Stroke Clinical Trials Update
Transitioning to an Anatomic Diagnosis in Ischemic Stroke

Alexander A. Khalessi MD MS
Director of Endovascular Neurosurgery
Surgical Director of NeuroCritical Care
University of California, San Diego
Disclosure Statement of Financial Interest

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

**Affiliation/Financial Relationship**
- Grant/Research Support
- Consulting Fees/Honoraria
- Major Stock Shareholder/Equity

**Company**
- Penumbra
- Covidien and Stryker Neurovascular
- Valor Medical (First Degree Relative)
Large Vessel Occlusion Carries a Distinct Natural History

iv tPA Rates of Revascularization

ICA-T: 4-8%
MCA-M1: 24-32%
MCA-M2: 31-44%

Del Zoppo et al., Ann Neurol 1992
Revascularization Improves Outcome at 3 Months in Large Vessel Occlusion

N=138

N=76 – median mRS=5 Thrombus >8mm

No recanalization by IV thrombolysis

N=6

N=55

N=17

N=62 – median mRS=2 Thrombus <8mm

Recanalization by IV thrombolysis

N=41

N=21

Riedel et al. Stroke. 2011;42:1775-1777
## Functional Outcome Based on Presenting NIHSS

<table>
<thead>
<tr>
<th>Site of Occlusion</th>
<th>6-Month mRS 0-2 Overall</th>
<th>6-Month Mortality Overall</th>
<th>6-Month mRS 0-2 NIHSS ≥10</th>
<th>6-Month Mortality NIHSS ≥10</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCA-M2</td>
<td>54% (26/48)</td>
<td>21% (10/48)</td>
<td>23% (5/22)</td>
<td>41% (9/22)</td>
</tr>
<tr>
<td>MCA-M1</td>
<td>38% (20/52)</td>
<td>23% (12/52)</td>
<td>23% (8/34)</td>
<td>32% (11/34)</td>
</tr>
<tr>
<td>ICA-T</td>
<td>38% (10/26)</td>
<td>23% (6/26)</td>
<td>7% (1/14)</td>
<td>36% (5/14)</td>
</tr>
</tbody>
</table>

Lima F, Nogueira RG et al. ISC 2010
Endovascular Stroke Therapy and the Lay Press
Broad Translational Questions

• To what extent did conduct of these trials mirror modern endovascular practice?

• What elements of endovascular practice are informed by data presented in these trials?
IMS III Post-Hoc Analysis with Confirmed LVO Demonstrate: Endovascular is Efficacious (pre-specified analysis)

**90-Day mRS Distribution, Baseline CTA Occlusion Present**

- **Endovascular N=180**
  - Endovascular: 13.3, 21.7, 12.2, 13.3, 17.8, 6.1, 15.6
- **IV tPA Alone N=91**
  - IV tPA Alone: 5.5, 14.3, 18.7, 11, 16.5, 7.7, 26.4

van Elteren test p-value 0.0114

Endovascular confers a statistically significant benefit across the spectrum of mRS

With CTA-confirmed occlusion at baseline, representative of current practice, IMS III has a statistically significant positive outcome for endovascular
Trials to Review

• IV TPA and Endovascular
  – THERAPY
  – SWIFT PRIME
  – EARLY
  – REVASCAT

• Imaging to Expand Patient Eligibility
  – POSITIVE
  – WASSABII
  – ESCAPE

• Technical Efficiency of Revascularization
  – ADAPT
  – RIVER JAPAN
IV TPA and Endovascular
THERAPY

• Assess the Penumbra System in the Treatment of Acute Stroke (THERAPY).
• Sponsor: Penumbra Inc.
• Primary objectives:
  – Assess the safety and effectiveness of the Penumbra System as an adjunctive treatment to intravenous (IV) recombinant human tissue plasminogen activator (rtPA) in patients with acute ischemic stroke from large vessel occlusion in the brain.
THERAPY

• Study type: Randomized controlled trial.
• Arms:
  – Control: IV rtPA (0.9 mg/kg to max of 90 mg)
  – Experimental: IV rtPA and IA Penumbra System aspiration embolectomy catheter and separator.
• Inclusion criteria:
  – 18 to 85 years old with symptomatic occlusion in the anterior circulation with clot burden > 8 mm presenting within 4.5 hours of last known normal and NIHSS > 8.
THERAPY

• Study period: 3 months
• Primary Outcome Measures:
  – Treatment blinded mRS score of 0-2 at 90 days.
• Secondary Outcome Measures:
  – 10 points or more improvement in the NIH stroke scale score at discharge.
  – Incidence of symptomatic and asymptomatic intracranial hemorrhage.
SWIFT PRIME

