Update on Acute Stroke Management

ACC Rockies, Banff
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Division of Neurology, Department of Medicine
University of Alberta
Disclosures

• None relevant to contents of presentation
Objectives

• Update on acute stroke management
• Focus two main areas of innovation:
  – Prehospital stroke care and stroke systems
    • Delivery of therapy in ambulance
    • Improvements in DTN
  – Endovascular stroke therapy
    • Review problems with previous trials
    • How the design of new trials has been adapted
It's fine to celebrate success but it is more important to heed the lessons of failure.

(Bill Gates)
Advances in Prehospital Stroke Care
Why is prehospital care essential?

- Time is still brain
  - 1.9 million neurons die per minute
  - Every 90 minute delay benefits of tPA halved

**Time to Treatment and Benefit of IV-TPA**
Pooled Analysis of 6 IV TPA Trials

![Graph showing the relationship between stroke onset to treatment time (OTT) and odds ratio (OR) for good outcome.](image-url)
Advances in Prehospital Stroke Care
Pitfalls of late reperfusion

5 hours post onset

7 hours post onset

ASA/Plavix
No lytics
Advances in Prehospital Stroke Care

• Are there ways to protect penumbral tissue pending reperfusion?
  – >49 neuroprotective agents studied
  – >114 trials
  – None successful
Advances in Prehospital Stroke Care: Problems with previous neuroprotective trials

More than 3 hrs: 92.3%
2-3 hrs: 6.3%
1-2 hrs: 1.2%
0-1 hrs: 0.2%
Advances in Prehospital Stroke Care: FAST-MAG Trial

- RCT, single region (LA/OC), population 13 million
- Placebo vs 4 gm Mg field plus 16 gm maintenance over 24 hours (within 2 hours stroke onset)
- 1700 patients enrolled over > 5 years

Saver et al, ISC 2014
Advances in Prehospital Stroke Care: FAST-MAG Trial

Primary Endpoint

CMH test: p = 0.28

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=843)</th>
<th>Magnesium (n=857)</th>
<th>Total (n=1700)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset* to Drug (mins)</td>
<td>46 (36-62)</td>
<td>45 (35-60)</td>
<td>45 (35-62)</td>
<td>0.24</td>
</tr>
<tr>
<td>Onset to Drug (categorical)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-1 hours</td>
<td>73.2%</td>
<td>75.3%</td>
<td>74.3%</td>
<td>0.61</td>
</tr>
<tr>
<td>1-2 hours</td>
<td>25.7%</td>
<td>23.7%</td>
<td>24.7%</td>
<td></td>
</tr>
<tr>
<td>&gt;2 hours</td>
<td>1.1%</td>
<td>0.9%</td>
<td>1.0%</td>
<td></td>
</tr>
</tbody>
</table>
Advances in Prehospital Stroke Care: FAST-MAG Trial

• Lessons from FAST-MAG
  – First phase 3, RCT, conducted in prehospital setting
  – Conducted without waiver of consent (innovative physician VOIP system)
  – Unable to separate ICH from ischemic stroke
    • Ischemic stroke 73%, ICH 23%, mimics 4%
  – Implications for future trials?
Advances in Prehospital Stroke Care: Challenges to EMS delivery of lytics in stroke

- No biomarkers to aid in prehospital diagnosis
  - No troponin, ECG
- Unable to differentiate ischemic (A) from hemorrhagic stroke (B)

Acute onset (within 2 hours) left sided weakness
Advances in Prehospital Stroke Care: What is the future?

Prehospital thrombolysis in acute stroke: Results of the PHANTOM-S pilot study.

DOI: 10.1212/WNL.0b013e31827b90e5

PHANTOM-S Pilot Study

152 patients included, 58% received tPA

Mean call to needle time: 62 minutes versus 98 minutes (controls)

No safety concerns
Advances in Prehospital Stroke Care: What is the future?

