Any Way You Want It: Treatment of Stroke with Thrombolytics

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Disclosures

- No financial relationships to disclose
- No non-financial relationships to disclose
Learning Objective

- Describe the differences between Alteplase and Tenecteplase, two thrombolytic agents used to treat acute ischemic stroke
Thrombolytics for Acute Ischemic Stroke (AIS)

- “Clot buster” for ischemic stroke symptoms
  - Alteplase is FDA approved for ischemic stroke
  - Tenecteplase is considered a reasonable alternative (not FDA approved)

- Must meet inclusion/exclusion criteria for use
  - Maximize benefit - should be administered as quickly as possible since benefit is time dependent
  - Minimize risk of bleeding

- Hemorrhagic complications occur in ~5-6%
- Increased independence at 3 months post stroke across all age groups in patients receiving thrombolytic
Thrombolytic Inclusion Criteria

- Age greater than 18
- Measurable deficit on NIH Stroke Scale
- Onset of symptoms < 4.5 hours (if NIHSS > 25 and time from symptom onset to time of treatment > 3 hours, benefit is uncertain)
- Head CT negative for hemorrhage
- Discussion of risk, alternatives, and benefits with patient or legal representative completed
- Patient or family members understand the potential risks and benefits from treatment
Thrombolytic Exclusion Criteria

- Significant head trauma or prior stroke in previous 3 months
- History of intracranial hemorrhage
- Evidence of intracranial hemorrhage on CT
- Symptoms suggestive of subarachnoid hemorrhage
- Arterial puncture at a non-compressible site in previous 7 days
- Intracranial neoplasm (an extra-axial neoplasm, e.g. meningioma, is not a contraindication)
- Untreated arteriovenous malformation, or > 10mm aneurysm
- Intracranial or intraspinal surgery in previous 3 months
- **Systolic blood pressure greater than 185 mmHg, diastolic blood pressure greater than 110 mmHg at the time of treatment despite attempts to lower**
- Active internal bleeding (including GI) in past 21 days
Thrombolytic Exclusion Criteria

- Active bleeding diathesis, including but not limited to platelet count <100,000/mm$^3$ (in patients without known history of abnormality, do not wait for lab results)

- **Therapeutic doses of enoxaparin or heparin** received within 24 hours (resulting in abnormally elevated aPTT > the upper limit of normal – prophylactic doses of heparin or LMWH are not contraindications)

- Current use of anticoagulant **warfarin with INR > 1.7 or PT > 15 seconds**

- Current use of **direct thrombin inhibitors** [e.g. dabigatran (Pradaxa)] or **direct factor Xa inhibitors** [e.g. rivaroxaban (Xarelto); apixaban (Eliquis)] taken within the previous 48 hours

- Current use of IV glycoprotein IIb/IIIa inhibitors (tirofiban and eptifibatide)
Thrombolytic Exclusion Criteria

- **Blood glucose concentration** < 50 mg/dL or > 400 (if symptoms persist after normalization, thrombolytic may be given)
- CT demonstrates multilobar infarction or hypodensity >1/3 cerebral hemisphere
- Intracranial arterial dissection or aortic dissection (if clinically appropriate, extracranial arterial dissection is not a contraindication)
- Infective endocarditis
Thrombolytic Relative Contraindications

- Minor or non-disabling stroke symptoms
- In pregnant patients, if severity of stroke is moderate or severe, and benefits of treatment felt to outweigh the anticipated risk of uterine bleeding, IV thrombolytic can be considered
- Seizure at onset with postictal residual neurological impairments
- Major surgery or serious trauma (not involving brain) within previous 14 days
- Minor stroke with acute pericarditis (thrombolytic administration may be reasonable if major ischemic stroke with urgent cardiology consultation)
- Recent acute left anterior myocardial infarction (within the previous 3 months), (thrombolytic considered safer if non-STEMI or a right or inferior MI)
- Minor stroke symptoms with known atrial or ventricular thrombus (thrombolytic administration may be reasonable if severe stroke likely to produce severe disability)
Alteplase vs Tenecteplase

