To tPA or not tPA

Disclosures

• None
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• Goals
• An analytical look at indications, warning and contraindications for alteplase

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• Strategy:
  • Make sure all reasonable cases can get Activase (Alteplase)
    • Alteplase is still only used in 5% of acute stroke cases
  • Contraindication should apply to situations where there is little or no clinical possible benefit
    • Known hazards
    • Not theoretical
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Age

- Age: older than 80
  - When compared to those younger patients
    - Lesser independence
    - Higher mortality
    - Greater chance of symptomatic ICH (sICH)
  - When compared to those who were treated to those not treated
    - Better outcomes (modified Rankin < 2) almost 2 x
    - Lesser mortality (OR 0.87)
    - Remains an increase sICH (OR 1.31)
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• Age: Pediatrics
  • Prothrombotic factors have greater role
    • 67% in newborns
    • >50% in infants and children
  • Other causes have greater importance
    • Vascular malformations
    • Congenital heart malformation
    • Infectious diseases
• Thrombolysis in Pediatrics (TIPS)
  • Stopped early due to lack of recruitment

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Table 11. Comparison of Stroke Diagnosis and Treatment Between Children and Adults

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Pediatric Population</th>
<th>Adult Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence of ischemic stroke</td>
<td>Lower 0.63–1.2/100,000, 1.2/100,000 per year</td>
<td>Higher, doubles for each decade after 55 y of age</td>
</tr>
<tr>
<td>Clinical presentation</td>
<td>Seizures, coma, and hemiparesis also common</td>
<td>Seizures or coma at onset is less common in adults</td>
</tr>
<tr>
<td>Stroke mechanism: prothrombotic factors</td>
<td>1/3 of stroke in newborns and 50% of stroke</td>
<td>Less common</td>
</tr>
<tr>
<td>Plasminogen levels</td>
<td>Reduced (neonates)</td>
<td>Normal</td>
</tr>
<tr>
<td>Response to tPA</td>
<td>Impaired (neonates), unknown efficacy</td>
<td>1/3 would have a better outcomes</td>
</tr>
<tr>
<td>Evidence of tPA</td>
<td>Limited to case reports or case series; no</td>
<td>6 RCTs and several observational studies</td>
</tr>
<tr>
<td>Dose of intravenous tPA</td>
<td>Unknown</td>
<td>0.9 mg/kg, 10% bolus</td>
</tr>
<tr>
<td>Legal framework</td>
<td>Off-label use</td>
<td>Approved for individuals ≥18 y of age</td>
</tr>
</tbody>
</table>

[^14]: American Heart Association; CHEST, American College of Chest Physicians; ESO, European Stroke Organisation; RCT, randomized, controlled trial; tPA, tissue-type plasminogen activator.
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• The initial study (NINDS trial): excluded patients > 80 yo
• Present AHA/ASA guidelines:
  • > 80 year olds
    • “...Older age is an adverse prognosticator but does not modify the treatment effect of thrombolysis...better chance of independence at 3 months” with treatment Class I; Level of Evidence (LoE) A
  • Pediatrics
    • Not recommended unless in a trial
      • “...not well established.” (Class IIb; LOE B)
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Stroke Severity

- Prior FDA labeling did recommend alteplase for
  - Minor stroke (NIHSS < 4)
  - Major stroke (NIHSS > 25)
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• Prior FDA labeling did recommend alteplase for
  • Major stroke (NIHSS > 25)
    • With 3 hrs. of symptom onset
    • Increase risk for sICH
    • “Based on available literature, there should no upper limit of NIHSS for patients
      • With in the 3 hr window
      • (Class I, LOE A)
    • It remains an exclusion for ECASS (3 to 4.5 hr window)

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• Prior FDA labeling did recommend alteplase for
  • Minor stroke (NIHSS < 4)
    • If considered disabling
    • Class I, LOE A
    • If not disabling...based on best clinical judgment
    • Class IIb, LOE C
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Rapidly improving

