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Expanding our horizons?

The role of extended-window fibrinolytics in acute ischemic stroke

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Disclosure

I do not have a vested interest in or affiliation with any corporate organization offering financial support or grant monies for this continuing education activity, or any affiliation with an organization whose philosophy could potentially bias my presentation (within the last 12 months).

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Pharmacist Learning Objectives

1. Review available pharmacologic options for treatment of acute ischemic stroke, including special populations such as pediatrics and pregnancy
2. Discuss limitations and current guideline recommendations for treatment of acute ischemic stroke
3. Appraise available literature for efficacy and safety of fibrinolytic use beyond 4.5 hours from last known well time
4. Apply current literature to a patient case to determine appropriateness of expanded-window fibrinolytic use

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Technician Learning Objectives

1. Review available pharmacologic options for treatment of acute ischemic stroke, including special populations such as pediatrics and pregnancy
2. Discuss limitations and current guideline recommendations for treatment of acute ischemic stroke

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Abbreviations

- ASPECTS: Alberta Stroke Program Early CT Score
- AIS: Acute ischemic stroke
- EQ-5D: EuroQol-5D
- EVT: Endovascular thrombectomy
- ICH: Intracerebral hemorrhage
  - sICH: Symptomatic ICH
- LKW: Last known well
- LVO: Large vessel occlusion
- mRS: Modified Rankin Scale
- NIHSS: National Institute of Health Stroke Scale
- CI: Confidence interval
- IQR: Interquartile range
- OR: Odds ratio
  - aOR: Adjusted OR
- RR: Risk ratio
  - aRR: Adjusted RR

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ACUTE ISCHEMIC STROKE

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Acute ischemic stroke

- Decreased blood flow to the brain caused by a sudden reduction in perfusion of brain tissue leading to reduced oxygenation and ischemia/infarction
  - Medical emergency – Delays in treatment worsen outcomes
- Represents about 87% of all strokes
- Nearly 800,000 patients annually have a stroke
  - Approximately 25% are recurrent strokes
- A leading cause of morbidity; 4th leading cause of mortality

American Stroke Association. *About Stroke*. https://www.stroke.org/en/about-stroke
Boehme AK, Esenwa C, Elkind MS. *Circ Res*. 2017;120(3):472-495.

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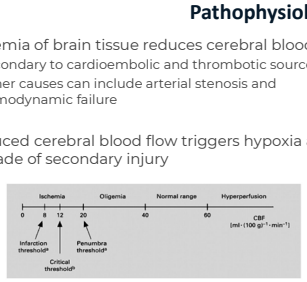
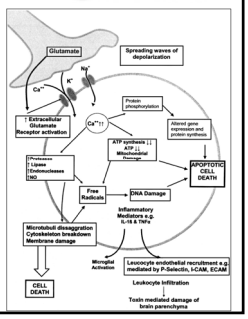
Pathophysiology

- Ischemia of brain tissue reduces cerebral blood flow
  - Secondary to cardioembolic and thrombotic sources
  - Other causes can include arterial stenosis and hemodynamic failure
- Reduced cerebral blood flow triggers hypoxia and cascade of secondary injury





Jovin T, et al. *Continuum (Minneap Minn)*. 2008;14(6):28-45.

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Stroke risk factors

- Risk for acute ischemic stroke increases with age
- Risk can vary with race and ethnicity
  - Risk for non-Hispanic Black adults nearly twice as high as for non-Hispanic White adults
- Modifiable risk factors: hypertension, dyslipidemia, smoking, obesity, and diabetes
  - One in three Americans has at least one of these risk factors
- Patients who experience a stroke are at an increased risk of experiencing recurrent stroke

Boehme AK, Esenwa C, Elkind MS. *Circ Res*. 2017;120(3):472-495.

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Deficit severity scales

Modified Rankin Scale (mRS)

Score	Description
0	No symptoms
1	No significant disability. Able to carry out all usual activities despite some symptoms
2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
3	Moderate disability; requiring some help, but able to walk without assistance
4	Moderately severe disability; unable to walk and attend to bodily needs without assistance
5	Severe disability; bedridden, incontinent, and requiring constant nursing care and attention
6	Dead

National Institute of Health Stroke Scale (NIHSS)

- Allows providers to quantify neurological symptoms and assess stroke severity
- Measured across 11 domains testing sensory and motor disability
  - Scored out of 42 points
- Severity:
  - Minor: 1-4
  - Moderate: 5-15
  - Moderate to severe: 16-20
  - Severe: 21-42

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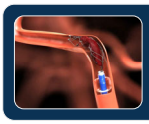
Treatment in the acute setting

