Acute Stroke and Transient Ischemic Attack - 2010

David Liebeskind, MD
UCLA Stroke Center

Acute Stroke: A Public Health Crisis

- Leading cause of adult disability in US
- 3rd leading cause of death (2nd worldwide)
- ~800,000 new strokes each year
- >5 million stroke survivors
- $70 billion per year in the United States
- 1 in 6 Americans will be affected
- Of those who survive, 90% have deficit

Cerebrovascular Disease: Pathogenesis

<table>
<thead>
<tr>
<th>Ischemic Stroke (83%)</th>
<th>Hemorrhagic Stroke (17%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atherothrombotic</td>
<td>Intracerebral Hemorrhage (10%)</td>
</tr>
<tr>
<td>Cerebrovascular Disease (30%)</td>
<td>Subarachnoid Hemorrhage (30%)</td>
</tr>
<tr>
<td>Lacunar (20%) (small vessel disease)</td>
<td>Other (vasculitis, dissection, hypercoagulable, etc (10%)</td>
</tr>
</tbody>
</table>
The Ischemic Penumbra

**Core Infarct**

**Ischemic Penumbra:** zone of salvageable tissue surrounding core infarct

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In a typical acute ischemic stroke, every minute the brain loses:

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

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Strategies to Identify Patients with Salvageable Ischemic Penumbra

<table>
<thead>
<tr>
<th>&lt; 3 Hrs</th>
<th>&gt; 3 Hrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperacute therapy when nearly all patients have penumbra</td>
<td>Imaging required to assess pathophysiology</td>
</tr>
</tbody>
</table>

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Strategies in Acute Ischemic Stroke Therapy

- **Proven**
  - Organized supportive Care
  - Recanalization
  - Prevent Clot Propagation
  - Early Implementation of Secondary Prevention
- **Experimental**
  - Neuroprotection
  - Reperfusion via Collateral Enhancement

Early Supportive Acute Stroke Care

5-15% Increase in Good Outcomes in Acute Stroke Unit Controlled Trials

- **Treat hypoxemia**
  - Continuous pulse oximetry, supplemental oxygen as needed
- **Maintain normothermia**
  - Early antipyretics/antibiotics
- **Avoid hyperglycemia**
  - Avoid glucose infusions/use Insulin/maintain glucose < 200 mg/dl
  - Early parental fluid to support collaterals
  - Maintain normotonic IV fluids (IV NS 75-100 cc/h)
- **Permissive hypertension to support collaterals**
  - Treat only if >220/120
- **DVT prophylaxis**
  - Compression boots/hep/LMWH
  - Early mobilization
- **Early swallow assessment to guide oral feeding**

Stroke Systems Controlled Trial

TEMPIS Study – Lancet Neurology 2006

- Controlled study of stroke systems
- 10 community hospitals in Bavaria
  - 5 intervention, 5 control
  - Matched in size, catchment area, infrastructure
- **Intervention**
  - Stroke wards in each hospital
  - Continuous onsite training of medical staff
  - 24/7 telemedicine consultation from academic centers (both ED and inpatient)
- **July 2003 – March 2005, 3122 ischemic and hemorrhagic stroke patients**
- Patients dead or disabled 3 months after stroke
  - 43.6% vs 54.0%, p<0.001,
  - OR for poor outcome 0.61, 95% CI .51-.73
Preventing Clot Propagation
Antithrombotics and Acute Stroke

- **Aspirin**
  - 9 trials, 41,399 patients (Cochrane 2004)
  - Minimally beneficial, OR = 0.94 (95% CI 0.91-0.98)
  - 13 more per 1000 alive and independent
  - NNT: 77

- **Heparin/LMWHs**
  - 21 trials, 23,427 patients (Cochrane 2004)
  - No net benefit
  - "Heparin/heparinoids are not recommended for acute ischemic stroke" AAN/AHA Joint Guideline 2002

Currently Available Recanalization Therapies in Acute Cerebral Ischemia

- **Intravenous**
  - IV TPA under 3 hours
    - FDA approved, guideline endorsed, RCT supported
  - IV TPA 3-4.5 hours
    - RCT supported, guideline endorsed, FDA approval likely
  - IV lytics 4.5-9 hours in advanced imaging selected patients
    - Weekly RCT supported, not guideline endorsed or FDA approved

