Interventional Management of Stroke
Past, Present and Future

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Comprehensive Stroke Center
Financial Disclosures

- Received study medication from Genentech for IMS III.
- Catheter devices supplied in early years of IMS III by Concentric, EKOS, and Cordis Neurovascular.
- Research monies from Genentech for PRISMS Trial – Executive Committee
Navigating the Future – Maps from Other Diseases

- Learn from colleagues within and outside of stroke, like cardiology.
- Therapeutic advances within the general population require not only science but advocacy, political will, changes in human behaviors, and organizational change locally, regionally, and nationally.
Reperfusion Is King for Acute Myocardial Infarction

- Lytic medications are effective but endovascular therapy, if delivered quickly, works better (although only about a 1% difference in mortality).
- Organizational triage in the U.S. has been driven by availability of interventional therapy.
- Very different triage system than trauma triage system nationally.
Advantages of Cardiologists in MI

- Don’t need to image heart like brain
- One primary type of pathology - thrombosis
- Endovascular access is much easier
- Often younger patients
- Patients can provide informed consent
- More common than stroke and thus more experience/power for pivotal trials
Advantages of Cardiology in MI

- 25 years of minimizing time to Rx, development of devices that treat consistent pathology, and standardization of training
- Distal embolization not as damaging
- And they have run up against limits of biology
The History and Future of Reperfusion in Acute Stroke
Reperfusion in Ischemic Stroke – Potential Advantages

- Imaging of brain provides potential measurement of salvageable brain
- Neurologic outcome/volume of brain infarction is a much more sensitive measure to measure treatment effect than mortality in MI trials
- Emboli – aspiration/removal versus fracturing and opening atherosclerotic plaque
MCA Reperfusion in the Primate

Crowell, 1981.
Stroke Care in the 1980s

- See patients the next day, no sense of urgency because no treatment that worked.
- All about diagnosis and secondary prevention (aspirin at that time, ticlopidine under testing).
- Treating patients within 90 minutes was seen as not possible (even though trauma patients and MI patients were).
NINDS Pilot rt-PA Trial
Changing Stroke Treatment

- First demonstrated the feasibility of treating stroke patients within 90 minutes of onset and developed the logistics for the “trauma model” of stroke treatment. (parallel processing, one of first cell-phone users, etc.). First users of cellphone technology to assist in treatment of stroke patients – the first “telemedicine”.
NINDS Pilot Trial of rt-PA Selection of Dose

- First dose-escalation trial in stroke
- 0/58 patients treated with IV rt-PA within 90 minutes at doses of 0.85 mg/kg or less as compared to 3/16 (19%) patients at doses of 0.95 mg/kg or higher with sICH.
  - Stroke; May, 1992.
- Small numbers of subjects in each dose-tier, non-randomized trial, but no outcome differences could be demonstrated among different doses
- Question of best dose of t-PA remains: ENCHANTED Trial – 2016 results
The NINDS rt-PA Stroke Trial

• Inclusion/exclusion criteria, the importance of time and the standard of care in this trial

• Results - 30% greater likelihood of better clinical outcome at 90 days

• Despite risk of symptomatic intracerebral hemorrhage
  • 6% of treated vs. 1% in placebo patients

• Benefit is sustained @ one year
Clinical Efficacy of t-PA by Time to Treatment


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Can We Do Better?
Limitations of IV t-PA

- Reperfusion is dependent upon available substrate and time to lyse clot
- Stimulates platelet activation
- May not be as effective with larger and older clots
- Hemorrhagic transformation
Logistic regression curve representing an estimate of the probability for successful recanalization of occluded vessels by intravenous thrombolysis (IVT) depending on thrombus length.  

