Thrombolytic Therapy for Ischemic Stroke: 0-3 hours and 3-4.5 hours

Shyam Prabhakaran, MD, MS
Associate Professor, Department of Neurology

TIME EQUALS BRAIN!

Per minute of ischemia, the following are destroyed:
• 1.9 million neurons
• 14 billion synapses

In an average stroke after 10 hours:
• 50 yo man ages 30 years cognitively

Predictors of outcome following acute ischemic stroke

Evidence-based treatment for acute ischemic stroke

<table>
<thead>
<tr>
<th>Time window</th>
<th>Treatment</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-4.5 hours</td>
<td>IV rt-PA 0.9 mg/kg</td>
<td>NINDS ECASS III</td>
</tr>
<tr>
<td>0-6 hours</td>
<td>IA pro-UK (rt-PA)</td>
<td>PROACT MELT</td>
</tr>
<tr>
<td>0-8 hours</td>
<td>mechanical extraction</td>
<td>MERCII PENUMBRA SOLITAIRE TREVO DEFUSE IMS MR-RESCUE</td>
</tr>
</tbody>
</table>

Thrombolysis in Stroke

Methodological Differences Among RCTs

1. Time windows:
   - <3 hrs: NINDS
   - 3-4.5 hrs: ECASS III
   - 3-5 hrs: ATLANTIS
   - <6 hrs: ECASS I, ECASS II

2. Dose: Cardiac (1.1 mg/kg) vs. Brain (0.9 mg/kg)

3. Use of concomitant therapy: heparin, aspirin

4. Blood pressure management: strict protocol in NINDS

NIH/NINDS rt-PA study

Design
Randomized, double-blind placebo-controlled trial

Raters different from baseline examiners

Two parts

Part 1: 24-hour improvement
- Complete resolution of deficit or improvement of 4 points on the NIH stroke scale

Part 2: 3-month outcome
- Consistent and persuasive difference in proportion of patients with minimal or no deficit
NIH/NINDS rt-PA study

Eligibility Criteria

- Ischemic stroke with clearly defined time of onset < 3 hours
- Baseline CT negative for hemorrhage
- Age > 18 years
- Moderate to severe symptoms

Exclusion criteria

- SBP > 185 or DBP > 110 despite treatment
- Elevated PTT > 5s ULN (on heparin)
- Platelet count < 100,000
- Warfarin with INR > 1.7
- Evidence of pericarditis, endocarditis, aortic dissection, septic emboli, pregnancy, acute IBI, etc
- CT with > 1/3 MCA infarct
- Rapidly improving symptoms
- Minor symptoms
- Seizure at stroke onset
- Glucose <50 or >400 mg/dL
- Injectable anticoagulants < 24 hours
- Novel anticoagulants < 48 hours
- Major active bleeding
- GI or GU hemorrhage within 21 days
- Prior major stroke, head trauma, or CNS surgery within 3 months
- Major surgery within 14 days
- History of non-traumatic hemorrhage (ICH or SAH)
- Prior MI within 3 months with unacceptable risks
- Non-compressible arterial puncture or internal biopsy within 7 days

Beware of rapid improvers!

Table 1: Patients with stroke excluded from alteplase treatment. Oxford Stroke Program Classification, NINDS; outcome at discharge in patients presenting within 2 hours of symptom onset.

