Endovascular Treatment of Acute Ischemic Stroke

William R. Stetler, Jr, MD
Assistant Professor
UAB, Dept of Neurosurgery

Disclosures

• No financial disclosures

IA Stroke Therapy

• 28 y/o F w/ h/o HTN, DM, Obesity, prior “clots” in legs w/ resulting toe amputations
• Acute onset R hemiplegia and aphasia at 14:30
• Went to OSH
• CT scan – no hemorrhage, hyperdense MCA
• IV tPA administered at 16:30
• Transferred to UAB
An estimated 795,000 Americans will suffer a new or recurrent stroke this year…

…that’s one every 40 seconds

87% of strokes are ischemic; only 1% of these patients get intervention.

13% of strokes are hemorrhagic:
- 10% intracerebral
- 3% subarachnoid

87% of strokes are ischemic; only 1% of these patients get intervention.
Physiological Impact of Stroke

Estimated Pace of Neural Circuitry Lost in a Typical Large Vessel Acute Ischemic Stroke

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Neurons Lost</th>
<th>Synapses Lost</th>
<th>Myelinated Fibers Lost</th>
<th>Estimated Aging</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.3</td>
<td>8.1 billion</td>
<td>800 billion</td>
<td>1.1 billion</td>
<td>0.3 years</td>
</tr>
<tr>
<td>1.6</td>
<td>130 million</td>
<td>14 billion</td>
<td>175 million</td>
<td>3.6 hours</td>
</tr>
<tr>
<td>5</td>
<td>12.5 trillion</td>
<td>1.8 trillion</td>
<td>218 million</td>
<td>4470 days</td>
</tr>
</tbody>
</table>


Stroke kills more women than breast, ovarian, uterine and cervical cancer combined.

US Prevalence of Stroke by Age and Sex

Race is a Risk Factor for Stroke

African-Americans have a risk of first-ever stroke that is almost twice that of Caucasians.
IV t-PA (alteplase)

- Currently the only FDA-approved medical treatment for acute ischemic stroke
- ≤ 3 hours since symptom onset
- Approved in Europe for ≤ 4.5 hours since symptom onset

NINDS: 0 to 3 hours

ECASS III: 3 to 4.5 hours
Benefit and harm of IV t-PA per 100 Patients

Significant IV t-PA related to previous 3 months
Significant IV t-PA related to subarachnoid hemorrhage
Arterial puncture at noncompressible site in previous 3 days
History of previous intracerebral hemorrhage
Intracerebral malignancies, arteriovenous malformation, or aneurysm
Recent intracranial or intraspinal surgery
Elevated systolic blood pressure (systolic >160 mm Hg or diastolic >110 mm Hg)
Active internal bleeding
Acute bleeding conditions, including but not limited to
Intracranial or intraspinal surgery
Hypertension within 24 hours, resulting in abnormal elevated aPTT greater than the upper limit of normal
Current use of anticoagulants with INR >1.7 or PT >15 seconds
Current use of direct thrombin inhibitors or direct factor Xa inhibitors with elevated sensitive laboratory tests such as aPTT, INR, platelet count, and ECT, TT, or appropriate factor for anticoagulant
Blood glucose concentration <50 mg/dL (2.7 mmol/L)
CT demonstrates multilobar hypodensity >1/3 cerebral hemisphere

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

*P-value with seeing statistically significant correlation

Impact of Clot Burden on Success Rate of IV tPA

50% recanalization

Successful Recanalization

$\text{Persistent Occlusion}$


35-40% of Ischemic Strokes are Considered “Large Vessel”

- This subset of ischemic stroke comprises blockages in the:
  - Internal Carotid Artery (ICA)
  - Middle Cerebral Artery (MCA)
  - Vertebral / Basilar Artery

- If left untreated, patient prognosis with these types of stroke is poor

<table>
<thead>
<tr>
<th>Vessel</th>
<th>Mortality Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICA</td>
<td>53%</td>
</tr>
<tr>
<td>MCA</td>
<td>27%</td>
</tr>
<tr>
<td>Basilar Artery</td>
<td>85-90%</td>
</tr>
</tbody>
</table>

