Prehospital and Endovascular Care in the New Era of Ischemic Stroke Treatment

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SA Vice-Chair and Professor of Neurology, DGSOM
JLS Disclosures

• Employee of the University of California. The University of California has patent rights in retrieval devices for stroke.
• Unpaid site investigator in multicenter trials run by Medtronic, Stryker, and Lundbeck, for which the UC Regents received payments on the basis of clinical trial contracts for the number of subjects enrolled.
• Receives funding for services as a scientific consultant regarding trial design and conduct to Medtronic/Covidien, Stryker, Neuravi, BrainsGate, Pfizer, Boehringer Ingelheim (prevention only), and St. Jude Medical.
• Serves as an unpaid consultant to Genentech advising on the design and conduct of the PRISMS trial; neither the University of California nor Dr. Saver received any payments for this voluntary service.
Talk Outline

• Fast - Time and Intravenous Therapies
  » IV TPA
  » Prehospital treatment

• Furious
  » Endovascular Therapies
  » Systems of Care

• Future
Strategies in Acute Ischemic Stroke Therapy

• Proven
  » Recanalization
  » Supportive Care
  » Prevent Clot Propagation

• Experimental
  » Neuroprotection
  » Collateral Enhancement
Two Major Strategies in Acute Ischemic Stroke Treatment

Reperfusion

Neuroprotection

--modified from M Tymianski
The Ischemic Penumbra

Irreversible Core Infarct

Ischemic Penumbra: zone of salvageable tissue surrounding core infarct
Brief Time Window in Animal Stroke Models

- Permanent
- Early
- Medium
- Late

• UCLA Stroke Center
In a typical acute ischemic stroke, every minute the brain loses

- 1.9 million neurons
- 14 billion synapses
- 7.5 miles myelinated fibers

--- Saver, Stroke 2006
Onset to Treatment Time for IV TPA and Odds of Excellent Outcome

- Pooled, patient level analysis
- 8 trials
  - NINDS 1 and 2
  - ATLANTIS A and B
  - ECASS 1, 2, and 3
  - EPITHET
- 3670 patients

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UCLA Stroke Center

--Lees et al, Lancet 2010
--Saver + Levine, Lancet 2010
--Saver, Stroke 2012
Among 1000 patients, for every 15 min acceleration of tPA treatment

- 18 more will have improved ambulation at discharge
  - Including 8 more who will ambulate fully independently
- 13 more will be discharged to a more independent environment
  - Including 7 more discharged to home
- 4 fewer patients will die prior to discharge

---

Saver et al, JAMA 2013

<table>
<thead>
<tr>
<th>Ambulatory Status</th>
<th>0-90</th>
<th>91-180</th>
<th>181-270</th>
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<tbody>
<tr>
<td>Ambulate Independently</td>
<td>25.8</td>
<td>22.7</td>
<td>18.8</td>
</tr>
<tr>
<td>Ambulate w/ Assistance</td>
<td>38.1</td>
<td>37.2</td>
<td>35.3</td>
</tr>
<tr>
<td>Non-Ambulatory</td>
<td>26.9</td>
<td>29.5</td>
<td>32.8</td>
</tr>
<tr>
<td>Dead</td>
<td>9.1</td>
<td>10.1</td>
<td>13.2</td>
</tr>
</tbody>
</table>
A Drop of Brain (1cc), A Week of Healthy Life Quality Adjusted Life-Years (QALYs)

DALYs = YLD + YLL

- DALYs: Disability Adjusted Life Years
- YLD: Years Lived with Disability
- YLL: Years of Life Lost

Penumbra (yellow) and core (blue) volumes on perfusion CT pre-tPA

Final infarct volume on 24h MRI

Pre-stroke, First 3m post-stroke, > 3m post-stroke

Expected Life-years

--Saver, Brain 2017
--Kawano et al, Brain 2017
Improvement Over Time in GWTG-Stroke in the Use of IV rt-PA in Eligible Patients

Substantial Opportunity to Improve Timeliness of IV rt-PA in Ischemic Stroke

Door-to-IV rt-PA within 60 minutes

- 2005: 24.10%
- 2006: 22.30%
- 2007: 24.70%
- 2008: 25.80%
- 2009: 27.40%

*GWTG-Stroke Database, data on file DCRI*
Target: Stroke  The Time is Now

Door-to-IV rt-PA within 60 minutes

- DTN within 60 min
  - 2009: 27.4%
  - Goal: 50.0%

*GWTG-Stroke Database, data on file DCRI
Target: Stroke
Best Practice Strategies

1. *EMS Pre-Notification
2. Stroke Toolkit
3. Rapid Triage and Stroke Team Notification
4. *Single Call Activation System
5. *Transfer Directly to CT
6. Rapid Brain Imaging
7. *POC Laboratory
8. *Premix TPA
10. Team approach
11. *Prompt data feedback

Target: Stroke Initiation

(P<0.0001 for comparison of the two slopes)
IV TPA Under 3 Hours – Patient Education

- Joint AHA-AAN-ACEP text tool to educate patients and families
- UCLA icon array tool based on AHA-AAN-ACEP

--Gadhia et al, Stroke 2010
Target: Stroke Phase 2

- Target: Stroke Elite
  - DTN ≤ 60m in 75%
  - DTN ≤ 45m in 50%
Time Trend in the Proportion of Patients with DTN Times within 45 Minutes Pre-Target: Stroke and During Target: Stroke Phase I and II

<table>
<thead>
<tr>
<th>Time Period (per year)</th>
<th>Estimate (95% CI)</th>
<th>P-value</th>
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</thead>
<tbody>
<tr>
<td>Pre-Target: Stroke</td>
<td>0.12 (-0.20, 0.43)</td>
<td>0.4741</td>
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<tr>
<td>Target: Stroke Phase I</td>
<td>2.87 (2.49, 3.25)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Target: Stroke Phase II</td>
<td>10.20 (5.92, 14.48)</td>
<td>0.0018</td>
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Door to Needle Times with “Direct to CT” or “ED Pitstop” in Best Practice Hospitals

<table>
<thead>
<tr>
<th>Stroke Center</th>
<th>Median Door to Needle Times</th>
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<tbody>
<tr>
<td>Helsinki, Finland</td>
<td>20 mins</td>
</tr>
<tr>
<td>Erlangen, Germany</td>
<td>25 mins</td>
</tr>
<tr>
<td>Wash U, St. Louis</td>
<td>39 mins</td>
</tr>
</tbody>
</table>

--Meretojoa et al, Neurology 2012  
--Korhmann et al, Int J Stroke 2011  
--Ford et al, Stroke 2012
Stroke Treatment in the Golden Hour

- **GWTG-Stroke**
  - 65,384 tPA patients
  - Jan 2009 – Sept 2013
  - 1456 hospitals

- **Onset to treatment time ≤ 60m**
  - 878 patients
  - 1.3% of under 4.5h tPA cohort
  - 15-60m vs 61-270m
    - Discharge to home OR 1.25
    - Indep ambulation at d/c OR 1.22
    - Nondisabled (mRS 0-1) OR 1.72

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**Shape of time-benefit curve**

Mildly nonlinear for mRS 0-1 and d/c home
More rapid decline first 100-170m

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--Kim JT et al. Circulation 2017
Stroke and the Golden Hour

- Narrow therapeutic time window
- Early intervention critical for stroke care
- Prehospital personnel
  » 35-70% of stroke patients arrive by ambulance
  » Unique position: first medical professional to come in contact with stroke patient

UCLA Stroke Center
<table>
<thead>
<tr>
<th>Trial</th>
<th>Intervention</th>
<th>Strategy</th>
<th>Design</th>
<th>Size</th>
<th>Status</th>
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</thead>
<tbody>
<tr>
<td>FAST-MAG Pilot</td>
<td>Magnesium</td>
<td>NP</td>
<td>Historical controls</td>
<td>20</td>
<td>2004</td>
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<tr>
<td>Helsinki EMS</td>
<td>IV + SQ Insulin</td>
<td>Homeo-Stasis</td>
<td>Randomized open / hist cont</td>
<td>23</td>
<td>2011</td>
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<tr>
<td>Aarhus University</td>
<td>Remote perconditioning</td>
<td>NP</td>
<td>Randomized open label</td>
<td>443</td>
<td>2013</td>
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<tr>
<td>RIGHT*</td>
<td>Glyceryl trinitrate</td>
<td>BP/NP</td>
<td>Randomized open label</td>
<td>41</td>
<td>2013</td>
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<tr>
<td>PIL-FAST*</td>
<td>Lisinopril</td>
<td>BP</td>
<td>Randomized open label</td>
<td>14</td>
<td>2013</td>
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<tr>
<td>FAST-MAG Pivotal</td>
<td>Magnesium</td>
<td>NP</td>
<td>Randomized, blinded placebo</td>
<td>1700</td>
<td>2014</td>
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<tr>
<td>FAST-BP*</td>
<td>Glyceryl trinitrate</td>
<td>NP/BP/CE</td>
<td>Dose escalation</td>
<td>45</td>
<td>Enrolling (California)</td>
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<tr>
<td>FRONTIER*</td>
<td>NA-1</td>
<td>NP</td>
<td>Randomized, 2B</td>
<td>500</td>
<td>Enrolling (Canada)</td>
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<tr>
<td>RIGHT-2*</td>
<td>Glyceryl trinitrate</td>
<td>NP/BP/CE</td>
<td>Randomized, sham-controlled</td>
<td>850</td>
<td>Enrolling (Great Britain)</td>
</tr>
</tbody>
</table>
The Ischemic Cascade and Neuroprotective Interventions

