Acute Ischemic Stroke: IV-tPA, Intervention, Surgery

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- **Stock:** Surpass Medical, Stryker Neurovascular, InNeuroCo, Inc
- **Speakers Bureau:** Covidien, Microvention
- **Consultant/Advisory Board:** Covidien, Microvention
Stroke Statistics

- Stroke is the 3rd leading cause of death in the US
- 795,000 strokes/year in the US
- 25% death within 1 year after the initial stroke
- Near 50% of stroke victims will not regain functional independence
- Estimated costs: $68.9 billion in 2009
• Assuming no change in the age-specific rates of stroke, approximately 1.1 million Americans will suffer a stroke in 2025¹

STROKE TYPES

Total Stroke
695,000

Ischemic Stroke (85%)
590,000

As many as 40% due to large vessel occlusion
236,000

Hemorrhagic Stroke (15%)
105,000

Ischemic Stroke Quantified

- The average number of neurons in the human forebrain is 22 billion.
- In 1 hour of a typical large vessel ischemic stroke a patient lose:
  - 120 million neurons
  - 830 billion synapses
  - 714 km (447 miles) of myelinated fibers

Saver JL Stroke 2006;37:263-6
Stroke Statistics

- Natural History of Acute Large Vessel Occlusion
  - ICA-T occlusion: ~50% mortality; 75% died or functionally dependent*
  - MCA occlusion: ~30% mortality**; 75% poor outcome
  - Basilar occlusion: 92% mortality***

*Paciaroni et al, Cerebrovasc Dis 2005
**Furlan et al, JAMA 1999
***Brandt et al, Stroke 1996
Dabus G et al. TVIR 2012
Intravenous thrombolysis

- NINDS study (1995): IV t-PA effective within 3 hours; ECASS III (2008) safe up to 4.5h
- Is IV rt-PA the ideal treatment?
  - 3% patients with acute stroke receive IV tPA (higher now???)
  - 6.4% symptomatic ICH
  - 30% recanalization of MCA occlusion
  - 10% recanalization of ICA occlusion
  - 12% absolute increase in good outcomes compared to placebo at 90 days – NNT: 8
IV tPA Reperfusion Limitations

- Location
  - Vessel occlusion location prognostic of response*
    - Distal ICA 4.4%  M1-MCA 32.3%
    - M2-MCA 30.8%  Basilar 4.0%
  - Reperfusion most predictive of outcome (RR 2.7)

- Clot size (<8mm)**
  - Reperfusion remains strongly predictive
    - Mean discharge mRS
      - Reperfused 1.9
      - No reperfusion 4.4

*Bhatia Stroke. 2010;41:2254-2258, **Riedel, Stroke. 2011;42:1775-1777
Endovascular Intervention

- Chemical thrombolysis (not FDA approved)
  - rt-PA
  - UK

- Mechanical techniques
  - Merci device (FDA approved)
  - Penumbra (FDA approved)
  - Stenting
  - Stentrievers (FDA approved)
Patient Selection for EVT

- Acute onset (up to 8h) of significant neurological deficit (NIHSS>=8)
- No significant previous disability
- CT/ MR: no evidence of hemorrhage or established infarct (>1/3 MCA territory)
- CTA/ MRA: large vessel occlusion (ICA, MCA, Basilar artery)
- CT/ MR Perfusion: presence of mismatch (salvageable tissue)
IA Chemical Thrombolysis

- **PROACT-II**
  - Designed to assess the clinical efficacy and safety of IA r-pro-UK
  - 180 patients were enrolled in a 2:1 randomization scheme to receive either 9 mg IA r-pro-UK plus 4 hours of low dose IV heparin, or low dose IV heparin alone

## PROACT-II

<table>
<thead>
<tr>
<th></th>
<th>rpro-UK + heparin (121)</th>
<th>Heparin (59)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recanalization</td>
<td>66%</td>
<td>18%</td>
</tr>
<tr>
<td>Slight or no neuro disability at 90 days</td>
<td>40%</td>
<td>25%</td>
</tr>
<tr>
<td>ICH and neuro deterioration</td>
<td>10%</td>
<td>2%</td>
</tr>
<tr>
<td>120 day Mortality</td>
<td>25%</td>
<td>27%</td>
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</tbody>
</table>

