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TenectePLACE in Acute Stroke Management

A presentation for HealthTrust members
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Speaker Disclosures

- The presenter has no real or perceived conflicts of interest related to this presentation

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Learning Objectives

- Explain the differences between recombinant tissue plasminogen activator (tPA) and tenecteplase
- Describe current practice guidelines for acute ischemic stroke
- Explain current literature for the use of tenecteplase in the setting of acute ischemic stroke

Epidemiology

Every 40 seconds an American suffers from a stroke

About 795,000 Americans experience a new or recurrent stroke annually

90% of stroke risk is due to modifiable risk factors

74% of stroke risk is due to behavioral risk factors

Source: Stroke. Center for Disease Control and Prevention. 2019.

Pathophysiology

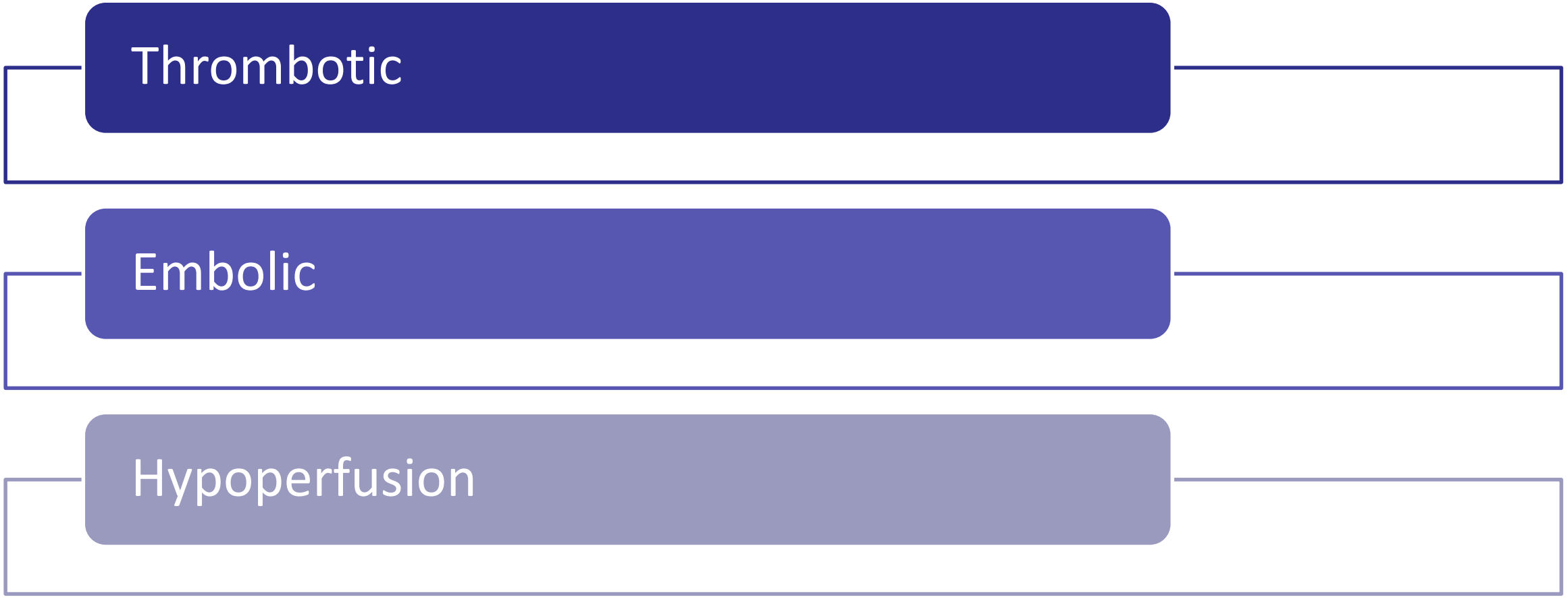
- A disease process that interrupts blood flow to the brain causing tissue injury due to lack of oxygen and glucose substrates

- **Ischemic** or hemorrhagic (intracerebral or nontraumatic subarachnoid hemorrhage)

https://www.medicinenet.com/stroke_symptoms_and_treatment/article.htm

Source: Tintinalli JE, et al. Tintinalli's Emergency Medicine. 2016.

Ischemic Stroke



Source: Tintinalli JE, et al. Tintinalli's Emergency Medicine. 2016.

Signs & Symptoms

Traditional

- Numbness or weakness (especially unilateral)
- Altered mental status
- Aphasia
- Memory deficit or spatial orientation or perception difficulties
- Visual deficit or diplopia
- Dizziness, gait disturbance, or ataxia
- Sudden severe headache with no known cause

Non-Traditional

- Loss of consciousness or syncope
- Generalized weakness
- Shortness of breath
- Sudden pain in the face, chest, arms, or legs
- Seizure
- Falls or accidents
- Sudden hiccups
- Sudden nausea
- Sudden fatigue
- Sudden palpitations
- Altered mental status

Source: Tintinalli JE, et al. Tintinalli's Emergency Medicine. 2016.

Diagnosis

Imaging

- Non-contrast head CT
- Diffusion-weighted MRI is superior to CT
  - Wake-up strokes
- CT angiography or magnetic resonance angiography

CT: computed tomography; MRI: magnetic resonance imaging
Source: Tintinalli JE, et al. Tintinalli's Emergency Medicine. 2016.

National Institutes of Health Stroke Scale (NIHSS)

- Tool used to objectively quantify the impairment caused by a stroke
- Composed of 11 items that are scored from 0 to 4 based on the patient's abilities
  - Level of consciousness, best gaze, visual, facial palsy, motor arm, motor leg, limb ataxia, sensory, best language, dysarthria, extinction and intention (formerly neglect)
- Score ranges from 0 – 42
  - 0 = No stroke
  - 1 – 4 = Mild
  - 5 – 20 = Moderate
  - > 20 = Severe

Source: Tintinalli JE, et al. Tintinalli's Emergency Medicine. 2016.

Modified Rankin Scale (mRS)

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

Source: Broderick JP, et al. Stroke. 2017.

Modified Treatment in Cerebral Ischemia (mTICI) Score

Grade 0	No perfusion
Grade 1	Antegrade reperfusion past the initial occlusion, but limited distal branch filling with little or slow distal reperfusion
Grade 2	• Grade 2a: antegrade reperfusion of less than half of the occluded target artery previously ischemic territory (e.g. in one major division of the middle cerebral artery (MCA) and its territory) • Grade 2b: antegrade reperfusion of more than half of the previously occluded target artery ischemic territory (e.g. in two major divisions of the MCA and their territories)
Grade 3	Complete antegrade reperfusion of the previously occluded target artery ischemic territory, with absence of visualized occlusion in all distal branches

Source: Dargazanli C, et al. Stroke. 2018.

