Treatment Swift and Treatment Sure: Prehospital Neuroprotection and Highly Effective Endovascular Recanalization Therapy for Acute Ischemic Stroke

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UCLA Ronald Reagan Medical Center
Stroke: Progress and Peril

- Number 1 cause of adult disability
- Number 2 cause of dementia
- Number 4 cause of death
  » Second leading cause of death worldwide
- 795,000 strokes per year
- ~137,000 deaths per year
- >5 million stroke survivors

--Recurrent stroke in trial control arms ↓50%
  --Hong, Saver, et al, Circulation 2011

--Stroke mortality rates ↓75%, 1960 - 2010
  --Towfighi + Saver, Stroke 2011

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Strategies in Acute Ischemic Stroke Therapy

- Proven
  - Recanalization
  - Supportive Care
  - Prevent Clot Propagation
- Experimental
  - Neuroprotection
  - Collateral Enhancement
Acute Ischemic Stroke Treatment 1.0: IV TPA and Moderately Effective Endovascular Therapy
Treatment Swift

Prehospital Neuroprotection
The Ischemic Penumbra

Irreversible Core Infarct

Ischemic Penumbra
zone of salvageable tissue surrounding core infarct
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

---Saver + Levine, Lancet 2010
Neuroprotection and the Ischemic Cascade

- 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)

--Dorman + Sandercock 1996; Heiss et al, 1999
Trials of Neuroprotective Agents for Stroke, 1955-2000

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

-- 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 (4-48 hrs)

--Ovbiagele, Saver, et al 2003
Enrollment Times in 6 Recent Neuroprotective Trials (n=5345)
--Ferguson, Kidwell, Starkman, Saver, JSCVD 2004

More than 3 hrs

92.3%

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Enrollment Times in 6 Recent Neuroprotective Trials (n=5345)
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- More than 3 hrs: 92.3%
- 2-3 hrs: 6.3%

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- More than 3 hrs: 92.3%
- 2-3 hrs: 6.3%
- 1-2 hrs: 1.2%
- 0-1 hrs: 0.2%
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

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Possible Therapeutic Effects of Magnesium in Stroke

**Vascular**
- Increased Cardiac Output
- Increased Regional CBF

**Neuronal**
- NMDA Ion Channel Blockade
- Enhanced ATP Recovery
- Ca\(^{2+}\) Channel Blockade
Trends Toward Benefit of Early Magnesium in Human Brain Ischemia

- Neuropsychologic deficits after carotid endarterectomy
  » Columbia CEA Trial
- Neuropsychologic deficits after CABG
  » Cleveland Clinic Trial
- Global brain ischemia after cardiac arrest
  » Brain-CPR Trial
- Cerebral palsy in preterm infants
  » ACTOMgS04 Trial
- Delayed cerebral infarction after SAH
  » MASH Trial
- Focal brain ischemia
  » IMAGES Trial <3h subgroup

Supported by NIH-NINDS
Prehospital Stroke Neuroprotective Trials: Distinctive Methodologic Aspects

- Diagnosing stroke in the field
  » LAPSS
- Rating stroke pretreatment severity
  » LAMS
- Randomization system
  » Pre-encounter randomization
- Eliciting consent
  » Field cellphone to MD simulating
Chain Cell Forwarding System

Direct Call

First On-Call Investigator

Call Forwarding (30 Seconds)

Second On-Call Investigator

Call Forwarding (30 Seconds)

Third On-Call Investigator

Call Forward to First Investigator (30 Seconds)

Voice-Over-Internet Phone (VOIP) System

Direct Call to VOIP System to English Line (Blue) and Spanish Line (Red)

Spanish-Line First On-Call Investigator

Spanish-Line Second On-Call Investigator

Spanish-Line Third On-Call Investigator

English-Line First On-Call Investigator

English-Line Second On-Call Investigator

English-Line Third On-Call Investigator
<table>
<thead>
<tr>
<th></th>
<th>Time (±SD)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>FAST-MAG (n=20)</td>
<td>23 min (±12)</td>
<td></td>
</tr>
<tr>
<td>Prior Trials (n=26)</td>
<td>141 min (±70)</td>
<td></td>
</tr>
</tbody>
</table>

\[ p < 0.0001 \]

*Time Savings: 1 hr 58 min*
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
  » 59 hospitals, Los Angeles and Orange Counties
- Prehospital patients within 2h of onset
- 4 gm Mg field, 16 gm Mg maintenance x 24h
- 1700 patients, 1st patient Jan 2005
- Primary endpoint: Rankin Scale shift

