

Clinical Practice Statement: Tissue Plasminogen Activator (tPA) and Stroke: A Clinical Practice Advisory (4/12/10)

tPA and Stroke: Clinical Practice Advisory

Alteplase therapy for acute ischemic stroke has been controversial in the emergency medicine community, although the therapy has been recommended by other bodies such as the American Heart Association.¹ We acknowledge that the controversy continues; however, important additional randomized clinical trial and registry data from phase IV studies have been published since the 1995 NINDS trial and are of relevance to the emergency physician.

Emergency physicians play a critical role in this process and often must discuss the benefits and risks of the therapy directly with patients and families; this is especially true in centers without organized acute stroke teams or substantial involvement from neurology. A pooled analysis of the three major thrombolytic trials utilizing alteplase at the established dosing confirmed benefit within three hours and suggested that benefit might exist up to 4.5 hours.² Data from several post-marketing surveillance and other observational studies has established that the complication rate from this therapy is similar to what was observed in clinical trials.³⁻⁵ An ongoing NIH funded cluster randomized trial (INSTINCT) will provide high quality, prospective data regarding use in community practice soon. Data from the recent ECASS III trial demonstrates a significantly improved chance of a good outcome in patients treated up to 4.5 hours after the onset of symptoms. While differences exist between the treatment and placebo groups for important prognostic variables (severity and history of prior stroke), the investigators performed adjustments to account for these baseline differences and continued to observe a persistent, significant clinical effect.⁶ The lower mean NIHSS and prevalence of prior stroke in the treatment group were not intentional but occurred by random chance. Further discussion is needed prior to widespread incorporation of the findings of ECASS III into broad clinical practice, although one important implication of this work is relevant to all emergency physicians now: it is unlikely that a therapy that has demonstrated efficacy between 3 and 4.5 hours would not be efficacious between 0 and 3 hours.

ECASS III was a randomized, double-blind, controlled clinical trial of 800 patients with acute stroke treated with tPA or placebo between 3 and 4.5 hours after symptom onset. The results of this trial were published in the NEJM on 25 September 2008. ECASS III shows an absolute benefit of 7% in good neurological outcomes at 3 months in patients treated with tPA. This is almost exactly the effect size that was predicted by the pooled analysis of the prior 5 randomized, controlled trials, none of which was itself powered to detect that size effect.² As in the previous ECASS trials they excluded the highest risk patients (elderly, extremely severe strokes, massive early ischemic signs on initial CT, etc.). This trial was mandated by the EMEA, the European equivalent of the

FDA, as a condition of approval of 0-3 hour alteplase for stroke in the EU, because they were afraid tPA would be used off label beyond 3 hours without data. While there are some details that would be interesting that were not presented in the paper (questions about randomization, distribution of severity, distribution over time, etc.), this paper, taken together with the pooled analysis of the 3 to 6 hour data in the previous ECASS, NINDS, and ATLANTIS trials, is positive. The symptomatic ICH rate was similar to that observed in prior trials, although the definition used by the ECASS III investigators (which more closely examined whether the ICH was the likely cause of the deterioration) yielded a rate of 2.4%. Mortality at 90 days was similar between treatment and placebo groups in ECASS III (7.7 and 8.4% respectively), and lower than the older tPA stroke trials in which mortality was around 20% in treatment and placebo groups.

These results represent the confirmatory trial data on the use of thrombolysis in acute ischemic stroke that many cautious colleagues have been requesting for years to settle disagreements about the adequacy of the supporting data for this rather persistent and often contentious clinical question. Alteplase has demonstrated benefit in academic centers and organized stroke centers but the benefit is not established at other types of hospitals. Additionally, all hospitals should have a protocol or plan in place (i.e. stroke team) for the care of suspected acute stroke patients. Emergency physicians working in sites without an institutional plan for stroke care is a suboptimal situation and the discussion regarding use of thrombolytics for acute stroke does not pertain to these settings.

Resources for developing local protocols and consent scripts or templates.

(We would urge clinicians to examine and become familiar with these tools PRIOR to considering using them as an adjunct to the standard consent process. Ideally, these tools would assist the clinician in developing a standardized consent process for their institution. Clinicians should consider discussing and documenting reasons for not offering treatment in both potentially eligible and non-eligible patients.)

1. The outcome wheel: a potential tool for shared decision making in ischemic stroke thrombolysis - <http://www.sem-bc.com/cvatoolkit/> - Provides a visual tool that estimates likelihood of being disability free, disabled, or dead when treated or not-treated with IV tPA and prompts for exclusions. Requires Microsoft Excel.
2. Stroke thrombolytic predictive instrument - <https://research.tufts-nemc.org/asat/> - Provides estimates of likelihood of good outcome with and without treatment based on age, glucose, blood pressure, and severity.
3. tPA for Stroke – Potential Benefit, Risk and Alternatives - <http://www.aaem.org/education/tpaedtool-AAEM.pdf> - Handout developed by AAEM
4. Activase patient information --

http://www.activase.com/media/Activase_PatientBroch.pdf -- Handout developed by the manufacturer, Genentech. As such the brochure is regulated and examined by the FDA for accuracy.

