

**The New England  
Journal of Medicine**

©Copyright, 1995, by the Massachusetts Medical Society

---

Volume 333                      DECEMBER 14, 1995                      Number 24

**TISSUE PLASMINOGEN ACTIVATOR FOR ACUTE ISCHEMIC STROKE**

THE NATIONAL INSTITUTE OF NEUROLOGICAL DISORDERS AND STROKE rt-PA STROKE STUDY GROUP\*

**Abstract** Background. Thrombolytic therapy for acute ischemic stroke has been approached cautiously because there were high rates of intracerebral hemorrhage in early clinical trials. We performed a randomized, double-blind trial of intravenous recombinant tissue plasminogen activator (t-PA) for ischemic stroke after recent pilot studies suggested that t-PA was beneficial when treatment was begun within three hours of the onset of stroke.

**Methods.** The trial had two parts. Part 1 (in which 291 patients were enrolled) tested whether t-PA had clinical activity, as indicated by an improvement of 4 points over base-line values in the score of the National Institutes of Health stroke scale (NIHSS) or the resolution of the neurologic deficit within 24 hours of the onset of stroke. Part 2 (in which 353 patients were enrolled) used a global test statistic to assess clinical outcome at three months, according to scores on the Barthel index, modified Rankin scale, Glasgow outcome scale, and NIHSS.

**Results.** In part 1, there was no significant difference between the group given t-PA and that given placebo in the percentages of patients with neurologic improvement at 24 hours, although a benefit was observed for the t-PA group at three months for all four outcome measures. In part 2, the long-term clinical benefit of t-PA predicted by the results of part 1 was confirmed (global odds ratio for a favorable outcome, 1.7; 95 percent confidence interval, 1.2 to 2.6). As compared with patients given placebo, patients treated with t-PA were at least 30 percent more likely to have minimal or no disability at three months on the assessment scales. Symptomatic intracerebral hemorrhage within 36 hours after the onset of stroke occurred in 8.4 percent of patients given t-PA but only 0.6 percent of patients given placebo ( $P < 0.001$ ). Mortality at three months was 17 percent in the t-PA group and 21 percent in the placebo group ( $P = 0.30$ ).

**Conclusions.** Despite an increased incidence of symptomatic intracerebral hemorrhage, treatment with intravenous t-PA within three hours of the onset of ischemic stroke improved clinical outcome at three months. (N Engl J Med 1995;333:1581-7)

**The NINDS rt-PA Stroke Trial**

*Prior information (Pre-Clinical, Phase I Studies, etc)*

- Thrombolytic canalization of occluded arteries may reduce the degree of brain injury if it is done before the process of infarction is completed.
- Thrombolysis of occluded coronary vessels improves outcome from AMI
- IV rt-PA recanalized cerebral arteries and reduced infarct volumes in a rabbit embolic stroke model (Zivin et al *Science* 1985)
- Many other experimental studies confirmed these observations
- Safety of IV rt-PA tested in 2 open-label, dose-escalation studies (Brott et al *Stroke* 1992 & Haley et al *Stroke* 1992)
- Emphasis on early treatment: > 90 min & between 91-180 min of stroke onset to reduce the risk of ICH and maximize potential for recovery
- Safety studies suggested that doses of < 0.95 mg/kg of rt-PA were relatively safe and resulted in early neurologic improvement in a substantial proportion of patients, with 8% ICH – enough to justify a larger, placebo-controlled RCT

**Study Questions**

1. Does IV rt-PA have clinical activity – specifically whether a greater proportion of patients treated with rt-PA, as compared with those given placebo, had early improvement (Part 1)?
2. Would there be a consistent and persuasive difference between rt-PA and placebo groups in terms of the proportion of patients who recovered with minimal or no deficit 3 months after treatment (part 2)?

