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[1] Health Services Research Unit, Institute of Applied Health Sciences, University of Aberdeen, UK

[2] Health Economics Research Unit, Institute of Applied Health Sciences, University of Aberdeen, UK

[3] Department of Public Health, Institute of Applied Health Sciences, University of Aberdeen, UK

[4] Nuclear Medicine Physics, Department of Bio-Medical Physics and Bio-Engineering, University of Aberdeen and Grampian University Hospitals NHS Trust, UK

[5] Cardiology Research Group, Department of Clinical Cardiology, University of Aberdeen and Grampian University Hospitals NHS Trust, UK

* Corresponding author

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Abstract

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

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[1] Health Services Research Unit, Institute of Applied Health Sciences, University of Aberdeen, UK
[2] Health Economics Research Unit, Institute of Applied Health Sciences, University of Aberdeen, UK
[3] Department of Public Health, Institute of Applied Health Sciences, University of Aberdeen, UK
[4] Nuclear Medicine Physics, Department of Bio-Medical Physics and Bio-Engineering, University of Aberdeen and Grampian University Hospitals NHS Trust, UK
[5] Cardiology Research Group, Department of Clinical Cardiology, University of Aberdeen and Grampian University Hospitals NHS Trust, UK
* Corresponding author

Objectives: To assess the effectiveness and cost-effectiveness of single photon emission computed tomography (SPECT) myocardial perfusion scintigraphy for the diagnosis and management of angina and myocardial infarction (MI).
Data sources: Major electronic databases.
Review methods: Two reviewers independently extracted data and assessed study quality. A decision tree model was used to model the diagnosis decision and a Markov model was developed for the management of patients with suspected coronary artery disease. Costs for the treatments and interventions within strategies were derived from the literature and expressed in 2001–02 pounds sterling. Quality-adjusted life-year (QALY) weights for the different Markov model states were also obtained from the literature.
Results: Twenty-one diagnostic and 46 prognostic studies were included, plus two studies comparing SPECT with electrocardiography (ECG)-gated SPECT and one study comparing SPECT with attenuation-corrected SPECT. The diagnostic values of SPECT were generally higher than those of stress ECG, indicating that SPECT provided a better diagnostic performance. SPECT also provided higher positive and lower negative likelihood ratios than stress ECG but heterogeneity was evident among studies. The subgroup of studies including patients with previous MI tended to report a better diagnostic performance for SPECT than stress ECG, but there were too few studies to assess this reliably. The extent and size of the perfusion defect, and whether reversible or fixed, were important factors in predicting future cardiac events such as cardiac death or non-fatal MI. SPECT may be able to identify lower risk patients for whom coronary angiography (CA) might be avoided. Normal SPECT scans were associated with a benign prognosis and the option of medical rather than invasive management. Four studies of patients post-MI reported SPECT to be valuable in stratifying patients into at-risk groups for further cardiac events. The two studies comparing SPECT with ECG-gated SPECT, one diagnostic and the other prognostic, found in favour of gated SPECT. The study comparing SPECT with attenuation-corrected SPECT reported the latter to be more accurate. The systematic review of economic evaluations indicated that strategies involving SPECT were likely either to be dominant or to produce more QALYs at an acceptable cost. There was less agreement about which of the strategies involving SPECT was optimal. The model suggested that, for low prevalence, the incremental cost per unit of output (true positives diagnosed, accurate diagnosis, QALY) for the move from stress ECG–SPECT–CA and from stress ECG–CA to SPECT–CA might be considered worthwhile. Even after allowing for different values for sensitivity or

specificity, the least costly and least effective strategy was stress ECG–SPECT–CA. The sensitivity analysis suggested that the cost-effectiveness of SPECT–CA improved if it was assumed that SPECT results allowed for the adoption of a management strategy without recourse to CA. As the time horizon reduced, the incremental cost per QALY increased (as the cost of initial diagnosis and treatment were not offset by survival and quality of life gains).

Conclusions: There was a considerable variability in terms of measurement of outcomes, management, setting and patient characteristics, however the direction of evidence tended to favour SPECT in terms of test sensitivity, although these conclusions are based on a relatively small number of diagnostic studies. SPECT, in a variety of settings and patient populations, provided valuable independent and incremental prognostic information to that provided by stress ECG and/or CA that helped to risk-stratify patients and influence the way in which their condition was managed. However, all of the prognostic studies were observational studies and may be biased by unknown confounding factors. Although the ECG-gated and attenuation-corrected SPECT findings seem promising, it is difficult to draw conclusions from so few studies. Further research is needed on the effectiveness and cost-effectiveness, diagnostically and prognostically, of (a) gated and attenuation-corrected SPECT compared with standard SPECT, (b) standard SPECT compared with stress echocardiography and (c) the uncertainty surrounding the results presented in the cost-effectiveness analysis.

Contents

List of abbreviations

2VD	two-vessel disease
3VD	three-vessel disease
AC	attenuation-corrected
ACER	average cost-effectiveness ratio
AMI	acute myocardial infarction
BMJ	*British Medical Journal*
BNCS	British Nuclear Cardiology Society
CA	coronary angiography
CABG	coronary artery bypass graft
CAD	coronary artery disease
CHD	coronary heart disease
CI	confidence interval
CRD	Centre for Reviews and Dissemination
DTM	decision tree model
EBCT	electron beam computed tomography
ECG	electrocardiography
ECHO	echocardiography
ExECG	exercise ECG
FN	false negative
FP	false positive
HCHS	Hospital and Community Health Services
HMIC	Health Management Information Consortium
HR	hazard ratio
ICER	incremental cost-effectiveness ratio
LAD	left anterior descending
LBBB	left bundle branch block
LMVD	left main vessel disease
LR	likelihood ratio
MI	myocardial infarction
MIBI	technetium-99m sestamibi
MPI	myocardial perfusion imaging
MPS	myocardial perfusion scintigraphy
MRI	magnetic resonance imaging
MVD	multivessel disease
NICE	National Institute for Clinical Excellence
NIDDM	non-insulin dependent diabetes mellitus
NSF	National Service Framework
OR	odds ratio
PET	positron-emission tomography
PTCA	percutaneous transluminal coronary angioplasty
QALY	quality-adjusted life-year
QoL	quality of life
QUADAS	quality assessment of diagnostic accuracy studies
RCT	randomised controlled trial
ROC	receiver operating characteristic
RR	relative risk
SA	sensitivity analysis
SPECT	single photon emission computed tomography
SRS	summed rest score
SVD	single-vessel disease
TN	true negative
TP	true positive

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure legend or at the end of the table.

Executive summary

Epidemiology and background

Coronary heart disease (CHD), secondary to coronary artery disease (CAD), is the most common cause of death in the UK, resulting in over 120,000 deaths in 2001. Prevalence, which varies across the UK, increases with age; it is estimated that around 2.65 million people in the UK have CHD. Over 378,000 people received inpatient treatment for CHD in NHS hospitals in 2000–01, representing 5% of all inpatient cases in men and 2% in women.

Methods of detecting the presence and assessing the extent of CAD have become increasingly important in informing therapies aimed at reducing mortality and morbidity. Coronary angiography (CA) is considered to be the 'gold standard' for defining the site and severity of coronary artery lesions. CA carries a small (<0.1%) risk of mortality and routine use is inadvisable. Stress (usually treadmill or bicycle exercise) electrocardiography (ECG) is widely used for non-invasive detection of CAD owing to its availability and low cost.

Myocardial perfusion scintigraphy (MPS) may be added to the diagnostic pathway to improve detection of CAD. MPS involves the injection of a radioactive tracer followed by the imaging of its distribution within the myocardium using a gamma camera. Single photon emission computed tomography (SPECT) MPS allows the creation of tomographic images. The images following stress and at rest are compared to assess whether defects are reversible (ischaemia) or fixed (infarction) and to allow the site, extent and depth of abnormalities to be determined. This review assesses the effectiveness and cost-effectiveness of SPECT MPS for the diagnosis and management of angina and myocardial infarction (MI).

Methods

Electronic searches were conducted to identify published and unpublished studies. The following databases were searched: MEDLINE (1966 to October 2002), EMBASE (1980 to week 44, 2002), PREMEDLINE (5 November 2002), BIOSIS (1985 to December 2002), Science Citation Index (1981 to December 2002), The Cochrane Library (Issue 3, 2002), Health Management Information Consortium (1979 to 2002), Health Technology Assessment Database (October 2002) and NHS Economic Evaluation Database (October 2002). Two reviewers independently extracted data and assessed study quality.

A decision tree model (DTM) was used to model the diagnosis decision and a simple Markov model was developed for the management of patients with suspected CAD. The strategies considered in the models were (a) stress ECG, followed by SPECT if stress ECG positive, followed by CA if SPECT positive; (b) stress ECG, followed by CA if stress ECG positive; (c) SPECT, followed by CA if SPECT positive; and (d) CA (invasive test as first option).

Costs for the treatments and interventions within strategies were derived from the literature and expressed in 2001–02 pounds sterling. Quality-adjusted life-year (QALY) weights for the different Markov model states were also obtained from the literature.

Number and quality of studies and direction of evidence

Twenty-one diagnostic and 46 prognostic studies were included plus two studies comparing SPECT with ECG-gated SPECT and one study comparing SPECT with attenuation-corrected SPECT. The quality of the diagnostic studies was assessed using the quality assessment of diagnostic accuracy studies (QUADAS) tool developed by the NHS Centre for Reviews and Dissemination. Most studies gave clearly described selection criteria. In 13 studies the spectrum of patients was not considered to be representative of those who would receive the test in practice. Eight studies described the index test (SPECT) and 12 described the reference standard (CA) sufficiently to permit its replication. In 14 studies the index test was interpreted without knowledge of the reference standard, whereas in nine studies the reference standard was interpreted without knowledge of the index test. It was unclear from 16 studies whether the same clinical data were

available when test results were interpreted as would be available were the test to be used in practice. The diagnostic values of SPECT were generally higher than those of stress ECG, indicating that SPECT provided a better diagnostic performance.

The prognostic studies were all observational studies and were assessed using a checklist designed to assess the methodological quality of both randomised and non-randomised studies. The overall mean score for the prognostic studies was 18.1 (out of a possible 27). The external validity of the studies was low. The evidence from the prognostic studies suggested that SPECT provided valuable independent and incremental information to that provided by stress ECG and/or CA.

Summary of benefits

Of 21 diagnostic studies, 16 included patients referred for suspected or known CAD, three evaluated patients following percutaneous transluminal coronary angioplasty (PTCA), one focused on patients suspected of asymptomatic coronary disease and one evaluated patients with left bundle branch block (LBBB). Among the largest subset of studies (those assessing patients with a suspicion or a history of CAD), sensitivity values tended to be higher for SPECT than for stress ECG whereas specificity values were similar. SPECT also provided higher positive and lower negative likelihood ratios than stress ECG but heterogeneity was evident amongst studies. The subgroup of studies including patients with previous MI tended to report a better diagnostic performance for SPECT than stress ECG, but there were too few studies to assess this reliably.

Twenty-one of the 46 prognostic studies provided general prognostic information. Important factors for predicting cardiac events included the extent and size of the perfusion defect and whether it was fixed or reversible. Normal SPECT scans were associated with a benign prognosis and the option of medical rather than invasive management. Two studies comparing different testing strategies found that a strategy incorporating SPECT with selective referral to CA resulted in lower rates of normal angiograms compared with a strategy of direct referral to CA, suggesting that SPECT was better able to identify lower risk patients for whom CA might be avoided.

The remaining prognostic studies examined the use of SPECT in different patient populations. Studies in relation to gender reported that SPECT provided important, independent prediction of survival in both men and women. Studies performed in patients following MI, and after PTCA and CABG, found that SPECT imaging provided important information for predicting future cardiac events.

Two studies, one diagnostic and the other prognostic, comparing SPECT with ECG-gated SPECT, found in favour of gated SPECT. One study comparing SPECT with attenuation-corrected SPECT reported the latter to be more accurate. Although these findings seem promising it is difficult to draw conclusions from so few studies.

Costs

For the base-case analysis, the results for costs and QALYs for the different strategies were: strategy (a) cost of £5190 and yielding 12.473 QALYs; strategy (b) £5395, 12.481 QALYs; strategy (c) £5529, 12.497 QALYs; and strategy (d) £5929, 12.506 QALYs.

Cost/QALY

The systematic review of economic evaluations indicated that strategies involving SPECT were likely either to be dominant or to produce more QALYs at an acceptable cost. There was less agreement, however, about which of the strategies involving SPECT was optimal.

At the baseline prevalence of 10.5%, SPECT–CA was cost-effective whereas CA, although generating more QALYs, did so at a relatively high incremental cost per QALY (£42,225). At 30% prevalence rates, whereas SPECT–CA was cost-effective, the CA strategy produced more QALYs at a relatively low incremental cost-effectiveness ratio (£7331). At higher prevalence rates (50 and 85%), the SPECT–CA strategy was extendedly dominated by the stress ECG–CA and CA strategies. In other words, over a defined range, if some patients received stress ECG–CA with the rest receiving CA, the costs would be lower and the QALYs higher than if SPECT–CA alone was used.

Sensitivity analyses

The model suggested that, for low prevalence, the incremental cost per unit of output (true positives diagnosed, accurate diagnosis, QALY) for the move from stress ECG–SPECT–CA and from stress

ECG–CA to SPECT–CA might be considered worthwhile. Even after allowing for different values for sensitivity or specificity, the least costly and least effective strategy was stress ECG–SPECT–CA. The sensitivity analysis suggested that the cost-effectiveness of SPECT–CA improved if it was assumed that SPECT results allowed for the adoption of a management strategy without recourse to CA. This would be the case if the assumption of perfect information from CA (sensitivity and specificity equal to 1) were relaxed.

Limitations of the calculations (assumptions made)

Linking diagnostic performance to long-term outcomes required a number of assumptions to be made about both the structure of the model and its parameters. Some assumptions were based on non-UK study data; it is unclear whether such data are applicable to a UK setting. Another assumption concerned the length of time over which the benefits from a diagnostic strategy might accrue. In the base-case analysis, a time period of 25 years was used, although the impact of shorter time horizons was explored in sensitivity analysis. As the time horizon reduced, the incremental cost per QALY increased (as the cost of initial diagnosis and treatment were not offset by survival and quality of life gains).

Other important issues regarding implications

Relatively poor data were available with which to consider longer term costs and consequences. The non-UK data used may not apply to a UK setting.

Notes on the generalisability of the findings

There was a considerable variability in terms of measurement of outcomes, management, setting and patient characteristics. Despite these differences the direction of evidence tended to favour SPECT in terms of test sensitivity, although these conclusions are based on a relatively small number of included studies.

All of the prognostic studies were observational studies and may be biased by unknown confounding factors. Thirty-four of the prognostic studies took place in North America and 12 were set in Europe. SPECT, in a variety of settings and patient populations, provided valuable independent and incremental information to that provided by stress ECG and/or CA. These results may not be generalisable to the UK as many studies were undertaken in countries with different healthcare systems to that of the UK.

Need for further research

Further research is needed on the effectiveness and cost-effectiveness, diagnostically and prognostically, of (a) gated and attenuation-corrected SPECT compared with standard SPECT, (b) standard SPECT compared with stress echocardiography and (c) the uncertainty surrounding the results presented in the cost-effectiveness analysis.

Chapter 1

Aim of the review

This review aims to assess the effectiveness and cost-effectiveness of single photon emission computed tomography (SPECT) myocardial perfusion scintigraphy (MPS) for the diagnosis and management of angina and myocardial infarction (MI). Where the evidence allows, the effectiveness of SPECT in specific patient populations (women and patients following myocardial infarction) is examined.

Chapter 2
Background

Description of underlying health problem

Epidemiology

Coronary heart disease (CHD) is the most common cause of death in the UK, causing over 120,000 deaths in 2001.[1] It is also the most common cause of premature death (death before the age of 75 years) in the UK: 23% of premature deaths in men and 14% of premature deaths in women are from CHD, accounting for nearly 43,000 premature deaths in 2001. Death rates vary across the UK (*Table 1*) and between population groups. They have been falling in the UK since the late 1970s. However, despite this improvement, death rates in the UK are amongst the highest in the world.[1]

Morbidity, in contrast to mortality, is rising, especially in older age groups. There has been a large increase in the number of people reported as having angina. Overall, 5% of men and 4% of women have or have had angina, giving a prevalence of just under 1.2 million people in the UK.[1] The incidence of angina is higher in men than women and increases with age. It is estimated that there are ~335,000 new cases of angina each year.[1]

The number of people experiencing a heart attack has fallen. On average, the incidence of MI, or heart attack, in the UK for those aged 30–69 years is about 600 per 100,000 for men and 200 per 100,000 for women. There were an estimated 275,000 heart attacks in people of all ages in 2001. Prevalence of heart attack increases with age. Combined data from prevalence studies suggest that ~4% of men and 2% of women have had a heart attack, resulting in an estimated 1.2 million people living in the UK who have had a heart attack.[1]

Overall, it is estimated that there are about 2.65 million people living in the UK who have CHD (either through angina or heart attack).[1] Prevalence of CHD is higher in the north than the south of the UK and is higher for lower socio-economic groups. Prevalence also varies between ethnic groups.[1]

Aetiology and pathology

Coronary artery disease (CAD) is the most common cause of CHD.[2] Most CAD is due to the insidious deposition of fibro-lipid (atheromatous) plaques in the large and medium-sized arteries serving the heart. The major complications of CAD are angina pectoris, unstable angina, MI, heart failure and sudden cardiac death due to arrhythmia.[3] Angina is the most common symptom of CAD and is caused by an inadequate supply of blood to the muscle of the heart. This is usually due to the arteries supplying the heart being gradually and progressively narrowed by atheromatous plaques.[4,5] Significant CAD is

TABLE 1 *Age-standardised death rates from CHD per 100,000 population by standard region, 2001*[1]

Region	Men aged 35–74 years	Women aged 35–74 years
United Kingdom	213	68
England	207	70
North	245	87
Yorkshire and Humberside	236	82
North West	254	92
East Midlands	202	71
West Midland	225	80
East Anglia	182	54
South East	180	60
South West	179	55
Wales	237	85
Scotland	261	98
Northern Ireland	228	83

usually defined angiographically as CAD with ≥70% diameter stenosis of at least one major epicardial artery segment or ≥50% diameter stenosis in the left main coronary artery. Lesions of less stenosis can cause angina, but they have less prognostic significance.[4]

Although the precise pathogenesis of CAD is unclear, risk is increased by tobacco use, hypertension, high blood cholesterol levels and diabetes; men and women with diabetes have a 2–5-fold greater annual risk.[3,4,6] Increased CAD risk is also associated with diets high in fat and calories and low in phytochemicals, fibre and vitamins E and C or diets with relatively low levels of omega-3 polyunsaturated fatty acids, obesity, poor stress management and inactivity.[1–4]

Prevention usually begins by addressing these risk factors through smoking cessation, diet modification, exercise and treating co-existing disorders such as diabetes. Cholesterol lowering with 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (statins) has been demonstrated to save lives, prevent unstable angina and MI and decrease coronary revascularisation rates.[3] It has been estimated that there will be a 28% reduction in CHD if government blood cholesterol, inactivity, blood pressure, smoking and obesity targets are met.[1] There is also good evidence that many people with CHD can have their symptoms relieved and/or their prognosis improved by revascularisation through coronary artery bypass surgery (CABG) or percutaneous transluminal coronary angioplasty (PTCA).[4]

Significance in terms of ill-health (burden of disease)

CHD makes a significant impact on every aspect of an individual's life, including their quality of life (QoL), future employment and personal relationships, and also increases their risk of dying prematurely.[5] Furthermore, in addition to human costs, CHD has major economic consequences for the UK. A recent study into the economic burden of CHD in the UK estimated the cost of CHD to the UK healthcare system in 1999 as £1.73 billion, rising to £7.06 billion when informal care and productivity losses were included.[7]

There has been a significant increase in prescriptions for the treatment and prevention of CHD since 1999. The combined cost of lipid-lowering drugs, including statins, and antihypertensive drugs in 2001 was £861 million, an increase of £171 million on the previous year. These drugs represent the first and second most costly classes of drugs in the NHS. As they are recommended in the National Service Framework (NSF), their use is likely to increase. The number of operations to treat CHD has also increased. Around 28,500 CABG operations and just under 39,000 PTCAs are now carried out each year in the UK. Overall, there were over 378,000 inpatient cases treated for CHD in NHS hospitals in 2000–01. These represent 5% of all inpatient cases in men and 2% in women.[1]

Current service provision

Current service provision and variation in services

Most patients with angina are referred to their hospital cardiology outpatient clinic for further assessment. The diagnosis of angina is predominantly based on clinical history. In addition, an exercise tolerance test is usually performed, both to assist with establishing the diagnosis and for risk stratification. A normal test generally excludes significant CAD and those with a positive test are referred for angiography, and a revascularisation procedure should there be significant disease.

The NSF for CHD was announced in March 2000 and sets out 12 national service standards for the prevention, diagnosis and treatment of CHD. These standards include ensuring that people with acute MI or angina receive appropriate assessment, investigations and treatment and to increase capacity so that all who need revascularisation are investigated and treated promptly.[4] Rapid access clinics supported by clear referral criteria and protocols for investigation should lead to more complete, more accurate and more rapid diagnosis and assessment of people with suspected angina.[4] Nationwide roll-out of rapid access chest pain clinics has been established by the NSF as a priority for the NHS, to meet the goal of assessment of new onset chest pain by a specialist within 2 weeks of GP referral. The NSF states that exercise electrocardiography (ECG) and MPS are useful for the assessment of severity of ischaemia; however, only exercise ECG (ExECG) is considered by the NSF within the context of rapid access chest pain clinics.[4]

The use of nuclear cardiology in the UK was investigated in 1988, 1994, 1997 and 2000 by the British Nuclear Cardiology Society (BNCS). The number of MPS studies performed each year

TABLE 2 *International variation and changes over time (between 1998 and 2002) in the use of MPS in known and suspected CAD*

Country	MPS procedures		Growth p.a. 1998–2002 (%)	Rate/1000 2001
	1998	2001		
UK	26,802	45,797	26.7	0.8
Germany	156,675	244,989	16.9	3.0
Italy	114,287	171,164	15.8	3.0
France	141,820	166,581	5.1	2.8
Spain	40,556	74,161	18.6	1.9
Europe	*480,140*	*702,692*	*14.2*	*2.4*
USA	4,088,454	5,588,733	11.0	20.3

Source: Amersham Health, 2003.

TABLE 3 *Target and actual waiting times for MPS at Royal Brompton Hospital, London*

Clinical urgency	Target waiting time	Actual waiting time
Routine	6 weeks	20 weeks
Soon	3 weeks	12 weeks
Urgent	1 week	2 weeks
Immediate	1 day	2 days

Source: Professional Groups' submission to NICE, 2003.

increased over this period; the figure for 2000 was 1.2 studies/1000 population/year compared with 0.86 studies/1000/year in 1997 [Professional Groups' submission to the National Institute for Clinical Excellence (NICE), 2003].[8] Despite nuclear cardiology activity rising, it remains below that recommended by the British Cardiac Society in 1994 as adequate to service the needs of patients with cardiac disease in the UK (2.6 nuclear studies/1000/year). It was significantly below the European average activity in 1994. Amersham Health (February 2003) also reported much lower levels of MPS within the UK than in Germany, Italy, France, Spain or the USA, as shown in *Table 2*. However, they reported levels of MPS activity lower than that reported by BNCS (Professional Groups' submission to NICE, 2003).

MPS activity is unevenly distributed between hospitals. In all but a handful of centres, MPS is performed in general nuclear medicine departments, outside the direct experience of referring cardiologists. Growth in MPS is concentrated in a small number of high-volume centres. These high-volume centres had shorter mean waiting times (17 weeks) than low-volume centres (27 weeks) in the BNCS 2000 survey. The overall mean waiting time was 20 weeks. Many centres prioritise referrals according to clinical urgency, as shown by Royal Brompton Hospital, London, the largest UK centre (*Table 3*) (Professional Groups' submission to NICE, 2003).

There are just over 250 nuclear medicine departments with about 500 gamma cameras in the UK. Over 80% of these cameras have the capability for SPECT.[9] The use of pharmacological stress for nuclear studies is increasing; 77% of studies used pharmacological stress in 2000 compared with 56 and 41% in 1997 and 1994, respectively. Attenuation correction was used in <4% of MPS studies in 1997. This value was concordant with US data suggesting that confidence in this variant of the technology is low.[8] ECG gating of MPS studies was used in 22% of studies in 2000 (Professional Groups' submission to NICE, 2003).

Current service costs

The current service costs may be estimated from the figures contained by Anagnostopoulos and colleagues in the Professional Groups' submission to NICE (2003). The average annual cost of the additional MPS suggested by this group was estimated to be £185 per study. In 2000, 600 studies were carried out per 500,000 population, giving the estimated cost to the NHS of MPS as £111,000 per annum per 500,000 population.

Description of new intervention

MPS uses an intravenously administered radiopharmaceutical tracer to evaluate regional coronary blood flow after stress and at rest. After delivery of the tracer, its distribution within the myocardium is imaged using a gamma camera. In SPECT imaging, the raw data are then processed to obtain tomographic images. Comparison of the distribution of tracer within the myocardium after stress and at rest can reveal the presence or absence of inducible ischaemia and/or infarction. Two tracers are approved and available commercially for use in MPS: thallium (^{201}Tl) and two classes of technetium (^{99m}Tc); sestamibi (MIBI) and tetrofosmin.[10] Technetium tracers now account for >59% of UK MPS practice (Professional Groups' submission to NICE, 2003). These tracers are avidly extracted by cardiac myocytes and hence their initial myocardial distribution reflects a combination of the distribution of myocytes and regional perfusion. Images are compared following stress and rest injections of tracer (or following redistribution for thallium) to assess myocardial viability and perfusion and allow the site, extent and depth of abnormalities to be determined (Professional Groups' submission to NICE, 2003). A problem with SPECT is that of non-uniform soft-tissue attenuation degrading SPECT image quality or creating artefacts that mimic true perfusion abnormalities. Although a variety of indirect measures have been used to reduce the impact of attenuation, the value of these techniques varies. At present, it is recommended that they are used only in experienced centres and attenuation-corrected images should be reviewed alongside non-corrected images.[9–11] The higher energy of technetium is less subject to attenuation than thallium and generally leads to better quality images and permits ECG gating. ECG gating synchronises the image with the patient's ECG. Multiple images are taken over the cardiac cycle. These images are aggregated and displayed by a computer as a continuous cinematic loop, which resembles a beating heart and provides additional functional information. By minimising artifacts caused by cardiac motion, the images are also clearer.[3,10]

Exercise and/or pharmacological agents are used to induce stress. When patients can exercise to develop an appropriate level of cardiovascular stress, exercise stress testing is preferable to pharmacological stress testing. Exercise stress testing is usually done on a conventional treadmill and ECG, heart rate, blood pressure and chest pain are carefully monitored. If no contraindications arise, exercise is continued to >85% of age-predicted maximum. Pharmacological stress testing is particularly useful in patients who cannot exercise. It may also be preferred in patients taking digitalis and those with bundle branch block. Coronary vasodilators, such as adenosine or dipyridamole, increase myocardial blood flow in normal coronary arteries but not in arteries distal to a stenosis. Both dipyridamole and adenosine are safe and well tolerated despite frequent mild side-effects, which occur in 50 and 80% of patients, respectively. These side-effects include angina, arrhythmia, shortness of breath, headache, dizziness, nausea and flushing. Severe side-effects are rare, but both drugs may cause severe bronchospasm in patients with asthma or chronic obstructive lung disease; therefore, they should be used with extreme caution, if at all, in these patients. Aminophylline may reverse these side-effects but is ordinarily not required after adenosine because of the latter's short half-life (<10 seconds).[4,10] Another agent, dobutamine, is a positive inotrope, eliciting a secondary increase in myocardial blood flow and provoking ischaemia. Although side-effects are frequent, dobutamine also appears to be relatively safe. Side-effects include nausea, anxiety, headache, tremors, arrhythmias, atypical chest pain and angina.[4]

Exercise testing is a low-risk investigation even in patients with known CAD, but serious complications occur in 2–4 per 1000 tests. Death may occur at a rate of 1–5 per 10,000 tests.[12] Absolute contraindications to exercise testing include acute MI within 2 days, cardiac arrhythmias causing symptoms or haemodynamic compromise, symptomatic and severe aortic stenosis, symptomatic heart failure, acute pulmonary embolus or pulmonary infarction, acute myocarditis or pericarditis and acute aortic dissection.[4]

Exercise testing must be performed by a healthcare professional who is appropriately trained. If a physician does not perform the test, a physician experienced in cardiovascular stress should be available for consultation, with appropriate accessibility. The healthcare professional conducting the stress test should be current in advanced life-support techniques and appropriate emergency support should be available. Emergency equipment, medications and support personnel should also be available. Processed MPS images should be inspected immediately after acquisition by a radiographer, technician or nuclear physician to identify

technical problems that might require repeat acquisition.[10]

MPS can be used to confirm or exclude the diagnosis of coronary obstruction in patients with clinically suspected CAD or to aid the management of patients with known CAD. In the latter group it can be used to determine prognosis (risk stratification) for example, post MI or before major surgery, to help target strategies for coronary revascularisation by determining the haemodynamic significance of angiographic coronary lesions and to assess the adequacy of percutaneous and surgical revascularisation.[10]

Diagnosis of CAD

Methods of detecting and assessing the extent of CAD have become increasingly important in applying therapies to decrease morbidity and mortality. Coronary angiography (CA) is considered the 'gold standard' for defining the site and severity of coronary artery lesions. However, it is not a reliable indicator of the functional significance of a coronary stenosis, is insensitive in detection of a thrombus owing to the limits to the resolution and ineffective in determining which plaques are likely to lead to an acute coronary event.[4,13] Routine use without prior non-invasive testing is not advisable, partly owing to the high cost but also because of the associated mortality and morbidity. The most serious complications of CA are death (0.1–0.2%), non-fatal MI (0.1%) and cerebrovascular accidents (0.1%). Other complications include arrhythmias, vasovagal reactions, infections and allergic dye reactions.[3,4,9]

ExECG is widely used for non-invasive detection of CAD owing to its ready availability and relatively low cost. However, a normal exercise ECG does not exclude CAD. ExECG is also a poor diagnostic test in low-risk populations owing to its low positive predictive value in a population with a low prevalence of the disease.[4] Imaging techniques such as SPECT are often added to improve detection and/or localisation of exercise-induced ischaemia. The number, size and location of abnormalities on SPECT images reflect the location and extent of functionally significant coronary stenosis.[4,12,14] In addition, ECG-gated SPECT allows for simultaneous imaging of perfusion and function and minimises artefacts caused by cardiac motion.[9]

Prognosis and risk stratification

In each affected person, CAD typically cycles in and out of clinically defined phases: asymptomatic, stable angina, progressing angina and unstable angina or acute MI (AMI). The patient's risk is usually a function of various patient characteristics, including:

- functioning of the left ventricle, most commonly measured by ejection fraction
- extent of inducible ischaemia
- anatomic extent and severity of atherosclerotic involvement of the coronary tree, most commonly measured by the number of diseased vessels
- evidence of a recent coronary plaque rupture, indicating a substantially increased short-term risk for cardiac death or non-fatal MI, and
- age, general health and non-coronary comorbidity.

Risk stratification of patients by stress testing permits the identification of groups of patients with low, intermediate or high risk of subsequent cardiac events.[4]

Exercise tolerance testing has been shown to be of value in assessing the prognosis of patients with CAD. An abnormal exercise ECG identifies a patient at higher risk of suffering new cardiac events in the subsequent year.[4,12] SPECT can also be used to estimate prognosis as it can reveal the extent of the perfusion abnormalities and extent of scarring from previous infarcts. Left ventricular ejection fraction may be measured at rest with ECG-gated SPECT perfusion imaging. Left ventricular ejection fraction may also be measured by radionuclide angiography. However, the ability of ECG-gated SPECT to assess both ventricular function and myocardial perfusion constitutes a definite advantage over radionuclide angiography.[3,4,10,15,16]

CA is used to identify the extent and severity of CAD and left ventricular dysfunction. These are powerful clinical predictors of long-term outcomes. Several prognostic indexes have been used to relate the severity of the disease identified by CA to the risk of subsequent cardiac events. The simplest and most widely used is the classification of disease into one-vessel, two-vessel, three-vessel or left main CAD.[4]

Important patient subgroups

Women

The exercise ECG test is less accurate for the diagnosis of CAD in women and is influenced by multiple factors including exercise capacity and hormonal status.[4,5,15] A growing body of evidence supports the diagnostic value of stress MPS in the detection of CAD in women. Artefacts due to

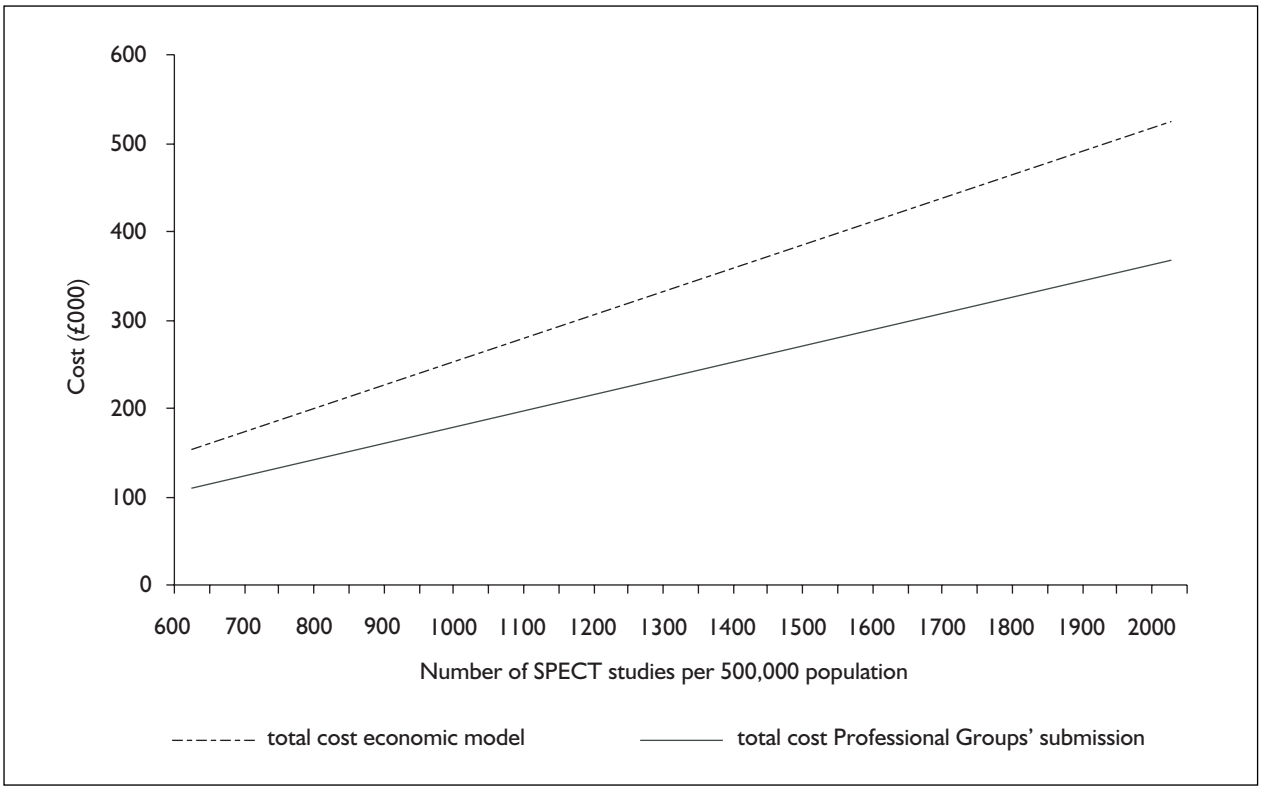

FIGURE 1 *Cost of SPECT to the NHS per 500,000 of the population as the number of studies increases*

breast attenuation, usually manifest in the anterior wall, can be an important consideration in the interpretation of women's scans, especially when thallium is used as a tracer. MIBI may be preferable to thallium scintigraphy for determining prognosis and diagnosing CAD in women with large breasts or breast implants.[4,10,15,16] Attenuation from breast tissue is particularly difficult because of the great individual variability in the amount of breast tissue over different sections of the field of view.[3] Therefore, women should be imaged with chest bands to minimise breast attenuation and to ensure reproducible positioning during later image acquisition. Chest bands can increase attenuation depending upon how they are applied. Thus, careful attention to technique must be used when breasts are strapped.[10] Using ECG-gated SPECT can assist in better differentiation of attenuation artefacts from infarcts and this is considered an effective non-invasive means of evaluating women with an intermediate to high pretest likelihood of CAD.[4,15,16]

People with diabetes

The diagnosis of chronic stable angina in people with diabetes can be particularly difficult because ischaemic symptoms may be reduced by autonomic and sensory neuropathy.[4,6] CAD, in this group, is typically diffuse and this has the potential to intensify ischaemia and make revascularisation more difficult.[6] The exercise ECG is often a less reliable indicator of significant CAD in the diabetic patient and MPS should be considered instead.[15]

After revascularisation

ExECG has a number of limitations after coronary artery bypass surgery. Rest ECG abnormalities are frequent, and more attention must be paid to symptom status, haemodynamic response and exercise capacity. Because of these considerations and the need to document the site of ischaemia, MPS is generally preferred for evaluation of patients in this group.[4] About 30% of patients have an abnormal ECG response on ExECG early after bypass surgery and these patients can be assessed by MPS for possible incomplete revascularisation and the extent of myocardium affected. Patients with initial negative postoperative ExECG who later become positive usually have progressive ischaemia due to graft closure or progression of the disease. MPS can be used to determine the location, extent and severity of such ischaemia. Restenosis is also a frequent problem after successful PTCA and stress SPECT

is thought to be particularly well suited for the functional evaluation of patients after PTCA and as a means of assessing the occurrence of restenosis.[16]

Expected costs

The submission by Anagnostopoulos and colleagues on behalf of various professional groups estimated that the current number of SPECT studies performed within the UK per 500,000 of the population is 600 per year. They suggested that the number of studies might reasonably be expected to expand to 4000 studies per million of the population per year (2000 per 500,000). Using data on the unit cost for a SPECT presented in Chapter 5 (£262 per study) and from the submission (£185 per study), the expected increase in cost to the NHS of an increase in the use of SPECT alone is presented (in *Figure 1*). In this figure, the costs of other investigations such as stress ECG and CA and also the effect on management costs have been excluded. As an illustration of the impact of the potential increase in studies at current rates of utilisation, the cost to the NHS per year of SPECT studies is between £111,000 and £157,200 per 500,000 of the population. At 1250 studies per year per 500,000 of the population, the extra cost to the NHS is between £120,000 and £170,000 per year.

Chapter 3

Effectiveness

Methods for reviewing effectiveness

Search strategy

Initial searches were undertaken to identify relevant systematic reviews, HTA reports and other evidence-based reports. A list of databases and web pages searched is given in Appendix 1.

Electronic searches were conducted to identify published and unpublished studies on the clinical and cost-effectiveness of SPECT MPS for the diagnosis and management of angina and MI. The following databases were searched and full details of the searches are documented in Appendix 1:

1. MEDLINE, 1966–October 2002, EMBASE 1980–2002 (to week 44)

   Separate search strategies were developed for each database and then combined to produce a final strategy that was run concurrently on the two databases. Duplicates were removed from the resulting set using Ovid's de-duplicating feature.

2. PREMEDLINE (Ovid), 5 November 2002
3. BIOSIS (Edina), 1985–December 2002
4. Science Citation Index (Web of Science), 1981–December 2002
5. The Cochrane Library (Issue 3, 2002) (CENTRAL)
6. Health Management Information Consortium (HMIC), 1979–2002
7. HTA Database [NHS Centre for Reviews and Dissemination (CRD)], October 2002.

References of included studies were also checked.

All titles and abstracts identified were assessed to identify potentially relevant items. For all these items, full-text papers were obtained and assessed independently for inclusion by two researchers, using a study eligibility form developed for this purpose. Any disagreements that could not be resolved through discussion were referred to an arbiter.

Inclusion and exclusion criteria

Types of study

Prospective and retrospective primary studies of SPECT MPS compared with any of the interventions noted under Types of interventions below for the diagnosis, prognosis, risk assessment, stratification and management of patients with suspected or confirmed coronary heart disease were included.

The following kinds of reports were not considered: abstracts; case reports; pictorial essays; pilot, volunteer, phantom, animal or safety studies; and studies investigating technical aspects of SPECT MPS or the development of imaging acquisition or processing. Studies reported in non-English languages were noted (details available from the authors) but not included in the review.

Studies with <100 participants were excluded.

Types of participants

Adults with suspected or diagnosed CHD were included, with the exception of pregnant women. Subgroup analysis was planned on:

- patients with previous MI
- women.

The following types of patients were excluded: patients who had received heart transplants; patients with hypertrophic cardiomyopathy, mitral valve prolapse, primary aldosteronism, lupus, acromegaly, cystic fibrosis, severe obstructive sleep apnoea or beta-thalassaemia; and patients who had undergone aortic reconstruction.

The role of MPS in patients unable to exercise or with abnormal resting ECG was not specifically considered.

Types of interventions

The interventions included were:

- SPECT (including ECG-gated SPECT and attenuation-corrected SPECT) as part of the clinical care pathways. Planar imaging was

excluded. The types of radionuclides considered relevant were thallium-201, MIBI and technetium-99m tetrofosmin. The types of stress included were exercise (treadmill or bicycle), pharmacological (adenosine or dipyridamole or dobutamine) or a combination of exercise and pharmacological means.
- Stress ECG.
- CA.

For studies of diagnostic accuracy, the interventions included were SPECT versus stress ECG, with CA as the reference standard test. In situations where CA would be an inappropriate reference standard (e.g. patients with mild clinical symptoms), clinical follow-up was accepted as the reference standard.

For prognostic studies, strategies involving SPECT were compared with strategies that did not. These included:

- stress ECG–SPECT–CA versus stress ECG–CA
- stress ECG–SPECT versus stress ECG alone
- SPECT–CA versus CA alone
- stress ECG versus SPECT versus CA
- SPECT versus CA
- stress ECG versus SPECT.

Studies were also included that compared SPECT with ECG-gated SPECT or attenuation-corrected SPECT (in any combination).

Types of outcomes

For studies of diagnostic accuracy, the types of outcomes included were either the absolute numbers of true positives (TPs), false positives (FPs), false negatives (FNs) and true negatives (TNs), or the sensitivity and specificity values.

For studies of prognosis, risk assessment, stratification and patient management, the types of outcomes included were: mortality; cardiac mortality; non-fatal MI; revascularisation (PTCA/CABG); occurrence of unstable angina; length of survival free of cardiac death; preservation of left ventricular function (after surgery); postoperative complications; number of CAs performed; hospital admissions; and QoL measures.

Data extraction strategy

A data extraction form was used (Appendix 2) to record details of study design, methods, participants, interventions, testing procedures, outcomes and follow-up. Two reviewers extracted data independently. Differences that could not be resolved through discussion were referred to an arbiter. Reviewers were not blinded to the names of study authors, institutions or publications.

Quality assessment strategy

The methodological quality of the diagnostic studies was assessed using the quality assessment of diagnostic accuracy studies (QUADAS) tool developed by the NHS CRD (Appendix 3). The tool did not incorporate a quality score but was a structured list of 12 questions, covering areas such as spectrum and verification bias, with each question to be answered 'Yes', 'No' or 'Unclear'. Two reviewers independently assessed the quality of the included studies. Any differences that could not be resolved through discussion were referred to an arbiter.

The prognostic studies were assessed using the Downs and Black checklist (Appendix 4).[17] The checklist assessed the quality of both randomised and non-randomised studies (including cohort studies). Question 27 (study power) was omitted as studies with <100 participants were excluded. The adapted checklist, therefore, contained 26 questions, covering the following subscales:

- reporting (10 questions)
- external validity (three questions)
- internal validity – bias (seven questions)
- internal validity – confounding (six questions).

An overall score and scores for each of the subscales were calculated. A list of principal confounders and possible adverse events was developed (Appendix 5) to provide supplementary information to questions 5 and 8 of the checklist. The maximum achievable scores within each subscale were reporting (11), external validity (3), internal validity – bias (7) and internal validity – confounding (6), providing an overall maximum achievable score of 27.

Synthesis of diagnostic studies

Diagnostic performance indexes [sensitivity, specificity, accuracy, predictive values and likelihood ratios (LRs)] were extracted and recalculated for each study for both tests (SPECT versus CA and stress ECG versus CA) and 2×2 contingency tables of TP, FP, FN and TN were generated. For studies with missing data (e.g. studies reporting only sensitivity and specificity values), an attempt was made to reconstruct the contingency tables from the data available in the published reports. This proved to be feasible only when the total number of participants, sensitivity, specificity and accuracy were provided or when the total number of participants, sensitivity, specificity and positive and negative LRs were known.

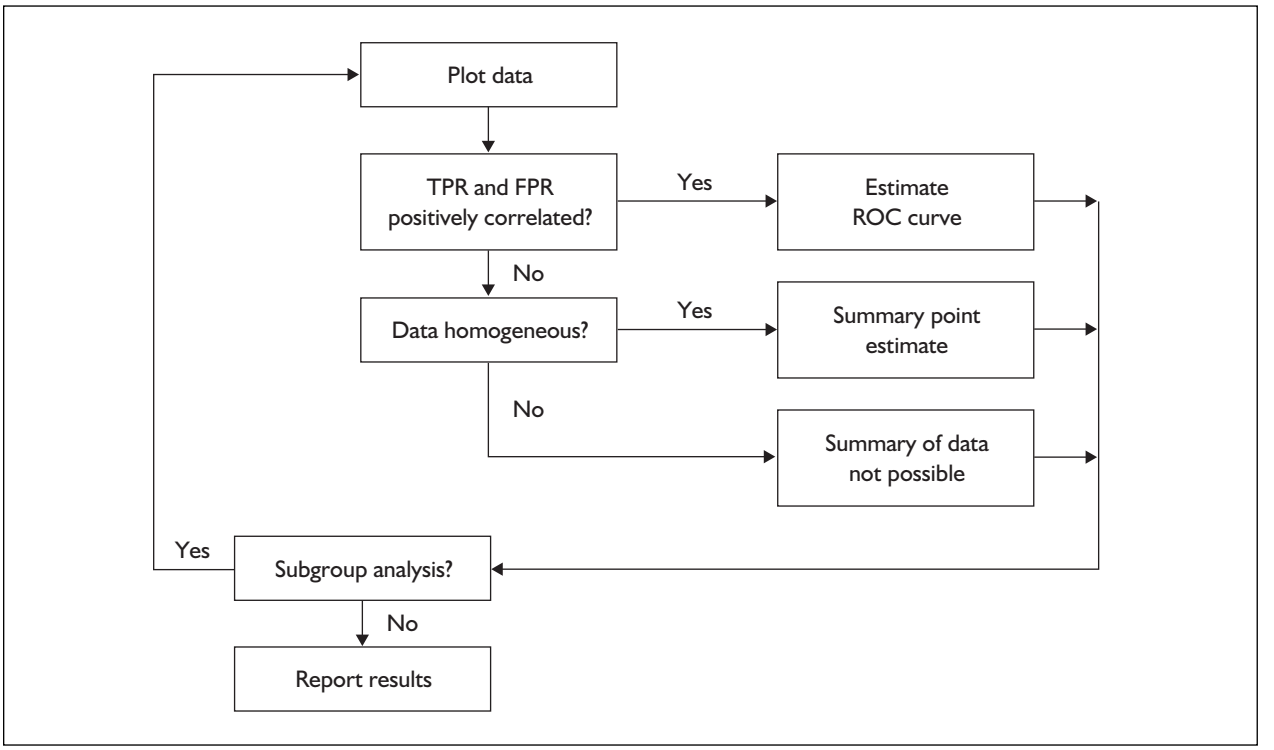

FIGURE 2 *Algorithm for performing a meta-analysis of studies of diagnostic test performance*[19]

Details of the mathematical equations applied are given in Appendix 6. Use of the equations was not always straightforward because in many cases they yielded non-integer values of TPs, FPs, FNs and TNs. This was usually because published values of sensitivity and specificity were often given to just two decimal places. In most cases it was possible to find integer values for the contingency tables that yielded the corresponding published values of sensitivity and specificity using the equations described above. There was, however, a minority of comparisons where no exact match could be found. For example, for Santana-Boado and colleagues' study[18] the chosen integer values for the 2×2 table for the SPECT versus CA comparison yielded a sensitivity of 0.917 but the reported value of sensitivity was 0.91 and not 0.92. In these cases it was decided to use the data providing the closest match to the published values as the differences were not great and it is likely that the discrepancies were caused by rounding errors.

For the statistical analysis of studies of diagnostic performance, the methods suggested by Midgette and colleagues were applied (*Figure 2*).[19] They first advocate plotting the TP rate (sensitivity) versus the FP rate (1 – specificity) and calculating the Spearman's rank correlation coefficient. If a large positive correlation is noted then this is an indication that calculation of a summary receiver operating characteristic (ROC) curve is desirable. In the absence of a positive correlation, heterogeneity between TP and FP rates is tested using a chi-squared test (or an extension of Fisher's exact test if the numbers are too small). If the data are homogeneous it is reasonable to conduct meta-analyses of sensitivities and specificities. Conversely, when data are heterogeneous and not positively correlated, a statistical summary is not recommended.

Summary ROC curves for SPECT versus CA and stress ECG versus CA were considered when a positive correlation between the TP and FP rates was found and when a sufficient number of studies was available for each comparison. A ROC curve for a test with high discriminatory power should yield a 'path' close to the top-left corner of the plot, indicating that it provides a high true-positive rate and a low false-positive rate. It is commonly used to describe how different test cut-off points affect the trade-off between sensitivity and specificity.[20,21]

If appropriate, it was planned to calculate pooled estimates of sensitivity and specificity and their confidence intervals for both SPECT and stress ECG for each comparison.[19,20] These are averages of the sensitivities and specificities weighted by the inverse of the variance of each study. Studies for

TABLE 4 *Number of hits and items selected by database*

Database searched	Number of hits screened	Number selected	Included studies
Multifile search (MEDLINE, EMBASE) after de-duplication	4079	1072	62
PREMEDLINE	28	2	2
BIOSIS	1284	228	33
SCI	2295	290	51
The Cochrane Library: CENTRAL	116	14	4
HTA	63	6	0
HMIC	36	0	0

which 2 × 2 table information could not be obtained could not be included in this analysis.

In addition, meta-analyses of positive and negative LRs were conducted where appropriate. LRs express the probability that a certain test result is expected in a patient with the target disorder, as opposed to a patient without the disorder. For instance, an LR of 10 means that a positive test result is 10 times more likely to occur in patients having the disease under investigation (i.e. CAD) than in healthy subjects. An LR of one means that the test result does not provide diagnostic information and does not change the probability of the target condition. LRs below one indicate a decrease in the probability of the target condition (the smaller the likelihood ratio, the greater the decrease). As LRs are identical in construction to risk ratios, meta-analyses of positive and negative LRs were conducted using a random effects model and treated as meta-analyses of risk ratios.[20]

Results

Quantity and quality of research available

Titles and abstracts of >7000 reports were identified by the search strategies (*Table 4*). After de-duplication, 1198 reports were identified as possibly relevant to the appraisal. Of these, 242 were papers written in a foreign language and were noted but not included. Hence, 956 reports were selected for further assessment and full-text articles, where possible, obtained. An additional 16 articles were obtained by scanning the reference lists of these papers. Of these 970 reports, 70 met the final inclusion criteria. No studies addressing the important issue of the role of SPECT in preoperative risk assessment were identified that met our inclusion criteria.

Most of the included studies were identified in more than one database. In comparing the results of the MEDLINE, EMBASE, BIOSIS and SCI searches, 24 reports were identified in all of them and a further 21 were identified in all in which they were indexed. Only nine papers were not identified by the MEDLINE/EMBASE search, five of which were identified by SCI; one by SCI and BIOSIS; and three were not identified from any electronic searches. One of these was identified from the subsequent search for cost-effectiveness studies and the other two were identified from references. The titles and abstracts of these three articles gave no indication that exercise ECG or CA had been undertaken.

Number and type of studies included

In total, 70 studies, published in 71 reports, met the inclusion criteria for studies of effectiveness. There were 21 diagnostic studies,[18,22–41] 46 prognostic studies,[42–88] two studies assessing ECG-gated SPECT[89,90] and one study assessing attenuation-corrected SPECT.[91]

Diagnostic studies

Overall, the quality of the diagnostic studies varied according to the methodological parameters considered (*Table 5*). Most studies clearly described their selection criteria. However, in the majority of studies spectrum bias was evident. In nearly all studies the index and reference tests were carried out within a period short enough to be reasonably sure that the target condition would not change in the intervening period. Eight of the studies described the SPECT test in sufficient detail to permit its replication; 12 described the reference standard test in sufficient detail to permit its replication. In the majority of studies the index test was interpreted without knowledge of the reference standard, and in just under half of the studies the reference standard was interpreted without knowledge of the index test. It was unclear from most studies whether the same clinical data were available when test results were interpreted as would be available if the test were to be used in practice.

TABLE 5 *Summary of quality assessment of included diagnostic studies*

NHS CRD QUADAS		Yes	No	Unclear
1.	Was the spectrum of patients representative of the patients who will receive the test in practice?	3	13	5
2.	Were selection criteria clearly described?	17	2	2
3.	Is the reference standard likely to correctly classify the target condition?	21	0	0
4.	Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?	17	1	3
5.	Did the whole sample, or a random selection of the sample, receive verification using a reference standard of diagnosis?	19	2	0
6.	Did patients receive the same reference standard regardless of the index test result?	21	0	0
7.	Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?	21	0	0
8a.	Was the execution of the index test described in sufficient detail to permit replication of the test?	8	13	0
8b.	Was the execution of the reference standard described in sufficient detail to permit its replication?	12	7	2
9a.	Were the index test results interpreted without knowledge of the results of the reference standard?	14	0	7
9b.	Were the reference standard results interpreted without knowledge of the results of the index test?	9	0	12
10.	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	1	4	16
11.	Were uninterpretable/intermediate test results reported?	10	8	3
12.	Were withdrawals from the study explained?	18	3	0

Prognostic studies

Table 6 summarises the overall and subscale scores from the quality assessment of the 46 included prognostic studies. The overall mean score for all prognostic studies was 18.1 (out of a possible 27). The mean scores within each of the subscales were as follows: reporting, 9.2 (out of a possible 11); external validity, 0.6 (out of a possible 3); internal validity – bias, 5.1 (out of a possible 7); and internal validity – confounding, 3.2 (out of a possible 6).

The overall methodological quality of the prognostic studies was good. The quality of the studies in terms of reporting of information was very good, but the external validity was low, with the internal validity higher in terms of preventing bias than in preventing confounding of study participants. Within the reporting subscale almost all items scored highly; the exception was that only three studies gave details of adverse events related to the intervention. On the whole, patients were not representative of the population from which they were drawn. In only one study were the staff, places and facilities where the patients were treated judged to be representative of the treatment that most patients would receive; in all other studies this was either not the case or could not be determined from the information provided.

Most items scored well on the internal validity – bias subscale. Given the nature of the intervention, blinding of participants was not possible; however, in just under half of the studies an attempt was made to blind those assessing test results. In nearly all studies the statistical tests used to assess the main outcomes were judged to be appropriate and the main outcomes were deemed to be valid and reliable. Many studies used survival analysis in an attempt to adjust for different lengths of patient follow-up. Most items scored well on the internal validity – confounding subscale. The majority of studies gave details of the period over which participants were recruited and reported losses to follow-up. Most studies adjusted for confounding in their analyses. The moderate overall score for the internal validity – confounding subscale was mainly a reflection of the lack of randomised trials.

Characteristics of studies

Appendix 7 provides details of the characteristics of the included studies (study design, participants,

TABLE 6 *Summary of quality assessment of included prognostic studies*

Study	Reporting (max. 11)	External validity (max. 3)	Internal validity – bias (max. 7)	Internal validity – confounding (max. 6)	Overall score (max. 27)
Amanullah, 1998[42]	10	2	4	3	19
Amanullah, 1999[43]	10	0	6	2	18
Ben-Gal, 2001[44]	11	2	3	4	20
Berman, 1995[45]	8	0	5	2	15
Candell-Riera, 1998[46]	10	0	6	4	20
Chatziioannou, 1999[47]	10	2	6	4	22
Chiamvimonvat, 2001[48]	10	0	6	4	20
Diaz, 2001[49]	9	0	6	4	19
Gibbons, 1999[50]	8	0	5	3	16
Giri, 2002[51]	10	0	6	2	18
Groutars, 2000[52]	9	2	6	3	20
Hachamovitch, 1996[53]	10	2	5	4	21
Hachamovitch, 1998[54]	9	2	5	3	19
Hachamovitch, 2002[55]	9	2	4	3	18
Ho, 1999[56]	9	0	5	3	17
Iskandrian, 1993[57]	6	0	4	1	11
Iskandrian, 1994[58]	9	0	4	4	17
Kamal, 1994[59]	10	2	4	4	20
Lauer, 1996[60]	10	0	6	3	19
Lauer, 1997[61]	10	0	6	4	20
Machecourt, 1994[62]	10	0	6	4	20
Marie, 1995[63]	10	0	6	4	20
Marwick, 1999[64]	10	2	6	4	22
Miller, 1998[65]	10	0	5	3	18
Miller, 2001[66]	8	0	5	3	16
Mishra, 1999[67]	8	0	5	2	15
Nallamothu, 1995[68]	9	2	4	2	17
Nallamothu, 1997[69]	9	0	6	3	18
O'Keefe, 1998[70]	10	1	5	4	20
Olmos, 1998[71]	10	0	6	4	20
Pancholy, 1994[72]	10	0	6	3	19
Pancholy, 1995[73]	9	0	5	3	17
Parisi, 1998[74]	5	0	5	3	13
Pattillo, 1996[75]	9	0	5	3	17
Schinkel, 2002[76]	11	2	6	4	23
Shaw, 1999[77]	9	0	6	3	18
Shaw, 1999[78]	4	0	4	2	10
Stratmann, 1994[80]	10	2	6	4	22
Travin, 1995[81]	9	0	4	3	16
Underwood, 1999[82]	10	1	5	2	18
Vanzetto, 1999[83]	10	0	6	4	20
Vanzetto, 1999[84]	9	0	5	4	18
Wagner, 1996[85]	10	0	4	3	17
Zanco, 1995[86]	8	0	4	2	14
Zellweger, 2002[87]	10	0	4	3	17
Zerahn, 2000[88]	10	1	5	3	19
Overall mean score	9.2	0.6	5.1	3.2	18.1

test characteristics and outcomes) for the diagnostic and prognostic studies.

Diagnostic studies

All diagnostic studies, apart from that of Vaduganathan and colleagues,[41] were observational studies comparing the diagnostic accuracy of SPECT versus stress ECG, with CA as the reference standard test. The study by Vaduganathan and colleagues[41] did not include stress ECG as a comparator, as the entire patient population presented with left bundle branch block (LBBB), for which the stress ECG test is non-diagnostic. Seventeen studies were prospective in design[18,22,24,26–33,35–38,40,41] while four were retrospective.[23,25,34,39] Thirteen

studies[18,22–25,29–31,33,36–38,41] employed a consecutive method of recruitment.

Five studies took place in the USA,[23,29,37,39,41] two each in Belgium,[28,36] France,[22,24] Japan[27,31] and Greece[38,40] and one each in Austria,[35] Canada,[25] Finland,[34] Italy,[26] Spain,[18] Sweden,[32] Taiwan[30] and the UK.[33] Nine studies gave details of the period during which they were carried out.[18,22,25–27,31,34,40,41] Of these, the study duration was from a minimum of 2 years[22,31,34] to a maximum of 9 years.[26]

The total number of people analysed in the studies was 4453; the smallest study contained 100 patients[33] and the largest 606 patients.[40] In 14 studies the number of patients analysed was <200.[18,22,25–30,32–36,41]

Across studies, the ages of the participant group as a whole ranged from <45 years[25] to a mean of 64 years. All studies apart from one[34] gave details of the numbers of men and women included; there was a total of 2868 men (66%) and 1468 women (34%). In two studies the participants consisted wholly of women[23,25] and in one they consisted wholly of men.[32]

Of the 4453 patients analysed, 960 (22%) had had a previous MI, 492 (11%) had previously undergone PTCA and 103 (2%) had previously undergone CABG. In the studies by Beygui and colleagues,[22] Hamasaki and colleagues[27] and Hecht and colleagues,[29] all patients had previously undergone PTCA.

In 15 studies the tracer used was Tl-201,[22–24,26,27,29–32,34,35,37–40] in five it was MIBI[18,25,28,33,36] and in one both Tl-201 and MIBI were use.[41] Fifteen studies used exercise as the means of stress, eight by treadmill[23,29,35–40] and six by bicycle,[22,27,28,30–32] and four studies used both exercise and pharmacological stress.[18,26,33,41] In two studies the pharmacological stress consisted of dipyridamole,[18,26] in one it was dobutamine or arbutamine[33] and in one[41] it was adenosine or dobutamine. Two studies[25,34] gave no information as to the type of stress used.

In 10 studies[18,22,24,26,27,30–32,35,36] image interpretation was visual, in eight[23,28,29,33,37–39,41] both visual and quantitative methods were used and in three[25,34,40] the method of image interpretation was not stated.

Prognostic studies

Of the 46 prognostic studies, four were comparative observational studies,[67,77,78,82] but only one of these was prospective.[77] Of the 42 cohort studies, 23 were prospective, 13 retrospective and for six it was unclear. Twenty-six studies employed a consecutive method of recruitment. Thirty-four studies used Cox proportional hazards regression analysis. Across studies, the mean length of follow-up ranged from a minimum of 3 months[67] to a maximum of 6.7 years.[49] The mean length of follow-up was 2 years or longer in 28 studies. One study gave no details of the length of follow-up.[42]

Thirty-three studies took place in the USA, four in France, two in The Netherlands, one each in Canada, Denmark, Germany, Israel, Italy and Spain and one study was a European multicentre study,[82] involving two hospitals from each of France, Germany, Italy and the UK. Thirty-one studies gave details of the period in which they were carried out. Of these, the study duration was from a minimum of 5 months[47] to a maximum of 10 years.[50]

The total number of people analysed in the studies was 83,138; the smallest study contained 106 patients[85] and the largest 11,249 patients.[77] In eight the number of patients analysed was <200. The mean age of the participant group ranged from 53 years[63,86] to 66 years.[78] All studies apart from one[88] gave details of the numbers of men and women included; there was a total of 50,041 men (61%) and 32,559 women (39%). In two studies the participants consisted wholly of women[73,78] and in one they consisted wholly of men.[74]

Of the patients analysed, 11,535 (14%) had suffered previous MI, 4806 (6%) had previously undergone PTCA and 5997 (7%) had previously undergone CABG. In four studies all patients had experienced previous MI.[48,81,85,87] In the study by Ho and colleagues[56] all patients had previously undergone PTCA and in the studies by Miller and colleagues[65] and Nallamothu and colleagues[69] all patients had previously undergone CABG.

In 23 studies the tracer used was Tl-201, in eight it was MIBI, in 12 both tracers were used, in one it was Tc-99m tetrofosmin and in two the type of tracer used was not stated. Twenty-seven studies used exercise as the means of stress. Three studies used pharmacological stress, one with dipyridamole,[48] one with adenosine[59] and one with dobutamine–arbutamine.[76] Twelve studies used both exercise and pharmacological stress; in four of these studies the pharmacological stressor

was adenosine,[43,52,54,87] in four it was dipyridamole,[44,62,64,83] in two studies both agents were used,[51,69] in one study[70] adenosine or dipyridamole or dobutamine were used and one study[77] did not give details of the pharmacological stressor used.

In 23 studies image interpretation was visual, in six it was quantitative, in 12 both visual and quantitative methods were used and in five the method of image interpretation was not stated.

Tabulation of results

The results of the studies are given in Appendix 8. All *p* values are those reported by the authors.

Discussion of results

Diagnostic studies

Twenty-one studies of variable methodological quality assessed the diagnostic accuracy of SPECT and stress ECG. Of these studies, 16 included patients referred for suspected or known CAD, three evaluated patients following PTCA, one focused on patients with asymptomatic coronary disease and one evaluated patients with LBBB.

Among the 16 studies assessing patients with a suspicion or a history of CAD, the largest subset, sensitivity values tended to be higher for SPECT than for stress ECG and the specificity values were similar. SPECT also provided higher positive LRs and lower negative LRs than stress ECG. The subgroup of studies including patients with previous MI tended to give better diagnostic performance but there were too few studies to assess this reliably. There were too few studies to assess the influence of other patients' characteristics on the accuracy of SPECT and stress ECG.

Comparison of SPECT and stress ECG in the other subsets of patients was also limited by the small number of included studies.

Prognostic studies

Twenty-one of the 46 prognostic studies provided general prognostic information. Sixteen of the general prognostic studies employed the Cox proportional hazards regression model. The Cox model is a regression technique that can be used to statistically adjust for baseline and other variables, such as those relating to the different tests used (for example, abnormal SPECT scan or ST-segment depression ≥ 1 mm) in order to calculate which variables in the model are predictive of the outcomes considered, over time. The variables included in the models generally appeared to be appropriate, although they differed to some extent across studies. Appendix 9 contains a list of the variables predictive of outcomes in studies employing multivariate analysis.

Four studies assessed the value of SPECT imaging in patients following MI.[48,81,85,87]

Six studies examined different gender issues relating to the use of SPECT, including post-test gender bias in referral for CA,[60] the value of SPECT in predicting cardiac mortality in men and women,[64] a comparison of two different testing strategies in women,[78] the incremental prognostic value of SPECT over clinical and exercise data in women compared with men,[54] the independent and incremental prognostic value of SPECT in women[73] and the prognostic value of SPECT compared with ExECG in men.[74]

Three studies assessed the value of SPECT in patients following revascularisation.[56,65,69] The remaining studies assessed the usefulness of SPECT in a number of specific areas/patient populations, including patients with an acute coronary syndrome, patients with diabetes, patients with left main/three-vessel disease, normal SPECT scans, asymptomatic coronary disease, high ExECG tolerance, normal resting ECG, prediction of early revascularisation and effect of age on referral.

