Thrombolysis Update 2025

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May 12, 2025

Disclosures

I have no financial relationships with the developers of any of the products discussed.

Clinical Trials

- NeuSTART - NINDS
- StrokeNET - NINDS
- ASPIRE - NINDS
- DISCOVERY - NINDS
- ESCAPE MeVO – Canadian Institutes of Health Research
- CAPTIVA – NINDS
- STEP – NINDS

Intra-Arterial Thrombolytics?

Future Directions

1. ***More comparisons of TNK and alteplase.***

2. ***Opportunities to extend the window for IV thrombolytics.***

3. ***Combination of IV thrombolytics and EVT in different subgroups.***

PROACT II

Intra-arterial Prourokinase for Acute Ischemic Stroke

The PROACT II Study: A Randomized Controlled Trial

Anthony Furlan, MD
Randall Higashida, MD
Lawrence Wechsler, MD
Michael Gent, DSc
Howard Rowley, MD
Carlos Kase, MD
Michael Pessin, MD†
Arvind Ahuja, MD
Fred Callahan, MD
Wayne M. Clark, MD
Frank Silver, MD
Frank Rivera, MD
for the PROACT Investigators

Context Intravenous tissue-type plasminogen activator can be beneficial to some patients when given within 3 hours of stroke onset, but many patients present later after stroke onset and alternative treatments are needed.

Objective To determine the clinical efficacy and safety of intra-arterial (IA) recombinant prourokinase (r-proUK) in patients with acute stroke of less than 6 hours' duration caused by middle cerebral artery (MCA) occlusion.

Design PROACT II (Prolyse in Acute Cerebral Thromboembolism II), a randomized, controlled, multicenter, open-label clinical trial with blinded follow-up conducted between February 1996 and August 1998.

Setting Fifty-four centers in the United States and Canada.

Patients A total of 180 patients with acute ischemic stroke of less than 6 hours' duration caused by angiographically proven occlusion of the MCA and without hemorrhage or major early infarction signs on computed tomographic scan.

Intervention Patients were randomized to receive 9 mg of IA r-proUK plus heparin (n = 121) or heparin only (n = 59).

Main Outcome Measures The primary outcome, analyzed by intention-to-treat,

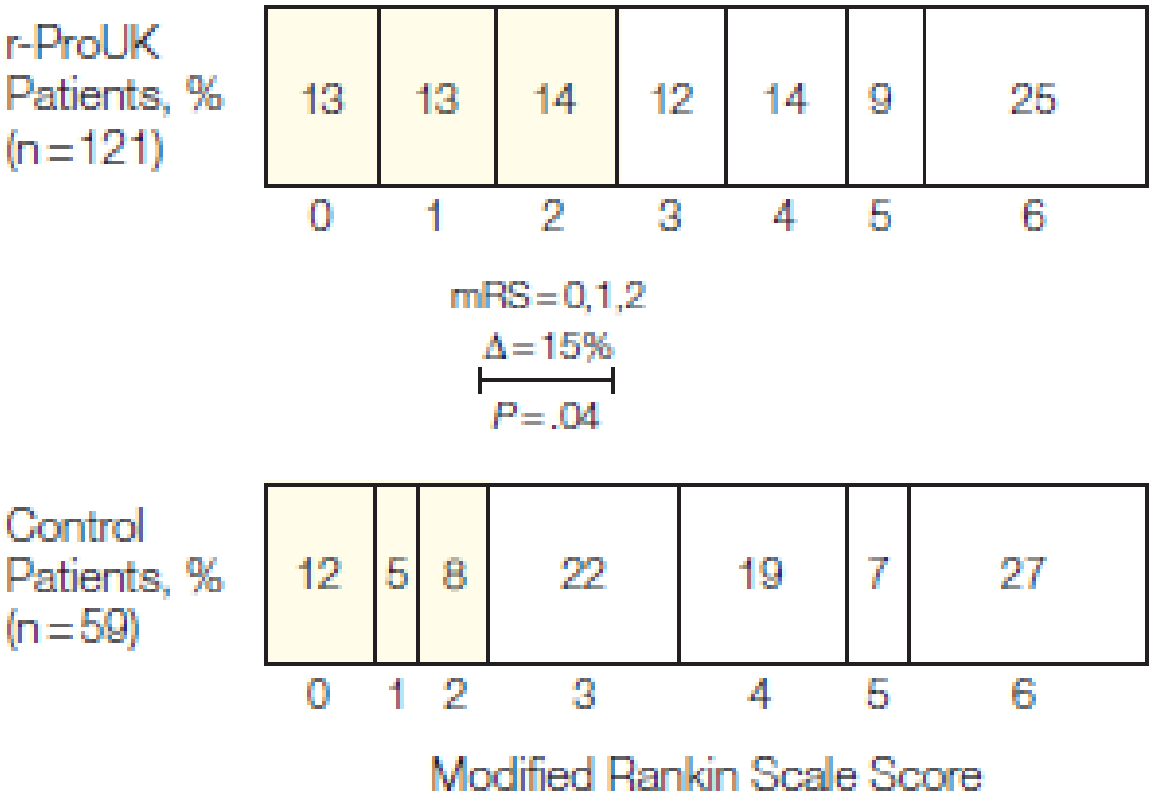
Furlan A, et al. PROACT II. JAMA 1999;282(21):2003

