Acute Stroke – Thrombolysis and EVT update

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Disclosures

The official ESCAPE trial sponsor was the “Governors of the University of Calgary” with grants from a consortium:

- Covidien AG (now Medtronic)
- University of Calgary (HBI, Dept Clin Neuroscience, Calgary Stroke Program)
- Alberta Health Services
- Heart & Stroke Foundation Canada
- Alberta Innovates Health Solutions
- CSPIN Network (ICRH-CIHR)

Medtronic – Grant to the University of Calgary for the HERMES Collaboration

NoNO Inc – Grant to the University of Calgary for the ESCAPE-NA1 trial

CIHR – Grant to the University of Calgary for the ESCAPE-NA1 trial

Alberta Innovates – Grant the University of Calgary for the QuICR Alberta Stroke Program

CIHR – Grant to the University of Calgary for the TEMPO-2 trial
The last slide....

1. EVT is a ground-breaking therapy for the big, ischemic strokes – probably 15%, maybe as much as 20% of the total ischemic stroke burden

2. Alteplase is a concurrent therapy for ischemic stroke, applying to many more ischemic stroke patients and working synergistically with EVT

3. Speed of treatment is critical to both success and safety

4. Teamwork and communication are vital
Age-specific acute vascular event rates in the general population

Data from Oxfordshire, UK, 2002-05. Lancet 2005;366:1773-83
For Many Strokes, There’s an Effective Treatment. Why Aren’t Some Doctors Offering It?
Existing data
IV tPA time relationship: time is brain

[Emberson et al. Lancet 2014]

- Early treatment with IV tPA reduced death and disability at 90 days
- The lower bound of the confidence interval cross unity at approximately 5 hours
- Speed is a critical factor in treatment
The neuron...

In a typical large vessel acute ischemic stroke...

1.9 million neurons
14 billion synapses
12 km of myelinated fibers

are destroyed each minute...

(Saver et al, 2006)

5 min ~ 10 million neurons, 60km of wires
10 min ~ 20 million neurons, 120km of wires
15 min ~ 30 million neurons, 180 km of wires...
Human Nature?

For each 10 minute delay in ER arrival, treatment was 18 minutes faster!
Helsinki: DTN 20 minutes
Meretoja et al. Neurology 2012
NNT = 5

Good is not Good Enough: The Benchmark Stroke Door-to-Needle Time Should be 30 Minutes


doi:10.1017/cjn.2014.41
tPA DTN Performance for Oct 29 - Nov 4, 2015

- Door-to-CT
- CT-to-Needle
- DTN Goal (30 min)

http://www.ucalgary.ca/quicr/files/quicr/sample-stroke-visualization-worksheet.xls
Absolute vs. Relative Contraindications
Real life use vs. Trial Criteria

• There are only TWO absolute contraindications to use of thrombolytic drugs:
  1. The patient is bleeding.
  2. The patient is about to (at high risk for) bleeding

• All other situations are relative.

• Examples are:
  • Recent of surgery
  • Hypoglycemia, seizure at presentation
ESCAPE

Endovascular treatment for Small Core and Anterior circulation Proximal occlusion with Emphasis on minimizing CT to recanalization times

Michael D Hill on behalf of the ESCAPE Trial Investigators
Inclusion and exclusion criteria

- > 5 NIHSS
- < 12 hours from symptom onset
- Adult; No age limit
- Good pre-morbid status

- CT head: ASPECTS > 5 (exclude large core)
- CTA: ICA + M1 or M1 or functional M1 (all M2s)
- CTA (preferably multiphase): moderate to good collaterals
Imaging - ASPECTS

Examine all the images at the ganglionic and supra-ganglionic levels.

Take off 1 pt from 10 for every region that is affected.

ASPECTS
8-10 core. Small
6-7 core. Moderate
0-5 core. Large
Imaging – CTA occlusion

Collapsed axial thick MIP images.