Several studies relied on the same patient population. The study by Marwick and colleagues[64] reported the same patient population as that reported by Shaw and colleagues.[79] For the purposes of this review, the former paper was considered the primary report of the study and the latter to be part of the same study. Although two other studies by Shaw and colleagues[77,78] contain different numbers of patients, it is likely that at least some of the same patients were included in both reports. This is probably also the case with the three studies by Hachamovitch and colleagues.[53–55] The two studies by Iskandrian and colleagues,[57,58] although containing different numbers of patients, report substantially the same patient population, the only difference being that the group of patients with normal CA were excluded from the 1993 paper.[57] Vanzetto and colleagues[84] reported a subset of the patient population reported by Machecourt and colleagues,[62] although this was not completely a subset as patients with previous revascularisation were excluded from the former study but not from the latter.

TABLE 7 *Sensitivity, specificity and accuracy for SPECT from the 16 included studies*

Study	*N*	Stenosis (%)	Tracer	Previous MI	Sensitivity	Specificity	Accuracy
Chae, 1993[23]	243	≥ 50	Tl-201	Yes	0.71	0.65	–
Daou, 2002[24]	338	≥ 50	Tl-201	Yes	0.63	0.77	0.66
De, 2002[25]	55	≥ 70	MIBI	Not stated	0.67	0.30	0.39
Gentile, 2001[26]	132	≥ 60	Tl-201	No	0.93	0.54	0.86
Hambye, 1996[28]	128	≥ 50	MIBI	No	0.82	0.76	–
Huang, 1992[30]	179	≥ 50	Tl-201	Yes	0.87	0.80	0.86
Kajinami, 1995[31]	251	≥ 75	Tl-201	Not stated	0.82	0.59	0.71
Karlsson, 1995[32]	170	≥ 50	Tl-201	Yes	0.68	0.65	–
Khattar, 1998[33]	100	≥ 50	MIBI	Yes	0.68	0.72	0.70
Koskinen, 1987[34]	100	≥ 50	Tl-201	Not stated	0.90	0.10	0.82
Mairesse, 1994[36]	129	≥ 50	MIBI	No	0.76	0.65	0.72
McClellan, 1996[37]	303	≥ 50	Tl-201	Yes	0.70	0.57	0.69
Michaelides, 1999[38]	245	≥ 70	Tl-201	No	0.93	0.82	0.91
Nallamothu, 1995[39]	321	≥ 50	Tl-201	Not stated	0.80	0.68	0.79
Psirropoulos, 2002[40]	606	≥ 50	Tl-201	Yes	0.93	0.44	0.73
Santana-Boado, 1998[18]	163	≥ 50	MIBI	No	0.91	0.90	0.91

TABLE 8 *Sensitivity, specificity and accuracy for stress ECG from the 16 included studies*

Study	*N*	Stenosis (%)	Previous MI	Sensitivity	Specificity	Accuracy
Chae, 1993[23]	243	≥ 50	Yes	0.62	0.60	0.61
Daou, 2002[24]	338	≥ 50	Yes	0.47	0.64	0.51
De, 2002[25]	55	≥ 70	Not stated	0.44	0.73	0.65
Gentile, 2001[26]	132	≥ 60	No	0.85	0.58	0.80
Hambye, 1996[28]	128	≥ 50	No	–	–	–
Huang, 1992[30]	179	≥ 50	Yes	0.50	0.76	0.54
Kajinami, 1995[31]	251	≥ 75	Not stated	0.74	0.75	0.74
Karlsson, 1995[32]	170	≥ 50	Yes	0.65	0.65	–
Khattar, 1998[33]	100	≥ 50	Yes	0.70	0.41	0.57
Koskinen, 1987[34]	100	≥ 50	Not stated	0.63	0.80	0.65
Mairesse, 1994[36]	129	≥ 50	No	0.42	0.83	0.57
McClellan, 1996[37]	303	≥ 50	Yes	–	–	–
Michaelides, 1999[38]	245	≥ 70	No	0.66	0.88	0.69
Nallamothu, 1995[39]	321	≥ 50	Not stated	0.46	0.59	0.49
Psirropoulos, 2002[40]	606	≥ 50	Yes	0.92	0.43	0.73
Santana-Boado, 1998[18]	163	≥ 50	No	0.67	0.71	0.69

Two studies, one diagnostic[90] and one prognostic[89] compared SPECT with gated SPECT, and one study[91] compared SPECT with attenuation-corrected SPECT.

Assessment of effectiveness

Critical review and synthesis of information – diagnostic studies

Results of the comparative diagnostic performance of SPECT and stress ECG are presented separately for the following identified categories of studies: (a) patients with suspected CAD; (b) patients with previous PTCA; (c) patients with asymptomatic coronary disease; and (d) patients with LBBB.

Patients with suspected CAD

Sixteen studies assessed the diagnostic accuracy of SPECT and stress ECG for the detection of coronary artery disease. In 12 studies the angiographic definition of CAD was ≥ 50% stenosis, in one study ≥ 60% stenosis and in three studies ≥ 70% stenosis. Two studies enrolled only women, one study only men and two studies provided results for women and men separately. The studies varied considerably with respect to size, characteristics of participants and methods.

Estimate of sensitivities and specificities

For each study the sensitivity, specificity and accuracy values for SPECT and stress ECG are shown in *Tables 7* and *8*, respectively. Only studies

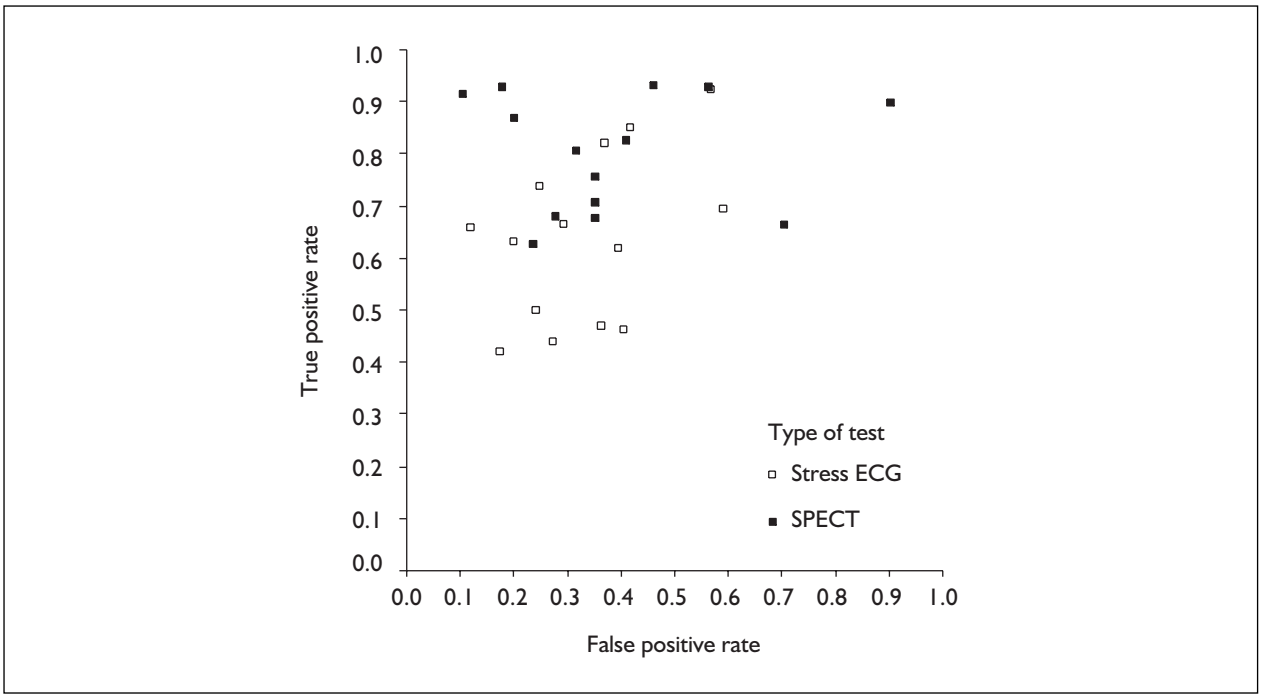

FIGURE 3 *Scatter plot of TP rate against FP rate showing the performance of SPECT and stress ECG*

in which patients underwent both SPECT and stress ECG, and where CA was used as the reference standard, were included in the analyses.

Owing to the significant heterogeneity among studies (chi-squared test: $p < 0.001$ in each case), no attempt was made to provide weighted averages of sensitivities and specificities for either SPECT or stress ECG.

Sensitivity and specificity values of both tests, SPECT and stress ECG, were available for only 14 studies. Two studies provided sensitivity and specificity for SPECT only and have been excluded from subsequent analyses. Sensitivity ranged from 0.63 to 0.93 (median 0.81) for SPECT and from 0.42 to 0.92 (median 0.65) for stress ECG. Specificity ranged from 0.10 to 0.90 (median 0.65) for SPECT and 0.41 to 0.88 (median 0.67) for stress ECG.

Figure 3 is a scatter plot showing the TP rate (sensitivity) and FP rate (1 – specificity) for SPECT and stress ECG for each of the 14 included studies. In qualitative terms, SPECT studies sat higher in the plot than stress ECG studies, suggesting a better diagnostic performance of SPECT. However, it was not possible to test this statistically.

Five of the 16 included studies clearly excluded patients with previous MI. Sensitivity and specificity values were available for both tests for only four studies (*Figure 4*). Sensitivity ranged from 0.76 to 0.93 (median 0.92) for SPECT and from 0.42 to 0.85 (median 0.66) for stress ECG and specificity ranged from 0.54 to 0.90 (median 0.72) for SPECT and from 0.58 to 0.88 (median 0.74) for stress ECG (*Table 9*). The range of sensitivity for the 10 studies that did include patients with previous MI was 0.63 to 0.93 (median 0.76) for SPECT and 0.44 to 0.92 (median 0.63) for stress ECG. Specificity for these ten studies ranged from 0.10 to 0.80 (median 0.65) for SPECT and from 0.41 to 0.80 (median 0.65) for stress ECG (*Table 10*).

Summary ROC curves for SPECT and stress ECG studies were not generated as the Spearman's rank correlation coefficient for the TP rates and FP rates in the 14 studies of SPECT was –0.02, indicating that the two values were not positively correlated. One explanation for the pattern observed is that the majority of the studies used the same cut-off for the definition of CAD (i.e. >50% stenosis). A ROC curve might have been more easily discerned if more of the studies had used different cut-off values. For stress ECG the Spearman's rank correlation coefficient was 0.46. Although a positive correlation was observed for stress ECG, it was decided not to produce summary ROC curves for either test.

It was also not possible to perform meaningful subgroup analyses to determine the differential

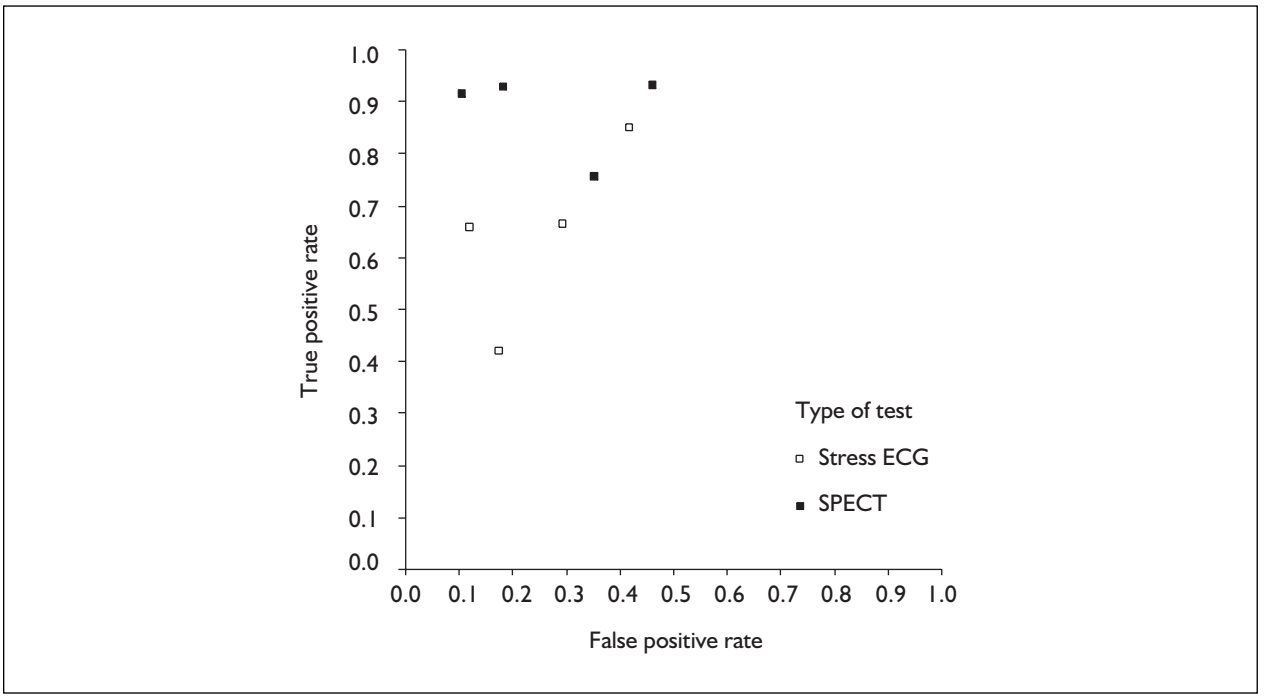

FIGURE 4 *Scatter plot of TP rate against FP rate for the subgroup of studies excluding patients with previous MI*

TABLE 9 *Sensitivity and specificity of studies excluding patients with previous MI*

	Sensitivity: median (range)	Specificity: median (range)
SPECT (n = 4)	0.92 (0.76–0.93)	0.74 (0.54–0.90)
Stress ECG (n =4)	0.66 (0.42–0.85)	0.77 (0.58–0.88)

TABLE 10 *Sensitivity and specificity of studies including patients with previous MI*

	Sensitivity: median (range)	Specificity: median (range)
SPECT (n = 10)	0.76 (0.63–0.93)	0.65 (0.10–0.80)
Stress ECG (n = 10)	0.63 (0.44–0.92)	0.77 (0.41–0.80)

effect of SPECT and stress ECG in patient subgroups (e.g. gender of participants, angiographic definition of CAD, patients taking beta-blockers) owing to the relatively small number of studies within each subgroup.

Likelihood ratios

LRs for both tests could be calculated for 12 of the 16 included studies (*Table 11*). The range of positive LRs was 0.95–8.99 (median 2.33) for SPECT and 1.14–5.60 (median 2.06) for stress ECG. It is worth noting that all positive LVs were <10 in both tests. Combining positive LRs using a random effects model yielded a higher overall estimate for SPECT (2.29, 95% CI 1.68 to 3.12) (*Figure 5*) compared with stress ECG (1.83, 95% CI 1.48 to 2.2.6) (*Figure 6*). However, for both tests there was significant heterogeneity among positive LRs ($p < 0.001$). Moreover, the overall estimate of 2.29 for SPECT was outside the 95% CIs of five of the 12 included studies. Similarly, the overall estimate of 1.83 for stress ECG was outside the 95% CIs of six of the 12 included studies.

Negative LRs ranged from 0.09 to 1.12 (median 0.29) for SPECT and from 0.18 to 0.91 (median 0.57) for stress ECG. Values varied considerably among studies. Two studies showed a negative LR for SPECT <0.1 (0.09) and LRs for SPECT

TABLE 11 *LRs for SPECT and stress ECG*

	Author(s)	*N*	Positive LR	Negative LR
SPECT	Daou, 2002[24]	338	2.71	0.48
	De, 2002[25]	55	0.95	1.12
	Gentile, 2001[26]	132	2.04	0.12
	Huang, 1992[30]	179	4.35	0.16
	Kajinami, 1995[31]	251	2.03	0.29
	Khattar, 1998[33]	100	2.49	0.44
	Koskinen, 1987[34]	100	1.00	1.00
	Mairesse, 1994[36]	129	2.18	0.37
	Michaelides, 1999[38]	245	5.26	0.09
	Nallamothu, 1995[39]	321	2.57	0.28
	Psirropoulos, 2002[40]	606	1.65	0.16
	Santana-Boado, 1998[18]	163	8.77	0.09
Stress ECG	Daou, 2002[24]	338	1.29	0.83
	De, 2002[25]	55	1.63	0.77
	Gentile, 2001[26]	132	2.04	0.25
	Huang, 1992[30]	179	2.08	0.66
	Kajinami, 1995[31]	251	3.00	0.35
	Khattar, 1998[33]	100	1.18	0.74
	Koskinen, 1987[34]	100	3.17	0.56
	Mairesse, 1994[36]	129	2.43	0.70
	Michaelides, 1999[38]	245	5.60	0.39
	Nallamothu, 1995[39]	321	1.14	0.91
	Psirropoulos, 2002[40]	606	1.63	0.18
	Santana-Boado, 1998[18]	163	2.28	0.47

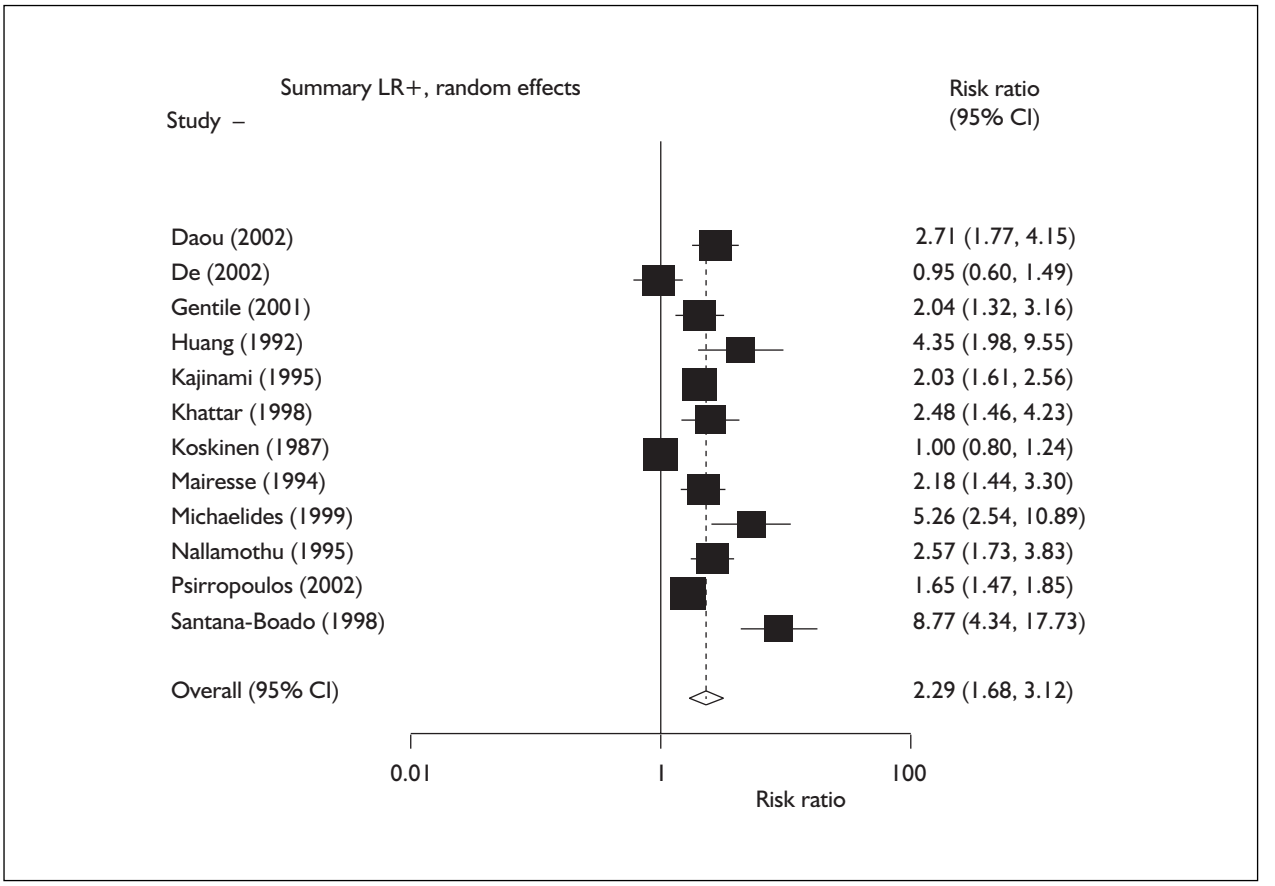

FIGURE 5 *Meta-analysis of positive LRs for SPECT (only studies with data for both SPECT and stress ECG)*

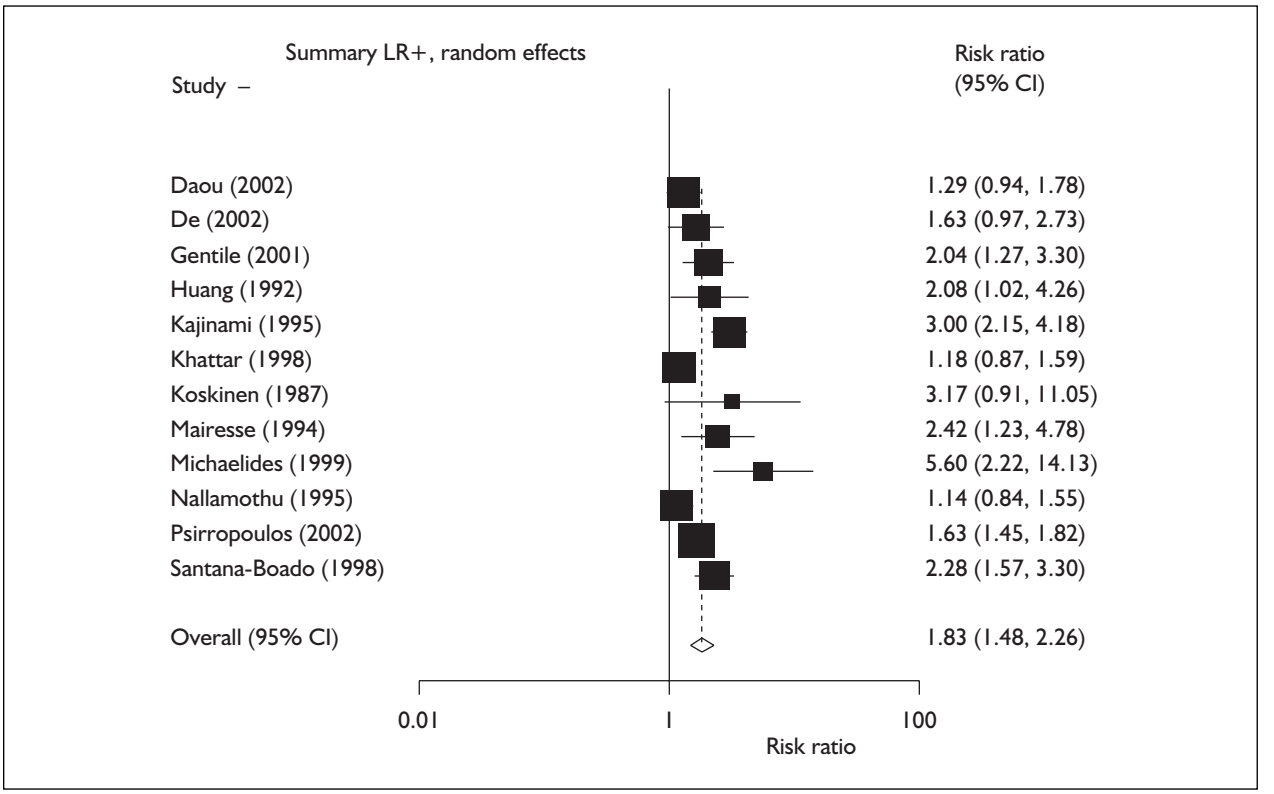

FIGURE 6 *Meta-analysis of positive LRs for stress ECG (only studies with data for both SPECT and stress ECG)*

tended to be smaller than those for stress ECG. The summary estimate of the negative LRs for SPECT was 0.25 (95% CI 0.17 to 0.37) (*Figure 7*) and 0.51 (95% CI 0.39 to 0.67) (*Figure 8*) for stress ECG, but again heterogeneity was evident among included studies ($p < 0.001$).

Patients who underwent PTCA

Three studies evaluated the diagnostic performance of SPECT and stress ECG in the detection of restenosis after PTCA.

Diagnostic data for both SPECT and stress ECG are shown in *Tables 12* and *13*. The range of sensitivities was 0.63–0.93 (median 0.79) for SPECT and 0.51–0.83 (median 0.52) for stress ECG. The range of specificities was 0.77–0.78 (median 0.77) for SPECT and 0.62–0.65 (median 0.64) for stress ECG.

Figure 9 shows the TP and FP rates for SPECT and stress ECG for the three included studies.

Two studies provided separate results for complete and partial revascularisation (*Table 14*). Sensitivity values of SPECT and stress ECG were similar whether or not revascularisation was complete. In contrast, specificity was lower for both tests for partial revascularisation. No further subgroup analyses could be performed.

Patients with asymptomatic coronary disease

One study[35] assessed the diagnostic performance of SPECT and stress ECG for the detection of CAD in asymptomatic patients. Patients were divided into two groups. Group I consisted of 46 asymptomatic patients with angiographically proven coronary stenosis and group II consisted of 60 asymptomatic patients with low-probability CAD. The sensitivity of SPECT for group I was 0.91 and the specificity was 0.96. The sensitivity of stress ECG in the same group was 0.43. In group II, the sensitivity of SPECT for CAD was 0.94 but its specificity was only 0.75, lower than in group I. The sensitivity of stress ECG was 0.70 and its specificity 0.56. Overall, SPECT performed better than stress ECG.

Patients with left bundle branch block

One study assessed the diagnostic value of SPECT during exercise and pharmacological stress in patients with LBBB and no diagnostic ECG for CAD.[41] A total of 383 consecutive patients were enrolled in the study. SPECT was performed in conjunction with exercise in 206, adenosine in 127 and dobutamine in 50 patients. Presence of

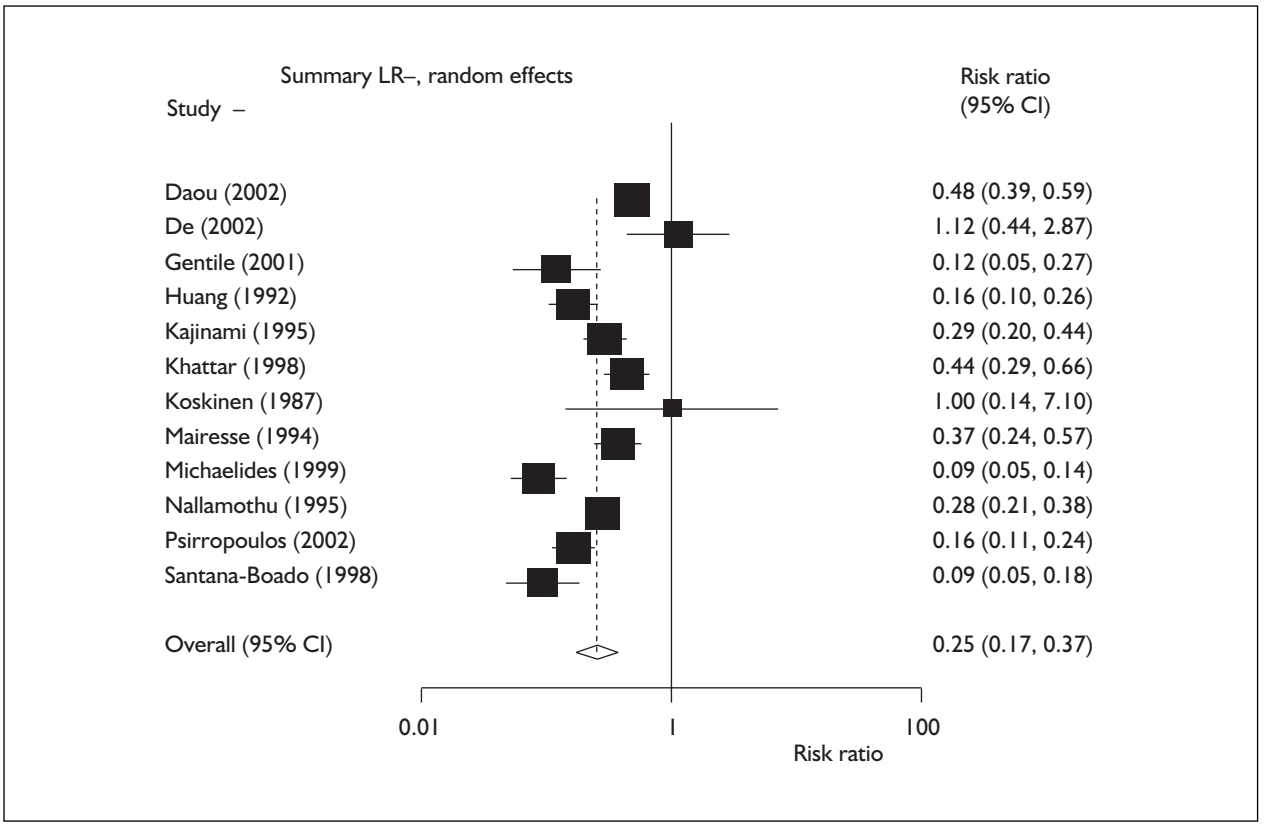

FIGURE 7 *Meta-analysis of negative LRs for SPECT (only studies with data for both SPECT and stress ECG)*

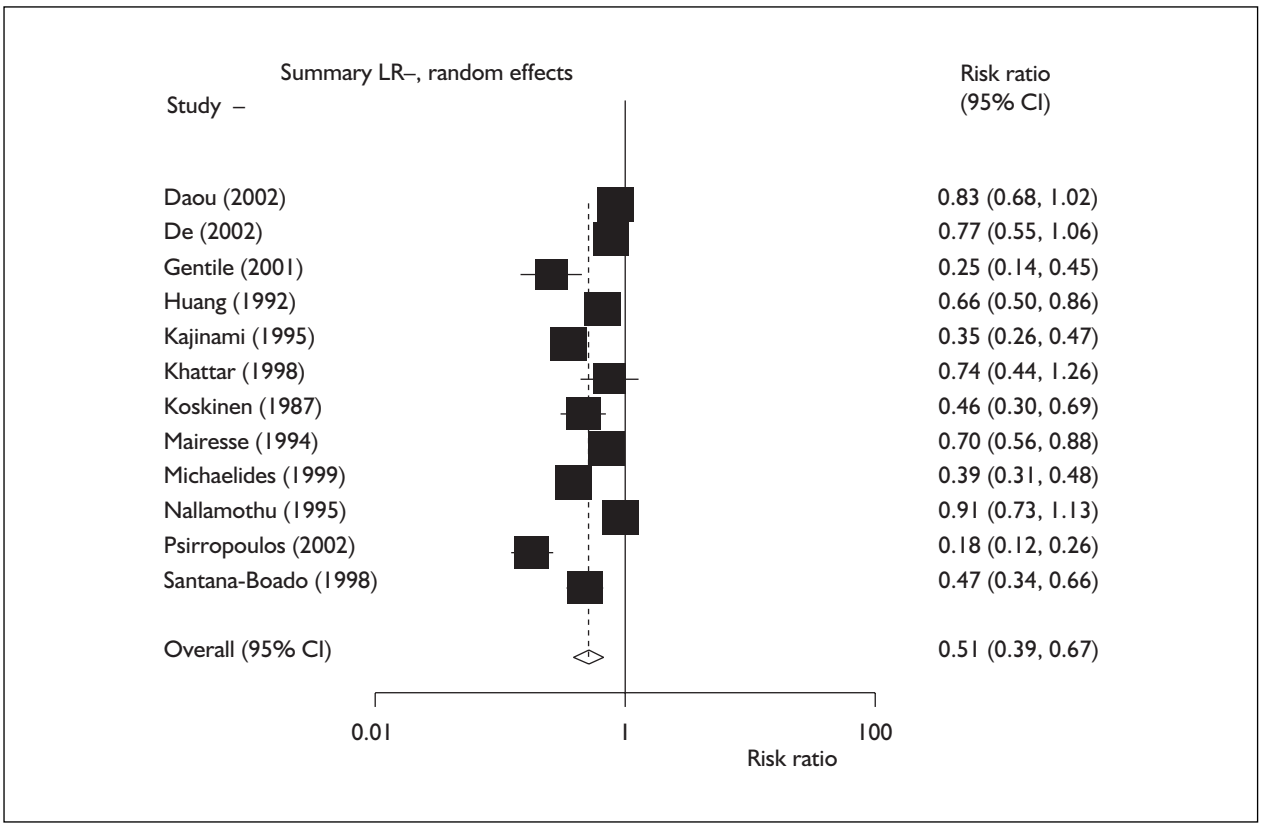

FIGURE 8 *Meta-analysis of negative LRs for stress ECG (only studies with data for both SPECT and stress ECG)*

TABLE 12 *Sensitivity, specificity and accuracy for SPECT from the three studies on PTCA*

Study	*N*	Stenosis (%)	Tracer	Previous MI	Sensitivity	Specificity	Accuracy
Beygui, 2000[22]	179	≥ 50	Tl-201	Yes	0.63	0.77	0.71
Hamasaki, 1996[27]	125	≥ 50	Tl-201	No	0.79	0.78	0.78
Hecht, 1990[29]	116	≥ 50	Tl-201	Yes	0.93	0.77	0.86

TABLE 13 *Sensitivity, specificity and accuracy for stress ECG from the three studies on PTCA*

Study	*N*	Stenosis (%)	Previous MI	Sensitivity	Specificity	Accuracy
Beygui, 2000[22]	179	≥ 50	Yes	0.51	0.62	0.58
Hamasaki, 1996[27]	125	≥ 50	No	0.83	0.65	0.72
Hecht, 1990[29]	116	≥ 50	Yes	0.52	0.64	0.57

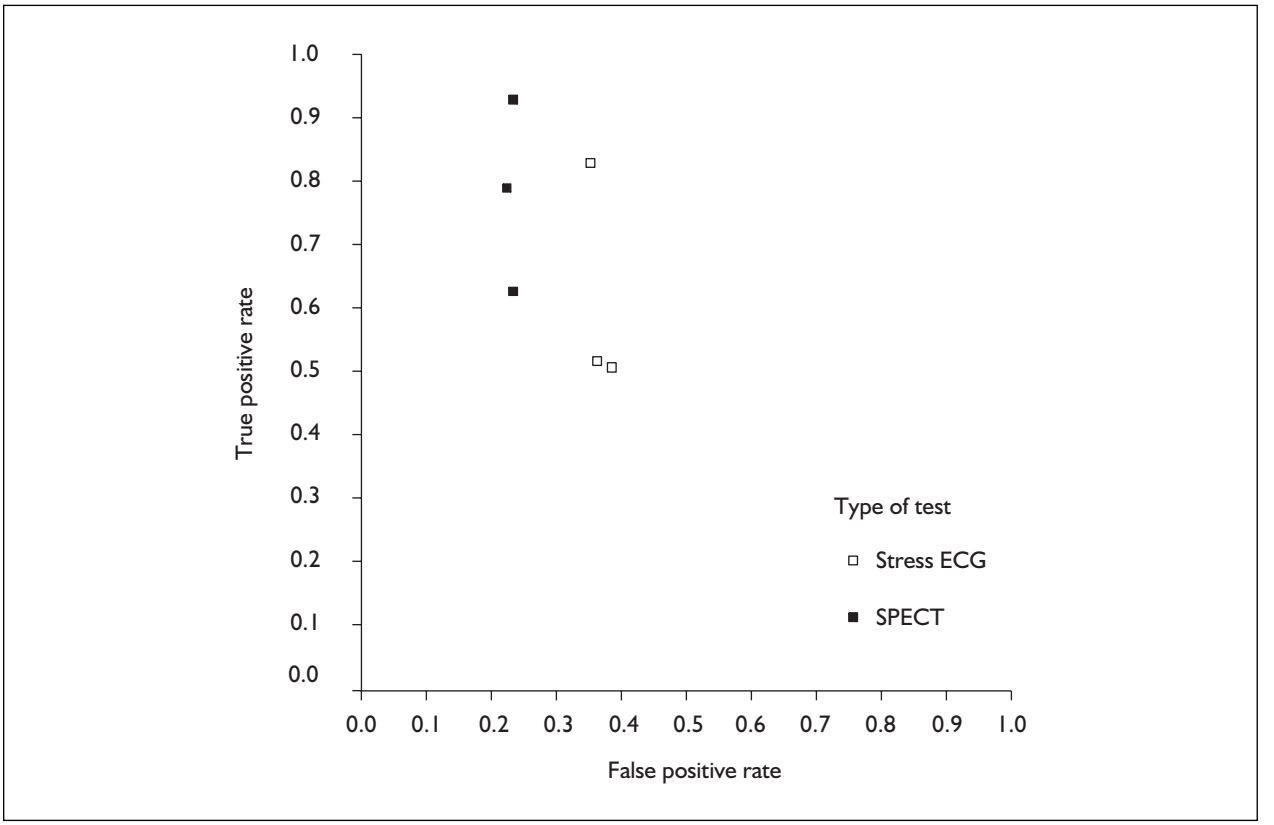

FIGURE 9 *SPECT and stress ECG scatter plot for detection of restenosis after PTCA*

stenosis was confirmed by CA within 1 month of SPECT. Exercise, adenosine and dobutamine SPECT had similar sensitivity for left anterior descending (LAD) coronary artery >50% stenosis (0.88, 0.79 and 1.0, respectively). The specificity and positive predictive value were 36 and 51% for exercise SPECT compared with 0.81 and 0.85 for adenosine and 0.80 and 0.90 for dobutamine. Pharmacological stress was shown to be more specific than exercise SPECT in the diagnosis of LAD coronary artery stenosis.

Critical review and synthesis of information – prognostic studies

Results of prognostic performance are presented separately for the following categories of studies: (a) general prognostic studies; (b) value of SPECT for the determination of prognosis in specific groups at risk of CAD; (c) use of SPECT in specific areas/patient populations; and (d) ECG-gated and attenuation-corrected SPECT.

TABLE 14 *Diagnostic data on complete and partial revascularisation*

	Study	*N*	Sensitivity	Specificity	Accuracy
SPECT complete revascularisation	Beygui, 2000[22]	150	0.62	0.84	0.76
	Hecht, 1990[29]	89	0.93	0.76	0.87
Stress ECG complete revascularisation	Beygui, 2000[22]	150	0.45	0.61	0.56
	Hecht, 1990[29]	89	0.52	0.64	0.57
SPECT partial revascularisation	Beygui, 2000[22]	58	0.67	0.58	0.60
	Hecht, 1990[29]	27	0.93	0.77	0.85
Stress ECG partial revascularisation	Beygui, 2000[22]	58	0.71	0.51	0.59
	Hecht, 1990[29]	27	0.50	0.62	0.56

TABLE 15 *Rate of revascularisation of SPECT–CA compared with CA*

Study	SPECT-CA: *n/N* (%)		CA: *n/N* (%)		*p*
Shaw, 1999[77]					
Low[a]	*n/N* not stated	(14)	*n/N* not stated	(16)	0.0001
Intermediate[a]		(13)		(27)	
High[a]		(16)		(30)	
Mishra, 1999[67]	123/2022 (6)		1692/4572 (37)		<0.001
Underwood, 1999[82]	10/48 (21)		33/75 (44)		<0.001

[a] Low, pretest probability of CAD ≤ 15%; intermediate, pretest probability of CAD ≤ 16–59%; high, pretest probability of CAD ≥ 60%.

General prognostic studies

Comparative observational studies

The three comparative observational studies[67,77,82] had quality assessment scores of 15, 18 and 18, respectively. One study was prospective[77] and two were retrospective.[67,82] Two compared a strategy of direct CA with a strategy of SPECT and selective use of CA.[67,77] A third study compared four strategies: stress ECG–CA (strategy one); stress ECG–SPECT-CA (strategy two); SPECT–CA (strategy three); and CA (strategy four).[82] The results of these studies are summarised in Appendix 8.

For the comparison of SPECT–CA with CA it was reported that the SPECT–CA strategy was associated with statistically significant lower rates of normal angiograms (33 versus 43%[77] (p value not reported) and 18 versus 33%,[67] $p < 0.001$). It was also reported that the rate of subsequent revascularisation was lower with the SPECT–CA strategy (*Table 15*). In the case of Shaw and colleagues, it was reported that this reduction in revascularisation rates was not accompanied by differences in rates of cardiac death or MI at 3 years.[77]

Underwood and colleagues[82] reported that there were significantly more deaths in patients in the SPECT–CA and CA strategies (10.4 and 5.3%, respectively) compared with the stress ECG–CA and stress ECG–SPECT-CA strategies (2.8 and 1.5%, respectively) ($p < 0.05$). They reported, however, that there were no significant differences in the total number of hard events (i.e. unstable angina, MI, death) between strategies (stress ECG–CA, $n = 15$; stress ECG–SPECT-CA, $n = 12$; SPECT–CA, $n = 8$; CA, $n = 13$). In patients with CAD, differences were evident between strategies with regard to freedom from symptoms, with stress ECG–CA having the lowest freedom from symptoms (37%) and CA the highest (64%) ($p = 0.05$). The prognostic power for the information available at the point of diagnosis differed between strategies ($p < 0.0001$), with SPECT being the single most powerful predictor of prognosis and having incremental value even when stress ECG or an angiogram had already been performed. Underwood and colleagues concluded that, although 2-year patient outcome was the same, strategies using SPECT were at least as effective as those not using SPECT.

Cohort studies

There were 12 prospective studies,[49,54,57,58,62,71,75,79,80,84,86,88] six of which employed consecutive recruitment. The study by Shaw and colleagues[79] was considered a subset of the study by Marwick and colleagues[64] that is considered in the section on the impact of gender on the effectiveness of SPECT-based strategies (see p. 29). There were also three retrospective studies[63,66,68] and three which did not provide information as to whether they were prospective or retrospective, although they used a consecutive method of recruitment.[55,59,76] The quality scores varied from between 14 to 23 out of 27. The results of these studies are detailed in Appendix 8.

Not all studies completely reported the structure of the statistical models used to assess the incremental value of SPECT. Furthermore, the variety of -independent predictors and the different outcome measures used hampered the comparison of the different studies.

The value of SPECT was compared with prognostic factors from other tests (stress ECG and angiography) and other clinical or natural history data in all cohort studies. In all except one study it was concluded that the addition of SPECT yielded incremental prognostic value. In the study by Miller and colleagues, which aimed to assess whether worsening clinical, exercise or SPECT variables could identify high-risk patients, the only prognostic variable that was predictive of cardiac death, MI or revacularisation was worsening clinical status.[66]

Variables shown by the included studies to be statistically significant independent predictors of death, cardiac death, cardiac events (cardiac death and non-fatal MI) and other outcomes are shown in *Tables 16–19*. What these tables do not show is the relative added value of these independent predictors, so where data have been reported in the form of odds ratios (ORs) or relative risks (RRs) this has been noted. Except where otherwise noted, an OR, RR or hazard ratio (HR) >1 indicates a greater risk of the outcome. The significance of these results is that if it is possible to predict who is at risk of these events, it may be possible to improve those patients' management and so avoid serious events (e.g. death or MI). For each study these data are summarised in Appendix 8.

Both Diaz and colleagues and Miller and colleagues concluded that SPECT had independent prognostic value even after accounting for treadmill variables,[49,66] heart rate recovery and other potential confounders (*Table 16*).[49] In terms of all cause death, Diaz and colleagues reported that SPECT provided little additional prognostic information at low risk and high risk, but for patients categorised as intermediate risk (impaired functional capacity or an abnormal heart rate recovery) SPECT was useful in stratifying risk.

All eight studies that reported on prediction of cardiac death concluded that the addition of SPECT provided important independent or incremental information. The most common conclusions were that the extent of perfusion defects was the most powerful predictor of events.[57,58,62,63,79] SPECT was reported as providing predictive information incremental to clinical and exercise data[76,84] or angiography.[58] Furthermore, SPECT had incremental value in patients at low,[62,76,84] intermediate[84] and high risk.[76]

Five studies also reported relative effectiveness data that enabled the importance of SPECT as an independent predictor of cardiac death to be judged.[63,71,76,84,88] In the study by Marie and colleagues,[63] when radionuclide left ventricular ejection fraction was excluded from the model, the SPECT total exercise defect extent was associated with a statistically significant ability to predict those most at risk of cardiac death (RR 1.06, 95% CI 1.03 to 1.08). Olmos and colleagues[71] in a model comprising clinical exercise test and SPECT variables, reported the perfusion defect size on a SPECT scan to be the strongest predictor of cardiac mortality (OR 1.41, 95% CI 1.1 to 1.82). In the study by Schinkel and colleagues,[76] two models were assessed. In the first an abnormal scan provided incremental ability to predict those at highest risk of cardiac death (HR 8.2, 95% CI 3.2 to 21) and in the second both reversible defects (HR 2.1, 95% CI 1.2 to 3.5) and fixed defects (HR 2.2, 95% CI 1.2 to 4.0) were incremental predictors of cardiac death. Similarly, Vanzetto and colleagues[84] and Zerahn and colleagues[88] reported that three or more abnormal SPECT segments (OR 4.83, 95% CI 2.22 to 9.54)[84] and fixed defects on a SPECT scan (RR 2.55, 95% CI 1.43 to 4.55)[88] were independent predictors of cardiac death.

Ten studies reported data on the independent predictive power of SPECT to identify patients at risk of cardiac death or non-fatal MI (*Table 18*). In all cases the statistical models used appeared to include appropriate clinical, ExECG and SPECT variables, although they differed between studies.

TABLE 16 *Statistically significant predictors of all cause death by multivariate analysis*

Study	Independent predictors[a]
Diaz, 2001[49]	High-risk SPECT scan; poor or fair fitness; abnormal heart rate recovery; intermediate-risk SPECT scan
Miller, 2001[66]	Worsening category summed stress score; worsening clinical status; worsening category summed reversibility score

[a] Ordered in terms of strongest evidence of statistical significance.

TABLE 17 *Statistically significant predictors of cardiac death by multivariate analysis*

Study	Independent predictors[a]
Iskandrian, 1994[58]	Combination of CA and SPECT data; extent of perfusion abnormality; extent of CAD by angiography[a]
Machecourt, 1994[62]	Abnormal SPECT scan; male gender; previous MI[a]
Marie, 1995[63]	Age; total exercise defect extent on SPECT scan
Olmos, 1998[71]	Perfusion defect size on SPECT scan
Schinkel, 2002[76]	Abnormal SPECT scan; congestive heart failure; diabetes mellitus; smoking; age[a]
Vanzetto, 1999[84]	≥ 3 abnormal segments; previous MI, non-diagnostic stress ECG; strongly positive ECG[a]
Shaw, 2000[79]	Pretest clinical risk; territories with infarction; territories with ischaemia[a]
Zerahn, 2000[88]	dPRP <2500 mmHg/min; fixed defects on SPECT scan; LBBB; digoxin; age ≥ 60 years[a]

[a] Ordered in terms of strongest evidence of statistical significance.
dPRP; the circulatory response expressed as the product of the increase in heart rate between rest and maximum workload and the difference in systolic blood pressure between rest and maximum workload.

TABLE 18 *Statistically significant predictors of cardiac events (cardiac death or non-fatal MI) by multivariate analysis*

Study	Independent predictors
Hachamovitch, 1998[54]	Improved prediction on addition of SPECT scan data to prescan information
Hachamovitch, 2002[55]	Summed stress score
Iskandrian, 1993[57]	Extent of total perfusion abnormality and extent of ischaemic abnormality and left ventricular dilation; extent of CAD and ejection fraction; gender; exercise work load[a]
Kamal, 1994[59]	Size of perfusion abnormality
Machecourt, 1994[62]	Submaximal exercise stress test; abnormal SPECT scan; previous MI; male gender[a]
Marie, 1995[63]	Age; total exercise defect extent on SPECT scan[a]
Miller, 2001[66]	Worsening clinical status
Olmos, 1998[71]	Abnormal SPECT scan
Pattillo, 1996[75]	Size of perfusion defect on SPECT scan
Stratmann, 1994[80]	Abnormal SPECT scan, or reversible defect when 'abnormal scan' replaced by 'fixed' and 'reversible' defect

[a] Ordered in terms of strongest evidence of statistical significance.

TABLE 19 *Statistically significant predictors of other outcome measures by multivariate analysis*

Outcome	Study	Independent predictors
Cardiac events and revascularisation	Miller, 2001[66]	Worsening clinical status
Non-fatal MI	Vanzetto, 1999[84]	≥ 3 abnormal segments on SPECT scan; 1–2 abnormal segments; previous MI; presence of risk factors[a]
Cardiac mortality, non-fatal MI, unstable angina	Zanco, 1995[86]	Abnormal SPECT scan, or reversible defect on SPECT; extent of the defect (>4 out of 18 segments) when 'abnormal scan' replaced by 'reversible defect' and 'extent of defect'

[a] Ordered in terms of strongest evidence of statistical significance.

All except one[66] concluded that SPECT provided additional independent or incremental information. Furthermore, in three studies it was reported that SPECT provided additional information to that provided by CA variables[57,59,63] and in one study the addition of CA variables to a strategy already including SPECT and stress ECG was no more powerful at predicting cardiac events.[75]

Three studies reported relative effectiveness data.[63,71,80] Marie and colleagues,[63] in a Cox multivariate analysis including SPECT and all other baseline variables, reported that the total extent of SPECT defects (RR 1.05, 95% CI 1.02 to 1.07) and age (RR 1.07, 95% CI 1.02 to 1.13) were directly predictive of cardiac events. Olmos and colleagues[71] reported that the main multivariate predictor of cardiac events from clinical, stress ECG and SPECT variables was an abnormal SPECT scan (OR 2.76, 95% CI 1.08 to 7.07). Stratmann and colleagues,[80] in a Cox multivariate analysis including clinical, exercise test and SPECT variables, reported that an abnormal SPECT scan was a statistically significant predictor of cardiac events (non-fatal MI or cardiac death) (RR 11.9, 95% CI 1.6 to 89.4). Five studies explicitly reported the comparison of a diagnostic strategy of clinical data and stress ECG compared with clinical data, stress ECG and SPECT.[55,62,63,71,75] All reported that the addition of SPECT to this pathway improved the ability to predict cardiac events.

Three studies also considered the independent or incremental prognostic value of SPECT in terms of other outcome measures (*Table 19*).[66,84,86] In the study by Mille and colleagues,[66] the only independent predictor of cardiac events and revascularisation from stress ECG, SPECT and clinical variables was worsening clinical status of patients.

Vanzetto and colleagues[84] reported on the incremental value of SPECT in predicting non-fatal MI. They found that the only independent predictors were SPECT and clinical variables. This study also reported that the most important predictors were three or more abnormal segments on a SPECT scan (OR 4.97, 95% CI 2.15 to 11.49), one to two abnormal SPECT segments (OR 4.20, 95% CI 1.93 to 9.14) followed by previous MI (OR 2.89, 95% CI 1.78 to 4.69) and the presence of one or more risk factors (OR 2.50, 95% CI 1.50 to 4.17).

Zanco and colleagues[86] considered two models: in model A, the abnormality of the SPECT scan was compared with stress ECG, clinical and other parameters such as age and gender, and in model B the 'abnormality of the SPECT scan' was replaced by the variables 'the presence of a reversible defect' and 'the extent and the score of the stress defect'. With model A, only 'abnormality of the SPECT scan' (RR 17.62. 95% CI 2.3 to 13.65%) was an independent predictor of increased risk. In model B, the two SPECT variables were the only independent predictors of increased risk, with the presence of a reversible defect having the largest effect (RR 5.11, 95% CI 1.5 to 17.36) with a smaller effect for a defect in more than four segments (RR 3.27, 95% CI 1.2 to 9.22). Zanco and colleagues concluded that SPECT was useful for risk stratification of CAD patients and that the presence of a reversible perfusion defect or an extensive defect appeared to indicate a clear increase in the likelihood of subsequent cardiac events.

Value of SPECT for the determination of prognosis in specific groups at risk of CAD

A number of studies also considered the prognostic value of SPECT in specific groups who were being diagnosed for CAD. These studies are considered below.

Gender

Six studies examined gender issues relating to the use of SPECT[53,60,64,73,74,78] and had quality assessment scores of 21, 19, 22, 17, 13 and 10, respectively. Three studies were prospective,[60,64,78] two were retrospective[53,73] and one[74] provided no information as to whether it was prospective or retrospective. Five studies employed a consecutive method of recruitment.[53,60,64,73,78] Of these studies, one examined post-test gender bias in referral for CA, two compared the value of SPECT in men and women, two considered the additional prognostic value of SPECT in women and one the additional prognostic value of SPECT in men.

Lauer and colleagues[60] examined the extent of post-test gender bias in referral for CA. In their Cox multivariate analysis they reported that, as for the whole population, an abnormal thallium SPECT scan (RR 2.34, $p = 0.08$) was predictive of increased mortality in women. Gender was not significantly associated with cardiac death (for women, RR 0.77, 95% CI 0.31 to 1.87) after adjusting for age, referral for CA and an abnormal SPECT scan. An abnormal SPECT scan was predictive of increased risk of fatal cardiac events (adjusted RR 4.37, 95% CI 2.03 to 9.40). The most

powerful predictor for referral for CA was an abnormal SPECT scan (OR 16.05, 95% CI 12.43 to 20.73); other independent predictors included anginal chest pain (OR 5.42, 95% CI 4.08 to 7.20), ventricular tachycardia (OR 4.95, 95% CI 3.01 to 13.17) and hypotensive response (OR 2.21, 95% CI 1.18 to 4.15). In logistic regression analysis with adjustment for SPECT results and age, women were as likely as men to be referred for CA (adjusted OR 1.00, 95% CI 0.75 to 1.34). Lauer and colleagues concluded that gender-related differences in referral for CA after treadmill SPECT were explained by a higher rate of abnormal tests in men. They detected no evidence of a post-test gender bias.

Marwick and colleagues[64] compared the value of SPECT for predicting cardiac mortality in men and women and sought to determine whether this information was independent from that available from clinical evaluation and exercise testing. They reported that the ST-segment response to stress predicted outcome in women but not men. They noted that independent predictors of cardiac death differed to some extent by gender. In women, clinical risk index and the number of territories with fixed defects were associated with increased risk of cardiac death, but the number of territories with stress-induced defects and exercise capacity were not. In men, clinical risk index, exercise time and the number of territories with stress-induced or fixed defects (but not ST-segment response) were associated with cardiac mortality. Marwick and colleagues concluded that the results of SPECT were important, independent predictors of survival in both women and men.

Hachamovitch and colleagues[53] examined whether SPECT added similar incremental prognostic information over that provided by clinical and exercise data in women compared with men and whether SPECT, incorporated in a clinical strategy, could be used to effectively risk stratify both men and women. Cox multivariate analysis was undertaken to determine the incremental prognostic value in men and women of three models: (1) clinical variables; (2) clinical plus exercise variables; and (3) clinical plus exercise plus SPECT variables. Model 3 provided significantly more prognostic information than model 2 in both men and women ($p < 0.0001$). In order to compare directly the relative discrimination of SPECT in men versus women with respect to identifying high-risk subjects, the areas under the ROC curves were compared for predicting events using the summed stress score. The area under the curve in women (0.84 ± 0.03) was significantly greater than that for men (0.71 ± 0.03, $p < 0.0005$ versus women), demonstrating that SPECT was better able to identify women at high risk of future events than men independently of baseline event rates, diagnostic thresholds or selection bias. SPECT also risk stratified women more effectively than men (OR for an event with abnormal versus normal scan results: men 4.4, women 22.8, Mantel–Haenszel OR 6.8, 95% CI 4.7 to 9.7). This significant difference in ability to stratify patients was present between men and women in all prescan likelihood categories, demonstrating that this effectiveness was independent of underlying patient characteristics and ExECG test results. Hachamovitch and colleagues[53] concluded that SPECT identified low-risk women and men equally well but relatively high-risk women were identified more accurately than relatively high-risk men and SPECT was therefore able to stratify women more effectively than men.

Shaw and colleagues[78] compared two alternative testing strategies, measuring the impact on cardiac outcomes (death or MI) in subsets of women with predefined and variable pretest probabilities of CAD. The two strategies were (1) referral directly to CA ($n = 4638$) or (2) SPECT imaging first ($n = 1263$) followed by CA if at least one reversible myocardial perfusion abnormality was detected. No statistically significant differences were found in cardiac mortality or non-fatal MI between the two diagnostic strategies compared. Shaw and colleagues, in a further multivariate analysis, demonstrated the incremental value of SPECT when compared with clinical history ($p < 0.0001$) and ExECG ($p < 0.0001$).

Pancholy and colleagues[73] sought to determine the independent and incremental prognostic value of exercise SPECT in women. They considered five strategies: (1) clinical data alone; (2) clinical and exercise data; (3) clinical, exercise and CA data; (4) clinical, exercise, CA and SPECT data; and (5) clinical, exercise and SPECT data. There were no statistically significant differences between strategies 1 and 2. Strategy 3 had incremental prognostic power compared with strategy 2 ($p < 0.01$) and strategy 4 had incremental prognostic power compared with strategy 3 ($p < 0.01$). However, there were no statistically significant differences between models 4 and 5. The SPECT variables included in their model (such as extent of total perfusion abnormality, extent of reversible perfusion abnormality,

multivessel abnormality and large perfusion abnormality) were strongly predictive of future cardiac events. The lung thallium uptake was a significant predictor of future cardiac events but not as strong as other scintigraphic variables. Pancholy and colleagues[73] concluded that SPECT imaging provided independent and incremental prognostic information to clinical, exercise and angiographic data in medically treated women with CAD, and that the extent of perfusion abnormality (reversible or fixed) was the most important predictor of prognosis.

In the study by Parisi and colleagues[74] set in the USA, 328 men were enrolled, with a follow-up of 5 years. The aim of the study was to compare the prognostic ability of SPECT and ExECG in low-risk men with CAD. In multivariate analysis, a reversible defect predicted significant risk (RR 2.23, $p = 0.04$); among other factors, only diabetes (RR 2.83) and current smoking (RR 2.19) had a significant relationship with subsequent mortality. A positive ExECG failed to distinguish survival from non-survival. Parisi and colleagues[74] concluded that in medically or angioplasty-treated middle-aged men with chronic stable angina and one- and two-vessel CAD, SPECT was superior to ExECG for predicting subsequent survival, although in this group of patients neither method was superior in predicting subsequent non-fatal coronary events.

Patients with diabetes

Two prospective studies,[51,83] with quality assessment scores of 18 and 20, respectively, assessed the usefulness of SPECT imaging in patients with diabetes. One aimed to evaluate the incremental role of stress SPECT imaging in the prediction of cardiac events in patients with diabetes[51] and the other prospectively evaluated the prognostic value of exercise stress testing and SPECT for the prediction of cardiac events in a homogeneous cohort of high-risk non-insulin-dependent diabetes mellitus (NIDDM) patients.[83]

Giri and colleagues[51] reported that in a Cox multivariate analysis, independent predictors of cardiac death were clinical risk ($p = 0.00001$), the number of ischaemic SPECT defects ($p = 0.00001$) and the number of fixed SPECT defects ($p = 0.00001$). For cardiac death or MI, independent predictors were clinical risk ($p = 0.0001$), the number of ischaemic SPECT defects ($p = 0.00001$) and the number of fixed SPECT defects ($p = 0.00001$). The presence of diabetes was not an independent predictor for either outcome. Giri and colleagues concluded that the presence of an abnormal SPECT scan and extent of the defect independently predicted subsequent cardiac events, and that using SPECT in conjunction with clinical information assisted in the risk stratification of patients with diabetes.

Vanzetto and colleagues[83] reported that, in Cox multivariate analysis, independent predictors of major cardiac events were age >60 years ($p = 0.02$), personal history of CAD ($p = 0.04$), presence of microalbuminuria ($p = 0.001$), inability to perform exercise stress testing ($p = 0.002$), presence of an abnormal SPECT scan ($p = 0.03$) and more than two abnormal segments on SPECT ($p = 0.002$). Vanzetto and colleagues reported that an abnormal SPECT image was an independent predictor of future cardiovascular events. In particular, the presence of a large defect, involving more than two myocardial segments, accurately identified higher risk patients. Vanzetto and colleagues concluded that in clinically selected high-risk diabetic patients, ability to exercise was related to a low probability of future cardiovascular events, and SPECT had little additive value in this case. Inability to exercise, however, was associated with a high risk of events, and in these patients SPECT imaging added incremental prognostic value over clinical and biological variables, with the presence of more than two abnormal segments identifying a very high-risk subset of patients.[83]

Left main and/or three-vessel disease

Amanullah and colleagues[43] (quality assessment score 18) examined the predictors of outcome of medically treated patients with left main and/or three-vessel CAD. In a Cox multivariate analysis, among clinical, stress and SPECT variables, the SPECT score was the only independent predictor of outcome ($p = 0.02$). Amanullah and colleagues concluded that SPECT was useful in predicting outcome in patients with left main and/or three-vessel CAD.

Normal SPECT scans

Four studies,[45,50,52,70] with quality assessment scores of 15, 16, 20 and 20, respectively, examined the value of SPECT when scan images were normal. Two studies were prospective.[45,52] Two studies employed a consecutive method of recruitment.[45,70]

Groutars and colleagues[52] evaluated the prognostic significance of normal dual-isotope (rest Tl-201, exercise Tc-99m tetrofosmin) SPECT studies in patients with suspected or known CAD. In 236 patients followed-up there were four cardiac events

and these occurred in patients with an intermediate to high pretest likelihood of CAD and negative or non-diagnostic exercise ECG results.

Berman and colleagues[45] assessed the prognostic implications of normal and equivocal exercise SPECT scans. SPECT provided incremental prognostic value in all patient subgroups analysed. For example, Berman and colleagues reported that, of the 1282 patients with interpretable ExECG responses (and a normal or abnormal scan), 548 had a low prestress ECG likelihood of CAD, of whom three (0.5%) had a hard event. Of these 548 patients, none of 441 with a normal or equivocal scan and three (2.8%) of 107 with an abnormal scan had a hard event. In patients with a low poststress ECG likelihood of CAD, those with a normal scan had a significantly lower hard event rate (0%, 0 of 167) than those with an abnormal scan (6.2%, four of 64), $p = 0.007$. Even greater stratification occurred in the patients with an intermediate to high poststress ECG likelihood of CAD [normal scan, 0.7% (2 of 274); abnormal scan, 7.9% (18 of 229), χ^2 18, $p < 0.001$]. Berman and colleagues concluded that normal or equivocal SPECT results were associated with a benign prognosis, even in patients with a high poststress ECG likelihood of CAD, and that there was incremental prognostic value for SPECT in all patient subgroups.

Gibbons and colleagues[50] evaluated the prognostic value of a normal or near-normal SPECT scan in patients with an intermediate risk by treadmill test. In a Cox multivariate analysis, they showed that variables demonstrating significant independent association with time to cardiac death were abnormal SPECT scan (OR 9.3, 95% CI 3.0 to 28.7) and cardiac enlargement (OR 4.3, 95% CI 1.5 to 12.2). Gibbons and colleagues concluded that patients with normal or near-normal exercise SPECT scans and normal cardiac size were at low risk for subsequent cardiac death and could be safely managed medically until their symptoms warranted revascularisation.

A study by O'Keefe and colleagues[70] evaluated the outcomes of patients with mild or moderate ischaemia but without high-risk features on SPECT scans in terms of whether they were managed medically or invasively. Cox multivariate analysis was performed assessing variables correlated with long-term outcome. Multivariate predictors of increased risk of referral for CA (invasive management) were angina (RR 2.71), transient ischaemic dilation (RR 2.1), angina while on the treadmill (RR 1.8) and absence of previous MI (RR 0.64). The analysis showed referral for CA (invasive management) as the only independent predictor of non-fatal MI or death during follow-up ($p = 0.0001$). The relative risk of infarction or death with invasive management compared with medical management was 11.6 (95% CI 4.8 to 27.9). O'Keefe and colleagues concluded that patients with non-high-risk ischaemia on SPECT imaging could be treated safely with a conservative medical management strategy.

Use of SPECT in specific areas/patient populations

SPECT imaging of patients after MI

Four studies[48,81,85,87] with quality assessment scores of 20, 16, 17 and 17, respectively, provided information on the prognostic utility of SPECT in patients after MI. Three studies were prospective.[48,81,85] All four employed a consecutive method of recruitment.

Chiamvimonvat and colleagues[48] assessed the utility of SPECT in a selected low-risk population following MI. They reported that, in a multivariate logistic regression model including clinical, SPECT and angiographic variables, the independent predictors of increased risk of cardiac events were the presence of reversible defects (OR 5.04, 95% CI 2.01 to 12.66) and the presence of multivessel stenosis ≥ 70% (OR 2.64, 95% CI 1.34 to 5.21). In addition, they reported a statistically significant incremental prognostic performance when moving from a strategy of (1) clinical data alone to (2) clinical and CA data to (3) clinical and SPECT to (4) clinical, CA and SPECT ($p < 0.05$ for all stepwise comparisons). Based on these results, they concluded that in low-risk populations after MI, the presence of reversible defects was a strong predictor of cardiac events, with greater prognostic value than angiographic data. As the extent of reversible defects correlated with subsequent cardiac events, SPECT imaging was useful for risk stratification in low-risk populations after MI.

The study by Travin and colleagues[81] assessed the value of SPECT in patients undergoing exercise stress testing after recent acute MI. In Cox multivariate analysis, the number of ischaemic defects on SPECT was the only significant predictor of an event ($p = 0.0317$). They concluded that exercise SPECT after MI frequently revealed residual ischaemia and was better than clinical data, symptoms and stress ECG in identifying patients at risk of a subsequent cardiac event.

