Stroke Therapy: What’s Proven, What’s Not and What’s Hot

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Stroke Program
Medical City Dallas
May 20, 2008
Acute Stroke Therapy

What’s Proven
- IV tPA
- Intra-arterial thrombolysis
- Mechanical thrombectomy

What’s Not
- Acute anticoagulation
- Carotid Stenting (general population)

What’s Hot
- Anti-thrombotics
- Multimodal revascularization
- Combined neuroprotection
- Stroke Center Designation/Stroke Systems of Care

Penumbra (20-50)
Core (0-20)

Tissue Status
Perfusion Status
Vessel Status
Infarct Core versus Penumbra:
Dead Tissue versus Salvageable Tissue
Only 1 FDA approved pharmacologic treatment for acute ischemic stroke...

INTRAVENTOUS TISSUE PLASMINOGEN ACTIVATOR

IV TPA
TPA Clot-Busting Action

- Fibrinolytic agent
- Short half life
- Rapid onset
IV TPA 0.9 mg/kg over 1 hr (90 mg max.); 10% bolus over 1 minute
More patients recover with minimal or no disability with Activase® (t-PA)

### NINDS results at 3 months*

<table>
<thead>
<tr>
<th>NIH Stroke Scale</th>
<th>0-1</th>
<th>2-8</th>
<th>≥9</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activase</td>
<td>31%</td>
<td>30%</td>
<td>22%</td>
<td>17%</td>
</tr>
<tr>
<td>Placebo</td>
<td>20%</td>
<td>32%</td>
<td>27%</td>
<td>21%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Barthel index</th>
<th>95-100</th>
<th>55-90</th>
<th>0-50</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activase</td>
<td>50%</td>
<td>16%</td>
<td>17%</td>
<td>17%</td>
</tr>
<tr>
<td>Placebo</td>
<td>38%</td>
<td>23%</td>
<td>18%</td>
<td>21%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Modified Rankin</th>
<th>0-1</th>
<th>2-3</th>
<th>4-5</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activase</td>
<td>39%</td>
<td>21%</td>
<td>23%</td>
<td>17%</td>
</tr>
<tr>
<td>Placebo</td>
<td>26%</td>
<td>25%</td>
<td>27%</td>
<td>21%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Glasgow outcome</th>
<th>1</th>
<th>2</th>
<th>3-4</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activase</td>
<td>44%</td>
<td>17%</td>
<td>22%</td>
<td>17%</td>
</tr>
<tr>
<td>Placebo</td>
<td>32%</td>
<td>22%</td>
<td>25%</td>
<td>21%</td>
</tr>
</tbody>
</table>

- Minimal or no disability
- Moderate disability
- Severe disability
- Death

*Values do not total 100% because of rounding.

NIH = National Institutes of Health.

Scores of ≤1 on the NIHSS, 95 to 100 on the Barthel index, ≤1 on the modified Rankin scale, and 1 on the Glasgow outcome scale were considered to indicate a favorable outcome.

NINDS rt-PA Stroke Study Parts 1 and 2
Relation of Time to Treatment to Odds of Ratio of Favorable Outcome

Data From 622 Patients. Odds Ratio of Minimal or No Disability At 3 Months For rt-PA Compared to Placebo-Treated Patients.
Incidence of Symptomatic ICH by Protocol Adherence/ Deviations

- NINDS Trial
- Phase IV Within Protocol
- Phase IV Protocol Deviations

% ICH
Just how risky is giving TPA?

- Benefit is not offset by risk
- Mortality: 17% TPA  20% Placebo
- Overall combined death & severity disability reduced by 10% with TPA...despite increased risk of ICH
Hemorrhagic Conversion: The Dreaded Consequence

NINDS: 6.4% symptomatic ICH
3.2% fatal ICH
Angioedema

More frequent with ACEI use (5.1%)

Neurology. 2003 May 13; 60(9): 1525
Recanalization and Dramatic Recovery

TPA bolus at 09:55
end of TPA infusion

NIH Stroke Scale Scores

Recanalization and Reocclusion post IV TPA

60 pts with MCA occlusion and TCD monitoring; NIHSS 16
Timing of Recanalization on TCD After TPA bolus

Christou et al. Stroke 2000;31:1812-16
Is Intravenous TPA Enough?