- Modulators of Excitatory Amino Acids
- Modulators of Calcium Influx
- Metabolic Activators
- Anti-edema Agents
- Inhibitors of Leukocyte Adhesion
- Free Radical Scavengers and Anti-Oxidants
- Promotors of Membrane Repair
- Unknown or Other Mechanism(s)

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45 mins

Standard Care

Neuroprotection

Collateral Enhancement

Neuroprotection + Collateral ↑

3 hours

Reperfusion

Final Infarct
Trials of Neuroprotective Agents for Stroke, 1955-2000

- Neuroprotective agents tested: 49
- RCTs performed: 114
- Patients enrolled: 21,445
- Neuroprotective agents approved: 0

Time windows: 4-48 hours

-- Kidwell, Liebeskind, Starkman, Saver, Stroke 2001
Six Design Defects of Past Neuroprotective Trials

- Dose too low
  » Side effects
- Enroll patients unlikely to respond to drug action
  » White matter strokes for EAA blockade agents
- Enroll uninformative patients
  » Too mild at entry – fare well with placebo
  » Too severe at entry – fare poorly with active
- Sample sizes too small
- Outcome measures insensitive to modest but important benefits
- Late time of treatment start
The Field Administration of Stroke Therapy – Magnesium (FAST-MAG) Phase III Trial
Field Administration of Stroke Treatment – Magnesium (FAST-MAG) Trial

- Placebo-controlled, double-blind, randomized
- Multicenter, single region
  » Los Angeles and Orange Counties
- 4 gm Mg field, 16 gm Mg maintenance x 24h
- 1700 patients, 1st patient Jan 2005
- Primary endpoint: Rankin Scale shift
FAST-MAG Trial Consortium

- Los Angeles and Orange Counties
  » Population 13.3 million
- 40 EMS Provider Agencies
  » 315 rescue ambulances
  » 2988 paramedics
- 60 receiving hospitals
  » 952 physician-investigators
    • 715 Emergency Medicine (site PIs)
    • 210 Neurologist
    • 26 Nsurg/Intensiv/Hosp
- 95 CCC coordinators and research assistants

Performance Sites in Los Angeles and Orange Counties

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Entry Criteria

Inclusion

• Suspected stroke identified by the Los Angeles Prehospital Stroke Screen (LAPSS)
• Age 40-95, inclusive
• Last known well time within 2h of treatment initiation
• Deficit present for ≥ 15 minutes

Exclusion

• Coma
• Rapidly improving neurologic deficit
• Pre-existing neurologic, psychiatric or advanced systemic disease that would confound outcome evaluations
• SBP<90 or>220
• Severe renal dysfunction
• Severe respiratory distress
• 2nd or 3rd degree heart block w/o pacemaker
• Major head trauma in last 24h
• Recent stroke within prior 30d,
• Patient/LAR unable to provide informed consent and EFIC not approved in catchment area

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FAST-MAG
Distinctive Methodologic Aspects

• Diagnosing stroke in the field
  » LAPSS
  » Physician cellphone review

• Rating pretreatment stroke severity
  » LAMS

• Eliciting consent
  » Physician cellphone elicitation (99%)
  » EFIC (1%)

• Prehospital treatment route
  » Fixed lumen, rate-limiting IV infusion

• Randomization
  » Pre-encounter randomization
FAST-MAG
Explicit Informed Consent Enrollment Process*

• Paramedics
  » Identify likely stroke patients using LAPSS
  » Call simultaneous ring enrolling line
    • English line – 4 English speaking MDs
    • Spanish line – 4 Spanish speaking MDs
    • First MD to answer proceeds
  » Give cellphone to patient/LAR
  » Give consent form to patient/LAR
    • Each ambulance has 8 consent forms
      » 4 most common hospitals (4 English, 4 Spanish)

• Cellphone Enrolling Physicians
  » Discuss trial with patient/LAR
    • While paramedic performs usual care
  » After patient/LAR signs form, instructs paramedic to start study infusion
  » Co-signs consent form after ED arrival

*99% enrolled by explicit consent; 1% by EFIC

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# Neurologic Features

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo (n=843)</th>
<th>Magnesium (n=857)</th>
<th>Total (n=1700)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prestroke Function</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Residence (home)</td>
<td>97.6%</td>
<td>97.3%</td>
<td>97.5%</td>
<td>0.16</td>
</tr>
<tr>
<td>Prestroke Rankin</td>
<td>0 (0-0)</td>
<td>0 (0-0)</td>
<td>0 (0-0)</td>
<td>0.83</td>
</tr>
<tr>
<td><strong>Final Diagnosis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebral Ischemia</td>
<td>72.8%</td>
<td>73.7%</td>
<td>73.3%</td>
<td>0.43</td>
</tr>
<tr>
<td>Intracranial Hemorrhage</td>
<td>22.8%</td>
<td>22.8%</td>
<td>22.8%</td>
<td>0.64</td>
</tr>
<tr>
<td>Mimic</td>
<td>4.4%</td>
<td>3.5%</td>
<td>3.9%</td>
<td>0.83</td>
</tr>
<tr>
<td><strong>Presenting Severity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAMS (Prehospital)</td>
<td>3.7 (±1.3)</td>
<td>3.7 (±1.3)</td>
<td>3.7 (±1.3)</td>
<td>0.57</td>
</tr>
<tr>
<td>NIHSS (Hospital)</td>
<td>11.2 (±9.8)</td>
<td>11.5 (±9.0)</td>
<td>11.3 (±9.9)</td>
<td>0.41</td>
</tr>
</tbody>
</table>

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## Time Intervals

<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>Onset* to Drug (mins)</td>
<td>46 (36-62)</td>
<td>45 (35-60)</td>
<td>45 (35-62)</td>
<td>0.24</td>
</tr>
</tbody>
</table>

*Onset = last known well time

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## Time Intervals

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<td>45 (35-62)</td>
<td>0.24</td>
</tr>
<tr>
<td>Onset to Drug (categorical)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-1 hours</td>
<td>73.2%</td>
<td>75.3%</td>
<td>74.3%</td>
<td>0.61</td>
</tr>
<tr>
<td>1-2 hours</td>
<td>25.7%</td>
<td>23.7%</td>
<td>24.7%</td>
<td></td>
</tr>
<tr>
<td>&gt;2 hours</td>
<td>1.1%</td>
<td>0.9%</td>
<td>1.0%</td>
<td></td>
</tr>
</tbody>
</table>

*Onset = last known well time

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<td>24.7%</td>
<td></td>
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<tr>
<td>&gt;2 hours</td>
<td>1.1%</td>
<td>0.9%</td>
<td>1.0%</td>
<td></td>
</tr>
<tr>
<td>On Scene to Drug</td>
<td>23 (19-28)</td>
<td>23 (18-27)</td>
<td>23 (18-27)</td>
<td>0.58</td>
</tr>
<tr>
<td>On Scene to Door**</td>
<td>33 (27-39)</td>
<td>32 (27-39)</td>
<td>33 (27-39)</td>
<td>0.91</td>
</tr>
</tbody>
</table>

*Onset = last known well time

**Historical comparator, pretrial LA scene to door times = 35 minutes (Stroke 2004;35:e106-108)

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Reperfusion Treatments After Arrival in FAST-MAG Cerebral Ischemia Patients (n=1235)

<table>
<thead>
<tr>
<th>Number of Patients</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV tPA</td>
<td>452</td>
</tr>
<tr>
<td>Endovascular</td>
<td>76</td>
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</tbody>
</table>


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Primary Endpoint: Global Disability at 3 Months (modified Rankin Scale)

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Magnesium</th>
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<tr>
<td>0</td>
<td>21.7</td>
<td>20.9</td>
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<tr>
<td>1</td>
<td>15.2</td>
<td>15.6</td>
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<tr>
<td>2</td>
<td>15.9</td>
<td>15.9</td>
</tr>
<tr>
<td>3</td>
<td>10.8</td>
<td>12.6</td>
</tr>
<tr>
<td>4</td>
<td>9.5</td>
<td>10.4</td>
</tr>
<tr>
<td>5</td>
<td>11.5</td>
<td>9.3</td>
</tr>
<tr>
<td>6</td>
<td>15.4</td>
<td>15.3</td>
</tr>
</tbody>
</table>

