ACUTE ISCHEMIC STROKE ALERT

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OBJECTIVES

- Review epidemiology and pathophysiology of acute ischemic stroke
- Recognize the signs and symptoms of a stroke
- Discuss initial evaluation and management of patients with suspected acute ischemic stroke
- State the contraindications to alteplase and recognize other relative exclusion and inclusion criteria
- Review the dosing, compounding, administration and monitoring for alteplase

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EPIDEMIOLOGY

- Stroke is the 5th leading cause of death in the US
- Stroke is the leading cause of serious, long term disability (reducing mobility in more than half of stroke survivors > 65 years)
- Every year, more than 795,000 people in the United States have a stroke
  - Someone in the US has a stroke every 40 seconds; every 4 minutes, someone dies of a stroke
- Every minute of delay in reperfusion → 2 million neurons are lost
  - Every 15 minutes decrease in delay of treatment = 1 month equivalent of disability-free life

https://www.cdc.gov/stroke/facts.htm
Merejota, et al. Stroke. 2014;45:00-00.

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RISK FACTORS

Non-Modifiable	Modifiable
• Age > 55 • Gender (Male > Female) • Race (African American, Asian-Pacific Islander, Hispanic)	• **Smoking** • **Hypertension** • **Diabetes** • **Dyslipidemia** • Obesity • **Atrial fibrillation** • Asymptomatic carotid stenosis • Sickle cell disease • Physical inactivity • Cardiac disease (CAD, CHF, PAD)

Meschia, et al. Stroke 2014;45(12):3754–3832.

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DIFFERENTIAL DIAGNOSIS

Table 6. Features of Clinical Situations Mimicking Stroke

Psychogenic	Lack of objective cranial nerve findings, neurological findings in a nonvascular distribution, inconsistent examination
Seizures	History of seizures, witnessed seizure activity, postictal period
Hypoglycemia	History of diabetes, low serum glucose, decreased level of consciousness
Migraine with aura (complicated migraine)	History of similar events, preceding aura, headache
Hypertensive encephalopathy	Headache, delirium, significant hypertension, cortical blindness, cerebral edema, seizure
Wernicke's encephalopathy	History of alcohol abuse, ataxia, ophthalmoplegia, confusion
CNS abscess	History of drug abuse, endocarditis, medical device implant with fever
CNS tumor	Gradual progression of symptoms, other primary malignancy, seizure at onset
Drug toxicity	Lithium, phenytoin, carbamazepine

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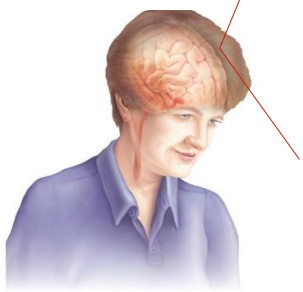
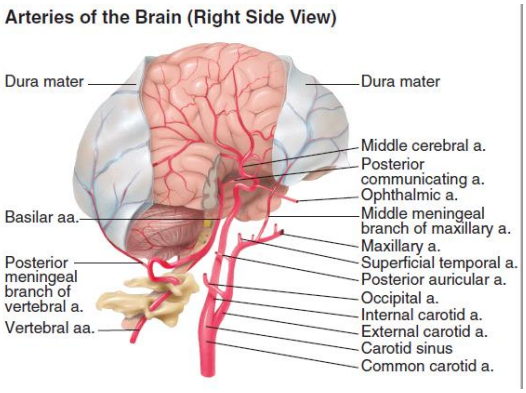
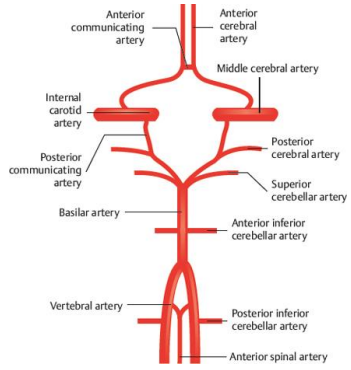
CEREBRAL PERFUSION







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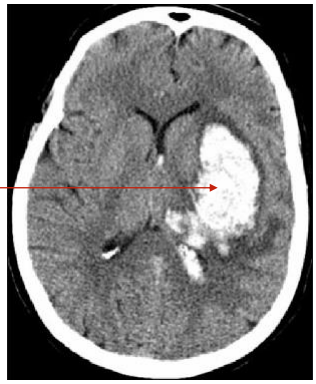
TYPES OF STROKE

- Stroke: neurological impairment caused by disruption in blood supply to a region of the brain
  - **Acute Ischemic Stroke** (~87%): brain ischemia due to thrombosis/embolism
  - **Hemorrhagic Stroke** (~13%): bleeding in the brain compresses the surrounding structures
    - Intracerebral hemorrhage
    - Subarachnoid hemorrhage



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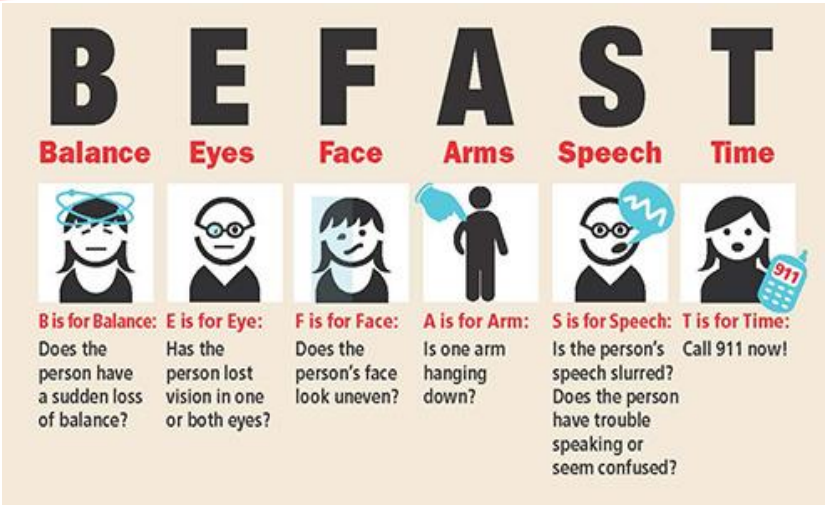
CLINICAL PRESENTATION



5 "SUDDENS" OF A STROKE
- Numbness or weakness of the face, arm or leg
- Trouble speaking or sudden confusion
- Vision changes
- Headache
- Dizziness, loss of balance

Only 1 in 3 people can name a single risk factor or warning sign of a stroke

Only 9% of people surveyed were aware of a time-sensitive treatment window from onset of stroke symptoms

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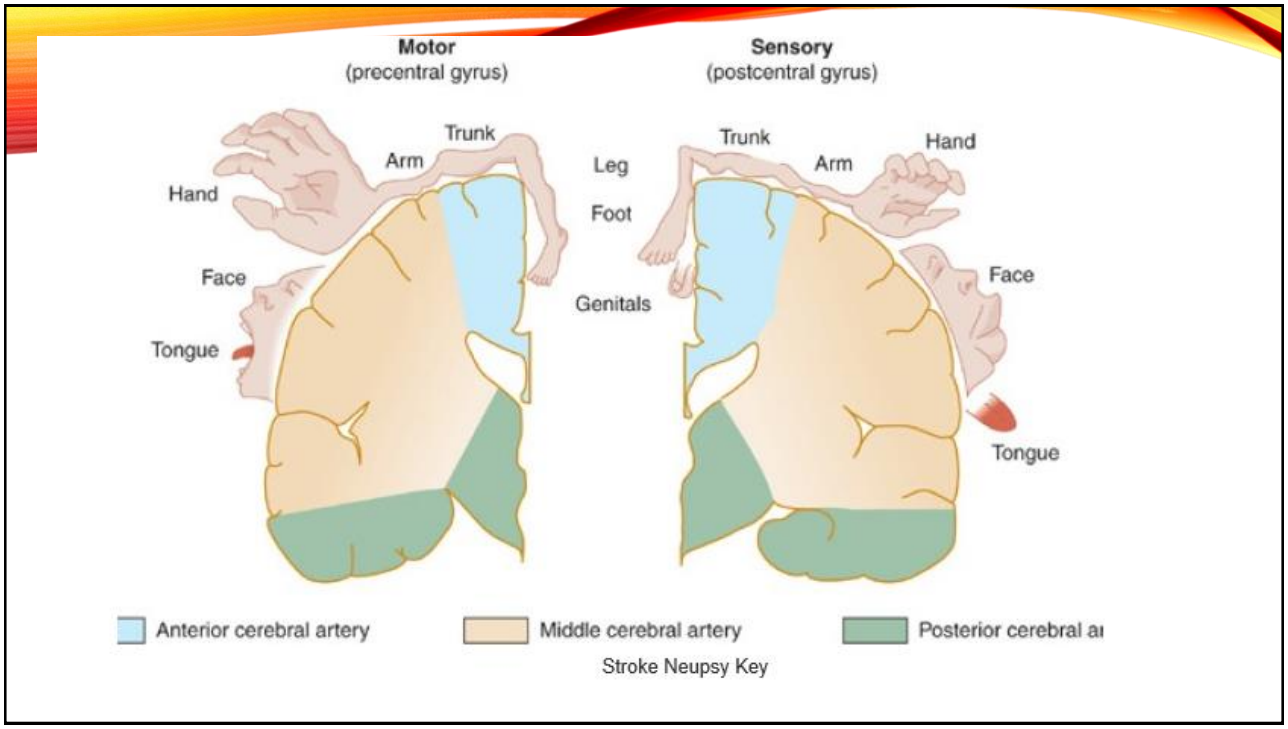