Wagner and colleagues[85] aimed to evaluate the predictive power of early postinfarction stress testing in survivors of uncomplicated MI treated with thrombolytics. They reported that in a multivariate analysis of clinical, exercise and SPECT variables the presence of reversible perfusion defects on SPECT was the only independent predictor of future cardiac events. No angiography variable was prognostically significant for these events. They concluded that SPECT imaging in the early postinfarction period was important in identifying patients at increased risk among clinically stable survivors of uncomplicated acute MI.

Zellweger and colleagues[87] assessed the incremental prognostic value of SPECT over clinical assessment in patients with remote prior MI who underwent SPECT imaging more than 6 months after MI. They showed that the most important independent predictors of cardiac death were non-reversible segments (RR 1.63, 95% CI 1.28 to 2.08), symptoms (RR 2.58, 95% CI 1.41 to 4.69), prior CABG (RR 0.47, 95% CI 0.27 to 0.82) (an RR of less than 1 indicates that prior CABG is associated with a lower risk of cardiac death) and age (RR 1.03, 95% CI 1.01 to 1.06). Similarly, predictors of cardiac death or non-fatal MI were symptoms (RR 3.84, 95% CI 2.28 to 6.45), prior CABG (RR 0.56, 95% CI 0.38 to 0.84), prescan likelihood of CAD (RR 2.57, 95% CI 1.43 to 4.64), summed difference score (RR 1.05, 95% CI 1.02 to 1.07) and presence of non-reversible segments (RR 1.13, 95% CI 1.07 to 1.19). When, for all patients, SPECT information was added to the prescan data, the ability to predict those most at risk of cardiac death ($p < 0.0001$) and all hard events ($p < 0.0001$) increased. Zellweger and colleagues concluded that, after adjustment for prescan information, the SPECT results (summed stress score) added incremental value to prescan and were highly predictive in the risk stratification of patients with remote prior MI.

Post-revascularisation

Three retrospective studies,[56,65,69] with quality assessment scores of 17, 18 and 18, respectively, assessed the prognostic value of SPECT in patients following revascularisation. One study investigated the usefulness of SPECT in patients following PTCA[56] and two assessed the role of SPECT in patients following CABG.[65,69]

Ho and colleagues[56] assessed univariate associations between ExECG and two SPECT variables. An abnormal SPECT scan, performed 1–3 years after PTCA, was found to be predictive of cardiac events.

Miller and colleagues[65] evaluated the prognostic value of exercise SPECT imaging in patients who had undergone CABG within 2 years of the SPECT test whereas Nallamothu and colleagues[69] considered the same question over a mean of 41 months of follow-up. Miller and colleagues,[65] in Cox multivariate analysis, reported the prognostic power of clinical, exercise and SPECT variables in predicting overall mortality. They reported that the significant independent predictors of increased mortality were increasing age (HR 1.40, 95% CI 1.00 to 1.96), shorter exercise duration (HR 1.24, 95% CI 1.09 to 1.41) and number of abnormal SPECT segments after exercise (HR 1.10, 95% CI 1.03 to 1.18). They also considered how well these variables predicted cardiac death or non-fatal MI and reported that the only independent predictors of increased risk were exercise angina score (HR 1.69, 95% CI 1.19 to 2.40) and number of abnormal SPECT segments after exercise (HR 1.12, 95% CI 1.04 to 1.20).

Both studies reported which variables were independent predictors of cardiac death, non-fatal MI or late PTCA/CABG. Miller and colleagues[65] found that the independent predictors of increased risk were chest pain class (HR 1.35, 95% CI 1.10 to 1.65) and number of abnormal SPECT segments after exercise (HR 1.10, 95% CI 1.03 to 1.18). Nallamothu and colleagues[69] reported that the extent of the perfusion abnormality, multivessel perfusion abnormality and increased lung thallium uptake were important independent predictors of events. Furthermore, they showed that SPECT added incremental prognostic information to clinical, stress ECG and angiographic variables (clinical plus stress ECG plus CA; clinical plus stress ECG plus CA plus SPECT, $p = 0.01$) and that neither clinical variables nor stress ECG variables provided prognostic information.

On the basis of the data presented in the studies, the authors concluded that SPECT was useful to stratify patients after CABG into low-, intermediate- and high-risk groups for future cardiac events.

Acute coronary setting

One study aimed to determine the utility of SPECT for predicting outcome of hospitalised patients with chest pain and a normal or non-diagnostic ECG.[44] In univariate analysis, hypertension, abnormal stress ECG, treatment with antianginal therapy and abnormal SPECT scan were found to be predictors of adverse cardiac events, and all parameters were entered into a multivariate regression model to assess their independent

predictive value. In this model, the only independent predictor of adverse cardiac events was an abnormal SPECT scan (OR 32.3, 95% CI 3.7 to 279). Ben-Gal and colleagues[44] concluded that the presence of SPECT distribution defects identified patients at higher risk for adverse cardiac events who may be referred for further invasive evaluation, whereas patients with normal scans were candidates for early hospital discharge.

Asymptomatic coronary disease

Two studies,[46,72] with quality assessment scores of 20 and 19, respectively, examined the value of SPECT in patients with asymptomatic coronary disease. Candell-Riera and colleagues[46] assessed the prognosis of medically treated patients who fulfilled the features that defined clandestine myocardial ischaemia (perfusion defect without angina and no ST-segment depression >1 mm during exercise test) and compared them with patients with asymptomatic coronary disease and angina pectoris. Pancholy and colleagues[72] examined the differences in the event-free survival rates between patients with CAD who had asymptomatic or symptomatic ischaemia during exercise testing.

Candell-Riera and colleagues[46] showed, in a Cox multivariate analysis, that neither ST-segment depression >1 mm during the exercise test nor multivessel disease on CA were predictive of worse prognosis. The presence of severe reversible SPECT defects was predictive of cardiac events only when the need for revascularisation was included as a complication ($p < 0.01$). The Cox multivariate analysis conducted by Pancholy and colleagues[72] revealed that the size of the perfusion abnormality and history of diabetes mellitus were independent predictors of prognosis. Patients with a history of diabetes mellitus and a large perfusion abnormality (≥ 15% of the myocardium) had the worst event-free survival rate ($p < 0.0001$). Angina was not a reliable marker of prognosis.

Both studies concluded that SPECT perfusion imaging could help identify high-risk patients with asymptomatic coronary disease. Furthermore, Candell-Riera and colleagues[46] reported that severe reversible SPECT defects were predictive of cardiac events only when the need for revascularisation was included as a cardiac event.

High exercise ECG tolerance

Chatziioannou and colleagues[47] assessed the predictive value of SPECT versus ExECG in patients with high exercise tolerance. In Cox multivariate analysis comparing four strategies, (a) SPECT, (b) stress ECG, (c) ECG and Duke treadmill score and (d) ECG, Duke treadmill score and SPECT, the only strategy that provided a statistically significant prediction of adverse cardiac events was SPECT alone. The presence of an abnormal SPECT scan was associated with an RR of 8 (95% CI 3 to 23) for adverse cardiac events. They concluded that, at high levels of exercise tolerance, the presence or absence of ST-segment changes and the Duke treadmill score risk categories had no predictive value. However, SPECT was an excellent prognostic indicator for adverse cardiac events in patients with known or suspected CAD and high exercise tolerance.

Predicting early revascularisation

Amanullah and colleagues[42] undertook a prospective cohort study (quality score 19) which assessed the predictors of early revascularisation. In multivariate logistic regression analysis, predictors of early revascularisation were (in order of statistical significance) reversible perfusion defects, extent of CAD by angiography and angina during exercise. They concluded that although referral for revascularisation may be conditional on the results of CA, SPECT provided enhanced information on which to base the decision to revascularise.

Age and referral for CA

Lauer and colleagues[61] investigated whether there was an association between age and referral to CA. All-cause mortality and cardiac death were associated with the total number of abnormal segments on SPECT (for each two additional abnormal segments, age-adjusted RR 1.41, 95% CI 1.06 to 1.88 for all-cause mortality and RR 1.60, 95% CI 1.03 to 2.48 for cardiac death), but not with referral to CA. After adjustment for the extent of ischaemia revealed by the SPECT scan, clinical characteristics and exercise findings including functional capacity, increasing age remained associated with a lower rate of referral to CA (for 5-year increase in age, adjusted OR = 0.81, 95% CI 0.73 to 0.90). Lauer and colleagues concluded that increasing age was associated with a lower rate of referral to CA following an abnormal SPECT scan.

ECG-gated and attenuation-corrected SPECT

Two studies[89,90] compared SPECT with ECG-gated SPECT and one compared SPECT with attenuation-corrected (AC) SPECT.[91] The diagnostic study by Shirai and colleagues[90] found that ECG-gated SPECT was more sensitive, with slightly lower but acceptable specificity, compared with the assessment of perfusion data alone for

detection of multivessel CAD. The prognostic study by Sharir and colleagues[89] concluded that ECG-gated SPECT provided incremental prognostic information in patients with known or suspected CAD over that provided by perfusion data alone. The diagnostic study by Gallowitsch and colleagues[91] found that SPECT was less sensitive and less specific than AC SPECT, both in patients with angina and no previous MI and also in patients with known CAD.

Summary and conclusions of the evidence for and against the intervention

Diagnostic studies

The sensitivity values of SPECT tended to be higher than those of stress ECG for the two main subsets of studies (patients suspected of CAD and patients who underwent PTCA). Specificity values of the two tests were similar for patients suspected of CAD, but higher values were reported for SPECT compared with stress ECG for patients who underwent PTCA. The sensitivity and specificity results of SPECT and stress ECG in the four studies excluding patients with previous MI were generally higher than those in the 10 studies that included patients with MI. However, this observation is based on a small number of studies with varied inclusion/exclusion criteria and patient characteristics. In addition, the 10 studies including patients with prior MI did not consist solely of patients with prior MI.

Summary ROC curves for both tests were not generated because the correlation between sensitivity and 1 – specificity for SPECT was close to zero. Although the correlation for stress ECG was higher (0.46), a summary ROC curve was not presented.

The overall estimate of positive LRs for SPECT was higher than that for stress ECG (2.29 versus 1.83) whereas the combined estimate of negative LRs for SPECT was slightly lower than that for stress ECG (0.25 versus 0.51). However, as in both instances significant heterogeneity was observed among included studies, it is questionable whether combining such results is appropriate and hence whether reliable conclusions can be drawn from them.

No firm conclusions about the overall accuracy of SPECT and stress ECG in different patient subgroups and for different angiographic definitions of CAD could be made owing to the small number of studies available in each subgroup.

Comparison of SPECT and stress ECG in the other categories was limited by the small number of included studies. Moreover, insufficient evidence was available to evaluate the incremental value of SPECT over stress ECG in the diagnosis of CAD.

Prognostic studies

There were 46 prognostic studies. Although they were all observational studies, the overall methodological quality was good. The quality of the studies in terms of reporting of information was very good, but their generalisability was fairly low, although internal validity was higher. Four studies compared different testing strategies,[67,77,78,82] whereas the remainder were cohort studies (23 prospective, 13 retrospective, six type not stated) in which substantially the same group of patients underwent the tests under investigation. Twenty-six studies employed a consecutive method of recruitment.

Twenty-one studies provided general prognostic information. The extent[57,58,62,63,68,79,84,86] and size[59,71,75] of the perfusion defect, and whether reversible or fixed,[76,80,86,88] were important factors in predicting prognosis. Other findings were that, compared with a direct CA strategy, SPECT imaging followed by selective CA resulted in lower rates of normal angiograms from those patients subsequently referred for CA.[67,77] SPECT also provided independent prognostic information for predicting MI,[80] provided incremental prognostic value over clinical and exercise testing data that was maintained at long-term follow-up,[71,75,76,84] was the single most powerful predictor of prognosis and had incremental value even when CA had already been performed.[58,63,82]

Sixteen of the general prognostic studies employed the Cox proportional hazards regression model. The variables included in the models generally appeared to be appropriate, although they differed to some extent across studies. Predicting variables related to SPECT included an intermediate risk-SPECT scan,[49] a high-risk SPECT scan,[49] extent of the perfusion defect,[57,58,63,79,84] size of the perfusion defect,[59,75] abnormal SPECT scan,[62,76,80] summed stress score,[55,66] summed reversibility score,[66] reversible perfusion defects[76,80] and fixed perfusion defects.[76,88]

The remaining prognostic studies addressed the use of SPECT in a variety of specific areas/populations. All four studies of patients post-MI[48,81,85,87] found that SPECT imaging was valuable in stratifying patients into at-risk groups for further cardiac events. The six studies addressing different questions relating to SPECT imaging and gender found that SPECT provided important, independent prediction of survival in both men and women[53,60,64,73,74,78] SPECT imaging performed 1–3 years after PTCA was predictive of cardiac events[56] and, in patients who had undergone CABG, SPECT was useful in stratifying patients into at-risk groups for future cardiac events.[65,69]

Our findings are in broad agreement with other published reviews assessing the prognostic usefulness of MPS. Travin and Laraia,[92] in a review of the prognostic value of stress myocardial perfusion imaging (MPI), concluded that it was a powerful method of risk stratification for patients with known or suspected ischaemic heart disease. Brown,[93] in a review of the prognostic value of Tl-201 MPI, concluded that it had been shown to have the ability to predict important cardiac events in a wide variety of clinical settings and was a powerful tool for risk stratification that could have a major impact on patient management.

In conclusion, the evidence from the included prognostic studies was consistent in suggesting that, as part of the stress ECG–SPECT–CA pathway, SPECT, in a variety of settings and patient populations, provided valuable independent and incremental information predictive of outcome that helped to risk-stratify patients and influence the way in which their condition was managed.

Although the limited evidence on ECG-gated and attenuation-corrected SPECT seems promising, it is difficult to draw conclusions from so few studies.

Clinical effect size

Of 46 prognostic studies, four were observational studies comparing different testing strategies.[67,77,78,82] In the study by Shaw and colleagues,[77] one group of patients underwent initial direct testing by CA and a second group underwent initial testing by stress SPECT, followed by selective catheterisation. For patients undergoing initial CA, the rate of subsequent revascularisation for clinically low-, intermediate- and high-risk catheterisation patients was 16, 27 and 30%, respectively, compared with 14, 13 and 16% for SPECT patients ($p = 0.0001$). In the study by Mishra and colleagues,[67] one group of patients underwent initial direct testing by CA and a second group underwent initial testing by stress SPECT. In the group undergoing initial CA, coronary revascularisation was performed in 51% of those with CAD and in 38% of the SPECT group who were found to have CAD on CA ($p < 0.001$).

Underwood and colleagues[82] compared four different testing strategies: (1) stress ECG–CA; (2) stress ECG–MPI–CA; (3) MPI–CA; and (4) CA. Patients in strategy 4 (CA) were found to have had significantly more revascularisations ($p < 0.001$). Shaw and colleagues[78] compared two different testing strategies: one group of women underwent initial direct testing by CA and a second group underwent initial testing by stress SPECT, followed by selective catheterisation. Rates of PTCA/CABG were significantly lower in the SPECT plus CA group than the CA group ($p < 0.005$).

The other prognostic studies were cohort studies and within each study substantially all patients received the various tests of interest. Many of these studies, using multivariate regression analysis, reported the statistical significance of SPECT and other variables in predicting outcomes and providing incremental information, and of SPECT adding statistically significant incremental information when incorporated into combinations of clinical, stress ECG and CA models. In these studies, the chi-squared or HR values favoured the SPECT variables when compared alone with other variables[42–44,47–51,55,57–61,63–66,69,71–76,80,81,83–86] or favoured the combination of variables including SPECT compared with combinations of variables excluding SPECT[47,48,53–55,57,58,63,69,71,73,75,76,84,87] (see Appendix 8).

Adverse effects of intervention

Four studies,[33,44,76,82] one of which was a diagnostic study,[33] gave details of adverse events resulting from the stress ECG or SPECT intervention. In the study by Khattar and colleagues,[33] angina was the most common end-point for exercise ECG, occurring in 49 of 100 patients, with inotropic stress testing precipitating angina in 23 cases. With respect to other causes leading to termination of inotropic stress, seven patients developed extensive wall thickening abnormality; hypotension occurred in 13 cases and five patients developed ventricular arrhythmias. Miscellaneous end-points included palpitations, tremor and nausea.[33]

In a prognostic study by Ben-Gal and colleagues,[44] one of 84 patients with a normal thallium SPECT

scan experienced a non-fatal MI. The patient was a 56-year-old woman with typical anginal chest pain and a non-diagnostic rest ECG at admission. During dipyridamole injection she experienced marked chest pain and the ECG showed ST-segment depression. The patient responded to antianginal therapy but 2 days later suffered a small inferior wall AMI.[44]

Schinkel and colleagues[76] reported that, out of 693 patients, side-effects during dobutamine–atropine stress were short ventricular tachycardia (<10 complexes) in 23 patients (3.3%), atrial fibrillation in seven patients (1.0%), severe hypotension (decrease in systolic blood pressure of >40 mmHg) in seven patients (1.0%) and severe hypertension (blood pressure of >240/130 mmHg) in five patients (0.7%). Minor side-effects included chills in 52 patients (7.5%), headache in 46 patients (6.6%) and nausea in 38 patients (5.5%). No patient, however, experienced a MI or ventricular fibrillation.[76]

In the study by Underwood and colleagues,[82] soft events included complications of diagnostic or therapeutic procedures. The number of complications reported for each strategy was three (out of 144 patients in strategy one); one (out of 130 patients in strategy two); one (out of 48 patients in strategy three); three (out of 75 patients in strategy four). There were three cases of complications in MPI user hospitals and five cases of complications in MPI non-user hospitals.[82]

Chapter 4

Systematic review of economic evaluations

Methods

Search strategies

Studies that reported both costs and outcomes of diagnostic strategies involving SPECT relative to strategies involving any of the other diagnostic interventions under investigation either with or without SPECT were sought from the systematic review of the literature. In addition, the Harvard database of cost–utility analyses was searched, and the Industry submissions for this Technology Assessment Review were checked. No language restrictions were imposed but the searching was limited to studies published after 1990. The following databases were searched for studies assessing cost-effectiveness.

1. MEDLINE, 1990–October 2002, EMBASE 1990–2002 (to week 44)
   Separate search strategies were developed for each database and then combined to produce a final strategy that was run concurrently. Duplicates were removed from the resulting set using Ovid's de-duplicating feature.
2. PREMEDLINE (Ovid), 5 November 2002
3. NHS–EED (NHS CRD), October 2002

Details of the final search strategies used can be found in Appendix 1. In addition, results of the searches of the HTA database and Health Management Information Consortium (HMIC) were also screened for potentially relevant articles. Other sources of information included references in relevant articles, selected experts in the field and references of consultees' submissions.

Inclusion and exclusion criteria

To be included, studies had to compare, in terms of both costs and outcomes for CAD, diagnostic strategies involving SPECT with alternative strategies, which may or may not have involved SPECT. Studies reported in languages other than English were identified from their abstracts but were not included in the review. Studies were excluded if they made no attempt to relate cost to outcome data. One reviewer assessed all abstracts for relevance and full papers were obtained for those that appeared potentially relevant. Results are given in *Table 20*.

Reviews of relevant studies were not considered eligible for inclusion. Nevertheless, as the submission by Amersham Health (February 2003) included a review of economic studies, a brief commentary has been included in the section 'Review of economic evaluations contained in the Industry submission' (p. 46).

Data extraction strategy

The following data were extracted for each included study.

1. Study identification information
   (a) author and year
   (b) the interventions studied
   (c) the type of economic evaluation
   (d) the country of origin and currency reported
2. the intervention, study design and main outcomes
   (a) fuller description of treatment
   (b) numbers receiving or randomised to each intervention
   (c) outcomes studied
3. sources of data
   (a) effectiveness data
   (b) mortality and comorbidity (if measured)
   (c) cost data
   (c) QoL (if measured)
4. methods and study perspective
5. results
   (a) costs
   (b) benefits

TABLE 20 *Results of searching for studies on cost-effectiveness*

Database	Number of hits screened	Number selected	Included studies
Multifile search (MEDLINE, EMBASE) after de-duplication	634	28	12
PREMEDLINE	28	2	2
NHS–EED	289	17	9

(c) incremental cost-effectiveness ratio (ICER)
(d) sensitivity analyses
6. additional comments.

Quality assessment strategy

Two economists independently assessed included studies using the *British Medical Journal* (*BMJ*) guidelines for reviewers.[94] The systematic review provided by Amersham Health was assessed using the following criteria adapted from Oxman and colleagues[95,96] and Mulrow and Cook,[97] which was used in a recent study of the quality of systematic reviews of economic evaluations:[98]

1. Is it unlikely that important relevant studies were missed?
2. Were the inclusion criteria used to select articles appropriate?
3. Was the assessment of studies reproducible?
4. Were the design and/or methods and/or topic of included studies broadly comparable?
5. How reproducible are the overall results?
6. Will the results help resource allocation in healthcare?

Each stem (1–6) was answered by one of the following: 'Impossible to judge', 'No', 'Partly', 'Yes'.

Data synthesis

No attempt was made to synthesise quantitatively the studies that were identified. Data from all included studies were instead summarised and appraised in order to identify common results, variations and weaknesses between studies. If a study only reported average cost-effectiveness ratios (ACERs) then, where possible, the data were reanalysed to provide estimates of incremental cost-effectiveness. The data were then interpreted alongside the results of the systematic review of effectiveness so that conclusions could be drawn on the relative efficiency of the different diagnostic strategies.

Systematic review of published economic evaluations

Number of studies identified

Twenty-two studies were identified. Two were not retrieved from the multifile search because they were pre-1990 papers but had been identified from the previous clinical effectiveness search. A further two studies were unpublished and were identified from reference lists.

Eleven studies were based on primary data and 11 used modelling techniques. These studies are summarised in Appendix 10. The following sub-section critiques and summarises those studies that have considered the diagnosis of coronary artery disease. The subsequent two sub-sections consider those studies that investigated the use of SPECT to diagnose coronary artery disease in those at high disease prevalence and women, respectively, the next sub-section considers the role of SPECT for those presenting with acute coronary syndromes and the final sub-section considers the role of SPECT in determining management following MI. The review provided by the Industry submission as well as the Amersham Health economic model are discussed separately in the sections 'Review of economic evaluations contained in the Industry submission' (p. 46) and 'Review of the Industry submission economic evaluation' (p. 47), respectively.

Diagnosis of coronary artery disease

Six studies[99–103] reporting the results of decision models considered the cost-effectiveness of different imaging strategies for a range of prevalence rates of CAD (Jacklin PB, Maisey MN, West PA, Sariklis D, Beech R. Guy's, King's and St Thomas' School of Medicine, King's College, London, unpublished studies, 2002) (subsequently referred to as 'Jacklin, 2002'). Two further studies based on models focused on patient groups at intermediate risk of disease (~25–75% prevalence).[104,105] There were also five primary studies.[55,77,82,106,107] Patients enrolled in the primary studies had either normal resting ECGs and/or cardiac symptoms and no known heart disease. Of these 13 studies, only two came from the UK or involved UK centres (Jacklin, 2002).[82] The strategies considered in each of the studies are summarised in *Tables 21* and *22*.

Quality of included studies

Of the studies based on models, three (Jacklin, 2002)[102,103] were developed from Patterson and colleagues.[101] The remaining four were based on models developed specifically for that study.[99,100,104,105]

The model structure built by Patterson and colleagues[101] was well reported, although it is unclear precisely how the model's effectiveness and utility parameters were derived. The later studies using updated parameters still did not adequately describe the source of model parameters. Although the data for sensitivity and specificity of stress ECG and sensitivity of SPECT were similar to those presented in Chapter 3, they tended to assume higher specificities for SPECT. This would tend to improve the cost-effectiveness

TABLE 21 *Summary of diagnostic strategies used in studies using models*

Study	Strategies
Jacklin, 2002	1. Stress ECG with CA if positive or inconclusive (or not feasible) 2. SPECT with CA if positive or non-diagnostic 3. Stress ECG with CA if positive or non-diagnostic. If still positive, then SPECT followed by CA if positive or non-diagnostic 4. Stress ECG with CA if positive. SPECT if stress ECG is negative and then CA if positive 5. CA with no prior diagnostic test
Garber, 1999[104]	1. Stress ECG 2. Planar SPECT 3. SPECT 4. Stress ECHO 5. Stress PET 6. CA
Kuntz, 1999[99]	1. No testing 2. CA alone 3. Stress SPECT; CA if positive 4. Stress ECG; CA if positive 5. Stress ECHO; CA if positive
Maddahi, 1997[100]	1. Direct referral for CA 2. PET if positive CA 3. SPECT if positive CA 4. Stress ECG, PET if stress ECG is positive and if positive CA 5. Stress ECG, SPECT if ECG is positive and if positive CA 6. Stress ECG and if positive CA
Patterson, 1984[101]	1. Stress ECG plus CA if stress ECG positive or non-diagnostic 2. Stress SPECT plus CA if SPECT positive or non-diagnostic 3. Direct CA 4. Stress ECG plus SPECT if positive non-diagnostic and CA if SPECT positive or non-diagnostic
Patterson, 1995[102]	1. Stress ECG plus CA if stress ECG positive or non-diagnostic 2. Stress SPECT plus CA if SPECT positive or non-diagnostic 3. Direct CA 4. Stress PET followed by CA if the PET was positive or non-diagnostic
Rumberger, 1999[103]	1. Stress ECG; CA if positive or if non-diagnostic 2. Stress ECHO; CA if positive or if non-diagnostic 3. SPECT; CA if positive or if non-diagnostic 4. EBCT; CA if positive or if non-diagnostic at 3 different cut-off points for scores 5. CA
Shaw, 2003[105]	1. CA 2. Stress ECG 3. Stress ECHO 4. Stress SPECT 5. Contrast-enhanced ECHO

EBCT, electron beam computed tomography; ECHO, echocardiography; PET, position emission tomography.

of SPECT. In terms of cost, the US studies focused on fees payable for tests and procedures, which may not be transferable to the UK.[101–103] The UK study provided reasonably good descriptions of resource use and cost. In none of these studies was it clear to which year cost data related and, despite three studies having 10-year time horizons, no discounting was performed (Jacklin, 2002).[101,102] The principal limitation of these studies is that they reported relative cost-effectiveness in terms of average cost-effectiveness ratios. Average cost-effectiveness ratios provide very limited information about whether a more costly but more effective strategy might be preferred. However, in two studies using the data provided it was possible to estimate incremental cost-effectiveness ratios and these data are presented in Appendix 11 (Jacklin, 2002).[103] Three studies (Jacklin, 2002)[101,102] provided estimates of cost per quality-adjusted life year (QALY) (although, as stated above, it was unclear how the QALY estimates were derived) and one only considered the cost per correct diagnosis.[103]

Of the other four models, three based cost estimates on Medicare fees[99,100,104] and the fourth

TABLE 22 *Summary of diagnostic strategies based on data from primary studies*

Study	Strategies
Christian, 1994[106]	1. Clinical data 2. Clinical data plus stress ECG 3. Clinical data plus stress ECG plus SPECT
Hachamovitch, 2002[55]	1. Clinical and history only 2. Stress ECG and clinical data and history 3. Stress SPECT plus strategy 2
Mattera, 1998[107]	1. Stress ECG 2. SPECT
Shaw, 1999[77]	3. SPECT, selective CA 4. Direct CA
Underwood, 1999[82]	1. Stress ECG followed by CA 2. Stress ECG plus SPECT followed by CA 3. SPECT followed by CA 4. CA alone

devoted considerable effort to identifying costs generalisable to a large healthcare provider in the USA.[105] One of these studies reported costs relative to the cost of an angiogram, which makes it more difficult to consider cost-effectiveness or make judgements about their applicability to the UK.[100]

All the studies took data on the sensitivity and specificity of tests from the literature. The most comprehensive description of how these data were assembled came from the study by Kuntz and colleagues.[99] The other studies were limited in terms of the searches performed (e.g. MEDLINE only) or because inadequate descriptions of the search strategy were provided. The rates of sensitivity and specificity of SPECT were all higher than those reported in Chapter 3 (although they were within the range provided by identified studies). The specificity of stress ECG was also higher, although sensitivity was similar.

All studies used incremental analysis and discounting as appropriate. Two studies focused on diagnostic accuracy[100,105] and two used QALYs.[99,104] The utility weights were taken from a previous survey of patients with stable angina. In one study utility scores were estimated using standard gamble methods[99] and in the other time trade-off values were obtained from the literature.[104] Two studies attempted a rigorous sensitivity analysis (SA) around all the main areas of uncertainty,[99,104] including a probabilistic analysis in one.[99] The other two studies either had limited[105] or no SA.[100]

Of the five studies based mainly on primary data, three were based on large retrospective cohorts,[55,77,107] one of which involved matched cohorts for the two diagnostic strategies considered.[77] Of the other two, one was based on a moderately sized (n = 411) cohort[106] and one involved the retrospective analysis of cost data from 396 patients selected from eight matched hospitals in the UK, Germany, Italy and France (two from each country).[82] This latter study based its effectiveness on data taken from the literature. The costs in three studies were based on very simplistic methods (only one or two cost events were included, costed using Medicare fees).[55,106,107] One converted Medicare charges into costs[77] and Underwood and colleagues applied unit costs from a single UK centre to resource use from other UK and European centres.[82] Descriptions of resource use were limited, which makes it difficult to judge how generalisable the data are to the UK. All studies adopted either an incremental analysis or a cost-minimisation approach. However, only one of the three studies where discounting should have been adopted did so[77] and only two used any form of SA, which in both cases involved the use of multivariate analysis to predict costs.[77,106]

Summary of results

The two studies that presented their results in terms of average cost-effectiveness ratios both showed that, for the strategies relevant to this technology assessment, a strategy of SPECT plus CA, if SPECT was positive or non-diagnostic, had the lowest average cost per QALY when the prevalence of CAD was <70%; >70% direct angiography had the lowest average cost per QALY.[101,102] As mentioned above, both the lack of explanation about how QALY estimates were derived and the difficulty of interpreting the relevance of average cost-effectiveness ratios make

TABLE 23 *ICERs for the comparison of stress ECG, SPECT in positives (non-diagnostics) versus stress ECG*

Study	Finding compared with stress ECG
Jacklin, 2002[a]	Stress ECG more effective but more costly. Incremental cost per true positive identified of stress ECG compared with ECG, SPECT £3038
Christian, 1994[106b]	US$20,550 per additional correct classification
Hachamovitch, 2002[55]	US$5417 per additional correct classification
Mattera, 1998[107]	SPECT reduced costs by 38%
Jacklin, 2002[a]	Stress ECG more effective and less costly
Hachamovitch, 2002[55]	US$25,134 per hard event avoided
Underwood, 1999[82]	Stress ECG, SPECT less costly more effective
Maddahi, 1997[100]	Stress ECG, SPECT most cost-effective
Jacklin, 2002[a]	Stress ECG more effective but more costly. Incremental cost per QALY of stress ECG compared with ECG, SPECT £854

[a] Costs in UK£; year of costs not stated.
[b] Costs in 1992 US$.

TABLE 24 *ICERs ratios for the comparison of SPECT versus stress ECG*

Study	Finding compared with stress ECG
Jacklin, 2002	£2774 per additional correct diagnosis
Rumberger, 1999[103]	US$12,278 per additional true positive diagnosed
Jacklin, 2002	£2863 per additional true positive diagnosed
Garber, 1999[104]	US$40,316 per additional QALY
Jacklin, 2002	£1991 per additional QALY
Kuntz, 1999[99]	US$38,000 per additional QALY

these data difficult to interpret. Two further studies also reported average cost-effectiveness ratios but provided sufficient information for incremental cost-effectiveness to be estimated (Appendix 11) (Jacklin, 2002).[103]

The comparison of the different diagnostic strategies was complicated by the multitude of strategies considered and the different ways in which outcomes were measured (not to mention differences in methodology adopted). Therefore, the results are summarised under a series of pairwise comparisons. These comparisons are made first for those at intermediate risk of disease and then, where information is available, for women and those at high risk.

Stress ECG, SPECT in positives (non-diagnostics) versus stress ECG
Six studies provided information on this comparison (*Table 23*).

There is little consistency between the studies, reflecting the different parameter values used. The studies by Christian and colleagues,[106] Hachamovitch and colleagues[55] and Mattera and colleagues[107] based their costs on no more than the cost of stress ECG and SPECT, so their results may be misleading. Underwood and colleagues showed that the cost of stress ECG, SPECT strategy is less (although no SA was reported).[82] The study by Jacklin and colleagues, while having reasonably strong costing methodology, reported that the stress ECG strategy was either dominant or more effective but more costly. This was caused by the low cost estimated for stress ECG (£7) (Jacklin, 2002).

SPECT versus stress ECG
Five studies provided information on the comparison of SPECT with stress ECG. In one a strategy of using SPECT to select those who would receive angiography was less costly and more effective than one using stress ECG.[82] In the other studies the SPECT strategy was more costly and more effective (*Table 24*).

The incremental cost per QALY in Jacklin and colleagues' study (Jacklin, 2002) is lower than that in the other two studies that report this outcome[99,104] because of the specificity rates used for SPECT and the assumptions made about QALY gains. If the cost and utility data used by the two US models were applicable to the UK, it is possible that the incremental cost per QALY might be deemed affordable.

TABLE 25 *ICERs for the comparison of SPECT versus coronary angiography*

Study	Incremental cost-effectiveness of coronary angiography
Jacklin, 2002	SPECT more costly and less effective[a]
Rumberger, 1999[103]	US$4140 per additional true positive diagnosed
Garber, 1999[104]	US$102,333 per additional QALY
Jacklin, 2002	£1017 per additional QALY[b]

[a] Costs of future treatments excluded.
[b] Costs of treatments included.

Stress ECG, SPECT in positives (non-diagnostics) versus SPECT
Three studies provided information on this outcome. In two it was concluded that the use of both stress ECG and SPECT was cost-effective.[82,100] and in one the use of SPECT alone provided more QALYs at greater cost (incremental cost per QALY was £1444 per QALY) (Jacklin, 2002).

Stress ECG, SPECT in positives (non-diagnostics) versus CA
Three studies considered this comparison and all found CA to be more costly but more effective (Jacklin, 2002).[82,100] This is due to the assumption made that CA provided perfect diagnostic information. Only one study provided information on incremental cost-effectiveness (incremental cost per QALY of CA was £1277). It should be noted that in the study by Jacklin and colleagues, stress ECG and SPECT in positives and non-diagnostics was reported to be the least effective of the five strategies considered (Jacklin, 2002).

SPECT versus CA
All of the six studies that provided data on this comparison found that CA was the more effective but more costly (Jacklin, 2002).[100,77,82,103,104] For one study, incremental cost-effectiveness could not be estimated[100] and two concluded that SPECT was more efficient.[77,82] The results for the remaining studies are summarised in *Table 25*.

Cost-effectiveness at high disease prevalence

Six studies considered the effect on cost-effectiveness of a high (> ~75%) prevalence of CAD. Four reported the results in terms of average cost-effectiveness ratios and found that CA was associated with the lowest average cost-effectiveness ratio (Jacklin, 2002).[101–103] Information on incremental cost-effectiveness was obtained from two of these studies (Jacklin, 2002)[103] and from the remaining two studies.[99,100] In three of these studies direct CA was less costly and more effective than any of the other strategies considered except for a strategy of stress ECG to select patients for CA.[99,100,103] In this situation, CA was more effective and more costly (incremental cost per QALY <US$25,000,[99] incremental cost per additional true positive diagnosed US$2363).[103] In the remaining study CA did not dominate any of the other strategies but was associated with an incremental cost per QALY of no more than £1285 (Jacklin, 2002).

Cost-effectiveness of alternative strategies amongst women at risk of coronary artery disease

Three studies reported the cost-effectiveness of alternative strategies to detect CAD in women.[78,108,109] Two of these were based on primary studies and one was based on a modelling exercise. A further three studies considered the cost-effectiveness of alternative strategies to detect CAD in women as part of an SA.[55,99,104] Interpretation is hampered by the differences in strategies compared and also limited reporting of results. Garber and Solomon estimated in their model that the incremental cost per QALY of using SPECT instead of stress ECG was ~US$50,000. This increased to US$100,000 for women aged 45 years (i.e. at lower risk) and US$61,500 for women aged 65 years (because of their lower life expectancy).[104] Similarly, Hachamovitch and colleagues showed that the incremental cost of adding SPECT to a strategy already involving stress ECG would be US$8092 per reclassification (US$3816 if limited to those positive on stress ECG).[55] Shaw and colleagues, in a large (N = 4638), reasonably well performed evaluation reported that for the comparison of a strategy of SPECT–CA with CA, the SPECT–CA strategy was less costly and that there was no evidence of worse outcomes.[78] A similar comparison was made by Amanullah and colleagues.[108] They reported that in their study, of limited methodological quality, SPECT strategies were dominated by a policy of direct angiography or that direct angiography was associated with a

modest cost per incremental case of severe or extensive case of CAD diagnosed.

Very few interpretable data on the cost-effectiveness of SPECT strategies were available from the studies of Kim and colleagues[109] and Kuntz and colleagues.[99] Nonetheless, Kuntz and colleagues reported that non-invasive strategies appeared to be associated with an incremental cost per QALY of <US$75,000, falling to more modest levels (>US$50,000 per QALY) as the prevalence of disease increased.[99]

Acute coronary syndromes

Four studies considered the strategies involving SPECT for those presenting to the emergency room with chest pain but normal resting ECGs.[110–113] All considered the added value of conducting a SPECT test at rest over and above the use of clinical and ECG information. Two were based on small prospective cohorts with between 9 and 12 months of follow-up[111,112] and one was a small randomised controlled trial (RCT) (n = 46) that had a 30-day follow-up.[113] The fourth used a decision model based on the results from an observational study (n = 102). The duration of time horizon was not stated but was likely to relate to the care episode.[110]

Quality of included studies

In all studies, the focus of the analysis was on costs as three showed that the addition of a rest SPECT would be at least as effective. Only in the RCT was this focus based on an explicit assumption of equal effectiveness.[113] In the other studies, the effectiveness data indicated that outcomes would be the same or better.[110–112] The small samples in all of the studies may make the results unreliable and two studies may have missed important costs and benefits owing to their short follow-up. Three studies focused on costs[110,111,113] and in two of these costs were obtained by converting Medicare charges into costs. In two studies, resource utilisation and unit cost data were not reported. One study reported resource utilisation rates[113] and the other only reported unit costs.[110] Costs were estimated in US$ in all studies but the price year was reported in one.[110] In three studies no sensitivity analysis was reported[111–113] and in the other SA was conducted on the incidence of acute events but did not consider uncertainty in the estimates of sensitivity and specificity except through the use of threshold analysis.[110]

Summary of results

In three studies the SPECT strategy was found to be less costly. Stowers and colleagues showed that patients in the SPECT arm had US$1843 (95% CI US$431–6171) lower median in-hospital costs and 2-day (95% CI 1–3 days) shorter hospital stay, but similar rates of in-hospital and 30-day follow-up events, compared with patients in the conventional arm.[113]

Radensky and colleagues using rest SPECT appeared to be on average US$1032 (17%) less costly (median US$453 or 10%) than a policy based on cardiac risk factors and finding of a rest ECG. Sensitivity analysis showed that the cost of the rest SPECT would have to be twice its baseline level (which was not stated) for the two strategies to have equal cost. It also showed that the specificity of the 'No SPECT' strategy would need to be 65% (baseline 37%) for the strategies to be equivalent. Cost-effectiveness was also influenced by the likelihood that chest pain would lead to an acute adverse cardiac event and only if the risk of an event was >60% would a strategy of 'No SPECT' be less costly.[110] Similarly, Weissman and colleagues showed that SPECT resulted in a cost saving of US$4786 per patient.[112]

In contrast to these results, Kosnik and colleagues found that although the use of SPECT saved treatment costs over a 12-month follow-up compared with a pretest judgement about management (US$1674 versus US$2626), it was more costly when the scan cost was included (US$2626 versus US$2096). This extra cost resulted in 27 patients receiving more appropriate management out of the 29 whose management changed as a result of the SPECT scan.[111]

Management following uncomplicated MI

Two studies were identified that looked at this group, one of which was based on a model[114] and the other on an RCT.[115] In the RCT reported by Barnett and colleagues, a policy of SPECT followed by selective CA was compared with a strategy of CA alone.[115] Dittus and colleagues considered seven strategies,[114] two of which were similar to those considered by Barnett and colleagues.[115] The seven strategies were:

1. medical management (use of beta-blockers, but no further diagnostic tests)
2. stress ECG, CABG surgical or medical treatment
3. stress ECG with selective SPECT and CA; aggressive CABG surgical or medical treatment
4. SPECT and selective CA; CABG surgical or medical treatment
5. SPECT and selective CA; aggressive CABG surgical or medical treatment

6. CA in all; CABG surgical or medical treatment
7. CA in all; aggressive CABG surgical or medical treatment.

Both studies were conducted in the USA and both based their costs on Medicare fees.

Quality of available evidence

Dittus and colleagues used a decision model to estimate the incremental cost per premature death avoided compared with current medical care for a 6-month follow-up period.[114] Data for model parameters came from a combination of published literature and clinical opinion. No additional details of the source of data/literature review methods were reported in the paper. The results relate to a 6-month time horizon, which may not be adequate to capture all relevant costs. Costs were based on charges for diagnostic tests, the costs of surgery and hospitalisation. The RCT reported by Barnett and colleagues was clearly reported and appeared to be competently performed.[115] It included a large number of patients (876) with clear inclusion/exclusion criteria. Although QALYs were not estimated, effectiveness was measured in terms of life-years, which aids comparability. The mean follow-up was only 23 months although results were extrapolated to a lifetime follow-up. The costing methodology, although not completely transferable to the UK, was clearly described. Costs were estimated using Medicare charges along with microcosting methods for the cost of hospital stay. Costs were discounted at 3% per year and reported in 1997 US$. Life-years were also discounted but it is unclear whether a 3% rate was used. Detailed sensitivity analysis was conducted along with bootstrapping of estimates of incremental cost per life-year saved, which facilitates consideration of the generalisability and precision of the results.

Summary of results

Dittus and colleagues reported all results relative to a strategy of standard medical care with 'No testing'.[114] The results showed that strategy 3 (stress ECG and selective use of MPS with positives receiving angiography and subsequent management with low treatment thresholds for the use CABG, surgical or medical treatment) was the most cost-effective. Comparisons between direct angiography and strategies that used SPECT as an initial test were not made and were not possible from the data reported. The incremental cost per death avoided compared with standard medical care was available and it was lower for direct angiography than for strategies based on the initial use of SPECT.

In the study by Barnett and colleagues,[115] the total cost of the SPECT strategy was significantly lower (US$39707) than that for the angiography strategy (US$41893) ($p = 0.04$). The difference in survival between the two strategies was also statistically significant, with those receiving the angiography strategy having an average of 1.79 years of survival compared with 1.86 years for the SPECT strategy over a 2-year follow-up. These results were stable over the SAs reported.

The two studies appeared to consider similar patient populations but they used different outcome measures, which makes it difficult to compare them. However, as the study by Barnett and colleagues[115] was a large, generally clearly reported, RCT whereas the study by Dittus and colleagues provided insufficient detail of how data were assembled,[114] it is likely that the data from Barnett and colleagues are the more reliable.

Review of economic evaluations contained in the Industry submission

The Industry submission was based on a review that involved the searching of the major relevant bibliographic databases and handsearching of journals. There is insufficient documentation provided on the electronic search strategies to comment on the adequacy of the database searching. It is unclear whether the search terms were restricted to subject headings only or if text word searching was also employed. It is also not stated whether any subject heading terms that were included were exploded to include more specific terms. However, the handsearching that was undertaken was comprehensive and included the most relevant journals. The quality of this review is summarised in *Table 26*.

More studies were identified in the Industry submission than were identified in the review reported in the section Number of studies identified (p. 40). In terms of the quality assessment tools used in the Industry submission, primary studies were assessed using the *BMJ* guidelines for reviewers of economic evaluations[94] and the reviews were assessed using the CRD quality assessment instrument. It was less clear precisely how studies that fared poorly using the *BMJ* criteria were excluded and for this reason the quality assessment of studies is only partly reproducible.

TABLE 26 *Quality assessment of the review*

Stem	Result
Is it unlikely that important relevant studies were missed?	Yes
Were the inclusion criteria used to select articles appropriate?	Yes
Was the assessment of studies reproducible?	Partly
Were the design and/or methods and/or topic of included studies broadly comparable?	Yes
Are the overall results reproducible?	Yes
Will the results help resource allocation in healthcare?	Partly

The studies included in the review used a variety of different methods, which limited their comparability. A number of studies included in the Industry review were excluded from our review as they were judged not to have attempted to combine costs and effects or to have explicitly made the assumption that effects were the same. In general, the interpretation of data by Industry is similar to that provided by this appraisal, although it is worth noting a number of key points:

1. The cost data used in US studies are greater than those used in UK studies especially for invasive tests. Therefore, strategies in which a large proportion of patients receive CA are less likely to be considered cost-effective.
2. For patients at intermediate pretest risk of coronary artery disease, CA is more costly but also more effective (although based on an assumption of perfect information). It is therefore a question for policy-makers to decide whether extra benefits are worth the extra cost.
3. It is unclear how applicable any of the QALY data provided are to decision-making in the UK. In all but two studies[99,104] the reader was left with no clear idea how QALY data were derived. Even in the two stronger studies QALYs were based on condition-specific time trade-off or standard gamble questions. These sources are far from ideal for priority setting.
4. The data are mixed as to whether a strategy of stress ECG followed by SPECT in positives is superior to a strategy of SPECT alone for those at intermediate risk of coronary artery disease.

Review of the Industry submission economic evaluation

In this section, the Amersham Health Industry submission is described and commented on. The first part provides a summary and this is followed by a critique of their methods of data collection and analytic approach.

Summary

The economic evaluation contained within the Amersham Health submission estimated the incremental cost per accurate result and incremental cost per life-year and QALY for seven diagnostic strategies for a time horizon of up to 25 years. Each diagnostic strategy consisted of between one and three sequential diagnostic tests. The strategies considered were:

1. direct CA
2. stress ECG, CA if stress ECG is positive or non-diagnostic (ECG–CA)
3. SPECT (MPS), CA if SPECT is positive or non-diagnostic (SPECT–CA)
4. stress ECG, SPECT if stress ECG is positive or non-diagnostic, CA if SPECT is positive or non-diagnostic (ECG–SPECT–CA)
5. stress ECG, SPECT if stress ECG is negative or non-diagnostic, CA if SPECT is positive or non-diagnostic (ECG–NegSPECT–CA)
6. stress ECG, SPECT if stress ECG is non-diagnostic, CA if SPECT is positive or non-diagnostic (ECG–NDSPECT–CA)
7. no testing.

These strategies are similar to those from the published economic evaluations, summarised in the section 'Systematic review of published economic evaluations' (p. 40). The evaluation comprises two components: (a) a decision tree model (DTM), focusing on diagnostic performance, and (b) a Markov model, estimating payoffs by extrapolating from diagnostic performance into longer term costs and consequences. The first 'decision model' component provided estimates of incremental cost per accurate diagnosis whereas the incorporation of the 'payoff' component facilitated the estimation of incremental cost per life-year and QALY.

The sensitivity and specificity of both stress ECG and SPECT, required for the DTM, were based on published reviews of the literature. Other

probabilities were taken from other previously published models, notably by Kuntz and colleagues (1999).[99] The payoff model was structured so that for individuals the initial treatment was decided on the basis of the severity of their disease and the likelihood that it was diagnosed. Although not stated in the text of the submission, it was assumed that following diagnosis all those with left main vessel disease (LMD) or three-vessel disease (3VD) would receive either CABG (100% LMD, 80% 3VD) or PTCA (20% 3VD). Rates of revascularisation were assumed to be lower for single vessel disease (SVD) (30%) and two-vessel disease (2VD) (40%). Those not receiving surgery were assumed to receive medical management. Subsequent costs and events were based on the effect that initial choice of management had on MI and revascularisation rates and mortality. The choice of many of the key parameter values required by the model was informed by the earlier evaluation by Kuntz and colleagues, although some parameter values are based on assumptions (e.g. the risk reduction provided by medical management).[99]

All costs were reported in UK£ for 2002 and costs occurring after the first year were discounted at a 5% rate. The costs of non-invasive diagnostic tests were based on a survey of three NHS hospitals; the costs of an angiogram, revascularisation and MI were based on NHS reference costs. Medical therapy costs were based on the recent literature inflated to 2002 UK£. Utility weights were based on a standard gamble survey conducted in the USA. The model differentiated between different severities of disease and whether disease was diagnosed. The weights were attached to the survival estimates provided by the payoff model to provide QALY estimates.

In common with the studies reported in the section 'Systematic review of published economic evaluations' (p. 40), judgements about cost-effectiveness were influenced by the prevalence of disease and that at high prevalences the CA strategy is more likely to be considered cost-effective. At low rates of prevalence (15% disease), SPECT–CA (strategy 3) dominates the CA strategy and ECG–NegSPECT–CA (strategy 5). It is further argued that because it has the lowest incremental cost versus 'No testing' (£3271 per extra accurate diagnosis; £30,887 per life-year; £14,125 per QALY) of the other strategies that are less costly but less effective it has extended dominance over them. At a 30% prevalence rate the SPECT–CA strategy dominates or has extended dominance over all strategies except ECG–NegSPECT–CA and CA, which are both associated with very high incremental costs per QALY. As the prevalence of coronary artery disease increases, the similarity of the incremental cost per QALY of the different strategies versus 'No testing' increases. At the 50% prevalence rate it is possible that CA would be considered cost-effective, as the incremental cost per QALY of moving from SPECT–CA to CA was £17,818. At 80% prevalence it was reported that CA dominated ECG–NegSPECT–CA and had extended dominance over the other strategies compared with 'No testing'.

SA was reported for changes in parameter values for three scenarios. Two relate to the comparison of SPECT–CA with 'No testing' at low risk (15%) and very low risk (10 and 5%) of disease. The third scenario involved the comparison of SPECT–CA and CA at a 50% prevalence level of disease. For the first and third scenarios, one-way SAs were conducted investigating (i) effect of discounting, (ii) time horizon over which costs and benefits accrue, (iii) time taken to identify and treat FNs, (iv) diagnostic performance of SPECT, (v) changes in costs of SPECT, (vi) changes in costs of an angiogram and (vii) mortality risk associated with an angiogram. The first analysis showed that adopting a 0% discount rate tended to improve the cost-effectiveness of the more costly but effective strategy as the later benefits of the more effective strategies were given more weight in the analysis. However, the overall effect of the change was small. The second analysis showed the importance of the time horizon, particularly for the comparison of SPECT–CA with CA. The rationale given for this was that the shorter time horizon of 10 years used in the sensitivity analysis reduced the time over which the benefits of a screening strategy could be accrued. In the third analysis, the time that it took false negatives to be identified was reduced from 5 to 2 years. This had the effect of reducing the penalties associated with an inaccurate diagnosis. As a result, SPECT–CA improved its cost-effectiveness compared with 'No testing', but paradoxically its cost-effectiveness reduced in comparison with CA. Reducing the sensitivity and specificity of SPECT (sensitivity changed from 89 to 88% and specificity changed from 91 to 77%) has little impact on the comparison of SPECT–CA to 'No testing'. For the comparison of CA and SPECT–CA, the CA strategy improved in cost-effectiveness. The fifth sensitivity analysis considered the effect of lowering the cost of obtaining a SPECT scan from £275 to £200. As would be expected, this improved the cost-effectiveness of strategies involving SPECT. Changing the cost of an

angiogram to £1000 from £734 led to a small increase in the incremental cost per QALY when SPECT–CA was compared with 'No testing', which in part is due to the relatively small proportion of patients with disease and the high sensitivity and specificity of SPECT. In contrast, the increase in the cost of an angiogram led to CA becoming less cost-effective. It would be expected that this effect would become less important at higher prevalence when a greater proportion of those screened using the SPECT–CA strategy would test positive and receive an angiogram. The seventh sensitivity analysis involved the increase in mortality risk of an angiogram from 0.15 to 0.5%. For comparison of SPECT–CA with 'No testing', the effect was not large as the likelihood of receiving an angiogram was not large. At a 50% prevalence rate, SPECT–CA dominated the CA strategy but it would be expected that as prevalence increased and the likelihood of receiving an angiogram with the SPECT–CA strategy increased then the difference between SPECT–CA and CA strategies would diminish.

A final sensitivity analysis showed that as the prevalence of disease fell to very low levels SPECT–CA became less cost-effective than 'No testing' with an incremental cost per QALY of nearly £29,000 being reported at a 5% prevalence.

Critique of Industry submission

The economic evaluation included in the Industry submission appeared to be comprehensive and competently performed. The main assumptions underpinning the model were highlighted and the sources of parameter values noted.

In the base-case analysis presented in the Industry submission, the sensitivity and specificity of SPECT were at the higher end of the spectrum of estimates used in previous economic analyses. The alternative values used in the sensitivity analysis still had a specificity of SPECT higher than that estimated in the review of diagnostic studies reported in Chapter 3. It is not inconceivable that the rates used in the Industry submission do represent the true sensitivity and specificity but the review presented in Chapter 3 indicated that there was strong statistical evidence of heterogeneity between diagnostic studies. Therefore, a larger variation in sensitivity and specificity values may need to be considered. If the sensitivity and specificity of SPECT were reduced, the relative cost-effectiveness of ECG- and angiography-based strategies would improve, perhaps to a level deemed acceptable.

The two comparisons that the sensitivity analysis focused upon were based on the consideration of which strategies were dominant (less costly and more effective) or had extended dominance. Extended dominance occurs when a strategy is more costly and less effective than a combination of two other strategies, one of which is less costly and less effective and the other is more costly and more effective. One of the implications of eliminating a strategy because of extended dominance is that a proportion of the treated population will receive the less effective treatment. In the Industry submission the comparison of SPECT with 'No testing' is justified because SPECT has extended dominance over the other non-invasive strategies. SPECT–CA only has extended dominance if it is accepted that a proportion of the eligible population will be screened using the SPECT–CA strategy and that the rest will receive the 'No testing' strategy. The impact of this particular implication is not considered within the Industry submission. If conclusions are not based on the use of extended dominance then the results of stepwise incremental analysis should be considered. *Table 27* presents a stepwise analysis for the comparison of the different screening strategies based on data presented in the Amersham Health submission. The results of this analysis provide information about whether the extra benefits of a more costly strategy are worthwhile.

When one of the screening strategies was extendedly dominated by the SPECT–CA strategy it meant that it was less costly and less effective but had a higher incremental cost-effectiveness ratio compared with no screening. In some circumstances it is conceivable that the uncertainty surrounding the results presented would be sufficient for conclusions about extended dominance to be reversed. This uncertainty could, as the Industry submission indicated, be formally considered in the analysis but it would greatly increase the complexity of the analysis and interpretation.

One of the most striking aspects about the results presented was the difference between the incremental cost per life-year and the incremental cost per QALY. For example, at a 50% risk of disease incremental cost per life-year for the comparison of the SPECT–CA strategy with the CA strategy was £375,100 but the incremental cost per QALY was only £17,862. The utility weights used in the Industry model are probably the best available but as noted earlier, they may not be wholly appropriate for priority setting in the UK.

TABLE 27 *Estimation of stepwise incremental cost per QALY at different prevalences of coronary artery disease (based on data presented in Table 22 of the Amersham Health submission)*

Prevalence (%)	Strategy	Diagnosis model				Payoff model		Stepwise incremental cost per QALY			
		Cost (£)	FNs	Acc.	DDs	Cost (£)	LYs	QALYs	Inc. cost (£)	Inc. QALYs	Inc. cost per QALY (£)
15	1. No testing (reference)	0	150	850	0	4833400	15516	13435			
	4. ExECG +ve MPS CA	366617	43.9	956	0.31	5534391	15538	13484	700991	48	14483
	2. ExECG CA	491203	33.6	966	0.81	5689297	15533	13482	Dominated	Dominated	Dominated
	3. MPS CA	445959	13.2	986	0.42	5710172	15544	13497	175781	14	12831
	5. ExECG –ve MPS CA	599952	6.9	992	0.65	5883108	15542	13497	Dominated	Dominated	Dominated
	6. ExECG ind. MPS CA	403988	37.6	962	0.49	5590919	15537	13484	Dominated	Dominated	Dominated
	7. CA (reference)	736429	0	999	1.5	6037856	15531	13489	Dominated	Dominated	Dominated
30	1. No testing (reference)	0	300	700	0	5384800	15183	13082			
	4. ExECG +ve MPS CA	450812	87.7	912	0.46	6505051	15230	13181	1120251	99	11316
	6. ExECG ind. MPS CA	464770	75.1	924	0.61	6558189	15231	13185	53138	4	12960
	2. ExECG CA	525986	67.2	932	0.88	6643350	15229	13185	Dominated	Dominated	Dominated
	3. MPS CA	532563	26.5	973	0.59	6780024	15244	13209	221835	24	9092
	5. ExECG –ve MPS CA	663126	13.9	985	0.8	6949553	15244	13213	169529	3	49861
	7. CA (reference)	736429	0	999	1.5	7063706	15236	13210	Dominated	Dominated	Dominated
50	1. No testing (reference)	0	500	500	0	6120000	14739	12610			
	4. ExECG +ve MPS CA	563033	146	853	0.66	7799226	14819	12776	1679226	166	10092
	6. ExECG ind. MPS CA	545788	125	874	0.78	7847860	14823	12785	48634	9	5527
	2. ExECG CA	572355	112	887	0.98	7915412	14823	12789	67552	4	17777
	3. MPS CA	647987	44.1	955	0.83	8206446	14843	12825	291034	36	8152
	5. ExECG –ve MPS CA	747327	23.1	976	1	8371451	14845	12833	165005	8	20626
	7. CA (reference)	736429	0	999	1.5	8431506	14843	12837	60055	5	13055
85	1. No testing (reference)	0	800	200	0	7222800	14073	11903	7222800	11903	
	4. ExECG +ve MPS CA	731281	234	765	0.95	9740405	14203	12170	2517605	268	9408
	6. ExECG ind. MPS CA	667266	200	799	1.02	9782316	14210	12186	41911	16	2669
	2. ExECG CA	641893	179	820	1.12	9823490	14214	12195	41174	9	4475
	3. MPS CA	821021	70.6	928	1.18	10345977	14241	12248	522487	53	9858
	7. CA (reference)	736429	0	999	1.5	10483206	14254	12279	137229	31	4485
	5. ExECG –ve MPS CA	873565	37	962	1.3	10504233	14248	12263	Dominated	Dominated	Dominated

Acc., accuracy; DDs, Diagnostic deaths; FNs, false negatives; Inc., incremental; ind., indeterminate; LYs, Life-years.

It would have been useful for the effect on the results of different utility values to be considered formally.

Summary of findings

Although prevalence of coronary artery disease has a large role to play in the determination of cost-effectiveness, the evidence is consistent that non-invasive strategies may be considered to be a better use of resources than the adoption of a strategy of direct angiography. Furthermore, the results generally indicate that strategies involving SPECT are likely to be either dominant or provide additional benefits that might be considered worth the additional cost compared with strategies involving stress ECG alone as a method of selecting patients for angiography.

There is less consistency about which of the various strategies that involve SPECT should be chosen. In part, this reflects the differing parameter values used and the different model structures. Only four studies, including the Industry submission, made the comparison between SPECT–CA and stress ECG followed by SPECT in positives and non-diagnostics (stress ECG–SPECT–CA). Of these, two concluded that stress ECG–SPECT–CA was cost-effective and two indicated that the extra benefits provided by SPECT–CA might be worth its additional cost. It is worth noting that three of these studies considered UK costs and that two studies used the same sensitivity and specificity data but came to different conclusions.

Although several studies including the Industry submission appeared to be of high quality and used data from existing reviews, the sensitivity and specificity used for SPECT varied. Higher rates were used in the Industry model than in many of the other evaluations and the extent to which these rates are appropriate is unclear. The results presented in Chapter 3 provide estimates of sensitivity and specificity that are lower than provided elsewhere but, perhaps more importantly, they indicate there is considerable uncertainty surrounding estimates of sensitivity and specificity that earlier reviews may not have fully reflected.

One of the common structural assumptions of many of the models is that the next test in a strategy is performed if the previous one is abnormal or inconclusive. The impact of this is that, depending on sensitivity and specificity data, a large proportion of patients would ultimately receive a coronary angiogram. The data reported in the section 'Critical review and synthesis of information – prognostic studies' (p. 25) suggest that SPECT has independent prognostic power over and above that provided by CA and may be useful for identifying patients with CAD for whom revascularisation is not an immediate treatment option. Allowing non-invasive strategies to identify these patients would tend to reduce the cost of the strategy with no significant impact on health, although this would depend on the accuracy of the test and consequences of misdiagnosis.

The evidence available for the use of SPECT-based strategies for the diagnosis of coronary artery disease in women is limited to a small number of studies conducted outwith the UK. These studies indicate that SPECT-based strategies may become cost-effective as the prevalence level of coronary artery disease increases. Similarly, only four studies considered the use of SPECT-based strategies for those with acute coronary syndrome. Three studies showed that the use of SPECT was likely to be less costly and at least as effective as a strategy based on clinical data and the findings of a rest ECG whereas one study showed it to be more costly but more effective.

The use of SPECT post-MI was limited but one RCT suggested that the use of SPECT would be cost saving. An earlier model-based analysis, however, reported that compared with standard care the incremental cost per death avoided was lower for a direct angiography strategy than a strategy involving SPECT.

The review identified seven studies which considered the cost-effectiveness of other diagnostic strategies for the diagnosis of CAD, such the use of positron emission tomography (PET) and stress echocardiography (ECHO). These interventions were not considered to be within the scope of this review. Of these tests, the most frequently used in diagnostic strategies was stress ECHO, and for this reason the results of comparisons between SPECT-based strategies and echocardiography-based strategies are summarised below.

Five of the seven studies were based in the USA, one in Korea and one in Australia. The number of comparator strategies differed between each study, but all studies included stress SPECT. Three of the studies used Markov modelling techniques to

compare the cost-effectiveness of the alternative strategies and results were estimated in terms of incremental cost per QALY ratios.[99,104,109] Of the other studies, Rumberger and colleagues estimated the average CEA of alternatives in terms of diagnostic accuracy.[103]

The patient populations and risk groups varied across the seven studies. All except one[116] categorised patients into risk groups according to pretest probability of CAD. Three studies included a very wide risk range (zero to one in five groups, Kuntz and colleagues;[99] zero to one in three groups, Shaw and colleagues;[78] 0.1 to one in four groups, Lee and colleagues[117]). Garber and Solomon[104] included only intermediate risk patients [p (CAD) = 0.25–0.75]. Kim and colleagues[109] based their three low- to intermediate-risk groups on three scenarios for women aged 55 years: definite angina [p (CAD) = 0.06], probable angina [p (CAD) = 0.31] and non-specific chest pain [p (CAD) = 0.71]. Lauffer and colleagues[116] did not describe patients in terms of pretest probability of CAD, but included a study population of patients referred for assessment of existing or suspected CAD.

Two studies based their data on the diagnostic performance of ECHO on the meta-analysis by Kuntz and colleagues[99,105] and one used an earlier review.[103] A further two used rates from their own reviews,[104,109] of which one assumed no difference in performance between SPECT and ECHO[117] and one based the results on an RCT which reported no difference in sensitivity and higher specificity for ECHO.[116] Overall, four studies assumed that ECHO was associated with lower sensitivity but higher specificity than SPECT.[99,103–105] One study comparing SPECT and ECHO in women reported higher sensitivity and specificity for ECHO.[109]

From their Markov model analysis, Garber and Solomon reported incremental cost per QALY results for SPECT compared with ECHO of US$64,000 (for men aged 65 years) and US$150,000 (for women aged 45 years).[104] The results from the model used by Kuntz and colleagues[99] included incremental cost per QALY estimates for SPECT compared with ECHO for patients with typical angina (US$62,800) and for patients with atypical angina (US$108,900). Kuntz and colleagues[99] and Kim and colleagues[109] reported results in a way which was difficult to interpret numerically in terms of cost-effectiveness, although they reported that exercise ECHO was more cost-effective than exercise SPECT at all levels of pretest risk of CAD. Rumberger and colleagues reported lower average cost-effectiveness for exercise ECHO than exercise SPECT at low, medium and high pretest CAD risk; despite SPECT being more costly than ECHO, SPECT was found to have better diagnostic accuracy than ECHO. When ICERs are estimated from these average CER results, the incremental cost per true positive diagnosis for SPECT compared with ECHO was >US$16,000 at all levels of prevalence.[103] Lee and colleagues considered the cost-effectiveness of stress ECHO compared with stress SPECT in terms of the prognostic value of FN results. For patients with a pretest CAD risk of ≥ 0.3, SPECT was found to be more cost-effective than ECHO, mainly owing to the lower rate of FNs from SPECT than from ECHO. At lower risk levels (<0.3) these results are reversed.[117] From their RCT (n = 115), Lauffer and colleagues reported both lower costs and higher specificity for exercise ECHO than for exercise SPECT, with no significant difference in test sensitivity.[116] Shaw and colleagues used pooled data from 210 US hospitals in a decision analytic study which included a comparison of stress ECHO and stress SPECT. Stress ECHO was reported to have the highest test sensitivity and a lower cost per patient than SPECT, but the data are presented in such a way as to preclude any accurate interpretation of ICERs.[105]

Although the underlying sources of the data on diagnostic performance have not been critically appraised, they appear to have been competently collected. Although none of the studies were conducted within the UK, their results indicate that echocardiography may be worth further consideration and may provide an alternative method of improving the management of people with CAD.

Chapter 5
Economic analysis

Economic modelling

The cost-effectiveness and economic evaluation of SPECT MPS relative to stress ECG and CA for the diagnosis and management of CAD have been assessed using economic evaluation modelling techniques. A DTM was used for the diagnosis decision (Appendix 12, *Figure 11*) and a simple Markov model (Appendix 12, *Figure 12*) for the management of patients with suspected CAD (both of them developed in Data 4.0[118]). The model structure has been developed following consultation with clinicians and consideration of the existing economic evaluation literature presented in Chapter 4.

