

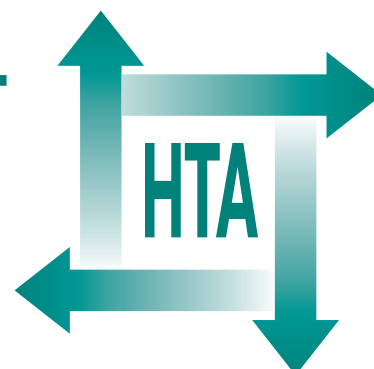
Cost-effectiveness of functional cardiac testing in the diagnosis and management of coronary artery disease: a randomised controlled trial. The CECaT trial

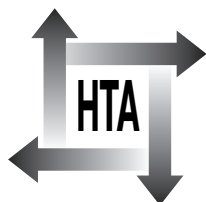
L Sharples, V Hughes, A Crean, M Dyer,
M Buxton, K Goldsmith and D Stone



December 2007

Health Technology Assessment
NHS R&D HTA Programme
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Cost-effectiveness of functional cardiac testing in the diagnosis and management of coronary artery disease: a randomised controlled trial. The CECaT trial

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Declared competing interests of authors: none

Published December 2007

This report should be referenced as follows:

Sharples L, Hughes V, Crean A, Dyer M, Buxton M, Goldsmith K, *et al.* Cost-effectiveness of functional cardiac testing in the diagnosis and management of coronary artery disease: a randomised controlled trial. The CECaT trial. *Health Technol Assess* 2007; **11**(49).

Health Technology Assessment is indexed and abstracted in *Index Medicus/MEDLINE*, *Excerpta Medica/EMBASE* and *Science Citation Index Expanded (SciSearch®)* and *Current Contents®/Clinical Medicine*.

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ISSN 1366-5278

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Abstract

Cost-effectiveness of functional cardiac testing in the diagnosis and management of coronary artery disease: a randomised controlled trial. The CECaT trial

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Objectives: To assess the acceptability and feasibility of functional tests as a gateway to angiography for management of coronary artery disease (CAD), the ability of diagnostic strategies to identify patients who should undergo revascularisation, patient outcomes in each diagnostic strategy, and the most cost-effective diagnostic strategy for patients with suspected or known CAD.

Design: A rapid systematic review of economic evaluations of alternative diagnostic strategies for CAD was carried out. A pragmatic and generalisable randomised controlled trial was undertaken to assess the use of the functional cardiac tests: angiography (controls); single photon emission computed tomography (SPECT); magnetic resonance imaging (MRI); stress echocardiography.

Setting: The setting was Papworth Hospital NHS Foundation Trust, a tertiary cardiothoracic referral centre.

Participants: Patients with suspected or known CAD and an exercise test result that required non-urgent angiography.

Interventions: Patients were randomised to one of the four initial diagnostic tests.

Main outcome measures: Eighteen months post-randomisation: exercise time (modified Bruce protocol); cost-effectiveness compared with angiography (diagnosis, treatment and follow-up costs). The aim was to demonstrate equivalence in exercise time between those randomised to functional tests and those randomised to angiography [defined as the confidence interval (CI) for mean difference from angiography within 1 minute].

Results: The 898 patients were randomised to angiography ($n = 222$), SPECT ($n = 224$), MRI ($n = 226$) or stress echo ($n = 226$). Initial diagnostic tests were completed successfully with unequivocal results for 98% of angiography, 94% of SPECT ($p = 0.05$), 78% of MRI ($p < 0.001$) and 90% of stress echocardiography patients ($p < 0.001$). Some 22% of SPECT patients, 20% of MRI patients and 25% of stress echo patients were not subsequently referred for an angiogram. Positive functional tests were confirmed by positive angiography in 83% of SPECT patients, 89% of MRI patients and 84% of stress echo patients. Negative functional tests were followed by positive angiograms in 31% of SPECT patients, 52% of MRI patients and 48% of stress echo patients tested. The proportions that had coronary artery bypass graft surgery were 10% (angiography), 11% (MRI) and 13% (SPECT and stress echo) and percutaneous coronary intervention 25% (angiography), 18% (SPECT) and 23% (MRI and stress echo). At 18 months, comparing SPECT and stress echo with angiography, a clinically significant difference in total exercise time can be ruled out. The MRI group had significantly shorter mean total exercise time of 35 seconds and the upper limit of the CI was 1.14 minutes less than in the angiography group, so a difference of at least 1 minute cannot be ruled out. At 6 months post-treatment, SPECT and angiography had equivalent mean exercise time. Compared with angiography, the MRI and stress echo groups had significantly shorter mean total exercise time of 37 and 38 seconds, respectively, and the upper limit of both CIs was 1.16 minutes, so a difference of at least 1 minute cannot be ruled out. The differences

were mainly attributable to revascularised patients. There were significantly more non-fatal adverse events in the stress echo group, mostly admissions for chest pain, but no significant difference in the number of patients reporting events. Mean (95% CI) total additional costs over 18 months, compared with angiography, were £415 (–£310 to £1084) for SPECT, £426 (–£247 to £1088) for MRI and £821 (£10 to £1715) for stress echocardiography, with very little difference in quality-adjusted life-years (QALYs) amongst the groups (less than 0.04 QALYs over 18 months). Cost-effectiveness was mainly influenced by test costs, clinicians' willingness to trust negative functional tests and by a small number of patients who had a particularly difficult clinical course.

Conclusions: Between 20 and 25% of patients can avoid invasive testing using functional testing as a gateway to angiography, without substantial effects on outcomes. The SPECT strategy was as useful as angiography in identifying patients who should undergo

revascularisation and the additional cost was not significant, in fact it would be reduced further by restricting the rest test to patients who have a positive stress test. MRI had the largest number of test failures and, in this study, had the least practical use in screening patients with suspected CAD, although it had similar outcomes to stress echo and is still an evolving technology. Stress echo patients had a 10% test failure rate, significantly shorter total exercise time and time to angina at 6 months post-treatment, and a greater number of adverse events, leading to significantly higher costs. Given the level of skill required for stress echo, it may be best to reserve this test for those who have a contraindication to SPECT and are unable or unwilling to have MRI. Further research, using blinded reassessment of functional test results and angiograms, is required to formally assess diagnostic accuracy. Longer-term cost-effectiveness analysis, and further studies of MRI and new generation computed tomography are also required.



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List of abbreviations

ACE	angiotensin-converting enzyme	MACE	major adverse cardiac event
CA	coronary angiography	MCS	mental component score
CABG	coronary artery bypass graft	MDCT	multi-detector computed tomography
CAD	coronary artery disease	MI	myocardial infarction
CCS	Canadian Cardiovascular Society	MM	medical management
CEAC	cost-effectiveness acceptability curve	MRI	magnetic resonance imaging
CECaT	Cost-Effectiveness of functional Cardiac Testing	NICE	National Institute for Health and Clinical Excellence
CI	confidence interval	NHP	Nottingham Health Profile
CT	computed tomography	PCI	percutaneous coronary intervention
DGH	district general hospital	PCS	physical component score
EBCT	electron beam computed tomography	PET	positron emission tomography
ECG	electrocardiogram	QALY	quality-adjusted life-year
ECS	Exertional Capacity Scale	RCA	right coronary artery
EET	exercise ECG test	RCT	randomised controlled trial
EQ-5D	EuroQoL utility measure	SAE	serious adverse event
DTPA	diethylenetriaminepentaacetic acid	SAQ	Seattle Angina Questionnaire
FFR	fractional flow reserve	SD	standard deviation
GLM	generalised linear model	SF-36	Short Form with 36 Items
HRG	Healthcare Resource Group	SPECT	single photon emission computed tomography
HRQoL	health-related quality of life	stress echo	stress echocardiography
ICER	incremental cost-effectiveness ratio	VF	ventricular fibrillation
LAD	left anterior descending	VT	ventricular tachycardia

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



Executive summary

Objectives

The objectives of this trial were to assess the following:

- acceptability and feasibility of functional tests as a gateway to angiography for the management of coronary artery disease (CAD)
- ability of diagnostic strategies to identify patients who should undergo revascularisation
- patient outcomes in each diagnostic strategy
- the most cost-effective diagnostic strategy for patients with suspected or known CAD.

Setting

The setting was Papworth Hospital NHS Foundation Trust, a tertiary cardiothoracic referral centre.

Participants

The trial participants were patients with suspected or known CAD and an exercise test result that required non-urgent angiography.

Exclusion criteria were: recent myocardial infarction or revascularisation, admission with chest pain; urgent revascularisation; contraindication to pharmacological stress testing on magnetic resonance imaging (MRI); incapable of performing modified Bruce exercise test; not available by telephone.

Interventions

Patients were randomised to one of four initial diagnostic tests: angiography (controls); single photon emission computed tomography (SPECT); MRI; stress echocardiography.

Main outcome measurements

The main outcome measurements were as follows:

- Primary: at 18 months post-randomisation: exercise time (modified Bruce protocol);

cost-effectiveness compared with angiography (diagnosis, treatment and follow-up costs). The aim was to demonstrate equivalence in exercise time between those randomised to functional tests and those randomised to angiography [defined as the confidence interval (CI) for mean difference from angiography within 1 minute].

- Secondary: exercise time at 6 months post-treatment; successful completion of initial diagnostic test; Canadian Cardiovascular Society (CCS) classification of angina; health-related quality of life (HRQoL) measured by the Seattle Angina Questionnaire, the Short Form with 36 Items and the EuroQoL; revascularisation rate; adverse events; clinician confidence in test results.

Results

Between September 2001 and September 2004, 898 patients were randomised to angiography ($n = 222$), SPECT ($n = 224$), MRI ($n = 226$) or stress echo ($n = 226$). There were no significant differences between the groups at baseline. At 18 months, compliance was 86% for the full protocol and 94% for cost-effectiveness data.

Initial diagnostic tests were completed successfully with unequivocal results for 98% of angiography, 94% of SPECT ($p = 0.05$), 78% of MRI ($p < 0.001$) and 90% of stress echocardiography patients ($p < 0.001$).

Some 22% of SPECT patients, 20% of MRI patients and 25% of stress echo patients were not subsequently referred for an angiogram. Positive functional tests were confirmed by positive angiography in 83% of SPECT patients, 89% of MRI patients and 84% of stress echo patients. Negative functional tests were followed by positive angiograms in 31% of SPECT patients, 52% of MRI patients and 48% of stress echo patients tested.

The proportions who had coronary artery bypass graft (CABG) surgery were 10% (angiography), 11% (MRI) and 13% (SPECT and stress echo) and percutaneous coronary intervention (PCI) 25%

(angiography), 18% (SPECT) and 23% (MRI and stress echo).

At 18 months, comparing SPECT and stress echo with angiography, a clinically significant difference in total exercise time can be ruled out. The MRI group had significantly shorter mean total exercise time of 35 seconds and the upper limit of the CI was 1.14 minutes less than in the angiography group, so a difference of at least 1 minute cannot be ruled out.

At 6 months post-treatment, SPECT and angiography had equivalent mean exercise time. Compared with angiography, the MRI and stress echo groups had significantly shorter mean total exercise time of 37 and 38 seconds, respectively, and the upper limit of both CIs was 1.16 minutes, so a difference of at least 1 minute cannot be ruled out. The differences were mainly attributable to revascularised patients.

There were significantly more non-fatal adverse events in the stress echo group [rate relative to angiography: 1.95 (95% CI: 1.23 to 3.08), $p = 0.012$], mostly admissions for chest pain, but no significant difference in the number of patients reporting events [1.59 (95% CI: 0.90 to 2.79), $p = 0.327$].

There was no significant difference among the groups in CCS class at either assessment. Clinically important differences in HRQoL could be ruled out.

Mean (95% CI) total additional costs over 18 months, compared with angiography, were £415 (–£310 to £1084) for SPECT, £426 (–£247 to £1088) for MRI and £821 (£10 to £1715) for stress echocardiography, with very little difference in quality-adjusted life-years (QALYs) amongst the groups (less than 0.04 QALYs over 18 months). Cost-effectiveness was mainly influenced by test costs, clinicians' willingness to trust negative functional tests and by a small number of patients who had a particularly difficult clinical course.

Conclusions

Between 20 and 25% of patients can avoid invasive testing using functional testing as a gateway to angiography without substantial effects on outcomes. The SPECT strategy was as useful as

angiography in identifying patients who should undergo revascularisation. The additional cost for the SPECT strategy was not significant and would be reduced further by restricting the rest test to patients who have a positive stress test.

MRI had the largest number of test failures and, in this study, had the least practical use in screening patients with suspected CAD, although it had similar outcomes to stress echo. This technology and decision rules for its interpretation are still evolving.

Stress echo patients had a 10% test failure rate, significantly shorter total exercise time and time to angina at 6 months post-treatment, and a greater number of adverse events, leading to significantly higher costs. Much of the excess costs were attributable to a small number of patients with particularly difficult clinical courses, unrelated to the diagnostic strategy. Given the level of skill required for stress echo, it may be best to reserve this test for those who have a contraindication to SPECT and are unable or unwilling to have MRI.

Implications for the NHS

Functional testing has a place in the diagnostic pathway for the assessment of chest pain in an outpatient population, avoiding invasive tests in a significant proportion of patients. The choice of test may be determined by local expertise and evolution of MRI. In this study, SPECT had the best outcomes, reflecting the greater experience of using this technique, although most differences between the tests were minor and there is a place for all three.

Recommendations for future research

Further research, using blinded reassessment of functional test results and angiograms, is required to formally assess diagnostic accuracy.

Longer-term cost-effectiveness analysis should assess whether decisions based on the functional tests have significant impact in the longer term.

Further studies of MRI and new generation computed tomography are required.

Chapter I

Introduction and background

Background

Introduction

Coronary artery disease (CAD) is the most common cause of death (both in the whole population and for premature deaths) in the UK, causing over 105,000 deaths in 2004.¹ The commonest symptom of CAD is angina. It is characterised by the gradual and progressive development of lipid-laden coronary arterial plaques, which reduce the blood supply to the heart muscle. CAD can lead to myocardial infarction (MI) and sudden cardiac death.

Although the mortality rate in the UK from CAD has been falling since the 1970s, the rate of morbidity is increasing especially in older age groups. Overall, the prevalence of CAD in the UK is estimated to be about 2.65 million people, of whom 1.2 million have had an MI. There were an estimated 275,000 MIs in the UK in 2001, and 335,000 new cases of angina are diagnosed each year.²

The cost of CAD to the NHS in 1999 was estimated at £1.7 billion and the total cost was around £7 billion when informal care and productivity costs were included.²

Diagnosis of CAD

For most patients, the diagnosis of chronic stable angina is based on a combination of medical history and exercise electrocardiogram (ECG) test (EET) results. Those patients with angina that is poorly controlled on medication and who are considered clinically suitable for revascularisation are referred for further investigation. Under most circumstances, a diagnosis of significant disease (i.e. $\geq 70\%$ diameter stenosis in a major vessel or $\geq 50\%$ in left main stem) results in a referral for intervention. In addition to symptomatic control, specific decisions regarding revascularisation depend on the presence and distribution of significant disease. If a stenosed or occluded vessel subtends non-functioning or infarcted myocardium, then the likely decision is to rely on medical management rather than revascularisation. The TIME trial provided some randomised controlled trial (RCT) evidence that there is significant symptom relief from referral

for further investigation, and revascularisation if subsequently indicated, particularly in elderly patients with poorly controlled symptoms.³

Exercise ECG test

EET is widely used for non-invasive detection of CAD owing to its ready availability (usually in District General Hospital Cardiology outpatient clinics), low risk and relatively low cost. However, a normal EET does not exclude CAD and EET is a poor diagnostic test in low-risk populations (such as women) owing to its low positive predictive value in a population with a low prevalence of the disease. A systematic review⁴ on stress single photon emission computed tomography (SPECT) imaging calculated the sensitivity and specificity of the two techniques against coronary stenosis in ten studies. The range of sensitivities was 0.44–0.92 (median 0.63) for EET and 0.63–0.93 (median 0.76) for SPECT. Specificity for these ten studies ranged from 0.41 to 0.80 (median 0.77) for EET and from 0.10 to 0.80 (median 0.65) for SPECT.

The limited accuracy of EET in diagnosing CAD is also due in part to its position near the bottom of the ischaemic cascade. Myocardial ischaemia develops during exercise when the increase in metabolism is not matched by an increase in perfusion. Prolonged hypoperfusion leads to wall motion abnormalities, initially diastolic and then systolic, followed by ECG changes and chest pain.

Exercise testing is a low-risk investigation even in patients with known CAD, but serious complications occur in 0.2–0.4% of tests. Deaths occur rarely, in $<0.05\%$ of tests.

Coronary angiography

Coronary angiography (CA) is considered the 'gold standard' for defining the site and severity of coronary artery lesions. CA provides mainly anatomical information, measures the degree of stenosis and is necessary prior to revascularisation to pinpoint the areas that are to be treated. However, it is not always a reliable indicator of the functional significance of coronary stenoses due to the limits of resolution and can be ineffective in determining those plaques that are liable to lead

to an acute coronary event.^{5,6} Routine use of CA without prior non-invasive testing is not advisable, except in those with a high pretest probability of significant disease, partly due to the high cost, but also because of the associated morbidity and mortality.² The most serious complications of CA are death (0.1–0.2%), non-fatal MI (0.1%) and cerebrovascular accidents (0.1%).

Currently, the majority of patients at most UK centres are investigated with an initial EET followed by CA if the EET is positive or if the EET is inconclusive and clinical suspicion of CAD is high. This diagnostic strategy has led to a proportion of patients having a diagnosis of normal coronary arteries or non-significant coronary disease following CA. Between June 2005 and March 2006, 15% of patients at Papworth had a diagnosis of normal coronary arteries and a further 36% continued on medical management (personal communications from Papworth Hospital Clinical Effectiveness Unit). The literature also suggests a rate of normal coronary angiography that may be as high as 20% overall and even higher in women.^{7,8}

Since the current study began, electron beam computed tomography (EBCT) and multi-detector computed tomography (MDCT) have become more common for non-invasive coronary assessment, but they were not routinely available when the study began and so are not reviewed here.