- **Catheter**
  - Mechanical embolectomy ≤ 8 h (Merci devices)
    - FDA approved for clot clearance, no RCTs
  - Mechanical aspiration ≤ 8 h (Penumbra device)
    - FDA approved for clot clearance, no RCTs
  - Mechanical angioplasty/stenting
    - FDA approved for secondary prevention, no RCTs
  - IA fibrinolytics ≤ 6 h
    - Off label, 1.5 positive RCTs, weakly guideline endorsed

NINDS tPA Stroke Trials 1 and 2

- Excellent Recovery (mRS 0-1)
- Death

- tPA tPA Placebo Placebo
- 38 26 9 20
- 4 1 0 1
- p < .001

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AAN-ACEP-AHA Jointly Developed TPA Patient Education Tool - 2008

- "If given promptly, 1 in 3 patients who receive tPA resolve their symptoms or have major improvement..."
- "In 6 out of 100 patients, bleeding may occur into the brain and cause further injury. For 1 of these 6 patients, it may cause death or long term serious disability."
- [Link to TPA Flyer]

IV TPA Under 3 Hours – Changes in Outcome Due to Treatment

<table>
<thead>
<tr>
<th>Outcome</th>
<th>NNTB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Near Normal</td>
<td>8.3</td>
</tr>
<tr>
<td>Improved</td>
<td>3.1</td>
</tr>
</tbody>
</table>

For every 100 patients treated with tPA, 32 benefit, 3 harmed

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Intravenous Treatment Beyond 3 Hours: Pooled Analysis of Initial IV TPA Trials (Lancet 2004)

- 6 trials, 4 with >3h data
  - ECASS 1, ECASS 2
  - ATLANTIS A, ATLANTIS B
  - NINDS Trial 1, NINDS Trial 2
- 2775 patients
- OR favorable outcome

<table>
<thead>
<tr>
<th>Time (hrs)</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.5-1.5</td>
<td>2.1</td>
</tr>
<tr>
<td>1.5-3.0</td>
<td>1.6</td>
</tr>
<tr>
<td>3.0-4.5</td>
<td>1.4</td>
</tr>
<tr>
<td>4.5-6.0</td>
<td>1.2</td>
</tr>
</tbody>
</table>

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Intravenous Treatment Beyond 3 Hours: ECASS 3 Trial (NEJM 2008)

- 821 patients, 130 European sites
- Entry criteria like <3h trials, except excluded:
  - Age > 80
  - NIHSS > 25
  - CT/MRI showing infarct > 1/3 MCA
  - On warfarin (at any INR, both < 1.7 and ≥ 1.7)
  - Combination of prior stroke and diabetes
- Primary endpoints
  - Safety: SICH (hemorrhage judged by blinded adjudicators to be predominant cause of NIHSS worsening by ≥ 4
  - Efficacy: Excellent functional outcome (modified Rankin Scale 0-1) at 3m

ECASS 3: Results

- SICH: 2.4% vs 0.2%, p=0.008
- Mortality: 6.7% vs 8.2%, p=0.68
- Excellent outcome: 52.4% vs 45.7%, p=0.04
- Shift toward favorable outcomes: p=0.02
Intravenous TPA in the 3-4.5 Hour Window

<table>
<thead>
<tr>
<th>Outcome</th>
<th>NNTB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal/Near Normal</td>
<td>14</td>
</tr>
<tr>
<td>Improved</td>
<td>7.1</td>
</tr>
</tbody>
</table>

For every 100 patients treated with tPA, 16 benefit, 3 harmed

--Saver et al, Stroke 2009

AHA/ASA Science Advisory

Expansion of the Time Window for Treatment of Acute Ischemic Stroke With Intravenous Tissue Plasminogen Activator

A Science Advisory From the American Heart Association/American Stroke Association

- "TPA should be administered to eligible patients who can be treated in the time period of 3 to 4.5 hours after stroke (Class I Recommendation, Level of Evidence B)."

- Exclusion criteria for recommendation
  - Same as in <3h, plus
    - Older than 80
    - Taking oral anticoagulants (even with normal INR)
    - NIHSS 25 or higher
    - History of stroke and diabetes
    - Established infarct signs on CT/MRI in > 1/3 MCA
  - "Although a longer time window for treatment with rtPA has been tested formally, delays in evaluation and initiation of therapy should be avoided, because the opportunity for improvement is greater with earlier treatment."