NIH-NINDS
FAST-MAG Trial Setting and Participating Sites

- Los Angeles and Orange Counties
- Ethnically diverse population 13.3 million
- 59 receiving hospitals
- 353 rescue ambulances
- 3300 paramedics
- > 400 emergency physicians
- >100 neurologists, neurosurgeons

NIH-NINDS
### Patient Characteristics (n=1470)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>69 (range 39-95)</td>
</tr>
<tr>
<td><strong>Female</strong></td>
<td>42%</td>
</tr>
<tr>
<td><strong>Index Event Diagnosis</strong></td>
<td></td>
</tr>
<tr>
<td>Cerebral ischemia</td>
<td>71.9%</td>
</tr>
<tr>
<td>Intracerebral hemorrhage</td>
<td>24.4%</td>
</tr>
<tr>
<td>Stroke Mimic</td>
<td>3.7%</td>
</tr>
<tr>
<td><strong>Stroke Severity</strong></td>
<td></td>
</tr>
<tr>
<td>LAMS (prehospital)</td>
<td>4.0 (range 1-5)</td>
</tr>
<tr>
<td>NIHSS (hospital arrival, after Rx start)</td>
<td>11.4 (range 0-40)</td>
</tr>
</tbody>
</table>

*NIH-NINDS*
Key Treatment Intervals
(n=1470)

Stroke onset to study drug (median) 46 mins
Paramedic arrival on scene to drug (mean) 25 mins
Paramedic arrival on scene to ED (mean) 35 mins
Treated within 1 hour of onset 73%
Treated 1-2 hr after onset 24%
Enrollment Times in 6 Recent Neuroprotective Trials (n=5345)

--Ferguson, Kidwell, Starkman, Saver, JSCVD 2004

More than 3 hrs: 92.3%
2 - 3 hrs: 6.3%
1 - 2 hrs: 1.2%
0 - 1 hrs: 0.2%

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Enrollments in the Golden Hour
6 Recent Neuroprotective Trials
Enrollments in the Golden Hour
6 Recent Neuroprotective Trials
vs FAST-MAG
FAST-MAG Innovations

• First “golden hour” (<1 hr) stroke treatment trial
• First acute (<3 hr) neuroprotective stroke treatment trial
• First trial of neuroprotective drugs before recanalization therapies
• First prehospital stroke RCT
• First prehospital RCT for any condition employing physician-elicited informed consent

NIH-NINDS
Treatment Sure

Highly Effective Cerebral Recanalization
Acute Mechanical Recanalization Strategy Depends on Target Occlusion Composition

In Situ Atherothrombosis
- Substantial local atherosclerotic plaque
- Strategy: Crack the plaque
  - Angioplasty
  - Stents
  - +/- Lytics

Embolus
- Relatively normal recipient artery
- Strategy: remove the thrombus
  - Retrievers
  - Aspirators
  - +/- Lytics
Approved Cerebral Endovascular Recanalization Devices

- Merci Retriever
- Penumbra System
- Phenox Retriever
- Catch Device

US + + + +
Europe + + + +
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>1</th>
<th>30 days post</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>mRS</td>
<td>5 days post</td>
<td>0</td>
<td>90 day post</td>
<td>0</td>
</tr>
</tbody>
</table>
Multicenter Trials of the Merci Retriever Devices

• Mechanical Embolus Removal in Cerebral Ischemia (MERCI) Trial
  » 25 sites in US, 141 pts
  » X5, X6
  » Up to 8 hours after onset, VA, BA, ICA, M1 MCA, M2 MCA
  » IV TPA patients excluded
  » Rescue IA therapies allowed
  » Primary endpoint: recanalization

• Multi-MERCI Trial
  » 14 sites US+Canada, 111 pts
  » X5, X6, L5, L6
  » Up to 8 hours after onset, VA, BA, ICA, M1 MCA, M2 MCA
  » “Failed” IV TPA patients permitted
  » Rescue IA therapies allowed
  » Primary endpoint: recanalization
Current Cerebral Recanalization Therapies Achieve Low Recanalization Rates

