Stroke Treatment Beyond Traditional Time Windows

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Endovascular Neurosurgery
Wellstar Health System
THE PAST

Endovascular Treatment for Acute Ischemic Stroke — Still Unproven

Marc I. Chimowitz, M.B., Ch.B.
Endovascular stent thrombectomy: the new standard of care for large vessel ischaemic stroke

Bruce C V Campbell, Geoffrey A Donnan, Kennedy R Lees, Werner Hacke, Pooja Khatri, Michael D Hill, Mayank Goyal, Peter J Mitchell, Jeffrey L Saver, Hans-Christoph Diener, Stephen M Davis

Summary

Background Results of initial randomised trials of endovascular treatment for ischaemic stroke, published in 2013, were neutral but limited by the selection criteria used, early-generation devices with modest efficacy, non-consecutive enrolment, and treatment delays.

Recent developments In the past year, six positive trials of endovascular thrombectomy for ischaemic stroke have provided level 1 evidence for improved patient outcome compared with standard care. In most patients, thrombectomy was performed in addition to thrombolysis with intravenous alteplase, but benefits were also reported in patients ineligible for alteplase treatment. Despite differences in the details of eligibility requirements, all these trials required proof of major vessel occlusion on non-invasive imaging and most used some imaging technique to exclude patients with a large area of irreversibly injured brain tissue. The results indicate that modern thrombectomy devices achieve faster and more complete reperfusion than do older devices, leading to improved clinical outcomes compared with intravenous alteplase alone. The number needed to treat to achieve one additional patient with independent functional outcome was in the range of 3–2–7 1 and, in most patients, was in addition to the substantial efficacy of intravenous alteplase. No major safety concerns were noted, with low rates of procedural complications and no increase in symptomatic intracerebral haemorrhage.

Where next? Thrombectomy benefits patients across a range of ages and levels of clinical severity. A planned meta-analysis of individual patient data might clarify effects in under-represented subgroups, such as those with mild initial stroke severity or elderly patients. Imaging-based selection, used in some of the recent trials to exclude patients with large areas of irreversible brain injury, probably contributed to the proportion of patients with favourable outcomes. The challenge is how best to implement imaging in clinical practice to maximise benefit for the entire population and to avoid exclusion of patients with smaller yet clinically important potential to benefit. Although favourable imaging identifies patients who might benefit despite long delays from symptom onset to treatment, the proportion of patients with favourable imaging decreases with time. Health systems therefore need to be reorganised to deliver treatment as quickly as possible to maximise benefits. On the basis of available trial data, intravenous alteplase remains the initial treatment for all eligible patients within 4.5 h of stroke symptom onset. Those patients with major vessel occlusion should, in parallel, proceed to endovascular thrombectomy immediately rather than waiting for an assessment of response to alteplase, because minimising time to reperfusion is the ultimate aim of treatment.
Patients eligible for intravenous rtPA should receive intravenous rtPA even if intra-arterial treatments are being considered.

Patients should receive endovascular therapy with a stent retriever if they meet all the following criteria:

- a) prestroke mRS score 0 to 1,
- b) acute ischemic stroke receiving intravenous r-tPA within 4.5 hours of onset according to guidelines from professional medical societies,
- c) causative occlusion of the internal carotid artery (ICA) or proximal MCA (M1),
- d) age ≥18 years,
- e) NIHSS score of ≥ 6,
- f) ASPECTS of ≥ 6, and

Class I Level of Evidence A New Recommendation

2015 American Heart Association/American Stroke Association Focused Update of the 2013 Guidelines for the Early Management of Patients With Acute Ischemic Stroke Regarding Endovascular Treatment

A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association

The American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists.

Endorsed by the American Association of Neurological Surgeons (AANS); Congress of Neurological Surgeons (CNS); AANS/CNS Cerebrovascular Section; American Society of Neuroradiology; and Society of Vascular and Interventional Neurology

Endovascular thrombectomy after large-vessel ischemic stroke: a meta-analysis of individual patient data from five randomised trials

HERMES Collaborators

Highly Effective Reperfusion evaluated in Multiple Endovascular Stroke trials (HERMES)

Endovascular thrombectomy after large-vessel ischemic stroke: a meta-analysis of individual patient data from five randomised trials


Summary

Background In 2015, five randomised trials showed efficacy of endovascular thrombectomy over standard medical care in patients with acute ischaemic stroke caused by occlusion of the proximal anterior artery circulation. In this meta-analysis we aimed to pool individual patient data from these trials to address remaining questions about whether the therapy is efficacious across the diverse populations of trials.