Impact of PSC Acute Ischemic Stroke Treatments

<table>
<thead>
<tr>
<th></th>
<th>NNTB</th>
<th>Benefit per 100 pts</th>
</tr>
</thead>
<tbody>
<tr>
<td>TPA 1-3h</td>
<td>3</td>
<td>32</td>
</tr>
<tr>
<td>TPA 3-4.5h</td>
<td>7</td>
<td>16</td>
</tr>
<tr>
<td>Stroke Unit</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Aspirin</td>
<td>77</td>
<td>1</td>
</tr>
</tbody>
</table>

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Using tPA in Routine Clinical Practice

- Overall only about 3%-4% of stroke patients receive tPA—mostly due to time delays
- Efficacy similar to NINDS trial
- Rate of ICH: 4%-6%
- Risk of ICH increases with protocol violations
  - Time >3 hours
  - Poor blood pressure control
  - Using prohibited agents
  - Wrong dose
    - 0.9 mg/kg
    - Maximum dose: 90 mg
  - Elevated blood sugar also increases risk


Time is Brain

- Door to treatment time 60 minutes
  - At least 80% of patients
  - Ambulance radio alert receiving hospital
  - Triage nurse alert stroke team
  - Team MD hx/exam within 20 minutes
  - CT within 40-45 minutes
  - Expedited pharmacy drug prep
  - Brain Attack/Code Stroke/STROK

  —NINDS Consensus Conference Guidelines

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TPA Door to Needle Times

- CDC 4 State Pilot Acute Stroke Registry
  - 98 hospitals, 6867 acute patients, 118 IV TPA
  - Treatment within target 60 minutes: 14.4%
- GWTG-S US National Registry
  - 905 hospitals, 106,924 ischemia pts, 12,141 TPA
  - Overall, mean door to needle time 86 mins
  - Among patients inED within 60 mins of onset, DTN ≤ 60 mins in 18.3%

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*Improvement Over Time in GWTG-Stroke in the Use of IV rt-PA in Eligible Patients

![Graph showing improvement over time in GWTG-Stroke in the use of IV rt-PA in eligible patients](image1)


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

*Door-to-IV rt-PA within 60 minutes

![Graph showing door-to-IV rt-PA within 60 minutes](image2)

*GWTG-Stroke Database, data on file DCRI

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

*Door-to-IV rt-PA within 60 minutes

![Graph showing door-to-IV rt-PA within 60 minutes](image3)

*GWTG-Stroke Database, data on file DCRI

TARGET: STROKE

TIME LOST IS BRAIN LOST.

STROKEASSOCIATION.ORG/TARGETSTROKE
**Target: Stroke  The Time is Now**

*Door-to-IV rt-PA within 60 minutes*

*GWTG-Stroke Database, data on file DCRI*  

**Target: Stroke  The Time is Now**

*Door-to-IV rt-PA within 60 minutes*

**Emergent Stroke Care and the Chain of Survival**

**Stroke Systems: Two 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

- **Primary Stroke Centers - Spokes**
  - Able to provide initial, acute care
  - Able to use rt-PA and other acute therapies in a safe and efficient manner
  - Can admit patients if they have a Stroke Unit

- **Comprehensive Stroke Centers - Hubs**
  - Able to care for complex patients
  - Advanced treatments (i.e. coils, stents, etc)
  - Trained specialists in key areas (Vascular neurology, Neurointerventional procedures, Neurocritical Care, Vascular Neurosurgery)
Certified Primary Stroke Centers in the United States

<table>
<thead>
<tr>
<th>Certification</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Joint Commission</td>
<td>545</td>
</tr>
<tr>
<td>HFAP (Osteopathic)</td>
<td>15</td>
</tr>
<tr>
<td>Dept of Health/EMS</td>
<td>290</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>850</td>
</tr>
</tbody>
</table>

Primary Stroke Center Coverage of US Population in 2009

- **States**
  - Delaware
  - Florida
  - Georgia
  - Illinois
  - Maryland
  - Massachusetts
  - Missouri
  - New Jersey
  - New Mexico
  - New York
  - Oklahoma
  - Texas
  - Virginia

