What’s the Deal with Endovascular Stroke Trials?

MICHAEL G. ABRAHAM, MD
NEUROINTERVENTIONALIST AND NEUROINTENSIVIST
Disclosures

- Consultant for Stryker Neurovascular
- Speaker’s Bureau for Boehringer Ingelheim
Outline

- Basics of endovascular stroke therapy
- Endovascular stroke trials that we stand on
- Endovascular stroke trials to embrace and believe in
How We Arrived Here...

TODAY!

Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy (MR RESCUE), 2004-2011

SYNTHESIS-Expansion, 2008-2012

Interventional Management of Stroke (IMS) III, 2006-2012

Middle Cerebral Artery Embolism Local Fibrinolytic Intervention Trial (MELT), 2002-05

Prolyse in Acute Cerebral Thromboembolism (PROACT I & II), 1996-1998

NINDS IV recombinant-tPA, 1995

Aspirin
Endovascular Stroke Treatments

- IA tPA – 1998/1999
- Merci Retriever – 2005
- Penumbra aspiration - 2008
- Solitaire Stent-Retriever (SWIFT) - 2010
- Trevo Stent-Retriever (Trevo) - 2012
- Penumbra 5 Max Aspiration (ADAPT) - 2013
TIMI (thrombolysis in myocardial infarction)

- 0 - no perfusion
- 1 - penetration without perfusion, faint antegrade coronary flow beyond the occlusion, with incomplete filling of the distal coronary bed
- 2 - partial reperfusion, delayed or sluggish antegrade flow with complete filling of the distal territory
- 3 – complete filling of the coronary
mTICI (modified thrombolysis in cerebral ischemia)

- 0 – no perfusion
- 1 – antegrade reperfusion past the initial occlusion, but limited distal branch filling with little or slow distal reperfusion
- 2a – antegrade reperfusion of <1/2 of the occluded target artery
- 2b – antegrade reperfusion of >1/2 of the previously occluded target artery
- 3 – complete antegrade perfusion
THE TRIALS
PROACT I

- IA pro-urokinase 6 mg + IV heparin over 2 hours vs saline placebo with IV heparin within 6 hours of symptom onset in a 2:1 fashion after NCCT (n = 26 vs 14)
- Recanalization (TIMI 2/3) was improved in treatment arm (57.7% vs 14.3%, 2P = 0.017)
- SICH was increased in treatment arm (15.4% vs 7.1%, 2P = 0.64)
- 10-12% absolute increase in excellent neurologic outcomes (mRS 0-1)
- IA pro-urokinase 9 mg + IV heparin over 2 hours vs IV heparin alone within 6 hours of symptom onset in a 2:1 fashion after NCCT (121 vs 59)
- Recanalization (TIMI 2/3) was improved in treatment arm (66% vs 18%, P <0.001)
- SICH was non-significantly increased in treatment arm (10% vs 2%)
- 90 day mRS ≤2: 40% vs 25%, p=0.04
IA urokinase + IV heparin vs standard therapy within 6 hours

- Primary end point of mRS ≤2 not significantly different between two arms (49.1% vs 38.6%, p=0.345)
- mRS ≤1 higher in the treatment arm (42.1% vs 22.8%, p=0.045)
- No significant difference between 90 day mortality and ICH
- TIMI 2/3 in 73.7%

Trial was aborted after IV tPA was approved in Japan
IMS-3
(Interventional Management of Stroke)

- Began enrolling 2006
- IV tPA vs IV tPA + endovascular therapy (EVT)
  - 1:2 randomization
- Group 1 - standard IV tPA within 3 hours
- Group 2 (<5-7 hours)
  - Received standard dose of IV t-PA*
  - Cerebral angiogram after tPA to check for persistent clot
  - If clot not seen then no further treatment
  - If clot seen neurointerventionalist chooses (based on the location and extent of the blood clot) a protocol approved endovascular treatment
    - IA tPA only, IA tPA with device intervention, or device intervention alone