Endovascular Horizon
Background : NIHSS

- Consciousness: 0-3
- Commands: 0-2
- Orientation: 0-2
- Language: 0-3
- Articulation: 0-2
- Neglect: 0-2
- Eye Movement: 0-2
- Motor:
  - Upper (R/L): 0-4
  - Lower (R/L): 0-4
  - Face: 0-3
- Sensory: 0-2
- Coordination: 0-2
- Visual Fields: 0-3

Total = 0-42

Minor = 1-4
Moderate = 5-15
Severe = 16-21

TICI Scale

Thrombolysis In Cerebral Infarction

- 0: No change
- 1: Slight partial recanalization
- 2a: Recanalization <50%
- 2b: Recanalization >50%
- 3: Complete recanalization
**ASPECTS**

- Systematic way to evaluate non-contrast CT head
- 1-10 scale:
  - 10 = completely normal
  - 0 = complete and total MCA completed infarction

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**PROACT II**
Furlan et al 1999

- 180 patients, < 6 hrs
- IA Urokinase vs IA heparin
- Primary outcome = mRS 2 or less
  - 40% vs. 25%, better in IA
- Symptomatic ICH 10% IA vs 2% control
- NNT = 7, NNH = 12

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**MERCI -2005**

- Phase I study, 161 ptnts, < 8 hrs, NIHSS > 8
- Recanalization ~ 50%
- Symptomatic ICH in 8%
- Good outcome more likely w/ recanalization
- Conclusion: OK to use when tpa contraindicated
Penumbra-2008

- Phase I study, 23 pts
- < 8 hrs, NIHSS > 8
- Primary outcome = recanalization → achieved in 100%
- Mortality 45%
- Good outcome in 45%
- F/u Study in 2009 with 27 pts
  - Recanalization in 93%

IMS III – Stroke 2013

- Phase III RTC of stroke pts NIHSS > 10
- IV alone vs. IA + IV (2/3 dose)
- MERCI Device predominantly
- 656 randomized, 58 centers, 6 years (<2 pts/center)
- Primary outcome = mRS 2 or less
- Stopped early secondary to futility
**MR RESCUE**

- Phase IIb RCT
- NIHSS > 5, < 8hrs
- 2004-2011, 127 pts, 118 analyzed (9 excluded)
- Randomized: embolectomy vs. medical care
  - Used only MERCI and Penumbra devices
  - Stratified based on penumbral imaging patterns
- Good outcome (mRS 0-2) not statistically significant
- Perfusion pattern didn’t fit with outcome
-Pts with revascularization had better outcome

**SYNTHESIS**

- Phase IIb RCT
- No minimum NIHSS, < 4.5hrs for randomization
- IV tpa vs. IA tpa
- 2008-2012, 362 pts
  - 181 to each group
  - Intervention = IA tpa +/- mechanical
- Primary outcome mRS 0-1 \(\rightarrow\) no statistical difference

**DOES ENDOVASCULAR THERAPY WORK?**
'Whoever wishes to foresee the future must consult the past; for human events ever resemble those of preceding times.'
- Machiavelli

Lessons Learned from Cardiology
- First document case of intracoronary administration of fibrinolysis in acute MI in 1976 (article in Russian)
- Then described again in 1982 via Meyer et al (article in German)
- Then multiple small series and abstracts that did not show significant benefit.
- Then.....
We conclude that in patients with initially successful thrombolysis and suitable coronary-artery anatomy, immediate angioplasty offers no clear advantage over delayed elective angioplasty. (N Engl J Med 1987; 317: 581–4.)
Question is answered, right?