Decision tree model

The DTM is a way of displaying the proper temporal and logical sequence of a clinical decision problem.[119] In this case, this decision tree is thought of as a static model although in actuality going from the first decision node to the final outcome may take weeks or even months.

The interventions considered in the DTM were SPECT, stress ECG and CA. Broadly, these are tests used for the diagnosis of heart disease. The results of these tests are positive or negative for stress ECG and SPECT and high, medium or low risk for CA (*Table 28*).

These diagnostic tests may be combined to produce the following strategies (thought representative of current practice):

1. stress ECG, followed by SPECT if stress ECG positive or indeterminate, followed by CA if SPECT positive or indeterminate
2. stress ECG, followed by CA if stress ECG positive or indeterminate
3. SPECT, followed by CA if SPECT positive or indeterminate
4. CA (invasive test as first option).

TABLE 28 *Results from the diagnostic tests*

Test	Result
Stress ECG	Positive or negative
SPECT	Positive or negative
CA	High risk, medium risk, low risk

Within the model described in Appendix 12 (*Figure 11*), a patient may, for example, arrive in the hospital with typical chest pain. Taking the patient's history and symptoms into account, the physician must decide between an invasive test (CA) or a non-invasive test as the first option (namely, stress ECG or SPECT) to assist in making the diagnosis. If the physician decides on an invasive test, then the patient has a risk of dying during the test. If the patient survives, then this will result in a final classification of his/her condition into one of three categories: high risk (i.e. 3VD and poor left ventricular function or LMD), medium risk (SVD or 2VD) or low risk (no significant heart disease present). This strategy is the one followed for patient A in *Table 29*.

In the same way, the physician could decide for patient B to adopt a non-invasive (stress ECG) test as the first option. If the result of this test is positive, another non-invasive test, SPECT, could be requested. Then, if the SPECT test result is positive, the patient could be diagnosed as high risk or a CA requested to help determine appropriate management. As a final outcome of this strategy for this particular patient, he/she will receive an LMD diagnosis and be classified as high risk. Similarly for patient C, the adoption of a non-invasive test decision first (SPECT), followed by a negative result enables the physician to classify the patient as low risk.

Each of these strategies considered by the model has associated expected costs and consequences. Depending on the probabilities of the occurrence of each event and on the accuracy of the tests, the relative efficiency of these strategies is estimated.

The importance of this model is to consider the different ways in which the SPECT intervention enters the different strategies. In strategy 1 SPECT is adopted as a method of confirming a positive result or dealing with an indeterminate result of stress ECG, whereas in strategy 3 SPECT is used as a substitute for stress ECG.

TABLE 29 *Examples of paths followed for different patients*

Patient	Path
A	CA → survive → positive result → 3VD → classified as high risk
B	Non-invasive test → stress ECG → positive result → SPECT → positive result → CA → positive result → LMVD and classified as high risk
C	Non-invasive test → SPECT → negative result → classified as low risk

TABLE 30 *Interventions and events considered in the Markov model*

Low-, medium- and high-risk states	Medical management MI
Low-, medium- and high-risk revascularisation states	Revascularisation, PTCA Revascularisation, CABG Further revascularisation Medical management MI
FN: true medium- or true high-risk states	Medical management MI Rediagnose (CA)
FP: true low-risk state	Medical management MI Rediagnose

Markov model

The Markov model can provide the estimated costs and outcomes over the lifetime period of a cohort of patients for the different management strategies adopted following diagnosis. Subject to the results of the clinical review and data availability, the model estimates of costs and outcomes were derived for women.

A Markov model of the type presented here has states in which patients stay for a period of time called a 'cycle'. The cycle must be a relevant period of time to the condition considered (e.g. 6 months, 1 year). At the end of the cycle, the individuals can remain in the state in which they started the cycle or can move to a different state. The probabilities of moving from one state to another are called transition probabilities. Finally, in these models there must be at least one absorbing state, that is, a state from which the patient will not be able to leave.

At the end of each branch of the decision tree, the patient will enter one of the following states of the Markov model: (a) low risk; (b) medium risk; (c) high risk; (d) FN (high risk); (e) FN (medium risk); (f) FP (medium risk) (an FP state has not been allowed for high risk as the model has assumed that all patients identified as high risk would receive an angiogram and therefore definitive diagnosis). Cycles last 1 year and the absorbing state is 'death', which can be reached from any of the other states. Patients who receive and survive a revascularisation move to a revascularisation state, in which they enjoy the benefits of the revascularisation (lower risk of death and MI) until they die or it is felt that the benefits of the revascularisation will no longer be obtained. The interventions and events considered in each state are shown in *Table 30*.

These states can be thought of as comprising a number of events that influence cost and outcome. For instance, when patients enter the high-risk state, they could have a revascularisation and move to the revascularisation state. Patients in the high-risk state will also receive medical management and during the cycle some patients could suffer MI and as a result a proportion will die, but others will survive and remain in the state. Patients moving to the high-risk revascularisation state will receive medical management, may experience a non-fatal MI, further revascularisation, which will be followed by medical management, or death. A similar process can be described for the other states.

In this model, there are a number of states that a patient may enter into as a result of being classified as TN or FP. The assumption within the

TABLE 31 *Interventions considered in the DTM*

	Total cost (£)	Source	Total cost (used in the model) (2001–02 £)	Method for actualisation
Stress ECG	107.00	Hartwell, 2004[120]	104.86	Assumption (2001–02 to 2002–03 2% inflation rate)
SPECT	220.00	Underwood, 1999[82] (1996–97 prices)	261.91	HCHS Pay and Prices Index
CA	1100	Underwood, 1999[82] (1996–97 prices)	1309.55	HCHS Pay and Prices Index

HCHS, Hospital and Community Health Services.

TABLE 32 *Interventions considered in the Markov model*

	Total cost (£)	Source	Total cost (used in the model) (2001–02 £)	Method for actualisation
Medical management	317.20	See Appendix 15	311.00	Assumption (2001–02 to 2002–03 2% inflation rate)
MI	1122.00	NHS cost 2001–02	1122.00	Not applicable
PTCA	2034.00	Hartwell, 2003[120]	1993.74	Assumption (2001–02 to 2002–03 2% inflation rate)
CABG	4397.00	NHS cost 2001–02	4397.00	Not applicable

model is that everyone is correctly diagnosed over a 10-year period either as a result of an additional scan or as a result of a non-fatal MI.

Costs

Decision tree model costs

The costs of the three interventions considered in the model are presented in *Table 31*.

The total costs for stress ECG and CA are £104.86 and £1309.55 and are based on data by Hartwell and colleagues[120] and Underwood 1999[82]; both figures are in 2001–02 pounds sterling. The cost of stress ECG was calculated from HRG V05 category.[124] As the authors reported in Appendix 6 of their report, it is Accident and Emergency direct cost plus a share of support services (pathology and radiology) and has been calculated in a top-down approach.

The SPECT total cost was obtained from Underwood and colleagues.[82] Their figures were derived by averaging 1996 data for UK centres and the Royal Brompton Hospital, London, which was judged to be the most meaningful by the authors. These costs were estimated using a very detailed bottom-up costing exercise where all resources were itemised and costed (Underwood SR, Imperial College of Science, Technology and Medicine, Royal Brompton Hospital, London, personal communication, 2003). The cost estimate was checked with an estimate derived using a top-down approach with data from different sources which confirm the figures from the EMPIRE study. The costs reported by Underwood and colleagues were inflated using the Hospital and Community Health Services (HCHS) Pay and Prices Index.[121]

Markov model costs

Table 32 shows the interventions considered for the Markov model, the cost as reported, the sources from where the figures were obtained, the cost in 2001–02 pounds sterling and the method of adjusting for inflation if applicable.

For the low-risk state, two interventions were considered: medical management and MI event

TABLE 33 *Cost for angioplasty (PTCA) (assumes 60 minutes in theatre; includes angiography)*

		Total for procedure (2002–03 £)	Total for procedure (2001–02 £)[a]
Staff	1 × cardiologist	46.35	45.42
	1 × radiographer	14.71	14.42
	1 × technician (= MTO)	17.75	17.40
	2 × nurses	22.63	22.18
	Total	101.40	99.40
Non-staff	Stents	825.00	808.50
	Drug-eluting stent	382.00	374.36
	Balloon catheter	317.00	310.66
	Guiding catheters (3 units)	159.00	155.82
	Fem stop	100.00	98.00
	Dyes and other consumables for angiography	150.00	147.00
	Total	1933.00	1894.30
	Overall total	2034.00	1994.00

Source: Hartwell 2004,[120] Appendix 6: Health Economics, p. 116.
[a] Actualised using HCHS Pay and Prices Index.
Items rounded to nearest £0.01, totals rounded to nearest £0.10, overall totals rounded to nearest £1.00. Note that number used in analysis was £1993.74.

management. Medical management for the different states was obtained from experts' opinion and checked with the literature; it was found that the final figure did not differ much from that presented by Sculpher and colleagues.[121] Prices for this calculation were obtained from the *British National Formulary*.[122] For MI event management cost, Boland and colleagues[123] were followed. The authors used NHS Reference Costs;[124] then, figures for 2001–02 and the same source were used in our model.

The cost for PTCA is £1993.74,[120] and the calculation assumes 60 minutes in theatre and an angiography, five professionals and non-staff items (*Table 33*). The cost for CABG was obtained from NHS Reference Costs.[124] The cost of managing an MI is the same as in the low-risk state. When appropriate, the figures were adjusted for inflation using HCHS Pay and Prices Index (see Appendix 14).

Finally, cost per year was calculated for each state in this model. The present value of these costs were calculated using the equation

$$PVC_A = TC_A + \sum_t P_{xt} P_{yt} C_A / (1 + 0.06)^t$$

where:
A is the possible states in the model and
$t = 1, \ldots, n$
PVC_A = present value of costs of state A over the n years
TC_A = total cost of diagnosis process
P_{xt} = probability of being alive in year t
P_{yt} = probability of remaining in actual state
C_A = cost associated with state A
0.06 = discount rate for costs as stated in NICE HTA guidelines.[125]

Probabilities

Decision tree model probabilities

DTM probabilities were assessed from the literature or calculated in the model. *Table 34* shows that many of these were derived from the results of the effectiveness review (see Chapter 3). The sensitivity and specificity of SPECT and stress ECG in *Table 34* were based on a simple synthesis of the mean data from each of the 16 studies reported in the section 'Critical review and synthesis of information – diagnostic studies' (p. 19), including the two studies which provided sensitivity and specificity for SPECT only and which were excluded from subsequent analysis in that section.

The prevalence of coronary heart disease was obtained from British Heart Foundation Statistics. With this, sensitivity, specificity from ER, positive and negative result rates were calculated for diagnostic strategy. Assuming sensitivity and specificity rates were independent of underlying prevalence of CAD, positive and negative result rates were calculated for diagnostic strategy at different pre-test risks of CAD.

Markov model probabilities

The time horizon for the Markov model was a maximum 25 years to enable comparisons with the

TABLE 34 A priori *probabilities for decision tree*

		Value	Range	Source
Prevalence of disease for patient cohorts	Males	10.5	10.5–90	BrHF Statistics, 2003[1]
	Females	5.5	5.5–90	BrHF Statistics, 2003[1]
Proportion of SVD		0.41		Shaw, 1999[77]
Proportion MVD and/or LMD		0.59		Shaw, 1999[77]
Intervention				
Stress ECG	Sensitivity	0.66	0.42–0.92	ER (pooled data)
	Specificity	0.60	0.43–0.83	ER
	Indeterminacy	0.18		Patterson, 1995[102]
	Positive result proportion	Calculated in the model		Calculated using Bayes with ER data
	Negative result proportion	Calculated in the model		Calculated using Bayes with ER data
	Mortality risk	0.00005		Patterson, 1995[102]
SPECT	Sensitivity	0.83	0.63–0.93	ER
	Specificity	0.59	0.44–0.90	ER
	Indeterminacy	0.09		Patterson, 1995[102]
	Positive result proportion	Calculated in the model		Calculated using Bayes with ER data
	Negative result proportion	Calculated in the model		Calculated using Bayes with ER data
	Mortality risk	0.00005		Patterson, 1995[102]
CA	Sensitivity	1.00		Assumption
	Specificity	1.00		Assumption
	Mortality risk	0.0015		Patterson, 1995[102]

ER, effectiveness review; MVD, multiple vessel disease.

Industry submission. In *Table 35* the usual transition probabilities scheme for Markov models is presented. The risk of dying from any of the states was calculated as the mortality rate for the corresponding age group with adjustments for the relative risk caused by the level of risk and beneficial effects of medical or surgical treatment. The mortality rate for men and women for England and Wales produced by the Government Actuary's Department was used to assess the mortality rate for the general population.[126]

Within the Markov model, states are defined for both FNs and FPs. The model allows for an increasing proportion of misclassified patients to be allocated properly in each cycle. For the base-case the complete cohort of misclassified patients is correctly allocated within 10 years.[126]

In our DTM, every patient classified as high risk had gone through CA. Given the assumption of perfect information for CA in the base-case of the model (i.e. specificity and sensitivity =1), the probability of FN results will be zero. Therefore, misclassification of patients will not occur and there is no chance that patients will be falsely diagnosed as at high risk. The implications of relaxing this assumption are discussed below. Similarly, patients at medium risk all receive CA in the base analysis and therefore FP rates are zero. The implications of relaxing this assumption are explored within the SA.

The risk of MI is considered for each state. The risk for the general population, used for the low-risk state, was obtained from Lampe and colleagues.[127] The relative risk for the other states was derived from Shaw and colleagues.[77] These proportions were split into fatal and non-fatal MI using data from Lampe and colleagues[127] and Volmink and colleagues.[128]

Annual revascularisation risk in medium and high-risk states and risk of second revascularisation when having PTCA or CABG were derived from Kuntz and colleagues.[99] *Table 35* shows the probability values used in the model with their sources.

Women

A subgroup analysis was conducted for women. This analysis made use of the relevant age-specific

TABLE 35 *Probabilities for the Markov model*

	Value	Source	Observations
Mortality			
Annual rate for age X		Interim life tables	Appendix 13
Relative risk medium risk	2.3	Yusuf, 1994[129]	
Relative risk high risk	3.6	Yusuf, 1994[129]	
Risk of MI			
Low risk FP	2.5%	Shaw, 1999[77]	
Medium risk and FN (medium risk)	5.0%	Shaw, 1999[77]	
High risk and FN (high risk)	9.0%	Shaw, 1999[77]	
Proportion fatal MI	44.84%, 51.08%	Based on Lampe, 2000[127] and Volmink, 1998[128]	Males, females
Revascularisation			
Proportion revascularisation	5%, 50%, 100%	Assumption	Low risk, medium risk, high risk
Proportion PTCA medium risk	61%	BrHF Statistics, 2003[1]	
Proportion CABG medium risk	39%	BrHF Statistics, 2003[1]	
Proportion PTCA	90%, 10%	Assumption	Low risk, high risk
Proportion CABG	10%, 90%	Assumption	Low risk, high risk
Proportion of patients with 2nd revascularisation		Kuntz, 1999[99]	
PTCA	3.6%		
CABG	1.8%		
Mortality risk reduction from revascularisation			
High risk	57%	Kuntz, 1999[99]	
Medium risk	15%	Kuntz, 1999[99]	
Risk reduction of MI			
PTCA	17%	Kuntz, 1999[99]	
CABG	40%	Kuntz, 1999[99]	
Procedures mortality			
PTCA	3.1%	Kuntz, 1999[99]	
CABG	0.75%	Kuntz, 1999[99]	
Time horizon	Max. 25 years		
Start age	60 years		

annual mortality obtained from Interim life tables[126] and the proportion of fatal MI (51.08%) constructed from Lampe and colleagues[127] and Volmink and colleagues.[128] Sensitivity and specificity for stress ECG and SPECT were obtained from the studies included in the effectiveness review reported in Chapter 3. The values applied were sensitivity stress ECG 0.67, specificity stress ECG 0.65, sensitivity SPECT 0.90 and specificity SPECT 0.80. Finally, prevalence for this subgroup was fixed at a lower rate (5.5%) than for the men subgroup.

Quality of life measures

One of the products of the economic evaluation is QALYs. QALYs combine estimates of survival time and the quality of that survival time. Survival is provided by the cumulative number of cycles spent in each state of the model other than death. QoL score weights time spent in each state.

Estimates of QALYs were required for each of the states in the Markov model. The best data for estimation of this would be UK studies with generic health status measures such as those provided by the EQ 5D. In the absence of such data, information was sought from other sources, notably the economic evaluations summarised in Chapter 4 and values from the CEA Registry.[130] Although relatively comprehensive, the data presented in the registry were methodologically no better (and more often of lower quality) than the results of the standard gamble exercise used by Kuntz and colleagues.[99] Moreover, the use of figures from Kuntz and colleagues[99] facilitates comparisons with the Industry submission. The utility scores used in the model are described in *Table 36*.

It is assumed in the Markov model that patients who have an MI or are revascularised will lose part of their QALYs as a result of the event and will recover their previous level of QoL in 3 months.[131]

TABLE 36 *Utility scores used in the estimation of QALYs*

State	Utility value (range)
Low risk (and FPs)	0.87 (0.77–1.00)
Untreated medium risk and FN medium risk	0.81 (0.68–1.00)
High risk and FN high risk	0.67 (0.4–0.98)
Adjustment for revascularisation or MI	0.1 (QALY loss)

The gain from revascularisation is the subsequent lower risk of death but not a higher QoL than before revascularisation.

Discounting

Guidelines of NICE[125] were followed for discounting costs and outcomes. Therefore, annual discount rates of 6 and 1.5% were used for costs and outcomes, respectively. The obvious result of this is that lower weights are given to costs and benefits that are further away in time.

Results

Base-case analyses

The parameters for costs of interventions, risks of events and QoL for the base-case analysis are summarised in *Table 37*. These parameters were entered in DTM and Markov model using the DATA software package. Payoffs for the DTM were obtained from the Markov model run for up to 25 cycles (i.e. 25 years follow-up period). The starting age for the hypothetical cohort of patients was 60 years.

Tables 38 and *39* show the results of the base-case analysis at a range of different prevalence rates. As prevalence increases, cost increases and the proportion of accurate diagnoses and QALYs decrease. At all prevalence levels the ordering of diagnostic strategies is the same. *Table 39* shows the incremental cost per true positive diagnosed, per accurate diagnosis and per QALY. The first two outcomes are based on the outputs of the DTM (diagnostic costs and diagnostic performance). The last outcome is based on both diagnostic and treatment costs (obtained from the payoff model) and estimated QALYs. As a consequence, the incremental cost per QALY is driven not only by diagnostic performance but also by the costs and consequences of management strategies chosen on the basis of diagnostic information. The results indicate that at lower levels of prevalence it is possible that the incremental costs per unit of output (TP diagnosed, accurate diagnosed, QALYs) for the move from stress ECG–SPECT–CA to stress ECG–CA and from stress ECG–CA to SPECT–CA might be considered worthwhile. Furthermore, stress ECG–CA is extendedly dominated by a combination of stress ECG–SPECT–CA and stress ECG–CA (over a defined range, allowing some patients to receive stress ECG–SPECT–CA with the rest receiving SPECT–CA would be less costly and result in more benefits overall than using stress ECG–CA alone). If stress ECG–CA is removed from the comparison then the incremental cost per unit of output at a 10.5% prevalence level for SPECT–CA versus stress ECG–SPECT–CA would be £13,715 per TP diagnosed, £13,873 per accurate diagnosis and £14,123 per QALY. These incremental cost-effectiveness ratios would decrease as prevalence increases. At high rates of prevalence (e.g. 50 or 85% risk of CAD) the stress ECG–SPECT–CA strategy is the one with lower cost. At these levels of prevalence the SPECT–CA strategy is extendedly dominated by stress ECG–CA and CA strategies for the three different types of outputs presented (TP diagnosis, accurate diagnosis and QALY) (over a defined range, allowing some patients to receive stress ECG–CA with the rest receiving CA would be less costly and result in more benefits overall than using stress SPECT–CA alone).

Sensitivity analysis

Effect of changing sensitivity and specificity

Tables 40 and *41* show the estimated incremental cost per QALY gained when the sensitivity or specificity of stress ECG or SPECT was varied. As expected, when the sensitivity or specificity of the tests is higher, the strategy that involves that test tends to perform better. For example, at a high sensitivity for stress ECG the stress ECG–CA strategy dominates SPECT–CA, whereas for low values of specificity of stress ECG the stress ECG–SPECT–CA strategy dominates stress ECG–CA. Moreover, for low values of SPECT sensitivity, stress ECG–CA dominates SPECT–CA, whereas for high values SPECT–CA dominates the CA strategy. Similarly, for high values of specificity

TABLE 37 *Summary of variables used in the analysis*

Costs	**Total cost (2001–02 £)**	**Source**
Stress ECG	104.86	Table 31
SPECT	261.91	Table 31
CA	1309.55	Table 31
Medical management	311.00	Table 32
MI	1122.00	Table 32
PTCA	1993.74	Table 32
CABG	4397.00	Table 32
Probabilities	**Parameter value**	**Source**
Prevalence of disease for patient cohorts	10.5	Table 34
Stress ECG		
Sensitivity	0.66	Table 34
Specificity	0.60	Table 34
Indeterminacy	0.18	Table 34
Mortality risk	0.00005	Table 34
SPECT		
Sensitivity	0.83	Table 34
Specificity	0.59	Table 34
Indeterminacy	0.09	Table 34
Mortality risk	0.00005	Table 34
CA		
Sensitivity	1.00	Table 34
Specificity	1.00	Table 34
Mortality risk	0.0015	Table 34
Mortality		
Annual rate for age X		Table 35
Relative risk medium risk	2.3	Table 35
Relative risk high risk	3.6	
Risk of MI		
Low risk (and FPs)	2.5%	Table 35
Untreated medium risk and FN medium risk	5.0%	Table 35
High risk and FN high risk	9.0%	Table 35
Proportion fatal MI	44.84%	Table 35
Proportion non-fatal MI	55.16%	Table 35
FN results		
Proportion to medium risk	41%	
Proportion to high risk	59%	
Revascularisation		
Proportion revascularisation low, medium, high risk	5, 50, 100%	Table 35
Proportion PTCA	90, 61, 10%	Table 35
Proportion CABG	10, 39, 90%	Table 35
Proportion of patients with 2nd revascularisation		Table 35
PTCA	3.6%	
CABG	1.8%	
Mortality risk reduction from revascularisation		
High risk	57%	Table 35
Medium risk	15%	Table 35
Risk reduction of MI		
PTCA	17%	Table 35
CABG	40%	Table 35
Procedures mortality		
PTCA	3.1%	Table 35
CABG	0.75%	Table 35
Utility	**Value**	**Source**
Low risk	0.87	Table 36
Medium risk	0.81	Table 36
High risk	0.67	Table 36
Adjustment for revascularisation or MI	0.1	Table 36
Other parameters		
Age at start of model	60 years	
Time horizon	25 years	

TABLE 38 *Estimated costs and outcomes for each diagnostic strategy*

Prevalence level (%)	Strategy	Diagnostic cost (£)	Diagnostic and treatment cost (£)	TPs diagnosed (%)	Accurate diagnoses (%)	QALYs
Baseline, 10.5	ECG–SPECT–CA	603	5190	6.39	95.85	12.473
	ECG–CA	799	5395	7.56	96.99	12.481
	SPECT–CA	921	5529	8.86	98.30	12.497
	CA	1310	5929	10.48	99.85	12.506
30	ECG–SPECT–CA	710	5780	18.26	88.23	11.689
	ECG–CA	854	5954	21.60	91.55	11.723
	SPECT–CA	1018	6153	25.32	95.27	11.765
	CA	1310	6484	29.96	99.85	11.811
50	ECG–SPECT–CA	819	6387	30.43	80.41	10.886
	ECG–CA	910	6528	36.00	85.96	10.946
	SPECT–CA	1119	6793	42.20	92.16	11.016
	CA	1310	7053	49.93	99.85	11.097
85	ECG–SPECT–CA	1010	7448	51.74	66.73	9.480
	ECG–CA	1007	7531	61.21	76.19	9.585
	SPECT–CA	1293	7914	71.74	86.73	9.703
	CA	1310	8049	84.87	99.85	9.849

TABLE 39 *Stepwise incremental cost-effectiveness*

Prevalence level (%)	Strategy	Incremental cost per TP diagnosed (£)	Incremental cost per accurate diagnosis (£)	Incremental cost per QALY (£)
Baseline, 10.5	ECG–SPECT–CA			
	ECG–CA	16761	17267	23648
	SPECT–CA	9339	9295	8723
	CA	23956	24998	42225
30	ECG–SPECT–CA			
	ECG–CA	5188	5230	5098
	SPECT–CA	5345	5339	4711
	CA	7143	7225	7331
50	ECG–SPECT–CA			
	ECG–CA	2526	2535	2345
	SPECT–CA	4285	4283	3807
	CA	3364	3380	3178
85	ECG–SPECT–CA			
	ECG–CA	882	882	792
	SPECT–CA	3630	3630	3242
	CA	1030	1030	927

TABLE 40 *Incremental cost per QALY (£): variation of sensitivity and specificity values for stress ECG*

	Sensitivity stress ECG		Specificity stress ECG		Base-case
	0.42	0.92	0.43	0.83	
ECG–SPECT–CA					
ECG–CA	53453	20214	45793	15406	23648
SPECT–CA	5398	Stress ECG dominant	SPECT dominant	35197	8723
CA	57214	57214	57214	57214	42225

TABLE 41 *Incremental cost per QALY (£): variation of sensitivity and specificity values for SPECT*

	Sensitivity SPECT		Specificity SPECT		Base-case
	0.63	**0.93**	**0.64**	**0.90**	
ECG–SPECT–CA					
ECG–CA	11689.73	754167	28002	SPECT dominant	23648
SPECT–CA	Stress ECG dominant	6869	4997	6706.57	8723
CA	17426.14	SPECT dominant	52221	158694.03	42225

TABLE 42 *Effect of changing proportion of patients that SPECT can identify as positive but not in need of an angiogram*

Strategy	Incremental cost per QALY (£)	Base-case results (£)
Stress ECG–SPECT–CA		
Stress ECG–CA	17928	23648
SPECT–CA	6495	8723
CA	16558[a]	42225

[a] This ICER strongly diminishes compared with the base-case as a result of a decrease in QALYs for the SPECT-CA strategy (base-case 12.497; this case 12.469).

of SPECT, the stress ECG–CA strategy is dominated by SPECT–CA (further results of the sensitivity analysis are presented in Appendix 16).

Effect of allowing SPECT to stratify patients into medium risk

Within Chapter 3, data were presented that suggested that SPECT may provide additional independent information to other tests in addition to being able to identify patients with CAD who would not need to progress to angiography. In this model, the effect of this was illustrated by varying the proportion of those tested positive whose condition might satisfactorily be managed medically. As this proportion increases from zero in the base-case analysis to ~50% then the SPECT-based strategies become more cost-effective (*Table 42*). Should SPECT have a higher specificity, as used in some of the economic evaluations and the Industry submission, and be able to risk stratify patients accurately, then its cost-effectiveness would further improve [incremental cost per QALY of SPECT–CA versus stress ECG–SPECT–CA <£5000 and SPECT–CA less costly (by an average of £324 per patient) and more effective (average of 0.03 per patient) than stress ECG–CA]. The estimates in *Table 42* are an overestimate as our model does not allow for the possibility that some high-risk patients may be misdiagnosed as positive but at lower risk (i.e. medium risk, and hence receive inappropriate management) but nevertheless illustrates the potential impact of this factor.

Effect of changing the rates of indeterminate results

Within the model presented in this section (and the Industry model), it has been assumed that for some strategies should the results of a test be indeterminate then the patient would proceed to the next test. The level of indeterminacy assumed for a test therefore has an impact on the cost, diagnostic performance and QALYs. In this model, the data from Patterson and colleagues[102] were used (*Table 34*). Alternative data are available from Kuntz and colleagues[99] and were used in the Industry model. These data suggest a rather higher rate of indeterminacy for stress ECG (30 versus 18%) and a lower level of indeterminacy for SPECT (2 versus 9%). *Tables 43* and *44* report the impact on cost-effectiveness of using these rates, which are more favourable to SPECT.

Effect of changes in cost of the diagnostic tests

Varying the cost of the tests between £25 and £225 for stress ECG and between £895 and £1724 for an angiogram had no impact on the rank ordering of the procedures. SPECT–CA still had extended dominance over stress ECG–CA and had an incremental cost per QALY compared with stress ECG–SPECT–CA of <£21,000 even when the cost of stress ECG was only £25. The CA option, even

TABLE 43 *Estimated costs and outcomes for each diagnostic strategy when indeterminacy stress ECG = 30% and indeterminacy SPECT = 2%*

Strategy	Diagnostic cost (£)	Diagnostic and treatment cost (£)	TP diagnosed (%)	Accurate diagnoses (%)	QALY
ECG–SPECT–CA	388	4983	7.26	96.74	12.49
ECG–CA	752	5353	8.14	97.57	12.49
SPECT–CA	511	5126	9.35	98.84	12.51
CA	1310	5929	10.48	99.85	12.51

TABLE 44 *Effect on cost-effectiveness when indeterminacy stress ECG = 30% and indeterminacy SPECT = 2%*

Strategy	Incremental cost per TP diagnosed (£)	Incremental cost per accurate diagnosis (£)	Incremental cost per QALY (£)	Base-case results (incremental cost per QALY) (£)
ECG–SPECT–CA				
ECG–CA	Dominated by SPECT–CA	Dominated by SPECT–CA	Dominated by SPECT–CA	23648
SPECT–CA	11419[a]	11419[a]	11422[a]	8723[b]
CA	25101	25101	41404	42225

[a] Incremental cost-effectiveness SPECT–CA versus stress ECG–SPECT–CA.
[b] Incremental cost per QALY for SPECT–CA versus stress ECG–SPECT–CA was £14,123.

when the low cost of an angiogram was used, was associated with an incremental cost per QALY compared with SPECT–CA of >£28,000. The cost of SPECT was varied between £128 to £340 and at the high cost of SPECT the incremental cost per QALY of SPECT–CA versus stress ECG–CA was <£16,000.

Effect of changing the time horizon of the analysis

In the base-case analysis, cumulative costs and QALYs were estimated for a 25-year period for a 60-year-old male. It may be unrealistic to assume that costs and outcomes over such a long period can be reliably estimated. For this reason, the effect of changing the time horizon was investigated. An example of the incremental cost per QALY changes as the time horizons change is shown in *Figure 10*. As the time horizon reduces the incremental cost per QALY increases (as the costs of initial diagnosis and treatment are not offset by survival and QoL gains).

Changes to the time it takes false negatives to be correctly diagnosed

One of the uncertainties within the model is the time that it takes for FNs to be correctly diagnosed. In the base-case analysis it was assumed that in the first year 10% are correctly rediagnosed and thereafter an increasing proportion are correctly rediagnosed such that all survivors are correctly diagnosed by year 10. Relaxing this assumption and allowing FNs to be rediagnosed sooner has the effect of reducing the penalty associated with making a false diagnosis (i.e. it improves the cost-effectiveness of non-invasive strategies compared with CA). Conversely, increasing the time until successful rediagnosis increases the penalty associated with misdiagnosis and reduces the cost-effectiveness of non-invasive strategies compared with CA (*Table 45*).

Summary of other sensitivity analysis

The payoff model estimates the costs and benefits associated with the consequences of diagnosis (choice of management) and the long-term effects of CAD. Changes in these parameters will affect the cost-effectiveness of the alternative strategies. *Table 45* shows, for example, the effect of changing the rate at which FNs are correctly diagnosed. Further changes could also be considered. For example, within the model it has been assumed that a coronary angiogram provides perfect diagnostic information. Should this assumption be relaxed then it might be expected that the relative cost-effectiveness of a non-invasive strategy would improve. Whether this would lead to an increased preference for SPECT-based strategies would in

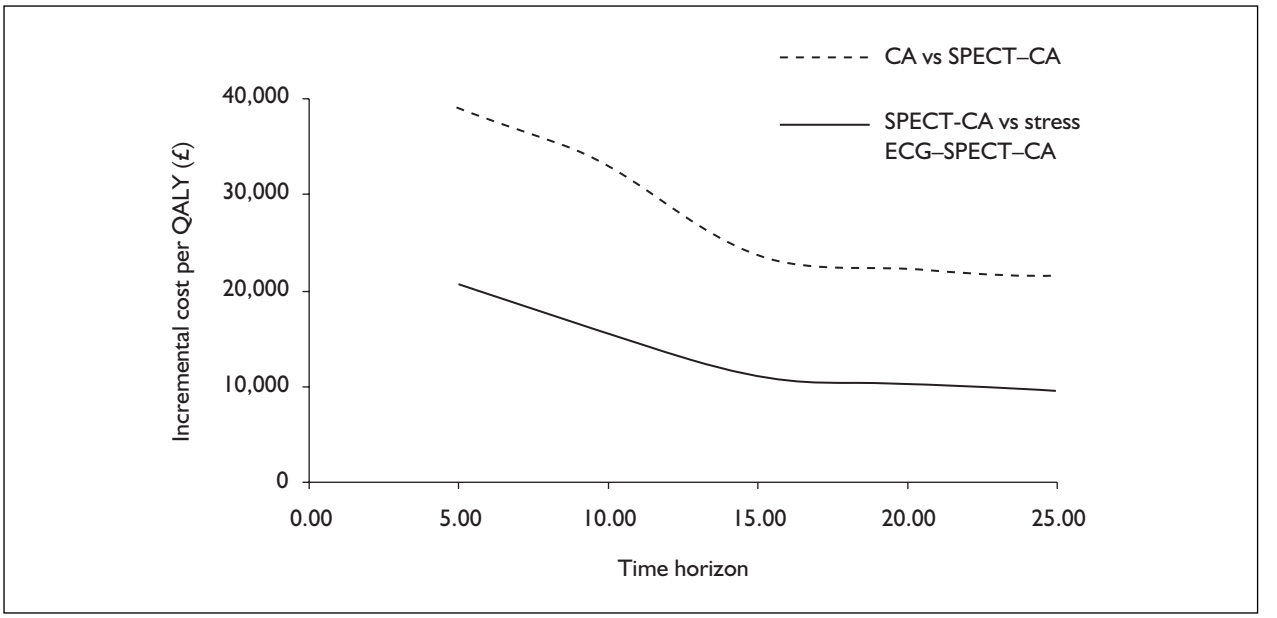

FIGURE 10 *Incremental cost per QALY at different time horizons for the comparison of CA with SPECT–CA and SPECT–CA with stress ECG–SPECT–CA*

TABLE 45 *Effect of changing the time until false negatives are correctly rediagnosed on the incremental cost per QALY*

Rediagnosis	Strategy	Cost (£)	QALY	Incremental cost per QALY (£)	Incremental cost per QALY (base-case) (£)
After 2 years	ECG–SPECT–CA	5415	12.312		
	ECG–CA	5587	12.320	19368	23648
	SPECT–CA	5708	12.336	7891	8723
	CA	6057	12.346	35194	42225
After 5 years	ECG–SPECT–CA	5374	12.305		
	ECG–CA	5558	12.316	16931	23648
	SPECT–CA	5692	12.333	7644	8723
	CA	6057	12.346	28868	42225
Never	ECG–SPECT–CA	5210	12.265		
	ECG–CA	5441	12.287	10442	23648
	SPECT–CA	5627	12.317	6190	8723
	CA	6057	12.346	15234	42225

part depend upon both the sensitivity and specificity of SPECT and also its ability to identify correctly patients with CAD who could be managed medically and may therefore not require an angiogram.

The values stated in the base-case analysis for risk of MI for all risk states in the payoff model were changed to allow for higher figures. As a result, all payoff cost values for the risk states rise, as there were more MIs to treat within the model. The payoff values for QALYs did not change widely as the fatal MIs were assumed to be included in the relative risk ratios of death of the different risk states. There was no difference in the order of the strategies selected when running the sensitivity analysis with this payoff and the ones obtained from the base-case run.

The discount rates were also changed following NICE guidelines to 0% for both cost and QALYs in first instance and 6% also for cost and QALYs in the second instance. There was only one change in the order of the strategies that differ from the sensitivity analysis done for base-case payoffs, namely, for low values of cost for SPECT and zero discount rates SPECT–CA dominates the stress ECG–CA strategy.

TABLE 46 *Estimated costs and outcomes for each diagnostic strategy for the women subgroup*

Strategy	Diagnostic cost (£)	Diagnostic and treatment cost (£)	TPs diagnosed (%)	Accurate diagnoses (%)	QALY
ECG–SPECT–CA	436	5241	3.64	98.12	14.08
ECG–CA	735	5541	4.01	98.43	14.08
SPECT–CA	664	5477	4.99	99.45	14.10
CA	1310	6121	5.49	99.85	14.09

TABLE 47 *Incremental cost per outcome for the women subgroup*

Strategy	Incremental cost per TP diagnosed (£)	Incremental cost per accurate diagnosis (£)	Incremental cost per QALY
ECG–SPECT–CA			
ECG–CA	82,133	93,988	ECG–SPECT dominant
SPECT–CA	SPECT dominant	SPECT dominant	SPECT dominant
CA	SPECT dominant	SPECT dominant	SPECT dominant

Finally, variations were made in QALY values and mortality risk reduction of MI resulting from revascularisation. No changes were observed in the order for the base-case DTM or in the subsequent SA.

Relative cost-effectiveness in women

One of the key subgroups for this analysis was the impact of the use SPECT-based strategies to diagnose CAD in women. This subgroup analysis used sensitivities and specificities for women and used a lower prevalence rate of CAD, different MI rates and mortality rates for women aged 60 years at diagnosis. The stress ECG–SPECT–CA strategy was less costly whereas stress ECG–CA and CA were dominated by the SPECT–CA strategy (less costly and slightly more effective in the second case). This is due to the higher specificity and sensitivity values for women than in the base-case analysis (*Tables 46* and *47*).

Comparison with the Industry submission

The model presented in this section and the model produced as part of the Industry review had broadly similar structures and produced similar results. The results are not identical and in some respects the model presented in this section is more favourable than the Industry model to the SPECT–CA strategy. Both models are similar to ones previously reported in the literature (see Chapter 4). There are discrepancies, however, due to differences in the structure and parameter values. In the Industry model there are seven diagnostic strategies. The model presented here considers only the four believed to be representative of usual practice. Despite this difference, the structures of these four strategies are very similar. In both cases (our model and the Industry model), a positive or indeterminate result in a test is followed by another test (in the usual order). Hence, a positive or indeterminate stress ECG will be followed by a SPECT test, and a positive or indeterminate SPECT test will be followed by a CA test. Moreover, the payoff Markov models are also very similar as in both cases the same scarce existing literature was used.

In order to facilitate comparison, the model presented here was run with the parameter values used by the Industry model. The results of this suggest that for prevalence levels of <50% SPECT–CA is associated with an incremental cost per QALY of not more than £14,600 compared with stress ECG–SPECT–CA and it dominates or has extended dominance over stress ECG–CA. Only at a prevalence of 30% does the incremental cost per QALY of CA compared with SPECT fall below £35,000. Between 50 and 65% prevalence levels, SPECT has extended dominance over stress ECG–CA. It is also associated with an incremental cost per QALY compared with stress ECG–SPECT–CA of <£1800. However, the incremental cost per QALY of CA compared with SPECT–CA is <£6000. Above 65% CA starts to have extended

dominance over SPECT–CA (at very high prevalence rates SPECT–CA is dominated). In the situation that occurs at these higher prevalence rates, the relevant comparison is between CA and stress ECG–CA, and the incremental cost per QALY of CA compared with stress ECG–CA is typically not greater than £4000.

It should be highlighted that the model presented in this section does not allow for higher QoL after revascularisation. In other words, the benefits of revascularisation come from a higher life expectancy but not from a higher QoL. If a higher QoL were achieved after revascularisation, those strategies that accurately identify patients for revascularisation (fewer FNs) would perform better (i.e. CA). Nevertheless, the rank ordering of the non-invasive strategies should not change as the QALY gain is still driven by sensitivity/specificity. It could be expected that SPECT–CA would perform better than stress ECG–CA, but this would be strongly dependent on the indeterminate results from stress ECG as they proceed to a CA test. Finally, if the 'No testing' strategy is dropped from the Industry submission model, the results are similar to those presented in our model, as stress ECG–SPECT–CA and SPECT–CA strategies dominate or extendedly dominate other strategies for low levels of prevalence, whereas stress ECG–CA and CA extendedly dominate the SPECT–CA strategy for high levels of prevalence.

Summary of results

The model presented in this section considered some of the strategies that are potentially relevant for managing CAD patients. The effectiveness data for the diagnostic tests came from the effectiveness review. However, few data were available from the UK. As a result, data from other countries were used, much of which came from studies conducted in the USA. In these cases, RRs and rates of utilisation were extrapolated but absolute rates of utilisation of interventions were not, as it is well known that there are differences in utilisation rates between the USA and UK and it was believed that the use of relative rates would result in less bias.

The model developed suggests that for low levels of prevalence it is possible that the incremental cost per unit of output (TPs diagnosed, accurate diagnosis, QALY) for the move from stress ECG–SPECT–CA and from stress ECG–CA to SPECT–CA might be considered worthwhile. At high rates of prevalence (e.g. 85% risk of CAD) the stress ECG–SPECT–CA strategy is dominated by the stress ECG–CA strategy. Furthermore, the CA option is associated with relatively modest ICERs.

In addition to allowing for different values for sensitivity or specificity, the most cost-effective strategy was stress ECG–SPECT–CA. For low levels of sensitivity for SPECT, stress ECG–CA dominates the SPECT–CA strategy, whereas for high levels SPECT–CA dominates CA. High levels of specificity for SPECT also result in the stress ECG–CA strategy being dominated by SPECT–CA.

The SA suggests that SPECT–CA improves its cost-effectiveness if it is assumed that SPECT gives information that will allow a management strategy to be decided upon without recourse to angiography. A further SA considering the extent to which non-invasive tests provide indeterminate results proved to be significant in the model. When the values used by Kuntz and colleagues[99] were applied, the results suggest that the SPECT–CA strategy dominates stress ECG–CA.

The results were not greatly sensitive to the cost of the diagnostic test but estimates of incremental cost per QALY are sensitive to the time horizon chosen. As the time horizon increases, the incremental cost per QALY declines. In the base-case model it was also assumed that those patients who were not correctly classified would be correctly diagnosed within 10 years. If this assumption was relaxed then those strategies that result in incorrect diagnoses would not be as heavily penalised.

In the model it was assumed that the specificity and sensitivity for CA equalled one. If this assumption is relaxed then it might be expected that the relative cost-effectiveness of a non-invasive strategy would improve. Whether this would lead to an increased preference for SPECT-based strategies would depend on both the sensitivity and specificity of SPECT and also its ability to identify correctly patients for whom management could be decided without the need for an angiogram.

For the subgroup analysis for women it was found that as the sensitivity and specificity for SPECT were higher than those adopted in the base-case (and the mortality and prevalence are lower), the SPECT–CA strategy dominates the stress ECG–CA and CA strategies.

Chapter 6

Implications for other parties

Quality of life for family and carers

Currently a patient with a positive stress ECG result would have to wait about 20 weeks before receiving a CA. This wait may cause a great deal of distress for patients and families. There are many causes of this distress, two of which are related to the delay in obtaining a definitive diagnosis and the nature of the testing required. Obviously, any intervention that reduces this wait would help to reduce this distress, for example movements towards achieving waiting time targets and the increased use of SPECT in rapid access chest pain clinics. Furthermore, the increased use of a non-invasive investigation such as SPECT in place of CA would also help reduce the anxiety associated with the prospect of undergoing a surgical procedure with an appreciable risk of mortality and morbidity.

Financial impact for patients and others

SPECT is not as widely available as stress ECG in the UK. As a result, patients who require SPECT may need to travel some distance. This has both time and financial costs which currently may fall on patients and their families. Should the use of SPECT increase then it might be expected that the magnitude of these costs would decline, especially if efforts were made to ensure equality of access.

Chapter 7

Factors relevant to the NHS

NSF for CHD

The NSF states that both ExECG and SPECT are useful for the assessment of severity of myocardial ischaemia. The data presented in this review suggest that SPECT-based strategies are effective and might also be considered cost-effective. It has been suggested by the relevant professional groups that as the NSF recommends a maximum 3-month gap between a decision to investigate and CA, then the waiting time target for SPECT should be 6 weeks for routine studies and 1 week for urgent studies.

Although not explicitly addressed within this review, it is likely that any increased adoption of SPECT through rapid access clinics might further facilitate the shortening of the waiting time for SPECT. Although such a service may face different costs and benefits (owing to possible changes in decision thresholds), the results of the available studies indicate that the use of SPECT in such circumstances might be cost-effective. It should be noted that although not formally evaluated in this study, ECHO, which can also be provided in open-access clinics, may potentially be a cost-effective method of diagnosing CAD.

In 2000, the number of SPECT studies performed was 1200 per million of the population, but a tentative assessment of the number of SPECT examinations needed is 4000 per million of the population per year (Professional Groups' submission to NICE, 2003).

Training issues

Clearly, the expansion of SPECT-based services would require considerable investment in infrastructure. It has been estimated that under very conservative assumptions some 84 additional gamma cameras would be required (Professional Groups' submission to NICE, 2003). In practice, it is unlikely that expansion would be via 84 dedicated centres undertaking 2000 studies per annum. It is more likely that this would be a progressive increase via many more centres undertaking extra studies. However, the former model could occur if centrally driven. If the latter model is adopted then the impact of this upon the need for more cameras is difficult to assess as it depends upon each centre's 'rate-limiting' step, that is, what the local need is and existing services. Furthermore, it is possible that the majority of nuclear medicine departments have an underprovision of modern gamma camera time, hence the real demand for hardware could be many times the estimate. It is possible that any residual camera time would be put to other potentially beneficial uses. Although the cost of equipment and the necessary staff and consumables is large (estimated at £31.07 million per year), it is more likely that the lack of trained staff would be the greatest obstacle. Professional groups have estimated that it would take 5–10 years for sufficient staff to be trained (Professional Groups' submission to NICE, 2003). However given that expansion will be by no means an overnight phenomenon, it might be possible to increase numbers progressively by ensuring that new-appointment consultant cardiologist, nuclear physician and radiology colleagues have dedicated sessions devoted to nuclear cardiology. Sufficient training for them may thereby be rapidly provided. It should also be noted that trained technologists and nurses would also be required. The timescale for this would be shorter, but would depend upon finance being available.

The limited ability to increase the use of SPECT may require the consideration of a second-best alternative, at least until sufficient trained staff are available. An alternative might be the adoption of a less SPECT-intensive option, for example only using SPECT in those tested positive at stress ECG. Such alternatives should be cost-effective in comparison with current practice but might be inferior to strategies using SPECT more intensively. Other potential options might involve the regional supervision and reporting of studies performed at the local level.

Equity issues

Growth in the use of SPECT is limited to a small number of high-using centres with the majority of centres performing relatively few studies (median number of studies per centre per annum 256). As

a result, staff may have limited experience of reporting SPECT studies, which may have an impact on patient outcomes. Furthermore, patients' access to SPECT is affected by their geographical proximity to high-using centres.

If a decision was taken to adopt a SPECT-based strategy then, given the limited number of trained staff available, service configuration would need to be carefully considered in order for equality of access to be maximised.

Chapter 8
Discussion

Effectiveness

Diagnostic studies

The 21 included studies assessing the diagnostic accuracy of both SPECT and stress ECG varied considerably with regard to their inclusion/exclusion criteria. Therefore, it was decided to analyse them according to the clinical characteristics of their patient populations. It was found that three studies exclusively assessed patients after PTCA, one study evaluated patients with asymptomatic coronary disease, one study focused on patients with LBBB and 16 studies assessed the diagnostic ability of SPECT and stress ECG to detect CAD in patients with a suspicion or a history of coronary disease.

The number of studies in each subset was small and their methodological quality varied considerably. In particular, they differed in terms of their definition of coronary stenosis, patients characteristics (mean age, gender, previous MI), severity of the disease (SVD versus MVD), use of beta-blocking medications, time between SPECT, stress ECG and CA, technical factors such as interpretation of test findings (visual versus quantitative reading analysis of SPECT, diagnostic versus non-diagnostic results of stress ECG), angiographic referral (the results of the SPECT and/or stress ECG determined who did or did not undergo CA) and blinding of test results.

Owing to the wide variation among primary studies in each of the two main subsets (patients with suspicion of CAD and patients who underwent PTCA), and the lack of a positive correlation between TP and FP rates, pooling of sensitivities and specificities and calculation of summary ROC curves were deemed inappropriate and as an alternative the medians and ranges were presented for both tests. For the two main subsets of studies (patients suspected of CAD and patients who underwent PTCA), the medians of sensitivity for SPECT were higher and their ranges narrower than those for stress ECG. Medians of specificity were similar between the two tests for patients suspected of CAD, with wider ranges for SPECT. Medians of specificity were higher for SPECT for patients who underwent PTCA, with wider ranges for stress ECG.

The inclusion of patients with previous MI has been reported to increase the sensitivity of SPECT significantly,[132] as patients with MI are more easily identified than patients without previous MI. Only four studies among our cohort of 16 included studies clearly excluded patients with previous MI. The median of sensitivity for SPECT in the subset of studies, excluding patients with MI, was higher (0.92, range 0.76–0.93) than that of the subset of studies enrolling patients with MI (0.76, range 0.63–0.93). The medians of sensitivity for stress ECG for patients with (0.63, range 0.44–0.92) and without previous MI (0.66, range 0.42–0.85) were similar. Specificity values of SPECT were akin to those of stress ECG in both subsets of studies but again values were higher among studies that did not include patients with previous MI. These findings can be explained by the small number of studies in the non-MI subset (four studies) compared with the MI subset (10 studies) and the great variation in the inclusion/exclusion criteria and patients' characteristics of primary studies. In addition, the 10 studies including patients with prior MI did not consist solely of patients with prior MI; rather, this category of patients was included within the broader patient populations contained in the studies.

There is evidence in the literature that studies free from verification bias show significantly higher specificities and relatively lower sensitivities than studies where only positive cases are verified by the reference standard.[20] Among the studies we identified, only two showed clear evidence of verification bias (i.e. results of SPECT were allowed to influence the decision to perform CA) and consequently were not included in the analyses.

The influence of other patients' characteristics that may affect the sensitivity of SPECT, such as gender of participants (studies with high proportions of men tend to report higher sensitivities), could not be assessed reliably owing to the small number of studies reporting this information.

Prognostic studies

Forty-six observational studies, of reasonable methodological quality, were included in this review.

In the 21 studies providing general prognostic information, the rates of cardiac events (cardiac mortality or non-fatal MI) were significantly higher for patients with abnormal SPECT scans compared with normal scans. Two comparative studies found that a strategy incorporating SPECT and selective CA resulted in lower rates of normal angiograms compared with patients referred to direct CA, suggesting that SPECT identified patients at lower risk for whom CA was not necessary.[67,77,82] Other findings were that SPECT provided independent prognostic information for predicting MI and provided incremental prognostic value over clinical and exercise testing data and even CA when it had already been performed.

Sixteen of the general prognostic studies employed the Cox proportional hazards model. The variables included in the models appeared to be appropriate, although they differed across studies, and not all studies provided comprehensive details of the variables included. SPECT variables found to be predictive of outcome included an abnormal SPECT scan, an intermediate-risk SPECT scan, a high-risk SPECT scan, the extent of the perfusion defect, the size of the perfusion defect, worsening category of summed stress score, worsening category of summed reversibility score and reversible and fixed perfusion defects.

The remaining studies addressed the use of SPECT in a variety of contexts or patient populations. The general conclusions were that, as part of the stress ECG–SPECT–CA pathway, SPECT imaging provided independent and incremental information that assisted in stratifying patients into at-risk groups and in influencing their treatment. All four studies assessing the usefulness of SPECT post-MI concluded that it was valuable for stratifying patients into at-risk groups.

SPECT appeared to provide independent prediction of survival in both men and women, although different aspects of the test results had different prognostic implications in terms of gender. In both men and women, the extent of total perfusion abnormality, extent of reversible perfusion abnormality, multivessel abnormality and large perfusion abnormality were all strongly predictive of future cardiac events.

Three studies concluded that SPECT was prognostically useful in patients following revascularisation. SPECT imaging performed 1–3 years after PTCA was found to be predictive of cardiac events, with summed stress score, summed reversibility score, and for stress ECG the Duke treadmill score, all strongly associated with PTCA/CABG within 3 months of SPECT imaging. In patients who had undergone CABG, the extent of the perfusion abnormality was an important independent predictor of events and SPECT was useful in stratifying patients into at-risk groups for future cardiac events.[69] Normal SPECT scans were associated with a benign prognosis that suggested medical rather than invasive management.

The other studies found SPECT to be prognostically useful in a variety of contexts/patient populations, including patients with normal resting ECG, asymptomatic coronary disease, high ExECG tolerance, LMD and/or 3VD and those hospitalised with chest pain who had a normal or non-diagnostic ECG.

In conclusion, the evidence from the included prognostic studies consistently suggested that, as part of the stress ECG–SPECT–CA pathway, SPECT, in a variety of settings and patient populations, provided valuable independent and incremental information in predicting outcome and helped to stratify patients into appropriate at-risk groups and influence decisions on how best their condition should be managed.

These findings are in broad agreement with other published reviews assessing the prognostic usefulness of MPS. Travin and Laraia,[92] in a review of the prognostic value of stress MPI, concluded that it was a powerful method of risk stratifying patients with known or suspected ischaemic heart disease. Brown,[93] in a review of the prognostic value of Tl-201 MPI, concluded that it had been shown to have the ability to predict important cardiac events in a wide variety of clinical settings and was a powerful tool for risk stratification that could have a major impact on patient management.

A secondary objective of this review was to attempt to summarise the limited evidence on gated and AC SPECT compared with standard SPECT. Two studies, one diagnostic and the other prognostic, comparing SPECT with gated SPECT found in favour of gated SPECT, and one diagnostic study comparing SPECT with AC SPECT found AC SPECT to be more accurate. Although these findings seem promising, it is difficult to draw conclusions from so few studies.

No studies meeting the inclusion criteria were identified that evaluated SPECT in the context of

rapid access chest pain clinics, or evaluated the role of SPECT in preoperative risk assessment of patients undergoing major surgery who were potentially at risk of coronary events. It should be noted, however, that risk stratification before non-cardiac surgery is listed as a class 1 indication for MPS in the guidelines for clinical use of cardiac radionuclide imaging developed by the American College of Cardiology/American Heart Association Task Force in collaboration with the American Society of Nuclear Cardiology.[133]

Cost and cost-effectiveness

Twenty-two economic evaluations were identified that compared strategies involving SPECT with alternative strategies that may or may not have included SPECT. One further economic evaluation was available from the submission by Amersham Health. Overall, the quality of the economic evaluations was very mixed. A number used either poor economic evaluation methodology or data of suspect validity. There were, however, a number of studies that used and clearly described strong methodology. These studies compared a wide variety of strategies and used different input parameters, especially for SPECT.

The available studies concluded that direct CA was cost-effective when the prevalence of disease was high (>75%) (although CA was generally more costly but more effective). At lower levels of prevalence, non-invasive strategies may be considered to be a better use of resources than a strategy of direct CA. Furthermore, strategies involving SPECT were likely to be either dominant or provide additional benefits that might be considered worth the additional cost compared with the stress ECG–CA strategy.

No single SPECT strategy was identified as being the most likely to be cost-effective. Four studies, including the Industry submission, compared SPECT–CA and stress ECG–SPECT–CA; two concluded that stress ECG–SPECT–CA was cost-effective and two reported that the extra benefits provided by SPECT–CA might be worth its additional cost.

The evidence for the use of SPECT in women is limited to non-UK studies and few data were available. The use of SPECT for acute coronary syndrome was again limited to non-UK studies, although three of the four available studies reported that SPECT was likely to dominate a strategy using clinical and rest ECG data alone.

One RCT suggested that the use of SPECT would be cost saving post-MI and a poorer quality model reported that compared with standard care the incremental cost per death avoided was lower for a direct CA strategy than for a strategy involving SPECT.

The model presented in this report considered some of the strategies currently used in the UK that are potentially relevant for the management of CAD. The results are broadly in accordance with those of the Industry submission.

The effectiveness data for the diagnostic tests came from the effectiveness review (Chapter 3). The results suggest that for low levels of prevalence the incremental cost per unit of output (TPs diagnosed, accurate diagnoses, QALY) for the move from both stress ECG–SPECT–CA and stress ECG–CA to SPECT–CA might be considered worthwhile. At 30% prevalence rates, although SPECT–CA is cost-effective, the CA strategy produces more QALYs at a relatively low ICER. At higher prevalence rates (50 and 85%), SPECT–CA strategy is extendedly dominated by stress ECG–CA and CA strategies.

Despite allowing for different values for sensitivity or specificity, the least costly and least effective strategy was stress ECG–SPECT–CA. For low levels of sensitivity for SPECT, stress ECG–CA dominates the SPECT–CA strategy, whereas for high sensitivity SPECT–CA dominates CA. At high levels of specificity for SPECT, the stress ECG–CA strategy is dominated by the SPECT–CA strategy.

SPECT–CA improves its cost-effectiveness if it can identify those patients who are positive but for whom an angiogram is not required. These results are tentative, however, as it has been assumed that SPECT can correctly stratify patients. The extent to which non-invasive tests provide indeterminate results in this model is very important. This was shown by adopting the values reported in the Industry submission. The results reported suggest that with those values of indeterminacy for stress ECG and SPECT, the SPECT–CA strategy dominates stress ECG–CA.

Estimates of incremental cost per QALY are sensitive to the time horizon chosen and as the time horizon increases the incremental cost per QALY declines. The results are also sensitive to assumptions about how long it takes for an incorrectly diagnosed patient to be correctly diagnosed. In the base-case model it was assumed that those patients who were not correctly classified

would be correctly allocated within 10 years. If this assumption is relaxed then those strategies that result in incorrect diagnoses improve in cost-effectiveness as the penalty associated with incorrect diagnosis is reduced. One of the assumptions of the model was that the specificity and sensitivity for CA equalled one. Relaxing this assumption would be expected to lead to improvement in the relative cost-effectiveness of the non-invasive strategy relative to CA. Whether this would lead to an increased preference for SPECT-based strategies would in part depend on both the sensitivity and specificity of SPECT and also its ability to identify correctly patients with CAD who could be managed medically and may therefore not require an angiogram.

Finally, a subgroup analysis was conducted for women. This analysis found that as the sensitivity and specificity for SPECT were higher than those adopted in the base-case (and the mortality and prevalence were lower), the SPECT–CA strategy dominates the stress ECG–CA and CA strategies.

Assumptions, limitations and uncertainties

Extensive literature searches were conducted. Nevertheless, they were restricted to major electronic databases and did not, for example, cover grey literature extensively. Because of time constraints, non-English language reports were not considered.

Studies with <100 participants were not included in the review. Small studies have been reported as tending to exaggerate treatment effects and also tending to be of poorer methodological quality compared with larger studies.[134] The median values for both sensitivity and specificity for SPECT in the set of studies excluded from the review because they contained <100 patients were higher than those of the set of included studies containing ≥100 patients. Including studies with <100 patients would therefore have resulted in the reporting of higher median sensitivity and specificity values for SPECT.

Planar imaging was excluded from this review because in the UK it has been superseded by tomographic imaging as the standard approach, and our choice of comparators was designed to reflect current practice. Much of the original work assessing the diagnostic and prognostic effectiveness of MPI was performed when tomographic imaging was less developed and planar imaging was common. The inclusion of planar imaging studies might have added power to the comparison of SPECT with stress ECG and might have provided greater statistical significance for the findings in favour of SPECT.

Although the role of SPECT for patients unable to exercise or with abnormal resting ECG was not specifically examined, such categories of patients may have been included within the larger patient population in those studies where ECG stress was produced pharmacologically rather than by exercise, and in studies where the stress part of SPECT was produced pharmacologically (adenosine, dipyridamole, dobutamine) rather than by exercise. One of the included diagnostic studies[41] was concerned with patients with LBBB, for whom stress ECG is non-diagnostic and was not included as a comparator, and where the diagnostic accuracy of SPECT was compared with CA as the reference standard.

No randomised trials were identified comparing outcomes after different diagnostic strategies with or without SPECT. For this reason, effectiveness was judged on SPECT's relative diagnostic and prognostic performance.

Effectiveness

Diagnostic studies

The number of diagnostic studies identified by the search strategy that met all the inclusion criteria was relatively small. The focus of the review was to assess the diagnostic ability of SPECT alongside existing tests (stress ECG) for the diagnosis of CAD. Several diagnostic studies assessing the performance of MPS versus CA are available in the literature, in addition to diagnostic studies based on the use of planar imaging. However, the evaluation of planar imaging studies was not within the scope of this review. In addition, studies assessing diagnostic accuracy separately for each test were also not considered for this review; in other words, included studies compared SPECT with another diagnostic procedure against the reference standard of CA. The decision to include only studies comparing SPECT with stress ECG, with CA as the reference standard, was taken in order to allow a direct comparison of the tests in the same patient populations over the same periods in the same settings. Although this decision resulted in fewer included studies than would have otherwise been the case, those studies that were included provided more useful comparative information between the tests than studies where SPECT alone or stress ECG alone was compared with CA and where indirect comparisons would then have to be made.

There are also a number of reports in the literature that compare the diagnostic performance of SPECT and exercise ECHO or assess the use of ECHO in addition to stress ECG in the diagnosis of CAD. Comparing the accuracy and relative effectiveness of SPECT and exercise ECHO was not within the remit of this review. However, it is worth mentioning the results of a recent meta-analysis evaluating the diagnostic performance of these two imaging techniques.[14] The meta-analysis included 44 studies comparing exercise ECHO with exercise SPECT, published between 1990 and 1997. SPECT yielded an overall sensitivity of 0.87 (95% CI 0.86 to 0.88) and an overall specificity of 0.64 (95% CI 0.60 to 0.80) whereas exercise ECHO had an overall sensitivity of 0.85 (95% CI 0.83 to 0.87) and an overall specificity of 0.77 (95% CI 0.74 to 0.80). It was concluded that exercise ECHO and exercise SPECT had similar sensitivities for the detection of CAD, but that exercise ECHO had better specificity, and therefore a higher overall discriminatory capability.

The studies included in this review varied considerably in terms of their inclusion/exclusion criteria, characteristics of participants, definition of positive test, definition of normal versus abnormal coronary angiograms and methods. This, together with the relatively small number of identified studies, hampered the possibility of combining diagnostic data using formal meta-analysis techniques and to ascertain whether certain factors could affect the accuracy of SPECT (e.g. gender, definition of CAD, severity of the condition).

Other limitations were related to the poor reporting of test results and the blinding of their interpretation. Although most of the selected studies provided estimates of sensitivity, specificity and accuracy, few provided such measures for patient subgroups and formally assessed test reproducibility. Interpretation of SPECT and stress ECG without knowledge of the results of CA and other clinical information is critical, especially for imaging techniques, which rely on subjective judgements. It was unclear from most studies whether the same clinical data were available when test results were interpreted as would be available if the test were to be used in practice. In studies of diagnostic accuracy where the SPECT images are interpreted in the absence of clinical information, this gives a lower specificity than would be the case in normal practice where the test is interpreted with clinical information present, since it is much more difficult to tell the difference between artefact and true perfusion abnormality if patient clinical data such as gender, breast size and build are not known.

Prognostic studies

Our findings are limited by the fact that all of the included studies were observational studies and susceptible to the biases inherent in such designs. Only four studies were comparative, in the sense that different groups had different testing strategies concurrently, usually with one group of patients allocated to a strategy of direct CA whereas a second group was managed with a strategy of SPECT, and selective CA.

The remaining studies were cohort studies in which substantially the same group of patients received all the tests of interest. Some form of multivariate regression, usually Cox proportional hazards regression analysis, was generally undertaken to calculate which variables associated with the tests were identifiable as independently and/or incrementally predicting the outcomes of interest, for example cardiac mortality or non-fatal MI. Although the direction of the evidence was consistent in favouring SPECT, the strength of the evidence from such study designs is not as strong as would be the case with RCTs.

Another limitation was that the generalisability of the included studies appeared to be low, in that study participants were not representative of the entire populations from which they were recruited, and insufficient information was provided to determine whether the staff, places and facilities where patients were treated were representative of the treatment that the majority of patients would receive.

Cost and cost-effectiveness

The review of existing economic evaluations focused solely on studies that attempted a formal cost-effectiveness/utility or cost-minimisation analysis. Cost analyses were not considered, as they provide no meaningful information about relative efficiency. Furthermore, a quantitative synthesis of the economic evaluations could not be undertaken.

Interpretation of the identified studies was complicated because so few of them were conducted in the UK and there were many different values used even for the sensitivity and specificity of SPECT. The extent to which data on longer term costs and effects are generalisable to the UK is unclear. Are rates of service utilisation used in the Amersham Health submission (and

also the model presented in Chapter 5) relevant to the UK, given that they are derived from non-UK-based studies where intervention is more likely? For example, RRs and relative rates of utilisation were extrapolated but absolute rates of utilisation of interventions were not, as it is well known that there are differences in utilisation rates between the USA and UK and it was believed that the use of relative rates would result in less bias.

These uncertainties present in the model have, in part, been addressed by the extensive SA. For example, within the model very conservative estimates for the sensitivity and especially for specificity of SPECT have been used. These estimates are lower than those used in the majority of economic evaluations and within the Industry model. Despite this, the SA has shown that over a range of plausible values the overall results remain stable.

One of the key areas of uncertainty was with respect to the ability of SPECT to identify patients at risk of CAD for whom CA would not be required. This was identified as a potential advantage of SPECT based both on the advice from clinicians and on the results of the prognostic studies reported in Chapter 3. However, the extent to which SPECT would be able to achieve this was unclear. Nevertheless, tentative results suggest that should SPECT be able to identify accurately those patients at risk of CAD for whom CA would not be required, then the cost-effectiveness of SPECT based strategies would improve.