- Majority of TPA-induced recanalizations occur within 60 minutes of treatment.
- Up to 30% patients re-occlude within 2 hours of TPA.
- Rescue reperfusion techniques should be considered if no flow improvement is detected or re-occlusion occurs within 60 minutes of TPA bolus.
Endovascular Thrombolysis

- Should **never** substitute for IV t-PA if patient is a candidate
- Used for patients excluded from IV t-PA either due to > 3 hour onset or risk of hemorrhage or as adjunctive therapy for patients who have clinically failed IV t-PA
- Pharmacologic
  - Intra-arterial t-PA
  - < 6 hours from onset
  - Not FDA approved
- Mechanical
  - Mechanical embolectomy devices
  - < 8 hours from onset
  - FDA approved
Acute Endovascular Rescue

![Graph showing outcomes of different treatment methods for acute ischemic stroke]

- **Recanal**: Treatment methods compared include Control, IMS, PROACT, MERCI, MultiMERCI, and Penumbra.
- **90 d mRS**: 90-day modified Rankin Scale scores for each method.
- **ICH**: Intracerebral hemorrhage rates for each treatment method.
**MERCI Trial**

- Merci Retriever, embolectomy device

- Prospective, non-randomized, multi-center trial investigating the safety and efficacy of embolectomy device to open occluded intracranial large vessels within 8 hours of stroke onset

- Primary outcome: recanalization and safety
# MERCI Neurological Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Overall</th>
<th>Recanalized</th>
<th>Not Recanal.</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 d mRS≤2</td>
<td>22.6</td>
<td>36.4</td>
<td>9.9</td>
<td>0.0002</td>
</tr>
<tr>
<td>30 d NIHSS improve &gt;10</td>
<td>34.1</td>
<td>54.0</td>
<td>15.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>90 d mRS≤2</td>
<td>27.7</td>
<td>46.0</td>
<td>10.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>90 d NIHSS improve &gt;10</td>
<td>32.4</td>
<td>50.0</td>
<td>17.5</td>
<td>0.0007</td>
</tr>
<tr>
<td>30 d mort.</td>
<td>37.1</td>
<td>23.9</td>
<td>49.3</td>
<td>0.0028</td>
</tr>
<tr>
<td>90 d mort.</td>
<td>43.5</td>
<td>31.8</td>
<td>54.2</td>
<td>0.0101</td>
</tr>
</tbody>
</table>
Multi MERCI Trial

- International, multi-center, prospective, single arm trial
- Mechanical thrombectomy of large vessel stroke within 8 hours of symptom onset
- Allowed use of IV and IA tPA
- Newer generation of device
- Primary outcome: recanalization
- Secondary outcomes: major device related complications, symptomatic ICH, clinical outcomes
MERCI & tPA

- **Recanalization**
  - Device alone 53%
  - Device/IV tPA 73%
  - Device/IA tPA 68%

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Overall</th>
<th>Recanalized</th>
<th>Not Recanalized</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favorable outcome (%)</td>
<td>36</td>
<td>49</td>
<td>9.6</td>
</tr>
<tr>
<td>90 day Mortality (%)</td>
<td>34</td>
<td>25</td>
<td>52</td>
</tr>
</tbody>
</table>

P<0.001
Penumbra Stroke Trial

- Advantages
  - Proximal working position
  - Continuous aspiration
  - Variable sizing

- Trial
  - 125 pt with proximal occlusion
  - 8 hours symptom onset
  - 81.6% revascularization
  - 3.2% procedural SAE
  - 11.2% sICH
  - 25% 90 day mRS < 2
**CLOTBUST**

Combined Lysis Of Thrombus in Brain ischemia using 2 MHz transcranial Ultrasound and Systemic TPA

<table>
<thead>
<tr>
<th></th>
<th>Ultrasound</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 Hr Complete Recanalization or Dramatic Recovery</td>
<td>49%</td>
<td>30%</td>
</tr>
<tr>
<td>3 Month Excellent Outcome (mRS 0-1)</td>
<td>42%</td>
<td>29%</td>
</tr>
</tbody>
</table>
Blood Pressure and TPA

- BP drop during thrombolysis is associated with greater DWI lesion volume and worse clinical outcome

