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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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;
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Contributions Of Interest

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.

Conflicts Of Interest

Howard Gemmell has a potential conflict of interest in that one of the suppliers to the Nuclear Medicine Physics department is Amersham Health, and the Nuclear Medicine Physics department are also negotiating with Amersham Health to fund a research project in brain receptor imaging.

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EXECUTIVE SUMMARY

Epidemiology and background

Coronary heart disease (CHD) is the commonest cause of death in the UK, causing over 120,000 deaths in 2001. Death rates 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. Morbidity, in contrast to mortality, is rising. Overall, it is estimated that there are about 2.65 million people living in the UK who have CHD (either angina or have had a myocardial infarction (MI)). Prevalence of CHD increases with age and varies across the UK and between population groups. There were over 378,000 inpatient cases treated for CHD in NHS hospitals in 2000/2001, representing 5% of all inpatient cases in men and 2% in women. The cost of CHD to the UK health care system in 1999 was estimated as £1.73 billion rising to £7.06 billion when informal care and productivity losses were included.

Coronary artery disease (CAD) is the most common cause of CHD and is the focus of this review. Methods of detecting and assessing the presence and extent of CAD have become increasingly important in applying therapies to reduce morbidity and mortality. Coronary angiography (CA) is considered the "gold standard" for defining the site and severity of coronary artery lesions. However, routine use without prior non-invasive testing is not advisable, due to the high cost and associated mortality and morbidity, including nonfatal MI and cerebrovascular accidents. Exercise electrocardiography (ECG) is widely used for non-invasive detection of CAD due to its ready availability and relatively low cost. Imaging techniques such as myocardial perfusion scintigraphy (MPS) are often added to improve detection and/or localisation of exercise-induced ischaemia. MPS can also be used to estimate prognosis, to help target strategies for coronary revascularisation and to assess the adequacy of revascularisation, as it can reveal the location and extent of the perfusion abnormalities and extent of scarring from previous infarcts.

MPS testing is a low risk investigation even in patients with known CAD. MPS uses an intravenously administered radiopharmaceutical to evaluate regional coronary flow after stress (induced by either exercise or pharmacological agents) and at rest. Two

tracers are approved and available commercially for use in MPS: thallium (^{201}Tl) and two classes of technetium (^{99m}Tc), sestamibi and tetrofosmin. These tracers are extracted by cardiac myocytes and their initial myocardial distribution reflects a combination of the distribution of myocytes and regional perfusion. The distribution of the tracer within the myocardium is imaged using a gamma camera. In single photon emission computed tomography (SPECT), the raw data are then processed to obtain tomographic images. Images are compared following stress and rest injections of the tracer (or following redistribution for thallium) to assess presence of inducible ischaemia and/or infarction and to allow the site, extent and depth of abnormalities to be determined. The higher energy of technetium generally leads to better quality images and permits ECG-gating, which gives additional functional information.

The number of MPS studies being performed is increasing; 600 MPS studies were carried out per 500,000 population in 2000, compared to 430 studies per 500,000 population in 1997. The cost of a SPECT scan has been estimated in two studies at £262 and £185. Therefore, at the current rates of utilisation the cost to the NHS per year of SPECT studies is estimated to be between £111,000 and £157,200 per 500,000 of the population.

This review assesses the effectiveness and cost-effectiveness of SPECT MPS for the diagnosis and management of angina and MI.

Number and quality of studies, and direction of evidence

Twenty-one diagnostic studies and 46 prognostic studies met our inclusion criteria in terms of types of study design, participants, interventions and outcomes. The methodological 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 and contained 12 questions. The quality of the diagnostic studies was variable. Most gave clearly described selection criteria. Spectrum bias (the spectrum of patients in the study was not representative of those who would receive the test in practice) was evident in 13 studies. In 17 studies the index test (SPECT) and reference test (CA) were carried out within a time period short enough to be reasonably sure that the target condition had not changed. Eight studies described the SPECT test in sufficient detail to permit its replication, while 12 met this criterion

with regard to the reference test. In 14 studies the index test was interpreted without knowledge of the reference standard, while 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 prognostic studies were assessed using a checklist designed to assess the methodological quality of both randomised and non-randomised studies and contained 26 questions. 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: 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 diagnostic values of SPECT were generally higher than those of stress ECG in all subsets of studies, indicating a possible better diagnostic performance of SPECT compared with stress ECG. The evidence from the prognostic studies suggested that SPECT provided valuable independent and incremental information predictive of future cardiac events, including cardiac death and nonfatal MI.

Summary of benefits

Of the 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 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 whilst specificity values were similar. SPECT also provided higher positive likelihood ratios and lower negative likelihood ratios compared with stress ECG but heterogeneity was evident among studies. The subgroup of studies including patients with previous MI tended to give better diagnostic performance for SPECT compared with stress ECG but there were too few studies to assess this reliably. There were also too few studies to assess the performance of SPECT and stress ECG in other patient subgroups and in other study subsets.

In the 20 general prognostic studies, the rates of cardiac events (cardiac mortality or nonfatal MI) were significantly higher for patients with abnormal SPECT scans compared with normal scans. The extent and size of the perfusion defect were important factors in predicting prognosis. Three 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 patients referred directly to CA. Other findings from the general prognostic studies were that SPECT provided independent prognostic information for predicting MI; provided incremental prognostic value over clinical and exercise testing data that was maintained at long-term follow-up; was the single most powerful predictor of prognosis; and had incremental value even when exercise ECG or CA had already been performed.

In patients post MI, those with a cardiac event had more ischaemic defects than those without. The presence of reversible perfusion defects was significantly associated with new cardiac events, while the absence of reversible defects had high negative predictive value. SPECT imaging was seen as valuable in risk stratifying patients following MI.

In relation to SPECT and gender, studies found that SPECT provided important, independent prediction of survival 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. One study reported that, in women, clinical risk and the number of territories with fixed defects were associated with cardiac mortality, while in men clinical risk, exercise time and the number of territories with stress-induced or fixed defects were associated with cardiac mortality, and that SPECT was better able to identify and stratify women at high risk of future events. Another study concluded that gender-related differences in referral for CA after exercise SPECT were explained by a higher rate of abnormal tests in men, rather than a possible post-test gender referral bias.

Three studies assessing SPECT, performed post-revascularisation, found it to provide useful information. SPECT imaging performed one to three years after PTCA was predictive of cardiac events, with summed stress score and summed reversibility score both strongly associated with future PTCA or coronary artery bypass graft (CABG)

within three months of the SPECT test. 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.

Normal SPECT scans were associated with a benign prognosis and the option of medical rather than invasive management. In one study of patients with normal resting ECG, summed stress score was a significant predictor of adverse events. In another study, SPECT perfusion imaging helped identify high-risk patients with silent ischaemia, while another found SPECT to be an excellent prognostic indicator for adverse cardiac events in patients with high exercise ECG tolerance. In one study of medically treated patients with left main and/or 3-vessel CAD, the SPECT score was the only independent predictor of cardiac mortality and nonfatal MI. Two studies found that the presence of an abnormal SPECT scan and the extent of the perfusion defects independently predicted subsequent cardiac events in patients with diabetes.

In conclusion, the evidence from the included prognostic studies was consistent in suggesting that SPECT, as part of the stress ECG/SPECT/CA pathway, in a variety of settings and patient populations, including women and patients with diabetes, provided valuable independent and incremental information predictive of outcome that helped to stratify patients into appropriate at-risk groups and influence the decisions on how best to manage their condition. Also, a normal SPECT scan, excluding clinically significant CAD, justifies avoiding invasive investigations such as CA.

Methods for economic evaluation

A Decision Tree Model (DTM) was used to model the diagnosis decision and a simple Markov Model for the management of patients with suspected CHD (both of them developed in Data 4.0). The strategies considered in the decision model 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; d) CA (invasive test as first option).

Costs

For the Base Case analysis the results for costs and QALYs for the different strategies were: strategy a), stress ECG-SPECT-CA, cost of £5,190 and yielding 12.473 QALY; strategy b) (£5,395; 12.481 QALY); strategy c) (£5,529; 12.497 QALY) and strategy d) (£5,929; 12.506 QALY).

Cost/QALY

The systematic review of economic evaluations indicated that strategies involving SPECT were likely to be either dominant or produced more QALYs at an acceptable cost, relative to those that did not contain SPECT. There was less consistency in the literature about which of the various strategies that involved SPECT should be chosen. The use of SPECT in the diagnosis of acute coronary syndromes or following MI was very limited but the evidence tentatively suggested that use of SPECT was cost saving and was as effective as the use of existing clinical data or coronary angiography.

At the baseline prevalence of 10.5%, SPECT-CA would be viewed as cost-effective whereas CA, which generated more QALYs, does so at an incremental cost per QALY, which might be viewed as relatively high. At 30% prevalence rates while SPECT-CA was cost effective, the CA strategy produced more QALYs at a relatively low Incremental Cost-Effectiveness Ratio (£7,331). At higher prevalence rates (50% and 85%) SPECT-CA strategy was extended dominated by stress ECG-CA and CA strategies.

Sensitivity analyses

The model developed suggested that for low levels of prevalence it was possible that the incremental cost per unit of output (true positives diagnosed, accurate diagnosed, 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 more cost-effective strategy was stress ECG-SPECT-CA. The sensitivity analysis suggested that SPECT-CA improved its cost-effectiveness if it was assumed that SPECT gave information that allowed a management strategy to be decided upon without recourse to angiography.

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 about parameters. Some of these assumptions were based on data from non-UK studies. It is unclear whether such data are applicable to the UK. Another assumption made related 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 sensitivity analysis the impact of using shorter time horizons has been explored. Furthermore, other data such as the utility values are not based on an UK population and may not be appropriate to priority setting in the UK. The model presented in Section 5 (unlike that presented in the Industry submission) did not allow for higher quality of life after revascularisation. Therefore the benefits of revascularisation were solely in the form of higher life expectancy. A further caveat related to the pay-off model is the extent to which severity of disease is linked to quality of life. The model presented and many of the models summarised in Section 4 made the assumption that there was a direct link. No utility data were identified with which to test this assumption and it remains unclear the extent to which relaxing this assumption would impact on relative cost-effectiveness.

Other important issues regarding implications

Relatively poor data were available with which to consider longer-term costs and consequences. Both the Industry submission from Amersham Health and the economic model presented in Section 5 used data from non-UK settings. Such data may not be generalisable to the UK.

Notes on the generalisability of the findings

The majority of diagnostic studies compared SPECT and stress ECG in patients with symptoms or history of coronary disease. There were few studies in other groups. Six studies took place in North America (five in the USA, one in Canada) 12 in Europe (two each in Belgium, France and Greece, and one in Austria, Finland, Italy, Spain, Sweden and the UK) and three in Asia (two in Japan and one in Taiwan). Studies differed in

terms of their definition of coronary stenosis, patients' characteristics, severity of the disease, use of beta-blocking medications, time between SPECT, stress ECG and coronary angiography, technical factors such as interpretation of test findings, angiographic referral and blinding of test results.

The 46 prognostic studies evaluated varying combinations of tests amongst varying types of patients. In one study all patients had a previous history of MI. In one study all patients had previously undergone PTCA and in two studies all patients had previously undergone CABG. In less than a third of studies, participants were judged to be representative of the entire population from which they were recruited. In only one study was sufficient information provided to determine that the staff, places and facilities where the participants were treated were representative of the treatment that the majority of people would receive. Of the 46 prognostic studies, 34 were set in North America (33 in the USA and one in Canada) and 13 were set in Europe (four in France, two in The Netherlands, one in Denmark, Germany, Israel, Italy and Spain, and one study was a European multicentre study). The fact that many of these studies were undertaken in other countries with different health care systems, in particular the USA, needs to be borne in mind when considering their relevance to a UK health setting.

Need for further 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 attenuation-corrected 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, diagnostically and prognostically, of SPECT compared with stress echocardiography.

List of abbreviations

3VD	Three-vessel disease	MET	Metabolic equivalents
AC	Attenuation-corrected	MI	Myocardial infarction
ACER	Average cost-effectiveness ratio	MIBI	Technetium-99m sestamibi
AMI	Acute myocardial infarction	MPI	Myocardial perfusion imaging
BMJ	British Medical Journal	MPS	Myocardial perfusion scintigraphy
BNCS	British Nuclear Cardiology Society	MRI	Magnetic resonance imaging
CA	Coronary angiography	MVD	Multi-vessel disease
CABG	Coronary artery bypass graft	NC	Non-corrected
CAD	Coronary artery disease	NIDDM	Non-insulin dependent diabetes mellitus
CEA	Cost-effectiveness analysis	N/S	Not stated
CHD	Coronary heart disease	NS	Non significant
CI	Confidence interval	NSF	National Services Framework
CMA	Cost minimisation analysis	OR	Odds ratio
CRD	Centre for Reviews and Dissemination	QALYs	Quality adjusted life years
DTM	Decision tree model	QoL	Quality of life
EBCT	Electron beam computed tomography	QUADAS	Quality assessment of diagnostic accuracy studies
ECG	Electrocardiography	PTCA	Percutaneous transluminal coronary angioplasty
ECHO	Echocardiography	RCA	Right coronary artery
EF	Ejection fraction	RCT	Randomised controlled trial
ESV	End-systolic volume	ROC	Receiver operating characteristic
ExECG	Exercise ECG	RR	Relative risk
FN	False negative	SA	Sensitivity analysis
FP	False positive	SDS	Summed difference score
HR	Hazard ratio	SPECT	Single photon emission computed tomography
HCHS	Hospital & Community Health Services	SRS	Summed rest score
ICER	Incremental cost-effectiveness ratio	SSS	Summed stress score
LAD	Left anterior descending	SVD	Single-vessel disease
LCX	Left circumflex	Tc-99m	Technetium-99m
LBBB	Left bundle branch block	TES	Treadmill exercise score
LMD	Left main disease	Tl-201	Thallium-201
LVH	Left ventricular hypertrophy	TN	True negative
LR	Likelihood ratio	TP	True positive

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. Where the evidence allows, the effectiveness of SPECT in specific patient populations (women and patients following myocardial infarction) is examined.