- **IV TPA**
  - Partial - 40%
  - Complete – 5%
- **IA Lysis**
  - Partial – 65%
  - Complete – 20%
- **Merci/Multi-Merci**
  - Partial – 65%
  - Complete – 23%
- **Penumbra**
  - Partial – (“82%”) 65%
  - Complete – 23%
Current Cerebral Recanalization Therapies Achieve Low Recanalization Rates

- **IV TPA**
  - Partial - 40%
  - Complete – 5%

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  - Complete – 20%

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  - Partial – 65%
  - Complete – 23%

- **Penumbra**
  - Partial – (“82%”) 65%
  - Complete – 23%
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

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Henkes et al, Stroke 2009, p410

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## Recanalization with the Solitaire Stent Retriever: Initial Series

<table>
<thead>
<tr>
<th>Report</th>
<th>Number of Pts</th>
<th>Partial</th>
<th>Complete</th>
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<tbody>
<tr>
<td>Castano 2010</td>
<td>20</td>
<td>100%</td>
<td>85%</td>
</tr>
<tr>
<td>Roth 2010</td>
<td>22</td>
<td>91%</td>
<td>55%</td>
</tr>
<tr>
<td>Miteff 2011</td>
<td>26</td>
<td>96%</td>
<td>42%</td>
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<tr>
<td>Stampfl 2011</td>
<td>18</td>
<td>89%</td>
<td>50%</td>
</tr>
<tr>
<td>Wehrscheutz 2011</td>
<td>11</td>
<td>100%</td>
<td>18%</td>
</tr>
<tr>
<td>Machi 2012</td>
<td>56</td>
<td>91%</td>
<td>82%</td>
</tr>
<tr>
<td>Mpotsaris 2012</td>
<td>26</td>
<td>88%</td>
<td>69%</td>
</tr>
<tr>
<td>Cohen 2012</td>
<td>17</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>196</strong></td>
<td><strong>93%</strong></td>
<td><strong>66%</strong></td>
</tr>
</tbody>
</table>

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Complete Recanalization Heart vs. Brain

--Patel + Saver, Submitted

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Complete Recanalization Heart vs. Brain

- Cardiac
- Stroke
Current Randomized Trials of Stent Retrievers

- **SWIFT Trial**
  - Solitaire vs Merci
  - Enrollment halted

- **TREVO Trial**
  - Trevo vs Merci
  - Recruiting

- **ReStore Trial**
  - ReStore vs Merci
  - Prelaunch
SWIFT Trial Design

• Multicenter, randomized, active comparator, non-inferiority trial
  – Solitaire as initial device, vs
  – Merci as initial device
• 20 sites (19 US, 1 Europe)
  – Roll-in phase in US
  – 2 patients treated with Solitaire
• Planned 200 randomized patients
• Primary efficacy endpoint
  – Successful recanalization with no hemorrhage (SRNH)
    • TIMI 2 or 3 flow in all treatable vessels without symptomatic intracranial hemorrhage
SWIFT Study Status

- **February 2010**
  - First patient enrolled

- **February 2011**
  - DSMB placed enrollment hold on the study
    - Detailed data analysis
    - Already enrolled patients followed through 90d

- **July 2011**
  - Steering Committee and DSMB permanently halted study
  - Ev3 plans to submit study results to FDA for 510K clearance of the Solitaire FR device
Bioenergetic Compromise

Perfusion Status

Hemodynamic Compromise

Vessel Status

Occlusions or Stenoses

CBV CT

PCT

CTA

DWI

PWI

MRA

Multimodal CT

Multimodal MRI

Tissue Status

Perfusion Status

Vessel Status

Bioenergetic Compromise

Hemodynamic Compromise

Occlusions or Stenoses
Patient Sure: Imaging Selection for Endovascular Recanalization

• **MR RESCUE (NIH)**
  » Multicenter, phase 2, 120 patients
  » Mechanical thrombectomy vs best medical care, up to 8h

--Kidwell, Jahan, MR RESCUE Trialists
Multivariate Models: Predicting Voxel Fate

Day 7 DWI Lesion = Final Infarct

Pretreatment PWI Lesion

--Kidwell, Alger, Saver
MR RESCUE

Case Example: Non-Penumbral Pattern

Day 90 MRS 5

Pre

Day 7

PWI

DWI/ FLAIR

Infarct Prediction
MR RESCUE
Case Example: Penumbral Pattern

Pre
Day 7
PWI
DWI
Infarct Prediction
Day 90 MRS 1
MRI Penumbral Pattern and Response to Embolectomy