- Every 10 mmHg SBP ↓, DWI lesion ↑ 7 cc

- Every 10 mmHg DBP ↓, DWI lesion ↑ 12 cc

- Impact of BP drop was more severe in non-recanalized patients
What’s New on the Horizon

- Use of MRI DWI/PWI mismatch to select patients with potentially salvageable penumbra
- Use of MRI to identify microhemorrhage
- Plasma biomarkers to predict hemorrhage after thrombolysis
- Alternative fibrinolytics (tenecteplase, desmotaplapse)
- Combined pharmacologic fibrino-thrombolysis
- Ultrasound-enhanced thrombolysis with microbubbles/microspheres
- Neuroprotection (so far all have failed, but we keep looking)
Acute Ischemic Stroke Studies

- DIAS—dose finding phase II trial of Desmoteplase in Acute Ischemic Stroke using MRI DWI/PWI mismatch criteria for patient selection within 3-9 hours onset (phase III ongoing)
  - Favorable outcome in 60% treated vs 22% control
  - Early reperfusion associated with favorable outcome
Acute Ischemic Stroke Studies

- **EPITHET:**
  - IV t-PA versus placebo
  - 3-6 hour time window; MR Diffusion/Perfusion
  - Non-significant trend to reduced infarct growth with t-PA
  - Significant increase in reperfusion with t-PA
  - Warrants further study

- **CLEAR:**
  - Eptifibatide (GP IIb/IIIa antagonist) plus 0.3 mg/kg IV t-PA versus 0.9 mg/kg IV tPA
  - 3 hour time window
  - 94 pt
  - sICH: 1.4% combo 8% t-PA
  - Non-significant trend to improved outcome with standard IV t-PA
  - No safety concerns

- Abest II—safety trial of abciximab in acute stroke terminated early for safety reasons
## Statin Withdrawal and Acute Ischemic Stroke

<table>
<thead>
<tr>
<th></th>
<th>Statin Withdrawn</th>
<th>Statin Continued</th>
<th>Statin Naive</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early Neuro Deterioration</td>
<td>65%</td>
<td>21%</td>
<td>27.8%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Infarct volume</td>
<td>74</td>
<td>26</td>
<td>53</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Poor 3 month outcome</td>
<td>60%</td>
<td>39%</td>
<td>42.1%</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Neurology. 2007 Aug 28; 69(9): 904
What’s Not Proven in Acute Stroke...

HEPARIN!!!!!!
Heparinoids for Ischemic Stroke

TOAST = Trial of ORG 10172 in Acute Stroke Treatment
HAEST = Heparin in Acute Embolic Stroke Trial
TAIST = Tinzaparin in Acute Ischemic Stroke

## Summary of Heparin/LMWH Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Drug</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canadian</td>
<td>225</td>
<td>Heparin IV</td>
<td>No Benefit</td>
</tr>
<tr>
<td>IST</td>
<td>19435</td>
<td>Heparin SQ</td>
<td>No Benefit</td>
</tr>
<tr>
<td>TOAST</td>
<td>1281</td>
<td>Heparinoid</td>
<td>No Benefit</td>
</tr>
<tr>
<td>HK</td>
<td>308</td>
<td>LMWH</td>
<td>↓ Death/Dependence at 6 months</td>
</tr>
<tr>
<td>FISS</td>
<td>767</td>
<td>LMWH</td>
<td>No Benefit</td>
</tr>
<tr>
<td>FISS-tris</td>
<td>599</td>
<td>LMWH</td>
<td>No Benefit</td>
</tr>
<tr>
<td>TAIST</td>
<td>1486</td>
<td>LMWH</td>
<td>No Benefit</td>
</tr>
<tr>
<td>TOPAS</td>
<td>404</td>
<td>LMWH</td>
<td>No difference among doses</td>
</tr>
</tbody>
</table>
# Hazards of Early Anticoagulation: Intracranial Hemorrhage