Appropriateness of coronary angiography/revascularisation

Although angiography remains the most frequently used investigation in the investigation of chest pain and in many cases is entirely appropriate, it remains true that angiographic appearances may be misleading and, without an assessment of the functional significance of lesions, are known to lead to inappropriate revascularisation. Rates of revascularisation are often influenced as much by local facilities and self-referral as by clinical necessity.⁹ When expert consensus panels meet and apply well-validated Delphi criteria to define appropriate indications for CA and revascularisation, there is a considerable proportion of potential indications for which angiography and subsequent revascularisation are considered uncertain or even inappropriate.^{10,11} Subsequent application of these agreed criteria suggests that a significant minority of revascularisation procedures are of questionable benefit. Up to 20% of patients in one large Swedish cohort were subsequently judged to have been inappropriately referred for coronary

revascularisation. This occurred significantly more often when percutaneous coronary intervention was performed (38%) than when a patient underwent bypass surgery (10%). The proportions who had revascularisation for indications classified as 'uncertain' were similar (30% and 12%, respectively).^{12,13} Application of RAND appropriateness criteria to a large prospective British cohort of patients under investigation of chest pain concluded that 5% underwent inappropriate CA and that a further 33% had CA for indications rated as uncertain by the consensus panel. Importantly, subsequent mortality and revascularisation rates were highest in the group rated appropriate for angiography and lowest in the group deemed inappropriate, suggesting that the criteria were effective in risk stratifying patients.¹⁴

Predicting stenosis severity at angiography

Visual assessment of angiographic severity is unreliable in predicting functional significance of a lesion and this is not improved greatly by quantitative measurements. Indeed, even experienced interventionalists may struggle to correctly identify significant lesions (as defined by fractional flow reserve) from the coronary angiograms alone, being incorrect in one study in 22–49% of cases, with disagreement between the readers in over half the cases.¹⁵ Invasive measurement of pressure drop across a lesion is currently regarded as one of the most accurate methods for assessing stenosis severity using a flow wire to assess distal coronary pressure in relation to aortic pressure under conditions of resting flow and also adenosine-induced hyperaemia.¹⁶ More importantly, fractional flow reserve (FFR) measurements also allow interventionalists to target which lesions to leave alone. One multi-centre European study randomised patients with intermediate severity coronary lesions to medical or interventional therapy according to FFR. All those with an FFR <0.75 (accepted as the cut-off for a significant lesion) had interventional management whereas those in whom FFR was >0.75 were randomised to either medical or interventional management. The greatest symptomatic benefit at 2-year follow-up was seen in the group with low FFR treated appropriately by revascularisation. However, in those without physiologically significant lesions (FFR >0.75), those treated by intervention were symptomatically worse than those treated with medical therapy alone.¹⁷ The medium- to long-term reliability of risk stratification by FFR has also been confirmed in recent publications.^{18,19} Several other studies

have confirmed that revascularisation may be safely deferred without adverse outcomes in both multi-vessel and left main stem coronary disease when FFR measurements fail to demonstrate significant flow limitation. These are both groups traditionally referred for coronary artery bypass surgery on prognostic grounds.^{18,20} Previous work has shown concordance between measurements of FFR and detection of ischaemia on stress echo, nuclear scintigraphy and stress perfusion MRI, which were the functional tests used in this study.²¹⁻²³

The data supporting the use of non-invasive imaging in the investigation of chest pain are reviewed in the following sections.

Functional tests

Non-invasive imaging tests are available that assess ischaemia higher up the cascade than EET, including stress echocardiography (stress echo) (to assess wall motion), SPECT and magnetic resonance imaging (MRI) (to assess myocardial perfusion) and positron emission tomography (PET) (to assess myocardial metabolism). In 2003, the National Institute for Health and Clinical Excellence (NICE) stated that imaging tests may be added in to the diagnostic schedule to improve detection and or localisation of exercise-induced ischaemia.²

All of these tests can use a pharmacological agent (adenosine or dobutamine) to induce stress. These drugs are safe and well tolerated with a low risk of serious adverse events (SAEs) (<0.01%).

Currently, stress echo and SPECT are used primarily for patients unable to complete an EET or in patients with angiographically detected stenosis of uncertain significance. Adenosine-stress MRI is, currently, rarely used in the diagnosis of CAD.

The use of radionuclide imaging varies widely in different countries. Lucas and colleagues²⁴ reported that in the USA the proportion of non-invasive imaging tests performed with radionuclide imaging increased from 50% to >80% between 1993 and 2001. The corresponding fraction in Canada rose from 33% to 50%.²⁵ The nearly 30% absolute rise in US rates of radionuclide imaging suggests that these imaging studies have become standard practice without clear evidence to support their routine use in place of exercise tests alone.

Stress echo

Echo is one of the most frequently used tools for the investigation of a wide range of cardiological problems. The portability and relative affordability of the equipment have led to a very rapid acceptance of the technique by the general medical community. Large numbers of staff have been trained to high operating standards across the world and standardised methods of examination and reporting are commonplace. Echo, which operates on the principle of differential absorption and reflection of sound waves by tissues of differing properties, utilises no ionising radiation and therefore could be an ideal modality for screening populations with symptoms of chest pain.

It has been known for many years that angina is a multi-step process sometimes described in terms of an 'ischaemic cascade'.²⁶ Microvascular perfusion abnormalities develop under conditions of 'stress' (which may be physiological or pharmacological). If a sufficient volume of local myocardium is involved, a regional wall motion abnormality will develop. The abnormality may be a subtle or obvious reduction in systolic thickening and contraction (hypokinesis) or development of an area of no thickening or movement at all (akinesis) or paradoxical motion (dyskinesis).

Stress echo makes use of this phenomenon. Regional wall motion abnormalities are sought by challenging the patient with (most commonly) an incremental infusion of intravenous dobutamine, which acts as a positive inotropic agent. Alternative methods of stress include treadmill or bicycle exercise and intravenous adenosine infusion. Continuous or staged echocardiographic monitoring is used throughout to look for changes in regional function. Dobutamine increases myocardial oxygen demand, which translates to an increased requirement for coronary blood flow. In the presence of a significant epicardial coronary stenosis, blood flow cannot increase by the amount required and so regional ischaemia and wall motion abnormalities develop. Responses may be biphasic, indicating the presence of hibernating myocardium within areas of impaired myocardium at rest, with transient regional improvement at low-dose dobutamine as myocardial function is recruited and subsequent decline due to increasing ischaemia. Biphasic responses have high positive predictive value for improvement in myocardial function following revascularisation.²⁷

Large studies suggest that approximately 5% of patients do not have an adequate acoustic

window.²⁸ The use of intravenous echo contrast, administered repeatedly during the study, improves endocardial definition and furthers appreciation of regional abnormalities. All stress echo examinations within the Cost-Effectiveness of functional Cardiac Testing (CECaT) trial were performed using dobutamine stress and with the benefit of intravenous microbubble contrast.

Diagnostic accuracy of stress echo

The sensitivity, specificity and accuracy of stress echo is in the range 80–85% with the highest sensitivity (>90%) for three-vessel disease and the lowest (75%) for single-vessel disease.²⁸ There are regional differences in sensitivity, however, with single-vessel circumflex disease being less well identified than isolated left anterior descending (LAD) or right coronary artery (RCA) disease – this is probably because acoustic shadowing often means the lateral wall is less well visualised than elsewhere. Recent work suggests further improvements in sensitivity and specificity may be possible with use of tissue Doppler imaging, which allows quantification of fractional area changes of left ventricular segments to be more accurately assessed compared with visual assessment alone.²⁹

Prognostic value of stress echo

There is strong evidence of the negative predictive value for a normal stress echocardiogram (irrespective of method of stress). In patients with normal wall motion at both rest and stress the event rate is extremely low and similar to that of an age-matched population.^{30–34}

Stress echo imaging in selected groups

Dobutamine stress echo has also been validated amongst populations who form a large percentage of real-life patients but are often under-represented in trials of new technology. The predictive outcome remains high among the elderly, in whom a positive study predicts an annual event rate of up to 8%.³⁵

Women have been extensively studied with the technique, with a higher reported sensitivity and specificity for detection of CAD than other modalities, including exercise testing and nuclear perfusion imaging.^{36–38} Similarly independent prognostic information has been demonstrated for prediction of all-cause mortality in women using this technique.³⁹

Diabetic patients are in a high-risk category for development of CAD and cardiac events. They are frequently unable to perform adequate exercise tests because of concomitant vascular disease in

the legs. Important prognostic information has been obtained for these individuals from pharmacological stress echo.^{40,41}

The final group of patients in whom standard exercise electrocardiography is often of low sensitivity and specificity includes those patients with systemic hypertension and/or abnormalities on the resting ECG. Hypertension is strongly associated with CAD,⁴² and may be better assessed by stress echo than nuclear perfusion techniques according to some reports.^{43,44}

Comparison with gated SPECT

There are limitations inherent to the stress echo technique. Chief among these is the problem of reliably obtaining good images and reproducible tomographic slices as the heart rate goes up with increasing rate of dobutamine infusion. Furthermore, there may be significant inter-observer variability in image interpretation due to the subjective nature of wall motion assessment. None of these are significant problems for myocardial SPECT, although the technique has its own limitations, namely attenuation artifacts, lower spatial resolution and the use of ionising radiation.

However, major advances in echo with the development of harmonic imaging and intravenous microbubble contrast in recent years have markedly improved image resolution and endocardial definition, increasing the reliability and reproducibility of the test, and allowing successful studies to be performed in the great majority of an unselected population. In one study, just over half of the participants required a nuclear perfusion study following an equivocal non-contrast stress echo, whereas only 3% did so if contrast was given at the time of echo examination.⁴⁵

In practice, sensitivity for detection of CAD is similar in head-to-head comparisons, although specificity appears higher for stress echo.⁴⁶

Safety of stress echo

Serious side-effects are uncommon, at less than one in 1000 studies.²⁸ The most common reasons for premature termination of the study (in up to 8% of cases) are arrhythmias, severe hypertension, severe hypotension or left ventricular outflow tract obstruction.^{47,48} The technique appears safe even in patients with left ventricular thrombi.⁴⁹

Stress perfusion MRI

MRI is a relatively new tool for the examination of the heart compared with the other non-invasive

modalities described. In the past 10 years there have been rapid advances in technology, both in hardware and in pulse sequence design, that now make it possible to image the whole heart volume during the bolus chase perfusion technique that is described below. The following summary will describe both the technique and the existing body of scientific evidence which supports it.

The physiological fundamentals of the stress perfusion process are exactly the same as for nuclear perfusion studies performed with adenosine. The adenosine is infused intravenously into the patient in order to cause maximal coronary vasodilatation. This has the effect of dramatically increasing coronary blood flow in normal vessels. In contrast, in those vessels containing a significant stenosis, generally regarded as 70% or more of the luminal diameter,⁵⁰ flow cannot increase significantly above baseline levels. A tracer agent that is injected at maximum hyperaemia will thus distribute within myocardium according to relative flow rates. This discrepancy in local concentrations of tracer agent can be discerned by specific MRI pulse sequences, which optimise the signal from the tracer, gadolinium chelate, that is used.

Magnetic resonance perfusion is currently performed as a first-pass bolus-tracking method. An intravenous adenosine infusion is given for a number of minutes just as in nuclear imaging. At peak stress, a bolus of gadolinium–diethylenetriaminepentaacetic acid (DTPA) is injected. The myocardium is imaged as a stack of short axis slices and recurrent images are acquired at each slice level, normally either every heartbeat or every other heartbeat depending on the extent of anatomical coverage required. The end result is a series of images in which dynamic passage of contrast agent through the ventricles and into the myocardium can be directly observed.⁵¹

Areas of relative hypoperfusion are identified as dark strips, either subendocardial or transmural depending on the severity of stenosis in the supplying epicardial coronary artery. After approximately 20 minutes to allow washout of contrast agent, a further ‘resting’ study is performed again with injection of gadolinium–DTPA, but without adenosine-induced hyperaemia. Thus the two perfusion series are analogous to the rest–stress studies in technetium or thallium imaging.

Quantitative and semiquantitative measurement of myocardial perfusion

Early work with MRI stress perfusion was limited by an inability to image the heart quickly enough

during the passage of a rapidly injected bolus of gadolinium in more than one or two sequential slices. This was because the available pulse sequences were not fast enough to permit data sampling at the spatial and temporal rate required. Even when several slices could be acquired there were often important baseline differences in signal (prior to injection of gadolinium) due to the application of a single preparation pulse at the beginning of the sequence with inevitable lengthening of the inversion–recovery time ‘seen’ by subsequent slices. Hence in the early days of MRI perfusion quantitative measurement was subject to a number of errors.

It was not until the advent of faster pulse sequences, often with an echoplanar readout,⁵² that multislice perfusion imaging became a genuine possibility. Development of a ‘notched’ saturation recovery pulse meant that every slice acquired was subject to the same degree of myocardial nulling prior to contrast arrival,⁵³ permitting flow quantification to be attempted. Nevertheless, problems remain with quantitative perfusion MRI. The reasons are complex and well described elsewhere.⁵⁴ They hinge on the imperfect nature of currently available preparations of gadolinium, none of which are true intravascular contrast agents but instead partition into the extracellular space with an extraction fraction that is, at least partly, dependent upon flow rate. Furthermore, many modelling assumptions have to be made when mathematically describing the behaviour of a bolus of contrast medium, that are unlikely to hold true in clinical practice.

Semiquantitative methods normalise peak flows to those obtained at rest, effectively generating a measure of myocardial perfusion reserve.^{55,56} This is similar to the concept of coronary flow reserve, which is widely used in the cardiology literature. Although perfusion reserve measured in this way tends uniformly to underestimate myocardial flow when compared with PET-derived estimates of flow reserve, there nonetheless remains a good correlation between the two across a wide range of flows. This is true both for normal volunteers and for individuals with angiographically documented CAD.^{57,58} Similar correlations are also seen when myocardial perfusion reserve is compared with indices of coronary flow derived from intra-coronary Doppler flow wire studies.⁵⁵ However, these methods are laborious in terms of post-processing and require adequate motion compensation on a slice-to-slice basis.

Results of clinical trials

There have been no large multi-centre trials of MRI myocardial perfusion as yet, although one small European study reported recently.⁵⁹

Interpretation of the current trials is hampered by highly selected patient groups, small numbers, differing perfusion sequences and wide variations in the anatomical and temporal coverage achieved depending upon the equipment available.^{60–69}

Furthermore, no common gold standard exists. Although, for pragmatic reasons, most authors have chosen to validate the technique against angiography, this is an imperfect gold standard.⁷⁰ Quantitative measurements of stenosis are better than visual estimation but remain a crude measure that fails to account for the effects of diffuse disease, length of diseased segment and serial stenoses. Defining a percentage diameter reduction in luminal area as the ‘cut-off’ point for defining a significant lesion is also a binary and simplistic approach. At least one paper has demonstrated convincingly the fallibility of comparing MRI perfusion against angiography rather than a more appropriate gold standard such as flow-tracer PET.⁷¹

Comparison with gated SPECT

There have been relatively few studies that compare MRI stress perfusion directly with gated SPECT and these have enrolled only small numbers of patients. These studies, however, have demonstrated higher sensitivities and specificities for the detection of CAD using MRI.^{72–75} In these studies, the reference gold standard of CA was applied. Clearly, much larger studies will be required to confirm the value of MRI. One such study involving over 700 patients is currently under way in the UK (JP Greenwood, Leeds University: personal communication, 2006). Encouragingly, patients appear to tolerate stress MRI examination at least as well as gated SPECT.⁷⁶

Prognostic data

As yet there are limited outcome data available for adenosine stress MRI. One recent study evaluated patients presenting as an emergency with symptoms of chest pain, negative troponin and equivocal resting ECG.⁷⁷ The patients underwent stress perfusion MRI and were followed up at 12 months to document cardiac events including death, MI, >50% stenosis at CA and need for revascularisation. Adenosine perfusion abnormalities had 100% sensitivity and 93% specificity as the single most accurate component of the cardiac MRI examination and added significant prognostic value in predicting future

diagnosis of CAD, MI or death over clinical risk factors.

One recent publication of more than 500 subjects undergoing stress perfusion MRI for known or suspected CAD demonstrated 3-year event-free survival of 99% following a negative study. Conversely, stress-induced ischaemia provided incremental information on risk of future events above and beyond other patient clinical data. These early data imply a useful prognostic role for stress perfusion MRI in coronary heart disease patients.⁷⁸

Nuclear perfusion

Nuclear perfusion has an extensive pedigree extending back over a quarter of a century, with hundreds of thousands of scans performed worldwide each year. Recent guidelines have suggested that the technique could be even more widely employed in the future,^{2,79} acting as a screening test in order to determine which patients proceed to CA.

The principle of stress perfusion testing is straightforward. One of several methods is used to increase coronary blood flow significantly above resting levels. In the presence of normal coronary anatomy, stress-induced vasodilatation leads to a uniform increase in coronary flow in each of the major epicardial coronary arteries. However, in the presence of a fixed stenosis of sufficient severity the distal microvascular bed, which is already maximally vasodilated, cannot increase flow to the same extent as unobstructed vessels and local perfusion reserve becomes exhausted. Such discrepancies in flow are revealed by injecting the patient with a tracer agent which partitions into myocardium according to local flow. Radionuclide pharmaceuticals of varying properties act as the tracer compound in this regard.

Stress nuclear perfusion thus reveals perfusion defects which are often absent on resting studies since basal coronary flow is generally very well preserved (through distal microvascular dilatation) under resting conditions until coronary stenoses become very severe, often >90% luminal narrowing. Use of a stress–rest protocol therefore dramatically improves the diagnostic accuracy of the study.

Many centres attempt exercise stress in the first instance with the patient exercising either on a

treadmill or stationary bicycle prior to tracer injection. Other centres have adopted a policy of near-routine use of pharmacological stress with either adenosine/dipyridamole or dobutamine. There are several papers attesting to the validity of each approach.^{80–83}

Since both stress and rest parts of the examination are required for diagnosis, two separate injections of radionuclide are required. There are good arguments for both the so-called “2 day” and “1 day” protocols.^{84–86} Experience at Papworth has always been to schedule rest and stress portions of the examination on different days in order to optimise administered radioactive dose (‘activity’) to the patient for both parts of the test.

Additional information may be gained at the time of the scan if cardiac gating is in use during data acquisition. The principles behind this are discussed elsewhere.⁶² Using this method, important additional information is derived, including ejection fraction, regional wall motion and thickening and left ventricular volumes. Since resting ejection fraction alone is a powerful determinant of prognosis,^{87,88} this is valuable additional information which effectively comes for ‘free’. The only disadvantage of gating the study is that effective acquisition times are somewhat longer in order to record sufficient counts per projection in each cardiac phase. The use of ECG gating in this way has been shown to increase diagnostic specificity without affecting sensitivity.^{89–92} As with all techniques which trigger data acquisition to the surface electrogram, a steady rhythm is a prerequisite for gated studies, which effectively excludes patients with arrhythmias such as atrial fibrillation.