Fibrinolytics
- Alteplase
- Tenecteplase



Mechanical thrombectomy
- Aspiration thrombectomy
- Stent retriever

Photo #1 by Genentech via https://www.activase.com/ais/dosing-and-administration/reconstituting.html
Photo #2 by Franciscan Health via https://www.franciscanhealth.org/community/blog/medical-thrombectomy

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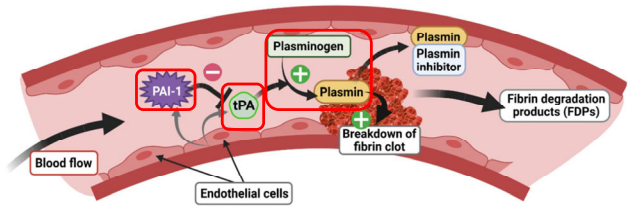
Fibrinolytic Mechanism



Mennesson M, Revest JM. *Int J Mol Sci*. 2023;24(5):4496

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Fibrinolytics

Alteplase (TPA)

- Approved in 1996 for acute ischemic stroke treatment in adults
- Dose of 0.9 mg/kg, max of 90 mg
  - 10% given as an IV push over one minute
  - 90% given as an infusion over one hour
- Half-life – 5 minutes

Tenecteplase (TNK)

- Approved in 2025 for acute ischemic stroke treatment in adults
- Dose of 0.25 mg/kg, max of 25 mg
  - Administered as an IV push over 2-5 minutes
- Terminal half-life – 90-130 minutes
- More specific to plasminogen, less specificity for Plasminogen activation inhibitor-1 (PAI-1)

Alteplase. In: Lexi-Drugs. UpToDate Lexidrug. UpToDate Inc.
Tenecteplase. In: Lexi-Drugs. UpToDate Lexidrug. UpToDate Inc.

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Special populations – Pregnancy

- Until 2018, pregnancy was considered a relative contraindication for fibrinolytic use
  - No randomized controlled trials examining efficacy and safety
- Use limited to case reports/case series
- Both agents are large molecules not expected to cross the placenta
- Risk of bleeding complications may be increased in pregnant patients
- Must weigh risk vs. benefit

Ryman KM, Pace WD, Smith S, Fontaine GV. *Pharmacotherapy.* 2019;39(7):767-774.

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Special populations - Pediatrics

- Not FDA-approved in this population for AIS
- Small studies pointing toward efficacy and safety with alteplase
  - Sporns, et al (2025): Improved mRS, NIHSS; no difference in sICH
  - Amlie-Lefond, et al. (2019): Overall risk for sICH is low and comparable to adult patients
- Very limited data for tenecteplase
  - Sun, et al. (2025): Case series signaling safety of TNK

2b	C-LD	14. In pediatric patients aged 28 days to 18 years with confirmed AIS presenting within 4.5 hours of symptom onset and disabling deficits, IVT with alteplase may be considered as it is safe, but efficacy is uncertain.[B-NR]

Sporns PB, et al. *JAMA Netw Open.* 2025;8(10):e2538191.
Amlie-Lefond C, et al. *Stroke.* 2020;51(2):542-548.
Sun LR, et al. *Neurology.* 2025;104(3):e210310.
Powers WJ, et al. *Stroke.* 2019;50(12):e344-e418.

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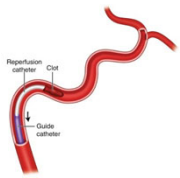
Mechanical thrombectomy

- Endovascular mechanical removal of a clot



- Performed in patients with LVOs
  - Comprise half of all acute ischemic strokes
- Ideal adult candidate:
  - LVO in the internal carotid or middle cerebral artery branch 1
  - Procedure initiated within 6 hours from last known well
  - Pre-stroke mRS of 0 or 1
  - ASPECTS ≥ 6
  - NIHSS ≥ 6

Al-Bayati, A.R., Nogueira, R.G., Samaniego, E.A., Haussen, D.C. (2019). Springer, Cham.
Waqas M, et al. *J. Stroke Cerebrovasc. Dis.* 2020;29(2):104504.

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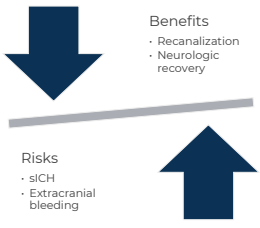
Balancing risk and benefit



- Considerations:
  - Age
  - Comorbidities
  - Severity of stroke
  - Location of stroke
  - Time from stroke onset
  - Pre-stroke level of function
  - Factors that can increase risk of bleeding

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EVOLUTION OF STROKE TREATMENT

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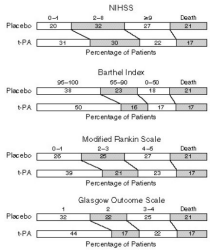
NINDS-TPA (1995)

- Randomized 624 patients to alteplase or placebo
  - Within 180 minutes of time from LKW
- Primary outcome
  - Part 1: Early neurological improvement at 24 hours
    - No significant difference; RR 1.2, 95% CI 1-1.4
  - Part 2: Sustained neurological improvement across four domains at three months
    - Significantly improved percentage of patients with favorable outcomes
- sICH: 6.3% vs. 0.6% (p < 0.001)
- Mortality: 17% vs. 21% (p = 0.30)



National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. *N Engl J Med.* 1995;333(24):1581-1587.