PHANTOM-S Pilot Study

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No safety concerns

Advances in Prehospital Stroke Care: Reducing DTN

Good outcome 80% of recanalizers

Stroke. 2013; 44: 270-277
Advances in Prehospital Stroke Care: Reducing DTN

Table 1: Twelve measures to reduce treatment delays

<table>
<thead>
<tr>
<th>Measure</th>
<th>Description</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMS involvement</td>
<td>Education of dispatchers and EMS personnel, stroke high priority dispatch</td>
<td>1998</td>
</tr>
<tr>
<td>Hospital prenotification</td>
<td>EMS contacts stroke physician directly via mobile phone</td>
<td>2001</td>
</tr>
<tr>
<td>Alarm and preorder of tests</td>
<td>Laboratory and CT computer-ordered and alarmed at prenotification</td>
<td>2001</td>
</tr>
<tr>
<td>No-delay CT interpretation</td>
<td>Stroke physician interprets the CT scan, not waiting for formal radiology report</td>
<td>2001</td>
</tr>
<tr>
<td>Premixing of tPA</td>
<td>With highly suspect thrombolysis candidates, tPA premixed prior to patient arrival</td>
<td>2002</td>
</tr>
<tr>
<td>Delivery of tPA on CT table</td>
<td>Bolus administered on CT table</td>
<td>2002</td>
</tr>
<tr>
<td>CT relocated to ER</td>
<td>Patient transfers of several hundred meters including elevators, were no longer needed</td>
<td></td>
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<tr>
<td>CT priority and CT transfer</td>
<td>CT emptied prior to patient arrival, and patient transferred straight onto CT table, not ER bed</td>
<td></td>
</tr>
<tr>
<td>Rapid neurologic evaluation</td>
<td>Patient is examined upon arrival, on CT table</td>
<td></td>
</tr>
<tr>
<td>Preacquisition of history</td>
<td>Statewide electronic patient records and eyewitness interview before/during transport</td>
<td></td>
</tr>
<tr>
<td>Point-of-care INR</td>
<td>Laboratory personnel draw blood while patient on CT table, and perform instant POC INR</td>
<td></td>
</tr>
<tr>
<td>Reduced imaging</td>
<td>While all patients have a CT, advanced imaging reserved for unclear cases only</td>
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Abbreviations: EMS = emergency medical service; ER = emergency room; CT = computed tomography; INR = international normalized ratio; POC = point-of-care; tPA = tissue plasminogen activator.
Advances in Prehospital Stroke Care: Reducing DTN

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Abbreviations: EMS = emergency medical service; ER = emergency room; DTN = door-to-needle time; CT = computerized tomography; INR = international normalized ratio; POC = point-of-care; tPA = tissue plasminogen activator.
Advances in endovascular stroke therapy
Problems with IV tPA

- IV tPA fails to open target arteries more often than it succeeds
- Obstructing thrombi highly variable composition and size
  - Main stem (M1) MCA, 3 mm diameter
  - Other clots >15 cm, extend from cervical ICA

<table>
<thead>
<tr>
<th>TPA Recanalization Rates</th>
<th>1h</th>
<th>2h</th>
<th>24h</th>
</tr>
</thead>
<tbody>
<tr>
<td>delZoppo et al 1992</td>
<td>8%</td>
<td>6%</td>
<td>46%</td>
</tr>
<tr>
<td>Saqqur et al 2007</td>
<td>26%</td>
<td>30%</td>
<td>53%</td>
</tr>
<tr>
<td>Zangerle et al 2007</td>
<td>35%</td>
<td>44%</td>
<td>68%</td>
</tr>
</tbody>
</table>

From A Demchuk
Advances in endovascular stroke therapy: Failed endovascular trials

Endovascular Therapy after Intravenous t-PA versus t-PA Alone for Stroke


for the Interventional Management of Strokes in Ischemic Stroke Study (INCIIDE) Investigators.