References:

1. Adams HP, Jr, del Zoppo G, Alberts MJ, et al. Guidelines for the Early Management of Adults With Ischemic Stroke: A Guideline From the American Heart Association/ American Stroke Association Stroke Council, Clinical Cardiology Council, Cardiovascular Radiology and Intervention Council, and the Atherosclerotic Peripheral Vascular Disease and Quality of Care Outcomes in Research Interdisciplinary Working Groups: The American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists. *Stroke*. May 1, 2007;38(5):1655-1711.
2. Hacke W, Donnan G, Fieschi C, et al. Association of outcome with early stroke treatment: pooled analysis of ATLANTIS, ECASS, and NINDS rt-PA stroke trials. *Lancet*. Mar 6 2004;363(9411):768-774.
3. Graham GD. Tissue plasminogen activator for acute ischemic stroke in clinical practice: a meta-analysis of safety data. *Stroke*. Dec 2003;34(12):2847-2850.
4. Lansberg MG, Bluhmki E, Thijs VN. Efficacy and safety of tissue plasminogen activator 3 to 4.5 hours after acute ischemic stroke: a metaanalysis. *Stroke*. Jul 2009;40(7):2438-2441.
5. Wahlgren N, Ahmed N, Dávalos A, et al. Thrombolysis with alteplase for acute ischaemic stroke in the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST): an observational study. *The Lancet*. 2007;369(9558):275-282.
6. Torbey MT, Jauch E, Liebeskind DS, et al. Thrombolysis 3 to 4.5 Hours after Acute Ischemic Stroke. *N Engl J Med*. December 25, 2008;359(26):2839-2841.

tPA and Stroke: Appendix - Literature Search Strategy

Using the AAEM methodology for literature search the following search was performed. Search terms CVA AND (thromboly* OR alteplase), limited to 1990-2009, English language. The clinical question: "Is intravenous thrombolysis safe and effective for stroke?" Guideline statements and non-systematic reviews were excluded. Studies targeting differences between specific populations (males versus females) were excluded.

Tier 1: Systematic Reviews – Provided 121 citations, the abstracts were scanned, yielding 11 manuscripts. One of these was identified in pubmed as a

meta-analysis, but actually no meta-analysis was performed; two of these were subsequent updates of earlier Cochrane Reviews and were excluded yielding 8 total Tier 1 manuscripts. As a large proportion of the reviews were performed by the same author, we decided to also include Tier 2 data:

Tier 2: High quality clinical trials and multicenter studies in core clinical journals – Provided 208 citations, for which the titles and abstracts were scanned to assess relevance to study questions, yielding 6 relevant citations, one of which was identified in Tier 1, leaving 5 randomized controlled trials.

Tier 1:

1: Stroke. 2009 Jul;40(7):2438-41. Epub 2009 May 28. Efficacy and safety of tissue plasminogen activator 3 to 4.5 hours after acute ischemic stroke: a metaanalysis. Lansberg MG, Bluhmki E, Thijs VN. Stanford Stroke Center, Stanford University Medical Center, Palo Alto, CA 94304-9705, USA. lansberg@stanford.edu

BACKGROUND AND PURPOSE: The Third European Cooperative Acute Stroke Study (ECASS-3) demonstrated a benefit of treatment with intravenous tissue plasminogen activator (tPA) for acute stroke in the 3- to 4.5-hour time-window. Prior studies, however, have failed to demonstrate a significant benefit of tPA for patients treated beyond 3 hours. The purpose of this study was to produce reliable and precise estimates of the treatment effect of tPA by pooling data from all relevant studies.

METHODS: A metaanalysis was undertaken to determine the efficacy of tPA in the 3- to 4.5-hour time-window. The effect of tPA on favorable outcome and mortality was assessed. **RESULTS:** The metaanalysis included data from patients treated in the 3- to 4.5-hour time-window in ECASS-1 (n=234), ECASS-2 (n=265), ECASS-3 (n=821) and The Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke (ATLANTIS) (n=302). tPA treatment was associated with an increased chance of favorable outcome (odds ratio 1.31; 95% CI: 1.10 to 1.56; P=0.002) and no significant difference in mortality (odds ratio 1.04; 95% CI: 0.75 to 1.43; P=0.83) compared to placebo treated patients.

CONCLUSIONS: Treatment with tPA in the 3- to 4.5-hour time-window is beneficial. It results in an increased rate of favorable outcome without adversely affecting mortality.

Evidence: Supporting, Grade A; Quality: Good

Comment: This meta-analysis addresses the question of whether tPA is safe and effective after 3 hours when combining data from several trials including the recent ECASS 3 trial. The authors concluded there was improved outcome

without excess mortality.

2: Stroke. 2008 Dec;39(12):3316-22. Epub 2008 Oct 16. Multivariable analysis of outcome predictors and adjustment of main outcome results to baseline data profile in randomized controlled trials: Safe Implementation of Thrombolysis in Stroke-MONitoring Study (SITS-MOST). Wahlgren N, Ahmed N, Eriksson N, Aichner F, Bluhmki E, Dávalos A, Eirilä T, Ford GA, Grond M, Hacke W, Hennerici MG, Kaste M, Köhrmann M, Larrue V, Lees KR, Machnig T, Roine RO, Toni D, Vanhooren G; Safe Implementation of Thrombolysis in Stroke-MONitoring Study Investigators. Department of Neurology, Karolinska University Hospital-Solna, Karolinska Institutet, Stockholm, Sweden. nils.wahlgren@karolinska.se

BACKGROUND AND PURPOSE: The Safe Implementation of Thrombolysis in Stroke-MONitoring Study (SITS-MOST) unadjusted results demonstrated that intravenous alteplase is well tolerated and that the effects were comparable with those seen in randomized, controlled trials (RCTs) when used in routine clinical practice within 3 hours of ischemic stroke onset. We aimed to identify outcome predictors and adjust the outcomes of the SITS-MOST to the baseline characteristics of RCTs.

METHODS: The study population was SITS-MOST (n=6483) and pooled RCTs (n=464) patients treated with intravenous alteplase within 3 hours of stroke onset. Multivariable, backward stepwise regression analyses (until $P \leq 0.10$) were performed to identify the outcome predictors for SITS-MOST. Variables appearing either in the final multivariable model or differing ($P < 0.10$) between SITS-MOST and RCTs were included in the prediction model for the adjustment of outcomes. Main outcome measures were symptomatic intracerebral hemorrhage, defined as National Institutes of Health Stroke Scale deterioration ≥ 1 within 7 days with any hemorrhage (RCT definition), mortality, and independency as defined by modified Rankin Score of 0 to 2 at 3 months.

