Stroke 2015:
Advances In Neurovascular Intervention

Matthew Lawson, MD
Disclosures

• No direct financial disclosures
  – No ownership interests
  – No consulting arrangements
Outline

• Case Presentation
• Stroke Treatment
  – NINDS Trial – IV TPA
  – Interventional Trials
Case 1 – 71 year old male

71 year old male is brought to the ER from Premier fitness after stumbling off an exercise bike. He had right hemi-body weakness and aphasia – EMS was activated and he was quickly brought to the Emergency Department – Initial head CT was negative for hemorrhage – Arrived 30 minutes after onset – NIHSS of 20
Case 1 – 71 year old male

• He met criteria for administration of TPA
  – IV Bolus given and infusion started

• CT Angiogram of the head and neck was performed, with a perfusion study
  – CTA helps identify treatable lesions
  – CT Perfusion helps assess dead brain tissue and viable “penumbra”
Case 1 - CTA

Axial

Coronal
Case 1 - CT Perfusion Images

MTT

CBV

At Risk

DEAD
Case 1 – 71 year old male

- He appeared to be a good candidate for endovascular intervention
  - Had a Left MCA occlusion (large vessel)
  - Had ~1/3 of the “at risk” territory with completed infarction (dead)
    - 2/3 of the “at risk” territory potentially salvageable!
      - Presented very early after onset of symptoms
- We took him directly to the neurovascular suite in the cath lab for intervention
Case 1 – Initial LICA Angiogram
Case 1 – 71 year old male

• Complete occlusion of the left MCA was identified at the level of the M1 segment
  – Proximal to the MCA trifurcation
• Trevo Pro device was used to perform a thrombectomy (remove the clot)
  – Total of 3 passes
• Complete removal of the thrombus
Case 1 – Final LICA Angiogram
Case 1 – Outcome

• He made a rapid improvement post procedure
• POD 1 his NIHSS was down to 3
  – NIHSS was 20 on presentation
    • 30% mortality at 30 days
• Discharged to rehab several days later
• On follow up at 3 weeks in the office...
  – NIHSS was 1
  – Mild residual facial droop on the right
Basic Premise: PENUMBRA

- **Core**: dead brain
- **Penumbra**: potentially salvageable brain
Time is Brain
Stroke

• Despite these basic principles, treatment options for acute stroke remained quite limited for most of the 20th century
  – Aspirin
  – Oxygen
  – Avoid Hypotension
TISSUE PLASMINOGEN ACTIVATOR FOR ACUTE ISCHEMIC STROKE

THE NATIONAL INSTITUTE OF NEUROLOGICAL DISORDERS AND STROKE rt-PA STROKE STUDY GROUP*

Abstract  Background. Thrombolytic therapy for acute ischemic stroke has been approached cautiously because there were high rates of intracerebral hemorrhage in early clinical trials. We performed a randomized, double-blind trial of intravenous recombinant tissue plasminogen activator (t-PA) for ischemic stroke after recent pilot studies suggested that t-PA was beneficial when treatment was begun within three hours of the onset of stroke.

Methods. The trial had two parts. Part 1 (in which 291 patients were enrolled) tested whether t-PA had clinical activity, as indicated by an improvement of 4 points over base-line values in the score of the National Institutes of Health stroke scale (NIHSS) or the resolution of the neurologic deficit within 24 hours of the onset of stroke. Part 2 (in which 333 patients were enrolled) used a global test statistic to assess clinical outcome at three months, according to scores on the Barthel index, modified Rankin scale, Glasgow outcome scale, and NIHSS.

Results. In part 1, there was no significant difference between the group given t-PA and that given placebo in the percentages of patients with neurologic improvement at 24 hours, although a benefit was observed for the t-PA group at three months for all four outcome measures. In part 2, the long-term clinical benefit of t-PA predicted by the results of part 1 was confirmed (global odds ratio for a favorable outcome, 1.7; 95 percent confidence interval, 1.2 to 2.6). As compared with patients given placebo, patients treated with t-PA were at least 30 percent more likely to have minimal or no disability at three months on the assessment scales. Symptomatic intracerebral hemorrhage within 36 hours after the onset of stroke occurred in 6.4 percent of patients given t-PA but only 0.6 percent of patients given placebo (P<0.001). Mortality at three months was 17 percent in the t-PA group and 21 percent in the placebo group (P=0.30).

