11 (0.51, 8.62)



Secondary Efficacy Outcomes

Outcome	Tenecteplase	Control	Measure of effect	Adjusted Value (95% CI)
mRS distribution	4 (1, 6)	3.5 (1, 6)	Common odds ratio	1.00 (0.61, 1.62)
mRS 0 to 2 at 90 days	40 (38.5)	42 (40.4)	Risk ratio	0.91 (0.66, 1.26)
mRS 0 to 3 at 90 days	50 (48.1)	52 (50.0)	Risk ratio	0.92 (0.70, 1.19)
NIHSS score at 24-72 hr	16 (6, 35)	16 (6, 35)	Beta coefficient	1.43 (-1.80, 4.67)
NIHSS score at 5–7 days or discharge	10 (2, 35)	8 (2, 28)	Beta coefficient	1.43 (-2.17, 5.04)
Barthel Index of 95 or 100 at 90 days	41 (39.4)	39 (37.5)	Risk ratio	1.01 (0.73, 1.39)
EQ-5D-5L score at 90 days	0.2 (0, 1)	0.6 (0, 0.98)	Beta coefficient	-0.06 (-0.19, 0.06)

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Primary Safety Outcomes

Outcome	Tenecteplase No. (%)	Control No. (%)	Adjusted Value (95% CI)
Death	29 (27.9)	28 (26.9)	1.12 (0.73, 1.71)
Death within 7 days	21 (20.2)	18 (17.3)	1.18 (0.69, 2.04)
Symptomatic ICH within 36 hours	8 (8.3)	3 (3.1)	2.87 (0.81, 10.24)

Secondary imaging and safety outcomes

Outcome	Tenecteplase No. (%)	Control No. (%)	Adjusted Value (95% CI)
Patency at 24-72 hr on CTA/MRA	63 (90.0)	64 (91.4)	0.98 (0.88, 1.10)
Radiological intracranial hemorrhage at 24-72h	26 (26.8)	15 (15.5)	1.94 (1.14, 3.29)
Asymptomatic ICH	18 (17.3)	12 (11.5)	1.63 (0.86, 3.10)

Discussion

- Tenecteplase over alteplase as the thrombolytic agent

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- Tenecteplase over alteplase as the thrombolytic agent
- Allowed stent placement

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- Allowed stent placement
- Included patients who had received IVT prior to EVT

Strengths & Limitations:

Strengths

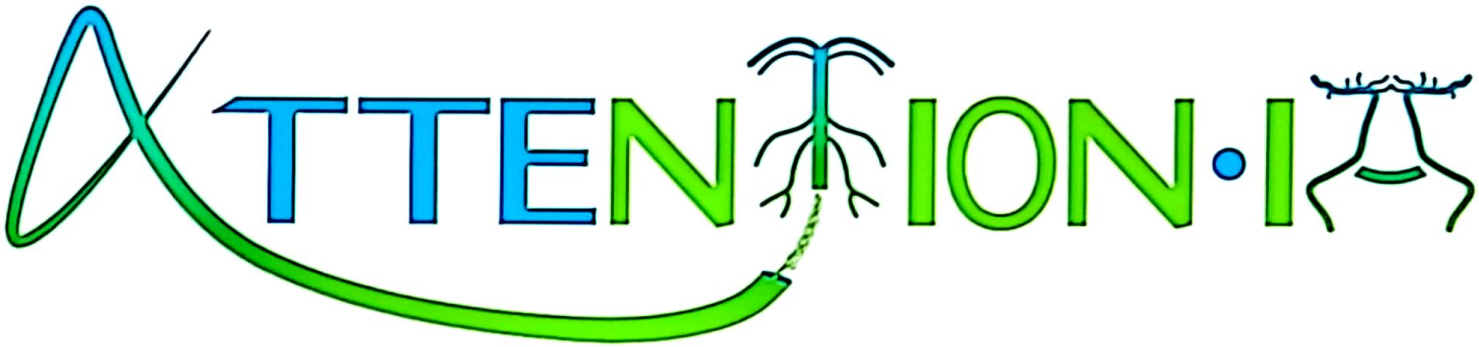
- Randomized clinical design
- Broad eligibility criteria
- Fast recruitment rate