RESULTS: The adjusted proportion of symptomatic intracerebral hemorrhage for SITS-MOST was 8.5% (95% CI, 7.9 to 9.0) versus 8.6% (6.3 to 11.6) for pooled RCTs; mortality was 15.5% (14.7 to 16.2) versus 17.3% (14.1 to 21.1); and independency was 50.4% (49.6 to 51.2) versus 50.1% (44.5 to 54.7), respectively. In the multivariable analysis, older age, high blood glucose, high National Institutes of Health Stroke Scale score, and current infarction on imaging scans were related to poor outcome in all parameters. Systolic blood pressure, atrial fibrillation, and weight were additional predictors of symptomatic intracerebral hemorrhage. Current smokers had a lower rate of symptomatic intracerebral hemorrhage. Disability before current stroke (modified Rankin Score 2 to 5), diastolic blood pressure, antiplatelet other than aspirin, congestive heart failure, patients treated in new centers, and male sex were related to high mortality at 3 months.

CONCLUSIONS: The adjusted outcomes from SITS-MOST were almost identical to those in relevant RCTs and reinforce the conclusion drawn previously in the unadjusted analysis. We identified several important outcome predictors to better identify patients suitable for thrombolysis.

Evidence: Supportive, Grade D; Quality: Adequate

Comment: One of the concerns about SITS-MOST was the overall stroke severity was low. This is a re-analysis where they adjusted the mortality and disability outcomes based on what was observed in the randomized controlled trials. The magnitude of effect and safety were both similar to prior RCT data when examined in this large registry. Patients who received alteplase outside the EMEA (European equivalent of FDA) label were not included in this registry. This effectively created a 0-3 hour window population similar to ECASS III's 3-4.5 hour window with no patients over 80 and no severe strokes. This population selection was likely responsible for the low mortality rates (about 11% versus 17-20% from NINDS).

This is not a controlled trial and is simply a registry.

3: Cochrane Database Syst Rev. 2004 Oct 18;(4):CD000514. Update of: Cochrane Database Syst Rev. 2000;(2):CD000514. Thrombolysis (different doses, routes of administration and agents) for acute ischaemic stroke. Mielke O, Wardlaw J, Liu M.

BACKGROUND: Thrombolytic therapy is effective for acute myocardial infarction, a disease with some similarities to acute ischaemic stroke. Meta-analyses suggest a net benefit in acute ischaemic stroke. **OBJECTIVES:** To assess different thrombolytic agents, and different regimens, in acute ischaemic stroke.

SEARCH STRATEGY: We searched the Cochrane Stroke Group trials register (last searched to June 2003), MEDLINE (1966 to July 2003) and EMBASE (1980 to July 2003). We hand searched four Japanese journals, contacted researchers and pharmaceutical companies, and attended relevant conferences.

SELECTION CRITERIA: Randomized and quasi-randomized trials of different doses of a thrombolytic agent, or different agents, or the same agent given by different routes, in people with confirmed acute ischaemic stroke.

DATA COLLECTION AND ANALYSIS: Two reviewers independently assessed trial eligibility and quality, and extracted the data.

MAIN RESULTS: Ten trials involving 1641 patients, 8 conducted in Japan, 1 in China and 1 in the USA, were included. Concealment of allocation was poorly described. Different doses (of tissue plasminogen activator or urokinase) were compared in seven trials (n = 1072 patients). Different agents (tissue

plasminogen activator versus urokinase; tissue-cultured urokinase versus conventional urokinase) were compared in three trials (n = 688 patients). One trial compared different routes of administration (intravenous plus intraarterial tissue plasminogen activator versus intraarterial tissue plasminogen activator alone, n = 35 patients). As some trials compared different agents and different doses, some patients contributed to two analyses. A higher dose of thrombolytic therapy was associated with a three-fold increase in fatal intracranial haemorrhages (Odds ratio (OR) 3.25, 95% confidence interval (CI) 1.32 to 7.97) compared with a lower dose of the same agent (based on 16 events among 539 higher-dose patients and 4 events among 533 lower-dose patients in 7 trials). There was no statistically significant difference in early (OR 1.01, 95% CI 0.58 to 1.74) or late (OR 0.94, 95% CI 0.58 to 1.53) deaths between lower and higher doses. Data were inadequate to assess the effect of dose on functional outcome. No statistically significant difference was shown between different thrombolytic agents tested. The data from the pilot trial comparing different routes of administration were inconclusive.

REVIEWERS' CONCLUSIONS: These scant data suggest that higher doses of thrombolytic agents may lead to higher rates of bleeding. However, the evidence is inadequate to conclude whether lower doses of thrombolytic agents are more effective than higher doses, or whether one agent is better than another, or which route of administration is the best, in acute ischaemic stroke.

PMID: 15494998 [PubMed - indexed for MEDLINE]

Evidence: Neutral, Grade B; Quality: Adequate

Comment: This meta-analysis focused on different agents and different routes and included semi RCT studies. It did not address the question of whether alteplase was safe and effective for acute ischemic stroke. Given the multiple comparisons between heterogeneous trials and dosing regimens the failure to reach any conclusions is not surprising

4: Lancet. 2004 Mar 6;363(9411):768-74. Association of outcome with early stroke treatment: pooled analysis of ATLANTIS, ECASS, and NINDS rt-PA stroke trials. Hacke W, Donnan G, Fieschi C, Kaste M, von Kummer R, Broderick JP, Brott T, Frankel M, Grotta JC, Haley EC Jr, Kwiatkowski T, Levine SR, Lewandowski C, Lu M, Lyden P, Marler JR, Patel S, Tilley BC, Albers G, Bluhmki E, Wilhelm M, Hamilton S; ATLANTIS Trials Investigators; ECASS Trials Investigators; NINDS rt-PA Study Group Investigators. Medical University at Heidelberg, Germany.