<table>
<thead>
<tr>
<th>Reason for exclusion</th>
<th>TACS</th>
<th>PACS</th>
<th>POS</th>
<th>LACs</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical improvement 18.5%</td>
<td>13</td>
<td>19</td>
<td>2</td>
<td>21</td>
<td>176</td>
</tr>
<tr>
<td>CT abnormality but no stroke</td>
<td>2</td>
<td>10</td>
<td>4</td>
<td>17</td>
<td>68</td>
</tr>
<tr>
<td>Potential contraindications</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protocol violations</td>
<td>3</td>
<td>6</td>
<td>0</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Hematoma</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>&quot;Early&quot; CT technical change</td>
<td>4</td>
<td>0</td>
<td>1</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>CT abnormality that preceded treatment</td>
<td>5</td>
<td>3</td>
<td>0</td>
<td>1</td>
<td>15</td>
</tr>
<tr>
<td>Recent surgery/neurosurgical interventions</td>
<td>5</td>
<td>2</td>
<td>0</td>
<td>5</td>
<td>12</td>
</tr>
<tr>
<td>Referral problems</td>
<td>0</td>
<td>11</td>
<td>5</td>
<td>5</td>
<td>20</td>
</tr>
<tr>
<td>Stroke not recognized by medical staff</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>14</td>
</tr>
<tr>
<td>Significant comorbidity</td>
<td>12</td>
<td>2</td>
<td>3</td>
<td>25</td>
<td>18.5</td>
</tr>
<tr>
<td>Intensive care</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>5</td>
</tr>
</tbody>
</table>

3% of these patients were disabled or dead at discharge
13.1%
18.2%

Barber PA, Neurology 2001; Smith EE, Stroke 2005
NIH/NINDS rt-PA study

Treatment

Dose 0.9 mg/kg (maximum 90 mg)
10% given as IV bolus
90% constant IV infusion over 1 hr

Other meds No other anticoagulants or antiplatelet agents for 24 hours post tPA

Strict BP control (< 180/105 mmHg) post-tPA

Outcomes at 24 hours

Outcomes at 3 months
Does Type of Stroke Matter?

90-Day Favorable Barthel Index (≥95)

<table>
<thead>
<tr>
<th>Type</th>
<th>rt-PA (%)</th>
<th>Placebo (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large-vessel</td>
<td>46%</td>
<td>36%</td>
</tr>
<tr>
<td>Cardioembolic</td>
<td>49%</td>
<td>37%</td>
</tr>
<tr>
<td>Small-vessel</td>
<td>50%</td>
<td>36%</td>
</tr>
</tbody>
</table>

Benefit to Harm Ratio

- Median NIHSS at 24 hours (tPA: 8, placebo: 12)

Myths about trial

- No early improvement
- Median NIHSS at 24 hours (tPA: 8, placebo: 12)
Myths about trial

• Only 1 trial with prior trials negative (ECASS)
  • It was actually 2 independent trials
  • Also differences in NINDS trial (dose, time window, post-TPA care)

• Modest benefits (NNT = 8)
  • Carotid endarterectomy (NNT = 11)
  • Warfarin for NVAF (NNT = 33)
  • Also the improvement to harm ratio is 33

• Symptomatic hemorrhage risk
  • Outcome benefits include sICH risks
  • sICH more likely with severe stroke (poor outcome even in placebo due to edema/progression)

<table>
<thead>
<tr>
<th>Study</th>
<th>Age group</th>
<th>tPA (n)</th>
<th>Control (n)</th>
<th>tPA (%)</th>
<th>Control (%)</th>
<th>OR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NINDS</td>
<td>&gt;80</td>
<td>40</td>
<td>29</td>
<td>9 (22.5)</td>
<td>6 (20.7)</td>
<td>1.11 (0.35-3.37)</td>
</tr>
<tr>
<td>IST-3</td>
<td>&gt;80</td>
<td>817</td>
<td>799</td>
<td>223 (27.3)</td>
<td>188 (23.5)</td>
<td>1.35 (0.97-1.88)</td>
</tr>
<tr>
<td>Total</td>
<td>&gt;80</td>
<td>857</td>
<td>828</td>
<td>232 (27.1)</td>
<td>194 (23.4)</td>
<td>1.21 (0.97-1.52)</td>
</tr>
</tbody>
</table>

• Can not be reproduced (special centers/systems)
  • Reproduced in community settings, other countries with similar results
  • ECASS-III and pooled meta-analyses confirm

• Symptomatic hemorrhage risk
  • Outcome benefits include sICH risks
  • sICH more likely with severe stroke (poor outcome even in placebo due to edema/progression)

• Small percentage of overall strokes treated (4%)
  • During an era of therapeutic nihilism about stroke
  • Now, most major centers average 10-20%
ECASS-3

