Thrombolysis and the transformation of stroke management: where next?

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Content

• **Thrombolysis**
  – IV thrombolysis from NINDS to ECASS 3 to IST-3
  – Pooled analyses: the most recent developments
  – Transvascular recanalisation: back to reality

• **Next steps in stroke care**
  – Stentrieverrs, imaging-based solutions and ultrasound-enhanced lysis
  – Neurovascular centers and telemedicine
  – Prehospital thrombolysis (CT-ambulances)
Relevant disclosures

• I have received financial compensation from Boehringer Ingelheim for my time and efforts as Chairman of the SC of ECASS 1-3
• I have received honoraria for lectures and advisory boards from BI
• I received a scientific grant from BI to organize ECASS 4
• I am a member of the SC of RIVER III and have received honoraria from CODMAN for my work
History: ground-breaking studies

- The NINDS Study leading to 3 h approval
- ECASS 3 confirming the 4.5h time window
- IST-3 showing that treatment outside the labelling does not cause harm
- The 2004 pooled analysis indicating benefit up to 4.5 h
- The second pooled analysis confirming the results of the previous one and indicating increased risk after 4.5h
- The on-going Stroke Thrombolysis Trialists' Collaborative Group analyses
Ground-breaking studies

- Two parts, a total of 600 patients randomized
- Positive in the combined endpoint with a roughly 15% improvement in outcome @ 3months
- The study was the basis for the 3h time window approval of rt-PA
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Outcome at Three Months in Part 2 of the Study, According to Treatment.
Scores of 1 on the NIHSS, 95 or 100 on the Barthel index, 1 on the modified Rankin scale, and 1 on the Glasgow outcome scale were considered to indicate a favorable outcome. Values do not total 100 percent because of rounding.
Ground-breaking studies

Thrombolysis with Alteplase 3 to 4.5 Hours after Acute Ischemic Stroke

Werner Hacke, M.D., Markku Kaste, M.D., Erich Bluhmki, Ph.D., Miroslav Brozman, M.D., Antoni Dávalos, M.D.; Donata Guidetti, M.D., Vincent Larrue, M.D., Kennedy R. Lees, M.D., Zakaria Medeghi, M.D., Thomas Machnig, M.D., Dietmar Schneider, M.D., Rüdiger von Kummer, M.D., Nils Wahlgren, M.D., and Danilo Toni, M.D., for the ECASS Investigators*

- 821 patients randomized
- Positive in the primary endpoint favourable outcome (mRS 0.1)
- (a 6.8% improvement in outcome @ 3 months)
- The study was the basis for the 4.5 h time window approval of rt-PA
Ground-breaking studies

The NEW ENGLAND JOURNAL of MEDICINE

Thrombolysis with Alteplase 3 to 4.5 Hours after Acute Ischemic Stroke

The benefits and harms of intravenous thrombolysis with recombinant tissue plasminogen activator within 6 h of acute ischaemic stroke (the third international stroke trial [IST-3]): a randomised controlled trial

The IST-3 collaborative group*

Summary

Background Thrombolysis is of net benefit in patients with acute ischaemic stroke, who are younger than 80 years of age and are treated within 4·5 h of onset. The third International Stroke Trial (IST-3) sought to determine whether a wider range of patients might benefit up to 6 h from stroke onset.

Methods In this international, multicentre, randomised, open-treatment trial, patients were allocated to 0·9 mg/kg intravenous recombinant tissue plasminogen activator (rt-PA) or to control. The primary analysis was of the proportion of patients alive and independent, as defined by an Oxford Handicap Score (OHS) of 0–2 at 6 months. The study is registered, ISRCTN25765518.

Findings 3035 patients were enrolled by 156 hospitals in 12 countries. All of these patients were included in the analyses (5515 in the rt-PA group vs 5280 in the control group), of whom 107 (53%) were older than 80 years of age. At 6 months, 554 (53%) patients in the rt-PA group versus 534 (53%) in the control group were alive and independent (OR 1.17 (95% CI 1.03—1.33; p=0.016).
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Findings 3,035 patients were enrolled by 156 hospitals in 12 countries. All of these patients were included in the analyses (3,135 in the rt-PA group vs 520 in the control group), of whom 1,075 (53%) were older than 80 years of age. At 6 months, 554 (53%) patients in the rt-PA group versus 534 (55%) in the control group were alive and independent (OHS 0–2; adjusted odds ratio [OR] 1.13, 95% CI 0.95–1.35, p=0.181; a non-significant absolute increase of 14/1000, 95% CI 28 to 48). An ordinal analysis showed a significant shift in OHS scores; common OR 1.29 (95% CI 1.10–1.49, p=0.001). Fatal or non-fatal symptomatic intracranial haemorrhage within 7 days occurred in 104 (7%) patients in the rt-PA group versus 16 (1%) in the control group (adjusted OR 6.94, 95% CI 4.07–11.8; absolute excess 5.8/1000, 95% CI 1.4–9.2). More deaths occurred within 7 days in the rt-PA group (163 [11%]) than in the control group (107 [7%]; adjusted OR 1.60, 95% CI 1.22–2.08, p=0.001; absolute increase 37/1000, 95% CI 17–57), but between 7 days and

• 3,035 patients randomized, 6h time window, uncertainty principle
• Missed primary endpoint, positive in shift
• Suggests safety and efficacy of rt-PA in elderly and severe strokes
• No extension of the time window granted so far
The most recent pooled analysis