PROACT II: Methods

- **All patients: heparin 2000 U bolus, 500 U/hr infusion x 4 hr**
- **Antithrombotic prohibited for 24 hr**
- **Infusion microcatheter placed in the proximal 1/3 of the MCA thrombus or as near to the thrombus as possible**
- **Mechanical disruption of the clot was not permitted**
- **r-ProUK infused at 30 cc/hr (4.5 mg) in 1st hour; 4.5 mg in 2nd hr**

Furlan A, et al. PROACT II. JAMA 1999;282(21):2003

PROACT II: mRS ≤ 2 at 90 days



rProUK: 40%

Control: 25%

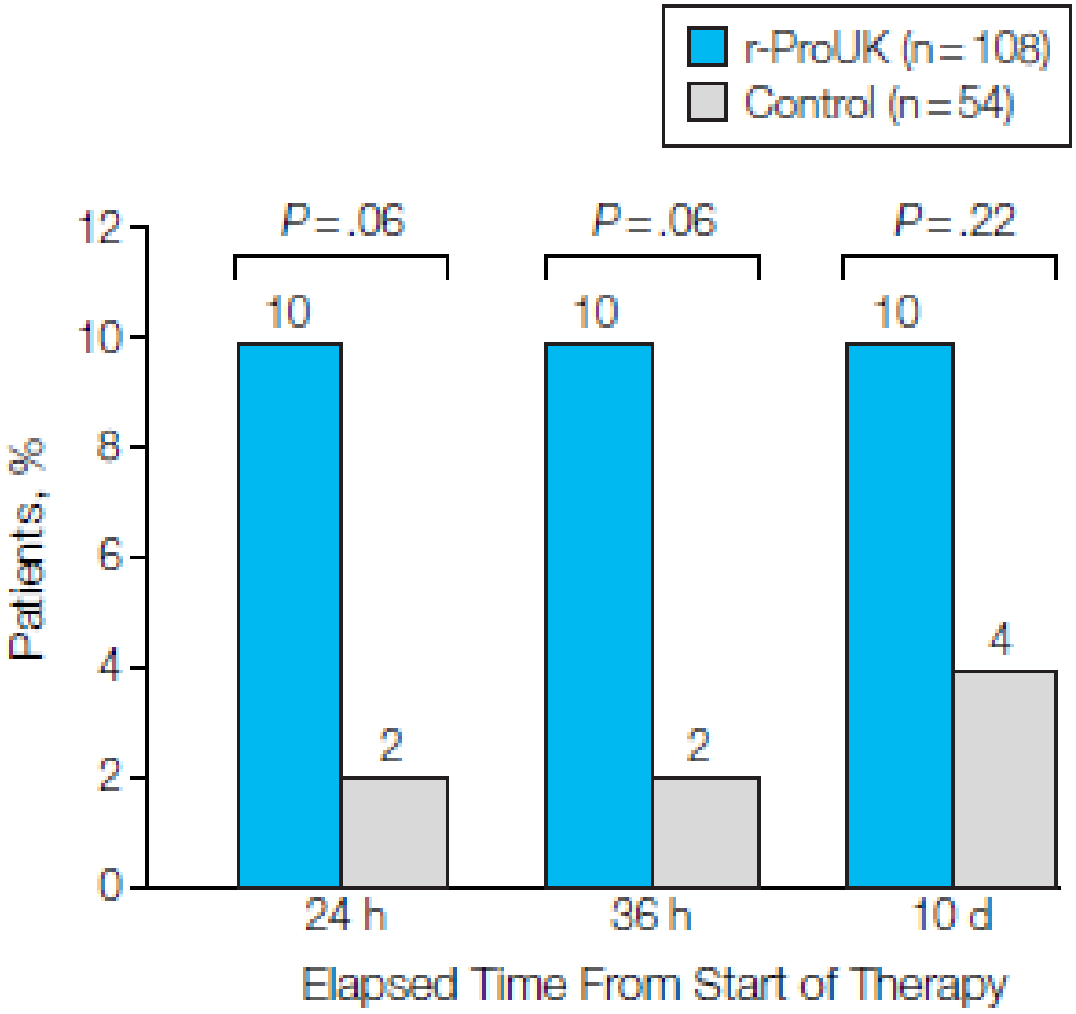
ARR: 15%

NNT: 7

Furlan A, et al. PROACT II. JAMA 1999;282(21):2003

PROACT II: sICH with neurologic deterioration

≥ 4 points deterioration on NIHSS or ≥ 1 point LOC



At 24 and 36 h

rProUK: 10%

Control: 2%

ARD: 8%

NNH: 12.5

At 10 days

rProUK: 10%

Control: 4%

ARD: 6%

NNH: 17

Furlan A, et al. PROACT II. JAMA 1999;282(21):2003

SYNTHESIS

ORIGINAL ARTICLE

Endovascular Treatment for Acute Ischemic Stroke

