



*tPA in Acute Stroke:
What We Know in 2004 From
the NINDS and other Studies*

Sidney Starkman, MD, FACEP

Professor & Emergency Neurology Director

**Departments of Emergency Medicine and
Neurology**

**University of California Los Angeles
Los Angeles, California**

tPA in Acute Stroke: What We Know in 2004 From the NINDS and other Studies

Key Learning Points

- The NINDS tPA Acute Stroke Trial published in the *New England Journal of Medicine* in 1995 reported a study of 624 patients, half of whom were randomly treated with tPA within 3 hours of stroke onset.
- The tPA group demonstrated an absolute benefit in favorable outcome of 12% (global odds ratio 1.7) with a symptomatic intracerebral hemorrhage rate of 6.4% (10 times the placebo group).
- Because of questions about the original analysis of the NINDS study, a reanalysis of the NINDS clinical trials data was conducted addressing specific concerns about the study and whether imbalances in the baseline stroke severity in the tPA treated and the placebo groups invalidated the entire trial. The NINDS Re-analysis was published in October 2004 in the journal *Stroke* stating that a clinically important and statistically significant benefit of tPA therapy was identified (adjusted tPA to placebo odds ratio of a favorable outcome of 2.1) despite baseline stroke severity imbalances and an increased incidence of symptomatic intracerebral hemorrhage. The NINDS trial was not powered to detect any subgroup differences.
- A meta-analysis of safety data from 15 published reports of postapproval tPA use in 2639 acute stroke patients was published in the journal *Stroke* in 2003. The symptomatic intracerebral hemorrhage rate was 5.2% with a mean total death rate of 13.4%, both slightly lower than in the NINDS trial.
- A pooled analysis of tPA therapy in the six randomized acute stroke trials was published in *Lancet* in 2004 and concluded that the sooner tPA therapy was given, the greater the benefit, especially if started within 90 minutes of stroke symptom onset.

Clinical Questions

- What are the benefits and the risks of tPA treatment for acute stroke as reported in the original NINDS trial?
- What are the benefits and the risks of tPA treatment for acute stroke as reported in the reanalysis of the NINDS trial data set?
- What did the reanalysis of the NINDS data tell us about the original data in regards to stroke severity imbalances in the treated and placebo groups, blood pressure management, risk factors for symptomatic intracerebral hemorrhage, and predicting subgroups more likely to have a favorable outcome as a result of tPA therapy?

- How does the meta-analysis of the safety data in postapproval use of tPA for acute stroke reports compare with the NINDS trial data?
- What can be learned from the report of the pooled analysis of the randomized, placebo controlled tPA trials for acute stroke?

Emergency Medicine Opportunities

- Emergency physicians and Emergency Medicine organizations should promulgate the information from the original NINDS report, the re-analysis of the NINDS dataset, the meta-analysis of postapproval tPA use in clinical practice, and the pooled analysis of randomized, placebo controlled tPA trials to better place into perspective the relative benefits and risks associated with tPA therapy in acute ischemic stroke.
- Academic emergency physicians should educate residents in training and practicing emergency physicians in the body of information regarding tPA for acute ischemic stroke including other reports from the NINDS trialists and others, such as the Calgary report regarding patients excluded from tPA therapy who proceeded to have a poor outcome and the Sacramento report regarding emergency physicians tPA experience.
- Emergency Medicine groups should utilize knowledgeable experts in tPA therapy for stroke to properly understand the published reports.
- Emergency Medicine groups should develop quality assessment tools devised to document and review their tPA experience and protocol adherence and compare their tPA treated and tPA-excluded patients' outcomes with published reports.
- Emergency physicians should actively participate in future studies designed to identify specific groups of acute stroke patients who are more or less likely to benefit from tPA therapy or in whom the risk of intracerebral hemorrhage is so high as to outweigh the potential benefit (e.g. age > 70 years, diabetes, pre-existing disability, differential stroke severity and stroke subtypes).

starkman@ucla.edu

310 794-0594

2004_stroke_adboard_starkman.doc