Conclusions...
Failures of Previous Trials

- Past trials of endovascular stroke treatment failed to show benefit in the intervention arm
- IMS 3, MR RESCUE, SYNTHESIS-Expansion
- Key learnings to improve IA Stroke trial results:
  - Imaging to confirm large vessel occlusion
  - Imaging to exclude patients with a large infarct core
  - Improve time to treatment
  - Use newest devices to improve recanalization rates

Turning Point
The Era of Stent-Retrievers

- Technological advances
  - Stent-retriever technology for safe, reliable performance
  - Significant improvement in revascularization and patient outcomes vs older technology, proven in randomized clinical trials

Stent Retrievers

- Two Devices:
  - Solitaire – eV3, 2012 FDA
  - TREVO – Stryker 2012 FDA
Stent-Retriever Studies

- **SWIFT** – Saver et al 2012
  - NIHSS > 8, < 8hrs, ineligible or failed tpa
  - 114 pts- Solitaire vs MERCI randomized
  - Primary outcome TIMI 2/3 – twice as likely Solitaire
  - mRS 2 or less twice as likely with Solitaire
  - Symptomatic ICH less in Solitaire

- **TREVO-2** – Nogueira et al 2012
  - NIHSS > 8, within 8hrs
  - 88 pts – Trevo vs MERCI
  - Primary outcome TICI 2b/3 – nearly twice as likely TREVO
  - mRS 2 or less twice as likely TREVO

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**MR CLEAN**
A Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands

- Multicenter (16 Centers in Netherlands), prospective, randomized trial, open-label treatment and:
  - Blinded assessment of functional outcome at 90 days
  - Blinded assessment of neuro-imaging at baseline and follow-up
  - Masked, web-based, 1:1 random treatment allocation
  - Intraarterial treatment (IA thrombolysis, mechanical treatment or both) plus usual care (could include IV tPA)
  - Usual care alone (control group)

- Inclusion Criteria
  - Acute ischemic stroke, Age ≥18, NIHSS ≥2
  - Intracranial anterior circulation occlusion (confirmed by CTA)
  - Initiation of IA treatment within 6 hours from onset

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**Design**

- Overview
  - Description of the study design and methodology
  - Analysis of patient outcomes and treatment effectiveness

- Results
  - Presentation of study findings and statistical analysis
  - Discussion of implications and future directions
Patients were randomized 1:1

Baseline Patient Characteristics

<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 (median)</td>
<td>9</td>
<td>9</td>
</tr>
</tbody>
</table>

Distribution of Occlusion Location at Baseline

* ICA with involvement of M1


Stent Retrievers were 97% of IAT Treatment in the Intervention Arm

Post-intervention TICI Scores In Treated Patients (N=196)
7x More Likely to Recanalize with Intra-Arterial Treatment*

Recanalization on CTA after 24 Hours

Control (68/207)  Intervention (141/187)

<table>
<thead>
<tr>
<th>Percentage</th>
<th>Control</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>0%</td>
<td>33%</td>
<td>75%</td>
</tr>
</tbody>
</table>

*Adjusted value odds ratio (95% CI) for “no intracranial occlusion on follow up CT angiography” in the intervention group versus the control group was 6.88 (4.34 to 10.94). Values were adjusted for age, NIHSS at baseline, time from onset to randomization, status with respect to previous stroke, atrial fibrillation, diabetes mellitus and occlusion of the ICAT. Data for follow up CT angiography were not available for 106 patients.


Effect Of Intervention On Primary Outcome

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

Serious Adverse Events

<table>
<thead>
<tr>
<th>Event Description</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 event 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 Within 7 days</td>
<td>27 (11.6%)</td>
<td>33 (12.6%)</td>
</tr>
<tr>
<td>Death Within 30 days</td>
<td>44 (18.9%)</td>
<td>49 (18.4%)</td>
</tr>
</tbody>
</table>

*No Significant Between-Group Difference in the Occurrence of Serious Adverse Events @ 90 days (P=0.31)

MR CLEAN Study Conclusion

- In patients with acute ischemic stroke caused by a proximal intracranial arterial occlusion of the anterior circulation, intraarterial treatment administered within 6 hours after stroke onset was effective and safe
- This treatment leads to a clinically significant increase in the functional independence in daily life by 3 months, without an increase in mortality
- Primary outcome measure: mRS at 90 days
  - mRS 0-2:
    - IA group: 32.6%
    - Control group: 19.1%