IMS-3

- Halted in 2012 due to futility (n=656)
  - No superiority of IV tPA + EVT vs IV tPA
    - Primary outcome of mRS ≤2 at 3 months (40.8% vs 48.7%)
  - No difference in safety outcomes, death, or SICH
Limitations of IMS-3

- **33% of patients had a CT-angiogram**
  - No large vessel occlusion (LVO) identified

- **~20% in the EVT arm had LVO**
  - 80% of patients with no LVO were exposed to an unnecessary procedure and its risks
  - Initially these patients received 2/3 dose of IV tPA
    - These are patients who would benefit most from IV tPA

- **Sub-group analyses**
  - Significant benefit in patients who underwent EVT in patients who did have a CT-angiogram demonstrating LVO

J NeuroIntervent Surg 2013;5:181-183
Patients were excluded if they had a large area of hypodensity suggesting completed infarct but not if other signs of completed infarct i.e. *sulcal effacement and loss of gray-white differentiation*

- 40% of patients had an Alberta Stroke Program Early CT score (ASPECTS) ≤7 (lower score = poorer prognosis)

- CT-perfusion and MR-perfusion were not used
Limitations of IMS-3

- Device of choice
  - Merci Retriever – 28.4%
    - antiquated device
  - Penumbra & Solitaire – 59 patients (13%)
  - TICI score 2b-3 in 23-44%

- SWIFT trial – TICI 2b-3 in 61% treated with Solitaire vs Merci Retriever
- Trevo 2 trial – TICI 2b-3 in 68% treated with Trevo vs Merci Retriever
MR-Rescue (Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy)

- Phase 2b randomized, open-label, blinded outcome, controlled trial
- Determine if neuroimaging (CT or MRI) can help predict better outcomes in patients undergoing EVT
- Patients randomized within 8 hours with anterior LVO to either Merci Retriever, Penumbra aspiration, or IA tPA vs IV tPA alone
  - Favorable penumbral pattern = substantial salvageable tissue + small infarct core (<90 mL)
  - Non-penumbral pattern = large core or small/absent penumbra
- $N = 64$ treatment arm
  - 34 vs 30
- $N = 54$ standard care arm
  - 34 vs 20
58% had a favorable penumbral pattern

TICI 2a/3 revascularization
- 67% penumbral embolectomy group
- No significant difference between all 4 groups

SICH – 3% vs 2%

Embolectomy vs. standard care was same across both groups
- Non-penumbral and favorable

90 day mRS ≤2 = 12% vs 11%
Limitations of MR RESCUE

- Antiquated devices
  - Merci Retriever
  - Early generation Penumbra aspiration
  - TICI 2b-3 in 25% (16/64)

- SWIFT trial – TICI 2b-3 in 61% treated with Solitaire vs Merci Retriever
- Trevo 2 trial – TICI 2b-3 in 68% treated with Trevo vs Merci Retriever

J NeuroIntervent Surg 2013;5:181-183
7 day revascularization and reperfusion associated with better outcomes regardless of treatment arm

- No patients in either group (favorable penumbra or non-penumbra) had a 90 day mRS ≤2 if not revascularized
- 35% of penumbral and 21% of non-penumbral patients who were revascularized had a 90 day mRS ≤2
• Open-treatment trial
• 181 patients randomized to IV tPA within 4.5 hours
• 181 patients randomized to endovascular therapy within 6 hours
  ○ Microwire clot maceration, IA tPA, other devices not outlined, “systems to capture and extract the thrombus, or more complex systems to crush and aspirate it”
• Primary outcome was mRS ≤1 at 90 days per telephone interview
**SYNTHESIS**

- **mRS ≤1 at 90 days**
  - 30.4% (55 patients) in EVT
  - 34.8% (63 patients) in the IV tPA group
  - $P=0.16$

