A systematic review of duplex ultrasound, magnetic resonance angiography and computed tomography angiography for the diagnosis and assessment of symptomatic, lower limb peripheral arterial disease


CRD summary
The authors concluded that contrast-enhanced magnetic resonance angiography appeared to have the highest diagnostic accuracy and, if available, may be a reasonable alternative to computed angiography. This was a well-conducted review and the authors' conclusions are likely to be robust.

Authors' objectives
To evaluate the diagnostic accuracy of duplex ultrasonography, magnetic resonance angiography (MRA) and computed tomography (CT) angiography for the diagnosis and assessment of symptomatic, lower limb peripheral arterial disease, and to assess the impact of these techniques on patient management and outcomes, patients' attitudes and adverse effects.

Searching
MEDLINE, EMBASE, BIOSIS Previews, Science Citation Index, NTIS, LILACS, SIGLE, Dissertation Abstracts Online, Inside Conferences and Pascal were searched from 1996 to April 2005; the search terms were reported. No language restrictions were applied. In addition, published and unpublished studies were sought through searches of the Cochrane Database of Systematic Reviews (Issue 3, 2005), six major journals of imaging and vascular disease, and the reference lists of included studies.

Study selection
Study designs of evaluations included in the review
Diagnostic cohort studies or case-control studies with 20 or more patients were eligible for inclusion in the review of diagnostic accuracy. Randomised controlled trials or controlled clinical trials with 20 or more patients were eligible for inclusion in the assessment of patient management and outcomes. Studies of any design with 20 or more patients, apart from case reports, were eligible for inclusion in the assessment of patient acceptability. Studies of any design and sample size, apart from case reports, were eligible for inclusion in the assessment of adverse effects. All of the included diagnostic accuracy studies were diagnostic cohorts.

Specific interventions included in the review
Studies that evaluated duplex ultrasonography, MRA and CT angiography, either alone or in combination, were eligible for inclusion. Most of the included studies evaluated duplex ultrasonography; other studies evaluated two-dimensional (2D) phase contrast MRA, 2D time-of-flight MRA and CT angiography.

Reference standard test against which the new test was compared
Studies that compared the specified tests with intra-arterial contrast angiography or findings at surgery or follow-up were eligible for inclusion in the review of diagnostic accuracy. All of the included studies used conventional angiography (CA) as the reference standard.

Participants included in the review
Studies of adults (aged at least 18 years) with symptoms of lower limb peripheral arterial disease were eligible for inclusion in the review.

Outcomes assessed in the review
Studies that reported sufficient information to construct relevant 2x2 tables were eligible for inclusion in the review of diagnostic accuracy. Studies that reported any treatment decision or long-term outcome measure were eligible for inclusion in the assessment of patient management and outcomes. Studies that reported any measure of patient
acceptability were eligible for inclusion in the assessment of patient acceptability. Studies that reported any adverse events associated with the index test or currently used contrast agents were eligible for inclusion in the assessment of adverse events.

The review assessed the accuracy of imaging tests in diagnosing stenosis 50% or more of the whole leg and stenosis 50% or more above and below the knee. The review assessed results for arterial segments.

How were decisions on the relevance of primary studies made?
Two reviewers independently selected studies from full papers and resolved any disagreements on inclusions through consensus or recourse to a third author.

Assessment of study quality
One reviewer assessed validity and a second reviewer checked the assessment. Any disagreements were resolved through consensus or recourse to a third author. The validity of diagnostic accuracy studies was assessed using the QUADAS (Quality Assessment of Diagnostic Accuracy Studies) checklist, which assesses bias, variability and the quality of reporting in test accuracy studies, or an appropriate quality checklist in the case of other study designs.

Data extraction
One reviewer extracted the data and a second reviewer checked the extraction. Any disagreements were resolved through consensus or recourse to a third author. For each diagnostic accuracy study, the numbers of true- and false-positive results and true- and false-negative results were extracted, and sensitivity and specificity values for the diagnosis of stenosis in arterial segments were calculated. The value of 0.5 was added to cells with zero events.

Methods of synthesis
How were the studies combined?
The diagnostic accuracy studies were grouped according to the imaging test examined and the specific outcome reported. Since there was significant heterogeneity, pooled data were reported as medians (with ranges). Sensitivity and specificity values were plotted on receiver operating characteristic (ROC) curves. Studies reporting other outcomes were combined in a narrative.

How were differences between studies investigated?
Statistical heterogeneity was assessed using the Q statistic and by visual inspection of forest plots. MRA studies were grouped by specific technique and discussed separately. Potential reasons for differences in the results between studies were discussed.

Results of the review
Fifty-eight studies (n=2,925 patients) evaluated diagnostic accuracy. Of these, duplex ultrasonography was evaluated in 28 studies, MRA in 25 studies (time-of-flight MRA was evaluated in eleven of these) and CT angiography in seven studies; two studies evaluated more than one index test. One trial with a historical control group (n=227 patients) assessed the effect of tests on patient management and outcome, four studies assessed patients' attitudes, and 55 studies reported adverse events.