CMH test: $p = 0.28$
(Means 2.7 v 2.7)
Discussion: Magnesium as a Neuroprotectant for Stroke

• FAST-MAG failed to confirm the primary hypothesis that prehospital magnesium sulfate is beneficial in likely stroke patients
• No increase in overall serious adverse events
• Potential reasons for neutral results
  » Slow magnesium passage across blood-brain barrier despite early systemic delivery
  » Magnesium as a single agent insufficient to suppress molecular ischemic cascade
  » Improving standard care reduced opportunity to demonstrate benefit
    • Interim analysis point estimates favorable for magnesium
    • Better supportive care at Primary Stroke Centers
    • TPA more often and faster
Discussion: Prehospital Delivery of Phase 3 RCT Stroke Therapy

- First prehospital stroke phase 3 randomized, controlled trial
- First acute (<3 hr) neuroprotective phase 3 trial
- First stroke phase 3 trial of neuroprotection before recanalization therapy
- First prehospital RCT for any condition employing physician-elicited informed consent
- First “golden hour” (<1 hr) stroke phase 3 trial
  » Over 1250 treated within 60 mins of last known well time
- Methods and patient data available for therapies in pipeline
FAST-MAG vs NINDS-TPA Study
Time to Treatment

Supported by NIH-NINDS

<table>
<thead>
<tr>
<th>Time to Treatment</th>
<th>FAST-MAG Study</th>
<th>NINDS-TPA Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1</td>
<td></td>
<td>0.3</td>
</tr>
<tr>
<td>1-2</td>
<td>55</td>
<td>55</td>
</tr>
<tr>
<td>&gt;2</td>
<td>44.8</td>
<td>44.8</td>
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FAST-MAG vs NINDS-TPA Study
Time to Treatment

Supported by NIH-NINDS

<table>
<thead>
<tr>
<th>Time (hrs)</th>
<th>FAST-MAG</th>
<th>NINDS-TPA</th>
</tr>
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<tbody>
<tr>
<td>0-1</td>
<td>75</td>
<td>0.3</td>
</tr>
<tr>
<td>1-2</td>
<td>24</td>
<td>55</td>
</tr>
<tr>
<td>&gt;2</td>
<td>44.8</td>
<td>1</td>
</tr>
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</table>
Mobile Stroke Units for Prehospital Thrombolysis

--Walter et al, PLOS One, 2010, Homburg

--Audebert et al, Berlin
Effect of the Use of Ambulance-Based Thrombolysis on Time to Thrombolysis in Acute Ischemic Stroke: A Randomized Clinical Trial

Martin Ebinger, MD; Benjamin Winter, MD; Matthias Wendt, MD; Joachim E. Weber, MD; Carolin Waldschmidt, MD; Michal Rozanski, MD; Alexander Kuzn, MD; Peter Koch, MD; Philipp A. Kalthoff, MD; Daniel Gerhards, MD; Kersten Wilfinger, MD; Jochen B. Friebich, MD; Ulrike Grittmann, PhD; Andreas Hartmann, MD; Bruno-Marcell Mackert, MD; Matthias Endres, MD; Heinrich J. Audszeit, MD; for the STEM Study Group

Original Investigation

April 23, 2014

Volume 311, Number 16
Pages 1529-1534

Research
<table>
<thead>
<tr>
<th></th>
<th>CT Ambulance Patients</th>
<th>p value</th>
<th>CT Ambulance Weeks</th>
<th>p value</th>
<th>Control Weeks</th>
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<tbody>
<tr>
<td>N</td>
<td>1804</td>
<td></td>
<td>3213</td>
<td></td>
<td>2969</td>
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<tr>
<td>Pct of AIS</td>
<td>32.6%</td>
<td>&lt;0.001</td>
<td>28.9%</td>
<td>&lt;0.001</td>
<td>21.1%</td>
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<tr>
<td>DTN Hosp (min)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>42</td>
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<tr>
<td>Alarm to Hosp (min)</td>
<td>85</td>
<td>&lt;0.001</td>
<td>67</td>
<td>&lt;0.001</td>
<td>35</td>
</tr>
<tr>
<td>Alarm to Imaging</td>
<td>38</td>
<td>&lt;0.001</td>
<td>44</td>
<td>&lt;0.001</td>
<td>52</td>
</tr>
<tr>
<td>Imaging to TPA</td>
<td>14</td>
<td>&lt;0.001</td>
<td>17</td>
<td>&lt;0.001</td>
<td>24</td>
</tr>
<tr>
<td>*Alarm to TPA</td>
<td>52</td>
<td>&lt;0.001</td>
<td>61</td>
<td>&lt;0.001</td>
<td>76</td>
</tr>
<tr>
<td>Onset to TPA</td>
<td>103</td>
<td>&lt;0.001</td>
<td>110</td>
<td>0.003</td>
<td>119</td>
</tr>
<tr>
<td>Onset to TPA &lt;90m</td>
<td>58%</td>
<td>&lt;0.001</td>
<td>48%</td>
<td>0.02</td>
<td>37%</td>
</tr>
</tbody>
</table>

*Primary Endpoint

No differences in efficacy or safety outcomes (not powered to detect)
Growing Worldwide Use of Mobile Stroke Units

UCLA Stroke Center -- Fassbender, Grotta, Walter, Grunwald, Ragoschke-Schumm, Saver. Lancet Neurol 2017
BE nefits of Stroke Treatment Delivered Using a Mobile Stroke Unit (BEST-MSU) Trial

- Cluster-control RCT
  - 5 EMS Regions USA
  - 1 week on, 1 week off
  - Patients
    - 6000 assessed
    - 1200 enrolled
      - 700 fully tPA eligible

- Key entry criteria
  - LKW within 4.5h prior to ambulance evaluation
  - tPA eligible prior to CT/labs

- Outcome
  - Utility-weighted mRS at 90d

- Timeline
  - 2014-2021
Trials of Novel Therapies Using Mobile Stroke Unit as Platform

• Intracerebral hemorrhage
  » Anticoag reversal
    • PRESTO-Reverse
    • B-SPATIAL
  » Hemostatic therapy
    • Aust transexamic acid RCT
  » BP control
    • HEME-MSU

• Acute cerebral ischemia
  » Neuroprotection
    • TEMPO-EMS

UCLA Stroke Center
1837 – First patented US ambulance in US

1889 – Patented ambulance with built-in stretcher

1914 – First x-ray ambulance – Madame Curie

2011 – First CT ambulance - Homburg

--Modified from Nour, Brain Attack 2017
Future Technology / Trials?

Helicopter MSU

Mobile Neurointervention Suite
Varieties of Treatment Strategies

Variants of the stroke rescue chain

Average times (in minutes)

0  30  60  90  120  150

Regular care
- Drive to scene
- First aid
- Transport to hospital
- In-hospital diagnostic work-up

Time to treatment

FAST-MAG
- Drive to scene
- First aid and study inclusion
- Transport + in-advance notification
- In-hospital diagnostic work-up

Brain "under protection"

Time to protection

STEMO
- Drive to scene
- First aid and diagnostic work-up
- Routing to specialized facility
- In-hospital work-up

Time of onset
Emergency call + dispatch

Intra-arterial treatment

--Audebert, Lees, Starkman, Saver, Endres, Neurology 2013
Catheter-Based Reperfusion Therapies
### Historical Development of Endovascular Technologies for Acute Recanalization

<table>
<thead>
<tr>
<th>Technology</th>
<th>First Human Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA microcatheter lysis</td>
<td>1988 (1999)</td>
</tr>
<tr>
<td>IA angioplasty</td>
<td>1994</td>
</tr>
<tr>
<td>IA aspiration thrombectomy</td>
<td>2001 (2009)</td>
</tr>
<tr>
<td>IA ultrasound sonothrombolysis</td>
<td>2003</td>
</tr>
<tr>
<td>IA implanted stents</td>
<td>2003</td>
</tr>
<tr>
<td>IA laser clot destruction</td>
<td>2004</td>
</tr>
<tr>
<td>IA Archimedes screw</td>
<td>2004</td>
</tr>
<tr>
<td>IA basket/brush retrievers</td>
<td>2006</td>
</tr>
<tr>
<td>IA stent retrievers</td>
<td>2010 (2010)</td>
</tr>
</tbody>
</table>

*UCLA Stroke Center*
Mechanical Thrombectomy Devices

Coil Retriever

UCLA Stroke Center
Mechanical Thrombectomy Devices

Coil Retriever

UCLA Stroke Center
Mechanical Thrombectomy Devices

Coil Retriever

UCLA Stroke Center
Mechanical Thrombectomy Devices

Coil Retriever

Stent Retriever
Mechanical Thrombectomy Devices

- Coil Retriever
- Stent Retriever
- Covered Stent Retriever

UCLA Stroke Center
Mechanical Thrombectomy Devices

- Coil Retriever
- Stent Retriever
- Covered Stent Retriever
- Basket Retriever

UCLA Stroke Center
Mechanical Thrombectomy Devices

Coil Retriever
Stent Retriever
Covered Stent Retriever
Basket Retriever
Brush Retriever

UCLA Stroke Center
Mechanical Thrombectomy Devices

- Coil Retriever
- Stent Retriever
- Covered Stent Retriever
- Basket Retriever
- Brush Retriever
- Aspiration Catheter
Acute Mechanical Recanalization Strategy Depends on Target Occlusion Composition

**Emboli**
- Relatively normal recipient artery
- Strategy: remove the thrombus
  - Retrievers
  - Aspirators
  - +/- Lytics

**In Situ Atherothrombosis**
- Substantial local atherosclerotic plaque
- Strategy: Crack the plaque
  - Angioplasty
  - Stents
  - +/- Lytics
Determinants of Thrombectomy Success

- Clot burden
- Clot composition
- Clot tensile properties
- Tortuosity of feeding arteries
- Target artery size
- Recipient artery branching curvature

UCLA Stroke Center
Should clot composition affect choice of endovascular therapy?