2 BACKGROUND

2.1 Description of underlying health problem

2.1.1 Epidemiology

Coronary heart disease (CHD) is the commonest 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) 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 2.1) 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]

Table 2.1 Age-standardised death rates from CHD per 100,000 population by standard region, 2001[1]

	Men aged 35-74	Women aged 35-74
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

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 approximately 335,000 new cases of angina each year.[1]

The number of people experiencing a heart attack has fallen. On average, the incidence of myocardial infarction (MI), or heart attack, in the UK for those aged 30 to 69 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 approximately 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]

2.1.2 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 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 two- to five-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 coexisting disorders such as diabetes. Cholesterol lowering with 3-Hydroxy-3-Methyl-Glutaryl 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]

2.1.3 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, future employment and personal relationships, as well as increasing their risk of dying prematurely.[5] Furthermore, as well as 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 health care 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 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, 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 2000/2001. These represent 5% of all inpatient cases in men and 2% in women.[1]

2.2 Current service provision

2.2.1 Current service provision and variation in services

Most patients with angina are referred to their hospital cardiology out-patient 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 while those with a positive test are referred for angiography, and a revascularisation procedure should there be significant disease.

The National Service Framework (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 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 two weeks of GP referral. The NSF states that exercise ECG and MPS are useful for assessment of severity of ischaemia, however, only exercise ECG 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 increased over this period; the figure for 2000 was 1.2 studies/1,000 population/year compared to 0.86 studies/1,000/year in 1997 (Professional Groups' submission to 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/1,000/year). It was significantly below the European average activity in 1994. Amersham Health (Feburary 2003) also reported much lower levels of MPS within the UK than in Germany, Italy, France, Spain, or USA as shown in Table 2.2. However, they reported levels of MPS

activity lower than that reported by BNCS (Professional Groups' submission to NICE, 2003).

Table 2.2 International variation and changes over time (between 1998 and 2002) in the use of MPS in known and suspected CAD

	MPS Procedures		Growth pa	Rate/1000
	1998	2001	1998-2002	2001
UK	26802	45797	26.7%	0.8
Germany	156675	244989	16.9%	3.0
Italy	114287	171164	15.8%	3.0
France	141820	166581	5.1%	2.8
Spain	40556	74161	18.6%	1.9
Europe	*480140*	*702692*	*14.2%*	*2.4*
USA	4088454	5588733	11.0%	20.3

Source: Amersham Health, 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 2.3) (Professional Groups' submission to NICE, 2003).

Table 2.3 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

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 single photon emission computed tomography (SPECT).[9] The use of pharmacological stress for nuclear studies is increasing; 77% of studies used pharmacological stress in 2000 compared to 56% and 41% in 1997 and 1994 respectively. Attenuation correction was used in less than 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).

2.2.2 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. 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.

2.3 Description of new intervention

MPS uses an intravenously administered radiopharmaceutical trace 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 and tetrofosmin.[10] Technetium tracers now account for more than 59% of UK myocardial perfusion scintigraphy 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 noncorrected 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 pharmacologic agents are used to induce stress. When patients can exercise to develop an appropriate level of cardiovascular stress, exercise stress testing is preferable to pharmacologic 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. Pharmacologic 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 1,000 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 accessability. The healthcare professional conducting the stress test should be current in advanced life support technique 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]

Myocardial perfusion scintigraphy 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) e.g. post myocardial infarction 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]

2.3.1 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 due 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 due to the high cost but also because of the associated mortality and morbidity. The most serious complications of CA are death (0.1 to 0.2%), nonfatal MI (0.1%) and cerebrovascular accidents (0.1%). Other complications include arrhythmias, vasovagal reactions, infections and allergic dye reactions.[3,4,9]

Exercise electrocardiography (ECG) is widely used for non-invasive detection of CAD due to its ready availability and relatively low cost. However, a normal ECG does not exclude CAD. Exercise ECG 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]

2.3.2 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. 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 nonfatal MI; and
- Age, general health and noncoronary comorbidity.

Risk stratification of patients by stress testing enables 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]

2.3.3 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 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. Technetium sestamibi 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

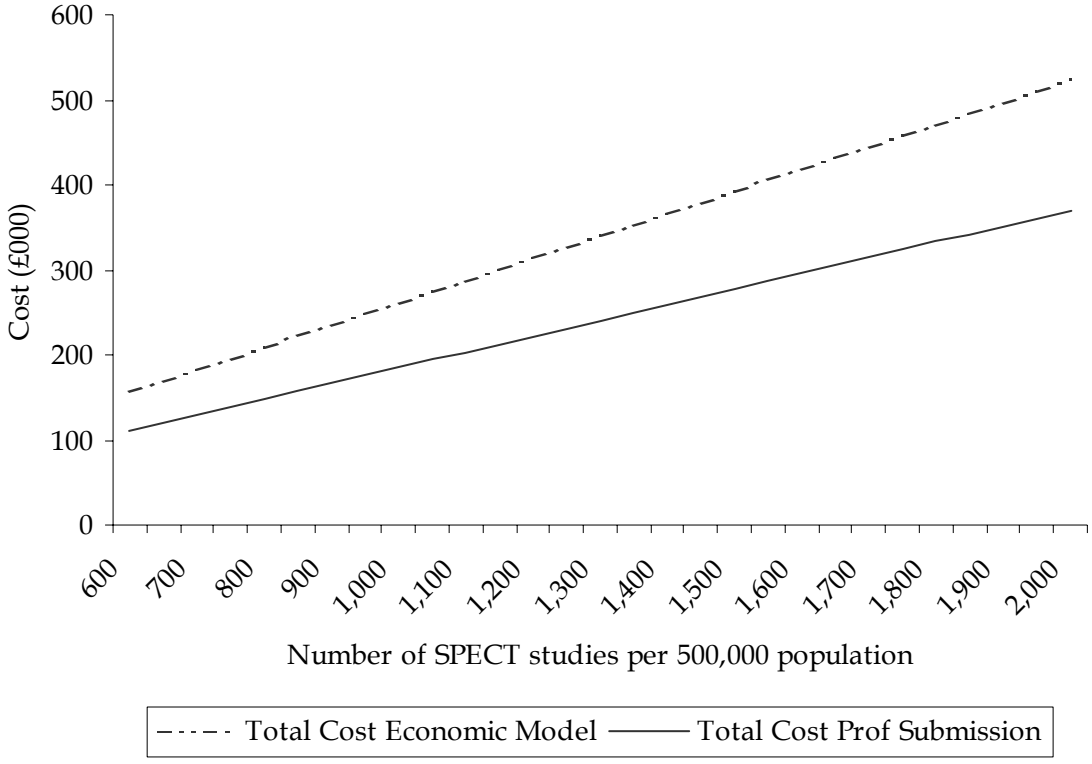
Exercise ECG has a number of limitations after coronary artery bypass surgery. Rest ECG abnormalities are frequent, and more attention must be paid to symptom status, haemodynamic response, and exercise capacity. Because of these considerations and the need to document the site of ischaemia, MPS is generally preferred for evaluation of patients in this group.[4] About 30% of patients have an abnormal ECG response on exercise ECG 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 exercise ECG 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]

2.4 Anticipated 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 Section 5 (£262 per study) and from the submission (£185 per study) the anticipated increase in cost to the NHS of an increase in the use of SPECT alone is presented (Figure 2.1). This figure has excluded the costs of other investigations such as stress ECG and CA as well as the effect on management costs. 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 populations, the extra cost to the NHS is between £120,000 and 170,000 per year.

Figure 2.1 Cost of SPECT to the NHS per 500,000 of the population as the number of studies increases



3 EFFECTIVENESS

3.1 Methods for reviewing effectiveness

3.1.1 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 are given in Appendix 1.

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

1. MEDLINE 1966 - Oct 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 four databases. Duplicates were removed from the resulting set using Ovid's de-duplicating feature.

2. PREMEDLINE (Ovid) 5th 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 (HCN) 1979 - 2002

7. HTA Database (NHS Centre for Reviews & Dissemination) 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.

3.1.2 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; 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 less than 100 participants were excluded.

Types of participants

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

(a) Patients who have experienced previous MI; and
(b) 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, beta-thalassemia, 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, technetium-99m sestamibi or technetium 99-m tetrofosmin. The types of stress included were exercise (treadmill or bicycle) or pharmacological (adenosine or dipyridamole or dobutamine) or a combination of exercise and pharmacological means.
- Stress ECG
- Coronary angiography (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, false positives, false negatives, and true negatives, 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; nonfatal MI; revascularisation (PTCA/CABG); occurrence of unstable angina; length of survival free of cardiac death; preservation of left ventricular function (after surgery); post-operative complications; number of CAs performed; hospital admissions; and quality of life measures.

3.1.3 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.

3.1.4 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 Centre for Reviews and Dissemination (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 less than 100 participants were excluded. The adapted checklist, therefore, contained 26 questions, covering the following subscales:

- reporting (ten questions)
- external validity (three questions)
- internal validity - bias (seven questions)
- internal validity - confounding (six questions)

An overall score as well as scores for each of the subscales was 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.

3.1.5 Synthesis of diagnostic studies

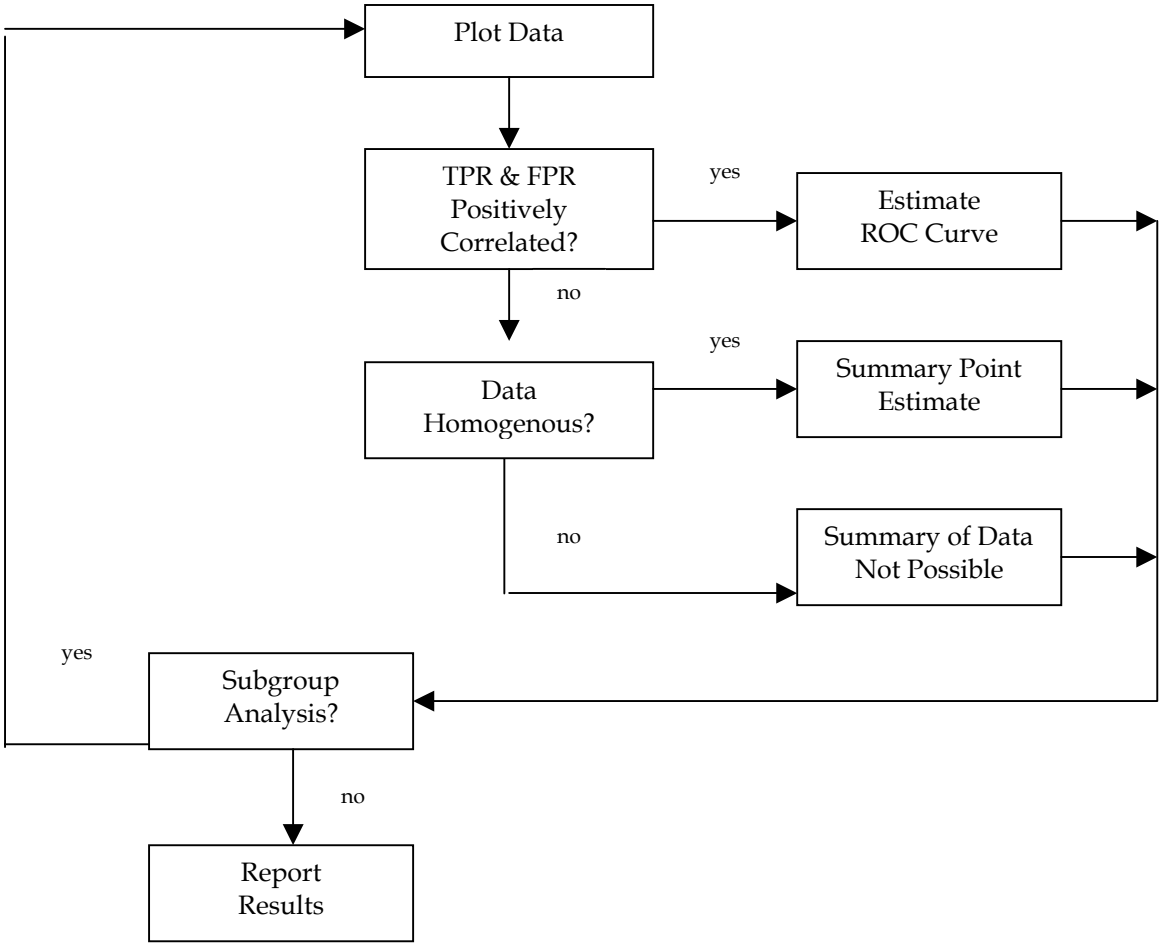
Diagnostic performance indexes (sensitivity, specificity, accuracy, predictive values, and likelihood ratios) were extracted and recalculated for each study for both tests (SPECT versus CA and stress ECG versus CA) and 2x2 contingency tables of true positive, false positive, false negative and true negative 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, positive and negative likelihood ratios were known.

Details of the mathematical formulae applied are given in Appendix 6. Use of the formulae was not always straightforward because in many cases they yielded non-integer values of true positives, false positives, false negatives and true negatives. 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 formulae described above. There was, however, a minority of comparisons where no exact match could be found. For example, for the Santana-Boado study[18] the chosen integer values for the 2x2 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 3.1).[19] They first advocate plotting the true positive rate (sensitivity) versus the false positive 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 true and false positive 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 homogenous 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.

Figure 3.1 Algorithm for performing a meta-analysis of studies of diagnostic test performance.[19]



Summary ROC curves for SPECT versus CA and stress ECG versus CA were considered when a positive correlation between the true and false positive 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 which 2x2 table information could not be obtained could not be included in this analysis.

