Treatment of Acute Ischemic Stroke
The Risk of NOT Giving Alteplase

June 11, 2019
James A. Bobenhouse MD
Disclosures

• None
Outline

• Introduction
• Demographics of Stroke
• Definition of Stroke
• Pathophysiology of Acute Stroke
• Stroke Chain of Survival and Recovery
• BE FAST/NIHSS Scores
• IV Alteplase in Acute Stroke
• RACE Score
• Mechanical Thrombectomy
  – <6 Hours
  – 6-24 Hours
TIME IS BRAIN!

- 1.9 Million Neurons
- 14 Billion Synapses
- 7.5 Miles of Myelinated Fibers

Saver, Stroke 2006
Stroke Overview

• Stroke Incidence
  – 795,000 Strokes/Year
  – 87% Ischemic
  – 13% Hemorrhagic
    • 10% Intracerebral
    • 3% Subarachnoid

• TIA Incidence
  – 500,000

• Stroke Prevalence
  – 7,000,000 (3%)

• Silent Stroke
  – 13,000,000

• Mortality
  – 136,000/Year

• Race
  – Blacks 2X
  – Hispanic 1.5X

• Cost to Society
  – 40.9 Billion/Year

• Lifetime Cost Stroke 2019
  CPI Adjusted
  – Ischemic
    • $175,475
  – Intracerebral Hemorrhage
    • $238,320
  – SAH
    • $439,801

Taylor et al, Stroke 1996
Roger et al, Circulation 2011
• **Stroke Working Definition:**
  – Vascular Insult to the brain

• **Stroke Types**
  – Ischemic (87%)
  – Hemorrhagic (13%)
    • SAH (3%)
    • ICH (10%)

• **TIA:**
  – Transient Neurologic Deficit generally < 1 Hour (60%)

SAH Subarachnoid Hemorrhage
ICH Intracerebral Hemorrhage
TIA Transient Ischemic Attack
The Heart, Aortic Arch and Carotid Arteries

Fig. 4.33  Diagram showing potential sources for emboli reaching the cerebral circulation.
Sensory and Motor Pathways
Symptoms of Acute Stroke

Sudden Onset of:
- Weakness/Numbness
- Speech/Language Difficulty
- Vision Disturbance
- Dizziness
- Gait Disturbance/Imbalance
- Confusion
- Severe Headache
Stroke Chain of Survival and Recovery

- **Early Detection**
- **Dispatch**
- **Door**
- **Data**
- **Decision about Potential Therapy**
- **Drug Therapy**
- **Rehabilitation**
- **Home**
Early Stroke Detection

- **Balance/Leg Weakness**
- **Eye (Gaze/Vision)**
- **Facial Droop**
- **Arm Drift**
- **Speech**
- **Time to Call 911**

Aroor et al, Stroke 2017 48:479-81
Initial Acute Stroke Work-Up

- CT Brain Without Contrast
- Electrocardiogram
- Chest X-Ray
- O₂
- Hematological Studies
  - CBC, Platelet Count, PT/INR, aPTT
- Chemistry Screen
  - Serum Electrolytes, Glucose, Renal and Hepatic Chemical Analysis
- Neurological Exam/ Swallowing Screen
- National Institute of Health Stroke Scale (NIHSS)
CAT SCAN
The National Institutes of Health Stroke Scale (NIHSS)
42 Point Scale

• Level of Consciousness
  — General
  — Questions
  — Commands

• Ophthalmologic
  — Gaze Abnormality
  — Vision Loss

• Motor Weakness
  — Face
  — Arm
  — Leg

• Limb Ataxia

• Sensory Loss

• Dysarthria

• Language Impairment

• Extinction
Stroke Work-Up

- RADIOGRAPHIC STUDIES:
  - Cranial CT
  - Magnetic Resonance Imaging
Stroke Work-Up

- **VASCULAR STUDIES:**
  - Carotid Duplex
  - CT Angiogram/CT Perfusion
  - Magnetic Resonance Angiogram
  - Four Vessel Cerebral Angiogram

- **CARDIAC STUDIES:**
  - EKG
  - Echocardiogram (Transthoracic or Transesophageal)
  - Telemetry, Holter Monitor, Event Monitor
Acute Stroke Treatment Timeline

Time From Stroke Onset

0  4.5 H  6 H  24 H

IV Alteplase

Mechanical Thrombectomy with Large Vessel Occlusion

Mechanical Thrombectomy with Large Vessel Occlusion and Mismatch
Criteria for IV tPA Use

- Acute Ischemic Stroke
- < 4.5 Hours duration
- >18 years old
- NIHSS 4-22
- Persistent/Significant Symptoms
Acute Ischemic Stroke: Contraindications for the Use of IV r-tPA

- Non-compressible IV Site or LP within the Last Week
- Severe Trauma or Intracranial Surgery within the Last 2 Weeks
- GI or GU Hemorrhage in the Last 3 Weeks
- Major Stroke or Severe Head Injury in the Past 3 Months
- **Hypoglycemia**
- Acute MI
- Seizure (Unless Confirmatory Evidence of Definite Stroke)