Diagnostic accuracy of myocardial perfusion imaging

The sensitivity and specificity of planar technetium-99m perfusion imaging is in the order of 90 and 70–80%, respectively, without significant difference between visual and semiquantitative methods of assessment.^{93,94} As explained above, the use of ECG gating with SPECT has increased specificity without detriment to sensitivity.⁸⁹ Nuclear perfusion testing is also well validated in the setting of acute chest pain, where one of the landmark studies demonstrated a sensitivity of 96% and specificity of 79% for the detection of CAD in patients without prior MI presenting with unstable angina.⁹⁵ Assessment within 12 hours of the episode of pain has shown a similar level of accuracy with a high negative predictive value for cardiac events in the subsequent 18 months.⁹⁶

Prognostic data

One of the main uses of non-invasive testing is in the prediction of future untoward events. Cardiac nuclear perfusion is well established in this regard, with the ability to distinguish individuals at high and low risk of adverse cardiac events. A normal scan predicts a low event rate no greater than that of an age-matched population or of a population with angiographically normal coronary arteries.^{97–99} Perhaps more surprisingly, a normal scan is also predictive of low risk in patient subsets with strongly positive exercise tests or evidence of epicardial coronary disease at angiography.^{100,101} On the other hand, multiple variables predict future hard cardiac events. These include reversible ischaemia in multiple segments, transient left ventricular cavity dilatation during stress and lung uptake of thallium-201.^{102–104} High-risk individuals have been shown to benefit from cardiac surgery.¹⁰⁵ However, both low- and moderate-risk patients experience equal mortality outcomes irrespective of whether they undergo medical therapy or a revascularisation strategy.^{106,107}

Myocardial perfusion imaging in selected groups

Diabetic patients are an important group with much higher rates of CAD than other populations.¹⁰⁸ Exercise testing alone is often inadequate as these individuals frequently suffer from peripheral vascular disease, which limits overall exercise capacity; pharmacological stress is therefore required in this situation.^{109,110} Published studies have demonstrated the validity of this approach with sensitivities and specificities for the detection of CAD equivalent to that in non-diabetic patients.^{111–113}

Female patients with chest pain pose particular problems for the physician. Published studies have demonstrated the unreliability of the clinical history with a high incidence of non-cardiac chest pain in premenopausal women referred for coronary angiography.^{114–116} Similarly, treadmill exercise testing was shown over 30 years ago to be unhelpful in women because of high rates of false-positive responses.¹¹⁷ At least one study has shown, however, that adenosine SPECT imaging is capable of yielding high levels of diagnostic accuracy in women with both low and high prescan likelihood of disease.¹¹⁸ Breast attenuation artifacts are of theoretical concern,¹¹⁹ although gated SPECT imaging serves to reduce false-positive results through demonstration of normal regional wall thickening and motion in the apparently hypoperfused anterior wall.¹²⁰

Comparison with stress echo

Stress echo has become popular in recent years as an alternative to gated SPECT for the non-invasive diagnosis of CAD. Early evidence suggested that annual cardiac event rates following a 'normal' stress echo can be as high as 7%, implying suboptimal sensitivity.^{121,122} This is much higher than the subsequent event rate following a normal myocardial perfusion study.¹²³ However, it is likely that the poorer sensitivity seen reflects a technology that was less mature than that of nuclear imaging at the time these studies were performed. There have been major improvements since then in both echo hardware and software and the widespread adoption of the use of bubble contrast agents for left ventricular cavity opacification. Despite these advances, one recent study comparing stress echo and gated SPECT for the detection of CAD demonstrated a much higher sensitivity for the nuclear study, although the specificity of stress echo was excellent.¹²⁴ However, another study, with relatively long-term follow-up, failed to show any difference in prognostic ability between the two modalities.¹²⁵

Treatment of CAD

Coronary revascularisation is a costly procedure and carries a significant peri-procedural risk [0.5% mortality with percutaneous coronary intervention (PCI) and 1.7% with coronary artery bypass graft (CABG) surgery] (Healthcare Commission website).⁵ However, the sum of evidence from clinical trials of CABG and of coronary angioplasty compared with medical therapy shows that mortality rates are reduced in patients with more severe disease. Bypass grafting prolongs life in patients with left main stem or triple-vessel disease, especially if the patient has concomitant left ventricular dysfunction.¹²⁶ The second Medicine, Angioplasty or Surgery Study (MASS-II)¹²⁷ reported significantly lower 1-year mortality among the patients randomised to the medical therapy arm (1.5%) compared with PCI (4.5%) and CABG (4.0%). Patients randomised to CABG had the lowest rate of subsequent MI and the highest proportion of event-free survival at 1 year (93%) compared with medical management (MM) (88%) and PCI (76%). They also had the highest proportion of patients free from angina at 1 year (61%) compared with MM (36%) and PCI (55%) (Table 1). Other studies have reported proportions of patients free from angina at 1 year to be 90% for patients having CABG compared with 75% of patients having PCI.¹²⁸ Other studies have shown a decrease in the occurrence in angina from 75%

TABLE 1 Results from MASS-II study

	MM	PCI	CABG
One-year mortality (%)	1.5	4.5	4.0
Event-free survival at 1 year (%)	88	76	93
Freedom from angina at 1 year (%)	36	55	61

before surgery to 3.7% at 12-month follow-up.¹²⁹ This means, however, that a significant proportion of recipients of cardiac revascularisation have some anginal symptoms 1 year later. There is a large body of evidence showing that coronary revascularisation improves patients' quality of life and this is related, in the most part, to reduction in angina classification.

Revascularisation does not necessarily prevent infarction. The incidence of MI following CABG is equal to or greater than that seen with medical therapy.¹³⁰ PCI may reduce acute reinfarction following thrombolysis, but there are few data to suggest a reduction in MI in chronic stable angina.¹³¹ Revascularisation is, therefore, primarily to relieve symptoms rather than improve prognosis. Revascularisation needs to be targeted at those who will benefit most and current evidence suggests this is the patient group with clearly defined reversible ischaemia in an area matched angiographically by significant disease.

There is growing evidence that revascularisation is not being targeted appropriately. In patients presenting with acute coronary syndrome, rates of CA, PCI and CABG were significantly higher in the USA than in Canada (69 versus 39%, 24 versus 13%, 24 versus 14%, respectively).¹³² However, there was no difference in the rates of MI or cardiac death. Overall, reported rates of PCI and CABG relative to angiography are similar in the two countries and are similar to those reported in the UK.

Review of health-related quality of life

In recent years there has been increased attention given to the measurement of health-related quality of life (HRQoL) as an indicator of health outcome. This has been particularly the case for CAD, where the goal of treatment is not only to prolong life, but also to relieve symptoms and improve function. A wide range of HRQoL instruments have been used in studies of CAD and revascularisation, both generic instruments such as

the Short Form with 36 Items (SF-36) and Nottingham Health Profile (NHP), and disease-specific instruments such as the Seattle Angina Questionnaire (SAQ). The SF-36 is a well validated, multi-dimensional and reliable questionnaire for many patient groups, including patients with CAD.^{133–135} The SAQ has also been well validated and is a reliable angina-specific, instrument suitable for self-administration.^{134–138}

Increases in HRQoL have been shown using both generic^{128,139,140} and disease-specific^{141–143} instruments following CABG and PCI. Kiebzak and colleagues¹²⁹ found that the pre-CABG HRQoL values were below published normative data with increases at 12 months post-surgery. These changes paralleled decreases in angina. Caine and colleagues¹³⁹ found that at 1 year post-surgery the NHP scores compared favourably with those from a normal male population and these changes persisted at 5 years after surgery.¹⁴⁴ Men have been found to show a greater increase in HRQoL than women^{40,141,143,145} and this is thought to be due, in part, to the differing presentation of CAD in women. Women were older, more severely ill with more co-morbidities and lower HRQoL scores prior to revascularisation. Various other factors have been identified as predictors of changes in HRQoL following CABG. Increases in HRQoL were associated with male sex, younger age and more-educated patients.¹⁴⁰ Poorer HRQoL was associated with current smoking, hypertension and lower ejection fraction prior to CABG.¹⁴⁶ A study by Lukkarinen and Hentinen¹⁴⁷ comparing the HRQoL in patients receiving either CABG, PCI or MM found that those patients who had revascularisation had significantly improved HRQoL up to 8 years after the procedure compared with before, but there was no change in the HRQoL at either 1 or 8 years of follow-up in patients who were managed medically.

There has been very little research published on the relationship between functional test results and HRQoL. Mattera and colleagues¹⁴⁸ evaluated the

SF-36 in 195 patients referred for EET and SPECT and found that the variation in the physical functioning and general health perception scales is not predicted well by the results of the diagnostic test. In a study comparing 93 consecutive patients, 45 of whom underwent CABG, a significant association was found between the results of the EET and the energy and pain scales from the NHP. This association was closer than that found between EET results and CCS classification.¹⁴⁹ In addition, Marwick and colleagues¹⁵⁰ reported results from 63 patients with left ventricular dysfunction and heart failure before and after CABG who all had PET scans and 47 of whom had stress echo. They found that HRQoL increased post-CABG but there was no correlation between HRQoL scores and the results of either PET scan or stress echo.

Summary

The preceding sections have provided a brief overview of the uses and limitations of the three main functional imaging tests employed as part of the CECaT trial pathways. The most established of the three tests, with the greatest weight of evidence behind it, is nuclear perfusion imaging. Stress echo is rapidly gaining acceptance as an alternative, with increasing data to support its use. Currently, stress perfusion MRI remains in the research arena, requiring further work and validation before its use as a routine clinical tool can be fully recommended.

Format of the report

This report is arranged as follows. A rapid systematic review of cost-effectiveness studies of diagnostic strategies in CAD is reported in Chapter 2. Study methods are described in Chapter 3. Chapters 4–6 summarise, respectively, basic clinical results, HRQoL including utilities, and resource use and cost-effectiveness analysis. Chapter 7 provides an overview of the trial results and its contribution to the evidence.

Chapter 2

Systematic review of economic evaluations

Introduction and methods

Introduction

This rapid, systematic review of economic evaluations of alternative diagnostic strategies for CAD patients uses similar methods to those reported by Mowatt and colleagues in their systematic review of the use of SPECT myocardial perfusion scintigraphy in the diagnosis and management of angina and MI.⁴ The same search strategies were used and expanded to include studies that involved comparisons of cardiac MRI, stress echo and CA in addition to SPECT and included studies published up to February 2006.

Search strategies

Studies that reported both the costs and outcomes of diagnostic strategies involving cardiac MRI, stress echo, SPECT and CA relative to each other or to other strategies involving any other types of diagnostic intervention were obtained from a (systematic) review of the literature. No language restrictions were imposed but searching was limited to studies published after 1990. The

following databases were searched for studies assessing cost-effectiveness:

- MEDLINE, 1990–February 2006; EMBASE, 1990–2006
- PreMEDLINE (Ovid), February 2006
- NHS-EED (NHS CRD), February 2006.

Inclusion and exclusion criteria

To be included, studies had to compare both costs and outcomes for patients with suspected CAD using diagnostic strategies involving cardiac MRI, stress echo, CA or SPECT, either with each other or against alternative diagnostic strategies (ECG, PET, etc.). Studies reported in languages other than English were identified from their abstract but were not included in the review. Studies were excluded from the review if they made no attempt to relate cost to outcome data. Review articles of relevant studies were also not considered for inclusion. *Figure 1* is a QUORUM diagram showing the number of studies identified in the initial search and the numbers excluded at each stage of the review.¹⁵¹

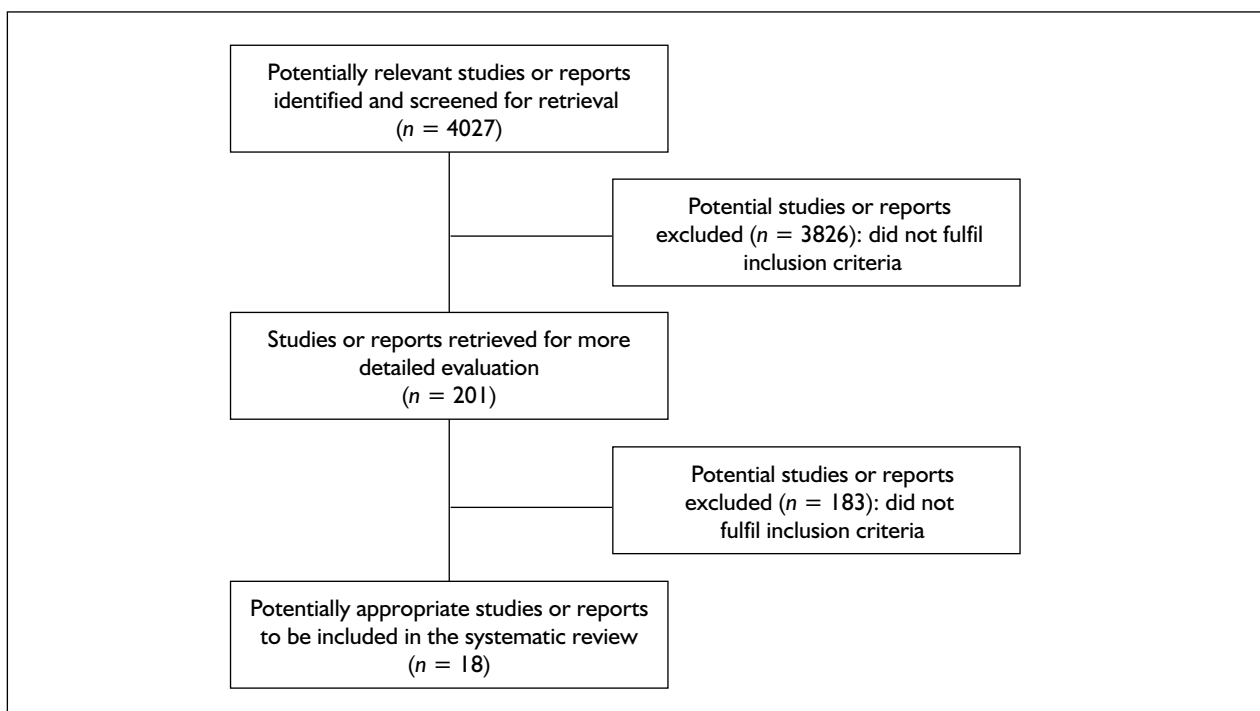


FIGURE 1 QUORUM study flow diagram

Number and quality of studies identified

Number of studies identified

Eighteen post-1990 studies were identified as being eligible for inclusion in the review (Table 2). Eight studies were based on primary data and ten used modelling techniques. The main section of this review provides a summary of those studies that have considered the diagnosis of CAD. The subsequent subsection considers studies that investigate the use of various diagnostic techniques amongst women at a range of prevalence rates. The literature search did not reveal any studies that considered the costs and

outcomes of functional cardiac MRI for the diagnosis of CAD.

Diagnosis of coronary heart disease

In total there were nine studies that used decision models^{4,152–159} (Table 3). Eight of these considered the cost-effectiveness of different diagnostic strategies for a range of prevalence rates of CAD.^{152–159} Another model-based study focused on patient groups at intermediate risk of disease (approximately 25–75% CAD prevalence).⁴ There were also six studies based on patient-level data^{160–165} (Table 4). In five studies, patients had either normal resting ECGs and/or cardiac symptoms and no known heart disease.^{160–164} In

TABLE 2 Eighteen studies included in systematic review of cost-effectiveness literature

Study, year	Study title
Mowatt, 2004 ⁴	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
Garber, 1999 ¹⁵²	Cost-effectiveness of alternative test strategies for the diagnosis of coronary artery disease
Kuntz, 1999 ¹⁵³	Cost-effectiveness of diagnostic strategies for patients with chest pain
Maddahi, 1997 ¹⁵⁴	Cost-effective selection of patients for coronary angiography
Patterson, 1984 ¹⁵⁵	Bayesian comparison of cost-effectiveness of different clinical approaches to diagnose coronary artery disease
Patterson, 1995 ¹⁵⁶	Comparison of cost-effectiveness and utility of exercise ECG, single photon emission computed tomography, positron emission tomography, and coronary angiography for diagnosis of coronary artery disease
Rumberger, 1999 ¹⁵⁷	Coronary calcification by electron beam computed tomography and obstructive coronary artery disease: a model for costs and effectiveness of diagnosis as compared with conventional cardiac testing methods
Lee, 2002 ¹⁵⁸	Comparison of the cost-effectiveness of stress myocardial SPECT and stress echocardiography in suspected coronary artery disease considering the prognostic value of false-negative results
Hayashino, 2004 ¹⁵⁹	Cost-effectiveness of screening for coronary artery disease in asymptomatic patients with Type 2 diabetes and additional atherogenic risk factors
Christian, 1994 ¹⁶⁰	Exercise tomographic thallium-201 imaging in patients with severe coronary artery disease and normal electrocardiograms
Hachamovitch, 2002 ¹⁶¹	Value of stress myocardial perfusion single photon emission computed tomography in patients with normal resting electrocardiograms: an evaluation of incremental prognostic value and cost-effectiveness
Mattera, 1998 ¹⁶²	Exercise testing with myocardial perfusion imaging in patients with normal baseline electrocardiograms: cost savings with a stepwise diagnostic strategy
Shaw, 1999 ¹⁶³	The economic consequences of available diagnostic and prognostic strategies for the evaluation of stable angina patients: an observational assessment of the value of pre-catheterization ischemia. Economics of Noninvasive Diagnosis (END) Multicenter Study Group
Underwood, 1999 ¹⁶⁴	Economics of myocardial perfusion imaging in Europe – the EMPIRE Study
Marwick, 2003 ¹⁶⁵	Clinical and economic impact of exercise electrocardiography and exercise echocardiography in clinical practice
Amanullah, 1997 ¹⁶⁷	Identification of severe or extensive coronary artery disease in women by adenosine technetium-99m sestamibi SPECT
Kim, 1999 ¹⁶⁸	Diagnosis of suspected coronary artery disease in women: a cost-effectiveness analysis
Shaw, 1999 ¹⁶⁹	Cost analysis of diagnostic testing for coronary artery disease in women with stable chest pain. Economics of Noninvasive Diagnosis (END) Study Group

TABLE 3 Summary of diagnostic strategies used in studies using models

Study	Strategies
Garber, 1999 ¹⁵²	<ol style="list-style-type: none"> 1. Stress ECG 2. Planar SPECT 3. SPECT 4. Stress echo 5. Stress PET 6. CA
Kuntz, 1999 ¹⁵³	<ol style="list-style-type: none"> 1. No testing 2. CA alone 3. Stress SPECT; CA if positive 4. Stress ECG; CA if positive 5. Stress echo; CA if positive
Maddahi, 1997 ¹⁵⁴	<ol style="list-style-type: none"> 1. Direct referral for CA 2. PET; CA if positive 3. SPECT; CA if positive
Patterson, 1984 ¹⁵⁵	<ol style="list-style-type: none"> 1. Stress ECG; CA if positive or non-diagnostic 2. Stress SPECT; CA if positive or non-diagnostic 3. Direct CA 4. Stress ECG; SPECT if positive or non-diagnostic and CA if SPECT positive or non-diagnostic
Patterson, 1995 ¹⁵⁶	<ol style="list-style-type: none"> 1. Stress ECG; CA if positive or non-diagnostic 2. Stress SPECT; CA if positive or non-diagnostic 3. Direct CA
Rumberger, 1999 ¹⁵⁷	<ol style="list-style-type: none"> 1. Stress ECG; CA if positive or non-diagnostic 2. Stress echo; CA if positive or non-diagnostic 3. SPECT; CA if positive or non-diagnostic 4. EBCT; CA if positive or non-diagnostic 5. Direct CA
Lee, 2002 ¹⁵⁸	<ol style="list-style-type: none"> 1. SPECT; CA if positive 2. Stress echo; CA if positive
Hayashino, 2004 ¹⁵⁹	<ol style="list-style-type: none"> 1. No testing 2. Stress ECG; CA if positive 3. Stress echo; CA if positive 4. Stress SPECT; CA if positive
Mowatt, 2004 ⁴	<ol style="list-style-type: none"> 1. Stress ECG; SPECT if positive or non-diagnostic and CA if SPECT positive or non-diagnostic 2. Stress ECG; CA if positive or non-diagnostic 3. SPECT; CA if positive or non-diagnostic 4. Direct CA

CA, conventional angiography; EBCT, electron beam computed tomography; PET, positron emission tomography.

only one study did patients have either known or suspected coronary disease.¹⁶⁵ Of these 15 studies identified, only two came from the UK or involved UK centres.^{4,164} Tables 3 and 4 provide summaries of the strategies considered in each of the studies based on models and patient-level data, respectively.