Alfonso Ciccone, M.D., Luca Valvassori, M.D., Michele Nichelatti, Ph.D., Annalisa Sgoifo, Psy.D., Michela Ponzio, Ph.D., Roberto Sterzi, M.D., and Edoardo Boccardi, M.D., for the SYNTHESIS Expansion Investigators*

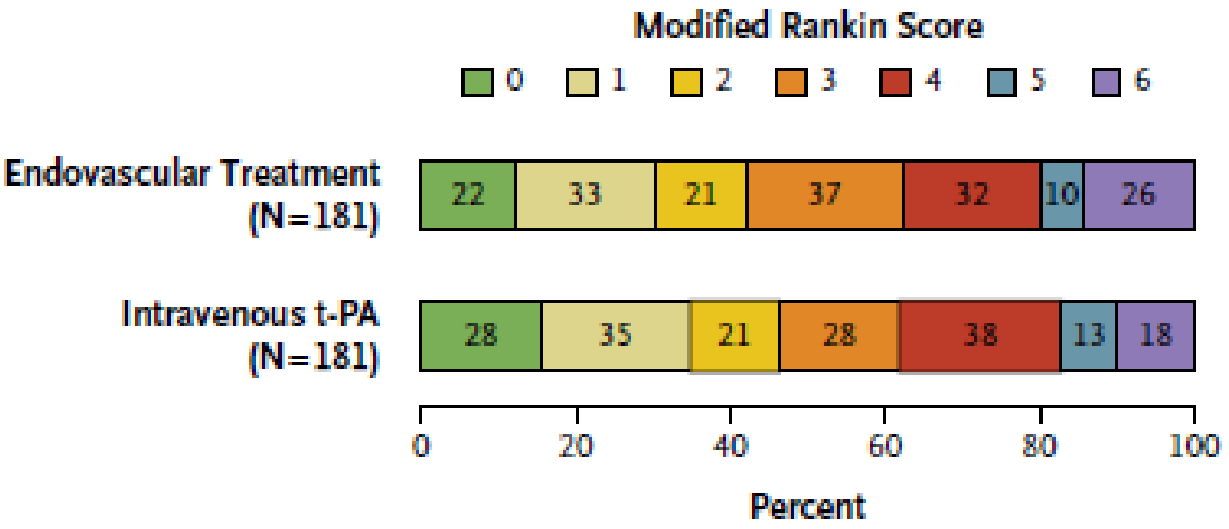
Ciccone A, et al. SYNTHESIS. NEJM 2013;368(10):904

SYNTHESIS: Methods

- **Anticoagulant recommended: heparin 5000 U bolus, 500 U/hr infusion during the procedure**
- **Pharmacologic or mechanical therapy or both allowed**
- **Infusion microcatheter placed close to (within or beyond) the thrombus**
- **t-PA up to 0.9 mg/kg (max 90 mg) until lysis (within 1 hr)**
- **"In patients with a neurologic deficit but no corresponding occlusion, t-PA was injected into the vascular area that was presumably affected." (up to 0.9 mg/kg [max 90 mg])**

Ciccone A, et al. SYNTHESIS. NEJM 2013;368(10):904

SYNTHESIS: mRS ≤ 1 at 90 days



mRS ≤ 1 (Primary)