- What are the major differences between alteplase and tenecteplase?
  - Efficacy
  - Safety
  - Dosing
  - Mechanism of action
  - Cost
  - Ease of administration
# AHA/ASA 2019 Update to 2018 Guidelines for Early Management of Acute Ischemic Stroke

## Recommendations

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>COR</th>
<th>LOE</th>
</tr>
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<tbody>
<tr>
<td>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.</td>
<td>Iib</td>
<td>B-R</td>
</tr>
<tr>
<td>2. 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.</td>
<td>Iib</td>
<td>B-R</td>
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</table>

**Class Iib (Moderate)**

**Level B-R**
- Moderate quality evidence from ≥ 1 randomized, controlled trials
- Meta-analyses of moderate quality randomized, controlled trials

Five clinical trials comparing tenecteplase with alteplase in a total of 1600 patients. Three doses of tenecteplase were compared to standard dose alteplase. In all five trials tenecteplase had similar safety and efficacy outcomes.

- **EXTEND-IA TNK:** Tenecteplase 0.25 mg/kg – more effective than alteplase in achieving recanalization in patients who were candidates for both IV thrombolysis and EVT; modestly better functional outcomes
- **NOR-TEST:** Tenecteplase 0.4 mg/kg had similar efficacy and safety in patients with minor neuro impairment and no major intracranial occlusion
- **ATTEST:** Tenecteplase 0.25 mg/kg as safe as standard dose alteplase, no difference in penumbral tissue salvaged, no mortality difference at 90 days
- **Parsons et al:** Both tenecteplase doses (0.1 mg/kg, 0.25 mg/kg) superior to standard dose alteplase
- **Haley et al:** Tenecteplase 0.4 mg/kg inferior; other doses (0.1 mg/kg, 0.25 mg/kg) were similar to standard dose alteplase
# Thrombolytic Dosing

<table>
<thead>
<tr>
<th>Medication</th>
<th>FDA approved</th>
<th>Recommended Dose</th>
<th>Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alteplase</td>
<td>Yes</td>
<td><strong>Bolus + 1 hour infusion</strong></td>
<td>Max: 90 mg</td>
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<tr>
<td></td>
<td></td>
<td>Total dose: 0.9 mg/kg</td>
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<td></td>
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<td>&lt;100 kg: 10% as IV bolus over 1 min,</td>
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<td></td>
<td></td>
<td>followed by 90% as continuous infusion over 60 min</td>
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<td></td>
<td></td>
<td>≥ 100 kg: 9 mg IV bolus over 1 min, 81 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>continuous infusion over 60 min</td>
<td></td>
</tr>
<tr>
<td>Tenecteplase</td>
<td>No, is off-label</td>
<td><strong>Bolus only</strong></td>
<td>Max: 25 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.25 mg/kg IV once (trials have looked at</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>0.1mg/kg and 0.4mg/kg dosing and</td>
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<td></td>
<td></td>
<td>0.25mg/kg has been the most effective dose</td>
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<tr>
<td></td>
<td></td>
<td>with the least adverse effects)</td>
<td></td>
</tr>
</tbody>
</table>

[https://www.uptodate.com/contents/tenecteplase-drug-information?search=tenecteplase&source=panel_search_result&selectedTitle=1~18&usage_type=panel&kp_tab=drug_general&display_rank=1#F23613417](https://www.uptodate.com/contents/tenecteplase-drug-information?search=tenecteplase&source=panel_search_result&selectedTitle=1~18&usage_type=panel&kp_tab=drug_general&display_rank=1)

[https://www.uptodate.com/contents/alteplase-drug-information?search=alteplase&source=panel_search_result&selectedTitle=1~86&usage_type=panel&kp_tab=drug_general&display_rank=1](https://www.uptodate.com/contents/alteplase-drug-information?search=alteplase&source=panel_search_result&selectedTitle=1~86&usage_type=panel&kp_tab=drug_general&display_rank=1)
# Thrombolytic Comparison

