Thrombolytics After the Window: Expanding the Stroke Treatment Timeline

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Aurora St. Luke's Medical Center | November 18, 2025

Disclosures

The planner(s) and speaker(s) have indicated that there are no relevant financial relationships with any ineligible companies to disclose.

Objectives

1. **Recall** the pharmacology and pharmacokinetics of thrombolytic agents used in acute ischemic stroke
2. **Outline** current guidelines and criteria for thrombolytic administration, including the traditional 4.5-hour window
3. **State** recent clinical trial data supporting thrombolytic use beyond the standard treatment window
4. **Select** an evidence-based approach to thrombolytic therapy timing for patients presenting outside the traditional window

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Abbreviations

- **ACA:** Anterior cerebral artery
- **AHA:** American Heart Association
- **ASA:** American Stroke Association
- **AIS:** Acute ischemic stroke
- **BA:** Basilar artery
- **CTA:** Computed tomography angiography
- **CT:** Computed tomography
- **CTP:** Computed tomography perfusion
- **DWI-FLAIR:** Diffusion-weighted imaging–fluid-attenuated inversion recovery
- **EVT:** Endovascular Thrombectomy
- **ICA:** Internal carotid artery
- **ICH:** Intracranial hemorrhage
- **IS:** Ischemic stroke
- **IVT:** Intravenous thrombolytics
- **LKW:** Last known well
- **LVO:** Large vessel occlusion

MCA: Middle cerebral artery

MeVO: Medium vessek occlusion

MRI: Magnetic resonance imaging

mRS: Modified Rankin Scale

NIHSS: National Institutes of Health Stroke Scale

PAI-1: Plasminogen activator inhibitor-1

PC-ASPECTS: Posterior Circulation Alberta Stroke Program Early CT Score

PCA: Proximal posterior artery

PCT: Perfusion computed tomography

SAH: Subarachnoid hemorrhage

sICH: Symptomatic intracranial hemorrhage

t1/2: Half life

TIA: Transient ischemic attack

TLKW: Time last known well

TNK: Tenecteplase

tPA: Alteplase

VA: Vertebral artery

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ACUTE ISCHEMIC STROKE (AIS)

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Epidemiology of Stroke

2nd most common cause of mortality

3rd most common cause of disability

68% = Ischemic

32% = Hemorrhagic

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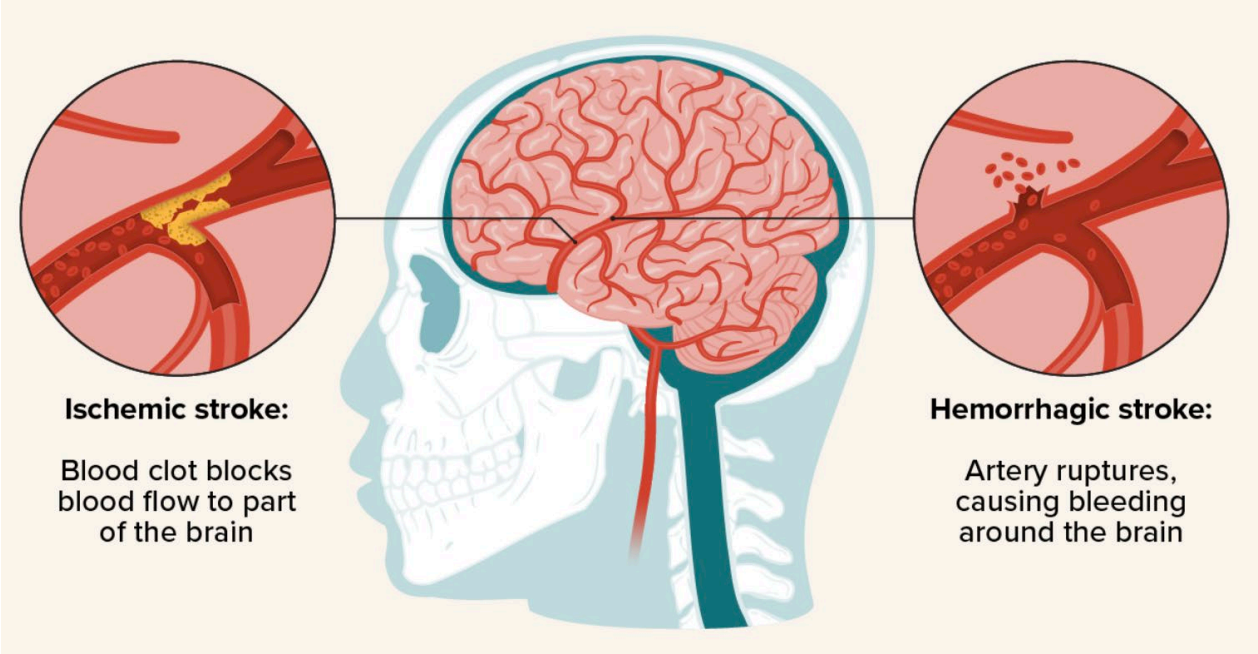
Gore M. StatPearls. March 10, 2024.

Types of Stroke



Chugh C. *Indian Journal of Critical Care Medicine*. 2019;23(S2):140-146.
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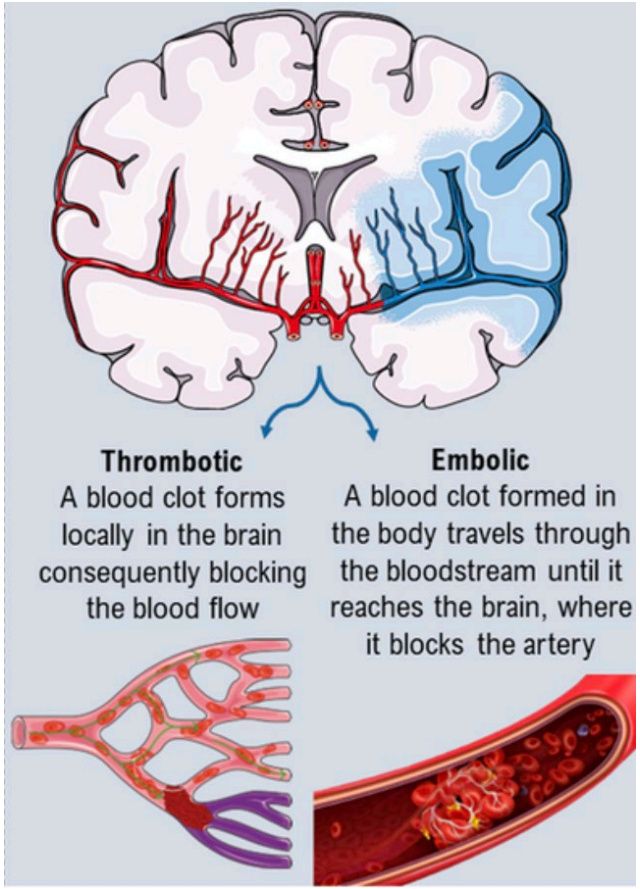

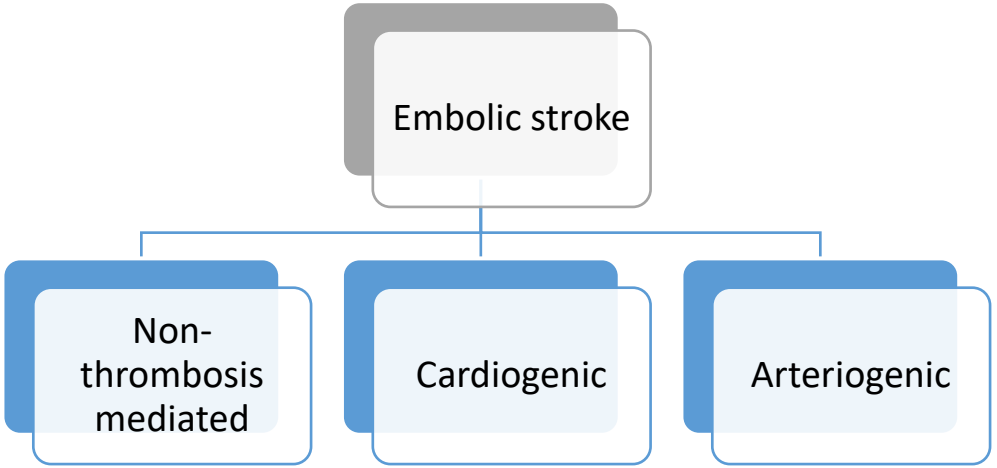

Tartari Neves L, et al. *Translational stroke research.* January 2023.