**Abstract**

Endovascular therapy has become a promising alternative for patients who are ineligible for IV thrombolysis or for whom it has failed. Greater knowledge about the composition of thromboembolic material underlying the vascular occlusion in stroke patients may provide the means for improving existing endovascular therapies and developing new treatment strategies. The objective of this article is to provide a review of clinical and experimental animal studies on the histology, imaging correlation, and ultrastructure of thromboemboli retrieved during acute ischemic stroke. *Neurology* 2012;78 (Suppl 1):S63–S67

Organized, Inelastic, Hard, Fibrin-Rich Clot

**Aspiration:**
- Cohesive = lower risk of clot stripping/fragmentation during aspiration

**Stentriever:**
- Inelastic so harder to be incorporated into the stent cells
- Push+Fluff Technique and/or larger or hybrid cells

Fresh, Elastic, Soft, RBC-Rich Clot

**Stentriever:**
- Elastic = easier to be incorporated into the stent cells

**Aspiration:**
- Friable = higher risk of clot stripping/fragmentation during aspiration
- Larger ID catheters closely matching vessel diameter
UCLA – MCA Occlusion
30-Year-Old Female – Baseline NIHSS 24
Symptom Onset to Final Angiogram – 5:37

<table>
<thead>
<tr>
<th>NIHSS</th>
<th>24 hours</th>
<th>mRS</th>
<th>5 days post</th>
<th>90 day post</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td></td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Complete Recanalization Heart vs. Brain

--Patel + Saver, Submitted
The New Wave in Endovascular Recanalization Devices: Retrievable Stents

• Advantages
  » Immediate reperfusion
  » Potential clot retrieval
  » Potential longterm stenting

• Devices
  » Solitaire stent
    • Ev3
    • SWIFT Trial
  » Mindframe stent
    • Mindframe, Inc
    • PRIISM Trial
  » ReStore stent
    • Reverse Medical
  » Trevo stent
    • Concentric
    • TREVO Trial

--Henkes et al, Stroke 2009, p410
JL Saver, R Jahan, E Levy, T G Jovin, B Baxter, R Nogueira, W Clark, R Budzik, OO Zaidat, for the SWIFT Trialists
## Primary Trial Endpoint

<table>
<thead>
<tr>
<th>Outcomes Among Randomized Patients</th>
<th>Randomized Solitaire FR N=58</th>
<th>Randomized Merci N=55</th>
<th>Non-inferiority P value(^1)</th>
<th>Superiority P value(^1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Successful recanalization without SICH(^2) (Core Lab)</td>
<td>60.7% (34/56)</td>
<td>24.1% (13/54)</td>
<td>&lt;0.0001</td>
<td>0.0001</td>
</tr>
<tr>
<td>Successful recanalization study device (Core Lab)</td>
<td>68.5% (37/54)</td>
<td>30.2% (16/53)</td>
<td>&lt;0.0001</td>
<td>0.0001</td>
</tr>
<tr>
<td>Successful recanalization study device (Site Assessed)</td>
<td>83.3% (45/54)</td>
<td>48.1% (26/54)</td>
<td>&lt;0.0001</td>
<td>0.0002</td>
</tr>
<tr>
<td>Use of rescue therapy</td>
<td>20.7% (12/58)</td>
<td>43.6% (24/55)</td>
<td>&lt;0.0001</td>
<td>0.015</td>
</tr>
<tr>
<td>End of procedure successful recanalization (Site)</td>
<td>88.9% (48/54)</td>
<td>67.3% (37/55)</td>
<td>&lt;0.0001</td>
<td>0.010</td>
</tr>
<tr>
<td>End of procedure successful recanalization (Core Lab)</td>
<td>80.4% (45/56)</td>
<td>57.4% (31/54)</td>
<td>&lt;0.0001</td>
<td>0.013</td>
</tr>
</tbody>
</table>

1. Noninferiority by Wald’s method, superiority by Fisher’s Exact test
2. Symptomatic Intracranial Hemorrhage - Any PH1, PH2, RIH, SAH, or IVH associated with a decline in NIHSS ≥ 4 within 24hrs.
Global Disability at 90 Days (Modified Rankin Score)

**MERCI**
- 10.4%
- 8.3%
- 10.4%
- 8.3%
- 16.7%
- 2.1%
- 43.8%

**SOLITAIRE FR**
- 12.7%
- 12.7%
- 10.9%
- 20.0%
- 21.8%
- 3.6%
- 18.2%

CMH, p = 0.04
Hemorrhagic Transformation Outcomes

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<tr>
<th>Outcomes Among Randomized Patients</th>
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<th>Randomized Merci N=55</th>
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<th>Superiority P value(^1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SICH</td>
<td>1.7% (1/58)</td>
<td>10.9% (6/55)</td>
<td>&lt;0.0001</td>
<td>0.057</td>
</tr>
<tr>
<td>All ICH</td>
<td>17.2% (10/58)</td>
<td>38.2% (21/55)</td>
<td>0.0001</td>
<td>0.020</td>
</tr>
</tbody>
</table>

\(^1\) Fisher’s Exact
TREVO 2 Trial

Rankin Shift

Trevo™ Device

Merci™ Device

---Nogueira et al, Lancet 2012
Complete Recanalization Heart vs. Brain

- Cardiac
- Stroke

UCLA Stroke Center
Era of Highly Effective Reperfusion Therapy
### Evidence of Benefit: Independence (mRS ≤ 2) at 3 Months

<table>
<thead>
<tr>
<th>Trial</th>
<th>ERT+MedRx</th>
<th>MedRx</th>
<th>OR</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MR CLEAN</td>
<td>32.6%</td>
<td>19.1%</td>
<td>2.05</td>
<td>0.0007</td>
</tr>
<tr>
<td>ESCAPE</td>
<td>53.0%</td>
<td>29.3%</td>
<td>2.73</td>
<td>0.00003</td>
</tr>
<tr>
<td>EXTEND-IA</td>
<td>71.4%</td>
<td>40.0%</td>
<td>3.75</td>
<td>0.009</td>
</tr>
<tr>
<td>SWIFT PRIME</td>
<td>60.2%</td>
<td>35.5%</td>
<td>2.75</td>
<td>0.0008</td>
</tr>
<tr>
<td>REVASCAT</td>
<td>43.7%</td>
<td>28.2%</td>
<td>1.98</td>
<td>0.021</td>
</tr>
<tr>
<td><strong>All (weighted avg)</strong></td>
<td><strong>46.1%</strong></td>
<td><strong>26.4%</strong></td>
<td><strong>2.39</strong></td>
<td><strong>&lt;0.00000001</strong></td>
</tr>
</tbody>
</table>

