Update on Acute Ischemic Stroke Treatment

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Disclosures

• None
Objectives

• Review the latest developments in the endovascular treatment of stroke
• Consider the implications for practice
#1 cause of disability among adults in the US

795,000 Americans each year suffer a stroke

40% are large vessel occlusion

KILLS 128,000 people a year. That’s about one out of every 19 deaths

EVERY 40 SECONDS someone has a stroke

#5 cause of death among adults in the US
STROKE DISEASE STATE
795,000 STROKES PER YEAR U.S.*

ISCHEMIC STROKE: 87%*

HEMORRHAGIC STROKE: 13%*

Acute Ischemic Stroke

Brain Aneurysm

Brain AVM

Angiographic Anatomy Review
Outcome at Three Months in Part 2 of the Study, According to Treatment.
The MERCI Device
<table>
<thead>
<tr>
<th></th>
<th>IMS III (Endovascular)++</th>
<th>IMS III (tPA)+++</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>434</td>
<td>222</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>69</td>
<td>68</td>
</tr>
<tr>
<td><strong>Male</strong></td>
<td>50.2%</td>
<td>55%</td>
</tr>
<tr>
<td><strong>Baseline NIHSS, median</strong></td>
<td>17</td>
<td>16</td>
</tr>
<tr>
<td><strong>% ICA occlusions</strong></td>
<td>15%</td>
<td>Unk</td>
</tr>
<tr>
<td><strong>% VBA occlusions</strong></td>
<td>1%</td>
<td>unk</td>
</tr>
<tr>
<td><strong>Successful recanalization</strong></td>
<td>38% (ICA)</td>
<td>Unk</td>
</tr>
<tr>
<td></td>
<td>44% (M1)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TICI &gt;2b</td>
<td></td>
</tr>
<tr>
<td><strong>mRS ≤ 2 at 3 months</strong></td>
<td>40.8%</td>
<td>38.7%</td>
</tr>
<tr>
<td><strong>Mortality at 3 months</strong></td>
<td>19.1%</td>
<td>21.6%</td>
</tr>
<tr>
<td><strong>Symptomatic ICH at 24 hrs</strong></td>
<td>6.2%</td>
<td>5.9%</td>
</tr>
</tbody>
</table>

***TREVO1 data from presentation by N. Wahlgren, International Stroke Congress 2012.
++Broderick, Joseph, et. Al. Endovascular Therapy after Intravenous t-PA versus t-PA Alone for Stroke. NEJM. vol. 368 no. 10

**Presented by Dr. Dippel, Erasmus University at World Stroke Congress 2014
Mechanical Thrombectomy

- Video
### Study Overview

#### Inclusion and Exclusion Criteria

<table>
<thead>
<tr>
<th>Study</th>
<th>MR CLEAN</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Enrollment Period</strong></td>
<td>December 2010 – March 2014</td>
</tr>
<tr>
<td><strong>Study Design</strong></td>
<td>Prospective, multi-center, randomized, controlled, blinded-endpoint trial</td>
</tr>
<tr>
<td><strong>Tx Window</strong></td>
<td>6 hrs</td>
</tr>
<tr>
<td><strong>NIHSS</strong></td>
<td>2 or more</td>
</tr>
<tr>
<td><strong>Study Arm</strong></td>
<td>Endovascular treatment: intra-arterial thrombolysis (urokinase or alteplase), mechanical treatment (retraction or aspiration of the thrombus with a catheter guided device, or stenting) or both</td>
</tr>
<tr>
<td><strong>Control Arm</strong></td>
<td>Medical management</td>
</tr>
<tr>
<td><strong>Target Vessels</strong></td>
<td>Distal ICA, middle (M1/M2) or anterior (A1/A2) cerebral artery</td>
</tr>
<tr>
<td><strong>Sample Size/Sites</strong></td>
<td>500 pts, 18 sites in Netherlands</td>
</tr>
<tr>
<td><strong>Primary Endpoints</strong></td>
<td>mRS at 90 days Rankin Shift</td>
</tr>
<tr>
<td><strong>Secondary Endpoints</strong></td>
<td>NIHSS at 24 hours, vessel patency at 24 hours, infarct size at day 5-7, and the occurrence of major bleeding</td>
</tr>
<tr>
<td><strong>Follow-up</strong></td>
<td>24 hrs, 5-7 days, discharge, 90 days</td>
</tr>
<tr>
<td><strong>Key In/Exclusion Criteria</strong></td>
<td>• Intracranial occlusion of the distal intracranial ICA, middle (M1/M2) or anterior (A1/A2) cerebral artery, demonstrated with CTA, MRA, DSA or transcranial Doppler/duplex (TCD).</td>
</tr>
</tbody>
</table>

Overall, even in this very complex population, the study observes that the addition of stent thrombectomy for acute ischemic stroke care significantly improves good neurological outcomes with no additional safety risks.