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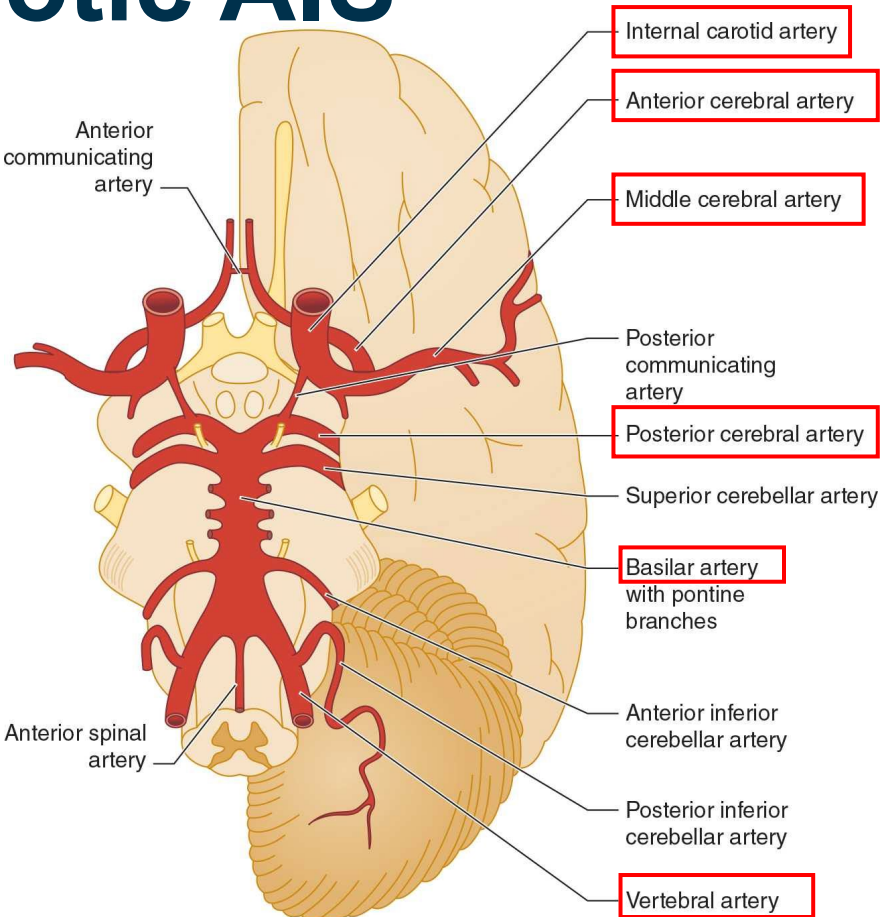
Types of Thrombotic AIS

LVO

- Acute blockages of intracranial ICA, proximal PCA, MCA, ACA, intracranial VA, and/or BA

Lacunar Stroke

- Marker of small vessel disease
- Small and located in noncortical areas



Gore M. StatPearls. March 10, 2024.
Neupsy Key. Stroke. November 8, 2016.

Medium Vessel Occlusions (MeVO)

Occlusions of the

- M2/3 segments of MCA
- A2/3 segments of ACA
- P2/3 segments of PCA

Thrombolysis with IV alteplase shows poor efficacy

- Recanalization rates at 2-6 hours <50%

EVT

- Feasible, but evidence is limited, and success varies

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Ospel JM, Nguyen TN, Jadhav AP, et al. *Stroke*. 2024;55(3):769-778.

Risk Factors

Non-Modifiable	Modifiable
• Age • Race • Sex • Ethnicity • History of migraine headaches • Fibromuscular dysplasia • Family history of stroke or TIAs	• Hypertension • Diabetes mellitus • High cholesterol • Previous stroke • Carotid stenosis • Excessive alcohol intake, tobacco use, illicit drug use, physical inactivity • Obesity • Oral contraceptive use/ postmenopausal hormone use

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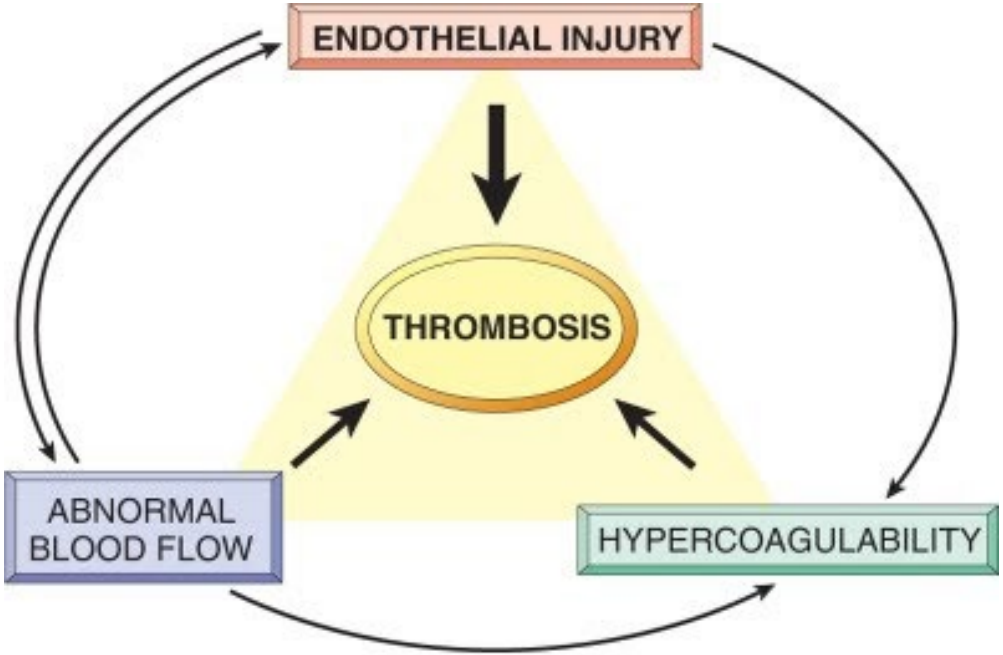
Boehme AK, Esenwa C, Elkind MSV. *Circulation Research*. 2017;120(3):472-495.

Virchow's Triad



Medicine Hack. Virchow's Triad. 2011.

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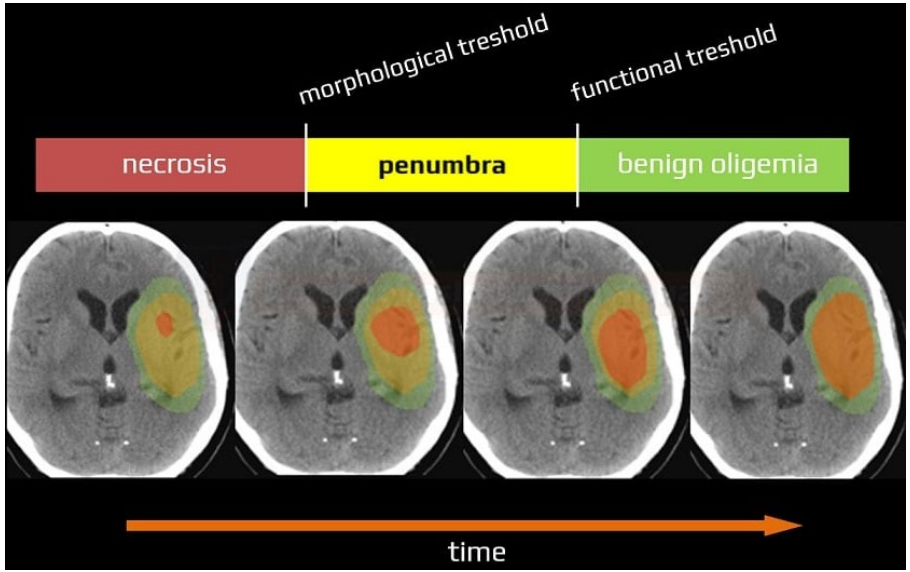
Ischemic Penumbra

Area of the brain that is ischemic

Remains viable for a limited time due to partially preserved collateral blood flow

Timely intervention can salvage this tissue



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Goldemund D. Stroke. September 24, 2025

Diagnosis

Imaging Technique	Use in Stroke	Benefits	Drawbacks
Non-contrast CT	Identify hemorrhage or large infarct Diagnose major stroke Identify brain tumor	Fast & widely available	Insensitive to diagnosis of minor stroke
CTA	Detect LVO	Detect LVO with almost 100% sensitivity	Contrast required
CTP or PCT	Identify & quantify volume of infarcted core and penumbra	Easier to interpret than CTA	Susceptible to motion artifact More radiation exposure vs CTA
MRI	Most sensitive technique for AIS detection Diagnose minor stroke	Can detect brain ischemia in TIA or minor IS	Susceptible to motion artifacts May not be available 24 hours

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Patil S, Rossi R, Jabrah D, Doyle K. *Frontiers in Medical Technology*. 2022;4.

TO SPOT THE SIGNS OF A STROKE,

B E F A S T

Balance: Loss of balance or coordination.

Eyes: Changes in vision.

Face: Drooping features on one side of the face.

Arms (and legs): Weakness in a limb.

Speech: Difficulty speaking or understanding others.

Time: Call 911 or emergency services right away.

Cleveland Clinic

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Cleveland Clinic. Cleveland Clinic. January 15, 2025.