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NATIONAL INSTITUTES OF HEALTH STROKE SCALE (NIHSS)

Table 4. National Institutes of Health Stroke Scale

Tested Item	Title	Responses and Scores
1A	Level of consciousness	0—Alert
		1—Drowsy
		2—Obtunded
		3—Coma/unresponsive
1B	Orientation questions (2)	0—Answers both correctly
		1—Answers 1 correctly
		2—Answers neither correctly
1C	Response to commands (2)	0—Performs both tasks correctly
		1—Performs 1 task correctly
		2—Performs neither
2	Gaze	0—Normal horizontal movements
		1—Partial gaze palsy
		2—Complete gaze palsy
3	Visual fields	0—No visual field defect
		1—Partial hemianopia
		2—Complete hemianopia
		3—Bilateral hemianopia
4	Facial movement	0—Normal
		1—Minor facial weakness
		2—Partial facial weakness
		3—Complete unilateral palsy
5	Motor function (arm)	0—No drift
	a. Left	1—Drift before 10 s
	b. Right	2—Falls before 10 s
		3—No effort against gravity
		4—No movement

Table 4. Continued

Tested Item	Title	Responses and Scores
6	Motor function (leg)	0—No drift
	a. Left	1—Drift before 5 s
	b. Right	2—Falls before 5 s
		3—No effort against gravity
		4—No movement
7	Limb ataxia	0—No ataxia
		1—Ataxia in 1 limb
		2—Ataxia in 2 limbs
8	Sensory	0—No sensory loss
		1—Mild sensory loss
		2—Severe sensory loss
9	Language	0—Normal
		1—Mild aphasia
		2—Severe aphasia
		3—Mute or global aphasia
10	Articulation	0—Normal
		1—Mild dysarthria
		2—Severe dysarthria
11	Extinction or inattention	0—Absent
		1—Mild loss (1 sensory modality lost)
		2—Severe loss (2 modalities lost)

Adapted from Lyden et al.[74] Copyright © 1994, American Heart Association, Inc.

- Measure of stroke severity
- 11 domains assessed

Scoring range is 0–42 points. The higher the number, the greater the severity.

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

American Stroke Association.

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NIHSS: SCORING

- 1a: LOC
  - 0 = Alert; keenly responsive
  - 1 = Not alert, but arousable by minor stimulation
  - 2 = Not alert; requires repeated stimulation/painful stimuli/obtunded
  - 3 = Responds only with reflex motor/autonomic effects or totally unresponsive/flaccid/areflexic
- 1b: LOC Questions
  - Ask the patient: "What month is it?" "How old are you?"
  - 0 = Answers both questions correctly
  - 1 = Answers one question correctly
  - 2 = Answers neither question correctly

National Institutes of Health. NIH Stroke Scale. https://stroke.nih.gov/documents/NIH_Stroke_Scale_Booklet.pdf

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NIHSS: SCORING

- 1c: LOC Commands
  - Ask the patient to: "Open and close your eyes." "Grip and release your hand."
  - 0 = Performs both tasks correctly
  - 1 = Performs one task correctly
  - 2 = Performs neither task correctly
- 2: Best Gaze
  - Establish eye contact and ask the patient to: "Follow my finger."
  - 0 = Normal
  - 1 = Partial gaze palsy
  - 2 = Forced deviation or total gaze paresis not overcome by oculocephalic maneuver

National Institutes of Health. NIH Stroke Scale. https://stroke.nih.gov/documents/NIH_Stroke_Scale_Booklet.pdf

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NIHSS: SCORING

- 3: Visual Fields
  - Use confrontation/finger counting/visual threat (upper & lower visual fields)

• 0 = No visual loss • 1 = Partial hemianopia	• 2 = Complete hemianopia • 3 = Bilateral hemianopia

- 4: Facial Palsy
  - "Show me your teeth." "Raise your eyebrows." "Close your eyes."
  - 0 = Normal symmetrical movements
  - 1 = Minor paralysis
  - 2 = Partial paralysis
  - 3 = Complete paralysis of one/both sides

National Institutes of Health. NIH Stroke Scale.
https://stroke.nih.gov/documents/NIH_Stroke_Scale_Booklet.pdf

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NIHSS: SCORING

- 5: Motor (Arm)
  - Alternately position patient's arms. Extend each arm with palms down.

• 0 = No drift • 1 = Drift • 2 = Some effort vs gravity	• 3 = No effort vs gravity • 4 = No movement • UN = Amputation/joint fusion

- 6: Motor (Leg)
  - Alternately position the patient's legs. Extend each leg (30 degrees while supine).

• 0 = No drift • 1 = Drift • 2 = Some effort vs gravity	• 3 = No effort vs gravity • 4 = No movement • UN = Amputation/joint fusion

National Institutes of Health. NIH Stroke Scale.
https://stroke.nih.gov/documents/NIH_Stroke_Scale_Booklet.pdf

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NIHSS: SCORING

- 7: Limb Ataxia
  - Ask patient to: "Touch your finger to your nose." "Touch your heel to your shin."

• 0 = Absent • 1 = Present in one limb	• 2 = Present in two limbs • UN = Amputation/joint fusion

- 8: Sensory
  - Test as many body parts as possible for sensation using pinprick/noxious stimulus (obtunded or aphasic patient).
  - 0 = Normal
  - 1 = Mild/moderate sensory loss
  - 2 = Severe/total sensory loss

National Institutes of Health. NIH Stroke Scale. https://stroke.nih.gov/documents/NIH_Stroke_Scale_Booklet.pdf

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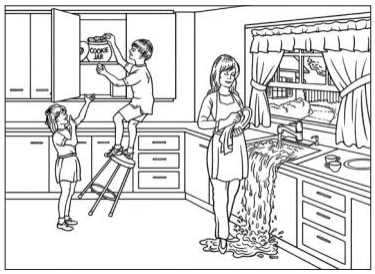
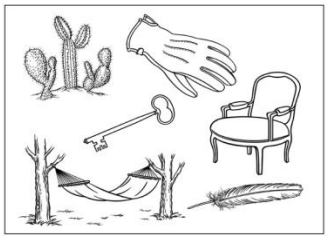
NIHSS: SCORING

- 9: Best Language
  - Using pictures and a sentence list, ask patient to:
    - "Describe what you see in this picture."
    - "Name the items in this picture."
    - "Read these sentences."
  - 0 = No aphasia
  - 1 = Mild/moderate aphasia
  - 2 = Severe aphasia
  - 3 = Mute/global aphasia





You know how.

Down to earth.

I got home from work.

Near the table in the dining room.

They heard him speak on the radio last night.

National Institutes of Health. NIH Stroke Scale. https://stroke.nih.gov/documents/NIH_Stroke_Scale_Booklet.pdf

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NIHSS: SCORING

MAMA

TIP-TOP

FIFTY-FIFTY

THANKS

HUCKLEBERRY

BASEBALL PLAYER

- 10: Dysarthria
  - Using simple word list, ask patient to: "Read/repeat these words."

• 0 = Normal articulation • 1 = Mild/moderate dysarthria	2 = Severe dysarthria UN = Intubated/other barrier

- 11: Extinction and Inattention
  - Sufficient information to determine these scores may have been obtained during prior testing
  - 0 = No abnormality
  - 1 = Visual, tactile, auditory, spatial, or personal inattention
  - 2 = Profound hemi-inattention or extinction to more than 1 modality

National Institutes of Health. NIH Stroke Scale.
https://stroke.nih.gov/documents/NIH_Stroke_Scale_Booklet.pdf

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LIMITATION OF NIHSS

- Example: JB is an 81/M who presents with sudden onset of nausea and dizziness while at a local casino (three hours ago). Symptoms are persistent and severe since initial onset. He denies any focal paresthesia or other symptoms. He was given Zofran by EMS and he is still retching during exam.
- NIH score = 0
  - The NIHSS has a known bias for anterior circulating strokes, especially with language deficits, and thus drastically underestimates the degree of stroke-associated functional impairment in posterior circulation stroke
  - The vast majority of PCS have NIHSS < 5, commonly presenting with symptoms such as headache, vertigo, nausea, and truncal ataxia ("drunken sailor" gait)
- CT with contrast demonstrated right vertebral occlusion, MRI acute right cerebellar infarct

Hoyer C, Szabo K. Front Neurol. 2021;12: 682827.