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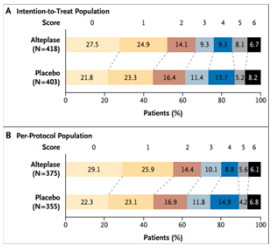
ECASS-III (2008)



- Randomized 821 patients to alteplase vs. placebo
  - Presented between 3 and 4.5 hours from LKW
- Favorable outcome, 90 days
  - Intention-to-treat: OR 1.42 (95% CI 1.02-1.98)
  - Per protocol: OR 1.47 (95% CI 1.1-1.97)
- Improvement in global outcome analysis for intention-to-treat and per-protocol cohorts

Hacke W, et al. *N Engl J Med.* 2008;359(13):1317-1329.

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ECASS-III (2008)

- Significant increase in:
  - Any ICH: 27% vs. 17.6%; OR 1.73 (95% CI 1.24-2.42)
  - sICH: 2.4% vs. 0.2%; OR 9.85 (95% CI 1.26-77.32)
- Fatal ICH: 0.7% vs. 0%
- Symptomatic edema: 6.9% vs. 7.2% (p=0.89)
- Death: 7.7% vs. 8.4% (p=0.68)
- Total serious adverse events: 25.1% vs. 24.6%

Hacke W, et al. *N Engl J Med.* 2008;359(13):1317-1329.

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EXTEND-IA TNK (2018)

- Randomized 202 patients to either tenecteplase or alteplase
  - Tenecteplase dose: 0.25 mg/kg, maximum of 25 mg
  - Patients were anticipated to undergo thrombectomy and presented within 4.5 hours of symptom onset
- Tenecteplase demonstrated improved rates of substantial reperfusion
  - 22% vs. 10%; aOR 2.6 (95% CI 1.1-5.9)
  - Higher rate of patients able to bypass thrombectomy
- Significant improvement in ordinal mRS analysis at 90 days
  - Reduced mortality; no difference in sICH

Campbell BC, et al. *Int J Stroke.* 2018;13(3):328-334.

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2019 guideline recommendations

Recommendations	Class of recommendation	Level of evidence
IV alteplase (0.9 mg/kg, maximum 90 mg over 60 minutes with initial 10% of dose given as a bolus over 1 minute) is **recommended for selected patients who can be treated within 3 hours of ischemic stroke symptom onset or patient last known well or at baseline state.**	I	A
IV alteplase (0.9 mg/kg, maximum 90 mg over 60 minutes with initial 10% of dose given as a bolus over 1 minute) is **also recommended for selected patients who can be treated within 3 and 4.5 hours of ischemic stroke symptom onset or patient last known well or at baseline state.**	I	B-R
It **may be reasonable to choose tenecteplase** (single IV bolus of 0.25 mg/kg, maximum 25 mg) **over IV alteplase in patients without contraindications** for IV fibrinolysis **who are also eligible to undergo mechanical thrombectomy.**	IIb	B-R

Powers WJ, et al. *Stroke.* 2019;50(12):e344-e418.

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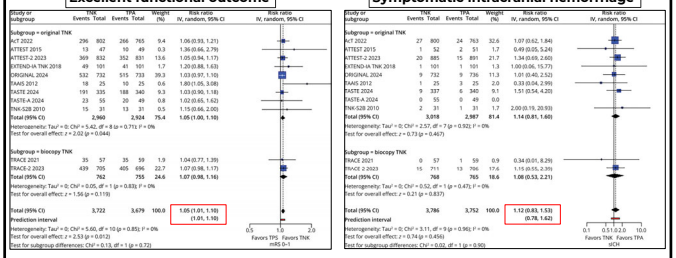
Excellent functional outcome

Symptomatic intracranial hemorrhage



Palaiodimou L, et al. *Neurology*. 2024;103(9):e209903.

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Contraindications to treatment

- Long checklist that should be reviewed prior to fibrinolytic administration
- Emphasizes the guiding principle of stroke treatment for optimization of the benefits and risks associated with treatment
  - Limiting fibrinolytic use to patients that are not expected to benefit OR in those that are at a high risk of harm
- Pharmacists can play a role in helping to rule out contraindicating factors
  - Medication reconciliation for anticoagulant use
  - Blood pressure management
  - Obtaining a blood glucose

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Gaps in treatment

- Most patients with acute ischemic stroke are not candidates for intravenous fibrinolysis
- Approximately 10% of all patients with suspected/confirmed acute ischemic stroke receive fibrinolysis
- Certain populations were less likely to receive this treatment
  - Racial gaps, economic disparities, and rural locations were predictors for lower odds of receiving thrombolytics

de Havenon A, et al. *Neurology*. 2021;97(23):e2292-e2303.