- Age > 80 years
- NIHSS score > 25
- >1/3 MCA hypodensity on CT
- Prior stroke AND diabetes
- Oral anticoagulation (regardless of INR)

**ECASS-3**

**Table 1: Major Inclusion and Exclusion Criteria**

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>Body Group</th>
<th>Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 80 years</td>
<td>Yes</td>
<td>3.17</td>
</tr>
<tr>
<td>NIHSS score &gt; 25</td>
<td>Yes</td>
<td>1.35</td>
</tr>
<tr>
<td>&gt;1/3 MCA hypodensity on CT</td>
<td>Yes</td>
<td>1.56</td>
</tr>
<tr>
<td>Prior stroke AND diabetes</td>
<td>Yes</td>
<td>1.51</td>
</tr>
<tr>
<td>Oral anticoagulation (regardless of INR)</td>
<td>Yes</td>
<td>1.34</td>
</tr>
</tbody>
</table>

**Table 2: Major Exclusion Criteria**

<table>
<thead>
<tr>
<th>Exclusion Criteria</th>
<th>Body Group</th>
<th>Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major surgery within 4 weeks</td>
<td>No</td>
<td>1.00</td>
</tr>
<tr>
<td>Major trauma within 4 weeks</td>
<td>No</td>
<td>1.00</td>
</tr>
<tr>
<td>Hemorrhagic transformation on CT</td>
<td>No</td>
<td>1.07</td>
</tr>
<tr>
<td>Prior stroke AND diabetes</td>
<td>No</td>
<td>1.00</td>
</tr>
<tr>
<td>Oral anticoagulation (regardless of INR)</td>
<td>No</td>
<td>1.00</td>
</tr>
</tbody>
</table>

**ECASS-3**
ECASS-3

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Alteplase Group (n=442)</th>
<th>Minaxi Group (n=485)</th>
<th>Odd Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-specified safety and points</td>
<td>133 (30.6)</td>
<td>71 (14.7)</td>
<td>1.79 (1.24-2.57)</td>
<td>0.001</td>
</tr>
<tr>
<td>Symptomatic ICH</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>According to ECASS III definition</td>
<td>10 (2.6)</td>
<td>1 (0.2)</td>
<td>9.85 (1.26-77.32)</td>
<td>0.006</td>
</tr>
<tr>
<td>According to ECASS III definition</td>
<td>22 (5.3)</td>
<td>9 (1.8)</td>
<td>2.43 (1.11-5.39)</td>
<td>0.02</td>
</tr>
<tr>
<td>According to NINDS-RT-PRO stroke definition</td>
<td>8 (1.9)</td>
<td>1 (0.2)</td>
<td>7.34 (1.98-29.30)</td>
<td>0.02</td>
</tr>
<tr>
<td>Fatal ICH</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 (0.7)</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptomatic deaths</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>29 (6.6)</td>
<td>29 (6.1)</td>
<td>0.98 (0.56-1.71)</td>
<td>0.89</td>
</tr>
<tr>
<td>Death</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>32 (7.2)</td>
<td>34 (7.0)</td>
<td>0.90 (0.54-1.48)</td>
<td>0.68</td>
</tr>
</tbody>
</table>

Results – Pooled Analysis

Every 10 minutes that goes by without tPA, 1 fewer patient experiences benefit from tPA

AHA/ASA Guidelines

Intravenous rt-PA is recommended for selected patients who may be treated within 3 hours of onset of ischemic stroke (Class I Recommendation, Level of Evidence A).

rt-PA should be administered to eligible patients who can be treated in the time period of 3 to 4.5 hours after stroke (Class I Recommendation, Level of Evidence B).
AHA/ASA Guidelines

EDs should establish standard operating procedures and protocols to triage stroke patients expeditiously (Class I, Level of Evidence B).

Standard procedures and protocols should be established for benchmarking time to evaluate and treat eligible stroke patients with rt-PA expeditiously (Class I, Level of Evidence B).

Target treatment with rt-PA should be within 1 hour of the patient’s arrival in the ED (Class I, Level of Evidence A).

IV tPA: who aren’t we treating?