Conclusions. Despite an increased incidence of symptomatic intracerebral hemorrhage, treatment with intravenous t-PA within three hours of the onset of ischemic stroke improved clinical outcome at three months. (N Engl J Med 1995;333:1581-7.)
NINDS Trial

• Inclusion criteria:
  – Ischemic stroke with a defined time of onset < 3 hours
  – Negative head CT for intracranial blood products
  – A measurable deficit using the NIHSS
    • 42 point scale to measure severity of stroke
NINDS Trial

• Exclusion criteria:
  – Recent stroke or head trauma within 3 months
  – Major surgery within 14 days
  – History of intracranial hemorrhage
  – SBP > 185 mm Hg and/or DBP > 110 mm Hg
  – Symptomatic improvement
  – Symptoms suggestive of subarachnoid hemorrhage
  – GI or urinary tract hemorrhage within the previous 21 days
  – Arterial puncture at a non-compressible site
  – Seizure at the time of ictus
  – Anticoagulants or systemic heparinization within 48 hours with an elevated PTT
  – Platelet count < 100,000
  – Glucose levels < 50 or > 400
NINDS Results

• rtPA-treated patients were 30% more likely to suffer minimal or no disability at 3 months compared to placebo.

• Symptomatic hemorrhage rates within 36 hours:
  – 6.4% rtPA
  – 0.6% placebo (P<0.001)

• 3-month mortality rates:
  – 17% rtPA
  – 21% placebo (P=0.3)
NINDS Functional Results

Independence at 30 Days
Placebo = 26%
TPA = 39%
NNT to increase independent outcome at 30 days... 7
rtPA Problems

• Not all patients improve with IV rtPA
  – Cross-over to other treatments

• Many patients are excluded from receiving rtPA:
  – Direct contraindications
  – Physician fear

• Less than 1% of eligible patients receive IV rtPA due largely to delay in presentation
Thrombolysis with Alteplase 3 to 4.5 Hours after Acute Ischemic Stroke

Werner Hacke, M.D., Markku Kaste, M.D., Erich Bluhmki, Ph.D., Miroslav Brozman, M.D., Antoni Dávalos, M.D., Donata Guidetti, M.D., Vincent Larrue, M.D., Kennedy R. Lees, M.D., Zakaria Medeghri, M.D., Thomas Machnig, M.D., Dietmar Schneider, M.D., Rüdiger von Kummer, M.D., Nils Wahlgren, M.D., and Danilo Toni, M.D., for the ECASS Investigators*
ECASS-3

- 821 patients enrolled
  - 375 received rtPA (0.9 mg/kg)
  - 355 controls

- Primary endpoints:
  - Favorable clinic outcome (mRS score ≤ 1) at 90 days

Table 1. Major Inclusion and Exclusion Criteria.