Eligible occlusions for the ESCAPE trial:

- Intracranial ‘T’ or ‘L’ ICA occlusion
- M1 occlusion
- M1 equivalent (all M2s)
ESCAPE Outcomes

**MEDICAL TREATMENT**
(No endovascular treatment)

- 29% Positive Outcome
- 52% Disability
- 19% Death

**ENDOVASCULAR TREATMENT**
(With medical treatment)

- 53% Positive Outcome
- 37% Disability
- 10% Death
Case Example

• 31 yo man

• St Jude mechanical AoV
  • Bicuspid native valve with subsequent endocarditis and valve replacement 1 year before
  • On coumadin

• Acute L MCA stroke, onset at 1500h

• Arrival at the hospital at 1543h

• Recent INR unknown, NIHSS 25
First slice NCCT at 16:04h
Baseline Occlusion

Groin puncture at 16:23h

TICI3 final reperfusion at 16:41h
Outcome

- mRS = 0
- Valve – ok on TEE
- INR was 1.3
- Continued coumadin for target INR 2.5-3.5
IV alteplase is effective

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV tPA</td>
<td>IV tPA</td>
</tr>
<tr>
<td>No IV tPA</td>
<td>No IV tPA</td>
</tr>
<tr>
<td>TICI 2b/3</td>
<td>70.5%</td>
</tr>
<tr>
<td>77.3%</td>
<td>---</td>
</tr>
<tr>
<td>mAOL 2-3</td>
<td>37.3%</td>
</tr>
<tr>
<td>---</td>
<td>7.1%</td>
</tr>
</tbody>
</table>

mAOL assessed on CTA done at 2-8h post randomization
Early recanalization pre-EVT

ESCAPE data

- 5.9% had TICI 2b/3 with IV alteplase, on the first run of the angio (before any intervention)
- 2.2% had TICI 2b/3 without IV alteplase, on the first run of the angio (before any intervention)
Reperfusion is no where near perfect

<table>
<thead>
<tr>
<th>HERMES</th>
<th>TICI 3</th>
<th>8%</th>
<th>30%</th>
<th>76%</th>
</tr>
</thead>
<tbody>
<tr>
<td>TICI 2c</td>
<td></td>
<td>22%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TICI 2b</td>
<td></td>
<td>46%</td>
<td>46%</td>
<td></td>
</tr>
<tr>
<td>TICI 2a</td>
<td></td>
<td>15%</td>
<td></td>
<td>24%</td>
</tr>
<tr>
<td>TICI 0-1</td>
<td></td>
<td>9%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Distal emboli – Clean-Up

**Graph: IV alteplase (Yes) vs IV alteplase (No)**

- **Follow-up on CT**
  - Treatment Arm (n=118): 1.1%
  - Control Arm (n=130): 6.9%
  - Treatment Arm (n=40): 2.9%
  - Control Arm (n=19): 3.6%

- **Follow-up on MRI**
  - Treatment Arm (n=118): 11.5%
  - Control Arm (n=130): 14.3%
  - Treatment Arm (n=40): 0%
  - Control Arm (n=19): 0%

**Table: Association of INT With Primary Clinical Outcome in I (Shift in Modified Rankin Scale at 90 d) After and Treatment Type**

<table>
<thead>
<tr>
<th></th>
<th>Common Odds Ratio*</th>
<th>95% Confidence Intervals</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV alteplase (Yes)</td>
<td>0.96</td>
<td>0.95–0.97</td>
</tr>
<tr>
<td>IV alteplase (No)</td>
<td>2.9</td>
<td>1.90–4.42</td>
</tr>
<tr>
<td>Treatment (yes vs no)</td>
<td>0.25</td>
<td>0.09–0.74</td>
</tr>
<tr>
<td>Ictory (yes vs no)†</td>
<td>1.75</td>
<td>1.04–2.95</td>
</tr>
</tbody>
</table>

