An Updated Systematic Review of rt-PA in Acute Ischaemic Stroke

Joanna M Wardlaw

COMPETING INTERESTS
The author is on the Steering Committees of the Third International Stroke Trial (IST3) and the Third European Cooperative Acute Stroke Study (ECASS 3), both testing rt-PA in acute ischaemic stroke; is involved in running the SHEFC Brain Imaging Research Centre for Scotland, established in 1997, and received 2% of its set-up funding from Boehringer Ingelheim UK; was an expert advisor to BI for the licensing application in Europe; further details are available at www.dcn.ed.ac.uk.

ABSTRACT
Since the last Karolinska Stroke Update (November 2000), no further new trials of rt-PA have been completed. However additional information has become available from existing rt-PA trials, and a new trial of urokinase has been completed in China. There are now data on nearly 3000 patients in rt-PA trials (nearly 6000 of any thrombolytic agent). The point estimates of treatment effects for key outcomes have remained similar since 1995, but the confidence intervals are still wide, there is between-trial heterogeneity for several important outcomes with rt-PA (death under three and six hours, death or dependency up to six hours), there is virtually no data from patients aged over 80, and the design of these trials did not ensure blinding or prevent modest but important imbalances in baseline prognosis which may have over or under estimated the rt-PA treatment effect in individual trials. Hence, although some patients may be treated within the rt-PA license, more trials are still needed to strengthen the evidence and encourage wider use.
**BACKGROUND**

Thrombolysis for stroke was first tested in 1958, but it was only after the invention of CT scanning that ischaemic stroke could be diagnosed accurately. Several trials of urokinase were conducted in the 1980’s but it was only in the 1990’s that the larger rt-PA trials were started. The National Institutes of Neurological Disorders and Stroke (NINDS) trial of recombinant tissue plasminogen activator (rt-PA) within three hours of stroke was published in 1995\(^1\) and a license was granted for use of rt-PA within three hours of stroke in the USA in 1996.

The NINDS trial was a major landmark in acute stroke treatment trials – it showed that patients could be assessed and treated within three hours and showed that rt-PA improved functional outcome despite an increase in symptomatic intracranial haemorrhage. However, despite subsequent licensing in Canada and now Europe, rt-PA has not been widely adopted into clinical practice, and if the result of the NINDS trial is correct, then rt-PA is probably being under-used.

The full details of all these trials are available in the Cochrane Database of Systematic Reviews (CDSR) Stroke Group’s review of Thrombolysis in Acute Ischaemic Stroke (update now submitted).\(^2\) The following review will briefly summarise the trial data available to date and highlight the gaps in the data (ie gaps in knowledge on the use of rt-PA) that may be discouraging its wider use in clinical practice.

**METHODS**

The data are taken from an ongoing, continuously updated, systematic review started in 1988 of thrombolysis in acute ischaemic stroke.\(^2\) Additional data to that appearing in the main publications was supplied by principle investigators of all trials, or for the NINDS trial, from the US Food and Drug Administration web site (www.fda.gov/cber/products/altegen061896.htm particularly the Clinical Review 2).

Data on key outcomes (early deaths, symptomatic and fatal intracranial haemorrhage, death, and death or dependency by the end of follow up) were extracted and verified with the principle investigators. Poor functional outcome was defined as a score of 3 to 6 on the modified Rankin scale. Details of the methodological quality of the trials are available in the CDSR thrombolysis review.\(^2\)

The effect of thrombolysis on the key outcomes is expressed as odds ratios (OR) using the fixed effects method. Heterogeneity between trials was tested using the Chi squared test. Where significant between-trial heterogeneity exists, an odds ratio using the random effects
method was also calculated. Absolute effects were calculated using the proportion with the outcome of note in the control group and the odds ratio. The main subgroup analysed was of patients randomised within three hours of stroke.

