Endovascular Therapy is the Standard of Care: Acute Ischemic Stroke Trials and Beyond

Italo Linfante MD, FAHA
Director Endovascular Neurosurgery
Interventional Neuroradiology
Miami Cardiac and Vascular Institute
Clinical Professor

Disclosures

Covidien: Consultant, Speaker, Proctor for Pipeline
Stryker: Consultant, Speaker
Codman Neurovascular: Consultant, Speaker
Surpass, InNeuroCo: Stock holder

Stroke is Team Work

Guilherme Dabus MD, FAHA
Michael Mayich, MD
Indiana Alcala RN, NP
Neurology and Neurosurgery Medical Staff
The BEST team
Baptist Hospital Neuroscience Center Nurses and staff
Endovascular Stroke Therapy

MR CLEAN - Design

- Phase III multicenter randomized clinical trial with blinded outcome assessment
- Endovascular treatment versus no endovascular treatment.
- Either treatment arms included optimal medical management, which may include IV tPA
- 500 patients were enrolled starting in December 2010 and completed in March of 2014.
Endovascular Wins 33-19

<table>
<thead>
<tr>
<th>mRS Score at 90 day</th>
<th>Endovascular (n=233)</th>
<th>Control (n=267)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>3%</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>9%</td>
<td>6%</td>
</tr>
<tr>
<td>2</td>
<td>21%</td>
<td>13%</td>
</tr>
<tr>
<td>3</td>
<td>18%</td>
<td>16%</td>
</tr>
<tr>
<td>4</td>
<td>22%</td>
<td>30%</td>
</tr>
<tr>
<td>5</td>
<td>6%</td>
<td>12%</td>
</tr>
<tr>
<td>6</td>
<td>21%</td>
<td>22%</td>
</tr>
</tbody>
</table>

Dominos Started to Fall

Results of MR Clean triggered suspension of enrollment in the ESCAPE, EXTEND IA and an interim analysis of SWIFT PRIME
Thrombectomy within 8 hours after Symptom Onset in Ischemic Stroke

Inclusion and exclusion criteria

- Acute ischemic stroke (NIHSS > 5)
- 12 hour window
- No upper age limit
- Good functional status

- CT head: ASPECTS > 5 (exclude large core)
- CTA: ICA + M1 or M1 or functional M1 (all M2s)
- CTA (preferably multiphase): moderate to good collaterals
**Outcomes (NNT = 4) (Traditional method I/rrt)**

<table>
<thead>
<tr>
<th>Modified Rankin Scale Score</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>Control (N=147)</td>
<td>7</td>
<td>10</td>
<td>12</td>
<td>15</td>
<td>24</td>
<td>12</td>
<td>19</td>
</tr>
<tr>
<td>Intervention (N=150)</td>
<td>15</td>
<td>21</td>
<td>18</td>
<td>16</td>
<td>13</td>
<td>7</td>
<td>10</td>
</tr>
</tbody>
</table>

**EXTEND - IA**

A randomized, controlled trial of thrombolysis in emergency neurological deficits: Intra-arterial

Bruce Campbell
Co-PI and Medical Coordinator

Peter Mitchell
Co-PI and Head of Neuroradiology

Stephen Davis and Geoffrey Donnan
Co-chairs

Trial design - PROBE design, planned 100 patients

Endovascular Wins 71-40

Day 90 mRS

Endovascular Therapy

Combined Intravenous t-PA and Endovascular Therapy

Ordinal p=0.006 (unadj), p=0.02 (adj)

NNT 3 for 21 point better on mRS

Intravenous t-PA alone

mRS 0-2 p=0.01

71% vs 46% - NNT 3.2 for independence

mRS 0-1 p=0.69

*co-primary outcome*
In Summary:

- With MR CLEAN, ESCAPE, EXTEND IA SWIFT-Prime, REVASCAT we have level 1A evidence in over 1000 patients
- Overwhelming superiority of Endovascular Treatment compared to IV tPA
- Endovascular Therapy is the Standard of Care for Acute Stroke Secondary to Large Vessel Occlusions
Reperfusion


- Independent predictors of good outcome in a multivariate analysis of Merci and Multi-merci trials (305 patients)
  - Revascularization (OR, 20.4; 95% CI, 7.7 to 53.9; P<0.0001)
Beyond the Trials

- Thank to ET, we are in the era of high percentage of TICI ≥2b recanalization
- In the RTC, good outcome (90 d mRS ≤2) was achieved in 33-71% of patients
- As we celebrate this monumental advancement, we are already finding ways to obtain even better outcomes