*Improvement of 1 point on the modified Rankin Scale.
†Test of interaction between Infarct in new territory and follow-up scan type in determining clinical outcome was nonsignificant.
No safety benefit to avoiding alteplase

sICH - Major Adverse Event rates

<table>
<thead>
<tr>
<th>Trials</th>
<th>sICH rate – EVT group</th>
<th>sICH rate – non-EVT group</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESCAPE</td>
<td>3.6%</td>
<td>2.7%</td>
</tr>
<tr>
<td>ESCAPE (tPA only)</td>
<td>4.2%</td>
<td>2.5%</td>
</tr>
<tr>
<td>ESCAPE (no tPA)</td>
<td>2.2%</td>
<td>3.1%</td>
</tr>
<tr>
<td>HERMES group</td>
<td>4.4%</td>
<td>4.3%</td>
</tr>
</tbody>
</table>
The WAKEUP trial

- Stroke on awakening
- MR – FLAIR_DWI mismatch
- Randomized 1:1 to alteplase or control
- 90d following
- 503 patients enrolled.

**Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Alteplase Group (N=254)</th>
<th>Placebo Group (N=249)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age ±SD — yr</td>
<td>65.3±11.2</td>
<td>65.2±11.9</td>
</tr>
<tr>
<td>Male sex — no. (%)</td>
<td>165 (65.0)</td>
<td>160 (64.3)</td>
</tr>
<tr>
<td>Reason for unknown time of symptom onset — no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nighttime sleep</td>
<td>227 (89.4)</td>
<td>222 (89.2)</td>
</tr>
<tr>
<td>Daytime sleep</td>
<td>12 (4.7)</td>
<td>11 (4.4)</td>
</tr>
<tr>
<td>Aphasia, confusion, or other</td>
<td>15 (5.9)</td>
<td>16 (6.4)</td>
</tr>
<tr>
<td>Median interval between last time the patient was known to be well and symptom recognition (IQR) — hr</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arterial hypertension</td>
<td>135 (53.1)</td>
<td>131 (52.6)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>43 (16.9)</td>
<td>39 (15.7)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>93 (36.6)</td>
<td>85 (34.1)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>30 (11.8)</td>
<td>29 (11.6)</td>
</tr>
<tr>
<td>History of ischemic stroke</td>
<td>37 (14.6)</td>
<td>31 (12.4)</td>
</tr>
<tr>
<td>Median NIHSS score (IQR)†</td>
<td>6 (4–9)</td>
<td>6 (4–9)</td>
</tr>
<tr>
<td>Vessel occlusion on time-of-flight MRA — no./total no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>84/249 (33.7)</td>
<td>84/246 (34.1)</td>
</tr>
<tr>
<td>Intracranial internal carotid artery</td>
<td>24/249 (9.6)</td>
<td>11/246 (4.5)</td>
</tr>
<tr>
<td>Middle cerebral artery main stem</td>
<td>33/249 (14.1)</td>
<td>37/246 (15.0)</td>
</tr>
<tr>
<td>Middle cerebral artery branch</td>
<td>32/249 (12.9)</td>
<td>36/246 (14.6)</td>
</tr>
<tr>
<td>Other†</td>
<td>12/249 (4.8)</td>
<td>12/246 (4.9)</td>
</tr>
<tr>
<td>Median lesion volume on diffusion-weighted imaging (IQR) — ml</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.0 (0.8–7.9)</td>
<td>2.5 (0.7–8.8)</td>
</tr>
<tr>
<td>Median time from symptom recognition to MRI (IQR) — hr</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.6 (1.9–3.3)</td>
<td>2.6 (2.1–3.3)</td>
</tr>
</tbody>
</table>
Outcomes

Table 2. Primary and Secondary Efficacy Outcomes (Intention-to-Treat Population), a