Quality of modelling studies

Of the studies based on models, two^{156,157} were developed from Patterson and colleagues¹⁵⁵ and another¹⁵⁸ was based on a model from the second study by Patterson and colleagues.¹⁵⁶ The study by Hayashino and colleagues¹⁵⁹ was based on an earlier model developed by Weinstein and

colleagues.¹⁶⁶ The remaining five studies were based on models developed specifically for that study.^{4,152–155}

The studies from outside of the UK (predominantly from the USA) focused on Medicare or insurance fees for tests and procedures, thus limiting transferability of costs to the UK setting. In most of these studies it was unclear which year costs referred to and in two of the studies^{155,156} no discounting was performed. Another limitation of some of these studies^{155–157} was that the relative cost-effectiveness of strategies was reported as average costs:effects ratios rather than the preferred

TABLE 4 Summary of diagnostic strategies based on data from primary studies

Study	Strategies
Christian, 1994 ¹⁶⁰	<ol style="list-style-type: none"> 1. Clinical data 2. Clinical data plus stress ECG 3. Clinical data plus stress ECG plus SPECT
Hachamovitch, 2002 ¹⁶¹	<ol style="list-style-type: none"> 1. Clinical and history only 2. Stress ECG and clinical data and history 3. Stress SPECT plus strategy 2
Mattera, 1998 ¹⁶²	<ol style="list-style-type: none"> 1. Stress ECG 2. SPECT
Shaw, 1999 ¹⁶³	<ol style="list-style-type: none"> 1. SPECT, selective CA 2. Direct CA
Underwood, 1999 ¹⁶⁴	<ol style="list-style-type: none"> 1. Stress ECG followed by CA 2. Stress ECG plus SPECT followed by CA 3. SPECT followed by CA 4. CA alone
Marwick, 2003 ¹⁶⁵	<ol style="list-style-type: none"> 1. Stress ECG 2. Stress echo

incremental cost-effectiveness ratios (ICERs), which compare a new treatment with standard practice. The only UK study⁴ provided a good description of the resource use and cost estimates.

Seven of the studies^{4,152,153,155,156,158,159} provided estimates of cost per quality-adjusted life-year (QALY). Briefly, QALYs are calculated by applying a weight (utility) to survival to reflect average quality of life during lifetime in a given health state. Three studies^{4,152,153} used utility weights taken from a previous survey of patients with stable angina whereas another used utility weights from surveys of patients who experienced angina and MI.¹⁵⁹ In the other three studies,^{155,156,158} it was unclear how the QALY estimates were derived. One study¹⁵⁷ considered the cost per correct diagnosis and another¹⁵⁴ used the percentage of patients correctly diagnosed (although costs and effects were not formally combined). Four studies attempted a rigorous sensitivity analysis around all the main areas of uncertainty^{4,152,153,159} with one of the studies conducting a probabilistic sensitivity analysis.¹⁵³ The other two studies either had limited¹⁵⁶ or no sensitivity analysis.¹⁵⁴

All studies populated their models with data on the sensitivity and specificity of the diagnostic tests based on estimates from the literature. Two studies^{4,153} provided a comprehensive description of how these data were assembled. The remaining studies were limited either in terms of the literature searches performed or because inadequate descriptions of the search strategy were provided, thus limiting the quality of the data used.

Quality of primary data studies

Of the six studies based mainly on primary data, four were based on large retrospective cohorts,^{161,162,163,165} one of which involved matched patient cohorts for the two diagnostic strategies considered.¹⁶³ The other two studies were based on moderately sized retrospective patient cohorts,^{160,164} with the second study based on a multinational cohort of patients from UK, Germany, Italy and France.¹⁶⁴ However, this study used effectiveness data taken from the literature. The costs in three studies from the USA were based on Medicare fees and descriptions of resource use were inadequate, again limiting the generalisability of the data to the UK setting.¹⁶⁰⁻¹⁶² One study¹⁶³ converted Medicare charges into costs, one study¹⁶⁴ applied unit costs from a single UK centre to resource use from other UK and European centres and another study¹⁶⁵ used a combination of Medicare fees and published cost data. All of the studies adopted either an incremental cost-effectiveness analysis or cost-minimisation approach. Two of the four studies with a time horizon greater than 1 year used discounting to downweight costs and effects incurred over time after 1 year^{163,165} and only two used any form of sensitivity analysis to assess alternative assumptions.^{160,163}

Results

Comparing and summarising the results of the studies were complicated by the large number of different strategies considered, outcome measures

used and methodologies adopted. Therefore, the results here are summarised under a series of pairwise comparisons. These comparisons are made for patients at different levels of risk of disease (about 25–100%), and also for women. All ICERs are presented in the currency specified for the study in question and based on prices for the year of the study.

Stress echo versus angiography

Only three studies provided information on this comparison and showed some consistency in their results (Table 5). In one study,¹⁵² stress echo alone was compared with CA, whereas in the other two^{153,157} stress echo followed by CA if positive or non-diagnostic was compared with CA alone. In one of the studies,¹⁵³ the ICER results were for men aged 50–59 years with mild chest pain (pretest risk of CAD of 25–75%) and in another study they were for 55-year-old men with a CAD prevalence of 50%.¹⁵² Similarly, the ICER results in Rumberger and colleagues¹⁵⁷ were based on a population with 50% prevalence of obstructive CAD. In two of the studies,^{153,157} stress echo was a cost-effective strategy in comparison with angiography, whereas in the other,¹⁵² angiography resulted in a slightly higher QALY gain compared with stress echo but at a higher cost, resulting in an ICER that would not be acceptable at current UK thresholds.

TABLE 5 ICERs for comparison of stress echo versus angiography

Study	Finding compared with angiography
Kuntz, 1999 ¹⁵³	US\$35,200 per additional QALY
Rumberger, 1999 ¹⁵⁷	US\$10,071 per additional true positive diagnosed
Garber, 1999 ¹⁵²	US\$88,000 per additional QALY (stress echo as comparator)

TABLE 6 ICERs for comparison of SPECT versus stress echo

Study	Finding compared with stress echo
Kuntz, 1999 ¹⁵³	US\$62,800 per additional QALY
Rumberger, 1999 ¹⁵⁷	US\$24,900 per additional true positive diagnosed
Garber, 1999 ¹⁵²	US\$78,444 per additional QALY
Hayashino, 2004 ¹⁵⁹	SPECT dominated by stress echo ?SPECT slightly more expensive and slightly less effective
Lee, 2002 ¹⁵⁸	Prevalence >0.3 SPECT was most cost-effective Prevalence <0.3 stress echo was most cost-effective

SPECT versus stress echo

In the comparison of SPECT versus stress echo (Table 6), the three studies described above also showed consistent results and indicated that the ICER for SPECT versus stress echo was fairly high. In the study by Hayashino and colleagues, a decision model was used to compare the cost-effectiveness of exercise echo with exercise SPECT in asymptomatic 55-year-old men with diabetes, two additional atherogenic risk factors and a CAD prevalence of 40%.¹⁵⁹ In this scenario, the SPECT strategy was slightly more expensive and slightly less effective than the stress echo strategy. The study by Lee and colleagues modelled the cost-effectiveness of stress echo against SPECT according to the prevalence of CAD, although the incremental cost-effectiveness could not be estimated.¹⁵⁸ The results of the study showed that at a prevalence of 30% or greater, SPECT was the most cost-effective strategy and when the prevalence was less than 30%, stress echo was the most cost-effective strategy.

Angiography versus SPECT

Table 7 presents the results for studies that considered this comparison. One study compared CA with SPECT alone¹⁵² and eight studies compared CA with SPECT followed by CA if positive or non-diagnostic.^{4,153–157,163,164} As a consequence, the ICER for angiography versus SPECT alone was very high in this first study.¹⁵² The remaining studies that estimated ICERs found that CA was the more effective but more costly strategy. This was also the case for three other studies that did not present ICERs.^{154–156}

The study by Maddahi and Gambhir¹⁵⁴ used a decision model to compare CA with SPECT at different pretest likelihoods of CAD. The authors concluded that at intermediate prevalence of CAD (~50%), SPECT was the more cost-effective strategy, whereas at higher prevalence (>~60%), CA was the more cost-effective strategy. Similarly,

TABLE 7 ICERs for comparison of angiography versus SPECT

Study	Finding compared with SPECT
Kuntz, 1999 ¹⁵³	US\$32,600 per additional QALY
Rumberger, 1999 ¹⁵⁷	US\$4140 per additional true positive diagnosed
Garber, 1999 ¹⁵²	US\$102,333 per additional QALY
Mowatt, 2004 ⁴	£42,225 per additional QALY
Shaw, 1999 ¹⁶³	No difference in effectiveness, SPECT 30–40% less costly
Underwood, 1999 ¹⁶⁴	No difference in effectiveness, SPECT £793 less costly
Maddahi, 1997 ¹⁵⁴	Angiography more effective and more costly (overall) Prevalence 50%, SPECT more cost-effective Prevalence 60% angiography more cost-effective
Patterson, 1984 ¹⁵⁵	Angiography more effective and more costly (overall) Prevalence <0.7 SPECT more cost-effective Prevalence >0.7 angiography more cost-effective
Patterson, 1995 ¹⁵⁶	Angiography more effective and more costly (overall) Prevalence <0.7 SPECT more cost-effective Prevalence >0.7 angiography more cost-effective

the two studies by Patterson and colleagues modelled the cost-effectiveness of the two strategies at different pretest likelihoods of CAD and found similar results, that is, SPECT had a lower cost per QALY at intermediate prevalence (<0.70) and CA had a lower cost per QALY at higher prevalence (>0.70).^{155,156}

The study by Mowatt and colleagues⁴ used a decision tree model for the diagnosis and a simple Markov model for the subsequent management of patients with suspected CAD. The base case results used a CAD prevalence of 10.5% obtained from British Heart Foundation statistics and a range of different prevalence rates for purposes of comparison (30, 50, 85%). At a prevalence of 10.5%, the costs:effects ratio for CA versus SPECT was £42,225 per QALY whereas for a prevalence of 85% this ratio decreased to £927 per QALY, thus confirming the findings of the earlier studies.^{154–156}

The two remaining comparisons were based on patient-level analyses.^{163,164} The first was a cost-minimisation analysis (because survival, MI, etc., did not appear to differ between the two strategies) based on matched cohorts of patients with stable angina who had received either CA or SPECT.¹⁶³ The results from this study showed that the use of SPECT was 30–40% less costly than CA. The second study was also a cost-minimisation analysis (as there were no significant differences in outcomes between groups) based on a multi-centre controlled study with patients presenting for CAD

diagnosis.¹⁶⁴ The results from this study were similar to the other patient-level study,¹⁶³ with the CA strategy costing on average £793 more than the SPECT strategy after 1-year follow-up.

Angiography versus stress ECG

One study compared CA with stress ECG alone,¹⁵² six studies compared CA with stress ECG followed by CA if positive or non-diagnostic,^{4,153,155–157,164} with three of these studies comparing CA with stress ECG followed by SPECT if positive or non-diagnostic.^{4,155,164} Again, the costs:effects ratio was higher in the study comparing CA with stress ECG alone, although to a lesser extent than the comparison with SPECT.¹⁵² There was consistency among the remaining studies, showing that CA was the more costly strategy but also the more effective (*Table 8*).

The base case ICERs for three studies using models^{152,153,157} were based on a prevalence of CAD of approximately 50% and one study used a prevalence of 10.5%.⁴ Again, when the CAD prevalence was increased in the sensitivity analyses, the costs:effects ratios for the two strategies both got smaller, as the cost increased and the effectiveness decreased. In the other studies using models, Patterson and colleagues¹⁵⁵ found that the strategy of stress ECG followed by SPECT had the lowest cost per QALY for a prevalence of CAD up to 80% and between 80 and 100% CA had the lowest cost per QALY. Similarly, in a subsequent study, Patterson and colleagues¹⁵⁶ concluded that the strategy of stress ECG followed

TABLE 8 ICERs for comparison of conventional angiography versus stress ECG

Study	Finding compared with stress ECG
Kuntz, 1999 ¹⁵³	US\$34,400 per additional QALY
Garber, 1999 ¹⁵²	US\$55,200 per additional QALY
Rumberger, 1999 ¹⁵⁷	US\$22,100 per additional true positive diagnosed
Mowatt, 2004 ⁴	£21,360 per additional QALY (ECG followed by CA) £22,394 per additional QALY (ECG followed by SPECT)
Patterson, 1984 ¹⁵⁵	CAD prevalence <80%, stress ECG more cost-effective CAD prevalence >80%, CA more cost-effective
Patterson, 1995 ¹⁵⁶	CAD prevalence <70%, stress ECG more cost-effective CAD prevalence >70%, CA more cost-effective
Underwood, 1999 ¹⁶⁴	CA cost £763 more (than ECG followed by CA) CA cost £844 more (than ECG followed by SPECT)

by CA had the lower costs:effects ratio up to a prevalence of 70% and above this CA had the lower costs:effects ratio. In the one primary study based on patient-level data,¹⁶⁴ the CA strategy cost on average £763 more than the stress ECG followed by CA strategy after 1-year follow-up, and on average £844 more than the stress ECG followed by SPECT strategy.

Stress echo versus stress ECG

Two studies evaluated stress echo versus stress ECG alone^{152,165} and three studies evaluated stress echo versus stress ECG followed by CA if positive or non-diagnostic^{153,157,159} (Table 9). Four of the studies^{152,153,157,159} were based on models and the study by Marwick and colleagues¹⁶⁵ was based on primary data. Although all the studies showed that stress echo was the more costly yet more effective strategy, there was little consistency between the studies in the magnitude of the ICERs. Both of the studies that compared stress echo with stress ECG alone had fairly low ICERs.^{152,156} The three studies that compared stress echo with stress ECG followed by CA generally had higher ICERs, although the study by Hayashino and colleagues¹⁵⁹ was based on a prevalence of CAD of 40% whereas the other two studies were based on a prevalence of 50%.^{153,157} However, it is difficult to compare these results directly given the underlying differences in the methodologies used, including differences in the sensitivity/specificity rates, the cost components and the year of the cost data, and differences in the way in which outcomes were measured.

SPECT versus stress ECG

Table 10 presents the results for studies that calculated ICERs for this comparison. Two studies compared SPECT alone with stress ECG alone,^{152,162}

TABLE 9 ICERs for comparison of stress echo versus stress ECG

Study	Finding compared with stress ECG
Kuntz, 1999 ¹⁵³	US\$32,000 per additional QALY
Garber, 1999 ¹⁵²	US\$6000 per additional QALY
Rumberger, 1999 ¹⁵⁷	US\$8671 per additional QALY
Marwick, 2003 ¹⁶⁵	€2615 per additional life-year saved
Hayashino, 2004 ¹⁵⁹	US\$72,522 per additional QALY

seven studies compared SPECT followed by CA if positive or non-diagnostic with stress ECG followed by CA if positive or non-diagnostic^{4,153,155–157,159,164} and two of these studies also compared SPECT followed by CA if positive or non-diagnostic with stress ECG plus SPECT if positive or non-diagnostic.^{4,155} Four studies compared stress ECG alone with stress ECG followed by SPECT if positive or non-diagnostic.^{154,160,161,164}

Of the four studies that compared stress ECG alone with stress ECG followed by SPECT, one was based on a model¹⁵⁴ and the remaining studies were based on primary level data.^{160,161,164} Two studies^{160,161} were both cost-effectiveness analyses based on large cohorts of patients with normal resting ECGs and both used 'correct disease classifications' as the outcome measure. Overall, there was little consistency between these four studies, reflecting the different parameters used. Some of the studies^{160,161} based their costs on no more than the cost of the two diagnostic strategies, and so their results may be misleading. The study by Underwood and colleagues¹⁶⁴ showed that the cost of the stress ECG plus SPECT strategy was less than that of the SPECT strategy alone and

TABLE 10 ICERs for comparison of SPECT versus stress ECG

Study	Finding compared with stress ECG
Christian, 1994 ¹⁶⁰	US\$20,550 per additional correct classification
Hachamovitch, 2002 ¹⁶¹	US\$5417 per additional correct classification
Kuntz, 1999 ¹⁵³	US\$38,000 per additional QALY
Garber, 1999 ¹⁵²	US\$40,316 per additional QALY
Rumberger, 1999 ¹⁵⁷	US\$12,278 per additional true positive diagnosed
Hayashino, 2004 ¹⁵⁹	US\$175,133 per additional QALY
Mowatt, 2004 ⁴	£8723 per additional QALY (ECG followed by CA) £14,125 per additional QALY (ECG followed by SPECT)
Mattera, 1998 ¹⁶²	SPECT more cost-effective
Patterson, 1984 ¹⁵⁵	SPECT + CA more cost-effective
Patterson, 1995 ¹⁵⁶	SPECT + CA more cost-effective
Underwood, 1999 ¹⁶⁴	SPECT + CA more cost-effective
Maddahi, 1997 ¹⁵⁴	SPECT more cost-effective

Maddahi and Gambhir¹⁵⁴ concluded that the SPECT strategy was more cost-effective.

The studies that compared SPECT plus CA versus stress ECG plus CA all found that the former strategy was more cost-effective, although the magnitude of the ICERs across the studies varied considerably, again reflecting the different parameters and methodologies used.^{4,153,155–157,159,164} The only study that was based on primary data found that the strategy of stress ECG plus CA was less costly than the strategy of SPECT plus CA over 1 year.¹⁶⁴ In the two studies comparing SPECT alone versus stress ECG alone, the SPECT strategy was the more cost-effective strategy with costs reduced by 38% in the study by Mattera and colleagues.¹⁶² Finally, in the two studies that compared SPECT plus CA versus stress ECG plus SPECT, one concluded that the former was the more cost-effective strategy⁴ and the other that the latter was the more cost-effective strategy.¹⁵⁵

Cost-effectiveness of alternative diagnostic strategies among women with suspected CAD

Three studies reported the cost-effectiveness of alternative strategies to detect CAD in women.^{167–169} Two of these studies were based on patient-level data^{167,169} and one on a decision model.¹⁶⁸ A further four studies considered the cost-effectiveness of alternative strategies to detect CAD in women as part of the sensitivity analysis,^{4,152,153,161} Again, the interpretation and comparison of the results of these studies were

complicated by the different strategies being compared and the way the results were reported.

In their study, Shaw and colleagues¹⁶⁹ used a cost-minimisation analysis based on matched cohorts of women with typical cardiac symptoms ($n = 4638$) who received either direct CA or SPECT (since there was no evidence of a statistically significant difference in cardiac deaths between the two strategies). At three different risk categories (low, medium, high), SPECT was the least costly strategy in each. A similar comparison was made by Amanullah and colleagues.¹⁶⁷ Their study used a cost-effectiveness analysis to compare CA with SPECT strategies in a cohort of women ($n = 130$) with no history of revascularisation or heart disease. The outcome measure was 'severe or extensive case of CAD diagnosed'. The results showed that the SPECT strategies were either dominated by CA or that CA had an ICER of US\$10,640 per incremental case of severe or extensive CAD diagnosed.

The study by Kim and colleagues¹⁶⁸ used a cost-utility analysis to compare four diagnostic strategies: SPECT, stress echo, CA and stress ECG based on a Markov model for 55-year-old women with chest pain. Estimates for the sensitivity/specificity of the various tests were based on a systematic review and utilities were taken from previous literature reporting the results of a time-trade-off survey, a study which assesses the amount of life an individual is prepared to give up in order to improve quality of life to a specified level. Unit costs were based on bottom-up costs

from a tertiary medical centre, although no description of the resource use was provided. The time horizon for the study was 35 years and QALYs but not costs were discounted at 5% per year. The results of the cost-effectiveness for patients with probable angina (pretest probability = 0.31) are as follows:

- Stress echo dominated the SPECT strategy.
- The ICER for stress echo versus stress ECG was US\$15,510.
- The ICER for CA versus stress echo was US\$75,333.
- CA dominated the SPECT strategy.
- The ICER for CA versus stress ECG was US\$26,904.