Within the model it has also been assumed that an angiogram provides perfect information. If this assumption were relaxed then it would be expected that those strategies that do not rely on angiography to the same extent would improve in cost-effectiveness.

The costs of the diagnostic tests used within the economic model are average costs and include elements for the capital and overheads of providing these services. The impact of using these costs was explored in the SA but there may be concerns that they do not adequately reflect opportunity costs. Therefore, careful consideration is required about whether these costs would apply to an increase in the use of SPECT suggested in the submission by the Professional Groups.

Linking diagnostic performance to long-term outcomes required a number of assumptions to be made about both the structure of the model and its parameters. Some of these assumptions were based on data from non-UK studies such as the proportion of positive patients with LMD and 3VD. It is unclear whether such data are applicable to the UK. Another assumption made relates to the duration of time over which the benefits from a diagnostic strategy might accrue. In the base-case analysis 25 years has been used. However, in the SA the impact of using shorter time horizons has been explored. Furthermore, other data, such as the utility values, are not based on a UK population and may not be appropriate to priority setting in the UK. The model presented in Chapter 5 (unlike that presented in the Industry submission) does not allow for higher QoL after revascularisation. Therefore, the benefits of revascularisation are solely in the form of higher life expectancy. If a higher QoL were achieved after revascularisation, those strategies that identify accurately patients for revascularisation (fewer FNs) would perform better.

A further caveat, related to the pay-off model, is the extent to which severity of disease is linked to QoL. The model presented in Chapter 5 and many of the models summarised in Chapter 4 make the assumption that there is a direct link. No utility data were identified with which to test this assumption and the impact of this assumption on relative cost-effectiveness is therefore unclear.

Need for further research

Further research is needed on the effectiveness and cost-effectiveness of SPECT compared with stress ECHO, both diagnostically and prognostically.

Ultimately, the decisions about the cost-effectiveness of strategies involving SPECT rely on information not only on their diagnostic performance but also on subsequent costs and effects of treatment. Relatively robust data can be obtained on, for example, the incremental cost per accurate diagnosis. Such data are of very limited value as a basis of decisions about allocative efficiency. Relatively poor data are available with which to consider longer term costs and consequences. Both the submission from Amersham Health and the economic model presented in Chapter 5 use data from non-UK settings. Such data may not be generalisable to the UK. Higher quality economic evaluations relevant to the UK require better information, especially on rates of service utilisation and on utilities.

By providing information on both function and perfusion, gated SPECT potentially has advantages over standard SPECT. In the same way, AC SPECT could potentially provide better quality images than standard SPECT. Additional research is needed to clarify the comparative effectiveness and cost-effectiveness of gated and AC SPECT compared with standard SPECT, diagnostically and prognostically, and whether these techniques are of particular benefit to specific patient groups.

Chapter 9
Conclusions

Implications for the NHS

- SPECT is more sensitive than stress ECG for the detection of CAD.
- SPECT provides independent and incremental information in predicting cardiac events in patients over and above that provided by stress ECG and CA.
- For the diagnosis of CAD in a low- to medium-risk population (<75% stenosis), SPECT-based strategies compared with those that rely on stress ECG are likely to be associated with additional benefits which may be considered affordable (i.e. SPECT can define the site and severity of ischaemia, providing important information that can guide patient management). It is currently unclear which of the SPECT-based strategies is likely to be most appropriate.
- At high risks of CAD, CA is associated with relatively modest estimates of incremental cost-effectiveness compared with SPECT-based strategies. SPECT, however, may identify patients with CAD for whom revascularisation is not an immediate treatment option, thus reducing the need for CA.
- SPECT-based strategies for the diagnosis of CAD in women may become cost-effective as the prevalence level of CAD increases.
- The use of SPECT-based strategies for the diagnosis of acute coronary syndromes or post-MI may be cost-effective, although the evidence base is small.
- Current services could not provide significantly more SPECT tests. Additional investment in facilities and training would be required.

Implications for patients and carers

- The increased use of SPECT-based strategies may reduce the number of invasive tests required.
- Although the use of non-invasive strategies may speed the time taken to provide a diagnosis, the expansion of services is likely to be slow because of the time needed to train staff adequately.

Implications for research

- Determination of the optimal diagnostic strategy requires information on longer term outcomes, especially rates of service utilisation and on utilities. Such information could be appropriately collected with observational studies and surveys of relevant patient groups.
- Further research is needed on the effectiveness and cost-effectiveness, diagnostically and prognostically, of gated and AC SPECT compared with standard SPECT, and whether these techniques are of particular benefit to specific patient groups.
- Further research is also needed on the effectiveness and cost-effectiveness of SPECT compared with stress ECHO.

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About 'Home Unit'

The Health Services Research Unit (HSRU), University of Aberdeen, has responsibility for the following general remit within Scotland:

1. to study or evaluate clinical activities with a view to improving effectiveness and efficiency in health care
2. to work for the implementation of proven changes in clinical activities
3. to encourage and support similar work throughout Scotland
4. to train NHS staff in Scotland, and others, in the principles and practice of health services research in general, and health care evaluation in particular.

Contributions of the authors

Graham Mowatt, Alison Murray, Miriam Brazzelli and Neil Scott completed the review of effectiveness. Luke Vale and Lynda McKenzie conducted the review of economic evaluations. Rodolfo Hernandez conducted the economic evaluation. Cynthia Fraser developed and ran search strategies and obtained papers. Neil Scott undertook statistical analyses. Malcolm Metcalfe, Graham Hillis and Howard Gemmell provided clinical advice and commented on drafts of the review.

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Appendix 1

Literature search strategies

Sources searched for systematic reviews and other evidence-based reports

1. The Cochrane Library (CDSR), Issue 3, 2002
2. Database of Abstracts of Reviews of Effects(DARE). NHS Centre for Reviews and Dissemination, October 2002
3. HTA Database, NHS Centre for Reviews and Dissemination, October 2002
4. Medion database of diagnostic met-analyses and reviews. University of Maastricht, October 2000. URL: http://www.hag.unimaas.nl/Internationalisering/onderzoek/Cochrane/database%20Frank%20Buntinx/welcome_on_the_webpage_of_medion.htm
5. National Guideline Clearinghouse. URL: http://www.guideline.gov/index.asp
6. Scottish Intercollegiate Guidelines Network. URL: http://www.show.scot.nhs.uk/sign/index.html
7. Trip database. URL: http://www.tripdatabase.com/
8. Agency for Healthcare Research and Quality. URL: http://www.ahrq.gov/
9. American College of Cardiology. URL: http://www.acc.org/index.htm
10. American Society of Nuclear Cardiology. URL: http://www.asnc.org/
11. British Cardiac Society. URL: http://www.bcs.com/resources/links.html
12. British Nuclear Cardiology Society. URL: http://www.bncs.org.uk/
13. Global Cardiology Network. URL: http://www.globalcardiology.org/index.html
14. European Society of Cardiology. URL: http://www.escardio.org/
15. Royal College of Physicians. URL: http://www.rcplondon.ac.uk/

Ovid multifile search: MEDLINE (1966–October 2002), EMBASE [1980–2002 (to week 44)], PREMEDLINE (5 November 2002) (using textword terms only)

1. myocardial ischemia/
2. coronary disease/
3. exp chest pain/
4. myocardial infarction/
5. exp heart infarction/
6. coronary arteriosclerosis/
7. exp coronary stenosis/
8. coronary thrombosis/
9. coronary artery constriction/
10. exp angina pectoris/
11. heart muscle perfusion/
12. (myocardi$ adj3 perfusion).tw.
13. coronary heart disease?.tw.
14. (isch?emi$ adj3 (heart or coronary or myocardial)).tw.
15. angina.tw.
16. chest pain?.tw.
17. ((myocardial or coronary) adj3 (infarct$ or thrombosis or stenosis or restenosis or arteriosclerosis)).tw.
18. or/1-17
19. Tomography, Emission-Computed, Single-Photon/
20. (spect or spet).tw.
21. single photon emission computed tomography.tw.
22. scintigraph$.tw.
23. or/19-22
24. 18 and 23
25. 23 and (heart or coronary or myocardi$).tw.
26. ((exercise or stress) adj3 test?).tw.
27. 18 and imag$.tw.
28. thallium.rw.
29. technetium tc 99m.rw.
30. 29 and (sestamibi or tetrofosmin).tw.
31. (26 or 27) and (28 or 30)
32. methoxy isobutyl isonitrile technetium tc 99m/
33. tetrofosmin tc 99m/
34. thallium 201/
35. thallium chloride tl 201/
36. (26 or 27) and (32 or 33 or 34 or 35)
37. 24 or 25 or 31 or 36
38. electrocardiography/
39. electrocardiograph$.tw.
40. (ecg or ekg).tw.
41. or/38-40
42. exercise test/
43. (exercise or stress or stressor or treadmill or bicycl$ or cycling).tw.
44. dipyridamole/

45. adenosine/
46. adenosine triphosphate/
47. dobutamine/
48. or/42-47
49. 41 and 48
50. exp coronary angiography/
51. ((coronary or myocardi$) adj3 (angiograph$ or angiogram$ or arteriograph$)).tw.
52. or/50-51
53. "sensitivity and specificity"/
54. roc curve/
55. predictive value of tests/
56. false positive reactions/
57. false negative reactions/
58. diagnostic accuracy/
59. diagnostic error/
60. diagnostic value/
61. differential diagnosis/
62. early diagnosis/
63. prediction/
64. prognosis/
65. risk assessment/
66. recurrence risk/
67. (ri or di or du).fs.
68. sensitivity.tw.
69. specificity.tw.
70. roc.tw.
71. (predictive adj4 value$).tw.
72. (prognosis or prognostic).tw.
73. (risk adj3 stratif$).tw.
74. (false adj3 (positive$ or negative$)).tw.
75. likelihood ratio$.tw.
76. (logistic adj2 (regression or model$)).tw.
77. (regression adj2 analys$).tw.
78. (distinguish$ or differentiat$).tw.
79. (identif$ or detect$ or diagnos$ or accura$).tw.
80. reproducibility of results/
81. or/53-80
82. exp myocardial revascularization/
83. exp coronary artery surgery/
84. atherectomy, coronary/
85. angioplasty, balloon/
86. revasculari?ation.tw.
87. angioplasty.tw.
88. coronary artery bypass.tw.
89. clinical pathways/
90. clinical protocols/
91. "referral and consultation"/
92. ((clinical or critical) adj3 (path? or pathway?)).tw.
93. protocol?.tw.
94. (referral or refer or referred).tw.
95. ((management or diagnos$ or investigat$) adj3 plan).tw.
96. myocardial reperfusion/
97. reperfusion.tw.
98. exp morbidity/
99. exp mortality/
100. death,sudden,cardiac/
102. major adverse cardiac event?.tw.
103. "Outcome Assessment (Health Care)"/
104. myocardial infarction/
105. exp heart infarction/
106. exp angina, unstable/
107. (evaluat$ or assess$ or increment$ or compara$).tw.
108. or/82-107
109. 37 and 81
110. 49 and 81
111. 52 and 81
112. 109 and (110 or 111)
113. 37 and (49 or 52)
114. 108 and 113
115. 112 or 114
116. (animal/ or nonhuman/) not human/
117. 115 not 116
118. (editorial or letter).pt.
119. 117 not 118
120. limit 119 to yr=1980-2002

BIOSIS (Edina) (1985–16 December 2002)

((al:spect or al: spet or al:scintigraph*
or
al:thallium or al:technetium or al:tetrofosmin
or
tal:computed tomography)
AND
(al:ecg or al:electrocardiogra* or al:angiogra*
or
al:stress test or al:exercise test)
AND
(al:myocardial or al:heart or al:coronary
or
al:chest pain or al:angina
or
al:ischemi* or al:ischaemi*))
AND
(al:diagnos* or al:detect*
or
al:sensitivity or al:specificity or al:roc
or
al:prognosis or al: prognositic or al:predict*
or
al:protocol* or al:pathway*
or
al:false positive or al:false negative or
al:incremental
or
al:risk stratif* or al:risk assess*)

Science Citation Index (Web of Science) and WOS Proceedings (1981–8 January 2003)

(spect or spet or scintigraph*
or
thallium or technetium or tetrofosmin
or
computed tomography)
AND
(ecg or electrocardiogra* or angiogra*
or
stress test or exercise test)
AND
(myocardial or heart or coronary
or
chest pain or angina
or
ischemi* or ischaemi*))
AND
(diagnos* or detect*
or
sensitivity or specificity or roc
or
prognosis or prognostic or predict*
or
protocol* or pathway*
or
false positive or false negative or incremental
or
risk stratif* or risk assess*)

HMIC (1979–2002)

(Spect or spet or scintigraph* or thallium or technetium or terofosmin or computed tomography
and
ecg or ekg or electrocardiogra* or angiogra* or stress test or exercise test)
or
(ischemi* or ischaemi* or chest pain or angina or myocardial or heart or coronary
and
diagnostic imaging in DE)

HTA and DARE (4 October 2002)

ECG or electrocardiograph* or angiogr*
Or
SPECT or scintigraphy or perfusion imag*
Or
Diagnos* and (coronary or myocardial or ischem* or ischaem*)

Medion (October 2002)

Spect; spet; scintigraph; coronary; perfusion in ti ,ab

Cochrane Library (Issue 3, 2002)

1. Tomography, Emission-Computed, Single-Photon (MESH)
2. spect or spet or scintigraph$. or computed tomography
3. #1 or #2
4. Electrocardiography (MESH)
5. ECG or EKG or electrocardiograph*
6. Coronary Angiography (MESH)
7. Coronary near angio*
8. Coronary near arteriograph*
9. #4 or #5 or #6 or #7 or #8
10. #3 and #9

MEDLINE (1966–October 2002), EMBASE [1980–October 2002 (to week 47)], PRE-MEDLINE (5 November 2002)

1. myocardial ischemia/
2. coronary disease/
3. exp chest pain/
4. myocardial infarction/
5. exp heart infarction/
6. coronary arteriosclerosis/
7. exp coronary stenosis/
8. coronary thrombosis/
9. coronary artery constriction/
10. exp angina pectoris/
11. heart muscle perfusion/
12. (myocardi$ adj3 perfusion).tw.
13. coronary heart disease?.tw.
14. (isch?emi$ adj3 (heart or coronary or myocardial)).tw.
15. angina.tw.
16. chest pain?.tw.
17. ((myocardial or coronary) adj3 (infarct$ or thrombosis or stenosis or restenosis or arteriosclerosis)).tw.
18. or/1-17
19. Tomography, Emission-Computed, Single-Photon/
20. (spect or spet).tw.
21. single photon emission computed tomography.tw.
22. scintigraph$.tw.
23. or/19-22
24. 18 and 23
25. 23 and (heart or coronary or myocardi$).tw.
26. ((exercise or stress) adj3 test?).tw.
27. 18 and imag$.tw.
28. thallium.rw.
29. technetium tc 99m.rw.
30. 29 and (sestamibi or tetrofosmin).tw.

31. (26 or 27) and (28 or 30)
32. methoxy isobutyl isonitrile technetium tc 99m/
33. tetrofosmin tc 99m/
34. thallium 201/
35. thallium chloride tl 201/
36. (26 or 27) and (32 or 33 or 34 or 35)
37. 24 or 25 or 31 or 36
38. *myocardial ischemia/di, du, ri use mesz
39. *myocardial ischemia/di
40. *coronary disease/di, du, ri use mesz
41. *coronary disease/di
42. exp *chest pain/di, du, ri use mesz
43. exp *chest pain/di
44. *myocardial infarction/di, du, ri use mesz
45. exp *heart infarction/di use emez
46. *coronary arteriosclerosis/di, du, ri use mesz
47. *coronary arteriosclerosis/di
48. exp *coronary stenosis/di, du, ri use mesz
49. exp *coronary stenosis/di
50. *coronary thrombosis/di, du, ri use mesz
51. *coronary thrombosis/di
52. *coronary artery constriction/di use emez
53. exp *angina pectoris/di, du, ri use mesz
54. exp *angina pectoris/di
55. *heart muscle perfusion/
56. or/38-55
57. economics/
58. exp "costs and cost analysis"/ use mesz
59. exp economics,hospital/ use mesz
60. exp models,economic/ use mesz
61. ec.fs. use mesz
62. exp economic evaluation/
63. exp hospital cost/
64. exp quality of life/
65. value of life/
66. cost of illness/
67. health status/
68. health status indicators/ use mesz
69. (qol or qaly?).tw.
70. (quality adj2 life).tw.
71. (health adj3 (indicator? or status or utilit$)).tw.
72. (cost? adj3 (analys?s or evaluat$ or effectiveness)).tw.
73. economic adj3 (analys?s or evaluat$ or effectiveness)).tw.
74. or/57-73
75. 37 and 74
76. 56 and 74
77. 75 or 76
78. limit 77 to yr=1990-2002

NHS–EED (4 October 2002)

ECG or electrocardiograph*
Or
SPECT or scintigraphy or perfusion imag*
Or
Diagnos* and (coronary or myocardial or ischem* or ischaem

Appendix 2

Data extraction form

Administration details

Paper number: _____ **Extractor initials:** _____ **Date information extracted:**

Date information extracted: _____

Study identifier: _____
(Surname of first author + year of publication)

Number of trials included in this paper: _____
(if more than one, complete separate extraction forms
for each, and add letters A, B, C, etc. to the study identifier)

Paper numbers of other trials with which this may link: _____ _____ _____ _____

Type of study

Diagnostic ☐

Prognostic: ☐

- General ☐
- Pre-operative risk assessment ☐
- Post-revascularisation assessment ☐

Aim of study:

Study Design

RCT ☐

Controlled Clinical Trial ☐

Prospective Comparative Observational Study ☐

Retrospective Comparative Observational Study ☐

Other _____

Characteristics of the participants					
Inclusion criteria:					
Exclusion criteria:					
Did the participants have suspected ☐ or confirmed ☐ CAD?					
Comparators/ pathways (please tick)	1	SPECT ☐	Stress ECG ☐	CA ☐	All
	2	Stress ECG/ SPECT ☐	Stress ECG ☐		
	3	SPECT/CA ☐	CA ☐		
	4	Stress ECG/ SPECT/CA ☐	Stress ECG/CA		
(Other)	5	☐	☐	☐	
Number of patients enrolled in trial					
Number of patients receiving intervention					
Number of patients lost to follow-up					
Age (mean, range)					
Gender		M: F:	M: F:	M: F:	M: F:
Ethnicity					
Number of patients with previous MI					
Number of patients with previous PTCA					
Number of patients with previous CABG					

Are all these characteristics approximately balanced amongst the groups receiving different tests?
If the trial does not consist wholly of patients with previous MI, are those patients with previous MI identifiable separately from the rest of the participants throughout the trial?
Source of participants:
Method of recruitment: (Consecutive etc.)
Dates for recruitment:
Characteristics of the intervention
Location and country of trial centre(s):
Duration of trial:
Length of follow-up:
Make and model of SPECT equipment:
Sequence and time between tests:
Radionuclide used: Thallium ☐ Technetium sestamibi ☐ Technetium tetrofosmin ☐ Dual isotope (give details) ☐

SPECT stress induced by: Exercise: Treadmill ☐ Bicycle ☐ Pharmacalogically: Adenosine ☐ Dipyridamole ☐ Dobutamine ☐ Combination of exercise/pharmacological means (give details)
ECG stress induced by: Treadmill ☐ Bicycle ☐ Pharmacalogically: Adenosine ☐ Dipyridamole ☐ Dobutamine ☐ Combination of exercise/pharmacological means (give details) ☐
Number of tests where patients reached at least 85% of their predicted maximal heart rate: Stress ECG: SPECT:
For diagnostic studies, was the reference test coronary angiography? (If not, give details of the reference test used)
What was the definition of a positive test result? Stress ECG: SPECT:
What was the authors' definition of significant CAD? (e.g. 50% stenosis, 70% stenosis etc.)

Concomitant interventions (interventions given to all participants in addition to SPECT/stress ECG/CA):

_____

_____

Outcomes (Diagnostic studies)			
Number of patients receiving test	SPECT	Stress ECG	CA
True positives			Notes
False positives			
True negatives			
False negatives			
Sensitivity			
Specificity			
Positive predictive value			
Negative predictive value			
Positive likelihood ratio			
Negative likelihood ratio			
Diagnostic accuracy			
Diagnostic odds ratio			

Outcomes (Prognostic studies.)				
Comparators/ pathways (please tick) 1 (Other) 2	SPECT ☐ --- ☐	Stress ECG ☐ --- ☐	CA ☐ --- ☐	All
Mortality				
Cardiac mortality				
Non fatal MI				
Revasc – PTCA				
Revasc – CABG				
Occurrence of unstable angina				
Other major cardiac events				
Survival free of cardiac death				
Preservation of left ventricular function				
Post-operative complications				
Number of CAs performed				
Hospital admissions				
Quality of Life (e.g. SF 36)				

Type of multivariate regression used:

Reference characteristic/factor:

Characteristic/factor	Odds ratio	Hazard ratio	Standard error	P value

Other comments

Appendix 3

QUADAS checklist for diagnostic tests

Paper number: _____ **Extractor initials:** _____ **Date study assessed:** _____

Study identifier: _____
(Surname of first author + year of publication)

Item	Yes	No	Unclear
1. Was the spectrum of patients representative of the patients who will receive the test in practice?			
2. Were selection criteria clearly described?			
3. Is the reference standard likely to correctly classify the target condition?			
4. Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?			
5. Did the whole sample or a random selection of the sample, receive verification using a reference standard of diagnosis?			
6. Did patients receive the same reference standard regardless of the index test result?			
7. Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?			
8a. Was the execution of the index test described in sufficient detail to permit replication of the test?			
8b. Was the execution of the reference standard described in sufficient detail to permit its replication?			
9a. Were the index test results interpreted without knowledge of the results of the reference standard?			
9b. Were the reference standard results interpreted without knowledge of the results of the index test?			
10. Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?			
11. Were uninterpretable/intermediate test results reported?			
12. Were withdrawals from the study explained?			

Appendix 4

Downs and Black quality assessment form

SPECT review

Quality assessment form – prognostic studies

Paper number: _____

Study identifier:
(surname of first author + year of publication)

_____

Assessor initials: _____

Date form completed: _____

Reporting

1. *Is the hypothesis/aim/objective of the study clearly described?*

Yes	
No	

2. *Are the main outcomes to be measured clearly described in the Introduction or Methods section?*

If the main outcomes are first mentioned in the Results section, the question should be answered no.

Yes	
No	

3. *Are the characteristics of the patients included in the study clearly described?*

In cohort studies and trials, inclusion and/or exclusion criteria should be given. In case-control studies, a case-definition and the source for controls should be given.

Yes	
No	

4. *Are the interventions of interest clearly described?*

Treatments and placebo (where relevant) that are to be compared should be clearly described.

Yes	
No	

5. *Are the distributions of principal confounders in each group of subjects to be compared clearly described?*

A list of principal confounders is provided.

Yes	
Partially	
No	

6. *Are the main findings of the study clearly described?*

Simple outcome data (including denominators and numerators) should be reported for all major findings so that the reader can check the major analyses and conclusions. (This question does not cover statistical tests which are considered below.)

Yes	
No	

7. *Does the study provide estimates of the random variability in the data for the main outcomes?*

In non-normally distributed data the inter-quartile range of results should be reported. In normally distributed data the standard error, standard deviation or confidence intervals should be reported. If the distribution of the data is not described, it must be assumed that the estimates used were appropriate and the question should be answered yes.

Yes	
No	

8. *Have all important adverse events that may be a consequence of the intervention been reported?*

This should be answered yes if the study demonstrates that there was a comprehensive attempt to measure adverse events. (A list of possible adverse events is provided.)

Yes	
No	

9. *Have the characteristics of patients lost to follow-up been described?*

This should be answered yes where there were no losses to follow-up or where losses to follow-up were so small that findings would be unaffected by their inclusion. This should be answered no where a study does not report the number of patients lost to follow-up.

Yes	
No	

10. *Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?*

Yes	
No	

External validity

All the following criteria attempt to address the representativeness of the findings of the study and whether they may be generalised to the population from which the study subjects were derived.

11. *Were the subjects asked to participate in the study representative of the entire population from which they were recruited?*

The study must identify the source population for patients and describe how the patients were selected. Patients would be representative if they comprised the entire source population, an unselected sample of consecutive patients, or a random sample. Random sampling is only feasible where a list of all members of the relevant population exists. Where a study does not report the proportion of the source population from which the patients are derived, the question should be answered as unable to determine.

Yes	
No	
Unable to determine	

12. *Were those subjects who were prepared to participate representative of the entire population from which they were recruited?*

The proportion of those asked who agreed should be stated. Validation that the sample was representative would include demonstrating that the distribution of the main confounding factors was the same in the study sample and the source population.

Yes	
No	
Unable to determine	

13. *Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients received?*

For the question to be answered yes the study should demonstrate that the intervention was representative of that in use in the source population. The question should be answered no if, for example, the intervention was undertaken in a specialist centre unrepresentative of the hospitals most of the source population would attend.

Yes	
No	
Unable to determine	

Internal validity – bias

14. *Was an attempt made to blind study subjects to the intervention they have received?*

For studies where the patients would have no way of knowing which intervention they received, this should be answered yes.

Yes	
No	
Unable to determine	

15. *Was an attempt made to blind those measuring the main outcomes of the intervention?*

Yes	
No	
Unable to determine	

16. *If any of the results of the study were based on 'data dredging', was this made clear?*

Any analyses that had not been planned at the outset of the study should be clearly indicated. If no retrospective unplanned subgroup analyses were reported, then answer yes.

Yes	
No	
Unable to determine	

17. *In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case–control studies, is the time period between the intervention and outcome the same for cases and controls?*

Where follow-up was the same for all study patients the answer should be yes. If different lengths of follow-up were adjusted for by, for example, survival analysis the answer should be yes. Studies where differences in follow-up are ignored should be answered no.

Yes	
No	
Unable to determine	

18. *Were the statistical tests used to assess the main outcomes appropriate?*

The statistical tests used must be appropriate to the data. For example non-parametric methods should be used for small sample sizes. Where little statistical analysis has been undertaken but where there is no evidence of bias, the question should be answered yes. If the distribution of the data (normal or not) is not described it must be assumed that the estimates used were appropriate and the question should be answered yes.

Yes	
No	
Unable to determine	

19. *Was compliance with the intervention/s reliable?*

Where there was non-compliance with the allocated treatment or where there was contamination of one group, the question should be answered no. For studies where the effect of any misclassification was likely to bias any association to the null, the question should be answered yes.

Yes	
No	
Unable to determine	

20. *Were the main outcome measures used accurate (valid and reliable)?*

For studies where the outcome measures are clearly described, the question should be answered yes. For studies which refer to other work or that demonstrate the outcome measures are accurate, the question should be answered yes.

Yes	
No	
Unable to determine	

Internal validity – confounding (selection bias)

21. *Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case–control studies) recruited from the same population?*

For example, patients for all comparison groups should be selected from the same hospital. The question should be answered unable to determine for cohort and case–control studies where there is no information concerning the source of patients included in the study.

Yes	
No	
Unable to determine	

22. *Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case–control studies) recruited over the same period of time?*

For a study which does not specify the time period over which patients were recruited, the question should be answered as unable to determine.

Yes	
No	
Unable to determine	

23. *Were study subjects randomised to intervention groups?*

Studies which state that subjects were randomised should be answered yes except where method of randomisation would not ensure random allocation. For example, alternate allocation would score no because it is predictable.

Yes	
No	
Unable to determine	

24. *Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?*

All non-randomised studies should be answered no. If assignment was concealed from patients but not from staff, it should be answered no.

Yes	
No	
Unable to determine	

25. *Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?*

This question should be answered no for trials if: the main conclusions of the study were based on analyses of treatment rather than intention to treat; the distribution of known confounders in the different treatment groups was not described; or the distribution of known confounders differed between the treatment groups but was not taken into account in the analyses. In non-randomised studies if the effect of the main confounders was not investigated or confounding was demonstrated but no adjustment was made in the final analyses the question should be answered as no.

Yes	
No	
Unable to determine	

26. *Were losses of patients to follow-up taken into account?*

If the numbers of patients lost to follow-up are not reported, the question should be answered as unable to determine. If the proportion lost to follow-up was too small to determine main findings, the question should be answered yes.

Yes	
No	
Unable to determine	

Power

27. *Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%?*

Sample sizes have been calculated to detect a difference of x% and y%.

	Size of *smallest* intervention group	
A	$<n_1$	0
B	n_1–n_2	1
C	n_3–n_4	2
D	n_5–n_6	3
E	n_7–n_8	4
F	n_8+	5

Appendix 5

List of principal confounders and possible adverse events

Question 5 List of principal confounders

- age
- gender
- previous MI
- previous PTCA
- previous CABG
- heart failure (only really a problem with thallium because of high lung uptake)
- weight.

Question 8 List of possible adverse events

- Coronary angiography:
  mortality; non-fatal MI; cerebrovascular accident; infection (rare); allergic dye reaction (rare); local vascular injury at site of catheterisation
- Stress test:
- Dipyridamole:
  mortality; non-fatal MI; ventricular tachycardia; pulmonary oedema; chest pain; headache; dizziness; ECG changes
- Adenosine:
  complete heart block; second-degree heart block; bronchospasm; refractory angina; flushing; headache
- Dobutamine:
  mortality; non-fatal MI; vent dysrhythmias; ventricular tachycardia; hypotension; headache; nausea; anxiety; chest pain; severe ischaemia.

Appendix 6

Equations used for deriving estimated numbers of true positives, false positives, false negatives and true negatives in diagnostic studies reporting sensitivity, specificity and accuracy values

Sensitivity, specificity, diagnostic accuracy and total number known

$$TN = [N(acc - sens) \times spec]/(spec - sens)$$

$$TP = acc \times N - TN$$

$$FP = (TN/spec) - TN$$

$$FN = (TP/sens) - TP$$

Sensitivity, specificity, positive predictive value, negative predictive value and total number known

$$TP = N/\{(1/PPV) + (1/sens) - 1 + [NPV/sens \times (1\text{-}NPV)] - [NPV/(1 - NPV)]\}$$

$$FP = (TP/PPV) - TP$$

$$FN = (TP/sens) - TP$$

$$TN = \{[(TP/sens) - TP] \times NPV\}/(1 - NPV)$$

Notation

TP = true positives

FP = false positives

FN = false negatives

TN = true negatives

sens = sensitivity

spec = specificity

acc = diagnostic accuracy

PPV = positive predictive value

NPV = negative predictive value

N = total number (= TP + FP + FN + TN)

Appendix 7

Characteristics of included studies of effectiveness

Diagnostic studies

Study and methods	Participants	Test characteristics and outcome measures
Beygui, 2000[22] **Study design**: Prospective observational comparison **Method of recruitment**: Consecutive **Dates**: Jan. 1995–Dec. 1996 **Country**: France **Focus**: Diagnostic values of ExECG and SPECT in asymptomatic patients and the discordance between follow-up functional tests and CA	**Inclusion criteria**: Asymptomatic patients with ExECG, SPECT and CA 6 ± 2 months after PTCA. All patients were symptomatic before PTCA **Exclusion criteria**: Patients unable to undergo ExECG, or those with rest ECG abnormalities receiving pharmacological stress **Enrolled**: 179 **Analysed**: 179 **Age**: 61 ± 10 years **Gender**: M 154, W 25 **History of**: **MI** 8; **PTCA** 179; **CABG** N/S	**SPECT**: **Tracer**: Tl-201. **Stress induced by**: Exercise (bicycle). **Image interpretation**: Qualitative. **Equipment**: APEX SPX-4 HR (Elscint, Haifa, Israel) gamma camera **CA methods**: Judkins technique **Interval between tests**: ECG/SPECT 1–7 days before CA **Definition of positive SPECT test**: Qualitative analysis using a 0–4 scale (0 = normal, 4 = severe reduction in Tl-201 uptake). Exercise perfusion defect: segment with a score of ≥2. Ischaemia: minimal improvement of 1 point on a visual scale. Presence of restenosis: ischaemic redistribution in the territory of individual vessels, guided by a pre-PTCA angiogram **Definition of positive stress ECG test**: ≥0.1 mV ST-segment depression with or without chest pain. **Angiographic definition of significant CAD**: Restenosis: >50% diameter stenosis **Outcome measures**: Sensitivity, specificity, positive predictive value, negative predictive value, accuracy for restenosis
Chae, 1993[23] **Study design**: Retrospective observational comparison **Method of recruitment**: Consecutive **Dates**: N/S **Country**: USA **Focus**: Ability of SPECT to identify high-risk women with LMD or 3VD	**Inclusion criteria**: Women who underwent SPECT within 3 months of CA **Exclusion criteria**: History of previous CABG, recent MI, unstable angina pectoris, valvular heart disease and congenital heart disease **Enrolled**: 243 **Analysed**: 243 **Age**: Group 1 65 ± 11, Group 2 61 ± 10 years **Gender**: M 0, W 243 **History of**: **MI** 103; **PTCA** N/S; **CABG** excluded	**SPECT**: **Tracer**: Tl-201. **Stress induced by**: Exercise (treadmill). **Image interpretation**: Visual, quantitative. **Equipment**: Large field of view gamma camera **CA methods**: Performed in multiple projections using standard techniques **Interval between tests**: ECG/SPECT performed within 3 months of CA **Definition of positive SPECT test**: Perfusion pattern in each vascular territory assessed as normal or with fixed or reversible abnormalities. Multivessel abnormality: >1 vascular territory involved. Quantitative analysis: perfusion abnormality – pixels with counts 2.5 SD below the mean normal value obtained from low-risk women; extent – per cent of total myocardium **Definition of positive stress ECG test**: ≥1 mm ST segment depression of the flat or downsloping variety in ≥3 consecutive beats at 8 ms after the J point or ≥1.5 mm upsloping ST-segment depression. Patients with baseline ST abnormalities, additional 2-mm ST depression in the leads showing changes at baseline **Angiographic definition of significant CAD**: ≥50% diameter stenosis **Outcome measures**: Sensitivity, specificity

continued

Study and methods	Participants	Test characteristics and outcome measures
Daou, 2002[24] **Study design**: Prospective observational comparison **Method of recruitment**: Consecutive **Dates**: N/S **Country**: France **Focus**: Values of SPECT, indirect scintigraphic markers of extensive CAD and total MPD criteria; additive value above clinical and stress test variables, for the diagnosis of extensive CAD	**Inclusion criteria**: Patients referred for SPECT who had CA within 3 months of SPECT **Exclusion criteria**: Valvular heart disease, cardiomyopathy, complete LBBB, atrial fibrillation, pacemaker, severe hypertension, advanced chronic bronchopulmonary disease, prior CABG or PTCA, dialysis or intervening acute coronary event between SPECT and CA **Enrolled**: 338 **Analysed**: 310 (pilot group; limited CAD 38, extensive CAD 122, validation group; limited CAD 32, extensive CAD 118) **Age**: Pilot group limited CAD 57 ± 10, pilot group extensive CAD 61 ± 9, validation group limited CAD 59 ± 12, validation group extensive CAD 60 ± 10 years **Gender**: M 282, W 28 **History of**: **MI** 202; **PTCA** excluded; **CABG** excluded	**SPECT**: **Tracer**: Tl-201. **Stress induced by**: Exercise. **Image interpretation**: Visual. **Equipment**: Elscint 1-head gamma camera (Hackensack, NJ, USA) **CA methods**: N/S **Interval between tests**: within a 3-month period **Definition of positive SPECT test**: Abnormalities in ≥ 2 vascular territories **Definition of positive stress ECG test**: Downsloping or horizontal ST-segment depression of ≥ 1 mmHg or upsloping ST depression of ≥ 2 mm measured 80 ms after the J point **Angiographic definition of significant CAD**: ≥ 50% diameter stenosis **Outcome measures**: Sensitivity, specificity, accuracy, incremental value (multivariable logistic regression analysis)
De, 2002[25] **Study design**: Retrospective observational comparison **Method of recruitment**: Consecutive **Dates**: Feb. 1997–Dec. 2000 **Country**: Canada **Focus**: Rate of CAD in women <45 years referred for chest pain; prevalence of cardiac risk factors, the role of non-invasive testing and the quality of medical management	**Inclusion criteria**: Women <45 years referred for CA because of chest pain that had not yet been diagnosed **Exclusion criteria**: Known history of CAD **Enrolled**: 187 **Analysed**: 187 **Age**: <45 years **Gender**: M 0, W 187 **History of**: **MI** N/S; **PTCA** N/S; **CABG** N/S	**SPECT**: **Tracer**: MIBI. **Stress induced by**: N/S. **Image interpretation**: N/S. **Equipment**: N/S **CA methods**: N/S **Interval between tests**: SPECT/ECG within 6 months before CA **Definition of positive SPECT test**: N/S **Definition of positive stress ECG test**: N/S **Angiographic definition of significant CAD**: ≥ 70% diameter stenosis in ≥ 1 coronary artery **Outcome measures**: Sensitivity, specificity

MPO, myocardial perfusion defect.

continued

Study and methods	Participants	Test characteristics and outcome measures
Gentile, 2001[26] **Study design**: Prospective observational comparison **Method of recruitment**: N/S **Dates**: Jan. 1990–Dec. 1998 **Country**: Italy **Focus**: Diagnostic accuracy and prognostic significance of stress ECG and SPECT in an elderly population	**Inclusion criteria**: Patients aged >65 years hospitalised because of cardiac events **Exclusion criteria**: Previous MI, revascularisation, significant valvular disease, idiopathic dilated cardiomyopathy, LBBB, equivocal ECG or SPECT or borderline lesion of a single vessel **Enrolled**: 195 **Analysed**: 132 **Age**: M 72.4 (range 62–76), W 68.2 (range 65–73) years **Gender**: M 90, W 42 **History of**: **MI** excluded; **PTCA** excluded; **CABG** excluded	**SPECT**: **Tracer**: Tl-201. **Stress induced by**: Exercise (bicycle), pharmacologically (dipyridamole). **Image interpretation**: Visual. **Equipment**: Rotating large-field gamma camera (Starcam 2000, General Electric, Milwaukee, WI, USA) **CA methods**: Judkins technique **Interval between tests**: CA performed within 2 weeks of ECG/SPECT **Definition of positive SPECT test**: An area of decreased activity seen during the peak stress that resolved, either partially or totally, during redistribution **Definition of positive stress ECG test**: >1 mm horizontal or downsloping depression of the ST segment 0.08 s after the J point **Angiographic definition of significant CAD**: Obstruction of 60% of lumen diameter. **Outcome measures**: Sensitivity, specificity, true positives for 1-, 2- and 3-vessel disease. Sensitivity, specificity, TPs and FPs and FNs and accuracy by gender and overall
Hamasaki, 1996[27] **Study design**: Prospective observational comparison **Method of recruitment**: N/S **Dates**: Oct. 1988–Sept. 1994 **Country**: Japan **Focus**: Clinical usefulness of the increase in the $\Delta ST/\Delta HR$ index from several days after angioplasty to follow-up for detection of restenosis after successful PTCA	**Inclusion criteria**: Patients with SVD, no prior MI, positive ExECG and SPECT, receiving antianginal therapy, previous PTCA and consent to (1) undergo ExECG after PTCA; (2) follow-up CA; (3) able to perform maximal exercise; and (4) ability to achieve ≥ 85% of the maximum age-predicted HR in the absence of diagnostic ECG. **Exclusion criteria**: LBBB or RBBB or non-specific intraventricular block patterns on resting ECG, taking digitalis or β-blocking agents **Enrolled**: 125 **Analysed**: 125 **Age**: 64 ± 9 years **Gender**: M 95, W 30 **History of**: **MI** excluded; **PTCA** 125; **CABG** N/S	**SPECT**: **Tracer**: Tl-201. **Stress induced by**: Exercise (bicycle). **Image interpretation**: Visual. **Equipment**: Gamma camera (ZLC-75; Shimadzu, Kyoto, Japan) **CA methods**: N/S **Interval between tests**: CA performed 7.5 ± 3.6 days after SPECT and 5.4 ± 1.3 days after ECG **Definition of positive SPECT test**: Perfusion defect on stress study absent on redistribution images, or defect on stress study larger than on redistribution study **Definition of positive stress ECG test**: Horizontal or downsloping ST-segment depression of ≥ 0.10 mV and an upsloping ST-segment depression of ≥ 0.20 mV measured 60 ms after the J point compared with the resting value **Angiographic definition of significant CAD**: Restenosis: increase in stenosis to >60% diameter **Outcome measures**: Sensitivity, specificity, positive predictive value, negative predictive value, TPs, FPs, TNs, FNs

continued

Study and methods	Participants	Test characteristics and outcome measures
Hambye, 1996[28] **Study design**: Prospective observational comparison **Method of recruitment**: N/S **Dates**: N/S **Country**: Belgium **Focus**: Incremental value of testing strategies for diagnosis of CAD in patients with an intermediate probability of CAD	**Inclusion criteria**: Patients referred for suspected or known CAD **Exclusion criteria**: History of MI, abnormal Q wave on the 12-lead ECG, LBBB, valvular or congenital heart disease, severe arrhythmias, or non-ischaemic cardiomyopathy **Enrolled**: 128 **Analysed**: 128 **Age**: 60 ± 9.2 (range 34–80) years **Gender**: M 90, W 38 **History of**: **MI** excluded; **PTCA** N/S; **CABG** N/S	**SPECT**: **Tracer**: MIBI. **Stress induced by**: Exercise (bicycle). **Image interpretation**: Visual, quantitative. **Equipment**: Single-head rotating gamma camera, 40-cm detector size (Orbiter Digitrac 7500; Siemens, Chicago, IL, USA) or a triple-head camera, 40 × 20 cm detector size **CA methods**: Performed in multiple views according to standard techniques **Interval between tests**: CA performed within 2 months of ECG/SPECT **Definition of positive SPECT test**: Reduced tracer uptake in ≥ 2 contiguous slices on two different orthogonal projections on the stress study that disappeared or improved by ≥ 10% on a colour scale on the rest image **Definition of positive stress ECG test**: Presence of clinical symptoms (typical angina, atypical chest pain, non-anginal pain, or miscellaneous) and ECG findings (significant changes, dubious results, no changes) **Angiographic definition of significant CAD**: ≥ 50% stenosis of ≥ 1 major epicardial coronary arteries or main side branches; ≥ 70% stenosis **Outcome measures**: Sensitivity, Specificity
Hecht, 1990[29] **Study design**: Prospective observational comparison **Method of recruitment**: Consecutive **Dates**: N/S **Country**: USA **Focus**: Detection of restenosis after PTCA and differentiation from other sources of myocardial ischaemia	**Inclusion criteria**: Patients referred for possible restenosis receiving SPECT and CA **Exclusion criteria**: N/S **Enrolled**: 116 **Analysed**: 116 **Age**: 58 ± 9 years **Gender**: M 93, W 23 **History of**: **MI** 49; **PTCA** 116; **CABG** N/S	**SPECT**: **Tracer**: Tl-201. **Stress induced by**: Exercise (treadmill). **Image interpretation**: Visual, quantitative. **Equipment**: Siemens Orbiter large field-of-view tomographic camera **CA methods**: Judkins or Sones approach **Interval between tests**: ECG/SPECT 1 week before CA **Definition of positive SPECT test**: Each segment scored on a 0–4 scale. Scores of ≥ 2 (mildly reduced uptake) abnormal. Myocardial ischaemia was categorised as either total or partial normalisation of a segment from exercise to redistribution imaging **Definition of positive stress ECG test**: ≥ 1 mm of horizontal or downsloping ST depression for ≥ 0.08 s after the J point compared with the resting tracing **Angiographic definition of significant CAD**: Restenosis; return of previously dilated vessel to a ≥ 50% diameter reduction **Outcome measures**: Sensitivity, specificity and accuracy for all, complete/partial revascularisation

continued

Study and methods	Participants	Test characteristics and outcome measures
Huang, 1992[30] **Study design**: Prospective observational comparison **Method of recruitment**: Consecutive **Dates**: N/S **Country**: Taiwan **Focus**: Accuracy of SPECT in diagnosis of CAD; the extent the level of exercise affects the sensitivity of the test	**Inclusion criteria**: Patients with chest pain receiving CA and SPECT **Exclusion criteria**: Cardiomyopathy, valvular or congenital heart disease **Enrolled**: 179 **Analysed**: 179 **Age**: Group 1 58 ± 9; Group 2 57± 9; Control 56 years **Gender**: M 144, W 35 **History of**: **MI** 70; **PTCA** 0; **CABG** 0	**SPECT**: **Tracer**: Tl-201. **Stress induced by**: Exercise (bicycle). **Image interpretation**: Visual. **Equipment**: Computerised dual-head imaging system (Picker International) **CA methods**: Judkins' technique **Interval between tests**: ECG/SPECT within 2 months of CA **Definition of positive SPECT test**: ≥ 50% decrease of thallium uptake in ≥ 2 contiguous slices and ≥ 2 tomographic planes **Definition of positive stress ECG test**: A horizontal or down-sloping ST-segment depression of ≥ 1 mm or upsloping depression of ≥ 1.5 mm, persisting ≥ 0.08 after the J point **Angiographic definition of significant CAD**: ≥ 50% stenosis in ≥ 1 major coronary artery **Outcome measures**: Sensitivity, specificity, TPs, FPs, TNs, FNs. SPECT sensitivity for 1-, 2- and 3-vessel CAD for all patients and those without MI, SPECT sensitivity for individual coronary artery stenosis
Kajinami, 1995[31] **Study design**: Prospective observational comparison **Method of recruitment**: Consecutive **Dates**: May 1991–May 1993 **Country**: Japan **Focus**: Usefulness of EBCT, ECG and SPECT for prediction of coronary stenosis	**Inclusion criteria**: Patients receiving elective CA and (1) chest pain suggesting angina pectoris or (2) possible myocardial ischaemia based on rest ECG **Exclusion criteria**: Patients in unstable condition, previous CABG or PTCA, abnormal Q waves in ≥ 2 ECG leads **Enrolled**: 251 **Analysed**: 251 **Age**: 56 ± 14 (range 16–86) years **Gender**: M 174, W 77 **History of**: **MI** N/S; **PTCA** excluded; **CABG** excluded	**SPECT**: **Tracer**: Tl-201. **Stress induced by**: Exercise (bicycle). **Image interpretation**: Visual. **Equipment**: Rotating gamma-camera SNC-510R (Shimadzu, Kyoto, Japan) **CA methods**: Performed in multiple projections using standard techniques **Interval between tests**: N/S **Definition of positive SPECT test**: Abnormal area in the initial images demonstrating complete or partial redistribution in the delayed images **Definition of positive stress ECG test**: (1) ≥ 0.1 mV depression 0.08 s from the J point, or (2) ≥ 0.1 mV elevation in a non-Q-wave lead in those without previous MI **Angiographic definition of significant CAD**: ≥ 75% occlusion in major coronary artery **Outcome measures**: Sensitivity, specificity, positive predictive value, negative predictive value, accuracy

continued

Study and methods	Participants	Test characteristics and outcome measures
Karlsson, 1995[32] **Study design**: Prospective observational comparison **Method of recruitment**: N/S **Dates**: N/S **Country**: Sweden **Focus**: Additional value of SPECT 1 month after an episode of unstable CAD over conventional ExECG for the identification of severe coronary lesions at CA	**Inclusion criteria**: Men 40–70 years; ongoing chest or anginal pain during the last 48 hours; occurrence of earlier unknown ST-depression ≥ 0.1 mV or T wave inversion by >0.1 mV in ≥ 2 adjacent leads in rest ECG **Exclusion criteria**: Increased risk of bleeding; indication for thrombolysis; acute Q wave MI; Q wave in ≥ 2 adjacent precordial leads or LBBB in ECG at rest; left ventricular failure; valvular heart disease; cardiomyopathy, pacemaker; CABG; poor short-term prognosis; or logistic difficulties with investigations or follow-up **Enrolled**: 205 **Analysed**: 170 **Age**: 59 years **Gender**: M 170, W 0 **History of**: **MI** 14%; **PTCA** N/S; **CABG** excluded	**SPECT**: **Tracer**: Tl-201. **Stress induced by**: Exercise (bicycle). **Image interpretation**: Qualitative. **Equipment**: Siemens Rotacamera (Siemens, The Netherlands) or Picker SX300 gamma-camera (Picker International, Ohio, USA) **CA methods**: Judkins technique **Interval between tests**: CA performed 1 day after ECG/SPECT **Definition of positive SPECT test**: Left ventricular myocardium divided into 9 segments. Each segment classified as 0 = normal uptake, 1 = reduced uptake, 2 = uptake defect. SPECT score = summation of score from all segments. **Definition of positive stress ECG test**: ST segment depression ≥ 0.1 mV 0.06 s after the J point **Angiographic definition of significant CAD**: ≥ 50% occlusion. Severe lesions defined as left main stenosis, 3VD, or 2VD with proximal LAD stenosis before first diagonal branch **Outcome measures**: Sensitivity, specificity
Khattar, 1998[33] **Study design**: Prospective observational comparison **Method of recruitment**: Consecutive **Dates**: N/S **Country**: UK **Focus**: SPECT and/or ECHO for detection of MVD versus clinical and ExECG data alone	**Inclusion criteria**: Patients with chest pain undergoing ExECG and subsequent CA **Exclusion criteria**: Unstable angina, significant arrhythmias, heart failure, uncontrolled hypertension, MI within 30 days, cardiomyopathy, significant valvular disease **Enrolled**: 100 **Analysed**: 100 **Age**: 62.2 (8.9) years **Gender**: M 70, W 30 **History of**: **MI** 29; **PTCA** N/S; **CABG** N/S	**SPECT**: **Tracer**: MIBI. **Stress induced by**: Exercise (treadmill) for ECG, pharmacologically (dobutamine, arbutamine) for SPECT. **Image interpretation**: Semiquantitative. **Equipment**: Large field of view gamma camera **CA methods**: Judkins technique **Interval between tests**: CA performed within 3 months of SPECT/ECG **Definition of positive SPECT test**: Resting or stress-induced perfusion defect, MVD if abnormalities in ≥ 2 coronary artery territories at peak stress **Definition of positive stress ECG test**: MVD: 1, ST depression ≥ 2 mm, ST depression ≥ 1 mm in ≥ 5 leads; 2, workload <6 MET; or 3, fall of systolic blood pressure >20 mmHg compared with the previous stage **Angiographic definition of significant CAD**: ≥ 50% stenosis, multivessel disease if ≥ 2 major coronary arteries involved **Outcome measures**: Sensitivity, specificity and accuracy for detecting multivessel disease in the total study group and excluding previous MI, incremental value

continued

Study and methods	Participants	Test characteristics and outcome measures
Koskinen, 1987[34] **Study design**: Retrospective observational comparison **Method of recruitment**: N/S **Dates**: 1983–84 **Country**: Finland **Focus**: SPECT versus CA	**Inclusion criteria**: Patients receiving SPECT and CA **Exclusion criteria**: CABG between CA and SPECT, patients whose imaging data had not been stored on magnetic tape, required stress level not achieved **Enrolled**: 117 **Analysed**: 117 **Age**: Proximal 3VD 50.1, peripheral 3VD 49.1, peripheral 2VD 49.1, peripheral SVD 47.6, CA healthy vessels 48.8, reference group 52.1, range 33–64 years **Gender**: N/S **History of**: **MI** N/S; **PTCA** N/S; **CABG** N/S	**SPECT**: **Tracer**: Tl-201. **Stress induced by**: N/S. **Image interpretation**: N/S. **Equipment**: N/S **CA methods**: N/S **Interval between tests**: N/S **Definition of positive SPECT test**: N/S **Definition of positive stress ECG test**: N/S **Angiographic definition of significant CAD**: Vessels with a 50% stenosis **Outcome measures**: Sensitivity and specificity
Lind, 1990[35] **Study design**: Prospective observational comparison **Method of recruitment**: N/S **Dates**: N/S **Country**: Austria **Focus**: SPECT versus ExECG for detection of silent myocardial ischaemia in patients with vascular risk factors	**Inclusion criteria**: Patients showing vascular risk factors, pathological ergometric findings without angina or signs of silent MI in the resting ECG **Exclusion criteria**: **Enrolled**: 106 **Analysed**: 106 **Age**: Group I 55 ± 10, Group II 60 ± 9 years **Gender**: Group I, M 38, W 8; Group II, M 43, W 17 **History of**: **MI** N/S; **PTCA** N/S; **CABG** N/S	**SPECT**: **Tracer**: Tl-201. **Stress induced by**: Exercise (treadmill). **Image interpretation**: Visual. **Equipment**: Elscint Apex 409 AG rotating gamma camera **CA methods**: Judkins technique **Interval between tests**: Maximum of 14 days between SPECT/ECG and CA **Definition of positive SPECT test**: N/S **Definition of positive stress ECG test**: N/S **Angiographic definition of significant CAD**: >75% coronary stenosis **Outcome measures**: Sensitivity, specificity plus true and false positives and negatives for ECG
Mairesse, 1994[36] **Study design**: Prospective observational comparison **Method of recruitment**: Consecutive **Dates**: N/S **Country**: Belgium **Focus**: Optimal ECG criteria for the diagnosis of CAD in association with dobutamine stress by use of precise computer measurements and comparing their accuracy with those of stress ECHO and MPS	**Inclusion criteria**: Patients referred for diagnostic CA **Exclusion criteria**: Clinical history or ECG evidence of previous Q wave MI, unstable angina, malignant arrhythmias, cardiomyopathy, severe valvular disease or severe hypertension, stress test interrupted prematurely, or uninterpretable ECG **Enrolled**: 129 **Analysed**: 129 **Age**: 56 ± 9 (range 31–78) years **Gender**: M 95, W 34 **History of**: **MI** (Q wave) excluded; **PTCA** N/S; **CABG** N/S	**SPECT**: **Tracer**: MIBI. **Stress induced by**: Pharmacologically (dobutamine). **Image interpretation**: Visual. **Equipment**: Large-field single-crystal camera **CA methods**: Judkins technique **Interval between tests**: CA within 2 days of stress ECG/SPECT **Definition of positive SPECT test**: N/S **Definition of positive stress ECG test**: Empirical ROC based on 0.2–1.8 mm of absolute ST segment shift of peak stress to define CAD at 0, 20, 40, 60 and 80 ms after the J point **Angiographic definition of significant CAD**: >50% stenosis of major epicardial coronary segment **Outcome measures**: Sensitivity, specificity, accuracy, TPs, FPs, TNs, FNs, sensitivity for SVD and MVD

continued

Study and methods	Participants	Test characteristics and outcome measures
McClellan, 1996[37] **Study design**: Prospective observational comparison **Method of recruitment**: Consecutive **Dates**: N/S **Country**: USA **Focus**: 1, Use of SPECT in a community hospital; 2, accuracy and additive value of SPECT versus ExECG	**Inclusion criteria**: Patients referred for treadmill exercise testing with SPECT. Indications for SPECT: diagnosis of CAD; evaluation and follow-up of patients with known CAD; and evaluation after MI, PTCA and CABG **Exclusion criteria**: N/S **Enrolled**: 501 **Analysed**: 492 **Age**: 58.9 (range 22–82) years **Gender**: M 322, W 179 **History of**: **MI** 170; **PTCA** 123; **CABG** 103	**SPECT**: **Tracer**: Tl-201. **Stress induced by**: Exercise (treadmill). **Image interpretation**: Visual, quantitative. **Equipment**: Rotating large field of view camera (GE 400 AC) **CA methods**: N/S **Interval between tests**: CA performed within 3 months of SPECT/ECG **Definition of positive SPECT test**: Presence of exercise-induced defects and partial, complete or absence of redistribution on delayed images **Definition of positive stress ECG test**: Normal resting ECG and ≥ 0.1 mV horizontal or downsloping depression during exercise **Angiographic definition of significant CAD**: ≥ 50% stenosis in ≥ 1 coronary artery **Outcome measures**: TPs, FPs, TNs, FNs, specificity, positive predictive value, diagnostic accuracy
Michaelides, 1999[38] **Study design**: Prospective observational comparison **Method of recruitment**: Consecutive **Dates**: N/S **Country**: Greece **Focus**: Sensitivity of exercise testing in the detection of CAD using right precordial leads V_3R, V_4R and V_5R and left precordial leads	**Inclusion criteria**: Patients referred to hospital with symptoms resembling angina **Exclusion criteria**: RBBB or LBBB, RVH or LVH, ventricular pre-excitation, history of MI or valvular or congenital heart disease, CABG or PTCA, and those receiving digitalis and those refusing CA **Enrolled**: 268 **Analysed**: 245 **Age**: 52 ± 8 (range 32–74) years **Gender**: M 218, W 27 **History of**: **MI** excluded; **PTCA** excluded; **CABG** excluded	**SPECT**: **Tracer**: Tl-201. **Stress induced by**: Exercise (treadmill). **Image interpretation**: Qualitatively, quantitatively. **Equipment**: Model 400 AC/T, General Electric, Milwaukee, WI, USA **CA methods**: Judkins technique **Interval between tests**: CA within 2 months after ECG/SPECT **Definition of positive SPECT test**: N/S **Definition of positive stress ECG test**: Horizontal or downsloping ST-segment depression of ≥ 1 mm 60 ms after the J point; upsloping ST segment with a depression of ≥ 1.5 mm 80 ms after the J point. In the presence of ST-segment depression at rest, an additional 2 mm of ST-segment depression, or an ST-segment elevation of ≥ 1 mm at the J point as compared with the baseline ECG recorded at rest **Angiographic definition of significant CAD**: narrowing of ≥ 70% of the diameter of the lumen in the LAD, LCX or RCA or narrowing of ≥ 50% of the diameter of the lumen in the left main coronary artery **Outcome measures**: Overall sensitivity and specificity plus sensitivity for 1-, 2- and 3-vessel disease, any CAD and LAD, RCA and LCX for SVD

continued

Study and methods	Participants	Test characteristics and outcome measures
Nallamothu, 1995[39] **Study design**: Retrospective observational comparison **Method of recruitment**: Identified from complete database according to inclusion criteria **Dates**: N/S **Country**: USA **Focus**: 1, Diagnostic accuracy of SPECT and ExECG response in patients with normal baseline ECG results; 2, differences in ability of each method to identify high-risk patients with extensive CAD	**Inclusion criteria**: Patients with 1, SPECT and CA within 3 months of each other; 2, normal baseline ECG results (no evidence of previous MI, conducting defects, ST-T wave changes, pre-excitation or pacemaker rhythm) **Exclusion criteria**: Patients taking digitalis **Enrolled**: 321 **Analysed**: 321 **Age**: 57 ± 10 years **Gender**: M 241, W 80 **History of**: **MI** N/S; **PTCA** 0; **CABG** 0	**SPECT**: **Tracer**: Tl-201. **Stress induced by**: Exercise (treadmill). **Image interpretation**: Visual, quantitative. **Equipment**: N/S **CA methods**: Performed in multiple projections using standard techniques **Interval between tests**: Stress ECG was part of SPECT test, CA within 3 months **Definition of positive SPECT test**: Presence and nature (fixed or reversible) of perfusion defects, site (vascular territory) of perfusion abnormality, size of perfusion defect (by polar maps), lung thallium uptake and left ventricular dilation. Multivessel thallium abnormalities were considered present when there were perfusion defects in >1 vascular territory **Definition of positive stress ECG test**: ≥1 mm downsloping or horizontal or ≥1.5 mm upsloping ST segment depression measured at 80 ms after the J point for ≥3 consecutive beats during or after exercise **Angiographic definition of significant CAD**: ≥50% diameter narrowing in any of the major coronary arteries or their major branches **Outcome measures**: Sensitivity, specificity, accuracy, positive predictive value, negative predictive value. Sensitivity in patients with 1-, 2- and 3-vessel disease
Psirropoulos, 2002[40] **Study design**: Prospective observational comparison **Method of recruitment**: N/S **Dates**: Sept. 1995–Dec. 2000 **Country**: Greece **Focus**: 1, MI development in elderly versus younger patients undergoing treatment for known CAD through conventional treadmill testing and scintigraphy; 2, relationship between the above non-invasive tests and CA confirmed important CAD	**Inclusion criteria**: Patients who had undergone CA, ExECG testing using Bruce protocol, and scintigraphy **Exclusion criteria**: Uncontrolled arterial hypertension, hypertrophic cardiomyopathy, severe valve disease, severe chronic obstructive lung disease, sever anaemia, peripheral atherosclerosis, orthopaedic problems and Parkinson's disease **Enrolled**: 606 **Analysed**: 606 **Age**: Group A 70.3 ± 5.3, Group B 54.4 ± 9.1 years **Gender**: M355, W251 **History of**: **MI** 309; **PTCA** N/S; **CABG** N/S	**SPECT**: **Tracer**: Tl-201. **Stress induced by**: Exercise (treadmill). **Image interpretation**: N/S. **Equipment**: N/S **CA methods**: N/S **Interval between tests**: ECG/SPECT performed 1 week to 2 months before CA **Definition of positive SPECT test**: N/S **Definition of positive stress ECG test**: (1) ST segment depression ≥0.15 mV at 80 ms after J point, (2) 0.1 mV flat or down-sloping ST segment depression and (3) ST segment upward slope >1 mV/s **Angiographic definition of significant CAD**: Important CAD was defined as (a) left main stem stenosis ≥50% with or without disease elsewhere, (b) proximal 3VD, (c) 3VD including the proximal LAD artery, (d) proximal 2VD including LAD and (e) 2VD including the proximal LAD **Outcome measures**: Sensitivity, specificity, positive predictive accuracy, negative predictive accuracy

continued

Study and methods	Participants	Test characteristics and outcome measures
Santana-Boado, 1998[18] **Study design**: Prospective observational comparison **Method of recruitment**: Consecutive **Dates**: Jan. 1992–Mar. 1995 **Country**: Spain **Focus**: Diagnostic accuracy of SPECT between sexes and the influence of analysing only the patients with CA instead of all the patients who are submitted to study	**Inclusion criteria**: Patients without previous MI in whom SPECT had been performed **Exclusion criteria**: previous MI **Enrolled**: 702 **Analysed**: 163 **Age**: M 60 ± 10, W 58 ± 8 years **Gender**: M 100, W 63 **History of**: **MI** excluded; **PTCA** N/S; **CABG** N/S	**SPECT**: **Tracer**: MIBI. **Stress induced by**: Exercise (bicycle) plus pharmacologically (dipyridamole) in 72 patients who performed an insufficient exercise test. **Image interpretation**: Visual. **Equipment**: SP4 (Elscint, Haifa, Israel) scintillation camera **CA methods**: Standard Seldinger's technique **Interval between tests**: Stress ECG was part of SPECT test, CA within <3 months after SPECT **Definition of positive SPECT test**: Mild, moderate or severe defect in ≥ 2 of 3 axes or 3 consecutive tomographic sections of the same axis, with reversibility at rest **Definition of positive stress ECG test**: N/S **Angiographic definition of significant CAD**: Stenoses >50% **Outcome measures**: Sensitivity, specificity, positive predictive value, negative predictive value, accuracy globally and for gender
Vaduganathan, 1996[41] **Study design**: Prospective observational comparison **Method of recruitment**: Consecutive **Dates**: Jan. 1990–Dec. 1994 **Country**: USA **Focus**: Diagnostic accuracy of exercise, adenosine and dobutamine imaging for the detection of LAD stenosis in patients with LBBB	**Inclusion criteria**: Patients with LBBB referred for perfusion scintigraphy **Exclusion criteria**: N/S **Enrolled**: 383 **Analysed**: 154 with CA **Age**: Exercise 61 ± 12, adenosine 69 ± 10, dobutamine 69 ± 10 years **Gender**: M 94, W 60 **History of**: **MI** 47; **PTCA** N/S; **CABG** N/S	**SPECT**: **Tracer**: Tl-201, MIBI. **Stress induced by**: Exercise (treadmill), pharmacologically (adenosine or dobutamine). **Image interpretation**: Visual, quantitative. **Equipment**: Single-crystal rotating gamma camera **CA methods**: Performed in multiple views using standard techniques **Interval between tests**: CA performed within 1 month of SPECT **Definition of positive SPECT test**: N/S **Definition of positive stress ECG test**: Non-diagnostic because of underlying LBBB **Angiographic definition of significant CAD**: ≥ 50% lumen diameter stenosis **Outcome measures**: Overall sensitivity, specificity, positive predictive value, and negative predictive value for each type of stress. Sensitivity and specificity for LAD, RCA and LCX for each type of stress

continued

Prognostic studies

Study and methods	Participants	Test characteristics and outcome measures
Amanullah, 1998[42] **Study design**: Cohort (prospective) **Method of recruitment**: Consecutive **Dates**: N/S **Follow-up**: N/S **Country**: USA **Focus**: Predictors of early revascularisation; to compare early revascularisation patients with those who had medical therapy	**Inclusion criteria**: Patients undergoing CA and SPECT for the evaluation of CAD **Exclusion criteria**: Patients with normal CA, previous CABG or recent MI or unstable angina **Enrolled**: 860 Lost to follow-up: 44 **Analysed**: 816 **Age**: 60 ± 10 years **Gender**: M 630, W 186 **History of**: **MI** 410; **PTCA** N/S; **CABG** excluded	**SPECT**: **Tracer**: Tl-201. **Stress induced by**: Exercise (treadmill). **Image interpretation**: Quantitative; visual. **Equipment**: N/S **CA**: Judkins methods **Interval between tests**: N/S **Definition of positive SPECT test**: Reversible abnormality: perfusion abnormality in the initial image that showed complete or partial redistribution on the delayed image involving 25% of the segment. Fixed abnormality: perfusion abnormality that remained unchanged in the delayed image. Multivessel abnormality: perfusion defects in 1 > vascular territory. **Definition of positive stress ECG test**: N/S **Angiographic definition of significant CAD**: >50% stenosis of major epicardial coronary artery or one of its major branches. Multivessel CAD: presence of significant CAD in ≥ 2 of the 3 major coronary arteries or their major branches **Multivariate analysis**: Yes **Outcome measures**: PTCA or CABG within 3 months of nuclear testing
Amanullah, 1999[43] **Study design**: Cohort **Method of recruitment**: N/S **Dates**: Jan. 1987–Mar. 1993 **Follow-up**: 36 ± 26 months **Country**: USA **Focus**: Predictors of outcome of medically treated patients with LMD and/or 3VD	**Inclusion criteria**: Patients who had documented LMD and/or 3VD noted on CA and had undergone SPECT within 3 months **Exclusion criteria**: History of previous MI, recent unstable angina, or coronary revascularisation **Enrolled**: 186 **Lost to follow-up**: 0 **Analysed**: 186 **Age**: 64 ± 9 years **Gender**: M 136, W 50 **History of**: **MI** excluded; **PTCA** excluded; **CABG** excluded	**SPECT**: **Tracer**: Tl-201. **Stress induced by**: Exercise (treadmill) 127; pharmacologically (adenosine) 59. **Image interpretation**: Quantitative; visual. **Equipment**: N/S **CA**: Judkins methods **Interval between tests**: 3 months **Definition of positive SPECT test**: Reversible abnormality: perfusion abnormality in the initial image that showed complete or partial redistribution on the delayed image involving 25% of the segment. Fixed abnormality: perfusion abnormality that remained unchanged in the delayed image. Multivessel abnormality: perfusion defects in >1 vascular territory. **Definition of positive stress ECG test**: N/S **Angiographic definition of significant CAD**: >50% stenosis of major epicardial coronary artery or one of its major branches **Multivariate analysis**: Cox proportional hazards regression model **Outcome measures**: Cardiac mortality; non-fatal MI