- One of the most common reasons for NOT giving alteplase
- Often misinterpreted exclusion
  - The original purpose was to exclude (in the original studies) those who have TIAs
  - Exclude those with "major, substantial improvements"
    - Who in the physician's "clinical judgement" will not be disabling
  - These lesions are dynamic
- Considered now to be reasonable
  - Class IIa, LOE A
To tPA or not tPA

- Rapidly improving
  - What about waiting to see if the patient continues to improve?
  - NIHSS of 20 to improve to 10
    - Is unlikely to completely resolve
  - Pure motor lacunar stroke (pons)
    - Frequently will progress
  - Delaying treatment anticipating further improvement is NOT recommended
    - Class III LOE C

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- What is a disabling stroke?

Table 12. Task Force Consensus: Definition and Clinical Context of Rapidly Improving Stroke Symptoms as an Exclusion Criterion for Intravenous Alteplase

<table>
<thead>
<tr>
<th>Improvement to a mild stroke such that any remaining deficits seem non-disabling</th>
</tr>
</thead>
<tbody>
<tr>
<td>The following typically should be considered disabling deficits:</td>
</tr>
<tr>
<td>Complete hemianopia (≥2 on NIHSS question 3) or severe aphasia (≥2 on NIHSS question 9), or</td>
</tr>
<tr>
<td>Visual or sensory extinction (≥1 on NIHSS question 11) or</td>
</tr>
<tr>
<td>Any weakness limiting sustained effort against gravity (≥2 on NIHSS question 6 or 7) or</td>
</tr>
<tr>
<td>Any deficits that lead to a total NIHSS score &gt;5 or</td>
</tr>
<tr>
<td>Any remaining deficit considered potentially disabling in the view of the patient and the treating practitioner. Clinical judgment is required.</td>
</tr>
</tbody>
</table>

NIHSS indicates National Institutes of Health Stroke Scale. Modified from Levine et al. 
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Time of onset

• 3 hrs.
  • Class I LOE A
• ECASS
  • 3 to 4.5 hrs. there are exclusions
    • >80 year of age
    • NIHSS > 25
    • More than 1/3rd of the MCA has early CT changes
    • DM AND prior stroke
    • Class I; LOE B
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• Time of onset
  • Cautionary notes
  • Don’t wait
    • Time to treatment is STRONGLY linked to outcome
    • Class I; LOE A
  • REMEMBER: Time is brain
    • Faster the better

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Pregnancy
To tPA or not tPA

• Pregnancy
  • Listed as a Category C
    • Potentially embryocidal at high doses
    • Animal studies at 1mg/kg there was no fetal toxicity
      • Alteplase at clinically relevant doses was not teratogenic

• Pregnancy
  • Minimal experience
    • 12 reported cases
      • 2 cases of systemic bleeding complications
        • 1 case of intrauterine bleeding – required surgical drainage and termination of pregnancy
        • 1 case of buttock bleeding treated conservatively and healthy infant
      • 2 fetal demise – (1 associated with a fatal sICH and spontaneous abortion)
    • 18 cases with thrombolysis for other indications
      • 1 additional serious bleeding – abruption utero with fetal demise
      • 2 cases

• Pregnancy
  • Listed as a Category C
    • Potentially embryocidal at high doses
    • Animal studies at 1mg/kg there was no fetal toxicity
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To tPA or not tPA

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    • 18 cases with thrombolysis for other indications
      • 1 additional serious bleeding – abruption utero with fetal demise
      • 2 cases
To tPA or not tPA

• Pregnancy
  • Alteplase administered for ischemic stroke
    • May be considered during pregnancy
    • For moderate to severe stroke
    • Outweighs the risks for bleeding or fetal survival
    • Class Iib; LOE C

• Early postpartum (<14 days)
  • Not well established
  • Class Iib; LOE C

• Urgent consult for GYN/OG and perinatologist is recommended
  • Class I; LOE C

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Coagulopathies
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• Labs test: INR > 1.7, elevated aPTT, platelet count of < 100,000 were removed
• Current AHA/ASA Guideline: “acute bleeding diathesis” as an exclusion. It does list as examples the following
  • Platelet count < 100,000
  • INR > 1.7
  • aPTT > 15 seconds
  • Not recommended
  • Class III; LOE C