Reasons for IV TPA exclusions:
Delay to ER 73%

Increasing tPA use
- Expanded time window (4.5 hours)
  - Up to 50% present in this window
- Public education and calling 911
  - Only 40% call 911 in Chicago
- EMS triage to primary stroke centers
  - Stroke centers deliver tPA more
- Primary Stroke Center Act in Illinois
- Telemedicine
  - Provides access to rural regions
  - Reduces delays in evaluation
- Improved reimbursement
  - DRG 559
Increasing tPA use

- Overcome physician/hospital barriers
- Fear of litigation for complication
  - Most claims are settled for plaintiff for failure to treat with tPA (9:1)
- Streamline acute stroke triage and pathways (stroke centers)
  - Goal door-to-tPA time < 60 minutes
  - Target: Stroke Initiative

<table>
<thead>
<tr>
<th>Allergic to tPA</th>
<th>Unknown Status</th>
<th>Unfed Status</th>
<th>Fed Status</th>
<th>目标</th>
<th>tPA Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>2%</td>
<td>4%</td>
<td>6%</td>
<td>9%</td>
<td>13%</td>
<td>26%</td>
</tr>
</tbody>
</table>

National time interval goals

1. Perform an initial patient evaluation within 10 minutes of arrival in the emergency department
2. Notify the stroke team within 15 minutes of arrival
3. Initiate a CT scan within 25 minutes of arrival
4. Interpret the CT scan within 45 minutes of arrival
5. Ensure a door-to-needle time for IV rt-PA within 60 minutes from arrival*

*Endorsed unanimously by National Quality Forum

EMS and Pre-notification

Lin C Circulation 2012
Stroke Team Activation

- Consider activation of stroke team earlier
  - When EMS or base station calls PSC with suspected stroke
  - At triage, nurse could use ROSIER scale

Labs and tPA delays

- Consider treating with tPA before labs are back
  - 0.4% chance of unsuspected coagulopathy (Rost, Neurology 2009)
  - 0.3% chance of unsuspected thrombocytopenia (Cucchiara, Stroke 2007)
  - Use a screening checklist:
    1. Taking warfarin or novel oral anticoagulants?
    2. Taking heparin or low-molecular weight heparinoid?
    3. On hemodialysis?
    4. Active malignancy?
    5. Liver dysfunction?
    6. Unable to obtain medical history?
      - If yes to any of the above, await labs and consider POC tests if average time to labs > 45 minutes

Mixing tPA delays

- 15-20 minutes for mixing tPA on average
- Consider pre-mixing tPA meeting criteria:
  - < 4.5 hours from onset
  - Measurable deficit on initial screen
  - CT head negative for hemorrhage
  - Glucose 50-400 mg/dL
  - Pharmacy paged with stroke team
  - Mix tPA

Genentech return policy
1. We believe you are having a stroke due to a clot blocking an artery in your brain.
2. We are recommending treatment with IV tPA, which is the only FDA approved treatment for thrombolysis or “clot busting.”
3. Studies have shown that if you receive IV tPA, you are at 11 times more likely to be helped than harmed by the drug (refer to chart).
4. There is a risk of bleeding with this medication. This could lead to significant worsening, but we believe the benefit outweighs the risk (refer to chart).
5. The benefit of tPA decreases with time, so the sooner we are able to treat you, the better.

Any questions?
National trends

Intracranial hemorrhage

- Asymptomatic in 5-10%
  - Observation only
- Symptomatic in 5-6%
  - Immediate CT head
  - Stop tPA if during infusion
  - Check CBC, coags, fibrinogen, and type/cross
  - Reversal required
- 6-8U cryoprecipitate and 6-8U platelets usually
  - Repeat CT head in 6 hours

Complications
tPA Complications

Angioedema – 1-5%
- Mild, transient, and contralateral to infarct side
- Associated with ACE-I use
- H2 blockers/steroids treat severe cases
- Emergent cricothyrotomy in some cases