No comparison of SPECT versus stress ECG was presented. Overall, the authors concluded that the optimal diagnostic strategy in terms of cost-effectiveness would be either CA or stress echo for this risk category.

Of the studies that considered the cost-effectiveness of alternative strategies among women as part of the sensitivity analysis, the study by Hachamovitch and colleagues¹⁶¹ showed that the incremental cost of adding SPECT to a strategy already involving stress ECG would be US\$8092 per reclassification (US\$3816 if limited to those positive on stress ECG). In their subgroup analysis, Mowatt and colleagues⁴ used higher sensitivities and specificities for women and a lower prevalence rate of CAD together with different MI and mortality rates. The results showed that the ECG followed by SPECT strategy dominated the ECG followed by CA strategy whilst the ECG followed by CA and CA alone strategies were both dominated by the SPECT followed by CA strategy. Unfortunately, very few interpretable data were available in the sensitivity analysis conducted by Kuntz and colleagues.¹⁵³

In the study by Garber and Solomon,¹⁵² the ICERs from their model for 55-year-old women with pretest probability of coronary disease of 50% are as follows:

- The strategy of CA had an ICER of over US\$100,000 per QALY compared with the SPECT and stress echo strategies and ~US\$70,000 per QALY compared with the stress ECG strategy.
- SPECT had an ICER of ~US\$95,000 per QALY and ~US\$55,000 per QALY compared with the stress echo and stress ECG strategies, respectively.

- The ICER for stress echo compared with stress ECG was ~US\$3000 per QALY. These ICERs were all consistent with the results for the male group although the magnitude of the costs per QALY for the women group was slightly higher in each scenario.

Summary

In summarising the overall findings from the literature on the relative cost-effectiveness of alternative diagnostic strategies, it is important to highlight the methodological differences across the studies included. These include, among other things, differences in the strategies considered, measures of effectiveness used, resource use and cost components considered and also the overall methodological quality. Similarly, the different levels of CAD prevalence across the different studies (about 25–100%) play an important role in determining the overall cost-effectiveness of alternative strategies. Nevertheless, it is possible to draw some general yet tentative conclusions based on the available published evidence.

First, there was limited evidence (based on three studies) to suggest that stress echo may be a more cost-effective strategy than angiography for men aged 50–60 years with CAD prevalence of 50%. In the comparison of SPECT versus stress echo, the available evidence suggested that ICER was fairly high, or in one case, the SPECT strategy was weakly dominated by the stress echo strategy. In general, studies that compared angiography with SPECT concluded that the former was the more costly yet more effective diagnostic strategy. Other model-based studies suggested that, at a more intermediate prevalence of CAD (50–60%), SPECT was more cost-effective whereas at a higher prevalence (>60%) angiography was the more cost-effective strategy.

The available evidence suggests that at an intermediate prevalence of CAD (about 50%), angiography alone was the more costly yet more effective strategy than stress ECG, followed by CA or SPECT if positive or non-diagnostic. Similarly, the comparison of stress ECG with stress echo suggested the latter to be the more cost-effective strategy at intermediate CAD prevalence, especially for the comparison with stress ECG alone. However, there was considerable variation in the magnitude of the ICER for this comparison. There was little consistency amongst studies comparing stress ECG plus SPECT versus SPECT alone, again reflecting the different parameters

and methodologies used. The studies that compared SPECT plus CA versus stress ECG plus CA all found that the former was the more cost-effective strategy, although again the magnitude of the ICERs across studies varied considerably.

For studies evaluating the cost-effectiveness of alternative strategies among women with suspected CAD, the overall results indicated that SPECT strategies were dominated by or were less

cost-effective than angiography, although the ICERs varied considerably in their magnitude. In one study, the SPECT strategy was dominated by the stress echo strategy and another study estimated an ICER of over \$95,000 per QALY. The overall evidence also suggested that the angiography, stress echo and SPECT strategies were all more cost-effective than the stress ECG strategies.

Chapter 3

Study objectives and methods

Study objectives

This RCT was designed to assess the use of functional cardiac tests as a gateway to angiography in patients with known or suspected CAD, who were referred for angiography in order to determine clinical management. Thus, the trial was designed to be (1) pragmatic, in that it reflects what is likely to happen in a clinical setting if the strategy is adopted, and (2) generalisable, in that it includes all patients for whom the diagnostic strategies could be applied. In addition, we were interested in assessing the value of functional tests as a gateway to angiography, rather than assessing other tests that provide anatomical imaging such as EBCT or MDCT, which were not generally available when this trial began.

Specific trial objectives were as follows:

- to assess the acceptability and feasibility of performing functional cardiac tests as a gateway to angiography in a clinical setting, in order to determine management for patients with known or suspected CAD
- to assess the ability of diagnostic strategies that include functional tests to identify patients who should undergo revascularisation
- to assess clinical and quality of life outcomes for patients randomised to one of the four alternative diagnostic strategies
- to identify the most cost-effective diagnostic strategy for patients with suspected significant CAD, including costs of the diagnostic strategies, revascularisation and other treatments and adverse events.

Patients and recruitment

All patients referred for non-urgent CA to Papworth Hospital, a tertiary referral centre, were eligible for the study.

The inclusion criteria were as follows:

- established or suspected chronic stable angina referred for angiography and
- an EET result which in the opinion of the referring clinician merited referral for

angiography (due to symptoms or ECG changes or inadequate exercise time).

The exclusion criteria were as follows:

- a functional test within the previous 12 months
- recent (<3 months) MI or admission with unstable angina
- urgent need for revascularisation
- revascularisation in the previous 6 months
- known to have adverse reactions to pharmacological stress testing
- physically incapable of performing modified Bruce EET
- pacemaker or other contraindication to MRI
- not available by telephone.

Prior MI (if >3 months from recruitment) was *not* an exclusion criterion. This is because the aim of the study was to investigate strategies for the detection of **ischaemia** in the presence of both known and suspected CAD. It was considered important not to exclude those with proven coronary disease since many such patients have repeated presentations to hospital with non-cardiac chest pain. Indeed, this is perhaps the group at highest risk of 'oculo-stenotic reflex' revascularisation.

Patients were enrolled within 1 month of the exercise test that resulted in the referral for angiography. Patients were informed about the study at one of the selected outpatient clinics in the surrounding district general hospitals (DGHs) (Addenbrooke's, Hinchingsbrooke, Peterborough and West Suffolk hospitals) or, if they had already been referred for CA, they were invited to participate by letter. At the DGH, the possibility of participating in the trial was discussed by the referring cardiologist. The patients were then seen by a Clinical Research Assistant, who discussed the trial in more detail, answered any questions and provided a copy of the patient information sheet to those who expressed an interest. The Clinical Research Assistant telephoned the clinic and waiting list patients 1 week after the initial contact had been made and invited patients who wanted to participate to attend a research recruitment clinic at Papworth hospital. The index ECG was not available to the trial personnel.

At the baseline research clinic, patients were checked for eligibility and those who consented were randomised to one of four diagnostic groups. Randomisation was supervised by the Project Statistician and performed centrally by the Papworth R&D Unit, with groups allocated by telephone. In order to ensure an even distribution of pretest risk between the groups, randomisation was stratified according to Pryor risk assessment (low- and high-risk groups).¹⁷⁰ The Pryor risk score uses a logistic regression equation to estimate the probability of having significant CAD, with 1 indicating certain disease and 0 indicating no chance of disease. The variables used in the regression are patient age, gender, age–gender interaction, typical/atypical angina, history of MI, ECG Q waves, history of MI–ECG Q waves interaction, smoking, hyperlipidaemia, diabetes, ECG ST-T wave changes, age–smoking interaction, age–hyperlipidaemia interaction and gender–smoking interaction. Definitions of these variables and their regression coefficients can be found in references by Pryor and colleagues.¹⁷⁰ High risk was defined *a priori* as a Pryor score of 0.8 or above. The study had local ethical committee approval and all patients gave informed written consent. Eligible patients who did not give consent proceeded to angiography as normal.

Study design

Patients entering the study were clinically assessed using the Canadian Cardiovascular Society (CCS) angina class and risk stratification as per Pryor and colleagues,¹⁷⁰ completed HRQoL questionnaires [generic SF-36 and EuroQoL utility measure (EQ-5D) and disease-specific SAQ] and performed a modified Bruce EET¹⁷¹ (see *Table 11* for the schedule of events).

Patients were randomised 1:1:1:1 to one of the four initial tests to occur within 4 weeks of recruitment:

- Group 1 (control) had angiography as planned.
- Group 2 had SPECT.
- Group 3 had stress cardiac MRI imaging.
- Group 4 had stress echo.

Within each Pryor risk group (high/low), randomisation was in blocks of length six or eight, using a random number-generating computer program. Sequentially numbered group designation was held in the R&D Unit and was not available to trial personnel. Patients were randomised to groups by R&D once they had given consent and were registered. Patients were randomised after (and not during) the trial

TABLE 11 Planned schedule of events

Outcome measures	Baseline assessment (n = 945)	Diagnostic test (n = 896)	Treatment (n = 896)	Follow-up 6 months post-treatment (n = 825)	Follow-up 18 months ^a post-randomisation (n = 756)
EET	×			×	×
HRQoL	×			×	×
CCS angina score	×			×	×
Formal risk assessment (Pryor <i>et al.</i> ¹⁷⁰)	×				
Clinician's opinion of IHD risk and need for revascularisation	×	×			
Revascularisation rate			×		
Hospital admission with:					
chest pain, acute MI, unplanned	×	×	×	×	×
revascularisation	×	×	×	×	×
cardiac deaths.	×	×	×	×	×
Resource use/EQ-5D	×	×	×	×	×

^a Primary analysis is based on results at 18 months post-randomisation. IHD, ischaemic heart disease.

assessment clinic and contacted by telephone or post.

Patients in group 1 were assigned to PCI or CABG (performed within 6 months of angiography) or to medical therapy according to standard practice. Those patients who were allocated to groups 2–4, the functional test groups, received their allocated test within 4 weeks of the baseline research clinic. The results were sent to the referring cardiologist with a strong recommendation to proceed with angiography only when the stress imaging test was 'positive' for reversible ischaemia (see the next section for the investigation protocols). The cardiologist's decision, however, was final and they were at liberty to proceed with angiography if they considered it clinically indicated. If angiography was considered necessary, it was performed within 3 months of the baseline research clinic. Revascularisation was decided on the basis of angiography, using the same criteria as for group 1. For those patients who did not require revascularisation, medical therapy was at the discretion of the referring clinician and depended on the history and symptoms of the patient. We stress that this was designed to be a pragmatic trial, reflecting use of these diagnostic strategies in a clinical setting.

To assess the perceived value of each of the four diagnostic strategies, the referring clinician was asked at the time of enrolment, and after the initial test, to estimate the risk of CAD being present (on a five-point scale: 1, definitely not present; 2, probably not present; 3, possibly present; 4, probably present; 5, definitely present). The clinician also recorded his/her opinion of the likelihood of the patient requiring revascularisation versus medical therapy (on a five-point scale: 1, definite medical therapy; 2, probable medical therapy; 3, possible revascularisation; 4, probable revascularisation; 5, definite revascularisation). For groups 2–4, the cardiologist's decision as to whether to proceed with angiography acted as the post-test indicator of clinical utility. The cardiologists also recorded whether or not the chest pain experienced by the patient was angina, or not cardiac in nature. In this clinic situation it was not possible to have patients reassessed by a second clinician for validation of the assessment of risk of CAD and need for revascularisation.

Outcome measures and their timings are summarised in the schedule of events in *Table 11*. All patients were reassessed 6 months after initiation of treatment. Because the timing of this

assessment relative to entry to the trial varied depending on waiting times for different treatments, the assessment was repeated 18 months after randomisation.

Longer term assessment of survival, cardiac events, quality of life and resource use will take place at 18 and 24 months post-treatment. These follow-up assessments will be completed in 2007 and will be reported separately.

Investigation protocols

Exercise ECG test

The exercise test prior to referral for angiography was performed according to practice at the local hospital and reported as positive or negative for ischaemia. The test was considered positive if there was ≥ 2 mm horizontal ST depression, 1 mm ST depression with chest pain or < 6 minutes of exercise had been achieved. Exercise testing was discontinued if there was exertional hypotension, life-threatening arrhythmia, ST depression ≥ 3 mm or limiting chest pain, breathlessness or fatigue.

The subsequent EET carried out as part of the study used a modified Bruce protocol.¹⁷¹ This protocol starts with a 0% gradient at 1.7 miles per hour and the speed and/or gradient increase every 3 minutes. An ischaemic response was defined as 1 mm ST depression associated with symptoms or 2 mm without. The primary measure was total exercise time.¹⁷² Time to onset of angina and reason for stopping the exercise test were also recorded. All the EETs performed as part of the study were carried out at Papworth by the research team.

Dobutamine stress echo

Dobutamine stress echo was performed at Papworth using a standard staged protocol of increasing doses of dobutamine infusion in stages of 3 minutes' duration. Imaging was performed with standard views (long axis parasternal, short axis parasternal, apical three chamber and apical two chamber) acquired using tissue harmonic imaging on a 3.5-MHz ultrasound probe in the last 1 minute of each 3-minute stage. Dobutamine was infused at rates of 10, 20, 30 and 40 μg per kg of body weight per minute, increased at 3-minute intervals. If necessary, 300–600 μg of atropine were added at peak stress to achieve 90% of target heart rate. Intravenous ultrasound contrast medium (microspheres) was used to delineate the left ventricular endocardial border. Beta-blocker medications were stopped 2 days prior to the test. Twelve-lead ECG, pulse and blood pressure

monitoring were performed at each stage and every 3 minutes during recovery. All examinations were performed by the same team and reported by one of two experienced cardiologists with special interests in echo who had access to patients' clinical details. Reports were either positive for ischaemia if they showed stress-related deterioration in contractility in functional or hibernating myocardial segments (i.e. in segments that were not akinetic or dyskinetic throughout), or negative. The distribution of ischaemic and infarcted myocardium was recorded for correlation with coronary anatomy at a later stage.

Nuclear perfusion imaging (SPECT)

Rest and stress ^{99m}Tc sestamibi (^{99m}Tc MIBI) SPECT imaging was performed at Papworth within 4 weeks of randomisation using a 2-day protocol for rest and stress studies in order to optimise the radioactive dose administered. Patients were asked to abstain from all caffeine-containing food and drink for 24 hours prior to the scan. Patients fasted for 6 hours preinjection and took a fatty meal postinjection; imaging was performed at 1 hour thereafter. In the CECaT study, we used adenosine stress routinely in all patients except those with contraindications such as asthma, in which case dobutamine was infused instead. Pharmacological stress was used (6-minute adenosine infusion, 140 $\mu\text{g}/\text{kg}/\text{minute}$ with tracer injected at 3 minutes). For each examination, the 400-MBq ^{99m}Tc MIBI was administered at 3 minutes after infusion of adenosine was started. SPECT imaging was performed at 60–90 minutes after injection.

Reconstructed tomographic images (three orthogonal planes) for rest and stress were assessed visually by a single observer who had access to the clinical history of the patients, looking for fixed and reversible defects (as per established criteria). Tomographic slices and bullseye plots were examined and wall motion was assessed where gated images were available. Examinations were reported as positive, that is, showing reversible ischaemia in at least one segment of a 20-segment model, or negative. Assessment of the distribution of ischaemia was made for correlation with angiography at a later stage.²²

Cardiac MRI

Patients were asked to abstain from all caffeine-containing food and drink for 24 hours prior to the scan. All examinations were performed at the Papworth Mobile MRI Unit on a 1.5-T magnet system (Signa CV/i, GE Medical Systems,

Milwaukee, WI, USA) by the same imaging team. Multi-slice first-pass contrast-enhanced MRI perfusion imaging was performed following adenosine stress and later at rest. A saturation recovery prepared hybrid fast gradient echo/echoplanar sequence was used in conjunction with a high-performance cardiac gradient insert and a four-channel phased array surface coil. Adenosine was infused at 140 $\mu\text{g}/\text{kg}/\text{minute}$. The infusion was run for 4 minutes under supervision. After 3 minutes, and during a breath hold, a rapid bolus of gadolinium-DTPA (0.1 mmol/kg) was delivered at 5 ml/s, followed by a 25-ml bolus of saline as flush. The heart was imaged after contrast infusion began, over 40 phases, with each phase the length of two R-R intervals, during the first pass through the heart. A volumetric notched saturation prepulse was applied in order to preserve a constant saturation recovery time during acquisition of every slice. Usually 6–8 short axis slices were obtained every two heart beats, depending on patient heart rate. Rest imaging without adenosine was repeated after an interval of at least 15 minutes. Examinations were performed by the same clinical team and reported by a single observer who had access to the patients' clinical details. Reports were either positive (i.e. showing reversible ischaemia with or without wall motion abnormality or thinning) or negative. The distribution of ischaemia was recorded for correlation with coronary anatomy at a later stage.

Coronary angiography

This standard management group acted as the control group. CA was performed and reported as per standard techniques from the right femoral artery approach using the Seldinger technique.¹⁷³ A minimum of five views of the left and three views of the right coronary system were taken. Left ventricular angiography was performed in the majority of cases. Extent of disease was determined by the performing cardiologist who recorded percentage diameter stenosis by visual assessment on a standard clinical template. Since the study was an attempt to investigate practice in real-world conditions, there was no requirement for more formal quantitative analysis of stenosis severity. For the same reason, there was no attempt to blind the operator to the patient's clinical history. Although subsequent clinical decision-making related to the extent of recorded coronary disease, it was not part of the trial design to attempt to influence subsequent patient management once coronary angiography had occurred. Since only a proportion of the trial subjects underwent angiography (by virtue of the

trial design), it was neither intended nor possible to evaluate formally sensitivity and specificity of the non-invasive tests – and indeed this has been done extensively elsewhere, as reported in Chapter 1. A positive angiogram was defined as having 50% stenosis in the left main stem or 70% stenosis in any other major vessel.

Outcome measurements

Primary outcomes

- exercise treadmill time according to modified Bruce protocol assessed at 18 months after randomisation, adjusted for baseline
- cost-effectiveness of each diagnostic group (diagnosis, treatment and follow-up costs).

Secondary outcomes

- exercise treadmill time at 6 months after treatment
- successful completion of the diagnostic test
- clinical utility
- CCS classification of angina as a four-point score
- two-class improvement in CCS of angina (clinically significant improvement commonly used in angina trials, e.g. Schofield and colleagues¹⁷²)
- HRQoL (generic SF-36, disease-specific SAQ and EQ-5D)
- revascularisation rate
- hospital admission with chest pain, acute MI, unplanned revascularisation and cardiac deaths
- clinician's opinion of risk of ischaemic heart disease before and after non-invasive diagnostic test.

The schedule of follow up assessments is summarised in *Table 11*. The primary analysis is based on follow-up from the first 18 months after randomisation. Subsequent follow-up will be completed in 2007 and will be reported elsewhere.

Test success

A test was defined as successful if it yielded a useful diagnostic answer and unsuccessful if any of the following occurred: allocated test was refused or declined immediately or during the test; test failed due to technical problems; test failed due to patient-related factors; test could not be interpreted definitively.

