Critical Review Form

Therapy

Thrombolysis with Alteplase 3 to 4.5 Hours after Acute Ischemic Stroke,
NEJM 2008; 359:1317-1329

Objective: **"To test the hypothesis that the efficacy of alteplase administered in patients with acute ischemic stroke can be safely extended to a time window of 3 to 4.5 hours after the onset of stroke symptoms." (p. 1318)**

Methods: **From July 2003 thru November 2007 patients from 130 sites in 19 European countries between ages 18 to 80 years of age presenting with clinically suspected acute ischemic stroke without pre-randomization intracranial hemorrhage or major cerebral infarction (> 1/3 of middle cerebral artery territory) via CT or MRI who could receive the study drug within 3 to 4.5 hours after symptom onset were randomized. The initial protocol had enrolled only subjects presenting within 3- to 4-hours, but was expanded by 0.5 hours in May 2005 after 228 patients had been enrolled. A significant number of exclusion criteria were applied:**

Intracranial hemorrhage
Time of symptom onset unknown
Symptoms rapidly improving or only minor before start of infusion
Severe stroke as assessed clinically (e.g., NIHSS score >25) or by appropriate imaging techniques*
Seizure at the onset of stroke
Stroke or serious head trauma within the previous 3 months
Combination of previous stroke and diabetes mellitus
Administration of heparin within the 48 hours preceding the onset of stroke, with an activated partial-thromboplastin time at presentation exceeding the upper limit of the normal range
Platelet count of less than 100,000 per cubic millimeter
Systolic pressure greater than 185 mm Hg or diastolic pressure greater than 110 mm Hg, or aggressive treatment (intravenous medication) necessary to reduce blood pressure to these limits
Blood glucose less than 50 mg per deciliter or greater than 400 mg per deciliter
Symptoms suggestive of subarachnoid hemorrhage, even if CT scan was normal
Oral anticoagulant treatment
Major surgery or severe trauma within the previous 3 months
Other major disorders associated with an increased risk of bleeding

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* A severe stroke as assessed by imaging was defined as a stroke involving more than one third of the middle cerebral artery territory. NIHSS denotes National Institutes of Health Stroke Scale in which total scores range from 0 to 42, with higher values reflecting more severe cerebral infarcts.

Eligible subjects were randomized via an interactive voice system in blocks of four. Patients, clinicians, outcome assessors and data safety board members were blinded to subject allocation arm. During the first 24-hours concomitant therapy with IV heparin, oral anticoagulants, aspirin or volume expanders after study drug

administration was prohibited. Clinical assessment occurred at 1, 2, and 24 hours as well as days 7, 30, and 90. CT or MRI was obtained before treatment and at 22 to 36 hours post-treatment.

The primary outcome was 90-day modified Rankin scale favorable outcome (a score of 0 or 1) versus an unfavorable outcome (mRS 2-6). The secondary outcome was a 90-day global outcome measure including mRS 0 or 1 and Barthel Index ≥ 95 and NIHSS 0 or 1 and a score of 1 on the Glasgow Outcome Scale. In the case of missing data among patients known to be alive, the worst possible outcome score was assigned. Initial analyses were performed without adjustment for confounding variables, but a *post- hoc* stratified analysis for mRS was performed adjusting for the two most strongly prognostic baseline variables (initial NIHSS and time to start of treatment). Based upon an odds ratio of 1.4, the study had *a priori* 90% power if 400 patients per group were enrolled.

Safety endpoints included 90-day mortality, any intracranial hemorrhage, symptomatic ICH, symptomatic cerebral edema, and "other serious adverse events". The chairs of the Safety Outcome Adjudication Committee and the steering committee (who remained unaware of the treatment assignments) together adjudicated whether each death or score change indicating neurological deterioration was likely to have been due to intracranial hemorrhage other brain injury or disease, or neither of these causes.

Monitoring and data management were undertaken by the sponsor of the trial (Boehringer Ingelheim). Statistical analyses were performed simultaneously by an independent external statistician and the statistician of the sponsor. "The steering committee had complete access to the trial data after the database had been locked and assumed complete responsibility for the final statistical analysis and interpretation of the results." (p. 1320)

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. "Eligible patients were randomly assigned, in a 1:1 ratio, to receive 0.9 mg of alteplase per kilogram administered intravenously (with an upper limit of 90 mg) or placebo." (p. 1318)

2.	Was randomization concealed (blinded)?	Yes, to patient, clinician, safety board and outcome assessors.
3.	Were patients analyzed in the groups to which they were randomized?	Yes. "Efficacy end points were assessed in the intention-to-treat population, which included all randomly assigned patients, whether or not they were treated." (p. 1321).
4.	Were patients in the treatment and control groups similar with respect to known prognostic factors?	"Baseline demographic and clinical characteristics of the two groups were similar, except that there were significant differences between the groups (before adjustment for multiple comparisons) with respect to the initial severity of the stroke and the presence or absence of a history of stroke." Table 2, (p. 1322).
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?	No. "Alteplase and matched placebo were reconstituted from lyophilized powder in sterile water for injection". Since placebo looked the same and no treating clinician or research associate knew the allocation arm patients would have had no way of knowing which compound (rt-PA or placebo) they received.
2.	Were clinicians aware of group allocation?	No. "The size of the (randomization) blocks was withheld from the investigators to make sure that they were unaware of the treatment assignments." (p. 1319).
3.	Were outcome assessors aware of group allocation?	No. "Patients were assessed by an examiner who was unaware of the treatment assignment." (p. 1320).
4.	Was follow-up complete?	23 subjects (13 rt-PA, 10 placebo) were lost to follow-up. (p. 1319).
II.	**What are the results (answer the questions posed below)?**	