- Solitaire™ FR With the Intention For Thrombectomy as Primary Endovascular Treatment for Acute Ischemic Stroke (SWIFT PRIME) Clinical Trial
- Sponsor: Covidien
- Primary objectives:
  - To determine if patients experiencing an Acute Ischemic Stroke due to large vessel occlusion, treated with combined IV t-PA and Solitaire FR within 6 hours of symptom onset have less stroke-related disability than those patients treated with IV t-PA alone.
SWIFT PRIME

• Study type: Randomized controlled trial.
• Arms:
  – Control: IV rtPA (appropriate weight based dose)
  – Experimental: IV t-PA with SOLITAIRE™ FR device embolectomy.
• Inclusion criteria:
  – 18-85 year olds with symptomatic large vessel occlusion with NIHSS > 8 and < 30 presenting within 4.5 hours of onset.
SWIFT PRIME

• Study period: 90 days
• Primary Outcome Measures:
  – 90-day global disability assessed via the blinded evaluation of modified Rankin score (mRS).
• Secondary Outcome Measures:
  – Death due to any cause.
  – Change in NIH Stroke Scale score at 27 ±3hrs post randomization.
• Feasibility Study of IV rtPA vs. Primary Endovascular Therapy for Acute Ischemic Stroke (EARLY)
• Sponsor: Mayo Clinic
• Primary objectives:
  – Direct comparison of delivery of endovascular reperfusion therapy to intravenous rt-PA in a time-to-treatment framework shown as most effective by the NINDS rt-PA Stroke Trial.
EARLY

• Study type: Randomized controlled trial.

• Arms:
  – Control: Intravenous thrombolysis (0.9 mg/kg max 90 mg).
  – Experimental: Mechanical thrombectomy and/or stent deployment. NO TPA

• Inclusion criteria:
  – Patients over 18 years old with large vessel occlusion of the ICA, M1 or M2 segments of the MCA, ACA, basilar artery, or PCAs presenting within 3.5 hours of onset.
EARLY

- Study period: 90 days
- Primary Outcome Measures:
  - Recanalization rate of primary occlusion (blinded assessment by CTA at 24 hours).
- Secondary Outcome Measures:
  - 90 day modified Rankin Scale.
REVASCAT

• Endovascular Revascularization With Solitaire Device Versus Best Medical Therapy in Anterior Circulation Stroke Within 8 Hours (REVASCAT)
• Sponsor: Fundacio Ictus Malaltia Vascular
• Primary objectives:
  – Compare mechanical embolectomy with the Solitaire FR device to medical management alone in achieving favorable outcome in the distribution of the modified Rankin Scale scores at 90 days in subjects presenting with acute large vessel ischemic stroke < 8 hours from symptom onset.
REVASCAT

• Study type: Randomized Controlled Trial

• Arms:
  – Control: Best medical therapy (including rtPA).
  – Experimental: Mechanical embolectomy with Solitaire FR device.

• Inclusion criteria:
  – Patients 18-80 with occlusion of M1 segment of MCA or intracranial ICA and NIHSS ≥ 8 presenting within 8 hours of symptom onset.
**REVASCAT**

- **Study period:** 90 days
- **Primary Outcome Measures:**
  - 90 days modified Rankin Scale scores (mRS)
- **Secondary Outcome Measures:**
  - Mortality at 90 days.
  - Deterioration of NIHSS $\geq 4$ within 24 hours of treatment and evidence of intra-parenchymal hemorrhage.
  - Vessel recanalization at 24 hours by CTA or MRA.
  - Intra-procedural related complications in the endovascular arm.
Imaging to Expand Patient Availability
• POSITIVE: PerfusiOn Imaging Selection of Ischemic STroke PatIents for EndoVascular ThErapy.
• Sponsor: Medical University of South Carolina
• Primary objectives:
  – Demonstrate the safety and efficacy of mechanical thrombectomy over medical therapy (MT) for treating acute ischemic stroke patients ineligible for IV-tPA with persistent symptoms within a 12 hour time window from symptom onset as selected by physiologic perfusion imaging criteria.
POSITIVE

• Study type: Randomized controlled trial.

• Arms:
  – Control: No Intervention or IV-rtPA: Best medical therapy.
  – Experimental: Endovascular treatment with standard thrombectomy with aspiration catheter or stent retriever.

• Inclusion criteria:
  – 18 to 80 year olds with symptomatic occlusion in the ICA or M1 of the MCA, NIHSS > 8, presenting within 12 hours of onset.
POSITIVE

• Study period: 90 days
• Primary Outcome Measures:
  – Treatment blinded mRS score of 0-2 at 90 days.
• Secondary Outcome Measures:
  – Mortality at 30 and 90 days.
  – ICH with neurological deterioration (NIHSS worsening >4).
  – Procedure related SAE's.
  – Arterial revascularization measured by TICI 2b or 3 following device use.
WASSABI

• Wake up Symptomatic Stroke - Benefit of Intravenous Clot Busters or Endovascular Intervention (WASSABI).

