Critical Review Form

Therapy

Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II), *Lancet* 1998; 352:1245-1251

Objectives: **"To find out whether alteplase given within 6 hours of symptom onset (patients were randomised equally to alteplase and placebo for both time strata of 0–3 h and 3–6 h) improved clinical outcome in comparison with placebo." (p. 1246).**

Methods: **Between October 1996 and January 1998 subjects were recruited from 108 centers in 14 European countries, Australia and New Zealand. Eligible subjects were age 18 – 80 years with clinical diagnosis of moderate to severe ischemic stroke with no or minimal CT evidence of cerebral infarction who could be treated within 6-hours of symptom onset Subjects were excluded if they had intracerebral hemorrhage, over 1/3 middle cerebral artery distribution hypoattenuation on CT, SAH, unknown symptom onset time, coma or stupor, hemiplegia with fixed eye deviation, minor stroke symptoms (Scandinavian Stroke Scale > 50) or rapid symptom improvement before t-PA, SBP > 185 or dBP > 110, traumatic brain injury within 14 days, CNS surgery within 3-months, GI or urinary tract hemorrhage, IV or SQ heparin, hereditary or acquired bleeding diathesis lactation, pregnancy, contraception, 50 mg/dL > glucose > 400 mg/dL, or participation in another drug trial within 3-months.**

A standard protocol was used to control blood pressure. Before and during the trial courses were run to improve the quality of CT-scanning and interpretation. Randomization occurred by a computer-generated procedure in blocks of four with investigators blinded to allocation arm except in emergencies. Treatment arm received alteplase 0.9 mg/ kg IV with 10% over 1-2 minutes and the remainder over the next 60-minutes (max dose 90 mg). SQ heparin was allowed during the first 24-hours, but not IV heparin, oral anticoagulants, antiplatelet agents, volume expanders or potential neuroprotective agents.

The primary endpoint was the proportion of subjects, with a favorable outcome (modified Rankin scale 0 or 1) at 90-days post-treatment. With 350 subjects in each arm the study had 80% power with (2-sided?) α level = 0.05 to detect an absolute difference in mRS proportion of 10% between treatment groups. Secondary outcomes included NIHSS, Barthel index, at 90 days, quality of life at 90 days, and hospital length-of-stay.

CT brain imaging was obtained at baseline, 22- 36 hours post-enrollment, and at Day 7. Adverse events monitored included symptomatic intracerebral hemorrhage and mortality at 30 and 90 days.

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. "A computer-generated randomisation procedure in blocks of four was used, with each centre allocated at least one block of the treatment groups at 0–3 h and 3–6 h to ensure a stratified distribution". (p. 1246).
2.	Was randomization concealed (blinded)?	Yes. "The randomisation schedule was known only to the Clinical Trial Support Unit at Boehringer-Ingelheim and to one member of the External Safety Committee. Treatment allocation was concealed from all investigators." (p. 1246).
3.	Were patients analyzed in the groups to which they were randomized?	Yes. "The primary analysis was by intention to treat, of all randomised patients". (p. 1247)
4.	Were patients in the treatment and control groups similar with respect to known prognostic factors?	Yes. "The alteplase and placebo groups were similar in terms of baseline variables (table 1)". (p. 1247)
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
2.	Were clinicians aware of group allocation?	No, except in cases of emergencies which happened five times.
3.	Were outcome assessors aware of group allocation?	No except in cases of emergencies.
4.	Was follow-up complete?	No significant lost to follow-up was reported.
II.	**What are the results (answer the questions posed below)?**	

1.	How large was the treatment effect?	• 800 patients were enrolled (409 t-PA, 391 placebo) and 72 protocol violations were reported (34 t-PA, 38 placebo). • 42.6% had no CT evidence of strokes on the initial scan. • For the *a priori* primary outcome (mRS 0 or 1 at 90 days) no difference between alteplase (40.3%) vs. placebo (36.6%) p = 0.277. However, **post-hoc analysis** of mRS 0, 1 or 2 favored t-PA group with ARR 8.3% (**NNT = 12**, p= 0.024). • No other secondary outcomes showed any clinically significant differences between t-PA and placebo. • Stratified analysis of treatment < 3 h vs. treatment 3 – 6 hours showed no significant difference (favorable mRS at 90 days 42% t-PA vs. 38% placebo in < 3 hours subset, p = 0.628), but only 19.8% of cohort had treatment < 3h. • 10.6% overall 90-day mortality, but no difference in 30- or 90-day mortality between treatment groups. • During the first 7-days more deaths in t-PA than placebo group from ICH (11 vs. 2). In the subgroup treated within 3 hours more deaths were noted up to 102-days in the t-PA group (14% vs. 8%). • No increase in other complications was noted in the t-PA group.
2.	How precise was the estimate of the treatment effect?	The Confidence Intervals cross one for the primary outcome, so not precise enough and possibly underpowered.
III.	**How can I apply the results to patient care (answer the questions posed below)?**	

1.	Were the study patients similar to my patient?	Uncertain since little hospital or patient specific data is provided. • Were patients treated in ED or on 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?
2.	Were all clinically important outcomes considered?	Yes, functional outcomes, adverse effects, QOL, and hospital LOS.
3.	Are the likely treatment benefits worth the potential harm and costs?	No, not based upon this study.

Limitations

1) **Uncertain since little hospital or patient specific data provided. Were patients treated in ED or on 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?**
2) **Underpowered for observed effect size so possible Type II error.**
3) **BP protocol not described.**
4) **<20% of subjects had treatment within 3h and no analysis of subset < 90 minutes or protocol violation report in the < 3 hours subset.**

Bottom Line

In highly select ischemic stroke patients (see exclusion criteria above) t-PA within 6-hours of symptom onset shows non-significant trend towards improve outcome (mRS 0 or 1, 40.3% t-PA vs. 36.6% placebo) while significantly increasing the risk of ICH within 7-days. In conjunction with the NINDS data with benefit dominated by the < 90-minute to treatment subset, future trials and clinical protocols

should focus resources on getting patients to the ED within 90 minutes (patient education, EMS protocols) rapidly accessible stroke teams and CT availability with Neuroradiology read pre-treatment and t-PA as close to 90 minutes as possible rather than extending the treatment window where the benefits are smaller and ICH rates are not trivial.