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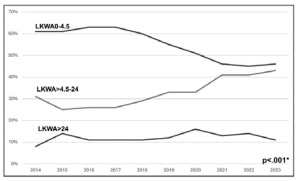
Gaps in patient treatment (cont'd)

- "I think it's great we have options! 4.5 hours feels restrictive though…"
- Only about half of all patients present within the 4.5-hour window



- (Some) Predictors for arrival beyond 4.5 hours
  - Age
  - Sex
  - Race
  - Median household income
  - Method of transport
  - Severity of stroke
  - Presence of multiple comorbid risk factors

Ferrone NG, et al. *Stroke*. 2025;56(3):591-602.

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EXPANDING THE TREATMENT WINDOW

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DAWN Trial (2017)

- Randomized 206 patients to thrombectomy or control (1:1) who presented between 6 and 24 hours from last known well
  - Identified patients with a "clinical deficit mismatch"
  - Randomized at a median 13.6 hours from last known well
- Improvement in utility-weighted mRS: Adjusted difference 2.0; 95% CI 1.1-3
- Rate of functional independence: Adjusted difference 33%; 95% CI 21-44%
- Rate of neurological deterioration: 14% vs. 26%; p=0.04
- No significant difference in serious adverse events, sICH, or mortality

Nogueira RG, et al. *N Engl J Med*. 2018;378(1):11-21.

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"Clinical deficit mismatch"

- Severe symptomatology over and above what would be expected based on stroke infarct size
  - Infarct size measured via CT perfusion or diffusion-weighted MRI
  - Indicates significant volume of salvageable tissue

Group	Patients	Criteria
A	80 years or older	NIHSS ≥ 10 with infarct volume < 21 mL
B	Younger than 80 years	NIHSS ≥ 10 with infarct volume < 31 mL
C	Younger than 80 years	NIHSS ≥ 20 with infarct volume of 31-51 mL

- Identified patients who are more likely to benefit from treatment

Nogueira RG, et al. *N Engl J Med.* 2018;378(1):11-21.

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DEFUSE 3 Trial (2018)

- Randomized 182 patients to thrombectomy vs. medical therapy alone who presented within 6-16 hours from time of last known well
  - Identified patients with a large volume of salvageable tissue
  - Median time from last known well of approx. 11 hours
- Median mRS at 90 days: 3 (1-4) vs. 4 (3-6); OR 2.77 (95% CI 1.63-4.7)
- Functional independence at 90 days: 45% vs. 17% (p<0.001)
- No difference in mortality, sICH, early neuro deterioration, or type 2 parenchymal hematoma rates

Albers GW, et al. *Int J Stroke.* 2017 Oct;12(8):896-905.

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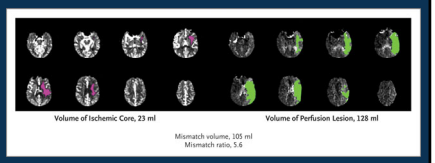
Perfusion-core mismatch

- CT Perfusion or diffusion-weighted MRI utilized
- Ischemic tissue to infarct volume ratio ('Mismatch ratio') of 1.8
  - Infarct size < 70 mL
  - Potentially large volume of salvageable tissue



Albers GW, et al. Int J Stroke. 2017 Oct;12(8):896-905.

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Takeaways from DAWN and DEFUSE 3

- Optimizing risk and benefit is key to stroke treatment
- Advanced imaging modalities can be leveraged to identify those who most benefit
  - Those with significant degree of salvageable tissue
- Expanding diagnostic evaluation beyond non-contrast head CT is crucial to expanding the treatable population

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Trial Design	Multicenter, randomized, double-blind, placebo-controlled trial
Patient population	Patients with an unknown time of onset for acute ischemic stroke
Inclusion	"MRI Diffusion-weighted/FLAIR mismatch"
Treatment	Intravenous alteplase (n=254) or placebo (n=249)
Median NIHSS (IQR)	6 (4-9)
Primary outcome	Favorable outcome at 90 days: 53.3% vs. 41.8% Adjusted OR 1.61 (95% CI 1.09-2.36)
Selected secondary outcomes	Median mRS (IQR): 1 (1-3) vs. 2 (1-3); adjusted OR 1.62 (95% CI 1.17-2.23) Global Outcome Score at 90 days: OR 1.47 (95% CI 1.07-2.04) EQ-5D at 90 days: 1.9 ± 2.1 vs. 2.4 ± 2.4 (p=0.004)
Safety outcomes	Death or dependency at 90 days: 13.5% vs. 18.3% (p=0.17) Symptomatic ICH: 2.4% vs. 0.4% (p=0.1) Major extracranial bleeding: 1.2% vs. 0%

WAKE-UP (2018)

Conclusion: "... Intravenous alteplase guided by a mismatch between diffusion-weighted imaging and FLAIR in the region of ischemic resulted in **significantly better functional outcome**..."