NASA Registry

- NASA Registry “real life” 20 sites in North America
- 354 acute stroke patients treated with Solitaire FR
- Data were housed and analyzed by a central coordinating site
- Differently from the 5 RCT, NASA included ICA+ MCA tandem and V-Basilar occlusions
- TICI ≥2b = 256 (72.3%)
- mRS ≤2 = 42%

Predictors of Mortality and Disability in Acute Ischemic despite Successful Recanalization

Italo Linfante, Amy K. Starosciak,+, Gail R. Walker, Osama O. Zaidi, Alicia C. Castonguay, Eugene Lin, †‡, Guilherme Dabus,§† for the NASA Investigators

†‡ Neuroscience Center, Baptist Hospital, Miami, FL USA
§† Center for Research and Grants, Baptist Health South Florida, Coral Gables, FL USA
+ Department of Neurology, Neuroradiology, and Neurosurgery, Baptist Hospital and Baptist Medical Center, Baptist Hospital, Miami, FL USA

Journal of NeuroInterventional Surgery

Solitaire™ FR: North American Multicenter Retrospective Data (NASA)

Delay in Recanalization in NASA

- 9% increased risk of Death or Severe Disability (mRS 3-5) per 30 min delay following successful recanalization
- Analyzed separately disability from death by multinomial logistic regression
- A 30-minute delay increased the risk of moderate/severe disability by 7%
- The risk of death increased by 11.8% (p=0.05)

Linfante et al Stroke 2015 46:2305-8

Final Infarct Volume

FIV is the ultimate bio marker for good outcome

Final infarct volume: A pivotal biomarker following IAT

Methods
Consecutive AIS pts treated with IAT:
- Anterior circulation PAO
- Final infarct imaging between 24 hrs and 2 weeks
- Available 90-day mRS

Results
107 pts with mean age 67 yrs and median NIHSSS 17
- TICI 2-3 reperfusion: 73%
- Median time to final infarct imaging: 41.8 hrs (NCCT in 58.9%)
- Median final infarct volume: 71.4 mL
- Only final infarct volume and age were independent predictors of 90-day mRS 0-2

Final infarct volume was the single best discriminator of 90-day good outcome (mRS 0-2; AUC=0.86)

Final infarct volume was the single best discriminator of 90-day good outcome


Volume thresholds for poor outcomes

<table>
<thead>
<tr>
<th>Volume threshold (cm³)</th>
<th>Specificity (95% CI) for poor outcome</th>
<th>Odds ratio (95% CI) for poor outcome</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;80</td>
<td>65.2% (66.3-65.8%)</td>
<td>8.63 (2.73-27.3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>&gt;90</td>
<td>88.9% (70.8-97.5%)</td>
<td>10.3 (2.86-37.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>&gt;100</td>
<td>92.6% (75.7-98.9%)</td>
<td>14.5 (3.22-65.5)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>&gt;110</td>
<td>96.3% (81.0-99.4%)</td>
<td>27.3 (3.54-211.2)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>&gt;120</td>
<td>100% (87.1-100%)</td>
<td>---</td>
<td>---</td>
</tr>
</tbody>
</table>

Poor outcome = mRS 3-6


MR CLEAN Infarct Volume (mL) at 7 day (mean)

Time is Not on Our Side

- Small FIV is our ultimate goal to achieve good outcomes
- Brain is extremely sensitive to ischemia
- What do we know about the relationship of time, core expansion and FIV?
Core Expansion and FIV

- How can we protect the penumbra and slow down or arrest core expansion?
- Time (we need to be faster)
- Brain arteries are different
- Collateral Circulation
- Pathophysiology of the endothelium in ischemia
- Cell dynamics that result in core expansion
Collateral Circulation: What do we know?

- In patients with acute ischemia, collateral circulation (CC) has high individual variability
- Poor CC is associated with rapid infarct growth
- Poor CC is a predictor of poor reperfusion despite recanalization

Collateral Circulation

- Nothing lasts forever
- “Robust” CC at the time of stroke does not last
- Failure of CC even in patients with initial good collateral circulation
CC and Ischemia

- Failure of CC in patients with initial good CC can be studied by experimental ischemia
- The robust CC present in MCAO in rats, tend to fade in approximately 2 hours after occlusion
- At the same time there is core expansion
Isolating & Pressurizing LMA (vs. non-LMA)