RESULTS

There are eight trials, NINDS,\textsuperscript{1} ATLANTIS A\textsuperscript{3} and B,\textsuperscript{4} ECASS\textsuperscript{5} and ECASS 2,\textsuperscript{6} and three small trials,\textsuperscript{7,9} testing intravenous rt-PA (total 2955 patients) up to six hours after stroke. Not all trials contribute data to analysis of all outcomes, but where available the data are included. Poor functional outcome: Within six hours (six trials, 2830 patients), rt-PA reduced significantly the odds of a poor functional outcome (OR 0.80, 95% CI 0.69 to 0.93, \(p=0.003\)) (Figure 1). There was significant between-trial heterogeneity (Chi squared \(p=0.02\)) justifying calculation of the OR also by the random effects method. When calculated by the random effects method, the reduction in poor functional outcomes was no longer statistically significant, although there was a trend towards a reduction in poor functional outcomes with rt-PA (OR 0.82, 95% CI 0.62, 1.09). This effect is equivalent to about 55 (95% CI 18 to 92) fewer patients being dead or dependent per 1000 treated (Table 1).

Figure 1. The effect of rt-PA given within six hours of stroke on poor functional outcomes (death or dependency).

<table>
<thead>
<tr>
<th></th>
<th>favours treatment</th>
<th>favours control</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATLANTIS A 2000</td>
<td>64/71</td>
<td>58/71</td>
</tr>
<tr>
<td>ATLANTIS B 1999</td>
<td>141/307</td>
<td>135/306</td>
</tr>
<tr>
<td>ECASS 1995</td>
<td>171/313</td>
<td>165/307</td>
</tr>
<tr>
<td>ECASS II 1998</td>
<td>167/409</td>
<td>211/391</td>
</tr>
<tr>
<td>Mori 1992</td>
<td>11/19</td>
<td>10/12</td>
</tr>
<tr>
<td>NINDS 1995</td>
<td>155/312</td>
<td>192/312</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>729/1431</td>
<td>780/1390</td>
</tr>
</tbody>
</table>

Test for heterogeneity chi-square=13.23 df=5 \(p=0.021\)
Test for overall effect \(z=2.97\) \(p=0.003\)
Restricting the analysis to patients randomised within three hours of stroke (5 trials, 930 patients) showed that rt-PA reduced the odds of a poor functional outcome even more (OR 0.64, 95% CI 0.5, 0.83) with no significant between-trial heterogeneity (Chi squared p = 0.77, Figure 2). This is equivalent to 110 fewer poor functional outcomes per 1000 patients treated (95% CI 45, 171 fewer). However this analysis is strongly influenced by the NINDS trial which contributed 624 patients (67% of the data) and may have been methodologically different from the other trials (ie one cannot assume that the positive result in NINDS was simply the result of the three hour time window).
Figure 2. The effect of rt-PA given within three hours of stroke on poor functional outcomes (death or dependency).

To compare the effect under three hours with that between three and six hours, we examined just trials that randomised patients in both time windows (thus each trial acts as its own “control”). The OR for patients randomised within three hours for death or dependency was 0.69 (95% CI 0.43, 1.09) and between three and six hours the OR was 0.85 (95% CI 0.72, 1.01), with no significant difference between the two and with no between-trial heterogeneity for either time window (Figure 3).