Odds that ERT is beneficial are more than 100,000,000 to 1
<table>
<thead>
<tr>
<th>Trial</th>
<th>Current N</th>
<th>Planned Max N</th>
<th>Intervention</th>
<th>CTA/MRA</th>
<th>Time</th>
<th>TPA</th>
<th>Imaging</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>MR CLEAN</td>
<td>500</td>
<td>500</td>
<td>Variable (97% SR)</td>
<td>+</td>
<td>6 hr</td>
<td>Y or Inel</td>
<td>&lt;1/3 MCA</td>
<td>Positive</td>
</tr>
<tr>
<td>ESCAPE</td>
<td>316</td>
<td>500</td>
<td>Variable (86% SR)</td>
<td>+</td>
<td>12 hr</td>
<td>Y or Inel</td>
<td>Collat &lt; 50%</td>
<td>Positive</td>
</tr>
<tr>
<td>EXTEND IA</td>
<td>70</td>
<td>100</td>
<td>Solitaire</td>
<td>+</td>
<td>6 hr</td>
<td>Y</td>
<td>RAPID Mismatch</td>
<td>Positive</td>
</tr>
<tr>
<td>SWIFT PRIME</td>
<td>196</td>
<td>833</td>
<td>Solitaire</td>
<td>+</td>
<td>6 hr</td>
<td>Y</td>
<td>A ≥ 6 RAPID</td>
<td>Positive</td>
</tr>
<tr>
<td>REVASCAT</td>
<td>206</td>
<td>690</td>
<td>Solitaire</td>
<td>+</td>
<td>8 hr</td>
<td>Inel or Failed</td>
<td>A ≥ 6/7</td>
<td>Positive</td>
</tr>
<tr>
<td>THRACE</td>
<td>~450</td>
<td>480</td>
<td>Variable</td>
<td>+</td>
<td>R 4h</td>
<td>Y</td>
<td></td>
<td>Positive</td>
</tr>
<tr>
<td>THERAPY</td>
<td>108</td>
<td>692</td>
<td>Penumbra 3D</td>
<td>HVS≥8 mm</td>
<td>(6 hr)</td>
<td>Y</td>
<td>&lt; 1/3 MCA</td>
<td>Trend Positive</td>
</tr>
<tr>
<td>PISTE</td>
<td>~75</td>
<td>800</td>
<td>Variable</td>
<td>+</td>
<td>6 hr</td>
<td>Y</td>
<td>CT hypo</td>
<td>Enrolling</td>
</tr>
</tbody>
</table>

UCLA Stroke Center
# Features of Second Generation Embolectomy Trials

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<thead>
<tr>
<th>Trial</th>
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</tr>
</tbody>
</table>

*UCLA Stroke Center*
Endovascular therapy if patients meet all the following criteria:
- Prestroke mRS score 0-1
- Received IV tPA (Ia) or tPA-ineligible (IIa)
- ICA or M1 MCA occlusion
- Age ≥ 18 yo
- NIHSS ≥ 6
- ASPECTS ≥ 6
- Treatment start (puncture) within 6h of onset
NNTs for Cerebral and Cardiac Ischemia Binary Outcomes

**Thrombectomy**
- for AIS (vs Lysis)
- Independence

**IV Lytics**
- for AIS (vs ASA)
- Nondisability

**PCI**
- for STEMI (vs Lysis)
- Mortality

(UCLA Stroke Center)

---

Cost Effectiveness
US Payer Perspective - Lifetime

• IV tPA vs supportive
  » QALY Gain
    • 0.39 yrs
  » Healthcare Costs
    • Reduced $25,000

• ET+IV TPA vs IV tPA
  » QALY Gain
    • 1.74yrs
  » Healthcare Costs
    • Reduced $23,203

---

UCLA Stroke Center

--Boudreau et al, Stroke 2014
--Shireman et al, Stroke 2017
Contribution of Intracranial Occlusions to Outcome in 643 Consecutive Ischemic Stroke and TIA Patients
--Reanalysis of Smith et al, Stroke 2009

<table>
<thead>
<tr>
<th>Occlusion</th>
<th>Proportion of All AIS and TIA</th>
<th>Proportion of Dependent or Worse (mRS 3-6) AIS or TIA</th>
<th>Proportion of Fatal AIS or TIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVO</td>
<td>44%</td>
<td>62%</td>
<td>72%</td>
</tr>
<tr>
<td>No LVO</td>
<td>56%</td>
<td>38%</td>
<td>28%</td>
</tr>
</tbody>
</table>
Time from Onset to Expected Puncture Odds of Reduced Disability with EVT vs Medical

Common Odds Ratio Using 6-Level mRS

7.3 hrs

Favors endovascular thrombectomy
Favors medical therapy alone

Time from Onset to Expected Puncture Odds of Reduced Disability with EVT vs Medical

Benefit Per Hundred

Common Odds Ratio Using 6-Level mRS

Time From Symptom Onset to Expected Arterial Puncture, min

7.3 hrs

Minutes Matter

- **IV TPA**
  - Every 8 minute delay causes 1 fewer of 100 treated patients to benefit in improved ambulation

- **IA Neurothrombectomy**
  - Every 4 minute delay causes 1 fewer of 100 reperfused patients to benefit in reduced final disability

---

Minutes Matter

• IV TPA
  » Every 8 minute delay causes 1 fewer of 100 treated patients to benefit in improved ambulation

• IA Neurothrombectomy
  » Every 4 minute delay causes 1 fewer of 100 reperfused patients to benefit in reduced final disability

UCLA Stroke Center

David Sacks, MD, Carl M. Black, MD, Christophe Cognard, MD, John J. Connors III, MD, Donald Frei, MD, Rishi Gupta, MD, Tudor G. Jovin, MD, Bryan Kluck, MD, Philip M. Meyers, MD, Kieran J. Murphy, MD, Stephen Ramee, MD, Daniel A. Rüfenacht, MD, M.J. Bernadette Stallmeyer, MD, PhD, and Dierk Vorwerk, MD
## Endovascular Time Targets

<table>
<thead>
<tr>
<th>Time Metric</th>
<th>Multi-Society Guideline 2013</th>
</tr>
</thead>
<tbody>
<tr>
<td>Door to Puncture</td>
<td>120 min</td>
</tr>
<tr>
<td>Picture to Puncture</td>
<td>95 min</td>
</tr>
<tr>
<td>Puncture to 1\textsuperscript{st} pass</td>
<td>45 min</td>
</tr>
<tr>
<td>Door to Revasc</td>
<td>210 min (3h 30m)</td>
</tr>
</tbody>
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# Endovascular Time Targets

<table>
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## Endovascular Time Targets

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<th>Multi-Society Guideline 2013</th>
<th>SWIFT PRIME</th>
<th>SNIS Guideline 2015 “Ideal”</th>
</tr>
</thead>
<tbody>
<tr>
<td>Door to Puncture</td>
<td>120 min</td>
<td>90 min</td>
<td>60 min</td>
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<td>30 min</td>
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<td>139 min (2h 19m)</td>
<td>90 min (1h 30m)</td>
</tr>
</tbody>
</table>

*UCLA Stroke Center*
Mapping the Responder Population

People react differently to drugs

“One size does not fit all ...”

Patient population with same disease phenotype

Ethnicity
Age
Pregnancy
Genetic factors
Disease
Drug interactions

Toxic responders
Non-responders
Responders

Patients with drug toxicity

Patients with non-response to drug therapy

Patients with normal response to drug therapy
Mapping the Responder Population

- More arteries
- MVOs (M2, etc)
- BA/VA
- Mild deficits
- Large cores
- Late-presenters

People react differently to drugs

“One size does not fit all ...”

Patient population with same disease phenotype

Ethnicity
Age
Pregnancy
Genetic factors
Disease
Drug interactions

Toxic responders
Non-responders
Responders

Patients with drug toxicity

Patients with non-response to drug therapy

Patients with normal response to drug therapy
Fast and Slow Progressors
Collateral Variability

Bioenergetic Compromise

Hemodynamic Compromise

Occlusions or Stenoses

Tissue Status
CBV CT

Perfusion Status
PCT

Vessel Status
CTA

Multimodal CT

Multimodal MRI

DWI

PWI

MRA

Bioenergetic Compromise

Hemodynamic Compromise

Occlusions or Stenoses
Strategies to Identify LVO Patients with Salvageable Ischemic Penumbra

< 6 Hrs

Hyperacute therapy when nearly all patients have penumbra

> 6 Hrs

Imaging required to assess pathophysiology

% Patients with Penumbra

Time From Onset (Hours)
Strategies to Identify LVO Patients with Salvageable Ischemic Penumbra

- **< 6 Hrs**
  - Hyperacute therapy when nearly all patients have penumbra

- **> 6 Hrs**
  - Imaging required to assess pathophysiology

% Patients with Penumbra vs Time From Onset (Hours)

Trials
- DAWN / DEFUSE 3
Potential Populations for Thrombectomy: Example of Time

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Trial Design Options for Expanding Eligible Patients

- **Older approaches**
  - Incremental expansion
    - From “sweet spot” out
    - Series of trials or adaptive expansion
  - Mega-trial
    - Wide entry criteria with enroll all or uncertainty principle
    - Sort it out in subgroup analysis

- **Newer approach**
  - Adaptive exploration
**DWI or CTP Assessment with Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention**

- **Entry criteria**
  - 6-24h after onset
  - Clinical-imaging mismatch on DWI MRI or CTP-rCBF
    - Age < 80 yo
      - NIHSS $\geq$ 10, 0-30 cc core
      - NIHSS $\geq$ 20, 31-50 cc core
    - Age $\geq$ 80 yo
      - NIHSS $\geq$ 10, 0-20 cc core
  
- **Sample size**
  - Adaptive Bayesian design
    - Up to 500 patients
    - Interim analyses at 150 and every 50 thereafter
**Entry criteria**
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- Clinical-imaging mismatch on DWI MRI or CTP-rCBF
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  • Age ≥ 80 yo
    » NIHSS ≥ 10, 0-20 cc core