Identify MCA & ACA
Look for connection points (vs. terminating arterioles)
Dissect from MCA to LMA to ACA

Response to potassium ion (in KCl aCSF)

Failure of CC after MCAO and Core expansion

Winship et al  JCBF  2014
Response to KCL and Diltiazem

- The ischemic penumbra is kept alive by collaterals that connect distal branches of major cerebral artery territories

- Improving CC in ischemia is a target for Neuroprotection

Collaterals: Target for Neuroprotection

- Endothelin receptor A antagonist BQ-610 block the loss of pial arterial dilation 2 h after the onset of MCAO (Cao et al. Am J Physiol. 2009;296:1412–1419)
Collaterals: Target for Neuroprotection

- Rho-associated protein kinase (ROCK) is a pleotropic downstream effector of Rho GTPases that regulates numerous cell processes including vascular contractility.
**Target Neuroprotection**

**Excitotoxicity**

- **Glutamate Receptors**
  - Impaired energy during HI injury:
    - $P_e$ depolarization and increased pre-synaptic glutamate release
  - Interference with re-uptake (mostly into astrocytes) of glutamate
  - Accumulation of synaptic glutamate
  - Excess and sustained activation of ionotropic glutamate receptors causes neuronal cell death
  - Antagonists of ionotropic glutamate receptors reduce brain injury in animal models

**Calcium Influx into Neurons**

- Ca$^{2+}$ overload and neuronal death during HI injury through numerous pathways:
  - $P_e$ depolarization and activation of VOCC
  - Activation of glutamate receptors by NMDA that is highly Ca$^{2+}$ permeable
  - Activation of other Ca$^{2+}$ permeable channels, including TRPM7 and ASICs
  - Calpains (Ca$^{2+}$ dependent proteases) inhibit Na$^+$/Ca$^{2+}$ (NCX) exchanger causing Ca$^{2+}$ accumulation

- Prolonged elevation of [Ca$^{2+}$]i activates numerous deleterious cell processes (PLA2, CaMKII, MAPK, ERK, JNK, endonucleases, cell death pathways, etc.)

**Reactive Oxygen Species (ROS)**

- NMDA receptor activation stimulates PLA2 and xanthine oxidase that produce O$_2^-$
- Increased O$_2$ during reperfusion uncouples e$^-$/transport chain of mitochondria
- Ischemia activates nNOS to increase NO production that is neurotoxic
- Transition metals (Fe$^{2+}$, Zn$^{2+}$) are released during hypoxia/ischemia and are neurotoxic via ROS production
Activation of NMDA receptors

- An example of one this target is an N-methyl-D-aspartate glutamate receptor (NMDA) antagonist known as NA-1
- NA-1 inhibits the neurotoxic signaling in ischemic neurons without inhibiting physiologic glutamate receptor activity


Neuroprotection and ET

- In the pre-ET era, although promising, several Neuroprotective agents failed phase II/III clinical trials
- However, we need to consider:
  1) potentially effective neuroprotecting agents are not likely to be beneficial in the absence of rapid recanalization of the occluded artery
  2) neuroprotective agents are not likely to be efficacious without a vascular route needed to reach the target tissue

In Summary:

- Combining Neuroprotection with Endovascular Intervention is a very promising next step
- Hopefully we can bridge this gap to obtain even better outcomes in acute stroke patients
Patient

- 65 y/o man presenting with left hemiplegia, profound neglect (NIHSS 18) 2:30 min after symptoms onset
- Decreased level of consciousness
- Intubated for airway protection
- 0.9 mg/kg of IV tPA
- Cerebral Angiogram started 4-hours after symptom onset

Acute ICA Stenting

- Microcatheter in the MCA
- Thrombectomy with Stent-Triever
Patient

- 74 year-old man
- Sudden onset of left arm and leg weakness with head and eyes deviation to the right and neglect
- Arrives to the ED 3 hours after symptom onset
- NIHSS 21
- In the angio room at 4 hours after symptom onset

Tandem Occlusion:

CTA extracranial Right ICA occlusion with intracranial MCA occlusion
Day after:
- NIHSS of 4
- mRS of 1 at 30 days
Patient

- 54 y/o man presenting with right hemiplegia, aphasia and INO (NIHSS 18)
- Top of the basilar artery occlusion on CTA
- No IV tPA due to recent STEMI
- Intubated for decrease level of consciousness
- Cerebral Angiogram started 4-hours after symptom onset

Final Angiogram after two passes
Patient

- Extubated the day after
- NIHSS of 4
- Home 5 days later