Methods We formed the HERMES collaboration to pool patient-level data from five trials (MR CLEAN, ESCAPE, REVASCAT, SWIFT PRIME, and EXTEND IA) done between December, 2010, and December, 2014. In these trials, patients with acute ischaemic stroke caused by occlusion of the proximal anterior artery circulation were randomly assigned to receive either endovascular thrombectomy within 12 h of symptom onset or standard care (control), with a primary outcome of reduced disability on the modified Rankin Scale (mRS) at 90 days. The principal investigators of the five trials, by direct access to the study databases, extracted individual patient data that we used to assess the primary outcome of reduced disability on mRS at 90 days and examine heterogeneity of this treatment effect across pre-specified subgroups. To account for between-trial variance we used mixed-effects modelling with random effects for parameters of interest. We then used mixed-effects ordinal logistic regression models to calculate common odds ratios (cOR) for the primary outcome of reduced disability (shift in analysis) and in subgroups after adjustment for age, sex, baseline stroke severity (National Institute of Health Stroke Scale score), site of occlusion (internal carotid artery vs M1 segment of middle cerebral artery vs M1 segment of middle cerebral artery, intravenous alteplase vs no), and baseline Alberta Stroke Program Early CT score, and time from stroke onset to randomisation.

Findings We analysed individual data for 1257 patients (634 assigned to endovascular thrombectomy, 623 assigned to control). Endovascular thrombectomy led to significantly reduced disability at 90 days compared with control (adjusted cOR 2.49, 95% CI 1.76–3.53; p < 0.0001). The number needed to treat with endovascular thrombectomy to reduce disability by at least one level on mRS for one patient was 2.6. Subgroup analysis of the primary endpoint showed no heterogeneity of treatment effect across pre-specified subgroups for reduced disability (p = 0.68). Effect size favouring endovascular thrombectomy was present in several states of special interest, including in patients aged 80 years or older (cOR 3.68, 95% CI 1.95–6.94), those randomised more than 304 min after symptom onset (1.76, 1.05–2.97), and those not eligible for intravenous alteplase (2.43, 1.30–4.55). Mortality at 90 days and of parenchymal haemorrhage and symptomatic intracranial haemorrhage did not differ between populations.

Interpretation Endovascular thrombectomy is of benefit to most patients with acute ischaemic stroke caused by occlusion of the proximal anterior circulation, irrespective of geographical location. These findings will have global implications on structuring systems of care to provide timely treatment to patients with acute ischaemic stroke due to large vessel occlusion.

Funding Medtronic.
Overall Treatment Effect NNT = 2.6
23 Randomized Trials of PCI vs Lytics: 30 day Events (n=7739)

ARR 6%, NNT= 29

Keeley & Grines, Lancet 2003;361:13-20
Ordinal (shift) analysis

Dichotomized analysis by functional independence (mRS)

**HERMES- SUBGROUP ANALYSIS – AGE**

### Shift on 90 day mRS stratified by age

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>n</th>
<th>cOR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-49</td>
<td>158</td>
<td>1.36 (0.75-2.46)</td>
</tr>
<tr>
<td>50-59</td>
<td>218</td>
<td>2.85 (1.72-4.72)</td>
</tr>
<tr>
<td>60-69</td>
<td>333</td>
<td>2.58 (1.49-4.48)</td>
</tr>
<tr>
<td>70-79</td>
<td>371</td>
<td>2.41 (1.55-3.74)</td>
</tr>
<tr>
<td>18-79</td>
<td>1080</td>
<td>2.44 (1.70-3.50)</td>
</tr>
<tr>
<td>≥80</td>
<td>198</td>
<td>3.68 (1.95-6.92)</td>
</tr>
</tbody>
</table>

