Timing and Choice of Fibrinolytic Agents in the Treatment of Acute Ischemic Stroke

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Speaker Disclosure

I have no financial relationships or affiliations to disclose.

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Objectives

- Differentiate between early and extended time windows for initiation of fibrinolytic therapy
- Compare alteplase and tenecteplase in the treatment of acute ischemic stroke
- Develop an appropriate treatment plan in the setting of acute ischemic stroke

Stroke Prevalence

Worldwide:

- 13 million people per year
- ~5.5 million deaths per year

United States:

- Stroke ranked 5th among all causes of death in 2019
- ~150,000 deaths per year

Alabama:

- Tied with MS for highest death rate (54.5%) in 2020

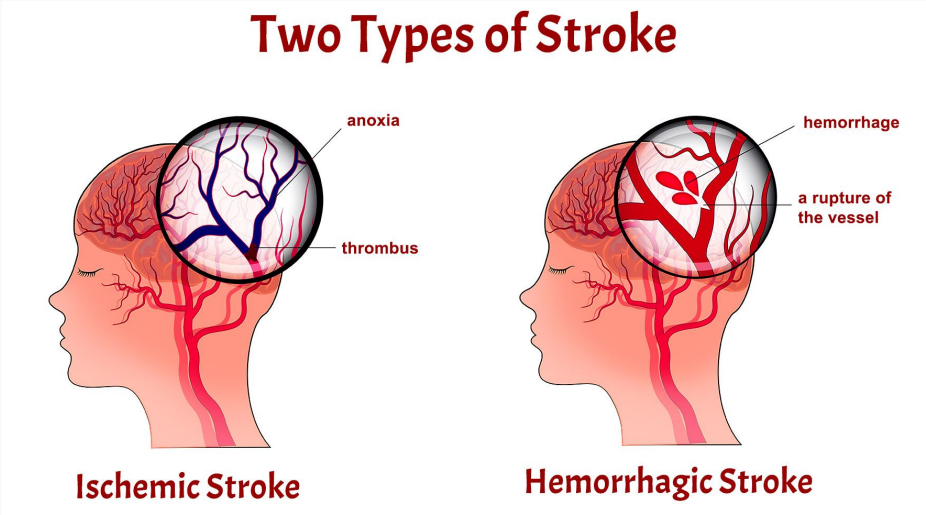
Common Stroke Types

Ischemic stroke:

- 87% of stroke cases

Hemorrhagic stroke:

- 13% of stroke cases



https://www.neofect.com/us/blog/what-are-the-different-types-of-stroke

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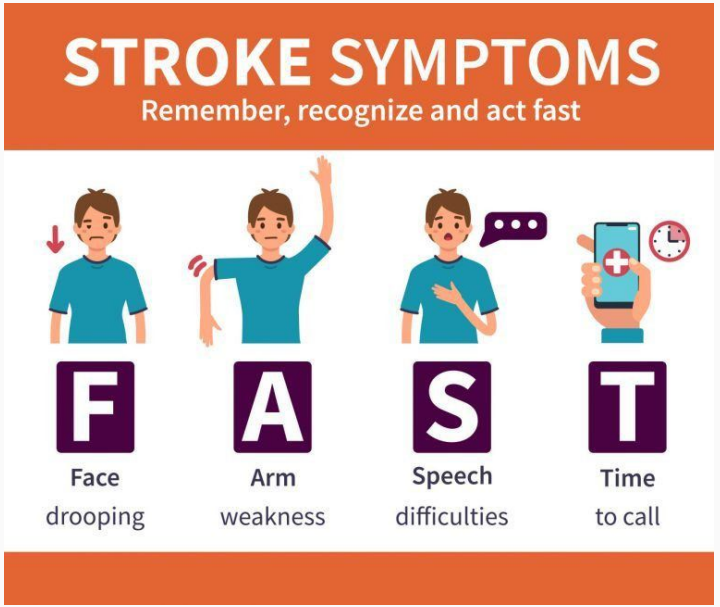
Clinical Presentation & Diagnosis