Canadian Cardiovascular Society score for angina

The CCS score was recorded as a four-point score and was elicited by Clinical Research Assistants

TABLE 12 HRQoL questionnaires administered

Type	Questionnaire
Generic	SF-36 – 8 dimensions + 2 composite scores: PCS, MCS EuroQoL – 5 dimensions + 1 derived utility measure: mobility; self-care; usual activities; pain/discomfort; anxiety/depression; EQ-5D utility
Disease specific	SAQ – 5 dimensions: exertional capacity scale; anginal stability scale; anginal frequency scale; treatment satisfaction scale; disease perception scale

using a standard form. A two-class improvement in CCS score has been frequently used in trials of angina treatments (see, for example, Schofield and colleagues¹⁷²).

Health-related quality of life

HRQoL interviews were conducted by Clinical Research Assistants in face-to-face interviews at hospital research clinics. The questionnaires administered are summarised in *Table 12*. A brief description of each questionnaire is given below. In addition, in this UK study, utility was assessed, to permit the calculation of QALYs.

Seattle Angina Questionnaire

The SAQ¹⁷⁴ was chosen as the disease-specific measure since angina was expected to be the main limiting symptom in these patients. The SAQ has five dimensions related to angina, named the exertional capacity scale, anginal stability scale, anginal frequency scale, treatment satisfaction scale and disease perception scale. Each scale has a range from 0 to 100, with higher values representing greater functioning/satisfaction and fewer limitations. In this scale item non-response was low and restricted to those patients for whom an activity or symptom was not present. For these patients the corresponding scale was treated as missing, as described in the original validation studies.¹⁷⁴

Short Form with 36 Items

The SF-36 was used as the generic health status measure since it has been validated in a number of populations, including those with CAD. The SF-36 aims to describe eight dimensions of HRQoL on a scale from 0 (minimum function) to 100 (maximum function). The dimensions are physical functioning, role limitations due to physical problems, pain, energy/vitality, social functioning,

mental health, role limitations due to emotional problems and general health. These scales can be combined into two composite scales named the physical component score (PCS) and the mental component score (MCS) (see, for example, Ware and colleagues¹⁷⁵). We have adopted the commonly used standardisation method so that for a general population the PCS and MCS are centred around 50 with a standard deviation (SD) of 10. Lower scores indicate worse physical and mental HRQoL. For missing items we used the methods recommended in the manual.¹⁷⁵ Briefly, if at least half the items were available for any scale, the mean of the recorded items was imputed for the missing items. If more than half the items for a scale were missing, the scale was coded as missing.

It is possible to derive a utility scale based on the SF-36.¹⁷⁶ The SF-6D consists of a multivariate health status classification system with six dimensions: physical functioning, role limitations, social functioning, pain, mental health and vitality, with each dimension consisting of 4–6 levels. This classification system was developed from 14 items of the SF-36 questionnaire.¹⁷⁷ Health status based on the levels of each dimension are scored using utility weights, scaled so that full health = 1 and dead = 0. The SF-6D was used here to investigate sensitivity of results to the choice of utility measure.

EuroQoL utility measure

The EuroQoL EQ-5D¹⁷⁸ has been used in many cost-effectiveness studies. It has been recommended for use in the economic evaluation of healthcare technologies within the UK in guidance issued by NICE¹⁷⁹ and has been used extensively across a wide range of studies within the cardiovascular area. It defines health in five dimensions, named morbidity, self-care, usual activities, pain or discomfort, anxiety or depression. Each dimension has three levels: no problems, a moderate problem or a severe problem. Health states defined by the level chosen for each dimension can be scored using utility weights reflecting the values from a representative sample of the UK population.¹⁸⁰ These utilities are scaled so that full health = 1 and death = 0 and they allow for severe health states for which HRQoL is valued lower than death. For patients with missing items the EQ-5D was coded as missing.

Adverse events

Because the main focus of this study was on cost-effectiveness, an adverse event was defined as mortality or any cardiac event that required

admission to hospital, prolonged stay in hospital or an unplanned intervention or outpatient episode. At each patient contact, details of inpatient or outpatient episodes were elicited by a Clinical Research Assistant and documented. Patient-reported admissions for MI were verified with the admitting hospital.

Blinding of patients and investigators

Since this was a trial of different diagnostic strategies, carried out on a clinical setting, both patient and clinician were necessarily aware of the allocated strategy. The primary outcome measurement, exercise time, was carried out by cardiac technicians who were not informed of the patients' diagnostic histories, although we cannot be absolutely confident that they were blind to patient group. Secondary outcome measures were elicited by Clinical Research Assistants who had access to each patient's group allocation, but were not involved in patient management.

Sample size calculation

The primary outcome was the 18-month post-randomisation exercise treadmill time using the modified Bruce protocol, in which exercise intensity was increased every 3 minutes.¹⁷¹ We based the study design on the premise that any of the alternative diagnostic strategies (groups 2–4) would better target patients who would benefit from revascularisation, but would not substantially change the mean exercise time in the group. Thus, for the primary outcome, this may be considered an equivalence study, although we might expect the proportion undergoing revascularisation to change and the costs associated with each strategy to differ. Therefore, we used the methods of Jones and colleagues to design the trial.¹⁸¹ A given diagnostic group would be considered to have equivalent exercise time to the angiography group if the two-sided 95% CI of the mean difference between the functional test group and the control group was within 1 minute. From previous experience of patients undergoing revascularisation procedures, the between-patient SD was assumed to be 3 minutes. Assuming 80% power, 189 patients were required per group available at 18 months after randomisation or a total of 756. Based on earlier trials at Papworth in similar patients,¹⁷² we assume that there would be 15% failure to reach the final end-point. Therefore, we planned to recruit 896 patients. This number also gave at least 80% power to exclude differences of 0.05 (SD 0.15) in the EQ-5D, the main measure of utility for the economic analysis.

Statistical analysis

Post-randomisation

Patients were analysed in the group to which they were randomised. Categorical measurements were summarised as number and percentage, continuous measurements as the mean and SD. Since this study aimed to establish equivalence in total exercise time on a treadmill test, despite changes in the proportion undergoing revascularisation, the analysis centred on estimation of CIs for differences in exercise time between the control group (angiography only) and each functional test group. These CIs were calculated independently for each functional test and were not adjusted for multiple testing (for example, using a Bonferroni correction). In addition, generalised linear models (GLMs) with normal link function were used to regress treadmill exercise time on the diagnostic test group as a factor and baseline exercise time. Global *p*-values presented are based on the likelihood ratio test comparing the model including group with that which did not include the group.

The CCS classification for angina, patient symptom scores, revascularisation rate and incidence of cardiac-related events were compared between groups using Mantel–Haenszel tests. A positive angiogram was defined as having 50% stenosis in the left main stem or 70% stenosis in any other major vessel. Clinician risk assessments and likelihood of disease were compared among the groups using the Mantel–Haenszel test, with risk scales included as a linear trend. Time to cardiac events (MI, cardiac-related death, hospitalisation for chest pain) and all-cause deaths were explored using Kaplan–Meier curves. Similarly, HRQoL scores and the EQ-5D utility scores were compared using likelihood ratio tests from generalised linear models with normal link function.

A small group of randomised patients were not available for either primary outcome measurement or HRQoL assessment. A range of assumptions about patient losses and protocol deviations were considered but were rejected since they led either to a more conservative estimate of group effect or to spurious increases in the precision of the estimates; hence they were not appropriate in an equivalence trial, in which we are trying to exclude clinically important differences.

Post-treatment

Our *a priori* hypothesis was that the number of unsuccessful revascularisation procedures

performed would be reduced by use of functional testing to target better those who benefit. Therefore, it was considered important to check that within each treatment subgroup (CABG, PCI, MM) we had at least equivalent results with these diagnostic strategies. For groups 1–4, we compared the proportion of patients allocated to each treatment using Pearson's χ^2 test. In addition, a follow-up assessment took place 6 months after revascularisation or treatment began. Within each treatment subgroup, groups 1–4 were compared for exercise time, symptoms and quality of life at 6 months after treatment.

In addition, survival and time to major adverse cardiac events (MACEs) will be analysed using data from follow-ups at 18 and 24 months post-treatment when these data become available in 2007, and reported separately.

Economic evaluation

An NHS perspective was adopted for the economic analysis. Therefore, only costs borne by the NHS and personal social services were considered in the overall analysis. For all four diagnostic imaging groups, patient-specific resource use data were collected for 18 months post-randomisation. Date of randomisation was designed to be no more than 1 month before the initial diagnostic test. All costs reported were based on 2005–6 prices unless specified otherwise. Costs available from previous years were inflated using the Hospital and Community Health Services Pay and Prices Index.¹⁸² According to current Department of Health guidelines,¹⁸³ an annual discount rate of 3.5% was applied to all costs incurred between 12 and 18 months post-randomisation. The following resource areas were measured and valued.

Cost of diagnostic imaging tests

Average unit costs for the four diagnostic tests were available from the Finance Department of Papworth NHS Trust, where all diagnostic imaging tests took place (*Table 13*).

TABLE 13 Unit costs of imaging tests

Diagnostic test	Average unit cost (£)
Angiography (day case)	625
Angiography (overnight)	935
SPECT	405
MR perfusion imaging	565
Stress echocardiography	435

TABLE 14 Summary of unit costs applied and source of information

Resource use component	Unit cost (£)	Source
Revascularisation procedures		
CABG	7,195	NHS Reference Cost 2005–6
PCI	3,660	NHS Reference Cost 2005–6
Admissions		
Papworth cardiac ward	240	Papworth NHS Trust 2005–6
Papworth cardiac surgical ward	290	Papworth NHS Trust 2005–6
Papworth ICU	475	Papworth NHS Trust 2005–6
Papworth day ward	150	Papworth NHS Trust 2005–6
Other hospital A&E admission	93	NHS Reference Cost 2005–6
Other hospital cardiac unit	467	NHS Reference Cost 2005–6
Other hospital day ward	132	NHS Reference Cost 2005–6
ICD implant	22,907	Papworth NHS Trust 2001–2
Pacemaker implant	3,500	Papworth NHS Trust 2005–6
Cardiac-related tests		
Echocardiogram	55	Papworth NHS Trust 2005–6
	59	NHS Reference Cost 2005–6
Exercise tolerance test	85	Papworth NHS Trust 2005–6
	81	NHS Reference Cost 2005–6
Computed tomography scan	150	Papworth NHS Trust 2005–6
	160	NHS Reference Cost 2005–6
24-hour ECG	55	Papworth NHS Trust 2005–6
	68	NHS Reference Cost 2005–6
24-hour blood pressure monitoring	55	Papworth NHS Trust 2005–6
	66	NHS Reference Cost 2005–6
Outpatient and GP visits		
Follow-up cardiac outpatient visit	85	Papworth NHS Trust 2005–6
	79	NHS Reference Cost 2005–6
GP home visit	49	Netten and Curtis, 2005 ¹⁸²
GP surgery visit	30	Netten and Curtis, 2005 ¹⁸²
Practice nurse visit	10	Netten and Curtis, 2005 ¹⁸²
Community occupational therapy services	59	NHS Reference Cost 2005–6
Health visitor services	29	NHS Reference Cost 2005–6
ICD, implantable cardioverter defibrillator; ICU, intensive care unit.		

Unit costs for the three imaging tests were based on an outpatient day-case basis (and included the cost of an EET which is carried out prior to angiography or imaging, based on clinical practice at Papworth hospital. For patients in the angiography group, information was recorded on whether the test was carried out as an outpatient day-case or an overnight stay in hospital, and appropriate unit costs were applied. The average costs of all four diagnostic tests were based on a combination of the capital cost of equipment, variable costs and staff costs.

Cost of subsequent treatment

Following the initial diagnostic test, resource use information was collected on admissions for the following: revascularisation procedures (CABG/PCI); other inpatient admissions due to cardiac-related adverse events; GP and outpatient

visits; any repeat imaging tests, including subsequent confirmatory angiography; and cardiac-related medications. A more detailed description of the resource use and cost components is given in the following subsections. A summary of the unit costs considered in the overall cost-effectiveness analysis is presented in *Table 14*.

Costs of revascularisation procedures

Unit cost estimates for the CABG and PCI procedures were taken from the latest NHS Reference Costs.¹⁸³ These costs were based on an elective Healthcare Resource Group (HRG) episode and included the cost of inpatient stay of 7 days for CABG and 1 day for PCI procedures. If patients were admitted to hospital for a longer or shorter period than the standard relevant HRG episode, the unit cost of an inpatient bed-day on the cardiac

ward (£132) multiplied by the difference in the length of stay was either subtracted or added, depending on the patient-specific length of stay. For example, a patient admitted for the CABG procedure for 4 days would incur a cost of £7195 – $(3 \times £132) = £6799$ and a patient admitted for the PCI procedure for 3 days would incur a cost of $£3660 + (2 \times £132) = £3924$.

Costs of adverse events

Throughout the 18-month period following randomisation, resource use data were collected for any further readmissions and interventions due to cardiac-related adverse events including any repeat imaging tests or revascularisation procedures. Most cardiac-related events such as angina or MI only required admission to hospital either in the cardiac ward or intensive care unit, which was costed by simply multiplying the relevant unit cost by the patient-specific length of stay. Any admissions, including A&E admissions, to hospitals other than Papworth were costed using NHS Reference Costs. A small number of patients were subsequently admitted to Papworth hospital for implantation of a cardioverter defibrillator ($n = 5$) or a pacemaker ($n = 3$) and unit costs were available for these procedures from Papworth NHS Trust. Any repeat imaging tests as well as other cardiac-related tests such as computed tomography (CT) scans or ECGs were also recorded and costed according to local and national estimates.

Costs of outpatient and GP visits

Any cardiac-related outpatient follow-up visits at either Papworth or other hospitals were recorded throughout the 18-month follow-up period and were costed according to both local and national estimates. Similarly, detailed resource use data were collected for any GP or nurse consultations (clinic/home visits) and also any occupational therapy or health visitor services. Unit costs for these episodes were available from either NHS Reference Costs¹⁸³ or Netten and Curtis.¹⁸²

Medications

Detailed data were collected on patient-specific, on-going, cardiac-related medication (drug, dose and frequency) from randomisation to 18 months' follow-up. The most regularly used cardiac-related drugs during this period included calcium channel blockers, beta-blockers, statins, anti-platelet medications, nitrates, angiotensin-converting enzyme (ACE) inhibitors and anti-arrhythmic drugs. Costing to 18 months post-randomisation was carried out on a patient-specific basis using the BNF.¹⁸⁴

Cost-effectiveness analysis methods

At baseline, 6 months post-treatment and 18 months post-randomisation, patients in all four diagnostic groups completed the EQ-5D questionnaire. The social tariff for the EQ-5D, as estimated by Dolan and colleagues, was applied to each patient's self-reported classification in order to calculate utility values for each patient.¹⁸⁰ Using actual rather than nominal times of assessment, and assuming a linear change in values between time points, patient-specific utility curves up to 18 months post-randomisation were calculated for patients from all four groups. Patients for whom EQ-5D data were missing for at least one particular follow-up appointment were not included in the estimation of mean QALYs. A value of zero was applied at the date of death for those patients who died. This base case analysis was repeated using Willan and colleagues' method for censored costs and QALY data,¹⁸⁵ but since the difference in results was negligible this analysis is not included here.

The proportion of a QALY experienced by each patient to 18 months post-randomisation was calculated as the area under their utility curve to 18 months or time of death if prior to 18 months post-randomisation. In order to adjust for differences in baseline utilities across the four test groups, two separate GLMs with a normal link function were fitted to the utilities at 6 months post-treatment and 18 months post-randomisation, with baseline utility and diagnostic test group as explanatory variables. Diagnostic test effects were taken from the treatment group coefficients of these GLMs. An annual discount rate of 3.5% was applied to all QALYs between 12 and 18 months post-randomisation.

The mean difference in costs and effects between randomisation and 18 months after randomisation were estimated using the sample mean. In order to generate CIs without assuming any parametric form for the distribution of the costs, bootstrapping was used to resample patients and repeat the calculations described above 1000 times.¹⁸⁶ The bootstrap samples for the comparison of each functional test with angiography were plotted on the cost-effectiveness plane. In addition, cost-effectiveness acceptability curves (CEACs) for these comparisons were plotted. The CEAC plots the probability that a functional test is cost-effective if we are willing to pay at most £X per QALY on the vertical axis against X on the horizontal axis.

Sensitivity analysis

Sensitivity of results to the following inputs was assessed:

- use of the SF-6D utility measure in place of the EQ-5D
- inclusion of uncertainty around the point estimates of unit test costs
- potential for cost savings if all negative functional tests were not followed by confirmatory angiography
- removing patients with the bottom and top 2.5 percentiles from the cost distributions to assess the influence of outliers
- subgroup analysis by type of referring clinician, classed as (i) interventional cardiologist or (ii) non-interventional cardiologist.

Chapter 4

Results: clinical

Recruitment and compliance

Between September 2001 and September 2004 there were 3201 patients assessed for entry into the trial (*Figure 2*). Of these patients, 1981 had one or more exclusion criteria and 322 refused entry to the trial.

No data were available for patients who were ineligible for the trial. An attempt was made to elicit reasons for refusal to participate and these are recorded in *Table 15*.

Of the patients who refused to participate, 147 (46%) were women, compared with 279/898 (31%) in the study group ($p < 0.001$). In addition, those who refused were significantly older than the study group (refusals mean age 64.6, SD 10.1 years compared with study group mean age 61.8, SD 9.4 years), $p < 0.001$.

The remaining 898 patients were recruited and randomised to angiography ($n = 222$), SPECT ($n = 224$), cardiac MRI ($n = 226$) or stress echo ($n = 226$) as the initial diagnostic test. These four groups were well matched for demographics and disease history (*Table 16*). Overall, the mean (SD) age at recruitment was 61.8 (9.4) years and 619 (69%) were men. Risk factors for CAD were common with 693 (77%) receiving treatment for hyperlipidaemia and 493 (55%) treated for

hypertension. There were no significant differences in mean systolic or diastolic blood pressure among the groups. A family history of CAD could be established in 237 (26%) patients, 113 (13%) had been diagnosed with diabetes and 395 (44%) were current tobacco smokers or had at least 25 pack-years of smoking experience. Previous cardiovascular events were reported as follows: 243 (27%) MI, 76 (9%) peripheral vascular disease and 43 (5%) cerebrovascular accident.

Table 17 records the main cardiovascular-related drugs prescribed for these patients. Most patients took a combination of drugs and the type of drugs prescribed at baseline was similar across the four groups. However, significantly more patients in the stress echo group were prescribed beta-blockers at baseline ($p = 0.034$) and significantly more patients in the cardiac MRI group were prescribed nitrates ($p = 0.037$). Otherwise, there were no significant differences among the groups at baseline. Since this was intended to be a pragmatic trial, there was no attempt to standardise drug therapies during the trial and these were left to the discretion of the local referring cardiologist.