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

3.2 Results

3.2.1 Quantity and quality of research available

Titles and abstracts of over 9,000 reports were identified by the search strategies (Table 3.1). 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. Thus, 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.

Table 3.1 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

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 while 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 ECG or CA had been undertaken.

3.2.2 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]

Table 3.2 Summary of quality assessment of included diagnostic studies

NHS CRD quality assessment checklist for diagnostic studies (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

Diagnostic studies

Overall, the quality of the diagnostic studies varied according to the methodological parameters considered (Table 3.2). 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 time 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, while 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.

Prognostic Studies

Table 3.3 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: 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).

Table 3.3 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[78]	4	0	4	2	10
Shaw 1999[77]	9	0	6	3	18
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[84]	9	0	5	4	18
Vanzetto 1999[83]	10	0	6	4	20
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

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 to this 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 time 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.

3.2.3 Characteristics of studies

Appendix 7 provides details of the characteristics of the included studies (study design, participants, test characteristics and outcomes) for the diagnostic and prognostic studies.

Diagnostic studies

All diagnostic studies, apart from 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, 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 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 time period during which they were carried out.[18,22,25-27,31,34,40,41] Of these, study duration lasted from a minimum of two years[22,31,34] to a maximum of nine years.[26]

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

Across studies, the ages of the participant group as a whole ranged from below 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] while in one they consisted wholly of men.[32]

Of the 4453 patients analysed, 960 (22%) had a previous MI, while 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 Tc-99m sestamibi[18,25,28,33,36] and in one both Tl-201 and Tc-99m sestamibi 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] while four studies used both exercise and pharmacological stress.[18,26,33,41] 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 ten 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 three months[67] to a maximum of 6.7 years.[49] The mean length of follow-up was two 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 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 time period in which they were carried out. Of these, study duration lasted from a minimum of five months[47] to a maximum of ten years.[50]

The total number of people followed-up in the studies was 83,138; the smallest study contained 106 patients[85] while the largest contained 11,249 patients.[77] In eight the number of patients analysed was less than 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] while in one they consisted wholly of men.[74]

Of the patients analysed, 11,535 (14%) had suffered previous MI, while 4806 (6%) had previously undergone PTCA and 5997 (7%) had previously undergone CABG. In the study by Travin and colleagues[81] all patients had experienced previous MI. 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 Tc-99m sestamibi, in twelve studies both tracers were used, in one it was Tc-99m tetrofosmin and in two studies 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] and in one study[70] adenosine or dipyridamole or dobutamine were used, while 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 studies both visual and quantitative methods were used, and in five the method of image interpretation was not stated.

3.2.4 Tabulation of results

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

3.2.5 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 sixteen 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 whilst specificity values were similar. SPECT also provided higher likelihood ratios and lower negative likelihood ratios compared with 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 patient 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 of the 46 prognostic studies provided general prognostic information. Fourteen 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 ≥ 1mm) 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 exercise ECG in men.[74]

Three studies assessed the value of SPECT in patients following revascularisation.[56,65,69] The remaining studies assessing the usefulness of SPECT in a number of specific areas/patient populations, including patients with an acute syndrome, patients with diabetes, patients with left main/3-vessel disease, normal SPECT scans, asymptomatic coronary disease, high exercise ECG 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 Marwick 1999 paper was considered the primary report of the study and the Shaw 2000 paper 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 Iskandrian 1993 paper. 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 study by Machecourt and colleagues but not from the study by Vanzetto and colleagues.

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

3.3 Assessment of effectiveness

3.3.1 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 left bundle branch block.

a) 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 $\geq$50% stenosis, in one study $\geq$60% stenosis, and in three studies $\geq$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 Table 3.4 and Table 3.5 respectively. Only studies in which patients underwent both SPECT and stress ECG, and where CA was used as the reference standard were included in the analyses.

Table 3.4 Sensitivity, specificity, and accuracy for SPECT from the 16 included studies

Author(s)	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 3.5 Sensitivity, specificity, and accuracy for stress ECG from the 16 included studies

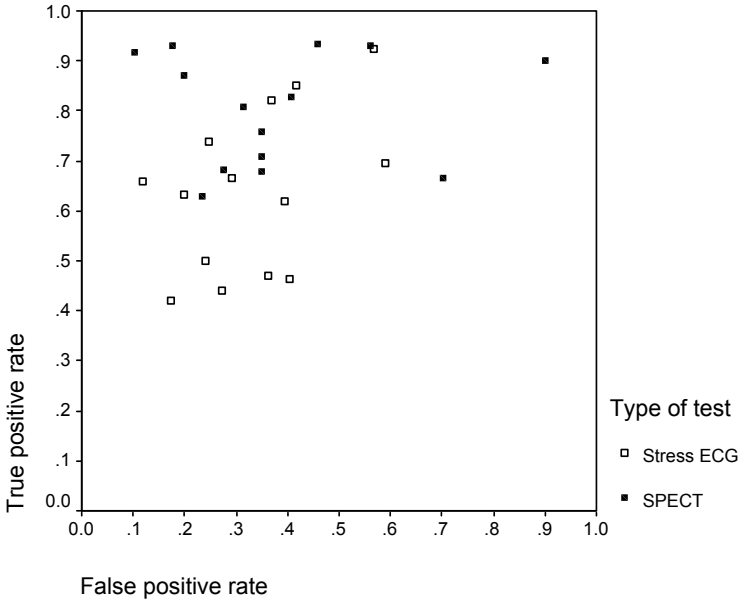
Author(s)	N	% stenosis	Previous MI	Sensitivity	Specificity	Accuracy
Chae 1993[23]	243	≥50%	Yes	0.62	0.60	0.61
Daou 2002[24]	338	≥50%	Yes	0.47	0.64	0.51
De 2002[25]	55	≥70%	Not stated	0.44	0.73	0.65
Gentile 2001[26]	132	≥60%	No	0.85	0.58	0.80
Hambye 1996[28]	128	≥50%	No	-	-	-
Huang 1992[30]	179	≥50%	Yes	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

Due to the significant heterogeneity among studies (χ^2 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 3.2 is a scatter plot showing the true positive rate (sensitivity) and false positive 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.

Figure 3.2 Scatter plot of true positive rate against false positive rate showing the performance of SPECT and stress ECG



Five of the 16 included studies clearly excluded patients with previous myocardial infarction. Sensitivity and specificity values were available for both tests for only four studies (Figure 3.3). 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 whilst 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 3.6). The range of sensitivity for the ten studies that did include patients with previous myocardial infarction 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 3.7).

Figure 3.3 Scatter plot of true positive rate against false positive rate for the subgroup of studies excluding patients with previous myocardial infarction

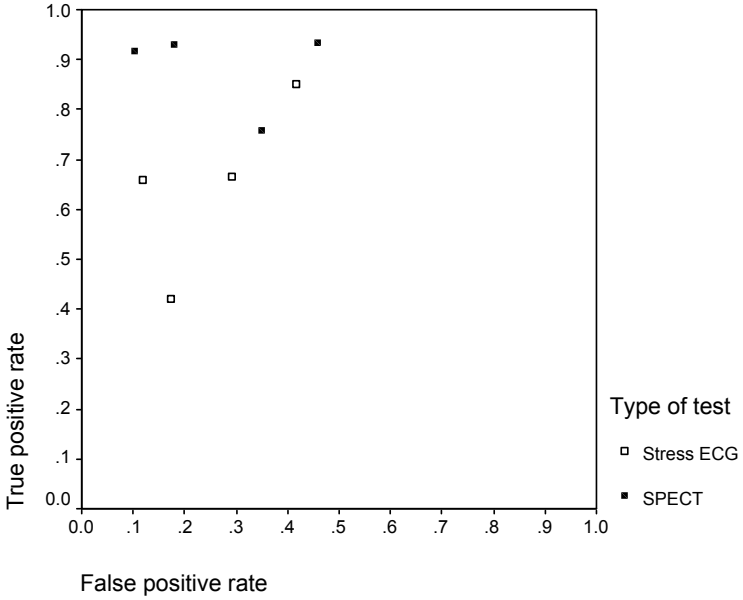


Table 3.6 Sensitivity and specificity of studies *excluding* patients with previous MI

	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 3.7 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)

Summary ROC curves for SPECT and stress ECG studies were not generated as the Spearman's rank correlation coefficient for the true positive rates and false positive 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 effect of SPECT and stress ECG in patient subgroups (e.g. gender of participants,

angiographic definition of CAD, patients taking beta-blockers) due to the relatively small number of studies within each subgroup.

- *Likelihood ratios*

Likelihood ratios for both tests could be calculated for 12 of the 16 included studies (Table 3.8). The range of positive likelihood ratios was 0.95 to 8.99 (median 2.33) for SPECT and 1.14 to 5.60 (median 2.06) for stress ECG. It is worth noting that all positive likelihood ratios were below ten in both tests. Combining positive likelihood ratios using a random effects model yielded a higher overall estimate for SPECT (2.29, 95% CI 1.68 to 3.12) (Figure 3.4) compared with stress ECG (1.83, 95% CI 1.48 to 2.2.6) (Figure 3.5). However, for both tests there was significant heterogeneity among positive likelihood ratios ($p<0.001$). Moreover, the overall estimate of 2.29 for SPECT was outside the 95% confidence intervals of five of the 12 included studies. Similarly, the overall estimate of 1.83 for stress ECG was outside the 95% CI of six of the 12 included studies.

Table 3.8 Likelihood ratios for SPECT and stress ECG

Author(s)	N	Positive LR	Negative LR
SPECT			
De 2002[25]	55	0.95	1.12
Daou 2002[24]	338	2.71	0.48
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			
De 2002[25]	55	1.63	0.77
Daou 2002[24]	338	1.29	0.83
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

Negative likelihood ratios 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 likelihood ratio for SPECT less than 0.1 (0.09) and likelihood ratios for SPECT tended to be smaller than those for stress ECG. The summary estimate of the negative likelihood ratios for SPECT was 0.25 (95%CI 0.17 to 0.37) (Figure 3.6) and 0.51 (95% CI 0.39 to 0.67) (Figure 3.7) for stress ECG but again heterogeneity was evident among included studies ($p<0.001$).

Figure 3.4 **Meta-analysis of positive likelihood ratios for SPECT (only studies with data for both SPECT and stress ECG)**

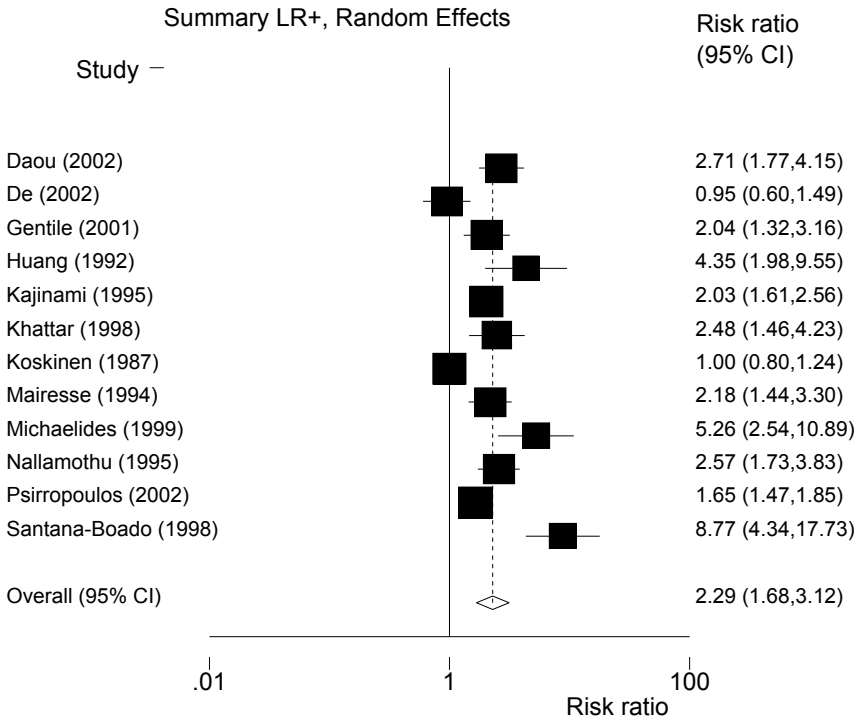


Figure 3.5 **Meta-analysis of positive likelihood ratios for stress ECG (only studies with data for both SPECT and stress ECG)**

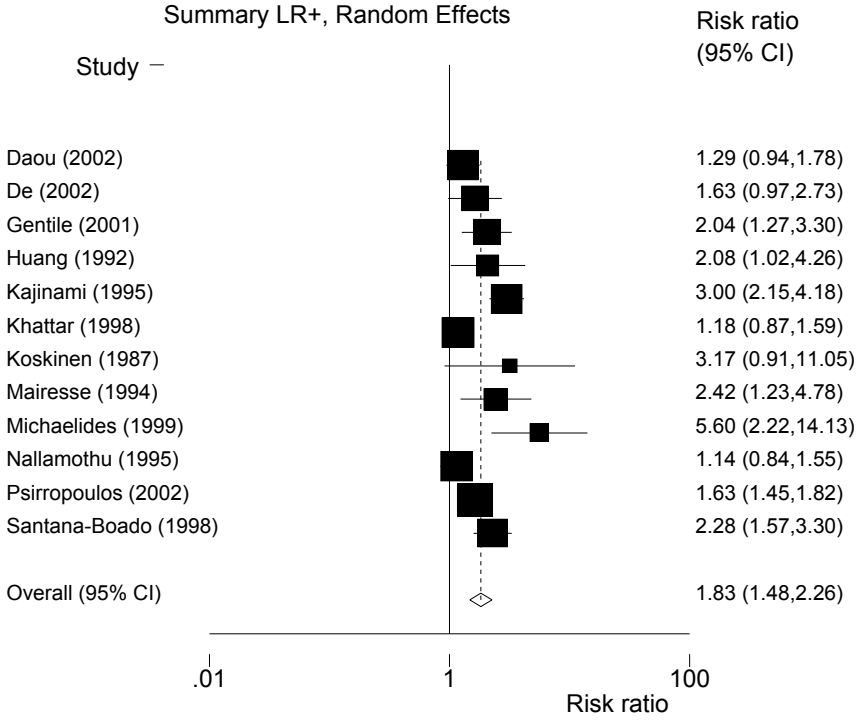


Figure 3.6 **Meta-analysis of negative likelihood ratios for SPECT (only studies with data for both SPECT and stress ECG)**

