Updated IV tPA Inclusion and Exclusion Criteria: the Scientific Evidence

Christopher Streib, MD, MS
Stroke Operations Director
University of Minnesota
Disclosures

- I have no financial relationships or other conflict of interests to disclose, and I will not discuss off label use and/or investigational use in my presentation
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Disclosures
Abbreviations Used

• AIS – acute ischemic stroke
• ICH – intracranial hemorrhage
  • sICH – symptomatic ICH
• IV tPA – intravenous tissue plasminogen activator
• NIHSS = NIH stroke scale
• TLSW – time last seen well (stroke onset time)
Objectives

1. Rationale for thrombolysis
2. History of IV tPA
3. Major recent revisions to the IV tPA inclusion-exclusion criteria
4. Additional relevant topics and common misconceptions
5. Summary
IV tPA Mechanism

- Fibrin stabilizes thrombus
- tPA activates conversion of Plasminogen to Plasmin resulting in Fibrin degradation
- tPA is selectively activated by Fibrin
Rationale for Thrombolysis

- At the onset of stroke symptoms, the stroke is evolving
- Rapid clot lysis reperfuses ischemic tissue limiting the eventual size of the infarct.
**Historical Context**

- **1960s-70s**: IV Thrombolysis tried in AIS, abandoned due to high rates of sICH
- **1972**: CT scan invented by Hounsfield and McCormack
- **1980s**: CT technology improved and becomes more widespread
- **1980s**: Early case series of IV thrombolysis
- **1990s**: Heterogeneous failed thrombolytic stroke trials with various agents, doses, time limits and protocols
- **1995**: NINDS IV tPA Trial
- **2008**: ECASS-III (4.5 hour time window)
- **Present**: Registry data and ongoing studies confirm consistent benefit of IV tPA for acute ischemic stroke
TPA for Cerebral Ischemia within 3 Hours of Onset-Changes in Outcome Due to Treatment

Changes in final outcome as a result of treatment:
- Normal or nearly normal
- Better
- No major change
- Worse
- Severely disabled or dead

Early course:
- No early worsening with brain bleeding
- Early worsening with brain bleeding
IV tPA in Acute Ischemic Stroke

- Received tPA: 4%
- Viable exclusion: 12%
- Hospital failure: 7%
- Overnight stroke: 8%
- Patient delay: 69%

Source: Neurology 2005;64;654
IV tPA Inclusion Criteria

• Diagnosis of ischemic stroke causing measurable neurological deficit
• Onset of symptoms < 3 hours before beginning treatment
  – or < 4.5 hours with stricter exclusion criteria
• Age ≥ 18 years
IV tPA Exclusion Criteria

- Significant head trauma or prior stroke in the previous 3 months
- Arterial puncture at non-compressible site in previous 7 days
- History of previous ICH or symptoms suggesting SAH
- Intracranial neoplasm, arteriovenous malformation, or aneurysm
- Recent intracranial or intraspinal surgery
- Elevated blood pressure (SBP >185 mm Hg or DBP >110 mm Hg)
- Active internal bleeding
- Platelet count <100,000
- Heparin within 48 hours with elevated aPTT
- Current use of anticoagulant with INR >1.7 or PT >15 seconds
- Use of direct thrombin inhibitors or direct factor Xa inhibitors
- Blood glucose concentration <50 mg/dL or > 400mg/dl
- CT demonstrates “large” infarction

IV tPA Relative Exclusion Criteria

• Minor or rapidly improving stroke symptoms
• Pregnancy
• Seizure at onset
• Major surgery or serious trauma within 14 days
• GI or urinary tract hemorrhage within 21 days
• Acute myocardial infarction within 3 months
  – Cardiac rupture leading to hemopericardium/tamponade

IV tPA Exclusion Criteria
4.5 HR window

- Age > 80 years
- Severe stroke (NIHSS > 25)
- Any anticoagulation regardless of INR
- History of both DM and prior ischemic stroke