IA: 30%

IV t-PA: 35%

ARR: - 4.4%

P = 0.37

- ***109 of 165 treated patients had only locoregional infusion and wire fragmentation; only 56 added device.***
- ***t-PA median dose 40 mg***
- ***57 were given IV heparin***

mRS ≤ 2

IA: 42%

IV t-PA: 46%

ARR: - 4%

Ciccone A, et al. SYNTHESIS. NEJM 2013;368(10):904

SYNTHESIS: Safety

- ***sICH – 6% in both groups***
- ***Death – EVT 8% v IV t-PA 6% (P=0.53)***

Ciccone A, et al. SYNTHESIS. NEJM 2013;368(10):904

CHOICE

JAMA | Preliminary Communication

Effect of Intra-arterial Alteplase vs Placebo Following Successful Thrombectomy on Functional Outcomes in Patients With Large Vessel Occlusion Acute Ischemic Stroke The CHOICE Randomized Clinical Trial

Arturo Renú, MD; Mónica Millán, MD; Luis San Román, MD; Jordi Blasco, MD; Joan Martí-Fàbregas, MD; Mikel Terceño, MD; Sergio Amaro, MD; Joaquín Serena, MD; Xabier Urra, MD; Carlos Laredo, PhD; Roger Barranco, MD; Pol Camps-Renom, MD; Federico Zarco, MD; Laura Oleaga, MD; Pere Cardona, MD; Carlos Castaño, MD; Juan Macho, MD; Elisa Cuadrado-Godia, MD; Elio Vivas, MD; Antonio López-Rueda, MD; Leopoldo Guimaraens, MD; Anna Ramos-Pachón, MD; Jaume Roquer, MD; Marian Muchada, MD; Alejandro Tomasello, MD; Antonio Dávalos, MD; Ferran Torres, MD; Angel Chamorro, MD; for the CHOICE Investigators

Renú A, et al. CHOICE. JAMA 2022;327(9):826-835

CHOICE

- **Hypothesis: In patient with LVO and successful MT, adjunctive IA t-PA will improve outcomes**
- **Multicenter, randomized, double-blind, placebo-controlled trial**
- **Population: ASPECTS ≥ 6 (if LKW > 4.5 h); LVO MCA, ACA, PCA MT within 24 h; successful MT (eTICI ≥ 2b50)**
- **Randomization: IA t-PA versus IA placebo**
- **Dose: 0.225 mg/kg (max 22.5 mg) over 30 min → 15 min)**
- **Primary Outcome: mRS 0-1 at 90 days**

Renú A, et al. CHOICE. JAMA 2022;327(9):826-835

CHOICE: 90-day mRS

- 7 sites in Catalonia, Spain
- 121 patients randomized; 113 in primary analysis
- Stopped early due to slow enrollment during pandemic

