Critical Review Form
Therapy

Tissue Plasminogen Activator for Acute Ischemic Stroke
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Objectives: **"To test whether t-PA had clinical activity — specifically, whether a greater proportion of patients treated with t-PA, as compared with those given placebo, had early improvement, defined as complete resolution of the neurologic deficit or an improvement from baseline in the score on the National Institutes of Health Stroke Scale (NIHSS) by 4 or more points 24 hours after the onset of stroke." An additional hypothesis was "that there would be a consistent and persuasive difference between the t-PA and placebo groups in terms of the proportion of patients who recovered with minimal or no deficit three months after treatment." (p. 1582)**

Methods: **Patients were recruited from 37 university affiliated hospitals with 24-hour access to third- or fourth- generation CT scanners. Subjects were eligible if they had an ischemic stroke with a clearly defined onset less than 180-minutes before t-PA administration if they had a measurable and sustained deficit on the NIHSS with no evidence of intracranial hemorrhage. Exclusion criteria included stroke or serious head trauma within preceding 3-months; major surgery within 14-days; history of intracranial hemorrhage, systolic blood pressure above 185 mm Hg or diastolic blood pressure above 110 mm Hg; rapidly improving or minor symptoms; symptoms suggestive of SAH; GI or urinary tract hemorrhage within 21-days; arterial puncture at a non-compressible site within 7-days; seizure at time of stroke; anticoagulants or heparin within 48-hours with elevated PTT; PT > 15-seconds; platelets < 100K; 50mg/dL > glucose > 400mg/dL; or if aggressive treatment is required to maintain the blood pressure within pre-specified limits.**

Subjects without exclusion criteria were randomized via permuted block design stratified by center and time-to-start of treatment (0-90 minutes or 91-180 minutes) to receive placebo or alteplase 0.9 mg/kg body weight (max 90 mg) with 10% as bolus and 90% as infusion over 60-minutes. No anticoagulants or antiplatelet agents were given for 24 hours after treatment. The first part of the study looked at 24 hour

symptom improvement and had 90% power to detect a 24% improvement if the baseline improvement in the placebo arm was 16% (two-sided α level = 0.05) if 280 subjects were enrolled. The second part of the study assessed 3-month functional recovery and had 95% power to detect 20% improvement if 320 subjects were enrolled.

The functional outcome at 3-months was assessed using four instruments: Barthel index, modified Rankin scale (mRS), Glasgow outcome scale and the NIHSS. Low scores on the Barthel index represent significant functional deficit (range 0-100). On the other hand, low scores on the mRS (range 0-5), Glasgow outcome scale (range 1-5), and NIHSS (range 0-42) represent a good functional outcome. Outcomes were "determined at 24 hours and three months by certified examiners who had not performed the baseline examination and had not been present during the initial treatment". (p. 1582) Patients who died before 3-month assessment were given the worst possible score for all outcomes. In surviving patients with missing data, results after 3-months were used or if that were absent results after 7-days closest to 3-months were used.

Interim analysis was performed after every three symptomatic intracranial hemorrhages and after every 10 deaths. Adverse events monitored included intracranial hemorrhage, serious systemic bleeding, death, and new stroke. Repeat CT scans were required at 24-hours and 7-10 days after stroke onset. All CT results were made available to treating clinicians, but later CT scans were reviewed by a neuroradiologist at the CT- reading center blinded to clinical information.

Genentech supplied and distributed both the alteplase and the placebo and monitored the clinical sites.

Guide		Comments
I.	**Are the results valid?**	
A.	**Did experimental and control groups begin the study with a similar prognosis (answer the questions posed below)?**	
1.	Were patients randomized?	Yes, using permuted block design with blocks of different sizes stratified by clinical center and time from stroke onset.
2.	Was randomization concealed (blinded)?	Outcome assessors were clearly blinded to treatment (p. 1582). The authors do not clearly state whether clinicians, patients, families, investigators, or consultants were blinded to treatment arm.
3.	Were patients analyzed in the groups to which they were randomized?	"All analyses were based on the intention to treat". (p. 1582).
4.	Were patients in the treatment and control groups similar with respect to known prognostic factors?	Subjects in treatment and placebo arms had no significant differences in prior strokes, DM, HTN, MI, A.fib, valvular heart disease, CHF, smoking, or pre-existing disability (Table 1, p. 1582). Additionally, the two treatment arms did not differ significantly by gender, race, NIHSS, glucose, or BP (Table 2, p. 1583). The t-PA arm in both phase I and phase II had more small vessel occlusive disease (13% vs. 7%) and less large vessel occlusive disease (24% vs. 29%). "The treatment groups were well matched with respect to all baseline characteristics except weight in part 1 of the clinical trial and age and aspirin use in part 2" (p. 1584).
B.	**Did experimental and control groups retain a similar prognosis after the study started (answer the questions posed below)?**	
1.	Were patients aware of group allocation?	Presumably no but not clearly stated.