### Risk Ratio 95% C.I.

<table>
<thead>
<tr>
<th>Age</th>
<th>N</th>
<th>Risk Ratio</th>
<th>95% C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-49</td>
<td>158</td>
<td>1.26</td>
<td>[0.81; 1.97]</td>
</tr>
<tr>
<td>50-59</td>
<td>218</td>
<td>2.40</td>
<td>[1.45; 4.00]</td>
</tr>
<tr>
<td>60-69</td>
<td>333</td>
<td>1.78</td>
<td>[1.25; 2.55]</td>
</tr>
<tr>
<td>70-79</td>
<td>371</td>
<td>1.71</td>
<td>[1.19; 2.45]</td>
</tr>
<tr>
<td>18-79</td>
<td>1080</td>
<td>1.69</td>
<td>[1.39; 2.07]</td>
</tr>
<tr>
<td>≥80</td>
<td>198</td>
<td>2.09</td>
<td>[1.03; 4.25]</td>
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</table>
### HERMES- SUBGROUP ANALYSIS – stroke severity

#### Ordinal (shift) analysis

<table>
<thead>
<tr>
<th>NIHSS score (p_{interaction} = 0.45)</th>
<th>n</th>
<th>cOR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤10</td>
<td>177</td>
<td>1.67 (0.80-3.50)</td>
</tr>
<tr>
<td>11-15</td>
<td>307</td>
<td>2.68 (1.39-5.19)</td>
</tr>
<tr>
<td>16-20</td>
<td>473</td>
<td>2.81 (1.80-4.38)</td>
</tr>
<tr>
<td>≥21</td>
<td>321</td>
<td>2.52 (1.40-4.54)</td>
</tr>
</tbody>
</table>

#### Dichotomized analysis by Functional independence (mRS)

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Risk Ratio</th>
<th>95% C.I.</th>
</tr>
</thead>
</table>

HERMES- SUBGROUP ANALYSIS – ASPECTS

Ordinal (shift) analysis

Dichotomized analysis by Functional independence (mRS)

<table>
<thead>
<tr>
<th>ASPECTS (p_interaction = 0.29)</th>
<th>n</th>
<th>Risk Ratio</th>
<th>95% C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-5</td>
<td>121</td>
<td>1.24</td>
<td>(0.62-2.49)</td>
</tr>
<tr>
<td>6-8</td>
<td>475</td>
<td>2.34</td>
<td>(1.68-3.26)</td>
</tr>
<tr>
<td>9-10</td>
<td>682</td>
<td>2.66</td>
<td>(1.61-4.40)</td>
</tr>
</tbody>
</table>
HERMES- SUBGROUP ANALYSIS – time to treatment

Ordinal (shift) analysis

Dichotomized analysis by Functional independence (mRS)

<table>
<thead>
<tr>
<th>Onset to Randomization</th>
<th>n</th>
<th>cOR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 300 mins</td>
<td>1070</td>
<td>1.76 [1.43; 2.16]</td>
</tr>
<tr>
<td>&gt; 300 mins</td>
<td>208</td>
<td>1.55 [0.93; 2.58]</td>
</tr>
</tbody>
</table>
7.3 hour onset to groin puncture time window for EVT

Infarct volume (both treatment groups) strongly correlates with clinical outcome ($p < 0.0001$)


IMS 3, Jovin T., et al, ISC 2015
TIME IS BRAIN REVISITED

Time = Brain
Imaging = Time

IMAGING = BRAIN
SHOULD THERE BE A TIME WINDOW FOR ACUTE STROKE INTERVENTIONS ???
SERIAL MRI'S (CORONAL SECTIONS) AT THREE LEVELS IN THE BRAIN DEPICTING THE APPARENT DIFFUSION COEFFICIENT OF WATER (ADC) (MARKED BY THE BLUE COLOUR) DEMONSTRATING THE TIME-DEPENDENT GROWTH OF THE ISCHEMIC CORE.
Initial Growth Rate: Known Onset & M1 Occlusion

Baseline DWI Volume (ml) vs. Time between Symptom Onset and Baseline MRI (hrs)

Initial Growth Rate: Known Onset & M1 Occlusion

Baseline DWI Volume (ml)

Time between Symptom Onset and Baseline MRI (hrs)