Treatment

- Goal: minimize neurologic injury by decreasing clot burden and restoring blood flow to the brain to reduce the likelihood of lifelong disability

- Standard of care
  - IV fibrinolytic therapy
  - Directed intra-arterial fibrinolytic therapy
  - Mechanical thrombectomy

Source: Nelson A, et al. Am J Emerg Med. 2019.

Room for Improvement

- Up to 2/3 of patients with large artery occlusions may not achieve recanalization
- Less than half of those treated have complete reperfusion by 24 hours
- Up to 40% of stroke patients who receive fibrinolytic pharmacotherapy may remain severely disabled or die

Source: Logallo N, et al. Lancet Neurol. 2017.

Current Practice Guidelines

Stroke
Volume 50, Issue 12, December 2019, Pages e344-e418
https://doi.org/10.1161/STR.0000000000000211

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

See related article, p 3331

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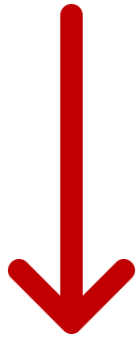
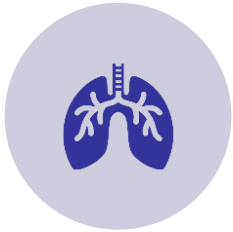
Source: Powers WJ, et al. Stroke. 2019.

Initial Management

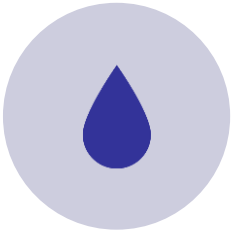




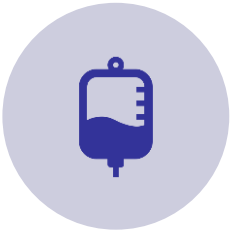
AIRWAY, BREATHING & OXYGENATION

BLOOD PRESSURE MANAGEMENT

TEMPERATURE MANAGEMENT



GLYCEMIC MANAGEMENT

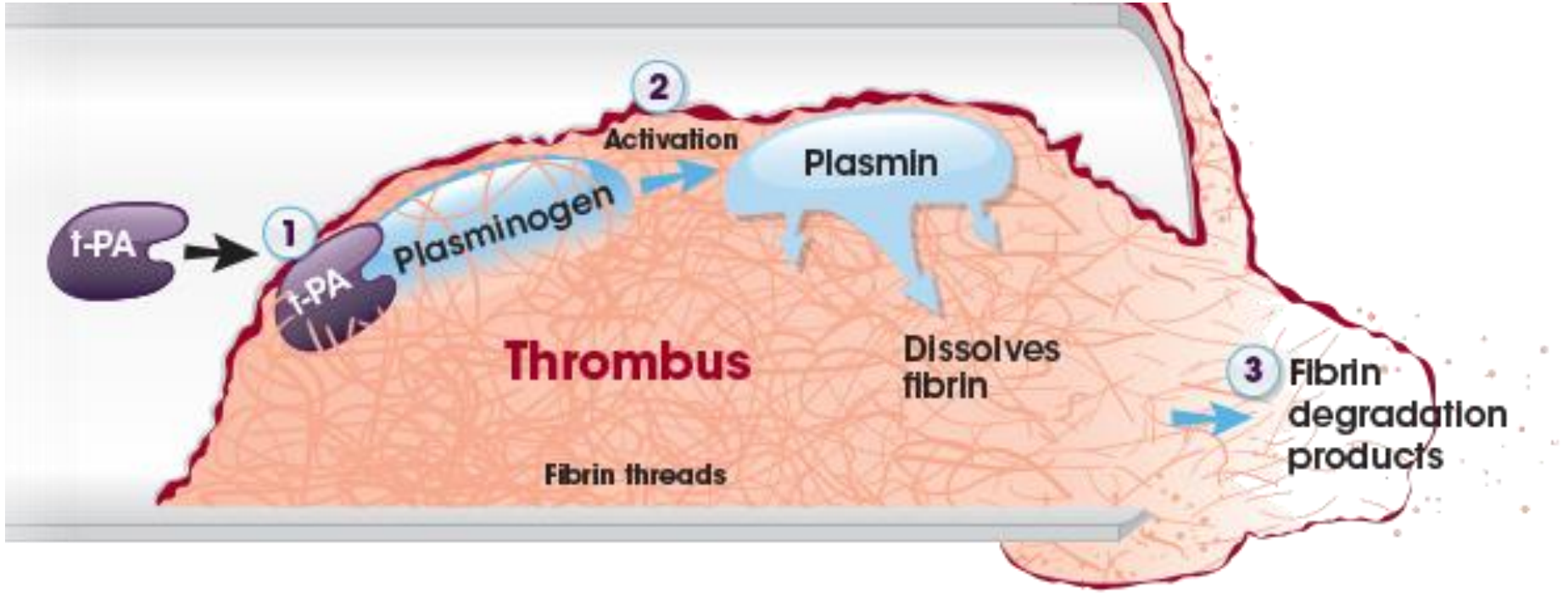


IV THROMBOLYTICS

MECHANICAL THROMBECTOMY

Source: Powers WJ, et al. Stroke. 2019.

Recombinant Tissue Plasminogen Activators



Source: Cathflo. https://www.cathflo.com/catheter-management/mechanism-of-action.html

Commercially Available Thrombolytics

Alteplase

Tenecteplase

Reteplase

Source: Activase ®. https://www.activase.com/ais/dosing-and-administration/reconstituting.html.
TNKase Tenecteplase. https://americanhistory.si.edu/collections/search/object/nmah_1445209
Retavase ®. https://retavase.com/dosing-administration/

Food For Thought

Efficacy with regards to neurologic improvement

Preparation and administration

Safety and adverse effect profile

Cost

Source: Zitek T, et al. West J Emerg Med. 2020.

IV Thrombolytic Recommendations

- In patients eligible for IV alteplase, benefit of therapy is time dependent, and treatment should be initiated as quickly as possible (Level IA)

- IV alteplase 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
(Level IA)

Source: Powers WJ, et al. Stroke. 2019.