Exclusion Criteria Origins

1. NINDS IV tPA Trial (many exclusions are untested, historical)
2. Avoid treating stroke mimics (i.e. seizure)
3. Avoid causing harm in patients with minor stroke
AHA Scientific Statement 2016*

• Comprehensive review of published evidence for IV tPA exclusion criteria in order to:
  1. Simplify IV tPA administration
  2. Assess validity of historical exclusion criteria
  3. Expand population of eligible stroke patients
  4. Inform physicians and patients of true risk vs. benefit

*http://stroke.ahajournals.org/content/strokeaha/47/2/581.full.pdf
## Grading the Evidence

<table>
<thead>
<tr>
<th><strong>SIZE OF TREATMENT EFFECT</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CLASS I</strong></td>
</tr>
<tr>
<td>Benefit &gt;&gt; Risk</td>
</tr>
<tr>
<td>Procedure/Treatment SHOULD be performed/administered</td>
</tr>
<tr>
<td><strong>PROCEDURE/TREATMENT MAY BE CONSIDERED</strong></td>
</tr>
</tbody>
</table>

### LEVEL A

- **Multiple populations evaluated***
- Data derived from multiple randomized clinical trials or meta-analyses

- Recommendation that procedure or treatment is useful/effective
- Sufficient evidence from multiple randomized trials or meta-analyses

- Recommendation in favor of treatment or procedure being useful/effective
- Some conflicting evidence from multiple randomized trials or meta-analyses

- Recommendation’s usefulness/efficacy less well established
- Greater conflicting evidence from multiple randomized trials or meta-analyses

### LEVEL B

- **Limited populations evaluated***
- Data derived from a single randomized trial or nonrandomized studies

- Recommendation that procedure or treatment is useful/effective
- Evidence from single randomized trial or nonrandomized studies

- Recommendation in favor of treatment or procedure being useful/effective
- Some conflicting evidence from single randomized trial or nonrandomized studies

- Recommendation’s usefulness/efficacy less well established
- Greater conflicting evidence from single randomized trial or nonrandomized studies

### LEVEL C

- **Very limited populations evaluated***
- Only consensus opinion of experts, case studies, or standard of care

- Recommendation that procedure or treatment is useful/effective
- Only expert opinion, case studies, or standard of care

- Recommendation in favor of treatment or procedure being useful/effective
- Only diverging expert opinion, case studies, or standard of care

- Recommendation’s usefulness/efficacy less well established
- Only diverging expert opinion, case studies, or standard of care

<table>
<thead>
<tr>
<th><strong>COR III: No benefit or Harmful</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Procedure/ Test</td>
</tr>
<tr>
<td>Excess Cost w/o Benefit or Harmful</td>
</tr>
</tbody>
</table>

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*For visualization purposes, it is important to note that the image captures the text-based grading system for the evidence, emphasizing the level of certainty (or precision) in treatment effect.**
1. Age

International Stroke Trial III (IST-III)

• RCT of IV-tPA from 0-6 hours of stroke onset
• Designed to expand indications for IV tPA
  – “Uncertainty principle”
• Prior to IST-III, only 79 patients > 80 yo had been enrolled in RCT trials of thrombolysis
  – 1616 patients > 80 yo in IST-3

**International Stroke Trial III**

### Table A

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Number of patients</th>
<th>Adjusted Odds Ratio (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>rt-PA</td>
<td>Control</td>
</tr>
<tr>
<td>Time to randomisation (hours)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤3</td>
<td>431</td>
<td>418</td>
</tr>
<tr>
<td>&gt;3, ≤4.5</td>
<td>577</td>
<td>600</td>
</tr>
<tr>
<td>&gt; 4.5</td>
<td>507</td>
<td>500</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18-60</td>
<td>157</td>
<td>172</td>
</tr>
<tr>
<td>61-70</td>
<td>188</td>
<td>177</td>
</tr>
<tr>
<td>71-80</td>
<td>353</td>
<td>371</td>
</tr>
<tr>
<td>81-90</td>
<td>706</td>
<td>701</td>
</tr>
<tr>
<td>≥90</td>
<td>111</td>
<td>99</td>
</tr>
</tbody>
</table>