National Institutes of Health (NIH) Stroke Scale

1a. Level of consciousness
Alert, Drowsy, etc

0 Alert | 1 Drowsy | 2 Stuporous | 3 Coma

1b. LOC Questions
Month, age

0 Answers both correctly | 1 Answers one correctly | 2 Incorrect

1c. LOC Commands
Open/close eyes, make a fist & let go

0 Obeys both correctly | 1 Obeys one correctly | 2 Incorrect

2. Best Gaze
Eyes open - pt follows examiner's fingers or face.

0 Normal | 1 Partial gaze palsy | 2 Forced deviation

3. Visual
Introduce visual stimulus/threat to pt's visual field quadrants. Cover 1 eye and hold up fingers in all 4 quadrants.

0 No visual loss | 1 Partial hemianopsia | 2 Complete hemianopsia | 3 Bilateral hemianopsia

4. Facial Palsy
Show teeth, raise eyebrows and squeeze eyes tightly shut.

0 Normal | 1 Minor | 2 Partial | 3 Complete

5.a Motor Arm - Left
Elevate extremity to 90 degrees and score drift/movement. Count to 10 out loud and use fingers for visual cue.

0 No Drift | 1 Drift | 2 Can't resist gravity | 3 No effort against gravity | 4 No Movement

NT = Amputation, joint fusion

5.b Motor Arm - Right
Elevate extremity to 90 degrees and score drift/movement. Count to 10 out loud and use fingers for visual cue.

0 No Drift | 1 Drift | 2 Can't resist gravity | 3 No effort against gravity | 4 No Movement

NT = Amputation, joint fusion

6.a Motor Leg - Left
Elevate extremity to 30 degrees and score drift/movement. Count to 5 out loud and use fingers for visual cue.

0 No Drift | 1 Drift | 2 Can't resist gravity | 3 No effort against gravity | 4 No Movement

NT = Amputation, joint fusion

6.b Motor Leg - Right
Elevate extremity to 30 degrees and score drift/movement. Count to 5 out loud and use fingers for visual cue.

0 No Drift | 1 Drift | 2 Can't resist gravity | 3 No effort against gravity | 4 No Movement

NT = Amputation, joint fusion

7. Limb Ataxia
Finger to nose, heal down shin

0 Absent | 1 Present in one limb | 2 Present in two limbs

8. Sensory
Pin prick to face, arms, trunk, and legs - compare sharpness side to side

0 Normal | 1 Partial loss | 2 Severe Loss

9. Best Language
Name items, describe picture, and read sentences. Don't forget glasses if they normally wear them.

0 No aphasia | 1 Mild to moderate aphasia | 2 Severe aphasia | 3 Mute

10. Dysarthria
Evaluate speech clarity by pt reading or repeating words on list.

0 Normal articulation | 1 Mild to moderate dysarthria | 2 Near to unintelligible or worse

NT = Intubated or other physical barrier

11. Extinction and Inattention
Use information from prior testing or double simultaneous stimuli testing to identify neglect. Face, arms, legs, and visual fields.

0 No neglect | 1 Partial neglect | 2 Complete neglect

NIH Stroke Scale Score	Stroke Severity
0	No stroke symptoms
1-4	Minor stroke
5-15	Moderate stroke
16-20	Moderate to severe stroke
21-42	Severe stroke

Saebo. Saebo. April 23, 2024.
Cohan AR. StrokeSciences. 2025.

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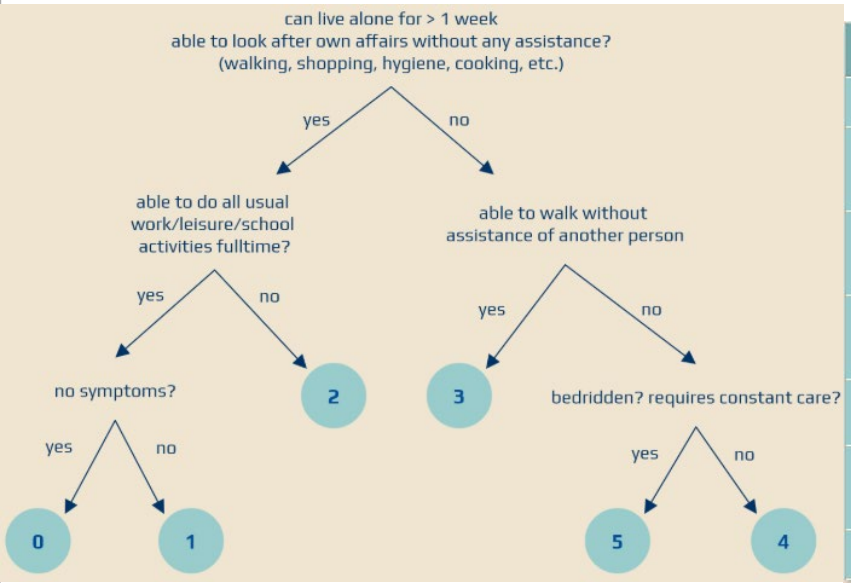
Modified Rankin Scale (mRS)

Assess functional outcomes in stroke patients



Modified Rankin Scale (mRS)	
0	• no symptoms
1	• mild deficit without significant disability • capable of performing all usual duties and activities
2	• mild disability • unable to carry out all previous activities, but able to manage own affairs **without any assistance**
3	• moderate disability, the patient requires assistance with some activities • **able to walk without another person's help**
4	• unable to walk and attend to bodily needs without assistance
5	• bedridden • incontinent, requiring constant nursing care
6	• dead

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Goldemund D. STROKE. September 29, 2025.

Stroke Mimics

Seizure disorder	Epidural/subdural hemorrhage	Migraine	Bell's palsy
Electrolyte dysfunction	Brain tumor	Hypoglycemia/ hyperglycemia	Multiple sclerosis
Hypertensive crisis	Aortic dissection	Depression/anxiety/ stress	Trauma

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H. Buck B, et al. *Annals of Medicine*. 2021;53(1):420-436.

Assessment Question #1

A 65-year-old man presents for a routine visit. His history includes hypertension, type 2 diabetes, atrial fibrillation, and he is a current smoker. He drinks alcohol occasionally and has a BMI of 29 kg/m^2. Which of the following is a **non-modifiable risk factor** for ischemic stroke in this patient?

A. Hypertension
B. Smoking
C. Age
D. Obesity

FIBRINOLYTICS

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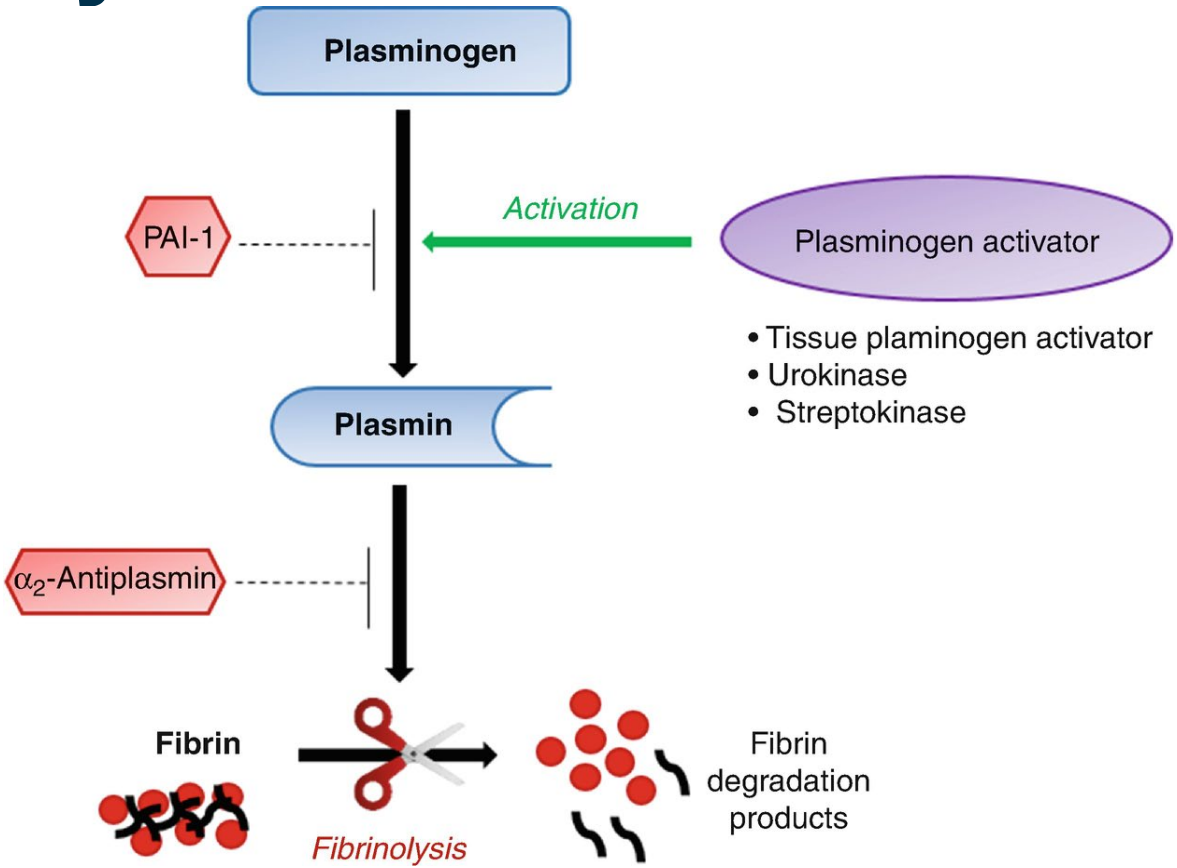
Fibrinolytics MOA



Baig MU. StatPearls. August 28, 2023.
Medicalbiochemist. 2024.