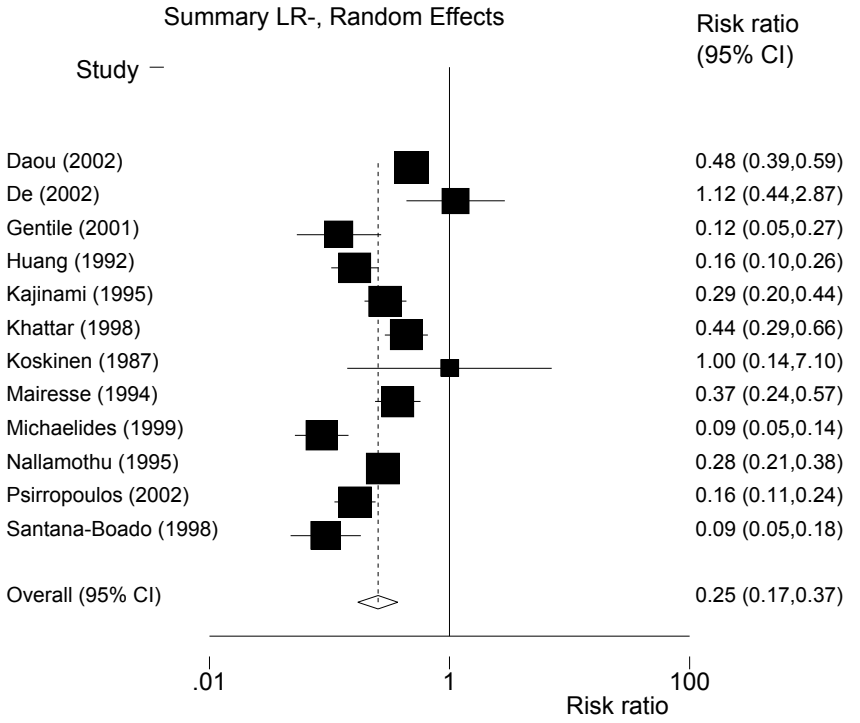
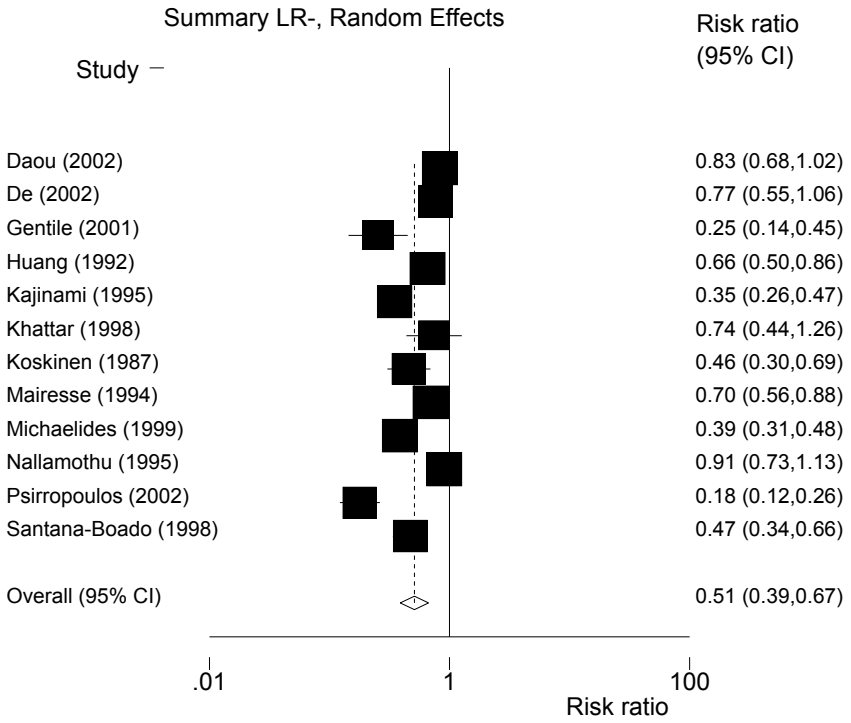


Figure 3.7 Meta-analysis of negative likelihood ratios for stress ECG (only studies with data for both SPECT and stress ECG)



b) 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 3.9 and 3.10. 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 3.8 shows the true positive and the false positive rates for SPECT and stress ECG for the three included studies.

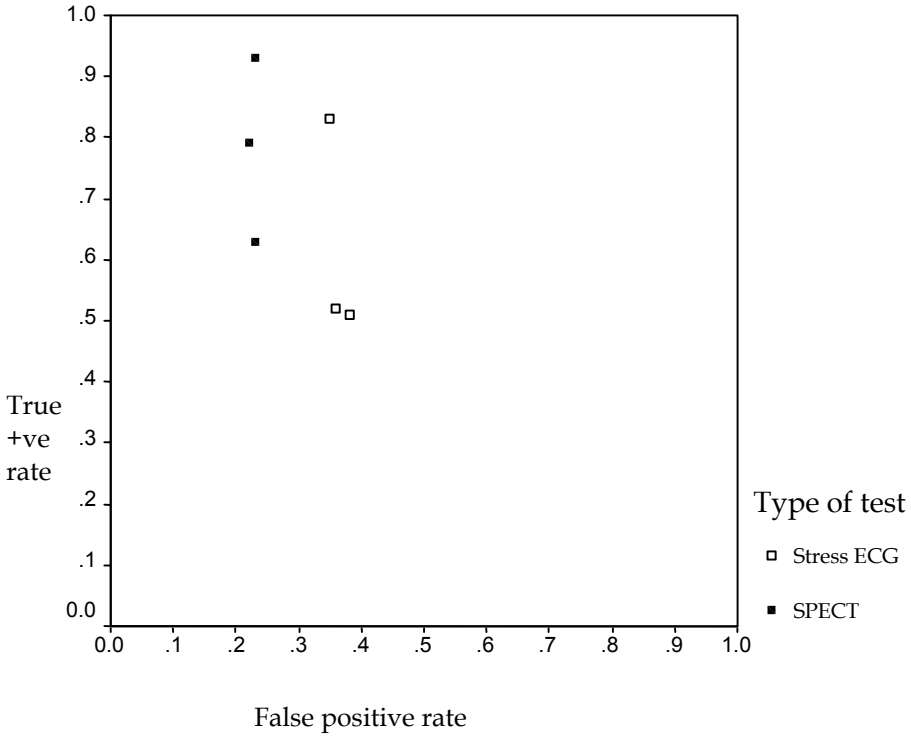
Table 3.9 Sensitivity, specificity, and accuracy for SPECT from the three studies on PTCA

Author(s)	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 3.10 Sensitivity, specificity, and accuracy for stress ECG from the three studies on PTCA

Author(s)	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 3.8 SPECT and stress ECG scatter plot for detection of restenosis after PTCA.



Two studies provided separate results for complete and partial revascularisation (see Table 3.11). 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.

Table 3.11 Diagnostic data on complete and partial revascularisation

Author	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

c) 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.

d) Patients with left bundle branch block

One study assessed the diagnostic value of SPECT during exercise and pharmacological stress in patients with left bundle branch block and no diagnostic ECG for CAD.[41] Three hundred and eighty-three consecutive patients were enrolled in the study. SPECT was performed in conjunction with exercise in 206 patients, adenosine in 127 patients and dobutamine in 50 patients. Presence of stenosis was confirmed by CA within a month of SPECT. Exercise, adenosine and dobutamine SPECT had similar sensitivity for left anterior descending 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 left anterior descending coronary artery stenosis.

3.3.2 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.

a) 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] while 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); 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 significantly lower rates of normal angiograms (33% vs 43%[77] (p values not reported) and 18% vs 33%[67] $p < 0.001$). It was also reported that the rate of subsequent revascularisation was lower with the SPECT-CA strategy (Table 3.12). 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 three years.[77]

Table 3.12 Risk of revascularisation of SPECT-CA compared to CA

Study		SPECT-CA % (n/N)	CA % (n/N)	Note
Shaw 1999[77]	Low	14%	16%	$p < 0.001$
	Intermediate	13%	27%	$p < 0.001$
	High	16%	30%	$p < 0.001$
Mishra 1999[67]		27% (123/450)	37% (1692/4572)	$p < 0.001$
Underwood 1999[82]		21%	44%	$p < 0.001$

Low – pretest probability of CAD $\leq$ 15%; Intermediate – pretest probability of CAD $\leq$ 16% to 59%; High – pretest probability of CAD $\geq$ 60%

Underwood and colleagues 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, while two-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 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. There were also three retrospective studies[63,66,68] and three which did not provide information as to whether they were prospective or retrospective; all however, 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 variable independent predictors and the different outcome measures used hampered the comparison of the different studies. In one study this resulted in no useable data being available.[68]

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 3.13 to 3.16 respectively. 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 or relative risks this has been noted. Except where otherwise noted, an odds ratio, relative risk or hazards ratio greater than one 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 a serious events (e.g. death or MI). For each study these data are summarised in Appendix 8.

Table 3.13 Statistically significant predictors of all cause death by multivariate analysis

Study id	Independent predictors
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*

* Ordered in terms of strongest evidence of statistical significance

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 3.13).[49] In terms of all cause death, Diaz and colleagues reported that SPECT provided little additional prognostic information at low-risk (< 1% per year for cardiac events) and high-risk (> 3% per year for cardiac events) but for patients categorised as intermediate-risk (impaired functional capacity or an abnormal heart rate recovery) SPECT was useful in stratifying risk.

Table 3.14 Statistically significant predictors of cardiac death by multivariate analysis

Study id	Independent predictors
Iskandrian 1994[58]	Extent of perfusion abnormality; extent of CAD by angiography*
Machecourt 1994[62]	Abnormal SPECT; previous MI; male*
Marie 1995[63]	Age; abnormal SPECT scan*
Schinkel 2002[76]	Abnormal SPECT scan; congestive heart failure; diabetes mellitus; smoking; Age*
Vanzetto 1999[84]	$\geq$ 3 abnormal segments; previous MI, non diagnostic stress ECG; strongly positive ECG; Age*
Shaw 2000[79]	Pretest clinical risk; territories with infarction; territories with ischaemia*
Zerahn 2000[88]	dPRP < 2500 mm Hg/min; Fixed defects; LBBB; digoxin; age 59+*

* Ordered in terms of strongest evidence of statistical significance

All seven studies that reported on prediction of cardiac death concluded that the addition of SPECT provided important incremental information. The most common conclusions were that the extent of perfusion defects was the most powerful predictor of events,[58,62,63,79] and that SPECT provided predictive independent information of clinical and exercise data[63,88] or angiography.[58] Shaw and colleagues,[79] in assessing the incremental value of perfusion imaging data, reported that these contributed 45.7% of new information above and beyond clinical history data ($p < 0.0001$). Furthermore, SPECT had incremental value in patients at low,[62 76,84] intermediate[84] and high risk.[76] The percentage of new prognostic information contributed by SPECT over and above clinical history data for low, intermediate and high risk patients was 24% ($p < 0.0001$), 48% ($p < 0.00001$), and 21% ($p < 0.001$) respectively.[79]

Four studies also reported data that enabled the relative importance of SPECT as an independent predictor of cardiac death to be judged.[63,76,84,88] In the study by Marie and colleagues,[63] the extent of SPECT defects 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). In 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 independent 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 defect on SPECT scan (RR 2.55, 95% CI 1.43 to 4.55)[88] were independent predictors of cardiac death.

Table 3.15 Statistically significant predictors of cardiac events by multivariate analysis

Study id	Independent predictors
Hachamovitch 1998[54]	Improved prediction on addition of Scan data based in summed stress score to prescan information
Hachamovitch 2002[55]	Summed stress score
Iskandrian 1993[57]	Extent of total perfusion abnormality & extent of ischaemic abnormality and LV dilation; extent of CAD & ejection fraction Gender; exercise work load*
Kamal 1994[59]	Size of perfusion abnormality
Marie 1995[63]	Age; abnormal SPECT scan*
Miller 2001[66]	Worsening clinical status
Olmos 1998[71]	Abnormal SPECT scan; normal ECG*
Pattillo 1996[75]	Size of perfusion defect
Stratmann 1994[80]	Abnormal SPECT scan
	Or reversible defect when abnormal scan replaced by fixed and reversible defect

* Ordered in terms of strongest evidence of statistical significance

Eight studies reported data on the independent predictive power of SPECT to identify patients at risk of cardiac death and MI (Table 3.15). In all cases the statistical models used appeared to include clinical, exercise and SPECT variables although they differed between studies. All except one concluded that the addition of SPECT provided additional independent information. Furthermore, in two studies it was reported that SPECT provided additional information to that provided by CA variables[63,75] 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.[57]

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 and stress ECG 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 (nonfatal MI or cardiac death) (RR 11.9, 95% CI 1.6 to 89.4). Three studies explicitly reported the comparison of a diagnostic strategy of clinical data and stress ECG versus clinical data, stress ECG and SPECT.[55,71,75] All three reported that the addition of SPECT to this pathway improved the ability to predict cardiac events.