Post-tPA Care

- Keep BP < 180/105 mmHg
- No antithrombotic therapy for 24 hours
- No lines, Foley if can wait for 24 hours
- Repeat CT if headache or deterioration in exam or at 24 hours
- Vitals and neuro checks q15min for 2 hours, q30min for 6 hours, and q1hr for 16hrs
- ICU or Stroke Unit for observation
Blood pressure in acute stroke

- Acute elevations in BP common after stroke
  - 85% of patients
  - Often declines spontaneously after 24-48 hours
- Cerebral autoregulation impaired in setting of stroke
- Acutely lowering BP may worsen ischemia based on clinical and PET studies

Blood pressure

![Graph showing baseline systolic blood pressure vs. death within 14 days and death or dependency](image)

AHA/ASA Guidelines, Stroke 2013

- For patients not eligible for tPA, treat only if > 220/120 mmHg
  - Unless other medical situations that require immediate lowering of blood pressure (hypertensive encephalopathy, aortic dissection, acute renal failure, acute MI, pulmonary edema), consensus is not to treat moderately elevated blood pressure
  - Treatment should be done cautiously
- For patient eligible for thrombolysis, blood pressure should be < 185/110 before tPA and < 180/105 after tPA
Blood pressure

Patients eligible for thrombolysis

- Prior to tPA (goal BP < 185/110)
  - SBP > 185 or DBP > 110
    - Labetalol 10-20 mg IV over 1-2 min (maximum 40 mg)
- During and after tPA treatment (goal BP < 180/105)
  - SBP 180-230 or DBP 105-120
    - IV labetalol 10 mg over 1-2 minutes (Repeat or double as necessary every 10 minutes up to max 150 mg)
    - Labetalol infusion @ 20 mg/hr (max 150 mg/hr)
  - SBP > 230 or DBP 121-140
    - Labetalol infusion @ 40 mg/hr (max 150 mg/hr) AND prn boluses (20-40 mg every 10-15 min)
    - Nicardipine infusion (5mg/hr upto max 15mg/hr)
  - DBP > 140
    - Labetalol infusion
    - Nicardipine infusion

Interventional Strategies for Ischemic Stroke: 0-8 hours

Shyam Prabhakaran, MD, MS
Associate Professor, Department of Neurology

Evidence-based treatment for acute ischemic stroke

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<td>IV rt-PA 0.9 mg/kg</td>
<td>NINDS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ECASS III</td>
</tr>
<tr>
<td>0-6 hours</td>
<td>IA pro-UK (rt-PA)</td>
<td>PROACT</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MELT</td>
</tr>
<tr>
<td>0-8 hours</td>
<td>mechanical extraction</td>
<td>MERCI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PENUMBRA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SOLITAIRE</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TREVO</td>
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<td></td>
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<td>DEFUSE</td>
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<tr>
<td></td>
<td></td>
<td>IMS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MR-RESCUE</td>
</tr>
</tbody>
</table>
IA therapy: the rationale

- Many patients arrive > 4.5 hours from onset or are ineligible for IV tPA
- Intravenous therapies may not work for large clots – 25% recanalization (MCA) and 10% (ICA)
- Large vessel occlusions portend worse prognosis – Only 20% achieve good neurologic outcome
- Intra-arterial therapies – Titrated and potentially more effective therapy

Drawbacks
- Riskier
- Takes longer
- Limited availability

IA thrombolysis: PROACT-II

N=12,323 screened
N=2095 clinically eligible
N=474 screening angiogram
N=180 randomized
N=121, r-proUK
N=108, received treatment as planned
N=59, control
N=54, received treatment as planned