AHA/ASA Guidelines Inclusion Criteria

Onset of symptoms **<4.5 hours**
Diagnosis of ischemic stroke causing neurological deficit
Age ≥18 years of age

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Demaerschalk BM, et al. *Stroke*. 2016;47(2):581-641.

AHA/ASA Guidelines Exclusion Criteria

Significant head trauma in previous 3 months
Symptoms suggest SAH
Arterial puncture at noncompressible site in previous 7 days
History of previous ICH
Intracranial neoplasm, arteriovenous malformation, or aneurysm
Recent intracranial or intraspinal surgery
Elevated blood pressure **(systolic >185 mmHg or diastolic >110 mmHg)**
Active internal bleeding
Blood glucose **<50mg/dL**
CT demonstrates multilobar infarction (hypodensity >1/3 cerebral hemisphere)
Heparin received **within 48 hours** resulting in abnormally elevated aPTT greater than the upper limit of normal
Current use of anticoagulant with **INR>1.7** or **PT>15 sec**
Current use of **direct thrombin inhibitors** or **DOACs** with elevated sensitive lab tests (eg, aPTT, INR, PLT, ECT, TT, or FXa assays)

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Demaerschalk BM, et al. *Stroke*. 2016;47(2):581-641.

AHA/ASA Guidelines Relative Exclusion Criteria

→	Major surgery or serious trauma within previous 14 days
→	Recent gastrointestinal or urinary tract hemorrhage (within previous 21 days)
	Recent acute myocardial infarction (within previous 3 months)
→	Only minor or rapidly improving stroke symptoms (clearly spontaneously)
	Pregnancy
	Seizure at onset with postictal residual neurological impairments

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Demaerschalk BM, et al. *Stroke*. 2016;47(2):581-641.

Blood Pressure Management

COR IIb	LOE C-EO
Patient otherwise eligible for emergency reperfusion therapy except that BP is >185/110 mm Hg:	
Labetalol 10–20 mg IV over 1–2 min, may repeat 1 time; or	
Nicardipine 5 mg/h IV, titrate up by 2.5 mg/h every 5–15 min, maximum 15 mg/h; when desired BP reached, adjust to maintain proper BP limits; or	
Clevidipine 1–2 mg/h IV, titrate by doubling the dose every 2–5 min until desired BP reached; maximum 21 mg/h	
Other agents (eg, hydralazine, enalaprilat) may also be considered	
If BP is not maintained ≤185/110 mm Hg, do not administer alteplase	
Management of BP during and after alteplase or other emergency reperfusion therapy to maintain BP ≤180/105 mm Hg:	
Monitor BP every 15 min for 2 h from the start of alteplase therapy, then every 30 min for 6 h, and then every hour for 16 h	
If systolic BP >180–230 mm Hg or diastolic BP >105–120 mm Hg:	
Labetalol 10 mg IV followed by continuous IV infusion 2–8 mg/min; or	
Nicardipine 5 mg/h IV, titrate up to desired effect by 2.5 mg/h every 5–15 min, maximum 15 mg/h; or	
Clevidipine 1–2 mg/h IV, titrate by doubling the dose every 2–5 min until desired BP reached; maximum 21 mg/h	
If BP not controlled or diastolic BP >140 mm Hg, consider IV sodium nitroprusside	

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Powers WJ, et al. *Stroke*. 2019;50(12).

Hemorrhagic Complications

ICH

- Fatal or result in severe neurological disability

Risk Factors

- Advanced age, hypertension, recent surgery, or a history of stroke

TNK shown to ↓systemic bleeding complications

- Proportion of patients with symptomatic ICH
  - 1.8% for TNK and 3.6% for alteplase ($P < .001$)

Bharatha A. Pharmacology Mentor. January 26, 2025.
Warach SJ, et al. JAMA neurology. 2023.

TNK versus Alteplase

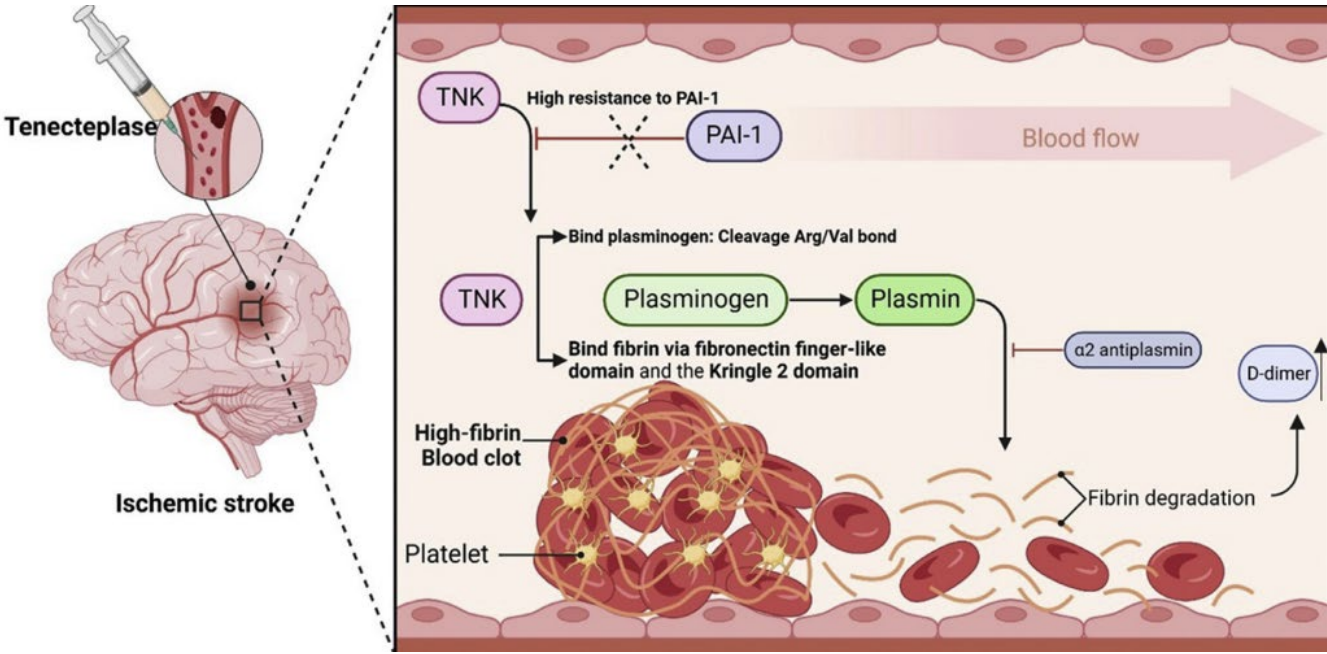
More fibrin specific → ↓systemic coagulopathy

More resistant to PAI-1

Longer duration of t½ (20 min vs. 4 min)

Slower plasma clearance

Both metabolized hepatically



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Haj Mohamad Ebrahim Ketabforoush A, et al. *Clinical Therapeutics*. 2024;46(11).

Tenecteplase versus alteplase for acute ischemic stroke: a systematic review and meta-analysis of randomized and non-randomized studies

Design

- Systematic review & meta-analysis (n=50,489) comparing TNK vs tPA in AIS

Results

- Functional outcome (mRS 0–1 at 90 days): No difference
- Symptomatic ICH: Similar between groups
- Mortality: Lower with TNK

Conclusion

- TNK shows similar functional outcomes and bleeding risk as tPA, but may reduce all-cause mortality

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Ma Y, Xiang H, et al. *Journal of Neurology*. 2024;271(5):2309-2323.

Costs

TNK at stroke dosage is less expensive than tPA in the U.S. market by

≈3000 USD

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Gao L, et al. *Stroke*. 2020;51(12):3681-3689.