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Alteplase Group (N = 254)</th>
<th>Placebo Group (N = 249)</th>
<th>Effect Variable</th>
<th>Adjusted Value (95% CI)††</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary efficacy end point</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Favorable outcome at 90 days — no. / total no. (%)</td>
<td>131/246 (53.3)</td>
<td>102/244 (41.8)</td>
<td>Odds ratio</td>
<td>1.61 (1.09 to 2.36)</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>Secondary efficacy end points</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median score on modified Rankin scale at 90 days (IQR)††</td>
<td>1 (1 to 3)</td>
<td>2 (1 to 3)</td>
<td>Common odds ratio</td>
<td>1.62 (1.17 to 2.23)</td>
<td>0.003†</td>
</tr>
<tr>
<td>Correlation between treatment response at 90 days and deficit level at baseline — no. / total no. (%)</td>
<td>72/246 (29.3)</td>
<td>44/244 (18.0)</td>
<td>Odds ratio</td>
<td>1.88 (1.22 to 2.89)</td>
<td>0.004†</td>
</tr>
<tr>
<td>Global Outcome Score at 90 days**</td>
<td></td>
<td></td>
<td>Odds ratio</td>
<td>1.47 (1.07 to 2.04)</td>
<td>0.02†</td>
</tr>
<tr>
<td>Median score on Beck Depression Inventory at 90 days (IQR)††</td>
<td>6.0 (2.0 to 11.0)</td>
<td>7.0 (2.0 to 14.0)</td>
<td>Mean difference (log)</td>
<td>-0.04 (-0.22 to 0.15)</td>
<td>0.69†</td>
</tr>
<tr>
<td>Total score on EQ-5D at 90 days‡‡</td>
<td>1.9±2.1</td>
<td>2.4±2.4</td>
<td>Mean difference (log)</td>
<td>-0.52 (-0.88 to -0.16)</td>
<td>0.004‡‡</td>
</tr>
<tr>
<td>Score on visual analog scale on EQ-5D at 90 days§§</td>
<td>72.6±19.7</td>
<td>64.9±23.8</td>
<td>Mean difference (log)</td>
<td>7.64 (3.75 to 11.51)</td>
<td>&lt;0.001‡‡</td>
</tr>
<tr>
<td>Median infarct volume at 22–36 hr (IQR) — ml</td>
<td>3.0 (0.8 to 17.7)</td>
<td>3.3 (1.1 to 16.6)</td>
<td>Mean difference (log)</td>
<td>-0.16 (-0.47 to 0.15)</td>
<td>0.32‡</td>
</tr>
</tbody>
</table>

Figure 2. Distribution of Scores on the Modified Rankin Scale at 90 Days (Intention-to-Treat Population).

Shown are the differences in the scores on the modified Rankin scale among patients in the alteplase group and the placebo group at 90 days. Scores range from 0 to 6, with 0 indicating no symptoms, 1 no clinically significant disability, 2 slight disability, 3 moderate disability, 4 moderately severe disability, 5 severe disability, and 6 death. Numbers indicate rounded proportions. There was a significant difference favoring the alteplase group over the placebo group in the overall distribution of scores (adjusted common odds ratio, 1.62; 95% confidence interval, 1.17 to 2.23; P = 0.003).
Observations on the trial

• Stroke severity was modest – median NIHSS 6
• Stroke volume was low – 2cc on DWI
• Only one third had proximal artery occlusion – time of flight MRA
• Clinical outcomes were uniformly better – it is very clear
• Adverse events were low – 4% PH2 rate compared to 0.4% control
• Radiological outcomes – no difference between groups
1. The term is a misnomer based upon our desire to time stroke from last known well.

2. There are multiple issues with timing of stroke onset
   • Many strokes are unwitnessed - by patient or family
   • Neurological deficits can occur without reaching consciousness

The true issue: We must abandon time as a criterion for treating stroke patients and select patients by clinical-imaging correlation
**DAWN trial**

**Study Objective:** To demonstrate superior functional outcomes at 90 days with Trevo plus medical management compared to medical management alone in appropriately selected patients treated six to 24 hours after last seen well

**Study design**
Global, multi-center, adaptive, population enrichment, prospective, randomized, open, blinded endpoint (PROBE), controlled FDA IDE trial

**Patient population**
Acute ischemic stroke (AIS) with large vessel occlusion
Able to be randomized between six to 24 hours after time last known well
Clinical imaging mismatch (CIM) defined by age, core, and NIHSS

**Target vessel**
Intracranial ICA, M1 segment of the MCA

**Randomization**
1:1 Trevo + medical management vs. medical management alone

**Sample size**
500 maximum subjects: 250 in the treatment arm and 250 in the control arm. Minimum sample size is 150 subjects.