IV Thrombolytic Recommendations

- IV alteplase 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. (Level I)

- IV alteplase 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
  - Are 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 (Level IIA)

AIS: acute ischemic stroke; DW-MRI: diffusion weighted magnetic resonance imaging
MCA: middle cerebral artery; FLAIR: fluid-attenuated inversion recovery
Source: Powers WJ, et al. Stroke. 2019.

IV Thrombolytic Recommendations

- For otherwise eligible patients with mild but disabling stroke symptoms, IV alteplase is recommended for patients who can be treated within 3 hours of ischemic stroke symptom onset or patient last known well or at baseline state. (Level I)

- For otherwise eligible patients with mild disabling stroke symptoms, IV alteplase may be reasonable for 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 (Level IIB)

Source: Powers WJ, et al. Stroke. 2019.

Alteplase Contraindications

- Mild nondisabling stroke presenting in the 0 to 4.5-hour window
- Intracranial hemorrhage
- Prior ischemic stroke within the past 3 months
- Severe head trauma within the past 3 months
- Intracranial/intraspinal surgery within the past 3 months
- History of intracranial hemorrhage
- Subarachnoid hemorrhage
- GI malignancy or GI bleed within the past 21 days
- Platelets <100,000/mm^3, INR >1.7, aPTT >40 seconds, or PT>15 seconds
- Received LMWH treatment dose within the past 24 hours
- Received thrombin inhibitor or DOAC within the past 48 hours
- Concomitant abciximab
- Concomitant IV aspirin
- Aortic arch dissection
- Intra-axial intracranial neoplasm

GI: Gastrointestinal; INR: international normalized ratio; aPTT: activated partial thromboplastin time
PT: prothrombin time; DOAC: direct oral anticoagulant
Source: Powers WJ, et al. Stroke. 2019.

Relative Alteplase Contraindications

- Patients presenting with very severe stroke (NIHSS>25) in the 3 to 4.5-hour window
- Arterial puncture of a non-compressible blood vessel within the past 7 days
- Major trauma within the past 14 days with injuries not involving the head
- Major surgery within the past 14 days
- GI/GU bleed within the past 21 days
- Active vaginal bleeding
- Extracranial cervical arterial dissections
- Intracranial arterial dissections
- Small or moderately sized (<10 mm) unruptured and unsecured intracranial aneurysm
- Unruptured and unsecured intracranial intracranial vascular malformations
- Concomitant tirofiban or eptifibatide
- Acute pericarditis
- Left atrial or ventricular thrombus
- Systemic malignancy
- Pregnancy

NIHSS: National Institutes of Health Stroke Scale
GI: gastrointestinal; GU: genitourinary
Source: Powers WJ, et al. Stroke. 2019.

IV Thrombolytic Recommendations

- 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 (Level IIB)

- Tenecteplase administered as a 0.4-mg/kg single IV bolus has not been proven to be superior or noninferior to alteplase but might be considered as an alternative to alteplase in patients with minor neurological impairment and no major intracranial occlusion (Level IIB)

- The administration of IV defibrinogenating agents or IV fibrinolytic agents other than alteplase and tenecteplase is not recommended (Level III)

Source: Powers WJ, et al. Stroke. 2019.

Tenecteplase (TNK)

- Modified tissue plasminogen activator
- More fibrin specific than alteplase
- Increases the conversion of plasminogen to plasmin
- Greater resistance to plasminogen activator inhibitor
- Administered as a single bolus injection

Source: Nelson A, et al. Am J Emerg Med. 2019.

Tenecteplase versus Alteplase

	Tenecteplase	Alteplase	Reteplase
FDA approved indications	Acute MI	Acute MI Acute ischemic stroke Acute massive PE	Acute MI
Binding affinity	Fibrin + + + PAI +	Fibrin + PAI + +	Potency expressed in units, so not comparable
Stroke dosing	Varies, 0.1 – 0.4 mg/kg IV bolus administered over 5 minutes	0.9 mg/kg (max 90 mg) administered as a 10% IV bolus followed by 90% IV infusion over 1 hour	Not applicable
Half-life	24 minutes	5 minutes	13-16 minutes
Average wholesale price	$7463 per 50 mg vial	$10,560 per 100 mg vial	$4,971 for 2 10 mg vials

PAI = plasminogen activator inhibitor

Source: REDBOOK Online. Accessed April 27, 2020.; Nelson A, et al. Am J Emerg Med. 2019.; Retavase (reteplase) [package insert]; August 2017.

Haley et al. Dose Finding Study

TNK dose 0.1 mg/kg vs. 0/25 mg/kg vs. 0.4 mg/kg vs. 0.5 mg/kg

Study terminated when 2 of 13 patients developed symptomatic ICH conversion within 36 hours of receiving 0.5 mg/kg dose

Increased rate of asymptomatic ICH in the other dosing arms: 8% (0.1 mg/kg TNK), 32%(0.2 mg/kg TNK), and 28%(0.4 mg/kg TNK)

Haley and colleagues conducted a second phase IIB/III trial on TNK vs tPA in acute ischemic stroke patients

TNK: tenecteplase; ICH: intracranial hemorrhage; tPA: tissue plasminogen activator (alteplase)
Source: Haley EC. Stroke. 2005.

Haley et al. IIB/III

- Randomized, multicenter, double-blind phase IIB/III
- Purpose:
  - To establish the dose of tenecteplase (0.1 mg/kg vs. 0.25 mg/kg vs. 0.4 mg/kg) for acute ischemic stroke using clinical outcome at 24 hours
  - To compare established tenecteplase dose to the standard alteplase dose 0.9 mg/kg (max 90 mg) using clinical outcome at 3 months
- Methods:
  - Inclusion: Patients aged ≥18 years presenting within 3 hours of symptom onset with at least a serious measurable deficit on the NIHSS in language, motor power, vision or attention
  - Used a response outcome score, Major Neurologic Improvement (MNI), which balanced neurologic improvement against risk of symptomatic ICH, to determine utility of each TNK dosing arm
  - Primary outcome: good neurologic outcome defined as mRS 0-1 at 3 months

NIHSS: National Institute of Health stroke Scale; ICH: intracranial hemorrhage
TNK: tenecteplase; mRS: modified rankin scale
Source: Haley EC, et al. Stroke. 2010.

Haley et al. Results

- Early termination due to lack of enrollment stopped the trial from proceeding to phase III testing
- Rate of good neurologic outcome (mRS 0-1) was highest with 0.25 mg/kg dose at 3 months, but no different when compared with other groups
- Number of patients with symptomatic intracranial hemorrhage did not differ between groups
- An interim analysis the study investigators concluded the 0.4mg/kg TNK arm to be inferior based on lower MNI score compared to other TNK arms

mRS: modified rankin scale; TNK: tenecteplase; MNI: major neurologic improvement
Source: Haley EC, et al. Stroke. 2010.