TNK Dosing

0.25 mg/kg/dose

Max: 25 mg/dose (>100 kg)

25 mg = 5 mL

Administration: 5 second IV bolus

Patient Weight (kg)	Tenecteplase (mg)	Volume of tenecteplase to administer (mL)
40-41.9	10	2
42-45.9	11	2.2
46-49.9	12	2.4
50-53.9	13	2.6
54-57.9	14	2.8
58-61.9	15	3
62-65.9	16	3.2
66-69.9	17	3.4
70-73.9	18	3.6
74-77.9	19	3.8
78-81.9	20	4
82-85.9	21	4.2
86-89.9	22	4.4
90-93.9	23	4.6
94-97.9	24	4.8
≥ 98	25	5

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Tenecteplase. *Lexi-Drugs.* 2025
Dahlgren M, George A. Sharepoint. 2022.

Alteplase Dosing

Patient weight **<100 kg**	0.09 mg/kg *(10% of 0.9 mg/kg dose)* as an IV bolus over 1 minute	0.81 mg/*kg (90% of 0.9 mg/kg dose)* as a continuous infusion over 60 minutes
Patient weight **≥100 kg**	9 mg *(10% of 90 mg)* as an IV bolus over 1 minute	81 mg *(90% of 90 mg)* as continuous infusion over 60 minutes

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Alteplase. *Lexi-Drugs*. 2025.

Assessment Question #2

Which best describes the mechanism of action of alteplase?

A. Directly activates factor X to promote clot formation
B. Converts plasminogen to plasmin, leading to fibrin degradation
C. Inhibits fibrin cross-linking by blocking thrombin
D. Enhances platelet aggregation to restore blood flow

Assessment Question #3

Compared to alteplase, tenecteplase is characterized by:

A. Shorter half-life and lower fibrin specificity
B. Longer half-life and greater fibrin specificity
C. Similar half-life but reduced resistance to PAI-1
D. Increased risk of systemic fibrinolysis

MECHANICAL THROMBECTOMY

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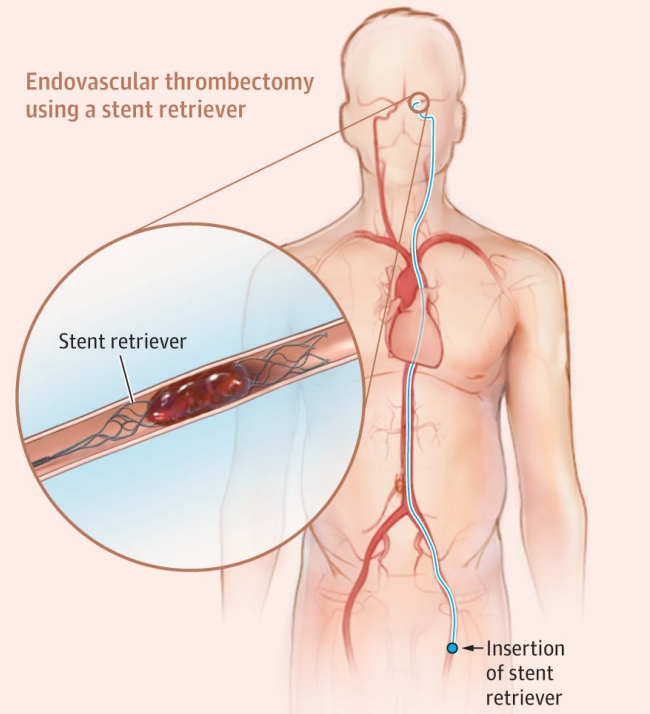
Introduction



Mechanical interventional procedure

- Remove clot from blood vessel

Receive thrombolytics if eligible

Endovascular thrombectomy compared with tPA alone

- Decreased severity of global disability
- Improved rates of functional independence at 90 days

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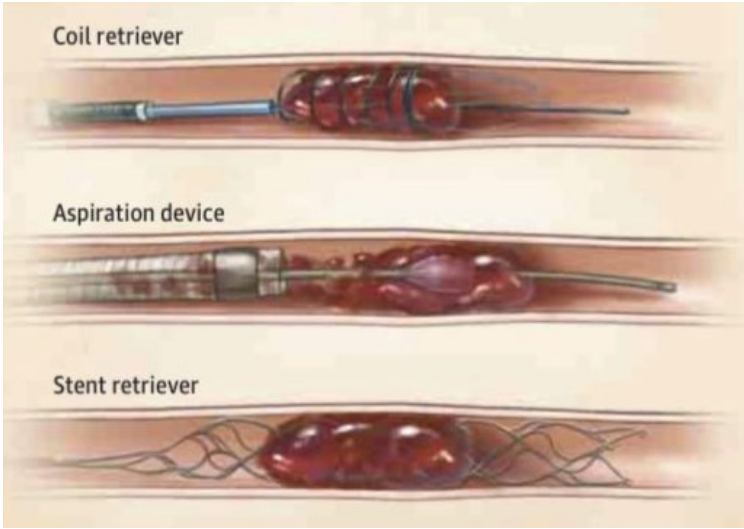
Thompson A. *JAMA*. 2015;314(4):331.

Types of Mechanical Thrombectomy

Coil Retrievers	• Deploys coil loops through the clot to capture it, then retracts both into the catheter
Aspiration Devices	• Employ vacuum aspiration to remove occlusive clot in acute ischemic stroke
Stent Retrievers	• Self-expanding stents are deployed within the thrombus to trap and retrieve it into the catheter



Raychev R, Saver JL. Neurology Clinical Practice. 2012;2(3):231-235.
Mehrotra A. JN Learning. 2020.

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Indication

AIS due to LVO

Within 24 hours of the time LKW

Regardless of whether thrombolytics were given

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Powers WJ, et al. *Stroke*. 2019;50(12).

Thrombectomy Trials

2015

MR CLEAN

- First breakthrough that EVT significantly improved functional outcomes with LVO treated within 6 hours

2015

EXTEND-IA

- EVT after tPA improved reperfusion, early neurologic improvement, and functional outcomes vs tPA alone

2015

SWIFT PRIME

- Thrombectomy plus tPA improved 90-day outcomes in anterior LVO without raising complications

2015

REVASCAT

- EVT within 8 hours improved functional outcomes in anterior circulation stroke compared to medication therapy alone

2016

HERMES

- Endovascular thrombectomy within 6 h became standard for acute ischemic stroke

2025

ESCAPE-MeVO

- EVT failed to improve outcomes in MeVO and increased sICH and mortality
- Stent retrievers may not be the best technique

Koriesh A. Neurology Residents. May 5, 2024.
Raha O, et al. BMJ Medicine. 2023;2(1).

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LITERATURE REVIEW

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0-4.5 Hour Landmark Trials

NINDS

- Clear benefit of tPA 0.9 mg/kg (max 90 mg (max 90 mg; 10% as bolus and rest over 60 minutes) over placebo within 3 hours of symptom onset, leading to its FDA approval

1995

ECASS III

- IV tPA given between 3-4.5 hours after symptom onset significantly improved functional outcomes vs placebo

2008

NOR-TEST

- TNK 0.4 mg/kg is as effective as tPA with a similar safety profile, potentially offering an alternative in acute stroke thrombolysis within 4.5 hours of onset

2017

EXTEND-IA TNK

- TNK 0.25 mg/kg was associated with higher early reperfusion rates and improved functional outcomes compared to tPA within 4.5 hours of onset and eligible for thrombectomy

2018

EXTEND-IA TNK Part 2

- In LVO patients undergoing planned thrombectomy, TNK 0.40 mg/kg did not improve reperfusion compared to 0.25 mg/kg, suggesting no added benefit of higher dose within 4.5 hours of onset

2020

Koriesh A. Neurology Residents. May 5, 2024.

4.5-9 Hour Landmark Trials

1995 NINDS
2008 ECASS III
2017 NOR-TEST
2018 EXTEND IA TNK
2020 EXTEND IA-TNK Part 2

0-4.5 Hour Landmark Trials

2019

EXTEND

- In patients with salvageable brain tissue, tPA given 4.5–9 hours post-onset or on awakening improved functional outcomes but increased sICH