BACKGROUND: Quick administration of intravenous recombinant tissue plasminogen activator (rt-PA) after stroke improved outcomes in previous trials. We aimed to analyse combined data for individual patients to confirm the

importance of rapid treatment.

METHODS: We pooled common data elements from six randomized placebo-controlled trials of intravenous rt-PA. Using multivariable logistic regression we assessed the relation of the interval from stroke onset to start of treatment (OTT) on favourable 3-month outcome and on the occurrence of clinically relevant parenchymal haemorrhage.

FINDINGS: Treatment was started within 360 min of onset of stroke in 2775 patients randomly allocated to rt-PA or placebo. Median age was 68 years, median baseline National Institute of Health Stroke Scale (NIHSS) 11, and median OTT 243 min. Odds of a favourable 3-month outcome increased as OTT decreased ($p=0.005$). Odds were 2.8 (95% CI 1.8-4.5) for 0-90 min, 1.6 (1.1-2.2) for 91-180 min, 1.4 (1.1-1.9) for 181-270 min, and 1.2 (0.9-1.5) for 271-360 min in favour of the rt-PA group. The hazard ratio for death adjusted for baseline NIHSS was not different from 1.0 for the 0-90, 91-180, and 181-270 min intervals; for 271-360 min it was 1.45 (1.02-2.07). Haemorrhage was seen in 82 (5.9%) rt-PA patients and 15 (1.1%) controls ($p<0.0001$). Haemorrhage was not associated with OTT but was with rt-PA treatment ($p=0.0001$) and age ($p=0.0002$). **INTERPRETATION:** The sooner that rt-PA is given to stroke patients, the greater the benefit, especially if started within 90 min. Our results suggest a potential benefit beyond 3 h, but this potential might come with some risks.

PMID: 15016487 [PubMed - indexed for MEDLINE]

Evidence: Supportive, Grade A; Quality: Good

This pooled analysis confirmed benefit of intravenous thrombolysis for stroke and illustrated that time to treatment is a very important prognostic factor.

5: Stroke. 2003 Dec;34(12):2847-50. Epub 2003 Nov 6. Tissue plasminogen activator for acute ischemic stroke in clinical practice: a meta-analysis of safety data. Graham GD. Albuquerque VA and University of New Mexico School of Medicine, Department of Neurology, VA Medical Center, Albuquerque, NM 87122, USA. graham@unm.edu

BACKGROUND AND PURPOSE: Concerns persist regarding the safety of tissue plasminogen activator (tPA) therapy for acute ischemic stroke. Numerous case series of clinical experience with tPA have been published that provide additional data on the safety of thrombolytic therapy. **METHODS:** This is a meta-analysis of 15 published, open-label studies that broadly followed approved indications and guidelines for tPA use in nonselective patient populations.

RESULTS: In 2639 treated patients, the symptomatic intracerebral hemorrhage

rate was 5.2% (95% confidence interval, 4.3 to 6.0), slightly lower than the 6.4% rate in the treated group of the randomized, placebo-controlled National Institute of Neurological Disorders and Stroke (NINDS) trial. The mean total death rate (13.4%) and proportion of subjects achieving a very favorable outcome (37.1%) were comparable to the NINDS trial results. Protocol deviations were reported in 19.8%. Comparing across studies showed that the mortality rate was correlated with the percentage of protocol violations ($r=0.67$, $P=0.018$).

CONCLUSIONS: Post approval data support the safety of intravenous thrombolytic therapy with tPA for acute ischemic stroke, especially when established treatment guidelines are followed.

PMID: 14605319 [PubMed - indexed for MEDLINE]

Evidence: Supportive, Grade B; Quality: Adequate

Comment: This meta-analysis included 10 prospective and 5 retrospective studies including open label reports in non selective patient populations.. Since this study focused on post-marketing surveillance derived safety data it could not address whether the treatment was efficacious. It did demonstrate a correlation between protocol violations and mortality which is not surprising. Additionally, the estimated rate of symptomatic ICH was 5.2%, similar to RCT data.

6: Cochrane Database Syst Rev. 2003;(3):CD000213. Update of: Cochrane Database Syst Rev. 2000;(2):CD000213. Thrombolysis for acute ischaemic stroke. Wardlaw JM, Zoppo G, Yamaguchi T, Berge E. Clinical Neurosciences, The University of Edinburgh, Western General Hospital, Crewe Rd, Edinburgh, UK, EH4 2XU.

BACKGROUND: The majority of strokes are due to blockage of an artery in the brain by a blood clot. Prompt treatment with thrombolytic drugs can restore blood flow before major brain damage has occurred. Successful treatment could mean that the patient is more likely to make a good recovery from their stroke. Thrombolytic drugs however, can also cause serious bleeding in the brain which can be fatal. Thrombolytic therapy has now been evaluated in several randomized trials in acute ischaemic stroke.

OBJECTIVES: The objective of this review was to assess the safety and efficacy of thrombolytic agents in patients with acute ischaemic stroke.

SEARCH STRATEGY: We searched the Cochrane Stroke Group Trials Register (last searched January 2003), MEDLINE (1966- January 2003) and EMBASE (1980-January 2003). In addition we contacted researchers and pharmaceutical companies, attended relevant conferences and hand searched four Japanese journals.

SELECTION CRITERIA: Randomized trials of any thrombolytic agent compared with control in patients with definite ischaemic stroke.

DATA COLLECTION AND ANALYSIS: One reviewer applied the inclusion criteria and extracted the data. Trial quality was assessed. The extracted data were verified by the principal investigators of all major trials. Thus published and unpublished data were obtained where available.