Haley et al. Conclusions

Additional studies are needed

Source: Haley EC, et al. Stroke. 2010.

ATTEST

- Single center, phase II, prospective, randomized, open-label, blinded end-point evaluation study
- Purpose: To assess the efficacy and safety of tenecteplase 0.25 mg/kg (Max 25 mg) IV versus alteplase 0.9 mg/kg (max 90 mg) IV
- Methods
  - Inclusion: patients aged ≥ 18 years presenting within 4.5 hours of symptom onset with measurable NIHSS and CT perfusion and CT angiogram prior to treatment
  - Primary outcome: Percent penumbral salvage at 24-48 hours
  - Secondary outcomes: 1)Recanalization 24-48 hours post treatment, 2) early clinical improvement at 24 hours, 3) symptomatic intracranial hemorrhage on 24-48 hour CT, 4)mRS at 30 days, 90 days, 5) mortality at 90 days

NIHSS: National Institute of Health Stroke Scale; CT: computed tomography
mRS: modified rankin scale
Source: Huang X, et al. Lancet Neurol. 2015.

ATTEST Results

	Tenecteplase (n=47)	Alteplase (n=49)	P value	Mean difference (95% CI)	Odds ratio (95% CI)
Primary outcome					
Percentage penumbral salvaged at 24–48 h	68% (28)	68% (23)	0.81	1.3% (−9.6 to 12.1)	
Secondary outcomes					
Recanalization at 24–48 h	21/32 (66%)	26/35 (74%)	0.38		0.6 (0.2 to 1.8)
mRS 0–1 at 90 days	13/47 (28%)	10/49 (20%)	0.28		1.8 (0.6 to 5.5)
Mortality at 90 days	8/47 (17%)	6/49 (12%)	0.51		1.3 (0.4 to −3.7)
Any ICH	8/52 (15%)	14/51 (27%)	0.09		0.4 (0.2 to 1.2)

mRS: modified rankin scale; ICH: intracranial hemorrhage
Source: Huang X, et al. Lancet Neurol. 2015.

ATTEST Conclusions

- Neurological and radiographical outcomes did not differ between groups
- Evaluation of tenecteplase in larger trials is warranted

Source: Huang X, et al. Lancet Neurol. 2015.

NOR-TEST

- Multicenter, prospective randomized, open-label, blinded endpoint
- Purpose: To establish superiority of tenecteplase 0.4 mg/kg IVP bolus versus alteplase 0.9 mg/kg (10% bolus, 90% infusion over 1 hour)
- Methods
  - Inclusion: admitted patients with acute ischemic stroke eligible for thrombolytic therapy
  - Eligibility: a) admitted <4.5 hours after symptom onset, b) admitted <4.5 hours after awakening with stroke symptoms, c) within 6 hours after the onset of symptoms if eligible for embolectomy
  - Primary endpoint: Modified Rankin Scale 0–1 at 90 days
  - Secondary endpoints: 1) hemorrhagic transformation, 2) symptomatic cerebral hemorrhage on CT at 24-48 hours, 3) major neurological improvement at 24 hours, 4) recanalization at 24–36 hours, 5) death

Source: Logallo N, et al. Lancet Neurol. 2017.

NOR-TEST Exclusion Criteria

- mRS score ≥3
- Patients for whom a complete NIHSS cannot be obtained
- Hemiplegic migraine with no arterial occlusion
- Seizure at stroke onset and no visible occlusion
- Intracranial hemorrhage
- Clinical presentation suggesting subarachnoid hemorrhage even if baseline CT is normal
- Large areas of hypodense ischemic changes on baseline CT
- Patients with primary endovascular treatment
- Patients with systolic blood pressure >180 mmHg or diastolic blood pressure >110 mmHg despite blood pressure lowering therapy
- Pregnant or breastfeeding
- Unlikely to complete follow-up
- Known bleeding diathesis; use of oral anticoagulants and INR ≥1.4; heparin <48 hours and increased aPTT; low molecular weight heparin(oid) <24 hours; new oral anticoagulants <12 hours; any other investigational drug <14 days
- Sepsis, endocarditis, pericarditis
- Arterial puncture at a non-compressible site or lumbar puncture <7 days
- Major surgery or serious trauma <14 days; gastrointestinal or urinary tract hemorrhage <14 days
- Clinical stroke <2 months
- History of ICH
- CNS neurosurgery <2 months
- Serious head trauma <2 months
- Any serious medical illness likely to interact with treatment
- Confounding pre-existent neurological or psychiatric disease

mRS: modified rankin scale; NIHSS: National Institute of Health Stroke Scale; CT: computed tomography
aPTT: activated partial thromboplastin time; ICH: intracranial hemorrhage; CNS: central nervous system
Source: Logallo N, et al. Lancet Neurol. 2017.

NOR-TEST Patient Population

	Tenecteplase (n=549)	Alteplase (n=551)
Major intracranial vessel occlusion	73 (13%)	92 (17%)
Premorbid modified Rankin Scale score		
0	435 (79%)	425 (77%)
1	62 (11%)	65 (12%)
2	25 (5%)	26 (5%)
≥3	27 (5%)	35 (6%)

	Tenecteplase (n=549)	Alteplase (n=551)
NIHSS Score		
Mean (SD)	5.6 (5.4)	5.8 (5.2)
Median (IQR)	4 (2–7)	4 (2–8)
Mild (0–7)	426 (78%)	401 (73%)
Moderate (8–14)	75 (14%)	98 (18%)
Severe (≥15)	48 (9%)	52 (9%)
Time (min)		
Onset to admission	79.0 (46–131)	74.5 (47–123)
Admission to thrombolysis	32.0 (22–47)	34.0 (25–50)
Onset to thrombolysis	118.0 (79–180)	111 (80–174)

NIHSS: National Institute of Health Stroke Scale
Source: Logallo N, et al. Lancet Neurol. 2017.