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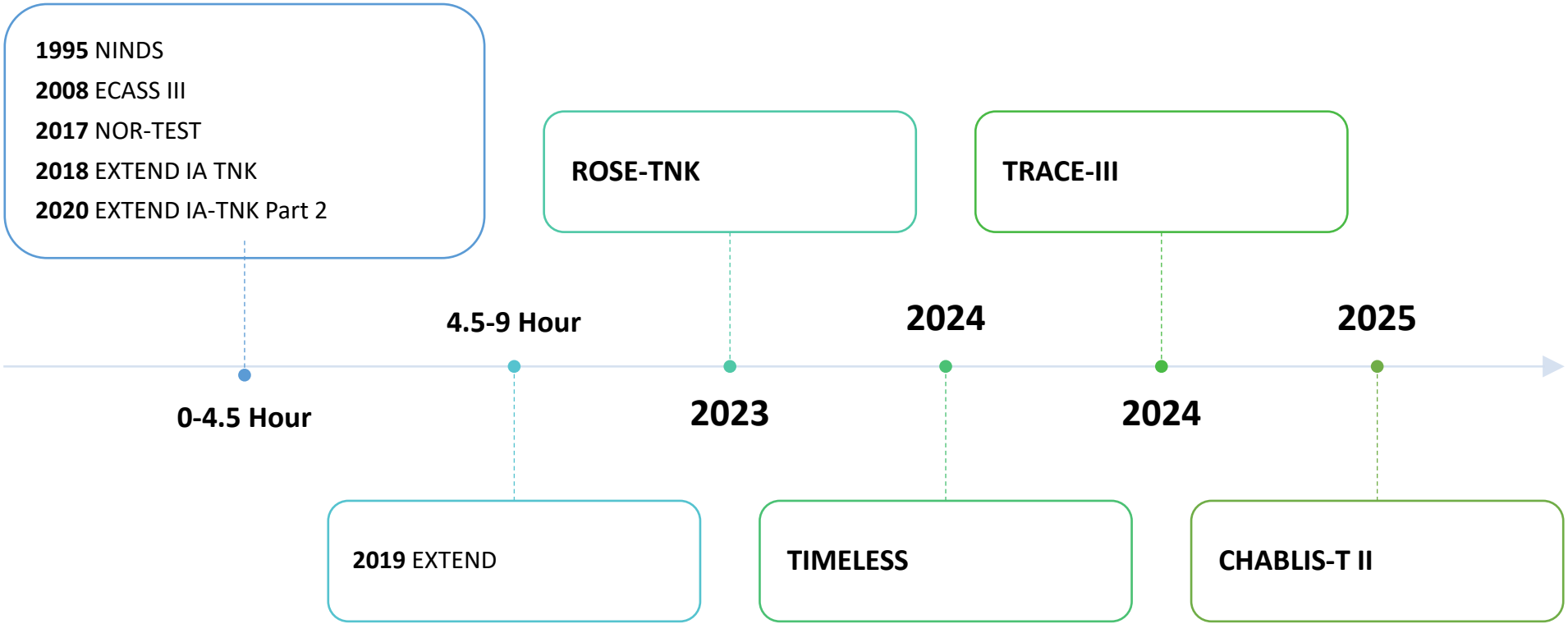
Koriesh A. Stroke trials . Neurology Residents. May 5, 2024.

4.5-24 Hour TNK Landmark Trials



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Koriesh A. Neurology Residents. May 5, 2024.

ROSE-TNK Trial

Design	Randomized, investigator-initiated, multicenter phase-2 trial in China with blinded endpoints between March 2021 and July 2022 (n=80)
Population	• 18-80 years old • With DWI-FLAIR mismatch • Acute moderate to severe stroke (NIHSS scores 6-25 at admission) • Functioning independently (mRS scores 0 to 1) before stroke • Enrolled within 4.5–24 hours after onset of stroke symptoms
Exclusion	• Planned endovascular treatment • Premorbid mRS ≥2
Intervention	TNK 0.25 mg/kg, max 25 mg (n=40) vs. standard care (n=40)

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Wang L, et al. Journal of Stroke. 2023;25(3):371-377.

Baseline Characteristics

	TNK group (n=40)	Control group (n=40)	P
Age (yr)	62.68 ± 8.87	62.80 ± 8.56	0.95
Male	31 (77.5)	26 (65.0)	0.22
Baseline NIHSS	7.50 [6.00–10.75]	7.00 [6.00–8.75]	0.21
Time from onset to randomization	10.97 ± 4.67 hours	11.01 ± 4.14 hours	0.97
Baseline infarct volume (mL)	0.32 [0.00–2.28]	0.40 [0.09–1.48]	0.78
LVO	17 (42.5)	18 (45.0)	0.82

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Wang L, et al. Journal of Stroke. 2023;25(3):371-377.

Results

	Outcome	TNK (n=40)	Control (n=40)	P
Primary Outcome	mRS (0–1) at 90 days	21 (52.5)	20 (50.0)	0.82
Secondary outcomes	mRS (0-2) at 90 days	26 (65.0)	26 (24 (60.0)	0.64
	Changes in NIHSS at 24 hours	-2.00 (-4.00 to 0.00)	7.00 [6.00–8.75]	0.07
	Changes in NIHSS at 7 days	-3.00 (-6.00 to 0.00)	-2.00 (-4.00 to -1.00)	0.31
	Early neurological improvement	11 (27.5)	3 (7.5)	0.03
Safety outcome	sICH	0 (0.0)	0 (0.0)	>0.99

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Wang L, et al. Journal of Stroke. 2023;25(3):371-377.

Limitations & Strengths

Limitation

- Small sample size
- Open-label
- More than half of the enrolled population had wake-up stroke
- Conducted in China

Strength

- Randomized multicenter design
- Blinded endpoint evaluations

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Wang L, et al. Journal of Stroke. 2023;25(3):371-377.

Conclusions

Suggests that IV administration of TNK within 4.5–24 hours of stroke onset may be safe and feasible, with the potential to improve early neurological outcomes in patients with a DWI-FLAIR mismatch

Wang L, et al. Journal of Stroke. 2023;25(3):371-377.

TIMELESS Trial

Design	Multicenter, double-blind, randomized, placebo-controlled trial in the United Sates and Canada from March 2019 through December 2022 (n=458)
Population	• ≥18 years old • 4.5-24 hours after LKW • Occlusion of MCA or ICA with salvageable tissue on CT perfusion imaging or perfusion-diffusion MRI
Exclusion	Patients who had no post-baseline mRS value
Intervention	TNK 0.25 mg/kg, max 25 mg (n=228) or placebo (n=230)

ADVOCATE HEALTH

Albers GW, et al. *New England Journal of Medicine*. 2024;390(8):701-711.

Baseline Characteristics

Characteristic	TNK group (N=228)	Control group (N=230)
Median age (IQR, year)	72 (62–79)	73 (63–82)
Female sex	122 (53.5)	123 (53.5)
Median NIHSS score (IQR)	12 (8–17)	12 (8–18)
Median duration from LKW to randomization (hour)	12.3 (9.2–15.6)	12.7 (8.7–16.5)
Endovascular thrombectomy performed	176 (77.2)	178 (77.4)

ADVOCATE HEALTH

Albers GW, et al. *New England Journal of Medicine*. 2024;390(8):701-711.

Results

	Outcome	TNK (N=228)	Control (N=230)	Adjusted Odds Ratio (95% CI)
Primary Outcome	Median mRS score at 90 days (IQR)	3 (1–5)	3 (1–4)	1.13 (0.82–1.57)
Secondary Outcomes (%)	Functional independence at 90 days	46.0	42.4	1.18 (0.80–1.74)
	Recanalization at 24 hr	76.7	63.9	1.89 (1.21–2.95)
	Reperfusion at the conclusion of endovascular thrombectomy	89.1	85.4	1.42 (0.75–2.67)
Safety Outcomes (%)	Death within 30 days	14.7	15.0	—
	Death within 90 days	19.7	18.2	—
	sICH within 36 hr	3.2	2.3	—

ADVOCATE HEALTH

Albers GW, et al. *New England Journal of Medicine*. 2024;390(8):701-711.

Limitations & Strengths

Limitation

- Inclusion criteria restrict generalizability
- Short interval between TNK or placebo administration and thrombectomy

Strength

- Double-blind randomized controlled trial
- Majority of participants from United States

ADVOCATE HEALTH

Albers GW, et al. *New England Journal of Medicine*. 2024;390(8):701-711.

Conclusion

TNK that was initiated 4.5 to 24 hours after stroke onset in patients with occlusions of the MCA or ICA, most of whom had undergone endovascular thrombectomy, did not result in better clinical outcomes than those with placebo

Albers GW, et al. *New England Journal of Medicine*. 2024;390(8):701-711.

TRACE-III Trial

Design	Phase 3, multicenter, prospective, open-label, randomized, blinded-outcome assessment in China from January 2022 through November 2023 (n=516)
Population	• ≥18 years old • Stroke, including stroke on awakening and unwitnessed stroke • Within 4.5 to 24 hours after LKW • Prestroke mRS score of 0 or 1 • NIHSS 6-25 • Evidence of occlusion of ICA or M1 or M2 segment of MCA on CTA or MRI • Evidence of salvageable brain tissue as identified on perfusion imaging
Exclusion	Access to endovascular thrombectomy
Intervention	TNK 25 mg/kg, max 25 mg (n=264) vs. standard therapy (n=252)

ADVOCATE HEALTH

Xiong Y, et al. New England Journal of Medicine. 2024;391(3):203-212.

Baseline Characteristics

Characteristic	TNK group (N=264)	Control group (N=252)
Median age (IQR, year)	67 (58–75)	68 (59–76)
Male sex	183 (69.3)	167 (66.3)
Median NIHSS score at randomization (IQR)	11 (7-15)	10 (7-14)
Known onset time	143 (54.2)	149 (59.1)
Median volume of irreversibly injured ischemic core at initial imaging (IQR, mL)	16.4 (5.7-28.4)	14.9 (6.0-29.3)

ADVOCATE HEALTH

Xiong Y, et al. New England Journal of Medicine. 2024;391(3):203-212.

