Future Interventions for Acute Stroke

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Thrombolysis Trials

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TISSUE PLASMINOGEN ACTIVATOR FOR ACUTE ISCHEMIC STROKE

The NEW ENGLAND JOURNAL OF MEDICINE

SOMEBODY IN ENGLAND

SEPTEMBER 28, 2000
VOL. 303
NO. 37

Thrombolysis with Alteplase 3 to 4.5 Hours after Acute Ischemic Stroke

Warren Higashida, M.D., Myriam Kates, M.D., Erich Hynek, Ph.D., Winicki Suwannawat, M.D., Atena Diodato, M.D., Donald Guetts, M.D., Vincent Lin, M.D., Kerrelise L. Low, M.D., Zhizhe Rong, M.D., Thomas Mischke, M.D., Dietmar Schneider, M.D., Rudolph von Kupffer, M.D., Niks Würflinger, M.D., and Christa Zoll, M.D., for the ECASS investigators
NINDS Trial of IV rtPA <3h:
3 Month Outcome

<table>
<thead>
<tr>
<th>rtPA</th>
<th>GOS</th>
<th>Barthel</th>
<th>Rankin</th>
<th>NIHSS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>GOS</td>
<td>Barthel</td>
<td>Rankin</td>
<td>NIHSS</td>
</tr>
</tbody>
</table>

Odds of Complete Recovery (mRS 0-1) in Individual Data Pooled Analysis from IV rtPA Trials

**Time is Brain:**
Current Stroke Treatment: Reperfusion Improves Outcomes

For every 100 patients treated with IV rtPA within 3 hours

Recanalisation of occluded blood vessel with IV rtPA

Changes in final outcome as a result of treatment:
- Normal or nearly normal
- Better
- No major change
- Worse
- Severely disabled or dead

Saver et al. Stroke. 2010;41:2381-2390

Current Stroke Treatment: Reperfusion Improves Outcomes...But with Some Risk

For every 100 patients treated with IV rtPA within 3 hours

Recanalisation of occluded blood vessel with IV rtPA

Changes in final outcome as a result of treatment:
- Normal or nearly normal
- Better
- No major change
- Worse
- Severely disabled or dead

The Downside of Recanalisation: Intracerebral Haemorrhage

Saver et al. Stroke. 2010;41:2381-2390
Why Are Patients Not Treated with IV rtPA?

**SINAPSE**

**Ischaemic Stroke**

- Presenting within Time Window (27%)
- Presenting outwith Time Window (73%)

**“Wake up” stroke**

No witness + communication difficulty

Barber et al Neurology 2001;56:1015-1020

**IST-3**

**SINAPSE**

- Distinctive features:
  - “uncertain” over indication
  - Predominantly very elderly (53% >80 years)
  - Predominantly late onset-to-treatment time
    - 72% >3 hours
    - 33% 4.5-6 hours
- OR for favourable outcome at 6 months
  - dichotomous (OHS 0-1 v OHS 2-6): **1.26** (1.04-1.53, p=0.018)
  - Ordinal shift (OHS 0, 1, 2, 3, 4-6): **1.27** (1.10–1.47, p=0.001)

IST-3 Collaborative Group. Lancet 2012,
ASIST Study:
Time to Presentation after Stroke

- 38% within <3h
- 37% within 3 to 6h
- 12% within 6 to 12h
- 13% >12h

- n=739
- unselected acute stroke patients
- 22 UK hospitals

Harraf et al. BMJ 2002;325:17

If You Have Longer, You Take Longer:
"Onset to Door" and "Door to Needle" Times in 11,833 patients treated with IV rtPA