2015: Important Clinical Trials

- MR CLEAN
- SYNTHESIS
- SWIFT PRIME
- EXTEND-IA
- REVASCAT

Stent Retriever Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Randomized Patients</th>
<th>Randomized Treatments</th>
<th>Blood Flow Restoration</th>
<th>Clinical Outcomes</th>
<th>mRS Improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>MR CLEAN</td>
<td>552</td>
<td>552</td>
<td>25</td>
<td>25</td>
<td>10</td>
</tr>
<tr>
<td>GLASPE</td>
<td>832</td>
<td>832</td>
<td>30</td>
<td>30</td>
<td>10</td>
</tr>
<tr>
<td>REVASCAT</td>
<td>960</td>
<td>960</td>
<td>40</td>
<td>40</td>
<td>15</td>
</tr>
<tr>
<td>SWIFT PRIME</td>
<td>196</td>
<td>196</td>
<td>90</td>
<td>90</td>
<td>25</td>
</tr>
<tr>
<td>EXTEND-IA</td>
<td>15</td>
<td>15</td>
<td>150</td>
<td>150</td>
<td>10</td>
</tr>
</tbody>
</table>

JAMA Neurol. 2015; 72:1101-1103
**Thrombectomy Trials**

- **Image 1:**
  - Title: Thrombectomy Trials
  - Bar chart showing recanalization rates for different trials.
  - Key points: Recanalization rates range from 66% to 88%, with TICI 2b-3 rates varying across different trials.

**IA Trials: Recanalization Rates**

- **Image 2:**
  - Title: IA Trials: Recanalization Rates
  - Bar chart illustrating recanalization rates for different trials.
  - Key points: Recanalization rates for TICI 2b-3 range from 27% to 66%.

**Stent Retriever Trials**

- **Image 3:**
  - Table summarizing stent retriever trials.
  - Key points: Various trials with different numbers of participants and outcomes detailed in the table.
2015 AHA/ASA Focused Update of the 2013 Guidelines for the Early Management of Patients With Acute Ischemic Stroke

- Patients should receive endovascular therapy with a stent retriever if they meet all of the following criteria:
  - Pre-stroke mRS score 0 to 1
  - Acute ischemic stroke receiving intravenous t-PA with 4.5 hour of onset
  - Causative occlusion of the internal carotid artery
  - Age ≥ 18 years
  - ASPECTS of ≥ 6 and
  - Treatment can be initiated within 6 hours of symptom onset
- Etc. etc...

Risks and benefits of IA thrombectomy summarized

- Chance of reopening the blocked artery: 60-80%
- Risk of a major complication (symptomatic hemorrhage): 5-15%
- Chance of providing some neurological benefit: 20-60%

Intra-arterial thrombectomy: Patient selection

- Intra-arterial treatment of acute ischemic stroke
  - Patients with acute ischemic stroke who cannot be treated with IV t-PA
    - Wake-up stroke
    - IV t-PA is contraindicated
  - Non-responders to t-PA
    - Large clot burden (large vessel occlusion or >8 mm in length)
  - May treat out to 6 hours after symptom onset
  - Favorable imaging - ? Perfusion
Perfusion Imaging

DEFUSE and DAWN Trials

- Both randomized trials to select patients for IA therapy beyond 6 hrs since last known normal
- Select patients with favorable perfusion imaging and randomize to IA therapy and best medical management
- UAB is a DEFUSE site, but currently on hold since DAWN trial has finished.
DAWN

- DAWN = DWI or CTP Assessment with Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention
- Randomized trial of ischemic stroke due to large artery occlusion treated 6-24 hours after symptom onset using perfusion imaging (CT or MRI)
- Inclusion:
  - Baseline NIHSS score ≥10
  - ICA or MCA M1 occlusion
  - +/− cervical occlusion
- Primary endpoint: 90 day mRS

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DAWN

- Planned enrollment of 500 patients
  - Recently stopped early after 204 patients given significant benefit
  - Primary endpoint met in 48.6% IA vs 13.1% BMT
  - Relative reduction in disability of 73%
  - NNT = 2.8
  - Industry sponsored; paper is pending
• Patient left hospital several days later, antigravity in RUE, speech intact