NOR-TEST Results – Efficacy (Intention-to-Treat)

	Tenecteplase (n=549)	Alteplase (n=551)	Odds Ratio (95% CI)	P value
Primary Outcome				
mRS 0-1 at 3 months	354/549 (64%)	345/551 (63%)	1.08 (0·84–1·38)	0.52
Secondary Outcomes				
Any ICH at 24-48 h	47/549 (9%)	50/551 (9%)	0.94 (0.60–1.45)	0.82
Symptomatic ICH at 24-48 h	15/549 (3%)	13/551 (2%)	1.16 (0.51–2.68)	0.70
Major clinical improvement at 24h	229/549 (42%)	214/551 (39%)	1.12 (0.89–1.43)	0.97
Death within 3 months	29/549 (5%)	26/551 (5%)	1.12 (0.63–2.02)	0.68

mRS: modified rankin scale; ICH: intracranial hemorrhage
Source: Logallo N, et al. Lancet Neurol. 2017.

NOR-TEST Results – Efficacy (Per Protocol)

	Tenecteplase (n=382)	Alteplase (n=391)	Odds Ratio (95% CI)	P value
Primary Outcome				
mRS 0-1 at 3 months	244/382 (64%)	250/391 (64%)	0.99 (0.74–1.33)	0.98
Secondary Outcomes				
Any ICH at 24-48 h	40/389 (10%)	39/400 (10%)	1.06 (0.67–1.67)	0.81
Symptomatic ICH at 24-48 h	11/389 (3%)	8/400 (2%)	1.42 (0.57– 3.58)	0.49
Major clinical improvement at 24h	140/381 (37%)	140/392 (36%)	1·04 (0·78–1·40)	0.76
Death within 3 months	20/382 (5%)	16/391 (4%)	1.29 (0.66–2.54)	0.49

mRS: modified rankin scale; ICH: intracranial hemorrhage
Source: Logallo N, et al. Lancet Neurol. 2017.

NOR-TEST Conclusions

- Stroke severity was lower than expected
- Tenecteplase was not superior to alteplase for treatment of acute ischemic stroke
- Adds to safety data for tenecteplase 0.4 mg/kg
  - "Might not be harmful"

Source: Logallo N, et al. Lancet Neurol. 2017.

EXTEND– IA TNK

- Phase III, investigator-initiated, multicenter, prospective, randomized, open-label, blinded-outcome
- Purpose: To test noninferiority of tenecteplase 0.25 mg/kg (max 25 mg) IV compared to alteplase 0.9 mg/kg (max 90 mg) IV, then to test superiority
- Methods
  - Inclusion: patients with ischemic stroke within 4.5 hours after onset who had large-vessel occlusion of the internal carotid, middle cerebral, or basilar artery and who were eligible to undergo intravenous thrombolysis and endovascular thrombectomy
  - Eligibility: 1) could receive IV thrombolysis within 4.5 hr, 2)cerebral vascular occlusion on CTA
  - Exclusion: mRS ≥ 3
  - Primary endpoint: reperfusion of >50% of the involved ischemic territory or an absence of retrievable thrombus at the time of initial angiographic assessment
  - Secondary endpoints: 1) mRS at 90 days, 2) safety (death and symptomatic intracerebral hemorrhage)

CTA: computed tomography angiography; mRS: modified rankin scale
Source: Campbell BCV, et al. NEJM. 2018.

EXTEND– IA TNK – Patient Population

	Tenecteplase (n=101)	Alteplase (n=101)
Median NIHSS score (IQR)	17 (12–22)	17 (12–22)
Median time from stroke onset to hospital arrival (IQR) — min	60 (44–89)	72 (53–104)
Median time from stroke onset to initiation of intravenous thrombolysis (IQR) — min	125 (102–156)	134 (104–176)
Median time from initiation of intravenous thrombolysis to arterial puncture (IQR) — min	43 (25–57)	42 (30–63)
Median time from initiation of intravenous thrombolysis to initial angiographic assessment (IQR) — min	54 (34–67)	56 (40–77)
Interhospital transfer for thrombectomy — no. (%)	27 (27)	23 (23)

NIHSS: National Institute of Health Stroke Scale
Source: Campbell BCV, et al. NEJM. 2018.

EXTEND– IA TNK – Primary Outcome

	Tenecteplase (n=101)	Alteplase (n=101)	Effect Size (95% CI)	P Value
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

Source: Campbell BCV, et al. NEJM. 2018.

