An Emerging Paradigm for Acute Stroke Care

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Ischemic Stroke
- PO aspirin
- IV TPA < 3 hrs
- IV TPA 3 to 4.5 hrs
- IA Merci Retriever < 8 hrs
- Endovascular temperature control

Intracerebral Hemorrhage
- IV Factor VIIa < 3 hrs
- Endovascular temperature control

Subarachnoid Hemorrhage
- GDC coil, Matrix coil, stent assisted coiling
- Endovascular temperature control
- IA angioplasty for vasospasm

Intraventricular Hemorrhage
- Intraventricular TPA and drainage
- Endovascular temperature control

Recanalization Treatments
Advances in Neuroimaging
- Identifying the Penumbra
- Salvaging the Penumbra

Ischemic Core
The area receiving little or no blood flow, where cells die rapidly, is known as the ischemic core
The ischemic core is where blood flow is severely reduced to <15 to 20%

**The Penumbra**

Surrounding this ischemic core is an area of reduced blood flow called the ischemic penumbra. The penumbra’s cells receive suboptimal blood flow (<40%)²


**Cells Within the Penumbra**

After a stroke, cells in the penumbra are in danger of cell death but are not immediately irreversibly damaged.


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**Ideal Model of Acute Ischemic Stroke Care**

- Symptoms
- Primary Stroke Center
- Neuroprotectants
- EMS
- 911
- Comp Stroke Center
- EMS IV Lytic
- Imaging
- Multi-modal imaging
- IA Mechanical or Lytic
- Angiogram
- Cath Lab
- Neuroprotectants
- Stroke Unit

**Neuroprotectants**

- Symptoms
- Primary Stroke Center
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**Role of neuroprotection**

Neuroprotection could help limit the damage caused by stroke.

- Without neuroprotection: Permanent ischemic damage
- With neuroprotection: Ischemic damage minimized


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**Neuroprotection may improve clinical outcomes**

Reducing free-radical-mediated damage is one approach.

Acute Ischemic Stroke

Ischemic Cascade

Repurpasion Cascade

Neuron Cell Death
Trials of Neuroprotective Agents for Stroke, 1958-2000

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

Time windows: 4-48 hours

Kidwell CS et al. Stroke 2001

Types of Neuroprotective Agents

- Glutamate antagonists
- Anti-inflammatory agents
- Calcium channel blockers
- Sodium channel blockers
- Potassium channel activators
- Free radical scavengers
- GABA receptor antagonists
- Serotonin antagonists
- Caspase inhibitors
- Others

The Ideal Neuroprotectant

- Safe in ischemic stroke
- Safe in hemorrhagic stroke
- Inexpensive
- Easily administered
- Easily stored
- Can be started quickly

Possible Therapeutic Effects of Magnesium in Stroke

- Mg2+ ions

  - NMDA Ion Channel Blockade
  - Ca2+ Channel Blockade

  - Enhanced ATP Recovery

  - Increased Cardiac Output
  - Increased Regional CBF

The Field Administration of Stroke Therapy – MAGnesium

- Phase 3 Clinical Trial
- NIH-NINDS-sponsored
- Goal: to evaluate the effectiveness and safety of field-initiated magnesium sulfate in improving the long-term functional outcome of patients with acute stroke

FAST-MAG

Investigative Setting

- Hospital Sites – Los Angeles County
  - > 6 million individuals
  - Up to 80 hospitals (69 in Wave 1)
  - > 16,000 stroke admissions yearly

- EMS Sites
  - Up to 31 EMS Provider Agencies
  - Up to 330 rescue vehicles
  - Up to 2000 paramedics

- Clinical Coordinating Center
  - UCLA Stroke Center

- Statistics Management Center
  - Stanford University and Mt. Tam Data Analysis

- Data Management Center
  - Pacific Data Designs (SF)
Age 69 (range 41-92)
Stroke subtype
- Cerebral ischemia 71%
- Ischemic stroke 82%
- TIA 18%
- Intracerebral hemorrhage 27%
- Momic 3%
- IV TPA
Among all cerebral ischemia 18%
Among all ischemic strokes 22%
Stroke Severity
- LAMS (prehospital) 4.0 (range 1-5)
- NIHSS (hospital arrival, after Rx start) 5.0 (range 0-40)

