A History of Systemic Thrombolysis for Stroke: Can We Trust the Clinical Guidelines?

Aaron Lane D.O.
Clinical Associate Professor of Emergency Medicine
OSU-CHS

Thrombolytics for Stroke

- Considered “settled science” and de facto standard of care.
- Code strokes, documentation mandates, stroke centers etc
- Guideline update from Dec 2015 recommend ever expanding inclusion criteria for thrombolysis.
- Age > 80 no longer reason to withhold thrombolysis
- Stroke severity (mild or severe) no longer a reason to withhold thrombolysis.
- Rapidly improving Sxs no longer a reason to withhold thrombolysis.
- Softens thrombolysis rec in recent surgical pts, recent MI pts, recent CVA pts and recent trauma pts.
- Ok to use thrombolytics in pts w/ incidental aneurysms?
- ESRD pts?, demented pts?, cancer pts?
- Hypo & hyperglycemia?
- Early CT findings?
- Recent LP?
- Psychogenic/Conversion/Malingering?

---

**Consent for the Incompetent Patient**

- “In an emergency when the patient is not competent and there is no immediately available legally authorized representative to provide consent, it is recommended to proceed with IV alteplase in an otherwise eligible patient with acute ischemic stroke”
How did we get here?

- Multiple trials have demonstrated a small but important benefit in mortality for STEMI pts treated with thrombolytics.
- Thrombolytics?
  - tPA
  - Streptokinase
    - Most data comparing these two drugs for MI did not demonstrate any difference in pt important outcomes

Thrombolysis in Myocardial Infarction (TIMI) Trial, Phase I: a comparison between intravenous tissue plasminogen activator and intravenous streptokinase*

Clinical findings through hospital discharge


- Stopped early
- At 90 min 60% of tPA group had reperfusion compared to 35% of streptokinase group
- Reperfusion is not a clinical outcome, and there were no differences in clinical outcomes.
- Initially there were plans to do a 2nd study examining clinically important outcomes (mortality) → never happened, WHY?
• Dr Elliot Grossbard MD a Genentech scientist
  — “We don’t know how another trial would turn out. And if we don’t come out ahead, we would have a tremendously self-inflicted wound...another study may be a good thing for America, but it wasn’t going to be good for us.”
• As you review these studies pay attention to:
  – Thrombolytic agent
  – Dose
  – Timing interval
  – Rate of intracranial hemorrhage (ICH)

**THE LANCET**

*Volume 348, Issue 8989, 9 December 1995, Pages 1509–1514*

**Articles**

Randomised controlled trial of streptokinase, aspirin, and combination of both in treatment of acute ischaemic stroke

*Multicentre Acute Stroke Trial—Italy (MAST-I) Group.†*

- Randomized, multicenter trial
- Enrolled 622 pts presenting within *6 hrs* of stroke onset
- Streptokinase 1.5 million units vs no treatment
- Primary outcome was death and disability at 6 months (Modified Rankin of 3–6)
- **Trial stopped early due to harm**
- Goal was to enroll 1,500 patients
- No difference of death/disability at 6 months (63% vs 65%)
- Mortality increased (36% with streptokinase and 24% without treatment)
October 4, 1995

Intravenous Thrombolysis With Recombinant Tissue Plasminogen Activator for Acute Hemispheric Stroke
The European Cooperative Acute Stroke Study (ECASS)
Werner Hacke, MD, Markku Kaste, MD; Cesare Fieschi, MD; et al.