Interventional Management of Stroke Study

- Recanalization
  - IMS-I: 56%
  - IMS-II: 60%
  - NINDS tPA: 43%

- 90 day mRS≤2
  - IMS-I: 46%
  - IMS-II: 39%
  - NINDS tPA: 6.30%

- Symptomatic ICH
  - IMS-I: 9.90%
  - IMS-II: 6.60%

- 90 day Mortality
  - IMS-I: 16%
  - IMS-II: 21%
Timing Is Critical – IMS I & II

Each 30 minutes = 10% loss!

(Khatri. Neurology, 2009)
MULTI-MERCI\textsuperscript{1}

- 164 patients, 15 centers
- Same design as Merci trial, but with newer retriever (L5) and failed IV tPA patients
- 8 hour window

Multi MERCI Clinical Outcomes

Recanalized

Not Recanalized

p < 0.001

ISC 2007, San Francisco
Mechanical Techniques

- The Penumbra POST (ISC 2009)
  - 139 patients in the study
  - 84% of patients revasc to a TIMI score of II or III
  - 5.8% procedural SAEs
  - 7.2% sICH
  - mortality is 22%
  - 40% had an mRS ≤ 2 at 90 days, indicating good functional outcome and the ability to live independently.
LANDMARK STUDIES SUMMARY

Landmark Study Results

<table>
<thead>
<tr>
<th>Trial</th>
<th>Percentage of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROACT II</td>
<td>Recanalization Rate (TIMI 2 or 3)</td>
</tr>
<tr>
<td>PROACT I</td>
<td>Symptomatic Hemorrhage</td>
</tr>
<tr>
<td>PROACT II</td>
<td>mRS≤2 @ 90 days</td>
</tr>
<tr>
<td>MERCI</td>
<td>Procedural Complications</td>
</tr>
<tr>
<td>Multi MERCI</td>
<td>Asymptomatic Hemorrhage</td>
</tr>
<tr>
<td>IMS</td>
<td>All Cause Mortality (90 days)</td>
</tr>
<tr>
<td>IMS II</td>
<td></td>
</tr>
<tr>
<td>Penumbra</td>
<td></td>
</tr>
</tbody>
</table>
Self-Expandable Stents in the Treatment of Acute Ischemic Stroke Refractory to Current Thrombectomy Devices

Italo Linfante, MD, FAHA; Edgar A. Samaniego, MD; Philipp Geisbüsch, MD; Guilherme Dabus, MD

**Background and Purpose**—Vessel recanalization is a strong predictor of good outcome in acute ischemic strokes (AIS) secondary to large vessel occlusions. We report our single-center experience with self-expandable stents in the treatment of AIS.

**Methods**—The stroke database of Baptist Cardiac and Vascular Institute in Miami was retrospectively reviewed from August of 2008 to September of 2010. All cases of AIS in which a self-expandable stents was deployed as acute endovascular intervention were included in the analysis. Criteria for intervention were the onset of neurological symptoms because of AIS, a National Institute of Health Stroke Scale score $\geq 4$ at presentation, stroke attributable to a large vessel occlusion, and failure of arterial thrombolysis or mechanical thrombectomy or both. Good outcome was defined as a modified Rankin Scale score $\leq 2$ at 1 month from hospital discharge.

**Results**—Nineteen patients with AIS who underwent stenting were identified. Median National Institute of Health Stroke Scale score on admission was 19. Six Enterprise and 13 Wingspan stents were deployed. Recanalization was achieved in 95% occlusions (63% thrombolysis in myocardial infarction grade 3 and 32% thrombolysis in myocardial infarction grade 2). Good clinical outcome was achieved in 42%. No intraprocedural complications occurred and all stents were successfully deployed. Symptomatic intracerebral hemorrhage occurred in 3 (16%) patients, 2 of whom died.