Key Time Intervals
- Stroke onset to study drug (median) 44 mins
- Paramedic arrival on scene to drug (mean) 28 mins
- Paramedic arrival on scene to ED (mean) 35 mins
- Treated within 1 hour of onset 73%
- Treated 1-2 hr after onset 23%

FAST-MAG Trial 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

Validation - Novel Techniques for Prehospital Stroke Trials
- Field recognition instrument (mLAPSS)
- Field stroke severity rating scale (LAMS)
- Prehospital explicit informed consent elicitation by cell phone

Evidence of Better Outcomes in Stroke Centers
- Stroke unit trialists’ collaboration meta-analysis
  - OR death: 0.82 (0.69, 0.98)
  - OR death/mst: 0.76 (0.64, 0.90)
  - OR death/dep: 0.71 (0.61, 0.84)

- In-hospital death less frequent in facilities with vascular neurologist; adjusted OR=0.49, P<0.0001
- Trend toward fewer deaths in facilities with dedicated stroke team available by pager
- JCAHO credentialing of stroke centers ensures that patients receive proper care

Impact of Establishing a Primary Stroke Center at a Hospital

Percentage of Patients Treated With tPA Related to the Establishment of a Primary Stroke Center

Pre-Stroke Center (9/1/98-9/14/99)
Pilot Period (9/15/99-1/2/00)
24-hour Stroke Team (1/3/00-12/31/01)


The New York State Stroke Center Designation Project

Stroke centers (n = 14) vs. Non-designated (n = 18)

Shorter median times
- from door to physician contact (10 vs 25 minutes, \( p < 0.001 \))
- Door to CT performance for potential t-PA candidates (31 vs 40 minutes, \( p = NS \))
- Door to t-PA administration (95 vs 115 minutes, \( p < 0.05 \))


Novel IV Thromolytic Strategies

Novel Agents
- Tenecteplase – NIH
- Reopenplase – CLEAR (NIH)
- Demoteplase – DIAS/DEDAS
- TPA Plus Ultrasound to Enhance Clot Lysis – CLOTBUST, TRUMBI
- Thrombolytic Plus GP IIb/IIIa or Direct Thrombin Inhibitors to Enhance Lysis – CLEAR, TARTS (NIH)
- TPA Plus Neuroprotective Agents
- Fibrinolytic Plus G2P or Direct Thrombin Inhibitors to Enhance Lysis
- Fibrinolytic Plus G2P or Direct Thrombin Inhibitors to Enhance Lysis – CLEAR, TARTS (NIH)
- TPA Plus Neuroprotective Agents
- Thrombolytic Plus GP IIb/IIIa
- IV Lytics Beyond 3 Hours
- Clinically selected
- ECASS III, 600 patients, 3.0-4.5 hours
- IST 3, 6000 patients, up to 6 hours
- Imaging selected
- DEFUSE, TPA, 3.0-3.5 hrs, pretreatment DWI/PWI MR, nonrandomized
- EPITHET, TPA, 3.0-3.5 hrs, pretreatment DWI/PWI MR, randomized
- DIAS/DEDAS, Desmoteplase, 3.0-3.9 hrs, multimodal MR, CT, 3-6 hrs

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 2004
mRS 0-1 at day 90
Adjusted odds ratio with 95% confidence interval by stroke onset to treatment time (OTT)

FDA approved for treatment of acute ischemic stroke up to 3 hours
ECASS 3
New AHA recommendations

Outcome was also improved with alteplase as compared with placebo (odds ratio, 1.28; P<0.05)
Intracranial hemorrhage more with alteplase than with placebo
- Any ICH, 27.0% vs. 17.6%; P=0.001
- Symptomatic ICH, 2.4% vs. 0.2%; P=0.008
Similar mortality (& other SAE)
- (7.7% and 8.4%, respectively; P=0.68)

For every 100 patients treated within 3 hours with tPA, 32 benefit, 3 harmed. For every 100 patients treated 3-4.5 hours 17 benefit and 3 are harmed
Inclusion criteria
• IV TPA ≤ 3 hours
• MCA occlusion on TCD (TIBI 0-3)

Treatment arms
• 2 hr continuous TCD monitoring, vs
• Helmet without TCD, except brief assessments at 30, 60, 90, 120 mins (total < 20 mins)
• IA rescue allowed after 2 hours