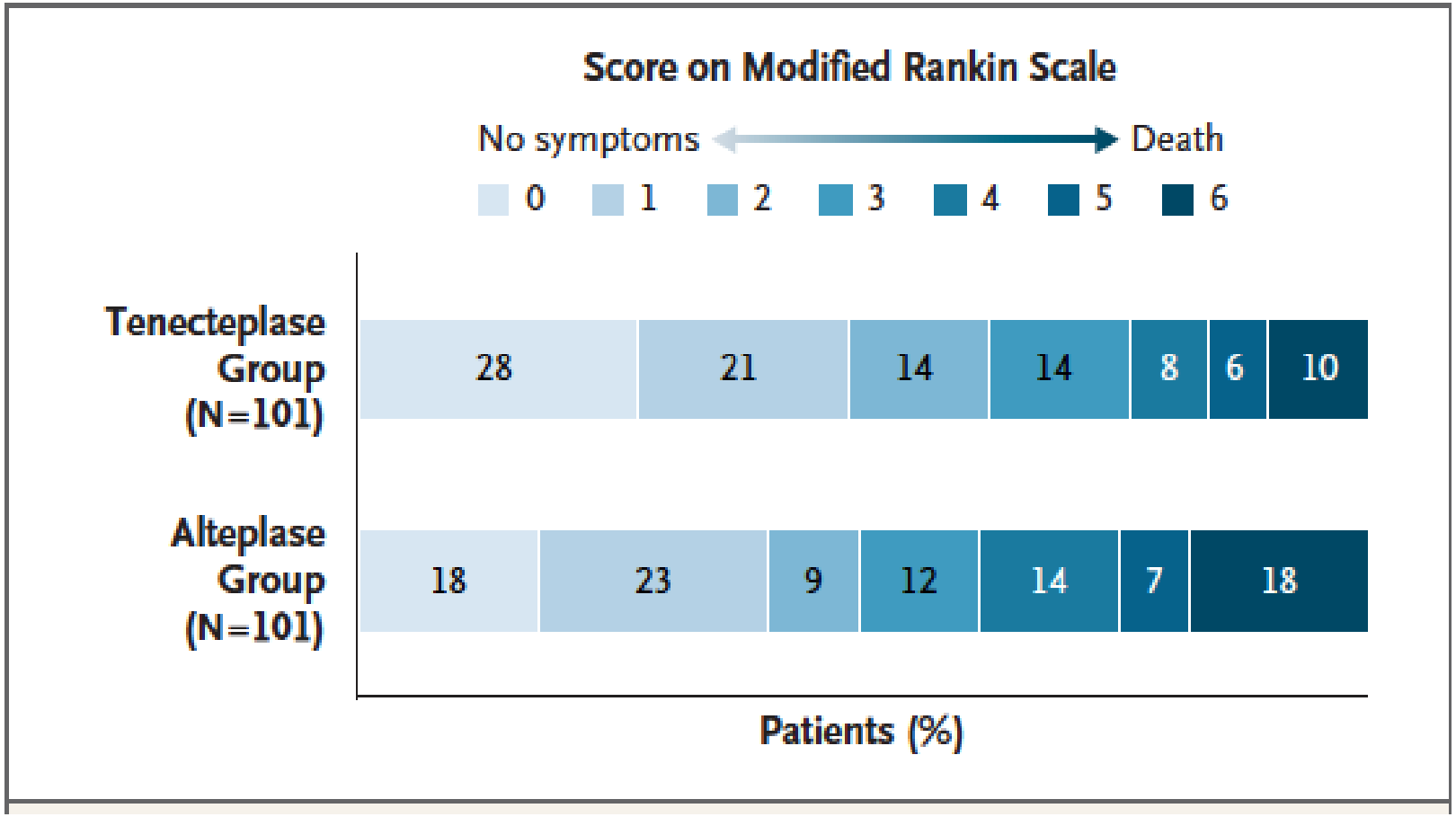
EXTEND– IA TNK – Secondary Outcomes

	Tenecteplase (n=101)	Alteplase (n=101)	Effect Size (95% CI)	P Value
mRS at 90 days				
Median score (IQR) on ordinal analysis	2 (0–3)	3 (1–4)	1.7 (1.0–2.8)	0.04
Death — no. (%)	10 (10)	18 (18)		
Adjusted risk ratio			0.5 (0.3–1.0)	0.049
Adjusted odds ratio			0.4 (0.2–1.1)	0.08
Symptomatic intracerebral hemorrhage — no. (%)	1 (1)	1 (1)		
Risk ratio			1.0 (0.1–15.9)	0.99
Odds ratio			1.0 (0.1–16.2)	0.99

mRS: modified rankin scale

Source: Campbell BCV, et al. NEJM. 2018.

EXTEND– IA TNK – Secondary Outcomes



Source: Campbell BCV, et al. NEJM. 2018.

EXTEND– IA TNK – Conclusions

- IV tenecteplase resulted in a higher incidence of reperfusion of the occluded vascular territory before thrombectomy than IV alteplase demonstrating non-inferiority
- Study was not powered for superiority
- Functional outcome (mRS) was better with tenecteplase than with alteplase, but the incidence of recovery to independent function did not differ significantly
- No significant difference in the incidence of cerebral hemorrhage

mRS: modified rankin scale
Source: Campbell BCV, et al. NEJM. 2018.

EXTEND– IA TNK, Part 2

- Phase II, multicenter, prospective, randomized, open- label, blinded endpoint
- Purpose: To compare efficacy and safety of tenecteplase 0.25 mg/kg (n=150) IV versus 0.4 mg/kg IV (n=150)
- Methods
  - Inclusion: Patients ≥ 18 years of age presenting with acute ischemic stroke eligible to receive IV thrombolysis within 4.5 hours of stroke onset, and ICA, M1, M2 or basilar artery occlusion on CTA
  - Primary Outcome: mTICI of 2b/3
  - Secondary Outcomes: 1) mRS, 2) NIHSS, 3) Symptomatic intracranial hemorrhage, 4) Death, 5) Angiographic reperfusion

ICA: internal carotid artery; ICM1: Horizontal segment of the MCA; MCA: middle cerebral artery; M2: sylvian segment of the MCA
mTICI: modified treatment in cerebral ischemia; mRS: modified rankin scale; NIHSS: National Institute of Health Stroke Scale
Source: Campbell BC, et al. Int J Stroke. 2019.

EXTEND– IA TNK, Part 2 Exclusion Criteria

- Intracranial hemorrhage (ICH) identified by CT or MRI
- Rapidly improving symptoms at the discretion of the investigator
- Pre-stroke mRS score of ≥ 4 (indicating previous disability)
- Hypodensity in >1/3 MCA territory or equivalent proportion of basilar artery territory on non-contrast CT
- Contraindication to imaging with contrast agents
- Any terminal illness such that patient would not be expected to survive more than 1 year
- Any condition that, in the judgment of the investigator could impose hazards to the patient if study therapy is initiated or affect the participation of the patient in the study.
- Pregnant women

Source: Campbell BC, et al. Int J Stroke. 2019.

EXTEND– IA TNK, Part 2 Results

Data presented at the 2020 International Stroke Conference

- 150 patients in each group
- All clots were largely dissolved prior to mechanical removal in 19.3% of patients in both groups
  - ARR 1.03, 95% CI (0.66 – 1.61), p = 0.89
- mRS scores were not statistically different between dose groups
  - Generalized odds ratio (gOR) 0.96, 95% CI (0.74 to 1.24), p = 0.73
- ~34% of patients treated in rural centers had substantially improved blood flow by the time they arrived at a hospital capable of performing mechanical clot removal
- Rates of symptomatic intracranial hemorrhage were numerically lower with the 0.25 mg/kg dosing
  - 1.3% versus 4.7%

Source: Hoffman M. NeurologyLive. 2020.

EXTEND– IA TNK, Part 2 Conclusions

- Tenecteplase 0.25 mg/kg is just as effective as the 0.4 mg/kg dose with lower rates of symptomatic intracranial hemorrhage

- 34% increase in blood flow following tenecteplase administration in patients who needed to be transferred for thrombectomy

Source: Hoffman M. NeurologyLive. 2020.

Trials in the Pipeline

ATTEST2

- Alteplase-Tenecteplase Trial Evaluation for Stroke Thrombolysis
- Randomized, parallel, open-label
- Purpose: To test for superiority of tenecteplase 0.25 mg/kg (max 25 mg) compared to alteplase 0.9 mg/kg (max 90 mg) in treating patients with acute ischemic stroke eligible for IV thrombolysis
- Methods
  - Inclusion: patients ≥ 18 years of age presenting <4.5 hours after acute ischemic stroke symptom onset with a mRS 0-1 prior to stroke
  - Primary outcome: mRS at 90 days
  - Secondary outcomes: 1) full neurologic recovery, 2) independent recovery, 3) early major neurological improvement or return to NIHSS of 0 or 1 at 24 hours, 4) Health Related Quality of Life, 5) Barthel Index Score, 5) mortality, 6) intracranial hemorrhage, 7) extracranial hemorrhage

Source: ClinicalTrials.gov. NCT02814409. Accessed April 27, 2020.