- MR CLEAN demonstrated a 71% improvement in good neurological outcomes for patients treated with intervention compared to medical management/TPA (32.6% (76/233) vs. 19.1% (51/267))
- There was no safety difference in adverse events (47% vs. 42%) , ICH (7.8% vs. 6.4%) or 90 day mortality (21% vs 22%) between the two groups.
- Lower absolute rates of 90 day mRS 0-2 and higher complication rates seen in MR CLEAN vs. prior studies reflect the ‘real-world’ experience in the Netherlands, particularly the relatively high rate of ICA lesions vs. prior studies like IMS3 (26% vs. 15%)
- 97% of interventions employed a stent retriever device the greatest contributor to the data was the Trevo™ Pro Retriever. The specific breakdown of device usage is unknown.
- Further studies are needed to confirm these results outside the Netherlands and examine the effect of stent thrombectomy in global systems of care and with varying patient populations.
MR CLEAN Rankin Shift Analysis**

Control (N=267)
- 6% 13% 16% 30% 12% 22%

Intervention (N=233)
- 3% 9% 21% 18% 22% 6% 21%

**Presented by Dr. Dippel, Erasmus University at World Stroke Congress 2014
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Intervention (N=233)</th>
<th>Control (N=267)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death Within 7 days – n (%)</td>
<td>27 (12%)</td>
<td>33 (12%)</td>
</tr>
<tr>
<td>Death Within 30 days – n (%)</td>
<td>44 (19%)</td>
<td>49 (19%)</td>
</tr>
<tr>
<td>Hemicraniectomy – n (%)</td>
<td>14 (6.0%)</td>
<td>13 (4.9%)</td>
</tr>
<tr>
<td>Patients with at least one SAE – n (%)</td>
<td>110 (47%)</td>
<td>113 (42%)</td>
</tr>
<tr>
<td>Symptomatic ICH – n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parenchymal hematoma type 1 (PH1)^</td>
<td>18 (7.8%)</td>
<td>17 (6.4%)</td>
</tr>
<tr>
<td>Parenchymal hematoma type 2 (PH2)^</td>
<td>14 (6.0%)</td>
<td>14 (5.2%)</td>
</tr>
<tr>
<td>Hemorrhagic infarction type 1 (HI1)</td>
<td>1 (0.4%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Hemorrhagic infarction type 2 (HI2)</td>
<td>1 (0.4%)</td>
<td>1 (0.4%)</td>
</tr>
<tr>
<td>Subarachnoid Hemorrhage</td>
<td>2 (0.9%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>New ischemic stroke in different vascular territory – n (%)</td>
<td>13 (5.6%)</td>
<td>1 (0.4%)</td>
</tr>
<tr>
<td>Progressive ischemic stroke – n (%)</td>
<td>46 (20%)</td>
<td>47 (18%)</td>
</tr>
<tr>
<td>Pneumonia – n (%)</td>
<td>25 (11%)</td>
<td>41 (15%)</td>
</tr>
<tr>
<td>Other infection – n (%)</td>
<td>16 (6.9%)</td>
<td>9 (3.4 %)</td>
</tr>
<tr>
<td>Cardiac ischemia – n (%)</td>
<td>1 (0.4%)</td>
<td>4 (1.5%)</td>
</tr>
<tr>
<td>Extracranial hemorrhage – n (%)</td>
<td>0 (0.0%)</td>
<td>2 (0.7%)</td>
</tr>
<tr>
<td>Allergic reaction – n (%)</td>
<td>1(0.4%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Other complication – n (%)</td>
<td>22 (9.4%)</td>
<td>33 (12%)</td>
</tr>
</tbody>
</table>

**Presented by Dr. Dippel, Erasmus University at World Stroke Congress 2014**
MR CLEAN (in summary)

- Groin puncture must be performed within 6 hrs of LKN
- No upward age restriction; NIHSS as low as 2
- tPA was given to 87% of patients
- CTA at 2 hrs showed MCA or ICA occlusion in 92% of patients
- Though randomization was 2 hrs after tPA, median ASPECTS score was 9
EXTEND-IA Study Overview

- **Background**: The EXTEND-IA trial was conducted to test the hypothesis that anterior circulation ischemic stroke patients, selected with a “dual target” of vessel occlusion and evidence of salvageable tissue on perfusion imaging within 4.5h of onset, would have improved reperfusion and early neurological improvement when treated with endovascular thrombectomy using the Solitaire™ stent thrombectomy device after intravenous (IV) alteplase, compared to alteplase alone.

