Evolving Treatment of Acute Ischemic Stroke

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Financial Disclosures

• IMS III – P.I., co-investigator MR Rescue
  – Receive drug from Genentech and devices from Concentric, EKOS, and Johnson & Johnson.
Take Away Points

• Chronologic and physiologic time are critical for any acute stroke therapy.
• Combination of drugs and/or devices is part of new paradigm which continues to undergo testing.
Take Away Points

• Device that opens arteries ≠ device that improves stroke outcome. This is because the positive effect of opening arteries is time-dependent as well dependent upon safety of approach.

• We don’t know which approach to recanalization is most efficacious – therefore we need randomized trials
Lessons from Cardiology

• No specific thrombolytic agent, including newer generation molecules such as tenecteplase (TNK), desmoteplase, etc., has shown any improvement in clinical outcome as compared to rt-PA alone in subjects with myocardial infarction.

• Studies for acute stroke: TNK (recently halted) and Desmoteplase (negative)
Lessons from Cardiology

• A combination of lower dose thrombolytic and moderate dose of glycoprotein (GP) IIb/IIIa platelet receptor blocker has been demonstrated to open arteries more quickly than full dose thrombolytic alone, but overall mortality was similar.
Lessons from Cardiology

• Combination therapy – mechanical devices + medications – open up arteries more quickly and improve outcome.

• But pathophysiology of acute MI has substantial differences from ischemic stroke
MCA Reperfusion in the Primate

Crowell, 1981.
“Time is Brain in IV t-PA Trials”

• “Time is brain” based on time from stroke symptom onset to INITIATION of IV rt-PA

Hacke, Lancet, 2004;
Thrombolysis with Alteplase 3 to 4.5 Hours after Acute Ischemic Stroke

Werner Hacke, M.D., Markku Kaste, M.D., Erich Bluhmki, Ph.D., Miroslav Brozman, M.D., Antoni Dávalos, M.D., Donata Guidetti, M.D., Vincent Larrue, M.D., Kennedy R. Lees, M.D., Zakaria Medeghri, M.D., Thomas Machnig, M.D., Dietmar Schneider, M.D., Rüdiger von Kummer, M.D., Nils Wahlgren, M.D., and Danilo Toni, M.D., for the ECASS Investigators*
Current Reality from Thrombolytic Stroke Trials

• IV rt-PA alone is an effective therapy – ASA Guidelines include treatment out to 4 ½ hours

• Angiographic recanalization rates at one hour in the pilot trials of IV rt-PA was only about 25-30% for M1 occlusions and 10% for ICA occlusions, with over two-thirds of recanalization being only partial reperfusion (TIMI 2).

• Higher rates of recanalization have been reported using TCD/MRA at 2-3 hours after treatment (Approximately 40% for M1)
Potential Limitations of t-PA

- Reperfusion is dependent upon available substrate and time to lyse clot
- Stimulates platelet activation
- May not be as effective with older clots
- Hemorrhagic transformation
First Intra-arterial Trial of Lytic: PROACT II

- 181 subjects with M-1 or M-2 occlusions were randomized within 6 hours of symptom onset to receive 9 mg of pro-urokinase plus heparin (low-dose) (n=121) versus placebo plus low-dose heparin (n=59).
- 40% of pro-urokinase group had a Rankin of 0-2 (mild or no significant disability) at 3 months compared to 25% of control patients (p = 0.04).
- Median time to treatment was > 5 hours.

Combination Approaches Under Study for Stroke

- IV t-PA plus other IV medications (anti-platelet or anti-thrombotic – e.g. argatroban)
- IV t-PA plus hypothermia
- IV t-PA plus ultrasound energy
- Other IV or IA lytics plus other therapies
- Mechanical Devices +/- thrombolytics/other medications
The CLEARERER Dosing

- **rt-PA**
  - 0.6 mg/kg (10% bolus, 40 min infusion)
  - This is “standard for 40 min”
  - Feasible – IMS III
  - Maintains Optimal Lytic Concentration
  - Standard of Care in Japan
The CLEARER Dosing

- **Eptifibatide**
  - 135 mcg/kg bolus
  - 0.75 mcg/kg/min infusion for 2 hours
  - 36% increase over CLEAR (front loaded)
  - Achieve/Maintain ≥50% plt inhibition
Potential Importance of Knowing Safety of Eptifibatide

- As we will discuss, stents are being tested as a potential device for acute stroke. If you leave a stent in place, it provides a major thrombogenic surface (in setting of acute stroke) that may require anti-platelet drugs for longer period (with associated additional risk).
Era of Devices
Device vs. Drug Approvals
Merci® Retriever – FDA 510(K) Approval - 2004

- Intended to restore blood flow...by removing thrombus in patients experiencing ischemic stroke.
- Patients who are ineligible for ... or who fail IV t-PA therapy are candidates for treatment.
- Also indicated for use in the retrieval of foreign bodies misplaced during interventional radiological procedures.