Older Age and IV tPA

- Benefit of reperfusion in the elderly has been shown consistently in IV tPA and endovascular trials.
- Older patients may be more dependent upon reperfusion due to limited cerebrovascular reserve.
- **Please do not withhold acute stroke treatment based upon age alone.**
- Medically eligible older patients should receive IV tPA (*Class I, Level A*)
2. Severe Stroke

• Use IV tPA “with caution” in patients with NIHSS > 22
  – due to higher rates of ICH, however, ICH more common in severe stroke with or without IV tPA
  – there is still a clear benefit for IV tPA in this subgroup

• Caveat: severe stroke defined radiographically carries different risks

• For stroke with severe clinical deficits, IV tPA is indicated. Despite increased risk of ICH, there is still proven clinical benefit (Class I, Level A)
Severe Stroke: Early Ischemic Change (EIC)

• Early ischemic change on Head CT has considered a relative contraindication
• No clear threshold to withhold IV tPA
• IV tPA is recommended in setting of EIC with exception of frank hypodensity *(Class I, Level A)*
• IV tPA for patients whose CT exhibits extensive regions of clear hypoattenuation is not recommended. Obvious hypodensity represents irreversible injury *(Class III, Level A)*
Severe Stroke: Malignant Profile

• Definition: Pre-treatment imaging pattern associated with sICH and poor outcome with reperfusion

• There are multiple definitions:
  1. “1/3 of the MCA territory” on Head CT
  2. Multiphase CT Angiography “poor” collateral score
  3. CT Perfusion with extensive hypoperfusion

• Malignant profile may exclude otherwise eligible patients from IV tPA/endovascular treatment
Example: Malignant Profile

- 24 yo with right ICA occlusion, NIHSS = 17
- 2 ½ hours from stroke onset
- ASPECTS: 3, plus anterior ACA territory shows early infarct
Malignant Profile: CT Perfusion

- Core infarct: 110cc
- Penumbra: 190cc
- Severe Hypoperfusion: 200cc
- IV tPA infusion had already been started
  - Infusion stopped
  - Early craniectomy for malignant cerebral edema
Malignant Profile: IV tPA

- Two trials, DEFUSE and EPITHET, assessed IV tPA in 3-6 hour window with baseline perfusion imaging
- Malignant profile: Hypoperfusion > 85cc tissue or core infarct > 80cc
- Without malignant profile reperfusion leads to good outcomes
- Malignant profile: reperfusion leads to bad outcomes
  - 89% with reperfusion vs. 39% w/o reperfusion
  - 67% parenchymal hematoma with reperfusion vs. 11% w/o reperfusion

Severe Stroke Summary

1. The clinical severity (NIHSS) alone is not a contraindication to IV tPA

2. Radiographic early ischemic change other than frank hypodensity does not contraindicate IV tPA
   - Frank hypodensity increases risk of sICH and calls into question the actual stroke onset time

3. Malignant profile as defined by frank hypodensity, edema, absent collateral circulation, or hypoperfusion volume may be a contraindication*
3. Minor & Improving Stroke

- There is no consensus about a lower limit, but many centers do not treat NIHSS ≤ 4 with IV tPA
- 1/3 of eligible patients not given IV tPA due to “mild symptoms”
- NIHSS is a crude tool, a better question is:
  - *Is this neurologic deficit disabling?*
- Exceptions to low NIHSS: aphasia, visual or sensory extinction, any weakness limiting effort against gravity, deficits that don’t score on NIHSS
Case 1: Minor Stroke

