Blood biomarkers in the diagnosis of ischemic stroke: a systematic review
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CRD summary
This review assessed the accuracy of blood biomarkers for the diagnosis of ischaemic stroke and concluded that deficiencies in the primary studies meant that no biomarker could be recommended for use in clinical practice. Despite some limitations in the presentation of the data, this conclusion appears reasonable.

Authors' objectives
To assess the accuracy of blood biomarkers for the diagnosis of ischemic stroke.

Searching
MEDLINE and EMBASE were searched to March 2007. The search strategy is available as a web supplement and a general description of the search terms was provided. The search included methodological terms for diagnostic accuracy studies. The bibliographies of retrieved articles, conference abstracts, books, personal files of the authors and the Internet were searched to identify additional studies. No language or publication status restrictions were applied.

Study selection
Studies that assessed the accuracy of blood biomarkers (singly or in combination) for the diagnosis of ischemic stroke were eligible for inclusion. Studies of cerebrospinal fluid biomarkers were excluded. Study populations could include patients with ischemic stroke and control without disease, stroke mimics, patients with other neurological diseases and patients with haemorrhagic stroke. Studies of any size that reported sufficient data to populate a 2x2 contingency table (numbers of true positives, false negatives, false positives and true negatives) were eligible for inclusion. No inclusion criteria were specified for the reference standard for diagnosis of ischaemic stroke.

The review reported data on 21 different biomarkers and diagnostic thresholds varied across studies of the same marker. Most studies defined patients as positive for ischaemic stroke only if they had both appropriate symptoms and a visible appropriate lesion on imaging; some studies classified transient ischaemic attack (TIA) as acute ischaemic stroke.

Two reviewers independently assessed the titles and abstracts of all retrieved articles against the stated inclusion criteria.

Assessment of study quality
The methodological quality of included studies was assessed using a modified version of the QUADAS tool (available as a web supplement).

The authors did not state how many reviewers performed the quality assessment.

Data extraction
Data to populate 2x2 contingency tables were extracted, along with the corresponding diagnostic thresholds. Where a study reported more than one data set, each data set was extracted separately. Sensitivity and specificity were the main outcome measures reported in the review.

Two reviewers independently extracted data. Any disagreements were resolved by discussion.

Methods of synthesis
Sensitivity and specificity, with 95% confidence intervals (CIs) were calculated for each data set.

Studies were combined in a narrative synthesis and comparative sensitivities and specificities were illustrated using
Results of the review
Twenty one studies that evaluated 58 single biomarkers and seven combinations were included in the review. Accuracy data were available for 21 biomarkers. Approximately 3,000 stroke patients and 1,500 controls were included in the review. Four of the 21 studies assessed biomarkers in patients with suspected stroke; the rest compared patients with stroke to a control group. Six of the 21 studies used a pre-specified diagnostic threshold; the rest derived the cut-off threshold from the cohort examined. Only two of the 21 studies reported assessment of the biomarker blind to stroke status, although all stroke diagnoses appeared to have been blind to biomarker results. Nine studies reported the delay between symptom onset and the drawing of blood for biomarkers (range 30 minutes to five days).

Single biomarkers: Five had reported sensitivities over 90% (NDKA, PARK7, UFD-1, NMDA receptor (NR) 2 fragment and NR2A/B antibodies) and 14 had reported specificities over 90% (PARK7/ RNA-BP, UFDP, NDKA, GSTP, ischemia modified albumin (IMA), visin like protein (VLP-1), beta globin DNA, NR2 fragments, S100 beta, FABP, neurone specific enolase (NSE), NR2A/2B antibodies, myelin basic protein (MBP) and thrombomodulin). Most markers were assessed in only one cohort of patients.

Combinations of markers: Data were extracted for five different combinations of markers, but none of the studies reported the regression equation for the combined panel of markers that would have allowed the calculation of the additional informative value provided by each biomarker.

Discrimination between ischaemic and haemorrhagic stroke: Five studies assessed six individual biomarkers and two panels of markers for discrimination between ischaemic and haemorrhagic stroke. Most studies defined a haemorrhagic stroke as the case-positive diagnosis. The two studies that reported a positive test as a diagnosis of ischaemic stroke both had high sensitivity and specificity (absolute values not reported); the markers assessed were apoprotein C1, apoprotein C3 and NR2A/2B antibodies.

Sensitivity and specificity values, with 95% CIs, for each data set were illustrated on forest plots, but numerical values were not reported.

Authors' conclusions
Although all of the biomarkers assessed showed either a high sensitivity or specificity, limitations in the design and reporting of all studies meant that no biomarker could be recommended for use in clinical practice.

CRD commentary
This review presented a clearly stated research question and defined appropriate inclusion criteria. The search strategy covered two bibliographic databases and a wide range of other sources. No language or publication status restrictions were applied. The use of methodological search terms for diagnostic accuracy studies is not generally recommended and was likely to lead to some studies being missed. Measures to minimise error and bias in the review process were reported and the methodological quality of included studies was assessed and fully reported. The authors’ decision to present a narrative synthesis appeared appropriate given the small number of data sets per marker and considerable heterogeneity in study characteristics. The results of individual studies presented were, however, difficult to interpret as no numerical data were provided (results were illustrated on forest plots only). In addition, the reference standard method(s) used to establish diagnoses were not reported. Despite some limitations in the presentation of the data, the poor quality of included studies and small size of data sets, the authors' conclusion that no biomarker could be recommended for use in clinical practice is a reasonable one.

Implications of the review for practice and research
Practice: The authors stated that no biomarker could be recommended for use in clinical practice.

Research: The authors stated that further research was needed to establish the performance of biomarkers in unselected cohorts of patients with suspected ischaemic stroke. Research should assess the accuracy of markers for diagnosing stroke where brain imaging was normal, the ability of markers to discriminate between ischaemic and haemorrhagic
stroke and the ability of markers to determine which patients required further, more invasive investigations.

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