Cerebrovascular Reperfusion: What Do We Have in Common?

Edward Jauch, MD MS
Disclosure Statement of Financial Interest

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

Affiliation/Financial Relationship
- Grant / Research Support
- Affiliations

Company
- NIH / NINDS: Research funding FAST-MAG DSMB
- STOP-IT Study: Novo Nordisk (drug in kind)
- PRISMS Study: Genentech
- POSITIVE Study: Covidiene, Stryker, Penumbra
- BASE Study: Ischemia Care
- Medical University of South Carolina
- American Heart Association
  - Past president, Stroke Council
  - Guidelines writing group chair
  - ACLS Stroke writing group chair
Current State of Stroke

- Growing global epidemic paralleling increase in cardiovascular disease
  - Share same risk factors
  - Similar need for reperfusion
  - A regional systems approach key to triaging patients to the level of necessary care
  - Stroke care has lagged STEMI care by decades
Phases of AMI Treatment

• Phase 1  1912 – 1961
  Bed rest, expectant treatment

• Phase 2  1961 – 1974
  Coronary care units

• Phase 3  1975 – present
  Myocardial reperfusion

• Phase 4  Future
  Reperfusion injury, regeneration
Development of Acute Stroke Treatments

400BC Hippocrates described “apoplexy”
1920s Contrast angiography developed
1950s First carotid endarterectomy performed
1960s Doppler ultrasonography developed.
1970s Development of computerized tomography (CT)
Aspirin shown to prevent stroke
1980s Development of magnetic resonance imaging
Interventional procedures more aggressive
1987 Beginning of NINDS t-PA Pilot trial
1990s Carotid endarterectomy proven to prevent stroke
## Development of Acute Stroke Treatments

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1991</td>
<td>Beginning of NINDS t-PA Stroke Trial</td>
</tr>
<tr>
<td>1993</td>
<td><em>Stroke units shown to save lives</em></td>
</tr>
<tr>
<td>1995</td>
<td>Publication of NINDS t-PA Stroke Trial(s); Start of EMS Trial</td>
</tr>
<tr>
<td>1996</td>
<td><em>FDA approval of t-PA for ischemic stroke</em></td>
</tr>
<tr>
<td>1999</td>
<td>Publication of PROACT II Trial</td>
</tr>
<tr>
<td>2000</td>
<td><em>Publication of Primary Stroke Center recommendations</em></td>
</tr>
<tr>
<td>2001</td>
<td>Start of IMS I Trial</td>
</tr>
<tr>
<td>2004</td>
<td>FDA clearance of Concentric Retriever</td>
</tr>
<tr>
<td>2005</td>
<td>Get With the Guidelines – Stroke begins</td>
</tr>
<tr>
<td>2005</td>
<td>Start of IMS III Trial</td>
</tr>
</tbody>
</table>
Development of Acute Stroke Treatments

2006  New DRGs for t-PA and thrombectomy
2007  AHA Guidelines for stroke system development
2008  *FDA approves thrombectomy device;* ECASS III
      Stroke drops from 3<sup>rd</sup> to 4<sup>th</sup> leading cause of death
2009  AHA guidelines rtPA 3-4 ½ hr window & telemedicine
2011  United Nations Summit on NCD, including stroke
      AHA guidelines for Comprehensive Stroke Centers
2012  JC develops criteria for CSC
      *Stent retrievers received FDA clearance*
2013  Large number of studies reporting neutral results
Similar Lessons to STEMI Care

- Reperfusion critical
  - Minimize delay
  - Maximize penumbral salvageability
    - Collateral flow
    - Physiologic optimization

- Time to reperfusion
  - Drives clinical outcomes
  - Affects likelihood of a trial success
  - *Should* drive all system development
Unique Features in Stroke

• Diagnostic challenge
  – No ECG, no troponin, no echo
  – Diagnosis of exclusion

• Clots vary
  – Source either embolic or *in situ* thrombotic
  – Clot size and location highly variable
  – Clot composition complex
  – Extremely tight but variable reperfusion window
  – Disability primary outcome (vs mortality)
Time Dependent Benefit of Reperfusion Therapy

IV rt-PA for Stroke

STEMI Reperfusion

Figure 3: Model estimating odds ratio for favourable outcome at 3 months in rt-PA-treated patients compared with controls by OTT

Adjusted for age, baseline glucose concentration, baseline NIHSS measurement, baseline diastolic blood pressure, previous hypertension, and interaction between age and baseline NIHSS measurement.
Time to Reperfusion: IA Treatment

Cases with angiographic reperfusion:
- <210 min
- 210-260 min
- >260 min

Cases without reperfusion

Probability of good clinical outcome

Time from symptom onset to angiographic reperfusion (minutes)

Khatri, *Stroke*. 2013
Impact of Time on Outcome

Comparison of the relative efficacies of thrombolysis in AMI and acute ischemic stroke (with endpoints of death and death and disability) per 1000 patients treated.