**Comparison: 01 Any thromolytic agent versus control**

**Outcome:** Death or dependency by time to treatment up to six hours - rt-PA

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment effect</th>
<th>Control effect</th>
<th>OR (95% CI Fixed)</th>
<th>Weight %</th>
<th>OR (95% CI Fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>01 treatment within three hours</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATLANTIS A 2000</td>
<td>7 / 10</td>
<td>7 / 12</td>
<td>0.7</td>
<td>1.62</td>
<td>[0.29, 8.96]</td>
</tr>
<tr>
<td>ATLANTIS B 1999</td>
<td>3 / 13</td>
<td>12 / 26</td>
<td>0.39</td>
<td>0.39</td>
<td>[0.16, 1.46]</td>
</tr>
<tr>
<td>ECASS 1995</td>
<td>26 / 49</td>
<td>25 / 38</td>
<td>0.70</td>
<td>0.70</td>
<td>[0.28, 1.66]</td>
</tr>
<tr>
<td>ECASS II 1998</td>
<td>36 / 81</td>
<td>44 / 77</td>
<td>0.70</td>
<td>0.70</td>
<td>[0.37, 1.30]</td>
</tr>
<tr>
<td>NNDS 1995</td>
<td>156 / 312</td>
<td>192 / 312</td>
<td>0.62</td>
<td>0.62</td>
<td>[0.45, 0.86]</td>
</tr>
<tr>
<td><strong>Subtotal (95%) CI</strong></td>
<td>232 / 465</td>
<td>280 / 465</td>
<td>0.64</td>
<td>0.64</td>
<td>[0.50, 0.83]</td>
</tr>
</tbody>
</table>

Test for heterogeneity chi-square=1.83 df=4 p=0.77
Test for overall effect z=-3.34 p=0.0008

favours treatment  favours control

**Figure 3**

Total (95%) CI

Test for heterogeneity chi-square=5.87 df=3 p=0.083
Test for overall effect z=-1.31 p=0.19

Test for heterogeneity chi-square=5.30 df=7 p=0.23
Test for overall effect z=-1.81 p=0.07
INTRACRANIAL HAEMORRHAGE

In patients treated up to six hours after stroke, there was a statistically significant increase in symptomatic and fatal intracranial haemorrhage (ICH) with rt-PA: symptomatic ICH OR 3.13 (95% CI 2.34, 4.19) and fatal ICH OR 3.6 (95% CI 2.28, 5.68), with no between-trial heterogeneity for either outcome. This is equivalent to an increase of 62 symptomatic ICHs (95% CI 40, 90), and of 25 fatal ICHs (95% CI 13, 44) per 1000 patients treated. In other words, treating 17 patients (95% CI 12, 26) will cause one symptomatic ICH, and 40 patients (95% CI 23, 80) will cause one fatal ICH (Table 1). Patients treated within three hours had a similar symptomatic ICH rate to those treated between three and six hours: OR under three hours 3.40 (95% CI 1.48, 7.84) and OR 3 – 6 hours 3.14 (95% CI 2.21, 4.47). However, there are two points to note: 1) the reduction in poor functional outcome is net of this increase in intracranial haemorrhage (ie it has already been accounted for); and 2) intracranial haemorrhage may have been over diagnosed as the cause of clinical deterioration. Several published examples of the symptomatic ICHs from various trials suggest that in some cases, a massive swollen infarct with a small amount of haemorrhagic transformation, which was not contributing to the mass effect, may have been counted as symptomatic ICH. Data on other cerebral complications was not systematically recorded, but for example there was a suggestion in the NINDS trial that rt-PA reduced the proportion of patients with massive infarct oedema (see FDA website quoted above).

EARLY AND TOTAL DEATHS

The trials that supplied the data showed, in patients treated up to six hours after stroke, a non-significant increase in early deaths (<10 days) in patients given rt-PA (OR 1.24, 95% CI 0.85, 1.81). At the end of follow-up, there was a non-significant increase in total deaths amongst patients allocated to rt-PA (OR 1.17, 95% CI 0.95, 1.45) but with significant between-trial heterogeneity (Chi squared 0.04), equivalent to 21 per 1000 more deaths (95% CI 18 fewer to 74 more).

In patients treated within three hours, there was no overall effect of rt-PA on total deaths – OR 0.97 (95% CI 0.69, 1.36) with no between-trial heterogeneity, equivalent to 4 per 1000 fewer deaths (95% CI 49 fewer to 47 more) Table 1. Comparison of patients treated within three hours with those treated between three and six hours in trials randomising in both time windows, showed, if anything, a trend towards later rt-PA treatment being associated with fewer deaths (Figure 4).
ARE THESE DATA COMPATIBLE WITH DATA FROM TRIALS OF OTHER THROMBOLYTIC AGENTS?