<table>
<thead>
<tr>
<th></th>
<th>High Dose</th>
<th>Low Dose</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>IST</td>
<td>1.8%</td>
<td>0.7%</td>
<td>0.4%</td>
</tr>
<tr>
<td>HK</td>
<td>0%</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>TOAST</td>
<td>2.2% *</td>
<td></td>
<td>0.6%</td>
</tr>
<tr>
<td>FISS</td>
<td>6.1% *</td>
<td>3.7%</td>
<td>2.8%</td>
</tr>
<tr>
<td>TAIST</td>
<td>1.4%</td>
<td>0.6%</td>
<td>0.2%</td>
</tr>
</tbody>
</table>
Anticoagulants in Acute Ischemic Stroke: Summary of RCTS

- In stroke patients, heparin or heparin like drugs at any dose do not produce any consistent benefit in:
  - Stroke progression
  - Early recurrence
  - Long-term outcome
- Low dose heparin reduces the incidence of DVT and PE without increasing the incidence of ICH
Secondary Stroke Prevention of Ischemic Stroke

What is the cause of the initial cerebrovascular event?

- Large-or small-vessel atherosclerosis
- Unknown
- Cardioembolic

Antiplatelet therapy

Warfarin

Aspirin in Stroke Prevention

- Proven first-line therapy

- Clinical trials do not support a dose-response effect above 75 mg qd

- Concern regarding “aspirin resistance” and “treatment failures”

- 30%-40% of patients admitted with an ischemic stroke are taking aspirin at the time of their stroke

- Aspirin is used increasingly in combination therapy
Efficacy of Aspirin at Various Doses in Reducing Vascular Events* in High-Risk Patients

<table>
<thead>
<tr>
<th>Daily Aspirin Dose</th>
<th>No. of Trials</th>
<th>Odds Reduction (%)</th>
<th>Odds Ratio (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>500 mg–1,500 mg</td>
<td>34</td>
<td>19</td>
<td>Antiplatelet</td>
</tr>
<tr>
<td>160 mg–325 mg</td>
<td>19</td>
<td>26</td>
<td>Control</td>
</tr>
<tr>
<td>75 mg–150 mg</td>
<td>12</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td>&lt;75 mg</td>
<td>3</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Any aspirin</td>
<td>65</td>
<td>23</td>
<td></td>
</tr>
</tbody>
</table>

*Vascular events included nonfatal MI, nonfatal stroke, and death from vascular causes.

CI, confidence interval. Treatment effect P<.0001.

Is Blocking Two Pathways Better Than Blocking One?

- European Stroke Prevention Study 2 (ESPS–2): aspirin/extended release dipyridamole combination effective in stroke

- Clopidogrel Studies
  - CAPRIE
  - MATCH
  - CHARISMA
Aspirin/Extended Release Dipyridamole

- ASA/ER DP has 20-23% RRR over aspirin alone (ESPS 2, ESPRIT)
- ASA/ER DP has 3% ARR over aspirin alone
- No increased bleeding
- Main side effect is headache
- HA may be prevented by pre-medication with acetaminophen
- Pleiotropic effects
Clopidogrel

- Clopidogrel, either alone or in combo with aspirin, has never shown a statistical benefit over aspirin in preventing stroke (nonsignificant 0.5% ARR of clopidogrel over aspirin)—3 large trials
- Combination of aspirin and clopidogrel doubles the risk of life threatening bleeding
- Reserved for patients with aspirin allergy, concomitant CAD/PVD or stents
- Cardiac indication is only for 1 year
Indirect Comparison of Stroke Prevention Therapy
Endpoint = Stroke

<table>
<thead>
<tr>
<th>Therapy (vs ASA)</th>
<th>NNT</th>
<th>Mean follow-up time years</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASA/ER-DP</td>
<td>33</td>
<td>2</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>121</td>
<td>1.91</td>
</tr>
<tr>
<td>Ticlopidine</td>
<td>40</td>
<td>3</td>
</tr>
</tbody>
</table>

Gorelick P. *Stroke* 2002;33:862-875
<table>
<thead>
<tr>
<th>Aggrenox &amp; Micardis</th>
<th>Plavix &amp; Micardis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aggrenox &amp; Placebo</td>
<td>Plavix &amp; Placebo</td>
</tr>
</tbody>
</table>
PRoFESS Results

- Stroke
- Stroke/MI/Death
- ICH
- Ischemic
- Benefit-risk Ratio

**Aggrenox**

**Plavix**
Antiplatelet Guidelines for Stroke Prevention

- Acceptable options for initial therapy:
  - Aspirin (50 mg qd–325 mg qd)
  - Aspirin (25 mg bid) + extended-release dipyridamole (200 mg bid)
  - Clopidogrel (75 mg qd)

- Recommendations above do not apply to those at risk of cardioembolic stroke
Combination of aspirin and extended release dipyridamole is suggested instead of aspirin alone.