mRS 0-1 at 90 days

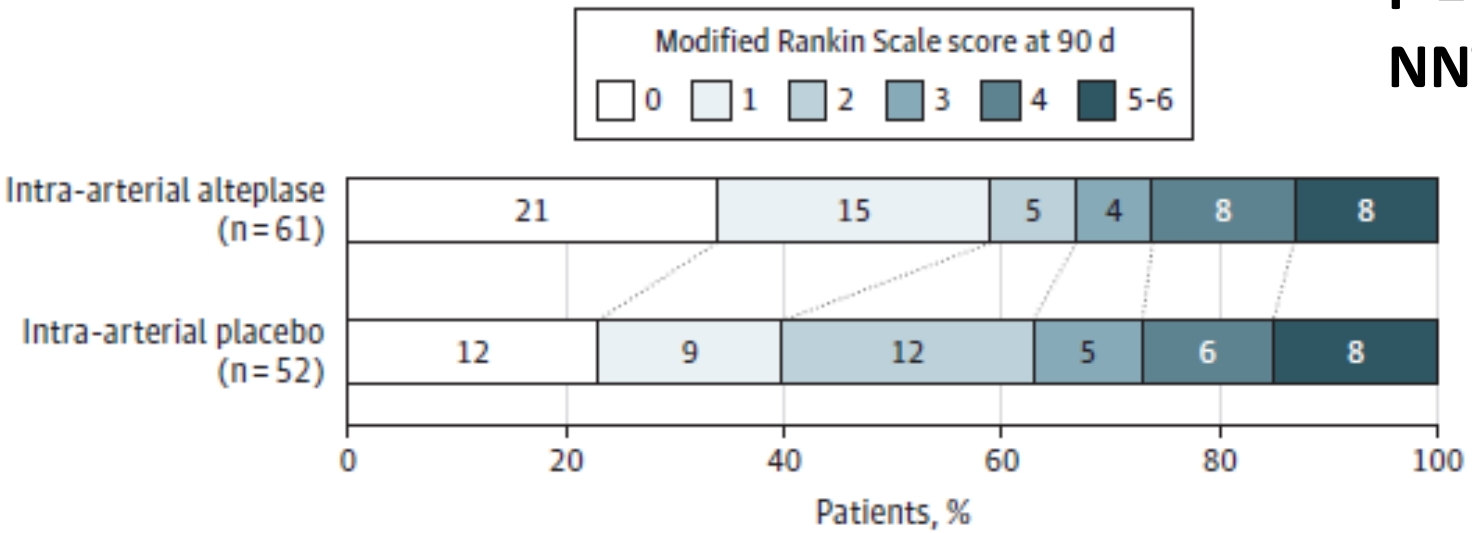
IA t-PA: 59%

Placebo: 40%

ARR: 18.4%

P = 0.047

NNT: 5



ARR = 18.4% (95% CI: 0.3 – 36.4)

Renú A, et al. CHOICE. JAMA 2022;327(9):826-835

CHOICE: Safety

Outcomes	No. (%) of participants	
	Alteplase (n = 61)	Placebo (n = 52)
Primary safety outcomes		
Symptomatic intracranial hemorrhage at 24 h	0	2 (3.8)
Death at 90 d	5 (8.2)	8 (15.4)
Additional safety outcomes		
Any serious adverse events[a]	10 (16.4)	15 (28.8)
Any cerebral hemorrhage	19 (31.1)	18 (34.6)
Hemorrhagic infarction		
Type 1[b]	11 (18.0)	8 (15.4)
Type 2[c]	1 (1.6)	0
Parenchymal hematoma		
Type 1[d]	0	0
Type 2[e]	2 (3.2)	4 (7.7)
Remote	1 (1.6)	0
Subarachnoid hemorrhage	4 (6.6)	6 (11.5)

Renú A, et al. CHOICE. JAMA 2022;327(9):826-835

CHOICE

Conclusions and Limitations

- ***Among patients with LVO and successful MT, adjunct IA t-PA resulted in higher likelihood of excellent neurologic recovery at 90 days with no increase in sICH or death. (preliminary)***

- ***Small size (60% of planned N) limited conclusions.***
- ***Wide confidence intervals (lower limit ARR only 0.3%)***
- ***Limited secondary outcome and subgroup data***
- ***Only 7% of treated population included***

Renú A, et al. CHOICE. JAMA 2022;327(9):826-835

POST-TNK

JAMA | Original Investigation

Intra-Arterial Tenecteplase Following Endovascular Reperfusion for Large Vessel Occlusion Acute Ischemic Stroke

The POST-TNK Randomized Clinical Trial

Jiacheng Huang, MD; Jie Yang, MD; Chang Liu, MD; Linyu Li, MD; Dahong Yang, MD; Changwei Guo, MD; Guoyong Zeng, MD; Jiaxing Song, MD; Jinfu Ma, MD; Xu Xu, MD; Xiaolei Shi, MD; Shihai Yang, MD; Wenzhe Sun, MD; Zhixi Wang, MD; Yufeng Tang, MD; Maojun Jiang, MD; Li Wang, MD; Xiangping Cheng, MD; Jun Luo, MD; Peiyang Zhou, MD; Xing Fang, MD; Guangsen Cheng, MD; Zhongfan Ruan, MD; Jinglun Li, MD; Jincheng Liu, MD; Bo Lei, MD; Yaoyu Tian, MD; Xiaolin Tan, MD; Guangxiong Yuan, MD; Jian Wang, MD; Xinyuan Huang, MD; Shengling Deng, MD; Zhenglong Jin, MD; Xin Zou, MD; Jie Zhang, MD; Daoyou Cheng, MD; Xiaojun Luo, MD; Jiasheng Liao, MD; Jian Miao, MD; Zhenqiang Li, MD; Yaxuan Sun, MD; Guohui Jiang, MD; Deyan Kong, MD; Shuyu Jiang, MD; Zhiyuan Wang, MD; Duolao Wang, MD; Johannes Kaesmacher, MD, PhD; Thanh N. Nguyen, MD; Raul G. Nogueira, MD; Jeffrey L. Saver, MD; Yangmei Chen, MD; Wenjie Zi, MD, PhD; for the POST-TNK Investigators

