A collaborative meta-analysis of individual participant data from all randomised trials of intravenous rt-PA versus control

The Stroke Thrombolysis Trialists' (STT) Collaboration

Protocol

Background

For the treatment of patients with ischaemic stroke, the only approved medical treatments for use within the first few hours of onset are thrombolytic therapy with intravenous (iv) recombinant tissue plasminogen activator (rt-PA) and aspirin. In 2004, a collaborative analysis of pooled individual patient data from some of the trials of iv rt-PA assessed the effects of time on benefit from treatment (1), an analysis that was subsequently updated in 2010 to include the results of the ECASS-3 (2) and EPITHET (3) trials. These analyses demonstrated reliably that thrombolysis with intravenous rt-PA is both effective and safe when administered to particular types of patient within 4.5 hours of having an ischaemic stroke, and that treatment benefit diminishes with increasing treatment delay. However, several uncertainties remain regarding the potential effects of rt-PA when administered in different circumstances, as well as in different subgroups of patients (4).

In May 2012, results from the IST-3 trial of 3035 patients randomised to rt-PA versus control were reported (5), while several other trials were still ongoing (see Appendix A). In this third phase of the collaborative analysis of pooled individual patient data from the rt-PA trials, results from the IST-3 trial (and, if possible, the TESPI trial (6)) will be included to help address several key questions, including:

1. After what treatment delay is benefit (defined by modified Rankin Score [mRS] 0-1 at final follow-up at 3-6 months) lost or does harm begin, and do age or stroke severity modify the proportional effect of rt-PA on stroke outcome?
2. What are the effects of rt-PA on a range of other secondary outcomes, including: death within 90 days; symptomatic intracranial haemorrhage, fatal symptomatic intracranial haemorrhage, symptomatic ischemic brain oedema and early oedema, effacement and/or midline shift.

These and other planned lines of investigation are described fully in the published Statistical Analysis Plan (7), which was agreed by the Stroke Thrombolysis Treatment (STT) Collaborative Group prior to becoming unblinded to the results from IST-3.

Importance of pre-specifying the planned analyses

To reduce the inevitable spurious findings that can result from post hoc analyses, it is important to pre-specify and limit the main subgroup analyses arising from the updated individual patient data meta-analysis. Whilst it might be tempting to suggest particular thresholds of data related to the eligibility of past and current trials, these, in general should be avoided or minimised (as these same trials will be included in the proposed analyses and circular estimation should be avoided). Furthermore, agreeing on a protocol and then progressing rapidly to data collection and organisation will allow the Collaboration to respond rapidly to the publication of new data from each of the other trials that will complete in the next few years.

Rationale

Good practice includes assessment of all new trial results in the context of all relevant prior completed trials. The principal aim of this new phase of analyses

would be to provide an updated guide on whom to treat. Robust data from an updated individual patient meta-analysis would not only provide the highest level of evidence, but consensus from ALL the trialists would be enormously powerful in promoting a substantial increase in the appropriate use of rt-PA and in silencing critics who have doubted the previous data.

Potential scope of updated meta-analysis

The main benefits of an individual participant data meta-analysis (sometimes referred to as a "pooled" analysis) include an ability to address some important outstanding questions, suggest new hypotheses and help identify future research questions. In addition to further increasing the precision of information on time to treatment, many outstanding questions about i.v. rt-PA therapy for acute ischaemic stroke will be informed by this collaborative meta-analysis. These are summarised in the Statistical Analysis Plan (7).

Study eligibility

All randomised trials with at least one randomised comparison of intravenous rt-PA with control that have completed and reported main results by 30th June 2012. The trials identified by the updated Cochrane Systematic review that meet this criterion are listed in Appendix A at the end of this protocol .

Identification of eligible trials

It is very unlikely that there are completed and potentially eligible trials that are not listed in Appendix A. However, for completeness, a further search of the Cochrane Stroke Group's Specialised Register of Trials will be conducted.

Data collection and checking

We will seek individual participant data for all randomised individuals in relevant trials. The requested data will comprise: baseline neurological, physiological, and imaging characteristics and concomitant medications recorded at randomisation, details of randomly allocated treatments (and the time from stroke onset that they were commenced), date and type of primary and secondary outcomes. The data will be checked carefully for internal consistency and completeness of individual participant records, and for other indicators of possible anomalies. All queries regarding particular trials will be referred back to the sponsors or principal investigators of the trials, and computer generated outputs consisting of detailed summary tabulations and consistency checks will be returned to each collaborator for review and confirmation.

Outcomes & Adjudication

Data will be sought on key primary and secondary outcomes, as defined and adjudicated in each trial (or adjudicated independently after trial completion [see the Statistical Analysis Plan (7)]). If adjudicated outcomes are not available, then the best available information on these outcomes will be recorded.

Analytical strategy

The analytical strategy, including definition of the primary and secondary outcomes, can be found in the published Statistical Analysis Plan (7), which was agreed by the STT Collaborative Group prior to becoming unblinded to the results from IST-3.