RELATIONSHIP BETWEEN TIME FROM ONSET TO REPERFUSION AND GOOD OUTCOMES IN DEFUSE 2

N= 46
Median baseline infarct volume = 16 cc

Lansberg M. et al., Neurology 2015
RELATIONSHIP BETWEEN TIME FROM ONSET TO REPERFUSION AND GOOD OUTCOMES IN REVASCAT

Ribo et al., Stroke 2016

28% favorable outcome
For 30 min reduction in time

44% favorable outcome
For 30 min reduction in time
Imaging-Based Endovascular Therapy for Acute Ischemic Stroke due to Proximal Intracranial Anterior Circulation Occlusion Treated Beyond 8 Hours From Time Last Seen Well

Retrospective Multicenter Analysis of 237 Consecutive Patients

Tudor G. Jovin, MD; David S. Liebeskind, MD; Rishi Gupta, MD; Marilyn Rymer, MD; Ansaar Rai, MD; Osama O. Zaidat, MD, MS; Alex Abou-Chebl, MD; Blaise Baxter, MD; Elad I. Levy, MD; Andrew Barreto, MD; Raul G. Nogueira, MD

Background and Purpose—Current selection criteria for intra-arterial therapies in the anterior circulation use time windows of 8 hours. Modern neuroimaging techniques have identified individuals with salvageable penumbra who present beyond this timeframe. We sought to assess safety, procedural, and clinical outcomes of MRI or CT perfusion imaging-based endovascular therapy in patients with anterior circulation stroke treated beyond 8 hours from time last seen well.

Methods—We conducted a multicenter retrospective review of consecutive patients meeting the following criteria: (1) acute proximal intracranial anterior circulation occlusion; (2) endovascular treatment initiated >8 hours from time last seen well; and (3) treatment selection based on MRI or CT perfusion imaging.

Results—Two hundred thirty-seven patients were identified (mean age, 63.8±16 years; mean baseline National Institutes of Health Stroke Scale, 15±5.5; mean time last seen well to treatment, 15±11.2 hours; male gender, 46%). Successful revascularization was achieved in 175 of 237 (73.84%) patients. Parenchymal hematoma occurred in 21 of 237 (8.86%) patients. The 90-day mortality rate was 21.5% (51 of 237). The rate of good outcomes was 45% (100 of 223) in the 223 patients with available modified Rankin Scale data at 90 days or time of hospital discharge. In multivariate analyses, age (OR, 0.96; 95% CI, 0.94 to 0.98; P=0.002), admission National Institutes of Health Stroke Scale (OR, 0.93; 0.87 to 0.98; P=0.016), and successful revascularization (OR, 4.32; 1.99 to 9.39; P<0.0001) were identified as independent predictors of good outcomes.

Conclusions—Endovascular therapy can be instituted with acceptable safety beyond 8 hours from time last seen well when selection is based on advanced neuroimaging. Successful revascularization is significantly associated with higher rates of good outcomes. The benefit of this approach compared with standard medical therapy should be assessed in a prospective randomized trial. (Stroke. 2011;42:2206-2211.)

Key Words: acute stroke ■ angiography ■ brain infarction ■ CT ■ endovascular treatment ■ interventional neuroradiology ■ MRI ■ stenting ■ thrombolysis
CASE SERIES

Outcomes after endovascular treatment for anterior circulation stroke presenting as wake-up strokes are not different than those with witnessed onset beyond 8 hours

Amin Aghaebrahim,¹ Carlos Leiva-Salinas,² Ashutosh P Jadhav,¹ Brian Jankowitz,³ Syed Zaidi,¹ Mouhammad Jumaa,¹ Xabi Urra,¹,⁴ Edilberto Amorim,¹ Guangming Zhu,² Dan-Victor Giurgiutiu,¹ Anat Horev,¹ Vivek Reddy,¹ Maxim Hammer,¹ Lawrence Wechsler,¹ Max Wintermark,² Tudor Jovin¹
WAKE UP STROKE VS WITNESED ONSET BEYOND 8 HRS - IS THERE A DIFFERENCE IN OUTCOMES WITH IAT?