MAIN RESULTS: Eighteen trials including 5727 patients were included, but not all trials contributed data to each outcome examined in this review. Sixteen trials were double-blind. The trials tested urokinase, streptokinase, recombinant tissue plasminogen activator or recombinant pro-urokinase. Two trials used intra-arterial administration but the rest used the intravenous route. About 50% of the data (patients and trials) come from trials testing intravenous tissue plasminogen activator. There are few data from patients aged over 80 years. Much of the data comes from trials conducted in the first half of the 1990s when, in an effort to reduce delays to trial drug administration, on site randomization methods were used that, in consequence, limited the ability to stratify randomization on key prognostic variables.

Several trials, because of the biological effects of thrombolysis combined with the follow-up methods used, did not have complete blinding of outcome assessment. Thrombolytic therapy, administered up to six hours after ischaemic stroke, significantly reduced the proportion of patients who were dead or dependent (modified Rankin 3 to 6) at the end of follow-up at three to six months (OR 0.84, 95% CI 0.75 to 0.95). This was in spite of a significant increase in: the odds of death within the first ten days (odds ratio [OR] 1.81, 95% confidence interval [CI] 1.46 to 2.24), the main cause of which was fatal intracranial haemorrhage (OR 4.34, 95% CI 3.14 to 5.99). Symptomatic intracranial haemorrhage was increased following thrombolysis (OR 3.37, 95% CI 2.68 to 4.22).

Thrombolytic therapy also increased the odds of death at the end of follow-up at three to six months (OR 1.33, 95% CI 1.15 to 1.53). For patients treated within three hours of stroke, thrombolytic therapy appeared more effective in reducing death or dependency (OR 0.66, 95% CI 0.53 to 0.83) with no statistically significant adverse effect on death (OR 1.13, 95% CI 0.86 to 1.48). There was heterogeneity between the trials that could have been due to many trial features including: thrombolytic drug used, variation in the use of aspirin and heparin, severity of the stroke (both between trials and between treatment groups within trials), and time to treatment.

Trials testing intravenous recombinant tissue plasminogen activator suggested that it may be associated with slightly less hazard and more benefit than other drugs when given up to six hours after stroke but these are non-random comparisons - death within the first ten days OR 1.24, 95% CI 0.85 to 1.81, death

at the end of follow-up OR 1.17, 95% CI 0.95 to 1.45, dead or dependent at the end of follow-up OR 0.80, 95% CI 0.69 to 0.93. However, no trial has directly compared rt-PA with any other thrombolytic agent. There is some evidence that antithrombotic drugs given soon after thrombolysis may increase the risk of death.

REVIEWER'S CONCLUSIONS: Overall, thrombolytic therapy appears to result in a significant net reduction in the proportion of patients dead or dependent in activities of daily living. However, this appears to be net of an increase in deaths within the first seven to ten days, symptomatic intracranial haemorrhage, and deaths at follow-up at three to six months. The data from trials using intravenous recombinant tissue plasminogen activator, from which there are the most evidence on thrombolytic therapy so far, suggest that it may be associated with less hazard and more benefit. There was heterogeneity between the trials for some outcomes and the optimum criteria to identify the patients most likely to benefit and least likely to be harmed, the latest time window, the agent, dose, and route of administration, are not clear. The data are promising and may justify the use of thrombolytic therapy with intravenous recombinant tissue plasminogen activator in experienced centres in highly selected patients where a licence exists. However, the data do not support the widespread use of thrombolytic therapy in routine clinical practice at this time, but suggest that further trials are needed to identify which patients are most likely to benefit from treatment and the environment in which it may best be given. To avoid the problem of data missing from some trials for some key outcomes encountered in this review to date, and to assist future metaanalyses, future trialists should try to collect data in such a way as to be compatible with the basic outcome assessments reviewed here (eg early death, fatal intracranial haemorrhage, poor functional outcome).

PMID: 12917889 [PubMed - indexed for MEDLINE]

Evidence: Supportive, Grade A; Quality: Adequate

Comment: This meta-analysis included RCTs and a few trials with possible RCT characteristics. It examined several heterogeneous stroke thrombolysis trials, which used different agents, dosages, and time windows. They found that thrombolysis within 3 hours was beneficial. The conclusion that future study was needed was based on some suggestion of excess harm, especially early. The SITS-MOST registry and ECASS III trial which were completed after this meta-analysis could be considered the sort of additional data that the authors of this review were looking for.

7: Stroke. 2003 Jun;34(6):1437-42. Epub 2003 May 1. Thrombolytic therapy with recombinant tissue plasminogen activator for acute ischemic stroke: where do we go from here? A cumulative meta-analysis. Wardlaw JM, Sandercock PA, Berge E. Department of Clinical Neurosciences, Western General Hospital, Edinburgh

EH42XU, Scotland, UK. jmw@skull.dcn.ed.ac.uk

BACKGROUND AND PURPOSE: Recombinant tissue plasminogen activator (rtPA; Actilyse) is not as widely used in clinical practice as it could be. Have new data since 1995 strengthened the evidence sufficiently to justify more widespread use of rtPA?

METHODS: We performed a sequential year-to-year cumulative meta-analysis of randomized controlled trials of rtPA in acute ischemic stroke. **RESULTS:** Although the amount of data has doubled since 1995, effect estimates for key outcomes remain imprecise, and significant between-trial heterogeneity persists. In the most recent analysis, rtPA up to 6 hours after stroke yielded 55 fewer dead or dependent people per 1000 treated (95% CI, 18 to 92) despite some risk (nonsignificant excess of 19 deaths per 1000 patients treated; 95% CI, 6 fewer to 48 more). Severity of stroke, patient age, and aspirin use were possible sources of heterogeneity.

CONCLUSIONS: Despite doubling of the data since 1995, the magnitude of risks and benefits with rtPA remains imprecise. This gap in knowledge may be hindering clinical use of rtPA and can be filled only by new trials designed to address these specific issues.

PMID: 12730560 [PubMed - indexed for MEDLINE]

Evidence: Supportive, Grade A; Quality: Adequate

Comment: This study performed a "cumulative" meta analysis of only RCTs over time. A significant reduction in disability was estimated, despite inclusion of trials enrolling most patients after 4.5 hours. Additionally, no excess mortality was observed.