- **Methods**: Stroke patients receiving 0.9mg/kg alteplase <4.5h after stroke onset, with internal carotid or middle cerebral artery occlusion and CT perfusion imaging evidence of salvageable tissue and ischemic core <70ml, were randomized to either alteplase followed by endovascular thrombectomy <6h with the Solitaire™ device, or alteplase alone. The co-primary outcomes were reperfusion at 24h and early neurological improvement (≥8 point reduction in National Institutes of Health Stroke Scale (NIHSS) or reaching 0-1 by day 3). The secondary outcome was modified Rankin scale (mRS) at day 90.

- The trial was stopped early because of efficacy after 70 patients had been randomized (35 patients in each group).
DWI (ADC<620) volume: 68.2 ml
Mismatch ratio: 2.0
Perfusion (Tmax>6.0s) volume: 139.3 ml

RAPID
EXTEND-IA Study Summary

Solitaire™ Device+ IV-TPA
N = 35

- Reperfusion at 24 hours: 100%
P < 0.0001

- MRS 0-2 at 90 days: 71%
P = 0.009

- Mortality at 90 days: 40%
P = 0.18

IV-TPA Alone
N = 35

- Reperfusion at 24 hours: 37%
P = 0.48

- MRS 0-2 at 90 days: 20%
P = 0.48

- Mortality at 90 days: 9%
P = 0.18

- SiCH: 0%
P = 0.48

Published in the New England Journal of Medicine. DOI: 10.1056/NEJMo1414792
Statistically significant improvement in rate of good outcomes at 90 days with intervention using the Solitaire™ device as primary treatment.
SWIFT PRIME Study Overview

• **Background:** Among patients with acute ischemic stroke due to occlusions in the proximal anterior intracranial circulation, less than 40% regain functional independence when treated with intravenous tissue plasminogen activator (t-PA) alone. Thrombectomy with the use of a stent retriever, in addition to intravenous t-PA, increases reperfusion rates and may improve long-term functional outcome.

• **Methods:** We randomly assigned eligible patients with stroke who were receiving or had received intravenous t-PA to continue with t-PA alone (control group) or to undergo endovascular thrombectomy with the use of a stent retriever within 6 hours after symptom onset (intervention group). Patients had confirmed occlusions in the proximal anterior intracranial circulation and an absence of large ischemic-core lesions. The primary outcome was the severity of global disability at 90 days, as assessed by means of the modified Rankin Scale (with scores ranging from 0 [no symptoms] to 6 [death]).

• The trial was stopped early because of efficacy after 98 patients had been randomized (196 patients in each group).

*Solitaire™ with the Intention for thrombectomy as primary endovascular treatment for acute ischemic stroke (SWIFT PRIME) trial. Saver JL, et al. New England Journal of Medicine In Press*
ASPECTS Score

- C - Caudate
- I - Insular ribbon
- IC - Internal Capsule
- L - Lentiform nucleus
- M1 - Anterior MCA cortex
- M2 - MCA cortex lateral to the insular ribbon
- M3 - Posterior MCA cortex
- M4 - Anterior MCA superior territory
- M5 - Lateral MCA superior territory
- M6 - Posterior MCA superior territory

ASPECTS Score = /10
SWIFT PRIME Study Summary

**Solitaire™ Device + IV-TPA**
N = 98

- Reperfusion at 27 hours: 83% (53/64) vs. 40% (21/52)
- mRS 0-2 at 90 days: 60% (59/98) vs. 35% (33/93)
- Mortality at 90 days: 9% (9/98) vs. 12% (12/97)
- SiCH: 0% (0/98) vs. 3% (3/98)

**IV-TPA Alone**
N = 98

- Reperfusion at 27 hours: 60% (59/98) vs. 35% (33/93)
- mRS 0-2 at 90 days: 60% (59/98) vs. 35% (33/93)
- Mortality at 90 days: 9% (9/98) vs. 12% (12/97)
- SiCH: 0% (0/98) vs. 3% (3/98)

*P < 0.001 for Solitaire™ Device + IV-TPA vs. IV-TPA Alone*

*P = 0.001 for Solitaire™ Device + IV-TPA vs. IV-TPA Alone*

*P = 0.50 for Solitaire™ Device + IV-TPA vs. IV-TPA Alone*

*P = 0.12 for Solitaire™ Device + IV-TPA vs. IV-TPA Alone*

*Solitaire™ with the Intention for thrombectomy as primary endovascular treatment for acute ischenmic stroke (SWIFT PRIME) trial. Saver JL, et al. New England Journal of Medicine In Press*
Statistically significant improvement in rate of good outcomes at 90 days with intervention using the Solitaire™ device.

*Solitaire™ with the Intention for thrombectomy as primary endovascular treatment for acute ischemic stroke (SWIFT PRIME) trial. Saver JL, et al. New England Journal of Medicine In Press*
Background: The REVASCAT study was aimed to assess safety and efficacy of thrombectomy for stroke in a trial embedded within a population based stroke reperfusion registry.