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LABORATORY MONITORING

- Glucose is the only lab that MUST be completed before administration of tPA
  - Hypoglycemia is a stroke mimic and can be quickly ruled out with point-of-care testing
- UNLESS patient is receiving warfarin prior to admission → then need INR
- IF patient had been receiving therapeutic heparin recently → then need aPTT
- IF CBC is available:
  - No tPA if platelet < 100

Table 8. Immediate Diagnostic Studies: Evaluation of a Patient With Suspected Acute Ischemic Stroke

All patients
Noncontrast brain CT or brain MRI
Blood glucose
Oxygen saturation
Serum electrolytes/renal function tests*
Complete blood count, including platelet count*
Markers of cardiac ischemia*
Prothrombin time/INR*
Activated partial thromboplastin time*
ECG*
Selected patients
TT and/or ECT if it is suspected the patient is taking direct thrombin inhibitors or direct factor Xa inhibitors
Hepatic function tests
Toxicology screen
Blood alcohol level
Pregnancy test
Arterial blood gas tests (if hypoxia is suspected)
Chest radiography (if lung disease is suspected)
Lumbar puncture (if subarachnoid hemorrhage is suspected and CT scan is negative for blood
Electroencephalogram (if seizures are suspected)

CT indicates computed tomography; ECG, electrocardiogram; ECT, ecarin clotting time; INR, international normalized ratio; MRI, magnetic resonance imaging; and TT, thrombin time.

*Although it is desirable to know the results of these tests before giving intravenous recombinant tissue-type plasminogen activator, fibrinolytic therapy should not be delayed while awaiting the results unless (1) there is clinical suspicion of a bleeding abnormality or thrombocytopenia, (2) the patient has received heparin or warfarin, or (3) the patient has received other anticoagulants (direct thrombin inhibitors or direct factor Xa inhibitors).

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STROKE DEFINITIONS

- **Time last known well (LKW)**
  - Time patient last known to be symptom free of current stroke or at his or her baseline status
- **Door to needle time (DTN)**
  - Time from patient arrival to administration of thrombolytic therapy
  - Goal: 60 minutes
    - Newer more aggressive goals:
      - 50% of tPA-eligible patients receive dose within 30 minutes
      - 75% of tPA-eligible patients receive dose within 45 minutes
      - 85% of tPA-eligible patients receive dose within 60 minutes

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TPA ELIGIBILITY WINDOW: TIME FROM LAST KNOWN WELL

- Traditionally 3-hour window to administer alteplase → **extended to 4.5 hours for most patients** (exception NIH > 25)
- NINDS study (1995): first study to demonstrate efficacy of tPA for AIS when administered in less than 3 hours
  - No difference between groups in early outcoe at 24 hours but treatment group showed benefit at 90 days (OR = 1.7)
- ECASS III (2008): verified NINDS trial and demonstrated efficacy of extended tpa eligibility window up to 4.5 hours (OR = 1.3)

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STROKE ALERT: CT

- Stroke Alert → Patient taken to for emergent imaging
- ED or RRT nurse usually accompanies patient
- IV access may be required for:
  - Contrast if CTA/perfusion ordered
  - IV alteplase if patient eligible
  - IV antihypertensives if alteplase to be administered and BP ≥ 185/110

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BLOOD PRESSURE GOALS

IV tPA

<185/110 mmHg (prior to tPA)

***Then* <180/105 mmHg** *for 24h post administration*

No IV tPA

Permissive HTN

→ No treatment unless **BP ≥ 220/120 mmHg**

Allow brain to autoregulate → increasing blood pressure may help to perfuse the ischemic penumbra

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BLOOD PRESSURE MANAGEMENT

- Monitor BP every 15 min for 2 hr from the start of alteplase, then every 30 min for 6h, then every hour for the next 16 hours
- If blood pressure lowering is indicated to obtain BP < 185/110 for alteplase administration treatment options include:

Agent	Dose
Labetalol	10 – 20 mg IV over 1 – 2 minutes; may repeat 1 time
Nicardipine	5 mg/hr IV continuous infusion, titrate up by 2.5 mg/hr every 5 – 15 minutes; maximum 15 mg/hour

Other agents (hydralazine, enalaprilat may also be considered)

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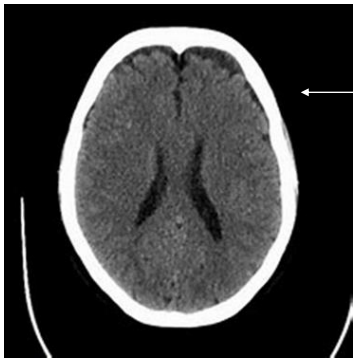
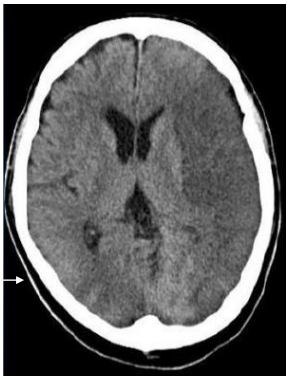
INITIAL IMAGING

- All patients with suspected acute stroke should receive emergency brain imaging on first arrival to hospital (or upon first recognition for inpatient)
- **Non-contrast enhanced head CT**
  - Exclude intracerebral hemorrhage (ICH)
  - Frank hypodensity on CT may increase the risk of hemorrhage with fibrinolysis and should be considered in treatment decision → If frank hypodensity involves more than one third of the MCA territory IV tPA should be withheld



< 3 hours from onset



12 hours from onset

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ADDITIONAL IMAGING

- Noninvasive intracranial vascular studies
  - Includes: CT angiography (CTA) or magnetic resonance imaging (MRI/MRA)
  - Strongly recommended during initial imaging evaluation if endovascular intervention is considered
  - Should not delay administration of IV tPA (if indicated)
- Benefits of additional imaging in select patients (MRA with diffusion weighted magnetic resonance imaging (DW-MRI) in select patients to identify diffusion positive but fluid attenuated inversion recovery (FLAIR) negative lesions which may benefit from tPA despite unknown last known well (LKW)

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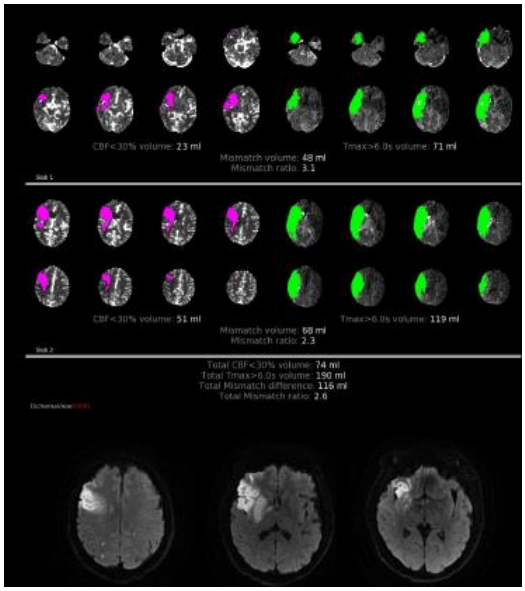
IMAGING IN STROKE

- **Core** = infarcted brain with severely reduced cerebral blood flow (< 30% normal CBF) = **not salvageable**
- **Penumbra** = hypoperfused brain at risk for progression to infarction = salvageable
  - Usually located around the ischemic core and represents target of reperfusion therapy
- CT perfusion study example:
  - 190 mL total volume of hypoperfused area in the brain
  - 74 mL core volume (infarcted brain with < 30% CBF)
  - 190 mL - 74 mL = 116 mL mismatch = the penumbra = salvageable tissue



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SUMMARY OF CHANGES IN 2019 AMERICAN HEART ASSOCIATION ACUTE ISCHEMIC STROKE GUIDELINES

	2013 Guidelines	2019 Guidelines
DTN Door-to-needle time	< 60 minutes	< 30 minutes in 50% < 45 minutes in 75% < 60 minutes in 85%
Tenecteplase	None	• Consider in LVO undergoing thrombectomy • Minor neurological impairment
3 - 4.5hr Window	**Contraindicated** in: • Warfarin regardless of INR • Age > 80 • Hx stroke/DM • NIHSS > 25	**Beneficial** in: • Warfarin if INR < 1.7 • Age > 80 • Hx stroke/DM Uncertain benefit in NIHSS > 25
Mild non-disabling stroke	Consider use	Contraindicated
Neuroimaging for guidance on IV thrombolysis	None	MRI to identify diffusion-positive flair-negative lesions
DAPT	None	Mild stroke no fibrinolysis – ASA + Plavix 21 days
Endovascular Therapy (EVT)	None (< 6 hours)	Extended up to 24hrs