A Trial of Imaging Selection and Endovascular Treatment for Ischemic Stroke

Chelsea S. Kidwell, M.D., Reza Jahan, M.D., Jeffrey Gornbein, Dr.P.H., Jeffry R. Alger, Ph.D., Val Nenov, Ph.D., Zahra Ajani, M.D., Lei Feng, M.D., Ph.D., Brett C. Meyer, M.D., Scott Olson, M.D., Lee H. Schwamm, M.D., Albert J. Yoo, M.D., Randolph S. Marshall, M.D., Philip M. Meyers, M.D., Dileep R. Yavagal, M.D., Max Wintemark, M.D., Judy Guzy, R.N., Sidney Starkman, M.D., and Jeffrey L. Saver, M.D., for the MR RESCUE Investigators.
Advances in endovascular stroke therapy: IMS III Results

- Multicentre, 656 patient, received IV randomized to endovascular therapy or standard of care
- Stopped early, futility
- No difference in primary endpoint (mRS 0-2),
- Similar safety outcomes

Advances in endovascular stroke therapy: How do we move forward from IMS-III?

1. Better patient selection:
   – Target proximal arterial occlusions
   – Brain to salvage

2. Better Devices

3. Faster more complete reperfusion
Advances in endovascular stroke therapy: Need proximal vessel occlusion

<table>
<thead>
<tr>
<th></th>
<th>ICA</th>
<th>M1 MCA</th>
<th>M2 MCA</th>
<th>Distal occlusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conservative</td>
<td>0</td>
<td>10</td>
<td>45.4</td>
<td>40</td>
</tr>
<tr>
<td>IV tPA alone</td>
<td>25</td>
<td>38.5</td>
<td>70.6</td>
<td>85.7</td>
</tr>
</tbody>
</table>

From MD Hill
Advances in endovascular stroke therapy: Need proximal vessel occlusion

Problem:
- IMS III did not require CTA
  - 1 in 4 patient randomized to IA, did not receive IA
  - 30% distal M2/M3/M4 occlusions

[Diagram of brain scan]
Advances in endovascular stroke therapy: Need salvageable brain

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Advances in endovascular stroke therapy: Need salvageable brain

Problem:
IMS-III ignored collaterals

Angiographic and clinical outcomes improve with better collaterals
Advances in endovascular stroke therapy: Need fast reperfusion

Time to Reperfusion and Good Clinical Outcome
Graphic – Observed Vs Predicted.

30 minute delay associated with 10% RR probably of good outcome

Observed values shown as horizontal bars for every ~20 subjects

ICAT, M1, and M2 Cases with Reperfusion with 95% confidence bands (p=0.0045)

P Khatri, 2013 unpublished
Advances in endovascular stroke therapy: Need fast reperfusion

Time from Symptom Onset to IA End/Reperfusion
Mean (SD) = 325 (±52) min
Range 180-418 min

Time from Onset to IV Start
121 ±34 min

Time from IV Start to Groin Puncture
81 ±27 min

Time from Groin Puncture to IA Start
42 ±21 min

Time from IA Start to IA End
81 ±43 min

Stroke System Related

Device related
Advances in endovascular stroke therapy: IMS-III Reperfusion Rates Suboptimal

Advances in endovascular stroke therapy: IMS-III Reperfusion Rates Suboptimal

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<th>Artery</th>
<th>N</th>
<th>TICI 2-3 (%)</th>
<th>TICI 2b-3 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Internal carotid artery</td>
<td>65</td>
<td>65</td>
<td>38</td>
</tr>
<tr>
<td>M1 of middle cerebral artery</td>
<td>135</td>
<td>81</td>
<td>44</td>
</tr>
<tr>
<td>M2 of middle cerebral artery</td>
<td>61</td>
<td>70</td>
<td>44</td>
</tr>
<tr>
<td>Multiple M2s</td>
<td>22</td>
<td>77</td>
<td>23</td>
</tr>
<tr>
<td>Basilar</td>
<td>4</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>
Stroke. 2013; 44: 2509-2512
Advances in endovascular stroke therapy: IMS-III Devices Less Effective
Advances in endovascular stroke therapy: IMS-III Devices Less Effective
Advances in endovascular stroke therapy: Stentretrievers

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</tbody>
</table>

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>SWIFT Solitaire (n=58)</th>
<th>Trevo2 Trevo (n=88)</th>
<th>TREVO EU (n=60)</th>
<th>STAR (n=202)</th>
<th>Solitaire EU Registry</th>
<th>Solitaire USA Registry (NASA)</th>
<th>START (n=105)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Successful Recanalization*</td>
<td>68.5% (37/54)</td>
<td>86.4% (76/88)</td>
<td>90.0%</td>
<td>84.2% (160/190)</td>
<td>85% (120/142)</td>
<td>87.2% (299/343)</td>
<td>85% (TIMI 2-3)</td>
</tr>
</tbody>
</table>
What have we learned about trial design?