Huang J, et al. POST-TNK. JAMA 2025;333(7):579

POST-TNK

- **Hypothesis: In patient with LVO and successful MT (near complete), adjunctive IA TNK will improve outcomes**
- **Multicenter, randomized, open-label, blinded outcome trial**
- **Population: ASPECTS ≥ 6 (if LKW ≤ 6 h; 7 if 6-24 h); LVO iICA, M1, M2 MT within 24 h; successful MT (eTICI ≥ 2c [90-99%]); no IV thrombolysis**
- **Randomization: IA TNK versus control**
- **Dose: 0.0625 mg/kg (max 6.25 mg) over 10-15 min**
- **Primary Outcome: mRS 0-1 at 90 days**

Huang J, et al. POST-TNK. JAMA 2025;333(7):579

POST-TNK: 90-day mRS

- 34 sites in China
- 541 patients randomized; 539 in primary analysis

mRS 0-1 at 90 days

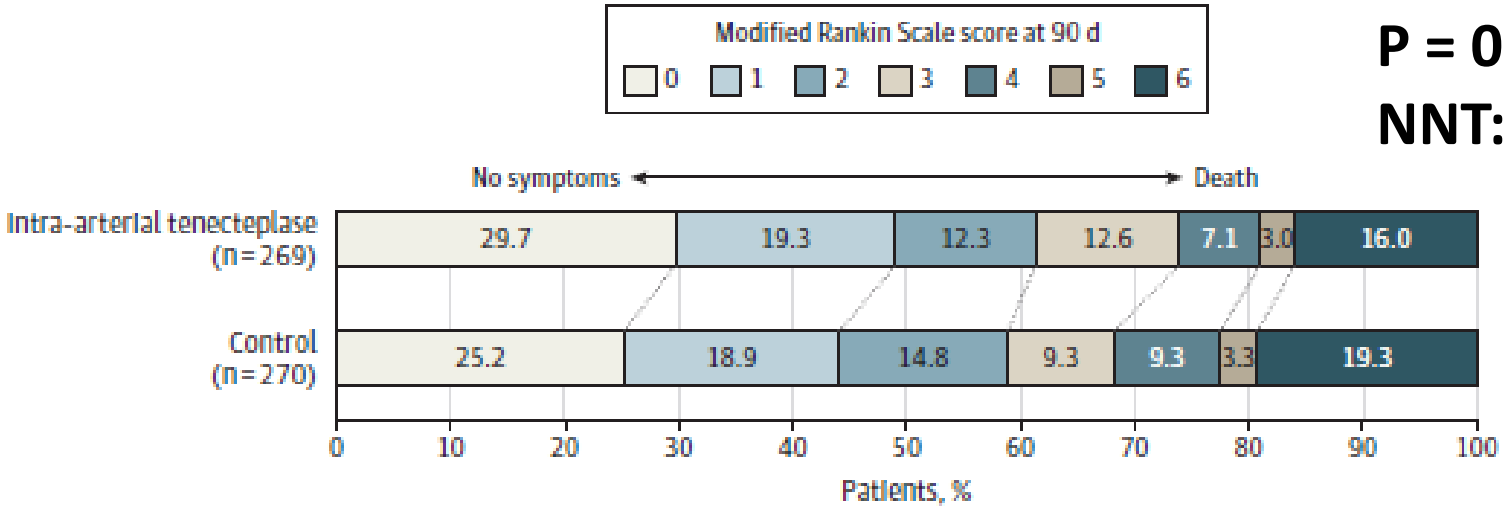
IA TNK: 49%

Control: 44%

ARR: 5%

P = 0.11

NNT: 20



ARR = 5% (95% CI: - 3.42 – 13.41)

Huang J, et al. POST-TNK. JAMA 2025;333(7):579

POST-TNK: Safety Outcomes

Outcome	*IA TNK*	*Control*	*P-value*
Death in 90d	16	19.3	0.16
sICH at 48h	6.3	4.4	0.35
Radiographic ICH at 48h	36.6	27.3	0.02
Systemic bleeding			0.11
• Mild	10	11.8	
• Moderate	0	0.7	
• Severe	38.7	30.3	

Huang J, et al. POST-TNK. JAMA 2025;333(7):579

POST-TNK: Safety Outcomes

Outcome	*IA TNK*	*Control*	*P-value*
Death in 90d	16	19.3	0.16
sICH at 48h	6.3	4.4	0.35
Radiographic ICH at 48h	36.6	27.3	0.02
Systemic bleeding			0.11
• Mild	10	11.8	
• Moderate	0	0.7	
• Severe	38.7	30.3	