2.	Were clinicians aware of group allocation?	Presumably no but not clearly stated.
3.	Were outcome assessors aware of group allocation?	No. "the outcome was determined at 24 hours and three months by certified examiners who had not performed the baseline examination and had not been present during the initial Treatment". (p. 1582)
4.	Was follow-up complete?	"Of the primary outcome measures for the 291 patients in part 1, data were missing for 1. Of the 1332 primary outcome measures in part 2 (333 patients), data were missing for 7 (4 patients)." (p. 1584)
II.	**What are the results (answer the questions posed below)?**	
1.	How large was the treatment effect?	• From January 1991 through October 1994, 624 patients underwent randomization. The investigators do not state whether these were consecutive patients or what proportion were excluded for various exclusion criteria. They also do not provide a CONSORT diagram. • As judged by complete medication administration, compliance with the protocol was excellent (90% t-PA arm, 92% placebo arm in part 1, 93% both groups in part 2). Investigators do not report any other measures of compliance such as proportion of subjects receiving t-PA or placebo with exclusionary criteria later identified, who screened subjects for eligibility (Neurology vs. EM), who interpreted initial CT (Neuro-radiology vs. non-neuroradiology vs. non-radiology), whether stroke teams were employed and what specific risk/benefit information was provided to subjects in consenting them. 24-hours post-randomization 2% of placebo group had complete resolution suggesting few cases of

		TIA mislabeled as stroke. • In part 1 of the study 24-hour outcomes were not significantly improved in either 0-90 minutes or 91-180 minutes subgroup but the trend favored t-PA in both groups. In part 2 and when part 1 and part 2 were combined the 0-90 minutes (157 combined patients) had a statistically significant ≥ 4 points on NIHSS improvement (55% t-PA vs. 42% placebo, NNT = 8) within 24 hours (Table 3, p. 1583). • **Three month outcomes in part 2 were consistently favorable in t-PA subset by all four outcome measures** (OR 1.7; 95% CI 1.2 – 2.6, p=0.008) with 12% absolute increase in subjects with no or minimal disability (**NNT = 8**). The inclusion of variables that differed at baseline (age, weight, ASA use) **magnified** this effect in favor of t-PA (OR 2.0; 95% CI 1.3 – 3.1) (Table 4, p. 1584). • The greater proportion of patients with minimal or no deficit at 3-months was not accompanied by an increase in severe disability or mortality. At 90-days 17% of t-PA subjects had died compared with 21% of placebo group. • All three stroke subtypes (small-vessel occlusive, cardio-embolic) favored t-PA for 3-month outcomes (Table 5, p. 1585). • **Symptomatic intracerebral hemorrhage** during the first 36-hours was **much more likely in the t-PA group** (8/144 vs. 0/147; **NNH = 18** [95% CI 18-49]), half of which were fatal. ICH was ore likely with more severe deficits (median NIHSS 20, range 3-29 vs. cohort median 14, range

		1-37). Additionally CT evidence of edema was present in 9% of ICH vs. 4% of study cohort. • At 3-months 17/28 (61%) symptomatic ICH had died
2.	How precise was the estimate of the treatment effect?	Sufficiently narrow CIs above and appropriately powered to believe the results.
III.	**How can I apply the results to patient care (answer the questions posed below)?**	
1.	Were the study patients similar to my patient?	Investigators do not provide sufficient detail to confidently answer this question. • Were consecutive patients enrolled? • How many community hospitals were among the 37? • Were study sites provided extra resources or personnel? • How was EMS employed to minimize the time-to-treatment?
2.	Were all clinically important outcomes considered?	No – functional outcomes and symptomatic ICH but not quality of life or hospital length-of-stay.
3.	Are the likely treatment benefits worth the potential harm and costs?	Uncertain without further details and confirmatory studies in non-academic centers.

Limitations

1) **Insufficient description of exclusionary criteria. What is a "significant and sustained" NIHSS score? What constitutes serious head trauma and "major surgery"? What is considered aggressive treatment to maintain blood pressure parameters?**

2) **No CONSORT diagram to illustrate excluded subjects or whether consecutive subjects were enrolled.**

3) **No details reported on the blood pressure protocol or how many subjects required this intervention.**

4) **Insufficient reporting of protocol violations. Did any subjects have unrecognized exclusion** criteria prior to randomization? Who assessed inclusion criteria (emergency physician, **Neurology, research personnel)?**

5) **No clear statement of blinding for patients, clinicians, or investigators.**

6) **Insufficient description of the study hospitals. How many community hospitals? Did hospitals receive any extra resources (money, equipment, personnel, neuro-radiologist)? Who assessed patients for inclusion and what sort of training did they receive? What consent information was provided to subjects and who provided it? How was EMS employed to reduce time-to-treatment?**

7) **How were the inclusion criteria assessed on aphasic or mentally impaired subjects?**

Bottom Line

In university-affiliated United States' hospitals, the NINDS trials demonstrated that t-PA within 3-hours of symptom onset to highly select patients (see the above exclusion criteria) significantly reduces functional deficit at 24-hours and 3-months (NNT = 8). These benefits are driven by the subset treated within 0-90 minutes and are associated with a significantly increased risk of symptomatic ICH within 36 hours (6% vs. 0%; NNH = 18), but no overall increase (or decrease) in 3-month mortality. Lacking other effective interventions for acute ischemic stroke the NNT, NNH, and limitations of this single study should be discussed with patients in collectively deciding upon the best option for an individual.