Intracranial Intervention and Acute Stroke Therapies

Philip M. Meyers, M.D.
Associate Professor, Radiology and Neurological Surgery
Columbia University, College of Physicians & Surgeons
Clinical Director, Neuroendovascular Service

THE NEUROLOGICAL INSTITUTE OF NEW YORK

COLUMBIA UNIVERSITY MEDICAL CENTER

NewYork-Presbyterian
The University Hospitals of Columbia and Cornell
Disclosure Statement of Financial Interest

I, Philip Meyers, DO NOT have a financial interest/arrangement or affiliation with one or more organizations that could be perceived as a real or apparent conflict of interest in the context of the subject of this presentation.
Survey Topics

- Cerebral Aneurysms
- Brain Arteriovenous Malformation
- Acute Ischemic Stroke
- Intracranial Revascularization
Hemorrhagic Stroke Aneurysm

- 1/3 of strokes age < 65\(^1\)
- 5-15\% of stroke overall\(^2\)
- 30-day mortality rate
  - 45\% 1\(^{st}\) rupture
  - 83\% 2\(^{nd}\)\(^4\)
- 50\% irreversible brain damage\(^3\)
- Rupture risk is LOW: 0.05-1\% for small aneurysms

\(^{1}\) Johnston Neurology 52: 1799-1805, 1999
\(^{2}\) Bederson Circulation 102: 2300-08, 2000
Hemorrhagic Stroke Aneurysm

- Surgical series
  - 0-6% mortality
  - 0-30% morbidity
- NY discharge data
  - 1987-1993
  - 4.6-8.1% mortality

1 Johnston Neurology 52: 1799-1805, 1999
2 Bederson Circulation 102: 2300-08, 2000
Endovascular Occlusion
International Subarachnoid Aneurysm Trial (ISAT)

Risk Analysis Coil vs. Clip, N=2143

- Relative reduction: 23.9%
- Absolute reduction: 7.4% \( p=0.00082 \)
- Point estimate: 0.76 (CI 0.64-.89)
- Equivalency: 76 pts/1000 treated

Significant disparity at 1 yr

Lancet 360: 1267-1274, 2002
ISAT

2002  2005

- Relative risk reduction: 23.9%  26.8%
- Absolute risk reduction: 7.4%  7.4%

Clip  Coil

- Death or disability @ 1 yr: 32.1%  23.4%
- Death or disability @ 1 yr: 30.9%  23.5% up to 7 yrs

Lancet 266: 809-17, 2005
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ISAT

- Follow up: 9 yrs, range 6-14 yrs
- 24 recurrent hemorrhage
  - Treated aneurysm: 13 patients (10 coil, 3 clip, $p=0.06$)
  - Pre-existing aneurysm: 4 patients
  - New aneurysm: 6 patients
- Risk of death remains lower in coil group, $p=0.03$
Size matters

All aneurysms, NY State, 1995-2000
By hospital volume

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Low</th>
<th>High</th>
<th>Improved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse outcome</td>
<td>15%</td>
<td>6.6%</td>
<td>16%</td>
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<tr>
<td>In hospital death</td>
<td>3.3%</td>
<td>1.5%</td>
<td>11%</td>
</tr>
</tbody>
</table>

Stroke 34: 2200-7. 2003
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Arteriovenous Malformation

Vein

Draining vein

Artery

AVM

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The University Hospital of Columbia and Cornell
Pial Arteriovenous Malformation

- **Prevalence**
  - $1.1-19/100000/yr$

- **Presentation**
  - 33 yrs mean age
  - 64% by age 40

- **Presentation**
  - Hemorrhage: >50%
  - Seizures: 20-25%
  - Headache (15%)
  - focal deficit/tinnitus (<5%)
AVM Hemorrhage

- **M&M**
  - 10% mortality
  - 30-50% morbidity
- **Location**
  - Parenchymal, 82%
  - Subarachnoid
  - Subdural
- **Risk** = 105 - (age in years)
- **Treatment**
  - Surgery
  - Embolization
  - Radiosurgery

**References**

Brown Neurosurg 46: 1024, 2000
Kondziolka Neurosurg 37: 851, 1995
Fults Neurosurg 15: 658, 1884
Forster J Neurosurg 37: 562, 1972
Effect of Clinical, and Morphological Variables on Follow-up AVM Hemorrhage (n=622)

Hemorrhage Rate per Year

- No Risk Factors: 0.9%
- Deep Drainage: 2.4%
- Deep Location: 3.1%
- Hem at Presentation: 4.5%
- Hem at Presentation + Deep Location + Deep Drainage: 34.4%