Saver et al. Stroke. 2010;41:1431-1439
The Scan in a Van

Better Brain Imaging Might Identify Patients Who Can Benefit from Treatment

**“Too Mild to Treat”: Outcomes**

<table>
<thead>
<tr>
<th>Reasons for exclusion</th>
<th>n</th>
<th>Median NIHSS</th>
<th>Dependent at discharge or died during admission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Too mild</td>
<td>41</td>
<td>3</td>
<td>7 (17%)</td>
</tr>
<tr>
<td>Clinical improvement</td>
<td>57</td>
<td>6</td>
<td>25 (44%)</td>
</tr>
<tr>
<td>Either</td>
<td>98</td>
<td>33%</td>
<td></td>
</tr>
</tbody>
</table>

Barber et al. Neurology 2001;56:1015–1020

**PRACTISE**

Patient fulfills Clinical Eligibility for IV rtPA (<4.5h)

NIHSS, Risk Factors, Blood glucose, BP, Clinical eligibility checklist

- NCCT only
- Multimodal CT (CT + CTA + CTP)
- ICH or other non-ischaemic stroke CT

Thrombolysis Decision

CT or MRI 24h

Clinical Outcome

NIHSS 24h, 72h, 7d, 30d, mRS 30d & 3m

Central Review

ICH classification

Brain swelling

Primary Outcome...

Secondary Outcome...

- 3 month mRS Outcome (CMH analysis) in ITT and Target Populations
- Safety - SICH rates
- 30m mRS in patients not treated with IV rtPA
- Diagnostic sensitivity and specificity
- Interobserver Agreement (Central vs local processing)
- Time to Decision for each imaging modality
- Time to IV rtPA treatment
Can Imaging Predict Risk of Intracerebral Haemorrhage with IV rtPA?
DEFUSE study: “Malignant Profile”

- Defined after DEFUSE interim analysis
- DWI volume >100ml and/or PWI volume >100ml and T\text{max} >8s
- Poor clinical outcome
- High risk (50%) of SICH with early reperfusion


Does Imaging Selection Improve Clinical Outcomes?

DEFUSE-2: Mismatch Predicts Benefit from Late Reperfusion

**OR for Favourable Outcome**

- **8.5 (95% CI 2.6 – 28)**
- **0.2 (95% CI 0.0 – 1.6)**

*Adjusted for age and baseline DWI volume

Lansberg et al. Lancet Neurol 2012 (in press)

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FLAIR as a Tissue Clock?

**DWI+ / FLAIR -**

<table>
<thead>
<tr>
<th>Onset</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive Predictive Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;3h</td>
<td>0.83</td>
<td>0.71</td>
<td>0.64</td>
</tr>
<tr>
<td>&lt;4.5h</td>
<td>0.74</td>
<td>0.85</td>
<td>0.87</td>
</tr>
<tr>
<td>&lt;6h</td>
<td>0.69</td>
<td>0.91</td>
<td>0.94</td>
</tr>
<tr>
<td>&lt;3h excl Lacunes and post fossa</td>
<td>0.93</td>
<td>0.77</td>
<td></td>
</tr>
</tbody>
</table>

WAKE-UP Flow Chart

IV rtPA Recanalisation Rates

Ribo et al. Stroke. 2006;37:1000-1004
Recanalisation and Occlusion Site: TIMI 2-3 Angiographic Outcomes 1h post-IV Duteplase

Del Zoppo et al Ann Neurol 1992;32:78-86

Better Thrombolytic Drugs?

Alteplase
Tenecteplase
### DIAS (part 2): Clinical Outcome by Dose

<table>
<thead>
<tr>
<th>Dose</th>
<th>Placebo</th>
<th>62.5ug/kg</th>
<th>90ug/kg</th>
<th>125ug/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Good Clinical Outcome</td>
<td>22.2</td>
<td>19.2</td>
<td>13.3</td>
<td>46.7</td>
</tr>
<tr>
<td>% Reperfusion</td>
<td>23.1</td>
<td>46.7</td>
<td>60</td>
<td>71.4</td>
</tr>
</tbody>
</table>

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**Hacke et al. Stroke 2005;36:66-73**

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### Better Thrombolytic Drugs?