- Patients will present with acute onset of symptoms
- Key next steps
  - **Confirming diagnosis/ type of stroke**
  - **Last well known of patient**
- Noncontrast CT is needed to rule out intracranial hemorrhage (ICH)
- Time is brain



https://comprehensiveprimarycare.com/what-are-the-signs-of-a-stroke/

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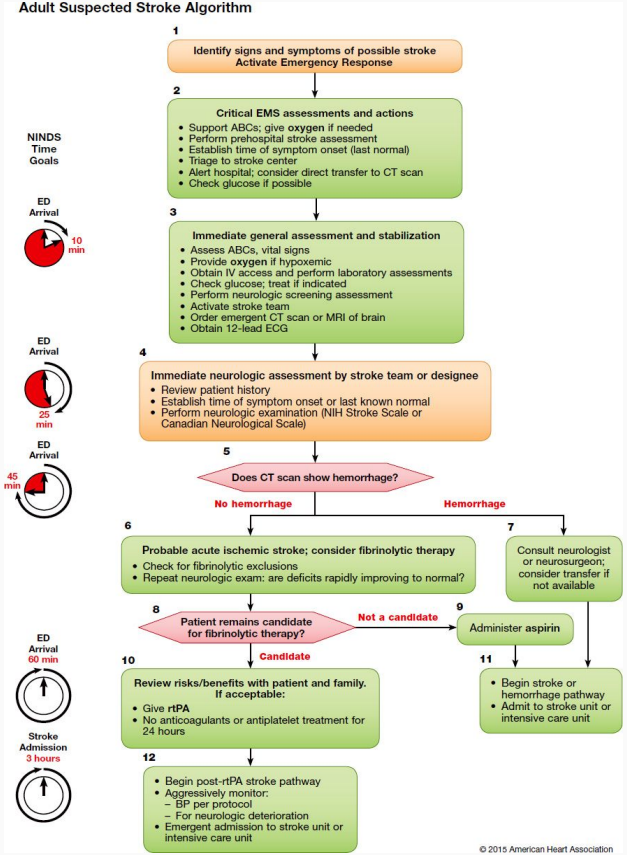
Time is brain



https://ebooks.heart.org/contentresolver/epub/50044708/OEBPS/Part5.html

Time Requirements (from arrival in ED)

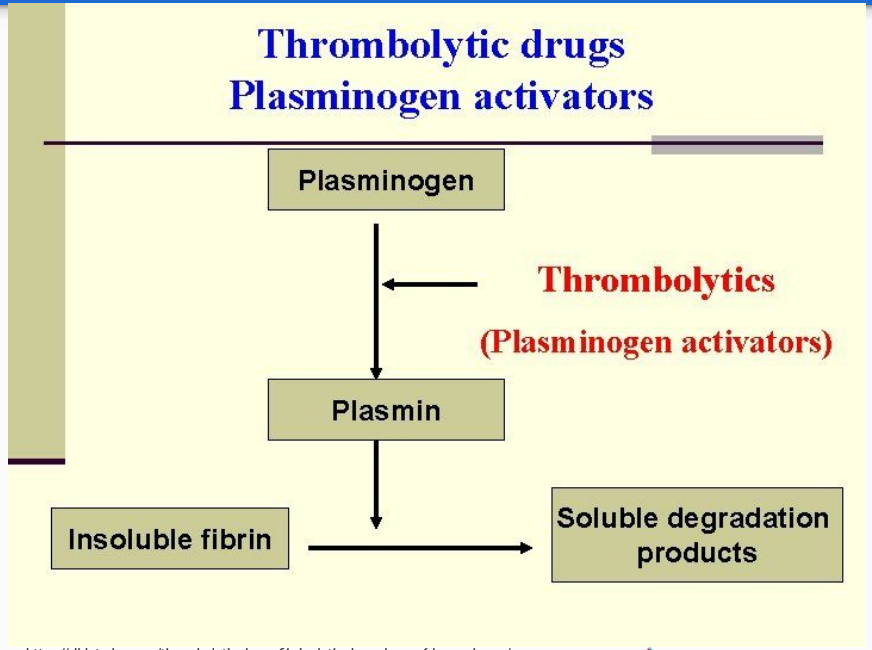
1. Within 10 minutes: initial assessment
2. Within 25 minutes: neurologic assessment
3. Within 45 minutes: hemorrhage present?
4. Within 60 minutes: begin treatment of stroke

Stroke Treatment Options

1. Fibrinolytics
2. Aspirin
3. Aspirin + clopidogrel
4. Mechanical thrombectomy

Fibrinolytics?