**Study Methodology**

- Part 1: To measure the activity of IV rt-PA within 180 minutes of stroke onset in improving neurological deficits. Early improvement was defined as complete resolution of the neurologic deficit or an improvement from baseline in the score on the NIH Stroke Scale (NIHSS) by 4 or more points 24 hours after stroke onset.
- Part 2: To measure if IV rt-PA can produce sustained clinical benefit. Sustained clinical benefit was defined as minimal or no disability on a global outcome assessment at 3 months post stroke.
- Randomized, placebo-controlled, clinical trial with the protocol exactly the same for Parts 1 and 2 (only difference between parts was the primary outcome measure)

**Study Methodology**

- Investigators blinded to Part 1 data during conduct of Part 2.
- Strict inclusion and exclusion criteria to maximize safety
- Results stratified by 0-90 minute and 91-180 minute treatment groups
- Part 1: Sample size of 70 per time strata and treatment group (N=280) based on 0.90 power to detect an absolute difference of 24 percentage points in outcome given a rate of 16% in the placebo group ( $\alpha = 0.05$ , 2-sided test)
- Part 2: Sample size of 160 per treatment group, the power was 0.95 to detect a difference of 20 percentage points between groups in a single measure. The power of the global test is equal to or greater than that of a single measure.
- Permuted-block design with blocks of various sizes

**Study Methodology**

- 0.9 mg/kg with maximum dose of 90mg, 10% as a bolus over 1 minute, the remainder IV drip over 1 hours
- No aspirin or anticoagulants for 24 hours post rt-PA, strict BP management guidelines in an ICU/ASU setting
- Outcome measures based on reliability:
  - Barthel Index (BI) – reliable and valid measure of ability to perform ADLs (100 = complete independence)
  - Modified Rankin Scale (mRS) – simplified overall assessment of function (0 = absence of symptoms, 5 = severe disability)
  - Glasgow Outcome Scale (GOS) global assessment of function (1 = good recovery, 5 = death)
  - NIHSS – quantitative, reliable, and valid measure of stroke severity (0 = no neurological deficit, 42 point scale)

### Study Methodology

- Favorable outcome in the Trial was defined as:
- BI 95-100 + 0-1 NIHSS + 0-1 mRS + 1 GOS
- Intention-to-treat analysis (no assessment defaulted to no improvement)
- Part 1: Comparison of proportion of patients with improvement in NIHSS 24 hours post stroke (Mantel-Haenszel tests)
- Part 2: Global statistic (the Wald test) – simultaneously tests for effect in all 4 outcomes measures specified. If no outcome data at least at 7 days post stroke, worst possible outcome assigned

### Study Methodology

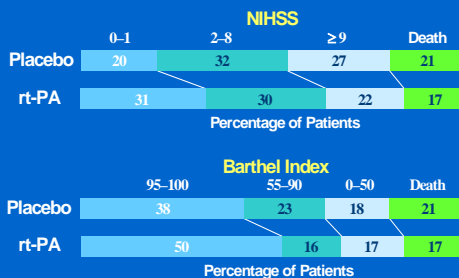
- Primary AEs: ICH, serious systemic bleeding, death, new stroke
- Head CTs required at 24 hours and 7- 10 days post stroke and when any clinical finding suggested hemorrhage. Central CT reading, blinded to treatment
- Interim analyses after every 3 ICHs and every 10 deaths. A lower boundary was set to allow the trial to be stopped if rt-PA was found to be harmful
- From January 1991 through October 1994, 624 patients underwent randomization

### Primary Study Findings

- Treatment groups well matched with respect to all base-line characteristic except weight in Part 1 and aspirin use in Part 2
- Protocol compliance was excellent:  $\geq 90\%$  of all patients received the full dose ( $\pm 5\%$ )
- Part 1: 291 patients – only 1 with missing primary outcome measure
- Part 2: 333 patients (1,332 primary outcome measures) – missing in 4 patients (7 measures)
- Part 1: No statistically significant differences were detected between groups in the primary outcome measure% improved by 4 or more points on the NIHSS or complete improvement. However post-hoc comparisons should significant improvement in the condition of patients (median NIHSSs) treated with rt-PA in most time strata in Parts 1 and 2 and in the combined analysis