**A Randomized Trial of Tenecteplase versus Alteplase for Acute Ischemic Stroke**

ATTEST: Alteplase v Tenecteplase <4.5h

Clinically eligible for IV thrombolysis pending CT
Consent for ATTEST randomisation dependent on CT result
NIHSS, glucose, BP, demographics
Routine CT confirms eligibility

Alteplase 0.9mg/kg (max 90mg)
10% bolus + 90% IVI over 1h

Tenecteplase 0.25mg/kg (max 25mg)
Bolus

24 hour CT, intracranial CTA NIHSS

Primary Outcome:
% Penumbra Salvaged at 24-28h
Secondary Outcomes:
Viability
Recanalisation
Microbleeds

Additional CTP, CTA

72h NIHSS

30 and 90 Day Follow-up
NIHSS, mRS, BI, Home Time

Device Studies

<table>
<thead>
<tr>
<th>MERCİ</th>
<th>Multi-MERCİ</th>
<th>Penumbra</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time Window</td>
<td>8h</td>
<td>8h</td>
</tr>
<tr>
<td>n Subjects</td>
<td>151</td>
<td>111</td>
</tr>
<tr>
<td>Median NIHSS</td>
<td>20</td>
<td>19</td>
</tr>
<tr>
<td>Onset to Treatment Time (h)</td>
<td>6.4h</td>
<td>5.8h</td>
</tr>
<tr>
<td>% Recanalised</td>
<td>46%</td>
<td>54%</td>
</tr>
<tr>
<td>Procedural Complications</td>
<td>7.1%</td>
<td>4.5%</td>
</tr>
<tr>
<td>SICH</td>
<td>7.8%</td>
<td>9.0%</td>
</tr>
<tr>
<td>Good Outcomes d90 (mRS 0-2)</td>
<td>28%</td>
<td>34%</td>
</tr>
<tr>
<td>Mortality d90</td>
<td>43.5%</td>
<td>31%</td>
</tr>
</tbody>
</table>


Smith et al AJNR 2006;27:1177-82.
Device Studies

<table>
<thead>
<tr>
<th>Device</th>
<th>MERCI</th>
<th>Multi-MERCI</th>
<th>Penumbra</th>
<th>NINDS IV rt-PA NHSS&gt;9</th>
<th>NINDS Placebo NHSS&gt;9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time Window</td>
<td>8h</td>
<td>8h</td>
<td>8h</td>
<td>3h</td>
<td>3h</td>
</tr>
<tr>
<td>n Subjects</td>
<td>151</td>
<td>111</td>
<td>125</td>
<td>182</td>
<td>211</td>
</tr>
<tr>
<td>Median NIHSS</td>
<td>20</td>
<td>19</td>
<td>18</td>
<td>17</td>
<td>17</td>
</tr>
<tr>
<td>Onset to Treatment Time (h)</td>
<td>6.4h</td>
<td>5.8h</td>
<td>4.3h</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% Recanalised</td>
<td>46%</td>
<td>54%</td>
<td>82%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Procedural Complications</td>
<td>7.1%</td>
<td>4.5%</td>
<td>12.8%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SICH</td>
<td>7.8%</td>
<td>9.0%</td>
<td>11.2%</td>
<td>7%</td>
<td>1%</td>
</tr>
<tr>
<td>Good Outcomes d90</td>
<td>28%</td>
<td>34%</td>
<td>25%</td>
<td>39%</td>
<td>28%</td>
</tr>
<tr>
<td>Mortality d90</td>
<td>43.5%</td>
<td>31%</td>
<td>33%</td>
<td>21%</td>
<td>24%</td>
</tr>
</tbody>
</table>


How Long to Intervene?

