Systematic review of the effectiveness and cost-effectiveness, and economic evaluation, of myocardial perfusion scintigraphy for the diagnosis and management of angina and myocardial infarction


CRD summary
This well-conducted review drew no firm conclusion on the diagnostic accuracy of single photon emission computed tomography (SPECT) myocardial perfusion scintigraphy compared to stress electrocardiography for the diagnosis and management of coronary artery disease, due to limited data available. The conclusion that SPECT is likely to add to the predictive power of risk assessment is supported by the data presented.

Authors' objectives
To assess the clinical and cost-effectiveness of single photon emission computed tomography (SPECT) myocardial perfusion scintigraphy for the diagnosis and management of angina and myocardial infarction.

Searching
The following databases were searched to December 2002: BIOSIS Previews, Cochrane Central Register of Controlled Trials, DARE, EMBASE, Health Management Information Consortium (HMIC), HTA, MEDION, MEDLINE, NHS-EED and Web of Science. Search strategies were reported in full in an appendix to the report. The bibliographies of included articles were screened to identify additional studies.

Study selection
Prospective or retrospective studies in adults with suspected or known coronary heart disease were eligible for inclusion. The following participant types were excluded: previous heart transplant; hypertrophic cardiomyopathy; mitral valve prolapse; primary aldosteronism; lupus; acromegaly; cystic fibrosis; severe obstructive sleep apnoea; beta-thalassaemia; and previous aortic reconstruction.

For diagnostic accuracy, included studies were required to compare SPECT myocardial perfusion scintigraphy (radionuclides: thallium-20, technetium-99m sestamibi or technetium-99m tetrofosmin) with stress electrocardiography (exercise or pharmacological stress). Included studies had to use coronary angiography or clinical follow-up for patients with mild symptoms, as the reference standard. Acceptable outcome measures for diagnostic accuracy were: numbers of true positives; false negatives; false positives and true negatives (2x2 contingency data); or sensitivity and specificity values.

For prognosis, studies which compared strategies with SPECT myocardial perfusion scintigraphy to strategies without (full details given in the report) were eligible for inclusion. Studies that compared SPECT with electrocardiography-gated or attenuation-corrected SPECT were also included. Acceptable outcome measures for prognosis/risk assessment were: mortality; cardiac mortality; non-fatal myocardial infarction; revascularization; unstable angina; survival time; preservation of post-surgical left ventricular function; post-operative complications; number of coronary angioplasty procedures; hospital admissions; and quality of life measures.

Non-English language studies were noted but not included in the review.

All studies deemed potentially relevant from their titles and abstracts were retrieved and independently assessed for inclusion by two reviewers. Disagreements were resolved by discussion, or referral to a third reviewer.

Assessment of study quality
The methodological quality of included studies was assessed using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) tool for diagnostic studies and the Downs and Black checklist for both randomised and non-randomised prognostic studies.
Two reviewers extracted data independently. Differences were resolved by discussion, or referral to a third reviewer. Reviewers were not blinded to study authors, institutions, or journal of publication.

**Data extraction**

Details of participants, test characteristics and outcome measures were extracted, along with 2x2 contingency data and sensitivity, specificity, likelihood ratios and accuracy, for diagnostic studies.

Predictive variables, relative risk (RR), odds ratio (OR), or hazard ratio (HR) were extracted for prognostic studies.

Two reviewers extracted data independently. Differences were resolved by discussion, or referral to a third reviewer. Reviewers were not blinded to study authors, institutions or journal of publication.

**Methods of synthesis**

Diagnostic accuracy studies:

Correlation between true positive rate (sensitivity) and false positive rate (1-specificity), or threshold effect was assessed using Spearman's rank correlation coefficient. Where a positive correlation was identified, Summary Receiver Operating Characteristic (SROC) curves were constructed. In the absence of a correlation, between study heterogeneity was assessed using $\chi^2$ or Fisher's exact tests. Where no evidence of heterogeneity was found, pooled estimates of sensitivity and specificity (weighted by inverse variance) were derived and pooled likelihood ratios were generated using a random-effects model. Accuracy studies were grouped separately for patients with suspected coronary artery disease, patients with previous percutaneous coronary angioplasty, patients with asymptomatic coronary disease, and patients with left bundle branch block.

Prognostic studies:

The results of prognostic studies were presented in a narrative synthesis, grouped into the following categories: general prognostic studies; value of SPECT for assessing prognosis in specific groups at risk of coronary artery disease (e.g. diabetes); specific patient populations (e.g. post-myocardial infarction); electrocardiography-gated and attenuation-corrected SPECT.

**Results of the review**

Diagnostic accuracy studies:

Twenty one diagnostic accuracy studies (n = 4,453 participants) were included in the review. Most studies clearly described selection criteria, but showed evidence of spectrum bias. The time between test and reference standard was generally sufficiently short to minimise disease progression bias. In just over half of the included studies, interpretation of the reference standard was made with knowledge of test results.