126 patients
99% completed 1 hr of assigned therapy
96% completed 2 hr of assigned therapy
Additional IA in 17% of control, 14% active
97% completed follow-up

CLOTBUST Results

<table>
<thead>
<tr>
<th>Active TCD</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median NIHSS</td>
<td>16</td>
</tr>
<tr>
<td>Time to IV TPA start</td>
<td>150</td>
</tr>
<tr>
<td>SICH (without IA)</td>
<td>3.2%</td>
</tr>
<tr>
<td>SICH (with IA)</td>
<td>4.8%</td>
</tr>
</tbody>
</table>

Primary endpoint | 49% | 30% |

p<.02, RR 1.6, NNT 5

*C: Complete recanalization on TCD, or early clinical recovery ≥ 10 NIHSS within 2 hours, or dramatic recovery to ≤ 3 NIHSS within 2 hours*
**ClotBust 3 Month Clinical Outcome (Rankin Global Disability)**

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Active TCD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>24</td>
<td>42</td>
</tr>
<tr>
<td>0-1</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>2-6</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>3-5</td>
<td>41</td>
<td>33</td>
</tr>
<tr>
<td>6</td>
<td>6</td>
<td>15</td>
</tr>
</tbody>
</table>

For binary 0-1 vs 2-6, p=0.21

**Evolving Developments in Therapeutic Ultrasound**

- ClotBust 3
  - Operator independent windowing
- Other Therapeutic Combinations for Lysis
  - Ultrasound alone
  - Ultrasound plus GPI, direct thrombin inhibitors
- Microbubbles
  - Further enhance lysis by local destruction
  - Microcapsule delivery of drug
  - External ultrasound to deliver drug specifically to occlusion
  - Add ligands to bubble surface to further enhance focal concentration and release

**Ideal Acute Ischemic Stroke Care**

1. Symptoms Primary Stroke Center
2. EMS 911
3. Comp Stroke Center
4. EMS IV Lytic
5. Imaging
   - Multi-modal imaging
   - Imaging required to assess pathophysiology
6. IA Mechanical or Lytic
7. Angiogram
8. Cath Lab Neuroprotectants
9. Stroke Unit

**Hyperacute therapy when nearly all patients have penumbra**

% Patients with Penumbra

Time From Onset (Hours)

**Strategies to Identify Patients with Salvageable Ischemic Penumbra**

- Imaging required to assess pathophysiology

**Multimodal CT Imaging**

- CT: Tissue Status
  - Bioenergetic Compromise
- PCT: Perfusion Status
  - Hemodynamic Compromise
- CTA: Vessel Status
  - Occlusions or Stenoses

**Multimodal MRI Imaging**

- DWI: Tissue Status
  - Bioenergetic Compromise
- PWI: Perfusion Status
  - Hemodynamic Compromise
- MRA: Vessel Status
  - Occlusions or Stenoses
Salvage of Mismatch Region: IA Thrombolysis and Basilar Artery Occlusion

DWI

PWI

Pre Post

DWI Reversal

Pre Post

Percent of Mismatch Salvaged With Intra-arterial Thrombolysis

Recanalization No Recanalization

Darby et al, Stroke 1999

Frequency of Mismatch

Frequency of Mismatch

0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%

<3 Hrs <6 6-12 12-18 18-24 Overall

100% 75% 71% 59% 44% 62%

TPA safe and effective in 0-3 hour window
TPA may be safe and effective in 3-6 hour window in select patients
- specific profiles on DWI and PWI predict a favorable clinical response

DEFUSE: Mismatch Pattern

DEFUSE: Mismatch Pattern

5:48 NIH 16

3 cc 65 cc ↓ M2 Flow

+4:32 hrs NIH 5

6 cc 0 cc Improved
DEFUSE: No Mismatch Pattern

5:15 NIH 14
- 20 cc
- 20 cc

+6.33 hrs NIH 11
- 31 cc
- 4 cc

? improved

DEFUSE: Malignant Infarct Pattern

5:10 NIH 9
- 94 cc
- 173 cc

+5 hrs NIH 9
- 111 cc
- 42 cc

Technically inadequate

DEFUSE, abcTIV, TPA 3-6 hours

3 populations now identified by MRI patterns

benefit from tPA
Target MM (40%)

no difference
Small / Matched (50%)

harm
Malignant (10%)