<table>
<thead>
<tr>
<th>Main inclusion criteria</th>
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</thead>
<tbody>
<tr>
<td>Acute ischemic stroke</td>
</tr>
<tr>
<td>Age, 18 to 80 years</td>
</tr>
<tr>
<td>Onset of stroke symptoms 3 to 4.5 hours before initiation of study-drug administration</td>
</tr>
<tr>
<td>Stroke symptoms present for at least 30 minutes with no significant improvement before treatment</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Main exclusion criteria</th>
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</thead>
<tbody>
<tr>
<td>Intracranial hemorrhage</td>
</tr>
<tr>
<td>Time of symptom onset unknown</td>
</tr>
<tr>
<td>Symptoms rapidly improving or only minor before start of infusion</td>
</tr>
<tr>
<td>Severe stroke as assessed clinically (e.g., NIHSS score &gt;25) or by appropriate imaging techniques*</td>
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<tr>
<td>Seizure at the onset of stroke</td>
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<tr>
<td>Stroke or serious head trauma within the previous 3 months</td>
</tr>
<tr>
<td>Combination of previous stroke and diabetes mellitus</td>
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<tr>
<td>Administration of heparin within the 48 hours preceding the onset of stroke, with an activated partial thromboplastin time at presentation exceeding the upper limit of the normal range</td>
</tr>
<tr>
<td>Platelet count of less than 100,000 per cubic millimeter</td>
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<tr>
<td>Systolic pressure greater than 185 mm Hg or diastolic pressure greater than 110 mm Hg, or aggressive treatment (intravenous medication) necessary to reduce blood pressure to these limits</td>
</tr>
<tr>
<td>Blood glucose less than 50 mg per deciliter or greater than 400 mg per deciliter</td>
</tr>
<tr>
<td>Symptoms suggestive of subarachnoid hemorrhage, even if CT scan was normal</td>
</tr>
<tr>
<td>Oral anticoagulant treatment</td>
</tr>
<tr>
<td>Major surgery or severe trauma within the previous 3 months</td>
</tr>
<tr>
<td>Other major disorders associated with an increased risk of bleeding</td>
</tr>
</tbody>
</table>
• **No difference in mortality rates** (7.7% rtPA versus 8.4% placebo)
• **Higher rate of ICH** in rtPA-treated patients (27%) compared to placebo (17.6%, P=0.001)
• (Note: NINDS trial had a 6.4% ICH rate)
Thrombectomy Trials

What if thrombolysis doesn’t work?

Can’t we just go remove the thrombus?
Mechanical Thrombectomy for Acute Ischemic Stroke
Final Results of the Multi MERCI Trial

Wade S. Smith, MD, PhD; Gene Sung, MD, MPH; Jeffrey Saver, MD;
Gary Duckwiler, MD; David S. Liebeskind, MD; Helmi L. Lutsep, MD;
Randall T. Higashida, MD; Sidney Starkman, MD; Y. F. for the Multi MERCI Investigators
Multi-MERCI Results

- **69.5% arterial recanalization rate** (TIMI Grade 2-3 flow) using the MERCI device +/- adjuvant thrombolytic therapy
  - 57.3% recanalization rate with device alone

- Favorable clinical outcomes (mRS scores ≤ 2) were observed in **36%** of patients

- Great results, at a price...
  - **34% mortality rate**
  - **16 intracranial hemorrhages (9.8%)**
Revascularization Improves Outcome

Revascularized

Non-revascularized
Meta-analysis Shows a Strong Correlation Between Revascularization and Good Patient Outcomes

Differences in sICH were not statistically significant between the revascularized and non-revascularized groups.


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The Penumbra Pivotal Stroke Trial

Safety and Effectiveness of a New Generation of Mechanical Devices for Clot Removal in Intracranial Large Vessel Occlusive Disease

The Penumbra Pivotal Stroke Trial Investigators

**Background and Purpose**—The purpose of this clinical evaluation was to assess the safety and effectiveness of the Penumbra System in the revascularization of patients presenting with strokes within 8 hours of symptom onset. Intracranial hemorrhage on 24-hour CT was seen in 14 (11.2%) of the patients, with 25% of the patients achieving a modified Rankin Score of 0 after 90 days.

**Conclusions**—These results suggest the Penumbra System allows safe and effective revascularization in patients experiencing ischemic stroke secondary to large vessel occlusive disease who present within 8 hours from symptom onset. *(Stroke. 2009;40:2761-2768.)*
82% recanalization (TIMI Grade 2 or 3 flow) in 125 treated arteries

28% intracranial hemorrhage rate

25% independent outcome at 90 days

Table 2. Neurological and Functional Outcomes From Open versus Closed Vessels

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Percent With Outcome</th>
<th>Overall (N=125)</th>
<th>TIMI 2–3 (N=102)</th>
<th>TIMI 0–1 (N=23)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discharge NIHSS 0–1 or improved by ≥10</td>
<td>27</td>
<td>32</td>
<td>5</td>
<td>0.0127</td>
<td></td>
</tr>
<tr>
<td>Good clinical outcome at 30 days†</td>
<td>30</td>
<td>35</td>
<td>9</td>
<td>0.0199</td>
<td></td>
</tr>
<tr>
<td>mRS ≤2 at 90 days</td>
<td>25</td>
<td>29</td>
<td>9</td>
<td>0.0596</td>
<td></td>
</tr>
<tr>
<td>Death at 90 days</td>
<td>33</td>
<td>29</td>
<td>48</td>
<td>0.1384</td>
<td></td>
</tr>
</tbody>
</table>