Thomalla G, et al. *N Engl J Med.* 2018;379(7):611-622.

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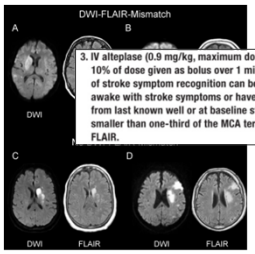
"Diffusion-weighted/FLAIR mismatch"



3. IV alteplase (0.9 mg/kg, maximum dose 90 mg over 60 minutes with initial 10% of dose given as bolus over 1 minute) administered within 4.5 hours of stroke symptom recognition can be beneficial in patients with AIS who awake with stroke symptoms or have unclear time of onset >4.5 hours from last known well or at baseline state and who have a DW-MRI lesion smaller than one-third of the MCA territory and no visible signal change on FLAIR.

- Fluid-attenuated inversion therapy (FLAIR) is a common MRI sequence that nullifies signals
- on
- Used to confirm stroke onset was within the previous 4.5 hours
  - Median interval from last known well ~7.1 hours
- No interaction between treatment effect and vessel status on post-hoc analyses

Thomalla G, et al. *N Engl J Med.* 2018;379(7):611-622.
Powers WJ, et al. *Stroke.* 2019;50(12):e344-e418.

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30,000-foot view

- WAKE-UP: We can use advanced imaging to our advantage
  - Timely MRI utilization might be a challenge
  - Our window hasn't been extended

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Trial Design	Multicenter, randomized, placebo-controlled trial
Patient population	Patients with acute ischemic stroke with time of last known well within 4.5 and 9 hours
Inclusion	Perfusion lesion-ischemic core mismatch ratio of 1.2
Treatment	Intravenous alteplase (n=113) or placebo (n=112)
Stroke characteristics	Median NIHSS (IQR): 12 (8-17) vs. 10 (6-16.5) Time from onset to treatment, min (IQR): 432 (374-488) vs. 450 (374-500) Large vessel occlusion: 69% vs. 72.3%
Primary outcome	Favorable outcome, 90 days: 35.4% vs. 29.5% aRR 1.44 (95% CI 1.01-2.06)
Selected secondary outcomes	Functional independence, 90 days: 49.6% vs. 42.9%; aRR 1.36 (95% CI 1.06-1.76) ≥90% reperfusion at 24 hours: 50% vs. 28.4%; aRR 1.73 (95% CI 1.22-2.46) Major neuro improvement, 24 hours: 28.3% vs. 11.6%; aRR 2.52 (95% CI 1.4-4.56)
Safety outcomes	90-day mortality: 11.5% vs. 8.9%; aRR 1.17 (95% CI 0.57-2.4) sICH at 36 hours: 6.2% vs. 0.9%; aRR 7.22 (95% CI 0.97-53.54)

EXTEND (2019)

Conclusion: "The use of alteplase therapy in patients who had a favorable perfusion-imaging profile between 4.5 and 9 hours after stroke onset or on awakening with stroke symptoms resulted in **no or minor neurologic deficits more often than the use of placebo**."

Ma H, et al. *N Engl J Med.* 2019;380(19):1795-1803.

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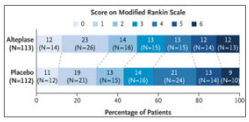
EXTEND (2019)

- Trial terminated early given positive results of the WAKE-UP Trial
- No significant difference in between-group functional improvement at 90 days on ordinal analysis
  - Common odds ratio: 1.55 (95% CI 0.96-2.49)



- Authors opined that further trials of expanded window utilization were needed

Ma H, et al. *N Engl J Med.* 2019;380(19):1795-1803.