8: Lancet. 1997 Aug 30;350(9078):607-14. Systematic review of evidence on thrombolytic therapy for acute ischaemic stroke. Wardlaw JM, Warlow CP, Counsell C. Department of Clinical Neurosciences, University of Edinburgh, UK. JMW@skull.dcn.ed.ac.uk

BACKGROUND: Recent trials of thrombolytic therapy in acute ischaemic stroke have given apparently conflicting results. Only one trial, the National Institute of Neurological Disorders and Stroke trial of tissue plasminogen activator (tPA), suggested that thrombolysis was definitely beneficial. To make sense of these results, we have done a systematic review of all available randomized trials of thrombolysis in acute ischaemic stroke.

METHODS: From all available completed randomized trials of thrombolytic therapy compared with control in acute ischaemic stroke (with prerandomization

CT), we checked tabular data on deaths during roughly the first 2 weeks, deaths from all causes and functional outcome (disability) at the end of the trial follow-up period, and early symptomatic and fatal intracranial haemorrhages.

FINDINGS: 12 trials included 3435 patients, of whom 694 (20%) were dead and 1001 (39%) of 2567 were functionally dependent at the end of follow-up (duration of follow-up varied between trials, but the longest was 6 months). 214 (6%) of the 3435 patients had early symptomatic or fatal intracranial haemorrhages.

Thrombolytic therapy was associated with a significant excess of early deaths (91 per 1000 patients treated [95% CI 54-134]), and total deaths (37 per 1000 [20-83]), but there was nevertheless a significant reduction in the number of patients in the combined outcome of dead or dependent (65 fewer per 1000 patients treated [28-107]). There was a substantial and significant excess of symptomatic and fatal intracranial haemorrhages with thrombolysis-which was similar in all recent trials-of about 70 extra symptomatic intracranial haemorrhages per 1000 patients treated (of which 51 per 1000 were fatal).

In the cohort of patients randomized within 3 h of stroke, there was a significant reduction in the number of patients who were dead or dependent at the end of follow-up (141 fewer dead or dependent per 1000 patients treated [75-206] and a non-significant increase in the number dead (nine per 1000 treated [-39 to 70]). There was significant heterogeneity between the trials for total deaths at the end of follow-up, which may be partly explained by differences in the use of antithrombotic drugs within the first 24 h of thrombolysis; the variation in severity of strokes included: the time window to thrombolytic treatment; and the dose of thrombolytic drug used. There were no direct comparisons of tPA with streptokinase or urokinase: much of the poor outcome in the streptokinase-treated patients might be explained by the inclusion of more severe strokes, greater use of antithrombotic drugs, higher doses, and the longer time to treatment compared with the trials that used tPA.

INTERPRETATION: Thrombolysis requires further testing in large randomized trials because the risks seem substantial, and the benefit uncertain. The time window for effective treatment remains unclear. There is no objective evidence to suggest that tPA is safer than streptokinase; the apparent hazards and benefits may be similar when differences in trial design and baseline variables are accounted for.

PMID: 9288042 [PubMed - indexed for MEDLINE]

Evidence: Supportive, Grade A; Quality: Adequate

Commentary: Similar to some of the later meta-analysis and most contemporary stroke trials, disability was reduced significantly, while there was not a significant increase in death with thrombolysis. This is despite the inclusion of several streptokinase trials and ECASS II, in which significant increases in death with

thrombolysis were observed, likely due to the timing, the protocol, and possibly the dosage/thrombolytic choice.

Tier 2

1. N Engl J Med. 2008 Sep 25;359(13):1317-29. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. Hacke W, Kaste M, Bluhmki E, Brozman M, Dávalos A, Guidetti D, Larrue V, Lees KR, Medeghri Z, Machnig T, Schneider D, von Kummer R, Wahlgren N, Toni D; ECASS Investigators. Department of Neurology, Universität Heidelberg, Heidelberg, Germany. werner.hacke@med.uni-heidelberg.de

BACKGROUND: Intravenous thrombolysis with alteplase is the only approved treatment for acute ischemic stroke, but its efficacy and safety when administered more than 3 hours after the onset of symptoms have not been established. We tested the efficacy and safety of alteplase administered between 3 and 4.5 hours after the onset of a stroke.

METHODS: After exclusion of patients with a brain hemorrhage or major infarction, as detected on a computed tomographic scan, we randomly assigned patients with acute ischemic stroke in a 1:1 double-blind fashion to receive treatment with intravenous alteplase (0.9 mg per kilogram of body weight) or placebo. The primary end point was disability at 90 days, dichotomized as a favorable outcome (a score of 0 or 1 on the modified Rankin scale, which has a range of 0 to 6, with 0 indicating no symptoms at all and 6 indicating death) or an unfavorable outcome (a score of 2 to 6 on the modified Rankin scale). The secondary end point was a global outcome analysis of four neurologic and disability scores combined. Safety end points included death, symptomatic intracranial hemorrhage, and other serious adverse events.

RESULTS: We enrolled a total of 821 patients in the study and randomly assigned 418 to the alteplase group and 403 to the placebo group. The median time for the administration of alteplase was 3 hours 59 minutes. More patients had a favorable outcome with alteplase than with placebo (52.4% vs. 45.2%; odds ratio, 1.34; 95% confidence interval [CI], 1.02 to 1.76; $P=0.04$). In the global analysis, the outcome was also improved with alteplase as compared with placebo (odds ratio, 1.28; 95% CI, 1.00 to 1.65; $P<0.05$). The incidence of intracranial hemorrhage was higher with alteplase than with placebo (for any intracranial hemorrhage, 27.0% vs. 17.6%; $P=0.001$; for symptomatic intracranial hemorrhage, 2.4% vs. 0.2%; $P=0.008$). Mortality did not differ significantly between the alteplase and placebo groups (7.7% and 8.4%, respectively; $P=0.68$). There was no significant difference in the rate of other serious adverse events.