Time to treatment with intravenous alteplase and outcome in stroke: an updated pooled analysis of ECASS, ATLANTIS, NINDS, and EPITHET trials

Kennedy R Lees, Erich Bluhmki, Rüdiger von Kummer, Thomas G Brott, Danilo Toni, James C Grotta, Gregory W Albers, Markku Kaste, John R Marler, Scott A Hamilton, Barbara C Tilley, Stephen M Davis, Geoffrey A Donnan, Werner Hacke, for the ECASS, ATLANTIS, NINDS, and EPITHET rt-PA Study Group Investigators*
IV rt-PA increases excellent outcome (mRS 0-1), n=3530

Updated pooled analysis

<table>
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<th>OTT (min)</th>
<th>NNT for mRS 0-1</th>
<th>NNT for any benefit</th>
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<tbody>
<tr>
<td>60</td>
<td>4.5</td>
<td>3.1</td>
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<tr>
<td>90</td>
<td>9.0</td>
<td>6.9</td>
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<tr>
<td>120</td>
<td>14.1</td>
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mRS: modified Rankin score; OTT: onset to treatment

p<0.0001 overall
p=0.03 for interaction with time to treat

The Stroke Thrombolysis Trialists' Collaborative Group

- The trialists of all thrombolysis RCTs have combined their efforts to prepare new analyses, not only for time effect of treatment but also for interaction with age and stroke severity.

- The statistical plan has just been published in the *Int J Stroke*. 

**Protocols**

Details of a prospective protocol for a collaborative meta-analysis of individual participant data from all randomized trials of intravenous rt-PA vs. control: statistical analysis plan for the Stroke Thrombolysis Trialists' Collaborative meta-analysis

The Stroke Thrombolysis Trialists' Collaborative Group

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2013-ISC Honululu: Doomsday for interventions

- The results of 3 randomized controlled trials studying transvascular thrombectomy against rt-PA were presented and published simultaneously in the *NEJM*
  - SYNTHESIS
  - IMS III
  - MR RESCUE
- None of them showed superiority of transvascular approaches

IMS III: Key results

**ORIGINAL ARTICLE**

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


February 7, 2013 DOI: 10.1056/NEJMoa1214300

- The study was stopped early because of futility after 656 randomized patients (434 endo and 222 to IV rt-PA)

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<th>IV/Endovascular (n=434)</th>
<th>IV rtPA Only (n=222)</th>
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<tr>
<td>mRS 0-2 (%)</td>
<td>177 (40.8%)</td>
<td>86 (38.7%)</td>
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Absolute difference, 1.5%; 95% CI –6.1 to 9.1
Explanations for this disaster

• All trials suffered from poor recruitment, up to 7 years for 120 patients
• Problems in trial design
  – Not on top of rt-PA, but against rt-PA or "standard treatment" which after 4.5h is nothing
  – Overestimation of effect size (based on uncontrolled data)
  – Underestimation of placebo (IV) response
• Mostly old devices
• Time window too long - 8 hours is too late
Summary for thrombolysis

• IV rt-PA is better established than ever
• Thrombectomy has so far failed to show superiority over rt-PA in proximal vessel occlusions
• Time window also counts in transvascular approaches
• Thrombolysis and interventional strategies have changed stroke infrastructure and will continue to do so
Content

- **Next steps in stroke care**
  - Stentriever, imaging-based solutions and ultrasound-enhanced lysis
  - Neurovascular centres and telemedicine
  - Prehospital thrombolysis (CT-ambulances)
Next steps: revascularisation

- Large RCTs using the most promising devices today (stentrievers) in an early time window against rt-PA are needed
- We hope that we will be able to combine forces to reach that goal, otherwise a promising strategy would be at risk
- We know that the new technologies are superior to the MERCI retriever (SWIFT; TREVO)
- We also know that MERCI was inferior to previously communicated recanalisation rates
Next steps: revascularisation

- Trials with new, probably more effective thrombolytics will come
  - Desmoteplase still around despite DIAS II
  - Plans for a tenecteplase RCT
- Revival of ultrasound-assisted thrombolysis
Next steps: imaging-based selection

- In some instances, e.g. late arrival, modern imaging technology may help to overcome the time window
  - Despite the negative result of DIAS II
  - And although MR RESCUE failed!

- However, this strategy still needs to be proven
  - EPITHET, DEFUSE, DEFUSE II indicate usefulness
  - DIAS II failed, desmoteplase ongoing
  - WAKE UP, EXTEND, ECASS 4 Extend

Next steps: infrastructure

- More stroke centres and neurovascular centres will be developed, providing IV lysis, transvascular approaches, stroke unit, ICU, neurosurgery, vascular surgery
- Conservative and interventional teams will both be needed
- The drip-and-ship approach may not be ideal because of time delays
- Telemedicine will help for decision-making strategies
Next steps: prehospital lysis

- First experiences of programs using ambulances with CT indicate that for selected settings treatment time can be shortened — > hundred patients have already been treated in Berlin and Homburg

- Whether this approach is cost effective remains to be proven
Summary

- Despite several failures, much energy is being put into the development of transvascular approaches, imaging-guided selection, new lytics and into the further advancement of stroke infrastructure.
- After all, it is the advance in stroke services as a whole that are responsible for the improved outcome of stroke patients, not only those who have been successfully recanalised.
- Stroke units, neurovascular centres, interdisciplinary teams and IV lysis are what really counts, and we must make them available to the majority of stroke victims.
- Time remains critical for better outcomes.