% Patients with Day 90 MRS 0-2

- Pen + Recan: 89%
- No Pen + Recan: 14%
- Pen + No Recan: 0%
- No Pen + No Recan: 0%

p < 0.01
Evidence Sure: Current US RCTs

- **MR RESCUE (NIH)**
  - Multicenter, phase 2, 120 patients
  - Mechanical thrombectomy vs best medical care, up to 8h

- **IMS 3 (NIH)**
  - Multicenter, phase 3, 900 patients
  - IV TPA vs IV TPA + IA (Merci or IA lytic or IA lytic + US), < 3h
MR RESCUE (NIH)

- Multicenter, phase 2,
- 120 patients
- Mechanical thrombectomy vs best medical care, up to 8h

IMS 3 (NIH)

- Multicenter, phase 3,
- 900 patients
- IV TPA vs IV TPA + IA (Merci or IA lytic or IA lytic + US), <3h

Evidence Sure: Current US RCTs
Access Sure: Certified Primary Stroke Centers in the United States

Joint Commission  708
HFAP (Osteopathic)  15
Dept of Health/EMS  290

Total  ~950

--Figure from Albright et al, Arch Neurol 2010
Dissemination of Preferential EMS Routing to PSCs

--Song and Saver, ISC 2011
Primary Stroke Center Coverage of US Population in 2011

20 states, multiple additional counties, 54% US population

- States
  - Arizona
  - Connecticut
  - Delaware
  - Florida
  - Georgia
  - Illinois
  - Maryland
  - Massachusetts
  - Missouri
  - Nevada
  - New Jersey
  - New York
  - North Carolina
  - North Dakota
  - Oklahoma
  - Rhode Island
  - South Carolina
  - Texas
  - Utah
  - Virginia
  - Washington

- Counties
  - Alabama
    - 7 counties
  - California (16 of 58)
    - Alameda
    - Butte
    - Colusa
    - Kern
    - Los Angeles
    - Nevada
    - Orange
    - Placer
    - Sacramento
    - San Diego
    - San Francisco
    - San Mateo
    - Santa Clara
    - Sutter
    - Yolo
    - Yuba
Comprehensive Stroke Center Buildout

- Feb 2011
  - AHA CSC metrics paper
- June 2011
  - TJC technical advisory panel
- 2012
  - TJC pilot testing
- 2012-2013
  - National CSC certification

(Courtesy G Houser)
Key Joint Commission CSC Criteria
Announced 1/30/12

- **Volume**
  - SAH – 20/yr
  - Aneurysm craniot – 10/yr
  - Aneurysm coiling – 15/yr
  - IV TPA – 25/yr

- **Facilities**
  - Cath angio 24/7
  - CTA 247
  - MRA, DWI 24/7
  - TCD
  - Neuro ICU

- **Peer review**
  - Monitor AIS, SAH, tPA

- **Patient-centered research**

- **Performance measures**
  - All PSC
  - CSC-specific
    - Including door to puncture for acute endovascular recanalization
History

- 83 yo RH woman
- 7:05 PM – acute onset wobbling gait, slurred speech, right body weakness
- 911 called
EMS Evaluation

- Pulse 75, BP 170/75
- Right weakness
- LAPSS positive for stroke
- Neurologist by phone confirms history and orders start of FAST-MAG neuroprotective trial study agent in ambulance
Primary Stroke Center

- BP 172/70
- Aphasic – says “hi” repetitively
- Severe right hemiparesis
- NIHSS 24
- H/o HTN, hypercholesterolemia
- Medications: Pravastatin, carvedilol, losartan, pantoprazole, levothyroxine
Noncontrast CT – L MCA hyperdense sign
Noncontrast CT – L MCA hyperdense sign
Primary Stroke Center

- IV TPA 0.9 mg/kg
- Transfer to UCLA CSC
An 83 yo RH woman with sudden speech difficulty and right body weakness

Last known well @ 7:05 PM
911 call @ 7 min
Field NP study drug @ 33 min
PSC ED arrival @ 49 min
IV TPA @ 1 hr 54 min
Air-Rescue Landed @ 3 h 24 min
Penumbral imaging @ 3 h 59 min
1st Merci pass @ 5 h 7 min
Recanalization @ 5 h 13 min
Acute Ischemic Stroke Treatment 1.0: IV TPA and Moderately Effective Endovascular Therapy
Acute Ischemic Stroke Treatment 2.0: Treatment Swift and Treatment Sure