- Randomized, double blind, placebo controlled, multicenter trial
- 620 pts with moderate to severe stroke without CT changes presenting within 6 hrs
- Compared tPA at 1.1mg/kg vs placebo
- Two primary outcomes (designed to look at functional outcomes at 90 days)
- Results = NO DIFFERENCE in either disability scale at 90 days
- Mortality higher in tPA group (17.95 vs 12.7%)
NINDS Criticisms

• Industry influence
• Baseline imbalance-> placebo group had more severe strokes
• No mortality benefit
• No control for post-thrombolytic therapy
• Issues with the 3 hour window:
  — benefit for up to 3 hours biased by 50% of the patients having thrombolysis <90 minutes
  — <90 min OR 1.71 (1.06-2.7)
  — 91-180 min OR 1.12 (0.71-1.76) (not significant)

Modified Rankin Scale

<table>
<thead>
<tr>
<th>Modified Rankin Scale (MRS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>4</td>
</tr>
<tr>
<td>5</td>
</tr>
<tr>
<td>6</td>
</tr>
</tbody>
</table>
Reliability of the Modified Rankin Scale
A Systematic Review

Terence J. Quinn, MRCP; Jesse Dawson, MRCP; Matthew R. Walters, MD; Kennedy R. Lees, MD

Background and Purpose—A perceived weakness of the modified Rankin Scale is potential for interobserver variability. We undertook a systematic review of modified Rankin Scale reliability studies.

Methods—Two researchers independently reviewed the literature. Crossdisciplinary electronic databases were interrogated using the following key words: Stroke; Cerebrovasc; Modified Rankin; Rankin Scale; Oxford Handicap; Observer variation. Data were extracted according to prespecified criteria with decisions on inclusion by consensus.

Results—From 3461 titles, 10 studies (587 patients) were included. Reliability of modified Rankin Scale varied from the weighted $\kappa$ of 0.55 to 0.25. Overall reliability of mRS was $\kappa=0.46$; weighted $\kappa=0.50$ (traditional modified Rankin Scale) and $\kappa=0.62$; weighted $\kappa=0.87$ (structured interview).

Conclusions—There remains uncertainty regarding modified Rankin Scale reliability. Interverberer studies closest in design to large-scale clinical trials demonstrate potentially significant interobserver variability. (Stroke. 2009;40:3383-3395)

Key Words: clinical trials ■ clinimetrics ■ modified Rankin Scales ■ outcome assessment ■ systematic review

The New England Journal of Medicine

© Copyright, 1996, by the Massachusetts Medical Society

VOLUME 335 JULY 18, 1996 NUMBER 3

THROMBOLYTIC THERAPY WITH STREPTOKINASE IN ACUTE ISCHEMIC STROKE

THE MULTICENTER ACUTE STROKE TRAIL — EUROPE STUDY GROUP

- Used a six hour time frame, streptokinase VS placebo
- Primary outcome was a binary criterion combining mortality and severe disability at six months (Modified Rankin Score of 3 or higher)
- Stopped early due to increased mortality and increased ICH
- ASK trial
- Used a 4 hour time frame
- Streptokinase VS placebo
- Primary outcome was death and disability at three months.
- Thrombolysis within 4 hours of acute stroke onset increased mortality at 3 months
- Treatment within 3 months of stroke was safer and associated with better outcomes than later treatment, but no significant benefit over placebo.

---

**THE LANCET**

Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II)

Prof Werner Hacke, MD, PhD, Prof Markku Kaste, MD, Prof Cesare Fieschi, MD, Prof Rüdiger von Kummer, MD, Prof Antoni Dávalos, MD, Dieter Meier, MD, Prof Vincent Larrue, MD, Erich Bluhmki, MD, Prof Stephen Davis, MD, Prof Geoffrey Donnan, MD, Dietmar Schneider, MD, Prof Exupero Diez-Tejedor, MD, Prof Paul Trouillas, MD, for the Second European-Australasian Acute Stroke Study Investigators

- 1998 ECASS II trial
- 
- Alteplase for acute ischemic stroke given within 6 hr of symptom onset
- Randomized double blinded placebo controlled
- Primary endpoint was disability at 90 days using a dichotimized Modified Rankin Scale (favorable score 0-1 & unfavorable 2-6)
- No difference in favorable outcomes at 3 months
- Treatment differences were similar whether pts were treated within 3 hours or 3-6 hours.
ATLANTIS B