- **Bleeding Diathesis**, INR > 1.6, PTT > 37, Platelets < 100,000,
- **Blood Pressure** > 185/110
- History of Cerebral Neoplasm, AVM, Cerebral Aneurysm, Intracranial or Subarachnoid Hemorrhage
“Pit Crew” Approach in Acute Stroke
Outcomes/Measures of Success

**Average Door-to-Needle tPA Times** (in minutes)

- **2015**: 61
- **2016**: 38

<table>
<thead>
<tr>
<th>Process</th>
<th>2015 (minutes)</th>
<th>2016 (minutes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Door to CT Ordered</td>
<td>11.52</td>
<td>3.43</td>
</tr>
<tr>
<td>Door to CT Complete</td>
<td>16.16</td>
<td>6.54</td>
</tr>
<tr>
<td>Door to CT Results</td>
<td>24.78</td>
<td>16.13</td>
</tr>
<tr>
<td>Door to Lab Drawn</td>
<td>13.63</td>
<td>11.64</td>
</tr>
<tr>
<td>Door to Lab Results</td>
<td>28.66</td>
<td>22.58</td>
</tr>
<tr>
<td>Door to EKG</td>
<td>19.94</td>
<td>17.39</td>
</tr>
</tbody>
</table>
Chances of Getting Back to Normal after IV tPA (<4.5 Hours)

**NNT** = Number Needed to Treat in Order to Help One Person with Acute Stroke get Back to Normal

**NNH** = Number Needed to Harm

11-12/100 Overall Benefit From Treatment with IV TPA

### Graph:
- **OR estimated by model**
- **95% CI for estimated OR**

- **1.5 H**
  - NNT=4-5
  - NNH=2.8 X 2
- **3 H**
  - NNT=9
  - NNH=42
  - 1.6 X
- **4.5 H**
  - NNT=14
  - NNH=20
  - 1.4 X
- **6 H**
  - NNH=14
  - 1.2 X (NS)

### References:
- Lansberg et al, Stroke 2009
- ECASS 1-3
- ATLANTIS 1-2
- NINDS 1-2
- EPITHET (7 RCTs+1)
- N=3670
### Results – Per Protocol Analysis: Other Endpoints

<table>
<thead>
<tr>
<th>Results</th>
<th>Placebo</th>
<th>tPA</th>
<th>Adjusted Relative Risk (CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>mRS 0-2 at 90 days</td>
<td>43%</td>
<td>51%</td>
<td>1.30 (1.00, 1.49)</td>
<td>0.049</td>
</tr>
<tr>
<td>mRS Shift at 90 days</td>
<td></td>
<td></td>
<td>Adjusted Common O.R. 1.43 (0.87, 2.34)</td>
<td>0.156</td>
</tr>
<tr>
<td>Early Neurological improvement</td>
<td>10%</td>
<td>25%</td>
<td>2.67 (1.41, 5.04)</td>
<td>0.002</td>
</tr>
<tr>
<td>NIHSS reduction =&gt;8 points or 0-1 at 24 hours</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reperfusion 90% at 24 hours</td>
<td>28%</td>
<td>51%</td>
<td>1.78 (1.24, 2.55)</td>
<td>0.001</td>
</tr>
<tr>
<td>Reperfusion 50% at 24 hours</td>
<td>53%</td>
<td>73%</td>
<td>1.33 (1.07, 1.64)</td>
<td>0.009</td>
</tr>
<tr>
<td>Recanalization at 24 hours</td>
<td>40%</td>
<td>70%</td>
<td>1.71 (1.31, 2.23)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

N=225  
IV tPA  113  
Placebo 112  

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Ma, H, et al NEJM 2019 380: 1795-1803
Stroke Mortality
Onset to Time to Treatment with IV TPA N=3670

For Every 15 Minutes Saved, 4% Lower Mortality

Saver et al, JAMA 2013 309:2480-2488
### IV TPA Symptomatic Hemorrhage

<table>
<thead>
<tr>
<th>N</th>
<th>tPA</th>
<th>Placebo</th>
<th>OR (95%CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>3670</td>
<td>1850</td>
<td>1820</td>
<td>5.37 (3.22-8.95)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

**PH2 Hemorrhage** 0-360 Min.

- **tPA** 5.2%/4.9%
- **Placebo** 1.0

For every 15 Minutes Saved 4% Fewer Hemorrhages

**References**

- Saver et al, JAMA 2013 309:2480-2488
- NINDS t-PA Stroke Study Group, Stroke 1997
Time to Treatment with Intravenous Alteplase and Outcome in Stroke Summary (<4.5 Hours)

• IV tPA is of Benefit up to 4.5 Hours After Onset of Acute Ischemic Stroke
• Overall, tPA increases the Chance of Returning to Normal or Near Normal by 11-12/100 but has a Risk of Serious or Fatal Hemorrhage in 5-6/100
• Earlier Treatment with IV tPA Improves the Likelihood of a Favorable Outcome
• Mortality and Symptomatic Hemorrhage Decreased by 4% With Every 15 Minutes Saved in IV tPA Treatment*
• Every 15 Minutes Saved Increases the Likelihood of Ambulation at Discharge by 4% and Home Discharge by 3%*

Lees et al, Lancet 2010 375:1695-1703
Mobile Stroke Unit

- Cost
  - Ambulance $600,000
  - CT $400,000
  - Other $100,000
  = $1,100,000
- Staffing (Paramedic, Nurse, Telemedicine Staff)
- 88% Agreement Between in Ambulance and Telemedicine TPA Decision Making
Mismatch?
What’s the Big Deal?