- **Counties**
  - Alabama
  - Arizona
  - Maricopa-Phoenix
  - California
  - Austin
  - Harris
  - Los Angeles (partial)
  - Orange
  - Sacramento
  - San Diego
  - San Francisco
  - San Mateo
  - Santa Clara

Primary Stroke Center Coverage of US Population in 2010

- Live in jurisdictions with direct routing to Stroke Centers
  - 154 million Americans
  - 51% of US population
- Live in jurisdictions with routing to nearest hospital, not PSCs
  - 150 million Americans
  - 49% of US population
Novel IV Fibrinolytic Strategies

- Novel Agents
  - Tenecteplase – NIH
  - Reptogen – CLEAR (NH)
  - Desmoteplase – DIAS/DEDAS
- TPA Plus Ultrasound to Enhance Clot Lysis
  - CLOTBUST, TRUMBI
- Fibrinolytic Plus GP2 or Direct Thrombin Inhibitors to Enhance Lysis
  - CLEAR (NH), TARTS (NH)
- TPA Plus Neuroprotectives
  - FAST-MAG (magnesium sulfate)
- IV Lytics Beyond 3 hours
  - TPA selection
    - IST 3, 6,000 patients, up to 6 hours
  - Imaging selected
    - DEFUSE, TPA, 3-6h, pretreatment DWI/PWI MR, nonrandomized
    - EPITHET, TPA, 3-6h, pretreatment DWI/PWI MR, randomized
    - DIAS/DEDAS, Desmoteplase, 3-6h, multivocal MRI, CT >3 hrs

Ticking Clock

Tissue Clock

Multimodal CT

Multimodal MRI

- CBV CT
- DWI
- Bioenergetic Compromise
- Occlusions or Stenoses

- PCT
- PWI
- Hemodynamic Compromise

- CTA
- MRA
- Vessel Status
Results of the DEFUSE Study

**DWI / PWI Evaluation**
**For Understanding Stroke Evolution**

Gregory W. Albers, MD
on behalf of the DEFUSE Investigators

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**DEFUSE: Mismatch Pattern**

- **6:48 NIH 16**
  - 3 cc
  - 65 cc
- **+4:32 hrs NIH 5**
  - 6 cc
  - 0 cc
  - ↓ M2 Flow
  - Improved

**DEFUSE: No Mismatch Pattern**

- **5:15 NIH 14**
  - 20 cc
- **+6:13 hrs NIH 11**
  - 31 cc
  - 4 cc
  - ↓ R MCA flow?
  - ? improved
**DEFUSE : Malignant Infarct Pattern**

- 5:10 NIH 9
  - 94 cc
  - 173 cc
  - 111 cc
  - 42 cc
  - Technically inadequate

+5 hrs NIH 9

**Frequency of Favorable Clinical Outcome**

<table>
<thead>
<tr>
<th>Mismatch</th>
<th>Early Reperfusion (ER) (+)</th>
<th>Baseline NIHSS (BN)</th>
<th>Frequency of Favorable Outcome (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(+)</td>
<td>ER (+) (n=17) BN:14.6</td>
<td>47</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ER (+) (n=16) BN:12.8</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>(-)</td>
<td>ER (-) (n=7) BN:13.0</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ER (-) (n=7) BN:12.1</td>
<td>43</td>
<td></td>
</tr>
</tbody>
</table>

- No significant difference in baseline NIHSS between groups
- Patients with baseline PWI of < 10cc excluded

**Key Results of the DEFUSE Study**

- **Target Mismatch** pattern (49%)
  - Benefit substantially from early reperfusion
- **Match** pattern (15%)
  - No benefit from early reperfusion
- **Small DWI / PWI lesions** (28%)
  - Associated with favorable outcomes
- **Malignant MRI** pattern (8%)
  - Predicts severe ICH following reperfusion
Intra-arterial Recanalization Therapies

**Advantages**
- Proven benefit within 3 hours of symptom onset
- Rapid initiation of thrombolysis
- Widely available

**Disadvantages**
- Low concentration of lytic agent at clot site
- Low early recanalization rates, 30-40%
- Systemic exposure to thrombolytic agent