- Ex: alteplase and tenecteplase
- For eligible patients with an ischemic stroke
- MOA: binds to fibrin and converts plasminogen to plasmin which then breaks down the fibrin into soluble derivatives
- Major warning: bleeding



https://slidetodoc.com/thrombolytic-drugs-fibrinolytic-drugs-by-prof-hanan-hagar/

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Fibrinolytic Therapy

- Treatment option for eligible patients
- Eligibility requirements:
  - Clinical diagnosis of ischemic stroke
  - Onset of symptoms less than 4.5 hours
  - BP less than 185/110 mmHg

Contraindications for Fibrinolytics

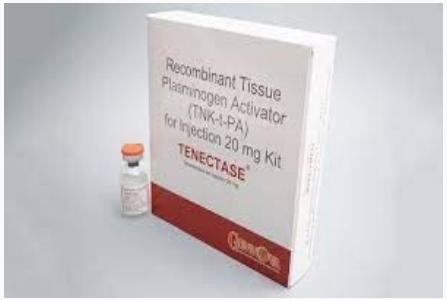
- Mild non-disabling stroke
- Ischemic stroke within 3 months
- Active or history of ICH
- Severe head trauma within 3 months
- Acute head trauma
- Intracranial/ spinal surgery within 3 months
- GI bleed within the previous 21 days
- Coagulopathy
- Full dose LMWH within the previous 24 hours
- DOAC within the previous 48 hours
- Infective endocarditis
- Aortic arch dissection
- Subarachnoid hemorrhage
- **Wake up stroke**

Wake Up Stroke

- Patient goes to bed fine and wakes up with stroke symptoms
- Their last well known time is unable to be calculated so we cannot administer a fibrinolytic

Alteplase and Tenecteplase

https://mms.mckesson.com/product/904182/Genentech-USA-50242008527



https://gennova.bio/tenectase/

- Currently alteplase is the only fibrinolytic that has an FDA approved indication for treatment of acute ischemic stroke
- Tenecteplase is used in acute ischemic stroke off label and is becoming the more desired agent

Alteplase vs Tenecteplase

Alteplase:

- Cost: 50 mg vial is $4,169.17, 100 mg vial is $8,338.34
- Dosing: 0.9 mg/kg (max dose of 90 mg)
- Administration: IV bolus 10% of total dose over 1 minute then continuous infusion of remaining over 60 minutes
- Dilution: compatible with normal saline or D5W

Tenecteplase:

- Cost: 50 mg vial is $6,564.22
- Dosing: 0.25 mg/kg (max dose of 25 mg)
- Administration: single IV bolus over 5 seconds
- Higher fibrin specificity compared to alteplase

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Fibrinolytic kits

Alteplase kit

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

Tenecteplase kit

https://americanhistory.si.edu/collections/search/object/nmah_1445209

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Monitoring of Fibrinolytics

Following administration of fibrinolytic

- Measure BP and perform neurological assessments Q15 min for 2 h, then Q30 min for 6 h, then hourly until 24 h after IV alteplase treatment.
- Obtain CT or MRI 24 hours after administration
- If patient develops severe headache, acute HTN, or worsening neurological examinations → d/c infusion and obtain emergency head CT scan

Last Well Known Window

Last Well Known

Within 3 hours

- Equally recommended for patients ≤ 80 or > 80 years of age
- Clinical benefit in severe stroke symptoms
- Mild but disabling stroke symptoms

3 hours to 4.5 hours

- Caution should be used in:
  - Older than 80 years of age
  - History of prior stroke and diabetes
  - Very severe stroke symptoms (NIHSS > 25)
  - Mildly disabling stroke

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NINDS Trial

National Institute of Neurological Disorders and Stroke

- Alteplase vs placebo (2 part study)
- Randomized, double blind, control trial
- Exclusion criteria: previous stroke, previous ICH, BP > 185/110, seizure at onset of stroke, and coagulopathies
- Part 1 included 291 patients
    - Primary outcome: whether t-PA had clinical activity, as indicated by an improvement of 4 points over baseline NIHSS score or resolution of neurologic deficit within 24 hours

- Part 2 included 333 patients
    - Primary outcome: assess clinical outcome at 3 months using the scores of different scales
- Administration method:
    - 3 hour treatment window
    - t-PA dose: 0.9 mg/kg (max 90 mg)
- Results:
    - Part 1: no significant difference in neurologic improvement at 24 hours
    - Part 2: t-PA group was at least 30% more likely to have minimal or no disability at 3 months
    - Occurence of ICH: 6.4% t-PA vs 0.6% placebo