Methods: Patients with acute ischemic stroke treatable within 8 hours of symptom onset with confirmed proximal anterior circulation occlusion and absence of large infarct on neuroimaging, were randomized to medical therapy (including iv t-PA when eligible) and endovascular treatment with Solitaire stent retriever versus medical therapy alone. Primary outcome measure was global disability at 90 days expressed as modified Rankin Scale (mRS, range 0 to 6, 0 indicates no symptoms, 5 severe disability, 6 death). Although maximum sample size was 690, enrolment was halted early following recommendation of the Data Safety Monitoring Board (DSMB) due to loss of equipoise given positive results from other trials.

The trial was stopped early because of efficacy after 206 patients had been randomized (103 patients in each group).

REVASCAT Study Summary

Solitaire™ with IV t-PA or Medical Management

- Reperfusion at 24 hours: 67/102 (66%)
- mRS 0-2 at 90 days: 45/103 (44%)
- Mortality at 90 days: 19/103 (18%)

IV t-PA or Medical Management alone

- Reperfusion at 24 hours: 29/103
- mRS 0-2 at 90 days: 28%
- Mortality at 90 days: 16/103 (16%)

OR=2.0, P=0.6, P=1.0

sICH: 2% in both groups

Statistically significant improvement in rate of good outcomes at 90 days with intervention using the Solitaire™ device as primary treatment.

Summary of Trials

• Thrombectomy is very effective in the treatment of patients with stroke from ICA or MCA occlusion.
  – Relatively normal CT scans, recanalization within 6 hrs
• IV t-PA should not be withheld if the patient meets criteria*
• Favorable results from thrombectomy at experienced endovascular centers with multidisciplinary teams
• Faster revascularization gives better results
Summary of Trials

- Increased mRS 0-2
- Decreased mortality
- TICI 2B/3
The typical LVO patient loses **2 million** neurons/min in the territory at risk

Probability of good clinical outcome over time to technically successful angiographic reperfusion
Family recognizes stroke symptoms

1. Call 911 ➔ EMS Assess ➔ EMS Identifies Stroke ➔ EMS Departs for Hospital ➔ Go to ER

2. Patient arrives at comprehensive stroke center ER

   - Symptom onset ≤ 3 hrs (4.5 hrs)
     - TPA Eligible YES ➔ CT/MR/IV TPA ➔ Start IV TPA ➔ CTP/CTA/MPR/MRA
     - TPA Eligible NO ➔ Large Mismatch ➔ To Angio
     - Small Mismatch or No Mismatch ➔ To MedTX

3. Patient arrives in Angio Suite

   - General Anesthesia ➔ Conscious Sedation ➔ Patient Prep ➔ Needle Stick
     - Carotid Access Easy ➔ Rapid Flow Restored ➔ Clot Removal
     - Carotid Access Difficult
Steps to Improving Door to Needle Time

• EMS Pre-Notification:
• Stroke Tools
• Rapid Triage Protocol
• Single Call Activation System
• Transfer Directly to CT Scanner
• Rapid Acquisition and Interpretation of Imaging
• Rapid Laboratory Testing
• Mix tPA ahead of time
• Rapid Administration of tPA
• Team Based Approach
• Prompt Data Feedback
Results at DRAH

- Door to Needle (min)
- %TICI 2b-3
- % mRS 0-2
Additional Issues: Imaging

• Do we need the CTA to show LVO?
• NIHSS >12 was used in MR CLEAN.
• Reasonable to not obtain CTA in patient with NIHSS >12, especially at spoke hospital where intervention will be > 1 hr away
• Are there tools to predict who may have an LVO
Additional Issues: Patients Excluded

• Wake up strokes and patients who were not t-PA candidates were not included.

• There may be a role for physiological imaging to drive patient selection
Who Does Not Benefit?

- Patients outside of the 6 hour time window
- Patients with large infarct on initial CT
- Patients with mild symptoms (NIHSS<2)
- Patients with distal occlusion (M2..)
- Patients not treated with stent retrievers (THERAPY)
Numbers Needed to Treat

• Only about 5-10% of all ischemic strokes will be candidates for thrombectomy.

• Excellent outcomes achieved in the 5 studies were in high volume referral centers with carefully selected interventionists, and carefully selected patients.

• In MR CLEAN there was 1 center per million population.
- Of 370,351 AIS primary diagnosis discharges, 14,926 (4%) received IV t-PA and 1889 (0.5%) had endovascular therapy
- By ground, 81% had access to IV-capable hospitals within 60 minutes and 56% had access to endovascular-capable hospitals
- By air, 97% had access to IV-capable hospitals within 60 minutes and 85% had access to endovascular hospitals
- More than half of the US population has geographic access to hospitals that actually deliver acute stroke care but treatment rates remain low
There is more to do

- 29% to 67% of patients had a poor outcome despite this treatment
Questions??