CONCLUSIONS: As compared with placebo, intravenous alteplase administered between 3 and 4.5 hours after the onset of symptoms significantly improved clinical outcomes in patients with acute ischemic stroke; alteplase was more frequently associated with symptomatic intracranial hemorrhage.

(ClinicalTrials.gov number, NCT00153036.) 2008 Massachusetts Medical Society

PMID: 18815396 [PubMed - indexed for MEDLINE]

See narrative section for commentary on ECASS III.

Evidence Supportive, Grade A, Quality Good.

2. JAMA. 1999 Dec 1;282(21):2019-26. Recombinant tissue-type plasminogen activator (Alteplase) for ischemic stroke 3 to 5 hours after symptom onset. The ATLANTIS Study: a randomized controlled trial. Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke. Clark WM, Wissman S, Albers GW, Jhamandas JH, Madden KP, Hamilton S. Oregon Stroke Center, Portland 97201, USA. clarkw@ohsu.edu

CONTEXT: Recombinant tissue-type plasminogen activator (rt-PA) improves outcomes for patients with acute ischemic stroke, but current approved use is limited to within 3 hours of symptom onset. This restricts the number of patients who can be treated, since most stroke patients present more than 3 hours after symptom onset.

OBJECTIVE: To test the efficacy and safety of rt-PA in patients with acute ischemic stroke when administered between 3 and 5 hours after symptom onset.

DESIGN: The Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke (ATLANTIS) study is a phase 3, placebo-controlled, double-blind randomized study conducted between December 1993 and July 1998, with up to 90 days of follow-up.

SETTING: One hundred forty university and community hospitals in North America.

PATIENTS: An intent-to-treat population of 613 acute ischemic stroke patients was enrolled, with 547 of these treated as assigned within 3 to 5 hours of symptom onset. A total of 39 others were treated within 3 hours of symptom onset, 24 were treated more than 5 hours after symptom onset, and 3 never received any study drug.

INTERVENTION: Administration of 0.9 mg/kg of rt-PA (n = 272) or placebo (n = 275) intravenously over 1 hour.

MAIN OUTCOME MEASURES: Primary efficacy was an excellent neurologic recovery at day 90 (National Institutes of Health Stroke Scale [NIHSS] score of < or =1); secondary end points included excellent recovery on functional outcome

measures (Barthel index, modified Rankin scale, and Glasgow Outcome Scale) at days 30 and 90. Serious adverse events were also assessed.

RESULTS: In the target population, 32% of the placebo and 34% of rt-PA patients had an excellent recovery at 90 days ($P = .65$). There were no differences on any of the secondary functional outcome measures. In the first 10 days treatment with rt-PA significantly increased the rate of symptomatic intracerebral hemorrhage (ICH) (1.1% vs 7.0% [$P < .001$]), a symptomatic ICH (4.7% vs 11.4% [$P = .004$]), and fatal ICH (0.3% vs 3.0% [$P < .001$]). Mortality at 90 days was 6.9% with placebo and 11.0% with rt-PA ($P = .09$). Results in the intent-to-treat population were similar. **CONCLUSIONS:** This study found no significant rt-PA benefit on the 90-day efficacy end points in patients treated between 3 and 5 hours. The risk of symptomatic ICH increased with rt-PA treatment. These results do not support the use of intravenous rt-PA for stroke treatment beyond 3 hours.

PMID: 10591384 [PubMed - indexed for MEDLINE]

At first glance, it is unclear why ECASS III even occurred based on these results. Upon detailed consideration, only about 20% of the patients in ATLANTIS presented from 3-4 hours, with most clustered near the 5 hour mark. It is also worth noting that this trial had an outcome measure that was different (NIHSS 0 or 1), than most other trials which used a disability scale.

Evidence Neutral, Grade A, Quality Good.

3. Lancet. 1998 Oct 17;352(9136):1245-51. Randomized double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II). Second European-Australasian Acute Stroke Study Investigators. Hacke W, Kaste M, Fieschi C, von Kummer R, Davalos A, Meier D, Larrue V, Bluhmki E, Davis S, Donnan G, Schneider D, Diez-Tejedor E, Trouillas P. Department of Neurology, University of Heidelberg, Germany. wernervhacke@ukl.uni.heidelberg.de

BACKGROUND: Thrombolysis for acute ischaemic stroke has been investigated in several clinical trials, with variable results. We have assessed the safety and efficacy of intravenous thrombolysis with alteplase (0.9 mg/kg bodyweight) within 6 h of stroke onset.

METHODS: This non-angiographic, randomized, double-blind, trial enrolled 800 patients in Europe, Australia, and New Zealand. Computed tomography was used to exclude patients with signs of major infarction. Alteplase ($n=409$) and placebo ($n=391$) were randomly assigned with stratification for time since symptom onset (0-3 h or 3-6 h). The primary endpoint was the modified Rankin scale (mRS) at 90 days, dichotomised for favourable (score 0-1) and unfavourable (score 2-6) outcome. Analyses were by intention to treat.

FINDINGS: 165 (40.3%) alteplase-group patients and 143 (36.6%) placebo-group patients had favourable mRS outcomes (absolute difference 3.7%, $p=0.277$). In a posthoc analysis of mRS scores dichotomised for death or dependency, 222 (54.3%) alteplase-group and 180 (46.0%) placebo-group patients had favourable outcomes (score 0-2; absolute difference 8.3%, $p=0.024$). Treatment differences were similar whether patients were treated within 3 h or 3-6 h. 85 (10.6%) patients died, with no difference between treatment groups at day 90 \pm 14 days (43 alteplase, 42 placebo). Symptomatic intracranial haemorrhage occurred in 36 (8.8%) alteplase-group patients and 13 (3.4%) placebo-group patients.

