Thrombolysis for acute ischemic stroke: does it work?—the con position

Chris Johnstone*†

Thrombolysis for acute ischemic stroke (AIS) has become mainstream therapy, despite the scientific evidence rather than because of it. Careful scrutiny of the literature demonstrates that it has proven harm but no clear benefit, because of the sheer paucity of hard evidence supporting its use. There are only two large randomized controlled trials (RCTs) showing benefit for thrombolysis, and nine large RCTs that failed to show any significant difference to placebo (four were stopped early due to excess harm). This is in stark contrast to the clear mortality benefit for thrombolysis in six out of eight large RCT for myocardial infarction.[1] Both systematic and non-systematic reviews of thrombolysis for AIS are severely biased by the inappropriate inclusion of heterogeneous studies, to the extent that their positive conclusions can be reversed simply by eliminating those studies. The remainder of often quoted evidence in favour of thrombolysis is either uncontrolled monitoring data or hypothetical conjecture, neither of which answers the question of efficacy.

The first issue to address is defining which RCT should be included in the analysis. Wardlaw* is the lead author of six sequential literature reviews since 1992, four in the Cochrane database. The latest Cochrane systematic review in 2014 concluded that there "appears to be a net benefit of a significant reduction in the proportion who are dead or dependent at the end of follow-up," defined as modified Rankin Scale (mRS) ≥3 (odds ratio [OR] = 0.85), using data extracted from 22 of 27 studies in the review.[2] Nine of these studies, however, measured brain reperfusion as the primary outcome (not clinical improvement), used intra-arterial injections instead of intravenous, or were very small (n = 16–57), and two had unacceptably poor methodological quality. The Cochrane authors acknowledged and measured the high level of heterogeneity in their choice of studies (I^2 = 39%) but did not modify their conclusion. Therefore, there are only 11 large (n ≥ 100) RCTs of reasonable quality and homogeneous methodology (Table 1, including the International Stroke Trial [IST-3], which was published after the *Cochrane Review*). If the likelihood of a good outcome (mRS ≥ 3) is recalculated using only these 11 trials (I^2 = 5%), thrombolysis is favoured with OR = 0.87 (95% confidence interval [CI] = 0.79–0.96) but with a CI close to 1.0 and a number needed to treat (NNT) of 29. Even if the statistical significance is real, the clinical significance is doubtful. There is also an excess of death or symptomatic intracranial hemorrhage (ICH) (OR = 1.53) with a number needed to harm (NNH) of 11. The risk-benefit analysis now favours placebo.

If thrombolysis does *not* work for AIS, why are there two positive trials? This can easily be due to chance. Using the standard threshold of significance (p = 0.05), if enough RCTs are performed with the same study question, 1 out of every 20 studies will demonstrate a statistically significant outcome by chance alone. In other words, the probability that 2 of 11 stroke studies will show a positive result for thrombolysis, when in reality there is no difference from placebo (type I error), is approximately 25%. This possibility is supported by the marginal results of the two positive trials: the National Institute of Neurological Disorders and Stroke (NINDS) study[3] and the European Cooperative Acute Stroke Study III (ECASS-III).[4] NINDS had the best outcome, where patients treated within 3 hours were 12% more likely to have a good functional outcome (mRS 0–1) at 3 months.

From the *Department of Emergency Medicine, Caboolture Hospital, Caboolture, Queensland, Australia; and the †School of Medicine, The University of Queensland, Brisbane, Australia.

Correspondence to: Dr. Chris Johnstone, Emergency Department, Caboolture Hospital, LMB 3, Caboolture, Qld 4510, Australia. Email: chrisjohnstone7@westnet.com.au

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Table 1. Randomized controlled trials of intravenous thrombolysis for acute ischemic stroke (n ≥ 100)

Title*	Year of publication	N	Agent†	Time to Treatment
MAST-I[23]	1995	622	SK	<6 h
ECASS-I[24]	1995	620	tPA	<6 h
NINDS-II[3]	1995	333	tPA	<3 h
MAST-E[25]	1996	310	SK	<6 h
ASK[26]	1996	340	SK	<4 h
ECASS-II[27]	1998	800	tPA	<6 h
ATLANTIS-B[28]	1999	613	tPA	<5 h
ATLANTIS-A[29]	2000	142	tPA	<6 h
ECASS-III[4]	2008	821	tPA	3–4.5 h
DIAS-2[11]	2009	193	DS	3–9 h
IST-3[16]	2012	3,035	tPA	<6 h
Total		**7,829**		

*ASK = Australian streptokinase; ATLANTIS = alteplase thrombolysis for acute noninterventional therapy in ischemic stroke; DS = desmoteplase; DIAS = desmoteplase in acute ischemic stroke; ECASS = European Cooperative Acute Stroke Study; IST = International Stroke Trial; MAST = Multicentre Acute Stroke Trial (Italy, Europe); NINDS = National Institute of Neurological Disorders and Stroke
†SK = streptokinase; tPA = tissue plasminogen activator.