### NINDS rtPA Stroke Trial

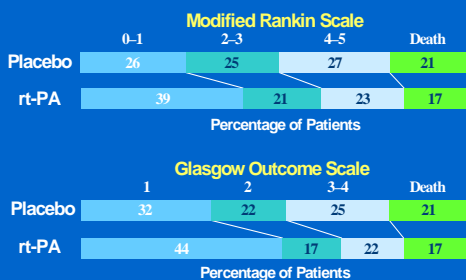
Outcome at 3 months in Part 2 of the study, according to treatment



From NINDS rt-PA Stroke Study Group, NEJM 1995;333:1581.

### NINDS rt-PA Stroke Trial

Outcome at 3 months in Part 2 of the study, according to treatment

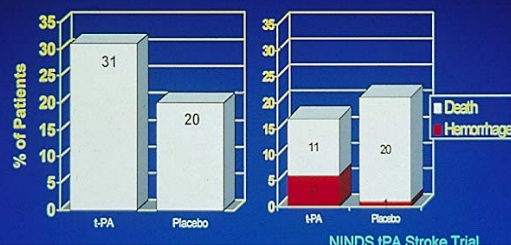


From NINDS rt-PA Stroke Study Group, NEJM 1995;333:1581.

### Results at 3 Months Part 2

Excellent Recovery NIH Scale

Total Death



### Primary Study Findings

- As compared to placebo, there was a 12% absolute (32% relative) increase in the number of patients with minimal or no disability (a score of 95 or 100 on the BI) in the rt-PA treated group.
- There was an 11% absolute (55% relative) increase in the number of patients with an NIHSS score of 0 or 1 with rt-PA. A similar magnitude of effect was seen with the mRS and GOS.
- There were no significant differences in mortality (17% rt-PA, 21% placebo) ( $p = 0.30$ ).
- Symptomatic ICH within 36 hours of treatment was significantly more common with rt-PA treatment (6.4% vs. 0.6%,  $p < 0.001$ )
- Asymptomatic ICH was similar between the 2 groups

### Primary Study Findings

- The positive effect of rt-PA on all outcome measures at 3 months was seen consistently in subgroups categorized according to age, base-line classification of the stroke subtype (small-vessel occlusive, large-vessel occlusive, cardioembolic), severity of the stroke, and use of aspirin before the stroke (i.e. generalized efficacy)

### Study Limitations

- Treatment result (favorable outcome) too limited – only “complete” recoveries counted (mRS 0-1)
- Should count any meaningful improvement (1 pt on mRS)
- Symptomatic ICH too strict – any transient decrease counted
- Should count only bad outcomes (mRS 3-6 at 3 months)
- Trade off of time to treat vs. imaging of vascular obstruction

### Practice Implications of the Study

- In June 1996, FDA approved IV rt-PA within 180 minutes of stroke onset as the first treatment for acute ischemic stroke, taken in conjunction with context/subgroup analyses of ECASS
- Stroke now considered a treatable medical emergency with a very narrow time window for opportunity of efficacy.
- Major paradigm shift/revolution in the triage and management of acute stroke
- Phase IV studies consistently demonstrated similar effects to the NINDS trial when the protocol was followed
- Current development of designated and certified stroke centers across the country

### How Could the Study Be Better Designed?

- Prespecified secondary hypotheses for other degrees of improvement
- Include vascular imaging

### Reanalysis NINDS tPA Trial

- Number needed to treat (NNT)  $\approx 3$  (to get any improvement mRS)
- Number needed to harm (NNH)  $\approx 30$  (to get poor mRS score  $\geq 3$ )
- Likelihood of being helped versus harmed (LHH = NNT/NNH)
- AAEM LLH  $\approx 2$
- Saver LLH  $\approx 10$