Data from trials testing streptokinase (SK), urokinase (UK), and recombinant pro-urokinase are available on another 2720 patients (ie nearly doubling the amount of data from rt-PA trials) and so are worth considering.² These other thrombolytic drugs are similar to rt-PA, increasing the robustness of the evidence for use of thrombolysis in stroke.

For example: the OR for poor functional outcome in patients treated within three hours of stroke is 0.66 (95% CI 0.53, 0.83) with no heterogeneity, equivalent to 102 fewer poor outcomes per 1000 patients treated (95% CI 45, 157); for symptomatic ICH in patients treated up to six hours is 3.37 (95% CI 2.68, 4.22) with no heterogeneity, equivalent to 51 extra symptomatic ICHs per 1000 patients treated (95% CI 36, 67).
IN WHAT WAY ARE THE DATA FROM RT-PA TRIALS DEFICIENT?

All the rt-PA trials had an upper age limit of 80 except for the NINDS trial, but the latter was only able to include 42 patients over the age of 80. The NINDS trial was published eight years ago, and demographic changes are occurring rapidly in society. Thus there are more people living longer and in good health to an old age, as well as in less good health, with each decade. This will lead to an increase in older stroke patients. Half of all strokes occur in patients aged over 72, thus it would be wrong to deny older patients an effective treatment. We cannot assume that the effect of rt-PA is the same in the 80 to 90 year olds as in the 50 to 60 year olds – while the direction of the effect is unlikely to change, its overall magnitude may do. Without data, these effects can only be guessed at.

The rt-PA trials did not collect data on use of aspirin prior to the stroke, and all used antithrombotic treatment differently after randomisation. Thus there are no reliable data on whether patients on aspirin at the time of the stroke are at increased risk of haemorrhage. There is randomised evidence from one trial of SK on the effect of aspirin immediately after thrombolysis (increases the hazard) and supporting non-random observational evidence that antithrombotic and anticoagulant drugs should be avoided for the first 24 hours after rt-PA. Information on what to do about the appearance of the CT scan is in a muddle. Some trials suggest that early infarct signs increase the risk of ICH, while others found no association with ICH, but rather that early infarct signs were an indication of severe stroke. The license in Europe now suggests that CT appearance of early infarction should not exclude the patient from rt-PA, but further standardisation of CT infarct reading will be necessary to resolve this debate.

The effect of stroke severity on outcome was not adequately accounted for. It is not possible to adjust for all aspects of the effects of stroke severity in the statistical analysis. It is much better to balance the treatment allocation prospectively at randomisation. However, none of the rt-PA trials were able to do this as none of them used central telephone randomisation with collection of key prognostic variables over the phone. This is important to secure the data so that patients cannot subsequently be “lost”, and to balance treatment allocation for key prognostic variables while retaining the random allocation (“minimisation” or “balanced stratified randomisation”). This avoids the problem of more severe strokes in either the treated or control groups, which may lead to an under or over estimate of rt-PA treatment effect.

This problem arose in the NINDS trial and has been the cause of considerable controversy in the USA. In NINDS, there were more patients with milder strokes and with lacunar as
opposed to cortical strokes in the rt-PA treated patients than in the controls.\textsuperscript{12} We have estimated the effect that this would have on the trial outcome using tabular data, and these were confirmed by the NINDS group.\textsuperscript{13} Overall, the trial suggested that rt-PA increased the absolute proportion of good functional outcomes by 14\% but in fact 3\% of this was attributable just to the imbalance in stroke severity, leaving about 11\% absolute benefit as the “true” rt-PA effect. Thus the NINDS trial was by chance more “positive” as a result of the randomisation method, but there was still a very worthwhile and positive treatment effect. ATLANTIS B was perceived as being “negative”, but it suffered from the opposite problem, i.e. more severe strokes in the rt-PA allocated patients, which reduced the apparent treatment effect of rt-PA.