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TPA INDICATION

- Acute ischemic stroke within 4.5 hours of symptom onset [(3 hours if very severe stroke (NIH > 25)]
- To administer tPA → BP < 185/110 mmHg and BG > 50 mg/dL
- Assess for anticoagulants → if warfarin INR ≤ 1.7 or PT < 15 seconds, no DOAC within 48 hours, no treatment dose of LMWH within 24 hours, if treatment dose heparin aPTT < 40 seconds
- Review absolute and relative contraindications

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TPA CONTRAINDICATIONS

ABSOLUTE CONTRAINDICATIONS
CT finding of intracranial hemorrhage
Active internal bleeding
Recent head trauma, intracranial/spinal surgery (within 3 months)
Uncontrolled blood pressure → initiate IV antihypertensives until BP < 185/110
Intracranial neoplasm, arteriovenous malformation
Arterial puncture of non-compressible blood vessel or lumbar puncture in the past 7 days
Full treatment dose of enoxaparin in the past 24 hours
Recent treatment dose of heparin with elevated aPTT (> 40 seconds)
Use of DOACs in the preceding 48 hours (longer if renal insufficiency)
*Platelet count < 100 (if available; not required before t-PA)
Blood glucose < 50 mg/dL

RELATIVE CONTRAINDICATIONS
History of intracranial hemorrhage
Recent history of acute ischemic stroke (within 3 months)
Recent head trauma (within 3 months)
Recent major surgery (within 14 days)
Structural GI malignancy or recent bleeding event (within 21 days)
Diabetic hemorrhagic retinopathy (or other hemorrhagic ophthalmic conditions)
Infective endocarditis
Acute aortic arch dissection
Mild non-disabling stroke (NIH < 5)
CT demonstrates multilobar infarction (hypodensity > 1/3 cerebral hemisphere)

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AHA/ASA Guideline

Guidelines for the Early Management of Patients With Acute Ischemic Stroke: 2019 Update to the 2018 Guidelines for the Early Management of Acute Ischemic Stroke

A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association

Endorsed by the Society for Academic Emergency Medicine and The Neurocritical Care Society

Reviewed for evidence-based integrity and endorsed by the American Association of Neurological Surgeons and Congress of Neurological Surgeons.

William J. Powers, MD, FAHA, Chair; Alejandro A. Rabinstein, MD, FAHA, Vice Chair;

AHA/ASA Scientific Statement

Scientific Rationale for the Inclusion and Exclusion Criteria for Intravenous Alteplase in Acute Ischemic Stroke

A Statement for Healthcare Professionals From the American Heart Association/American Stroke Association

The American Academy of Neurology affirms the value of this statement as an educational tool for neurologists.

Endorsed by the American Association of Neurological Surgeons and Congress of Neurological Surgeons

Bart M. Demaerschalk, MD, MSc, FRCPC, FAHA, Chair;
Dawn O. Kleindorfer, MD, FAHA, Vice-Chair; Opeolu M. Adeoye, MD, MS, FAHA;

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MILD NON-DISABLING STROKE

Contraindications (COR III: No Benefit)	And (COR III: Harm)
0- to 3-h window–Mild nondisabling stroke	For otherwise eligible patients with mild nondisabling stroke (NIHSS score 0–5), IV alteplase is not recommended for patients who could be treated within 3 h of ischemic stroke symptom onset or patient last known well or at baseline state. (*COR III: No Benefit, LOE B-R*)‡

- Example: 66/M construction worker presents with 2.5 hr duration of left hand "weakness" including difficulty flexing the wrist and straightening fingers. ED provider calculates initial NIH 2.
- PMH: smoker, cocaine abuse, (transient episode of atrial fibrillation at MCE in October 2021 after cocaine overdose – not anticoagulated)
- Initial head CT negative for bleed. BG 101 mg/dL. BP 132/78 mmHg
- CT perfusion and MRI negative
- Neurologist interviews patient and discovers he slept at a "campground" the night before, "leaning against a pallet" and may have injured his arm → neurology concerned for radial nerve palsy

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SEVERE STROKES AND ALTEPLASE

Within 3 h–Severe stroke	For severe stroke, IV alteplase is indicated within 3 h from symptom onset of ischemic stroke. Despite increased risk of hemorrhagic transformation, there is still proven clinical benefit for patients with severe stroke symptoms.† (*COR I; LOE A*)
3 to 4.5 h–Severe stroke	The benefit of IV alteplase between 3 and 4.5 h from symptom onset for patients with very severe stroke symptoms (NIHSS score >25) is uncertain.† (*COR IIb; LOE C-LD*)§

- Higher stroke severity has been associated with an increased risk of hemorrhagic transformation, with or without alteplase treatment
- Alteplase may improve the final functional outcome for more severe stroke and it is controversial whether NIH > 25 should alone be interpreted as a rationale for withholding treatment if otherwise indicated

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UNKNOWN LAST KNOWN WELL (WAKE UP STROKE)

Wake-up and unknown time of onset	IV alteplase (0.9 mg/kg, maximum dose 90 mg over 60 min with initial 10% of dose given as bolus over 1 min) administered within 4.5 h of stroke symptom recognition can be beneficial in patients with AIS who awake with stroke symptoms or have unclear time of onset >4.5 h 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. (*COR IIa; LOE B-R*)‡

- 80/M patient presents at 06:30 with left sided facial droop and speech difficulty. He went to bed normal at 21:00 and woke up this way at 06:00. He is not considered a t-PA candidate since time of stroke onset cannot be assessed.
- *What if the stroke had just occurred? Couldn't imaging be helpful to estimate the time of onset of the stroke?*
- DWI changes occur within minutes after ischemic stroke
- FLAIR changes are often delayed up to 3 – 4 hours (vasogenic edema of the brain parenchyma)
- Therefore, ischemic lesion visible on diffusion-weighted imaging but with no parenchymal hyperintensity on FLAIR suggests the stroke occurred within the previous 4.5 hours and patient may still be potentially considered for thrombolytic (i.e. DWI-FLAIR mismatch)

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RECENT MAJOR SURGERY WITHIN 14 DAYS

Recent major surgery	Use of IV alteplase in carefully selected patients presenting with AIS who have undergone a major surgery in the preceding 14 d may be considered, but the potential increased risk of surgical-site hemorrhage should be weighed against the anticipated benefits of reduced stroke related neurological deficits.† (*COR IIb; LOE C-LD*)§

- Examples of "major" surgery in alteplase package insert = CABG, obstetrical delivery, or organ biopsy
  - Note: intracranial/intraspinal surgery is considered separately and is a contraindication within the preceding 3 months
- The rationale for this warning is potential for surgical site or systemic hemorrhage, but very little supporting evidence
- Provided that clinical services are available to manage surgical site hemorrhage, IV alteplase remains reasonable in select stoke patients with recent surgery

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PROCEDURAL STROKES

Procedural stroke	IV alteplase is reasonable for the treatment of AIS complications of cardiac or cerebral angiographic procedures, depending on the usual eligibility criteria.† (*COR IIa; LOE A*)§
Arterial puncture	The safety and efficacy of administering IV alteplase to acute stroke patients who have had an arterial puncture of a noncompressible blood vessel in the 7 d preceding stroke symptoms are uncertain.† (*COR IIb; LOE C-LD*)§

- LP 67/F with scheduled catheterization for preinfarction angina. Post cath patient experienced left sided weakness upper and lower extremity. NIHSS = 7
- PMH DM2, HLD, HTN, subclavian artery stenosis
- Note: due to subclavian stenosis, patient had femoral artery access for catheterization. Safeguard placed on right groin.
- CT w/o contrast negative
- CT perfusion: right anterior cerebral artery territory 26 mL penumbra, 0 mL core
- Transferred to MCE and attempted embolectomy but anterior circulation occlusion resolved without intervention

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RECENT HISTORY OF AIS WITHIN 3 MONTHS

Ischemic stroke within 3 mo	Use of IV alteplase in patients presenting with AIS who have had a prior ischemic stroke within 3 mo may be harmful.† (*COR III: Harm; LOE B-NR*)§‖

- How soon after an acute ischemic stroke is it relatively safe to administer t-PA for a recurrent acute ischemic stroke?
- Theoretical risk of hemorrhagic transformation of a recent stroke

- ST 73/F presenting at 14:00 with AMS (not following any commands) with right side paralysis. NIH 26. Last known well 11:00.
- PMH: large left-sided MCA stroke in May 2022
- HR 124, BP 80/67, Tmax 100.1, BG 855 mg/dL, lactate 4.1
- Head CT without contrast progression of left MCA infarct