1.	How large was the treatment effect?	• 821 patients were randomly assigned (418 rt-PA, 403 placebo) with 10% within 3- to 3.5-hours, 46.8% within 3.5- to 4-hours, and 39.2% between 4- and 4.5-hours. • Favorable outcome (mRS 0 or 1) was found in 219/418 (52.4%) of rt-PA compared with 182/403 (45.2%) of the placebo group (OR 1.34; 95% CI 1.02-1.76, p = 0.04) which is **NNT = 14** (95% CI 7 – 255). • In the post-hoc intention-to-treatment analysis several significant (p < 0.10) variables were identified by logistic regression analysis: study-group assignment, baseline, NIHSS score, smoking status, time from stroke onset to treatment, presence/absence of hypertension. • In the adjusted analysis rt-PA remained associated with a favorable outcome (OR 1.42, 95%, CI 1.02-1.98). • Treatment with rt-PA also improved secondary outcomes (global OR 1.28, 95% CI 1.0-1.65, p < 0.05). • In the per-protocol analysis (rt-PA 375, placebo 355) significantly more subjects had mRS = 0 (29.1% vs. 22.3%) or 1 (25.9% vs. 23.1%). • Post-hoc adjusted analysis (for NIHSS and time to treatment) also showed favorable outcome in favor of rt-PA (p = 0.02). • Death occurred equally (rt-PA 7.7%, placebo 8.4%) with no trends noted in time-to-death. • rt-PA had significantly more cases of symptomatic ICH regardless of which definition was used (ECASS-III, ECASS-II, SITS-MOST, or NINDS): 2.4% vs. 0.8% p = 0.008. (**NNH = 47**; 95% CI 39-161). • All symptomatic ICH occurred within 22-36 hours of treatment. • rt-PA was administered a median of 3 hours 59 minutes after the onset.

2.	How precise was the estimate of the treatment effect?	See CI above.
III.	**How can I apply the results to patient care (answer the questions posed below)?**	
1.	Were the study patients similar to my patient?	Yes, based upon Table 2 though racial profile and hospital characteristics not described.
2.	Were all clinically important outcomes considered?	Yes.
3.	Are the likely treatment benefits worth the potential harm and costs?	Yes, based upon the combination of two recent meta-analysis (Lansberg 2009 and Hacke 2004) and the results of ECASS III. Furthermore, a recent repeat analysis of the ECASS III data to calculate an effect size incorporating benefit and harm across all levels of post-stroke disability derived a NNT 6 (95% CI 5.6 – 6.7) and NNH 38 (95% CI 34.6-40.5) – even better than the estimates derived from the raw data above!

Limitations

Few and quite minor. This was a well-conducted, explicitly reported study.

1) **Pharma sponsored trial for an expensive, controversial treatment that divides our specialty and acts as a significant source of litigation regardless of the physicians' decision to administer or not.**
2) **Poor description of patient population ethnic profile or capacity of study hospital**
    - **Were patients treated in ED or on a Neurology floor?**
    - **Who treated them (Neurology or EM)?**
    - **Who read the CT?**

- **Did participating hospitals receive extra resources for study participation?**
- **Are these community or academic hospitals or a mix?**
- **Were communities educated on signs/symptoms of stroke?**
- **What was the role of EMS?**

Bottom Line

Intravenous alteplase administered from 3 – 4.5 hours after symptom onset for ischemic stroke in select patients (see exclusion criteria above and below) in a research environment is associated with a clinically significant improvement in the proportion of patients with functionally independent favorable outcomes (NNT = 14; 95% CI 7 – 255) without increasing mortality or symptomatic ICH rates (NNH = 47; 95% CI 39-161). Patients who can be treated within 3 hours should not have their treatment delayed. Optimally, these results will be expeditiously replicated in future studies but this currently represents the best-evidence by which to treat (otherwise untreatable) ischemic strokes and ought to be discussed with patients and families in conjunction with a local neurological protocol.

ECASS III Exclusion Criteria

- Age < 18 or > 80 years
- Onset of stroke > 4.5 hours before drug administration or symptom onset unknown
- Stroke symptoms present < 30 minutes or significantly improving before treatment
- Intracranial hemorrhage
- Severe stroke as defined by NIHSS > 25 or imaging (CT or MRI) displaying > 1/3 of middle cerebral artery territory involved
- Seizure at the onset of stroke
- Stroke or serious head trauma within the previous 3-months
- Combination of previous stroke and diabetes mellitus
- Heparin within the preceding 48 hours with PTT above normal limit
- Platelet count < 100,000 mm^3
- Systolic blood pressure > 185 mm Hg or diastolic > 110 mm Hg or aggressive treatment (intravenous medication) to reduce blood pressure to these limits
- Glucose < 50 mg/dL or > 400 mg/dL
- Symptoms suggestive of subarachnoid hemorrhage even if CT normal
- Oral anticoagulation therapy
- Major surgery or severe trauma within 3-months
- Other major disorders with an increased risk of bleeding