The tPA Cage Match

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Disclosures

- Advisory Boards
  - Astra Zeneca, Pfizer, CSL Behring, Janssen, Lundbeck
- Past Chair, ACEP Clinical Policies Committee
- Executive Board, NINDS BAC
- Executive Board, FERNE (received educational grants from Genetech)

Cage Match

- Cage Match: Round after round of meaningless sex with someone you are extremely sexually attracted to.

Cage Match

- Cage match: A gimmick match in pro wrestling
  - A cage surrounds the wrestling ring. Both wrestlers start inside the ring (and thus inside the cage). In order to win, BOTH of your feet have to hit the ground outside of the cage.

Key Questions

- Does Alteplase improve functional outcomes in patients with an acute ischemic stroke presenting within 3 hours of symptom onset?
- Does the risk of symptomatic ICH (sICH) outweigh the benefit to functional outcomes?
  - Any CT documented hemorrhage within 36 hours temporally related to deterioration in the patient's clinical condition (NINDS) vs related to a 4 point change in the NIHSS score (SITS-MOST)
- Is there a subset of strokes where the risk of sICH is less than the composite risk of all stroke types?

Key Points

- Alteplase is FDA approved treatment for acute ischemic stroke and its use in the appropriate setting is a Level I recommendation by ACEP, AAEM, AAN, ASA/AHA, ESO, NICE
- The risk of symptomatic hemorrhagic conversion in properly selected patients is < 2% with no increase in disability or mortality
- A decision **not** to use Alteplase in the appropriate setting is acceptable but clinical decision making must be well supported in the medical record

The Facts: Ischemic Stroke

- Acute Ischemic stroke
  - Hemorrhagic conversion within 36 hours: 0.6% symptomatic, 4% asymptomatic
  - 26% have little or no disability at 3 months
  - 25% have mild to moderate disability at 3 months
  - 27% have severe disability
  - 22% dead at 3 months

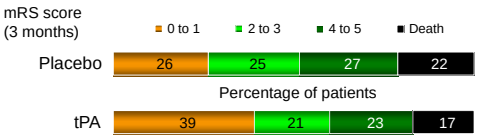
NINDS t-PA Acute Ischemic Stroke

NEJM 1995

- A two part, double blind study: 624 patients
  - Randomized to t-PA or placebo
- "Favorable outcome" defined as normal or near normal at 90 days
  - 4 outcome measures: Barthel Index, Modified Rankin Scale, Glasgow Outcome Scale, NIHSS

IV tPA for Acute Ischemic Stroke: NINDS Trial

- Primary end point: Favorable outcome at 24 hours and 3 months
  - Defined as normal or near normal neurological function using a global scale that incorporated 4 commonly used scales
  - Odds ratio: 1.7 (95% CI, 1.2-2.6) favoring tPA over placebo
    - Includes an increased incidence of symptomatic ICH (6.4% vs 0.6%) – associated with a 45% mortality



NINDS Trial Criticism

- No benefit demonstrated in first 24 hours
- External validity
- Imbalance of baseline NIHSS between the t-PA and placebo groups
- Treatment effect favored those patients treated within 90 minutes
- Unclear which patients were at risk for intracerebral hemorrhage

NINDS Date Re-analysis Committee

Stroke 2004

- Kjell Asplund MD
  Umeå, Sweden
- Lewis R. Goldfrank MD
  New York, USA
- Timothy Ingall MD
  Mayo Clinic Scottsdale
- Vicki Hertzberg PhD
  Emory University
- Thomas Louis PhD
  Johns Hopkins
- MichaelO'Fallon PhD
  Mayo Clinic Rochester

ICH Analysis

Risk Factors for ICH:

- Baseline NIHSS > 20
- Age > 70 years
- Ischemic changes present on initial CT
- Glucose > 300 mg/dl (16.7 mmol/L)

# of Risk Factors	# of patients treated with t-PA (n=310)	# of Symptomatic ICH's (# of placebo patients with ICH)	Percentage (%)
0	114	2 (1)	1.8
1	144	7 (1)	4.9
> 1	52	11	21.2

NINDS Re-analysis

Stroke 2004

- Initial NIHSS <20, no diabetes, age <70, normal CT predict best outcome from t-PA and low risk for ICH
- The committee concluded, despite an increased incidence of symptomatic intracerebral hemorrhage in t-PA treated patients and subgroup imbalances in baseline stroke severity, there was a statistically significant benefit of t-PA treatment measured by an adjusted t-PA to placebo global odds ratio of 2.1 (95% CI: 1.5-2.9) for a favorable clinical outcome at 3 months

Predicting sICH

J Neuro Sci 2013

- 518 patients treated with Alteplase
- 434 anterior circulation – 8.1% sICH
- 84 posterior circulation – 1.2% sICH