Ticking Clock

Tissue Clock

Ideal Acute Ischemic Stroke Care

Multi-modal imaging
IA Mechanical or Lytic
Angiogram
Cath Lab Neuroprotectants Stroke Unit

Recanalization
- Endovascular Recanalization Devices
  - Mechanical embolectomy – Merci Retriever (Concentric);
  - Neuronet (Guidant)
  - Angioplasty/stent
  - Embolic thrombectomy – Angiojet (Possis)
  - Ultrasound – EKOS
  - Laser - EPAR

- External Recanalization Promoting Devices
  - Diffuse Ultrasound (TRUMBI - Neuroflow); Focused ultrasound (CLOTBUST)

- Hypothermia/Normothermia
  - Internal – Celsius CS (Innercool), SetPoint (Radiant), CoolGard (Alinum)
  - External – Arctic Sun (CHILI)

Other Strategies
- CBF Enhancement
  - Controlled aortic occlusion – NeuroFlo (CoAxia)
  - Cerebral retrograde perfusion – Neurep/NeuroPerfusion, Inc

- Hypothermia/Normothermia
  - Internal – Cerebel CS (Innerecool), SetPoint (Radiant), CoolGard (Alinum)
  - External – Arctic Sun (CHILI)

- Regional – cooling helmet
**Merci® Retrieval System**

Flexible, helical shaped, tapered tip made of nitinol wire

Merci = mechanical embolus retrieval in cerebral ischemia

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**MCA Occlusion**

30-Year-Old Female – Baseline NIHSS 24

Symptom Onset to Final Angiogram – 5:37

<table>
<thead>
<tr>
<th>NIHSS 24 hours</th>
<th>30 days post</th>
<th>mRS 5 days post</th>
<th>90 day post</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

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**MERCI Trial Primary Endpoints**

<table>
<thead>
<tr>
<th></th>
<th>Revascularization</th>
<th>Serious Complications (Device Related)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total n=114</td>
<td>54% (61)</td>
<td>3.5% (4)</td>
</tr>
<tr>
<td>95% Confidence Interval: 44% to 63%</td>
<td></td>
<td></td>
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</tbody>
</table>

*p < 0.001†

† p-value for showing superiority over a 16% (PROACT II Placebo Group) success rate using the exact binomial test


* ICA and ICA T (ICA/MCA/ACA) occlusions were combined into the ICA group

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**Successful Revascularization by Vessel**

<table>
<thead>
<tr>
<th>Vessel</th>
<th>Overall (61/114)</th>
<th>ICA* (21/57)</th>
<th>MCA (33/65)</th>
<th>Vert Bas (7/12)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>54%</td>
<td>57%</td>
<td>51%</td>
<td>58%</td>
</tr>
<tr>
<td>0%</td>
<td>10%</td>
<td>20%</td>
<td>30%</td>
<td>40%</td>
</tr>
<tr>
<td>50%</td>
<td>60%</td>
<td>70%</td>
<td>80%</td>
<td>90%</td>
</tr>
</tbody>
</table>

* ICA and ICA T (ICA/MCA/ACA) occlusions were combined into the ICA group
**FD A Approval of Merci Retriever August 2004**

Indications for use

“The Merci Retriever is intended to restore blood flow in the neurovasculature by removing thrombus in patients experiencing ischemic stroke. Patients who are ineligible for treatment with intravenous tissue plasminogen activator (IV t-PA) or who fail IV t-PA therapy are candidates for treatment.”

**Merci Retriever: Current Trials**

**MR RESCUE (NIH)**
- Randomized trial Merci Retriever vs best medical care, <8h

**Multi-MERCI (Concentric)**
- Next generation Merci LX device
- Cylindrical helices
- Attached filaments
- Combined IV TPA – Rescue Merci

**IMS 3 (NIH)**
- IV TPA vs IV TPA + IA (Merci or IA lytic), < 3h

**A New Approach to Cerebral Ischemia**

Globally increase cerebral perfusion

Utilize extensive cerebral collateral network to perfuse the ischemic penumbra

Salvage ‘at risk’ tissue immediately

Treat later in time while minimizing risk of hemorrhagic conversion (not disturbing clot)