• Sponsor: Jacobs Neurological Institute

• Primary objectives:
  – To study the safety and the effectiveness of using CT Perfusion studies as an indicator to treat stroke patients with unknown time of onset.
WASSABI

• Study type: **Randomized controlled trial.**
• Arms:
  – Control: Best medical therapy.
  – Experimental 1: IV thrombolytics. (Weight based IV-rtPA upto 90 mg)
  – Experimental 2: IA therapy with IA Activase, MERCI device, or PENUMBRA device.
• Inclusion criteria:
  – Patients 18-80 presenting with ischemic wake up stroke with unknown time of onset less than 24 hours, NIHSS 8-22, evidence of penumbra on CTP, and ASPECTS of 7 or greater.
WASSABI

• Study period: 90 days
• Primary Outcome Measures:
  – Modified Rankin Scale (mRS).
• Secondary Outcome Measures:
  – National Institute of Health Stroke Scale (NIHSS)
  – Thromboylsis in Cerebral Ischemia (TICI) flow
  – Symptomatic intracranial Hemorrhage (ICH)
ESCAPE

• Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion With Emphasis on Minimizing CT to Recanalization Times (ESCAPE) Trial.
• Sponsor: University of Calgary
• Primary objectives:
  – To show that rapid endovascular revascularization amongst radiologically selected (small core/proximal occlusion) patients with ischemic stroke results in improved outcome compared to patients treated in clinical routine.
ESCAPE

• Study type: Randomized, open-label blinded outcome.

• Arms
  – Control: No intervention; best medical therapy.
  – Experimental: Endovascular mechanical thrombectomy or endovascular delivery of thrombolytic agent.

• Enrollment:
  – Must be enrolled within 12 hours of last seen normal with a baseline NIHSS > 5 and confirmed symptomatic intracranial occlusion, based on single phase, multiphase or dynamic CTA.
ESCAPE

• Study period: 90 days
• Primary Outcome Measures:
  – NIHSS score of 0-2 OR a mRS score of 0-2 at 90 days.
• Secondary Outcome Measures:
  – Barthel Index > 90 at 90 days.
  – Cognitive outcomes:
    • Trailmaking A, B
    • MOCA
    • Boston Naming Test
    • Sunnybrook hemi-spatial neglect battery.
Technical Efficiency of Revascularization
ADAPT

• ADAPT: A Direct Aspiration, First Pass Technique for the Endovascular Treatment of Stroke.
• Sponsor: Medical University of South Carolina.
• Primary objectives:
  – To prospectively collect experiences where direct aspiration as a first pass technique is used for thrombectomy procedures and compare specific characteristics from these cases to other stroke cases where traditional thrombectomy devices were used.
ADAPT

• Study type: Retrospective observational study.
• Arms:
  – Experimental: Embolectomy performed by large bore aspiration catheter via direct aspiration, first pass technique.
  – Control: Embolectomy performed with traditional techniques and devices.
• Inclusion criteria:
  – All patients who were treated with direct aspiration as a first pass choice or treated with a stent retriever will be included.
ADAPT

- Study period: 90 days
- Primary Outcome Measures:
  - Discharge NIHSS score.
- Secondary Outcome Measures:
  - 90 day modified Rankin Score (mRS)
RIVER JAPAN

• Reperfuse Ischemic Vessels With Endovascular Recanalization Device in JAPAN (RIVER JAPAN)
• Sponsor: Johnson & Johnson K.K. Medical Company
• Primary objectives:
  – Document that the thrombectomy catheter (Rev-01) is effective and safe when used for revascularization in subjects with acute ischemic stroke within 8 hours of symptom onset who are ineligible for treatment with IV t-PA, or in whom treatment with IV t-PA has been ineffective.
RIVER JAPAN

• Study type: Prospective case controlled study.
• Arms: Embolectomy with Johnson and Johnson thrombectomy catheter (Rev-01)
• Inclusion criteria:
  – Patients 20-85 years old with symptomatic occlusion of M1, M2, basilar artery, or vertebral artery, NIHSS 8-30, presenting within 8 hours of onset of symptoms.
RIVER JAPAN

• Study period: 90 days
• Primary Outcome Measures:
  – Proportion of patients who have recanalization.
• Secondary Outcome Measures:
  – 90 day mRS score, NIHSS score, and BI score.
  – Proportion of patients with ICH (symptomatic and asymptomatic).
  – Mortality due to any cause.
Conclusions

• Next Generation Trials appropriately target Large Vessel Occlusion

• Preponderance of Large Scale Trials continue to Target iv TPA Eligible Patients

• Expansion of Patients Eligible for Endovascular Rely on Imaging Triage

• Continued iterative efforts to improve technical efficiency of revascularization.