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**IV Fibrinolysis**

**Advantages**
- High concentration of lytic agent at clot site
- Gentle mechanical disruption of clot
- Option of pure mechanical strategy
- High early recanalization rates, 60-80%
- Precise knowledge of occlusion, recanalization

**Disadvantages**
- Delayed start of therapy
- Procedural risks - vessel rupture, dissection, etc
- Available only at specialized centers

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**IA Recanalization Therapies**

**Advantages**
- High concentration of lytic agent at clot site
- Gentle mechanical disruption of clot
- Option of pure mechanical strategy
- High early recanalization rates, 60-80%
- Precise knowledge of occlusion, recanalization

**Disadvantages**
- Delayed start of therapy
- Procedural risks - vessel rupture, dissection, etc
- Available only at specialized centers

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Meta-analysis IA Fibrinolysis

A. Good outcome (modified Rankin Scale 0–2)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Mean Apparent</th>
<th>Control</th>
<th>Peto Odds Ratio</th>
<th>Peto Odds Ratio 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large Pro-UK trials</td>
<td>29</td>
<td>20</td>
<td>1.68</td>
<td>(1.05, 2.68)</td>
</tr>
<tr>
<td>Large IA trials</td>
<td>18</td>
<td>12</td>
<td>1.54</td>
<td>(1.05, 2.27)</td>
</tr>
<tr>
<td>Meta-regression</td>
<td>24</td>
<td>17</td>
<td>1.54</td>
<td>(1.05, 2.27)</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>57</td>
<td>37</td>
<td>1.58</td>
<td>(1.05, 2.41)</td>
</tr>
</tbody>
</table>

Heterogeneity: Q = 4.54, df = 1, P = 0.099
Total test effect: Z = 2.19 (P = 0.029)

B. Excellent outcome (modified Rankin Scale 0–1)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Mean Apparent</th>
<th>Control</th>
<th>Peto Odds Ratio</th>
<th>Peto Odds Ratio 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large Pro-UK trials</td>
<td>22</td>
<td>15</td>
<td>1.42</td>
<td>(1.05, 1.92)</td>
</tr>
<tr>
<td>Large IA trials</td>
<td>14</td>
<td>9</td>
<td>1.53</td>
<td>(1.05, 2.26)</td>
</tr>
<tr>
<td>Meta-regression</td>
<td>16</td>
<td>12</td>
<td>1.49</td>
<td>(1.05, 2.13)</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>38</td>
<td>27</td>
<td>1.50</td>
<td>(1.05, 2.14)</td>
</tr>
</tbody>
</table>

Heterogeneity: Q = 5.77, df = 1, P = 0.016
Total test effect: Z = 2.19 (P = 0.029)

Number Needed to Treat to Benefit from IA Pro-UK
Across Full Range of Functional Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>NNT</th>
</tr>
</thead>
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<tr>
<td>Normal/Near Normal</td>
<td>11.1</td>
</tr>
<tr>
<td>Improved</td>
<td>4.8</td>
</tr>
</tbody>
</table>

For every 100 patients treated with IA Pro-UK, 21 benefit, 4 harmed

--Saver, Stroke 2007; 38;3055-3062

Mechanical Endovascular Recanalization Devices in Acute Stroke

- Endovascular Thrombectomy
  - Clot Retrieval Devices
    - Merci Retriever
    - Retrievable Stents
    - Phenox Retriever
    - Catch Device
    - Microsnare
  - Suction Thrombectomy
    - Penumbra system
    - Syringes suction
    - Angiojet/Neurojet

- Mechanical Disruption
  - Stenting
  - Angioplasty
  - Laser
    - EPAR Device
    - LaTIS Device
  - Augmented Fibrinolysis
    - Microwire passage
    - Endovascular ultrasound
Approved Cerebral Endovascular Recanalization Devices

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

US: + + + +
Europe: + + + +

Merci® Retrieval System

Flexible, helical shaped, tapered tip made of nitinol wire
Merci = mechanical embolus retrieval in cerebral ischemia

Find it, Engage it, Retrieve it
Merci Retriever Devices

X5, X6
Five helical loops, conical; X6 more resistant to stretching

L5, L6
Helical loops, cylindrical, arcading filaments

K-mini
Helical loops with counter-twist, cylindrical, smaller diameter

V-Series
7 helical loops (2 small distal loops), filaments, variable spring rate

UCLA – MCA Occlusion
30-Year-Old Female – Baseline NIHSS 24
Symptom Onset to Final Angiogram – 5:37