Limitations

- Exclusive enrollment of Chinese patients
- No IA placebo group (PROBE)

CONCLUSION

- In patients with acute ischemic stroke due to proximal large or medium vessel occlusions of the posterior intracranial circulation, addition of intra-arterial tenecteplase to endovascular therapy:
  - Does NOT provide any added benefit
  - May potentially increase the risk of symptomatic ICH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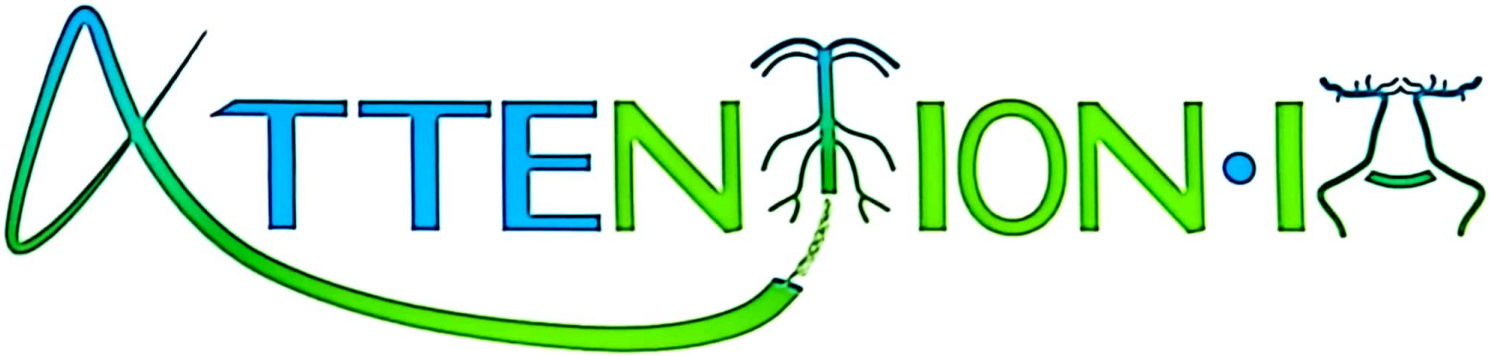

- Thanks to All Participating Patients and their Families, and the ATTENTION IA Investigators!

Disclosure of conflict of interest

- RGN reports consulting fees for advisory roles with Anaconda, Biogen, Cerenovus, Genentech, Philips, Hybernia, Imperative Care, Medtronic, Phenox, Phillips, Prolong Pharmaceuticals, Stryker Neurovascular, Shanghai Wallaby, Synchron, and stock options for advisory roles with Astrocyte, Brainomix, Cerebrotech, Ceretrieve, Corindus Vascular Robotics, Vesalio, Viz-AI, RapidPulse and Perfuze. RGN is one of the Principal Investigators of the "Endovascular Therapy for Low NIHSS Ischemic Strokes (ENDOLOW)" trial Funding for this project is provided by Cerenovus. RGN is the Principal Investigator of the "Combined Thrombectomy for Distal MedIUm Vessel Occlusion StroKe (DUSK)" trial. Funding for this project is provided by Stryker Neurovascular. RGN is an investor in Viz-AI, Perfuze, Cerebrotech, Reist/Q'Apel Medical, Truvic, Tulavi Therapeutics, Vastrax, Piraeus Medical, Brain4Care, Quantanosis AI, and Viseon.
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- T.Nguyen reports Associate Editor of Stroke; advisory board of Brainomix.
- Wei Hu, Chunrong Tao, Li Wang, Zhongjun Chen, Adnan I. Qureshi and Xinfeng Liu have no financial conflicts of interest.