Riedel et al, 2011
Potential Approaches

- Improve time to treatment
- New thrombolytic agents (tNK and desmoteplase).
- Add an agent which is synergistic (eptifibatide, argatroban)
- Combine with transcranial ultrasound energy (CLOTBUSTER)
- Cool brain while reperfusion is still ongoing (neuroprotection) and other neuroprotective strategies
Potential Approaches

- Use imaging to select patients better
- Devices to remove clot not lysed by t-PA
FIRST GENERATION
ENDOVASCULAR TRIALS
# Meta-analysis of 5 IA Trials

<table>
<thead>
<tr>
<th>Study (No, Time)</th>
<th>Intervention</th>
<th>Control</th>
<th>Odds ratio (95% C.I.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keris et al (N = 45, &lt; 6 hrs)</td>
<td>IV+IA t-PA+ IV heparin</td>
<td>IV heparin</td>
<td>7.39 (1.85, 29.54)</td>
</tr>
<tr>
<td>Macleod et al (N = 16, &lt;24 hrs)</td>
<td>IA UK + IV heparin</td>
<td>IV heparin</td>
<td>5.14 (0.66, 39.78)</td>
</tr>
<tr>
<td>MELT (N = 114, &lt;6 hrs)</td>
<td>IA UK + IV heparin</td>
<td>IV heparin</td>
<td>1.53 (0.73, 3.19)</td>
</tr>
<tr>
<td>PROACT (N = 40, &lt;6 hrs)</td>
<td>IA pro-UK + IV heparin</td>
<td>IV heparin</td>
<td>1.58 (0.38, 6.64)</td>
</tr>
<tr>
<td>PROACT II (N = 180, &lt;6 hrs)</td>
<td>IA pro-UK + IV heparin</td>
<td>IV heparin</td>
<td>1.86 (0.97, 3.57)</td>
</tr>
</tbody>
</table>
Meta-analysis of 5 IA Trials

Odds ratio for meta-analysis of mROS 0-2
2.05 (95% CI = 1.33, 3.14)

BUT:

PROACT II is the only positive modestly-sized study and just barely

No trial data comparing IA to IV t-PA alone within 4 ½ hrs

No clear evidence of effectiveness beyond 4 ½ hrs against standard care
NEXT GENERATION TRIALS
Next Generation Trials

- IMS III, SYNTHESIS and MR RESCUE all negative trials with regards to primary endpoint.

- Limitations:
  - All had minimal use of stent-retrievers
  - IMS III had CTA in nearly 50% and SYNTHESIS had CTAs in 30%.
  - MR RESCUE had long delay from onset and imaging to endovascular therapy
Technology is Rapidly Changing

![Graph showing changes in IMS III Protocol Version](image)

- Baseline CTA (%)*
- Use of IA t-PA alone (%)†

*p<0.0001, †p<0.05
Time to Start of Endovascular Therapy Can Be Improved

![Graph showing the improvement in time to start of endovascular therapy with increasing IMS III Protocol Version. The x-axis represents IMS III Protocol Version 1 to 5, and the y-axis represents time in minutes (0 to 400). The graph includes two lines: one for Onset to groin (min) mean† and another for Onset to last angio image (min) mean*. The legend indicates that *p<0.0001, †p<0.05.]}
IMS III: Patients with Severe Stroke May Benefit from Additional Endovascular Therapy

Palesch, Stroke: 2015, In Press
### Benefit for Subjects with CTA Occlusions at Baseline

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Endovascular</strong>&lt;br&gt;N=180</td>
<td>13.3</td>
<td>21.7</td>
<td>12.2</td>
<td>13.3</td>
<td>17.8</td>
<td>6.1</td>
<td>15.6</td>
</tr>
<tr>
<td><strong>IV tPA Alone</strong>&lt;br&gt;N=91</td>
<td>5.5</td>
<td>14.3</td>
<td>18.7</td>
<td>11</td>
<td>16.5</td>
<td>7.7</td>
<td>26.4</td>
</tr>
</tbody>
</table>

van Elteren test p-value 0.01

Demchuk et al, Radiology, 2014
## Particularly For ICA Occlusions

<table>
<thead>
<tr>
<th>Baseline Primary Occlusion Vessel Category</th>
<th>Endovascular</th>
<th>IV tPA Only</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Subjects with Baseline CTA</td>
<td>mRS 0-2</td>
</tr>
<tr>
<td>All</td>
<td>189</td>
<td>44.44%</td>
</tr>
<tr>
<td>ICA-T/L</td>
<td>39</td>
<td>23.08%</td>
</tr>
<tr>
<td>Tandem M1 with ICAo</td>
<td>7</td>
<td>42.86%</td>
</tr>
<tr>
<td>Combined</td>
<td>46</td>
<td>26.09%*</td>
</tr>
</tbody>
</table>