Table 3.16 Statistically significant predictors of other outcome measures by multivariate analysis

Outcome	Study id	Independent predictors
Cardiac events and revascularisation	Machecourt 1994[62]	Submaximal exercise stress test; Abnormal SPECT; Previous MI; male*
	Miller 2001[66]	Worsening clinical status
Nonfatal MI	Vanzetto 1999[84]	$\geq$ 3 abnormal segments; 1-2 abnormal segments; previous MI, presence of risk factors*
Cardiac mortality, nonfatal 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 and extent of defect

* Ordered in terms of strongest evidence of statistical significance

Four studies also considered the incremental prognostic value of SPECT in terms of other outcome measures (Table 3.16). In one of the two studies that considered the incremental prognostic value of SPECT in predicting cardiac events and revascularisation, SPECT variables were important independent predictors.[62] This study by Machecourt and colleagues went on to conclude that, in patients with stable angina, a normal SPECT scan indicated low risk, while the extent of the perfusion defect was an important factor for predicting prognosis. In the other study, the only independent

predictor from stress ECG, SPECT and clinical variables was worsening clinical status of patients.[66]

A further study reported on the incremental value of SPECT in predicting non-fatal MI. This study found that the only independent predictors were SPECT and clinical variables.[84] This study also reported that the most important predictors were 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, p = 0.03).

Zanco and colleagues[86] considered two models: in model A, the abnormality of the SPECT scan was compared with clinical findings 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.

b) Value of SPECT for the determination of prognosis in specific groups at risk of coronary artery disease

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 they 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] while 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 examine 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 - 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 result 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 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 directly compare 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 pre-scan likelihood categories, demonstrating that this effectiveness was independent of underlying patient characteristics and exercise ECG 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 nonfatal MI between the two diagnostic strategies compared. Shaw and colleagues, in a further multivariate analysis, demonstrated the incremental value of SPECT ($p < 0.0001$) when compared with clinical history ($p < 0.0001$) and exercise ECG ($p < 0.00010$).

Pancholy and colleagues[73] sought to determine the independent and incremental prognostic value of exercise SPECT in women. They considered 5 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 five years. The aim of the study was to compare the prognostic ability of SPECT and exercise ECG 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 exercise ECG failed to distinguish survival from nonsurvival. Parisi and colleagues[74] concluded that in medically or angioplasty-treated middle-aged men with chronic stable angina and 1- and 2-vessel CAD, SPECT was

superior to exercise ECG for predicting subsequent survival, although in this group of patients neither method was superior in predicting subsequent nonfatal 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 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 independent predictor for either outcome. Giri and colleagues concluded that the presence of an abnormal SPECT scan and extent of 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 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 3-vessel disease*

Amanullah and colleagues[43] (quality assessment score 18) examined the predictors of outcome of medically treated patients with left main and/or 3-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 3-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 pre-test likelihood of CAD and negative or nondiagnostic 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 exercise ECG responses (and a normal or abnormal scan), 548 had a low pre-stress ECG likelihood of CAD, of whom 3 (0.5%) had a hard event. Of these 548 patients, none of 441 with a normal or equivocal scan and 3 (2.8%) of 107 with an abnormal scan had a hard event. In patients with a low post-stress 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%, 4 of 64), $p = 0.007$. Even greater stratification

occurred in the patients with an intermediate to high post-stress ECG likelihood of CAD (normal scan, 0.7% [2 of 274]; abnormal scan, 7.9% [18 of 229], chi-square 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 post stress 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. Multivariable 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 nonfatal 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 (CI 4.8 - 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.

c) 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 use 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, in a multivariate logistic regression model including clinical, SPECT and angiographic variables, that 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 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 showed that in the 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 post-infarction 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 six 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)[1] and age (RR 1.03, 95% CI 1.01 to 1.06). Similarly, predictors of cardiac death or nonfatal 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); pre-scan 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 pre-scan 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 pre-scan information, the SPECT results (summed stress score) added incremental value to pre-scan 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] while the other two assessed the role of SPECT in patients following CABG.[65,69]

Ho and colleagues[56] assessed univariate associations between exercise ECG and two SPECT variables. An abnormal SPECT scan, performed one to three years after PTCA, was found to be predictive of cardiac events.

[1] A relative risk of 1 indicates that prior CABG is associated with a lower risk of cardiac death

Miller and colleagues[65] evaluated the prognostic value of exercise SPECT imaging in patients who had undergone CABG within two years of the SPECT test whereas Nallamothu and colleagues[69] considered the same question over a mean of 41 month 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 nonfatal 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, nonfatal 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 anti-anginal

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 noted that the presence of SPECT defects identified patients at higher risk for adverse cardiac events who may be referred for further invasive evaluation. It was concluded that 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-depression > 1mm 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 > 1mm 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 (equal to or greater than 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 for 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 exercise ECG in patients with high exercise tolerance. In Cox multivariate analysis comparing four strategies a) SPECT b) Stress ECG c) ECG and Duke treadmill score 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 was associated with a relative risk 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.

d) ECG-gated and attenuation-corrected SPECT

Two studies[89,90] compared SPECT with ECG-gated SPECT, while one compared SPECT with attenuation-corrected SPECT.[91] The diagnostic study by Shirai and colleagues[90] found that ECG-gated SPECT was more sensitive, with slightly lower but acceptable specificity, when 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 attenuation-corrected SPECT, both in patients with angina and no previous MI and also in patients with known CAD.

3.4 Summary and conclusions of the evidence for and against the intervention

3.4.1 Diagnostic studies

The sensitivity values of SPECT tended to be higher that those of stress ECG for the two main subsets of studies (patients suspected of CAD and patients who underwent PTCA) whilst specificity values of the two tests were similar. The sensitivity and specificity results of SPECT and stress ECG in the four studies excluding patients with previous myocardial infarction were generally higher than those in the ten studies that included patients with myocardial infarction. However, this observation is based on a small number of studies.

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 likelihood ratios for SPECT was higher than that for stress ECG (2.29 versus 1.83) whilst the combined estimate of negative likelihood ratios for SPECT was slightly smaller than that of 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 sensible 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 due 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.

3.4.2 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] while the remainder were cohort studies (23 prospective, 13 retrospective, six type not stated) in which substantially the same group of patients underwent both the tests under investigation and the reference standard. Twenty-six studies employed a consecutive method of recruitment.

Twenty studies provided general prognostic information. The extent[57,62,63,68,86] and size[58,59,75] of the perfusion defect was an important factor in predicting prognosis. Other findings were that SPECT imaging: resulted in lower rates of normal angiograms from those patients subsequently referred for CA;[67,77,82] 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;[76,84] was the single most powerful predictor of prognosis and had incremental value even when exercise ECG or CA had already been performed.[82]

Fourteen 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] size of the perfusion defect;[59,75] abnormal SPECT scan;[62,63,71,76,80,84,86] worsening category summed stress score;[66] worsening category summed reversibility score;[66] and fixed perfusion defects.[88]

The remaining 26 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 one to three years after

PTCA was predictive of cardiac events[56] and in patients who had undergone CABG, SPECT was useful in stratifying patients into risk groups for future cardiac events.[65,69]

Our findings are in broad agreement with other published reviews assessing the prognostic usefulness of myocardial perfusion scintigraphy. Travin and Laraia,[92] in a review of the prognostic value of stress myocardial perfusion imaging, 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 myocardial perfusion imaging, 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.

3.4.3 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, while 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, while 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 four (CA) were found to have had significantly more revascularisations ($p < 0.001$). Shaw and colleagues[78] compared two different testing strategies: one group of patients underwent initial direct testing by CA, while 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 compared with 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-square or hazard ratio values favoured the SPECT variables when compared each alone[42-44,48-51,57-66,72,74,76,77,80,81,84-88] or in combination[47,48,55,69,71,73,75] (see Appendix 8).

3.4.4 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 endpoint for exercise ECG, occurring in 49 of the patients, with inotropic stress testing precipitated 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 endpoints included palpitations, tremor and nausea.[33]

In a prognostic study by Ben-Gal and colleagues,[44] one of the 84 patients with a normal thallium SPECT scan experienced a nonfatal 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 anti-anginal therapy but two days later suffered a small inferior wall acute MI.[44]

Schinkel and colleagues[76] reported that 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 mm Hg) in seven patients (1.0%), and severe hypertension (blood pressure of > 240/130 mm Hg) 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 were: three (strategy one); one (strategy two); one (strategy three); three (strategy four). There were three cases of complications in MPI user hospitals and five cases of complications in MPI non user hospitals.[76,82]

4 SYSTEMATIC REVIEW OF ECONOMIC EVALUATIONS

4.1 Methods

4.1.1 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-Oct 2002, EMBASE 1990-2002 (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) 5th November 2002

3 NHS-EED (NHS Centre for Reviews and Dissemination) October 2002

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

4.1.2 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.

Table 4.1 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

Reviews of relevant studies were not considered eligible for inclusion. Nevertheless, as the submission by Amersham Health (Amersham Health, February 2003) included a review of economic studies a brief commentary has been included in Section 4.3.

4.1.3 Data extraction strategy

The following data were extracted for each included study.

1. *Study identification information*
    - Author and year
    - The interventions studied
    - The type of economic evaluation
    - The country of origin and currency reported
2. *The intervention, study design and main outcomes*
    - Fuller description of treatment
    - Numbers receiving or randomised to each intervention
    - Outcomes studied
3. *Sources of data*
    - Effectiveness data
    - Mortality and comorbidity (if measured)
    - Cost data
    - Quality of life (if measured)

4. *Methods and study perspective*
5. *Results*
    - Costs
    - Benefits
    - Incremental cost-effectiveness/utility ratio (ICER)
    - Sensitivity analyses
6. *Additional comments*

4.1.4 Quality assessment strategy

Two economists independently assessed included studies using the 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]

A. Is it unlikely that important relevant studies were missed?
B. Were the inclusion criteria used to select articles appropriate?
C. Was the assessment of studies reproducible?
D. Were the design and/or methods and/or topic of included studies broadly comparable?
E. How reproducible are the overall results?
F. Will the results help resource allocation in healthcare?

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

4.1.5 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.

4.2 Systematic review of published economic evaluations

4.2.1 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. Section 4.2.2 critiques and summarises those studies that have considered the diagnosis of coronary artery disease. Sections 4.2.3 and 4.2.4 consider those studies that have investigated the use of SPECT to diagnose coronary artery disease in those at high disease prevalence and women respectively. Section 4.2.5 considers the role of SPECT for those presenting with acute coronary syndromes and Section 4.2.6 considers the role of SPECT in determining management following myocardial infarction. The review provided by the Industry submission as well as the Amersham Health economic model are discussed separately in Sections 4.3 and 4.4 respectively.

4.2.2 Diagnosis of coronary artery disease

Six[99-103] studies reporting the results of decision models considered the cost-effectiveness of different imaging strategies for a range of prevalence rates of coronary artery disease (Jacklin 2002). Two further studies based on models focused on patient groups at intermediate risk of disease (approximately 25% to 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 4.2 and 4.3.

Table 4.2 Summary of diagnostic strategies used in studies using models

Study	Strategies
Jacklin 2002 (unpublished)	1. Stress ECG with CA if positive or non conclusive (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 1997[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 echocardiography; CA if positive
Maddahi and Gambhir 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. Electron beam computed tomography (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

Table 4.3 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 two above
Mattera 1998[107]	1. Stess 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

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 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 that presented in Section 3 they tended to assume higher specificities for SPECT. This would tend to improve the cost-effectiveness 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 which year cost data related to and despite three studies having ten 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 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] while the fourth devoted considerable effort to identifying costs generalisable to a large health care 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 Section 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 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 sensitivity analysis.[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, 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 and this 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 sensitivity analysis 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 positive or non-diagnostic, had the lowest average cost per QALY when the prevalence of coronary artery disease was below 70%. Above 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 this 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 4.4).

Table 4.4 Incremental cost-effectiveness ratios for the comparison of stress ECG, SPECT in positives (non diagnostics) versus stress ECG

Study	Finding compared with stress ECG
Jacklin 2002 (unpublished)*	Stress ECG more effective but more costly. Incremental cost per true positive identified of stress ECG compared with ECG, SPECT £3038
Christian# 1994[106]	$20,550 per additional correct classification
Hachamovitch 2002[55]	$5417 per additional correct classification
Mattera 1998[107]	SPECT reduced costs by 38%
Jacklin 2002 (unpublished)*	Stress ECG more effective and less costly
Hachamovitch 2002[55]	$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 (unpublished)*	Stress ECG more effective but more costly. Incremental cost per QALY of stress ECG compared with ECG, SPECT £854

* costs in UK £; year of costs not stated
# costs in 1992 US

There is little consistency between the studies, reflecting the different parameter values used. The studies by Christian and colleagues, Hachamovitch and colleagues, and Mattera and colleagues based their costs on no more than the cost of stress ECG and SPECT, so their results may be misleading.[55,106,107] Underwood and colleagues showed that the cost of stress ECG, SPECT strategy is less (although no sensitivity analysis 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 4.5)

Table 4.5 Incremental cost-effectiveness ratios for the comparison of SPECT versus stress ECG

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

The incremental cost per QALY in the 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.

- *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 coronary angiography*

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 coronary angiography*

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 4.6.

Table 4.6 Incremental cost-effectiveness ratios for the comparison of SPECT versus coronary angiography

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

* Costs of future treatments excluded. ** Costs of treatments included

4.2.3 Cost-effectiveness at high disease prevalence

Six studies considered the effect on cost-effectiveness of a high (approximately >75%) prevalence of coronary artery disease. 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] as well as 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 less than $25,000,[99] incremental cost per additional true positive diagnosed $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).