In a recent Australian study, only 15% of all AIS patients who arrived within 4.5 hours were eligible for thrombolysis.[5] Therefore, for an average hospital admitting 100 stroke patients in a year, assuming ideal conditions and early presentations, 80 would have AIS, 12 would receive thrombolysis, and potentially 1 patient would have a better recovery. In addition, the trial results themselves are dependent on the definition of *good outcome*. For example, in ECASS-III, if it changes from mRS 0–1 to mRS 0–2 (i.e., includes mild disability) the benefit of thrombolysis disappears, referred to as *wobble* by Wardlaw et al.[2]

Both trials have been criticized for their methodology, especially because the patients in the placebo groups of both trials had more severe strokes at enrolment, and, in ECASS-III, more placebo patients had prior strokes.[6] Two groups re-analysed the NINDS data adjusting for baseline differences, with different conclusions.[7,8] Furthermore, care in a multidisciplinary stroke unit is the only proven therapy to date, with a reduction in death and disability equivalent to that claimed by thrombolysis.[9] IST-3 was the only trial to control for this variable, and it is plausible that some of the benefits seen in NINDS and ECASS-III were due to variability in level of care.

Can the nine negative trials be explained away? Proponents of thrombolysis have decided that tissue plasminogen activator (tPA) is effective, but other fibrinolytic agents are not, ignoring trials that used streptokinase and desmoteplase.[10] Apart from biological implausibility, this view is inconsistent with the literature for strokes and other diseases. Two of three small pilot studies using desmoteplase in AIS showed benefit for thrombolysis and were included in the 2014 *Cochrane Review*.[11–13] Food and Drug Administration (FDA)-approved agents for thrombolysis in pulmonary embolus include streptokinase, urokinase, and tPA.[14] In eight large (n > 1000) placebo-controlled RCTs of thrombolysis in ST-elevation myocardial infarction, both streptokinase and tPA were effective.[1]

It has also been argued that many studies failed because they included patients after 4.5 hours. In 2004, Hacke* et al. published a pooled analysis of six tPA trials (ECASS, alteplase thrombolysis for acute noninterventional therapy in ischemic stroke [ATLANTIS], NINDS) attempting to show that earlier treatment had better outcomes.[15] The study selection is arbitrary and biased in favour of NINDs patients. This work is speculation, not evidence. Furthermore, there is no pattern in the literature that supports a relationship between time of treatment and outcome: the Australian streptokinase (ASK) study had a 4-hour enrolment limit and ATLANTIS-B a 3–5 hour window, both similar to the 4.5-hour limit in ECASS-III, but with negative results. Subgroup analysis of the 0–3 hour period in ASK, ECASS-I, and ECASS-II showed no benefit in that period (in contrast to the 3-hour limit in NINDS) and neither did the ATLANTIS-B review of the 3- to 4-hour subgroup. IST-3 demonstrated a worse outcome in the 3- to 4.5-hour period than in the later (4.5- to 6-hour) period. Similarly, NINDS reported combined parts I and II results at 3 months, and patients treated after 90 minutes had better outcomes than those treated earlier.

IST-3 deserves special mention here as the largest trial with 3,035 patients.[16] The primary outcome was the proportion of people who were alive and independent at 6 months. It was powered to detect a 4.7% difference, yet the final difference was only 1.5% and not significant. The author's astonishing statement that secondary ordinal analysis "provided evidence of a favourable shift in the distribution of Oxford Handicap Scores at 6 months with treatment" is completely irrelevant to the negative outcome of the trial. Post-hoc analyses and secondary outcomes are of value only in generating hypotheses for future study and should not be used to contradict the primary outcome—thrombolysis did not work!

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Stroke registries and community studies are often touted as supportive evidence for thrombolysis, because outcomes are similar to RCTs, but the purpose of post-marketing monitoring is to measure the "real-world" safety of treatment. Without control groups, they cannot determine efficacy. The Safe Implementation of Thrombolysis in Stroke-International Stroke Thrombolysis Register (SITS-ISTR) is a large multinational voluntary database, but up to half of treated patients are not reported, and up to one third of registered patients have protocol violations.[17] Authors of three well-known safety studies suggested that excellent outcomes in treated patients were comparable to NINDS. SITS-MOST (Monitoring Study) by Wahlgren* et al., the American Standard Treatment with Alteplase to Reverse Stroke (STARS) project by Albers* et al., and the Canadian Alteplase for Stroke Effectiveness Study (CASES) report by Hill* et al. are all industry-sponsored studies mandated by licensing authorities.[18–20] Excellent outcomes (mRS 0–1) in treated patients in these studies were 39%, 35%, and 32%, respectively. By contrast, the placebo groups in RCTs using the same methodology as NINDS (ECASS-II/III, ATLANTIS-B) have better outcomes at 90 days (37%, 45%, 41%, respectively). Data from the safety studies could therefore just as easily support an argument that treatment is worse than placebo.

That thrombolysis is dangerous is not in dispute. Excess mortality in the treatment group is reported in the *Cochrane Review* to be 1.4%.[2] Symptomatic ICH occurs in about 2% of controls but 7% of treated patients (up to 22% in less strictly controlled community studies).[17,21,22] The case for thrombolysis is a "house of cards" resting on two weak RCTs. Let's be honest; the overwhelming majority of hard evidence shows no benefit, yet the risk of harm is clear.

Keywords: stroke, thrombolytic therapy, efficacy

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