Methodological limitations in the diagnostic accuracy studies included an inappropriate range of patients, inadequate description of the patients and selection criteria, failure to report the time interval between index and reference tests, and availability of clinical data. In most studies, the index tests were interpreted blind to the reference test results and the reference tests were interpreted blind to the index test results.

Detection of stenosis 50% or more, or occlusion of the whole leg: The highest diagnostic accuracy was obtained with contrast-enhanced MRA; the median sensitivity was 95% (range 92 to 99.5%) and specificity 97% (range 64 to 99%), based on seven studies. 2D time-of-flight MRA had a lower diagnostic accuracy; the median sensitivity was 92% (range 79 to 94%) and specificity 88% (range 74 to 92%), based on five studies. One study evaluated 2D phase contrast MRA.
and reported a sensitivity of 98% and specificity of 74%. CT angiography had a median sensitivity of 91% (range 89 to 90%) and specificity of 91% (range 93 to 97%), based on six studies. Duplex ultrasonography had a median sensitivity of 88% (range 80 to 98%) and specificity of 96% (range 89 to 99%), based on seven studies.

Results were also reported for the detection of 50% or more stenosis above and below the knee and the detection of occlusion in the foot.

**Effect of the tests on patient management and outcome:** One controlled trial with a historical control group (n=227 patients) compared duplex ultrasonography plus contrast angiography where indicated with contrast angiography. In 78% of cases, management was based on duplex ultrasonography alone. There were no significant differences between testing regimens for immediate or intermediate outcomes.

**Patients' attitudes:** The studies only included patients who were suitable for MRA. In two studies, patients expressed a preference for MRA over CT angiography. The most uncomfortable was reported to be contrast angiography, followed by contrast-enhanced MRA, with CT angiography the least uncomfortable (based on one study that compared all three methods). Half of the patients expressed no preference between [A: contrast enhanced MRA] and duplex ultrasonography.

**Adverse events:** The studies did not always report the methods used to monitor and record adverse events. The review authors stated that adverse events reported in the review should not be accepted as being an accurate indication of their frequency. The highest frequency of adverse events was reported for MRA but most adverse events were mild. Major adverse events (death, severe vascular adverse events) were most common in patients undergoing contrast angiography, but the percentage affected was low: 5% (1 out of 19 patients) with contrast angiography versus 0.5% (2 out of 435 patients) with MRA.

**Cost information**
For assessment of the whole leg pre-operatively, duplex ultrasonography showed the lowest cost per quality-adjusted life-year (\(\text{£13,646 per QALY}\)). For pre-operative assessment of a section of leg (either above or below the knee), 2D time-of-flight MRA showed the lowest cost per QALY (\(\text{£13,646 per QALY}\)). For below-knee assessment, the incremental cost per QALY was \(\text{£37,024 per QALY}\) compared with duplex ultrasonography. For above-knee assessment, 2D time-of-flight MRA showed the lowest costs and slightly lower effectiveness (\(\text{£13,442 per QALY}\)) than the most effective strategy (i.e. contrast-enhanced MRA). The economic analysis was based on six economic evaluations.

**Authors' conclusions**
Contrast-enhanced MRA appeared to have the highest diagnostic accuracy and, if available, may be a reasonable alternative to CT angiography.

**CRD commentary**
The review addressed a clear question that was defined in terms of the participants, intervention, outcomes and study design. The strategy undertaken to identify trials was extensive and attempts were made to minimise both publication and language bias. Appropriate methods were used in the study selection, validity assessment and data extraction processes, thereby reducing the potential for reviewer bias and errors. Validity was assessed using specified criteria and the results of this assessment were reported. Adequate information about the included studies was presented. The studies were appropriately grouped and combined. Differences between the studies in diagnostic accuracy were illustrated graphically and potential reasons for outliers were discussed. This was a well-conducted review and the authors' conclusions are likely to be robust.

**Implications of the review for practice and research**
Practice: The authors stated that, where available, contrast-enhanced MRA may be a reasonable alternative to CT angiography.

Research: The authors stated that future evaluations of diagnostic tests should adhere to the Standards for the Reporting
of Diagnostic Accuracy Studies (STARD) guidelines. They also stated that research in the following areas is required: the relative effects of available imaging tests on surgical planning, post-operative outcomes and cost-effectiveness in a large multicentre randomised controlled trial; comparison of adverse events associated with different tests and their incidence, and the most appropriate methods for collecting data on adverse events; patients' attitudes regarding different tests; the true diagnostic accuracy of duplex ultrasonography compared with CT angiography; the effects of the skill, training and experience of test operators on all imaging tests; and the diagnostic accuracy and clinical effectiveness of imaging tests for arteries in different locations in the leg, especially the foot, and for clinically important subgroups of patients (e.g. those with diabetes).

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