TABLE 15 Patient-reported reasons for refusal to participate in the trial

Reason given	Number (%)
Patient would not give a reason	196 (61%)
Patient wanted an angiogram	25 (8%)
Patient did not want additional tests or visits	25 (8%)
Family/pet commitments or recent bereavement	18 (6%)
Work commitments or too busy	12 (4%)
Felt too sick or too old	8 (2%)
Patient had a phobia of hospitals or needles	8 (2%)
Patient decided to 'go private'	6 (2%)
Patient did not want a functional test	5 (2%)
Patient did not want an angiogram	5 (2%)
GP or family advised against trial	5 (2%)
Patient refused all diagnostic tests	4 (1%)
Current mental health or nervous problems	4 (1%)
Patient felt too well	1 (0%)
Total	322 (100%)

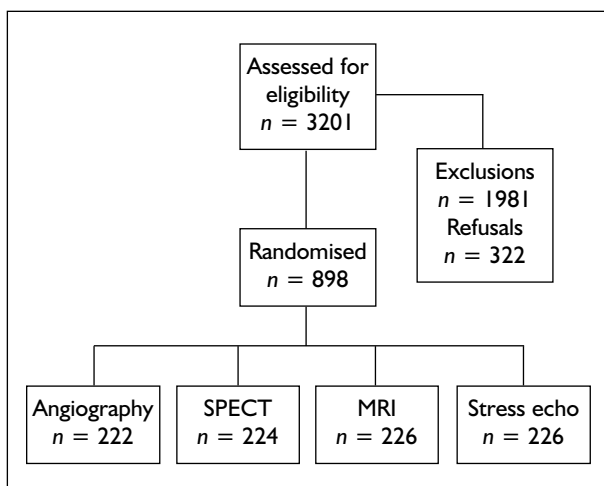


FIGURE 2 Patient recruitment and randomisation to initial diagnostic test

TABLE 16 Baseline characteristics^a

Demographics	Angiography (n = 222)	SPECT (n = 224)	Cardiac MRI (n = 226)	Stress echo (n = 226)
Mean (SD) age (years)	60.7 (9.1)	62.1 (9.5)	62.2 (9.0)	61.9 (9.9)
Males (%)	149 (67%)	157 (70%)	153 (68%)	160 (71%)
Mean (SD) body mass index (kg/m ²)	27.6 (4.2)	27.3 (4.3)	28.0 (4.4)	27.9 (4.2)
History/risk factors				
Previous MI (%)	63 (28%)	52 (23%)	69 (31%)	59 (26%)
Previous CVA (%)	10 (5%)	13 (6%)	8 (4%)	12 (5%)
Peripheral VD (%)	20 (9%)	21 (9%)	17 (8%)	18 (8%)
Diabetes (%)				
IDDM	12 (5%)	8 (4%)	11 (5%)	5 (2%)
NIDDM	16 (7%)	18 (8%)	21 (9%)	22 (10%)
Family history CAD	60 (27%)	55 (25%)	63 (28%)	59 (26%)
Smoking history (%)				
Never/ex-light	118 (53%)	130 (58%)	128 (57%)	127 (56%)
Current light ^b	31 (14%)	32 (14%)	20 (9%)	28 (12%)
Heavy ^c	73 (33%)	62 (28%)	78 (35%)	71 (31%)
Treated hyperlipidaemia (%)	164 (74%)	171 (76%)	179 (79%)	179 (79%)
Mean (SD) systolic blood pressure (mmHg)	148.3 (23.4)	152.8 (23.1)	149.2 (21.7)	151.3 (24.0)
Mean (SD) diastolic blood pressure (mmHg)	84.5 (10.2)	86.3 (9.9)	84.1 (10.0)	84.4 (11.0)
Treated hypertension (%)	117 (53%)	132 (59%)	115 (51%)	129 (57%)

CVA, cerebrovascular accident; IDDM, insulin-dependent diabetes mellitus; NIDDM, non-insulin dependent diabetes mellitus; VD, vascular disease.

^a There were no significant differences between the groups in any variable.

^b Light smoking refers to less than 25 pack-years of smoking.

^c Heavy smoking refers to a current smoker or an ex-smoker with at least 25 pack-years of smoking.

TABLE 17 Cardiovascular-related medication at baseline^a

	Angiography (n = 222)	SPECT (n = 224)	Cardiac MRI (n = 226)	Stress echo (n = 226)
Anti-platelets	168 (76%)	167 (75%)	179 (79%)	182 (81%)
Statins	141 (64%)	149 (67%)	164 (73%)	157 (69%)
Beta-blockers	126 (57%)	112 (50%)	126 (56%)	144 (64%)
ACE inhibitors	77 (35%)	71 (32%)	74 (33%)	71 (31%)
Calcium-channel blockers	60 (27%)	70 (31%)	71 (31%)	64 (28%)
Nicorandil/potassium-channel activators	42 (19%)	40 (18%)	36 (16%)	54 (24%)
Nitrates	35 (16%)	35 (16%)	56 (25%)	39 (17%)
Diuretics	38 (17%)	30 (13%)	21 (9%)	33 (15%)
Angiotensin-II receptor antagonists	15 (7%)	10 (4%)	17 (8%)	15 (7%)

^a Stress echo group was more likely to be on beta-blockers and cardiac MRI group more likely to be on nitrates, otherwise there were no significant differences between groups.

There were no significant differences between the groups at baseline in mean total exercise time, time to angina onset, ECG changes, CCS angina class or Pryor risk assessment at recruitment (Table 18). Mean (SD) time on the treadmill using the modified Bruce test was 10.77 (4.44) minutes, with 432 (48%) experiencing angina during the test. Mean (SD) time to angina in those who experienced it was 7.38 (4.20) minutes. ST depression on ECG was noted in 291 (32%) patients, including 84 (9%) who had one

≥2-mm ST depression but no other symptoms. There were six patients with an ST elevation on exercise ECG. The majority of patients (786; 88%) were in CCS classes 0–II and 69% were classed as high risk for CAD (Pryor score ≥0.8). There were no differences between the groups at baseline.

Patients were assessed for outcome at two periods, 6 months after treatment and 18 months after randomisation, the latter defined as the time of

TABLE 18 Baseline angina and exercise tolerance^a

	Angiography (n = 222)	SPECT (n = 224)	Cardiac MRI (n = 226)	Stress echo (n = 226)
Exercise tolerance^b				
Mean (SD) total exercise time (minutes)	11.29 (4.56)	10.46 (4.41)	10.43 (4.43)	10.89 (4.36)
Angina during ETT	108 (49%)	96 (43%)	111 (49%)	117 (52%)
Mean (SD) time to angina (minutes) ^c	7.61 (4.23)	7.59 (4.68)	7.34 (4.11)	7.03 (3.86)
Mean (SD) total exercise time (minutes) ^c	10.86 (4.38)	9.88 (4.38)	10.23 (4.18)	10.56 (3.86)
ECG changes on exercise test				
1–2-mm ST depression with symptoms	53 (24%)	43 (19%)	54 (24%)	57 (25%)
≥2-mm ST depression without symptoms	16 (7%)	24 (11%)	20 (9%)	24 (11%)
ST elevation/no change	153 (69%)	157 (70%)	152 (67%)	145 (64%)
CCS class				
0	11 (5%)	17 (8%)	18 (8%)	13 (6%)
I	49 (22%)	37 (17%)	60 (27%)	45 (20%)
II	138 (62%)	144 (64%)	122 (54%)	132 (58%)
III	23 (10%)	22 (10%)	23 (10%)	32 (14%)
IV	1 (1%)	4 (2%)	3 (1%)	4 (2%)
Prior risk assessment				
Low	69 (31%)	69 (31%)	69 (31%)	70 (31%)
High	153 (69%)	155 (69%)	157 (69%)	156 (69%)

^a There were no significant differences between the groups.
^b 4 patients completed the full Bruce protocol test in error and are excluded.
^c Times for those patients who experienced angina during exercise only.

primary outcome. *Figure 3* summarises the numbers in each group who attended these assessments.

Overall there were 788 (88%) patients who returned to Papworth for assessment at 6 months post-treatment, and a further 50 (6%) patients agreed to complete CCS assessment and quality of life questionnaires by post. At 18 months post-randomisation 773 (86%) had full follow-up assessment and 58 (6%) provided CCS class and quality of life information only. This compared favourably with the assumed 'failure to reach end-point' rate of 15% in the study proposal.

Feasibility of tests

Figure 3 summarises the progress of patients through the trial. In the group allocated to angiography, three patients refused the test and were not investigated further. These three patients were followed up under intention-to-treat. One patient allocated to the control group was taken off the waiting list due to renal failure and withdrew from the study. The remaining 218 (98%) underwent angiography successfully. Of the

224 patients in the SPECT arm, two required an urgent angiogram, one refused the test, one withdrew from the study and nine provided an equivocal result; 211 (94%) had a successful test. This was marginally significantly lower than the control group success rate ($p = 0.05$). Of those allocated to cardiac MRI, 25 did not have the test for the following reasons: claustrophobia (11); too large (4); asthma/chronic obstructive airways disease (COAD) (3); required urgent angiogram (2); arrhythmia or frequent ectopic heart beats (2); technical reasons (1); withdrew (1); died before referral (1). A further 10 patients attended for the MRI but the test could not be completed for the following reasons: patient refused due to claustrophobia (5); patient refused following a panic attack (1); arrhythmia or frequent ectopic beats (2); foreign body in the eye (1); technical failure of the magnet (1). A further 15 resulted in an equivocal result, giving 176 (78%) successful tests, significantly lower than controls ($p < 0.001$). Similarly, stress echo provided unequivocal test results for 203 (90%) patients, with eight not having the test [urgent angiogram required (2), withdrew (2), COAD (1), cardiac hypertrophy (1), hyperthyroidism (1), administration error (1)], a further eight having a failed test [inadequate stress achieved due to either vasovagal response (2) or

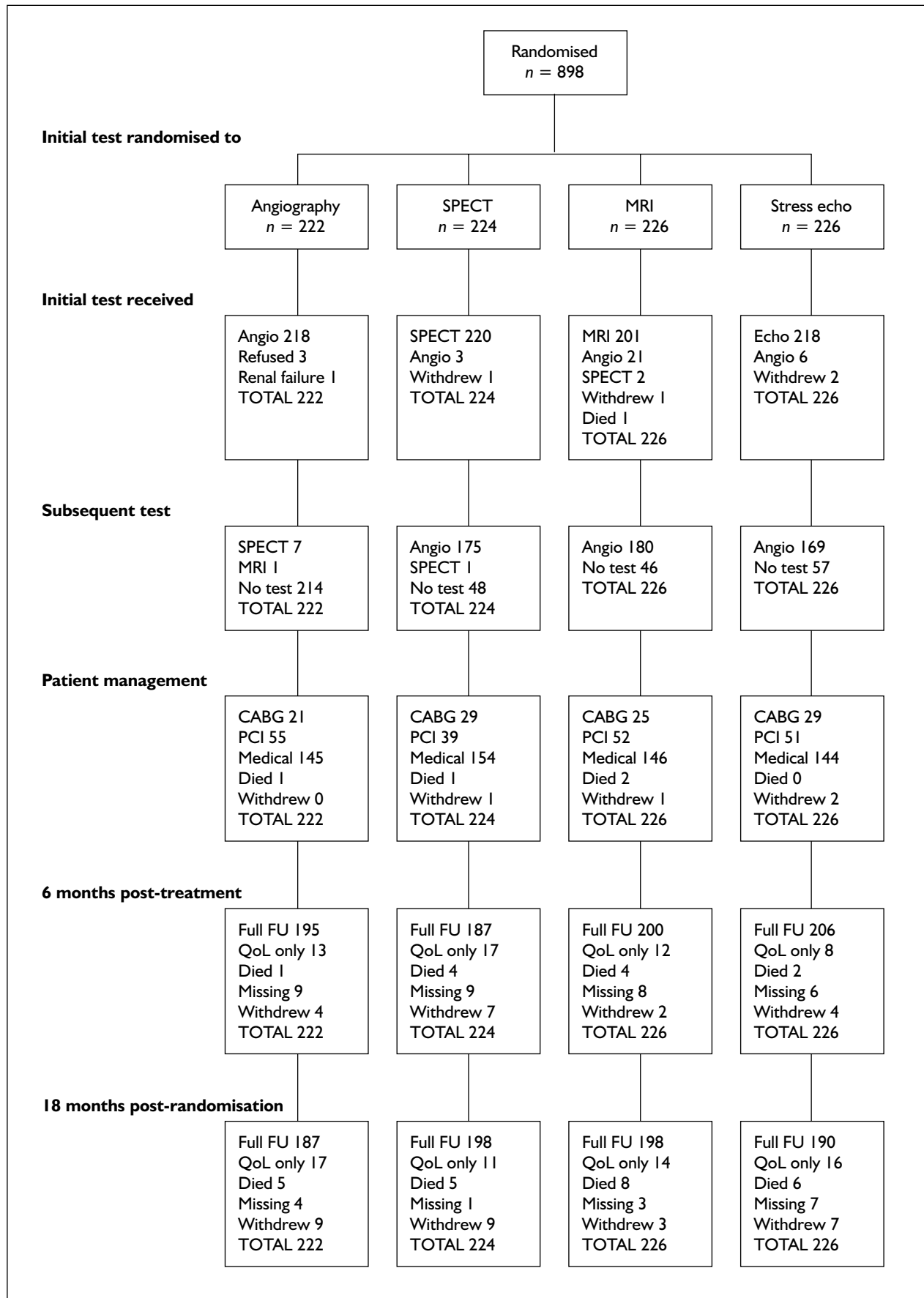


FIGURE 3 Patient progress through the trial. FU, follow-up.

other reasons (2), poor imaging due to obesity (2), hypertension (1), arrhythmia (1)] and seven not providing a definitive result. This was significantly lower than the control group ($p < 0.001$).

Confining the analysis to those who actually completed the allocated test, all 218 angiograms provided definitive information but equivocal results were found for 4% (9/220) of SPECT patients, 8% (15/191) of cardiac MRI patients and 3% (7/210) of stress echo patients. These equivocal results rates are all significantly higher than angiography ($p < 0.02$) but the difference among the three functional tests was not significant ($p = 0.09$). For the purposes of clinical management, all equivocal tests were treated as positive and patients were referred for angiography.

Clinician risk rating

Appendix 1 and *Figures 4* and *5* summarise the cardiologist's assessment of risk of serious CAD and likelihood of revascularisation at baseline, prior to and after the initial test procedure. There was no significant difference between the groups in baseline assessment of risk ($p = 0.79$) or likelihood of revascularisation ($p = 0.48$).

After the initial test, as expected with the 'gold standard' test, clinicians had confidence in the results of angiography, with assessment polarised at the highest and lowest risk categories, and the functional tests were more evenly spread across risk categories (Appendix 1 and *Figures 4* and *5*).

There was a significant difference in risk assessment patterns between angiography and functional tests ($p < 0.001$) but the three functional tests had similar patterns ($p = 0.86$). Similarly, clinicians' opinions of the need for revascularisation showed similar levels of confidence in the three functional tests ($p = 0.55$) and this was true whether the functional test result was positive or negative.

Subsequent angiography results

Of the 224 SPECT patients, 175 (78%) were subsequently referred for an angiogram (*Table 19*). Similarly, 180 (80%) MRI patients and 169 (75%) stress echo patients were referred on for an angiogram. Thus, between 20 and 25% of patients undergoing functional tests did not require further diagnostic tests. For patients who had a positive functional test the diagnosis was confirmed by angiography (50% stenosis in LAD or 70% stenosis in any other major vessel) in 83% (96/116) of SPECT patients, 89% (74/83) of MRI patients and 84% (85/101) of stress echo patients. The proportion of people with both positive functional tests and positive angiography who were managed medically was 43% in the SPECT group, 34% in the cardiac MRI group and 29% in the stress echo group. The proportion of these who required bypass surgery was 27% in the SPECT group, 27% in the cardiac MRI group and 28% in the stress echo group. The remaining patients had PCI and there were no significant differences in these proportions ($p = 0.364$). In the angiography

TABLE 19 Functional test results compared with angiography in patients who had both a functional test and an angiogram

Initial test		Result of subsequent angiography				
		Positive	Negative	Equivocal	Referred and not done	Not referred/died
SPECT	Positive	96	20	0	1	4
	Negative	14	31	0	1	44
	Equivocal	2	7	0	0	0
	Failed/not done	2	1	0	0	1
	Total	114	59	0	2	49
Cardiac MRI	Positive	74	9	0	1	6
	Negative	26	24	0	0	36
	Equivocal	7	7	0	0	1
	Failed/not done	16	15	0	0	4
	Total	123	55	0	1	47
Stress echo	Positive	85	15	1	0	2
	Negative	23	25	0	0	52
	Equivocal	3	2	0	0	2
	Failed/not done	7	6	0	0	3
	Total	118	48	1	0	59

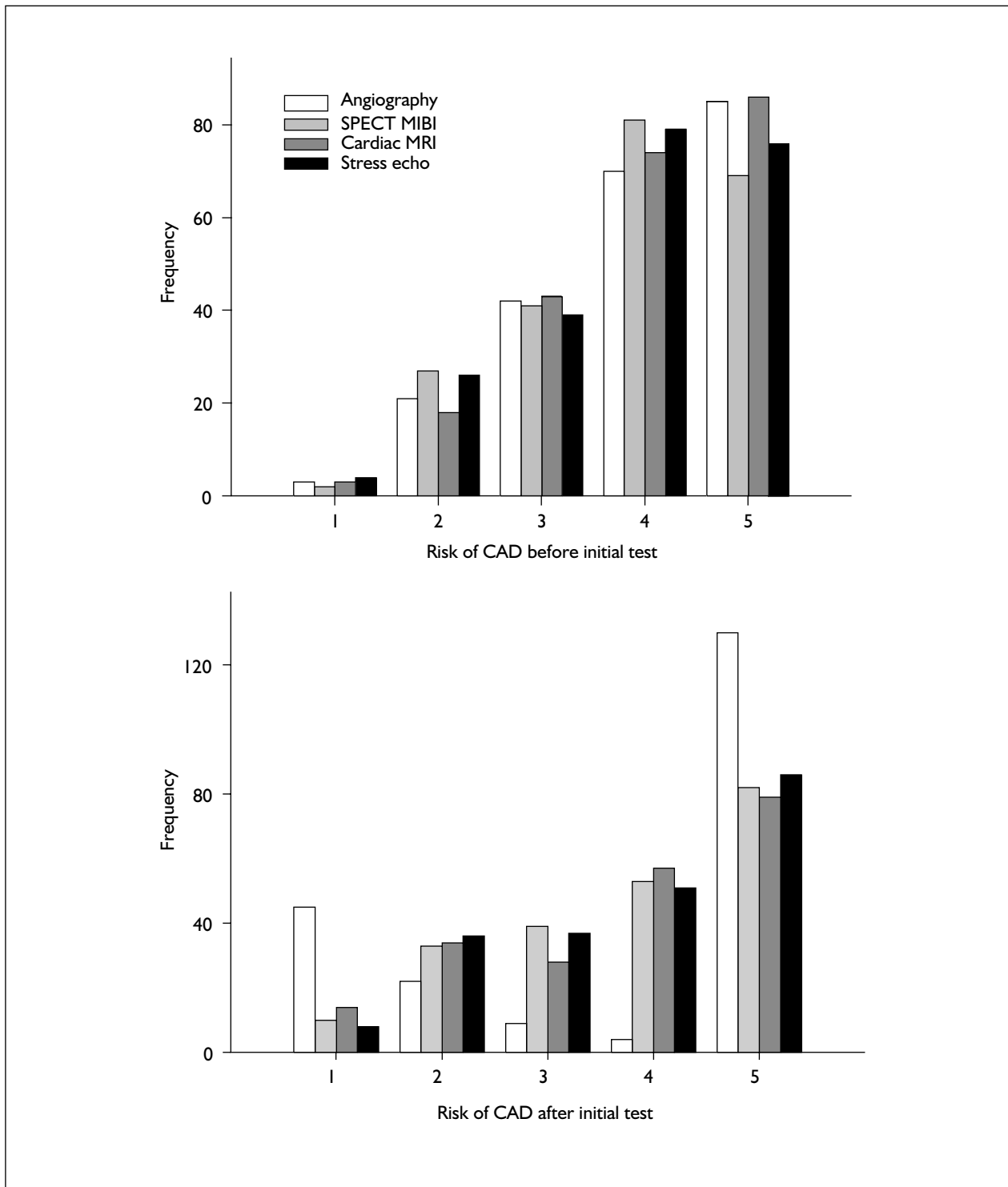


FIGURE 4 Clinician's assessment of risk of CAD. Risk was scored from 1 (lowest risk) to 5 (highest risk).

group, three patients subsequently required CABG; all had positive tests but were initially managed with PCI (2) or medically (1).