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SEIZURE AT ONSET OF STROKE

Seizure at onset	IV alteplase is reasonable in patients with a seizure at the time of onset of acute stroke if evidence suggests that residual impairments are secondary to stroke and not a postictal phenomenon.† (*COR IIa; LOE C-LD*)§
Stroke mimics	The risk of symptomatic intracranial hemorrhage in the stroke mimic population is quite low; thus, starting IV alteplase is probably recommended in preference over delaying treatment to pursue additional diagnostic studies.† (*COR IIa; LOE B-NR*)§

- A clinical suspicion of seizure at onset of stroke was traditionally considered a contraindication to t-PA based on the rationale that a focal neurological deficit in this setting was more attributable to a stroke mimic (postictal Todd paralysis) than to acute cerebral ischemia
- Note: the risk of sICH after thrombolysis of stoke mimics is exceedingly low

- 80/F presents unresponsive and stroke alert called.
- Patient's eyelid and lip are rhythmically twitching during CT without contrast.
- Pharmacist reviews home medication list from nursing home which includes antiepileptics
- Lorazepam 4 mg IV x 1 given and soon after patient begins to respond

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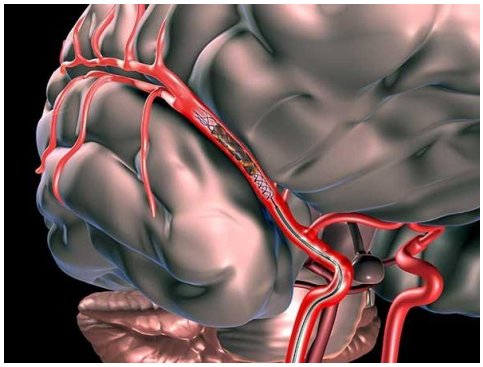
AHA 2019 GUIDELINES: ENDOVASCULAR

- Patients presenting with AIS beyond the 4.5 hour window for tPA may still be considered for mechanical thrombectomy for up to 24 hours (very specific selection criteria)
- Patient's eligible for IV tPA should receive tPA even if endovascular treatments are being considered (Class 1; Level of Evidence A)
  - IV thrombolytic should be offered to all eligible patients with large vessel occlusion (LVO) of the anterior circulation
  - Mechanical thrombectomy + IV thrombolytic (IVT) is superior to IVT alone in LVO



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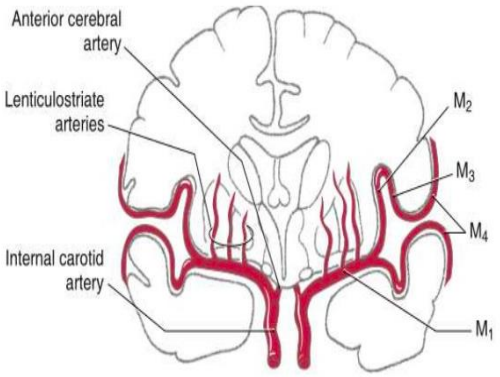

WHY IS MECHANICAL THROMBECTOMY SO IMPORTANT IN ANTERIOR CIRCULATION LVO?

Vessel	Relevant recanalization with tPA before EVT
ICA	5/93 (5.4%)
M1	12/148 (8.1%)
M2	6/34 (17.6%)

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HOW TO RECOGNIZE LVO OCCLUSION

Los Angeles Motor Scale (LAMS) ☆

Stratifies stroke severity in the field.

When to Use ⌄ | Pearls/Pitfalls ⌄ | Why Use ⌄

Facial droop	Absent 0	Present +1
Arm drift	Absent 0	Drifts down +1 / Falls rapidly +2
Grip strength	Normal 0	Weak grip +1 / No grip +2

FORMULA

Addition of the selected points:

	0 points	1 point	2 points
Facial droop	Absent	Present	--
Arm drift	Absent	Drifts down	Falls rapidly
Grip strength	Normal	Weak grip	No grip

FACTS & FIGURES

Interpretation:

LAMS	Interpretation
<4	LVO less likely. Stroke is minor or moderate in severity, but may still benefit from acute treatment.
≥4	LVO likely. Stroke is severe and requires acute treatment. Transfer to stroke center with endovascular capabilities.

In the derivation study, lower mean LAMS correlated with lower Modified Rankin Scale score (i.e., better functional outcome) at 3 months (mean entry LAMS 2.2 versus 3.7 for mRS ≤1 or >1, respectively).

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INFECTIVE ENDOCARDITIS

Infective endocarditis	For patients with AIS and symptoms consistent with infective endocarditis, treatment with IV alteplase should not be administered because of the increased risk of intracranial hemorrhage.† (*COR III: Harm; LOE C-LD*)§‖ (Recommendation wording modified to match COR III stratifications.)

- Cerebral embolic stroke is a frequent complication of infective endocarditis (especially left-sided endocarditis)
- Histopathological examination shows vegetations are composed of platelets and fibrin but also microorganisms and inflammatory cells
- Septic emboli are particularly prone to hemorrhagic transformation as a result of septic arteritis with erosion of the arterial wall in the recipient vessel, with or without formation of mycotic aneurysms

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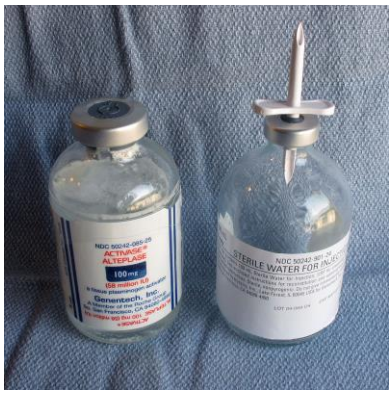
ALTEPLASE: DOSING

- Acute ischemic stroke
  - Total dose: Alteplase 0.9 mg/kg (actual body weight)
    - **Maximum dose = 90mg (there is always waste volume that should be discarded)**
  - Administration
    - **Bolus** Dose 0.09 mg/kg: 10% of total dose given over one minute as slow IV push
    - **Infusion** Dose 0.81 mg/kg: 90% of total dose infused over 60 minutes using Plum360 infusion pump
      - Pharmacist will calculate dose on ALL stroke alerts



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ADMINISTRATION OF ALTEPLASE

- Example: 80 kg patient
  - 0.9 mg/kg x 80 kg = 72 mg total dose

    - Alteplase vial contains 100 mg and is reconstituted with 100 mL → final concentration is 1 mg = 1 mL
    - WASTE volume: 100 mL – 72 mL = 28 mL (throw away)
    - 10% as bolus = 7.2 mg as slow IV push over 1 minutes
    - 90% as infusion = 64.8 mg infused over 60 min (64.8 mL/hr)
    - THEN flush line at same rate with saline to clear the ~ 25 mL of alteplase still in the tubing to ensure entire dose

What is the total dose of tpa for patient that weighs 111 kg?

111 x 0.9 mg/kg = 99.9 mg → MAXIMUM 90 MG TOTAL DOSE → 9 MG BOLUS AND 81 MG INFUSION

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TPA COMPLICATIONS: HEMORRHAGIC CONVERSION

- Symptomatic intracranial hemorrhage occurs in ~6% of patients with acute ischemic stroke treated with alteplase → likely due to reperfusion of damaged brain tissue
- Although the half-life of alteplase is very short (~ 5 minutes), its fibrinolytic activity persists creating a consumptive coagulopathy for approximately 24 hours → especially suppression of fibrinogen

Monitor patients post- tPA for 24 hours for signs and symptoms of ICH:

- Nausea/vomiting
- Headache
- Neurological deterioration
- Acute hypertension

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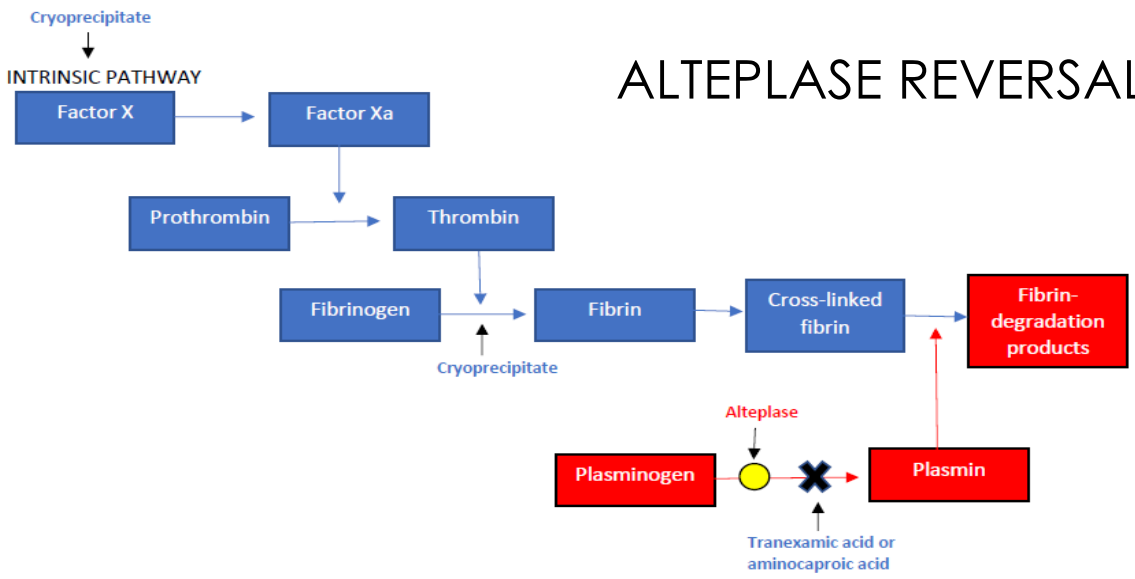
ALTEPLASE REVERSAL