Addition of aspirin to clopidogrel increases the risk of hemorrhage & is not routinely recommended.

No evidence that increased aspirin dose is effective.

For patients allergic to aspirin the guidelines recommend clopidogrel.
Carotid Stenting: an Emerging Option

PRE

POST

R CAROTID

L CAROTID

PRE

POST
Stenting and Angioplasty With Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) Trial

- High-risk patients (CHF, recent MI, or unstable angina)
- Symptomatic carotid disease with at least 50% stenosis or asymptomatic carotid stenosis of at least 80%

- 30-day periprocedural stroke/MI/death rate:
  - 5.8% for carotid angioplasty stenting
  - 12.6% for endarterectomy

Primary Endpoint: Composite of death/stroke/MI at 30 days or ipsilateral stroke within 1 year
Ongoing Stent vs CEA Trials

- **CREST—United States**
  - 2500 patients
  - ACCULINK™ carotid stent system, ACCUNET™ embolic protection device

- **CAVATAS II—United Kingdom**
  - 2000 patients
  - No protection device required

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*Carotid Revascularization Endarterectomy versus Stenting Trial (CREST).
†Carotid And Vertebral Artery Transluminal Angioplasty Study 2 (CAVATAS II).

SPARCL: Stroke Prevention by Aggressive Reduction in Cholesterol Levels

- Double blind, randomized, placebo-controlled
- Stroke/TIA patients (< 6 months) with LDL 100-190 mg/dL
- Atorvastatin 80 mg/d versus placebo
- 5 yr ARR Fatal/Nonfatal stroke: 2.2%, \( p=0.03 \)
- No difference in mortality
Stroke Reduction with Ideal Implementation of Therapies

In patients with history of stroke/TIA, total strokes prevented 221,420/yr (80% of total)

Impetus for Stroke Centers

- **Mandate:** Texas Stroke Legislation (SB 330 & HB 2344)
- **Definition:** Brain Attack Coalition Recommendations for Primary Stroke Centers
- **Implementation:** American Stroke Association Get With The Guidelines—Stroke (clinical practice guidelines)
- **Certification:** Primary Stroke Center certification by Joint Commission
Bridging the Gap Between Efficacy and Effectiveness

Efficacy

• Outcomes associated with an intervention under ideal circumstances
  – Clinical trial reported in literature
  – Guidelines

Effectiveness

• Outcomes associated with an intervention in the real world
  – Hospital
  – Outpatient
  – Across Continuum

Systems to Translate Efficacy → Effectiveness
Implement Guidelines HERE

- Healthy Population
- Undiagnosed or Untreated
- In Treatment
- Acute Event
- Post Event
Stroke Units

Systematic review of 19 RCT of stroke unit care:

- Improved functional outcome
- Increased discharge to home
- Decreased mortality
- Reduced LOS
- Improved 10 year survival- (the “pixie dust” of stroke unit care)


Joint Commission: Performance Measures

- Deep Vein Thrombosis Prophylaxis
- Discharged on Antithrombotic Therapy
- Patients with Atrial Fibrillation Receiving Anticoagulation Therapy
- Thrombolytic Administered
- Antithrombotic Therapy by End of HD2
- Discharged on Cholesterol Reducing Medication
- Dysphagia Screening
- Stroke Education
- Smoking Cessation Advice/Counseling
- Assessed for Rehabilitation
Medical City Stroke Initiative

- **ED Acute Stroke Protocol**
- **Stroke Units**
  - NVICU
  - 5 South
- **Written Care Protocols**
  - Admission Orders
  - Stroke Care Pathway
- **Staff Education**
  - Formal seminars
  - Stroke rounds
  - Healthstream courses
- **Patient Education**
  - Education binder
  - Patient Satisfaction survey
Summary

There are acute stroke treatments that have proven efficacy for improving outcome.

There are effective preventive strategies to reduce secondary stroke.

We must implement these through organized systems of stroke care.