The Penumbra Aspiration System: FDA 510 (K) Approval in 2008

System Components

- **Reperfusion Catheter**
  - Optimized design for efficient navigation and aspiration

- **Separator**
  - Operator controlled movement cleans and clears Reperfusion Catheter enabling continuous aspiration.

- **Thrombus Removal Ring**
  - If thrombus remains after aspiration, the Ring is designed to capture calcified, hard clot

McDougall, ISC, 2008.
Recanalization and Clinical Outcome: A common viewpoint

– Recanalization = Good Outcome (PROACT II – only randomized endovascular trial where two are linked)

– Device that opens arteries better than medical therapy (historically) = Device that is effective in opening arteries = Device that is effective for acute ischemic stroke

– Higher Recanalization Rate = Clinically More Effective Therapy
Related Trial Comparisons*
Revascularization

Penumbra Pivotal (N=125)
Merci 2 (N=141)
Multi Merci (N=111)
PROACT II (N=121)
Clotbust (N=63)

Revascularization Rate


* Population observation rates, and 95% Exact Binomial Confidence Intervals
Related Trial Comparisons*

mRS ≤ 2 at 90 Days

- Penumbra Pivotal (N=120)
- Merci 2 (N=130)¹
- Multi Merci (N=108)²
- PROACT II (N=121)³
- Clotbust (N=63)⁴

Proportion of Patients with mRS ≤ 2 at 90 Days


*Population observation rates, and 95% Exact Binomial Confidence Intervals
“Time is Brain in IV t-PA Trials”

- “Time is brain” based on time from stroke symptom onset to INITIATION of IV rt-PA

- BUT how does this time window relate to the actual restoration of blood flow?

Good Clinical Outcome over Time after Technically Successful Reperfusion

Cases with Reperfusion (p=0.02)

95% Prediction Bands

Cases without Reperfusion

Khatri, ISC, 2008.
Timing Is Critical

Cases with Reperfusion (p=0.02)

30 minutes=10%!

95% Prediction Bands

Cases without Reperfusion

Neurology, in press.
Recanalization = Good Clinical Outcome: Problems with That Belief

– Recanalizers may be different than non-recanalizers and those differences may affect outcome (collaterals, age, site of occlusion, etc.)
– Nonrecanalizers can be harmed by an intervention(s) – “piling on” therapies
– The limitations of historical comparisons with PROACT II and NINDS Trials
  • Role of medical comorbidities for comparisons
  • Medical management in that time period
  • Changes in earlier use of DNR
MERCI/Penumbra: What We Know

- Both open arteries better than PROACT II historical controls
- Patients with recanalization have better clinical outcomes than those without recanalization within the study
- Similar rate of sICH as other treatments
- Mortality is higher (but confounding factor of stroke severity)
MERCI/Penumbra: What We Don’t Know

• Is it efficacious?
  – As adjunct to IV t-PA within 3 hours?
    • IMS III:* Large (n=900) randomized trial of severe strokes (NIHSS≥10) within 3 hours
    • IV r-tPA versus combined IV + IA approach (more rt-PA via standard cath/EKOS) or clot removal via Retriever/Penumbra (additional IA t-PA allowed)
  – Beyond 3 hours?
    • MR-Rescue:* Phase II trial
    • Med mgmt versus IA or combined approach – mostly beyond 3 hours
    • POC trial of MRI mismatch – now includes CT mismatch as well
Advantages of Combined IV/IA Approach

• IV t-PA is started ASAP no matter where the patient is initially evaluated.
• Patients can be referred for interventional approaches, if appropriate.
The Combined IV/IA Approach to Recanalization

- EMS Study – Completed 1994-95
- IMS I Study – Completed 2001*
- IMS II Study – Completed 2005*
- IMS II-b Study – Completed 2006*
### IV/IA Experience – Flaherty et al