Sample size
» Adaptive Bayesian design
  • Up to 500 patients
  • Interim analyses at 150 and every 50 thereafter
DAWN in Full Daylight

DWI or CTP Assessment with Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention with Trevo

Tudor G. Jovin MD & Raul G. Nogueira MD
on behalf of the DAWN investigators
Study Methods: Workflow

NCCT/DWI:
<1/3 MCA Territory

CTA/MRA:
ICA-T and/or MCA-M1 (Tandem Occlusions Allowed)

RAPID CTP/DWI CIM:
A. ≥80 y/o:
   1. NIHSS ≥10 + core <21cc
B. <80 y/o:
   2. NIHSS ≥10 + core <31cc
   3. NIHSS ≥20 + core <51cc

1:1 Randomization:
- CIM subgroup
- ICA-T vs M1
- 6-12 vs 12-24h

Informed Consent

Control

90-day mRS
- U-W mRS
- mRS 0-2

Thrombectomy
TRIAL ENROLLMENT RATE AND TERMINATION

<table>
<thead>
<tr>
<th>Site Status</th>
<th>Actual</th>
<th>Projected</th>
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<tbody>
<tr>
<td>Sites Qualified</td>
<td>36</td>
<td>31</td>
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<tr>
<td>Sites Initiated</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>IRB/EC Approvals</td>
<td>31</td>
<td>206</td>
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</tbody>
</table>

Actual / Projected Enrollment

*Boundary for first enrichment not crossed.*

Enrollment stopped at DSMB recommendation.
Results

CBF (<30%) volume: 2.0 ml
Perfusion (Tmax > 6.0s) volume: 100.0 ml
Mismatch volume: 98.0 ml
Mismatch ratio: 50.0

This image is not intended for primary diagnosis.
Patient presentation

<table>
<thead>
<tr>
<th>Time since time last seen well to randomization (hrs)</th>
<th>Treatment arm N=107</th>
<th>Control arm N=99</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ± SD</td>
<td>13.4 ± 4.1</td>
<td>13.0 ± 4.5</td>
<td>0.53</td>
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<tr>
<td>Median (Q1, Q3)</td>
<td>12.2 (10.2, 16.0)</td>
<td>13.2 (9.4, 15.8)</td>
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<tr>
<td>Range (min, max)</td>
<td>6.1, 23.5</td>
<td>6.4, 23.9</td>
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<tr>
<th>Stroke sub-population</th>
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<tr>
<td>Wake up stroke</td>
<td>64.5%</td>
<td>47.5%</td>
<td>0.01</td>
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<tr>
<td>Witnessed stroke</td>
<td>10.3%</td>
<td>14.1%</td>
<td>0.52</td>
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<tr>
<td>Un-witnessed stroke</td>
<td>25.2%</td>
<td>38.4%</td>
<td>0.05</td>
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</table>
Co-primary endpoints

<table>
<thead>
<tr>
<th></th>
<th>Trevo</th>
<th>MM</th>
<th>Treatment benefit (95% CI)</th>
<th>Bayesian probability of superiority</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 90 weighted mRS</td>
<td>5.5 ± 3.8</td>
<td>3.4 ± 3.1</td>
<td>2.1 (1.20, 3.12)</td>
<td>&gt;0.9999*</td>
</tr>
<tr>
<td>Day 90 mRS (0-2)</td>
<td>48.6%</td>
<td>13.1%</td>
<td>35.5% (23.9%, 47.0%)</td>
<td>&gt;0.9999*</td>
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NNT for 90-day functional independence = 2.8

*Similar to p<0.0001
Primary outcome

TREVO
- mRS 0/uW mRS 10: 9%
- mRS 1/uW mRS 9.1: 17%
- mRS 3/ uW mRS 6.5: 22%
- mRS 4/ uW mRS 3.3: 13%
- mRS 5-6/ uW mRS 0: 13%
- mRS 2/ uW mRS 7.6: 26%

Probability of superiority >0.9999

CONTROL
- mRS 0/uW mRS 10: 4%
- mRS 1/uW mRS 9.1: 16%
- mRS 3/ uW mRS 6.5: 5%
- mRS 4/ uW mRS 3.3: 34%
- mRS 5-6/ uW mRS 0: 36%

73% relative risk reduction of dependency in ADL’s NNT for any lower disability 2.0

DAWN TRIAL
90 Day mRS 0-2 by TLSW to Randomization

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<td>6-12h</td>
<td>55.1%</td>
<td>20.0%</td>
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Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke 3

- **Entry criteria**
  - 6-16h after onset
  - Target mismatch profile on DWI/PWI MRI or CTP
    - Ischemic core < 70 cc
    - Mismatch ratio ≥ 1.8
    - Penumbra (mismatch) volume ≥ 15 cc

- **Sample size**
  - Adaptive design
    - Up to 476 patients
    - First interim efficacy analysis planned at 200
    - (Stopped for efficacy at 182)
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July 26, 2017

DEFUSE 3 – DSMB has halted the trial permanently because of a high likelihood of efficacy in the endovascular treatment group. The Study is currently under continuing review.

Data cleaning is underway. Please complete the 90 day visits as soon as possible so they can get the database cleaned and locked.
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<td>✔</td>
</tr>
<tr>
<td>100-149%</td>
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<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
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<td>✔</td>
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<td>✔</td>
</tr>
<tr>
<td>50-99%</td>
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<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>20-49%</td>
<td></td>
<td></td>
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<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
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</table>
### Acute (<24h) Ischemic Stroke Subtypes

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Percent</th>
<th>Number per Year</th>
</tr>
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<tbody>
<tr>
<td>All</td>
<td>100%</td>
<td>600,000</td>
</tr>
<tr>
<td>LVO</td>
<td>40%</td>
<td>240,000</td>
</tr>
<tr>
<td>LVO &lt; 6h (70%)</td>
<td>28%</td>
<td>168,000</td>
</tr>
</tbody>
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--Smith et al, Stroke 2009; van Seeters et al, Cerebrovasc Dis 2015; Tong et al, Stroke 2012; Malhotra and Saver, Stroke 2017 (abstract); Darby et al, Stroke 1999
Population Impact of Imaging Selection for Additional Patients Who Benefit from Thrombectomy

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</tr>
<tr>
<td>LVO 6-24h (30%)</td>
<td>12%</td>
<td>72,000</td>
</tr>
<tr>
<td>LVO 6-24h DAWN eligible (15%)</td>
<td>2%</td>
<td>12,240</td>
</tr>
<tr>
<td>LVO 6-24h DEFUSE 3 eligible (30%)</td>
<td>4%</td>
<td>24,480</td>
</tr>
</tbody>
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<td>4%</td>
<td>24,480</td>
</tr>
<tr>
<td>LVO 6-24h all who benefit (50%?)</td>
<td>6%?</td>
<td>36,720?</td>
</tr>
</tbody>
</table>

---

--Smith et al, Stroke 2009; van Seeters et al, Cerebrovasc Dis 2015; Tong et al, Stroke 2012; Malhotra and Saver, Stroke 2017 (abstract); Darby et al, Stroke 1999
Stroke Systems: Two Four Tier US Model

- **EMS**
  - Trained dispatchers, high priority triage
  - Paramedics trained in stroke recognition (e.g. LAPSS)
  - Deliver patients to nearest stroke capable hospital
  - Pre-arrival notification

- **Spokes**
  - Stroke Ready Hospitals (SRHs)
    - Able to provide initial, ED care, often via telemedicine
    - Able to use rt-PA and other acute therapies safely and efficiently
  - Primary Stroke Centers (PSCs)
    - Able to provide initial, ED care
    - Able to use rt-PA and other acute therapies in a safe and efficient manner
    - Have Stroke Units and can admit patients

- **Hubs**
  - Thrombectomy Stroke Centers (TSCs)
    - Able to provide endovascular thrombectomy but not other advanced care
  - Comprehensive Stroke Centers (CSCs)
    - Able to care for all complex patients
    - Advanced treatments (i.e. coils, clips, stents, endovascular recanalization, etc)
    - Trained specialists in key areas (Vascular neurology, Neurointerventional procedures, Neurocritical Care, Vascular Neurosurgery)
Warning Signs and Activation of EMS System

**SPOT A STROKE**

- **F**ACE drooping
- **A**rm weakness
- **S**peech difficulty
- Time to call 911

**BE FAST**

- **B**alance loss: Does the person have trouble keeping balance or falling?
- **E**yes: Is one eye closed or unable to open?
- **F**ace: Is the person’s face drooping on one side?
- **S**peech: Is the person speaking slurred or unable to speak?
- **T**ime: Call 911 immediately.

Every second counts!