**Table 1** Baseline characteristics and outcomes

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>Group 1 (n=78)</th>
<th>Group 2 (n=128)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) (mean SD)</td>
<td>67 (13.8)</td>
<td>64 (13.6)</td>
<td>0.11</td>
</tr>
<tr>
<td>Male (%)</td>
<td>53</td>
<td>59</td>
<td>0.45</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>73</td>
<td>71</td>
<td>0.74</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>18</td>
<td>17</td>
<td>0.83</td>
</tr>
<tr>
<td>Dyslipidemia (%)</td>
<td>36</td>
<td>44</td>
<td>0.27</td>
</tr>
<tr>
<td>Atrial fibrillation (%)</td>
<td>30</td>
<td>21</td>
<td>0.15</td>
</tr>
<tr>
<td>Current smoker (%)</td>
<td>33</td>
<td>35</td>
<td>0.80</td>
</tr>
<tr>
<td>Baseline NIHSS (mean SD)</td>
<td>15 (4.6)</td>
<td>14 (5.4)</td>
<td>0.14</td>
</tr>
<tr>
<td>OTT (h) (mean SD)</td>
<td>14.9 (11.2)</td>
<td>18.2 (33.6)</td>
<td>0.40</td>
</tr>
<tr>
<td>Tandem occlusion (%)</td>
<td>37</td>
<td>24</td>
<td>0.047</td>
</tr>
<tr>
<td>M1 (%)</td>
<td>56</td>
<td>68</td>
<td>0.09</td>
</tr>
<tr>
<td>M2 (%)</td>
<td>14</td>
<td>15</td>
<td>0.80</td>
</tr>
<tr>
<td>ICAT (%)</td>
<td>36</td>
<td>20</td>
<td>0.006</td>
</tr>
<tr>
<td>Manual aspiration (%)</td>
<td>54</td>
<td>55</td>
<td>0.90</td>
</tr>
<tr>
<td>Intubated state (%)</td>
<td>22</td>
<td>20</td>
<td>0.70</td>
</tr>
<tr>
<td>TICI ≥2b (%)</td>
<td>68</td>
<td>70</td>
<td>0.70</td>
</tr>
</tbody>
</table>

**Outcomes**

| mRS 0–2 at 90 days (%) | 43 | 50 | 0.30 |
| PH (%)                 | 9  | 5.5| 0.30 |
| Mortality at 90 days (%)| 21 | 22 | 0.89 |

**Table 2** Radiographic findings

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline MRI (%)</td>
<td>40</td>
<td>47</td>
<td>0.30</td>
</tr>
<tr>
<td>Baseline PCT (%)</td>
<td>73</td>
<td>66</td>
<td>0.30</td>
</tr>
<tr>
<td>Baseline MRI or PCT (%)</td>
<td>89</td>
<td>94</td>
<td>0.11</td>
</tr>
<tr>
<td>Baseline infarct volume (mL) (mean SD)</td>
<td>18.4 (20.2)</td>
<td>16.7 (19.2)</td>
<td>0.50</td>
</tr>
<tr>
<td>Final infarct volume (mL) (mean SD)</td>
<td>75.2 (93)</td>
<td>61.4 (73)</td>
<td>0.60</td>
</tr>
<tr>
<td>Infarct growth (mL) (mean SD)</td>
<td>59 (93)</td>
<td>54 (71)</td>
<td>0.70</td>
</tr>
</tbody>
</table>

PCT, perfusion CT.

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Aghaebrahim A. et al., JNIS 2015
SHOULD WE TREAT PATIENTS WITH LVO AND MISMATCH BEYOND 6 HOURS WITH NO TIME LIMIT ???
88 year old woman with L M1 occlusion, TLSW 22 hours, NIHSS 21, no intervention
mRS at 3 weeks: 3

Baseline MRI/MRA – NIHSS 21

MCA partially recanalized

4 day MRI/MRA – NIHSS 11
88 year old woman with R M1 occlusion, TLSW 20 hours, NIHSS 17, no intervention
mRS at 30 days 1

Baseline MRI/MRA

Follow-up MRI/MRA at 24 hours (NIHSS 17) – no infarct growth and partial recanalization
61 year old man with R M1 occlusion, TLSW 14 hours, NIHSS 21, no intervention
3 months mRS 4
DAWN Trial: Why Do We Need to Do It?
# DAWN STUDY OVERVIEW