NIHSS 24 hours 1
30 days post 0

mRS 5 days post 0
90 day post 0
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

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Recanalization: Primary Endpoint of Merci and Multi-Merci Trials

<table>
<thead>
<tr>
<th></th>
<th>Recanalization</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROACT Controls (n=59)</td>
<td>18%</td>
</tr>
<tr>
<td>MERCI Retriever (n=141)</td>
<td>48% (60%)</td>
</tr>
<tr>
<td>Multi-MERCI Retriever (n=111)</td>
<td>54% (69%)</td>
</tr>
</tbody>
</table>

p < 0.00001

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Successful Revascularization by Vessel

90-Day Modified Rankin Score
Revascularized vs. Unrevascularized

MCA Patients in PROACT 2 and Merci/Multi-Merci Trials
—Josephson, Saver, Smith et al, Neurocritical Care 2008
Penumbra System: Registration Trial

- 125 patients
- NIHSS 17.6
- Recanalization (TIMI 2-3)
  - Reported "82%"
  - Likely lower using standard ratings
- SICH 11.2%
- Nondisabled (mRS 0-2) outcome 90 d 25%
- Death 90 d 33%

Penumbra System in Glass Model: Operator Controlled Separator
Movement Clears Catheter and Permits Continuous Aspiration

Distinctive Aspects of Cerebral Recanalization

- Composition of occlusion – clot (vs athero + clot)
  - Angioplasty and stenting often unsuccessful
  - Vessel wall more vulnerable to mechanical stress
  - Dissection, perforation, and rethrombosis greater threats
- Large volume of clot
  - Mechanical disposition of large clot burden desirable
- Emboli matter
  - Concurrent thrombolysis of distal emboli frequently required
  - Advantage of "clean" over "dirty" techniques
- The brain bleeds
  - Limit on dosage/combinations of lytics/antithrombotics
  - Potential for severe worsening
**New Approaches to TIA: Definition, Diagnosis, Early Triage**

**Evolution of the Definition of TIA**

- **Traditional Time Definition**
  - 1950s–2000
  - Symptom duration used as a rough indicator of brain injury
  - TIA defined as symptoms < 24h
  - Definition becomes untenable as CT and then DWI MRI show up to half of all <24h episodes associated with underlying acute brain infarction

- **New Tissue Definition**
  - 2000s – Proposal of tissue defns of TIA
  - 2009 – Formal endorsement in AHA/ASA Scientific Statement
  - "a brief episode of neurological dysfunction caused by focal brain or retinal ischemia, and without evidence of acute infarction"


**Epidemiology of Transient Ischemic Attacks**

- Frequency estimates vary widely
  - Underestimate – non-reporting by patients, underinclusive diagnostic criteria
  - Overestimate – overinclusive diagnostic criteria

- **Incidence**
  - 0.37-1.1 per 1000 per year
  - 200,000–500,000 per year in US

- **Prevalence**
  - 2.3%
  - 5 million individuals in US
Epidemiology of Transient Ischemic Attacks

- Frequency estimates vary widely
  - Underestimate – non-reporting by patients, underinclusive diagnostic criteria
  - Overestimate – overinclusive diagnostic criteria
- Incidence
  - 0.37-1.1 per 1000 per year
  - 200,000–500,000 per year in US
- Prevalence
  - 2.3%
  - 5 million individuals in US

Prognosis in TIAs

- Signal of cerebrovascular instability
- After TIA, 10 X the risk of ischemic stroke
  - Risk highest in first 48 hours
  - Remains high over first 3 months
  - 35% stroke risk within 3–5 years after TIA
- A key opportunity to prevent stroke

Short Term Prognosis After Emergency Department Diagnosis of TIA

- 1707 patients, Kaiser Northern Calif
- Mean age 72
- 90 day prognosis
  - Stroke: 10.5%
  - TIA: 12.7%
  - Death: 2.6%
- 2 day prognosis
  - Stroke: 5.3%
The ABCD² Scale
Unified Scale to Predict Stroke Risk After TIA