*P is for testing of the difference in outcome rates using a 2-tailed Fisher exact test.
†A composite of the discharge NIHSS score of 0–1 or improved by ≥10 points or a 30-day mRS score of ≤2.
Findings Between Feb 3, 2011, and June 30, 2011, 90 patients to Merci Retriever group and 100 patients to the primary endpoint after the assigned treatment in the primary safety endpoint did not differ between the Merci group; \( p=0.1826 \).

Interpretation Patients who have had a stroke due to tissue plasminogen activator showed...
TREVO 2

- Randomized trial for stroke patients with large vessel occlusion, NIHSS 8-29, and within 8 hours of symptom onset
  - 88 patients randomized to TREVO device
  - 90 patients randomized to MERCI device

- Results
  - Revascularization (TICI 2) was superior in TREVO (86%) compared to MERCI (60%), p < 0.0001
  - Safety profiles were similar (no significant difference in hemorrhage, death, etc)
Thrombectomy Works!

- Multi-MERCI, Penumbra, TREVO 2, and SWIFT all have similar results
  - Increasing ability to get the vessel open
<table>
<thead>
<tr>
<th></th>
<th>PROACT II</th>
<th>MULTI-MERCi</th>
<th>MERCI 2</th>
<th>CLOTBUST</th>
<th>EKOS 1</th>
<th>Penumbra</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>121</td>
<td>164</td>
<td>141</td>
<td>63</td>
<td>14</td>
<td>125</td>
</tr>
<tr>
<td>Age, years</td>
<td>64</td>
<td>68</td>
<td>67</td>
<td>67</td>
<td>64</td>
<td>64</td>
</tr>
<tr>
<td>Baseline NIHSS</td>
<td>17</td>
<td>19</td>
<td>20</td>
<td>16</td>
<td>18</td>
<td>18</td>
</tr>
<tr>
<td><strong>Revascularization, %</strong></td>
<td><strong>66</strong></td>
<td><strong>68</strong></td>
<td><strong>48</strong></td>
<td><strong>38</strong></td>
<td><strong>57</strong></td>
<td><strong>82</strong></td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(57.0–74.5)</td>
<td>(61–75)</td>
<td>(39.7–56.8)</td>
<td>(26.2–51.2)</td>
<td>(28.9–82.3)</td>
<td>(73.7–88.0)</td>
</tr>
<tr>
<td>Symptomatic ICH, %</td>
<td>10.9‡</td>
<td>9.8*</td>
<td>7.8*</td>
<td>4.8†</td>
<td>14</td>
<td>11.2</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(5.9–17.7)</td>
<td>(5.2–14.3)</td>
<td>(3.5–12.7)</td>
<td>(1–13.3)</td>
<td>(0.2–33.9)</td>
<td>(6.3–18.1)</td>
</tr>
<tr>
<td>Asymptomatic ICH, %</td>
<td>25</td>
<td>30.5</td>
<td>27.7</td>
<td>N/R</td>
<td>N/R</td>
<td>16.8</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(17.4–33.5)</td>
<td>(24–38)</td>
<td>(20.5–35.8)</td>
<td>N/R</td>
<td>N/R</td>
<td>(10.7–24.5)</td>
</tr>
<tr>
<td>90-day mortality</td>
<td>25</td>
<td>34</td>
<td>43.5</td>
<td>15</td>
<td>36</td>
<td>32.8</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(17.4–33.5)</td>
<td>(26–41)</td>
<td>(35.0–51.9)</td>
<td>(6.8–25.4)</td>
<td>(12.8–64.9)</td>
<td>(24.7–41.8)</td>
</tr>
<tr>
<td><strong>90-day mRS ≤2</strong></td>
<td><strong>40</strong></td>
<td><strong>36</strong></td>
<td><strong>27.7</strong></td>
<td><strong>42</strong></td>
<td><strong>43</strong></td>
<td><strong>25</strong></td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(31.7–49.8)</td>
<td>(29–44)</td>
<td>(21.1–36.6)</td>
<td>(at 0–1)</td>
<td>(30.5–56.0)</td>
<td>(23.0–77.0)</td>
</tr>
</tbody>
</table>

CLOTBUST indicates The Combined Lysis of Thrombus in Brain Ischemia Using Transcranial Ultrasound and Systemic t-PA Trial; EKOS, MicroLys US System Trial.