- Fatal or nonfatal SICH was 6% in both groups

- No significant difference in other serious adverse events

- Study conclusion: EVT is not superior to standard IV tPA
Limitation in SYNTHESIS

- **Experimental algorithm**
  - mRS ≤1
  - 90 day follow up via telephone interview

- **Treatment was based on a non-contrast CT**
  - No CT-angio or MR-angio
  - No evidence of an LVO
Limitation in SYNTHESIS

- Median NIHSS 13, >50% were <11
  - Suggesting no LVO but rather perforator or small vessel occlusion
  - Patients receiving EVT did not receive IV tPA
    - IV tPA would more likely benefit lower NIHSS patients than EVT
- EVT arm treated 1 hour later than IV tPA
Limitation in SYNTHESIS

- Antiquated devices
  - Mircowire maceration
  - IA tPA at IV tPA doses (up to 0.9 mg/kg)
  - PROACT I and II used 6 and 9 mg, respectively
  - 66% treated with microwire maceration and/or IA tPA
  - If no LVO was found, then protocol called for IA tPA into the presumed affected vascular area
  - 56 (33%) stent-retriever, aspiration, Merci

- Results did not report percent who had LVO or TICI scores
THE COOL STUFF
Primary outcome of mRS ≤2 had 1.67 higher OR for EVT
Shift toward better outcomes in favor of intervention in all categories of mRS except death
mTICI 2b/3 achieved in 115/196 patients (58.7%) in EVT group
reperfusion at 24 hours
  75.4% vs 32.9%
5.6% in the EVT group vs 0.4% in the control group had clinical signs of a new ischemic stroke in a different vascular territory within 90 days
No significant difference in adverse events or mortality at 7, 30, and 90 days
Endovascular Stroke Trials

- Meta-analysis of above 6 endovascular stroke trials
  - Fargen et al, January 2015
  - Primary outcome mRS ≤2 at 90 days
- Pre-randomization LVO confirmation (dataset 1, 1183 total patients)
- Pre-randomization regardless of LVO confirmation (dataset 2, 1903 patients)
Table 1  Characteristics of the six included studies

<table>
<thead>
<tr>
<th>Trial</th>
<th>Trial period</th>
<th>Location</th>
<th>No of centers</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROACT II</td>
<td>1996–1998</td>
<td>North America</td>
<td>54</td>
</tr>
<tr>
<td>MELT</td>
<td>2002–2005</td>
<td>Japan</td>
<td>57</td>
</tr>
<tr>
<td>IMS III</td>
<td>2006–2012</td>
<td>North America, Europe, Australia</td>
<td>58</td>
</tr>
<tr>
<td>SYNTHESIS</td>
<td>2008–2012</td>
<td>Europe</td>
<td>24</td>
</tr>
<tr>
<td>MR RESCUE</td>
<td>2004–2011</td>
<td>North America</td>
<td>22</td>
</tr>
<tr>
<td>MR CLEAN</td>
<td>2010–2014</td>
<td>Europe</td>
<td>30</td>
</tr>
</tbody>
</table>