• 50 year old right-handed male with sudden onset weakness of the right wrist and complete paralysis of right hand
• NIHSS = 0
• Car mechanic => reliant on his hand dexterity
• Consented for and received IV tPA with a full recovery
Case 2: Minor Stroke

- 62 yo healthy female
- Presented with NIHSS = 1 for difficulty speaking (expressive aphasia)
- Did not receive IV tPA because symptoms were “mild” and improving
Three Month Follow-up

• Her aphasia was stable, she continued to have difficulty with word finding and speech
• She no longer socialized with her friends, her quality of life was severely impacted
• “I used to be known for my outgoing personality, now it’s so hard for me to talk”
Too Good to Treat?

Table 2. Discharge Outcomes According to Stroke Severity for Patients With Mild or Improving Stroke

<table>
<thead>
<tr>
<th>Mild/Improving Stroke, NIHSS Score</th>
<th>Discharge Destination</th>
<th></th>
<th>Ambulatory Status at Discharge</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>Not Discharged Home</td>
<td>Percent</td>
</tr>
<tr>
<td>0</td>
<td>3229</td>
<td>500</td>
<td>15.5</td>
</tr>
<tr>
<td>1</td>
<td>2932</td>
<td>535</td>
<td>18.2</td>
</tr>
<tr>
<td>2</td>
<td>3100</td>
<td>735</td>
<td>23.7</td>
</tr>
<tr>
<td>3</td>
<td>2475</td>
<td>715</td>
<td>28.9</td>
</tr>
<tr>
<td>4</td>
<td>1682</td>
<td>596</td>
<td>35.4</td>
</tr>
<tr>
<td>5</td>
<td>1045</td>
<td>411</td>
<td>39.3</td>
</tr>
<tr>
<td>6–10</td>
<td>2338</td>
<td>1074</td>
<td>46.0</td>
</tr>
<tr>
<td>&gt;10</td>
<td>1266</td>
<td>729</td>
<td>57.6</td>
</tr>
</tbody>
</table>

Stroke patients with NIHSS=0 had either imaging evidence of infarction or stroke symptoms not quantifiable on the NIHSS. Outcomes were strongly associated with initial NIHSS score (P<0.001).

NIHSS indicates National Institutes of Health Stroke Scale.

Smith et al. Outcomes in Mild or Rapidly Improving Stroke not Treated with tPA. Stroke 2011
## sICH Risk in Mild Stroke

<table>
<thead>
<tr>
<th>Authors</th>
<th>Study</th>
<th>Definition</th>
<th># of Pts</th>
<th>sICH</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urra, 2013¹</td>
<td>Single-center, prospective</td>
<td>NIHSS ≤5</td>
<td>119</td>
<td>0</td>
<td>0–3.1</td>
</tr>
<tr>
<td>Greisenegger, 2014²</td>
<td>National registry</td>
<td>NIHSS ≤5</td>
<td>445</td>
<td>11 (2.4%)</td>
<td>1.3–4.5</td>
</tr>
<tr>
<td>Huisa, 2012³</td>
<td>Single-center, prospective</td>
<td>NIHSS ≤5</td>
<td>59</td>
<td>3 (5%)</td>
<td>1–15</td>
</tr>
<tr>
<td>Hassan, 2010⁴</td>
<td>Single-center, retrospective</td>
<td>NIHSS &lt;7</td>
<td>27</td>
<td>0</td>
<td>0–12</td>
</tr>
<tr>
<td>Steffenhagen, 2009⁵</td>
<td>National, prospective</td>
<td>NIHSS ≤5</td>
<td>77</td>
<td>2 (2.6%)</td>
<td>0.8–9</td>
</tr>
<tr>
<td>Kohrmann, 2009⁶</td>
<td>Single-center, prospective</td>
<td>MD judgment</td>
<td>32</td>
<td>0</td>
<td>0–11</td>
</tr>
<tr>
<td>Gonzales, 2006⁷</td>
<td>Single-center, retrospective</td>
<td>NIHSS &lt;8</td>
<td>146</td>
<td>3 (2.1%)</td>
<td>0.7–6</td>
</tr>
<tr>
<td>Baumann, 2006⁸</td>
<td>Single-center, prospective</td>
<td>NIHSS range was 1–6</td>
<td>19</td>
<td>0</td>
<td>0–17</td>
</tr>
<tr>
<td>NINDS, 1997, 2010⁹,¹⁰</td>
<td>Clinical trial</td>
<td>NIHSS ≤5</td>
<td>42</td>
<td>1 (2.4%)</td>
<td>0.6–12</td>
</tr>
<tr>
<td>Romano, 2014¹¹</td>
<td>National registry</td>
<td>NIHSS ≤5</td>
<td>5910</td>
<td>109 (1.8%)</td>
<td>NA</td>
</tr>
</tbody>
</table>