Results

	Outcome	TNK (N=264)	Control (N=252)	Effect Size (95% CI)
Primary Outcome	mRS 0-1 at 90 days	87 (33.0)	61 (24.2)	1.37 (1.04 to 1.81)
Secondary Outcomes (%)	mRS score ≤2 at 90 days	43.6	33.3	1.31 (1.05 to 1.63)
	Major neurologic improvement at 72 hr	16.0	6.0	2.66 (1.51 to 4.69)
	Reperfusion at 24 hr	20.1	11.8	1.70 (1.10 to 2.64)
	Change in NIHSS at 7 days	−4 (−6 to −1)	−2 (−5 to 0)	−1.47 (−2.30 to −0.64)
Safety Outcomes (%)	sICH within 36 hr after randomization	3.0	0.8	3.82 (0.82 to 17.87)
	Death within 90 days	13.3	13.1	1.01 (0.65 to 1.58)

ADVOCATE HEALTH

Xiong Y, et al. New England Journal of Medicine. 2024;391(3):203-212.

Limitations & Strengths

Limitation

- Open-label
- Excluded EVT patients
- Conducted in China

Strength

- Blinded endpoint assessment

ADVOCATE HEALTH

Xiong Y, et al. New England Journal of Medicine. 2024;391(3):203-212.

Conclusion

TNK administered 4.5 to 24 hours after stroke onset resulted in less disability and similar survival as compared with standard medical treatment, but the incidence of sICH appeared to be higher

Xiong Y, et al. New England Journal of Medicine. 2024;391(3):203-212.

CHABLIS-II Trial

Design	Multicenter, prospective, block-randomized, open-label, blinded-end point, phase IIb study from October 21, 2021, to June 13, 2023 (n=224)
Population	• 18-80 years old • Premorbid mRS 0-2 • 4.5-24 hours after LKW • Clinically significant acute neurological deficit • Large or medium vessel occlusion in anterior circulation on baseline CTA • Favorable penumbral mismatch profile on baseline CTP
Exclusion	Extensive hypoattenuation region (more than 1/3 of the MCA territory) identified on baseline non-contrast CT
Intervention	TNK 0.25 mg/kg, max 25 mg (n=111) vs. standard therapy (n=113)

ADVOCATE HEALTH

Cheng X, et al. Stroke. 2025;56(2):344-354.

Baseline Characteristics

Characteristic	TNK group (N=111)	Control group (N=113)
Age, mean (SD), year	64.2 (10.4)	63.6 (11.0)
Male sex	80 (72.1%)	80 (70.8%)
NIHSS score at randomization, median (IQR)	9 (5–14)	9 (6–16)
Transferred for preplanned endovascular treatment	59 (53.2%)	64 (56.6%)
TLKW to hospital arrival, min, medium (IQR)	595.0 (398.0–818.0)	525.0 (368.5–778.5)
Ischemic core volume at baseline, mL, median (IQR)	6.0 (2.0-25.0)	9.0 (3.0-22.0)

ADVOCATE HEALTH

Cheng X, et al. Stroke. 2025;56(2):344-354.

Results

	Outcome	TNK (N=111)	Control (N=113)	95% CI	P
Primary Outcome (%)	Major reperfusion without sICH within 24 to 48 hours post-randomization	33.3	10.8	1.6 to 5.7	0.001
Secondary Outcome (%)	Recanalization	35.8	14.3	1.4 to 4.4	0.002
	mRS 0-2 at 90 days	50.5	58.4	0.6 to 1.2	0.4
	Major neurological improvement at 24–48 hours	21.8	23.1	0.5 to 1.6	0.8
	Change in NIHSS score at 24–48 hours, median (IQR)	−1 (−4 to 0)	1 (−5 to 0)	−1.0 to 1.4	0.7
Safety Outcome (%)	SICH	5.4	4.4	0.4 to 4.2	0.7
	Any ICH	24.3	18.6	0.8 to 2.4	0.3
	mRS score 5–6 at 90 d	9.8	17.7	0.6 to 2.1	0.7

Cheng X, et al. Stroke. 2025;56(2):344-354.

Limitations & Strengths

Limitation

- Limited sample size
- Open-label
- Optional EVT
- Conducted in China

Strength

- Multicenter, randomized design
- Blinded endpoint assessment

ADVOCATE HEALTH

Cheng X, et al. Stroke. 2025;56(2):344-354.

Conclusion

TNK 0.25 mg/kg increased reperfusion without sICH in patients with ischemic stroke selected by imaging in late-time window treatment but did not change clinical outcomes at 90 days

ADVOCATE HEALTH

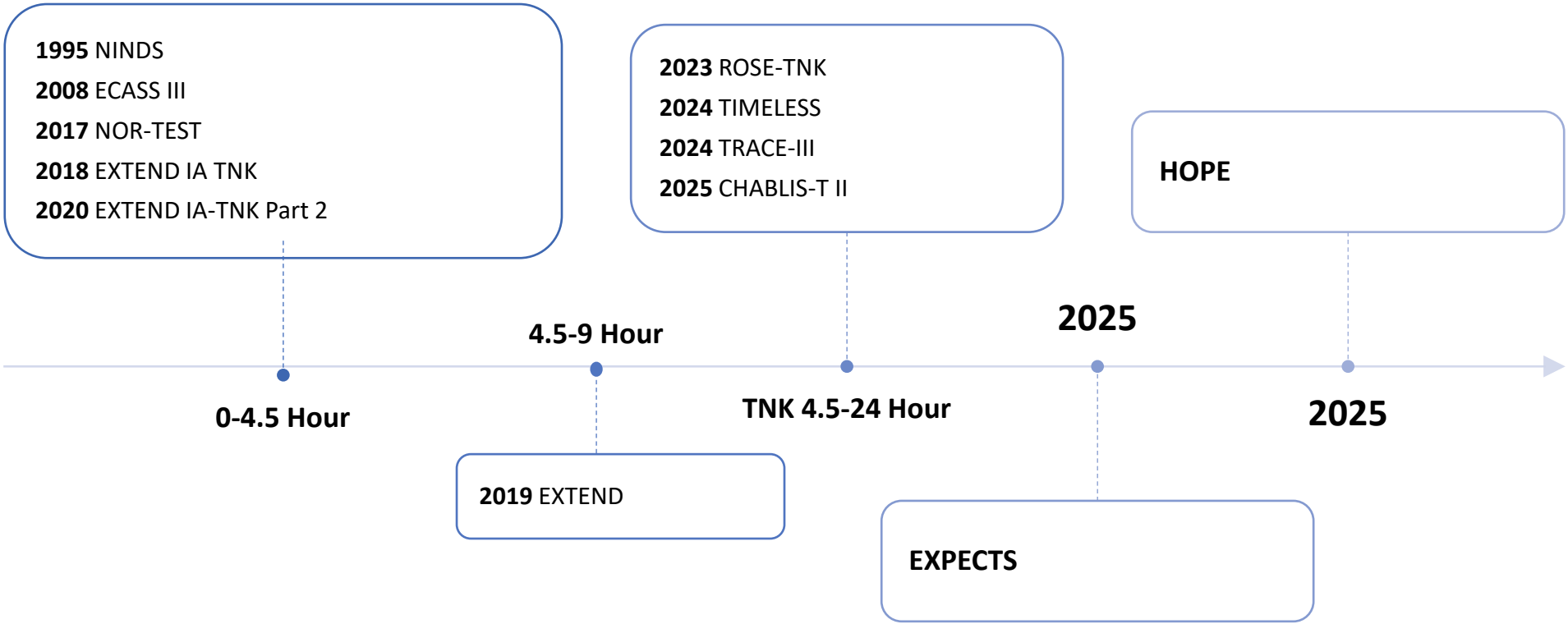
Cheng X, et al. Stroke. 2025;56(2):344-354.

Assessment Question #4

In the CHABLIS-II trial comparing TNK to best medical therapy for patients with acute ischemic stroke due to LVO, which of the following was a key finding?

A. TNK significantly increased the rate of sICH compared to best medical therapy
B. TNK significantly improved major reperfusion without increasing sICH
C. There was no difference in early recanalization rates between TNK and best medical therapy
D. Patients with planned endovascular thrombectomy were included and had better outcomes with TNK

4.5-24 Hour tPA Landmark Trials



ADVOCATE HEALTH

Koriesh A. Neurology Residents. May 5, 2024.

EXPECTS Trial

Design	Prospective, multicenter, open-label, randomized trial with blinded outcome assessment in China from August 2022 through May 2024 (n=234)
Population	• ≥18 years old • Clinical signs of posterior circulation stroke with confirmation on diffusion-weighted MRI or lack of an alternative diagnosis on CT • 4.5-24 hours from onset of stroke • NIHSS ≥1 • Prestroke mRS score 0-1
Exclusion	Thrombectomy planned
Intervention	Alteplase 0.9 mg/kg, max 90 mg (n=117) vs. standard therapy (n=117)

ADVOCATE HEALTH

Yan S, et al. *New England Journal of Medicine*. 2025;392(13):1288-1296.