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• The risk of finding in otherwise unsuspected patient (no history for a coagulopathy) is low
  • INR that were abnormal (0.4%)
  • Platelet < 100,000 (0.3%)
  • Not recommended to wait for these tests
  • Class IIa; LOE B
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• What about patients with a clinical history of potential bleeding diathesis or coagulopathy
  • Cirrhosis – liver failure
  • Sepsis
  • Congenital disorders
  • Hematological malignancies (leukemia)
  • Post-chemotherapy (<1 month)
  • Renal failure (abnormal platelet function)
  • Antiphospholipid antibody syndrome

To tPA or not tPA

• What about patients with a clinical history of potential bleeding diathesis or coagulopathy – for example:
  • Cirrhosis – liver failure
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  • Hematological malignancies (leukemia)
  • Post-chemotherapy (<1 month)
  • Renal failure (abnormal platelet function)
  • Antiphospholipid antibody syndrome
To tPA or not tPA

- What about patients with a clinical history of potential bleeding diathesis or coagulopathy
- Use of alteplase may be considered on a case to case bases
  - Class IIb; LOE C

To tPA or not tPA

- What about the use of alteplase with a history of OAC use?
- Warfarin use
  - INR < 1.7 may be reasonable – Class IIb; LOE B
  - INR > 1.7 NOT recommended – Class III; LOE B
- LMWH use
  - For prophylaxis and treatment doses
  - NOT recommended
  - Class III; LOE B
- NOACs – not recommended if used in 48 hrs
  - Class III; LOE C
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Major surgery
Trauma
TBI

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• Major surgery with 14 days
  • Lack of information
  • Case reports usually done within 3 months
    • Blepharoplasty
    • Helsinki Stroke Registry
      • 8 cases
To tPA or not tPA

• Major surgery with 14 days
  • AHA/ASA recommendation:
    • Alteplase may be given AFTER careful consideration of the potential increase risk of surgical site bleeding verses stroke related deficit
    • Class IIB; LOE C
  • May want to consider IA especially of there is an occlude major feeding vessel

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• Major trauma (Not TBI)
  • Mechanism of cerebral infarction (trauma related cases)
    • Dissection (carotid, vertebral arteries)
    • Compression of intracranial arteries (edema, blood, ICP)
  • AHA/ASA recommendation:
    • Alteplase may be given AFTER careful consideration of the potential increase risk of surgical site bleeding verses stroke related deficit
    • Class IIB; LOE C
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• Major TBI
  • Within 3 months
  • IV Alteplase is CONTRAINDICATED
  • Class IIb; LOE C

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Cardiac Conditions
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• Recent acute MI
  • Concurrent acute MI and stenting and ischemic stroke
  • IV Alteplase is reasonable
    • Class IIa; LOE C
  • IA would be favored

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• Recent acute MI
  • Acute ischemic stroke and non-STEMI MI within 3 months
    • Is reasonable
    • Class IIa; LOE C
  • Acute ischemic stroke and a STEMI MI (right sided or inferior wall)
    • Is reasonable
    • Class IIa; LOE C
  • Acute ischemic stroke and an anterior wall STEMI MI
    • MAY be reasonable
    • Class IIa; LOE C
  • Mechanical thrombectomy is favored
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• Pericarditis
  • From an MI
  • Urgent cardiology consultation
  • If the stroke disability will be major IV alteplase may be considered
    • Class IIb; LOE C
  • If the stroke disability will be moderated or minor IV alteplase has uncertain value
    • Class IIb; LOE C
  • Mechanical thrombectomy is favored