**Conclusions**—Use of self-expandable stents in AIS appears to be safe and may be considered when currently available thrombectomy devices and/or intraarterial thrombolysis fail. *(Stroke. 2011;42:2636-2638.)*
Real Life Experience:
EVT for acute stroke at NMH

- 40 patients – mean NIHSS 17
- median time from stroke onset to EVT: ~ 4h
- Merci 55%; Penumbra 23%; Angioplasty 37%; IA 57%; intracranial stent 5%
- Multiple methods were used in 58% of cases
- Recanalization rate: 71% to TIMI 2/3
- sICH in 8%
- mRS 2 or less achieved in 37%
- Overall mortality 27%

Real Life Experience: EVT for acute stroke at NMH

- Patients who were successfully revascularized tended to have better outcomes
- 44% of revascularized pts had mRS 2 or less
- 14% of not revascularized pts had mRS 2 or less
- Correspondingly, the revascularized groups had lower mortality, 25% (4/16) versus 42.8 % (3/7) of the non-revascularized cases

Stentrieverers

- SWIFT Trial (Solitaire) and TREVO-2 Trial (Trevo)
- Both trials demonstrated significantly better recanalization rates with the stentriever compared to Merci
- Outcomes were also better in the stentriever group

<table>
<thead>
<tr>
<th></th>
<th>Solitaire (roll-in; n=31)</th>
<th>Solitaire (randomly allocated; n=58)</th>
<th>Merci (randomly allocated; n=55)</th>
<th>Odds ratio (95% CI) for comparison between randomised groups</th>
<th>Non-inferiority p value for comparison between randomised groups</th>
<th>Superiority p value for randomised comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>Successful recanalisation without symptomatic intracranial haemorrhage (primary endpoint)</td>
<td>55% (16/29)</td>
<td>61% (34/56)</td>
<td>24% (13/54)</td>
<td>4.87 (2.14-11.10)</td>
<td>&lt;0.0001</td>
<td>0.0001</td>
</tr>
<tr>
<td>Angiographic efficacy endpoints</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Successful recanalisation with study device (assessed by core laboratory)</td>
<td>63% (17/27)</td>
<td>69% (37/54)</td>
<td>30% (16/53)</td>
<td>5.03 (2.22-13.66)</td>
<td>&lt;0.0001</td>
<td>0.0001</td>
</tr>
<tr>
<td>Successful recanalisation with study device (assessed at study site)</td>
<td>77% (24/31)</td>
<td>83% (45/54)</td>
<td>48% (26/54)</td>
<td>5.38 (2.21-13.15)</td>
<td>&lt;0.0001</td>
<td>0.0002</td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th></th>
<th>Trevo group</th>
<th>Merci group</th>
<th>Odds ratio (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary efficacy endpoint</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Assigned device TICI ≥2</td>
<td>76/88 (86%)</td>
<td>54/90 (60%)</td>
<td>4.22 (1.92-9.69)</td>
<td>&lt;0.0001; &lt;0.0001†</td>
</tr>
</tbody>
</table>
EVT Stroke Trials

IMS III
MR RESCUE
SYNTHESIS

NEJM February 7, 2013
Endovascular Therapy after Intravenous t-PA versus t-PA Alone for Stroke


for the Interventional Management of Stroke (IMS) III Investigators
Primary and Safety Endpoints