continued

Study and methods	Participants	Test characteristics and outcome measures
Ben-Gal, 2001[44] **Study design**: Cohort **Method of recruitment**: Consecutive **Dates**: July 1996–Sept. 1997 Follow-up: Mean 11.7 ± 5.3 months **Country**: Israel **Focus**: Utility of SPECT for predicting outcome of hospitalised patients with chest pain and a normal or non-diagnostic ECG	**Inclusion criteria**: Patients admitted due to angina-like chest pain and a normal or non-diagnostic 12 lead ECG **Exclusion criteria**: Patients with suspected acute MI, known previous MI, PTCA or CABG **Enrolled**: 109 Lost to follow-up: 0 **Analysed**: 109 **Age**: 60.7 ± 13.7 years **Gender**: M 57, W 52 **History of**: **MI** excluded; **PTCA** excluded; **CABG** excluded	**SPECT**: **Tracer**: Tl-201. **Stress induced by**: Exercise (treadmill, 37 patients); pharmacologically (dipyridamole, 72 patients). **Image interpretation**: Visual. **Equipment**: Digital gamma camera (Apex SP 4-HR, Elscint) **CA**: Judkins technique **Interval between tests**: N/S **Definition of positive SPECT test**: Fixed defects: defects in ≥ 2 consecutive images present and unchanged in stress and rest scans. Reversible defects: defects on stress images absent or less prominent on rest images. Scans abnormal if any perfusion defect present **Definition of positive stress ECG test**: 1 mV of horizontal or downsloping ST-segment depression that persisted for 80 ms after the J point **Angiographic definition of significant CAD**: N/S **Multivariate analysis**: Yes **Outcome measures**: Cardiac mortality; non-fatal MI, PTCA, CABG
Berman, 1995[45] **Study design**: Cohort (prospective) **Method of recruitment**: Consecutive **Dates**: Jan. 1991–Jan. 1993 **Follow-up**: ≥ 1 year, mean 20 ± 5 months. **Country**: USA **Focus**: Prognostic implications of normal and equivocal SPECT scans	**Inclusion criteria**: Patients in whom SPECT was performed **Exclusion criteria**: Previous PTCA or CABG **Enrolled**: 1811 of whom 7 had a technically inadequate study for interpretation or incomplete data **Lost to follow-up**: 102 **Analysed**: 1702 **Age**: Normal scan results 60 ± 13; abnormal scan results 65 ± 12 years **Gender**: M 1037, W 665 **History of**: **MI** 182; **PTCA** excluded; **CABG** excluded	**SPECT**: **Tracer**: Tl-201 rest, MIBI stress. **Stress induced by**: Exercise (treadmill). **Image interpretation**: Visual. **Equipment**: Scintillation camera/computer system **CA**: No **Interval between tests**: N/S **Definition of positive SPECT test**: Tomograms divided into 20 segments for each study and scored on a 5-point scale at rest and stress (0 = normal, 4 = absence of detectable tracer uptake). Study results normal, probably normal, equivocal, probably abnormal or definitely abnormal on the basis of number of segments with scores ≥ 2 **Definition of positive stress ECG test**: N/S **Angiographic definition of significant CAD**: N/S **Multivariate analysis**: No **Outcome measures**: Hard events – cardiac mortality; non-fatal MI. Soft events – PTCA or CABG >60 days after testing

continued

Study and methods	Participants	Test characteristics and outcome measures
Candell-Riera, 1998[46] **Study design**: Cohort (prospective) **Method of recruitment**: N/S **Dates**: Nov. 1993–Nov. 1995 **Follow-up**: ≥ 6 months, max. 5.5 years (mean 3.6 years) **Country**: Spain **Focus**: Prognosis of medically treated patients with clandestine myocardial ischaemia compared with patients with silent myocardial ischaemia and angina pectoris	**Inclusion criteria**: Medically treated patients with confirmed CAD demonstrated by SPECT and CA **Exclusion criteria**: Previous MI; previous revascularisation; another type of heart disease; normal CA; negative SPECT; patients who received dipyridamole simultaneously **Enrolled**: 112 **Lost to follow-up**: 0 **Analysed**: 112 **Age**: 57 ± 10 years **Gender**: M 95, W 17 **History of**: **MI** excluded; **PTCA** excluded; **CABG** excluded	**SPECT**: **Tracer**: MIBI. **Stress induced by**: Exercise (bicycle). **Image interpretation**: Visual. **Equipment**: Elscint SP4 scintillation camera **CA**: Seldinger's technique **Interval between tests**: Within 3 months **Definition of positive SPECT test**: SPECT image divided into 13 segments and scored from 1 to 5 (1 = normal, 5 = severe defect) according to the severity of the ischaemia **Definition of positive stress ECG test**: Horizontal or descending ST-segment depression ≥ 1 mm at 0.08 s after the J point **Angiographic definition of significant CAD**: = 50% stenoses **Multivariate analysis**: Cox proportional hazards regression model **Outcome measures**: Cardiac mortality; non-fatal MI; need for revascularisation
Chatziioannou, 1999[47] **Study design**: Cohort (retrospective) **Method of recruitment**: Consecutive **Dates**: Feb. 1996–June 1996 **Follow-up**: 18 ± 2.7 months (range 15–24 months) **Country**: USA **Focus**: Predictive value of SPECT versus ExECG in patients with high exercise tolerance	**Inclusion criteria**: Patients receiving SPECT who reached at least Bruce stage IV **Exclusion criteria**: N/S **Enrolled**: 388 **Lost to follow-up**: 0 **Analysed**: 388 **Age**: 54 ± 10 years **Gender**: M 337, W 51 **History of**: **MI** 19% of 348 patients with no event; 48% of 21 patients with event; **PTCA** N/S; **CABG** 17% of 348 patients with no event; 34% of 21 patients with event	**SPECT**: **Tracer**: MIBI. **Stress induced by**: Exercise (treadmill). **Image interpretation**: Visual. **Equipment**: 1, PRISM 3000XP triple-headed detector camera; 2, Starcam 3000 (General Electric) single-headed detector camera **CA**: No **Interval between tests**: Same day protocol **Definition of positive SPECT test**: Abnormal MPI scans had ≥ 1 reversible, fixed or mixed defects **Definition of positive stress ECG test**: Horizontal or downsloping ST-segment depression of ≥ 1 mm or an upsloping ST-segment depression of ≥ 2 mm 0.08 s after the J point **Angiographic definition of significant CAD**: N/S **Multivariate analysis**: Cox proportional hazards regression model **Outcome measures**: Hard events – cardiac mortality; non-fatal MI. Soft events – PTCA or CABG. Revascularisations due to SPECT or to the patients' condition at the time of SPECT not included in the analysis, and the patients involved were excluded from follow-up

continued

Study and methods	Participants	Test characteristics and outcome measures
Chiamvimonvat, 2001[48] **Study design**: Cohort (prospective) **Method of recruitment**: Consecutive **Dates**: 1994–1996 **Follow-up**: Min. 12 months, average 15 ± 3 months **Country**: Canada **Focus**: Utility of SPECT in a low-risk population after MI	**Inclusion criteria**: Patients who were stable with no complications 3–21 days after MI **Exclusion criteria**: CABG; other significant life-threatening illnesses; found on CA to require revascularisation **Enrolled**: 203 **Lost to follow-up**: 0 **Analysed**: 203 **Age**: 56 ± 11 years **Gender**: M 178, W 25 **History of**: **MI** 17; **PTCA** 2; **CABG** excluded	**SPECT**: **Tracer**: Tl-201 rest, MIBI stress. **Stress induced**: Pharmacologically (dipyridamole). **Image interpretation**: Visual; quantitative. **Equipment**: N/S **CA**: Predetermined protocol **Interval between tests**: Same day **Definition of positive SPECT test**: Fixed defect: no change between rest and stress images. Reversible defect: decrease in stress score by ≥ 1. Abnormality: uptake of ≥ 2.5 SDs below lower limits of normal **Definition of positive stress ECG test**: N/S **Angiographic definition of significant CAD**: N/S **Multivariate analysis**: Yes **Outcome measures**: Cardiac mortality; non-fatal MI; PTCA; CABG; occurrence of unstable angina requiring hospitalisation. Late revascularisation occurring > 1 month after study entry, CA, and SPECT included. Patients excluded after the first occurrence of any of the above end-points
Diaz, 2001[49] **Study design**: Cohort (prospective) **Method of recruitment**: Consecutive **Dates**: Sept. 1990–Dec. 1993 **Follow-up**: Mean 6.7 years, min. 4.5 years **Country**: USA **Focus**: Value of SPECT for prediction of all-cause mortality when considered along with functional capacity and heart rate recovery	**Inclusion criteria**: Adults aged ≥ 30 years referred for SPECT in conjunction with symptom-limited exercise testing **Exclusion criteria**: Heart failure, left ventricular dysfunction, valvular disease, pacemaker or foreign nationals **Enrolled**: 7163 **Lost to follow-up**: 0 **Analysed**: 7163 **Age**: 60 ± 10 years **Gender**: M 5354, W 1809 **History of**: **MI** N/S; **PTCA** 1196; **CABG** 1736	**SPECT**: **Tracer**: Tl-201. **Stress induced by**: N/S. **Image interpretation**: Quantitative. **Equipment**: N/S **CA**: No **Interval between tests**: Stress ECG was part of SPECT test **Definition of positive SPECT test**: Heart divided into 12 segments, each segment weighted according to its relative contribution to total left ventricular mass. Segments coded as normal, fixed or reversible. Normal: count variation within the segment ≤ 20% compared to segment with highest count rate. Reversible: count increased by 20% on redistribution. Fixed: count increased by <20% on redistribution. Segments abnormal if defect on ≥ 2 consecutive slices and verified in an orthogonal plane **Angiographic definition of significant CAD**: N/S **Multivariate analysis**: Cox proportional hazards regression model **Outcome measures**: Mortality

continued

Study and methods	Participants	Test characteristics and outcome measures
Gibbons, 1999[50] **Study design**: Cohort (retrospective) **Method of recruitment**: N/S **Dates**: Jan. 1985–Jan. 1995 **Follow-up**: 3 ± 2 years (min. 1 year, median 2 years) **Country**: USA **Focus**: The hypothesis that normal or near-normal SPECT in a patient with an intermediate-risk treadmill test would be associated with a very low long-term risk of subsequent cardiovascular events	**Inclusion criteria**: Patients who underwent SPECT for evaluation of known or suspected CAD, had a calculable Duke treadmill score and had an intermediate-risk treadmill score and normal or near-normal SPECT **Exclusion criteria**: Previous PTCA or CABG, valvular heart disease, cardiomyopathy, congenital heart disease, uninterpretable exercise test due to LBBB, paced rhythm or preexcitation syndrome **Enrolled**: 4649 **Lost to follow-up**: 176 **Analysed**: 4473 **Age**: 61.2 ± 11.4 years **Gender**: M 2046, W 2427 **History of**: **MI** 241; **PTCA** excluded; **CABG** excluded	**SPECT**: **Tracer**: Tl-201 and/or MIBI. **Stress induced by**: Exercise (treadmill). **Image interpretation**: Visual. **Equipment**: N/S **CA**: No **Interval between tests**: Stress ECG was part of SPECT test **Definition of positive SPECT test**: Images were categorised as normal, near-normal or abnormal. Near-normal: non-specific abnormalities judged subjectively not to represent evidence of CAD. **Definition of positive stress ECG test**: N/S **Angiographic definition of significant CAD**: N/S **Multivariate analysis**: Cox proportional hazards regression model **Outcome measures**: Cardiac mortality; non-fatal MI; PTCA; CABG; number of CAs performed
Giri, 2002[51] **Study design**: Cohort (prospective) **Method of recruitment**: N/S **Dates**: N/S **Follow-up**: 2.5 ± 1.5 years (minimum 6 months) **Country**: USA **Focus**: Incremental role of SPECT in diabetic patients in the prediction of cardiac events and the possibility of a sex-ischaemia interaction	**Inclusion criteria**: Patients with symptoms suggestive of CAD **Exclusion criteria**: Hospitalised for unstable angina or MI or received revascularisation within 3 weeks of presentation **Enrolled**: 4755 [diabetic 929 (20%), non-diabetic 3826 (80%)] **Lost to follow-up**: 0 **Analysed**: 4755 **Age**: Diabetic 65 ± 11, non-diabetic 64 ± 11 years **Gender**: M 2669, W 2086 (diabetic M 478, W 451; non-diabetic M 2191, W 1635) **History of**: **MI** 1414 (diabetic 329, non-diabetic 1085); **PTCA** N/S; **CABG** N/S	**SPECT**: **Tracer**: Tl-201 and/or MIBI. **Stress induced by**: Exercise (treadmill), pharmacologically (adenosine or dipyridamole). **Image interpretation**: Visual. **Equipment**: N/S **CA**: Method N/S (597 patients) **Interval between tests**: N/S **Definition of positive SPECT test**: Stress defects: defects present at rest and remained unchanged during stress. Ischaemic: new or worsening defects (40% activity reduction) after stress. Extent of perfusion defects coded as 0, 1, 2 and 3 vascular territory involvement. **Definition of positive stress ECG test**: N/S **Angiographic definition of significant CAD**: N/S **Multivariate analysis**: Cox proportional hazards regression model **Outcome measures**: Cardiac mortality; PTCA

continued

Study and methods	Participants	Test characteristics and outcome measures
Groutars, 2000[52] **Study design**: Cohort (prospective) **Method of recruitment**: N/S **Dates**: Apr. 1996–Dec. 1996 **Follow-up**: Mean 25 ± 3 months **Country**: The Netherlands **Focus**: Prognostic significance of normal SPECT studies in patients with suspected or known CAD	**Inclusion criteria**: Patients referred for SPECT **Exclusion criteria**: Unstable angina pectoris, recent MI (within 6 weeks) **Enrolled**: 246 **Lost to follow-up**: 10 **Analysed**: 236 **Age**: 61 ± 11 (range 27–85) years **Gender**: M 106, W 140 **History of**: **MI** (Q wave) 14; **PTCA** 22; **CABG** 9	**SPECT**: **Tracer**: Tl-201 rest, MIBI stress. **Stress induced by**: Exercise (bicycle) 125; pharmacologically (adenosine) 121. **Image interpretation**: Semiquantitative visual. **Equipment**: Toshiba triple-detector gamma camera **CA**: No **Interval between tests**: Stress ECG part of SPECT test **Definition of positive SPECT test**: Semiquantitative visual analysis of myocardial scintigrams with a 5-point scoring system (1 = normal, 5 = absence of tracer uptake) over 20 segments **Definition of positive stress ECG test**: Horizontal or downsloping ST-segment depression of ≥ 1 mm lasting >80 ms after the J point for ≥ 3 consecutive beats **Angiographic definition of significant CAD**: N/S **Multivariate analysis**: No **Outcome measures**: Primary end-points – cardiac mortality; non-fatal MI. Secondary end-points – PTCA; CABG
Hachamovitch, 1996[53] **Study design**: Cohort (retrospective) **Method of recruitment**: Consecutive **Dates**: Jan. 1991–Dec. 1993 **Follow-up**: ≥ 1 year. Mean 20 ± 5 months **Country**: USA **Focus**: Prognostic value of SPECT over clinical and exercise data in women versus men	**Inclusion criteria**: Patients who underwent SPECT **Exclusion criteria**: Valvular heart disease, primary cardiomyopathy **Enrolled**: 4620 of whom 16 excluded because of missing data and 270 excluded because of early revascularisation **Lost to follow-up**: 198 **Analysed**: 4136 **Age**: M 61.7 ± 12.2, W 64.5 ± 11.8 years **Gender**: M 2742, W 1394 **History of**: **MI** M 666, W 198; **PTCA** M 398, W 91; **CABG** M 466, W 86	**SPECT**: **Tracer**: Tl-201 rest, MIBI stress. **Stress induced by**: Exercise (treadmill). **Image interpretation**: Semiquantitative visual. **Equipment**: N/S **CA**: No **Interval between tests**: Stress ECG part of SPECT test **Definition of positive SPECT test**: Summed stress score obtained by adding the score of the 20 segments of the stress images. Summed rest score obtained by adding the score of the 20 segments of the rest images. Summed difference score: sum of the differences between each of the 20 segments on the stress and rest images and represents amount of ischaemia present **Definition of positive stress ECG test**: >1 mm horizontal or downsloping ST-segment elevation or depression except in leads without significant Q waves or in lead aVR **Angiographic definition of significant CAD**: N/S **Multivariate analysis**: Cox proportional hazards regression model **Outcome measures**: Cardiac mortality; non-fatal MI. Patients receiving revascularisation within 60 days of index SPECT censored from analysis

continued

Study and methods	Participants	Test characteristics and outcome measures
Hachamovitch, 1998[54] **Study design**: Cohort (prospective) **Method of recruitment**: Consecutive **Dates**: Jan. 1991–Dec. 1993 **Follow-up**: ≥ 1 year, mean 642 ± 226 days **Country**: USA **Focus**: 1, Incremental prognostic value of SPECT for the prediction of cardiac death; 2, ability of SPECT to risk stratify patients; 3, impact on cost of testing if patients at low risk for cardiac death but intermediate risk for non-fatal MI are not referred to CA as initial therapy	**Inclusion criteria**: Patients who underwent SPECT **Exclusion criteria**: Valvular heart disease; non-ischaemic cardiomyopathy; early (<60 days after SPECT) revascularisation. **Enrolled**: 5456 of whom 4 were excluded because of missing data **Lost to follow-up**: 269 **Analysed**: 5183 **Age**: Exercise 62.6 ± 12.1; adenosine 70.4 ± 11.3 years **Gender**: Exercise M 2723, W 1381; Adenosine M 541, W 538 **History of**: **MI** exercise 850; adenosine 346; **PTCA** exercise 473; adenosine 143; **CABG** exercise 544; adenosine 219	**SPECT**: **Tracer**: Tl-201 rest, MIBI stress. **Stress induced by**: Exercise (treadmill) 4104; pharmacologically (adenosine) 1079. **Image interpretation**: Semiquantitative visual. **Equipment**: N/S **CA**: No **Interval between tests**: Stress ECG was part of SPECT test **Definition of positive SPECT test**: Summed stress score obtained by adding the score of the 20 segments of the stress images. Summed stress scores <4 normal; 4–8 mildly abnormal; 9–13 moderately abnormal; >13 severely abnormal. Summed rest score obtained by adding the scores of the 20 segments of the rest images. Summed difference score: sum of the differences between each of the 20 segments on stress and rest images **Definition of positive stress ECG test**: N/S **Angiographic definition of significant CAD**: N/S **Multivariate analysis**: Cox proportional hazards regression model **Outcome measures**: Cardiac mortality; non-fatal MI
Hachamovitch, 2002[55] **Study design**: Cohort **Method of recruitment**: Consecutive **Dates**: Jan. 1991–Dec. 1993 **Follow-up**: 1.6 ± 0.5 years **Country**: USA **Focus**: 1, Incremental prognostic value of SPECT in patients with normal resting ECG over pre-SPECT information; 2, ability to risk-stratify patients; 3, cost-effectiveness of SPECT as part of a testing strategy	**Inclusion criteria**: Patients who underwent SPECT **Exclusion criteria**: Abnormality on rest ECG other than sinus bradycardia; early (<60 days after SPECT) revascularisation **Enrolled**: 3224 **Lost to follow-up**: 166 **Analysed**: 3058 **Age**: No hard event 61 ± 12; hard event 64 ± 13 years **Gender**: No hard event M 1956, W 1032; hard event M 52, W 18 **History of**: **MI** no hard event 520; hard event 33; **PTCA** no hard event 347; hard event 18; **CABG** no hard event 299; hard event 11	**SPECT**: **Tracer**: Tl-201 rest, MIBI stress. **Stress induced by**: Exercise (treadmill). **Image interpretation**: Semiquantitative visual. **Equipment**: N/S **CA**: No **Interval between tests**: Stress ECG was part of SPECT test **Definition of positive SPECT test**: 20 segments scored on a 5-point scale (0 = normal, 4 = absence of tracer uptake in a segment). Summed score obtained by summing scores of 20 segments. Summed stress scores <4 normal, 4–8 mildly abnormal, >8 moderately to severely abnormal **Definition of positive stress ECG test**: N/S **Angiographic definition of significant CAD**: N/S **Multivariate analysis**: Cox proportional hazards regression model **Outcome measures**: Cardiac mortality; non-fatal MI

continued

Study and methods	Participants	Test characteristics and outcome measures
Ho, 1999[56] **Study design**: Cohort (retrospective) **Method of recruitment**: N/S **Dates**: Jan. 1989–Dec. 1991 **Follow-up**: Median duration of 7.3 years in patients alive at follow-up **Country**: USA **Focus**: Prognostic value of SPECT performed 1–3 years after PTCA	**Inclusion criteria**: Patients who had performed an exercise tomographic Tl-201 test and had undergone PTCA 1–3 years preceding the Tl-201 study **Exclusion criteria**: Technically poor images, LBBB or paced ventricular rhythm, valvular heart disease, MI sustained between PTCA and SPECT study. CABG before PTCA **Enrolled**: 211 **Lost to follow-up**: 0 **Analysed**: 211 **Age**: 60 ± 10 years **Gender**: M 158, W 53 **History of**: **MI** 68; **PTCA** 211; **CABG** excluded if CABG before PTCA	**SPECT**: **Tracer**: Tl-201. **Stress induced by**: Exercise (treadmill). **Image interpretation**: Visual. **Equipment**: N/S **CA**: No **Interval between tests**: Stress ECG was part of SPECT test **Definition of positive SPECT test**: 14 segments graded subjectively on a 5-point scale (0 = absent uptake, 4 = normal). Redistribution: improved uptake ≥ 1 grade. Segments with mild fixed defects (scored as 3) considered normal and recoded 4 for this study. Summed stress scores obtained by adding the stress scores (normal = 56). Summed reversibility score: difference between summed stress and delayed scores **Definition of positive stress ECG test**: ≥ 1mm horizontal or downsloping ST-segment depression 0.08 s after the J point **Angiographic definition of significant CAD**: N/S **Multivariate analysis**: No. Cox univariate proportional hazards regression model **Outcome measures**: Mortality; cardiac mortality; non-fatal MI; repeat PTCA; repeat CABG; survival free of cardiac death
Iskandrian, 1993[57] **Study design**: Cohort (prospective) **Method of recruitment**: N/S **Dates**: N/S **Follow-up**: 28 ± 15 (range 1–60) months **Country**: USA **Focus**: Ability of SPECT to provide independent and incremental prognostic information above clinical, exercise and CA data in medically treated patients with CAD	**Inclusion criteria**: Patients receiving, within a 3-month period, SPECT and CA for evaluation of stable chest pain due to suspected or proven CAD **Exclusion criteria**: Normal angiograms, previous CABG or PTCA, recent acute MI (within 3 months) or unstable angina. **Enrolled**: 316 **Lost to follow-up**: 0 **Analysed**: 316 **Age**: 62 ± 10 years **Gender**: No cardiac event M 217, W 64; cardiac event M 21, W 14 **History of**: **MI** N/S; **PTCA** excluded; **CABG** excluded	**SPECT**: **Tracer**: Tl-201. **Stress induced by**: Exercise (treadmill). **Image interpretation**: Quantitative. **Equipment**: N/S **CA**: Method N/S **Interval between tests**: Within 3 months **Definition of positive SPECT test**: Reversible abnormality: perfusion abnormality in the initial image showing complete or partial redistribution on the delayed image involving ≥ 25% of the segment. Fixed abnormality: perfusion abnormality that remained unchanged in the delayed image. Multivessel abnormality: perfusion defects in ≥ 1 vascular territory. Abnormality: data points 2.5 SD below the mean normal limit **Definition of positive stress ECG test**: N/S **Angiographic definition of significant CAD**: ≥ 50% diameter stenosis of ≥ 1 major coronary artery **Multivariate analysis**: Cox proportional hazards regression model **Outcome measures**: Survival free of cardiac events. Patients receiving revascularisation (CABG or PTCA) within 3 months excluded

continued

Study and methods	Participants	Test characteristics and outcome measures
Iskandrian, 1994[58] **Study design**: Cohort (prospective) **Method of recruitment**: N/S **Dates**: N/S **Follow-up**: Mean follow-up 29 months **Country**: USA **Focus**: Value of the treadmill exercise score versus SPECT in medically treated patients with CAD	**Inclusion criteria**: Patients receiving SPECT and CA for evaluation of chest pain caused by suspected or proven CAD **Exclusion criteria**: Previous revascularisation, recent acute MI, unstable angina pectoris or revascularisation within 3 months of stress test **Enrolled**: 437 Lost to follow-up: 0 **Analysed**: 437 **Age**: 61 ± 10 years **Gender**: M 310, W 127 **History of**: **MI** (Q wave) 77; **PTCA** excluded; **CABG** excluded	**SPECT**: **Tracer**: Tl-201. **Stress induced by**: Exercise (treadmill). **Image interpretation**: Quantitative. **Equipment**: N/S **CA**: Method N/S **Interval between tests**: N/S **Definition of positive SPECT test**: N/S **Definition of positive stress ECG test**: Treadmill angina index: a score of 0 for no angina, 1 for non-limiting angina and 2 for exercise-limiting angina **Angiographic definition of significant CAD**: ≥ 50% diameter stenosis of ≥ 1 vessel **Multivariate analysis**: Cox proportional hazards regression model **Outcome measures**: Cardiac mortality; non-fatal MI
Kamal, 1994[59] **Study design**: Cohort **Method of recruitment**: Consecutive **Dates**: Feb. 1989–Jan. 1993 **Follow-up**: Average follow-up interval 22 ± 13 months **Country**: USA **Focus**: Prognostic value of adenosine SPECT in medically treated patients with CAD	**Inclusion criteria**: Patients receiving SPECT and CA within 3 months of each other for evaluation of chest pain **Exclusion criteria**: Coronary revascularisation within 3 months of SPECT, sick sinus syndrome, second-degree or greater atrioventricular block in the absence of a functioning pacemaker, or bronchospasm **Enrolled**: 177 **Lost to follow-up**: 0 **Analysed**: 177 **Age**: 64 ± 11 years **Gender**: M 109, W 68 **History of**: **MI** (Q wave) no cardiac event 45 of 163; cardiac event 4 of 14; **PTCA** N/S; **CABG** N/S	**SPECT**: **Tracer**: Tl-201. **Stress induced**: Pharmacologically (adenosine). **Image interpretation**: Semiquantitative. **Equipment**: N/S **CA**: Performed in multiple projections according to standard techniques **Interval between tests**: Within 3 months **Definition of positive SPECT test**: Perfusion pattern in each of vascular territories assessed as normal or showing fixed or reversible abnormalities. Multivessel thallium abnormality present when ≥ 1 vascular territory involved. **Definition of positive stress ECG test**: Horizontal or downsloping ST-segment depression ≥ 1 mm 80 ms after the J point **Angiographic definition of significant CAD**: ≥ 50% diameter stenosis in any major coronary arteries or their branches **Multivariate analysis**: Cox proportional hazards regression model **Outcome measures**: Cardiac mortality; non-fatal MI

continued

Study and methods	Participants	Test characteristics and outcome measures
Lauer, 1996[60] **Study design**: Cohort (prospective) **Method of recruitment**: Consecutive **Dates**: Sept. 1990–Dec. 1993 **Follow-up**: 1.8 years (for all-cause mortality) **Country**: USA **Focus**: Possible post-test gender bias for referral for CA	**Inclusion criteria**: Patients referred for SPECT **Exclusion criteria**: Prior invasive cardiac procedures, congestive heart failure, cardiomyopathy, valvular disease, heart transplant evaluation, or congenital heart disease **Enrolled**: 3669 **Lost to follow-up**: 0 **Analysed**: 3669 **Age**: M 58 ± 12, W 59 ± 12 years **Gender**: M 2351, W 1318 **History of**: **MI** M 167, W 41; **PTCA** excluded; **CABG** excluded	**SPECT**: **Tracer**: Tl-201. **Stress induced by**: Exercise (treadmill). **Image interpretation**: Quantitative. **Equipment**: 3-headed camera **CA**: Method N/S **Interval between tests**: Within 90 days **Definition of positive SPECT test**: N/S **Definition of positive stress ECG test**: ≥ 1 mm of horizontal or downsloping ST-segment depression 80 ms after the J point **Angiographic definition of significant CAD**: ≥ 50% stenosis in proximal or middle coronary vessel or major branch. Severe coronary disease: (1) ≥ 50% left main stenosis, (2) 3VD (≥ 70% stenosis in each major coronary artery system) or (3) 2VD with a ≥ 70% proximal LAD artery lesion **Multivariate analysis**: Cox proportional hazards regression model **Outcome measures**: Mortality; cardiac catheterisation performed within 90 days of stress testing
Lauer, 1997[61] **Study design**: Cohort (prospective) **Method of recruitment**: Consecutive **Dates**: Sept. 1990–Dec. 1993 **Follow-up**: ~2 years **Country**: USA **Focus**: Associations between age and referral to CA among adults undergoing noninvasive evaluation of known or suspected coronary disease	**Inclusion criteria**: Adults, ≥ 30 years old, under the care of cardiologists, with abnormal symptom-limited SPECT **Exclusion criteria**: Prior cardiac procedures (including CA), congestive heart failure, or valvular congenital heart disease **Enrolled**: 416 **Lost to follow-up**: 0 **Analysed**: 416 **Age**: 30–49 years group, 43 ± 5; 50–64 years group, 58 ± 4; 65–74 years group, 69 ± 3; ≥ 75 years group, 78 ± 3 **Gender**: M 354, W 62 **History of**: prior coronary events 155; **PTCA** excluded; **CABG** excluded	**SPECT**: **Tracer**: Tl-201. **Stress induced by**: Exercise (treadmill). **Image interpretation**: Visual. **Equipment**: N/S **CA**: Method N/S **Interval between tests**: Within 90 days **Definition of positive SPECT test**: Ischaemia: presence of >20% reversibility. Scarring: presence of counts <80% of maximum (<70% for the posterior wall). 12-segment system – each segment coded as normal ischaemic or scarred **Definition of positive stress ECG test**: ≥ 1 mm horizontal or downsloping ST-segment depression occurring 80 ms after the J point, or if ≥ 1 mm of additional ST-segment elevation occurred in leads without pathological Q waves **Angiographic definition of significant CAD**: ≥ 50% stenosis in any proximal or middle coronary vessel or major branch. Severe coronary disease: ≥ 50% left main artery stenosis, 3VD (≥ 70% stenosis in each major coronary artery system) or 2VD with a ≥ 70% proximal LAD artery lesion **Multivariate analysis**: Cox proportional hazards regression model **Outcome measures**: Mortality; cardiac mortality; CA performed within 90 days of SPECT

continued

Study and methods	Participants	Test characteristics and outcome measures
Machecourt, 1994[62] **Study design**: Cohort (prospective) **Method of recruitment**: Consecutive **Dates**: Jan. 1987–Dec. 1989 **Follow-up**: Mean 33 ± 10 months **Country**: France **Focus**: Prognostic value of SPECT in patients with suspected stable CAD **Note**: A subset of these patients is reported on in Vanzetto, 1999[84]	**Inclusion criteria**: Patients with suspected stable CAD **Exclusion criteria**: Prior CABG or PTCA; revascularisation performed <2 months after SPECT; MI <1 month; age >76 years; SPECT at rest; planar scintigraphy; missing administrative data **Enrolled**: 2013 **Lost to follow-up**: 87 **Analysed**: 1926 **Age**: 56.8 ± 9 years **Gender**: M 1303, W 623 **History of**: **MI** 357; **PTCA** excluded; **CABG** excluded	**SPECT**: **Tracer**: Tl-201. **Stress induced by**: Exercise (bicycle) 1121 (58%), pharmacologically (dipyridamole) 805 (42%). **Image interpretation**: Visual. **Equipment**: Rotating gamma camera. **CA**: No **Interval between tests**: Stress ECG was part of SPECT test **Definition of positive SPECT test**: Left ventricle divided into 6 segments, each segment classified as normal or abnormal **Definition of positive stress ECG test**: Horizontal or downsloping ST-segment depression >1 mm **Angiographic definition of significant CAD**: N/S **Multivariate analysis**: Cox proportional hazards regression model **Outcome measures**: Main criteria – mortality; cardiac mortality. Ancillary criteria – non-fatal MI; PTCA or CABG beyond the second month following the SPECT test
Marie, 1995[63] **Study design**: Cohort (retrospective) **Method of recruitment**: N/S **Dates**: 1982–1987 **Follow-up**: 70 ± 19 months **Country**: France **Focus**: Long-term prognostic value of SPECT in patients with known or suspected CAD compared with clinical history, exercise testing, CA and radionuclide ventricular angiography	**Inclusion criteria**: 1, Presence of known or suspected CAD and SPECT, CA and rest radionuclide angiographic results over a <1.5-month period; 2, subsequent medical therapy **Exclusion criteria**: Previous cardiac surgery or PTCA; congenital or valvular heart disease; hypertrophic or idiopathic dilated cardiomyopathy; decision to revascularise at hospital discharge; or revascularisation within 3 months **Enrolled**: 221 **Lost to follow-up**: 4 **Analysed**: 217 **Age**: 53 ± 9 (range 25–72) years **Gender**: M 188, W 29 **History of**: **MI** 143; **PTCA** excluded; **CABG** excluded	**SPECT**: **Tracer**: Tl-201. **Stress induced by**: Exercise (treadmill). **Image interpretation**: Visual. **Equipment**: N/S **CA**: Method N/S **Interval between tests**: Within 1.5 months **Definition of positive SPECT test**: Tl-201 uptake scored using a 4-point scale on a 20-segment division of the left ventricle (0 = normal, 3 = severely reduced). Extent of exercise defects: percent of segments with an uptake score ≥2 after exercise. Extent of reversible defects: percent of segments with exercise defects with a ≥1 point decrease in the uptake score at redistribution **Definition of positive stress ECG test**: ≥1 mm horizontal or downsloping depression occurring 0.08 s after the J point compared with baseline values **Angiographic definition of significant CAD**: Number of diseased coronary segments and vessels calculated using ≥70% and ≥50% diameter reduction **Multivariate analysis**: Cox proportional hazards regression model **Outcome measures**: Major ischaemic events (cardiac death or MI; other major cardiac events)

continued

Study and methods	Participants	Test characteristics and outcome measures
Marwick, 1999[64] **Study design**: Cohort (prospective) **Method of recruitment**: Consecutive **Dates**: 1990–1995 **Follow-up**: Mean 2.4 ± 1.5 years **Country**: USA **Focus**: Value of SPECT for prediction of cardiac mortality in men and women and whether this is independent of clinical evaluation and exercise testing **Note**: Shaw, 2000[79] reports on the same patient population and is considered as part of Marwick, 1999[64]	**Inclusion criteria**: Patients with cardiac symptoms of known or suspected CAD **Exclusion criteria**: Recent hospitalisation for unstable angina, MI and coronary revascularisation **Enrolled**: 8411 **Lost to follow-up**: 0 **Analysed**: 8411 **Age**: M 60.3 ± 12, W 62.9 ± 12 years **Gender**: M 5009, W 3402 **History of**: **MI** 1428 (M 952, W 476); **PTCA** 571 (M 401, W 170); **CABG** 671 (M 501, W 170)	**SPECT**: **Tracer**: Tl-201 (17% of patients), MIBI (83% of patients). **Stress induced by**: Exercise (treadmill 7486 patients), pharmacologically (dipyridamole 925 patients). **Image interpretation**: Visual. **Equipment**: N/S **CA**: No **Interval between tests**: Stress ECG was part of SPECT test **Definition of positive SPECT test**: Fixed defects: similar defects on both stress and redistribution images. Stress-induced defects: defects present in the stress image and absent in the redistribution image, or defects greater following stress than at redistribution. Fixed and stress-induced defects in each of the vascular territories of the 3 major coronary arteries coded 1, 2 or 3 **Definition of positive stress ECG test**: N/S **Angiographic definition of significant CAD**: N/S **Multivariate analysis**: Cox proportional hazards regression model **Outcome measures**: Mortality; cardiac mortality
Miller, 1998[65] **Study design**: Cohort (retrospective) **Method of recruitment**: N/S **Dates**: Dec. 1985–Dec. 1993 **Follow-up**: Median duration of follow-up 5.8 years **Country**: USA **Focus**: Prognostic value of SPECT performed relatively early after CABG	**Inclusion criteria**: Patients receiving SPECT and undergone CABG within the 2 years preceding SPECT **Exclusion criteria**: Technically poor images, LBBB or paced ventricular rhythm on the rest ECG, valvular heart disease or PTCA before CABG **Enrolled**: 411 **Lost to follow-up**: 0 **Analysed**: 411 **Age**: 62 ± 9 years **Gender**: M 329, W 82 **History of**: **MI** 189; **PTCA** excluded; **CABG** 411	**SPECT**: **Tracer**: Tl-201. **Stress induced by**: Exercise (treadmill). **Image interpretation**: Visual. **Equipment**: N/S CA: No **Interval between tests**: Stress ECG was part of SPECT test **Definition of positive SPECT test**: 14 short-axis segments. Redistribution: improved uptake of ≥ 1 grade. Mild fixed defects (score of 3 on stress and delayed images) considered normal. Ischaemia proximal to bypass graft insertion defined as redistribution confined to a basal segment or segments without redistribution in the apical or mid-segments of a coronary artery distribution. **Definition of positive stress ECG test**: ≥ 1 mm horizontal or downsloping ST-segment depression 0.08 s after the J point **Angiographic definition of significant CAD**: N/S **Multivariate analysis**: Cox proportional hazards regression model **Outcome measures**: Cardiac mortality; PTCA/repeat CABG early (≤ 3 months following the SPECT test); PTCA/repeat CABG late (>3 months following the SPECT test)

continued

Study and methods	Participants	Test characteristics and outcome measures
Miller, 2001[66] **Study design**: Cohort (retrospective) **Method of recruitment**: N/S **Dates**: Jan. 1989–Dec. 1991 **Follow-up**: Median follow-up 4.9 years **Country**: USA **Focus**: Identification of high-risk patients by worsening clinical, exercise or SPECT variables	**Inclusion criteria**: Symptomatic patients receiving SPECT and a second SPECT ≥ 6 months later without revascularisation or MI during this period **Exclusion criteria**: Congenital, cardiomyopathic or valvular heart disease; prior PTCA or CABG; LBBB, pacemaker, LVH or ventricular pre-excitation; technically poor SPECT images; or refusal of research authorisation **Enrolled**: 375 patients of whom 47 were excluded because magnitude of ST-segment depression was not retrievable **Lost to follow-up**: 0 **Analysed**: 328 **Age**: 62 ± 10 years **Gender**: M 262, W 113 **History of**: **MI** 65; **PTCA** excluded; **CABG** excluded	**SPECT**: **Tracer**: Tl-201. **Stress induced by**: Exercise (treadmill) . **Image interpretation**: Visual. **Equipment**: N/S **CA**: No **Interval between tests**: Stress ECG was part of SPECT test **Definition of positive SPECT test**: Tl-201 uptake in 24 segments for resting and exercise SPECT graded on a 5-point scale (0 = absent uptake, 4 = normal uptake). Summed stress and resting scores calculated by adding the grades in each of the 14 short-axis segments. Summed reversibility score calculated as the difference between the summed resting and stress scores **Definition of positive stress ECG test**: ≥ 1 mm horizontal or downsloping ST-segment depression 0.08 s after the J point **Angiographic definition of significant CAD**: N/S **Multivariate analysis**: Cox proportional hazards regression model **Outcome measures**: Mortality; non-fatal MI; early PTCA ≤ 3 months of SPECT test; late PTCA >3 months of SPECT test; early CABG ≤ 3 months of SPECT test; late CABG >3 months of SPECT test
Mishra, 1999[67] **Study design**: Retrospective comparative observational **Method of recruitment**: N/S **Dates**: N/S **Follow-up**: 3 months for CA, 2 weeks for revascularisation **Country**: USA **Focus**: Downstream utilisation rate in cohorts of patients with intermediate pretest probability of CAD, receiving either CA or SPECT for initial screening	**Inclusion criteria**: Patients being evaluated for chest pain suspected of being due to CAD **Exclusion criteria**: Previous revascularisation, cardiomyopathy or valvular heart disease **Enrolled**: Group 1 (CA) 4572; group 2 (SPECT) 2022 **Lost to follow-up**: N/S **Analysed**: Group 1 4572; Group 2 2022 **Age**: Group 1 59 ± 11; Group 2 57 ± 12 years **Gender**: Group 1 M 62%, W 38%; Group 2 M 55%, W 45% **History of**: **MI** N/S; **PTCA** excluded; **CABG** excluded	**SPECT**: **Tracer**: N/S. **Stress induced by**: N/S. **Image interpretation**: N/S. **Equipment**: N/S **CA**: Using standard techniques **Interval between tests**: CA within 3 months of SPECT (Group 2) **Definition of positive SPECT test**: Presence, extent, site(s) and nature of abnormality (fixed or reversible) **Definition of positive stress ECG test**: N/S **Angiographic definition of significant CAD**: ≥ 50% diameter stenosis in ≥ 1 of the major vessels **Multivariate analysis**: No **Outcome measures**: Coronary revascularisation (Group 1); CA and coronary revascularisation (Group 2)

continued

Study and methods	Participants	Test characteristics and outcome measures
Nallamothu, 1995[68] **Study design**: Cohort (retrospective) **Method of recruitment**: Consecutive **Dates**: N/S **Follow-up**: Mean 37 ± 29 months **Country**: USA **Focus**: Impact of SPECT on patient management and outcome	**Inclusion criteria**: Patients with suspected CAD receiving SPECT **Exclusion criteria**: N/S **Enrolled**: 2700 **Lost to follow-up**: 0 **Analysed**: 2700 **Age**: 59 ± 13 years **Gender**: M 1510, W 1190 **History of**: **MI** 0; **PTCA** 0; **CABG** 0	**SPECT**: **Tracer**: Tl-201. **Stress induced by**: Exercise (treadmill). **Image interpretation**: N/S. **Equipment**: N/S **CA**: Method N/S **Interval between tests**: N/S **Definition of positive SPECT test**: N/S **Definition of positive stress ECG test**: N/S **Angiographic definition of significant CAD**: N/S **Multivariate analysis**: No **Outcome measures**: Mortality; non-fatal MI; PTCA; CABG; need for subsequent CA (following SPECT study)
Nallamothu, 1997[69] **Study design**: Cohort (retrospective) **Method of recruitment**: N/S **Dates**: N/S **Follow-up**: Mean 41 ± 28 months (mean of 5 years after CABG (58 ± 50 months)) **Country**: USA **Focus**: Prognostic value of SPECT after CABG	**Inclusion criteria**: Prior CABG for angina pectoris, SPECT and CA within 3 months of each other after CABG, and no repeat CABG within 3 months of SPECT **Exclusion criteria**: Patients not receiving repeat CA **Enrolled**: 255 **Lost to follow-up**: 0 **Analysed**: 255 **Age**: 64 ± 9 years **Gender**: M 206, W 49 **History of**: **MI** (Q-wave) 64; **PTCA** N/S; **CABG** 255	**SPECT**: **Tracer**: Tl-201. **Stress induced by**: Exercise (treadmill) 134 (53%), pharmacologically (adenosine 100 (39%), dipyridamole 21 (8%)). **Image interpretation**: N/S. **Equipment**: N/S **CA**: Multiple projections using standard techniques **Interval between tests**: Within 3 months **Definition of positive SPECT test**: N/S **Definition of positive stress ECG test**: N/S **Angiographic definition of significant CAD**: ≥ 50% diameter stenosis in any one of the non-grafted coronary arteries, grafted vessels distal to the graft anastomoses, or in the grafts **Multivariate analysis**: Cox proportional hazards regression model **Outcome measures**: Cardiac mortality; non-fatal MIPTCA or CABG >3 months after stress testing

continued

Study and methods	Participants	Test characteristics and outcome measures
O'Keefe, 1998[70] **Study design**: Cohort (retrospective) **Method of recruitment**: Consecutive **Dates**: June 1991–Aug. 1993 **Follow-up**: Mean 19 ± 10 months **Country**: USA **Focus**: Outcomes of patients with mild or moderate ischaemia but without high-risk features on SPECT as a function of whether they were managed medically or invasively	**Inclusion criteria**: Patients with non-high-risk classification from SPECT **Exclusion criteria**: CA <90 days before SPECT **Enrolled**: 1352 (medically managed 1236, invasively managed 116) **Lost to follow-up**: 28 **Analysed**: 1324 **Age**: Medically managed 64.4 ± 10.2, invasively managed 61.8 ± 10.5 years **Gender**: M 1078, W 274 (medically managed M 974, W 262, invasively managed M 104, W 12) **History of**: **MI** 615 (medically managed 577, invasively managed 38); **PTCA** 743 (medically managed 679, invasively managed 64); **CABG** 375 (medically managed 347, invasively managed 28)	**SPECT**: **Tracer**: Tl-201 (97% of patients), MIBI (3% of patients). **Stress induced by**: Exercise (type N/S), pharmacologically (adenosine or dipyridamole or dobutamine). **Image interpretation**: Visual, quantitative. **Equipment**: N/S **CA**: No **Interval between tests**: Stress ECG was part of SPECT test **Definition of positive SPECT test**: Perfusion defects scored: severe = 3, moderate = 2, mild/equivocal = 1, normal = 0. Ischaemia: change in segmental score between stress and rest of 3–0, 3–1, 2–0 and 2–1. Non-reversible: scores of 3–3, 3–2 and 2–2. Scans categorised into 3 classifications: 1, high risk – two or three of multivessel ischaemia, ischaemia in the LAD coronary territory or abnormal lung uptake of thallium on the stress anterior view; 2, non-high risk – ischaemic but not meeting criteria for high risk; 3, normal/non-ischaemic **Definition of positive stress ECG test**: N/S **Angiographic definition of significant CAD**: N/S **Multivariate analysis**: Cox proportional hazards regression model **Outcome measures**: Cardiac mortality; non-fatal MI; PTCA or CABG excluding procedures performed within first 30 days in invasively managed group
Olmos, 1998[71] **Study design**: Cohort (prospective) **Method of recruitment**: N/S **Dates**: 1986–1993 **Follow-up**: Up to 8 years, mean 3.7 ± 2 years **Country**: USA **Focus**: Incremental prognostic value of exercise echocardiography and SPECT with clinical variables and ExECG in patients with suspected or known CAD	**Inclusion criteria**: Patients evaluated for suspected or known CAD **Exclusion criteria**: Recent MI (<2 months), valvular heart disease, dilated or hypertrophic cardiomyopathy or previous cardiac transplantation **Enrolled**: 248 **Lost to follow-up**: 23 **Analysed**: 225 **Age**: 56.3 ± 12 years **Gender**: M 189, W 59 **History of**: **MI** 86; **PTCA/CABG** 57	**SPECT**: **Tracer**: Tl-201. **Stress induced by**: Exercise (treadmill). **Image interpretation**: Visual. **Equipment**: ADAC, ARC 3000-3300 large field-of-view, single-crystal, rotating gamma camera **CA**: Method N/S **Interval between tests**: Within 3 months (84 patients had CA) **Definition of positive SPECT test**: Tl-201 uptake was scored: 1 = normal, 2 = mildly reduced, 3 = moderately reduced, 4 = severely reduced. Perfusion defects analysed for complete redistribution (ischaemia), no redistribution (fixed defect), or partial redistribution (mixed defect) **Definition of positive stress ECG test**: ≥ 1 mm horizontal or downsloping ST-segment depression 0.08 s after the J point **Angiographic definition of significant CAD**: N/S **Multivariate analysis**: Yes **Outcome measures**: Mortality; cardiac mortality; non-fatal MI; PTCA; CABG; unstable angina requiring hospitalisation; congestive heart failure; cardiac transplantation

continued

Study and methods	Participants	Test characteristics and outcome measures
Parisi, 1998[74] **Study design**: Cohort **Method of recruitment**: N/S **Dates**: N/S **Follow-up**: 5 years **Country**: USA **Focus**: Prognostic ability of SPECT and ExECG after commonly accepted treatments in low-risk men with CAD	**Inclusion criteria**: Men with chronic stable angina referred for CA found to have SVD or 2VD and no prior revascularisation. Positive baseline test with stress ECG or SPECT required for study entry **Exclusion criteria**: N/S **Enrolled**: 328 of whom 3, with uninterpretable ECGs, were excluded **Lost to follow-up**: 3 **Analysed**: 297 **Age**: 60 years **Gender**: M 297 **History of**: **MI** N/S; **PTCA** excluded; **CABG** excluded	**SPECT**: **Tracer**: Tl-201. **Stress induced by**: N/S. **Image interpretation**: Visual. **Equipment**: N/S CA: No **Interval between tests**: Stress ECG was part of SPECT test **Definition of positive SPECT test**: ≥ 1 regional perfusion deficit apparent in the exercise images **Definition of positive stress ECG test**: ≥ 1 mm exercise-induced ST-segment depression 0.08 s after the J point persisting for ≥ 15 s and reverting to baseline thereafter **Angiographic definition of significant CAD**: N/S **Multivariate analysis**: Yes **Outcome measures**: Mortality; MI; PTCA; CABG; occurrence of unstable angina
Pattillo, 1996[75] **Study design**: Cohort (prospective) **Method of recruitment**: N/S **Dates**: N/S **Follow-up**: 41 ± 22 months **Country**: USA **Focus**: Relative independent and incremental prognostic value of clinical evaluation, exercise testing, CA and SPECT with quantitative assessment	**Inclusion criteria**: Patients receiving SPECT, during symptom-limited exercise testing, and CA within 3 months of each other because of chest pain **Exclusion criteria**: Previous CABG, PTCA, acute MI within 3 months, unstable angina pectoris, or revascularisation within 3 months of exercise testing **Enrolled**: 732 **Lost to follow-up**: 0 **Analysed**: 732 **Age**: 59 ± 11 years **Gender**: M 519, W 213 **History of**: **MI** 343; **PTCA** excluded; **CABG** excluded	**SPECT**: **Tracer**: Tl-201. **Stress induced by**: Exercise (treadmill). **Image interpretation**: Quantitative. **Equipment**: N/S **CA**: Performed with standard techniques **Interval between tests**: Within 3 months **Definition of positive SPECT test**: Interpreted as normal or showing fixed or reversible abnormality, multivessel abnormality, left ventricular dilation and increased lung thallium uptake. Size of the perfusion abnormality determined from polar map plots, by sum of number of segments with abnormal perfusion pattern and sum of number of segments with reversible defects **Definition of positive stress ECG test**: Treadmill exercise score calculated according to the method of Mark and colleagues.[136,137] A score of <–10 was considered high risk, –10 to 4 moderate risk and ≥ 5 low risk **Angiographic definition of significant CAD**: Number of vessels with ≥ 50% diameter stenosis and by the Gensini score. Gensini score based on the number, degree and sites of stenoses and collateral vessels. Score of < 10 mild disease; 10–34 moderate disease and ≥ 35 severe disease **Multivariate analysis**: Cox proportional hazards regression model **Outcome measures**: Cardiac mortality; non-fatal MI

continued

Study and methods	Participants	Test characteristics and outcome measures
Schinkel, 2002[76] **Study design**: Cohort **Method of recruitment**: Consecutive **Dates**: 1994–2000 **Follow-up**: 37 ± 17 months **Country**: The Netherlands **Focus**: Prognostic value of dobutamine–atropine SPECT in patients with known or suspected CAD	**Inclusion criteria**: Patients with limited exercise capacity **Exclusion criteria**: 28 patients who underwent coronary revascularisation within 3 months of SPECT were excluded from the analysis **Enrolled**: 721 **Lost to follow-up**: 2 **Analysed**: 693 **Age**: 60 ± 10 years **Gender**: M 419, W 274 **History of**: **MI** 194; **PTCA** 111; **CABG** 100	**SPECT**: **Tracer**: Tc-99m tetrofosmin. **Stress induced**: Pharmacologically (dobutamine–atropine). **Image interpretation**: Semiquantitative. **Equipment**: PRISM 3000 XP (Picker International) triple-headed gamma camera system **CA**: No **Interval between tests**: Stress ECG was part of SPECT test **Definition of positive SPECT test**: Reversible perfusion defect: perfusion defect on stress images that partially or completely resolved at rest in ≥ 2 contiguous segments or slices in the 47-segment model. Fixed perfusion defect: perfusion defect on stress images in ≥ 2 contiguous segments or slices, which persisted on rest images in the 47-segment model. Abnormal study: presence of a fixed or reversible perfusion defect (or both) **Definition of positive stress ECG test**: N/S **Angiographic definition of significant CAD**: N/S **Multivariate analysis**: Cox proportional hazards regression model **Outcome measures**: Mortality; cardiac mortality; non-fatal MI; PTCA/CABG later than 3 months following the SPECT test
Shaw, 1999[77] **Study design**: Prospective comparative observational **Method of recruitment**: N/S **Dates**: N/S **Follow-up**: Mean 2.5 ± 1.5 years **Country**: USA **Focus**: Observational differences in costs of care by the coronary disease diagnostic test modality	**Inclusion criteria**: Patients with typical cardiac symptoms enrolled into a registry of stable angina pectoris patients including patients receiving initial direct diagnostic CA and those receiving SPECT **Exclusion criteria**: Patients undergoing a predischarge evaluation or recently hospitalised for unstable angina, MI or revascularisation **Enrolled**: Group 1 (CA) 5423; Group 2 (MPI) 5826 **Lost to follow-up**: N/S **Analysed**: Group 1 5423; Group 2 5826 **Age**: Group 1 62 ± 12; Group 2 64 ± 12 years **Gender**: Group 1 M 62%, W 38%; Group 2 M 64%, W 36% **History of**: **MI** N/S; **PTCA** N/S; **CABG** N/S	**SPECT**: **Tracer**: Tl-201 (17%), MIBI (83%). **Stress induced by**: Exercise (treadmill 4901); pharmacologically 925 (agent N/S). **Image interpretation**: Visual. **Equipment**: N/S **CA**: Method N/S **Interval between tests**: N/S **Definition of positive SPECT test**: Fixed defects: defects at rest and remained unchanged during stress. Reversible defects: new or worsening defects after stress. Perfusion defect extent coded as 0, 1, 2 or 3 vascular territory involvement **Definition of positive stress ECG test**: ≥ 1 mm of horizontal or downsloping ST-segment depression **Angiographic definition of significant CAD**: N/S **Multivariate analysis**: Cox proportional hazards regression model **Outcome measures**: Cardiac mortality; non-fatal MI; death or MI; revascularisation

continued

Study and methods	Participants	Test characteristics and outcome measures
Shaw, 1999[78] **Study design**: Prospective comparative observational **Method of recruitment**: Consecutive **Dates**: N/S **Follow-up**: 2.5 ± 1.5 years and a minimum of 6 months after initial testing for each patient **Country**: USA **Focus**: Medical costs and clinical outcomes of women referred for CA or non-invasive stress myocardial imaging to evaluate chest pain, incremental costs of diagnostic testing and subsequent medical care of 2 testing strategies, and impact on cardiac outcomes	**Inclusion criteria**: Women referred for testing to evaluate known or suspected CAD based on stable chest pain consistent with angina pectoris **Exclusion criteria**: Women undergoing predischarge risk stratification after recent (<3 weeks) MI, prior coronary revascularisation, recent valvular disease, or cardiac catheterisation **Enrolled**: 4638 **Lost to follow-up**: 0 **Analysed**: 4638. Strategy 1. 3375, Strategy 2. 1263 **Age**: 66 ± 11 years **Gender**: W 4638 **History of**: **MI** N/S; **PTCA** excluded; **CABG** excluded	**SPECT**: **Tracer**: MIBI. **Stress induced by**: Exercise (type N/S), pharmacologically (dipyridamole) 525. **Image interpretation**: N/S. **Equipment**: N/S **CA**: Method N/S **Interval between tests**: N/S **Definition of positive SPECT test**: ≥ 1 reversible myocardial perfusion defect **Definition of positive stress ECG test**: ≥ 1 mm electrocardiographically detected ST-segment depression beyond baseline **Angiographic definition of significant CAD**: stenosis of >70% luminal diameter reduction **Multivariate analysis**: Cox proportional hazards regression model **Outcome measures**: Cardiac mortality; non-fatal MI; revascularisation
Shaw, 2000[79] **Study design**: Cohort (prospective) **Method of recruitment**: N/S **Dates**: 1991–1996 **Follow-up**: Mean 2.5 ± 1.5 years **Country**: USA **Focus**: Value of non-invasive risk stratification relative to clinical assessment in a stable chest pain population **Note**: this study reports on the same patient population as Marwick, 1999,[64] which is considered as the primary report	**Inclusion criteria**: Patients with typical cardiac symptoms referred for SPECT **Exclusion criteria**: Undergoing a predischarge evaluation, or recently hospitalised for acute coronary syndromes or coronary revascularisation **Enrolled**: 8411 **Lost to follow-up**: N/S **Analysed**: 8411 **Age**: 69 ± 11 years **Gender**: M 5009, W 3402 **History of**: **MI** 1414; **PTCA** 4458; **CABG** 5467	**SPECT**: **Tracer**: Tl-201 (17% of patients); MIBI (83% of patients). **Stress induced by**: Exercise (treadmill); pharmacologically (adenosine or dipyridamole). **Image interpretation**: Visual. **Equipment**: N/S **CA**: No **Interval between tests**: Stress ECG was part of SPECT test **Definition of positive SPECT test**: Fixed defects: defects at rest and unchanged during stress. Ischaemic: new or worsening defects after stress. Perfusion defect extent coded as 0, 1, 2 or 3 vascular territory abnormalities **Definition of positive stress ECG test**: ≥ 1 mm horizontal or downsloping ST-segment depression at 80 ms after the J point **Angiographic definition of significant CAD**: N/S **Multivariate analysis**: Cox proportional hazards regression model **Outcome measures**: Cardiac mortality; MI; coronary revascularisation

continued

Study and methods	Participants	Test characteristics and outcome measures
Stratmann, 1994[80] **Study design**: Cohort (prospective) **Method of recruitment**: Consecutive **Dates**: Mar. 1991–Sept. 1992 **Follow-up**: 13 ± 5 months (range 1–24 months), ≥ 6 months for patients without cardiac events **Country**: USA **Focus**: Relative prognostic value of exercise stress with SPECT and clinical risk variables in patients presenting for evaluation of stable chest pain consistent with angina pectoris	**Inclusion criteria**: Patients with stable chest pain consistent with angina pectoris referred for exercise testing and SPECT **Exclusion criteria**: Unstable angina, acute MI ≤ 3 months before testing, or early (<6 months after SPECT) revascularisation **Enrolled**: 531 **Lost to follow-up**: 10 **Analysed**: 521 **Age**: No cardiac event 59 ± 11; cardiac event 62 ± 8 years **Gender**: No cardiac event M 487, W 10; cardiac event M 24 **History of**: **MI** No cardiac event 172; cardiac event 12; **PTCA** N/S; **CABG** N/S	**SPECT**: **Tracer**: MIBI. **Stress induced by**: Exercise (treadmill). **Image interpretation**: Visual. **Equipment**: Siemens Orbiter-75 single-headed SPECT gamma camera **CA**: No **Interval between tests**: Stress ECG was part of SPECT test **Definition of positive SPECT test**: Presence of perfusion defect. Fixed defect: defect present and unchanged on both stress and rest images. Reversible defect: defect on stress images absent or less prominent on rest images **Definition of positive stress ECG test**: Horizontal or downsloping ST-segment depression ≥ 1 mm **Angiographic definition of significant CAD**: ≥ 50% stenosis (as determined in ≥ 2 angiographic views) **Multivariate analysis**: Cox proportional hazards regression model **Outcome measures**: Cardiac mortality; non-fatal MI; PTCA/CABG performed ≥ 6 months after exercise testing; survival free of cardiac events at 1 year
Travin, 1995[81] **Study design**: Cohort (prospective) **Method of recruitment**: Consecutive **Dates**: N/S **Follow-up**: 15 ± 10 months (range <1–37 months) **Country**: USA **Focus**: Clinical utility of SPECT in patients undergoing exercise stress testing after recent acute MI	**Inclusion criteria**: Patients who had an acute MI within 14 days and were referred for SPECT **Exclusion criteria**: N/S **Enrolled**: 134 of whom 33 underwent coronary revascularisation **Lost to follow-up**: 14 **Analysed**: 87 **Age**: 60.5 ± 11.9 years **Gender**: M 90, W 44 **History of**: MI 17 although all patients in the study had recent **MI**; **PTCA** N/S; **CABG** N/S	**SPECT**: **Tracer**: MIBI. **Stress induced by**: Exercise (treadmill). **Image interpretation**: Visual. **Equipment**: ADAC ARC 4000 or Cirrhus camera. **CA**: No **Interval between tests**: Stress ECG was part of SPECT test **Definition of positive SPECT test**: Left ventricular myocardium divided into 5 segments. Each segment classified as normal, ischaemic (perfusion defect on stress images that improved ≥ 30% visually on rest images) or fixed **Definition of positive stress ECG test**: ≥ 3 consecutive beats showing ≥ 0.1 mV of horizontal or downsloping ST-segment depression beyond baseline that persisted for ≥ 80 ms after the J point **Angiographic definition of significant CAD**: N/S **Multivariate analysis**: Cox proportional hazards regression model **Outcome measures**: Cardiac mortality; non-fatal MI; hospital admissions for unstable angina

continued

Study and methods	Participants	Test characteristics and outcome measures
Underwood, 1999[82] **Study design**: Retrospective observational comparison **Method of recruitment**: Consecutive within each centre **Dates**: Presenting after 1 July 1993 **Follow-up**: 2 years **Country**: France, Germany, Italy, UK **Focus**: Cost-effectiveness of 4 diagnostic strategies in patients newly presenting with possible CAD, and to compare cost-effectiveness in centres that routinely use MPI with those that do not	**Inclusion criteria**: Patients newly presenting with symptoms suggestive of CAD **Exclusion criteria**: Presenting with MI or unstable angina; those in whom coronary disease had been previously confirmed or excluded **Enrolled**: Strategy 1, 146; strategy 2, 131; strategy 3, 48; strategy 4, 76 **Lost to follow-up**: Strategy 1, 2; strategy 2, 1; strategy 3, 0; strategy 4, 1 **Analysed**: Strategy 1, 144; strategy 2, 130; strategy 3, 48; strategy 4, 75 **Age (mean)**: Strategy 1, 55; strategy 2, 53; strategy 3, 61; strategy 4, 61 years **Gender**: Strategy 1, M 85, W 61; strategy 2, M 85, W 46; strategy 3, M 31, W 17; strategy 4, M 48, W 28 **History of**: **MI** excluded; **PTCA** excluded; **CABG** excluded	**SPECT**: **Tracer**: N/S. **Stress induced by**: N/S. **Image interpretation**: N/S. **Equipment**: N/S **CA**: Yes **Interval between tests**: N/S **Definition of positive SPECT test**: Taken as recorded in the notes **Definition of positive stress ECG test**: N/S **Angiographic definition of significant CAD**: N/S **Multivariate analysis**: No **Outcome measures**: Hard events – mortality; MI; occurrence of unstable angina. Soft events – PTCA; CABG; worsening of angina; complications; other
Vanzetto, 1999[83] **Study design**: Cohort (prospective) **Method of recruitment**: N/S **Dates**: 1989–1994 **Follow-up**: 23 ± 17 months (range 3–78 months) **Country**: France **Focus**: Prognostic value of exercise stress testing and SPECT for the prediction of cardiac events in a homogeneous cohort of high-risk NIDDM patients	**Inclusion criteria**: NIDDM patients presenting with ≥2 of the following risk factors: age ≥65 years; active smoker; high blood pressure, hypercholesterolaemia or LDL cholesterol >3.10 mmol/l; history of CAD; PVD; abnormal rest ECG; microalbuminuria **Exclusion criteria**: Myocardial revascularisation <3 months; episode of unstable angina <3 months; acute MI <3 months; severe angina under medical therapy **Enrolled**: 158 **Lost to follow-up**: 0 **Analysed**: 158 **Age**: 63 ± 9 years **Gender**: M 105, W 53 **History of**: **MI** 20; **PTCA** N/S; **CABG** N/S	**SPECT**: **Tracer**: Tl-201. **Stress induced by**: Exercise (bicycle, $n = 78$); pharmacologically (dipyridamole, $n = 80$). **Image interpretation**: Visual. **Equipment**: N/S **CA**: No **Interval between tests**: Stress ECG was part of SPECT test **Definition of positive SPECT test**: Left ventricle divided into 9 segments. Each segment classified as normal or abnormal, and if abnormal as reversible (partial or total normalisation after reinjection) or fixed (persistent defect after reinjection) **Definition of positive stress ECG test**: Horizontal or downsloping ST-segment depression >1 mm measured 0.08 s after the J point. In patients with ST segment abnormalities on rest ECG, stress ECG positive when ST depression >2 mm during exercise **Angiographic definition of significant CAD**: N/S **Multivariate analysis**: Cox proportional hazards regression model **Outcome measures**: Cardiac mortality; non-fatal MI; need for revascularisation; occurrence of unstable angina; acute congestive heart failure