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• Left-sided thrombus
  • The presence of a high likelihood of a left heart thrombus
    • Mitral stenosis with AF
    • At risk for thrombus disintegration and early distal embolization and possible early (within 3 days) recurrent cerebral infarction
    • Thromboembolic complications – 1.5%
  • AHA/ASA recommendation are based on anticipated disability
    • If major then IV alteplase is reasonable – Class IIb; LOE C
    • If mild or moderate then uncertain – Class IIb; LOE C
  • Mechanical thrombectomy is favored
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• Bacterial endocarditis
  • IV alteplase is NOT recommended
  • Class III, LOE C
• Mechanical thrombectomy is favored but this approach may be too risky

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Intracranial or Spinal Surgery
To tPA or not tPA

• Intracranial or Spinal Surgery
  • If within 3 months
  • AHA/ASA recommendations IV alteplase
    • Potentially harmful
    • Class III; LOE C
  • Mechanical thrombectomy is favored

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Prior Stroke
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• Prior Stroke within 3 months
  • Trend for sICH
  • 2 case reports of alteplase given IV at 40 and 90 hrs. without sICH complication
  • AHA/ASA recommendation:
    • May be harmful – Class III; LOE C
    • Potential for sICH and death – Class IIb; LOE B
    • Potential risk should be discussed and weighted against anticipated benefits – Class I; LOE C
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GI Bleeding within 21 days

- Separates out
  - Active internal bleeding – a contraindication
  vs.
  - History of recent GI/GU bleeding (21 days)
    - Now there is no specific number of days
    - Reported literature – low bleeding risk with IV Alteplase
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- GI Bleeding within 21 days
  - AHA/ASA recommendations:
    - History of PAST GI/GU bleeding may be reasonable – Class IIb; LOE C
    - Structural GI malignancy, or recent bleeding event with 21 days of the stroke
      - Considered high risk and potentially – Class III; LOC

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- Arterial puncture at a non-compressible vessel within 7 days
  - It is considered a contraindication – was a consensus opinion
  - Most likely case scenarios
    - Subclavian or internal jugular catheterization
    - Dialysis
    - Pacing
    - Transcatheter heart valve placement
      - These patients are generally sicker
      - The risk benefit needs to be considered
  - AHA/ASA recommendation:
    - Safety is uncertain – Class IIb; LOE C
    - Mechanical thrombectomy may be an option
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Uncontrolled hypertension

- Uncontrolled hypertension
  - Uncontrolled or severe hypertension
    - Defined as SBP > 185, DBP > 110 on ≥ 2 measurements
    - Common exclusion
      - There is a correlation with higher the BP the greater the sICH risk
  - How low?
    - There is a correlation with lower BP and poorer outcomes
      - ENCHANTED Study (in progress)
To tPA or not tPA

- Uncontrolled hypertension
  - AHA/ASA recommendations
    - IV alteplase is **recommended** for patients SBP and DBP are < 185 and 110 respectively the BP should be stabilized – Class I LOE B
    - If medication is needed to lower BP the BP should be **stabilized** and should be maintained at the lower level for the first 24 hours after IV alteplase – Class I; LOE B

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History of Intracranial Hemorrhage
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• History of Intracranial Hemorrhage
  • Cerebral microbleeds (CMB)
  • CMB is not the same as ICH
  • Cause is not known – possible causes
    • Reperfusion injury
    • Disrupted autoregulation
    • No substantial increase in sICH

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• History of Intracranial Hemorrhage
  • Individual cases reports of alteplase was given to patients with a past history of ICH
    • Results were mixed
    • One case had a recurrence of ICH
    • Another case without recurrence of ICH
To tPA or not tPA

- History of Intracranial Hemorrhage
  - IV alteplase in patients with a history of CMH
    - Is considered reasonable
    - Class IIa; LOE B
  - IV alteplase in patients with a history of ICH
    - Is potentially harmful
    - Class III; LOE C

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Unruptured Intracranial Aneurysm
Intracranial Vascular Malformation
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- **Unruptured** Intracranial Aneurysm
  - 2 to 3% occurrence in the general population
  - Once case series: 22 cases
  - Similar ICH risk for these patients
  - No data on the size