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Definition of Time Interval</th>
<th>Number of Patients</th>
<th>Age (Mean)</th>
<th>NIHSS (Median)</th>
<th>Time Interval to Minimize (Mean)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wells et al., 2008</td>
<td>Onset to treatment</td>
<td>65</td>
<td>68.1</td>
<td>15</td>
<td>261</td>
</tr>
<tr>
<td>Perry/pace et al., 2007</td>
<td>Onset to start of treatment</td>
<td>100</td>
<td>54.2</td>
<td>16</td>
<td>330</td>
</tr>
<tr>
<td>Onset to start of treatment</td>
<td>100</td>
<td>57.3</td>
<td>16</td>
<td>306</td>
<td></td>
</tr>
<tr>
<td>O'connor et al., 2007</td>
<td>Onset to intraarterial balloon occlusion</td>
<td>56</td>
<td>60.9</td>
<td>14</td>
<td>207</td>
</tr>
<tr>
<td>Studeni et al., 2007</td>
<td>Symptoms onset to intraarterial bolus</td>
<td>69</td>
<td>59.8</td>
<td>18</td>
<td>285</td>
</tr>
<tr>
<td>Matia et al., 2006</td>
<td>Onset to intraarterial treatment</td>
<td>53</td>
<td>58</td>
<td>172</td>
<td>244</td>
</tr>
<tr>
<td>Kim et al., 2008</td>
<td>Onset to localised intraarterial thrombolyis</td>
<td>18</td>
<td>65.4</td>
<td>17</td>
<td>312</td>
</tr>
</tbody>
</table>

* Treatment group; † Control group; ‡ Mean values.

Intra-Arterial Device Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>IMI 3</th>
<th>MR CLEAN</th>
<th>SYNTHESIS expansion</th>
<th>THRACE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Country</td>
<td>USA, selected European Centres</td>
<td>Netherlands</td>
<td>Italy</td>
<td>France</td>
</tr>
<tr>
<td>Time window</td>
<td>1h</td>
<td>6h</td>
<td>1h (IV) / 6h (IA)</td>
<td>2h</td>
</tr>
<tr>
<td>Armes</td>
<td>IV rtPA v IV rtPA (2/3 dose) + IA rtPA ± mechanical thrombectomy</td>
<td>Standard medical care (including IV rtPA, if indicated) v IA rtPA, mechanical thrombectomy or both</td>
<td>IV rtPA v IV rtPA ± mechanical thrombectomy</td>
<td>IV rtPA v IV rtPA+ ± mechanical thrombectomy</td>
</tr>
<tr>
<td>Patients</td>
<td>18-80 years NIHSS ≥ 10</td>
<td>&gt;18 years</td>
<td>18-80 years</td>
<td>18-80 years</td>
</tr>
<tr>
<td>Angiographic inclusion criteria</td>
<td>ICA, M1, M2, basilar or vertebral arteries</td>
<td>Intracranial ICA, M1, M2, A1 or A2 occlusion</td>
<td>Not specified</td>
<td>ICA, MCA, M1 or distal BA</td>
</tr>
<tr>
<td>Imaging Modalities</td>
<td>CTA, MRA, DSA or TCD</td>
<td>Not specified</td>
<td>Not specified</td>
<td>Not specified</td>
</tr>
<tr>
<td>Devices</td>
<td>Merci, Penumbra, EKOS</td>
<td>Investigator discretion</td>
<td>Investigator discretion</td>
<td>Merci, Penumbra, Catch, SoftBank</td>
</tr>
<tr>
<td>IA lytic drug allowed</td>
<td>Yes (IA; max. 22mg)</td>
<td>Yes (IA; rtPA)</td>
<td>50% randomised to IA rtPA</td>
<td></td>
</tr>
<tr>
<td>IV lytic drug pre-intervention</td>
<td>Mandatory (IV rtPA ≤3h), full or reduced dose</td>
<td>Allowed (IV rtPA ≤3.5h), not mandatory</td>
<td>Not in intervention arm</td>
<td></td>
</tr>
</tbody>
</table>

PISTE: Pragmatic Ischaemic Stroke Thrombectomy Evaluation

>18 years
ICA-T, MCA M1 or M2 occlusion
NIHSS ≥ 6
No Major CT Contraindication

IV rtPA 0.9mg/kg

IV rtPA + IA Device (as per Neurointerventionalist) <6h

Primary Outcome: mRS 0-2 versus 3-6 at 3m

Secondary Outcomes:
- 24h Recanalisation %
- Early major neurological improvement (≥8 points NIHSS)