**Follow-up**
24 hours (-6/+24), day 5-7/discharge, day 30 (± 14), and day 90 (± 14)
Stroke-on-awakening in DAWN

### Table 1. Characteristics of the Patients at Baseline.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Thrombectomy Group (N=107)</th>
<th>Control Group (N=99)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of stroke onset — no. (%)‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>On awakening</td>
<td>67 (63)</td>
<td>47 (47)</td>
</tr>
<tr>
<td>Unwitnessed stroke</td>
<td>29 (27)</td>
<td>38 (38)</td>
</tr>
<tr>
<td>Witnessed stroke</td>
<td>11 (10)</td>
<td>14 (14)</td>
</tr>
</tbody>
</table>
**Primary outcome**

- **TREVO**
  - mRS 0/uW: 9%
  - mRS 1/uW: 22%
  - mRS 3/uW: 17%
  - mRS 4/uW: 13%
  - mRS 5-6/uW: 13%
  - mRS 7.6: 26%

- **CONTROL**
  - mRS 0/uW: 4%
  - mRS 1/uW: 5%
  - mRS 3/uW: 4%
  - mRS 4/uW: 16%
  - mRS 9.1: 34%
  - mRS 7.6: 36%

- **Probability of superiority >0.9999**

- **73% relative risk reduction of dependency in ADL’s**

- **NNT for any lower disability 2.0**

**DAWN Trial**
Imaging and Time

• DAWN, DEFUSE-3 and WAKEUP
  • Build on multiple prior studies

• Model –
  • “Good scan – occlusion model”
    → Small core
    → Evidence of brain at risk (CTA, mCTA, CTP, MRI, clinical examination)

• Time is convenient surrogate for physiology but prone to much measurement error
Tenecteplase

• TASTE
• ATTEST-2
• TWIST
• TEMPO-2
• EXTEND-IA TNK, part 2
TNK-tPA (Tenecteplase)

- Genetically engineered, mutant tissue plasminogen activator
- Advantages compared to tPA (alteplase):
  - Higher fibrin specificity,
  - Longer half-life,
  - More resistant to plasminogen activator
- May result in more rapid reperfusion and lower intracranial hemorrhage

Parsons et al. NEJM 2012, 366;1099.
Phase II TNK vs alteplase

- Individual dose tier analysis

Distribution of reperfusion

Distribution of change in NIHSS
# Table 2. Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Tenecteplase Group (N=101)</th>
<th>Altepase Group (N=101)</th>
<th>Effect Size (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary efficacy outcome</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Substantial reperfusion at initial angiographic assessment — no. (%)*</td>
<td>22 (22)</td>
<td>10 (10)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Difference — percentage points</td>
<td>12 (2–21)</td>
<td></td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td>Adjusted incidence ratio</td>
<td>2.2 (1.1–4.4)</td>
<td></td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>Adjusted odds ratio</td>
<td>2.6 (1.1–5.9)</td>
<td></td>
<td>0.02</td>
<td></td>
</tr>
</tbody>
</table>
The last slide....

1. EVT is a ground-breaking therapy for the big, ischemic strokes – probably 15%, maybe as much as 20% of the total ischemic stroke burden

2. Alteplase is a concurrent therapy for ischemic stroke, applying to many more ischemic stroke patients and working synergistically with EVT

3. Speed of treatment is critical to both success and safety

4. Teamwork and communication are vital
Stroke Resources

www.aspectsinstroke.ca
[Imaging cases, teaching and practice]

https://cumming.ucalgary.ca/cme/programs/acute-stroke-care-e-learning
[Acute stroke e-learning course. For all nurses, EMTs, paramedics, ED physicians, general physicians, neurologists, radiologists]

http://www.ucalgary.ca/quicr/files/quicr/sample-stroke-visualization-worksheet.xls
[Worksheet for presenting DTN]
Calgary Stroke Fellowship Program

We have funding!
150 thrombectomy+150 IV tPA cases per year
75+ fellows trained so far from 15 countries
Weekly half day teaching, weekly case rounds
5 stroke clinician scientists: to find fun projects
10 stroke neurologists under one roof: to debate