Current Stroke Care

- Public education
- Systems development
- Focus on EMS and Emergency Department care
- Reperfusion drives system
- Specialized hospital-based stroke care
- Early secondary prevention
- Aggressive and early rehabilitation
Stroke Systems of Care

Nonstroke Center

Primary Stroke Center

Acute Stroke Ready Hospital

Comprehensive Stroke Center

Acute Stroke Ready Hospital

Primary Stroke Center

Schwamm, Circulation. 2005;111:1078-191
Higashida, Stroke. 2013;44
Stroke Chain of Survival

- Detection: Early recognition
- Dispatch: Early EMS activation
- Delivery: Transport & management
- Door: ED triage
- Data: ED evaluation & management
- Decision: Neurology input, therapy selection
- Drug: Thrombolytic, drugs, device
- Disposition: Admission or transfer

Jauch, ACLS Stroke 2010
Door Emergent Triage Data ED Evaluation (Triad)
Current ACLS Guidelines

- Door-to-MD: 10 minutes
- Door-to-Team: 15 minutes
- Door-to-CT scan: 25 minutes
- Door-to-Drug: 60 minutes
- Door-to-Unit: 3 hours
Decision  A Team Approach
Drug(s) / Device
Recanalization Strategies

• FDA approved / cleared interventions:
  – IV tPA (0-3 hours)  Approved 1996
  – IV tPA (3-4.5 hours)  Denied request 2012
  2013 AHA Recommends
  – Thrombectomy devices  Cleared for clot removal

<table>
<thead>
<tr>
<th>Time Window</th>
<th>0-3 hrs</th>
<th>3-4.5 hrs</th>
<th>3-6 hrs</th>
<th>8 hrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Options</td>
<td>• IV tPA • Device</td>
<td>• IV tPA • Device</td>
<td>• IA Lytic • Device</td>
<td>• Device</td>
</tr>
</tbody>
</table>
Intra-arterial Strategies
Recanalization Trials

Impact of Time

Hypothetical Benefit of Cardiac Reperfusion

Intraarterial Reperfusion in Stroke

Gersh, *JAMA*. 2005;293:979-986

Clotbust, IMS I, II, PROACT II, MELT, Penumbra, Merci, MMerci, SWIFT, Trevo
The Future of Stroke Treatments

- **Prevention**
- **Stroke Systems of Care**
- **Stroke Research**
  - Stroke clinical trial networks
  - New diagnostic tools
  - Thrombolytics
  - Intra-arterial approaches
  - Combination agents
  - Refining and defining windows
  - Cerebral protection
  - Surgical
  - Rehabilitation

- Neuroimaging, markers
- ProUK, TNK, rPA, Ancrod
- IA, specialty catheters, devices
- Antiplatelets, LMWH
- Clinically, imaging based
- Hypothermia, neuroprotection
- Hemicraniectomy, cell transplant
- Constraint therapy
Penumbral Imaging

Top: ↑CBV ↑MTT with penumbra → small stroke
Bottom: ↓CBV ↑MTT → no penumbra to save → big stroke

Majda Thurnher, Medical University of Vienna
Parsons, Neurology. 2007;68:730–736
The Future: Full Integration of Care

Diagnosis and Treatment During Transport

Thrombolytic and Neuroprotective Drugs / Direct Reperfusion Strategies

Prompt Recognition 911 Activation Priority Dispatch

EMS Triage to Most Appropriate Regional Stroke Center

Advanced Brain Imaging / Diagnostic Markers

Stem cells / Nerve growth stimulants

Stroke Unit / NSICU

Thrombolytic and Neuroprotective Drugs / Direct Reperfusion Strategies

Full Recovery Prevention Strategies

Computer Assisted Therapy
Will Give $PA For Food
Lecture Overview

• Review current state of acute stroke
• Review similarities and differences in cerebrovascular and cardiovascular reperfusion
• Review other acute strategies at improving functional outcomes