Baseline Characteristics

Characteristics	Alteplase (N=117)	Standard Treatment (N=117)
Median age (IQR), year	64 (57–76)	63 (55–74)
Male sex	75 (64.1)	78 (66.7)
Median NIHSS score at randomization	3 (2–6)	3 (1–6)
mRS 0 before stroke	114 (97.4)	114 (97.4)

ADVOCATE HEALTH

Yan S, et al. *New England Journal of Medicine*. 2025;392(13):1288-1296.

Results

	Outcome	Alteplase (N=117)	Control (N=117)	Treatment Effect (95% CI)
Primary Outcome (%)	mRS 0-2 at 90 days	89.6	72.6	1.16 (1.03–1.30)
Secondary Outcomes (%)	Major neurologic improvement at 24 hr	36.2	35.9	0.97 (0.69–1.37)
	Major neurologic improvement at 7 days	56.0	48.7	1.11 (0.87–1.42)
Safety Outcomes (%)	Death within 90 days	5.2	8.5	0.61 (0.23–1.62)
	sICH within 36 hr after randomization	1.7	0.9	1.98 (0.18–21.56)

ADVOCATE HEALTH

Yan S, et al. *New England Journal of Medicine*. 2025;392(13):1288-1296.

Limitations & Strengths

Limitation

- Excluded patients with EVT planned
- Mild strokes
- Open label
- Conducted in China
- 31.2% were enrolled on noncontrast CT findings

Strength

- Excluded patients with EVT planned
- Multicenter, randomized trial
- Blinded outcome assessment

Conclusion

Among patients with mainly mild posterior circulation stroke who did not receive thrombectomy, tPA administered 4.5 to 24 hours after stroke onset resulted in a higher frequency of functional independence at 90 days than standard medical care

Yan S, et al. *New England Journal of Medicine*. 2025;392(13):1288-1296.

HOPE Trial

Design	Randomized, multicenter, open-label, blinded end-point trial between June 21, 2021, and June 30, 2024 (n=372)
Population	• 18 years or older • Clinical signs of stroke that began within 4.5 to 24 hours of presentation • NIHSS 4-26 • Prestroke mRS 0-1 • Potentially salvageable tissue on CT perfusion imaging
Exclusion	Thrombectomy planned
Intervention	Randomly assigned (1:1) to tPA 0.9 mg/kg, max 90 mg (n=186) or standard medical treatment (n=186)

ADVOCATE HEALTH

Zhou Y, et al. *JAMA*. 2025;334(9):788.

Baseline Characteristics

Characteristic	Alteplase (N=186)	Control (N=186)
Age, median (IQR), year	72 (62-80)	73 (65-80)
Male sex	102 (54.8)	110 (59.1)
NIHSS score at randomization, median (IQR)	10 (6-15)	10 (6-14)
Onset to randomization time, median (IQR), min	411 (328-551)	427 (352-542)
Ischemic core at initial imaging, median (IQR), mL	12 (4-28)	14 (4-28)
Endovascular Treatment	3 (1.6)	7 (3.8)
MeVO	74 (39.8)	69 (37.1)

ADVOCATE HEALTH

Zhou Y, et al. *JAMA*. 2025;334(9):788.

Results

	Outcome	Alteplase (N=186)	Control (N=186)	Effect Size (95% CI)	P
Primary Outcome	mRS score 0-1 at 90 days	75 (40.3)	49 (26.3)	1.52 (1.14 to 2.02)	0.004
Secondary Outcome	mRS score 0-2 at 90 days	103 (55.4)	85 (45.7)	1.20 (1.00 to 1.45)	0.052
	Major neurologic improvement at 24 hours	39 (21.0)	24 (12.9)	1.66 (1.03 to 2.66)	0.04
	Major neurologic improvement at 7 days	35.5%	27.2%	1.30 (0.95 to 1.77)	0.10
Safety Outcome	Death within 90 days	20 (10.8)	20 (10.8)	0.91 (0.52 to 1.62)	0.76
	sICH within 36 hours	3.8%	0.5%	7.34 (1.54 to 34.84)	0.01

ADVOCATE HEALTH

Zhou Y, et al. *JAMA*. 2025;334(9):788.

Limitations & Strengths

Limitation

- Open-label
- Excluded patients with planned EVT

Strength

- Included MeVO
- Randomized trial
- Blinded end points
- Excluded patients with planned EVT

ADVOCATE HEALTH

Zhou Y, et al. *JAMA*. 2025;334(9):788.

Conclusion

In patients with acute ischemic stroke with salvageable brain tissue identified by perfusion imaging who did not initially receive thrombectomy, tPA administered 4.5-24 hours after onset provided functional benefit, despite an increase in sICH

ADVOCATE HEALTH

Zhou Y, et al. *JAMA*. 2025;334(9):788.

Assessment Question #5

A 68-year-old man presents 6 hours after onset of left-sided weakness and slurred speech. Perfusion imaging shows salvageable brain tissue, and imaging confirms a distal M2 middle cerebral artery (MCA) occlusion. He did not receive thrombectomy. Based on the HOPE trial, which of the following is the most evidence-based next step?

A. Administer alteplase 0.9 mg/kg (10% bolus, remainder over 60 minutes)
B. Proceed with endovascular thrombectomy
C. Start dual antiplatelet therapy only
D. Observe and repeat imaging in 24 hours

SUMMARY

ADVOCATEHEALTH

Tenecteplase for Acute Ischemic Stroke at 4.5 to 24 Hours: A Meta-Analysis of Randomized Controlled Trials

Improves excellent functional outcomes and recanalization

Without increasing risks of sICH or mortality

Provides greater additional benefits when EVT is inaccessible, establishing its role as an alternative reperfusion strategy in resource-limited settings

ADVOCATE HEALTH

Wang Z, et al. *Stroke*. 2025.

Potential Impact

Expect that findings from these trials could be incorporated into upcoming guidelines

These trials could shape future guidelines and prompt practice changes, especially in rural hospitals

	Trial	N	LVO?	Imaging	Safety (sICH)	mRS Outcome (0-1)	EVT	Notes
TNK	**ROSE-TNK 2023**	80	Yes 44%	MR DWI-FLAIR	No increase	**No change** (52.5% vs 50%)	Excluded	Safe but small number of patients
	Timeless 2024	458	Yes 100%	CT Perfusion	No increase (3.2% vs 2.3%)	**No change** (46% vs 42%) (mRS 0-2)	Permitted 77%	Safe but didn't affect outcome
	TRACE III 2024	516	Yes 100%	CT Perfusion	No significant increase (3% vs 0.8%)	**Improved** (33% vs 24%)	Excluded	Safe and effective in LVO patients not going for EVT
	CHABLIS-T II 2025	224	Yes 100%	CT Perfusion	No significant increase (5.4% vs 4.4%)	**No change** (39.6% vs 36.3%)	Permitted 55%	Safe and improved reperfusion
tPA	**EXPECTS 2025**	234	Yes 30%	CT or CTP or DWI	No significant increase (1.7% vs 0.9%)	**Improved** (74% vs 61%)	Excluded	Safe and effective in larger selection of patients
	HOPE 2025	372	Yes 63%	CT Perfusion	No significant increase (3.8% vs 0.5%)	**Improved** (40% vs 26%)	Excluded	Safe and effective for posterior circulation stroke (not going for EVT) with 38% MeVO

TNK Trials Summary

ROSE-TNK (2023)

- TNK within 4.5-24 hours was safe with no sICH events
- Early neurological improvement was significantly higher with TNK
- No difference in 90-day functional outcome (mRS 0-1)

TIMELESS (2024)

- TNK did not significantly improve 90-day mRS in LVO patients 4.5-24 hours after stroke onset
  - M1 occlusion showed possible benefit
- sICH and mortality were similar
- Most underwent thrombectomy (77%)

TRACE-III (2024)

- In patients with LVO who did not undergo thrombectomy, TNK in an extended window of 4.5-24 hours was associated with less disability

CHABLIS-T II

- TNK significantly increased reperfusion without increasing sICH
- No signidiacnt different in 90-day clinical outcomes (mRS 0-2 or NIHSS)
- Safety outcomes were similar

tPA Trials Summary

EXPECTS (2025)

- tPA between 4.5-24 hours after onset improved functional independence at 90 days in patients with posterior circulation strokes

HOPE (2025)

- tPA 4.5-24 hours after stroke onset provided a functional benefit, despite an increase in sICH, using CT Perfusion
- Improved functional independence at 90 days with tPA (40% vs. 26%)
- No significant difference in all-cause mortality at 90 days between groups

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Questions?

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