*Fisher p value 0.0471 (% mRS)

**Chi-square p-value 0.0001 (% recanalized)
STENT RETRIEVER TRIALS
<table>
<thead>
<tr>
<th>Study Groups</th>
<th>No. of patients</th>
<th>TIMI 2-3 or TICI 2-3 after primary device and after procedure</th>
<th>Rankin 0-2</th>
<th>90-day Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>SWIFT Solitaire*</td>
<td>58</td>
<td>69% (89%+)</td>
<td>36%</td>
<td>17%</td>
</tr>
<tr>
<td>SWIFT Merci*</td>
<td>55</td>
<td>30% (67%+)</td>
<td>29%</td>
<td>38%</td>
</tr>
<tr>
<td>TREVO II** Retriever</td>
<td>88</td>
<td>86% (92%+)</td>
<td>40%</td>
<td>33%</td>
</tr>
<tr>
<td>TREVO II** Merci</td>
<td>90</td>
<td>60% (77%+)</td>
<td>22%</td>
<td>24%</td>
</tr>
</tbody>
</table>

Prior IV t-PA in 47% of Merci vs. 33% of Solitaire group. Prior IV t-PA in 58% Merci and 50% of Trevo retriever.

+ As assessed by study site
Disclosures

Funded by the Dutch Heart Foundation

Nominal, unrestricted grants from

• AngioCare BV
• Covidien/EV3®
• MEDAC Gmbh/LAMEPRO
• Penumbra Inc.
• Top Medical/Concentric

NEJM – Dec, 2014
Patient Flow in the Study

Baseline CT, CTA N=502

Allocation

Intervention N=233

17 did not reach angiosuite

20 DSA only

Received Rx

IAT N=196

mRS N=233

Control N=267

1 pt IAT

2 pts refused participation

End of FU

Standard Rx N=266

mRS N=267

Received Rx

IAT N=196

mRS N=233

Control N=267

1 pt IAT

End of FU

Baseline CT, CTA N=502

Allocation

Intervention N=233

17 did not reach angiosuite

20 DSA only

Received Rx

IAT N=196

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1 pt IAT

End of FU

Standard Rx N=266

mRS N=267

Received Rx

IAT N=196

mRS N=233

Control N=267

1 pt IAT

End of FU
## Main Clinical Characteristics at Baseline

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Intervention (N=233)</th>
<th>Control (N=267)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years</td>
<td>65 (55 to 76)</td>
<td>66 (56 to 76)</td>
</tr>
<tr>
<td>Male sex</td>
<td>135 (58%)</td>
<td>157 (59%)</td>
</tr>
<tr>
<td>NIHSS score</td>
<td>17 (14 to 21)</td>
<td>18 (14 to 22)</td>
</tr>
<tr>
<td>Treatment with IV alteplase</td>
<td>203 (87%)</td>
<td>242 (91%)</td>
</tr>
</tbody>
</table>
Distribution of Occlusive Lesions at Baseline

- ICA terminus
- M1
- M2
- A1/A2

- Control
- Intervention
Timing

- **Time from onset to start of IV alteplase**
  - Intervention: 85
  - Control: 87

- **Time from onset to randomization**
  - Intervention: 204
  - Control: 196

- **Time from onset to groin puncture**
  - Intervention: 260

Legend:
- Red: Intervention
- Light blue: Control
Intervention Details

- N=196
- N=190 (97%)
- N=5 (2.6%)
- N=1 (0.4%)