Lancet 1997; 350:1065 - 1068

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<table>
<thead>
<tr>
<th>Variable</th>
<th>HR</th>
<th>Attributable Risk</th>
<th>P</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>1.05</td>
<td></td>
<td>&lt;0.0001</td>
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<tr>
<td>Female gender</td>
<td>0.64</td>
<td>47.4%</td>
<td>0.21</td>
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<tr>
<td>Hemorrhagic presentation</td>
<td>5.38</td>
<td>9.4%</td>
<td>&lt;0.0001</td>
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<tr>
<td>Deep brain location</td>
<td>3.25</td>
<td></td>
<td>0.01</td>
</tr>
<tr>
<td>AVM size (mm)</td>
<td>0.99</td>
<td>13.9%</td>
<td>0.34</td>
</tr>
<tr>
<td>Deep drainage only</td>
<td>2.39</td>
<td></td>
<td>0.04</td>
</tr>
<tr>
<td>Associated aneurysms</td>
<td>1.62</td>
<td></td>
<td>0.17</td>
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</table>
Acute Ischemic Stroke
Pre-treatment Imaging
Commonly still CT based

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Viability Imaging – Role Undefined

Computed Tomography

Magnetic Resonance
Intravenous Thrombolysis (t-PA)

- Treatment window 0-3 hours post ictus
- NINDS showed 30% increase of favorable outcome at 90 days versus placebo
- Limited efficacy:
  - IV t-PA opens 30 – 50% of major occluded intracranial vessels within 1 – 2 hours*
- The ONLY Class I Evidence for acute stroke treatment - FDA Approved


Stroke rtPA Study. NEJM. 333:1581-7, 1995
ECASS-III
European Cooperative Acute Stroke Study

- 821 patients
  - 418 rt-PA
  - 403 placebo
- Median time to treat: 3 hr 59 min
- Favorable outcome: 52% vs. 42%, P<.05
- Hemorrhage Rate: 27% vs. 18%, P=.001
- Mortality: 7.7 vs. 8.4%, P=0.68

Recanalization Rates: IV tPA ≤ 8 hrs

- M3,4: 40
- M2: 35
- M1: 26
- ICA: 8

del Zoppo Ann Neurol 32: 78, 1992
## ProACT II
Prolyse in Acute Cerebral Thromboembolism

<table>
<thead>
<tr>
<th></th>
<th>rPro-UK</th>
<th>Control</th>
<th>(P)</th>
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<tbody>
<tr>
<td>90 Day Good/Excellent Outcome:</td>
<td>40%</td>
<td>25%</td>
<td>0.04</td>
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<tr>
<td>Recanalization:</td>
<td>66%</td>
<td>18%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mortality (90 day):</td>
<td>25%</td>
<td>27%</td>
<td></td>
</tr>
<tr>
<td>Symptomatic Cerebral Hemorrhage &lt;24 hrs:</td>
<td>10%</td>
<td>2%</td>
<td>0.06</td>
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</table>
PROACT II Summary

- Provides **proof of principle** in a worst-case scenario:
  - Late *time* to treatment (5.3 hours)
  - Limited manipulation, no mechanical maceration of clot
  - Patient selection, NIHSS=17
  - **NOT** Class I Evidence – **NOT** FDA approved.
Bridging Protocols: Outcome Percent mRS ≤ 2 vs. Time

Lewandowski Stroke 30: 2598, 1999
IMS Investigators. Stroke 35: 904, 2004
Kathri P Stroke 39: 560, 2008
Concentric Merci Trial
Mechanical Thrombectomy
Concentric Merci Trial
Mechanical Thrombectomy
Multi MERCI Clinical Outcomes

- **Good Outcome**
  - Recanalized: 49.1%
  - Not Recanalized: 9.6%
  - *p* < 0.001

- **Mortality (90 day)**
  - Recanalized: 24.8%
  - Not Recanalized: 51.9%
  - *p* < 0.001

Smith ISC 2007, San Francisco

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13 year old boy s/p Fontan Procedure
Futile Revascularization

• Recanalization correlate with favorable neurological outcomes in several studies BUT
• Risk of death following stroke remains stable despite revascularization
• “Futile recanalization” – up to 36%!
• Patient selection remains limited
<table>
<thead>
<tr>
<th>Study</th>
<th>NIHSS</th>
<th>% Recanalization, TIMI 2-3</th>
<th>% mRS 0-2 @ 90 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROACT I</td>
<td>17</td>
<td>58%</td>
<td>-</td>
</tr>
<tr>
<td>PROACT II</td>
<td>17</td>
<td>66</td>
<td>40</td>
</tr>
<tr>
<td>IMS I</td>
<td>18</td>
<td>56</td>
<td>43</td>
</tr>
<tr>
<td>IMS II</td>
<td>19</td>
<td>60</td>
<td>46</td>
</tr>
<tr>
<td>MERCI</td>
<td>22</td>
<td>46</td>
<td>28</td>
</tr>
<tr>
<td>Multi MERCI</td>
<td>19</td>
<td>68</td>
<td>36</td>
</tr>
<tr>
<td>Penumbra</td>
<td>18</td>
<td>82</td>
<td>25</td>
</tr>
<tr>
<td>PROACT II Control</td>
<td>17</td>
<td>18</td>
<td>25</td>
</tr>
<tr>
<td>NINDS IV rtPA</td>
<td>18</td>
<td>-</td>
<td>28</td>
</tr>
<tr>
<td>NINDS placebo</td>
<td>18</td>
<td>-</td>
<td>39</td>
</tr>
</tbody>
</table>
# Mortality and ICH