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30,000-foot view (cont'd)

- WAKE-UP: We can use advanced imaging to our advantage
  - Timely MRI utilization might be a challenge
  - Our window hasn't been extended
- EXTEND: Fibrinolytics up to 9 hours from LKW may be safe
  - Mixed findings on overall effectiveness

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Trial Design	Multicenter, randomized, open-label trial
Patient population	Patients with moderate-severe acute ischemic stroke with time of last known well within 4.5 and 24 hours
Inclusion	ICA or MCA branch 1 or 2 occlusion, mismatch ratio of 1.8
Treatment	Intravenous tenecteplase (n=264) or placebo (n=252)
Stroke characteristics	Median NIHSS (IQR): 11 (7-15) vs. 10 (7-14) mRS of 0 at baseline: 87.1% vs. 85.7% Median time from last known well (IQR): 12.3 hours (8.5-16.4)
Primary outcome	mRS of 0 or 1, 90 days: 33% vs. 24.2% Relative rate 1.37 (95% CI 1.04-1.81)
Selected secondary outcomes	Functional independence: 43.6% vs. 33.3%; RR 1.31 (95% CI 1.05-1.63) Reperfusion at 24 hours: 20.1% vs. 11.8%; RR 1.7 (95% CI 1.1-2.64) Major improvement, 72 hours: 16% vs. 6%; RR 2.66 (95% CI 1.51-4.69)
Safety outcomes	90-day mortality: 13.3% vs. 13.1%; RR 1.01 (95% CI 0.65-1.58) sICH at 36 hours: 3% vs. 0.8%; RR 3.82 (95% CI 0.82-17.87)

TRACE-III (2024)

Conclusion: "… tenecteplase administered between 4.5 hours and 24 hours after the patients were last known to be well was shown to **improve disability-free recovery."**

Xiong Y, et al. *N Engl J Med.* 2024;391(3):203-212.

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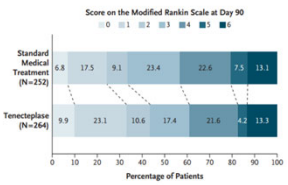
TRACE-III (2024)



- No significant difference in between-group functional improvement at 90 days on ordinal analysis
  - Common odds ratio: 1.33 (95% CI 0.98-1.81)

Xiong Y, et al. *N Engl J Med.* 2024;391(3):203-212.

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30,000-foot view (cont'd)

- WAKE-UP: We can use advanced imaging to our advantage
  - Timely MRI utilization might be a challenge
  - Our window hasn't been extended
- EXTEND: Fibrinolytics up to 9 hours from LKW may be safe
  - Mixed findings on overall effectiveness
- TRACE-III: Fibrinolytics may be safe up to 24 hours
  - The effectiveness question hasn't been fully answered
  - Limited generalizability – patients were largely thrombectomy-ineligible

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Trial Design	Multicenter, randomized, placebo-controlled trial
Patient population	Patients with acute ischemic stroke with time of last known well within 4.5 and 24 hours
Inclusion	ICA or MCA branch 1 or 2 occlusion with a perfusion lesion-ischemic core mismatch ratio of 1.8
Treatment	Intravenous tenecteplase (n=228) or placebo (n=230)
Stroke characteristics	Median NIHSS: 12 (8-17) vs. 12 (8-18) Time from onset to randomization, hrs (IQR): 12.3 (9.2-15.6) vs. 12.7 (8.7-15.6) Thrombectomy performed: 77.2% vs. 77.4% Median TICI grade (IQR): 0 (0-0) vs. 0 (0-0)
Primary outcome	Median mRS at 90 days (IQR): 3 (1-5) vs. 3 (1-4) Adjusted common odds ratio 1.13 (95% CI 0.82-1.57)
Selected secondary outcomes	Functional independence, 90 days: 46% vs. 42.4%; aOR 1.18 (95% CI 0.8-1.74) Reperfusion, 24 hours: 56.9% vs. 57.7%; aOR 1.04 (95% CI 0.69-1.57)
Safety outcomes	30-day mortality: 14.7% vs. 15% sICH at 36 hours: 3.2% vs. 2.3%

TIMELESS (2024)

Conclusion: "**No benefit in functional outcome with tenecteplase as compared with placebo** administered 4.5 to 24 hours after symptom onset in patients with ischemic stroke who had been selected on the basis of a favorable perfusion-imaging profile."

Albers GW, et al. *N Engl J Med.* 2024;390(8):701-711

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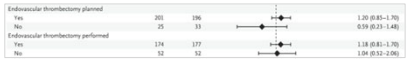
TIMELESS (2024)

- No benefit to extended-window thrombolytics in a *predominantly thrombectomy-eligible population*
  - TRACE-III included patients unable to undergo thrombectomy
- Subgroup analysis did not demonstrate a benefit in the non-thrombectomy cohort



- 15 patients in the tenecteplase arm vs. 4 in the placebo arm avoided planned EVT

Albers GW, et al. *N Engl J Med.* 2024;390(8):701-711

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30,000-foot view (cont'd)

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- TIMELESS: Fibrinolytics do not appear to be effective in the expanded window
  - A majority underwent thrombectomy

