Intravenous thrombolysis in acute ischaemic stroke: a systematic review and meta-analysis to aid decision making in patients over 80 years of age

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CRD summary
The authors concluded that patients aged over 80 years receiving thrombolysis with alteplase for acute ischaemic stroke may have lower functional recovery rates and higher mortality than younger patients, but appear not to have increased symptomatic cerebral haemorrhage rates.

In view of limitations in the review, particularly potential selection bias in the primary studies, these conclusions require cautious interpretation.

Authors' objectives
To evaluate the effectiveness and safety of intravenous thrombolytic therapy with alteplase for the treatment of acute ischaemic stroke in people aged over 80 years compared with those under 80 years old.

Searching
MEDLINE, EMBASE and CINAHL were searched from inception to September 2010. Search terms were reported. Leading journals and the reference lists of selected articles were checked for further studies.

Study selection
Comparative observational cohort studies of intravenous thrombolysis with alteplase after acute ischaemic stroke in people aged at least 80 years versus those under 80 years were eligible for inclusion. Outcomes of interest in the review were mortality, functional recovery and symptomatic intracranial haemorrhage; all at three month follow-up. Outcomes reported at other time frames were excluded. Functional recovery was measured with the modified Rankin scale: the review defined a favourable outcome as an modified Rankin scale score of 0 to 1.

In each study, the over 80 years old group was smaller with 12% to 32% of the total sample size and, where stated, this group was more likely to be female. Baseline risk factors in the two groups differed substantially in all studies. Most studies used the National Institute of Neurological Diseases and Stroke management protocol. All studies defined symptomatic intracranial haemorrhage with Neurological Diseases and Stroke management or European Cooperative Stroke Study III trial criteria. Most studies reported the review outcomes of interest, but a few studies used different time-frames for some outcomes (or their definitions for outcomes differed from those used in the review). The studies were set in a variety of European and North American countries.

Two authors independently selected the studies, with disagreements resolved by discussion with a third author.

Assessment of study quality
The following aspects of study quality were assessed: whether prospective; whether recruitment consecutive; reporting of methods, protocol violations and losses to follow-up; assessment of baseline comparability of groups and adjustment for potential confounders.

The authors did not state how the assessment was performed.

Data extraction
Odds ratios (ORs) with 95% confidence intervals (CIs) were extracted or calculated from the numbers of events in the two groups of each study. A study that only reported stroke-related deaths and three studies that defined functional recovery as an modified Rankin scale score of 0-2 were excluded from the main analyses.

The authors did not state how many reviewers performed data extraction.

Methods of synthesis
The studies were pooled using a Mantel-Haenszel fixed-effect model to calculate pooled odds ratios and 95%
confidence intervals. Heterogeneity was assessed using $X^2$ and publication bias with funnel plots. Sensitivity analyses included exclusion of one of the studies in which the data may have overlapped with another study, sequential removal of studies with minor variations (e.g. differing stroke management protocols) and exclusion of an outlying study. A subgroup analysis including only studies that defined recovery as modified Rankin scale 0-2 was performed.

Results of the review
Thirteen comparative cohort studies were included (3,556 participants, range 72 to 1,135). All were prospective and had well defined methodology, four studies did not clearly report whether participants were enrolled consecutively, 11 compared the groups at baseline for most potential confounders, nine adjusted statistically for baseline differences and seven described protocol violations. Only two of eleven studies that reported death and recovery rates at three months described losses to follow-up.

By three month follow-up, the over 80 years old group were significantly more likely to die (OR 2.77, 95% CI 2.25 to 3.40; 10 studies) and less likely to have functional recovery (OR 0.49, 95% CI 0.40 to 0.61; eight studies). There was no significant difference between the groups in the incidence of symptomatic intracranial haemorrhage (OR 1.31, 95% CI 0.93 to 1.84; 13 studies). There was no significant heterogeneity for any of these analyses (P>0.1) and sensitivity analyses did not substantially change the main findings. There was no indication of publication bias.

Pooling of the subgroup of studies that defined recovery as modified Rankin scale 0-2 resulted in significant heterogeneity (p=0.06) so were considered invalid.

Authors’ conclusions
Patients aged over 80 years receiving thrombolysis with alteplase for acute ischaemic stroke may have lower functional recovery rates and higher mortality than younger patients, but appear not to have increased symptomatic cerebral haemorrhage rates.

CRD commentary
The objectives of the review were clear, but not all review outcomes were defined in detail. Relevant sources were searched for studies, but no specific efforts were made to locate unpublished studies; funnel plots did not suggest publication bias. It was unclear whether the search was restricted by language. These factors meant that it was unclear whether studies could have been missed. Steps were taken to minimise the risk of reviewer bias and error by having more than one reviewer independently select studies, but the processes used for validity assessment and data extraction were not described.

Overall study quality appeared low: as the authors noted, there was strong potential for selection bias, losses to follow-up were poorly reported and sample sizes were small. The methods used to pool the studies and to assess and explore heterogeneity were appropriate in most respects. The issues explored in sensitivity analyses were not described in detail.

In view of limitations in the review, particularly potential selection bias in the primary studies, the authors’ conclusions required cautious interpretation.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that patients aged 80 years or over should be recruited into ongoing randomised controlled trials of thrombolysis for acute ischaemic stroke.

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Not stated.

Bibliographic details
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.