



## **tPA in Acute Ischemic Stroke: The NINDS Reanalysis & Meta-analysis Data**

Sidney Starkman, MD, FACEP

Professor & Emergency Neurology Director  
Departments of Emergency Medicine and Neurology  
University of California, Los Angeles  
Los Angeles, CA

### **Case Presentation**

A 46 year old emergency physician with 20 years of Emergency Medicine experience ponders the use of tPA in the treatment of ED patients with acute ischemic stroke. He is aware of the medical literature, and has read the 1995 *NEJM* NINDS clinical trial study that established the efficacy of the tPA in improving outcome in acute stroke patients. He understands the risks and benefits of tPA use, and knows that a recent reanalysis of the data has been conducted. He has heard lectures presented by emergency physicians, some who state that the drug is the industry standard, and others that are concerned that there is insufficient data to support its broad use. He has read the many statements from Emergency Medicine societies, most of which suggest that the drug is effective when used properly.

This EM physician has used tPA in stroke patients with success. He has heard from colleagues that there are lawsuits out there, most related to a failure to use tPA, not because of complications following tPA use.

What approach should this EM physician take in learning more about tPA use in the Emergency Department?

## Key Clinical Questions and Learning Points

**What were the results of the original NINDS trial, in which tPA was used as treatment for acute ischemic stroke?**

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).

**Why was a reanalysis of the NINDS tPA data performed? What did it show?**

A reanalysis of the NINDS clinical trials data was conducted because of questions about the original analysis of the NINDS study. The committee was charged with addressing specific concerns about the study, specifically 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). This improved outcome was noted despite baseline stroke severity imbalances and an increased incidence of symptomatic ICH. Because the NINDS trial was not powered to detect any subgroup differences, the committee could not specifically state that any one subgroup did better or worse.

**What did the reanalysis of the NINDS data tell us regarding: stroke severity imbalances, blood pressure management, risk factors for symptomatic ICH, and predicting subgroups more likely to have a favorable outcome as a result of tPA therapy?**

The committee adjusted for baseline stroke severity in the two treatment groups when calculating the global odds ratio of a favorable outcome. The committee stated: “Despite an increased incidence of symptomatic intracerebral hemorrhage in t-PA treated patients and subgroup imbalances in baseline stroke severity

subgroup imbalances, the adjusted analysis demonstrated a statistically significant, and clinically important, benefit for treating acute ischemic stroke patients with IV t-PA within three hours of symptom onset.”

Regarding blood pressure management, the committee stated: “We concluded that a number of problems preclude the use of the study’s blood pressure information in either statistical analyses or clinical management.”

When analyzing the ability to predict complications, including ICH, the committee observed that age, baseline NIHSS, and the interaction between the two, were related to a decreased likelihood of having a favorable outcome. A risk factor score using combinations of age, baseline NIHSS, admission glucose, and CT scan findings predicted ICH occurrence and a decreased likelihood of a favorable outcome. However, this information must be utilized very cautiously in the management of individual patients, since the study was not powered to study outcome in particular subgroups.

### **What did the NINDS reanalysis tell us about OTT (stroke onset time to treatment time) and patient outcome?**

Regarding time to treatment, the committee stated: “Based on our analyses, and the observation that the distribution of the OTT values was substantially nonlinear, the Review Committee concluded there was no evidence that the effectiveness of tPA treatment decreased as the time from stroke onset increased.”

### **How does the meta-analysis of the safety data in post approval use of tPA for acute stroke reports compare with the NINDS trial data?**

A meta-analysis of safety data from 15 reports of post-approval tPA use in 2639 acute stroke patients was published in the journal *Stroke* in 2003. The very favorable outcome rate was 37%, 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. The author suggests that when the protocol utilized in the NINDS trial is followed, it is possible to replicate the beneficial outcome and adverse event profiles seen in the original study and reanalysis.

**What can be learned from the report of the pooled analysis of the randomized, placebo controlled tPA trials for acute stroke?**

A pooled analysis of tPA therapy in the six randomized acute stroke trials was published in *Lancet* in 2004. This analysis included data from the NINDS Parts I and II, Atlantis A and B, and ECASS I and II studies. The report concludes that the sooner tPA therapy was given, the greater the benefit, especially if tPA is started within 90 minutes of stroke symptom onset. This may be due, in part both to improved favorable outcome odds ratios and lower ICH rates in patients treated prior to 90 minutes from the stroke onset time.

**Patient Case Outcome – A true story**

The emergency physician learned more about the use of tPA in the ED. After reading the most recent analyses and reviewing lectures on the FERNE website, [www.ferne.org](http://www.ferne.org), he understood that tPA probably can be used efficaciously when it is provided *per the NINDS protocol*.

He met with the neurologists, radiologists, primary care providers, and administrators at his hospital. They agreed that a protocol for the rapid assessment and treatment of stroke patients, including the use of tPA and necessary adjuncts, should be developed. They developed a protocol off-line, one that incorporated the specific NINDS treatment protocol. They then planned to utilize the protocol in treating acute ischemic stroke patients once the hospital staff was in-serviced on the agreed upon treatment plan. Patients are now being treated using the new protocol and patient outcomes are expected to match those found in the NINDS trial.

This new stroke collaborative group is also looking into becoming a designated primary stroke center. They look forward to new data that will allow them to continue to improve the care of the stroke patients that they treat in the Emergency Department.