**Stroke 2004**

<table>
<thead>
<tr>
<th></th>
<th>Current Series</th>
<th>IMS Study</th>
<th>EMS Trial*</th>
<th>NINDS rt-PA (NIHSS&gt;10, age ≤ 80)</th>
<th>NINDS Placebo (NIHSS&gt;10, age ≤ 80)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients</strong></td>
<td>62</td>
<td>54</td>
<td>80</td>
<td>17</td>
<td>182</td>
</tr>
<tr>
<td><strong>Median NIHSSS#</strong></td>
<td>18</td>
<td>18</td>
<td>18</td>
<td>16</td>
<td>17</td>
</tr>
<tr>
<td><strong>3 mo mRS 0-2 (%)</strong></td>
<td>31 (50)</td>
<td>29 (54)</td>
<td>34 (43)</td>
<td>8 (47)</td>
<td>71 (39)</td>
</tr>
<tr>
<td><strong>SICH (%)</strong></td>
<td>5 (8)</td>
<td>3 (6)</td>
<td>5 (6)</td>
<td>2 (12)</td>
<td>13 (7)</td>
</tr>
<tr>
<td><strong>Mortality (%)</strong></td>
<td>11 (18)</td>
<td>6 (11)</td>
<td>13 (16)</td>
<td>5 (29)</td>
<td>39 (21)</td>
</tr>
</tbody>
</table>

NIHSSS = NIH Stroke Scale Score, mRS = modified Rankin Scale score, SICH = symptomatic intracerebral hemorrhage  *combined IV/IA group only
EKOS MicroLysus® Ultrasound Catheter*

* CAUTION: Investigational Device limited by US law to investigational use
# IMS I and II Safety Results

<table>
<thead>
<tr>
<th></th>
<th>IMS II N = 81</th>
<th>IMS I N = 80</th>
<th>NINDS rt-PA N = 182</th>
<th>NINDS Placebo N = 211</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality (at 3 Months)</td>
<td>16%</td>
<td>16%</td>
<td>21%</td>
<td>24%</td>
</tr>
<tr>
<td>Symptomatic ICH (≤36 hrs)</td>
<td>9.9%</td>
<td>6.3%</td>
<td>6.6%</td>
<td>1%</td>
</tr>
<tr>
<td>PH2s</td>
<td>8.8%</td>
<td>7.5%</td>
<td>3.6%</td>
<td>0.5%</td>
</tr>
<tr>
<td>Asymptomatic ICH (≤ 36 hrs)</td>
<td>32.1%</td>
<td>42.5%</td>
<td>6.0%</td>
<td>5.7%</td>
</tr>
<tr>
<td>Serious Bleeding (Non ICH)</td>
<td>2.5%</td>
<td>2.7%</td>
<td>1%</td>
<td>0.5%</td>
</tr>
</tbody>
</table>
# IMS II Efficacy

<table>
<thead>
<tr>
<th>3-month outcome</th>
<th>IMS II N=81</th>
<th>NINDS Placebo N=211</th>
<th>Odd Ratio* (95% CI)</th>
<th>NINDS rt-PA N=182</th>
<th>Odds Ratio* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>mRS 0-1</td>
<td>33%</td>
<td>18%</td>
<td>2.78 (1.46, 5.31)</td>
<td>32%</td>
<td>1.36 (0.72, 2.56)</td>
</tr>
<tr>
<td>mRS 0-2</td>
<td>46%</td>
<td>28%</td>
<td>2.82 (1.54, 5.16)</td>
<td>39%</td>
<td>1.74 (0.95, 3.19)</td>
</tr>
<tr>
<td>NIHSS &lt;=1</td>
<td>27%</td>
<td>15%</td>
<td>2.84 (1.40, 5.73)</td>
<td>25%</td>
<td>1.85 (0.92, 3.70)</td>
</tr>
<tr>
<td>BI 95-100</td>
<td>53%</td>
<td>30%</td>
<td>3.24 (1.80, 5.85)</td>
<td>42%</td>
<td>2.29 (1.24, 4.23)</td>
</tr>
<tr>
<td>Global Test Statistic</td>
<td>NA</td>
<td>NA</td>
<td>2.88 (1.66, 4.99)</td>
<td>NA</td>
<td>1.85 (1.06, 3.23)</td>
</tr>
<tr>
<td>NIHSS 0-2 @24 hours</td>
<td>19%</td>
<td>3%</td>
<td>7.07 (2.54, 19.63)</td>
<td>14%</td>
<td>2.27 (0.996, 5.16)</td>
</tr>
</tbody>
</table>