<table>
<thead>
<tr>
<th>End Point</th>
<th>Endovascular Therapy (N=434)</th>
<th>Intravenous t-PA Alone (N=222)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death — no. (%)</td>
<td>52 (12.0)</td>
<td>24 (10.8)</td>
<td>0.57</td>
</tr>
<tr>
<td>Within 7 days</td>
<td>83 (19.1)</td>
<td>48 (21.6)</td>
<td>0.52</td>
</tr>
<tr>
<td>Intracerebral hemorrhage within 30 hr — no. (%)</td>
<td>27 (6.2)</td>
<td>13 (5.9)</td>
<td>0.83</td>
</tr>
<tr>
<td>Symptomatic</td>
<td>119 (27.4)</td>
<td>42 (18.9)</td>
<td>0.01</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parenchymal hematoma identified within 30 hr</td>
<td>25/417 (6.0)</td>
<td>13/207 (6.3)</td>
<td>0.90</td>
</tr>
<tr>
<td>no./total no. (%)†</td>
<td>15/417 (3.6)</td>
<td>3/207 (1.4)</td>
<td>0.12</td>
</tr>
<tr>
<td>Type 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemorrhage — no./total no. (%)</td>
<td>48/417 (11.5)</td>
<td>12/207 (5.8)</td>
<td>0.02</td>
</tr>
<tr>
<td>Subarachnoid</td>
<td>27/417 (6.5)</td>
<td>10/207 (4.8)</td>
<td>0.40</td>
</tr>
<tr>
<td>Intraventricular</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major complication due to nonintracerebral bleeding within 5 days — no. (%)‡</td>
<td>13 (3.0)</td>
<td>5 (2.3)</td>
<td>0.55</td>
</tr>
<tr>
<td>Recurrent stroke within 90 days — no. (%)</td>
<td>22 (5.1)</td>
<td>14 (6.3)</td>
<td>0.54</td>
</tr>
<tr>
<td>Device or procedural complication — no. (%)‡</td>
<td>70 (16.1)</td>
<td>—</td>
<td></td>
</tr>
</tbody>
</table>
IMS III problems

- Basic Head CT only in most patients
  - More than 40% of IMS III patients had baseline CT with ASPECTS ≤ 7

ASPECTS 0-7

Small Infarct
15/30 pts

ASPECTS 8-10

Large Infarct
8/53 pts

mRS ≤ 2

Goyal M. Stroke 2010
IMS III problems

- Basic Head CT only in most patients
- Patients with “large clear regions of hypodensity” (darker than white matter and brighter than CSF) on CT, greater than 1/3rd of MCA territory were excluded
  - Sulcal effacement and loss of grey-white matter differentiation were not contraindications
  - Many patients would have likely been excluded with more conservative CT reading (ASPECTS), CTA-SI (source image) ASPECTS, MR Diffusion ASPECTS, CT Perfusion or MR Perfusion
IMS III: Baseline CTA Occlusion Present – 90 day mRS

van Elteren test p-value 0.0114
IMS III: Baseline CTA Occlusion Present - NIHSS ≥ 20

<table>
<thead>
<tr>
<th>NIH ≥ 20</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endovascular N= 58</td>
<td>5.2</td>
<td>12.1</td>
<td>12.1</td>
<td>19</td>
<td>13.8</td>
<td>8.6</td>
<td>29.3</td>
</tr>
<tr>
<td>IV t-PA Alone N= 30</td>
<td>3.3</td>
<td>10</td>
<td>6.7</td>
<td>16.7</td>
<td>13.3</td>
<td>46.7</td>
<td></td>
</tr>
</tbody>
</table>

van Elteren test p-value 0.0330
IMS-III

- Endovascular group: 434 patients
- Good reperfusion (TICI 2b-3): 40% of total
  - 38% for ICA occlusion
  - 44% for M1 or M2 occlusion
- MRS 0-2 increase with better reperfusion
  - 12.7% TICI 0; 27.6% TICI 1; 34.3% TICI 2a
  - 47.9% TICI 2b; 71.4% TICI 3
- Most patients treated with Merci or IA tPA; Only 4 patients treated with Solitaire
IMS III patients further suffered a significant lag between groin access and initiation of IAT at the lesion. Forty-four minutes is far beyond reported standards with modern guide and distal access catheter technology.
Time to Treatment

- **IMS III**
  - Onset to arrival: 57 min
  - Arrival to IV tPA: 66 min
  - IV to groin puncture: 86 mins
  - Groin puncture to IA: 44 mins
  - Mean time from imaging to groin puncture: 2h 4 min