**FAST**

- **F**ace drooping
- **A**rm weakness
- **S**peech difficulty
- Time to call 911

**FASTER**

- **F**ace drooping
- **A**rm weakness
- **S**peech difficulty
- **E**yes
- **T**alking
- **R**eacting
- **E**yes

**UCLA Stroke Center**
Ubiquitous Computing and Ambient Intelligence
Accelerated Stroke Onset Detection

Las Vegas Casinos

Home Cameras
Home Health Robots

Computer Vision and Accelerometer Fall Detection
(also wearable pajamas)

---Example: Leone et al. Detecting falls with 3d range camera in ambient assisted living applications. Medical Engineering & Physics 2011

UCLA Stroke Center
Advanced Stroke Center Buildout

- Comprehensive Stroke Centers
  - 2011
    - AHA CSC metrics paper
    - TJC technical advisory panel
  - 2012
    - TJC pilot testing
  - 2012-2013
    - National CSC certification
  - 2014
    - CSC Performance Measures
- Thrombectomy Stroke Centers
  - 2018
    - National TSC certification

--Saver et al, Stroke Interventionalist 2013
Identifying Likely Large Vessel Occlusion Patients in Field

• Medium (distal) vessel and small (penetrator) occlusions
  » IV tPA - works well, want asap
  » Thrombectomy – not an option
  » Primary Stroke Center or Acute Stroke Ready Hospital

• Large vessel occlusions
  » IV tPA - works poorly
  » Thrombectomy – works well
  » Comprehensive Stroke Center
Routing Protocols in Tiered Systems: ASRHs, PSCs, CSCs

• Tiered routing options
  » None
  » Time (e.g. 3.5-6h)
  » Severity (e.g. LAMS 4-5)
  » Type (H/A, ICH)

• Considerations
  » Urban v rural
  » Geography
  » Traffic
  » Resources
  » Minimize time out of service area

UCLA Stroke Center
Comprehensive Stroke Center Routing Within Regional Systems of Care

- **IV TPA ineligible**
  - Direct to CSC
  - 3.5-7 hours after onset

- **IV TPA eligible**
  - Drip and ship
    - Faster IV TPA, slower cath
  - Mothership
    - Slower IV TPA, faster cath
    - Large vessel occlusion
      - LAMS 4-5
    - Likely hemorrhage
  - BATmobile trip (mobile CT)
    - Fastest IV TPA, fast cath

*UCLA Stroke Center*
**Severity-Based Stroke Triage Algorithm for EMS**

- **EMS Dispatch** notifies responding EMS unit of possible stroke call. EMS crew dispatched per regional stroke protocol or on-scene suspicion of acute stroke by EMS providers.

- **Upon arrival**, provide any needed ABC interventions, request dispatch of higher level of provider if necessary for unstable patients and interview patient, family and other witnesses.

- Perform and document results of pre-hospital stroke identification screen (PREHIS, LAPIS, etc.) and POC blood glucose.

- **Stroke Screen Positive? Stroke Suspected?**
  - Yes, treat and transport as indicated per patient presentation.
  - No, Stroke not suspected.

- **LVO Suspected?**
  - Yes, perform and document results from severity tool used to assess potential LVO (LAMS, RACE, CISTR, FAST-ED, etc.).
  - No, low less than 6 hours?

- **Low less than 6 hours?**
  - Yes, direct transport to CSC and less than or equal to 15 minutes.
  - No, transport to CSC will not preclude use of IV alteplase.

- **Transport to CSC will not preclude use of IV alteplase?**
  - Yes, call Stroke Alert, pre-onset receiving facility and transport directly to an appropriately certified CSC that is within the acceptable transport time, if no CSC meets the criteria then transport to the nearest designated EVT-capable center, or closest appropriate stroke center (AMRR, PSC, CSC) per your regional stroke system of care plan.
  - No, treat and transport as indicated per patient presentation.

**Mission:** Lifeline Stroke has developed this algorithm to help ensure the RIGHT patient is brought to the RIGHT stroke center RIGHT on time.
Go Directly to CSC IF:

Severity Screen (++)
+
LKW < 6 Hours
+
Transport to CSC Adds < 15 min
+
Transport to CSC Does Not Place Patient Outside Thrombolysis Window

Any ‘NO’ then Go to Nearest/Closest Appropriate Facility Per Regional Plan

Call Stroke Alert, pre-notify receiving facility and transport directly to an appropriately certified CSC that is within the acceptable transport time, if no CSC meets the criteria then transport to the nearest designated EVT-capable center, or closest appropriate stroke center (ASRH, PSC) per your regional stroke system of care plan.
Examples of Prehospital Stroke Scales to Identify LVO

- Los Angeles Motor Scale (LAMS)
  - 3 elements
  - Facial droop, arm drift, grip weakness
- 3 Item Stroke Scale (3I-SS)
  - 6 elements
  - Level of consciousness, gaze deviation, facial droop, arm drift, R/L leg weakness
- Rapid Arterial Occlusion Evaluation Score (RACE)
  - 7 elements
  - Facial droop, arm drift, R/L leg weakness, gaze deviation, aphasia, denial of hemiparesis
- Cincinnati Prehospital Stroke Severity Scale (CPSSS)
  - 4 elements
  - Gaze deviation, arm drift, LOC command, LOC questions
- Field Assessment Stroke Triage for Emergency Destination (Fast-ED)
  - 5 elements
  - Face, Arm weakness, speech, eye deviation, Denial/Neglect
- VAN
  - 3 elements
  - Vision, Aphasia, Neglect
### KISS Principle in Prehospital Care

<table>
<thead>
<tr>
<th>LAMS</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Facial Droop</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>0</td>
</tr>
<tr>
<td>Present</td>
<td>1</td>
</tr>
<tr>
<td>Arm Drift</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>0</td>
</tr>
<tr>
<td>Drifts Down</td>
<td>1</td>
</tr>
<tr>
<td>Falls Rapidly</td>
<td>2</td>
</tr>
<tr>
<td>Grip Strength</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>0</td>
</tr>
<tr>
<td>Weak Grip</td>
<td>1</td>
</tr>
<tr>
<td>No Grip</td>
<td>2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>RACE</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Facial Palsy</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>0</td>
</tr>
<tr>
<td>Mild</td>
<td>1</td>
</tr>
<tr>
<td>Mod-severe</td>
<td>2</td>
</tr>
<tr>
<td>Arm Motor Func</td>
<td></td>
</tr>
<tr>
<td>Normal to mild</td>
<td>0</td>
</tr>
<tr>
<td>Moderate</td>
<td>1</td>
</tr>
<tr>
<td>Severe</td>
<td>2</td>
</tr>
<tr>
<td>Leg Motor Func</td>
<td></td>
</tr>
<tr>
<td>Normal to mild</td>
<td>0</td>
</tr>
<tr>
<td>Moderate</td>
<td>1</td>
</tr>
<tr>
<td>Severe</td>
<td>2</td>
</tr>
<tr>
<td>Head + Gaze Dev</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>0</td>
</tr>
<tr>
<td>Present</td>
<td>1</td>
</tr>
<tr>
<td>Aphasia (if right HP)</td>
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<tr>
<td>Normal to mild</td>
<td>0</td>
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<tr>
<td>Moderate</td>
<td>1</td>
</tr>
<tr>
<td>Severe</td>
<td>2</td>
</tr>
<tr>
<td>Agnosia (if left HP)</td>
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</tr>
<tr>
<td>Normal to mild</td>
<td>0</td>
</tr>
<tr>
<td>Moderate</td>
<td>1</td>
</tr>
<tr>
<td>Severe</td>
<td>2</td>
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</table>
LAMS Comparable to or Better than 6 Other Proposed Prehospital LVO Scales and the Full NIHSS

<table>
<thead>
<tr>
<th>LVO among All Acute Cerebral Ischemia Transports</th>
<th>CSC-Appropriate (LVO+ICH) among All Suspected Stroke Transports</th>
</tr>
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<tbody>
<tr>
<td><strong>Sensitivity</strong></td>
<td><strong>Specificity</strong></td>
</tr>
<tr>
<td><strong>Prehospital</strong></td>
<td></td>
</tr>
<tr>
<td>LAMS</td>
<td>0.74</td>
</tr>
<tr>
<td>ED</td>
<td>0.63</td>
</tr>
<tr>
<td>LAMS</td>
<td>0.54</td>
</tr>
<tr>
<td>CPSSS</td>
<td>0.54</td>
</tr>
<tr>
<td>FAST-ED</td>
<td>0.57</td>
</tr>
<tr>
<td>PASS</td>
<td>0.54</td>
</tr>
<tr>
<td>RACE</td>
<td>0.57</td>
</tr>
<tr>
<td>VAN</td>
<td>0.41</td>
</tr>
<tr>
<td>NIHSS ≥ 7</td>
<td>0.65</td>
</tr>
<tr>
<td>NIHSS ≥ 10</td>
<td>0.54</td>
</tr>
<tr>
<td><strong>Sensitivity</strong></td>
<td><strong>Specificity</strong></td>
</tr>
<tr>
<td><strong>Prehospital</strong></td>
<td></td>
</tr>
<tr>
<td>LAMS</td>
<td>0.67</td>
</tr>
<tr>
<td>CPSSS</td>
<td>0.53</td>
</tr>
<tr>
<td>FAST-ED</td>
<td>0.55</td>
</tr>
<tr>
<td>PASS</td>
<td>0.56</td>
</tr>
<tr>
<td>RACE</td>
<td>0.57</td>
</tr>
<tr>
<td>VAN</td>
<td>0.59</td>
</tr>
<tr>
<td>NIHSS ≥ 7</td>
<td>0.71</td>
</tr>
<tr>
<td>NIHSS ≥ 10</td>
<td>0.56</td>
</tr>
</tbody>
</table>