*Adjusted for age, baseline NIHSS, and time to treatment
## Recanalization Scores

<table>
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<tr>
<th></th>
<th>IMS I</th>
<th>IMS II</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIMI 2-3 for IA Treated</td>
<td>55.0%*</td>
<td>57.7%*</td>
</tr>
<tr>
<td>AOL Recanalization 2-3 scores</td>
<td>55.6%</td>
<td>69.0%</td>
</tr>
</tbody>
</table>

Includes thrombi in larger vessels than in PROACT Studies – e.g. ICA occlusions
Scientific Rationale and IMSIII Trial Design
GRANT SUPPORT:
NIH/NINDS U01-NS052220

PRINCIPAL INVESTIGATORS:
Joseph P. Broderick, MD
Thomas Tomsick, MD

FDA IND: #5785
Study Drug: Genentech, Inc.
Key Design Features

- Randomized trial of planned 900 subjects with moderate to severe stroke at 50 centers

- Randomization of subjects to combined IV/IA approach or standard IV t-PA in a 2:1 ratio within 3 hours of stroke onset.

- IA therapy includes choice of catheter/devices (Concentric retriever, Penumbra catheter, EKOS catheter, standard micro-catheter) and IA t-PA depending upon lesion, experience and training of investigator, and specified use of devices.
Key Inclusion Criteria

• Age: **18 through 82 years** (i.e., candidates must have had their 18th birthday, but not had their 81st birthday)

• **Within 3 hours** of symptom onset (i.e., the last time when patient was witnessed @ baseline)

• NIHSS \( \geq 10 \), or NIHSS 8-9 with CTA evidence of ICA, M1 or basilar occlusion prior to initiation of IV rtPA

• Consent/randomization prior to **40-minute** rt-PA IV infusion completed
IMS III Study Design

IV Activase® 0.9 mg/kg
(10% Bolus + Infusion over 40 minutes)
Total N: 900

Meets All Inclusion /Exclusion Criteria and Consent obtained

Randomized 2:1 (IV/IA to IV)

IA *
0-22 mg

IV 0.9mg/kg additional 20 min.
IV Drug

• If randomized to IV t-PA group, subject will receive the remainder of standard IV t-PA dose over an hour.

• If randomized to IV/IA group, the IV infusion is stopped at 40 minutes and the patient is taken to angiography for additional IA treatment.
If No Arterial Occlusion on Angiogram: No IA t-PA Therapy Administered
IF   YES

Chose only **ONE** of the following treatment options

But Remember

Merci Retriever Contraindications to Use:
- Dissection precluding safe passage
- Significant (≥50%) proximal vessel stenosis/occlusion
- Prominent vessel tortuosity

EKOS Microcatheter contraindications to Use:
- Etiologies or suspected etiologies preventing safe passage of device such as: dissection, chronic atherosclerosis, vasculitis, arterial spasm, moyamoya, arteriopathy, fibromuscular dysplasia, etc.

Standard Microcatheter IA rt-PA by local infusion (or by regional infusion if inaccessible) w/ every 15 min. assessments
Time-line of Procedure

• 1) Deployment of catheter (Concentric/Penumbra) or infusion of IA rt-PA via EKOS or standard micro-catheter must begin within 5 hours of stroke onset.

• 2) IA procedure must be completed within 7 hours of stroke onset.
IMS I, II, and III

Minutes

Stroke Onset to IV Start
IV Start to IA Start

IMS I
IMS II
IMS III

136
141
123
133
N = 355
randomized

N = 77
randomized
Figure. Example of acute stenting cases before and after stenting: Case A developed acute in-stent thrombosis with resolution post-balloon angioplasty and GP-IIb/IIIa inhibitor. Case D developed a small asymptomatic basal ganglia bleed.

Zaidat et al: Stroke 2008
First Food and Drug Administration-Approved Prospective Trial of Primary Intracranial Stenting for Acute Stroke

SARIS (Stent-Assisted Recanalization in Acute Ischemic Stroke)

Elad I. Levy, MD; Adnan H. Siddiqui, MD, PhD; Annemarie Crumlish, CCRC; Kenneth V. Snyder, MD, PhD; Erik F. Hauck, MD, PhD; David J. Fiorella, MD, PhD; L. Nelson Hopkins, MD; J Mocco, MD, MS

Stroke, 2009
Summary – Reperfusion

• No matter what the reperfusion approach – time to start and time to reperfusion is critical.