Safety Outcomes:
- SICH (ECASS 2) 24-48h
- Mortality
- Any ICH
- Extracranial bleeding
**CLOTBUSTe: Ultrasound Therapy?**

Fibrin strands – no ultrasound

Fibrin strands in the presence of 2 MHz ultrasound


---

**Extending Reperfusion Strategies**

<table>
<thead>
<tr>
<th>Study</th>
<th>Imaging Selection</th>
<th>Active Treatment</th>
<th>Route</th>
<th>Time Window</th>
</tr>
</thead>
<tbody>
<tr>
<td>DIAS 4</td>
<td>CT, CTA or MRI, MRA</td>
<td>Desmoteplase</td>
<td>IV</td>
<td>4.5-9h</td>
</tr>
<tr>
<td>Talecris</td>
<td>CT, angio</td>
<td>Plasmin</td>
<td>IA</td>
<td>0-8h</td>
</tr>
<tr>
<td>WAKE-UP</td>
<td>MR DWI/FLAIR, Alteplase</td>
<td></td>
<td>IV</td>
<td>4.5h</td>
</tr>
<tr>
<td>PISTE</td>
<td>CT, angio</td>
<td>Device</td>
<td>IA</td>
<td>0-6h</td>
</tr>
<tr>
<td>ECASS-4</td>
<td>MR mismatch, Alteplase</td>
<td></td>
<td>IV</td>
<td>4.5-8h</td>
</tr>
<tr>
<td>ENCHANTED</td>
<td>CT</td>
<td>Reduced dose alteplase</td>
<td>IV</td>
<td>4.5h</td>
</tr>
<tr>
<td>PRACTISE</td>
<td>CT, CT/CTA/CTP, Alteplase</td>
<td></td>
<td>IV</td>
<td>4.5h</td>
</tr>
<tr>
<td>CLOTBUSTER</td>
<td>CT</td>
<td>TCD</td>
<td>IV</td>
<td>4.5h</td>
</tr>
<tr>
<td>BASICS</td>
<td>CT</td>
<td>Alteplase</td>
<td>IV or IA</td>
<td>0-6h</td>
</tr>
</tbody>
</table>
**Primary objective:**
To determine whether systemic cooling to a target temperature between 34 and 35°C, started within 6 hours of symptom onset and maintained for 24 hours, improves functional outcome at 3 months in patients with acute ischaemic stroke.

**Key facts:**
- N=1500; 1:1
- Cooling methods: induction by cold iv fluid or new surface device
- Maintainance phase by endovascular or surfache cooling

---

**Intracerebral Haemorrhage:**
Growth Predicts Poor Outcome

<table>
<thead>
<tr>
<th>Growth (%)</th>
<th>3h</th>
<th>5h</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;33%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤33%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>n</th>
<th>27</th>
<th>76</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-Point drop in GCS</td>
<td>31%</td>
<td>10%</td>
</tr>
<tr>
<td>30-Day mortality</td>
<td>44%</td>
<td>34%</td>
</tr>
</tbody>
</table>

CTA “Spot Sign”: Contrast Extravasation and ICH Expansion

Summary

- Reperfusion with IV rtPA <4.5h is the only proven acute treatment for ischaemic stroke
  - Improved access to IV rtPA for appropriate patients can come from better acute care systems
  - Imaging selection may stratify patients according to potential to respond
- Future:
  - Better drugs (eg ATTEST)
  - Imaging selection – vascular (eg DIAS-4), tissue viability (DEFUSE-2, ECASS-4), multimodal (PRACTISE)
  - Interventional procedures
  - Adjuvants (sonothrombolysis)
- Protecting the brain may be possible: Hypothermia to be tested in EuroHyp-1
- Intracerebral haemorrhage lacks treatments and radiological features may facilitate clinical trials