IA thrombolysis: PROACT-II

<table>
<thead>
<tr>
<th></th>
<th>r-ProUK</th>
<th>Control</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>121</td>
<td>59</td>
<td>NS</td>
</tr>
<tr>
<td>Mean age</td>
<td>64.4 yrs</td>
<td>64.4 yrs</td>
<td>NS</td>
</tr>
<tr>
<td>Mean NIHSS</td>
<td>17</td>
<td>17</td>
<td>NS</td>
</tr>
<tr>
<td>Median time Rx</td>
<td>5.3 hrs</td>
<td>5.3 hrs</td>
<td>NS</td>
</tr>
<tr>
<td>3-month outcomes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rankin &lt;2</td>
<td>46%</td>
<td>25%</td>
<td>0.043</td>
</tr>
<tr>
<td>Barthel ≥90</td>
<td>41%</td>
<td>32%</td>
<td>NS</td>
</tr>
<tr>
<td>36 hr ICH</td>
<td>46.3%</td>
<td>16.4%</td>
<td>0.001</td>
</tr>
<tr>
<td>Symptomatic ICH</td>
<td>10.2%</td>
<td>1.8%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>90 day mortality</td>
<td>24</td>
<td>27</td>
<td>NS</td>
</tr>
</tbody>
</table>

MELT

- 114 patients randomized to urokinase vs. placebo in the 0-6 hour window
- Japanese version of PROACT
- 90-day mRS 0-1: 42.1% vs. 22.8% (P = 0.045)
- Mortality: 5.3% vs. 3.5% (P = 1.000)
- sICH: 9% vs. 2% (P = 0.206)
Evidence-based treatment for acute ischemic stroke

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Mechanical thrombectomy: MERCI

<table>
<thead>
<tr>
<th></th>
<th>MERCI</th>
<th>PROACT Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>151</td>
<td>59</td>
</tr>
<tr>
<td>Mean age</td>
<td>67.0</td>
<td>64.4</td>
</tr>
<tr>
<td>Mean NIHSS</td>
<td>20</td>
<td>17</td>
</tr>
<tr>
<td>Median time to Rx (hrs)</td>
<td>4.3</td>
<td>5.3</td>
</tr>
<tr>
<td>Outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recanalization</td>
<td>46%</td>
<td>18%</td>
</tr>
<tr>
<td>90 d Rankin ≤2</td>
<td>28%</td>
<td>25%</td>
</tr>
<tr>
<td>Symptom, ICH</td>
<td>7.8%</td>
<td>1.8%</td>
</tr>
<tr>
<td>90 d Mortality</td>
<td>43.5%</td>
<td>27%</td>
</tr>
</tbody>
</table>

Smith WS et al. Stroke 2005
Mechanical thrombectomy: Penumbra

<table>
<thead>
<tr>
<th></th>
<th>Penumbra</th>
<th>PROACT Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>125</td>
<td>59</td>
</tr>
<tr>
<td>Mean age</td>
<td>64.0</td>
<td>64.4</td>
</tr>
<tr>
<td>Mean NIHSS</td>
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<td>17</td>
</tr>
<tr>
<td>Outcomes</td>
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<td></td>
</tr>
<tr>
<td>Recanalization</td>
<td>82%</td>
<td>18%</td>
</tr>
<tr>
<td>90 d Rankin ≤2</td>
<td>25%</td>
<td>25%</td>
</tr>
<tr>
<td>Symptom. ICH</td>
<td>11.2%</td>
<td>1.8%</td>
</tr>
<tr>
<td>90 d Mortality</td>
<td>32.8%</td>
<td>27%</td>
</tr>
</tbody>
</table>

Mechanical thrombectomy: SOLITAIRE and TREVO
Recanalization and ICH rates by mode of therapy

<table>
<thead>
<tr>
<th></th>
<th>Spontaneous</th>
<th>IV-tPA alone</th>
<th>IA-tPA alone</th>
<th>MERCI alone</th>
<th>Penumbra</th>
<th>Solitaire/ Trevo</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIMI 2-3</td>
<td>18% (MCA)</td>
<td>10% (ICA)</td>
<td>66% (MCA)</td>
<td>46-54%</td>
<td>32%</td>
<td>90%</td>
</tr>
<tr>
<td>ICH</td>
<td>0.6%</td>
<td>6.4%</td>
<td>10% (MCA)</td>
<td>6.7%</td>
<td>11.2%</td>
<td>2.4%</td>
</tr>
<tr>
<td>mRS 0-2</td>
<td>25% (MCA)</td>
<td>30-35%</td>
<td>40% (MCA)</td>
<td>33.3%</td>
<td>27%</td>
<td>37-40%</td>
</tr>
</tbody>
</table>