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ECASS III Trial

- Alteplase vs placebo (821 patients)
- Randomized, placebo-controlled, phase 3 trial
- Administration between 3 hours and 4.5 hours after onset of ischemic stroke
- Pertinent exclusion criteria:
  - Greater than 80 years old
  - NIHSS score > 25 (severe stroke)
  - Prior stroke and history of DM
- Primary outcome: disability at 90 days
- Safety outcomes: death, ICH, and other serious adverse effects

- Results
  - Primary outcome: more favorable outcome at 90 days in the alteplase group (52.4% to 45.2%)
  - Higher incidence of ICH in alteplase group (27.0% to 17.6%)
  - Mortality did not differ between the two groups (7.7% t-PA vs 8.4 placebo)
- Conclusion
  - Alteplase administered between 3 and 4.5 hours after onset of symptoms significantly improved clinical outcomes in patients with acute ischemic stroke

Comparing Fibrinolytics

TASTE-A Trial

- Tenecteplase (0.25 mg/kg) vs Alteplase (0.9 mg/kg)
- Phase 2, randomized, open-label, blinded endpoint trial (104 patients)
- Administration of fibrinolytic within 4.5 hours of onset of ischemic stroke
- Primary outcome:
  - Volume of perfusion lesion on arrival after administration of fibrinolytic
- Secondary efficacy:
  - Percent reperfusion
  - Infarct core growth
  - Reduction in NIHSS

- Results
  - Perfusion lesion volume: alteplase 35 mL vs tenecteplase 12 mL
  - mRS of 5 to 6 at 90 days: alteplase 20% vs tenecteplase 15%
  - Death at 90 days: alteplase 10% vs tenecteplase 9%
  - 90 days serious adverse events: alteplase 8% vs tenecteplase 5%
- Conclusion
  - Treatment with tenecteplase resulted in superior rate of early reperfusion compared to alteplase, and no safety concerns were noted

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NOR-TEST 2 Part A

- Tenecteplase (0.4 mg/kg) vs alteplase (0.9 mg/kg)
- Phase 3, multicenter randomized, open label, blinded endpoint, non-inferiority trial
- Administration of a fibrinolytic within 4.5 hours of onset of symptoms
- Primary outcome:
  - Favorable functional outcome (mRS 0 to 1) at 3 months

- Secondary outcomes: efficacy and safety endpoints
- Trial was ended early due to safety review that showed an imbalance regarding the rate of symptomatic ICH
- Results
  - Any ICH: TNK 21% vs tPA 7%
  - Symptomatic ICH: TNK 6% vs tPA 1%
- Conclusion: tenecteplase of 0.4 mg/kg lead to worse safety and functional outcomes compared to alteplase

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Patient Case

Patient Case

https://healthcare.ascension.org/locations/alabama/albir/birmingham-ascension-st-vincents-birmingham

68 yo male presents to the ED at an Ascension emergency department with his wife at 1245.

- CC: slurred speech, facial droop, and loss of balance
- PMH: hypertension, dyslipidemia, COPD
- Wife states he was fine at breakfast and noticed his symptoms mid morning (around 1015)

What do we do next?

- What we know:
  - Symptoms are in line with an acute stroke
  - Last well known is at 2.5 hours
  - NIHSS score = 18
- What do we do next?
  A. Administer fibrinolytic
  B. Just monitor symptoms
  C. Send patient for CT scan of brain
  D. Administer aspirin + clopidogrel

Results and Next Step

- CT scan shows no hemorrhage, diagnose is acute ischemic stroke (30 minutes)
- Labs are within normal limits
- BP: 178/98 mmHg
- Decision is made to administer a fibrinolytic, what doses are appropriate? (Wt: 75 kg)
  A. Alteplase 68 mg (0.9 mg/kg)
  B. Alteplase 19 mg (0.25 mg/kg)
  C. Tenecteplase 68 mg (0.9 mg/kg)
  D. Tenecteplase 19 mg (0.25 mg/kg)

New Things Coming to Ascension St. Vincent's

- Tenecteplase is now the preferred drug of choice for the treatment of acute ischemic stroke

- Ascension St. Vincent's is in the process of becoming a certified Stroke Center

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