- 1999
- Placebo-controlled, randomized, double blinded
- Sought to determine efficacy of alteplase administered to acute ischemic stroke pts presenting 3-5 hours after symptom onset.
- Favorable outcome at 3 months, (32% of placebo and 34% of thrombolytic pts P=0.65)
- No differences in any secondary functional outcome measures
- Alteplase significantly increased the rate of ICH
- Mortality at 90 days was 6.9% in placebo group and 11% in the alteplase group.
ATLANTIS - A

- Trial started in 1991
- Placebo controlled, double blind, randomized study comparing alteplase to placebo for acute ischemic stroke pts presenting within 6 hrs.
- Primary endpoint was the # of pts with a decrease in the NIHSS of 4 or more at 24 hours, and day 30, along with infarct volume at 30 days.
- Stopped in 1993 by the safety committee
- In Dec 1993 the study was restarted and the time frame was changed 6 hours to 5 hours → PART B.
- Part A = results of the original study that was stopped.
ATLANTIS-A

- Higher percentage of alteplase pts had a 4 point improvement in the NIHSS at 24 hours (24% vs 40%).
- This early effect was reversed at 30 days with more placebo pts having a 4 point improvement (75%) than pts treated with alteplase (60%)
- Alteplase significantly increased the risk of ICH within the first 10 days (11% vs 0%)
- Mortality at 90 days was 23% for alteplase pts and 7% for placebo.

---

**Stroke**

The Desmoteplase in Acute Ischemic Stroke Trial (DIAS)
A Phase II MRI-Based 9-Hour Window Acute Stroke Thrombolysis Trial With Intravenous Desmoteplase

Werner Hacke, MD; Greg Albers, MD; Yasir Al-Rawi, MD; Julien Bogousslavsky, MD; Antonio Davalos, MD; Michael Eliaziw, PhD; Michael Fischer, PhD; Anthony Furlan, MD; Markku Kaste, MD; Kennedy R. Lees, MD; Mariola Soehngen, MD; Steven Warach, MD; for The DIAS Study Group

- 2008
- Placebo controlled, double-blinded, randomized, dose finding phase 2 trial
- Eligibility $\rightarrow$ NIHSS of 4 – 20 with MRI evidence of diffusion/perfusion
- The dose finding phase was prematurely terminated due to increased ICH
- Favorable 90 day outcomes was found in 22% of placebo pts and 13% of desmoteplase treated pts.
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*

- 2012 study
- A multicenter open-label, randomized, controlled trial
  Patients: 3035 adult patients with acute stroke within 6 hours of symptom onset. Patients were excluded if they “had a clear indication” for t-Pa and if there was a clear contraindication. Then, only if both the physician and the patient thought that the treatment was “promising, but not proven” would the patient be enrolled. 53% of the patients were older than 80 (excluded from other trials.)
- Intervention: t-Pa 0.9mg/kg
- Comparison: standard care
- Primary outcome: Proportion of patients alive and independent at 6 months

IST-3

- There was no difference in the primary outcome: 35% of the placebo group and 37% of the tPa group were alive and independent at 6 months.
- Mortality at 6 months was unchanged (27% vs 27%, p=0.672)
- Mortality was increased at 7 days with t-Pa (11% vs 7%, OR 1.59, 95%CI 1.23-2.07, p=0.0004).
- Symptomatic intracranial hemorrhage was increased with t-Pa (7% vs 1%, p<0.0001).
IST - 3

- Largest thrombolytic for stroke trial
- Worst methods → bias towards tPA group but still no treatment benefit demonstrated.
- Follow-up was by mail
- 3 hr subgroup did better, but the 3 – 4.5 hr group did much worse, while the 4.5 -6 hr group did better again = CHANCE