NOR-TEST 2

- Norwegian Tenecteplase Stroke Trial 2
- Multicenter, prospective randomized, open-label, blinded endpoint trial
- Purpose: To compare efficacy and safety of tenecteplase 0.4 mg/kg compared to alteplase 0.9 mg/kg (max 90 mg) a) within 4½ hours after symptom onset; b) within 4½ hours after awakening with stroke symptoms, and c) as bridging therapy within 4½ hours before thrombectomy
- Methods
  - Inclusion: All patients admitted to hospital with acute ischemic stroke eligible for standard iv thrombolysis with alteplase and with pre-stroke mRS<3 and NIHSS score of >5 on admission
  - Primary outcome: Favorable functional outcome defined as mRS 0-1 at 90 days
  - Secondary outcomes: 1) symptomatic cerebral hemorrhage, 2) any cerebral hemorrhage, 3) major neurologic improvement, 4) functional handicap, 5) mortality

Source: ClinicalTrials.gov. NCT03854500. Accessed April 27, 2020.

TIMELESS

- Tenecteplase in Stroke Patients Between 4.5 and 24 Hours
- Phase III, Prospective, Double-blind, Randomized, Placebo-controlled Trial
- Purpose: To evaluate the efficacy and safety of tenecteplase 0.25 mg/kg (max 25 mg) compared with placebo in patients with acute ischemic stroke
- Methods:
  - Inclusion: Patients ≥ 18 years of age presenting 4.5 to 24 hours after acute ischemic stroke symptom onset with an mRS 0-2 prior to stroke and NIHSS ≥5 prior to randomization
  - Primary outcome: mRS at 90 days
  - Secondary Outcomes: 1) Functional independence (mRS), 2) Reperfusion rate, 3) Barthel Index score ≥95, 4) Glasgow Outcome Scale, 5) NIHSS, 6) Recanalization at 24 hours post randomization, 7) symptomatic intracranial hemorrhage, 8) ADEs, 9) mortality, 10) parenchymal hemorrhage

Source: ClinicalTrials.gov. NCT03785678. Accessed April 27, 2020.

Assessment Question 1

The following statements regarding the differences between alteplase and tenecteplase are true **except**:

A. Alteplase has the FDA indications for the treatment of ST-Elevation MI, PE and acute ischemic stroke
B. Tenecteplase has higher specificity and better binding to fibrin
C. Tenecteplase has a longer half-life
D. Tenecteplase is administered as an IV bolus followed by an IV infusion
E. Alteplase has a maximum dose of 90 mg

Assessment Question 1: Response

The following statements regarding the differences between alteplase and tenecteplase are true **except**:

A. Alteplase has the FDA indications for the treatment of ST-Elevation MI, PE and acute ischemic stroke
B. Tenecteplase has higher specificity and better binding to fibrin
C. Tenecteplase has a longer half-life
D. Tenecteplase is administered as an IV bolus followed by an IV infusion
E. Alteplase has a maximum dose of 90 mg

Assessment Question 2

According to the *2018 AHA/ASA Guidelines for the Early Management of Patients with Acute Ischemic Stroke,* what is the level of evidence for tenecteplase administration?

A. Ia

B. IIa

C. IIb

D. IIc

E. III

Assessment Question 2: Response

According to the *2018 AHA/ASA Guidelines for the Early Management of Patients with Acute Ischemic Stroke,* what is the level of evidence for tenecteplase administration?

A. Ia

B. IIa

C. IIb

D. IIc

E. III

Assessment Question 3

Which of the following statements presents the best interpretation of the following data from the NOR-TEST Trial: The primary outcome of modified Rankin Scale (mRS) score 0-1 at 3 months was achieved by 354 (64%) patients in the tenecteplase group and 345 (63%) patients in the alteplase group (odds ratio 1.08, 95% CI 0.84-1.38; p=0.52).

A. Patients who received tenecteplase were 1.08 times more likely to have excellent functional outcomes at 3 months, but it was not statistically significant

B. Patients who received alteplase were 1.08 times more likely to have excellent functional outcomes at 3 months, but it was not statistically significant

C. Patients who received tenecteplase were 1.08 times more likely to have statistically significant excellent functional outcomes at 3 months

D. Patients who received tenecteplase were 1.08 times more likely to die from any cause within 3 months

E. Patients who received alteplase were 1.08 times more likely to die from any cause within 3 months

Assessment Question 3: Response

Which of the following statements presents the best interpretation of the following data from the NOR-TEST Trial: The primary outcome of modified Rankin Scale (mRS) score 0-1 at 3 months was achieved by 354 (64%) patients in the tenecteplase group and 345 (63%) patients in the alteplase group (odds ratio 1.08, 95% CI 0.84-1.38; p=0.52).

A. Patients who received tenecteplase were 1.08 times more likely to have excellent functional outcomes at 3 months, but it was not statistically significant

B. Patients who received alteplase were 1.08 times more likely to have excellent functional outcomes at 3 months, but it was not statistically significant

C. Patients who received tenecteplase were 1.08 times more likely to have statistically significant excellent functional outcomes at 3 months

D. Patients who received tenecteplase were 1.08 times more likely to die from any cause within 3 months

E. Patients who received alteplase were 1.08 times more likely to die from any cause within 3 months

Take Home Points

- Tenecteplase has a longer half-life compared to alteplase allowing for administration as a single IV bolus
- Tenecteplase may not be worse than alteplase
- Tenecteplase 0.25 mg/kg is as effective as the 0.4 mg/kg dose with lower rates of symptomatic intracranial hemorrhage
- Promising studies in the pipeline addressing superiority