<table>
<thead>
<tr>
<th>Title</th>
<th>DWI or CTP Assessment with Clinical Mismatch in the Triage of Wake Up and Late Presenting Strokes Undergoing Neurointervention (DAWN)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sponsor</td>
<td>Stryker Neyrovascular Inc.</td>
</tr>
<tr>
<td>PI</td>
<td>Tudor Jovin, MD and Raul Nogueira, MD</td>
</tr>
<tr>
<td>Study device</td>
<td>Trevo® ProVue™ and Trevo® XP ProVue™ Retrievers</td>
</tr>
<tr>
<td>Control intervention (IV-tPA yes/no?)</td>
<td>Best medical therapy including iv t-PA in eligible patients (which will be estimated to make up maximum 20% of total)</td>
</tr>
<tr>
<td>Study population</td>
<td>Acute stroke patients with no upper age limit presenting in the 6-24 hour time window with proximal anterior circulation occlusions (M1, ICA T) and substantial clinical/core mismatch</td>
</tr>
<tr>
<td>Objective</td>
<td>To evaluate the hypothesis that Trevo thrombectomy plus medical management leads to superior clinical outcomes at 90 days as compared to medical management alone in appropriately selected subjects experiencing an acute ischemic stroke when treatment is initiated within 6-24 hours after last seen well.</td>
</tr>
</tbody>
</table>
Counterpoints Supporting Equipoise: Why DAWN Can Fail?

Longer Time from Stroke Onset to Treatment = Better Collaterals = ? Better Natural History

Longer Time from Stroke Onset to Treatment = ? Increased Risk of Hemorrhagic Transformation

Longer Time from Stroke Onset to Treatment = ? Worse Reperfusion Rates

RCTs of Delayed IV Thrombolysis (including Mismatch-Based) Have Failed to Show a Benefit
DAWN™ Trial Design

- Prospective, randomized (1:1), multi-center, Phase II/III (feasibility/pivotal), adaptive, population enrichment, blinded endpoint, controlled trial
- Up to 50 sites (worldwide)
- 150 subjects (feasibility) up to 500 (pivotal) max
- Primary endpoint:
  - Difference between the average weighted mRS at 90 days between treatment and control groups
DAWN™ Trial Unique Design

Primary Endpoint: Weighted mRS

- Designed to capture health state transitions across the entire spectrum
- Endpoint that is a combination of both efficacy and safety
- Differentiates outcomes
- Patient-centered outcomes analysis

<table>
<thead>
<tr>
<th>mRS</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>Weight</td>
<td>10</td>
<td>9.1</td>
<td>7.6</td>
<td>6.5</td>
<td>3.3</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Enrichment

- Designed to fine tune the patient population based on core infarct size
- Identify subgroups experiencing clinical benefit

0-50 cc → 0-45 cc → 0-40 cc → 0-35 cc → 0-30 cc
Origin of the Utility – Weighted mRS

Chasnaianunkul et al., Stroke. 2015;46:2238-2243.
DAWN™ Clinical Trial

Goal: To identify the Target Mismatch Patient in the 6-24h Window (including Wake-Up Strokes)

- Clinical Mismatch: NIHSS ≥10 + Small Infarct
- Proximal Occlusion: ICA-T and/or MCA-M1 Occlusion
- Standardized RAPID software

Randomization Balanced re: CIM subgroup, time and occlusion location
CLINICAL EXAM (NIHSS): A GOOD ESTIMATION OF THE AT RISK TERRITORY ??

The clinical-DWI mismatch

A new diagnostic approach to the brain tissue at risk of infarction

A. Dávalos, MD, PhD; M. Blanco, MD, PhD; S. Pedraza, MD; R. Leira, MD, PhD; M. Castellanos, MD; J.M. Pumar, MD, PhD; Y. Silva, MD; J. Serena, MD, PhD; and J. Castillo, MD, PhD