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

Three studies reported the cost-effectiveness of alternative strategies to detect coronary artery disease in women.[78,108,109] Two of these were based on primary studies and one was based on a modeling exercise. A further three studies considered the cost-effectiveness of alternative strategies to detect coronary artery disease in women as part of a sensitivity analysis.[55,99,104] Interpretation is hampered by the differences in strategies compared and also limited reporting of results. Garber and colleagues estimated in their model that the incremental cost per QALY of using SPECT instead of stress ECG was approximately $50,000. This increased to $100,000 for women aged 45 (i.e. at lower risk) and $61,500 for women aged 65 (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 $8092 per reclassification ($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. 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 coronary artery disease diagnosed.[108]

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

4.2.5 Acute coronary syndromes

Four studies considered the strategies involving SPECT for those presenting to the emergency room with chest pain but normal resting ECG's.[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 nine and 12 months follow-up[111,112] and one was a small 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 due 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 sensitivity analysis 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 $1843 (95% CI $431-$6171) lower median in-hospital costs and 2 day (CI 1-3 days) shorter hospital stay, but similar rates of in-hospital and 30 day follow-up events, compared to patients in the conventional arm.[113]

Radensky and colleagues using rest SPECT appeared to be on average $1032 (17%) less costly (median $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 above 60% would a strategy of 'No SPECT' be less costly.[110] Similarly, Weissman and colleagues showed that SPECT resulted in a cost saving of $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 pre-test judgement about management ($1674 versus $2626) it was more costly when the scan cost was included ($2626 versus $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]

4.2.6 Management following uncomplicated myocardial infarction

Two studies were identified that looked at this group, one of which was based on a model[114] and the other based 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 six 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 six-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

In Dittus and colleagues all results were reported relative to a strategy: 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 more cost-effective strategy. Direct 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 to standard medical care was available and it was lower for direct angiography than for strategies based on the initial use of SPECT.

In Barnett and colleagues[115] the total cost of the SPECT strategy was significantly lower ($39707) than that for the angiography strategy ($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 to 1.86 for the SPECT strategy over a two-year follow-up. These results were stable over the sensitivity analyses reported.

The two studies appeared to consider similar patient populations but they used different outcome measures and this makes it difficult to compare them. However, as the study by Barnett and colleagues[115] was a large, generally clearly reported, randomised controlled trial while 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.

4.3 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 4.7.

Table 4.7 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

More studies were identified in the Industry submission than were identified in the review reported in Section 4.2.1 above. 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.

The studies included in the review used a variety of different methods and this 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 is greater than that 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 pre-test 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 respectively. 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.

4.4 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.

4.4.1 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 Section 4.2. The evaluation comprises two components: a) a decision

model, focusing on diagnostic performance and b) a Markov model, estimated 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 while 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 decision model, were based upon published reviews of the literature. Other probabilities were taken from other previously published models, notably 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 or three-vessel disease would receive either CABG (100% left main vessel disease, 80% three-vessel disease) or PTCA (20% three-vessel disease). Rates of revascularisation were assumed to be lower for single vessel (30%) and two-vessel (40%) disease. Those not receiving surgery were assumed to receive medical management. Subsequent costs and events were based upon the effect that initial choice of management had on myocardial infarction 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 GBP 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 myocardial infarction were based on NHS reference costs. Medical therapy costs were based on the recent literature inflated to 2002 GBP. 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 Section 4.2 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 strategy 5, ECG-negSPECT-CA. 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 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 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'.

Sensitivity analysis was reported for changes in parameter values for three scenarios. Two relate to the comparison of SPECT-CA to '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 oneway sensitivity analyses were conducted investigating (i) effect of discounting (ii) time horizon over which costs and benefits accrue (iii) time taken to identify and treat false negatives (iv) diagnostic performance of SPECT (v) changes in costs of SPECT (vi) changes in costs of an angiogram (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 ten 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 five years to two years. This had the effect of reducing the penalties associated with an

inaccurate diagnosis. As a result SPECT-CA improved its cost-effectiveness compared to 'No testing' but paradoxically its cost-effectiveness reduced in comparison to 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 from £275 to £200. As would be expected it 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 to '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 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 in comparison to 'No testing' with an incremental cost per QALY of nearly £29,000 being reported at a 5% prevalence.

4.4.2 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 Section 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 Section 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 the 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 4.8 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.

Table 4.8 Estimation of stepwise incremental cost per QALY at different prevalences of coronary artery disease. Table is based on data presented in Table 22 of the Amersham Health submission

Strategy	Diagnosis model				Payoff Model			Stepwise incremental cost per QALY		
	Cost	FNs	Acc	DDs	Cost	LYs	QALYs	Inc Cost	Inc QALYs	Inc C per QALY
Prevalence: 15%										
1. No testing (reference)	£0	150	850	0	£4,833,400	15,516	13,435			
4. ExECG +ve MPS CA	£366,617	43.9	956	0.31	£5,534,391	15,538	13,484	£700,991	48	14,483
2. ExECG CA	£491,203	33.6	966	0.81	£5,689,297	15,533	13,482	Dominated	Dominated	Dominated
3. MPS CA	£445,959	13.2	986	0.42	£5,710,172	15,544	13,497	£175,781	14	12,831
5. ExECG –ve MPS CA	£599,952	6.9	992	0.65	£5,883,108	15,542	13,497	Dominated	Dominated	Dominated
6. ExECG ind MPS CA	£403,988	37.6	962	0.49	£5,590,919	15,537	13,484	Dominated	Dominated	Dominated
7. CA (reference)	£736,429	0	999	1.5	£6,037,856	15,531	13,489	Dominated	Dominated	Dominated
Prevalence: 30%										
1. No testing (reference)	£0	300	700	0	£5,384,800	15,183	13,082			
4. ExECG +ve MPS CA	£450,812	87.7	912	0.46	£6,505,051	15,230	13,181	£1,120,251	99	11,316
6. ExECG ind MPS CA	£464,770	75.1	924	0.61	£6,558,189	15,231	13,185	£53,138	4	12,960
2. ExECG CA	£525,986	67.2	932	0.88	£6,643,350	15,229	13,185	Dominated	Dominated	Dominated
3. MPS CA	£532,563	26.5	973	0.59	£6,780,024	15,244	13,209	£221,835	24	9092
5. ExECG –ve MPS CA	£663,126	13.9	985	0.8	£6,949,553	15,244	13,213	£169,529	3	49,861
7. CA (reference)	£736,429	0	999	1.5	£7,063,706	15,236	13,210	Dominated	Dominated	Dominated

Table 4.8 (Cont)

Strategy	Diagnosis model				Payoff Model			Stepwise incremental cost per QALY		
	Cost	FNs	Acc	DDs	Cost	LYs	QALYs	Inc Cost	Inc QALYs	Inc C per QALY
Prevalence: 50%										
1. No testing (reference)	£0	500	500	0	£6,120,000	14,739	12,610			
4. ExECG +ve MPS CA	£563,033	146	853	0.66	£7,799,226	14,819	12,776	£1,679,226	166	10,092
6. ExECG ind MPS CA	£545,788	125	874	0.78	£7,847,860	14,823	12,785	£48,634	9	5527
2. ExECG CA	£572,355	112	887	0.98	£7,915,412	14,823	12,789	£67,552	4	17,777
3. MPS CA	£647,987	44.1	955	0.83	£8,206,446	14,843	12,825	£291,034	36	8152
5. ExECG –ve MPS CA	£747,327	23.1	976	1	£8,371,451	14,845	12,833	£165,005	8	20,626
7. CA (reference)	£736,429	0	999	1.5	£8,431,506	14,843	12,837	£60,055	5	13,055
Prevalence: 85%										
1. No testing (reference)	£0	800	200	0	£7,222,800	14,073	11,903	£7,222,800	11903	
4. ExECG +ve MPS CA	£731,281	234	765	0.95	£9,740,405	14,203	12,170	£2,517,605	268	9408
6. ExECG ind MPS CA	£667,266	200	799	1.02	£9,782,316	14,210	12,186	£41,911	16	2669
2. ExECG CA	£641,893	179	820	1.12	£9,823,490	14,214	12,195	£41,174	9	4475
3. MPS CA	£821,021	70.6	928	1.18	£10,345,977	14,241	12,248	£522,487	53	9858
7. CA (reference)	£736,429	0	999	1.5	£10,483,206	14,254	12,279	£137,229	31	4485
5. ExECG –ve MPS CA	£873,565	37	962	1.3	£10,504,233	14,248	12,263	Dominated	Dominated	Dominated

FN = false negatives; Acc = accuracy; DD = Diagnostic deaths; LYs = Lifeyears; Inc cost = incremental cost; Inc QALYs = Incremental QALYs;

Inc C per QALY = Incremental cost per QALY

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

4.5 Summary of findings

While 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 to 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 it is unclear the extent to which these rates are appropriate. The results presented in Section 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 Section 3.3.2 suggest that SPECT has independent prognostic power over and above that provided by CA and may be useful to identify 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 upon 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 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 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 while one showed it to be more costly but more effective.

The use of SPECT post myocardial infarction was limited but one RCT suggested that the use of SPECT would be cost saving. An earlier model based analysis however reported that compared to 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 PET and stress echocardiography. 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 echocardiography 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 pre-test probability of CAD. Three studies included a very wide risk range (zero to one in five groups Kuntz;[99] zero to one in three groups Shaw;[78] 0.1 to one in four groups Lee.[117]) Garber included only intermediate risk patients (pCAD from 0.25 to 0.75). Kim and colleagues based their three low to intermediate risk groups on three scenarios for women aged 55 years; definite angina (pCAD 0.06); probable angina (pCAD 0.31); and non-specific chest pain (pCAD 0.71). Lauffer does not describe patients in terms of pre-test probability of CAD, but includes a study population of patients referred for assessment of existing or suspected CAD.

Two studies based their data on the diagnostic performance of echocardiography on the meta-analysis by Fleischmann 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 echocardiography[117] and one based the results on an RCT which reported no difference in sensitivity and higher specificity for echocardiography.[116] Overall, four studies assumed that echocardiography was associated with lower sensitivity but higher specificity than SPECT.[99,103-105] One study comparing SPECT and echocardiography in women reported higher sensitivity and specificity for echocardiography.[109]

From their Markov model analysis Garber and Solomon reported incremental cost per QALY results for SPECT compared to ECHO of $64,000 (for men aged 65 years) and $150,000 (for women aged 45 years).[104] The results from the model used by Kuntz and colleagues included incremental cost per QALY estimates for SPECT compared with ECHO for patients with typical angina ($62,800) and for patients with atypical angina ($108,900). Kuntz, Kim and colleagues report results in a way which was difficult to interpret numerically in terms of cost-effectiveness, although the authors report that exercise ECHO was more cost-effective than exercise SPECT at all levels of pre-test risk of CAD.[109] Rumberger and colleagues report lower average cost-effectiveness for exercise ECHO compared to exercise SPECT at low, medium and high pre-test 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 greater than $16,000 at all levels of prevalence.[103] Lee and colleagues considered the cost-effectiveness of stress ECHO compared to stress SPECT in terms of the prognostic value of false negative results. For patients with a pre-test CAD risk of 0.3 or higher, SPECT was found to be more cost-effective than ECHO, due mainly to the lower rate of false negatives from SPECT than from ECHO. At lower risk levels (< 0.3) these results are reversed.[117] From their RCT (n = 115), Lauffer and colleagues report 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 be 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 coronary artery disease.

5 ECONOMIC ANALYSIS

5.1 Economic modelling

The cost-effectiveness and economic evaluation of single photon emission computed tomography (SPECT) myocardial perfusion scintigraphy (MPS) relative to stress electrocardiography (stress EGC), and coronary angiography (CA), for the diagnosis and management of coronary artery disease (CAD) have been assessed using economic evaluation modelling techniques. A decision tree model (DTM) was used for the diagnosis decision (Appendix 12, Figure 1) and a simple Markov Model (Appendix 12, Figure 2) 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 Section 4.

5.1.1 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. These are all, broadly speaking, 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 5.1).

Table 5.1 Results from the diagnostic tests

Test	Result
Stress ECG	Positive or Negative
SPECT	Positive or Negative
CA	High Risk, Medium Risk, Low Risk

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

a) Stress ECG; followed by SPECT if stress ECG positive or indeterminate; followed by CA if SPECT positive or indeterminate
b) Stress ECG; followed by CA if stress ECG positive or indeterminate
c) SPECT; followed by CA if SPECT positive or indeterminate
d) CA (invasive test as first option).

Within the model described in Appendix 12 (Figure 1) 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. three vessel disease and poor left ventricular function or left main disease), Medium Risk (single or double vessel disease), or Low Risk, (no significant heart disease present). This strategy is the one followed for patient A in Table 5.2.

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 could diagnose the patient as High Risk or request a CA to help determine appropriate management. As a final outcome of this strategy for this particular patient he/she will receive a left main disease 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.

Table 5.2 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→LMD and Classified as High Risk
C	Non-invasive test → SPECT → Negative result → Classified as Low Risk

3VD = three vessel disease; LMD = left main disease

Each of these strategies considered by the model has associated expected costs and consequences. Depending on the probabilities of 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 (a) SPECT is adopted as a method of confirming a positive result or dealing with an indeterminate result of stress ECG while in strategy (c) SPECT is used as a substitute for stress ECG.

5.1.2 Markov Model

The Markov Model can provide the estimated costs and outcomes over the life-time 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. six months, one year). At the end of the cycle, the individuals can remain in the state they started the cycle in 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) false negative (high risk); e) false negative (medium risk) f) false positive (medium risk) (a false positive 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 one 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 the patient dies or it is felt the benefits of the revascularisation will no longer be obtained. The interventions and events considered in each state are shown in Table 5.3.

Table 5.3 Interventions and events considered in the Markov Model

Low, medium and high risk states:	Medical Management
	Myocardial Infarction
Low, medium and high risk revascularisation states:	Revascularisation, percutaneous transluminal coronary angioplasty (PTCA)
	Revascularisation, coronary artery bypass grafting (CABG)
	Further revascularisation
	Medical Management
	Myocardial Infarction
False negative: true medium or true high risk states	Medical Management
	Myocardial Infarction
	Rediagnose (CA)
False positive: true low risk state	Medical Management
	Myocardial Infarction
	Rediagnose

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 true negative, or false positive. The assumption within the 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.

5.2 Costs

5.2.1 Decision Tree Model Costs

The costs of the three interventions considered in the model are presented in Table 5.4.