PVD, peripheral vascular disease.

continued

Study and methods	Participants	Test characteristics and outcome measures
Vanzetto, 1999[84] **Study design**: Cohort (prospective) **Method of recruitment**: N/S **Dates**: 1987–1989 **Follow-up**: 72 ± 18 months (11 days to 8 years) **Country**: France **Focus**: Prognostic value of SPECT in patients with low to intermediate likelihood of future cardiac events at long-term follow-up; incremental prognostic value of SPECT over clinical and ETT data **Note**: This study focuses on a subset of the patient population reported on by Machecourt, 1994[62]	**Inclusion criteria**: Patients referred for SPECT **Exclusion criteria**: Myocardial revascularisation within 3 months of SPECT, MI <3 months before SPECT or age >75 years **Enrolled**: 1182 **Lost to follow-up**: 45 **Analysed**: 1137 **Age**: 55.3 ± 9.2 years **Gender**: M 857, W 280 **History of** (>3 months): **MI** 270; **PTCA** 91; **CABG** 148	**SPECT**: **Tracer**: Tl-201. **Stress induced by**: Exercise (bicycle). **Image interpretation**: Visual. **Equipment**: N/S **CA**: No **Interval between tests**: N/S whether stress ECG was within SPECT test **Definition of positive SPECT test**: Left ventricle divided into 6 segments. Segments scored as abnormal in the event of decreased tracer uptake in a surface large enough to be considered significant. Abnormal segments defined as reversible (partial or total normalisation on redistribution images) or fixed **Definition of positive stress ECG test**: Positive: horizontal or downsloping ST-segment depression of 1–2 mm measured 0.08 s after the J point, occurring for a workload >75 W, with or without chest pain. Strongly positive: ST-segment depression >2 mm at any workload or >1 mm for a workload ≤ 75 W or ST depression postexercise duration >6 minutes **Angiographic definition of significant CAD**: N/S **Multivariate analysis**: Cox proportional hazards regression model **Outcome measures**: Mortality; cardiac mortality; non-fatal MI; PTCA/CABG >3 months after SPECT
Wagner, 1996[85] **Study design**: Cohort (prospective) **Method of recruitment**: Consecutive **Dates**: Feb. 1992–Dec. 1994 **Follow-up**: Mean 13.5 months **Country**: Germany **Focus**: Relative predictive power of 3 types of stress tests without knowledge of contributory risk factors 1 year after transmural MI and subsequent to treatment with thrombolytics	**Inclusion criteria**: Patients hospitalised with acute transmural MI, treated with thrombolytic therapy, clinically stable in the post-MI course and able to exercise **Exclusion criteria**: Death, unstable angina, >75 years, severe concomitant disease, or refusal **Enrolled**: 106 **Lost to follow-up**: 4 **Analysed**: 102 **Age**: 57 ± 11 years **Gender**: M 89, W 13 **History of**: **MI** N/S; **PTCA** N/S; **CABG** N/S	**SPECT**: **Tracer**: MIBI. **Stress induced by**: Exercise (bicycle). **Image interpretation**: Visual. **Equipment**: APEX 409 AG system **CA**: Judkins technique **Interval between tests**: Within 18 days **Definition of positive SPECT test**: Persistent defects: defects at stress and at rest. Reversible defects (ischaemia): difference from rest ≥ 10% **Definition of positive stress ECG test**: Horizontal or downsloping ST-segment depression ≥ 1 mm in any lead measured 80 ms after the J point. Occurrence of angina pectoris an additional parameter for stress-induced ischaemia **Angiographic definition of significant CAD**: Stenoses of ≥ 50% of the arterial intraluminal diameter **Multivariate analysis**: Yes **Outcome measures**: Mortality; PTCA; CABG; occurrence of unstable angina; occurrence of reinfarction

continued

Study and methods	Participants	Test characteristics and outcome measures
Zanco, 1995[86] **Study design**: Cohort (prospective) **Method of recruitment**: Consecutive **Dates**: Jan. 1988–Dec. 1990 **Follow-up**: ≥ 36 months; mean 43 months (range 36–60 months) **Country**: Italy **Focus**: Incremental prognostic value of SPECT in CAD patients	**Inclusion criteria**: Patients who underwent SPECT for diagnosis or evaluation of CAD **Exclusion criteria**: Previous revascularisation **Enrolled**: 176 **Lost to follow-up**: 29 **Analysed**: 147 **Age**: 53 ± 9 (range 27–68) years **Gender**: M121, W 26 **History of**: **MI** 61; **PTCA** excluded; **CABG** excluded	**SPECT**: **Tracer**: MIBI. **Stress induced by**: Exercise (bicycle). **Image interpretation**: Visual. **Equipment**: Single-head large field-of-view rotating gamma camera. **CA**: No **Interval between tests**: Stress ECG was part of SPECT test **Definition of positive SPECT test**: 18 segments per study. Each segment scored on a 4-point scale, in comparison with a linear colour scale (0 = activity >80% of the maximum, 1 = 80–50%, 2 = 50–20%, 3 = <20%). Parameters evaluated: (1) presence of abnormal scan (fixed or reversible defect); (2) presence of reversible defect (increase ≥ 2 in total score of stress images compared with rest images); (3) extent of stress perfusion defect (number of segments with score ≥ 1); (4) score of stress perfusion defect, including extent and severity of defect (calculated by sum of score of all segments in stress images) **Definition of positive stress ECG test**: N/S **Angiographic definition of significant CAD**: N/S **Multivariate analysis**: Yes **Outcome measures**: Cardiac mortality; non-fatal MI; occurrence of unstable angina
Zellweger, 2002[87] **Study design**: Cohort (retrospective) **Method of recruitment**: Consecutive **Dates**: N/S **Follow-up**: Mean 667 ± 185 days; min. 1 year **Country**: USA **Focus**: 1, Incremental prognostic value of SPECT over clinical assessment; 2, potential usefulness and cost-effectiveness in clinical risk stratification; 3, impact of SPECT on the subsequent referral to early CA	**Inclusion criteria**: Patients with remote prior MI receiving their first SPECT study >6 months after MI **Exclusion criteria**: Early (<60 days after SPECT) revascularisation **Enrolled**: 1663 **Lost to follow-up**: 59 **Analysed**: 1413 **Age**: Exercise 66.8 ± 10.5, adenosine 71.9 ± 10.5 years **Gender**: M 1068, W 345 **History of**: **MI** 1413; **PTCA** 383; **CABG** 571	**SPECT**: **Tracer**: Tl-201 or MIBI. **Stress induced by**: Exercise [treadmill 899 (64%), pharmacologically, adenosine 514 (36%)]. **Image interpretation**: Semiquantitative. **Equipment**: N/S **CA**: No **Interval between tests**: Stress ECG was part of SPECT test **Definition of positive SPECT test**: Perfusion images scored on a 20-segment, 5-point model (0 = normal, 5 = no uptake) for the left ventricle. SSS and SRS calculated by adding scores of segments in stress and rest image, respectively. SDS derived as the difference between stress and rest scores. SSS <4 normal, 4–8 mildly abnormal, 9–13 moderately abnormal, >13 severely abnormal. Degree of reversibility: SDS <2 non-ischaemic, 2–6 mildly ischaemic, >6 moderately or severely ischaemic **Definition of positive stress ECG test**: Horizontal or downsloping ST-segment depression of ≥ 1 mm or upsloping of ≥ 1.5 mm at 80 ms after the J point **Angiographic definition of significant CAD**: N/S **Multivariate analysis**: Cox proportional hazards regression model **Outcome measures**: Cardiac mortality; non-fatal MI; PTCA; CABG

continued

Study and methods	Participants	Test characteristics and outcome measures
Zerahn, 2000[88] **Study design**: Cohort (prospective) **Method of recruitment**: Consecutive **Dates**: Jan. 1991–Aug. 1997 **Follow-up**: Mean 59.1 months ± 22.1. Follow-up until death or end Dec. 1998 **Country**: Denmark **Focus**: Prognostic power of SPECT in combination with ExECG	**Inclusion criteria**: Patients referred for SPECT **Exclusion criteria**: N/S **Enrolled**: 697 **Lost to follow-up**: N/S **Analysed**: N/S **Age**: 56.9 ± 9.6 years **Gender**: N/S **History of**: MI 356; PTCA 6; CABG 30	**SPECT**: **Tracer**: MIBI. **Stress induced by**: Exercise (bicycle). **Image interpretation**: Visual. **Equipment**: N/S **CA**: No **Interval between tests**: Stress ECG was part of SPECT test **Definition of positive SPECT test**: Reversible or irreversible perfusion defect present **Definition of positive stress ECG test**: Horizontal or downsloping ST-segment depression 80 ms after the J point of ≥ 1 mm compared with the rest ECG **Angiographic definition of significant CAD**: N/S **Multivariate analysis**: Cox proportional hazards regression model **Outcome measures**: Cardiac mortality

ECG-gated SPECT

Study and methods	Participants	Test characteristics and outcome measures
Sharir, 1999[89] **Study design**: Cohort **Method of recruitment**: Consecutive **Dates**: N/S **Follow-up**: Minimum of 1 year. Mean follow-up interval 569 ± 106 days (range 365–968 days) **Country**: USA **Focus**: Incremental prognostic value of poststress ejection fraction and left ventricular volume, measured by gated SPECT, over clinical, exercise and perfusion data in predicting cardiac death in patients referred for SPECT	**Inclusion criteria**: Patients receiving separate acquisition gated SPECT **Exclusion criteria**: Non-ischaemic cardiomyopathy or revascularised <60 days after SPECT **Enrolled**: 1924 **Lost to follow-up**: **Analysed**: 1680 **Age**: Exercise 64 ± 12, adenosine 71 ± 11 **Gender**: M 1034, W 646 **History of**: **MI** 418; **PTCA** 305; **CABG** 336	**SPECT**: **Tracer**: Tl-201 (rest), MIBI (stress). **Stress induced by**: Exercise (treadmill, 1029); pharmacological (adenosine, 651). **Image interpretation**: Quantitative, visual. **Equipment**: 2-detector (Vertex, ADAC), 3-detector (PRISM, Picker) or 1-detector (Orbiter, Siemens) camera **CA**: No **Interval between tests**: N/S **Definition of positive SPECT test**: Perfusion images scored on 20-segment, 5-point model for LV (0 = normal uptake, 4 = no uptake). SSS and SRS calculated by adding the scores of segments in stress and rest images, respectively. SDS derived as the difference between stress and rest scores. SSS <4 normal, 4–13 mildly/moderately abnormal, >13 severely abnormal **Definition of positive stress ECG test**: Horizontal or downsloping ST-segment depression ≥ 1 mm or upsloping ≥ 1.5 mm at 80 ms after the J point was considered positive. Failure to achieve 85% of maximal predicted heart rate or ischaemic ECG response during exercise was followed by conversion to an adenosine stress test **Angiographic definition of significant CAD**: N/S **Multivariate analysis**: Cox proportional hazards regression model **Outcome measures**: Cardiac mortality, non-fatal MI, PTCA later than 60 days following SPECT, CABG later than 60 days following SPECT
Shirai, 2002[90] **Study design**: Prospective observational comparison **Method of recruitment**: Consecutive **Dates**: Jan. 1999–Oct. 2000 **Country**: Japan **Focus**: Incremental diagnostic value of worsening of regional wall motion, assessed by an automated algorithm in ECG-gated SPECT, over perfusion data for detection of multivessel CAD	**Inclusion criteria**: Patients with normal sinus rhythm and known or suspected CAD who received SPECT and CA **Exclusion criteria**: Previous CABG **Enrolled**: 201 **Analysed**: 201 **Age**: 63 ± 10 years **Gender**: M 153, W 48 **History of**: **MI** 63; **PTCA** 97; **CABG** Excluded	**SPECT**: **Tracer**: Tl-201. **Stress induced by**: Exercise (bicycle). **Image interpretation**: Visual (perfusion defects and LV regional wall motion). Quantitative (LV ejection fraction). **Equipment**: 2-detector gamma camera (Vertex, ADAC). **CA**: Yes. Method N/S **Interval between tests**: Within 10 weeks **Definition of positive SPECT test**: LV divided into 9 segments. Tl-201 uptake of each segment assessed with a 4-point scoring system (3 = normal, 0 = severely reduced or absent). Reversible perfusion defect: ≥ 1 grade improvement in any segment on the delayed images or reinjection images compared with the initial images. **Regional wall motion**: Regional wall motion graded as 3 = normal or hyperkinetic, 2 = mildly hypokinetic, 1 = severely hypokinetic, 0 = akinetic or dyskinetic. Worsening of wall motion: ≥ 1 grade worsening in any segment on initial images compared with rest images. Individual segments assigned to 3 coronary territories **Angiographic definition of significant CAD**: ≥ 70% narrowing of the internal diameter of the LAD, the LCX, the RCA or their major branches and ≥ 50% narrowing of the left main coronary artery. Multivessel disease: significant LMD or 3VD or 2VD **Outcome measures**: TPs, FPs, TNs, FNs, sensitivity, specificity, diagnostic accuracy

Attenuation-corrected SPECT

Study and methods	Participants	Test characteristics and outcome measures
Gallowitsch, 1998[91] **Study design**: Prospective observational comparison **Method of recruitment**: Consecutive **Dates**: N/S **Country**: Austria **Focus**: Sensitivity and specificity of AC SPECT, impact on the extent and severity of perfusion abnormalities and comparison with CA	**Inclusion criteria**: Patients in whom CA was planned because of suspected CAD **Exclusion criteria**: LBBB **Enrolled**: All: 107 **Analysed**: 107 **Age**: All: 63.8 ± 9.5 (range 33–77) years **Gender**: All: M 69, W 38 **History of**: **MI** 42; **PTCA** 22; **CABG** 8	**SPECT**: **Tracer**: Tl-201. **Stress induced by**: Exercise (treadmill, 69); pharmacological (dipyridamole, 39). **Image interpretation**: Visual, quantitative. **Equipment**: Biplane high-resolution gamma camera (APEX SP-X , Cardia-L, Elscint). **CA**: Seldinger technique **Interval between tests**: 1–14 days **Definition of positive SPECT test**: Positivity and reversibility on the redistribution images. Semiquantitative analysis using polar maps for non-corrected and AC images. Segmental perfusion defects classified as moderate (50–75% of maximal counts), severe (25–50%) or complete (0–25%). Extent of ischaemia determined by number of segments affected out of 31 segments. Segments assigned to vascular territories **Angiographic definition of significant CAD**: ≥ 70% narrowing of lumen diameter **Outcome measures**: TPs, FPs, TNs, FNs, false negatives, sensitivity, specificity

LCX, left circumflex; LV, left ventricular; LVH, left ventricular hypertrophy; M, men; MET, metabolic equivalents; N/S, not stated; RBBB, right bundle branch block; RCA, right coronary artery; RVH, right ventricular hypertrophy; SD, standard deviation; SDS, summed difference score; SRS, summed rest score; SSS, summed stress score; W, women.

Appendix 8

Results of included studies of effectiveness

Diagnostic studies

Study	Definition of CAD (% stenosis)	Test	No. of patients	Sensitivity	Specificity	Accuracy	True positives	False positives	False negatives	True negatives
Beygui, 2000[22]	≥ 50	SPECT	179	0.63	0.77	0.70	48	24	28	79
		Stress ECG	179	0.51	0.62	0.58	33	43	32	71
Chae, 1993[23]	≥ 50	SPECT	243	0.71	0.65					
		Stress ECG	243	0.25	0.38	0.29	44	42	131	26
Daou, 2002[24]	≥ 50	SPECT	338	0.63	0.77	0.66	167	17	98	56
		Stress ECG	338	0.47	0.64	0.51	121	29	137	51
De, 2002[25]	≥ 70	SPECT	55	0.67	0.30	0.39	8	26	4	11
		Stress ECG	55	0.44	0.73	0.65	15	23	19	62
Gentile, 2001[26]	≥ 60	SPECT	132	0.93	0.54	0.86	101	11	7	13
		Stress ECG	132	0.85	0.58	0.80	92	10	16	14
Hamasaki, 1996[27]	≥ 60	SPECT	125	0.78	0.78	0.78	37	17	10	61
		Stress ECG	125	0.83	0.65	0.72	39	27	8	51
Hambye, 1996[28]	≥ 50	SPECT	128	0.82	0.76					
		Stress ECG	128							
	≥ 70	SPECT	128							
		Stress ECG	128							
Hecht, 1990[29]	≥ 50	All patients:								
		SPECT	116	0.92	0.76	0.85	61	12	5	39
		Stress ECG	116	0.51	0.65	0.57	35	17	33	31
		With complete revascularisation:								
		SPECT	89	0.93	0.77	0.88	54	7	4	24
		Stress ECG	89	0.52	0.65	0.57	27	13	25	24
		With incomplete revascularisation:								
		SPECT	27	0.93	0.77	0.85	13	3	1	10
		Stress ECG	27	0.5	0.61	0.56	7	5	7	8
Huang, 1992[30]	≥ 50	SPECT	179	0.87	0.8	0.86	134	5	20	20
		Stress ECG	179	0.5	0.76	0.54	77	6	77	19
Kajinami, 1995[31]	≥ 75	SPECT	251	0.82	0.59	0.71	110	48	23	70
		Stress ECG	251	0.74	0.75	0.74	98	29	35	89
Karlsson, 1995[32]	≥ 50	SPECT	170	0.68	0.65					
		Stress ECG	170	0.82	0.63					

continued

Study	Definition of CAD (% stenosis)	Test	No. of patients	Sensitivity	Specificity	Accuracy	True positives	False positives	False negatives	True negatives
Khattar, 1998[33]	≥ 50	SPECT	100	0.68	0.72	0.7	41	11	19	29
		Stress ECG	100	0.7	0.41	0.57	39	26	17	18
Koskinen, 1987[34]	≥ 50	SPECT	100	0.9	0.1	0.82	81	9	9	1
		Stress ECG	100	0.63	0.8	0.65	57	2	33	8
Lind, 1990[35]	>50	SPECT	157	0.91	0.96	0.94	72	3	7	75
		Stress ECG	46	0.43		0.43	20	0	26	0
Mairesse, 1994[36]	>50	SPECT	129	0.76	0.65	0.72	63	16	20	30
		Stress ECG	129	0.42	0.83	0.57	35	8	48	38
McClellan, 1996[37]	≥ 50	SPECT	303	0.7	0.57	0.69	193	12	82	16
		Stress ECG								
Michaelides, 1999[38]	≥ 70 (≥ 50 for LMD)	SPECT	245	0.93	0.82	0.91	196	6	15	28
		Stress ECG	245	0.66	0.88	0.69	139	4	72	30
Nallamothu, 1995[39]	≥ 50	SPECT	321	0.8	0.68	0.79	216	17	51	37
		Stress ECG	321	0.46	0.59	0.49	114	30	133	44
Psirropoulos, 2002[40]	≥ 50 LMD	SPECT	606	0.93	0.44	0.73	338	136	26	106
		Stress ECG	606	0.92	0.43	0.73	335	138	28	105
Santana-Boado, 1998[18]	>50	All patients:								
		SPECT	163	0.91	0.9	0.91	88	7	8	60
		Stress ECG	163	0.67	0.71	0.69	54	24	27	58
		Men:								
		SPECT	100	0.93	0.88	0.92	70	3	5	22
		Stress ECG	100	0.69	0.8	0.71	55	4	25	16
		Women:								
		SPECT	63	0.86	0.9	0.89	18	4	3	38
		Stress ECG	63	0.61	0.67	0.65	11	15	7	30
Vaduganathan, 1996[41]	≥ 50	SPECT								
		Overall performance with:								
(LBBB – no stress ECG performed)		Exercise		0.91	0.2	0.64	43	24	4	6
		Adenosine		0.89	0.67	0.84	34	4	4	8
		Dobutamine		0.92	0.5	0.89	23	1	2	1
		LAD:								
		Exercise		0.88	0.36	0.58	29	28	4	16
		Adenosine		0.79	0.81	0.8	23	4	6	17

Prognostic studies

Study	Results
Amanullah, 1998[42]	**Multivariate analysis**: Independent predictors of early revascularisation: Variable χ^2 Reversible perfusion defects 43 Extent of CAD by angiography 23 Angina during exercise 10 Rate of early revascularisation: 48% in patients with reversible perfusion defects, angina during exercise and MVD; 12% in patients with SVD and no exercise-induced angina or reversible defects ($p < 0.01$)
Amanullah, 1999[43]	**Cox multivariate analysis** Independent predictors of outcome χ^2 SPECT score 6 ($p = 0.02$) Cardiac event rate at 30 months: 30% in the high-risk group (SPECT score 5–7); 19% in the medium or intermediate risk group (SPECT score 2–4); 7% in the low-risk group (SPECT score 0–1) (RR = 4.6, 95% CI = 1.2 to 5.8; $p = 0.01$)
Ben-Gal, 2001[44]	**Multivariate analysis**: Logistic regression models were fitted to the data to predict the occurrence of cardiac events. Abnormal thallium SPECT scan identified as the only independent predictor of adverse cardiac events (OR 32.3, 95% CI 3.7 to 279, $p = 0.0016$)
Berman, 1995[45]	**Multivariate analysis**: No SPECT provided incremental prognostic value in all patient subgroups analysed. In patients with an interpretable ExECG and a low post-ETT likelihood of CAD, those with a normal scan had a significantly lower hard event rate than those with an abnormal scan ($\chi^2 = 7$, $p = 0.007$). Even greater stratification occurred in the patients with an intermediate to high post-ETT likelihood of CAD ($\chi^2 = 18$, $p < 0.001$). In patients with uninterpretable ExECG responses an abnormal scan and a low pre-ETT likelihood of CAD significantly stratified patients with respect to total events ($\chi^2 = 7$, $p = 0.01$). A normal or equivocal scan significantly stratified patients with an intermediate to high pre-ETT likelihood of CAD ($\chi^2 = 15$, $p < 0.001$)
Candell-Riera, 1998[46]	**Cox multivariate analysis**: Neither ST-segment depression >1 mm during ExECG nor MVD on CA were predictive of worse prognosis. Presence of severe reversible SPECT defects predictive of cardiac events only when the need for revascularisation included as a complication ($p < 0.01$)
Chatziioannou, 1999[47]	**Cox multivariate analysis** Indicator of risk of adverse cardiac events — Global χ^2 — RR — 95% CI — p Abnormal SPECT — 13.2 — 8 — 3 to 23 — < 0.001 ExECG — 0.05 — 1 — 0.4 to 3 — 0.8 ExECG + Duke treadmill score — 0.17 — (no significant improvement over ExECG alone) ExECG + Duke treadmill score + SPECT — 13.5 — (no significant improvement over SPECT alone)

continued

Study	Results				
	Patients with known CAD:	Global χ^2	RR	95% CI	p
	Abnormal SPECT	5	4	1 to 14	0.02
	ExECG	0.2	0.8	0.2 to 2.3	0.6
	ExECG + Duke treadmill score	0.8	(no significant improvement over ExECG alone)		
	ExECG + Duke treadmill score + SPECT	5.4	(no significant improvement over SPECT alone)		
Chiamvimonvat, 2001[48]	**Multivariate analysis**:				
	Prediction of cardiac events with a multivariate logistic regression model with clinical, SPECT and CA variables				
		OR	95% CI	p	
	Presence of scintigraphic reversibility	5.04	2.01 to 12.66	0.0006	
	Presence of multivessel stenoses = 70%	2.64	1.34 to 5.21	0.003	
	Incremental prognostic power (depicted by global χ^2) of CA and SPECT variables over clinical model in predicting all cardiac events after MI:				
		χ^2	p		
	1. Clinical variable	3.3			
	2. Clinical + CA variables	14.5	<0.05 compared with 1		
	3. Clinical + SPECT variables	20.5	<0.05 compared with 2		
	4. Clinical + CA + SPECT variables	29.4	<0.05 compared with 3		
Diaz, 2001[49]	**Cox multivariate analysis**:				
	Nuclear and exercise predictors of risk of death after adjustment for potential confounders including ECG findings of Q waves:				
	Variable	Adjusted HR	95% CI	p	
	Intermediate-risk nuclear scan	1.50	1.28 to 1.76	<0.0001	
	High-risk nuclear scan	2.13	1.76 to 2.56	<0.0001	
	Poor or fair fitness	2.34	2.00 to 2.76	<0.0001	
	Abnormal heart rate recovery	1.60	1.37 to 1.87	<0.0001	
Gibbons, 1999[50]	**Cox multivariate analysis**:				
	Variables demonstrating significant ($p < 0.01$) independent association with time to cardiac death:				
	Variable	χ^2	p	OR	95% CI
	Near normal SPECT scan	14.9	0.0001	9.3	3.0 to 28.7
	Cardiac enlargement	7.3	0.007	4.3	1.5 to 12.2
	No association existed between treadmill score and cardiac mortality				
Giri, 2002[51]	**Cox multivariate analysis**:				
	Predicting variables	Cardiac death		Cardiac death or MI	
		χ^2	p	χ^2	p
	Diabetes	0.37	0.55	2.4	0.13
	Clinical risk	52.2	0.00001	16.1	0.0001
	Number of ischaemic SPECT defects	39.2	0.00001	40.9	0.00001
	Number of fixed SPECT defects	54.6	0.00001	30.8	0.00001

continued

<table>
<tr><th>Study</th><th>Results</th></tr>
<tr><td>Groutars, 2000[52]</td><td>All 4 cardiac events occurred in patients with an intermediate-to-high pretest likelihood of CAD (83.3–100%) and negative or non-diagnostic exercise ECG results

Multivariate analysis: No</td></tr>
<tr><td>Hachamovitch, 1996[53]</td><td>Cox multivariate analysis:
Results of determination of incremental prognostic value in men and women for the 3 models tested:
<table>
<tr><th></th><th colspan="2">χ^2</th></tr>
<tr><th></th><th>Men</th><th>Women</th></tr>
<tr><td>Clinical variables</td><td>56</td><td>48</td></tr>
<tr><td>Clinical + exercise variables</td><td>75</td><td>75</td></tr>
<tr><td>Clinical + exercise + SPECT variables</td><td>90*</td><td>120*</td></tr>
</table>
* $p < 0.0001$ compared with clinical + exercise

The areas under the ROC curves were compared for predicting events using the summed stress score. The area under the curve in women (0.84 ± 0.03) was significantly greater than that for men (0.71 ± 0.03, $p < 0.0005$ versus women), demonstrating that SPECT is better able to identify women at high risk of future events than men independently of baseline event rates, diagnostic thresholds or selection bias

SPECT also risk stratified women more effectively than men (OR for an event with abnormal versus normal scan results: men 4.4, women 22.8, Mantel–Haenszel OR 6.8, 95% CI 4.7 to 9.7, $\chi^2 = 109$, $p < 0.0001$). This significant difference was present in all prescan likelihood categories, demonstrating that this effectiveness was independent of underlying patient characteristics and ExECG test results [Mantel–Haenszel OR 5.1, 95% CI 2.2 to 11.9 for low (<0.15) prescan likelihood of CAD; OR 8.0, 95% CI 4.2 to 15.4 for intermediate (0.15–0.85) prescan likelihood of CAD; OR 3.6, 95% CI 1.9 to 6.9 for high (>0.85) prescan likelihood of CAD]</td></tr>
<tr><td>Hachamovitch, 1998[54]</td><td>Cox multivariate analysis:
The Cox proportional hazards model was applied to 3 models with cardiac death and MI as separate end-points. Significant information was contained in the model containing clinical, historical and exercise data and the model containing SPECT variables alone. Significant increases in global χ^2 ($p < 0.00001$) occurred after adjustment for the SPECT data for prescan information, including the type of stress performed. Therefore, after consideration of all prescan information, SPECT provided statistical incremental prognostic value toward the prediction of MI and cardiac death</td></tr>
<tr><td>Hachamovitch, 2002[55]</td><td>Cox multivariate analysis:
A statistically significant increase in the global χ^2 of the model after the addition of nuclear variables defined incremental prognostic value.

Prediction of hard events:
<table>
<tr><th></th><th colspan="2">χ^2</th></tr>
<tr><th>Variable</th><th>Model using pre-SPECT data</th><th>Model with addition of SPECT data</th></tr>
<tr><td>Men</td><td>16</td><td>47*</td></tr>
<tr><td>Women</td><td>20</td><td>45*</td></tr>
<tr><td>Prior history of CAD</td><td>7</td><td>20*</td></tr>
<tr><td>No prior history of CAD</td><td>20</td><td>76*</td></tr>
</table>
* $p < 0.001$</td></tr>
</table>

continued

Study	Results
	Multivariable survival analysis revealed that after adjusting for clinical and historical information (post-ExECG likelihood of CAD, history of prior MI; global $\chi^2 = 52$, $p < 0.001$), the addition of the most predictive nuclear variable, summed stress score, additionally increased the global χ^2 to 85 ($p < 0.001$). Even after adjusting for pre-SPECT data, SSS was a significant predictor of adverse events in men, women, and patients with and without history of prior CAD. Risk-adjusted survival curves generated from the initial model demonstrated that even after adjusting for pre-SPECT data, a significant ($p < 0.001$) difference was present with respect to event-free survival between the normal SPECT patients and the patients with mildly, and moderately to severely, abnormal SPECT
Ho, 1999[56]	**Multivariate analysis**: No **Univariate analysis**: None of the variables was significantly associated with overall mortality. Both SSS ($p = 0.106$) and SRS ($p = 0.078$) showed insignificant trends. SSS demonstrated a significant association ($p = 0.047$) with the end-point cardiac death or MI. The Duke score was predictive of the combination end-point that included hard and soft cardiac events. All 3 variables were also analysed and found to be strongly associated with early PTCA/CABG
Iskandrian, 1993[57]	**Cox multivariate analysis**: Predictors of events: Variable — χ^2 Gender — 5.1 Exercise work load — 3.1 Extent of CAD and ejection fraction — 14.8 Extent of total perfusion abnormality, extent of ischaemic abnormality and LV dilation — 22.7 Independent and incremental prognostic power of diagnostic procedures: χ^2 Gender + exercise work load — 7.4 Gender + exercise + CA — 25 — $p < 0.01$ compared with gender + exercise Gender + exercise + SPECT — 33.5 — $p < 0.01$ compared with gender + exercise + CA Gender + exercise + SPECT + CA — 33.7 — p: NS compared with gender + exercise + SPECT
Iskandrian, 1994[58]	**Multivariate analysis**: Of the SPECT variables, the extent of perfusion abnormality was the single most important predictor of prognosis by multivariate analysis ($\chi^2 = 29$). The extent of CAD by CA was also prognostically important ($\chi^2 = 27$, p: NS compared with SPECT). The combination of CA and SPECT data improved the χ^2 to 37 ($p < 0.05$). The TES provided no incremental prognostic value to the CA or SPECT data. Therefore, SPECT provided prognostic information independent of and incremental to that provided by CA
Kamal, 1994[59]	**Cox multivariate analysis**: The size of the perfusion abnormality was the strongest predictor of events ($\chi^2 = 9$). There were 93 patients with a defect size of ≥ 15% and 84 patients with a defect size of <15%; cardiac events were observed in 13 patients in the former group Actuarial life-table analysis showed that the patients with perfusion abnormality <15% had better event-free survival than patients with perfusion defects ≥ 15% (Mantel–Cox statistic = 13, $p < 0.001$). The extent of CAD and ST-segment depression during the adenosine infusion did not separate patients with and without events

continued

Study	Results
Lauer, 1996[60]	**Cox multivariate analysis**: Independent predictors of referral for CA: Entire population: Abnormal SPECT: OR 16.05, 95% CI 12.43 to 20.73, χ^2 452, p <0.0001 Anginal chest pain: OR 5.42, 95% CI 4.08 to 7.20, χ^2 137, p <0.0001 Ventricular tachycardia: OR 4.95, 95% CI 3.01 to 13.17, χ^2 10, p 0.001 Hypotensive response: OR 2.21, 95% CI 1.18 to 4.15, χ^2 6, p 0.01 Patients with interpretable ECG ST-segment (n = 2696): Abnormal SPECT: OR 17.93, 95% CI 12.94 to 24.83, χ^2 301, p <0.0001 Ischaemic ST-segments: OR 4.75, 95% CI 3.46 to 6.52, χ^2 93, p <0.0001 Anginal chest pain: OR 4.98, 95% CI 3.48 to 7.14, χ^2 76, p <0.0001 Failure to reach target heart rate: OR 2.00, 95% CI 1.37 to 2.94, χ^2 13, p 0.0004 Age (10 years): OR 0.86, 95% CI 0.75 to 0.98, χ^2 5, p 0.03 Ventricular tachycardia: OR 5.36, 95% CI 1.13 to 25.47, χ^2 4, p 0.03 Gender was not independently predictive of referral for CA As in the whole population, abnormal SPECT was predictive of mortality in analyses confined to women (after adjusting for age and smoking status, RR = 2.34, p = 0.08). Gender was not significantly associated with cardiac death (for women RR = 0.77, 95% CI 0.31 to 1.87, p < 0.5) after adjusting for age, referral for CA and abnormal SPECT. Abnormal SPECT was predictive of fatal cardiac events (adjusted RR = 4.37, 95% CI 2.03 to 9.40, p = 0.0002)
Lauer, 1997[61]	**Cox multivariate analysis**: Predictors for referral to CA: Adjusted OR, 95% CI, p Presence of ischaemia revealed by SPECT: 4.66, 2.93 to 7.41, <0.0001 Anginal chest pain on treadmill: 4.62, 2.65 to 8.07, <0.0001 Presence of ischaemia revealed by SPECT: 50–64 years: 6.61, 2.96 to 14.70, <0.001 65–74 years: 3.46, 1.83 to 8.55, 0.0007 Anginal chest pain on treadmill: 50–64 years: 4.96, 1.85 to 13.10, 0.001 65–74 years: 3.96, 1.69 to 7.06, 0.0005 Patients aged >74 years: Anginal chest pain on treadmill: 7.26, 0.88 to 59.79, 0.07 After adjustment for the extent of ischaemia revealed by SPECT, clinical characteristics and exercise findings including functional capacity, increasing age remained associated with a lower rate of referral to CA (for 5-year increase in age, adjusted OR = 0.81, 95% CI 0.73 to 0.90, p < 0.0001) All-cause mortality rates were associated with the total number of abnormal segments on SPECT (for each 2 additional abnormal segments, age-adjusted RR = 1.41, 95% CI 1.06 to 1.88, p = 0.02), but not with referral to CA (RR = 0.73, 95% CI 0.36 to 1.50, p > 0.3). Cardiac death was also associated with the total number of abnormal segments on SPECT (for each 2 additional abnormal segments, RR = 1.60, 95% CI 1.03 to 2.48, p = 0.04), but it was not associated with referral to CA (RR = 1.14, 95% CI 0.40 to 3.30, p > 0.8).

continued

Study	Results
Machecourt, 1994[62] Note: a subset of these patients are reported on by Vanzetto, 1999[84]	**Cox multivariate analysis**: Cox multivariate stepwise analysis performed to compare the prognostic value of risk factors, clinical variables, ExECG and SPECT data (significant variable $F > 4$). The following were predictive of future cardiovascular death: Variable — *F* Male gender — 7 Previous MI — 6.9 Abnormal SPECT result — 9.6 Comparison with ExECG stress testing – variables predictive of future cardiovascular death: Variable Previous MI — 4.2 Submaximal exercise stress test — 8.6 Abnormal SPECT image — 6.5 Variables predictive of major cardiovascular events: Male gender — 4.1 Previous MI — 7.2 Submaximal exercise stress test — 10.5 Abnormal SPECT image — 8.3
Marie, 1995[63]	**Cox multivariate analysis**: Prediction of cardiac death: — RR — 95% CI — *p* Model – all variables used Radionuclide LV EF (%) — 0.93 — 0.90 to 0.97 — 0.00006 Age (years) — 1.07 — 1.01 to 1.14 — 0.032 Model – radionuclide LV EF excluded SPECT TDE (% of LV) — 1.06 — 1.03 to 1.08 — 0.0001 Age (years) — 1.07 — 1.01 to 1.14 — 0.026 Prediction of major ischaemic events (cardiac death or MI): Model – all variables used SPECT TDE (% of LV) — 1.05 — 1.02 to 1.07 — 0.00005 Age (years) — 1.07 — 1.02 to 1.13 — 0.008 Model – radionuclide LV EF excluded SPECT TDE (% of LV) — 1.05 — 1.02 to 1.07 — 0.00005 Age (years) — 1.07 — 1.02 to 1.13 — 0.008 Total extent of exercise SPECT defects provided marked incremental prognostic information with regard to clinical and exercise testing variables. This additional prognostic information was found both for the prediction of major events and cardiac death (both $p < 0.001$). When clinical, exercise testing and CA variables were included in the initial model, the total extent of SPECT defects also provided additional prognostic information, for both major events and cardiac death (both $p < 0.02$)

continued

Study	Results
Marwick, 1999[64] Note: This is considered to be the primary report for this study, which is also reported on by Shaw, 2000[79]	**Cox multivariate analysis**: Models for total and cardiac mortality Total mortality model: Pretest clinical risk index: RR 1.02, 95% CI 1.00 to 1.95, p 0.08; Women: RR 1.04, 95% CI 0.99 to 1.09, p 0.13; p for interaction 0.73 Extent of stress-induced defects: RR 1.06, 95% CI 1.02 to 1.10, p 0.003; Women: RR 1.15, 95% CI 1.09 to 1.21, p 0.0001; p for interaction 0.15 Extent of fixed defects: RR 0.98, 95% CI 0.94 to 1.01, p 0.40; Women: RR 0.98, 95% CI 0.91 to 1.06, p 0.73; p for interaction 0.71 ST-segment depression > 0.1 mV: RR 1.02, 95% CI 0.95 to 1.09, p 0.59; Women: RR 0.90, 95% CI 0.83 to 0.99, p 0.03; p for interaction 0.0002 Exercise time: RR 0.84, 95% CI 0.83 to 0.85, p 0.0001; Women: RR 0.80, 95% CI 0.78 to 0.81, p <0.0001; p for interaction 0.006 Cardiac mortality model: Pretest clinical risk index: RR 2.6, 95% CI 1.9 to 3.4, p <0.0001; Women: RR 1.9, 95% CI 1.3 to 2.8, p 0.001; p for interaction 0.20 Extent of stress-induced defects: RR 1.7, 95% CI 1.4 to 2.1, p <0.0001; Women: RR 1.2, 95% CI 0.8 to 1.7, p 0.38; p for interaction 0.04 Extent of fixed defects: RR 1.7, 95% CI 1.4 to 2.0, p <0.0001; Women: RR 2.8, 95% CI 2.0 to 3.8, p <0.001; p for interaction 0.01 ST-segment depression > 0.1 mV: RR 0.9, 95% CI 0.5 to 1.4, p 0.54; Women: RR 0.3, 95% CI 0.06 to 1.1, p 0.07; p for interaction 0.41 Exercise time: RR 0.84, 95% CI 0.83 to 0.85, p 0.0001; Women: RR 0.80, 95% CI 0.78 to 0.81, p <0.001; p for interaction 0.0001 RR = relative risk (95% CI) expressed per increment of 10 points of risk score, 1 vascular territory of stress-induced or fixed defects, 1 minute of exercise time, or the presence of ST depression >0.1 mV In multivariable models, total mortality was somewhat greater in men than in women (RR = 1.07, 95% CI 1.02 to 1,12; p = 0.003). The independent predictors of cardiac death differed by gender
Miller, 1998[65]	**Cox multivariate analysis**: Associations between clinical, exercise and SPECT: Total mortality: Shorter exercise duration: χ^2 10.7, HR 1.24, 95% CI 1.09 to 1.41, p 0.001 Number of abnormal SPECT segments after exercise: χ^2 7.3, HR 1.10, 95% CI 1.03 to 1.18, p 0.007 Increasing age: χ^2 3.9, HR 1.40, 95% CI 1.00 to 1.96, p 0.049 Initial cardiac death or non-fatal MI: Exercise angina score: χ^2 8.7, HR 1.69, 95% CI 1.19 to 2.40, p 0.003 Number of abnormal Tl-201 segments after exercise: χ^2 8.1, HR 1.12, 95% CI 1.04 to 1.20, p 0.004 Initial cardiac death, non-fatal MI or late PTCA/CABG: Chest pain class: χ^2 8.5, HR 1.35, 95% CI 1.10 to 1.65, p 0.004 Number of abnormal Tl-201 segments after exercise: χ^2 7.8, HR 1.10, 95% CI 1.03 to 1.18, p 0.005

continued

Study	Results
	Post hoc analysis: Associations between global stress and reversibility scores and outcome Total mortality: SSS: χ^2 13.2, HR 1.05, 95% CI 1.01 to 1.10, p <0.001 Shorter exercise duration: χ^2 6.3, HR 1.23, 95% CI 1.05 to 1.44, p 0.01 Increasing age: χ^2 5.2, HR 1.64, 95% CI 1.07 to 2.51, p 0.02 Cardiac death/MI: Exercise angina score: χ^2 9.7, HR 1.82, 95% CI 1.25 to 2.65, p 0.002 SSS: χ^2 4.9, HR 1.04, 95% CI 1.01 to 1.07, p 0.03 Cardiac death/MI/late PTCA/CABG: Chest pain class: χ^2 9.3, HR 1.42, 95% CI 1.13 to 1.79, p 0.002 SSS: χ^2 6.2, HR 1.04, 95% CI 1.01 to 1.07, p 0.01 Variables not shown were not significantly associated with outcome. HRs for all variables are expressed for 1 unit of change (e.g. 1 MET or 1 SPECT segment). For *post hoc* analysis the HR is for a decrease in SSS and increase in SRS The single variable independently predictive of all 3 outcome endpoints was the number of abnormal SPECT segments on the postexercise images
Miller, 2001[66]	**Cox multivariate analysis**: Associations between outcome and serial changes in clinical and SPECT variables Overall mortality: Worsening clinical status χ^2 8.5, p 0.004; Lower Duke score by ≥ 4 points <1, NS; Worsening category Duke score <1, NS; Worsening category SSS 10.7, 0.001; Worsening category SRS 5.1, 0.02; New coronary territory <1, NS Cardiac death or MI: Worsening clinical status 7.0, 0.008; Lower Duke score by ≥ 4 points <1, NS; Worsening category Duke score <1, NS; Worsening category SSS <1, NS; Worsening category SRS <1, NS; New coronary territory <1, NS Cardiac death or MI or late revascularisation: Worsening clinical status 7.5, 0.006; Lower Duke score by ≥ 4 points <1, NS; Worsening category Duke score <1, NS; Worsening category SSS 1.5, NS; Worsening category SRS <1, NS; New coronary territory 2.0, NS Worsening clinical status and worsening SPECT on follow-up testing identified higher risk patients. Changes in treadmill variables did not predict outcome

continued

Study	Results
Mishra, 1999[67]	**Multivariate analysis**: No Coronary revascularisation was performed in 1692 of 4572 patients (37%) in group 1 (CA) and in 123 of 2022 patients (6%) in group 2 (SPECT as the initial screening test), $p < 0.001$. In patients with intermediate pretest probability of CAD, selective CA after stress SPECT resulted in lower rates of normal angiograms (18 versus 33%), and a lower rate of coronary revascularisation (38% versus 51%). However, the pretest probability of CAD was higher in group 1 than group 2 (76 ± 27% versus 44 ± 30%, $p = 0.001$)
Nallamothu, 1995[68]	**Multivariate analysis**: No In group 1 (normal SPECT), 3% of patients subsequently underwent CA compared with 36% in group 2 (abnormal SPECT) ($p = 0.0001$). CA showed MVD in 13% of patients in group 1 and 55% of patients in group 2 ($p < 0.001$). The need for coronary revascularisation was significantly higher (30 versus 2%, $p < 0.0001$) and the event rate in medically treated patients was significantly higher (10 versus 0%, $p = 0.02$) in patients with abnormal than normal SPECT
Nallamothu, 1997[69]	**Cox multivariate analysis**: Variables — Global χ^2 — p 1. Clinical — 3 2. Clinical + stress — 5 — NS between 1 and 2 3. Clinical + stress + CA — 6 — NS between 2 and 3 4. Clinical + stress + CA + SPECT — 14 — 0.01 between 3 and 4 Multivariate Cox survival analysis of clinical factors, stress, angiographic variables and SPECT variables showed that the extent of the perfusion abnormality, multivessel perfusion abnormality and increased lung thallium uptake were important independent predictors of events. SPECT added incremental prognostic information to clinical, stress and angiographic variables. Clinical variables did not provide prognostic information and stress variables were also not useful in predicting outcome
O'Keefe, 1998[70]	**Cox multivariate analysis**: Multivariable predictors of referral for invasive management angiography were angina (RR 2.71), transient ischaemic dilation (RR 2.1), angina while on the treadmill (RR 1.8) and absence of previous MI (RR 0.64) The analysis showed referral for CA (invasive management) as the only independent predictor of non-fatal MI or death during follow-up ($p = 0.0001$). RR of infarction or death with invasive management compared with medical management was 11.6 (95% CI 4.8 to 27.9)

continued

Study	Results
Olmos, 1998[71]	**Multivariate analysis**: Clinical models and multivariate predictors of all cardiac events: OR / 95% CI / *p* Clinical + ExECG: Normal ExECG: 0.39 / 0.21 to 0.75 / 0.004 Smoking: 2.16 / 1.15 to 4.05 / 0.016 Max. exercise heart rate (bpm): 0.89 / 0.79 to 1.00 / 0.056 Clinical + ExECG + SPECT: Ischaemia by SPECT: 4.93 / 1.72 to 14.08 / 0.003 Normal ExECG: 0.47 / 0.24 to 0.93 / 0.030 Incremental value of multivariate models for prediction of cardiac events: AUC / SE / χ^2 / *p* All cardiac events: Clinical + ExECG: 0.68 / 0.04 / 18.04 / 0.0004 Clinical + ExECG + SPECT: 0.78 / 0.039 / 41.20 / <0.0001 Ischaemic events and cardiac death: Clinical + ExECG + SPECT: 0.70 / 0.06 / 8.86 / 0.03 Cardiac death: Clinical + ExECG + SPECT: 0.81 / 0.10 / 12.56 / 0.02 Clinical models and multivariate predictors of ischaemic events and/or cardiac death: Ischaemic events and cardiac death: OR / *p* / 95% CI Cardiac death: OR / *p* / 95% CI Significant models and predictors: Clinical + ExECG + SPECT: Abnormal SPECT: 2.76 / 0.03 / 1.08 to 7.07 Perfusion defect size by SPECT: 1.41 / 0.007 / 1.1 to 1.82 Ischaemia by SPECT was the main multivariate predictor of all cardiac events. However, perfusion defect size successfully separated the study population into low and high risk and was the sole multivariate predictor of cardiac death
Pancholy, 1994[72]	**Cox multivariate analysis**: The size of the perfusion abnormality and history of diabetes mellitus were independent predictors of cardiac death or non-fatal MI. Patients with a history of diabetes mellitus and a large perfusion abnormality (≥ 15% of the myocardium) had the worst event-free survival rate (Mantel–Cox statistic = 21, $p < 0.0001$)
Pancholy, 1995[73]	**Cox multivariate analysis**: Independent predictors of future cardiac events: χ^2 Large perfusion abnormality: 16 Age: 3

continued

Study	Results
	Incremental prognostic value of clinical, exercise, catheterisation, and SPECT variables: 1. Clinical — Global χ^2 4 2. Clinical + exercise — 5 3. Clinical + exercise + catheterisation — 10 — p <0.01 between 2 and 3 4. Clinical + exercise + catheterisation + SPECT — 19 — p <0.01 between 3 and 4 5. Clinical + exercise + SPECT — 19 — p NS between 4 and 5 Actuarial survival analysis revealed a significantly better event-free survival rate in patients with no or a small perfusion abnormality (<15% of myocardium) than in patients with a large abnormality (Mantel–Cox statistic = 16, p = 0.0001)
Parisi, 1998[74]	**Multivariate analysis**: In a multivariate model, a reversible defect on SPECT continued to predict significant risk (RR = 2.23, p = 0.04); among other factors, only diabetes (RR = 2.83) and current smoking (RR = 2.19) had a significant relationship with subsequent survival A positive exercise ECG failed to distinguish survival from non-survival in the patient cohort
Pattillo, 1996[75]	**Cox multivariate analysis**: 1. Clinical — χ^2 1 2. TES — 1 — p NS between 1 and 2 3. Gensini — 5 — p 0.05 between 2 and 3 4. SPECT — 15 — p 0.001 between 3 and 4 5. Clinical + TES — 1 6. Clinical + TES + Gensini — 5 — p 0.05 between 5 and 6 7. Clinical + TES + Gensini + SPECT — 16 — p 0.001 between 6 and 7 8. Clinical + TES + SPECT — 15 — p NS between 7 and 8 SPECT thallium imaging variables were significantly different between patients with and without events. The patients with events had more abnormal images, more reversible defects, larger defects and more left ventricular dilation than did patients without events
Schinkel, 2002[76]	**Cox multivariate analysis**: Predictors of cardiac death: Clinical characteristics: Age (per year) — Clinical data: HR 1.05, 95% CI 1.02 to 1.08; Model 1: HR 1.05, 95% CI 1.02 to 1.08; Model 2: HR 1.04, 95% CI 1.01 to 1.07 Diabetes mellitus — Clinical data: HR 2.00, 95% CI 1.1 to 3.4; Model 1: HR 1.9, 95% CI 1.1 to 3.2; Model 2: NS Smoking — Clinical data: HR 2.1, 95% CI 1.2 to 3.6; Model 1: HR 1.9, 95% CI 1.1 to 3.2; Model 2: HR 1.8, 95% CI 1.0 to 3.0 Congestive heart failure — Clinical data: HR 4.2, 95% CI 2.5 to 7.0; Model 1: HR 3.9, 95% CI 2.3 to 6.6; Model 2: HR 3.7, 95% CI 2.2 to 6.2

continued

Study	Results						
		Clinical data		Model 1		Model 2	
		HR	95% CI	HR	95% CI	HR	95% CI
	Stress test results:						
	Typical angina			NS		NS	
	ST-segment changes			NS		NS	
	Scan parameters:						
	Abnormal scan			8.2	3.2 to 21	Variable excluded	
	Reversible defect			Variable excluded		2.1	1.2 to 3.5
	Fixed defect			Variable excluded		2.2	1.2 to 4.0
	Model 1: presence of an abnormal scan added to the clinical characteristics, stress ECG data, and haemodynamic data. Model 2: presence of a fixed or reversible perfusion defect added separately						
	An abnormal scan was the strongest independent predictor of cardiac death. The presence of an abnormal scan (model 1) provided incremental prognostic value over clinical, stress ECG and haemodynamic data (log-likelihood, –324 to –305, $p < 0.0001$). Model 2 also offered incremental prognostic information compared with the clinical, stress ECG and haemodynamic parameters (log-likelihood, –324 to –313, $p < 0.0001$)						
Shaw, 1999[77]	Cardiac mortality: group 1 3.3%, group 2 2.8% ($p > 0.20$)						
	Non-fatal MI: group 1 3.0%, group 2 2.8% ($p > 0.20$)						
	Patient clinical risk	Group 1 (%)	Group 2 (%)				
	Death or MI:						
	Low	2.5	2.1				
	Intermediate	5	4.7				
	High	9	8.3				
	Revascularisation:						
	Low	16	14				
	Intermediate	27	13				
	High	30	16				
	Number of CAs performed: group 2, 34%						
Shaw, 1999[78]	**Cox multivariate analysis**:						
		χ^2	p	Information (%)		Change in p value	
	Multivariate predictors of catheterisation:						
	Global model	293.98	<0.00001				
	Probability of coronary disease	41.25	<0.00001				
	ST-segment depression	5.76	0.01				
	Reversible defect	196.45	<0.00001				
	Incremental value of stress MPI:						
	Clinical history	89.20	<0.00001	30.3			
	Exercise ECG	102.15	<0.00001	4.4		0.02	
	Nuclear	293.97	<0.00001	65.3		0.00001	

continued

Study	Results
	Group 1 patients underwent initial direct diagnostic CA. Group 2 patients underwent SPECT Primary end-point: occurrence of cardiac death. Secondary events: occurrence of coronary revascularisation procedures and cardiac hospitalisations (e.g. MIs) **Cox multivariate analysis**: Cox proportional hazard regression analysis, including assessment of clinical history and demonstrable evidence of ischaemic heart disease (as determined by the varying testing strategies) in standard, risk-adjusted methodologies
Shaw, 2000[79] Note: This study reports on the same population as Marwick, 1999,[64] and is considered to be part of that study	**Cox multivariate analysis**: Risk-adjusted Cox proportional hazards model predicting cardiac death: χ^2 p Clinical history risk-adjusted model: Number of vascular territories with ischaemia 38.6 <0.0001 Number of vascular territories with infarction 61.5 0.00001 Pretest clinical risk 65.3 <0.0001 Age risk–adjusted model: Number of vascular territories with ischaemia 45.4 <0.0001 Number of vascular territories with infarction 92.9 0.00001 Age (years) 40.5 <0.0001

	RR	95% CI	p	Death rate (%)
Relative risk of cardiac death for clinically high-risk patients compared with low-intermediate risk patients:	2.3	1.7 to 3.0	<0.00001	8
Ischaemic defects. Patients with:				
1-vessel involvement	2.3	1.5 to 3.4		2.8
2-vessel involvement	2.8	1.8 to 4.5		3.1
3-vessel involvement	5.2	2.9 to 9.5	<0.00001	5.6
Infarction. Patients with:				
1-vessel involvement	3.8	2.4 to 5.9		2.8
2- to 3-vessel involvement	5.3	3.1 to 5.9	<0.00001	6.9
Subset of patients who underwent exercise testing:				
Shorter exercise duration	0.83	0.75 to 0.95	0.0005	

Incremental value of perfusion imaging data – these values contributed 45.7% of new information above and beyond clinical history data ($p < 0.0001$). The percentages of new prognostic information varied by pretest clinical risk patient subsets. The percentages of new prognostic information contributed by the imaging data were 24% ($p < 0.0001$), 48% ($p < 0.00001$) and 21% ($p < 0.001$) in clinically low-, intermediate- and high-risk patients, respectively

continued

Study | **Results**

Stratmann, 1994[80]

Cox multivariate analysis:
Relative risks of clinical, exercise testing and MIBI variables for cardiac events:

	Model 1			Model 2		
	RR	95% CI	*p*	RR	95%CI	*p*
Abnormal scan	11.9	1.6 to 89.4	<0.05			
Reversible defect				2.9	1.2 to 7.0	<0.05
Fixed defect				1.4	0.6 to 3.3	
Ischaemic ST depression	2.2	0.9 to 5.0		2.0	0.8 to 4.6	
History of congestive heart failure	1.6	0.6 to 4.2		1.9	0.7 to 5.2	
History of old MI	1.2	0.5 to 2.8		1.3	0.6 to 3.2	
History of diabetes mellitus	1.5	0.6 to 4.1		1.6	0.6 to 4.2	

Model 1: scintigraphic variables included 'abnormal scan'
Model 2: scintigraphic variables included 'reversible defect' and 'fixed defect'; 'abnormal scan' excluded

Travin, 1995[81]

Cox multivariate analysis:
The number of ischaemic defects on SPECT was the only significant predictor of a cardiac event (χ^2 4.62, $p = 0.0317$). Previous acute MI was the only significant multivariate correlate of an event ($p = 0.0001$)

Underwood, 1999[82]

Outcomes

Hard events	Patients	Unstable angina	MI	Death	Any event
Stress ECG/CA	144	1	10	4	15
Stress ECG/MPI/CA	130	1	9	2	12
MPI/CA	48	0	3	5*	8
CA	75	0	9	4*	13
MPI users	190	1	18	8	27
MPI non-users	207	1	13	7	21

*Statistically significant difference ($p < 0.05$)

Soft events	Complications	Worse angina	CABG	PTCA	Other	Any event
Stress ECG/CA	3	2	11	8	1	25
Stress ECG/MPI/CA	1	1	2	10	2	16
MPI/CA	1	0	4	6	1	12
CA	3	1	14**	19**	2	39**
MPI users	3	1	11	27	2	44
MPI non-users	3	1	11	27	2	44

**Statistically significant more revascularisation procedures ($p < 0.001$)

continued

Study	Results
	Prognostic power (mean global χ^2) for the information available at the point of diagnosis. This differed between strategies and type of hospital, with the scintigraphic strategies and hospitals having significantly greater prognostic power: Stress ECG/CA: mean global $\chi^2 \pm$ SD = 20 ± 4.5 Stress ECG/MPI/CA: 25 ± 7.6 MPI/CA: 25 ± 0.2 CA: 9 ± 0.2; p < 0.0001 User hospitals: 22 ± 8.0 Non-user hospitals: 18 ± 6.8; p < 0.0001 MPI is the single most powerful predictor of prognosis and it has incremental value even when stress ECG or CA have already been performed
Vanzetto, 1999[83]	**Cox multivariate analysis**: Independent predictors of major events: age >60 years (p = 0.02); personal history of CAD (p = 0.04); presence of microalbuminuria (p = 0.001); inability to perform ExECG (p = 0.002); presence of an abnormal SPECT (p = 0.03); more than 2 abnormal segments on SPECT (p = 0.002) SPECT imaging was an independent predictor of future cardiovascular events. Especially the presence of a large defect, involving more than 2 myocardial segments, accurately identified higher risk patients. SPECT has an incremental prognostic value over clinical and biological variables, the presence of an abnormal scan and especially of more than 2 abnormal segments, being independent predictors of outcome
Vanzetto, 1999[84] Note: this study reports on a subset of the patient population reported on by Machecourt, 1994[62]	**Cox multivariate analysis**: Multivariate predictors of cardiac death and non-fatal MI: Cardiac deaths: Age >60 years: OR 1.78; 95% CI 1.02 to 3.11; p 0.05 Previous MI: 3.50; 2.06 to 5.96; 0.006 Positive ExECG: 0.83; 0.25 to 2.80; NS Strongly positive ExECG: 2.66; 1.23 to 5.76; 0.02 Non-diagnostic ExECG: 2.48; 1.31 to 4.69; 0.006 1 or 2 abnormal segments on SPECT: 2.20; 0.97 to 4.98; 0.08 ≥ 3 abnormal segments on SPECT: 4.83; 2.22 to 9.54; 0.001 MI: Presence of ≥ 1 risk factor: 2.50; 1.50 to 4.17; 0.03 Previous MI: 2.89; 1.78 to 4.69; 0.01 Positive ExECG: 1.14; 0.60 to 2.18; NS Strongly positive ExECG: 0.89; 0.43 to 1.85; NS Non-diagnostic ExECG: 0.93; 1.54 to 1.60; NS Maximum ST-segment depression ≥ 2: 1.34; 0.76 to 2.37; NS 1 or 2 abnormal segments on SPECT: 4.20; 1.93 to 9.14; 0.002 ≥ 3 abnormal segments on SPECT: 4.97; 2.15 to 11.49; 0.004

continued

Study	Results
	In patients who survived the first 3 years of follow-up, the relationships between the results of the tests and the occurrence of death was maintained for SPECT ($p = 0.01$) but not for ExECG
	Age ($p = 0.04$), ExECG ($p = 0.03$) and SPECT ($p = 0.003$) were independent predictors of overall mortality. SPECT and ExECG were independent predictors of cardiac death. SPECT was also predictive of future MI, whereas ExECG was not. The incremental prognostic value of SPECT over clinical and ExECG data for the prediction of cardiac events was maintained at long-term follow-up in patients with low to intermediate likelihood of CAD
	Additive prognostic value of SPECT over ExECG for prediction of major cardiac events: Negative ExECG: abnormal SPECT compared with normal SPECT, OR = 2.58, $p = 0.02$ Strongly positive ExECG: abnormal SPECT compared with normal SPECT, OR = 4.24, $p = 0.053$ Non-diagnostic ExECG : abnormal SPECT compared with normal SPECT, OR = 2.62, $p = 0.04$
	When performed after ExECG, SPECT accurately identified higher and lower risk patients, whatever the results of ExECG
Wagner, 1996[85]	**Multivariate analysis**: Relative risk of various parameters for cardiac events:

	χ^2	OR	95% CI
Baseline data:			
Age >60 years	NS	2.1	0.9 to 5.1
Gender, male	NS	1.4	0.4 to 5.7
Location of infarction, anterior MI	NS	1.5	0.6 to 3.5
Vessel disease, 2VD + 3VD	NS	1.6	0.7 to 3.8
LV ejection fraction, ≤45%	NS	1.6	0.2 to 2.1
TIMI classification,[138] 0–2	NS	1.3	0.3 to 2.0
Residual stenosis of infarct-related artery, >75%	NS	3.8	0.9 to 16.5
Bicycle ergometry:			
Maximal exercise stage, ≤75 W	NS	3.9	0.7 to 22.2
Systolic BP increase during exercise, ≤30 mmHg	NS	1.4	0.6 to 3.4
Downsloping ST-segment, ≥1 mm	NS	1.4	0.5 to 3.5
Angina pectoris	NS	0.9	0.3 to 2.7
Duration of exercise, ≤4 min	NS	0.4	0.2 to 1.0
Downsloping ST-segment ≥1 mm and angina pectoris	NS	2.3	1.0 to 5.4
Perfusion scintigraphy:			
Reversible defects	0.006	4.2	1.5 to 11.8
Fixed defects	NS	3.1	0.4 to 24.3

	Analysis of clinical and exercise variables demonstrated that reversible perfusion defects in SPECT were significantly associated with new cardiac events. ST depression was not prognostically significant for future cardiac events. None of the variables determined by CA correlated with future cardiac events in stable patients post-acute MI after thrombolysis

continued

Study	Results

	Model A			Model B		
	RR	95% CI	*p*	RR	95% CI	*p*
Abnormal stress SPECT scan	17.62	2.3 to 136.5	0.006	Variable excluded		
Reversible defect with SPECT scan	Variable excluded			5.11	1.5 to 17.36	0.0089
Extent of the defect (>4)	Variable excluded			3.27	1.2 to 9.22	0.0255
Typical angina	2.45	1.0 to 6.0	0.051			NS

Other parameters not statistically significant in both models: score of the defect (>7), age, gender, risk factor (clinical or laboratory), previous MI, stress double product, stress ECG downsloping ST, stress submaximal heart rate.

Zanco, 1995[86]

Model A: scintigraphic variables included abnormal SPECT. Model B: scintigraphic variables included reversible defect with SPECT, extension of the defect (>4) and extension severity score (>7); abnormal SPECT excluded. In model B, continuous variables evaluated in a dichotomous manner

RR calculated as the OR

Zellweger, 2002[87]

Cox multivariate analysis:

	p	RR	95% CI
Predictors of cardiac death:			
Age	0.017	1.03	1.01 to 1.06
Symptoms	0.002	2.58	1.41 to 4.69
Prior CABG	0.008	0.47	0.27 to 0.82
Non-reversible segments	0.0001	1.63	1.28 to 2.08
Predictors of cardiac death or non-fatal MI:			
Symptoms	0.0001	3.84	2.28 to 6.45
Prior CABG	0.005	0.56	0.38 to 0.84
Prescan likelihood of CAD	0.002	2.57	1.43 to 4.64
Summed difference score	0.0008	1.05	1.02 to 1.07
Non-reversible segments	0.0001	1.13	1.07 to 1.19

Incremental χ^2 values with respect to prescan and nuclear information:
All patients:

	χ^2 prescan	χ^2 prescan + nuclear	*p*
Cardiac death	50.7	76.9	<0.0001
Hard events	55.4	75.6	<0.0001

Patients who underwent exercise stress testing:

	χ^2 Duke	χ^2 Duke + nuclear	*p*
Cardiac death	14.2	19.3	<0.05
Hard events	15.7	16.5	NS

After adjustment for prescan information, the SPECT results (SSS) added incremental information with regard to cardiac death and hard events

continued

Study	Results			
Zerahn, 2000[88]	**Cox multivariate analysis**:			
	Relative risk of cardiac death:			
		RR	95% CI	*p*
	SPECT variables:			
	Fixed defects	2.55	1.43 to 4.55	0.0008
	Exercise test variables:			
	dPRP <2500 mmHg/minute	3.26	1.74 to 6.08	0.0001
	Clinical variables:			
	Age ≥ 60 years	1.69	1.04 to 3.76	0.034
	Ex-smokers and smokers	1.72	0.96 to 3.07	0.068
	LBBB	1.88	1.07 to 3.46	0.041
	Pharmacological variables:			
	Digoxin	1.79	1.04 to 3.10	0.036
	The major prognostic information of SPECT was the ability to detect patients with a definitely low risk. Patients with impaired circulatory response to exercise test and fixed perfusion defects were at a very high risk			
	There was a trend towards lower mortality in the group of patients with reversible defects who underwent revascularisation compared with those with reversible defects who did not ($p = 0.09$), whereas the impact of dPRP and fixed defects on survival was independent of revascularisation			

ECG-gated SPECT

Study	Results
Sharir, 1999[89]	**Cox multivariate analysis** Multivariate models for the prediction of cardiac events. Wald χ^2 / p Cardiac death: Type of stress 8.29 0.004 EF 9.0 0.004 ESV 5.11 0.024 Cardiac death or MI: EF 11.97 0.0005 ESV 4.6 0.03 Cardiac death, MI or late revascularisation: History of MI 8.76 0.003 Likelihood of CAD 11.36 0.0007 Type of stress 4.04 0.044 SSS 18.23 0.00002 SRS 11.97 0.0005 ESV 15.52 0.00008 The addition of EF and ESV (gated SPECT variables) to perfusion data resulted in a significant improvement in the global χ^2 in the prediction of cardiac death compared with the model that contained perfusion data only ($\chi^2 = 72.13$ versus 31.1, respectively; $p < 0.0001$)

Study	Definition of CAD (% stenosis)	Test	No. of patients	Sensitivity	Specificity	Accuracy	True positives	False positives	False negatives	True negatives
Shirai, 2002[90]	≥ 70 (≥ 50% for LMD)	Overall:								
		SPECT	603	0.46	0.96	0.77	110	14	127	352
		Gated SPECT	603	0.45	0.96	0.76	106	13	131	353
		Both	603	0.61	0.93	0.81	145	24	92	342
		LAD:								
		SPECT	201	0.55	0.93	0.74	55	7	45	94
		Gated SPECT	201	0.53	0.95	0.74	53	5	47	96
		Both	201	0.68	0.9	0.79	68	10	32	91
		RCA:								
		SPECT	201	0.51	0.96	0.81	34	6	32	129
		Gated SPECT	201	0.54	0.97	0.83	36	4	30	131
		Both	201	0.71	0.93	0.86	47	9	19	126
		LCX:								
		SPECT	201	0.3	0.99	0.75	21	1	50	129
		Gated SPECT	201	0.24	0.97	0.71	17	4	54	126
		Both	201	0.42	0.96	0.77	30	5	41	125

Attenuation-corrected SPECT

Study	Definition of CAD (% stenosis)	Test	No. of patients	Sensitivity	Specificity	Accuracy	True positives	False positives	False negatives	True negatives
Gallowitsch, 1998[91]	≥ 70%	All:								
		SPECT – NC	107	0.79	0.94		42	11	11	43
		SPECT – AC	107	0.8	0.91		50	5	3	49
		Men:								
		SPECT – NC	69	0.86	0.76		31	25	5	8
		SPECT – AC	69	0.94	0.91		34	30	2	3
		Women:								
		SPECT – NC	38	0.65	0.86		11	18	6	3
		SPECT – AC	38	0.94	0.9		16	19	1	2

AUC, area under the curve; EF, ejection fraction; ESV, end systolic volume; ETT, exercise treadmill test; NC, non-corrected; NS, not significant; SE, standard error; SRS, summed rest score; SSS, summed stress score; TDE, total exercise defect extent; TES, treadmill exercises score.