*Four-point or greater decline in the NIHSS score within 24 hours with any blood products on head CT at 24 hours (petechial bleeding, hematoma, or subarachnoid hemorrhage) or any intracranial hemorrhage in which no further NIHSS scores were available beyond baseline and the patient died.

†Hemorrhage with clinical worsening (indicated by an NIHSS score of 4) within 72 hours of the onset of stroke.

‡If it was associated with a clinical deterioration of >4 points on the NIHSS or 1-point deterioration in level of consciousness.

N/R indicates not reported.
Current Controversy: Does this stroke intervention stuff work?
December 2014

Validation of Thrombectomy for Acute Ischemic Stroke
A Randomized Trial of Intraarterial Treatment for Acute Ischemic Stroke


ABSTRACT
MR CLEAN

• Randomized trial of intraarterial thrombectomy + usual care compared to usual care alone
  ─ Within 6 hours of stroke symptom onset
  ─ Large vessel occlusion (ICA, MCA, ACA)
  ─ 500 patients in 16 centers in the Netherlands
    • 233 intraarterial thrombectomy + usual care
    • 267 usual care alone
  ─ Blinded mRS evaluation at 90 days
  ─ Intention to treat analysis
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Intervention (N=233)</th>
<th>Control (N=267)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years (median)</td>
<td>65.8</td>
<td>65.7</td>
</tr>
<tr>
<td>Male sex</td>
<td>135 (57.9%)</td>
<td>157 (58.8%)</td>
</tr>
<tr>
<td>NIHSS score (median)</td>
<td>17</td>
<td>18</td>
</tr>
<tr>
<td>Treatment with IV alteplase</td>
<td>203 (87.1%)</td>
<td>242 (90.6%)</td>
</tr>
<tr>
<td>Extracranial ICA occlusion</td>
<td>32.2%</td>
<td>26.3%</td>
</tr>
<tr>
<td>ASPECTS</td>
<td>9</td>
<td>9</td>
</tr>
</tbody>
</table>
MR CLEAN – Recanalization Rates

Recanalization on CTA after 24 Hours

Control (68/207) 33%

Intervention (141/187) 75%
MR CLEAN - Primary Outcome

mRS at 90 days

Common adjusted odds ratio: 1.67 (95% CI: 1.21 to 2.30)


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### Serious Adverse Events @ 90 days (P=0.31)

<table>
<thead>
<tr>
<th>Serious Adverse Events</th>
<th>Intervention (N=233)</th>
<th>Control (N=267)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any serious adverse event</td>
<td>110 (47.2%)</td>
<td>113 (42.3%)</td>
</tr>
<tr>
<td>Parenchymal hematoma type 2</td>
<td>14 (6.0%)</td>
<td>14 (5.2%)</td>
</tr>
<tr>
<td>New ischemic stroke in different vascular territory*</td>
<td>13 (5.6%)</td>
<td>1 (0.4%)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>25 (10.7%)</td>
<td>41 (15.4%)</td>
</tr>
<tr>
<td>Hemicraniectomy</td>
<td>14 (6.0%)</td>
<td>13 (4.9%)</td>
</tr>
<tr>
<td>Death</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Within 7 days</td>
<td>27 (11.6%)</td>
<td>33 (12.4%)</td>
</tr>
<tr>
<td>Within 30 days</td>
<td>44 (18.9%)</td>
<td>49 (18.4%)</td>
</tr>
</tbody>
</table>
Stroke in 2015

• MR CLEAN data demonstrates *improved outcomes* with stroke intervention
  – Other studies in process of publication seem to confirm the findings of MR CLEAN

• Stroke centers nationally are working on treatment algorithms to implement strategies used in the trial
Thank you!

• Questions???

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References