Outcomes for Minor Stroke Treated with IV tPA

Oxfordshire Handicap Score (OHS) at 6 Months

Control Arm (n=51)
- OHS 0: 16%
- OHS 1: 35%
- OHS 2: 14%
- OHS 3: 14%
- OHS 4: 10%
- OHS 5: 6%
- OHS 6: 6%

IV rt-PA Arm (n=55)
- OHS 0: 25%
- OHS 1: 35%
- OHS 2: 24%
- OHS 3: 13%
- OHS 4: 2%

Figure. Distributions of clinical outcomes in International Stroke Trial (IST)-3 mild stroke subcohort. IV r-tPA indicates intravenous recombinant tissue-type plasminogen activator.
Mild and Rapidly Improving Stroke

• For patients with mild, but disabling symptoms there is proven benefit *(Class I, Level A)*

• For treatment with mild, but non-disabling symptoms, IV tPA may be considered *(Class IIb, Evidence C)*

• IV tPA is indicated for rapidly improving symptoms, whose deficits remain disabling *(Class IIa, Level A)*

• Delaying treatment to monitor for improvement is not recommended *(Class III, Level C)*
4. Stroke Mimics

- Seizure: 38%
- Migraine: 37%
- Conversion disorder: 21%
- Aseptic meningitis: 1%
- Epidural spinal mass: 1%
- Heat stroke: 1%
- Syncope/VT: 1%
## IV tPA in Stroke Mimics

<table>
<thead>
<tr>
<th>Study</th>
<th>Total Patients</th>
<th>Neuro Imaging negative</th>
<th>Stroke Mimics</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Winkler et al. Stroke 2009</td>
<td>250</td>
<td>7 (2.8%)</td>
<td>7 (2.8%)</td>
<td>0</td>
</tr>
<tr>
<td>Chernyshev et al. Neurology 2010</td>
<td>512</td>
<td>107 (20.8%)</td>
<td>71 (13.8%)</td>
<td>0</td>
</tr>
<tr>
<td>Scott et al. A Emerg Med. 2003</td>
<td>151</td>
<td>10 (6.6%)</td>
<td>6 (3.9%)</td>
<td>0</td>
</tr>
<tr>
<td>Artto et al. A Emerg Med. 2012</td>
<td>985</td>
<td>275 (27.9%)</td>
<td>14 (1.4%)</td>
<td>0</td>
</tr>
<tr>
<td>Tsivgoulis et al. Stroke 2011</td>
<td>539</td>
<td>56 (10.3%)</td>
<td>56 (10.3%)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>399</strong></td>
<td><strong>164</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Stroke Mimics

• The risk of sICH in stroke mimics is quite low; thus, starting IV tPA is recommended over delaying treatment to pursue additional diagnostic studies (*Class IIa, Level B*)
5. Extended Time Window (3.0-4.5 Hours)

• In 2008, ECASS-III demonstrated benefit of IV tPA for AIS patients 3.0-4.5 hours from TLSW