Supported by NIH-NINDS
RACECAT Trial

• Cluster-control RCT Spain
  » 12 hospitals, 1754 patients
• Key entry criteria
  » LVO by RACE and teleneurology
  » Can reach an EVT-SC within 7h of onset
• Randomized strata
  » Daytime vs evening
  » Weekday vs weekend
  » Urban vs rural
• Outcome: mRS 0-2
• Timeline: 2017-2020
Stroke physician prehospital real-time telestroke assessment of the National Institutes of Health Stroke Scale in the moving ambulance

Liman T G et al. Stroke 2012;43:2086-2090
Mobile Technologies
(Other than CT)

- Ultrasound
  » Burl – Sonas
  » Neural Analytics

- EEG
  » Samsung – EDSAP

- Near infra-red
  » B+W Tek – i-Spec

- Microwave
  » Australia - Strokefinder helmet

UCLA Stroke Center
Acute Ischemic Stroke Treatment 1.0: IV TPA and Moderately Effective Endovascular Therapy
Acute Ischemic Stroke Treatment 2.0: Highly Effective Recanalization - Fast and Furious

- Symptoms
  - EMS
  - Neuroprotectants
  - Primary Stroke Center
  - Imaging

- Imaging
  - Comp Stroke Center
  - EMS
  - IV Lytic

- Cath Lab
  - Angiogram
  - IA Mechanical or Lytic
  - Stroke Unit

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Are We Done Yet?
Second Generation Neurothrombectomy Therapy
Outcome Across All Disability Levels (5 Trials – HERMES)

UCLA Stroke Center
Are We Done Yet?
Second Generation Neurothrombectomy Therapy Outcome Across All Disability Levels (5 Trials – HERMES)

<table>
<thead>
<tr>
<th></th>
<th>No Endovascular</th>
<th>Endovascular</th>
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<tbody>
<tr>
<td>5,0</td>
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<td>13,6</td>
<td>19,1</td>
<td></td>
</tr>
<tr>
<td>16,4</td>
<td>16,9</td>
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</tr>
<tr>
<td>24,7</td>
<td>15,6</td>
<td></td>
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<tr>
<td>13,5</td>
<td>6,2</td>
<td></td>
</tr>
<tr>
<td>18,9</td>
<td>15,3</td>
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UCLA Stroke Center
Are We Done Yet?
Second Generation Neurothrombectomy Therapy
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Are We Done Yet?
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UCLA Stroke Center
What Do We Need

• More REPERFUSION
• More SALVAGEABLE BRAIN
• Less BLEEDING
• More PATIENTS
What Do We Need

- More REPERFUSION
  » Better devices
  » Better combinations of lytics and devices
- More SALVAGEABLE BRAIN
  » Preprocedure neuroprotection / collateral enhancement
  » Faster onset to puncture
    • Hospital processes of care
    • EMS systems of care
- Less BLEEDING
  » Skip tPA (?)
  » Deter reperfusion injury
- More PATIENTS
  » Expand time window with standard selection
  » Expand time window with imaging selection

UCLA Stroke Center
# Building Next Generation of Clinical Trials that Will Positively Impact an Emerging Field

<table>
<thead>
<tr>
<th>Intervention Type</th>
<th>Special Trial Aspects</th>
<th>Example Comparisons</th>
<th>Target Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>New Devices</td>
<td>TICI reperfusion as primary surrogate endpoint</td>
<td>Device A vs B</td>
<td>Large artery occlusions</td>
</tr>
<tr>
<td>Reperfusion Strategies</td>
<td>Active Comparator</td>
<td>IVT+ERT vs ERT alone</td>
<td>ICA occlusions</td>
</tr>
<tr>
<td></td>
<td>IVT+ERT vs IVT alone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prehospital Neuroprotection</td>
<td>ED imaging endpoints</td>
<td>NA1, hypothermia, RIPC, NTG vs control</td>
<td>EMS transported patients</td>
</tr>
<tr>
<td>Systems of Care</td>
<td>Cluster randomization; stepped wedge</td>
<td>EMS routing – PSCs first versus CSCs first</td>
<td>Severe deficits</td>
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<tr>
<td>Deter Reperfusion Injury</td>
<td>IA admin</td>
<td>Free radical scavengers vs control</td>
<td>Post-successful TICI 2b/3 reperfusion</td>
</tr>
<tr>
<td>Imaging Selection</td>
<td>6-24h</td>
<td>ERT vs no ERT</td>
<td>Wake-up and late</td>
</tr>
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</table>
Improved Reperfusion Rates via Novel Devices

• Retrievers
  » Solitaire (Medtronic)
  » Trevo (Stryker)
  » Catch (Balt)
  » Preset (Phenox)
  » EmboTrap (Neuravia)
  » Separator 3D (Penumbra)
  » Revive (Codman)
  » Mindframe (Medtronic)
  » Golden (Amnis)
  » Tigertriever (Rapid Medical)

• Aspiration catheters
  » Max ACE (Penumbra)
  » Arc (Medtronic)
  » SOFIA (Microvention)
  » Cat-6 (Stryker)
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---

**UCLA Stroke Center**

- LVO
- MVO - M2, M3/4, P1/2 PCA, A1/2 ACA

---

**Graph:**

- Complete Recanalization Heart vs. Brain
- Points represent data points over the years from 1975 to 2015.
Improved Reperfusion Rates via Novel Devices

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  - Trevo (Stryker)
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  - EmboTrap (Neuravia)
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- **Aspiration catheters**
  - Max ACE (Penumbra)
  - Arc (Medtronic)
  - SOFIA (Microvention)
  - Cat-6 (Stryker)

**Trials**
- ARISE II
- ASTER / Penumbra 3D / COMPASS
Neuroprotective Trial Designs in the Thrombectomy Era

NP in the Ambulance

• Enroll at PSCs, ASRHs
  » Tele-enrollment
• NP infusion during interval from OSH to endovascular hospital
• “Drip, ship, NiP, and grip”

NP during Hosp Tx

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NP Door to Reperf

FAST-MAG

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<tr>
<th>Number of Patients</th>
<th>NP to Reperf Tx Start Time</th>
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<tr>
<td>IV tPA 452 (27%)</td>
<td>1h 32m</td>
</tr>
<tr>
<td>EVT 76 (5%)</td>
<td>3h 50m</td>
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Door to needle in ≤60 min

- 0 min: Suspected stroke patient arrives at ED
- ≤10 min: Indicate ID and alert neurologist
- ≤15 min: Notify stroke team; imaging scan
- ≤25 min: Complete lab work; order EDCT
- ≤45 min: Start IV tPA; perform imaging scan
- ≤60 min: Initiate treatment; check for eligibility for alteplase
- ≤60 min: Give alteplase; avoid long delays in eligible patients
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### Give or Skip IV tPA

#### Pro Combination
- Faster reperfusion
  - Faster start of IV Rx - faster reperfusion in IV responders
  - Increased first-pass response
- More reperfusion
  - Higher ERT reperfusion rate
  - Reperfusion in ERT non-deployable pts
  - High IV Rx reperfusion in EMVO
- Cleaner distal vessels
  - Dissolve distal thrombus fragments from ERT
- Target occlusion characterization
  - Reveal *in situ* athero

#### Against Combination
- Slower reperfusion
  - Consent and set-up of IV Rx may slow start of ERT
- Little additional reperfusion
  - Low IV Rx reperfusion in ELVO
- More hemorrhage
- Higher cost

*UCLA Stroke Center*
Give or Skip IV tPA

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**Trials**
- MR CLEAN Family
- SWIFT Direct
"The outcome of any serious research can only be to make two questions grow where only one grew before" (Veblen)

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<tr>
<th>Intervention Type</th>
<th>Special Trial Aspects</th>
<th>Example Comparisons</th>
<th>Target Patients</th>
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<td></td>
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<td>IVT+EVT vs IVT alone</td>
<td>M2 occlusions</td>
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<tr>
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<td>Free radical scavengers vs control</td>
<td>Post-successful TICI 2b/3 reperfusion</td>
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<tr>
<td><strong>Imaging Selection</strong></td>
<td>6-24h</td>
<td>ERT vs no ERT</td>
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</table>
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