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ALTEPLASE REVERSAL

Table 6. Management of Symptomatic Intracranial Bleeding Occurring Within 24 Hours After Administration of IV Alteplase for Treatment of AIS

COR IIb	LOE C-EO
Stop alteplase infusion	
CBC, PT (INR), aPTT, fibrinogen level, and type and cross-match	
Emergent nonenhanced head CT	
Cryoprecipitate (includes factor VIII): 10 U infused over 10–30 min (onset in 1 h, peaks in 12 h); administer additional dose for fibrinogen level of <150 mg/dL	
Tranexamic acid 1000 mg IV infused over 10 min OR ε-aminocaproic acid 4–5 g over 1 h, followed by 1 g IV until bleeding is controlled (peak onset in 3 h) (Potential for benefit in all patients, but particularly when blood products are contraindicated or declined by patient/family or if cryoprecipitate is not available in a timely manner.)	
Hematology and neurosurgery consultations	
Supportive therapy, including BP management, ICP, CPP, MAP, temperature, and glucose control	

Cryoprecipitate contains **fibrinogen**, factor VIII (activates intrinsic pathway), factor XIII, and von Willebrand factor

Tranexamic acid and aminocaproic acid inhibit proteolytic enzymes such as plasmin that mediate the action of alteplase

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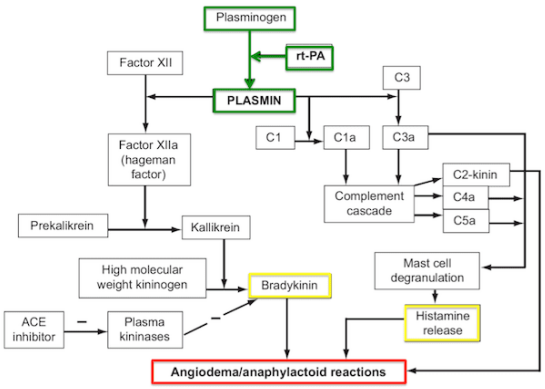
TPA COMPLICATIONS: OROLINGUAL ANGIOEDEMA

- Alteplase increases plasmin which activates the complement cascade causes histamine release and increase in circulating bradykinin
- Incidence: 1 – 5% patients who receive alteplase → higher risk in patients taking ACE inhibitors
- Usually self-limiting → need for advanced airway is extremely rare



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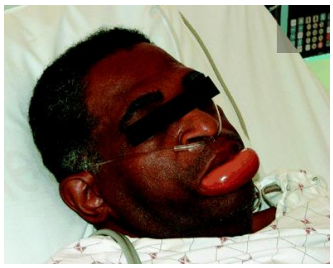
TREATMENT ALTEPLASE-INDUCED ANGIOEDEMA

- Stop alteplase (assess for ACE inhibitor use and stop)
- Administer methylprednisolone 125 mg IV x 1, diphenhydramine 50 mg IV x1 , and famotidine 20 mg IV x 1



Assess for ACE inhibitor use.

Begin by examining the tongue & oral cavity before Alteplase infusion for baseline

If angioedema suspected:

- Immediately turn off Alteplase infusion
- Immediately administer steroids (methylprednisolone or dexamethasone)
- Immediately administer diphenhydramine injection, then consider famotidine injection (famotidine is our formulary H2 blocker)

Other medications to consider:

- Epinephrine 0.1% 0.3ml IM or SQ
- Fresh frozen plasma(FFP)
- Nebulized Epinephrine

Consider airway interventions:

- Early intubation, difficult airway cart and glidescope to bedside
- Consider ENT or anesthesia consult
- Emergency tracheostomy

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MAIN POINTS

- Acute Ischemic Stroke is a time-sensitive diagnosis and early goals of therapy involve restoring cerebral blood flow and determining eligibility for thrombolytics or mechanical thrombectomy
- Review absolute and relative contraindications to tPA
- If any relative contraindications present, discuss risks and benefits with specialty providers and patient to make decision
- Patients with large vessel occlusion should additionally be referred to interventional specialist for mechanical thrombectomy
- Monitor patient closely for tPA complications such as hemorrhagic transformation and be prepared with reversal plan if indicated

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FUTURE DIRECTION

- Bonus slides (informational)
- Tenecteplase is a non-FDA approved thrombolytic with the same mechanism of action as alteplase but with easier drug administration as IV push only as compared to a bolus followed by 1-hour infusion
- Many hospitals are switching from alteplase to tenecteplase for AIS ahead of AHA guideline recommendation or FDA approval

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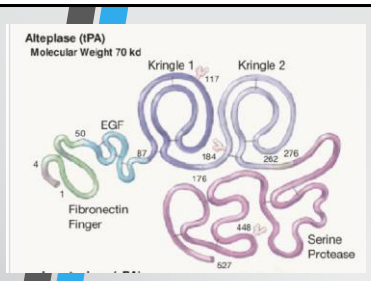
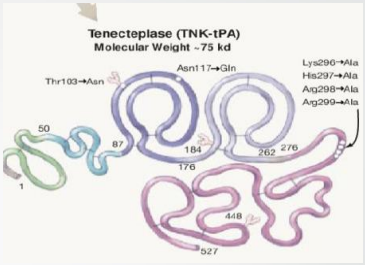


Tenecteplase



- Tenecteplase is genetically engineered with 3-point amino acid substitution (Threonine (T), Asparagine (N), Lysine(K) = TNK) from alteplase for preferential pharmacokinetics
  - 14-fold greater specificity for fibrin
  - 80-fold increased resistance to plasminogen activator inhibitor-1 (PAI-1)
  - Enhanced affinity to clot-bound fibrin and extended duration of action allow for administration as single bolus (circulating half-life 20-24 minutes)

Rabinstein AA, et al. CNS Drugs. 2020 Oct;34(10):1009-1014.

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Comparison Tenecteplase and Alteplase

	Alteplase	Tenecteplase
Administration	10% bolus, 90% as 60-minute IV infusion	Rapid bolus IV push
Plasma half-life	5 minutes	20 – 24 minutes
Terminal half-life		2 hours
Fibrin Specificity	+	+++

Efficacy:
- Tenecteplase has demonstrated consistent superiority in early reperfusion for patients with LVO undergoing mechanical thrombectomy
- Prospective, retrospective, and real-world data demonstrates non-inferiority for 90-day neurological recovery

Safety:
- Similar rates of bleeding including symptomatic intracranial hemorrhage for Tenecteplase 0.25 mg/kg dose compared to alteplase

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2018 AHA Guidelines Recommended Tenecteplase for LVO undergoing Embolectomy

3.6. Other IV Fibrinolytics and Sonothrombolysis

3.6. Other IV Fibrinolytics and Sonothrombolysis	COR	LOE	New, Revised, or Unchanged
1. 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	New recommendation.

Recommendation based on EXTEND-IA TNK (2018) trial demonstrating superiority of Tenecteplase over alteplase for early reperfusion

EXTEND-IA TNK

Tenecteplase versus Alteplase before Thrombectomy for Ischemic Stroke

Table 2. Outcomes.

Outcome	Tenecteplase Group (N = 101)	Alteplase Group (N = 101)	Effect Size (95% CI)	P Value
Primary efficacy outcome				
Substantial reperfusion at initial angiographic assessment — no. (%)*	22 (22)	10 (10)		
Difference — percentage points			12 (2–21)	0.002
Adjusted incidence ratio			2.2 (1.1–4.4)	0.03
Adjusted odds ratio			2.6 (1.1–5.9)	0.02
Secondary outcomes				
Score on the modified Rankin scale at 90 days†				
Median score (IQR) on ordinal analysis‡	2 (0–3)	3 (1–4)	1.7 (1.0–2.8)	0.04
Functionally independent outcome — no. (%)§	65 (64)	52 (51)		
Adjusted incidence ratio			1.2 (1.0–1.5)	0.06
Adjusted odds ratio			1.8 (1.0–3.4)	0.06

Campbell BCV, et al. N Engl J Med. 2018;378(17):1573-82.