- CT Perfusion Imaging Mismatch
  - Cerebral Blood Flow
  - Mean Transit Time
- Clinical Core Mismatch
  - Severity of Stroke Clinically (NIHSS)
  - CT Perfusion or MRI Diffusion
- MRI Flair Diffusion Mismatch
  - MRI Flair
  - MRI Diffusion
Fantastic Five Reboot 2015

- MR CLEAN
- SWIFT PRIME
- ESCAPE
- REVASCAT
- EXTEND IA

HERMES Collaboration (N=1287)
EVT + Medical  Medical  OR

<table>
<thead>
<tr>
<th></th>
<th>EVT+Medical</th>
<th>Medical</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>mRS 0-2</td>
<td>64%</td>
<td>46%</td>
<td>2.32</td>
</tr>
<tr>
<td>Mortality</td>
<td>18.9%</td>
<td>15.3%</td>
<td></td>
</tr>
<tr>
<td>Sympt Hem</td>
<td>4.4%</td>
<td>4.2%</td>
<td></td>
</tr>
<tr>
<td>NNT=2.6</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

EVT + IV tPA vs IV tPA <6 Hours
(HERMES Collaboration)

Odds Ratio for Less Disability at 3 Months in Endovascular Thrombectomy vs. Medical Therapy Alone Groups By Time to Treatment

- 3 Hours: cOR 2.79, ARD 39.2%
- 6 Hours: cOR 1.98, ARD 30.2%
- 7.3 Hours: NS

Favors Endovascular Thrombectomy
Favors Medical Therapy Alone

Time From Symptom Onset to Expected Arterial Puncture, Minutes.

cOR = Common Odds Ratio   ARD = Absolute Risk Difference

# Large Vessel Occlusions

A Score of >5 Suggests a Large Vessel Occlusion!

## South Carolina EMS R.A.C.E. Stroke Scale

**Rapid Arterial Occlusion Evaluation Scale**

<table>
<thead>
<tr>
<th>ITEM</th>
<th>Instruction</th>
<th>Result</th>
<th>Score</th>
<th>NIHSS Equivalent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Facial Palsy</td>
<td>Ask patient to show their teeth (smile)</td>
<td>Absent (symmetrical movement)</td>
<td>0</td>
<td>0-3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mild (slight asymmetrical)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Moderate to Severe (completely asymmetrical)</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Arm Motor Function</td>
<td>Extending the arm of the patient 90° (if sitting) or 45° (if supine)</td>
<td>Normal to Mild (limb upheld more than 10 seconds)</td>
<td>0</td>
<td>0-4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Moderate (limb upheld less than 10 seconds)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Severe (patient unable to raise arm against gravity)</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Leg Motor Function</td>
<td>Extending the leg of the patient 30° (in supine)</td>
<td>Normal to Mild (limb upheld more than 5 seconds)</td>
<td>0</td>
<td>0-4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Moderate (limb upheld less than 5 seconds)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Severe (patient unable to raise leg against gravity)</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

**RACE SCALE TOTAL**

Any score above 4 is a Stroke Alert and high likelihood of an LVO


Perez de la Ossa et al. *Stroke*. 2014. 45 (1) :87-91
Solitaire Retractable Stent
Solitaire Retractable Stent
Thrombus from Solitaire Mechanical Thrombectomy

Courtesy Michael Budler MD and Jeff Himmelberg MD
EVT for Acute Ischemic Stroke 6-24 Hours
With a Large Vessel Occlusion

• Pivotal Trials
  – DAWN Trial 6-24 Hours
    • Clinical (NIHSS) – Infarct Core Mismatch
    • EVT + Medical vs Medical
    • Median NIHSS 17
    • Reperfusion 2b,3 84%
    • mRS 0-2 49% vs 13% at 90 days
    • Symptomatic Hem 6% vs 3%
    • Mortality 19% vs 18%
    • NNT = 2.8
  – DEFUSE Trial 6-16 Hours
    • EVT + Medical vs Medical
    • CTP or MRI Perfusion Diffusion Mismatch
    • Median NIHSS 16
    • Reperfusion 2b,3 76%
    • mRS 0-2 45% vs 17% at 90 Days
    • Symptomatic Hem 7% vs 4%
    • Mortality 14% vs 26%

EVT Endovascular Therapy

Questions?