Early signs of brain infarction at CT: observer reliability and outcome after thrombolytic treatment. Systematic review

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CRD summary
The review examined inter-observer variation in early computed tomographic (CT) scans in acute ischaemic stroke and the relationship between early CT signs and outcome. The authors concluded that further research is required. Limitations in the validity assessment and analysis mean that the results of the meta-analyses may not be reliable. However, the authors’ conclusions about the need for further research appear reasonable.

Authors' objectives
To determine the relationship between early computed tomography (CT) signs in acute ischaemic stroke and patient outcome (with or without thrombolysis), and to assess inter-observer agreement.

Searching
MEDLINE and EMBASE were searched from January 1990 to May 2003; a full search strategy was reported. The reference lists of identified articles were checked for additional publications. Conference abstracts were also examined, but were only included if they were subsequently published in full. Studies published before 1990 were excluded as early signs of infarction were not well recognised, thrombolysis was not widely used before this time, and because CT technology has since changed. No language restrictions were applied.

Study selection
Study designs of evaluations included in the review
The studies had to have at least 10 patients; no other inclusion criteria were specified for studies of inter-observer agreement. All included studies of inter-observer agreement appeared to be diagnostic cohorts. Studies comparing CT signs and outcome were randomised controlled trials (RCTs) and observational studies.

Specific interventions included in the review
Studies of early signs of brain infarction at CT, in acute ischaemic stroke, were eligible for inclusion. Early signs were defined as any evidence of infarction (e.g. hypoattenuation, swelling) or pathologic vascular condition (e.g. hyperattenuating vessels). Studies in which only radiological markers of outcome (e.g. infarct volume) were given, without clinical outcome data, were excluded. Studies comparing CT signs and outcome had to report whether or not thrombolysis was given. Included studies of inter-observer agreement used printed hard-copy CT scans and analysed between one and five early signs on CT.

Reference standard test against which the new test was compared
Studies of inter-observer agreement were required to compare CT signs with a defined reference standard. The reference standard in most studies of inter-observer agreement was reading by a neuroradiologist with follow-up imaging.

Participants included in the review
Eligible studies were of adult patients who underwent CT within 6 hours of stroke.

Outcomes assessed in the review
Studies of inter-observer agreement were required to report agreement statistics (e.g. kappa values) or to report reader sensitivity or agreement compared with the reference standard. Studies comparing CT signs and outcome were required to assess death or dependency according to a recognised standard scale (e.g. Rankin or Barthel) at least 1 month after stroke.

How were decisions on the relevance of primary studies made?
Studies were formally assessed for eligibility using a standardised assessment form. The authors did not state how many reviewers selected studies from the databases. Two reviewers independently screened reference lists and abstracts of meetings.

**Assessment of study quality**
The authors did not state that they formally assessed validity. However, they did report on blinding and definitions of CT signs for studies of inter-observer agreement.

**Data extraction**
Two reviewers independently extracted the data using a standardised form. Both reviewers independently checked all extracted data twice. Any disagreements were resolved by consensus. For studies of inter-observer agreement, measures of agreement were extracted or calculated where possible. For studies comparing CT signs and outcome, the proportions of patients with early signs of infarction and good or poor outcomes were extracted. These were used to calculate odds ratios (ORs) for a poor outcome associated with each particular sign.

**Methods of synthesis**
How were the studies combined?
For studies of inter-observer agreement, the results of individual included studies were tabulated and summarised in a narrative synthesis; mean values (with ranges) were reported. For studies comparing CT signs and patient outcome, the summary OR for a poor outcome (death or dependency) in the presence of each CT sign was calculated; the overall OR for any sign present was also calculated.

How were differences between studies investigated?
The authors did not report a method for assessing heterogeneity between studies of inter-observer agreement. However, statistical heterogeneity between studies examining the relationship between early CT signs of infarction and clinical outcome was assessed using the chi-squared test. The authors planned to assess the effects of observer experience, knowledge of symptoms and prevalence of early infarction signs on inter-observer agreement. An assessment of any differences in the effect of thrombolytic therapy between patients with and without early signs of infarction was also planned.

**Results of the review**
Fifteen studies assessing inter-observer agreement were included in the review. These studies assessed a total of 1,300 scans, with 707 readers.

Fifteen studies comparing CT signs and outcome were included in the review (3,481 patients). Five studies were secondary analyses of 7 published RCTs and 10 (n=947) were observational studies.

Assessment of inter-observer agreement.

Eight of the 15 studies gave explicit definitions of early signs of infarction. In 9 studies the readers were blinded to clinical factors.

Studies included a median of 30 scans and 6 observers. The prevalence of all early infarction signs (15 studies) was 61% +/- 21 (standard deviation). Inter-observer agreement (kappa statistic) ranged from 0.14 to 0.78 (6 studies). The mean sensitivity and specificity values for the detection of early infarction signs with CT were 66% (range: 20 to 87) and 87% (range: 56 to 100), respectively. The data were insufficient to allow a reliable determination of the effects of observer experience, knowledge of symptoms, or prevalence of early signs on inter-observer agreement; data from individual included studies indicated that experience improved detection, but knowledge of symptoms did not.

Comparison of CT signs and patient outcome.

The presence of any early infarction sign at CT increased the risk of poor outcome (death or dependency) (OR 3.11,
95% CI: 2.77, 3.49). The presence of each of five individual infarction signs also increased the risk of poor outcome in each case (full data reported in the article). Statistically significant between-study heterogeneity was present in all but one of the five groups of studies used to generate pooled ORs. Two studies that examined the relationship between early infarction signs and the effectiveness of thrombolysis found no evidence that thrombolysis resulted in worse outcomes.

Authors' conclusions
Further work is needed to identify those infarction signs that are most reliably detected, to assess whether scoring systems are useful, and to determine whether any infarction sign should influence the decision to give thrombolysis.

CRD commentary
The article stated a clear research question and reported appropriate inclusion criteria for the participants, intervention and outcome; inclusion criteria were not defined for the reference standard or study design. The search strategy was reported in full and appeared appropriate, though the exclusion of abstracts not published in full might have resulted in the omission of relevant data; an assessment of publication bias was not reported. Some details of the included studies were reported. However, there was a very limited assessment of the methodological quality of the included studies. In addition, observational studies and trials were pooled in meta-analyses examining the relationship between early infarction signs and patient outcome. This factor, along with significant between-study heterogeneity in the majority of the pooled groups and a failure to report the model used to generate pooled estimates, makes the value of these estimates doubtful. The use of simple means to indicate overall sensitivity and specificity was inappropriate. However, the authors’ conclusions were not dependent upon the pooled data presented and represent reasonable recommendations for future research.

Implications of the review for practice and research
Practice: The authors made no specific recommendations for practice.

Research: The authors stated that further research is needed. Such research should improve definition and standardisation of early infarction signs at CT; determine which signs are most reliably detected; determine the utility of scoring systems; determine whether early infarction signs should be a factor in the decision to give thrombolysis and, if so, what degree of infarction sign is significant; assess observer variability across the range of relevant backgrounds; and determine the relationship between early infarction signs and outcome with thrombolysis.

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Record Status
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