• Even the best reperfusion therapy, given at the wrong time, may not be useful and may be harmful
To Randomize or Not?
Example: EC-IC Bypass

- “...An exquisite procedure that technically could successfully bypass arterial blood from extracranial arteries to intracranial arteries. It had to work, but it didn't....Many of us had been sure that the surgery would be effective for these patients.”
  - Dr. Dyken, Willis Lecture, 1993.
What do we know about ICA-T Occlusions?

Issues with comparisons: Age, NIHSS, time, revascularization rates, exact ICA locations, pre-IA treatment with IV rt-PA, treatment details

<table>
<thead>
<tr>
<th>STUDY</th>
<th>N</th>
<th>mRS 0-2</th>
<th>STUDY</th>
<th>N</th>
<th>mRS 0-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLOTBUST (ICA-T)</td>
<td>11</td>
<td>18%</td>
<td>MERCI + multi MERCI; ALL intracranial ICAO (Flint, 2007)</td>
<td>80</td>
<td>25.3%</td>
</tr>
<tr>
<td>(Saqqur, 2007)</td>
<td></td>
<td></td>
<td>IMS I and II (after IV; C5, C6, C7)</td>
<td>21</td>
<td>14.3%</td>
</tr>
</tbody>
</table>

- Also, a prospective series of consecutive pts:
  - Jansen et al, AJNR, 1995 (n=32 ICAT; 16 IV, 16 IA)
    - mRS 0-3: 19% IV group versus 6% IA group (IA lytics)
Always New Questions

• ECASS III results – impact on practice and trials
• New devices and older ones under study (e.g. Wingspan, Solitaire, Trevo, and other stents)
• What is sufficient training/experience for interventional stroke and for a given device
• How much sedation is needed for IA Rx and does this impact outcome?
• The impact of hospital and physician reimbursement on clinical trials and scientific study
SUMMARY

1) Combination therapies represent the future of stroke as in acute MI.

2) Randomization is critical to control for important determinates of outcome such as stroke severity, age, and time-to-Rx.

3) A combined IV/IA approach to recanalization may be more effective than standard IV t-PA alone with similar safety and IMS III will answer this question.
• BOCA RATON, Fla. (EGMN) – Acute stroke patients who have their blood flow restored by a retrievable stent may avoid the need for post-procedure antiplatelet therapy if the stent is removed afterward, according to Dr. Thomas Liebig’s experience with the device in Germany.

• “Stents and other permanent intravascular implants can activate blood-platelets and therefore lead to thrombus formation. This is why patients
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Crowell, 1981.
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  • Dr. Dyken, Willis Lecture, 1993.
Recanalization and Clinical Outcome: Problems with that viewpoint

– IA recanalization comes with risk
  • Time, device and procedure-related complications
– IA procedure involves risks associated with sedation and contrast
Device-Related Complications

- **Embolization (0-15%)**
  - King, AJNR, 2007; Grolla, AJNR, 2008

- **Arterial puncture or avulsion (0-3.5%)**
Examples of *Procedure*-Related Complications

- **Sedation**

  Is peri-procedural sedation during acute stroke therapy associated with poorer functional outcomes?
  Christopher Nichols, MD; Janice Carrozzella, RN; Sharon Yeatts, PhD; Thomas Tomsick, MD; Joseph Broderick, MD; Pooja Khatri MD, FAHA
  Journal of Neurointerventional Surgery, 2009

- **Contrast**

  Does Application of Radio Contrast Media Prior to Thrombolysis Impact Thrombolytic effect in Acute Ischemic Stroke?
  Imanuel Dzialowski, Univ of Dresden, Dept Neurology, Dresden, Germany; Volker Puetz, Andrew M Demchuk, Univ of Calgary, Dept of Clinical Neurosciences, Stroke Program, Calgary, Canada; Alastair M Buchan, Univ of Oxford, Dept. Geratology, Oxford, United Kingdom; Michael D Hill, Univ of Calgary, Dept of Neurosciences, Stroke Program, Calgary, Canada; for the Calgary CTA Study Group