The NEW ENGLAND JOURNAL of MEDICINE

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 Medeghri, M.D., Thomas Machni, M.D., Dietmar Schneider, M.D., Rüdiger von Kummer, M.D., Nils Wahlgren, M.D., and Danilo Toni, M.D., for the ECASS Investigators*

- ECASS III Trial
- A multicenter, placebo controlled, double-blind, randomized trial
- 821 adult stroke patients (aged 18-80) who were able to received the drug with a 3-4 hours time frame after symptom onset (later extended to 3-4.5 hours). They excluded patients with a NIHSS >25
- tPA 0.9mg.kg
ECASS III

- Primary outcome: Disability at 90 days (looking at a modified Rankin scale 0-1)
- More people in the treatment group ended up with a favourable modified Rankin score (0-1): 52.4% with t-Pa vs 45.2% with placebo.
- There was not a statistically significant difference in the Glasgow outcome scale or the Barthel index between the two groups.

ECASS III

- Mortality was unchanged: 7.7% with t-Pa and 8.4% with placebo, p=0.68
- Symptomatic hemorrhage was higher. 2.4% vs 0.2%
  - According to the NINDS definition, 7.9% vs 3.5%.
NINDS Concerns

• Aug 2000 AHA upgraded its recommendation of alteplase for stroke from optional to recommended.
  – Most randomized control trials showed no benefit or harm.
  – Validity of NINDS trial was questionable because the proportion of pts enrolled in 0-90 min group was artificially increased due to study design.
  – Chance alone could explain the benefit found in this trial.

NINDS Concerns

• Efficacy in expert hands is not the same as effectiveness in usual clinical practice.
• 20% of pts initially Dx’d with stroke by expert stroke teams were subsequently found to not have a stroke.
• “Selective emphasis of a single study is scientific folly.”
Repeat the Trial!!!!!!

• “There are numerous examples in medicine where a single small study (or even a few studies) seemed to support a promising hypothesis but subsequent larger work failed to confirm that benefit (or even cause significant harm).”

• It took 8 years and a Freedom of Information Act Request through the FDA to obtain raw data from the NINDS trial.
AHA Conflicts of Interest

- Minutes of the AHA Board of Directors meeting reveal that Genentech contributed $2.5 million to build the AHA headquarters.
- Genentech has given over $11 million to the AHA in the last decade.
- 2000 AHA Stroke Guidelines were adopted by a panel of 9 experts.
  - 8 of 9 supported the guidelines
  - Four panelists received lecture fees as member of Genentech speakers bureau.
  - One served as a consultant to Boehringer-Ingelheim (development and marketing partner of Genentech).
  - 2 received research funding from Genentech
Dr Jerome Hoffman MD was the lone dissenter, and also had no industry ties.

After providing expert testimony at the conference he was asked to provide written commentary providing the basis of his disent.

He submitted his paper 1 year before the guideline were released but it was never published and the guidelines never mentioned it.

• A study to verify the outcomes of NINDS could benefit the public, it could only harm those who stand to financially.

• Remember Dr Grossbard’s comments!
"There is a treatment we sometimes use for stroke that is supposed to break down the clot causing the stroke. The treatment is controversial, and you will probably hear different things from different doctors. The issue is that out of 12 major trials, only 2 have shown benefit, and both of those trials have some problems, and they were both paid for by the people who make the drug. There are some risks that we’re certain about: about 1 in 12 patients will have severe bleeding resulting in worse neurologic outcome. Despite that risk, in the best case scenario, about 1 in 10 people given this drug early will have a noticeable improvement in their function after 3 months. Unfortunately, it isn’t clear how reliable the science has been, and we don’t know which patients have the greatest chance at benefit or harm. The choice to receive this medication remains up to each individual patient.”
Not Just Genentech and AHA!

• American Cancer Society – sponsored by AstraZeneca, Johnson & Johnson, Bristol-Myers Squibb, and Eli Lilly

• National Alliance of the Mentally Ill → Eli Lilly (manufactures >17 psych drugs) donated $11.72 million.