Powers WF, et al. Stroke 2019;50:e344-418.

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Should Tenecteplase be used for all AIS?

- There is clear benefit of tenecteplase over alteplase for patients with LVO
- Many clinical trials over the last 5 years have demonstrated the safety and efficacy (non-inferiority) of tenecteplase compared to alteplase for <u>all</u> acute ischemic strokes
- Considering the ease of administration compared to alteplase, many hospitals around the world have moved towards tenecteplase as the exclusive formulary agent for AIS with and without LVO
  - Trinity Health anticipated go-live September 27, 2022

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Differences in Compounding and Administration

Alteplase Dose Calculation:
0.9 mg/kg (max 90 mg)

Draw up and discard waste

10% given as a bolus over 1 min

90% given as infusion over 1 hour

Tenecteplase Dose Calculation:
0.25 mg/kg (max 25 mg)

Reconstitute with 10 mL (final concentration 5 mg/mL)

Administer as IV push and flush

Example Dosing Chart:

Weight	Dose
< 60 kg	15 mg (3 mL)
60 – 69.9 kg	17.5 mg (3.5 mL)
70 – 79.9 kg	20 mg (4 mL)
80 – 89.9 kg	22.5 mg (4.5 mL)
≥ 90 kg	25 mg (5 mL)

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Door-to-Needle Time: Real-World Evidence

Door to Needle time presented in clinical studies Alteplase versus Tenecteplase

Acute Ischemic Stroke (AIS)	
2021 Hall[15]	58 (IQR 45, 70) vs 41 (IQR 34, 62) minutes, **p<0.01**
2021 Lucas[16]	39 (SD 36) vs 35 (SD 19) minutes, p=0.4666
2021 Mahawish[17]	61 (IQR 45, 86) vs 53 (IQR 38, 74) minutes, **p=0.0002**
2021 Zhong[18]	48 (IQR 33, 66) vs 47 (IQR 33, 69) minutes, p=0.93

IQR = interquartile range; SD = standard deviation

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Previous Clinical Trials: Tenecteplase vs. Altepase AIS

Trial	Intervention	Results (Efficacy)	Safety
NORTEST (2017) 1100 patients AIS eligible for tPA *superiority trial*	TNK 0.25 mg/kg vs Alteplase *(mostly mild strokes, average NIH = 6)*	Early improvement: TNK 41.7% vs. ALT38.8% Excellent recovery (mRS 0 -1 at 90 days): TNK 64% vs. 63%, p = 0.52)	sICH: TNK 2.73% vs ALT 2.35%
Zhong ,et al (Stroke 2021) 419 patients *Retrospective*	TNK 0.25 mg/kg vs Alteplase	90-day functional independence 61% vs 57%, p = 0.47	1.8% vs 2.7%, p = 0.75
NORTEST 2 (2022) 204 patients Terminated early	TNK 0.4 mg/kg vs Alteplase	Favorable functional outcome TNK 32% vs. ALT 51%, p = 0.006	Any ICH TNK 21% vs.ALT 7%, p=0.0031

Logallo N, et al. *Lancet Neurol.* 2017;16(10):781-788.
Kvistad CE, et al. Lancet Neurol 2022 Jun;21(6)511-519.
Zhong CS, Beharry J, Salazar D, et al. Stroke 2021 Mar;52(3):1087-1090.

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AcT Trial 2022

- Tenecteplase 0.25 mg/kg (max 25 mg) vs alteplase 0.9 mg/kg (max 90 mg) for acute ischemic stroke in tPA eligible patients
- Randomized, prospective, outcome assessment blinded
- Largest head-to-head trial to date: 1,577 patients included in intention to treat analysis
- Tenecteplase shown to be non-inferior to alteplase for AIS within similar risk of bleeding

Articles

Intravenous tenecteplase compared with alteplase for acute ischaemic stroke in Canada (AcT): a pragmatic, multicentre, open-label, registry-linked, randomised, controlled, non-inferiority trial

Bijoy K Menon, Brian H Buck, Nishita Singh, Yan Deschaintre, Mohammed A Almekhlafi, Shelagh B Coutts, Sibi Thirunavukkarasu, Houman Khosravani, Ramana Appireddy, Francois Moreau, Gord Gubitz, Aleksander Tkach, Luciana Catanese, Dar Dowlatshahi, George Medvedev, Jennifer Mandzia, Aleksandra Pikula, Jai Shankar, Heather Williams, Thalia S Field, Alejandro Manosalva, Muzaffar Siddiqui, Atif Zafar, Oje Imoukhuede, Gary Hunter, Andrew M Demchuk, Sachin Mishra, Laura C Gioia, Shirin Jalini, Caroline Cayer, Stephen Phillips, Elsadig Elamin, Ashkan Shoamanesh, Suresh Subramaniam, Mahesh Kate, Gregory Jacquin, Marie-Christine Camden, Faysal Benali, Ibrahim Alhabli, Fouzi Bala, MacKenzie Horn, Grant Stotts, Michael D Hill, David J Gladstone, Alexandre Poppe, Arshia Sehgal, Qiao Zhang, Brendan Cord Lethebe, Craig Doram, Ayoola Ademola, Michel Shamy, Carol Kenney, Tolulope T Sajobi, Richard H Swartz, for the AcT Trial Investigators

Summary

Background Intravenous thrombolysis with alteplase bolus followed by infusion is a global standard of care for patients with acute ischaemic stroke. We aimed to determine whether tenecteplase given as a single bolus might increase reperfusion compared with this standard of care.

Methods In this multicentre, open-label, parallel-group, registry-linked, randomised, controlled trial (AcT), patients were enrolled from 22 primary and comprehensive stroke centres across Canada. Patients were eligible for inclusion if they were aged 18 years or older, with a diagnosis of ischaemic stroke causing disabling neurological deficit, presenting within 4·5 h of symptom onset, and eligible for thrombolysis per Canadian guidelines. Eligible patients were randomly assigned (1:1), using a previously validated minimal sufficient balance algorithm to balance allocation by site and a secure real-time web-based server, to either intravenous tenecteplase (0·25 mg/kg to a maximum of 25 mg) or alteplase (0·9 mg/kg to a maximum of 90mg; 0·09 mg/kg as a bolus and then a 60 min infusion of the remaining 0·81 mg/kg). The primary outcome was the proportion of patients who had a modified Rankin Scale (mRS) score of 0–1 at 90–120 days after treatment, assessed via blinded review in the intention-to-treat (ITT) population (ie, all patients randomly assigned to treatment who did not withdraw consent). Non-inferiority was met if the lower 95% CI of the difference in the proportion of patients who met the primary outcome between the tenecteplase and alteplase groups was more than –5%. Safety was assessed in all patients who received any of either thrombolytic agent and who were reported as treated. The trial is registered with ClinicalTrials.gov, NCT03889249, and is closed to accrual.

Lancet 2022; 400: 161–69

Published Online June 29, 2022 https://doi.org/10.1016/S0140-6736(22)01054-6

See Comment page 138

Department of Clinical Neurosciences (Prof B K Menon MD, Prof S B Coutts MD, Prof A M Demchuk MD, S Subramaniam MD, F Benali MD, I Alhabli MD, F Bala MD, M Horn BSc,

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Patient Population

	Tenecteplase group (n=806)	Alteplase group (n=771)
Age, years	74 (63–83)	73 (62–83)
Sex		
Female	382 (47·4%)	373 (48·4%)
Male	424 (52·6%)	398 (51·6%)
Baseline NIHSS score (n=1569)	9 (6–16)	10 (6–17)
Baseline NIHSS score categories		
<8	325/803 (40·5%)	294/766 (38·4%)
8–15	247/803 (30·8%)	256/766 (33·4%)
>15	231/803 (28·8%)	216/766 (28·2%)
Occlusion site on baseline CT angiography (n=1558)*		
Intracranial internal carotid artery	69/801 (8·6%)	66/757 (8·7%)
M1 segment MCA	118/801 (14·7%)	119/757 (15·7%)
M2 segment MCA	174/801 (21·7%)	141/757 (18·6%)
Other distal occlusions†	130/801 (16·2%)	138/757 (18·2%)
Vertebrobasilar arterial system	26/801 (3·2%)	38/757 (5·0%)
Cervical internal carotid artery	17/801 (2·1%)	9/757 (1·2%)
No visible occlusions	267/801 (33·3%)	246/757 (32·5%)
Presence of large vessel occlusion on baseline CT angiography (n=1558)	196/801 (24·5%)	193/757 (25·5%)