<table>
<thead>
<tr>
<th>Medication</th>
<th>Mechanism of action</th>
<th>Metabolism/Elimination</th>
</tr>
</thead>
</table>
| **Alteplase**| Initiates *local fibrinolysis* by binding to fibrin in a thrombus and converts entrapped plasminogen to plasmin | - Initial half-life = 5 minutes  
- >50% present in plasma cleared in ~5 minutes after infusion terminated, ~80% cleared within 10 minutes |
| **Tenecteplase** | 3rd generation variant of alteplase molecule with *more fibrin specificity*, more resistant to plasminogen activator inhibitor-1 (PAI-1) with *longer duration of action* than alteplase | - Metabolized hepatically  
- Excreted renally  
- Half-life elimination (biphasic): Initial ~20-24 minutes; terminal ~90-130 minutes |
On-Going Tenecteplase Trials

**ATTEST-2**
- Tenecteplase superiority in thrombolysis up to 4.5 hrs

**TASTEa**
- Tenecteplase superiority in thrombolysis up to 4.5 hrs
- Thrombolytic administered in mobile stroke units

**NOR-TEST-2**
- Tenecteplase non-inferiority in thrombolysis up to 4.5 hrs
- Wake-up stroke patients within 4.5 hrs
- Utilizing 0.4mg/kg dosing

**TEMPO-2**
- Compared to antiplatelet agents
- Extended time window (Up to ~12 h) in NIHSS <6

**TIMELESS**
- Compared to placebo
- Extended time window from >4.5 to 24 hours

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Tenecteplase for thrombolysis in stroke patients: Systematic review with meta-analysis (clinicalkey.com)

https://www.clinicalkey.com/service/content/pdf/watermarked/1-s2.0-S0735675720311451.pdf?locale=en_US&searchIndex=
Thrombolytic Timing

- Administer as soon as possible after determining the patient is a candidate
- Give within 4.5 hours of symptom onset
  - Within 3 hours of symptom onset if NIHSS > 25
- Certified Stroke Center goal
  - 75% within 60 minutes of arrival at emergency department
  - 50% within 45 minutes of arrival at emergency department

TIME IS BRAIN!
Alteplase Administration

- Dilute alteplase powder with 100 mL sterile water using transfer device
  - Insert transfer device into sterile water
  - Do not invert sterile water – push alteplase vial on top of sterile water / transfer device
  - Invert vials so sterile water flows into alteplase vial
- Swirl gently to dissolve – DO NOT SHAKE
- Withdraw appropriate bolus dose in syringe

- Withdraw excess drug volume with syringe from vial
- Administer bolus over 1 minute
- Set up infusion portion: prime tubing, program pump, attach to patient
- Hang normal saline flush bag (50-100 mL) after alteplase infusion is nearly complete to deliver the full dose

https://www.activase.com/ais/dosing-and-administration/reconstituting.html
Tenecteplase Administration

- Dilute Tenecteplase powder with 10 mL sterile water
- Swirl gently to dissolve – DO NOT SHAKE
- Withdraw the appropriate volume for patient dose (max 25mg for ischemic stroke)
- Administer bolus over 5 seconds

Cost Implications

- Pricing depends on your institution
- May be some savings with tenecteplase
- Alteplase offers product replacement if drug is mixed but not administered
- Tenecteplase does not offer replacement for ischemic stroke since use is off-label

<table>
<thead>
<tr>
<th>Drug</th>
<th>U.S. Priced Intravenous Drug</th>
<th>Lexicomp</th>
<th>Drugs.com</th>
</tr>
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<tbody>
<tr>
<td>Alteplase</td>
<td></td>
<td>100 mg:</td>
<td>$10,560.43</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$7,462.63</td>
<td>$6,501.99</td>
</tr>
<tr>
<td>Tenecteplase</td>
<td></td>
<td>50 mg:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>$7,462.63</td>
<td></td>
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Alteplase: Drug information - UpToDate
https://www.uptodate.com/contents/alteplase-drug-information?search=alteplase&source=panel_search_result&selectedTitle=1~86&usage_type=panel&kp_tab=drug_general&display_rank=1#F16322973
Dosing Tools