For patients with suspected coronary artery disease (14 studies): sensitivities for SPECT ranged from 0.63 to 0.93 (median 0.81) and for stress electrocardiography from 0.42 to 0.92 (median 0.65); specificities for SPECT ranged from 0.10 to 0.90 (median 0.65) and for stress electrocardiography from 0.41 to 0.88 (median 0.67).

For the evaluation of restenosis in patients who had previously undergone percutaneous coronary angioplasty (three studies) sensitivities for SPECT ranged from 0.63 to 0.93 (median 0.79) and for stress electrocardiography from 0.51 to 0.83 (median 0.52); specificities for SPECT ranged from 0.77 to 0.78 (median 0.77) and for stress electrocardiography from 0.62 to 0.65 (median 0.64).

One study assessed patients with asymptomatic coronary artery disease and reported sensitivities of 0.91 for SPECT and 0.43 for electrocardiography in patients with angiographically proven stenosis; the specificity of SPECT in these patients was 0.96. For patients with low probability of coronary artery disease, in the same study, sensitivity for SPECT was 0.94 and electrocardiography was 0.70; with specificity for SPECT 0.75 and electrocardiography 0.56.
In one study of patients with left bundle branch block, pharmacological stress was shown to be more specific than exercise stress for left anterior descending coronary artery disease. The overall pooled positive likelihood ratio was higher for SPECT (2.29) than for stress electrocardiography (1.83) and the pooled negative likelihood ratio was lower (0.25 versus 0.51). However, significant heterogeneity was present.

Two studies comparing SPECT with electrocardiography-gated SPECT found SPECT to be more accurate, and one study comparing SPECT with attenuation-corrected SPECT found the latter to be more accurate.

Prognostic studies:

Forty-six prognostic studies (n = 83,138 participants) were included in the review. The overall methodological quality of these studies was good, with a mean overall score 18.1 out of a possible 27. Full results tables were presented in Appendix 8 of the report and independent predictive variables identified by studies employing multi-variate analyses were presented in Appendix 9.

For general prognostic studies (21 studies), the extent (eight studies) and size (three studies) of perfusion defect and whether it was fixed or reversible (four studies) were found to be important predictors of prognosis.

Two studies compared a direct coronary angiography strategy with selective coronary angiography following SPECT and found that the latter strategy reduced the rate of normal angiograms (i.e. unnecessary coronary angiography).

SPECT was also found to be an independent predictor of myocardial infarction (one study), to provide incremental prognostic value over clinical and exercise testing (four studies) and coronary angiography (three studies).

SPECT was found to be useful in stratifying patients into risk groups for further cardiac events post-myocardial infarction (four studies) and after coronary artery bypass graft (two studies) and, when performed one to three years after percutaneous coronary angioplasty, was also predictive of cardiac events (one study).

Adverse events data were also reported.

Cost information

For the base-case analysis, the costs were: £5,190 (yielding 12.473 quality-adjusted life-years (QALYs)) for strategy a (stress electrocardiography, followed by SPECT if stress electrocardiography positive, followed by coronary angiography if SPECT positive); £5,395 (yielding 12.481 QALYs) for strategy b (stress electrocardiography, followed by coronary angiography if stress electrocardiography positive); £5,529 (yielding 12.497 QALYs) for strategy c (SPECT, followed by coronary angiography if SPECT positive); £5,929 (yielding 12.506 QALYs) for strategy d (coronary angiography as first option).

Authors' conclusions

No firm conclusions could be drawn about the comparative accuracy of SPECT and stress electrocardiography, in different patient subgroups and for different definitions of coronary artery disease, due to the small numbers of studies available in each subgroup. Insufficient data were available to assess the incremental value of SPECT over electrocardiography in the diagnosis of coronary artery disease.

Evidence from prognostic studies suggested that SPECT, as part of the stress electrocardiography-SPECT-coronary angiography pathway, provides independent, incremental information that is predictive of outcome and can help in risk stratification, in a variety of settings and populations.

CRD commentary

The review addressed a clearly stated research question and gave a full definition of appropriate inclusion criteria. The search strategy was extensive and fully reported but the restriction to English language studies means that language bias remains a possibility. The review methodology was fully reported and included appropriate measures to minimise error and bias. The methodological quality of included studies was assessed using appropriate tools and the results of this assessment were fully reported. Although pooled estimates of likelihood ratios were presented, the focus was generally
on a narrative summary with ranges of results. This approach seems reasonable, given the heterogeneous data available. The authors make no firm conclusions with regard to the diagnostic accuracy of SPECT and electrocardiography, which is reasonable, given the limited and variable data available. The conclusion that SPECT is likely to add to the predictive power of existing prognostic algorithms is supported by the data presented.

**Implications of the review for practice and research**

Research: The authors stated that further research is needed on the diagnostic and prognostic clinical and cost-effectiveness of gated and attenuation-corrected SPECT compared with standard SPECT, standard SPECT compared with electrocardiography, and the uncertainties around cost-effectiveness analyses.

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