<table>
<thead>
<tr>
<th>Item</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥60</td>
<td>1</td>
</tr>
<tr>
<td>Blood pressure, SBP ≥140 or DBP ≥90</td>
<td>1</td>
</tr>
<tr>
<td>Clinical features of TIA</td>
<td></td>
</tr>
<tr>
<td>Unilateral weakness</td>
<td>2</td>
</tr>
<tr>
<td>Speech impairment without weakness</td>
<td>1</td>
</tr>
<tr>
<td>Duration of TIA</td>
<td></td>
</tr>
<tr>
<td>≥60 mins</td>
<td>2</td>
</tr>
<tr>
<td>10–59 mins</td>
<td>1</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1</td>
</tr>
</tbody>
</table>

Johnston, Rothwell et al, Lancet 2007

Short Term Risk of Stroke by ABCD² Score Among 4799 Patients

Johnston, Rothwell et al, Lancet 2007
**Imaging Predictors of Early Stroke**

- CT or MR
  - Any prior infarcts
- DWI MR
  - Acute DWI abnormality
  - Multiple recent lesions
- Vessel imaging
  - Vessel Occlusion

**MRI Predictors of Early Risk of Stroke**

120 TIA and Minor Infarct (NIHSS ≤ 3) imaged within 24h

<table>
<thead>
<tr>
<th>Condition</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal DWI</td>
<td>4.3%</td>
</tr>
<tr>
<td>DWI lesion, Open Arteries</td>
<td>10.6%</td>
</tr>
<tr>
<td>DWI lesion, Occluded Artery</td>
<td>52.6%</td>
</tr>
</tbody>
</table>

Coutts et al, Ann Neurol 2005

**The ABCD² + MRI Scale**

<table>
<thead>
<tr>
<th>Item</th>
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<tr>
<td>Age ≥ 60</td>
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<td></td>
</tr>
<tr>
<td>Unilateral weakness</td>
<td>2</td>
</tr>
<tr>
<td>Speech impairment w/o weakness</td>
<td>1</td>
</tr>
<tr>
<td>Duration of TIA</td>
<td></td>
</tr>
<tr>
<td>≥ 60 mins</td>
<td>2</td>
</tr>
<tr>
<td>10–59 mins</td>
<td>1</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1</td>
</tr>
<tr>
<td>MRI DWI lesion positive</td>
<td>1</td>
</tr>
<tr>
<td>MRA Vessel Occlusion</td>
<td>1</td>
</tr>
</tbody>
</table>
Admitting TIA Patients for 24 Hours is Cost-Effective if TPA Delivered to Early Recurers

<table>
<thead>
<tr>
<th></th>
<th>Admit for 24 H</th>
<th>Send Home</th>
</tr>
</thead>
<tbody>
<tr>
<td>24h Hospital Costs</td>
<td>$696</td>
<td>0</td>
</tr>
<tr>
<td>24h Stroke Risk</td>
<td>4.2%</td>
<td>4.2%</td>
</tr>
<tr>
<td>Rate of TPA</td>
<td>53%</td>
<td>8%</td>
</tr>
<tr>
<td>Cost saved per Rx</td>
<td>$5700</td>
<td>$5700</td>
</tr>
<tr>
<td>QALY per Treatment</td>
<td>0.564</td>
<td>0.564</td>
</tr>
</tbody>
</table>

$55,000/QALY

*Nguyen-Huynh + Johnston, Neurology 2005
*UCLA Stroke Center

Rapid Implementation of Definitive Secondary Prevention

- Underlying risk factor management: HTN, DM, Cholesterol, Tobacco, Exercise
- Carotid stenosis
  - Carotid endarterectomy / Carotid Stenting
  - Especially early revascularization in TIA
  - High early recurrence rate
  - No or minimal disturbed autoregulation
- Atrial fibrillation
  - Anticoagulation
  - Consider early initiation in TIA
  - Reduced HT risk compared with tissue infarction
- LAA or SVD
  - Antiplatelet therapies

*UCLA Stroke Center

Rapid Evaluation and Treatment of TIA Improves Outcome (EXPRESS Study)

- Prospective, population-based, Oxford
- Daily urgent TIA/minor stroke specialist clinic
  - 2002–Appointments, recommendations to PMD
  - 2004–Immediate eval w/o appt, immediate Rx