Enrollment criteria

<table>
<thead>
<tr>
<th>Trial</th>
<th>Time from symptom onset</th>
<th>Age (years)</th>
<th>NIHSS</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROACT II</td>
<td>&lt;6 h</td>
<td>18–85</td>
<td>4–30</td>
</tr>
<tr>
<td>MELT</td>
<td>&lt;6 h</td>
<td>20–75</td>
<td>5–22</td>
</tr>
<tr>
<td>IMS III</td>
<td>&lt;3 h</td>
<td>18–82</td>
<td>≥10 (≥8)*</td>
</tr>
<tr>
<td>SYNTHESIS</td>
<td>&lt;4.5 h</td>
<td>18–80</td>
<td>Any</td>
</tr>
<tr>
<td>MR RESCUE</td>
<td>&lt;8 h</td>
<td>18–85</td>
<td>6–29</td>
</tr>
<tr>
<td>MR CLEAN</td>
<td>&lt;6 h</td>
<td>≥18</td>
<td>≥2</td>
</tr>
<tr>
<td>Outcome measure</td>
<td>IA arm (n (%) unweighted)</td>
<td>Medical arm (n (%) unweighted)</td>
<td>OR (95% CI), p value</td>
</tr>
<tr>
<td>----------------------------------------------------</td>
<td>---------------------------</td>
<td>-------------------------------</td>
<td>---------------------</td>
</tr>
<tr>
<td><strong>Included studies with LVO confirmed at time of randomization</strong> (dataset 1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary outcome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mRS 0–2 at 90 days</td>
<td>251 (38.3)</td>
<td>136 (25.8)</td>
<td>1.67 (1.29 to 2.16), p=0.0001</td>
</tr>
<tr>
<td>Secondary outcomes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mRS 0–1 at 90 days</td>
<td>156 (23.8)</td>
<td>66 (12.5)</td>
<td>1.93 (1.39 to 2.68), p&lt;0.0001</td>
</tr>
<tr>
<td>mRS 0–3 at 90 days</td>
<td>348 (53.1)</td>
<td>224 (42.4)</td>
<td>1.46 (1.16 to 1.85), p=0.002</td>
</tr>
<tr>
<td>Mortality at 90 days</td>
<td>122 (18.6)</td>
<td>114 (21.6)</td>
<td>0.80 (0.60 to 1.07), p=0.13</td>
</tr>
<tr>
<td>mRS shift analysis (mean)</td>
<td>3.35</td>
<td>3.73</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td><strong>All included studies</strong> (dataset 2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary outcome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mRS 0–2 at 90 days</td>
<td>419 (39.1)</td>
<td>271 (32.6)</td>
<td>1.27 (1.04 to 1.54), p=0.018</td>
</tr>
<tr>
<td>Secondary outcomes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mRS 0–1 at 90 days</td>
<td>270 (25.2)</td>
<td>169 (20.3)</td>
<td>1.22 (0.97 to 1.53), p=0.09</td>
</tr>
<tr>
<td>mRS 0–3 at 90 days</td>
<td>600 (56.0)</td>
<td>412 (49.5)</td>
<td>1.25 (1.04 to 1.51), p=0.019</td>
</tr>
<tr>
<td>Mortality at 90 days</td>
<td>203 (19.0)</td>
<td>156 (18.8)</td>
<td>0.96 (0.76 to 1.22), p=0.73</td>
</tr>
<tr>
<td>mRS shift analysis (mean)</td>
<td>3.16</td>
<td>3.42</td>
<td>p=0.003</td>
</tr>
</tbody>
</table>

IA, intra-arterial; LVO, large vessel occlusion; mRS, modified Rankin score.
Even with 3 “negative” trials better OR of good outcome with EVT

Patients randomized to endovascular therapies had almost a 2 times greater odds of a good outcome at 90 days compared with those randomized to medical management with a mean time of groin puncture >4 hours
Limitations
- Retrospective
- Different inclusion/exclusion criteria of trials
- Different devices/therapies
- Different outcome measures

ANOVA testing was done to evaluate the potential discrepancies
- study year, location, number of centers, difference in mean NIHSS between the endovascular and medical arms, difference in mean age between endovascular and medical arms, and mean time to endovascular treatment and treatment modality
- None were associated with clinical outcome
EVT Trials Hot Off the Press
SWIFT PRIME

- Solitaire FR With the Intention For Thrombectomy as Primary Endovascular Treatment for Acute Ischemic Stroke Clinical Trial
- IV tPA alone within 4.5 hours vs IV tPA and Solitaire FR within 6 hours of symptom onset
SWIFT-PRIME

- N = 196
- Mean image to groin time 58 minutes
- Mean image to recanalization time 252 minutes
- 88% mTICI 2b/3
- 90 day mRS ≤2
  - 60% vs 35.5%
- SICH
  - 1 vs 3.1% (NS)
ESCAPE Trial

- Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion With Emphasis on Minimizing CT to Recanalization Times
- Investigator initiated
- Ischemic stroke $\leq 12$ hours of last seen normal treated with best standard of medical care (n=118) vs endovascular therapy $\pm$ IV tPA (n=120) $\leq 4.5$ hours
- Endovascular treatment - stentriever $\pm$ other at discretion of neurointerventionalist

N Engl J Med. 2015 Feb 11
ESCAPE

- No upper age limit, BI 90-100
- CT → groin time mean 51 minutes
- CT → recanalization time mean 84 minutes
- Recommended balloon-guide catheter
- Recommended stentriever (86.1%)
- Avoid general anesthesia
- November 6th, 2014 – stopped due to efficacy
- 72% IV tPA
- enrolled 1.44 participants per center per month
ESCAPE Trial

- Multi-phase CTA to assess collaterals

**Radiology. 2015 Jan 29:142256**
<table>
<thead>
<tr>
<th></th>
<th>ESCAPE</th>
<th>EVT</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>90 d mortality</td>
<td></td>
<td>10%</td>
<td>19%</td>
</tr>
<tr>
<td>SICH</td>
<td>3.6%</td>
<td></td>
<td>2.7%</td>
</tr>
<tr>
<td>Recanalization</td>
<td>72.4% - TICI 2b/3</td>
<td>31.2% mAOL 2-3</td>
<td></td>
</tr>
<tr>
<td>90 d mRS ≤2 (p&lt;0.001)</td>
<td>53%</td>
<td></td>
<td>29.3%</td>
</tr>
<tr>
<td>90 d NIHSS 0-2</td>
<td>51.6%</td>
<td></td>
<td>23.1%</td>
</tr>
<tr>
<td>Adjusted OR</td>
<td>3.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;80 y/o</td>
<td>3.01 OR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;80 y/o</td>
<td>2.67 OR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11 (3.6%) ASPECTS &lt;6</td>
<td></td>
<td></td>
<td>ASPECTS &lt;6</td>
</tr>
<tr>
<td>Gen Anesthesia</td>
<td></td>
<td>15 (9.1%)</td>
<td></td>
</tr>
<tr>
<td>Median Sx onset to Reperfusion</td>
<td></td>
<td>241 minutes</td>
<td></td>
</tr>
<tr>
<td>NNT</td>
<td>4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
EXTEND-IA

- A multicenter, randomized, controlled study to investigate EXtending the time for Thrombolysis in Emergency Neurological Deficits with Intra-Arterial therapy
  - Investigator-initiated
  - All patients receive IV tPA 0.9 mg/kg within 4.5 h of stroke onset undergo multimodal CT or MRI
  - Dual target imaging criteria: vessel occlusion (ICA or MCA) and mismatch (perfusion lesion: ischemic core mismatch ratio >1.2, absolute mismatch >10 ml, ischemic core volume <70 ml)
  - Randomized to either clot retrieval with the Solitaire FR device (6-8 hours) or IV tPA alone (4.5 hours)
  - No age limit, mRS 0-1

EXTEND-IA

- Primary outcomes
  - reperfusion at 24 hours
  - early neurologic improvement (≥8-point reduction on the NIHSS or a score of 0 or 1 at day 3)
- Treated patients only during “normal” hours
- $N = 70$ (35 vs 35)
- 10% reperfusion by angio time
- 30% ICA occlusion in both arms
- Median time from onset to EVT was 50 minutes shorter than in MR CLEAN

EXTEND-IA

- Stopped at 70 patients due to MR CLEAN results
- 225 (22%) patients out of operating hours
- reperfusion at 24 hours (P<0.001)
  - Median 100% endovascular-therapy group
  - Median 37% IV tPA-only group
- EVT initiated at a median of 210 minutes after the onset of stroke
- 86% mTICI 2b/3
- Decrease in NIHSS ≥8 within 3 days
  - 80% vs 37% (P=0.002)
- 90 day mRS ≤2
  - 71% vs 40% (p=0.01)

90 day mortality
- 9% vs 20%

SICH
- 0 vs 6%

Median number of days spent at home vs in hospital/inpatient facility) in first 90 days after stroke was 64 days greater in the endovascular-therapy group than in the IV tPA-only group (P=0.001)

NNT 3

Why the Better Outcomes?