Abstract—Objective: To evaluate the usefulness of a mismatch between the severity of acute clinical manifestations and the diffusion-weighted imaging (DWI) lesion in predicting early stroke outcome and infarct volume. Methods: One hundred sixty-six patients with a hemispheric ischemic stroke of <12 hours’ duration were studied. The NIH Stroke Scale (NIHSS) score and the volume of DWI lesion were measured on admission and at 72 ± 12 hours. Infarct volume was measured on T2-weighted or fluid-attenuated inversion recovery images at day 30. Early neurologic deterioration (END) was defined as an increase of ≥4 points between the two NIHSS evaluations. Thirty-eight patients received IV thrombolysis or abciximab. Clinical-DWI mismatch (CDM) was defined as NIHSS score of ≥8 and ischemic volume on DWI of ≥25 mL on admission. The adjusted influence of CDM on END, DWI lesion enlargement at 72 hours, and infarct growth at day 30 was evaluated by logistic regression analysis and generalized linear models. Results: CDM was found in 87 patients (52.4%). Patients with CDM had a higher risk of END than patients without CDM because NIHSS < 8 (odds ratio [OR], 9.0; 95% CI, 1.9 to 42) or DWI lesion > 25 mL (OR, 2.0; 95% CI, 0.8 to 4.9). CDM was associated with an increase of 46 to 68 mL in the mean volume of DWI lesion enlargement and infarct growth in comparison with non-CDM. All the effects were even greater and significant in patients not treated with reperfusion therapies. Conclusions: Acute stroke patients with an NIHSS score of ≥8 and DWI volume of ≥25 mL have a higher probability of infarct growth and early neurologic deterioration. The new concept of CDM may identify patients with tissue at risk of infarction for thrombolytic or neuroprotective drugs.

NEUROLOGY 2004;62:2187-2192

Davalos et al., Neurology 2004
DEFUSE 3: NIH-funded, prospective, randomized, multi-center, adaptive, blinded endpoint trial

- Paradigm shift
  - From time-based selection to imaging-based selection

- Target population
  - Anterior circulation ischemic stroke; ICA or M1 occlusions (CTA/MRA)
  - Salvageable tissue on CT perfusion or MR diffusion / perfusion
  - Endovascular therapy within 6-16 hours of last known well

- Design
  - 1:1 randomization; standard medical therapy vs. endovascular
  - 45 sites
Neuroimaging Inclusion Criteria

MRA / CTA reveals
  ◦ M1 segment MCA occlusion, or
  ◦ ICA occlusion (cervical or intracranial; with or without tandem MCA lesions)

AND

Target Mismatch Profile on CT perfusion or MRI (RAPID)
  ◦ Ischemic core volume < 70 mL
  ◦ Mismatch ratio > 1.8
  ◦ Mismatch volume ≥ 15 mL
Dear DAWN Investigators:

Today, the DAWN DSMB has performed an interim analysis of the first 200 enrolled subjects in DAWN. It is with great excitement that we announce that based on crossing of pre-specified probability thresholds for efficacy, the DSMB recommended trial enrollment to be stopped.

According to the message from DSMB chair, Wade Smith, MD, PhD, “The DSMB has concluded that the DAWN trial should be considered for stopping further enrollment for efficacy. This is based on incomplete follow-up, but the DSMB is convinced by the excellent statistical work done by Berry Consultants that the conclusion of efficacy - when all data is obtained and the dataset closed - will not change.”

The DAWN steering committee has voted to accept the recommendation of the DSMB and, therefore, enrollment will be stopped as of now. The DAWN randomization site has been closed and no further subjects can be entered in the study.

We would like to remind all investigators that due to pending follow-up evaluations, the results reviewed by the DSMB are preliminary. Therefore, until the final follow-up information of the last subject enrolled is obtained, it is essential that the all data remains blinded and that follow-up of subjects who have not yet achieved 90 days follow-up continues in unchanged fashion. The final results of the trial will be available after completion of all pending follow-up data.

We would like to thank each and every one of you for achievement of this historical milestone which, if confirmed by the final results, has the potential to change stroke care across the world.

Sincerely,

Tudor Jovin, Raul Nogueira, and Christine Toruno on behalf of Stryker Neurovascular
Conclusions

- Endovascular stroke therapy is a game changer for patient outcomes

- Patients with larger stroke syndromes regardless of time of last known normal should be screened

- Worse to under treat than over treat this disease

- Community, Hospital, EMS discussions of how to triage patients to CSC and Endovascular hospitals