INTERPRETATION: The results do not confirm a statistical benefit for alteplase. However, we believe the trend towards efficacy should be interpreted in the light of evidence from previous trials. Despite the increased risk of intracranial haemorrhage, thrombolysis with alteplase at a dose of 0.9 mg/kg in selected patients may lead to a clinically relevant improvement in outcome.

PMID: 9788453 [PubMed - indexed for MEDLINE]

ECASS II was an improvement over the first ECASS, but only 20% of patients were enrolled within 3 hours of onset. In addition, about 10% of enrolled patients had protocol violations-mainly CT scan exclusions such as early ischemic changes. It is reasonable to suspect that most of the patients were clustered with treatment near 6 hours from onset. There was a significant effect on reduction in "death or dependency (good = mRS 0-2)," but this was a post-hoc analysis and as such was hypothesis generating.

Evidence Neutral, Grade A, Quality Adequate.

4. N Engl J Med. 1995 Dec 14;333(24):1581-7. Tissue plasminogen activator for acute ischemic stroke. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group.

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 333 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 6.4 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.

PMID: 7477192 [PubMed - indexed for MEDLINE]

This trial (or two trials, technically) provided the basis for the FDA approval of alteplase for acute ischemic stroke. The primary outcome was met in Part 2 -- disability was reduced. While symptomatic ICH was increased with treatment, the proportion of patients who were dead or severely disabled was not different between the groups. Half the patients were treated really early (less than 90 minutes from onset), which may not be reflective of routine clinical practice; although the better results noted in this group should provide the clinician with incentive to try to initiate treatment as fast as their system will allow it. Also, by chance there were differences between the tPA (less severe strokes) and placebo (more patients who were old) groups. Subsequent re-analysis of the data (Stroke. 2004;35:2418), confirmed the treatment effect while adjusting for stroke severity, age and other important prognostic factors. The adjusted odds ratio for improvement was 2.1 (95% CI 1.5 – 2.9). To make a long story short, this was a randomized trial. The alteplase group received an advantage from less severe strokes, while the placebo group was advantaged by younger patients.

Evidence: Supportive, Grade A, Quality Good.

5. JAMA. 1995 Oct 4;274(13):1017-25. Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke. The European Cooperative Acute Stroke Study (ECASS). Hacke W, Kaste M, Fieschi

C, Toni D, Lesaffre E, von Kummer R, Boysen G, Bluhmki E, Höxter G, Mahagne MH, et al. Department of Neurology, University of Heidelberg, Germany.

OBJECTIVE: To evaluate the efficacy and safety of intravenous thrombolysis using recombinant tissue plasminogen activator (rt-PA) in patients with acute ischemic stroke.

DESIGN: Randomized, prospective, multicenter, double-blind, placebo-controlled clinical trial.

SETTING: A total of 75 hospitals in 14 European countries. **PATIENTS--**A total of 620 patients with acute ischemic hemispheric stroke and moderate to severe neurologic deficit and without major early infarct signs on initial computed tomography (CT).

INTERVENTION: Patients were randomized to treatment with 1.1 mg per kilogram of body weight of rt-PA (alteplase) or placebo within 6 hours from the onset of symptoms.

OUTCOME MEASURES: Primary end points included Barthel Index (BI) and modified Rankin Scale (RS) at 90 days. Secondary end points included combined BI and RS, Scandinavian Stroke Scale (SSS) at 90 days, and 30-day mortality. Tertiary end points included early neurologic recovery (SSS) and duration of in-hospital stay. Safety parameters included mortality and incidence of intracranial or extracranial hemorrhage.

RESULTS: The distribution of demographic variables was similar among patients in the rt-PA and placebo treatment arms in both the intention-to-treat (ITT) analysis and the explanatory analysis for the target population (TP). A total of 109 patients (17.4%) were included in the trial despite major protocol violations but excluded from the TP. There was no difference in the primary end points in the ITT analysis, while the TP analysis revealed a significant difference in the RS in favor of rt-PA-treated patients ($P = .035$). Of the secondary end points, the combined BI and RS showed a difference in favor of rt-PA-treated patients in both analyses ($P < .001$). Neurologic recovery at 90 days was significantly better for rt-PA-treated patients in the TP ($P = .03$). The speed of neurologic recovery assessed by the SSS was significantly better up to 7 days in the ITT analysis and up to 30 days for the TP in the rt-PA treatment arm. In-hospital stay was significantly shorter in the rt-PA treatment arm in both analyses. There were no statistically significant differences in the mortality rate at 30 days or in the overall incidence of intracerebral hemorrhages among the rt-PA and placebo treatment arms in either analysis. However, the occurrence of large parenchymal hemorrhages was significantly more frequent in the rt-PA-treated patients.

CONCLUSIONS--Intravenous thrombolysis in acute ischemic stroke is effective in improving some functional measures and neurologic outcome in a defined

subgroup of stroke patients with moderate to severe neurologic deficit and without extended infarct signs on the initial CT scan. However, the identification of this subgroup is difficult and depends on recognition of early major CT signs of early infarction. Therefore, since treating ineligible patients is associated with an unacceptable increase of hemorrhagic complications and death, intravenous thrombolysis cannot currently be recommended for use in an unselected population of acute ischemic stroke patients.

PMID: 7563451 [PubMed - indexed for MEDLINE]

This trial used a higher dose of alteplase (1.1 mg/kg). The mean time to enrollment from onset to symptoms was about 4.5 hours. There were a large number of patients with major protocol violations (mainly CT scan problems such as early ischemic changes). Given the inclusion of so many high risk patients in the trial, it appears that the results were biased towards finding no effect. On the secondary outcomes, such as achieving independence within the protocol treated patients, a positive effect was observed – this served as the rationale for the design of ECASS II.

Evidence Neutral, Grade A, Quality Adequate