- Retrievable stent
- Thrombolytics only
- Other mechanical

N=196
## Serious Adverse Events

<table>
<thead>
<tr>
<th>Serious Adverse Events</th>
<th>Intervention (N=233)</th>
<th>Control (N=267)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with at least one SAE</td>
<td>110 (47%)</td>
<td>113 (42%)</td>
</tr>
<tr>
<td>Parenchymal hemorrhage type 2 (PH2)</td>
<td>14 (6.0%)</td>
<td>14 (5.2%)</td>
</tr>
<tr>
<td><strong>New ischemic stroke in different vascular territory</strong></td>
<td><strong>13 (5.6%)</strong></td>
<td><strong>1 (0.4%)</strong></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>25 (11%)</td>
<td>41 (15%)</td>
</tr>
<tr>
<td>Hemicraniectomy</td>
<td>14 (6.0%)</td>
<td>13 (4.9%)</td>
</tr>
</tbody>
</table>
Safety data: mortality
Pre- and Post Intervention mTICI Scores

- Pre: 92%
- Post: 59%

Categories:
- mTICI 3: 35%
- mTICI 2b: 24%
- mTICI 2a: 14%
- mTICI 1: 0%
- mTICI 0: 0%
Effect of Intervention on Primary Outcome

Common adjusted odds ratio: 1.67 (95% CI: 1.21 to 2.30)
Subgroup analyses: age and NIHSS

<table>
<thead>
<tr>
<th>Age</th>
<th>No. of patients</th>
<th>acOR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>500</td>
<td>1.67 (1.21 to 2.30)</td>
</tr>
<tr>
<td>&lt;80</td>
<td>419</td>
<td>1.6 (1.13 to 2.27)</td>
</tr>
<tr>
<td>≥80</td>
<td>81</td>
<td>3.24 (1.21 to 8.62)</td>
</tr>
<tr>
<td>NIHSS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-15</td>
<td>164</td>
<td>1.71 (.96 to 3.02)</td>
</tr>
<tr>
<td>16-19</td>
<td>153</td>
<td>1.5 (.83 to 2.67)</td>
</tr>
<tr>
<td>≥20</td>
<td>183</td>
<td>1.85 (1.06 to 2.31)</td>
</tr>
</tbody>
</table>
Subgroup Analyses: Neuro-imaging

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of patients</th>
<th>acOR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>500</td>
<td>1.67 (1.21 to 2.30)</td>
</tr>
<tr>
<td>ICA terminus occlusion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>absent</td>
<td>366</td>
<td>1.61 (1.10 to 2.33)</td>
</tr>
<tr>
<td>present</td>
<td>134</td>
<td>2.43 (1.24 to 4.77)</td>
</tr>
<tr>
<td>ASPECTS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-4</td>
<td>28</td>
<td>1.09 (.14 to 8.46)</td>
</tr>
<tr>
<td>5-7</td>
<td>92</td>
<td>1.97 (.89 to 4.35)</td>
</tr>
<tr>
<td>8-10</td>
<td>376</td>
<td>1.61 (1.11 to 2.33)</td>
</tr>
<tr>
<td>Extracranial ICA occlusion&lt;sup&gt;+&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>absent</td>
<td>354</td>
<td>1.85 (1.25 to 2.72)</td>
</tr>
<tr>
<td>present</td>
<td>146</td>
<td>1.43 (.77 to 2.64)</td>
</tr>
</tbody>
</table>
Subgroup analyses: time from onset and IV alteplase