Huang J, et al. POST-TNK. JAMA 2025;333(7):579

POST-UK

JAMA | Original Investigation

Intra-Arterial Urokinase After Endovascular Reperfusion for Acute Ischemic Stroke

The POST-UK Randomized Clinical Trial

Chang Liu, MD; Changwei Guo, MD; Fengli Li, MD; Nizhen Yu, MD; Jiacheng Huang, MD; Zhouzhou Peng, MD; Weilin Kong, MD; Jiaxing Song, MD; Xiang Liu, MD; Shitao Fan, MD; Chengsong Yue, MD; Boyu Chen, MD; Chong Zheng, MD; Xingyun Yuan, MD; Jian Sheng, MD; Youlin Wu, MD; Bo Sun, MD; Zengqiang Zhao, MD; Minzhen Zhu, MD; Ling Han, MD; Qiang Shi, MD; Zhongbin Xia, MD; Xianjin Shang, MD; Fengguang Li, MD; Rongzong Li, MD; Feixue Yue, MD; Shunfu Jiang, MD; Dengwen Song, MD; Min Song, MD; Yuanjun Shan, MD; Chawen Ding, MD; Li Yao, MD; Yong Yang, MD; Junbin Chen, MD; Wencheng He, MD; Feibao Pan, MD; Wensheng Zhang, MD; Tieying Cai, MD; Shibo Han, MD; Wei Li, MD; Gongbo Li, MD; Chen Gong, MD; Liping Huang, MD; Cheng Huang, MD; Duolao Wang, PhD; Johannes Kaesmacher, MD, PhD; Thanh N. Nguyen, MD; Raul G. Nogueira, MD; Jeffrey L. Saver, MD; Wenjie Zi, MD; Yangmei Chen, MD; Qingwu Yang, MD; for the POST-UK investigators

Liu C, et al. POST-UK. JAMA 2025;333(7):589

POST-UK

- **Hypothesis: In patient with LVO and successful MT (near complete), adjunctive IA UK will improve outcomes**
- **Multicenter, randomized, open-label, blinded outcome trial**
- **Population: ASPECTS ≥ 6 (if LKW ≤ 6 h; 7 if 6-24 h); LVO iICA, M1, M2 MT within 24 h; successful MT (eTICI ≥ 2c [90-99%]); no IV thrombolysis**
- **Randomization: IA UK versus control**
- **Dose: 100,000 IU over 10-15 min**
- **Primary Outcome: mRS 0-1 at 90 days**

Liu C, et al. POST-UK. JAMA 2025;333(7):589

POST-UK: 90-day mRS

- **35 sites in China**
- **535 patients randomized; 532 in primary analysis**

mRS 0-1 at 90 days

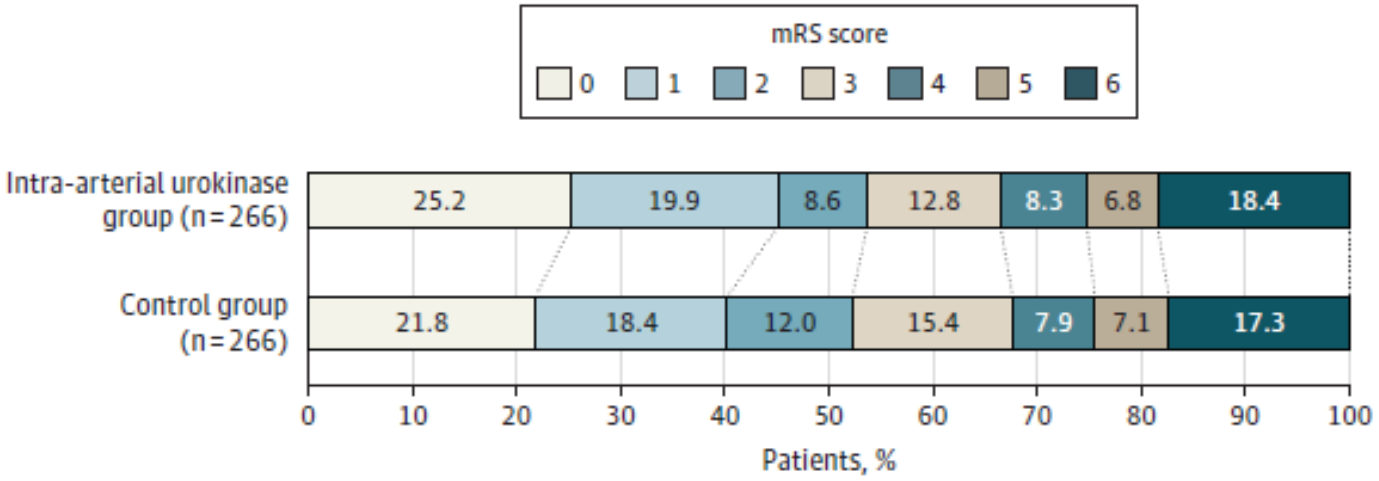
IA TNK: 45%

Control: 40%

ARR: 5%

P = 0.19

NNT: 20



ARR = 4.89% (95% CI: - 3.51 – 13.28)