Other problems present in all the rt-PA trials include sub-optimal blinding of treatment allocation and of follow-up assessments. Although all had a placebo, the protocols varied in how much they insisted that the early and late follow-up was by an independent person who had not been involved in the treatment of the patient. An identical appearing placebo in the syringe will not blind the biological effects of rt-PA, hence independent blinded follow-up is essential to avoid bias. There is no way of knowing what influence this opportunity for lack of blinding might have had on the results. However as the primary outcome in all trials was functional outcome, patients would only have to move one point on the Rankin scale to go from counting as a “bad” to “good” outcome. Death is a harder endpoint, less open to investigator bias, so it is important as a key endpoint.

\textbf{WHAT ELSE IS NEW?}

An individual patient data metaanalysis of NINDS, ECASS and ECASS2 and ATLANTIS A and B was prepared in support of the application for a license in Europe by Boehringer Ingelheim in collaboration with the individual trialists (T Brott, personal communication, presented spring 2002). Full details are yet to be published, but the analysis found similar effects of rt-PA under three hours to the Cochrane review, and suggested that the latest time window for treatment might be about four hours. However, there are limitations: as the database had no trials which randomised beyond six hours, it would be unlikely to show the true final latest time window; as there were few data on older subjects (see below); it will not provide information on rt-PA in older patients; and as the original trials did not use methods to balance the treatment allocation for key prognostic variables at randomisation, it can only provide a limited analysis of the interaction between rt-PA and stroke severity.
The NINDS trial has been the corner stone of the pro rt-PA lobby, yet it was small (624 patients) and there are other methodological problems recently come to light which mean that further data are needed to confirm the benefit. For example, in addition to the above, the NINDS randomisation process was complex and resulted in some confusion about what time window and group the patient had been entered into (further details are available at12). Many drug packs were opened in preparation for randomising a patient, but then discarded as “unused” if the patient turned out to be unsuitable. This may have added to the complexity. The true time of treatment may have been different to that specified by the investigator as the graph of time to randomisation shows two concentrated peaks at 90 and 180 minutes. The interested reader should read Clinical Review 2 on the FDA website to judge the potential impact of these points for themselves.12 In any event and bearing these points in mind, it is not realistic to expect clinical practice to change on a wide scale without more robust data.

CONCLUSION

Overall the analysis is in keeping with a clinically and statistically important effect of rt-PA in reducing poor functional outcomes if given within three hours to selected patients, and probably up to six hours in many other patients. However, this is at a cost - one symptomatic ICH for every 17 patients treated. At this rate, it would be much better to be able use specific patient characteristics more carefully to define the risk benefit ratio in individual patients, and this will not be possible without more data. The existing data simply do not exist to look at the effect of rt-PA with increasing patient age, differing stroke severities and syndromes, prior aspirin or other antithrombotic use, more subtle CT appearances, etc.

Trials are currently underway in different parts of the world, notable the Third International Stroke Trial (IST3) www.dcn.ed.ac.uk/IST3, the third European Cooperative Acute Stroke Study (ECASS 3), EPITHET (evaluating diffusion/perfusion mismatch as a guide to rt-PA treatment), and several other trials of other thrombolytic drugs. The existence of a license should not preclude further collection of new data under and beyond three hours after stroke as there are many patients for whom the existing data do not provide strong evidence for routine treatment, but who are likely to benefit nonetheless.

The use of rt-PA is unlikely to be cost-effective unless it can be given to a much larger proportion of stroke patients – there is not point in having fast track stroke assessment and care in place if a key piece of that care (rt-PA) which improves outcome, is not being offered as often as it could be.
ACKNOWLEDGEMENTS

The principle investigators and collaborators of all trials of thrombolysis (especially rt-PA) in acute ischaemic stroke. The University of Edinburgh, the Scottish Higher Education Funding Council, and the UK National Health Service fund the author.

REFERENCES


12. [www.fda.gov/cber/products/altegen061896.htm](http://www.fda.gov/cber/products/altegen061896.htm)