Type of enrolling centre		
Primary stroke centre	56/806 (6·9%)	43/771 (5·6%)
Comprehensive stroke centre	750/806 (93·1%)	728/771 (94·4%)
Workflow times, min		
Stroke symptom onset to hospital arrival (n=1560)	82 (54–140)	83 (55–138)
Stroke symptom onset to randomisation (n=1570)	121 (85–179)	123 (88–179)
Door (hospital arrival) to baseline CT (n=1561)	15 (12–21)	16 (12–22)
Stroke symptom onset to needle (intravenous thrombolysis start; n=1562)	128 (93–186)	131 (95–188)
Door (hospital arrival) to needle (intravenous thrombolysis start; n=1556)	36 (27–49)	37 (29–52)
Baseline CT to arterial puncture (in patients undergoing EVT; n=505)	60 (43–88)	58 (41–85)
Arterial puncture to successful reperfusion (in patients undergoing EVT; n=445)	31 (19–47)	27 (17–45)

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Results

- 1577 patients in ITT population (806 tenecteplase vs 771 alteplase)
- Primary outcome (mRS 0-1 at 90 days)
  - 296 (36.9%) tenecteplase vs 266 (34.8%) alteplase (unadjusted risk difference 2.1% [95% CI -2.6 to 6.9])

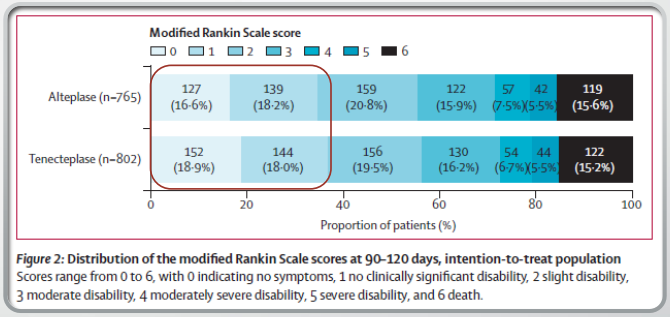

Figure 2: **Distribution of the modified Rankin Scale scores at 90–120 days, intention-to-treat population**
Scores range from 0 to 6, with 0 indicating no symptoms, 1 no clinically significant disability, 2 slight disability, 3 moderate disability, 4 moderately severe disability, 5 severe disability, and 6 death.

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Results

	Tenecteplase group (n=806)	Alteplase group (n=771)	Unadjusted difference in proportion	Adjusted risk ratio*	Difference in medians	Adjusted common odds ratio*†	Adjusted β coefficient*
Primary outcome							
mRS score 0–1 at 90–120 days (n=1567)	296/802 (36·9%)	266/765 (34·8%)	2·1 (−2·6 to 6·9)	..	..	..	..
Secondary outcomes*							
mRS score 0–1 at 90–120 days (n=1567)	296/802 (36·9%)	266/765 (34·8%)	..	1·1 (1·0 to 1·2)	..	..	..
mRS score 0–2 at 90–120 days (n=1567)	452/802 (56·4%)	425/765 (55·6%)	0·8 (−4·1 to 5·7)	1·0 (1·0 to 1·1)	..	..	..
Actual mRS score at 90–120 days (n=1567)	2 (1 to 4)	2 (1 to 4)	..	..	0	0·9 (0·8 to 1·1)	..
Return to baseline function (n=1454)	219/740 (29·6%)	199/714 (27·9%)	1·7 (−2·9 to 6·4)	1·1 (0·9 to 1·2)	..	..	..
EQ-VAS at 90–120 days (n=1262)	70·5 (21·3)	68·1 (22·6)	2·4 (−0·1 to 4·8)	..	..	..	2·1 (−0·3 to 4·5)
Endovascular thrombectomy use (n=1577)	258/806 (32·0%)	248/771 (32·2%)	−0·2 (−4·8 to 4·5)	1·0 (0·8 to 1·2)	..	..	..
eTICI score of ≥2b on initial angiography of EVT (n=502)‡	26/256 (10·2%)	27/256 (10·5%)	−0·8 (−6·3 to 4·6)	0·9 (0·6 to 1·6)	..	..	..
rAOL score of ≥2b on initial angiography of EVT (n=499; post hoc)§¶	48/253 (19·0%)	40/246 (16·3%)	2·7 (−4·0 to 9·4)	1·1 (0·7 to 1·7)	..	..	..
Length of hospital stay (n=1479; post hoc)	5 (2 to 11)	5 (3 to 11)	..	1·0 (0·9 to 1·1)	0	..	..

Data are n/N (%), median (IQR), mean (SD), or effect estimate with 95% CI in parentheses. EQ-VAS=EuroQol visual analogue scale. eTICI=extended Thrombolysis in Cerebral Infarction. EVT=endovascular thrombectomy. mRS=modified Rankin Scale. rAOL=revised Arterial Occlusive Lesion score. *Adjusted for age, sex, baseline stroke severity, stroke symptom onset-to-needle time, and source registry as fixed-effects variables, and site as a random effects variable. †Common odds ratio is the odds ratio for a unit increase in the modified Rankin scale score for tenecteplase vs alteplase. ‡Four patients did not have initial intracranial endovascular thrombectomy images. §Scored as follows: 0, primary occlusive thrombus remains same; 1, debulking of proximal part of the thrombus but without any recanalisation; 2a, partial or complete recanalisation of the primary thrombus with occlusion in major distal vascular branch; 2b, partial or complete recanalisation of the primary thrombus with occlusion in minor distal vascular branch, or partial recanalisation of the primary thrombus with no thrombus in the vascular tree at or beyond the primary occlusive thrombus; and 3, complete recanalisation of the primary occlusive thrombus with no clot in the vascular tree beyond. ¶rAOL was not assessable in six patients because of missing initial intracranial angiography or missing baseline CT angiography images.

Table 2: **Efficacy outcomes in the intention-to-treat population**

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Results

	Tenecteplase group (n=800)	Alteplase group (n=763)	Risk difference (95% CI)
Death within 90 days of randomisation (n=1554)	122/796 (15·3%)	117/758 (15·4%)	−0·1 (−3·7 to 3·5)
24 h symptomatic intracerebral haemorrhage	27/800 (3·4%)	24/763 (3·2%)	0·2 (−1·5 to 2·0)
Extracranial bleeding requiring blood transfusions	6/800 (0·8%)	6/763 (0·8%)	0·0 (−0·9 to 0·8)
Orolingual angio-oedema	9/800 (1·1%)	9/763 (1·2%)	−0·1 (−1·1 to 1·0)
Other serious adverse events	81/800 (10·0%)	69/763 (9·1%)	1·1 (−1·8 to 4·0)
Imaging-identified intracranial haemorrhage	154/800 (19·3%)	157/763 (20·6%)	−1·3 (−5·3 to 2·6)
Subarachnoid haemorrhage	53/800 (6·6%)	52/763 (6·8%)	−0·2 (−2·7 to 2·3)
Subdural haemorrhage	2/800 (0·3%)	5/763 (0·7%)	−0·4 (−1·1 to 0·3)
Intraventricular haemorrhage	24/800 (3·0%)	17/763 (2·2%)	0·8 (−0·8 to 2·3)
Haemorrhagic infarction type 1 (scattered small petechiae)	18/800 (2·3%)	24/763 (3·2%)	−0·9 (−2·5 to 0·7)
Haemorrhagic infarction type 2 (confluent petechiae)	62/800 (7·8%)	67/763 (8·8%)	−1·0 (−3·8 to 1·7)
Parenchymal haematoma type 1 (haematoma occupying <30% of infarct with no substantive mass effect)	28/800 (3·5%)	20/763 (2·6%)	1·1 (−1·0 to 2·6)
Parenchymal haematoma type 2 (haematoma occupying ≥30% of infarct with obvious mass effect)	21/800 (2·6%)	18/763 (2·4%)	0·3 (−1·3 to 1·8)
Remote parenchymal haematoma type 1†	6/800 (0·8%)	9/763 (1·2%)	−0·4 (−1·4 to 0·5)
Remote parenchymal haematoma type 2‡	2/800 (0·3%)	3/763 (0·4%)	−0·1 (−0·7 to 0·4)

Data are n/N (%) or risk difference with 95% CI in parentheses. Imaging-identified intracranial haemorrhages were assessed in a central core laboratory in a blinded manner and classified using the Heidelberg classification.[19] *Within the intention-to-treat population. †Remote parenchymal haematoma type 1 was defined as haematoma outside the infarcted tissue with no substantive mass effect. ‡Remote parenchymal haematoma type 2 was defined as haematoma outside the infarcted tissue, with obvious mass effect.

Table 3: **Safety outcomes in patients who received at least some dose of either thrombolytic agent and reported as treated***

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Author's Conclusion

"The AcT trial provides robust empirical evidence that tenecteplase is comparable to alteplase in patients presenting with acute ischemic stroke, with similar function, quality of life, and safety outcomes. Given the ease of administration compared with alteplase, these results provide a compelling rationale to support switching the standard-of-care intravenous thrombolytic agent for acute ischemic stroke from alteplase to tenecteplase at a dose of 0.25 mg/kg."

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