<table>
<thead>
<tr>
<th></th>
<th>Standard</th>
<th>Express</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>310</td>
<td>281</td>
</tr>
<tr>
<td>Delay to encounter (d)</td>
<td>3 (2–5)</td>
<td>1 (0–3)</td>
</tr>
<tr>
<td>Delay to prescription (d)</td>
<td>20 (8–53)</td>
<td>1 (0–3)</td>
</tr>
<tr>
<td>Stroke by 90d</td>
<td>10.3%</td>
<td>2.1%</td>
</tr>
</tbody>
</table>

(p=0.0001)

*Rothwell et al, Lancet 2007
*UCLA Stroke Center
EXPRESS: Processes of Care at 1 Month in TIA and Minor Stroke Patients

<table>
<thead>
<tr>
<th>Phase 1 (n=302)</th>
<th>Phase 2 (n=179)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>On antithrombotic or anticoagulant</td>
<td>232 (77%)</td>
<td>269 (97%)</td>
</tr>
<tr>
<td>On aspirin or clopidogrel</td>
<td>26 (8%)</td>
<td>37 (18%)</td>
</tr>
<tr>
<td>On warfarin</td>
<td>196 (65%)</td>
<td>233 (14%)</td>
</tr>
<tr>
<td>On or more blood pressure-lowering drugs</td>
<td>66 (22%)</td>
<td>23 (13%)</td>
</tr>
<tr>
<td>On or more blood pressure-lowering drugs</td>
<td>163 (48%)</td>
<td>168 (60%)</td>
</tr>
<tr>
<td>Clot in middle cerebral artery</td>
<td>14 (30%)</td>
<td>39 (78%)</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>80 (10)</td>
<td>75 (10)</td>
</tr>
</tbody>
</table>

Time to carotid surgery
- < 4 days: 15 (51%) vs 14 (49%) | ns |
- 4+ days: 1 (3%) vs 3 (6%) | ns |

Rapid Evaluation and Treatment of TIA Improves Outcome (SOS-TIA Study)
- 24/7/365 TIA clinic in Paris, 1085 patients
- Rapid standardized evaluation
  - Vascular neurologist
  - MRI (or CT)
  - Carotid duplex and TCD
  - EKG, blood work
  - As needed, outpatient echo, inpatient admission
  - Eval within 24h in 53%, 7 days in 75%
- Interventions
  - Risk factor management and antithrombotics - 100%
  - Urgent carotid revascularization - 5%
  - Anticoagulation for atrial fibrillation - 5%
  - Sent home from clinic on day of evaluation - 74%
- Stroke Rates by 90 days
  - Actual: 1.2% (CI 0.7–2.1)
  - Predicted (ABCD²): 6.0%

TIA and Hospital Admission
- Why admit
  - If early recurrence, can intervene with TPA, other rescue therapy
  - Rapidly complete etiologic work-up
  - Rapidly start etiology-targeted, secondary prevention therapies
- Who to admit
  - AHA/ASA 2009 TIA Guidelines
  - "It is reasonable to hospitalize patients with TIA if they present within 72 hours of the event and any of the following criteria are present:
    a. ABCD² score of 3 (Class IIa, Level of Evidence C).
    b. ABCD² score of 0 to 2 and uncertainty that diagnostic workup can be completed within 2 days as an outpatient (Class IIa, Level of Evidence C).
    c. ABCD² score of 0 to 2 and other evidence that indicates the patient’s event was caused by focal ischemia (Class IIa, Level of Evidence C)."
New Approaches to TIA
Key Take-Home Messages

- Tissue, not time
- High early stroke rate
- Stratify risk
  - ABCD²
  - MR DWI, Artery occlusion
- Rapid evaluation and start of 2nd prevention improves outcome

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
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
An 83 yo RH woman with sudden speech difficulty and right body weakness

Last known well @ 5:00 PM
911 call @ 7 min
Field NP study drug @ 33 min
PSC ED arrival @ 49 min
IV TPA @ 1 hr 54 min
CSC ED arrival @ 3 hr 17 min
Multimodal MRI @ 3 hr 39 min
1st Merci pass @ 4 hr 22 min
Recanalization @ 4 hr 51 min

Acute Ischemic Stroke Care in the 21st Century