- Merci Retriever
Why the Better Outcomes?

- MR CLEAN
  - TICI 2b/3a 58%

- SWIFT
  - Solitaire TICI 2b/3a 61%

- TREVO
  - Trevo TICI 2b/3a 68%

- ADAPT
  - Penumbra 5 Max Ace TICI 2b/3a 78%
  - With stent-retriever 95%

- IMS 3
  - TICI 2b/3a 23-44%
National Multicenter Registries

- **North American Solitaire Acute Stroke registry (NASA)**
  - post-marketing, retrospective registry on use of the Solitaire FR device in acute stroke patients
  - primary outcomes were 90 day mRS, mortality, and symptomatic intracranial hemorrhage
  - 281 patients (KUMC 9)

- **Trevo Acute Ischemic Stroke Thrombectomy Registry (TRACK)**
  - post-marketing, retrospective registry on the use of Trevo Device in acute ischemic stroke patients
  - primary outcomes were 90 day mRS, mTICI, symptomatic intracranial hemorrhage
  - 409 patients (KUMC 21)
National Multicenter Registries

- **NASA**
  - 42.5% mRS ≤2
  - TICI 2b/3 = 87.2%
  - SICH 9.9%

- **TRACK**
  - 43.4% mRS ≤2
  - TICI 2b/3 = 73.3%
  - SICH 9%
<table>
<thead>
<tr>
<th>Study</th>
<th>mTICI 2b/3</th>
<th>90 day mRS ≤2 (EVT vs SC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMS 3</td>
<td>23-44%</td>
<td>40.8% vs 48.7%</td>
</tr>
<tr>
<td>MR RESCUE</td>
<td>25%</td>
<td>12% vs 11%</td>
</tr>
<tr>
<td>SYNTHESIS-EXPANSION</td>
<td>Not reported</td>
<td>30.4% vs 34.8%*</td>
</tr>
<tr>
<td>MR CLEAN</td>
<td>58.7%</td>
<td>32.6% vs 19.1%</td>
</tr>
<tr>
<td>SWIFT PRIME</td>
<td>88%</td>
<td>60% vs 35.5%</td>
</tr>
<tr>
<td>ESCAPE</td>
<td>72.4%</td>
<td>53% vs 29.3%</td>
</tr>
<tr>
<td>EXTEND-IA</td>
<td>86%</td>
<td>71% vs 40%</td>
</tr>
</tbody>
</table>
Final Thoughts...

- IV tPA standard of care for AIS patients within 4.5 hours
- NINDS recombinant tPA Stroke Study Group trial, published in 1995
  - part 1 of the trial (291 patients) demonstrated no benefit of IV tPA
  - part 2 (333 patients) demonstrated IV tPA beneficial in improving outcomes with a requirement that half of the patients be enrolled within 90 min
Reflections

- to extend IV tPA beyond 3 hours, European Cooperative Acute Stroke Study (ECASS) 1 and 2 trials, enrolled >1400 patients treated between 3-6 hours, demonstrated no benefit of IV tPA >3 hours
- Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke (ATLANTIS) trial with 613 patients of a planned enrollment of >900, treated from 3-5 hours with IV tPA, was halted for futility
- ECASS 3 in 2008 extended window to 4.5 hours
Reflections...

- The negative trials were not bad or ill thought of, they just took place at a time when good endovascular stroke therapies were not available
- New standard of care
- Educate
- Efficient patient transport