<table>
<thead>
<tr>
<th>Study</th>
<th>% Mortality @ 90 days</th>
<th>% Symptomatic ICH</th>
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<tbody>
<tr>
<td>PROACT I</td>
<td>27</td>
<td>15</td>
</tr>
<tr>
<td>PROACT II</td>
<td>25</td>
<td>10</td>
</tr>
<tr>
<td>IMS I</td>
<td>16</td>
<td>6</td>
</tr>
<tr>
<td>IMS II</td>
<td>16</td>
<td>10</td>
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<tr>
<td>MERCI</td>
<td>44</td>
<td>8</td>
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<tr>
<td>Multi MERCI</td>
<td>34</td>
<td>10</td>
</tr>
<tr>
<td>Penumbra</td>
<td>33</td>
<td>11</td>
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<tr>
<td>PROACT I</td>
<td>43</td>
<td>7</td>
</tr>
<tr>
<td>PROACT II Control</td>
<td>27</td>
<td>2</td>
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<tr>
<td>NINDS IV rtPA</td>
<td>24</td>
<td>1</td>
</tr>
<tr>
<td>NINDS placebo</td>
<td>21</td>
<td>7</td>
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Intracranial Atherosclerosis
Ischemic Stroke Subtypes
Northern Manhattan

- Cryptogenic: 43%
- Lacunar: 19%
- Atherosclerotic (Intracranial): 6%
- Atherosclerotic (Extracranial): 7%
- Cardioembolic: 21%
- Other: 4%

Boden-Albala Neurology 1999;52:A557
Ischemic Stroke Subtypes
Improved Imaging

- Cryptogenic: 39%
- Cardioembolic: 21%
- Lacunar: 19%
- Atherosclerotic (Intracranial): 11%
- Atherosclerotic (Extracranial): 7%
- Other: 3%
Risk Factors

- In general, IA is part of diffuse disease process
- Populations most at risk
  - Asian (Japanese, Chinese, Korean) \(^1\)
  - African-American \(^2\)
  - Hispanics \(^3\)
- Other risk factors
  - Diabetes mellitus, hypercholesterolemia
  - Hypertension, smoking

\(^1\) Caplan Stroke 17: 648-655, 1986
\(^3\) Sacco Stroke 26:14-20, 1995
Degree of Stenosis

Kasner. Circulation 2006;113:555-563
Intracranial Atherosclerosis: Therapeutic Options

- **Medical Therapy**
  - Anti-platelet therapy > anti-coagulant therapy
  - Statins
  - ACE inhibitors
- **Bypass Surgery** – largely discredited
- **Endovascular Revascularization**
  - Angioplasty – effective but high recurrence
  - Stent Angioplasty – HDE devices but unreimbursed
Identification of patients for stent-angioplasty

- Symptomatic disease
- Stroke syndrome must correlate with imaging
- Alternative diagnoses, e.g. inflammatory, neoplastic, metabolic diseases
- Perfusion failure vs. arterio-arterial embolization
- Large vessel disease vs. perforator ischemia
Mild Vessel Dilatation
Wingspan Registry

- Periprocedural M&M: 12.8%
  - Major Stroke or Death: 6.4%
  - Minor complications: 6.4%
- 34.2% (13) had new DWI+ ischemic lesions
- 23% of new strokes were severe
- 30% restenosis at 6 mo. mean F/U
- 9.5% occlusion at 6 mo. mean F/U

SAMMPRIS
Stenting and Aggressive Medical Management for Preventing Recurrent stroke in Intracranial Stenosis

- Stenting vs. intensive medical care
- 764 patients 1:1 random, 50 US Centers
- Intracranial stenosis 70-99%
- TIA or stroke within 30 days
- 2 yr average follow-up
- Primary hypothesis: 35% stroke or death with stenting in 2 yrs
SAMMPRIS Enrollment
Stenting and Aggressive Medical Management for Preventing Recurrent stroke in Intracranial Stenosis

Target = 764 Patients

Courtesy of Colin Derdeyn, PI
Neurointervention

- Aneurysms – especially for SAH
- AVM – pre-operative adjunct
- Acute Ischemic Stroke – when IV thrombolysis is contra-indicated
- Intracranial atherosclerosis
  - HDE for symptomatic patients refractory to medical therapy
  - SAMMPRIS

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