- **MR RESCUE**
  - Mean time from imaging to groin puncture: 2h 4 min

- **SYNTHESIS**
  - Time from onset to start of treatment
    - EVT 3.75 hrs
    - IV 2.75 hrs

By comparison STAR registry:
- Groin Puncture to guide cath placement: 12 mins
- Guide cath to TICI 2B/3 flow: 20 mins

Critical as IA group did **NOT** receive IV tpa
Newer Technologies = Better Recanalization

- **Solitaire FR**
- **Trevo**
- **Separator 3-D**
- **Penumbra Max System**
MR CLEAN

- Multicenter, blinded, randomized trial
- IA treatment + usual care vs usual care alone
- LVO in anterior circulation
- IA treatment up to 6h after symptom onset
500 pts enrolled (age 23 to 96; mean 65)
- Median NIHSS 17 (IA) and 18(control)
- 233 IA vs 267 usual care alone
- 89% (445) received IV tPA
- Stentretrievers used in 81% of IA cohort
- TICI 2b/3 achieved in 58.7% IA cohort
- Absolute difference of 13.5% in the rate of functional independence favoring IA (32.6% vs 19.1%)
- No significant difference in mortality (21% IA; 22% control) or hemorrhage (7.7% IA; 6.4% control)
<table>
<thead>
<tr>
<th>Trial</th>
<th>Rationale</th>
<th>Device</th>
<th>Selection</th>
<th>Time imaging to groin puncture</th>
<th>Primary outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESCAPE</td>
<td>Optimize Time</td>
<td>Any FDA approved mechanical thrombectomy device</td>
<td>CT/CTA</td>
<td>60 min</td>
<td>mRS 0-2 at 90 days</td>
</tr>
<tr>
<td>POSITIVE</td>
<td>Imaging Selection (Advanced Imaging)</td>
<td>Any FDA approved mechanical thrombectomy device (excluding MERCI)</td>
<td>CT/CTA/CTP or MRI/MRP</td>
<td></td>
<td>mRS (Rankin Shift and minimum 5% difference in mRS 0-2) at 90 days</td>
</tr>
<tr>
<td>SWIFT PRIME</td>
<td>Imaging Selection (Advanced Imaging)</td>
<td>Solitaire</td>
<td>CT/CTA/CTP or MRI/MRP</td>
<td>90 min</td>
<td>mRS at 90 days</td>
</tr>
<tr>
<td>THERAPY</td>
<td>Imaging Selection (Clot length)</td>
<td>Penumbra Aspiration System/3D Separator</td>
<td>Thin slice CT, clot length &gt; 8mm</td>
<td></td>
<td>mRS 0-2 at 90 days</td>
</tr>
</tbody>
</table>
81 yo wake up stroke at 5am – last seen normal at 11pm
Aphasia, right hemiparesis NIHSS 20
3 month f/u
46 F history of hypothyroidism who presents from home with an initial NIHSS of 23 with symptoms of a left hemispheric stroke. She received full dose tPA. She presented within 3 to 4 hours after symptom onset and she was referred for further cerebral angiogram and mechanical thrombectomy.
CT Perfusion
CT 36h after EVT NIHSS 2
2 month f/u NIHSS 0
63M wake up stroke NIHSS19 with right hemiparesis, left gaze preference, and right neglect with aphasia
MRI 3 days later
Surgery - Hemicraniectomy

- 17 yo M high school athlete presenting with left hemiparesis followed by LOC
- 2h after the onset
Should we go ahead?
Should we go ahead?
Should we go ahead?
Should we go ahead?

CT 24h post rx

CT 36h post rx
Should we go ahead?

CT 4d post rx

CT 8d post rx
Conclusions

- IV-tPA is standard of care and needs to be given to all eligible patients.
- Endovascular intervention improves the rates of recanalization in patients presenting with proximal occlusion of the intracranial arteries.
- MR Clean first RCT to demonstrate better results with EVT in the modern era.
- New trials comparing IV and IA using the new EVT technology (Therapy, Swift Prime) are currently halted waiting for analysis of current sample.
Thank You!

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