• Additional exclusion criteria in ECASS-III:
  1. Age > 80 years
  2. Severe stroke (NIHSS>25)
  3. Any anticoagulation regardless of INR
  4. History of both DM and prior ischemic stroke
3.0-4.5 Hour Time Window

**B  Favorable Outcome (modified Rankin Scale 0-1)**

<table>
<thead>
<tr>
<th>Study</th>
<th>tPA (events/total)</th>
<th>Placebo (events/total)</th>
<th>Odds Ratio, 95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECASS-1</td>
<td>42/114</td>
<td>35/120</td>
<td>1.42 (0.82-2.45)</td>
<td>0.21</td>
</tr>
<tr>
<td>ECASS-2</td>
<td>52/131</td>
<td>40/134</td>
<td>1.55 (0.93-2.57)</td>
<td>0.09</td>
</tr>
<tr>
<td>ECASS-3</td>
<td>219/418</td>
<td>182/403</td>
<td>1.34 (1.02-1.76)</td>
<td>0.04</td>
</tr>
<tr>
<td>ATLANTIS</td>
<td>50/145</td>
<td>56/157</td>
<td>0.95 (0.59-1.52)</td>
<td>0.83</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>363/808</strong></td>
<td><strong>313/814</strong></td>
<td><strong>1.31 (1.07-1.59)</strong></td>
<td><strong>0.01</strong></td>
</tr>
</tbody>
</table>


- For patients > 80 yo, IV tPA in the 3-4.5-hour window is safe and may be as effective as in younger patients *(Class IIa, Level B)*
- For patients with an INR < 1.7, IV tPA in the 3-4.5-hour window appears safe and may be beneficial *(Class IIb, Level B)*
3.0-4.5 Hour Time Window

• The benefit of IV tPA in the 3-4.5 hour time window for NIHSS score > 25 is uncertain \((\text{Class IIb, Level C})\)

• For patients with prior stroke and diabetes mellitus, IV tPA in the 3-4.5 hour window may be as effective as the 0-3 hour window \((\text{Class IIb, Level B})\)

• In summary, there is no evidence for additional exclusion criteria for patients presenting 3.0-4.5 hours after stroke onset
6. Platelets, INR, aPTT, PT

- The safety and efficacy of IV tPA in patients with platelets < 100,000, INR > 1.7, aPTT > 40, PT > 15 seconds is unknown and IV tPA is not recommended (Class III, Level C)

- Given low risk of unsuspected thrombocytopenia or coagulopathy, it’s reasonable not to wait for lab results to administer IV tPA unless an underlying abnormality is suspected (Class IIa, Level B)
7. Anticoagulation

• IV tPA is not recommended in patients taking direct oral anticoagulants within the last 48 hours unless the appropriate laboratory tests are available and normal *(Class III, Level C)*

• IV tPA is not recommended in patients who have received a therapeutic dose of LMWH in the last 24 hours* *(Class III, Level B)*
8. Recent Stroke, Trauma & Surgery

- Major Surgery within 14 days: the potential risk of surgical site hemorrhage should be weighed against the anticipated benefit of IV tPA (*Class IIb, Level C*)

- Major Trauma within 14 days: IV tPA may be considered, weighing the risks of bleeding from trauma against the stroke severity (*Class IIb, Level C*)

- Severe Head Trauma within 3 months: IV tPA is contraindicated (*Class III, Level C*)

- Stroke within 3 months: IV tPA may be harmful (*Class III, Level B*), potential risks should be weighed against the anticipated benefits during decision making (*Class I, Level C*)
9. Endocarditis – New

• Embolic stroke related to septic emboli are especially prone to hemorrhage due to local inflammation and erosion of the vessel wall

• For patients with acute ischemic stroke and symptoms consistent with IE, IV tPA is not recommended because of the increased risk of ICH (*Class III, Level C*)
10. Pre-existing Dementia/Debility