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- **Unruptured** Intracranial Aneurysm

  - AHA/ASA recommendations:
    - For patients with small or moderate size (<10mm) aneurysm
      - Is reasonable
      - Class IIa; LOE C
    - For patients with a large (>10mm) aneurysm
      - Is not established
      - Class IIb; LOE C
To tPA or not tPA

- Intracranial Vascular Malformations
- AHA/ASA recommendations:
  - Patient presenting with acute ischemic stroke who also has an intracranial vascular malformation. The risk benefit is not established
    - Class IIb; LOE C
  - Patients with similar vascular malformation who has an acute large stroke. The mortality and morbidly risk is high if nothing is done. Alteplase may be considered.
    - Class IIb; LOE C

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Intracranial Neoplasms
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• Intracranial Neoplasms

• Split brain tumor into
  • Intra-axial (i.e. glioblastoma)
  • Extra-axial (acoustic neuroma, meningioma)

• AHA/ASA recommendation:
  • Extra-axial tumors is probably recommended
    • Class IIa; LOE C
  • Intra-axial tumors is potentially harmful
    • Class III; LOE C
To tPA or not tPA

- Serious Comorbid Illnesses
  - Dementia
    - Generally associated with worse outcomes
    - Potential for ICH because of
      - Amyloid angiopathy
      - Microbleeds
  - Malignancy
    - There is no specific contraindication
    - Generally in case reports there isn't an increase sICH
  - Recrudescence
    - Patients with past stroke who develop may develop the old symptoms/signs with the development of AKI, hypo/hyper glycaemia, systemic infection etc

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- AHA/ASA Recommendations:
  - ESRD on HD and normal PT and APTT is recommended Class I; LOE C
  - Pre-existing dementia may benefit BUT should also consider life-expectancy and premorbid level of functioning Class IIb; LOE B
  - Safety of alteplase with current malignancy is not studied
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Preexisting Disability

• Preexisting Disability
  • With the aging population, preexisting disability (modified Rankin > 2) is an independent predictor for
    • Worse outcomes – more likely to have a worse outcome
      • Modified Rankin > 3 more likely to die after receiving alteplase
    • Longer length of stays
    • Does not increase risk for sICH after alteplase
      • Demonstrate less neurological improvement
To tPA or not tPA

• Preexisting Disability
  • Nursing home residents
    • Use of alteplase is controversial
    • Implies a level of preexisting dependence
    • Lower likelihood to receive alteplase
  • Life expectancy < 12 months
    • May have malignancy or metastatic cancer
  • Preexisting neurological or psychiatric disorders
    • At a greater risk for a stroke mimic

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• Preexisting Disability
  • AHA/ASA recommendations:
    • Alteplase may be reasonable BUT decisions should take into account "relevant" factors
    • Class IIb; LOE b
  • Relevant factors are the following
    • Quality of life
    • Social support
    • Place of residence
    • Caregiver need
To tPA or not tPA

• Blood Glucose (BG)
  • BG should be between 50 to 400
  • Low BG <1% of contraindications
    • Low BG may mimic a stroke
  • High BG >400
    • May also mimic stroke

To tPA or not tPA

• Blood Glucose (BG)
• AHA/ASA recommendations
  • Alteplase is recommended for patients wit BG >50 or <400
    • Class I; LOE A
  • Caution with hypoglycemia or hyperglycemia. Alteplase is NOT indicated for patients with a BG > 50
    • Class III; LOE B
  • Patients with reporting BG >400
    • May be reasonable
    • Class IIb; LOE C
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• The initial study (NINDS trial): would exclude patients who had a seizure upon presentation
  • Concern about post-ictal neurological deficits
    • Class IIa; LOE C