Liu C, et al. POST-UK. JAMA 2025;333(7):589

POST-UK: Safety Outcomes

Outcome	*IA TNK*	*Control*	*P-value*
Death in 90d	**18**	**17.3**	**0.77**
sICH at 48h	**4.1**	**4.1**	**0.91**
Radiographic ICH at 48h	**25.8**	**24.7**	**0.52**
Systemic bleeding			**0.25**
• **Mild**	**13.1**	**9.4**	
• **Moderate**	**0**	**0.7**	
• **Severe**	**27.0**	**25.8**	

Liu C, et al. POST-UK. JAMA 2025;333(7):589

Intra-arterial Thrombolytics?

PEARL ISC 2025
Intra-arterial alteplase for acute ischemic stroke after mechanical thrombectomy (PEARL).
Multicenter, open-label, blind-endpoint, RCT
28 centers in China
IA-tPA (0.225 mg/kg, max 20 mg) after MT
NIHSS 6-25, within 24 hr LKW, CT ASPECTS ≥ 6, confirmed occlusion terminal ICA, M1, M2; stable eTICI score 2b50-3 after MT, prestrike mRS 0-1
Stents and planned DAPT excluded

Pooled analysis of

MeVO-IA

PEARL

- **Hypothesis: In patient with LVO and successful MT, adjunctive IA t-PA will improve outcomes**
- **Multicenter, randomized, open-label, blinded outcome trial**
- **Population: ASPECTS ≥ 6; LVO iICA, M1, M2 MT; successful MT (eTICI ≥ 2b50)**
- **Randomization: IA t-PA versus control**
- **Dose: 0.225 mg/kg (max 20 mg)**
- **Primary Outcome: mRS 0-1 at 90 days**

ISC 2025, and Yang X et al. (PEARL). BMJ Open 2024;14(11):e091059. Published 2024 Nov 5. doi:10.1136/bmjopen-2024-091059

PEARL

Outcomes

- **28 centers in China**
- **324 patients; 164 IA-tPA and 160 standard care**
- **Median age 65.8; NIHSS 15; ASPECTS 9**
- **41.7% got IV tPA before MT**
- **Primary outcome: mRS 0-1 IA-tPA (44.8%) v standard care (30.2%) (p=0.01)**
- **Safety outcomes: sICH at 36h: IA-tPA 4.3 v standard care 5.0% (p = 0.67)**

  Death at 90d: IA-tPA 17.1% v standard care 11.3% (p = 0.2)

ISC 2025, and Yang X et al. (PEARL). BMJ Open 2024;14(11):e091059. Published 2024 Nov 5. doi:10.1136/bmjopen-2024-091059

ANGEL-TNK

- **Hypothesis: In patient with LVO and successful MT, adjunctive IA TNK will improve outcomes**
- **Multicenter, randomized, open-label, blinded outcome trial**
- **Population: ASPECTS ≥ 6; LVO iICA, M1, M2 MT; successful MT (eTICI ≥ 2b50); IV tPA before MT was excluded**
- **Randomization: IA TNK versus control**
- **Dose: 0.125 mg/kg (max 12.5 mg)**
- **Primary Outcome: mRS 0-1 at 90 days**

ISC 2025 and Huo X, et al. ANGEL-TNK Stroke Vasc Neurol 2024; doi:10.1136/svn-2024-003318

ANGEL-TNK

Outcomes

- **19 centers in China**
- **255 patients**
- **Median age 72; (45% women)**
- **IV tPA before MT was excluded**
- **Primary outcome: mRS 0-1 IA-tPA (40.5%) v standard care (26.4%) (p=0.02)**
- **Safety outcomes: sICH at 48h: IA-tPA 24.6 v standard care 27.9% (p = NS)**

  Death at 90d: IA-tPA 21.4% v standard care 21.7% (p = NS)

ISC 2025 and Huo X, et al. ANGEL-TNK Stroke Vasc Neurol 2024; doi:10.1136/svn-2024-003318