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of patients</th>
<th>acOR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>500</td>
<td>1.67 (1.21 to 2.30)</td>
</tr>
<tr>
<td>Onset to randomization</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥120 min</td>
<td>449</td>
<td>1.69 (1.20 to 2.38)</td>
</tr>
<tr>
<td>&lt;120 min</td>
<td>51</td>
<td>1.57 (.50 to 4.85)</td>
</tr>
<tr>
<td>IV alteplase*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>no</td>
<td>55</td>
<td>2.06 (.69 to 6.13)</td>
</tr>
<tr>
<td>yes</td>
<td>445</td>
<td>1.71 (1.21 to 2.40)</td>
</tr>
</tbody>
</table>
## Summary of Stent-Retriever Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Time Window</th>
<th>Imaging Selection</th>
</tr>
</thead>
<tbody>
<tr>
<td>MR CLEAN</td>
<td>6 hours (90%) t-PA</td>
<td>CT, CTA</td>
</tr>
<tr>
<td>SWIFT PRIME</td>
<td>4 1/2 hours (100% t-PA)</td>
<td>CT, CTA, CT/MR perfusion core/mismatch and ASPECTS</td>
</tr>
<tr>
<td>ESCAPE</td>
<td>12 hours (76% t-PA)</td>
<td>CT, CTA (good/moderate collaterals), CTA ASPECTS</td>
</tr>
<tr>
<td>EXTEND IA</td>
<td>4 1/2 hours (100% t-PA)</td>
<td>CT, CTA, CT perfusion core/ mismatch - RAPID</td>
</tr>
<tr>
<td>REVASCAT</td>
<td>8 hours (73 % t-PA)</td>
<td>CT, CTA, CT ASPECTS</td>
</tr>
</tbody>
</table>

Minutes (median) from last seen normal to groin puncture in the IAT group for each trial

Grotta, Stroke, 2015
Complete Recanalization Heart vs. Brain

SWIFT and Trevo 2 Trials

SWIFT PRIME EXTEND IA
ESCAPE
REVASCAT
MR CLEAN

Cardiac
Stroke

IMS III Trial
(a) prestroke mRS score 0 to 1,
(b) acute ischemic stroke receiving intravenous t-PA within 4.5 hours of onset according to guidelines
(c) causative occlusion of the internal carotid artery or proximal MCA (M1)
(d) age \( \geq 18 \) years
(e) NIHSS score of \( \geq 6 \)
(f) ASPECTS of \( \geq 6 \)
(g) treatment can be initiated (groin puncture) within 6 hours of onset
Information in Time Windows Beyond 6 hours

- ESCAPE: 49 patients underwent randomization 6 or more hours after stroke onset; in the analysis of a modified Rankin score of 0 to 2 at 90 days, the direction of effect favored the intervention in these patients (rate ratio, 1.7; 95% CI, 0.7 to 4.0), but the between-group difference was not significant.
- REVASCAT out to 8 hours: 20 patients between 6-8 hours
- EXTEND IA, SWIFT PRIME, THERAPY, THRACE – all randomized within 4 ½ hours
WHAT IS CURRENT ROLE OF IMAGING FOR REPERFUSION THERAPY?
Guiding Principle: Don’t treat patients with reperfusion therapy who have very large core of already dead brain.

Options:
- Greater than clear hypodensity in 1/3 territory of middle cerebral artery
- ASPECTS score
  - Defines process for review and scoring of all regions
ASPECTS Score: Predictor of Outcome vs Predictor of Response to Therapy

- Excellent predictor of outcome in all reperfusion trials
- Not a good predictor of the effect of IV t-PA therapy
- Three of the five endovascular trials used ASPECTS entirely or in part to select patients (ASPECTS >5 or >6).
- MR CLEAN did not use ASPECTS to select patients.

- ASPECTS of 6 or more currently recommended. Use in patients with ASPECTS < 6 requires more study.
Importance of CTA for Endovascular Therapy

- CTA is not needed for use of IV t-PA. T-PA works in patients with small artery occlusions.
- Documentation of a large artery occlusion CTA (or MRA) is critical to define need for endovascular therapy.
- All of successful recent endovascular trials required CTA (MRA) to document major arterial occlusion.
Goal: Identify patients who have salvageable brain amenable to reperfusion and exclude those with large areas of brain that is already dead or destined to die.