Table 5.4 Interventions considered in the Decision Tree Model

	Total Cost (£)	Source	Total Cost (used in the model) (2001/02 £ sterling)	Method for actualisation
Stress ECG	107.00	Hartwell 2003[120]	104.86	Assumption (2001/02 – 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

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 A+E direct cost plus 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 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 (personal communication, Professor Underwood, February 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]

5.2.2 Markov Model Costs

Table 5.5 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 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 the one 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] was followed. The authors used NHS Reference Costs;[124] then, figures for 2001/02 and the same source is 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 5.6). 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).

Table 5.5 Interventions considered in the Markov Model

	Total Cost (£)	Source	Total Cost (used in the model) (UK £ 2001/02)	Method for actualisation
Medical Management	317.20	See Appendix 15	311.00	Assumption (2001/02 – 2002/03 2% inflation rate)
MI	1,122.00	NHS Cost 2001/02	1,122.00	Not applicable
PTCA	2,034.00	Hartwell 2003[120]	1,993.74	Assumption (2001/02 – 2002/03 2% inflation rate)
CABG	4,397.00	NHS Cost 2001/02	4,397.00	Not applicable

Table 5.6 Cost for Angioplasty (PTCA) (assumes 60 minutes in theatre. Includes angiography)

		Total for procedure (£ 2002/03)	Total for procedure (£ 2001/02) *
Staff:	1 x cardiologist	46.35	45.42
	1 x radiographer	14.71	14.42
	1 x technician (=MTO)	17.75	17.40
	2 x nurses	22.63	22.18
	Total	101.43	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	1,933.00	1894.34
Angioplasty Total Staff and non-staff costs		2,034.00	1993.74

Source: Hartwell 2003[120] Appendix 6: Health Economics, page 116* Actualised using HCHS Pay and Prices Index

Finally, cost per year was calculated for each state in this model. The present value of these costs were calculated as follows:

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

Where:
A being the possible states in the model and t = 1,…,n
PVC_A = Present value of costs of state A over the n years
TC_A = Total cost of diagnosis process
Pxt = probability of being alive in year t
Pyt = 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]

5.3 Probabilities

5.3.1 Decision Tree Model Probabilities

Decision tree probabilities were assessed from the literature or calculated in the model. Table 5.7 shows that many of these were derived from the results of the effectiveness review (see Section 3).

Table 5.7 A priori probabilities for decision tree

		Value	Range	Source
Prevalence of disease for patient cohorts	Males	10.5	10.5 – 90	BrHF Stats 2003[1]
	Females	5.5	5.5 – 90	BrHF Stats 2003[1]
Proportion of Single Vessel Disease		0.41		Shaw 1999[77]
Proportion Multiple Vessel Disease and/or Left Main Vessel Disease		0.59		Shaw 1999[77]
Intervention:		**Value**	**Range**	**Source**
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[99,102]
CA	Sensitivity	1.00		Assumption
	Specificity	1.00		Assumption
	Mortality risk	0.0015		Patterson 1995[102]

ER = Effectiveness Review

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.

5.3.2 Markov Model Probabilities

The time horizon for the Markov Model was a maximum 25 years to enable comparisons with the Industry submission. In Table 5.8 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 false negatives and false positives. 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 decision model 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 equal 1), the probability of false negative 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 false positive rates are zero. The implications of relaxing this assumption are explored within the sensitivity analysis.

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. 2000.[127] The relative risk for the other states was derived from Shaw and colleagues 1999.[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 states as well as risk of second revascularisation when having PTCA or CABG were derived from Kuntz and colleagues.[99] Table 5.8 shows the probability values used in the model with their sources.

Table 5.8 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 & false positive	2.5%	Shaw 1999[77]	
Medium Risk & false negative (medium risk)	5.0%	Shaw 1999[77]	
High Risk & false negative (high risk)	9.0%	Shaw 1999[77]	
Prop 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, medium, high risk, respectively)
Prop PTCA Medium Risk	61%	BrHF Stats 2003[1]	
Prop CABG Medium Risk	39%	BrHF Stats 2003[1]	
Proportion PTCA	90%; 10%	Assumption	(low - high risk)
Proportion CABG	10%; 90%	Assumption	(low - high risk)
Prop of patients with 2nd Revasc		Kuntz 1999[99]	
PTCA	3.6%		
CABG	1.8%		
Mortality risk reduction from revasc:			
High Risk	57%	Kuntz 1999	
Medium Risk	15%	Kuntz 1999	
Risk reduction of MI:			
PTCA	17%	Kuntz 1999	
CABG	40%	Kuntz 1999	
Procedures mortality:			
PTCA	3.1%	Kuntz 1999	
CABG	0.75%	Kuntz 1999	
Time Horizon	Max. 25 years		
Start Age	60 years		

5.3.3 Females

A sub-group analysis was conducted for females. This analysis made use of the relevant age specific 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 Section 3. The values applied were: sensitivity stress ECG, 0.67, specificity stress ECG, 0.65, sensitivity SPECT, 0.90, specificity SPECT, 0.80. Finally, prevalence for this sub-group was fixed at a lower rate than males sub-group: 5.5%.

5.4 Quality of life measures

One of the products of the economic evaluation is quality adjusted life years (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. Quality of life 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 Section 4 and values from the CEA Registry.[130] While 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, using figures from Kuntz and colleagues[99] facilitates comparisons with the Industry submission. The utility scores used in the model are described in Table 5.9.

Table 5.9 Utility scores used in the estimation of Quality Adjusted Life Years

State	Utility value (range)
Low Risk (and false positives)	0.87 (0.77-1.00)
Untreated Medium Risk and false negative medium risk	0.81 (0.68-1.00)
High Risk and false negative high risk	0.67 (0.4-0.98)
Adjustment for revascularisation or MI	0.1 (QALY loss)

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 quality of life in three month.[131] The gain from revascularisation is the subsequent lower risk of death but not a higher quality of life than before revascularisation.

5.5 Discounting

Guidelines of the National Institute for Clinical Excellence[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.

5.6 Results

5.6.1 Base case analyses

The parameters for costs of interventions, risks of events and quality of life for the base case analysis are summarised in Table 5.10. These parameters were entered in decision tree and Markov models using the DATA software package. Payoffs for the decision tree model were obtained from the Markov models 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.

Table 5.10 Summary of variables used in the analysis

Costs		Total Cost (2001/02 £ sterling)	Source
Stress ECG		104.86	See Table 5.4
SPECT		261.91	See Table 5.4
CA		1309.55	See Table 5.4
Medical Management		311.00	See Table 5.5
MI		1,122.00	See Table 5.5
PTCA		1,993.74	See Table 5.5
CABG		4,397.00	See Table 5.5
Probabilities		**Parameter value**	**Source**
Prevalence of disease for patient cohorts		10.5	See Table 5.7
Stress ECG	Sensitivity	0.66	See Table 5.7
	Specificity	0.60	See Table 5.7
	Indeterminacy	0.18	See Table 5.7
	Mortality risk	0.00005	See Table 5.7
SPECT	Sensitivity	0.83	See Table 5.7
	Specificity	0.59	See Table 5.7
	Indeterminacy	0.09	See Table 5.7
	Mortality risk	0.00005	See Table 5.7
CA	Sensitivity	1.00	See Table 5.7
	Specificity	1.00	See Table 5.7
	Mortality risk	0.0015	See Table 5.7
Mortality			
Annual rate for age X			See Table 5.8
Relative Risk Medium Risk		2.3	See Table 5.8
Relative Risk High Risk		3.6	
Risk of MI:			
Low Risk (& false positives)		2.5%	See Table 5.8
Untreated Medium Risk & false negative medium risk		5.0%	See Table 5.8
High Risk & false negative high risk		9.0%	See Table 5.8
Prop fatal MI		44.84%	See Table 5.8
Prop non-fatal MI		55.16%	See Table 5.8
False Negative Results			
Prop to Med Risk		41%	
Prop to High Risk		59%	
Revascularisation:			
Proportion revascularisation Low, Medium, High risk.		5%; 50%; 100%	See Table 5.8
Prop PTCA		90%; 61%; 10%	See Table 5.8
Prop CABG		10%; 39%; 90%	See Table 5.8
Prop of patients with 2nd revascularisation			See Table 5.8
PTCA		3.6%	
CABG		1.8%	
Mortality Risk reduction from revasc:			
High Risk		57%	See Table 5.8
Medium Risk		15%	See Table 5.8
Risk reduction of MI:			
PTCA		17%	See Table 5.8
CABG		40%	See Table 5.8
Procedures mortality			
PTCA		3.1%	See Table 5.8

Table 5.10 (cont)

CABG	0.75%	See Table 5.8
Utility	**Value**	**Source**
Low Risk	0.87	See Table 5.9
Medium Risk	0.81	See Table 5.9
High Risk	0.67	See Table 5.9
Adjustment for revascularisation or MI	0.1	See Table 5.9
Other parameters		
Age at start of model	60 years	
Time horizon	25 years	

ER: Effectiveness Review

Tables 5.11 and 5.12 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 5.12 shows the incremental cost per true positive diagnosed, per accurate diagnosis and per QALY. The two former outcomes are based on the outputs of the decision model (diagnostic costs and diagnostic performance). The latter outcome is based upon 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 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 (true positive 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[2]. 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 true positive 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 SPECT-CA strategy is extended dominated by stress ECG-CA

[2] 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.

and CA strategies for the three different types of outputs presented (true positives diagnosis, accurate diagnosis and QALY)[3].

Table 5.11 Estimated costs and outcomes for each diagnostic strategy

Strategy	Diagnostic cost	Diagnostic and treatment cost	% True positive diagnosed	% Accurate diagnoses	QALYs
Prevalence level: 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
Prevalence level: 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
Prevalence level: 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
Prevalence level: 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

[3] 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.

Table 5.12 Stepwise incremental cost-effectiveness

Strategy	Incremental cost per true positive diagnosed	Incremental cost per accurate diagnosis	Incremental cost per QALY
Prevalence level: Baseline 10.5%			
ECG-SPECT-CA			
ECG-CA	£16761	£17,267	£23,648
SPECT-CA	£9339	£9295	£8723
CA	£23956	£24,998	£42,225
Prevalence level: 30%			
ECG-SPECT-CA			
ECG-CA	£5188	£5230	£5098
SPECT-CA	£5345	£5339	£4711
CA	£7143	£7225	£7331
Prevalence level: 50%			
ECG-SPECT-CA			
ECG-CA	£2526	£2535	£2345
SPECT-CA	£4285	£4283	£3807
CA	£3364	£3380	£3178
Prevalence level: 85%			
ECG-SPECT-CA			
ECG-CA	£882	£882	£792
SPECT-CA	£3630	£3630	£3242
CA	£1030	£1030	£927

5.6.2 Sensitivity Analysis

Effect of changing sensitivity and specificity

Tables 5.13 and 5.14 show the estimated incremental cost per QALY gained when the sensitivity or specificity of stress ECG or SPECT was varied. As expected, when 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, while 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; while for high values SPECT-CA dominates the CA strategy. Similarly, for high values of specificity of SPECT the stress ECG-CA strategy is dominated by SPECT-CA (further results of the sensitivity analysis are presented in Appendix 16).

Table 5.13 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	£53,453	£20,214	£45,793	£15,406	£23,648
SPECT-CA	£5,398	stress ECG dominant	SPECT dominant	£35,197	£8,723
CA	£57,214	£57,214	£57,214	£57,214	£42,225

Table 5.14 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	£754,167	£28,002	SPECT dominant	£23,648
SPECT-CA	stress ECG dominant	£6,869	£4,997	£ 6,706.57	£8,723
CA	£17426.14	SPECT dominant	£52.221	£158,694.03	£42,225

Effect of allowing SPECT to stratify patients into medium risk

Within Section 3 data were presented that suggested that SPECT may provide additional independent information to other tests as well as 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 approximately 50% then the SPECT-based strategies become more cost-effective (Table 5.15). Should SPECT have a higher specificity, as used in some of the economic evaluations and the Industry submission, and be able to accurately risk stratify patients then its cost-effectiveness would further improve (incremental cost per QALY of SPECT-CA versus stress ECG-SPECT-CA less than £5000 and SPECT-CA less costly [by average of £324 per patient] and more effective [average of 0.03 per patient] than stress ECG-CA). The estimates in Table 5.15 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 get inappropriate management) but nevertheless illustrates the potential impact of this factor.

Table 5.15 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	£17,928	£23,648
SPECT-CA	£6495	£8723
CA	£16,558[4]	£42,225

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] was used (Table 5.7). 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% vs 18%) and a lower level of indeterminacy for SPECT (2% vs 9%). Tables 5.16 and 5.17 report the impact on cost-effectiveness of using these rates which are more favourable to SPECT.

Table 5.16 Estimated costs and outcomes for each diagnostic strategy when indeterminacy stress ECG = 30% and indeterminacy SPECT = 2%

Strategy	Diagnostic cost	Diagnostic and treatment cost	% True positive diagnosed	% Accurate diagnoses	QALY
ECG-SPECT-CA	£388	£4,983	7.26%	96.74%	12.49
ECG-CA	£752	£5,353	8.14%	97.57%	12.49
SPECT-CA	£511	£5,126	9.35%	98.84%	12.51
CA	£1310	£5,929	10.48%	99.85%	12.51

[4] This Incremental Cost-Effectiveness Ratio strongly diminishes compared with Base Case as a result of a decrease in QALYs for SPECT-CA strategy (Base Case 12.497; this case 12.469).