References

1. Stroke. Center for Disease Control and Prevention website. https://www.cdc.gov/stroke/index.htm. Updated April 7, 2020. Accessed May 6, 2020.
2. Go S. Stroke Syndromes. In: Tintinalli JE, Ma O, Yealy DM, Meckler GD, Stapczynski J, Cline DM, Thomas SH. eds. *Tintinalli's Emergency Medicine: A Comprehensive Study Guide, 9e* New York, NY: McGraw-Hill; . http://accessmedicine.mhmedical.com.proxy.libraries.rutgers.edu/content.aspx?bookid=2353&sectionid=220293532. Accessed May 06, 2020.
3. Broderick JP, Adeoye O, Elm J. Evolution of the Modified Rankin Scale and Its Use in Future Stroke Trials. Stroke. 2017;48(7):2007-2012.
4. Dargazanli C, Fahed R, Blanc R, et al. Modified Thrombolysis in Cerebral Infarction 2C/Thrombolysis in Cerebral Infarction 3 Reperfusion Should Be the Aim of Mechanical Thrombectomy: Insights From the ASTER Trial (Contact Aspiration Versus Stent Retriever for Successful Revascularization). Stroke. 2018;49(5):1189-1196.
5. Nelson A, Kelly G, Byyny R, Dionne C, Preslaski C, Kaucher K. Tenecteplase utility in acute ischemic stroke patients: A clinical review of current evidence. Am J Emerg Med. 2019;37(2):344-348.
6. Logallo N, Novotny V, Assmus J, et al. Tenecteplase versus alteplase for management of acute ischaemic stroke (NOR-TEST): a phase 3, randomised, open-label, blinded endpoint trial. Lancet Neurol. 2017;16(10):781-788.
7. Powers WJ, Rabinstein AA, Ackerson T, et al. 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. Stroke.
8. Mechanism of Action. Cathflo ® Activase ® (alteplase) website. https://www.cathflo.com/catheter-management/mechanism-of-action.html. Accessed May 6, 2020.
9. Reconstitute Activase ® immediately before administration. Activase ® Alteplase A recombinant tissue plasminogen activator website. https://www.activase.com/ais/dosing-and-administration/reconstituting.html. Accessed May 6, 2020.
10. TNKase Tenecteplase. National Museum of American History website. https://americanhistory.si.edu/collections/search/object/nmah_1445209. 2020. Accessed May 6, 2020.
11. Retavase ® (reteplase) dosing and administration. Retavase ® (reteplase) for injection website. https://retavase.com/dosing-administration/. 2017. Accessed May 6, 2020.
12. Zitek T, Ataya R, Brea I. Using Tenecteplase for Acute Ischemic Stroke: What Is the Hold Up?. *West J Emerg Med*. 2020;21(2):199-202. Published 2020 Feb 24. doi:10.5811/westjem.2020.1.45279

References (continued)

13. IBM Micromedex ® Red Book ®. (electronic version), IBM Watson Health information, https://www-micromedexsolutions-com.proxy.libraries.rutgers.edu/micromedex2/librarian/CS/04C94F/ND_PR/evidencexpert/ND_P/evidencexpert/DUPLICATIONSHIELDSYNC/D4B4BF/ND_PG/evidencexpert/ND_B/evidencexpert/ND_AppProduct/evidencexpert/ND_T/evidencexpert/PFActionId/redbook.ShowProductSearchResults?SearchTerm=tenecteplase&searchType=redbookGenericName&searchTermId=925249&searchContent=REDBOOK&searchFilterAD=filterADActive&searchFilterRepackager=filterExcludeRepackager&searchPattern=%5Etenecteplase. Accessed April 27, 2020.
14. IBM Micromedex ® Red Book ®. (electronic version), IBM Watson Health information, https://www-micromedexsolutions-com.proxy.libraries.rutgers.edu/micromedex2/librarian/CS/687A58/ND_PR/evidencexpert/ND_P/evidencexpert/DUPLICATIONSHIELDSYNC/BEF4DB/ND_PG/evidencexpert/ND_B/evidencexpert/ND_AppProduct/evidencexpert/ND_T/evidencexpert/PFActionId/redbook.ShowProductSearchResults?SearchTerm=alteplase%2C%20recombinant&searchType=redbookGenericName&searchTermId=20930&searchContent=%24searchContent&searchFilterAD=filterADActive&searchFilterRepackager=filterExcludeRepackager&searchPattern=%5Ealteplase. Accessed April 27, 2020.
15. IBM Micromedex ® Red Book ®. (electronic version), IBM Watson Health information, https://www-micromedexsolutions-com.proxy.libraries.rutgers.edu/micromedex2/librarian/CS/2D13D8/ND_PR/evidencexpert/ND_P/evidencexpert/DUPLICATIONSHIELDSYNC/C00379/ND_PG/evidencexpert/ND_B/evidencexpert/ND_AppProduct/evidencexpert/ND_T/evidencexpert/PFActionId/redbook.ShowProductSearchResults?SearchTerm=reteplase%2C%20recombinant&searchType=redbookGenericName&searchTermId=924138&searchContent=%24searchContent&searchFilterAD=filterADActive&searchFilterRepackager=filterExcludeRepackager&searchPattern=%5Ereteplase. Accessed April 27, 2020.
16. Haley EC, Thompson JLP, Grotta JC, et al. Phase IIB/III trial of tenecteplase in acute ischemic stroke: results of a prematurely terminated randomized clinical trial. *Stroke*. 2010; 41:707–11.
17. Huang X, Cheripelli BK, Lloyd SM, et al. Alteplase versus tenecteplase for thrombolysis after ischaemic stroke (ATTEST): a phase 2, randomised, open-label, blinded endpoint study. Lancet Neurol 2015;14:368–76.
18. Campbell BCV, Mitchell PJ, Churilov L, et al. Tenecteplase versus Alteplase before Thrombectomy for Ischemic Stroke. N Engl J Med. 2018;378(17):1573-1582.
19. Campbell BCV, Mitchell PJ, Churilov L, et al. Effect of Intravenous Tenecteplase Dose on Cerebral Reperfusion Before Thrombectomy in Patients With Large Vessel Occlusion Ischemic Stroke: The EXTEND-IA TNK Part 2 Randomized Clinical Trial. *JAMA*. 2020;323(13).

References (continued)

20. Alteplase-Tenecteplase Trial Evaluation for Stroke Thrombolysis (ATTEST2). ClinicalTrials.gov website. https://clinicaltrials.gov/ct2/show/NCT02814409. Updated March 29, 2018. Accessed April 27, 2020.
21. The Norwegian Tenecteplase Stroke Trial 2 (NOR-TEST 2). ClinicalTrials.gov website. https://clinicaltrials.gov/ct2/show/NCT03854500?term=NOR-TEST+2&draw=2&rank=1. Updated October 31, 2019. Accessed April 27, 2020.
22. Tenecteplase in Stroke Patients Between 4.5 and 24 Hours (TIMELESS). ClinicalTrials.gov website. https://www.clinicaltrials.gov/ct2/show/NCT03785678. Updated April 13, 2020. Accessed April 27, 2020.

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