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Trial Design	Multicenter, block-randomized, open-label trial
Patient population	Patients with acute ischemic stroke with time of last known well within 4.5 and 24 hours
Inclusion	ICA, MCA branch 1 or 2, or ACA occlusion with a perfusion lesion-ischemic core mismatch ratio of 1.2
Treatment	Intravenous tenecteplase (n=111) or best medical treatment (n=113)
Stroke characteristics	Median NIHSS (IQR): 9 (5-14) vs. 9 (6-16) Time from onset to treatment, hrs (IQR): 12.3 (8.7-15.9) vs. 10.1 (7.8-13.6) Underwent thrombectomy: 53.2% vs. 56.6%
Primary outcome	Major reperfusion without sICH: 33.3% vs. 10.8% Adjusted RR 3 (95% CI 1.6-5.7)
Selected secondary outcomes	Recanalization: 35.8% vs. 14.3 % (p=0.002) Infarct growth at 3-5 days, mL (IQR): 18.9 (4.2-59.6) vs. 16.5 (2.6-42.3) (p=0.2) Major neurologic improvement, 24-48 hours: 21.8% vs. 23.1% (p=0.8) mRS 0-1 at 90 days: 39.6% vs. 36.3% (p=0.8)
Safety outcomes	mRS 5-6 at 90 days: 19.8% vs. 17.7%; adjusted RR 1.1 (95% CI 0.6-2.1) sICH: 5.4% vs. 4.4%; adjusted RR 1.33 (95% CI 0.4-4.2)

CHABLIS-T II (2025)

Conclusion: "… Tenecteplase 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.**"

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

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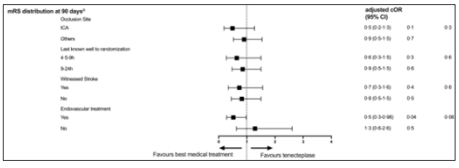
CHABLIS-T II (2025)

- 28 patients in the Best Medical Treatment arm received a fibrinolytic
- No significant difference in ordinal distribution of mRS scores
  - Common odds ratio: 0.8 (95% CI 0.5-1.3)



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

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30,000-foot view (cont'd)

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- TIMELESS: Fibrinolytics do not appear to be effective in the expanded window
  - A majority underwent thrombectomy
- CHABLIS-T II: Does not add much to assuage concerns about efficacy

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Trial Design	Multicenter, randomized, open-label trial
Patient population	Patients with acute ischemic stroke with time of last known well within 4.5 and 24 hours.
Inclusion	Non-LVO; core mismatch ratio of 1.2
Treatment	Intravenous tenecteplase (n=282) or placebo (n=284)
Stroke characteristics	Median NIHSS (IQR): 7 (5-9) Time from LKW to randomization, hrs (IQR): 12 (8.6-16.7)
Primary outcome	Excellent functional outcome, 90 days: 43.6% vs. 34.2% Adjusted RR 1.28 (95% CI 1.04-1.57)
Selected secondary outcomes	mRS 0-2 at 90 days: 62.8% vs. 55.3%; aRR 1.16 (95% CI 1.02-1.32) 90% reperfusion at 24 hours: 37.7% vs. 28.8%; aRR 1.31 (95% CI 1.03-1.68) Early clinical response at 24 hours: 11.4% vs. 5%; aRR 2.37 (95% CI 1.3-4.34)
Safety outcomes	90-day mortality: 5% vs. 3.2%; adjusted RR 1.48 (95% CI 0.65-3.36) sICH at 36 hours: 2.8% vs. 0%; unadjusted RR 2.85 (95% CI 1.16-5.54)

OPTION (2026)

Conclusion: "**Intravenous tenecteplase administered 4.5 to 24 hours after stroke onset** in patients with non–large vessel occlusion and salvageable brain tissue resulted in a **higher likelihood of an excellent functional outcome than standard medical care**..."

Ma G, et al. *JAMA*. 2026;335(13):1137-1147.

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30,000-foot view (cont'd)

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- TIMELESS: Fibrinolytics do not appear to be effective in the expanded window
  - The majority underwent thrombectomy
- CHABLIS-T II: Did not add much to assuage concerns about efficacy
- OPTION: Fibrinolytics appear to be safe and effective in a non-LVO cohort
  - Generalizable to more severe stroke?