1. Better patient selection:
   – Target proximal arterial occlusions
   – Require CTA, good collaterals
2. Better Devices
3. Faster more complete reperfusion
   – Innovate on stroke systems
ESCAPE is novel and different from past stroke trials

**WORKFLOW**
- 24*7 Stroke and Interventional Teams
- Rapid Access to CT. Optimizing speed of image acquisition and interpretation
- Rapid access to IV tPA and Cath Lab
- Co-ordination with allied services like ER, Anesthesia and Critical Care
- High Quality Post Stroke Care and Rehab

**IMAGING**
- Detection of target occlusion using CTA
- Excluding patients with large baseline infarct using CT ASPECTS
- Detecting salvageable brain using CTA collateral imaging
- Teaching advanced imaging interpretation

**TECHNOLOGY**
- Using latest device technology: >80% reperfusion
- Using safe device technologies
- Using optimal interventional techniques

**CULTURE**
- Multiple manuscripts, editorials, opinion pieces on consecutive enrollment, workflow, imaging and technology
- Waiver of Consent
- Signed agreement on consecutive enrollment
- Intense QA process within trial focusing on enrollment, efficiency and safety
- Highest historical enrollment rate at 1.5 subjects/site/month. 5X faster than IMS-III

**ESCAPE TRIAL**
- 90th percentile Picture to Puncture Time < 60 mins
- 90th percentile Picture to Perfusion Time < 90 mins
- 90%+ of subjects have target lesion
- 90%+ of subjects have good collaterals
- 85% TICI 2b/3 reperfusion rates
<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Status (enrolled/target N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MR Clean</td>
<td>Endovascular Tx vs. Standard TX &lt;6h</td>
<td>~455/500</td>
</tr>
<tr>
<td>THRACE</td>
<td>Endovascular Tx+iv tPA vs iv tPA</td>
<td>~350/480</td>
</tr>
<tr>
<td>REVASCAT</td>
<td>SOLITAIRE FR tx vs no tx &lt;8h</td>
<td>100/690</td>
</tr>
<tr>
<td>ESCAPE</td>
<td><strong>Endo tx vs standard of care&lt;12h</strong></td>
<td>125/400</td>
</tr>
<tr>
<td>Therapy</td>
<td>Penumbra + iv tPA vs iv tPA</td>
<td>~64/692</td>
</tr>
<tr>
<td>SWIFT-Prime</td>
<td>SOLITAIRE FR+iv tPA vs iv tPA</td>
<td>47/883</td>
</tr>
<tr>
<td>EXTEND-IA</td>
<td>SOLITAIRE tx vs standard care &lt;6h</td>
<td>~45/100</td>
</tr>
<tr>
<td>EASI</td>
<td><strong>Endo tx vs standard of care&lt;6h</strong></td>
<td>~36/400</td>
</tr>
<tr>
<td>BASICS</td>
<td>iv tPA vs iv tPA/endo</td>
<td>~32/750</td>
</tr>
<tr>
<td>PISTE</td>
<td>Endovascular tx +iv tPA vs iv tPA &lt;4.5h</td>
<td>12/70</td>
</tr>
<tr>
<td>POSITIVE</td>
<td>Endo tx vs standard of care&lt;12h</td>
<td>1/750</td>
</tr>
<tr>
<td>DAWN</td>
<td>TREVO tx vs no tx &gt;8h</td>
<td>0/600</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td><strong>&gt;1100 randomized</strong></td>
</tr>
</tbody>
</table>
Conclusions

• Prehospital stroke care expanding
• Future endovascular trials will require:
  – Improved systems of care to reduce DTN, P2P
  – Small infarct core, CTA target lesion, good collaterals
  – Faster reperfusion using next generation endovascular devices
  – Target TICA 2b/3 reperfusion