Appendix 9

Predictors of events by multivariate analysis

Study	Outcome	Independent predictors
Amanullah, 1998[42]	Early revascularisation	Reversible perfusion defects on SPECT scan; extent of CAD by angiography; angina during exercise
Amanullah, 1999[43]	Cardiac death or non-fatal MI	SPECT score
Ben-Gal, 2001[44]	Adverse cardiac events	Abnormal SPECT scan
Chatziioannou, 1999[47]	Cardiac death, non-fatal MI, revascularisation	Abnormal SPECT scan
Chiamvimonvat, 2001[48]	Cardiac death, non-fatal MI, unstable angina, revascularisation	Presence of scintigraphic reversibility on SPECT scan; presence of multivessel stenoses
Diaz, 2001[49]	All-cause mortality	Intermediate-risk SPECT scan; high-risk SPECT scan; poor or fair fitness; abnormal heart rate recovery
Gibbons, 1999[50]	Time to cardiac death	Near-normal SPECT scan; cardiac enlargement
Giri, 2002[51]	Death or MI; cardiac death	LV EF; ischaemic defects on SPECT scan; fixed defects on SPECT scan
Hachamovitch, 2002[55]	Cardiac events	SSS from SPECT scan
Iskandrian, 1993[57]	Cardiac events	Extent of total perfusion abnormality, extent of ischaemic abnormality and LV dilation on SPECT scan; gender; exercise work load; extent of CAD and EF
Iskandrian, 1994[58]	Cardiac death	Extent of perfusion abnormality on SPECT scan; extent of CAD by angiography
Kamal, 1994[59]	Cardiac events	Size of perfusion abnormality on SPECT scan
Lauer, 1996[60]	Referral for CA	Abnormal SPECT scan; anginal chest pain; ventricular tachycardia; hypotensive response
Lauer, 1997[61]	Referral for CA	Presence of any ischaemia revealed by SPECT; anginal chest pain on the treadmill
Machecourt, 1994[62]	Cardiac death or non-fatal MI	Abnormal SPECT scan; male gender; previous MI; submaximal ExECS
Marie, 1995[63]	Cardiac death or non-fatal MI	Total exercise defect extent on SPECT scan; age
Marwick, 1999[64]	Total mortality	Exercise capacity; number of territories with reversible defects on SPECT scan
Miller, 1998[65]	All-cause mortality	Shorter exercise duration; number of abnormal SPECT segments after exercise; increasing age
Miller, 2001[66]	All-cause mortality	Worsening clinical status; worsening category SSS; worsening category SRS from SPECT scan
Nallamothu, 1997[69]	Cardiac death or non-fatal MI	Extent of perfusion abnormality; multivessel perfusion abnormality on SPECT scan; increased lung thallium uptake on SPECT scan
O'Keefe, 1998[70]	Cardiac death or non-fatal MI	Referral for CA
Olmos, 1998[71]	Cardiac death or non-fatal MI	Abnormal SPECT scan

continued

Study	Outcome	Independent predictors
Pancholy, 1994[72]	Survival	History of diabetes mellitus; size of perfusion abnormality on SPECT scan
Pancholy, 1995[73]	Cardiac death or non-fatal MI	Large perfusion abnormality on SPECT scan; age
Parisi, 1998[74]	Survival	Reversible defect on SPECT scan; diabetes; current smoking
Pattillo, 1996[75]	Cardiac death or non-fatal MI	Size of perfusion defect on SPECT scan
Schinkel, 2002[76]	Cardiac death	Abnormal SPECT scan; age; diabetes mellitus; smoking; congestive heart failure
Shaw, 1999[78]	Catheterisation	Probability of CAD; ST-segment depression; reversible defect on SPECT scan
Shaw, 2000[79]	Cardiac death	Number of ischaemic myocardial perfusion territories on SPECT scan; number of infarcted myocardial perfusion territories on SPECT scan; pretest clinical risk
Stratmann, 1994[80]	Cardiac death or non-fatal MI	Abnormal SPECT scan;
Travin, 1995[81]	Cardiac death or non-fatal MI or hospitalisation for unstable angina	Number of SPECT ischaemic defects
Vanzetto, 1999[83]	Cardiac death or non-fatal MI	Age >60 years; personal history of CAD; presence of microalbuminaria; inability to perform exercise stress test; abnormal SPECT scan; >2 abnormal segments on SPECT scan
Vanzetto, 1999[84]	Overall mortality	Age; exercise ECG; abnormal SPECT scan
Vanzetto, 1999[84]	Cardiac death	≥ 3 abnormal segments on SPECT scan; previous MI; non-diagnostic EXECG; strongly positive ECG
Wagner, 1996[85]	Death, unstable angina, reinfarction, revascularisation	Reversible perfusion defects on SPECT scan
Zanco, 1995[86]	Cardiac death, non-fatal MI, unstable angina	Abnormal SPECT scan; typical angina
Zellweger, 2002[87]	Cardiac death or non-fatal MI	Symptoms; prior CABG; prescan likelihood of CAD; summed difference score from SPECT scan; non-reversible segments on SPECT scan
Zerahn, 2000[88]	Cardiac death	Fixed defects on SPECT scan; dPRP <2500 mmHg/minute; age ≥ 60 years; LBBB; digoxin

SRS, summed rest score; SSS, summed stress score.

Appendix 10

Summary of economic evaluations

Summary of included economic evaluations: patient-level analyses

Study and sample	Type of study	Eligibility/ patient group	Comparators	Outcome measures	Follow-up	Unit costs/ resource use	Results/authors' conclusions	Comments
Amanullah, 1997[108] USA *N* = 130	CEA Prospective cohort study Two scenarios considered: 1. whole patient cohort 2. patients with prescan likelihood of CAD ≥ 15% No sensitivity analysis	Women without a history of revascularisation or known valvular heart disease	1. CA 2. SPECT, CA if positive 3. SPECT, CA if SPECT summed stress score ≥ 8	Severe or extensive CAD on CA identified	Not stated but short	Medicare reimbursement for Minnesota costs in 1992 US$ Ex SPECT $700 unit costs Only costs included are SPECT and CA	All patients: Strat. Cost Effect 1 364,000 54 2 375,200 53 3 310,800 49 Prescan risk ≥ 15%: 1 333,200 52 2 346,400 51 3 284,800 47 Incremental cost-effectiveness All patients: 1 vs 2 1 dominant 1 vs 3 $10,640 Prescan risk ≥ 15%: 1 vs 2 1 dominant	Results presented in the study as average cost-effectiveness ratio. Data presented here are estimated incremental ratios

continued

Study and sample	Type of study	Eligibility/ patient group	Comparators	Outcome measures	Follow-up	Unit costs/ resource use	Results/authors' conclusions	Comments
Barnet, 2002[115] USA *N* = 876 – a substudy of the VANQUISH trial	Incremental cost-effectiveness analysis based on an RCT SA Discount rate (5%) Veterans administration unit cost Estimation of lifetime survival and costs	Diagnosed AMI Mean age 61 years Men 98% Previous MI 43% Diabetes 25%	1. CA 2. SPECT, CA if myocardial ischaemia	Survival Life-years Life-years discounted, rate not stated Costs discounted at 3%	Mean 23 months	Unit costs: Microcosting Hospital stay from Medicare 1997 $US Resource use data on cost drivers provided	Higher initial costs for CA (14733:19,256, $p < 0.001$); total for initial stay and follow-up care for CA = 41,893; SPECT = 39,707 ($p = 0.037$) Survival with SPECT strategy significantly higher than invasive strategy at 1 year. 1.86 life-years (conservative): 1.79 invasive at 2 years Bootstrapping results: 76.5% of bootstrap iterations had better outcomes and lower costs for SPECT strategy In 96% of replication SPECT preferred at a CE threshold of $50,000 per life year saved	Cost differences compared using non-parametric Wilcoxon rank sum test. Bootstrapping to assess uncertainty surrounding incremental cost per life-year gained

continued

Study and sample	Type of study	Eligibility/ patient group	Comparators	Outcome measures	Follow-up	Unit costs/ resource use	Results/authors' conclusions	Comments
Christian, 1994[106] (also Evans, 1996[135]) USA *N* = 411	CEA Prospective cohort study Data analysed using effectiveness were assessed using an MV analysis SA using a cross-validation MV comparing predictions based on 9 deciles with data from the tenth	Normal resting ECG, no previous MI	1. Clinical data 2. Clinical data plus ExECG 3. Clinical data plus ExECG plus SPECT for detection of 3VD or LMD	Disease reclassified based on findings of angiography Telephone follow-up for details of cardiac events	2.8 ± 1 year	Medicare reimbursement for Minnesota costs in 1992 US$ ExECG $89 ExSPECT $700 Resource use not reported	ExECG vs clinical data: ExECG led to an additional 24 correct classifications. Cost per additional correct reclassification $1524 SPECT vs ExECG: SPECT led to cost per additional correct reclassification $20,550 Cross-validation exercise greatly increased the incremental cost per correct classification, £14,3880 Conclusion: SPECT not cost-effective	Although the analysis of effectiveness was sophisticated, the estimation of cost-effectiveness was simple and only two costs were included. Limited nature of costs and benefits included mean important costs and benefits may have been missed. Effect of this on CEA is uncertain
Hachamovitch, 2002[55] USA *N* = 3058	CEA based on a retrospective observational study MV analysis to assess differences between strategies but simple patient-level analysis to assess cost-effectiveness	Patients with abnormalities on resting ECG; those undergoing early revascularisation or who were lost to follow-up were excluded. 3058 patients with normal resting ECGs were identified from 4572 consecutive patients who had undergone exercise SPECT between January 1991 and December 1993	1. Clinical and history only 2. ExECG and clinical data and history 3. ExSPECT plus strategy 2 above	Correct classification Hard event rate: 1. Cardiac death 2. Non-fatal MI 3. Incremental cost per correct classification 4. Incremental cost per hard event	Telephone interview 1.6 ± 0.5 years	Cost for SPECT of $840 was used to make it comparable to previous studies. No cost for ExECG stated Cost date: unsure Resource use not reported	Cost-effective except for low-risk patients. For intermediate to high post-ExECG risk $5417 per reclassification overall; $3816 per reclassification for women subgroup. Incremental cost per hard event rate: SPECT for patients $44,288* SPECT vs clinical for those at low risk of CAD $211,470 SPECT vs clinical for those at high risk $31,904 SPECT vs ExECG $25,134 * Reviewers' estimate	Appropriateness of CEA calculations inferred from the results of the MV analysis. Limited incremental analysis due to choice of outcome measures and exclusion of other costs notably the cost of ExECG. Data on incremental cost per hard event rate can be used to illustrate a number of scenarios

continued

Study and sample	Type of study	Eligibility/ patient group	Comparators	Outcome measures	Follow-up	Unit costs/ resource use	Results/authors' conclusions	Comments
Kosnik, 2001[111] USA *N* = 69	CMA Prospective cohort study No sensitivity analysis reported in the paper	Adults (mean age 56 years; 43% men) with abnormalities on resting ECG, suspected AMI and without cardiac complications (heart failure, arrhythmias, shock)	1. SPECT 2. Clinical data	Acute coronary events Change in management strategy from pre- and post-test assessment of risk	12 months	Cost-based decision support systems for 3 Detroit hospitals. Unit costs or resource use were not reported. Costs included all direct and indirect (overhead) costs US$; year to which costs relate not stated	Clinical judgement alone mean treatment scenario cost was $2096. Clinical judgement and SPECT mean treatment scenario cost was $1674. Adding the scan cost increases the cost to $2626 Inclusion of SPECT led to 29 changes to management, 27 of which were optimal	
Mattera, 1998[107] USA *N* = 313	CMA based on a retrospective observational study Three subgroups based on pretest risk of CAD: ≤20%, 21–70%, ≥71%	Patients included if they had normal resting ECG regardless of known history of CAD/MI. Univariate analysis used to test for the association between test results and outcomes	1. Stress ECG 2. SPECT	Diagnostic accuracy re hard cardiac events (cardiac death, non-fatal MI)	397 days (±151 days)	Connecticut Medicare fees in 1996 US$ Exercise ECG $120 SPECT $745	Stepwise approach reduced costs by 38% in patients with normal resting ECGs. Both ECG and SPECT associated with prediction of cardiac events	Both SPECT and planar imaging occurred. No distinction drawn between the two. Only costs included were SPECT and ExECG Effects not directly related to costs within the analysis

continued

Study and sample	Type of study	Eligibility/ patient group	Comparators	Outcome measures	Follow-up	Unit costs/ resource use	Results/authors' conclusions	Comments
Shaw, 1999[77] USA *N* = 11372	CMA based on matched cohorts of patients who had received either direct CA or SPECT CMA chosen as risk profiles were similar SA: changes in costs by 50% Comparison of patient level analysis with a multivariate linear regression to estimate costs	Patients with typical cardiac symptoms referred for invasive or non-invasive testing. Patients were excluded if tests for a predischarge evaluation, recent hospitalisation for unstable angina, MI or coronary revasculisation	1. ExSPECT, selective CA 2. Direct CA	Cardiac survival MI Admission for unstable angina	2.5 ± 1.5 years	Diagnostic costs + follow-up costs (including cardiac hospitalisations over 3 years Direct costs from microcost accounting system; Medicare hospital charges; hospital specific Medicare charges Costs in 1995 US$ Costs discounted at a 3% discount rate	Outcomes did not appear to differ between the two strategies Rates of revascularisation were higher for direct CA strategy Costs increased as pretest risk of CAD increased for both strategies Initial use of non-invasive stress imaging decreased overall cost of care over 3 years Use of SPECT was 30–40% less costly than direct CA Results of an SA were similar	Risk of disease may differ between the two cohorts. Effect is unclear as there were more people with no or SVD disease in the direct CA group – this would magnify cost savings. There were fewer with MVD in the direct CA group, which would tend to reduce differences

continued

Study and sample	Type of study	Eligibility/ patient group	Comparators	Outcome measures	Follow-up	Unit costs/ resource use	Results/authors' conclusions	Comments
Shaw, 1999[78] USA *N* = 4638	CMA based on matched cohorts of women who received either direct CA or SPECT CMA as no evidence of a statistically significant difference in cardiac deaths	Patients with typical cardiac symptoms referred for invasive or non-invasive testing. Patients were excluded if tests for a predischarge evaluation, recent hospitalisation for unstable angina, MI or coronary revasculisation	1. Ex SPECT, selective CA 2. Direct CA	Cardiac survival Revascular-isation	3 years	Diagnostic costs + follow-up costs (including cardiac hospitalisations) over 3 years Medicare hospital charges converted to costs using the hospitals cost to charge ratio; hospital costs in 1995 US$ Not reported if discounting performed	No evidence of a statistically significant difference in cardiac deaths Rates of revascularisation were higher for direct CA strategy Low risk: CA $2490 SPECT $1587 Medium risk: CA $2740 SPECT $1693 High risk: CA $3687 SPECT $2585 All differences statistically significant at the 5% level	
Stowers, 2000[113] USA *N* = 46	RCT with all patients receiving SPECT but clinicians blinded to results in conventional treatment arm Random block randomisation; unclear how performed CMA as no difference in outcome was assumed Differences in cost tested using Wilcoxon rank sum test	Patients presenting to emergency departments with chest pain <12 h and normal ECG, chest pain score >10, age >50 years and 3 high-risk factors Excluded pregnant women, prior MI, use of investigatory drugs <30 days	1. SPECT and clinical data, followed by ExECG if negative, CA if any test positive 2. Clinical data (conventional treatment)	In-hospital events	30 days	Clinical and in-hospital costs from bills/patient charges converted to costs using institutions cost/charge ratio Date to which costs relate is unclear	Patients in SPECT arm had median hospital cost $1843 (95% CI $431 to 6171) lower than conventional arm Mean costs were $4620 for SPECT and $9054 for conventional arm	Focus of cost analysis was on medians rather than means differences No SA reported

continued

Study and sample	Type of study	Eligibility/ patient group	Comparators	Outcome measures	Follow-up	Unit costs/ resource use	Results/authors' conclusions	Comments
Underwood, 1999 EMPIRE study[82] UK/Europe *N* = 396	Multicentre (UK, France, Germany, Italy), 2 hospitals from each country Controlled clinical study Hospitals were defined as regular or non-users of SPECT CMA using retrospective data Sensitivity and specificity based on published figures rather than study specific figures (rates were similar)	Patients presenting for CAD diagnosis	1. ExECG followed by CA 2. ExECG plus SPECT followed by CA 3. SPECT followed by CA 4. CA alone	Hard and soft cardiac events Secondary outcomes included prognostic power and the number of coronary angiograms	2 years	Cost of diagnosis (assuming out- not inpatient) plus the cost of management over 2 years (outpatient, inpatient, further investigations). Excludes inpatient stay costs Costs: Rest ECG £20 ExECG £70 SPECT £220 CA £1100 PTCA £3700 CABG £6900 Outpatient £70 Inpatient day £300 1996 UK costs, NHS perspective	Reports mean cost of diagnosis by strategy and centre. Scintigraphic strategies cheaper than non-scintigraphic Mean cost (£) of diagnosis ($p < 0.0001$) Strategy 1. 490 2. 409 3. 460 4. 1253 Mean 2 year costs also reported, £208, 207, 358, 463 Costs differ between centres who were users/non-users No significant difference in outcomes (final CAD diagnosis) Prognostic power of scintigraphic strategies and users greater than other strategies/non-users SPECT strategies (2 and 3) less costly and similar effectiveness	No SA, no discounting. The inclusion of discounting would be unlikely to change costs greatly

continued

Study and sample	Type of study	Eligibility/ patient group	Comparators	Outcome measures	Follow-up	Unit costs/ resource use	Results/authors' conclusions	Comments
Weissman, 1996[112] USA *N* = 50	CMA based on a prospective cohort study	Unexplained chest pain, non-diagnostic ECG, history, cardiac enzyme levels (when available) and non-diagnostic history and physical examination	1. Rest or stress SPECT and clinical data 2. Clinical data alone	Physician diagnostic confidence on a 1–5 scale Cardiac events	9–12 months	Comparison of pre-SPECT costs based on previous 6 months' patient data and costs following introduction of SPECT Year and currency not specified	No patients diagnosed as normal had an adverse event; 1 patient with an adverse event who would have been discharged without SPECT identified. SPECT imaging resulted in a cost saving of $786 per patient. Initially extra time in emergency room but earlier discharge	

Summary of included economic evaluations: models

Study and setting	Target population	Strategies	Type of study	Outcome measures	Source of data	Follow-up/ time horizon	Unit costs	Results/authors' conclusions	Comment
Dittus, 1987[114] USA	After uncomplicated MI	1. Medical management 2. ExECG, CABG surgical or medical treatment 3. ExECG with selective SPECT and CA. Aggressive CABG surgical or medical treatment 4. MPS and selective CA. CABG surgical or medical treatment 5. MPS and selective CA. Aggressive CABG surgical or medical treatment 6. CA in all. CABG surgical or medical treatment 7. CA in all. Aggressive CABG surgical or medical treatment	CEA Decision model results relative to baseline standard medical care SA on: 1. Proportions with one- and two-vessel or left main vessel or triple-vessel disease changed 2. Effectiveness of therapy 3. Changes to the cost of revascularisation	Cost per premature death avoided	Data on effectiveness: review of published literature plus experience of American College of Cardiology. Details not reported Unit costs: standard charges in US$. Year not reported Resource use: not reported	6 months Unclear if capital costs annuitised using a discount rate	ExECG $150 SPECT $750 CA $2500 CABG $15000 Non-fatal AMI $1500	Incremental cost per death avoided at 6 months compared with strategy 1: 2. $496,140 3. $217,000 4. $988,550 5. $245,850 6. $1,167,530 7. $241,510	The choice of outcome measure and the short follow-up make the results difficult to interpret in terms of outcomes

continued

Study and setting	Target population	Strategies	Type of study	Outcome measures	Source of data	Follow-up/ time horizon	Unit costs	Results/authors' conclusions	Comment
Garber, 1999[104] USA	Population with pretest risk of coronary artery disease of between 25% and 75% (intermediate risk)	1. ExECG 2. ExPlanar SPECT 3. ExSPECT 4. ExECHO 5. ExPET 6. CA	CEA based on a Markov model SA on population age and sex, prevalence of disease, cost of PET, risk and strategy following a non-diagnostic test, complications of angiography	QALYs Life-years	Data on effectiveness: Sensitivity and specificity based on a systematic review based around a MEDLINE search Utilities: Previous literature reporting results of TTO survey Unit costs: Medicare payment schedules reported in 1996 US$ Resource use: not explicitly stated	30 years 1996 $US 3% discount rate used for costs, life-years and QALYs	SPECT $475 ExECG $110 CA $1810 CABG for single and 2-vessel $32,390 CABG for 3-vessel and left main vessel $32,824 MI admission $7415 PTCA $11,685 Utility values not stated	Illustrative results for 55-year-old men and women and prevalence of 50% Men: CA vs SPECT $102,333 SPECT vs ExECG $40,316 Women: CA vs SPECT $118,200 SPECT vs ExECG $53,462	ICERs estimated using a stepwise approach. More costly, less effective alternative excluded

continued

Study and setting	Target population	Strategies	Type of study	Outcome measures	Source of data	Follow-up/ time horizon	Unit costs	Results/authors' conclusions	Comment
Jacklin, 2002 UK	Those at risk of CAD Cohort with pretest prevalence of CAD 10, 50 and 90%	1. ExECG; CA in positives or if non-diagnostic 2. SPECT; CA in positives or if non-diagnostic 3. ExECG, SPECT in positives or non-diagnostics; CA in positives 4. ExECG, CA in positives; SPECT in negatives or non-diagnostic, CA in positives 5. CA	Average CEA/QALY Decision model with QALY estimates attached as payoffs One-way SA range of parameter values in model. MV analysis parameter affecting CA at high risk of CAD	Correct diagnosis of disease QALY	Data on effectiveness: same data as used in Patterson, 1995[102] Utilities: unclear how assessed Unit costs: single UK centre, descriptions reasonably comprehensive Date of costs not stated Resource use: not provided	10 years Discounting not performed	SPECT £190 ExECG £7 (£7–55) CA £375 (£375–459) CABG £4732 PTCA £1140 Drug tx £1500 Weighted tx average (based on Tx data from Patterson 1995[102]) £3200 (£1500–7000) Complications £1500 (£500–5000)	Pretest CAD risk 10%, lowest av. cost per QALY was for strategy 3 Pretest CAD risk 50%, lowest av. cost per QALY was for strategy 1 Pretest CAD risk 10%, lowest av. cost per QALY was for strategy 5	Results presented as a series of average cost-effectiveness ratios. ICERs can be estimated from the data provided (Appendix 13). Stepwise ICERs show the gain from adopting more effective but costly strategies
Kim, 1999[109] USA	Diagnosis of CAD in women. 3 scenarios considered: 55-year-old women 1. with definite angina 2. probable angina 3. non-specific chest pain	1. Stress ECG 2. SPECT 3. Stress ECHO 4. CA 5. No test	CUA based on a Markov model. One way SA on all variables. Changes to time horizon	QALYs	Data on effectiveness: sensitivity and specificity based on a systematic review not described in the paper Utilities: previous literature reporting TTO results Unit costs: bottom-up costs from two organisations reported in 1996 US$ Resource use: not explicitly stated	35 years QALYs discounted at 5% rate Unclear if costs discounted	SPECT $1379 ExECG $282 CA $1672 ECHO $435 PTCA $4333 CABG $21,131 Medical management $863 AMI $7797 AMI follow-up treatment $863 QALYs Angiogram 0.0027 AMI 0.0190 PTCA 0.00822 CABG 0.0822	Separate cost data not reported CA dominates SPECT at high and intermediate risks Comparisons of SPECT vs ECG not presented	Sensitivity and specificity

continued

Study and setting	Target population	Strategies	Type of study	Outcome measures	Source of data	Follow-up/ time horizon	Unit costs	Results/authors' conclusions	Comment
Kuntz, 1999[99]	Those with chest pain and no MI history for three age cohorts, 40–49, 50–59 and 60–69 years, presenting symptoms	1. No testing; medical therapy as appropriate 2. CA alone 3. ExSPECT; CA if positive 4. ExECG; CA if positive 5. ExECHO; CA if positive Criterion for further work-up further split into strongly positive or positive	Diagnostic strategies assessed using a decision model Lifetime costs and QALYs estimated using a Markov model One- and two-way analysis on all variables Monte Carlo simulation incorporating parameter uncertainty Subgroup analysis	Estimated lifetime: QALYs Costs Incremental cost per QALY	Data on effectiveness: sensitivities/ specificities taken from recent meta-analyses. Other risks and long-term prognoses from the literature but method of assembly not reported Utilities based on a SG exercise of 211 patients Unit costs: Medicare allowable charges Costs in 1996 US$. Methods for any price adjustment reported Resources: not stated	Lifetime costs and QALYs Utilities No chest pain 0.87 (0.77–1) Mild chest pain 0.81 (0.68–1) Severe 0.67 (0.4–0.98) 3% discount rate for costs and life-years	ExECG $110 (77–143) Echo $262 (183–341) SPECT $574 (402–746) CA $4741 (3319–6163) PTCA $12,476 (8733–16,219) CABG $33,088 (23,162–43,014) MI $14,168 (9918–12,983) Annual medical management 160–3500 depending on severity	ICER results for men aged 50–59 year with mild chest pain (a) Typical angina: SPECT: exercise ECG = $38,000; SPECT: no testing = $27,600. (b) Atypical angina: SPECT: ECG = $54,900; SPECT: no testing = $33,300 Higher ICERs for women and younger men (lower risk of CAD)	ICERs estimated using a stepwise approach More costly, less effective alternative excluded, as were options with higher ICERs than preceding options (defined as weakly dominated)

continued

Study and setting	Target population	Strategies	Type of study	Outcome measures	Source of data	Follow-up/ time horizon	Unit costs	Results/authors' conclusions	Comment
Maddahi, 1997[100] USA	Those at risk of CAD at various pretest prevalence rates	1. Angiography, 2. PET, CA if positive 3. SPECT, if positive 4. ECG, PET if positive; if PET positive) 5. ECG, SPECT if positive, CA if SPECT positive 6. ECG, CA if positive	Decision analysis. Costs and effects not formally combined based on review/meta-analysis No SA	% correctly diagnosed Relative costs compared with angiography	Data on effectiveness: review of studies published between 1967 and 1996. Methods of the review are not well documented Unit costs: relative prices only. Price year and currency not stated Resource use: not reported	Unclear but likely to be short	Relative rates compared with CA only reported	For all risk categories the authors conclude that strategies (4) and (5) are the most cost-effective	The results are difficult to interpret as only relative costs are used Sensitivity and specificities for SPECT are higher than those estimated in Chapter 3 Sensitivity of ExECG is approximately the same but specificity is higher
Patterson, 1984[101] USA	Those at risk of CAD Prevalence of CAD varied between 0 and 100%	1. ExECG; CA in positives or if non-diagnostic 2. SPECT; CA in positives or if non-diagnostic 3. CA 4. ExECG, SPECT in positives; CA in positives	Average CEA/QALY Decision model with QALY estimates attached as pay-offs SA on risk of CA, risk following FNs; changes in QALYs, low cost CA or SPECT	Accurate diagnosis of CAD QALYs	Data on effectiveness: data from a single centre, existing literature. Unclear how data chosen Utilities: unclear Unit costs: Medicaid–Medicare for New York City in 1981 US$ Resource use: not provided	10 years Discounting not performed	SPECT $385 ExECG $175 CA $2825 Post-CAD diagnosis change in QALYs (over 10 years) = 2	The lowest average cost per QALY was for strategy 4 for a prevalence of CAD up to 80%. Thereafter, direct CA had the lowest cost per QALY. Results most sensitive to QALY estimates	Unclear from the data provided whether the results relate to planar imaging. ICERs are not readily estimable. Unclear if cost of diagnostic complications included productivity costs

continued

Study and setting	Target population	Strategies	Type of study	Outcome measures	Source of data	Follow-up/ time horizon	Unit costs	Results/authors' conclusion	Comment
Patterson 1995[102] USA	Those at risk of CAD Prevalence of CAD varied between 0 and 100% and presented for specific scenarios	1. ExECG; CA in positives or if non-diagnostic 2. SPECT; CA in positives or if non-diagnostic 3. PET; CA in positives or if non-diagnostic 4. CA	Average CEA per QALY Decision model with QALY estimates attached as payoffs SA low fees for tests, lower accuracy of PET, SPECT and ExECG, low risk of FNs, low benefit from treatment	QALYs	Data on effectiveness: unclear Utilities: unclear how obtained Unit costs: fee for tests Currency: US$, year is unclear. Resource use: not provided	10 years Discounting not performed	SPECT $1200 ExECG $330 PET $1800 CA $4800	For pretest CAD risk <0.7; stress PET had lowest average cost per QALY, followed by SPECT, ExECG and CA >70 Lowest average cost per QALY was CA	ICERs are not readily estimable. Unclear how the incremental value of a SPECT strategy can be defined
Radensky, 1997[110]	Those presenting to emergency rooms with normal or non-diagnostic ECG	1. Rest SPECT (scan) 2. Stratification on the basis of clinical and ECG variables (no scan)	Decision analysis SA on cost of SPECT Threshold of the specificity of no scan strategy; probabilistic analysis on cost distributions	Cost Model set-up with data that show that the scan strategy is more effective in terms of diagnosing those most at risk of cardiac events	Data on effectiveness: taken from a single study performed by the authors. Unit costs: Medicare fees converted into costs. Methods for adjusting for inflation reported Currency: 1994 US$ Resource use: not provided	Hospital stay	Not stated	Medicare mean costs: scan cost $1032 (17%) less than no scan. Median costs: scan 453 (10%) less costly SA showed specificity of no scan would need to be 65% for the two strategies to be equivalent. No scan should be less costly if >60% patients had an adverse event	Short-term follow-up and crude estimates of effectiveness limit applicability

continued

Study and setting	Target population	Strategies	Type of study	Outcome measures	Source of data	Follow-up/ time horizon	Unit costs	Results/authors' conclusions	Comment
Rumberger, 1999[103] USA	Those at risk of CAD presenting with normal resting ECG Prevalence of CAD varied between 0 and 100%	1. ExECG; CA in positives or if non-diagnostic 2. ExECHO; CA in positives or if non-diagnostic 3. SPECT; CA in positives or if non-diagnostic 4. EBCT; CA in positives or if non-diagnostic 5. CA alone	Average CEA	Correct diagnosis with CAD	Data on effectiveness: existing literature. Unclear how data chosen Unit costs: Medicare fees, Currency US$, year not stated Resource use: not provided	Follow-up not stated. Likely to be short	EBCT = $377 ExECG = $302 SPECT = $1244 CA = $2941 ECHO = $943	Lowest ACERs Low (10%) pretest risk of CAD: EBCT score 180 Medium (50%): EBCT score 37 High (100%): CA Of the interventions of interest (strategies 1, 3, 5) rank ordering of ACERs were: Low (10%), strategy 1, 3, 5, Medium (50%), strategy 1, 5, 3, High (100%), strategy 5, 1, 3	Results presented as a series of average cost-effectiveness ratios. ICERs can be estimated from the data provided (Appendix 13). Stepwise ICERs show the gain from adopting more effective but costly strategies. Incremental cost per true positive of strategy 3 above strategy 2 was always >$16,000
Shaw, 2003[105] USA	Hypothetical cohort of 1000 patients with suspected CAD 30% low risk (15% risk of CAD), 10% high risk (>80% risk of CAD), 60% intermediate risk	1. CA 2. Stress ECG 3. Stress ECHO 4. Stress SPECT 5. Contrast-enhanced ECHO Pathways validated by survey of those hospitals which had care pathways in a large group purchasing organisation in the USA	CEA based on a decision analysis SA: changes by 1 SD in the diagnostic accuracy of tests	Diagnostic accuracy Incremental cost per additional accurate diagnosis	Data on effectiveness: from a literature review described as systematic but with no details provided Unit costs: procedural cost database of the purchasing organisation adjusted by number of procedures per hospital. Currency: 1998 US$ Resource use: not stated	2 years Costs discounted at 5%	ExECHO = $188 SPECT = $330 CA = $851 ExECG = $122	Low risk: not reported in detail Intermediate risk: ACER reported as $267–355 for contrast-enhanced ECHO and stress SPECT, $1320 for ExECG High risk: not reported in detail SPECT and contrast-enhanced ECHO are dominant	From the data presented it is not possible to replicate any of the ACERs or ICERs reported, suggesting that the model is not sufficiently transparent. This limits applicability of the model

CEA, cost-effectiveness analysis; CMA, cost minimisation analysis; CUA, cost utility analysis; MV, multivariate; TTO, time trade-off.

Appendix 11

Estimation of incremental cost-effectiveness from data presented in the economic evaluation

Incremental cost per true positive (Jacklin, 2002)

Risk (%)		Stepwise incremental analysis						Pairwise comparisons				
		True +ves	**Cost (£)**	**Av CER**	**Incr +ves**	**Incr £**	**ICER**	**ECG, +ves SPECT**	**Ex ECG**	**SPECT**	**ECG, –ves SPECT**	**CA**
10	ECG, +ves SPECT	619	1488000	2404	619	1488000		NA				
	ExECG	724	1807000	2496	105	319000	3038	3038	NA			
	SPECT	836	3045000	3642	112	1238000	11054	7175	11054	NA		
	ECG, –ves SPECT	914	3248000	3554	78	203000	2603	5966	7584	2603	NA	
	CA	979	4050000	4137	65	802000	12338	7117	8796	7028	12338	NA
		True +ves	**Cost (£)**	**Av CER**	**Incr +ves**	**Incr £**	**ICER**	**Ex ECG**	**ECG, +ves SPECT**	**ECG, –ves SPECT**	**CA**	**SPECT**
50	ExECG	3622	2630000	726	3622	2630000		NA				
	ECG, +ves SPECT	3093	2944000	952	–529	314000	Dominated	Dominated	NA			
	ECG, –ves SPECT	4569	3966000	868	947	1336000	1411	1411	Not est	NA		
	CA	4893	4050000	828	324	84000	259	1117	Not est	259	NA	
	SPECT	4178	4222000	1011	–715	172000	Dominated	2863	Not est	352	298	NA
		True +ves	**Cost (£)**	**Av CER**	**Incr +ves**	**Incr £**	**ICER**	**Ex ECG**	**CA**	**ECG, +ves SPECT**	**ECG, –ves SPECT**	**SPECT**
90	ExECG	6520	3453000	530	6520	3453000		NA				
	CA	8807	4050000	460	2287	597000	261	261	NA			
	ECG, +ves SPECT	5568	4499000	808	–3239	449000	Dominated	Dominated	Dominated	NA		
	ECG, –ves SPECT	8224	4684000	570	–583	634000	Dominated	722	Dominated	70	NA	
	SPECT	7520	5399000	718	–1287	1349000	Dominated	1946	Dominated	461	Dominated	NA

Incremental cost correct diagnosis (Jacklin, 2002)

Risk (%)		Stepwise incremental analysis						Pairwise comparisons				
		True diag	**Cost (£)**	**Av CER**	**Incr diag**	**Incr £**	**ICER**	**ECG, +ves SPECT**	**Ex ECG**	**SPECT**	**ECG, –ves SPECT**	**CA**
10	ECG, +ves SPECT	9597	1488000	155	9597	1488000		NA				
	ExECG	9647	1807000	187	50	319000	6380	6380	NA			
	SPECT	9790	3045000	311	143	1238000	8657	8067	8657	NA		
	ECG, –ves SPECT	9836	3248000	330	46	203000	4413	7364	7624	4413	NA	
	CA	9785	4050000	414	–51	802000	Dominated	13628	16254	Dominated	Dominated	NA
		True diag	**Cost (£)**	**Av CER**	**Incr diag**	**Incr £**	**ICER**	**Ex ECG**	**ECG, +ves SPECT**	**ECG, –ves SPECT**	**CA**	**SPECT**
50	ExECG	8579	2630000	307	8579	2630000		NA				
	ECG, +ves SPECT	8081	2944000	364	–498	314000	Dominated	Dominated	NA			
	ECG, –ves SPECT	9526	3966000	416	947	1336000	1411	1411	Not est	NA		
	CA	9785	4050000	414	259	84000	324	1177	Not est	324	NA	
	SPECT	9153	4222000	461	–632	172000	Dominated	2774	Not est	Dominated	Dominated	NA
		True +ves	**Cost (£)**	**Av CER**	**Incr +ves**	**Incr £**	**ICER**	**Ex ECG**	**CA**	**ECG, +ves SPECT**	**ECG, –ves SPECT**	**SPECT**
90	ExECG	7512	3453000	460	6520	3453000		NA				
	CA	9785	4050000	414	2273	597000	263	183	NA			
	ECG, +ves SPECT	6565	4499000	685	–3220	449000	Dominated	Dominated	Not est	NA		
	ECG, –ves SPECT	9216	4684000	508	-569	634000	Dominated	457	Not est	Not est	NA	
	SPECT	8515	5399000	634	–1270	1349000	Dominated	975	Not est	Not est	Not est	NA

Incremental cost per QALY (Jacklin, 2002)

Risk (%)		Stepwise incremental analysis						Pairwise incremental analysis				
		QALYs	Cost (£)	Av CER	Incr QALYs	Incr £	ICER	ECG, +ves SPECT	Ex ECG	SPECT	ECG, –ves SPECT	CA
10	ECG, +ves SPECT	1867	3531000	1891	1867	3531000		NA				
	ExECG	2147	4188000	1951	280	657000	2346	2346	NA			
	SPECT	2513	5789000	2304	366	1601000	4374	3495	4374	NA		
	ECG, –ves SPECT	2727	6260000	2296	214	471000	2201	3173	3572	2201	NA	
	CA	2834	7245000	2556	107	985000	9206	3841	4450	4536	9206	NA
		QALYs	Cost (£)	Av CER	Incr QALYs	Incr £	ICER	ECG, +ves SPECT	Ex ECG	SPECT	ECG, –ves SPECT	CA
50	ECG, +ves SPECT	9444	13119000	1389	9444	13119000		NA				
	ExECG	11030	14474000	1312	1586	1355000	854	854	NA			
	SPECT	12741	17880000	1403	1711	3406000	1991	1444	1991	NA		
	ECG, –ves SPECT	13923	18911000	1358	1182	1031000	872	1293	1534	872	NA	
	CA	14852	20026000	1348	929	1115000	1200	1277	1453	1017	1200	NA
		QALYs	Cost (£)	Av CER	Incr QALYs	Incr £	ICER	ECG, +ves SPECT	Ex ECG	SPECT	ECG, –ves SPECT	CA
90	ECG, +ves SPECT	17016	22708000	1335	17016	3453000		NA				
	ExECG	18911	24760000	1309	1895	2052000	1083	1083	NA			
	SPECT	22966	29971000	1305	4055	5211000	1285	1221	1285	NA		
	ECG, –ves SPECT	25118	31563000	1257	2152	1592000	740	1093	1096	740	NA	
	CA	26869	32807000	1221	1751	1244000	710	1025	1011	727	710	NA

Incremental cost per true positive (Rumberger and colleagues)[103]

Risk (%)		Stepwise incremental analysis						Pairwise incremental analysis							
		True +ves (%)	Cost (£)	Av CER	Incr +ves (%)	Incr £	ICER	EBCT 168	EBCT 80	EBCT 37	ECG	ECHO	SPECT	EBCT 0	CA
10	EBCT 168	70	1051	15014	70	1051		NA							
	EBCT 80	80	1264	15800	10	213	21300	21300	NA						
	EBCT 37	90	1512	16800	10	1299	24800	23050	24800	NA					
	ECG	70	1660	23714	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	NA				
	ECHO	90	1913	21256	Dominated	Dominated	Dominated	43100	64900	Dominated	12650	NA			
	SPECT	90	2411	26789	Dominated	Dominated	Dominated	68000	114700	Dominated	37550	Dominated	NA		
	EBCT 0	100	2470	24700	10	958	95800	47300	60300	95800	27000	55700	5900	NA	
	CA	100	3540	35400	Dominated	Dominated	Dominated	82967	113800	202800	62667	162700	112900	Dominated	NA
		True +ves (%)	Cost (£)	Av CER	Incr +ves (%)	Incr £	ICER	EBCT 168	EBCT 80	EBCT 37	ECG	ECHO	EBCT 0	SPECT	CA
20	EBCT 168	70	1264	9029	70	1264		NA							
	EBCT 80	85	1512	8894	15	248	8267	8267	NA						
	EBCT 37	90	1725	9583	5	1477	21300	11525	21300	NA					
	ECG	75	1802	12013	Dominated	Dominated	Dominated	53800	Dominated	Dominated	NA				
	ECHO	85	2161	12712	Dominated	Dominated	Dominated	29900	Dominated	Dominated	17950	NA			
	EBCT 0	95	2612	13747	5	887	88700	26960	55000	88700	20250	22550	NA		
	SPECT	90	2659	14772	Dominated	Dominated	Dominated	34875	114700	Dominated	28567	49800	Dominated	NA	
	CA	100	3540	17700	5	881	92800	37933	67600	90750	34760	45967	92800	44050	NA
		True +ves (%)	Cost (£)	Av CER	Incr +ves (%)	Incr £	ICER	EBCT 168	EBCT 80	ECG	EBCT 37	ECHO	EBCT 0	SPECT	CA
50	EBCT 168	72	1867	5186	72	1867		NA							
	EBCT 80	84	2222	5290	12	355	5917	5917	NA						
	ECG	72	2228	6189	Dominated	Dominated	Dominated	Dominated	Dominated	NA					
	EBCT 37	90	2435	5411	6	213	7100	6311	7100	2300	NA				
	ECHO	86	2835	6593	Dominated	Dominated	Dominated	13829	61300	8671	Dominated	NA			
	EBCT 0	96	3038	6329	6	603	20100	9758	13600	6750	20100	4060	NA		
	SPECT	90	3333	7407	Dominated	Dominated	Dominated	16289	37033	12278	Dominated	24900	Dominated	NA	
	CA	100	3540	7080	4	502	25100	11950	16475	9371	22100	10071	25100	4140	NA

continued

Risk (%)		Stepwise incremental analysis						Pairwise incremental analysis							
		True +ves (%)	Cost (£)	Av CER	Incr +ves (%)	Incr £	ICER	EBCT 168	ECG	EBCT 80	EBCT 37	ECHO	EBCT 0	CA	SPECT
70	EBCT 168	71	2293	4614	71	2293		NA							
	ECG	73	2476	4845	2	183	13071	13071	NA						
	EBCT 80	84	2683	4563	11	207	2688	4286	2688	NA					
	EBCT 37	90	2896	4597	6	213	5071	4534	3529	5071	NA				
	ECHO	86	3297	5477	Dominated	Dominated	Dominated	9562	9022	43857	Dominated	NA			
	EBCT 0	96	3321	4942	6	425	10119	5874	5248	7595	10119	343	NA		
	CA	100	3540	5057	4	219	7821	6143	5630	7652	9200	2480	7821	NA	
	SPECT	90	3759	5967	Dominated	Dominated	Dominated	11023	10782	25619	Dominated	16500	Dominated	Dominated	NA
		True +ves	Cost (£)	Av CER	Incr +ves (%)	Incr £	ICER	ECG	EBCT 168	EBCT 80	CA	EBCT 37	EBCT 0	ECHO	SPECT
100	ECG	0.73	2902	3975	73	2902		NA							
	EBCT 168	0.72	2931	4071	Dominated	Dominated	Dominated	Dominated	NA						
	EBCT 80	0.84	3357	3996	11	455	4136	4136	3550	NA					
	CA	1	3540	3540	16	609	1144	2363	2175	1144	NA				
	EBCT 37	0.9	3570	3967	Dominated	Dominated	Dominated	3929	3550	3550	Dominated	NA			
	EBCT 0	0.95	3748	3945	Dominated	Dominated	Dominated	3845	3552	3555	Dominated	3560	NA		
	ECHO	0.85	3971	4672	Dominated	Dominated	Dominated	8908	8000	61400	Dominated	Dominated	Dominated	NA	
	SPECT	0.91	4469	4911	Dominated	Dominated	Dominated	8706	8095	15886	Dominated	89900	Dominated	8300	NA

CER, cost-effectiveness ratio; AV, average; +ves, positives; –ves, negatives; Incr, increment; diag, diagnosis; est, estimated.

Appendix 12

The models

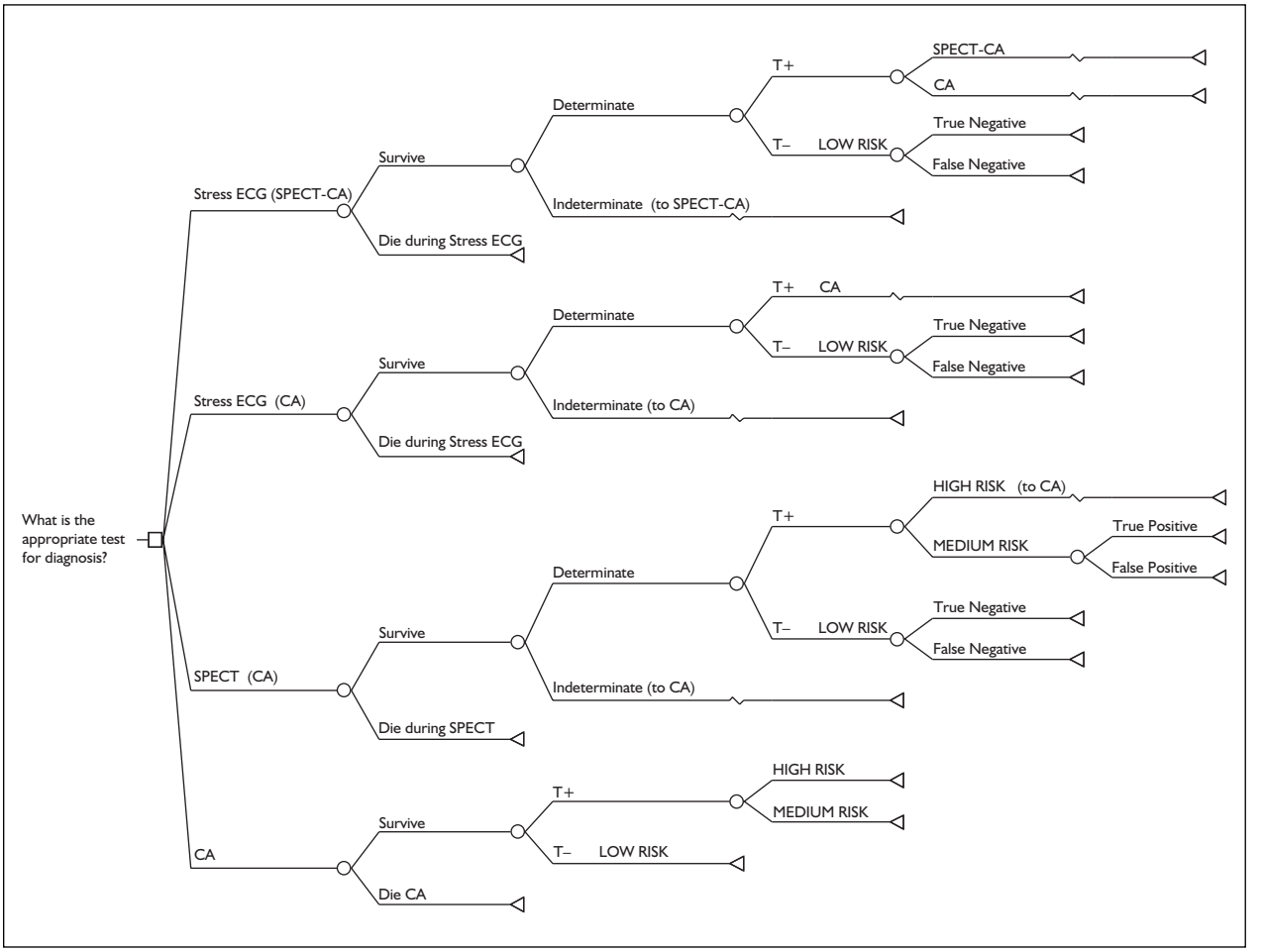

FIGURE 11 *Decision tree model (short-term diagnosis model)*

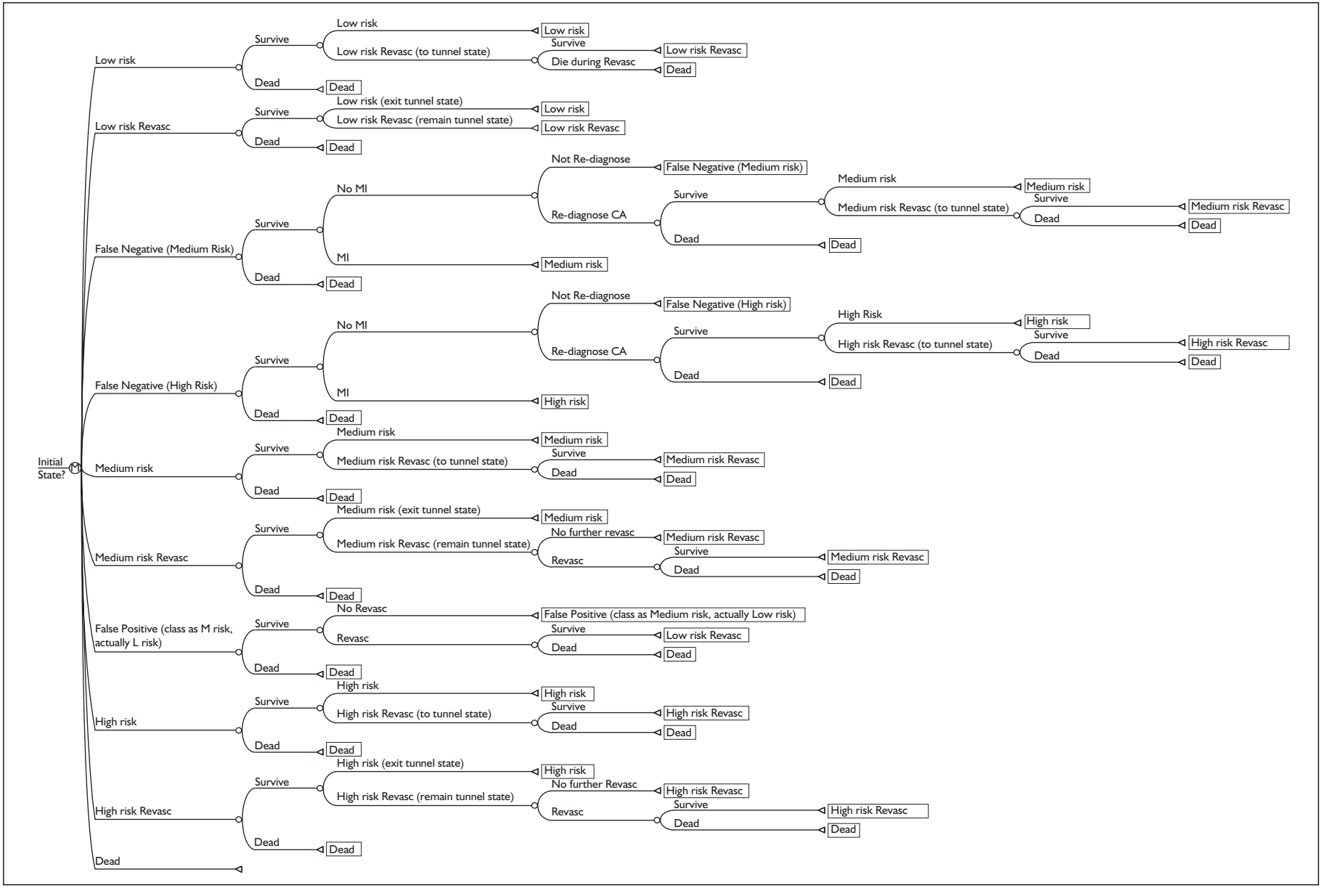

FIGURE 12 *Simple Markov model for prognosis and management of CAD*

Appendix 13

Life tables

Mortality general population (q_x)[a]

Age$_x$ (years)	Males	Females	Age$_x$ (years)	Males	Females
0	0.006159	0.005020	51	0.004260	0.002805
1	0.000468	0.000349	52	0.004626	0.003120
2	0.000284	0.000215	53	0.005160	0.003292
3	0.000185	0.000189	54	0.005655	0.003821
4	0.000156	0.000132	55	0.006306	0.004094
5	0.000113	0.000121	56	0.007209	0.004509
6	0.000145	0.000105	57	0.008034	0.005003
7	0.000127	0.000092	58	0.008703	0.005363
8	0.000112	0.000114	59	0.009744	0.006052
9	0.000104	0.000090	60	0.010872	0.006729
10	0.000128	0.000105	61	0.012025	0.007349
11	0.000123	0.000121	62	0.013157	0.007877
12	0.000163	0.000105	63	0.014426	0.008762
13	0.000170	0.000108	64	0.015749	0.009735
14	0.000222	0.000135	65	0.017873	0.010716
15	0.000237	0.000161	66	0.019823	0.011768
16	0.000371	0.000218	67	0.022256	0.013184
17	0.000587	0.000257	68	0.024278	0.014480
18	0.000774	0.000305	69	0.027316	0.016281
19	0.000785	0.000285	70	0.030222	0.018326
20	0.000779	0.000285	71	0.033944	0.020606
21	0.000809	0.000303	72	0.037650	0.022932
22	0.000805	0.000317	73	0.041882	0.025704
23	0.000833	0.000309	74	0.046243	0.028836
24	0.000902	0.000304	75	0.051249	0.031856
25	0.000866	0.000302	76	0.055974	0.035567
26	0.000854	0.000359	77	0.061938	0.039250
27	0.000952	0.000340	78	0.068115	0.043221
28	0.000914	0.000376	79	0.074030	0.047603
29	0.001029	0.000374	80	0.079333	0.052758
30	0.000979	0.000414	81	0.086789	0.059054
31	0.001049	0.000462	82	0.096967	0.066227
32	0.001077	0.000484	83	0.109904	0.075432
33	0.001121	0.000533	84	0.120204	0.084005
34	0.001176	0.000584	85	0.132078	0.094072
35	0.001200	0.000686	86	0.141829	0.102922
36	0.001249	0.000724	87	0.153119	0.114779
37	0.001319	0.000730	88	0.170537	0.126904
38	0.001382	0.000809	89	0.183982	0.141894
39	0.001528	0.000880	90	0.195068	0.156488
40	0.001650	0.000990	91	0.206710	0.173781
41	0.001768	0.001123	92	0.227749	0.189181
42	0.001867	0.001239	93	0.243303	0.208578
43	0.001973	0.001431	94	0.262304	0.223075
44	0.002183	0.001474	95	0.281455	0.242673
45	0.002435	0.001629	96	0.295060	0.263861
46	0.002776	0.001830	97	0.330229	0.282011
47	0.003054	0.001988	98	0.342677	0.304412
48	0.003242	0.002169	99	0.353111	0.315921
49	0.003732	0.002412	100	0.373571	0.344946
50	0.004067	0.002742			

[a] Defined as: is the mortality rate between age x and $(x + 1)$, that is the probability that a person aged x exactly will die before reaching age $(x + 1)$. Source: *Interim Life Tables*. Government Actuary's Department. England and Wales, based on data for years 1999–2001.

Appendix 14

Price index

Hospital and community health services pay and prices index

Year	Hospital and Community Health Services	
	Pay and prices index (1987–88 = 100)	Annual increase (%)
1993–94	155.5	3.40
1994–95	159.6	2.64
1995–96	166.0	4.01
1996–97	170.6	2.77
1997–98	173.5	1.70
1998–99	180.4	3.98
1999–00	188.5	4.49
2000–01	196.4	4.19
2001–02	203.1	3.41

Source: Netten A, Curtis L. *Unit Costs of Health and Social Care 2002*. Personal Social Services Research Unit, downloaded publication, p. 187. URL: http://www.ukc.ac.uk/PSSRU/

Appendix 15

Medical management costs

TABLE 48 *Patients' characteristics from EMPIRE study for Aberdeen and Leicester (Underwood, 1999[82])*

	Aberdeen	Leicester	Average
Angina (%)	50.0	97.0	73.5
Smoking (%)	62.0	59.0	60.5
Cholesterol (%)	25.0	44.0	34.5
Hypertension (%)	14.0	28.0	21.0
Presenting probability of CAD (%)	43.0	56.0	49.5
Actual CAD (%)	29.0	47.0	38.0

TABLE 49 *Medical management*

Treatment[a]	mg/day	Prices[b]			Costs	
		1	2	3	Average per unit	Daily
Basic (for all):						
Aspirin	75					0.01
Beta-blockers (atenolol)	200	0.98	3.83	8.12	0.15	0.31
If hypertension:						
ACE inhibitors (enalapril)	10	5.2	10.53		0.28	0.28
If high cholesterol:						
Statins	40	29.69	29.69		1.06	1.06
If with angina chest pain:						
Long-acting nitrates	2.6–3	19.56	5.12		0.25	0.25

[a] Alternative trademarks:

Beta-blockers	1	Non-proprietary
	2	Co-tenidone
	3	Tenoretic
Enaprapil	1	Non-proprietary
	2	Innovace
	3	Innozide
Statins	1	Lipitor
	2	Lipostat
	1	Suscard
	2	Sustac

[b] Source: *British National Formulary*. URL: http://bnf.vhn.net/home/ (March 2003).

TABLE 50 *Medical management cost (2001–02£)*

	Daily	Annual	% Patients applied to	Annual cost for typical cohort
Basic treatment	0.32	116.02	100	116.00
Angina	0.25	92.16	50	46.10
Cholesterol	1.06	387.03	35	133.50
Hypertension	0.28	102.53	21	21.50
Total annual cost for typical cohort of patients	317.20			

Appendix 16

Economic model sensitivity analysis: sensitivity and specificity variation results

TABLE 51 *Estimated costs and outcomes when sensitivity of ECG varies*

Strategy	Diagnostic cost (£)	Diagnostic and treatment cost (£)	True positives diagnosed (%)	Accurate diagnoses (%)	QALY
ECG sensitivity = 0.42:					
ExECG (SPECT–CA)	575	5146	4.65	94.10	12.46
ExECG (CA)	772	5349	5.5	94.92	12.47
SPECT (CA)	921	5529	8.86	98.29	12.50
CA	1310	5929	10.48	99.85	12.51
ECG sensitivity = 0.92:					
ExECG (SPECT–CA)	634	5238	8.28	97.74	12.50
ExECG (CA)	829	5445	9.8	99.22	12.51
SPECT (CA)	921	5529	8.86	98.29	12.50
CA	1310	5929	10.48	99.85	12.51

TABLE 52 *Stepwise cost-effectiveness when sensitivity of ECG varies*

Strategy	Incremental cost per true positive diagnosed (£)	Incremental cost per accurate diagnosis (£)	Incremental cost per QALY (£)
ECG sensitivity = 0.42:			
ExECG (SPECT–CA)			
ExECG (CA)	23930	24941	53453
SPECT (CA)	5334	5324	5398
CA	24689	25763	57214
ECG sensitivity = 0.92:			
ExECG (SPECT–CA)			
ExECG (CA)	13663	13981	20214
SPECT (CA)	–8981	–9041	Dominated
CA	24689	25763	57214

TABLE 53 *Estimated costs and outcomes when specificity of ECG varies*

Strategy	Diagnostic cost (£)	Diagnostic and treatment cost (£)	True positives diagnosed (%)	Accurate diagnoses (%)	QALY
ECG specificity = 0.43:					
ExECG (SPECT–CA)	712	5298	6.39	95.84	12.48
ExECG (CA)	963	5558	7.56	96.97	12.48
SPECT (CA)	921	5529	8.86	98.30	12.50
CA	1310	5929	10.48	99.85	12.51
ECG specificity = 0.83:					
ExECG (SPECT–CA)	457	5044	6.39	95.87	12.48
ExECG (CA)	578	5175	7.56	97.01	12.49
SPECT (CA)	921	5529	8.86	98.29	12.50
CA	1310	5929.18	10.48	99.85	12.51

TABLE 54 *Stepwise cost-effectiveness when specificity of ECG varies*

Strategy	Incremental cost per true positive diagnosed (£)	Incremental cost per accurate diagnosis (£)	Incremental cost per QALY (£)
ECG specificity = 0.43:			
ExECG (SPECT–CA)			
ExECG (CA)	22217	23081	45793
SPECT (CA)	–2227	–2186	–1842
CA	24689	25763	57214
ECG specificity = 0.83:			
ExECG (SPECT–CA)			
ExECG (CA)	11228	11438	15406
SPECT (CA)	27176	27583	35197
CA	24689	25763	57214

TABLE 55 *Estimated costs and outcomes when sensitivity of SPECT varies*

Strategy	Diagnostic cost (£)	Diagnostic and treatment cost (£)	True positives diagnosed (%)	Accurate diagnoses (%)	QALY
SPECT sensitivity = 0.63:					
ExECG (SPECT–CA)	585	5159	5.01	94.47	12.47
ExECG (CA)	799	5395	7.56	96.99	12.49
SPECT (CA)	896	5486	6.95	96.39	12.48
CA	1310	5929	10.48	99.85	12.51
SPECT sensitivity = 0.93					
ExECG (SPECT–CA)	612	5205	7.08	96.54	12.49
ExECG (CA)	799	5395	7.56	96.99	12.49
SPECT (CA)	933	5550	9.82	99.25	12.51
CA	1310	5929	10.48	99.85	12.51

TABLE 56 *Stepwise cost-effectiveness when sensitivity of SPECT varies*

Strategy	Incremental cost per true positive diagnosed (£)	Incremental cost per accurate diagnosis (£)	Incremental cost per QALY (£)
SPECT sensitivity = 0.63			
ExECG (SPECT–CA)			
ExECG (CA)	11689.73	9392.14	11689.73
SPECT (CA)	–17889.45	–15175.37	–17889.45
CA	17426.14	12791.97	17426.14
SPECT sensitivity = 0.93			
ExECG (SPECT–CA)			
ExECG (CA)	39422	42461	754167
SPECT (CA)	6865	6846	6869
CA	56764	63151	–171397

TABLE 57 *Estimated costs and outcomes when specificity of SPECT varies*

Strategy	Diagnostic cost (£)	Diagnostic and treatment cost (£)	True positives diagnosed (%)	Accurate diagnoses (%)	QALY
SPECT specificity = 0.64:					
ExECG (SPECT–CA)	576	5163	6.39	95.86	12.47
ExECG (CA)	799	5395	7.56	96.99	12.48
SPECT (CA)	868	5476	8.86	98.30	12.50
CA	1310	5929	10.48	99.85	12.51
SPECT specificity = 0.90:					
ExECG (SPECT–CA)	435.34	5022.62	6.39	95.87	12.48
ExECG (CA)	799.39	5395.03	7.56	96.99	12.48
SPECT (CA)	590.26	5199.64	8.86	98.33	12.50
CA	1309.55	5929.18	10.48	99.85	12.51

TABLE 58 *Stepwise cost-effectiveness when specificity of SPECT varies*

Strategy	Incremental cost per true positive diagnosed (£)	Incremental cost per accurate diagnosis (£)	Incremental cost per QALY (£)
SPECT specificity = 0.64:			
ExECG (SPECT–CA)			
ExECG(CA)	19851	20506	28002
SPECT (CA)	6191	6133	4997
CA	27960	29290	52221
SPECT specificity = 0.90:			
ExECG-SPECT–CA			
ExECG–CA	Dominated	Dominated	Dominated
SPECT–CA	7164.19	7192.14	6706.57
CA	44966.53	48093.94	158694.03

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Professor Ala Szczepura, Professor of Health Service Research, Centre for Health Services Studies, University of Warwick

Dr Ross Taylor, Senior Lecturer, Department of General Practice and Primary Care, University of Aberdeen

Mrs Joan Webster, Consumer member, HTA – Expert Advisory Network

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We look forward to hearing from you.

The National Coordinating Centre for Health Technology Assessment,
Mailpoint 728, Boldrewood,
University of Southampton,
Southampton, SO16 7PX, UK.
Fax: +44 (0) 23 8059 5639 Email: hta@soton.ac.uk
http://www.ncchta.org

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