Challenges: different definitions and imaging of “ischemic core” and salvageable brain (brain regions not yet dead but with decreased perfusion)
Perfusion-Diffusion Imaging

A: NIHSS 14, MRI 1.5 h after symptom onset, i.v. thrombolysis, non MMI

B: NIHSS 21, MRI 2h after symptom onset, MMI, hemicraniectomy

Stroke. 2003; 34: 1892-1899
Collateral Flow Imaging on CTA

**Site of Occlusion**

**Good collaterals**

**Intermediate collaterals**

**Poor collaterals**
Proportion (95% confidence interval) of vascular and clinical outcomes by collateral grade. AOL indicates arterial occlusive lesion; mRS, modified Rankin Scale; and mTICI, modified Thrombolysis in Cerebral Infarction.

David S. Liebeskind et al. Stroke. 2014;45:759-764

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## IMS III: Collateral Flow on Pre-treatment CTA and Outcome

<table>
<thead>
<tr>
<th>Collateral Score</th>
<th>Endovascular Treatment</th>
<th>IV tPA Only</th>
<th>Treatment Difference (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>% mRS 0-2</td>
<td>N</td>
</tr>
<tr>
<td><strong>Score 1</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Good (8-10)</td>
<td>46</td>
<td>56.5</td>
<td>24</td>
</tr>
<tr>
<td>Intermediate (6-7)</td>
<td>42</td>
<td>45.2</td>
<td>18</td>
</tr>
<tr>
<td>Poor (0-5)</td>
<td>38</td>
<td>18.4</td>
<td>17</td>
</tr>
<tr>
<td><strong>Score 2</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Good (3-5)</td>
<td>47</td>
<td>57.4</td>
<td>26</td>
</tr>
<tr>
<td>Intermediate (2)</td>
<td>60</td>
<td>40</td>
<td>26</td>
</tr>
<tr>
<td>Poor (0-1)</td>
<td>19</td>
<td>5.3</td>
<td>7</td>
</tr>
</tbody>
</table>

The effectiveness of t-PA, and endovascular therapy, is strongly correlated with time to start of therapy.

Advanced perfusion/core imaging provides a measure of remaining physiologic time but shouldn’t delay treatment.

CTA, and particularly perfusion/diffusion imaging, can be done after IV t-PA is started.

The role of perfusion/diffusion imaging in patient selection, particularly in later time windows, remains an important area of research.
Pre-treatment non-contrast CT is the current basic imaging requirement in the decision for reperfusion therapy – both for t-PA and endovascular therapy.

For endovascular therapy, an ASPECTS of 6 or more marks a patient group who has been demonstrated to have better outcomes. For patients < 6, more data are needed to determine the usefulness of EVT in this subgroup.

CTA (or MRA) demonstrates the need for endovascular therapy, can be done before or after t-PA is initiated, but should not delay start of t-PA.

CT and MR perfusion/diffusion imaging is an area of intense study.
Endovascular Therapy
A New Clinical Standard

- As compared to standard therapy, current endovascular therapy improves outcome in subjects with major arterial occlusions when treatment is begun within 6 hours of onset.
- Potential benefit and less adverse events are likely greatest with earlier reperfusion.
- Ongoing analyses of collateral flow and perfusion imaging from completed studies will help to further clarify subgroups most likely to benefit and whether imaging can select patients at later time window.
Other Questions Besides Imaging Selection?

- Conscious sedation vs anesthesia?
- Better ways to prevent embolization/fragmentation?
- Safer reperfusion?
Improving Medical Reperfusion Therapies (all tested in Phase II)

- T-PA plus eptifibatide
- T-PA plus argatroban
- TNK (3 trials ongoing)
- Desmoteplase (just reported – neutral)
- T-PA with MR imaging and longer time window
- T-PA plus transcranial ultrasound

NONE OF THESE THERAPIES REQUIRE ENDOVASCULAR THERAPY AND CAN BE DONE AT COMMUNITY HOSPITALS OR IN MOBILE CARE UNITS AND REMOTE SITES VIA TELEMEDICINE
Next Steps