Japan Alteplase Clinical Trial

Stroke 2006

- Prospective, multicenter, single arm, open lable trial
- 100 patients; outcome mRS 0-1 at 3 months; sICH at 36 hours
- 38% mRS 0-1 at 3 months
  - Historical Japanese controls: 21%
- 6% symptomatic hemorrhage

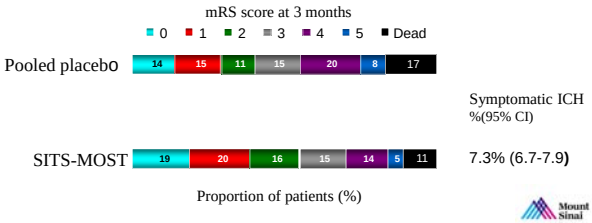
Thrombolysis with Alteplase for acute ischaemic stroke (SITS-MOST)

Lancet 2007

- Prospective, open, multicentre, multinational, observational monitoring study established as a condition by the European Union for licensing
- 6483 patients
- 4.6% symptomatic hemorrhage at 24 hours
- 39% with no or mild disability at 3 months (vs 29% in pooled placebo)

SITS-MOST

- Safe Implementation of Thrombolysis in Stroke–Monitoring Study (SITS-MOST)
  - Prospective, open, observational study
  - 6483 patients, 285 centers in 14 European countries
    - Half of centers had little experience with stroke thrombolysis



Third International Stroke Trial – 3

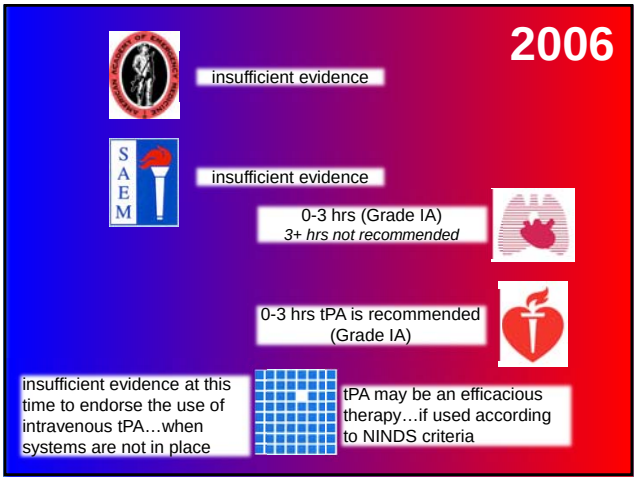
Lancet 2012

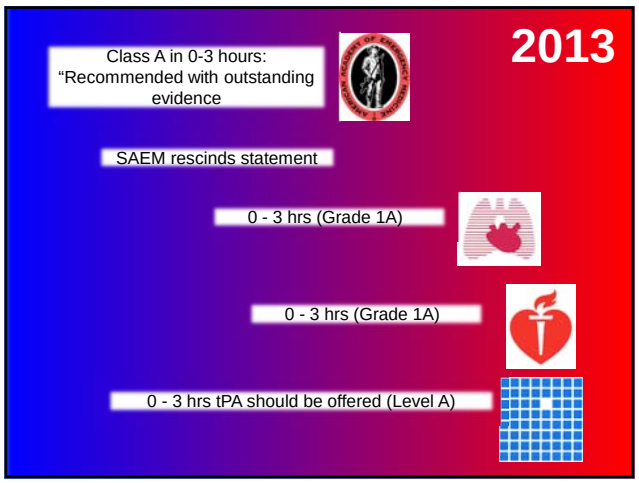
- Multicentre, randomized, open treatment trial
- Treatment within 6 hours of symptom onset
- Outcome measure: independent at 6 months; symptomatic hemorrhage at 7 days
- 3035 patients enrolled; 53% older than 80
- 431 patients treated 0-3 hrs vs 418 controls
  - 31% independent at 6 months vs 23% of controls

Third International Stroke Trial – 3

Lancet 2012

- GWTG-Stoke Program analysis
  - 1647 hospitals / 1,154,247 stroke patients
  - 58,353 Alteplase treated patients, 0 – 4.5 hours
  - April 1, 2003 – April 1, 2012
  - 8.8% mortality / 4.9% sICH
  - 33.4% independent ambulation at hospital discharge / 38.6% discharged home
  - Time to treatment (0-90 vs 90 – 180)was associated with decreased mortality, decreased sICH (4% vs 5%), and improved outcome





Putting Policy into Practice

- 0 – 3 hours
- Level A – IV tPA should be **offered** to patients who meet NINDs criteria*

*The effectiveness of tPA has been less well established in institutions without the systems in place to safely administer the medication

Key Points

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