Steering Group
The conduct of the data collection, analysis, preparation of manuscripts will be overseen by the Steering Group. This will include a lead representative from each trial, responsible for consulting with members of the trial they represent (eg to collate comments on circulated materials), for participating in manuscript preparation and editing, and for agreeing all procedural issues.

Publication policy
All publications will be in the name of the Stroke Thrombolysis Trialists' (STT) Collaboration, with the names of collaborators listed at the end of the paper. All collaborators will be expected to participate fully in manuscript preparation and editing, and will be expected to consult with, and collate comments from, colleagues from the trials they represent. Publications will be circulated for comments and approval before submission to peer review. The principles for agreeing the text of papers are that any such papers should**:**

- focus on conveying clear findings on which all trial groups are agreed, with controversial findings labelled as such;
- where there is disagreement, the aim should be to moderate language to try to reach agreement; BUT
- if agreement cannot be reached, then trials have the right to remove their data from an analysis.

Confidentiality, data storage and handling
All trial data will be regarded as strictly confidential, and will not be provided to any third party without the prior written permission of the owners of the data. However, if appropriate, and agreed by the steering group, the same data set may be held elsewhere, and if so, strict confidentiality and data security at each data repository will be maintained. The secretariat will be responsible for collating and checking the data (in one location until complete, then will ensure the final locked analysis dataset is held in each data repository).

Funding and grant applications
Collaborators will be asked to fund their own travel costs for initial meetings (accommodation and meals will be provided). The secretariat will prepare grant applications as appropriate for support for the costs of research staff, data management and meeting (travel and accommodation) costs. Such applications will be submitted in the name of the group as a whole, with the members of the Steering Group named as co-applicants.

References

1. The ATLANTIS, ECASS and NINDS rt-PA Study Group Investigators. Association of Outcome With Early Stroke Treatment: Pooled Analysis of ATLANTIS, ECASS, and NINDS Rt-PA Stroke Trials. Lancet 2004; 363: 768-74.
2. Lees KR, Bluhmki E, von Kummer R, Brott TG, Toni D, Grotta JC et al. Time to Treatment With Intravenous Alteplase and Outcome in Stroke: an Updated Pooled Analysis of ECASS, ATLANTIS, NINDS, and EPITHET Trials. Lancet 2010; 375: 1695-703.
3. Davis SM, Donnan GA, Parsons MW, Levi C, Butcher KS, Peeters A et al. Effects of alteplase beyond 3 h after stroke in the Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET): a placebo-controlled randomised trial. Lancet Neurol 2008; 7: 299-309
4. Wardlaw JM, Murray V, Berge E, del Zoppo GJ. Thrombolysis for acute ischemic stroke. *Stroke* 2010;41:e445-e446
5. The IST-3 Collaborative Group. The benefits and harms of intravenous thrombolysis with recombinant tissue plasminogen activator within 6 h of acute ischaemic stroke (the third international stroke trial [IST-3]): a randomized controlled trial. Lancet 2012; 379: 2352-2363.
6. Lorenzano S and Danilo Toni, for the TESPI trial Investigators. TESPI (Thrombolysis in Elderly Stroke Patients in Italy): a randomized controlled trial of alteplase (rt-PA) versus standard treatment in acute ischaemic stroke in patients aged more than 80 years where thrombolysis is initiated within three hours after stroke onset. Int J Stroke. 2012; 7:250-7
7. The Stroke Thrombolysis Trialists' Collaborative Group. Details of a prospective protocol for a collaborative meta-analysis of individual participant data from all randomised trials of intravenous rt-PA versus control: Statistical Analysis Plan for the Stroke Thrombolysis Trialists' Collaborative Meta-Analysis. Int J Stroke 2013; 8: 278-83

Appendix A:
List of eligible trials and STT lead investigators

Trial	Lead investigators	Status in Third Phase
ATLANTIS (A&B)	Gregory Albers, James Grotta, Maarten Lansberg, Jean Marc Olivot	Included
ECASS-1, ECASS-2, ECASS-3	Erich Bluhmki, Werner Hacke, Markku Kaste, Greg del Zoppo, Kennedy Lees, Ruediger von Kummer, Nils Wahlgren	Included
EPITHET	Stephen Davis, Geoffrey Donnan, Mark Parsons	Included
IST-3	Peter Sandercock, Joanna Wardlaw, Richard Lindley, Gordon Murray, Geoff Cohen, William Whiteley	Included
NINDS (A & B)	James Grotta, Patrick Lyden, John Marler, Barbara Tilley	Included
TESPI	Danilo Toni	Not included
EXTEND	Davis, Donnan	Not included
Haley	Haley	Not included
ICTUS-L	Lyden	Not included
JTSG	Masatoshi Koga, Kazunori Toyoda, Takenori Yamaguchi	Not included
Mori	Etsuro Mori	Not included
Wang	Wang	Not included

STT Statistical Analysis Centre and Secretariat

Colin Baigent, Lisa Blackwell, Erich Bluhmki, Kelly Davies, Jonathan Emberson, Heather Halls, Lisa Holland, George Howard, Clare Mathews, Samantha Smith, Kate Wilson