Other factors affecting recanalization:
- Thrombus burden
- Composition of clot (white vs. red, fibrin vs. platelet, new vs. old)
- Location of clot (ICA-T occlusion = BA < M1 < M2 < ACA = PCA)
- Underlying anatomy (atherosclerotic stenosis)
- Time to treatment

Other predictors of ICH:
- Stroke severity and age
- Elevated blood pressure
- Early ischemic changes on CT
- Hyperglycemia / diabetes
- Low platelets, coagulopathy
- Reperfusion

Lansberg MG et al. Lancet Neurol 2012

Clinical trials: DEFUSE-2
Clinical trials: IMS-3

- Comparison of 0.9 mg/kg IV tPA vs. 0.6 mg/kg plus IA therapy in AIS patients presenting < 3 hours (IAT completed within 7 hours)
  - Age 18-82
  - Consent within 40 minutes of IV tPA
  - 2:1 randomization in favor of IV+IAT
  - NIHSS > 9 or NIHSS 8-9 with CTA+ M1, ICA, or BA
  - Study stopped after 656 patients enrolled (futility)
- 40.8 vs. 38.7% good outcomes (not significant)
- No safety concerns (similar hemorrhage and mortality rates) though higher SAH and asymptomatic hemorrhages in IA groups

• Onset to IAT 249 minutes
  - 127 minutes from IV tPA start to IA start (86 minutes from IV completion to IA start)
• 89 of 423 (21%) did not have clot
• Most patients received IA tPA (80%) compared to mechanical embolectomy (57%)
  - Solitaire only used in 5 cases
• IMS-3 subgroups (trends for IAT benefit)
  - NIHSS score > 19
  - Onset to IV tPA < 120 minutes
  - IV tPA to IA start < 90 minutes
• Every 30 minute delay → 10% relative reduction in probability of good outcome
Clinical trials: MR-RESCUE

- Comparison of perfusion hypothesis and embolectomy vs. standard of care
  - < 8 hours from onset, NIHSS 7-29, Age 18-85
  - MCA/ICA occlusion by MRA/CTA
  - Penumbra: core < 90 cc and core/penumbra ≤ 70%
  - Allowed IV tPA if LAO after tPA (37% of patients)
- Enrolled 120 patients into 4 categories
  - Penumbra vs. non-penumbra; SOC vs. embolectomy
- No benefit of embolectomy vs. SOC
  - Penumbral pattern predicted better outcome

Clinical trials: MR-RESCUE

- Onset to IAT > 6 hours
  - Onset to randomization after MRI 5.5 hours
  - Used 1st generation embolectomy devices
  - Mismatch ratio may have been too low and included oligemia
- 80% MRP (included 20% CT perfusion)
- Reperfusion/revascularization at 7 days had less infarct growth and lower mRS than those without reperfusion
  - 50% of SOC had reperfusion at 7-day MRP/CTP!!
Clinical trials: SYNTHESIS

- Pragmatic, multi-center, open-treatment with blinded end-point
  - Comparison of IV tPA vs. IA therapy in AIS patients < 4.5h (IAT < 6h)
  - NIHSS score > 2, age 18-80 years
- Good outcome: mRS 0-1 at 3 months
- Enrolled 362 patients
- No difference in primary outcome
  - 34.8% vs. 30.4%
- No safety concerns related to hemorrhage

Clinical trials: SYNTHESIS

- NIHSS score cut-point > 2
- 8% had no IA therapy
- Onset to therapy 2.5h for IVT vs. 3.5h for IAT
- Majority of patients received IA tPA or local fragmentation (67%) while remainder used devices
- No groups favored IA therapy
  - NIHSS < 11 favored IV tPA alone
Ongoing trials

- THERAPY (IV vs. IAT within 4.5 hours) using clot length as selection criteria
  - Large clots will not respond to IV therapy and do worse?
- SWIFT-PRIME (IV vs. IAT within 4.5 hours) using stent retrievers as primary device
- Novel lytic trials
  - Desmoteplase
  - Tenecteplase
  - Eptifibatide
- IMS-4?

Thank You!