- Multi-arm Optimization of Stroke Thrombolysis (MOST) Stroke Trial (Argatroban or Eptifibatide)
  - Age $\geq 18$, NIHSS $\geq 6$, rt-PA within 3 hours, NCCT only
  - Includes endovascular therapy in those for whom it is indicated.
5MAX™ Direct Aspiration™ Enables Choice
CAN WE BUY TIME FOR REPERFUSION’S BENEFITS WITH NEUROPROTECTION?
Neuroprotection – New Trials

Pre-conditioning
Tri-nitrate
NA-1
Reorganization of Stroke Triage

- How do we organize stroke triage in our communities?
  - EMS recognition of patients with severe stroke and likely to have large artery occlusion
  - When to transfer to CSC directly and when to primary stroke center/other hospital to start t-PA?
  - Trauma vs acute MI triage approach – or something in between?
Acute Ischemic Stroke Treatment

Symptoms

911

Dispatch

EMS

IV Reperfusion

Imaging

Mobile Stroke Unit
Mobile Stroke Unit and Standard EMS – Not Mutually Exclusive

**Mobile Stroke Unit**
- Major new infrastructure and cost for region
- Not available 24 hr/7 days
- Better identification of stroke and stroke subtype although takes time to image
- Can initiate t-PA quickly
- Better determination of severe stroke and triage

**EMS**
- Uses existing infrastructure
- Available 24 hr/7 days
- Can identify most focal neurologic problems clinically and minimizes time to a hospital
- t-PA cannot be started until imaging at hospital
- No current way to triage mild and severe strokes
Triage of Acute Stroke
Prehospital Identification of Severe Strokes and Large Artery Occlusion

- NIHSS by trained EMS/MD telemedicine
- Abbreviated pre-hospital stroke scales
- CT angiography in mobile CT
Prehospital Triage

**MSU- CT angiography**
- Identifies large artery occlusion and proper triage
- Takes additional time, use of contrast, potential renal testing, etc.
- Could activate interventional team earlier if positive

**Pre-hospital scales**
- Can be done without technology or by telemedicine
- NIHSS – best data about score and large artery occlusion, however, takes more time, training and sophistication for EMS
- Shorter pre-hospital scores easier to train and still sensitive
Cincinnati Stroke Triage Assessment Tool (C-STAT)

Cincinnati Prehospital Stroke Severity Scale

2 points: Conjugate gaze deviation (≥1 on NIHSS item for Gaze)

1 point: Incorrectly answers at least one of two level of consciousness questions on NIHSS (age or current month) and does not follow at least one of two commands (close eyes, open and close hand) (≥1 on the NIHSS item for Level of Consciousness 1b and 1c)

1 point: Cannot hold arm (either right, left or both) up for 10 seconds before arm(s) falls to bed (≥2 on the NIHSS item for Motor Arm)

Brian S. Katz et al. Stroke. 2015;46:1508-1512
The receiver operating characteristic curve for Cincinnati Prehospital Stroke Severity Scale in detecting stroke severity and large vessel occlusion in the validation data set.

Brian S. Katz et al. Stroke. 2015;46:1508-1512
## Prehospital Stroke Severity Scales

<table>
<thead>
<tr>
<th></th>
<th>C-STAT</th>
<th>LAMS</th>
<th>RACE</th>
<th>I3SS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N in derivation dataset</strong></td>
<td>624</td>
<td>119</td>
<td>654</td>
<td>171</td>
</tr>
<tr>
<td><strong>Validated independent</strong></td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td><strong>dataset (Y/N)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Number of items scored</strong></td>
<td>3</td>
<td>3</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td><strong>Sensitivity/Specificity for</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>severe stroke</strong></td>
<td>89%/72%</td>
<td>NA</td>
<td>NA</td>
<td>86%/95%†</td>
</tr>
<tr>
<td><strong>Sensitivity/Specificity - LVO</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>‡</td>
<td>83%/40%</td>
<td>81%/89%*</td>
<td>85%/67%**</td>
<td>67%/92% §</td>
</tr>
<tr>
<td><strong>Evaluated in Prehospital</strong></td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td><strong>Setting (Y/N)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Acute Ischemic Stroke Treatment