No intracranial access required

**NeuroFlo Treatment Example:**

**Pre Treatment**

**Post Treatment**

<table>
<thead>
<tr>
<th>Core Penumbra</th>
<th>PRODUCT / PROCEDURE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dual balloon aortic catheter</td>
</tr>
<tr>
<td></td>
<td>9 Fr sheath; simple femoral access</td>
</tr>
<tr>
<td></td>
<td>Balloons advanced to supra- and infra-renal</td>
</tr>
<tr>
<td></td>
<td>45 minute inflation; removal</td>
</tr>
<tr>
<td></td>
<td>No effect on mean arterial blood pressure; bypasses cerebral autoregulation (does lower iliac and femoral pressures)</td>
</tr>
<tr>
<td></td>
<td>Cerebral perfusion increases average +30% and persists beyond balloon deflation</td>
</tr>
<tr>
<td></td>
<td>Unique, supra- &amp; infra-renal design preserves renal perfusion</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Non-Recan</th>
<th>Recan</th>
</tr>
</thead>
<tbody>
<tr>
<td>n= 51</td>
<td>n= 47</td>
</tr>
<tr>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>10%</td>
<td>10%</td>
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<td>20%</td>
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<td>80%</td>
<td>80%</td>
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<tr>
<td>90%</td>
<td>90%</td>
</tr>
<tr>
<td>100%</td>
<td>100%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>mRS 0-2</th>
<th>mRS 3-5</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>53%</td>
<td>16%</td>
<td>31%</td>
</tr>
<tr>
<td>32%</td>
<td>62%</td>
<td>0%</td>
</tr>
</tbody>
</table>
A randomized trial comparing 90 day clinical outcome between NeuroFlo and standard medical management in patients not qualifying for IV tPA or IA interventions

- FDA controlled pivotal trial currently enrolling at 47 North American sites
- 149 patients enrolled to date
- 100 patient safety data reviewed by DSMB
  - safety remains very positive – no higher mortality or clinically significant bleeds in treatment patients vs. control
  - outcomes blinded until final analysis

### Treated (n = 27) vs. Control (n = 20)

<table>
<thead>
<tr>
<th>Event</th>
<th>Treated</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>2 (7.4%)</td>
<td>4 (20%)</td>
</tr>
<tr>
<td>SAEs - fatal and non-fatal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptomatic hemorrhagic</td>
<td>1 (3.7%)</td>
<td>1 (5.0%)</td>
</tr>
<tr>
<td>Fatal hemorrhagic transformation</td>
<td>0</td>
<td>N/A</td>
</tr>
<tr>
<td>Procedure-related cardiac SAEs</td>
<td>0</td>
<td>N/A</td>
</tr>
<tr>
<td>Procedure-related groin/aorta SAEs</td>
<td>0</td>
<td>N/A</td>
</tr>
<tr>
<td>Procedure-related renal injury</td>
<td>0</td>
<td>N/A</td>
</tr>
<tr>
<td>Stroke Unit</td>
<td>0</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Note: 3 patients randomized to treatment but not treated.

### Ideal Model of Acute Ischemic Stroke Care

1. **Symptoms**
   - Primary Stroke Center

2. **EMS**
   - 911

3. **Comp Stroke Center**
   - Neuroprotectants

4. **EMS IV Lytic**

5. **Imaging**
   - Multi-modal imaging

6. **IA Mechanical or Lytic**
   - Angiogram
   - Cath Lab
   - Neuroprotectants

7. **Stroke Unit**

### Stroke Expertise and Patient Outcome

1073 VA acute stroke patients, national sample
- Primary attending: neurologist or non-neurologist
- Outcomes at discharge

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Neurologist</th>
<th>Non-Neurologist</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dependent/dead</td>
<td>46.1%</td>
<td>57.1%</td>
</tr>
<tr>
<td>Dead</td>
<td>5.6%</td>
<td>13.5%</td>
</tr>
</tbody>
</table>

Differences significant after controlling for severity and comorbidities.
**Acute Stroke Care: Summary**

- Time
- Penumbra
- Recanalization
- Organization of stroke care
- Stroke prevention starts on admission

Prevention is still the most effective means of reducing stroke impact and disability.