- Dosing charts
- "Badge buddy" hang tag for RNs/pharmacists
- Double check dose with electronic order

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**TENECTEPLASE WEIGHT TIERED DOSING CHART FOR ACUTE ISCHEMIC STROKE**

[Using Concentration 50 mg / 10 mL TNK] = 5 mg per 1 mL

**Dosing for Ischemic Stroke** = 0.25 mg / kg, *Max dose of 25 mg*

<table>
<thead>
<tr>
<th>WT IN LBS</th>
<th>WT IN KG</th>
<th>BOLUS DOSE IN MG</th>
<th>BOLUS DOSE IN ML</th>
<th>AMOUNT TO DISCARD IN ML</th>
</tr>
</thead>
<tbody>
<tr>
<td>90</td>
<td>40.9</td>
<td>10.225</td>
<td>2.0</td>
<td>8.0</td>
</tr>
<tr>
<td>92</td>
<td>41.8</td>
<td>10.45</td>
<td>2.1</td>
<td>7.9</td>
</tr>
<tr>
<td>94</td>
<td>42.7</td>
<td>10.875</td>
<td>2.2</td>
<td>7.9</td>
</tr>
<tr>
<td>96</td>
<td>43.6</td>
<td>10.9</td>
<td>2.2</td>
<td>7.8</td>
</tr>
<tr>
<td>98</td>
<td>44.6</td>
<td>11.15</td>
<td>2.2</td>
<td>7.8</td>
</tr>
<tr>
<td>100</td>
<td>45.5</td>
<td>11.375</td>
<td>2.3</td>
<td>7.7</td>
</tr>
<tr>
<td>102</td>
<td>46.4</td>
<td>11.6</td>
<td>2.3</td>
<td>7.7</td>
</tr>
<tr>
<td>104</td>
<td>47.3</td>
<td>11.825</td>
<td>2.4</td>
<td>7.6</td>
</tr>
<tr>
<td>106</td>
<td>48.2</td>
<td>12.05</td>
<td>2.5</td>
<td>7.5</td>
</tr>
<tr>
<td>108</td>
<td>49.1</td>
<td>12.275</td>
<td>2.5</td>
<td>7.5</td>
</tr>
</tbody>
</table>

**TENECTEPLASE in Acute Stroke**

**BP Parameters:**
- Before administering bolus: 185/110, must be maintained before bolus given
- Post bolus (x24 hrs): 180/105
- *Notify provider if BP above parameters

**Recommended Dose:**
- *TOTAL Dose: 0.25mg/kg IV (Max: 25mg, or 5mL). There will always be waste using 50mg/10mL vial.

**Steps to Administer TENECTEPLASE:**
1. Determine total dose to be given: 0.25mg/kg (Max of 25mg, or 5mL).
2. Mix Tenecteplase per guidelines (50mg/10mL).
3. Prepare bolus: remove desired weight-based dose from vial.
4. Administer TNK IV bolus over 5 seconds.
5. Flush line with 10mL NS.

**Prior to TENECTEPLASE Administration**
Ensure the following:
- Blood sugar checked, not hypoglycemic
- BP within parameters
- NIHSS completed
- PT/INR and/or PTT resulted, within parameters (if applicable)
- Verbal consent for Tenecteplase obtained (by provider)

**Tenecteplase monitoring requirements:**
- Neuro Assessment (LOC/Orientation, Pupils, Motor strength, sensation, and speech, angioedema or other reaction) AND Vital Signs (BP, MAP, P, R, *O2 and Temp (q2hr24hr)) to be complete:
  - Within 15 minutes prior to administration of Tenecteplase bolus AND
  - Every 15 minutes x2 post bolus, THEN
  - Every 30 minutes x6, THEN
  - Every one-hour x 16h (total of 24 hours of monitoring)

*O2 to be maintained to 94% for acute stroke unless contraindicated.