Symptoms

Primary Stroke Center/telemedicine

Neuroprotectants EMS 911

Comp Stroke Center EMS IV Lytic

Imaging

IA Mechanical Angiogram

Cath Lab Reperfusion Neuroprotectants

Stroke Unit

Imaging

Courtesy of Jeff Saver
Future of Ischemic Stroke Therapy

- Reperfusion is king but its reign is short
- Medical reperfusion during first hours is key because of speed and availability
- Endovascular therapy for subjects with large artery occlusions within 6 hours with or without t-PA is more effective than t-PA alone
- Organization of entire system from first call to hospital is critical — triage to give the patients the right cost-effective treatment at the right time
THE FUTURE OF ACUTE STROKE THERAPY IS NOT JUST IN NEW TRIALS BUT THE WAY WE DO TRIALS
Maximizing efficiencies in cerebrovascular research
NIH StrokeNet is Something New

- National Network that includes stroke prevention, acute treatment, and recovery trials.
- Multi-site Phase 1 to Phase 3 Trials, biomarkers studies.
- Centralized infrastructure for contracts, IRBs, managing data, and running trials.
- Big – 25 regional centers and 270+ associated hospitals thus far.
StrokeNet Sites – 50% of U.S. Population within 40 miles
Summary

- We are making great progress and have very interesting potential new treatments (including treatments for ICH) but we have to change and standardize the process of acute stroke treatment.
- We need to mobilize stroke networks worldwide to do the big trials
- Tremendous opportunities but also challenges
Extra slides
Common Themes of Stroke Systems

- Systems accomplish acute stroke delivery through a variety of means - phone, video, or in-person
- They require multidisciplinary stroke team with 24/7 coverage
- Hub relationships provide neurointerventional, neurosurgical, and neurointensive care as needed
  - Acute IA reperfusion, hemicraniectomy, aneurysm clipping/coiling, IV drains, hematoma evacuation
- These robust infrastructures can have a major impact on acute stroke care in a region
## Hospital Cost in 2012 US Currency

<table>
<thead>
<tr>
<th>Treatment Group Description</th>
<th>Total N=430</th>
<th>Mean Cost per Admission (SD)</th>
<th>Estimated* Mean Cost per Admission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized to endovascular therapy</td>
<td>284</td>
<td>$35,175 (20,702)</td>
<td>$35,130**</td>
</tr>
<tr>
<td>Randomized to IV t-PA alone</td>
<td>146</td>
<td>$26,266 (24,042)</td>
<td>$25,630</td>
</tr>
<tr>
<td>IV t-PA alone, no intubation</td>
<td>135</td>
<td>$22,982 (14,745)</td>
<td>$23,027</td>
</tr>
<tr>
<td>IV t-PA alone, with medically indicated intubation</td>
<td>9</td>
<td>$59,784 (61,035)</td>
<td>$57,145</td>
</tr>
<tr>
<td>Endovascular therapy, no intubation</td>
<td>186</td>
<td>$30,216 (57,114)</td>
<td>$30,350</td>
</tr>
<tr>
<td>Endovascular therapy with medically indicated intubation</td>
<td>45</td>
<td>$42,760 (20,196)</td>
<td>$41,690</td>
</tr>
<tr>
<td>Endovascular therapy with procedural intubation</td>
<td>53</td>
<td>$46,139 (28,912)</td>
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*multivariable models adjusted for age, sex, baseline NIHSS, diabetes, stroke location and early tPA administration,**

(p<0.0001)
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Factors Related to Cost

- Endovascular treatment group (higher costs)
- Baseline NIH Stroke Scale (higher costs with higher severity)
- Time from stroke onset to IV t-PA (lower costs with earlier treatment)
- Age (higher costs with older age)
- Stroke location (higher cost with right hemispheric location)
- Diabetes (higher costs with diabetes).
Rapid Treatment May Save Money As Well as Brain

*P<0.05
Note: Anesthesia is grouped with Operating costs, blood products are grouped with Other cost.