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Special circumstances
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• Special circumstances
  • Early ischemic changes (EIC)
    • Defined as parenchymal hypodensity or focal edema or mass effect
    • Represents decrease in X-ray attenuation
      • A marker of irreversible brain damage
    • EIC on plan CT if > 1/3rd MCA – alteplase is contraindicated
    • If EIC is < 1/3rd MCA then alteplase increases the odds of good outcome
      • OR 3.43
    • In practice this >1/3rd MCA rule is hard to apply
    • ASPECTS (Alberta Stroke Program Early CT Score)

• ASPECTS (Alberta Stroke Program Early CT Score)
  • Initially scores 7
  • Scores > 7 was associated with a trend for reduced mortality

• The final word is neither the 1/3rd rule or ASPECTS could establish a clear and certain threshold below which IV alteplase have no effect (when given within 3 hrs)
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- Special circumstances
  - AHA/ASA recommendation - Early ischemic changes (EIC)
    - IV alteplase is recommended if EICs are mild to moderate (other than frank hypodensity)
      - Class I; LOE A
    - There is insufficient evidence for a specific threshold of hypodensity severity or extent which affects treatment response to alteplase. If there is extensive regions of clear hypodensity IV alteplase in NOT recommended. These patients have poor outcomes.
      - Class III; LOE A

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- Special circumstances
  - Diabetic retinopathy
    - Should not be considered an absolute contraindication for IV alteplase
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• Special circumstances
  • AHA/ASA recommendation – diabetic retinopathy
    • History of diabetic retinopathy or other hemorrhagic conditions is reasonable to recommend IV alteplase BUT there is potential for increased vision loss. One needs to weight the potential benefits of decrease neurological disability vs vision loss
      • Class IIa; LOE B

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• Special circumstances
  • Suspicion of SAH
    • In 2013 guidelines was an exclusion
  • Now list SAH as an exclusion
  • Work up for a possible aneurysm
    • CTA or MRA
    • LP is not recommended (would exclude IV alteplase)
  • AHA/ASA recommendation
    • IV alteplase is contraindicated in patients with S/S most consistent with SAH
      • Class III; LOE C
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• Special situations – Menstruation and Menorrhagia

• IV alteplase is
  • Probably indicated menstruating patient presenting with AIS. The patient should be warned of likely increase in menstrual flow
    • Class IIa; LOE C
  • Patients with menorrhagia with non-critical anemia or hypotension likely will benefit from IV Alteplase
    • Class IIb; LOE C

• Patient with active vaginal bleeding with significant anemia an urgent GYN consultation is indicated
  • Class IIa; LOE C

• Patients given IV alteplase who have active vaginal bleeding should be monitored for 24 hrs
  • Class I; LOE C
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- Special situations – Intracardiac Mass
  - Myxomas are the most common
    - IV alteplase may be reasonable in patient likely to have severe disability
    - Class IIb; LOE C
  - Fibroelastoma
    - IV alteplase may be reasonable in patients likely to have severe disability
      - Class IIb; LOE C

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Warning and Precautions
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- Warning and precautions:
  - A set of adverse reactions (AR) and other potentially safety hazards
  - Serious
  - Clinically significant which will affect patient management
  - These AR should have at least a causal relationship
    - Need not be definitive

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- New Section: Oral Lingual Angioedema
  - Physicians who prescribe alteplase should be prepared to treat
    - Bleeding complication
    - Angioedema – may cause airway obstruction
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- Patient who received alteplase
- Had left sided weakness

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- Oral lingual angioedema – mechanism
  - The increase in plasmin may play a role in the development of angioedema by activating the kinin pathway and leading to the formation of the vasodilator bradykinin.
  - Plasmin also activates the complement system and leads to the production of the anaphylaxis C3a, C4a, and C5a, which also cause mast cell degranulation and histamine release.
  - The lateralization of the edema was hypothesized to be due to the loss of autonomic innervation of that side.
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- Oral lingual angioedema – who are at risk
  - Previously treatment with alteplase
  - Currently on ace inhibitors
  - Hereditary deficiency in C1-esterase

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- Oral lingual angioedema – treatment
  - Intubation
  - Steroids
  - Ranitidine
  - Diphenhydramine
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