**Non-intervention stroke patients:**
- Vital Signs: ES11: q30min; ES12: q15 min until stable, then q1h
- Neuro Assessments—Hourly (more frequently if unstable). Notify physician of changes in neuro condition.

*All suspected stroke or TIA patients must have a Modified Massey Dysphagia Screen completed before any PO intake, including medications. Be mindful that documentation time reflects the correct time of the screening. Consider performing dysphagia screening on any patient that gets a non-contrast head CT so appropriate patients aren’t missed.
Dosing Safety with Tenecteplase

- Tenecteplase box includes mixing instructions and myocardial infarction dosing on the inside flap.
- **Dosing for myocardial infarction and ischemic stroke differ.**

![Dosing Information Chart]

*From one vial of TNKase reconstituted with 10 mL SWFI.*
Dosing Safety with Tenecteplase

- Provide education on stroke dosing
- If using for stroke, provide dosing reminder on packaging
Monitoring after Thrombolytic Administration

- ICU admission for monitoring
- Maintain SBP < 180 and DBP < 105 during infusion and 24 hours post-infusion
- Neuro checks and vitals
  - Within 15 min prior to giving thrombolytic
  - Q15min during infusion
  - Q15min x 2 hours post-infusion
  - Q30min x 6 hours thereafter
  - Q1h until 24 hours post-infusion

Monitoring after Thrombolytic Administration

- Notify provider if any of the following occur:
  - Severe headache
  - Acute hypertension
  - Nausea or vomiting
  - Worsening neuro evaluation
  - Angioedema symptoms
- Obtain emergent head CT if any of the above symptoms occur

Management of Angioedema with Thrombolytic Administration

- Maintain airway
- Hold any ACE-inhibitor therapy
- Administer medications
  - Methylprednisolone 125 mg IV
  - Diphenhydramine 50 mg IV
  - Famotidine 20 mg IV
  - If angioedema increases, may administer Epinephrine 0.1% 0.3 mL subcutaneously or 0.5 mL inhaled via nebulizer
### Antithrombotic Therapy

- **Dysphagia (swallow) screen prior to any oral intake**
- **Antithrombotic therapy by end of hospital Day 2**
  - No thrombolytic given = start within 24 hours of onset of symptoms
  - **Thrombolytic given** = do **NOT** start within 24 hours of thrombolytic
    - Aspirin, Aggrenox, Plavix
- **Venous thromboembolism prophylaxis** – day of or day after admission
  - Pneumatic compression stockings
  - Benefit of prophylactic enoxaparin or subcutaneous unfractionated heparin is not well established
    - May increase risk of hemorrhage
    - **If used, must be 24 hours after thrombolytic complete**

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Conclusions

- Alteplase or tenecteplase can be considered within 4.5 hours of the onset of ischemic stroke symptoms if inclusion/exclusion criteria have been met.
- Patient selection should maximize benefit and minimize bleeding risk.
- Alteplase and tenecteplase have similar efficacy and safety profiles.
- Decision to administer thrombolytic should be shared between provider, patient, and/or family.
References

References

- *UpToDate.* (n.d.-b). UpToDate. [https://www.uptodate.com/contents/alteplase-drug-information?search=alteplase&source=panel_search_result&selectedTitle=1~86&usage_type=panel&kp_tab=drug_general&display_rank=1%E2%80%8B](https://www.uptodate.com/contents/alteplase-drug-information?search=alteplase&source=panel_search_result&selectedTitle=1~86&usage_type=panel&kp_tab=drug_general&display_rank=1%E2%80%8B)
- *UpToDate.* (n.d.). UpToDate. [https://www.uptodate.com/contents/tenecteplase-drug-information?search=tenecteplase&source=panel_search_result&selectedTitle=1~18&usage_type=panel&kp_tab=drug_general&display_rank=1#F23613417%E2%80%8B%E2%80%8B](https://www.uptodate.com/contents/tenecteplase-drug-information?search=tenecteplase&source=panel_search_result&selectedTitle=1~18&usage_type=panel&kp_tab=drug_general&display_rank=1#F23613417%E2%80%8B%E2%80%8B)
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