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Trial name	Treatment	LKW window	LVO?	EVT?	Selection criteria	Findings
WAKE-UP (2018)	Alteplase	Unknown onset	n/a	N	MRI "Diffusion-weighted/FLAIR mismatch"	Improved 90-day favorable outcomes; no difference in mortality or sICH
EXTEND (2019)	Alteplase	4.5-9 hours	71%	N	Perfusion mismatch ratio of 1.2, Core < 70 mL with >10 mL difference from penumbra	Improved 90-day favorable outcomes; no difference in mortality or sICH
THAWS (2020)	Alteplase 0.6 mg/kg	>4.5 hours	30%	N	MRI "Diffusion-weighted/FLAIR mismatch"	No change in 90-day favorable outcomes, sICH, or mortality
ROSE-TNK (2023)	Tenecteplase	4.5-24 hours	43%	N	MRI "Diffusion-weighted/FLAIR mismatch"	No change in 90-day functional independence, sICH, or mortality
HOPE (2024)	Alteplase	4.5-24 hours	50%	N	Perfusion mismatch ratio of 1.2; Core < 70 mL with >10 mL difference from penumbra	Improved 90-day favorable outcomes; increased sICH; no change in mortality
TRACE-III (2024)	Tenecteplase	4.5-24 hours	100%	N	Perfusion mismatch ratio of 1.8; Core < 70 mL with >15 mL difference from penumbra	Improved 90-day favorable outcomes; increased sICH; no change in mortality
TIMELESS (2024)	Tenecteplase	4.5-24 hours	95.4%	77.3%	Perfusion mismatch ratio of 1.8; Core < 70 mL with >15 mL difference from penumbra	No change in 90-day functional independence, sICH, or mortality
CHABLIS-T II (2025)	Tenecteplase	4.5-24 hours	72%	54.9%	Perfusion mismatch ratio of 1.2; Core < 70 mL with >10 mL difference from penumbra	No change in 90-day favorable outcomes, sICH, or mortality
OPTION (2026)	Tenecteplase	4.5-24 hours	N	N	Perfusion mismatch ratio of 1.2; Core < 50 mL with >10 mL difference from penumbra	Improved 90-day favorable outcome; increased sICH; no change in mortality
TNK-PLUS (2026)	Tenecteplase	4.5-24 hours	Y	Y	Perfusion mismatch ratio of 1.8; Core < 70 mL with >15 mL difference from penumbra	No change in 90-day functional independence, sICH, or mortality

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Meta-analyses

Günkan, et al. (2025)

- 8 RCTs; Included patients that did not undergo thrombectomy
  - Included TPA and TNK trials
- Improved rates of 90-day excellent outcomes, early reperfusion, and neurologic improvement
- Significantly increased symptomatic ICH rates
  - No difference in mortality
- No effect of treatment selection on outcomes

Wang, et al. (2026)

- 4 trials; included EVT candidates and non-EVT candidates
  - Trials included only tenecteplase
- Improved rates of 90-day excellent functional outcomes
  - No change in rate of good functional outcome
  - Driven primarily by effect in non-EVT trials
- No difference in rates of sICH
  - Consistent within subgroup analysis

Günkan A, et al. *Stroke*. 2025;56(3):580-590.
Wang Z, Li J, et al. *Stroke*. 2026;57(1):50-62.

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2026 AHA/ASA Acute Ischemic Stroke Guidelines

Recommendations	Class of recommendation	Level of evidence	
In patients with AIS who (a) **have unknown time of onset and are within 4.5 hours from symptom recognition** and (b) have an **MRI-DWI lesion smaller than one-third of the MCA territory and no marked signal change on FLAIR**, IVT administered within 4.5 hours of stroke symptom recognition can be beneficial to improve functional outcomes.	IIa	B-R	**WAKE UP Trial**
In patients with AIS who have **salvageable ischemic penumbra** detected on automated perfusion imaging and who (a) **awake with stroke symptoms within 9 hours from the midpoint of sleep or (b) are 4.5-9 hours from last known well**, IV thrombolysis may be reasonable to improve functional outcomes.	IIa	B-R	**EXTEND Trial**
In patients with AIS due to LVO with **salvageable ischemic penumbra**, presenting **within 4.5 to 24 hours** from symptom onset or last known well, **and who cannot receive EVT**, treatment with IVT directed by individuals with expertise in thrombolytic stroke care may be beneficial to improve functional outcomes.	IIb	B-R	**TRACE-III Trial**

Prabhakaran S, et al. *Stroke*. Published online January 26, 2026.

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"What should I do?"

I can't [illegible] for you

- Need to weigh the risks an[illegible]
- Operational constraints ne[illegible]
- Provider comfort will impa[illegible]
- Extending beyond 4.5 hou[illegible]
  - Inconsistent findings in a he[illegible]
- Future trials may better de[illegible]

[illegible]commendation
[illegible]es it difficult to draw conclusions
[illegible]r treatment

Picture credit: https://www.shutterstock.com/g/Goga3

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Summary

- Most patients with acute ischemic stroke present outside of the historical treatment window of 4.5 hours from last known well
- Emerging evidence suggests that expanded-window fibrinolytic use may be safe and effective in an appropriately selected patient
- Patients who are not eligible or able to undergo thrombectomy are the most likely to benefit from late thrombolytic use
- Further research would allow for a more refined approach to optimizing risks and benefits in this patient population

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Questions?

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Expanding our horizons?

The role of extended-window fibrinolytics in acute ischemic stroke

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Thank you!

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