• Pre-existing dementia and debility are not contraindications, but may limit neurologic recovery

• Patients with pre-existing dementia may benefit from IV alteplase (*Class IIb, Level B*)

• IV tPA for patients with debility is reasonable, but should account for factors such as quality of life, post-stroke residence, and patient preferences (*Class IIb, Level B*)
11. Consent

- IV tPA is standard of care
- IV tPA is not FDA approved in the United States in the 3.0-4.5 hour window, however, is considered standard of care
- If the patient is not competent and no one is available to provide consent, it is recommended to give IV tPA to an eligible patient (Class I, Level C)
12. Medicolegal Considerations

• Review of 789 AIS stroke litigation cases
• 46 cases were related to IV tPA
  – 38 cases: failure to administer IV tPA (95%)
  – 2 cases: complications of IV-tPA. (5.0%)
  – ED physicians (60.52%), Neurologists (20.0%)
• 65% verdicts favored defense, 30% plaintiffs

13. Time to Treatment

Ratio of IV tPA patients who benefit vs harm by time (minutes)

Lansberg et al, Stroke 2009
Statistically significant benefits are seen by accelerating IV tPA administration 15 minutes.

For every 1000 patients:
- 18 more patients have improved ambulation
- 8 more ambulate independently
- 13 more discharged to a more independent environment
- 4 fewer patients die prior to discharge

Summary

Prior Exclusion Criteria

• Significant head trauma or prior stroke in the previous 3 months
• Arterial puncture at non-compressible site in previous 7 days
• History of previous ICH or symptoms suggesting SAH
• Intra-axial neoplasm, arteriovenous malformation, or aneurysm
• Recent intracranial or intraspinal surgery
• Elevated BP (SBP >185, DBP >110)
  – (post-aggressive treatment)
• Active internal bleeding
• Platelet count <100,000
• Therapeutic heparin within 48 hours and elevated aPTT
• INR >1.7 or PT >15 seconds
• Use of direct thrombin inhibitors or direct factor Xa inhibitors within 48 hrs
• Blood glucose concentration <50 mg/dL or >400mg/dL
• CT demonstrates “large” infarction

Prior Relative Exclusion Criteria

• Minor or rapidly improving stroke symptoms
• Pregnancy
• Seizure at onset
• Major surgery or serious trauma within 14 days
• GI or urinary tract hemorrhage within 21 days (due to malignant or structural lesion)
• Acute myocardial infarction within 3 months

Prior 3.0-4.5 Hour Exclusion Criteria

• Age > 80 years
• Severe stroke (NIHSS > 25)
• Any anticoagulation regardless of INR
• History of both DM and prior ischemic stroke

New

• Acute ischemic stroke due to infective endocarditis
Summary: IV tPA Exclusion Criteria

Revised Exclusion Criteria
• Head CT demonstrates “large” infarction
• History of previous ICH or symptoms suggesting SAH
• Significant head trauma or prior stroke in the previous 3 months
• Intra-axial neoplasm
• Recent intracranial or intraspinal surgery
• Platelet count <100,000, INR >1.7 or PT >15 seconds
• Therapeutic heparin and elevated aPTT, direct thrombin inhibitors, or direct factor Xa inhibitors within 48 hrs
• GI or urinary tract hemorrhage within 21 days due to malignancy or structural lesion or other active internal bleeding
• Acute ischemic stroke secondary to infective endocarditis

Readily Treatable Exclusion Criteria
• Elevated BP (SBP >185, DBP >110)
• Blood glucose concentration <50 mg/dL
Conclusions

1. IV tPA inclusion-exclusion criteria for ischemic stroke are “soft”, few absolute exclusion criteria
2. Each case must be assessed on an individual basis, with a unique risk-benefit assessment
3. The treatment effect is strongly time dependent
4. Treat patients based upon debility, not NIHSS score
5. There is no age limit
6. We are not giving enough tPA!
Questions

Contact: streib@umn.edu