Table 5.17 Effect on cost-effectiveness when indeterminacy stress ECG = 30% and indeterminacy SPECT = 2%

Strategy	Incremental cost per true positive 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	£23,648
SPECT-CA	£11,419**	£11,419**	£11,422**	£8723*
CA	£25,101	£25,101	£41,404	£42,225

* Incremental cost per QALY for SPECT-CA versus stress ECG-SPECT-CA was £14,123

** Incremental cost-effectiveness SPECT-CA versus stress ECG-SPECT-CA

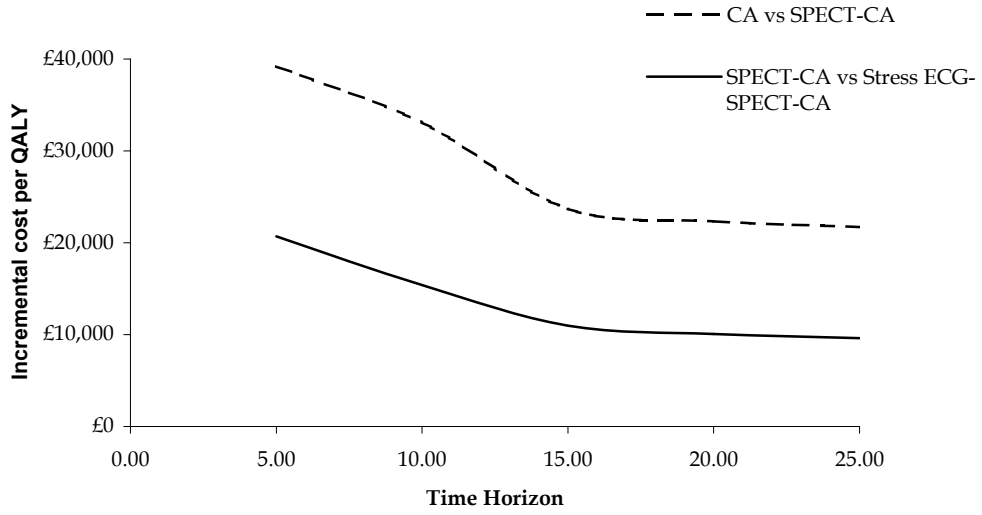
Effect of changes in cost of the diagnostic tests

Varying the cost of the tests between £25 to £225 for stress ECG and £895 to £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 less than £21,000 even when the cost of stress ECG was only £25. The CA option even when the low cost of an angiogram was used was associated with an incremental cost per QALY compared to SPECT-CA of more than £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 less than £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 5.1. 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 quality of life gains).

Figure 5.1 Incremental cost per QALY at different time horizons for the comparison of CA with SPECT-CA and SPECT-CA with stress ECG-SPECT-CA



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 false negatives 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 false negatives 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 5.18)

Table 5.18 Effect of changing the time until false negatives are correctly rediagnosed on the incremental cost per QALY

	Cost	QALY	Incremental cost per QALY	Incremental cost per QALY(base case)
Rediagnosis - after two years				
ECG-SPECT-CA	£5415	12.312		
ECG-CA	£5587	12.320	£19,368	£23,648
SPECT-CA	£5708	12.336	£7891	£8723
CA	£6057	12.346	£35,194	£42,225

Rediagnosis - after five years				
ECG-SPECT-CA	£5374	12.305		
ECG-CA	£5558	12.316	£16,931	£23,648
SPECT-CA	£5692	12.333	£7644	£8723
CA	£6057	12.346	£28,868	£42,225
Rediagnosis – never				
ECG-SPECT-CA	£5210	12.265		
ECG-CA	£5441	12.287	£10,442	£23,648
SPECT-CA	£5627	12.317	£6190	£8723
CA	£6057	12.346	£15,234	£42,225

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 5.18 shows for example the effect of changing the rate at which false negatives 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 anticipated 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 part depend upon both sensitivity and specificity of SPECT and also its ability to correctly identify 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 was 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.

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 decision tree model, or in the subsequent sensitivity analysis.

5.7 Relative cost-effectiveness in females

One of the key subgroups for this analysis was the impact of the use SPECT based strategies to diagnose CAD in females. This subgroup analysis used sensitivities and specificities for females and used a lower prevalence rate of CAD, different MI rates, as well as mortality rates for females aged 60 at diagnosis. The stress ECG-SPECT-CA strategy was less costly while 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 5.19 and 5.20).

Table 5.19 Estimated costs and outcomes for each diagnostic strategy for female subgroup

Strategy	Diagnostic cost	Diagnostic and treatment cost	% True positive diagnosed	% Accurate diagnoses	QALY
ECG - SPECT - CA)	£436	£5,241	3.64%	98.12%	14.08
ECG – CA	£735	£5,541	4.01%	98.43%	14.08
SPECT – CA	£664	£5,477	4.99%	99.45%	14.10
CA	£1,310	£6,121	5.49%	99.85%	14.09

Table 5.20 Incremental cost per outcome for female subgroup

Strategy	Incremental cost per true positive diagnosed	Incremental cost per accurate diagnosis	Incremental cost per QALY
ECG - SPECT – CA			
ECG – CA	£82,133	£93,988	ETT-SPECT dominant
SPECT – CA	SPECT dominant	SPECT dominant	SPECT dominant
CA	SPECT dominant	SPECT dominant	SPECT dominant

5.8 Comparison with the Industry submission

The model presented in this section and the model produced as part of the Industry review had a broadly similar structure and produced similar results. The results are not identical and in some respects the model presented in this section is more favourable to the SPECT-CA strategy than the Industry model. Both models are similar to ones previously reported in the literature (see Section 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). So, 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 less than 50% SPECT-CA is associated with an incremental cost per QALY of no more than £14,600 compare 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 a 50% and 65% prevalence level, SPECT has extended dominance over stress ECG-CA. It is also associated with an incremental cost per QALY compare with stress ECG-SPECT-CA of less than £1800. However, the incremental cost per QALY of CA compare with SPECT-CA is less than £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 no greater than £4000.

It should be highlighted that the model presented in this section does not allow for higher quality of life after revascularisation. In other words, the benefits of revascularisation come from a higher life expectancy but not from a higher quality of life. If a higher quality of life were achieved after revascularisation, those strategies that accurately identify patients for revascularisation (fewer false negatives) 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, results are similar to those presented in our model, as stress ECG-SPECT-CA[5] and SPECT-CA strategies dominate or extendedly dominate other strategies for low levels of prevalence, while stress ECG-CA and CA extendedly dominate the SPECT-CA strategy for high levels of prevalence.

5.9 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, little 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, relative risks 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 (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. At high rates of prevalence (e.g. 85% risk of CAD) the stress ECG-SPECT-CA strategy is dominated by the stress ECG-CA

[5] ECG positive result followed by SPECT-CA

strategy. Furthermore, the CA option is associated with relatively modest incremental cost-effectiveness ratios.

Besides allowing for different values for sensitivity or specificity, the more cost-effective strategy was stress ECG-SPECT-CA. For low levels of sensitivity for SPECT, stress ECG-CA dominates the SPECT-CA strategy, while 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 sensitivity analysis 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 sensitivity analysis 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 specificity and sensitivity for CA equalled one. If this assumption is relaxed then it might be anticipated 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 upon both the sensitivity and specificity of SPECT and also its ability to correctly identify patients for whom management could be decided without the need for an angiogram.

For the sub-group analysis for females 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.

6 IMPLICATIONS FOR OTHER PARTIES

6.1 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.

6.2 Financial impact for patients and others

SPECT is not as widely available in the UK as stress ECG. 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 are made to ensure equality of access.

7 FACTORS RELEVANT TO THE NHS

7.1 National Service Framework for coronary heart disease

The National Service Framework (NSF) states that both exercise ECG 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 three month gap between a decision to investigate and CA then the waiting time target for SPECT should be six weeks for routine studies and one week for urgent studies.

While 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 (due 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 echocardiography, which can also be provided in open access clinics, may be a (more) 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).

7.2 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 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 i.e. what is the local need, existing services, etc. Furthermore, it is possible that the majority of Nuclear Medicine departments have an underprovision of modern gamma camera time and hence the real demand for hardware could be therefore many times the estimate. It is possible that any residual camera time would be put to other potentially beneficial uses. While the cost of equipment and the necessary staff and consumables is large (estimated at £31.07m 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 five to ten years to 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 progressively increase numbers by insisting that new appointment Consultant Cardiologist and Radiology Colleagues have dedicated sessions devoted to Nuclear Cardiology. Sufficient training for them may be rapidly provided. It should also be noted that trained technologists and nurses would also be required. The timescale for this would be much 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 to 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.

7.3 Equity issues

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

8 DISCUSSION

8.1 Effectiveness

8.1.1 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 percutaneous transluminal coronary angioplasty (PTCA), one study evaluated patients with asymptomatic coronary disease, one study focused on patients with left bundle branch block 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, patient characteristics (mean age, gender, previous myocardial infarction), severity of the disease (single vessel versus multivessel disease) 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.

Due 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 true and false positive 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 the medians of sensitivity for SPECT were higher and their ranges smaller than those for stress ECG. Medians of specificity were similar between the two tests, but with wider ranges for SPECT.

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

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

The influence of other patient 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 due to the small number of studies reporting this information.

8.1.2 Prognostic studies

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

In the 20 studies providing general prognostic information, the rates of cardiac events (cardiac mortality or nonfatal MI) were significantly higher for patients with abnormal SPECT scans compared with normal scans. Three 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.

Fourteen 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 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 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 one to three 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 three 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 remaining studies found SPECT to be prognostically useful in a variety of contexts/patient populations, including patients with normal resting ECG, asymptomatic coronary disease, high exercise ECG tolerance, left main and/or 3-vessel CAD 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 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 myocardial perfusion scintigraphy. Travin and Laraia,[92] in a review of the prognostic value of stress myocardial perfusion imaging, 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 myocardial perfusion imaging, 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 attenuation-corrected, SPECT compared with standard SPECT. Two studies, one diagnostic and one prognostic, comparing SPECT with gated SPECT found in favour of gated SPECT and one diagnostic study comparing SPECT with attenuation-corrected SPECT found attenuation-corrected 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, nor evaluated the role of SPECT in pre-operative risk assessment of patients undergoing major surgery who were potentially at risk of coronary events.

8.2 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 quite 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 to 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 and 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 little data were available. 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 myocardial infarction and a poorer quality model reported that compared to standard care the incremental cost per death avoided was lower for a direct CA strategy than 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, Section 3. The results suggest that for low levels of prevalence the incremental cost per unit of output (true positives 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 while SPECT-CA is cost effective, the CA strategy produces more QALYs at a relatively low Incremental Cost-Effectiveness Ratio. At higher prevalence rates (50% and 85%) SPECT-CA strategy is extended dominated by stress ECG-CA and CA strategies.

Besides allowing for different values for sensitivity or specificity, the more cost-effective strategy was stress ECG-SPECT-CA. For low levels of sensitivity for SPECT, stress ECG-CA dominates the SPECT-CA strategy, while 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 upon both sensitivity and specificity of SPECT and also its ability to correctly identify patients with CAD who could be managed medically and may therefore not require an angiogram.

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

8.3 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. Because of time constraint reports published in language other than English were not considered. For the same reason, studies with fewer than 100 participants were not included in the review.

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

8.3.1 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 myocardial perfusion scintigraphy versus CA are available in the literature as well as 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 comparing SPECT with another diagnostic procedure against the reference standard of CA.

There are also a number of reports in the literature that compare the diagnostic performance of SPECT and exercise echocardiography (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) whilst exercise echocardiography had an overall sensitivity of 0.85 (95% CI 0.83 to 0.87) and an overall specificity of 0.77 (0.74 to 0.80). It was concluded that exercise ECHO and exercise SPECT had similar sensitivities for the detection of coronary artery disease, 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 to combine 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.

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, while a second group was managed with a strategy of SPECT, and selective CA.

The remaining studies were cohort studies in which all the 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 nonfatal 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 randomised controlled trials.

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.

8.3.2 Cost and cost-effectiveness

The review of existing economic evaluations focused solely on studies that attempted a formal cost-effectiveness/utility of 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. It is unclear the extent to which data on longer term costs and effects are generalisable to the UK. Are rates of service utilisation used in the Amersham Health submission (as well as the model presented in Section 5) relevant to the UK given that they are derived from non-UK-based studies where they are known to be more likely to intervene? For example, relative risks 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.

These uncertainties present in the model have, in part, been addressed by the extensive sensitivity analysis. 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 sensitivity analysis 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 Section 3. It was unclear, however, the extent to which SPECT would be able to achieve this. 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 sensitivity analysis but there may be concerns that they do not adequately reflect opportunity costs. Therefore, careful consideration is required about whether these costs would apply for an increase in the use of SPECT suggested in the submission by the professional group.

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 left main disease and three-vessel disease. 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 sensitivity analysis 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 Section 5 (unlike that presented in the Industry submission) does not allow for higher quality of life after revascularisation. Therefore the benefits of revascularisation are solely in the form of higher life expectancy. If a higher quality of life were achieved after revascularisation, those strategies that identify accurately patients for revascularisation (fewer false negatives) would perform better.

A further caveat, related to the pay-off model, is the extent to which severity of disease is linked to quality of life. The model presented in Section 5 and many of the models summarised in Section 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.

8.4 Need for further research

Further research is needed on the effectiveness and cost-effectiveness of SPECT compared with stress echocardiography, 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 is of very limited value as a basis of decisions about allocative efficiency. Relatively poor data is available with which to consider longer-term costs and consequences. Both the submission from Amersham Health and the economic model presented in Section 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, attenuation–corrected

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 attenuation-corrected SPECT compared with standard SPECT, diagnostically and prognostically, and whether these techniques are of particular benefit to specific patient groups.

9 CONCLUSION

9.1 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 outcomes in patients as part of a stress ECG-SPECT-CA pathway.
- For the diagnosis of coronary artery disease 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, coronary angiography is associated with relatively modest estimates of incremental cost-effectiveness compared with SPECT-based strategies.
- SPECT-based strategies for the diagnosis of coronary artery disease is women may become cost-effective as the prevalence level of coronary artery disease 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.

9.2 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.

9.3 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 attenuation-corrected 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 echocardiograph.

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