One patient with a positive cardiac MRI and three with positive echoes were initially managed with PCI and subsequently required bypass surgery.

Negative functional tests were followed by positive angiograms in 14/45 (31%) SPECT patients, 26/50 (52%) MRI patients and 23/48 (48%) stress echo patients. In each of the three groups, one of the false negatives was referred for bypass surgery as the initial management. In addition, in the SPECT group eight of the 14 false negatives were referred

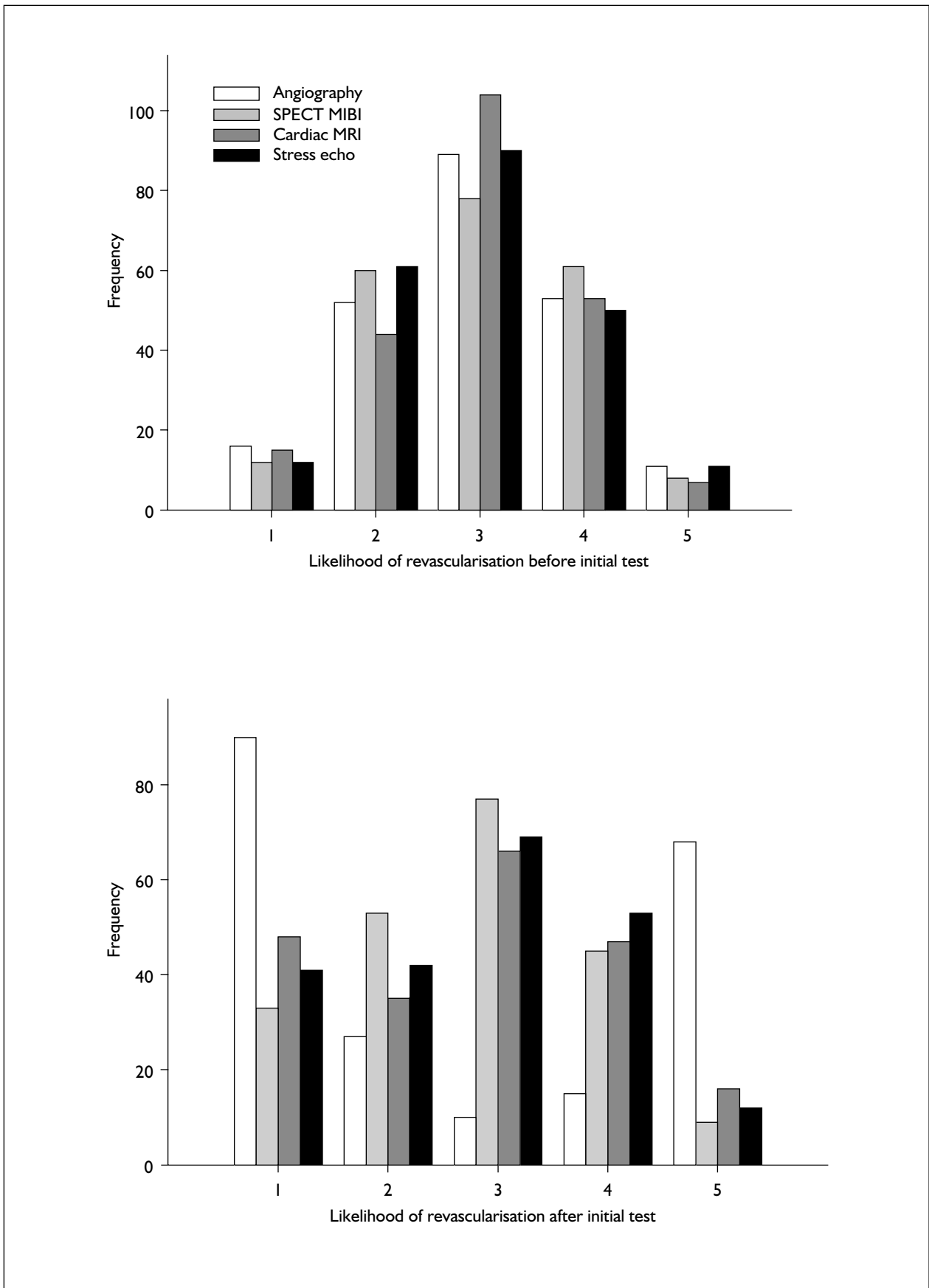


FIGURE 5 Clinician's assessment of the likelihood of revascularisation. Likelihood was scored from 1 (definitely MM) to 5 definitely revascularisation.

for PCI, compared with 15 of 26 in the MRI groups and 12 of 23 in the stress echo group. Of these false negatives initially managed with PCI, one SPECT and one stress echo patient subsequently required bypass surgery in the 18-month follow-up period.

We stress here that the study was designed to be pragmatic, reflecting current clinical practice. Formal assessment of sensitivity and specificity was not one of our objectives.

Patient management

Figure 3 and Tables 20–22 summarise patient management decisions on the basis of the initial and subsequent diagnostic tests. Four patients died and four patients withdrew from the trial before management was decided. Of the remaining patients, revascularisation was required in just over one-third (301/890, 34%) and the remaining patients had their medical management reassessed by the referring cardiology team. There was no significant difference between the groups in patient management. The proportions who had CABG were similar at 10% for the angiography group, 11% for the cardiac MRI group and 13% for both the SPECT and stress echo groups. The proportions who had PCI were 25% for the

angiography group, 18% for the SPECT group and 23% for both the cardiac MRI and stress echo groups.

Primary outcome: exercise time

18 months post-randomisation

The primary outcome measurement was total exercise time using a modified Bruce protocol treadmill test at 18 months after randomisation. Although 773 completed the exercise test, the test was completed according to the protocol in only 771 cases and results from these patients are reported here. The aim was to demonstrate equivalence in outcome between the functional tests and angiography. Clinical significance was defined *a priori* as the confidence interval for mean difference from angiography lying within ± 1 minute.

Appendix 2 summarises total exercise time for the four groups. Although the mean total exercise time for the angiography group was slightly longer than that for the functional tests, these patients had slightly longer exercise time at baseline, indicating that it was important to adjust for baseline exercise time in the analysis. Table 23 shows the difference in mean exercise time between each functional test group and controls, both unadjusted and adjusted for baseline exercise

TABLE 20 SPECT patients trial progress

Functional test result	Angiography result	Actual management
Positive (n = 121)	Positive (n = 96, 79%)	CABG (n = 26, 27%) PCI (n = 29, 30%) MM (n = 41, 43%)
	Negative (n = 20, 17%)	MM (n = 20, 100%)
	Declined (n = 1, 1%)	MM (n = 1, 100%)
	Not referred (n = 4, 3%)	MM (n = 3, 75%) Died (n = 1, 25%)
Negative (n = 90)	Positive (n = 14, 16%)	CABG (n = 1, 7%) PCI (n = 8, 57%) MM (n = 5, 36%)
	Negative (n = 31, 34%)	MM (n = 31, 100%)
	Declined (n = 1, 1%)	MM (n = 1, 100%)
	Not referred (n = 44, 49%)	MM (n = 44, 100%)
Equivocal (n = 9)	Positive (n = 2, 22%)	CABG (n = 1, 50%) PCI (n = 1, 50%)
	Negative (n = 7, 78%)	MM (n = 7, 100%)
Not done (n = 4)	Positive (n = 2, 50%)	CABG (n = 1, 50%) PCI (n = 1, 50%)
	Negative (n = 1, 25%)	MM (n = 1, 100%)
	Not referred (n = 1, 25%)	MM (n = 1, 100%)

TABLE 21 Cardiac MRI patients trial progress

Functional test result	Angiography result	Actual management
Positive (<i>n</i> = 90)	Positive (<i>n</i> = 74, 82%)	CABG (<i>n</i> = 20, 27%) PCI (<i>n</i> = 29, 39%) MM (<i>n</i> = 25, 34%) MM (<i>n</i> = 9, 100%) MM (<i>n</i> = 1, 1%)
	Negative (<i>n</i> = 9, 10%)	MM (<i>n</i> = 1, 1%)
	Declined (<i>n</i> = 1, 1%)	
	Died (<i>n</i> = 1, 1%)	
Negative (<i>n</i> = 86)	Positive (<i>n</i> = 26, 30%)	CABG (<i>n</i> = 1, 4%) PCI (<i>n</i> = 15, 58%) MM (<i>n</i> = 10, 38%) MM (<i>n</i> = 24, 100%) MM (<i>n</i> = 36, 100%)
	Negative (<i>n</i> = 24, 28%)	
	Not referred (<i>n</i> = 36, 42%)	
Equivocal (<i>n</i> = 15)	Positive (<i>n</i> = 7, 47%)	CABG (<i>n</i> = 1, 14%) PCI (<i>n</i> = 2, 29%) MM (<i>n</i> = 4, 57%) MM (<i>n</i> = 7, 100%) MM (<i>n</i> = 1, 100%)
	Negative (<i>n</i> = 7, 47%)	
	Not referred (<i>n</i> = 1, 7%)	
Test failed (<i>n</i> = 10)	Positive (<i>n</i> = 7, 70%)	CABG (<i>n</i> = 1, 14%) PCI (<i>n</i> = 2, 29%) MM (<i>n</i> = 4, 57%) MM (<i>n</i> = 3, 100%)
	Negative (<i>n</i> = 3, 30%)	
Not done (<i>n</i> = 25)	Positive (<i>n</i> = 9, 36%)	CABG (<i>n</i> = 2, 22%) PCI (<i>n</i> = 4, 44%) MM (<i>n</i> = 3, 33%) MM (<i>n</i> = 12, 100%) MM (<i>n</i> = 3, 75%) Died (<i>n</i> = 1, 25%)
	Negative (<i>n</i> = 12, 48%)	
	Not referred (<i>n</i> = 4, 16%)	

time. These differences, adjusted for baseline, are plotted in *Figure 6*. When adjusted for baseline exercise time, the differences between SPECT and angiography and between stress echo and angiography were not significant. For these groups we can also rule out a clinically significant difference in total exercise time since the upper limit of the CI was <1. However, the cardiac MRI group had a significantly shorter mean total exercise time of 35 seconds and the upper limit of the CI was 1.14 minutes less than in the angiography group, so that we cannot rule out a difference of at least 1 minute with 95% confidence.

Appendix 2 shows the proportion of patients who had angina during the modified Bruce treadmill test. At baseline, the proportion ranged from 43% for the SPECT group to 52% for the stress echo group, but the variation among the groups was not significant ($p = 0.322$). At 18 months post-randomisation, the proportion of patients experiencing angina during exercise time was significantly lower in all four groups ($p < 0.001$ for

all groups). The proportion of patients with angina during the test at 18 months ranged from 21% for the angiography group to 29% for the cardiac MRI group and the variation among the groups was not significant ($p = 0.313$). Since not all patients experienced angina during exercise, the time to angina is estimated using Kaplan–Meier curves, with those not having angina censored at the end of their exercise time. Time to angina curves are plotted in *Figure 7*. At baseline and 18 months post-randomisation there was no significant difference among the curves ($p = 0.287$ and 0.159, respectively).

6 months post-treatment

Table 23 also summarises the difference in mean exercise time between each functional test group and controls at 6 months post-treatment. These differences, adjusted for baseline, are plotted in *Figure 6*. When adjusted for baseline exercise time, the difference between SPECT and angiography was not significant and for this group we can rule out a clinically significant difference in total

TABLE 22 Stress echo patients trial progress

Functional test result	Angiography result	Actual management
Positive (n = 103)	Positive (n = 85, 83%)	CABG (n = 24, 28%) PCI (n = 36, 42%) MM (n = 25, 29%)
	Negative (n = 15, 15%)	MM (n = 15, 100%)
	Equivocal (n = 1, 1%) Not referred (n = 2, 2%)	MM (n = 1, 100%) MM (n = 2, 100%)
Negative (n = 100)	Positive (n = 23, 23%)	CABG (n = 2, 9%) PCI (n = 12, 52%) MM (n = 9, 39%)
	Negative (n = 25, 25%)	MM (n = 25, 100%)
	Declined (n = 1, 1%) Not referred (n = 51, 51%)	MM (n = 1, 100%) MM (n = 51, 100%)
Equivocal (n = 7)	Positive (n = 3, 43%)	CABG (n = 1, 33%) PCI (n = 2, 67%)
	Negative (n = 2, 29%)	MM (n = 2, 100%)
	Not referred (n = 2, 29%)	MM (n = 2, 100%)
Not done (n = 8)	Positive (n = 3, 38%)	CABG (n = 1, 33%) PCI (n = 1, 33%) MM (n = 1, 33%)
	Negative (n = 3, 38%)	MM (n = 3, 100%)
	Not referred (n = 2, 25%)	MM (n = 2, 100%)
Test failed (n = 8)	Positive (n = 4, 50%)	CABG (n = 1, 25%) MM (n = 3, 75%)
	Negative (n = 3, 38%)	MM (n = 3, 100%)
	Not referred (n = 1, 12%)	MM (n = 1, 100%)

TABLE 23 Mean difference between functional test groups and controls (95% CI) in exercise test results using the modified Bruce protocol treadmill test

	SPECT	Cardiac MRI	Stress echo	p-Value
Total exercise time (minutes)^a				
Unadjusted				
6 months	0.59 (-0.27 to 1.44)	1.39 (0.55 to 2.23) ^b	0.95 (0.11 to 1.79) ^c	0.011
18 months	0.75 (-0.10 to 1.59)	1.12 (0.27 to 1.96) ^b	0.69 (-0.16 to 1.54)	0.074
Adjusted for baseline				
6 months	-0.06 (-0.61 to 0.48)	0.62 (0.08 to 1.16) ^c	0.63 (0.09 to 1.16) ^c	0.010
18 months	0.14 (-0.42 to 0.71)	0.58 (0.01 to 1.14) ^c	0.44 (-0.13 to 1.01)	0.165
^a Positive difference indicates angiography group have longer mean total exercise time.				
^b p < 0.01.				
^c p < 0.05.				

exercise time at 6 months after treatment. However, both the cardiac MRI group and the stress echo group had significantly shorter mean total exercise times of 37 and 38 seconds, respectively, and the upper limits of both CIs was 1.16 minutes, so a difference of at least 1 minute with 95% confidence at 6 months cannot be ruled out. However, patients in these groups had a

range of treatments so these effects need to be investigated for each treatment.

Appendix 2 shows the proportion of patients who had angina during exercise testing at 6 months post-treatment. This ranged from 23% for the angiography group to 35% for the cardiac MRI group and the variation among the groups was

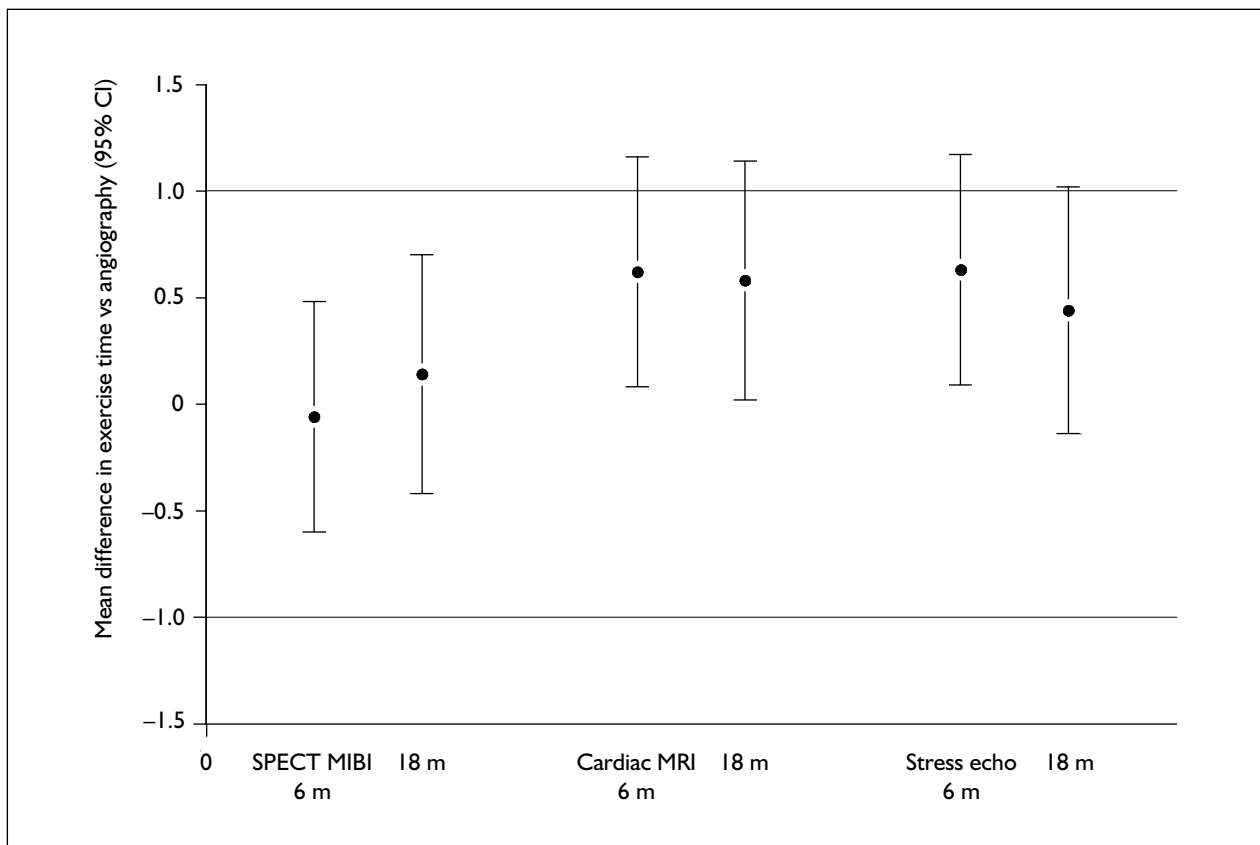


FIGURE 6 Difference in mean total exercise time (95% CI) between functional test groups and angiography group. Differences within ± 1 minute were defined a priori as not clinically significant. Values above zero favour angiography and values below zero favour the functional test. m, month.

TABLE 24 Significant improvement in CCS angina class (>2 decrease in CCS class)

	Angiography (n = 222)	SPECT (n = 224)	Cardiac MRI (n = 226)	Stress echo (n = 226)
6 months post-treatment ($p = 0.757$)				
<2 decrease in CCS class	142 (68%)	137 (68%)	152 (72%)	147 (69%)
≥ 2 decrease in CCS class	66 (32%)	66 (33%)	59 (28%)	67 (31%)
18 months post-randomisation ($p = 0.059$)				
<2 decrease in CCS class	138 (68%)	122 (58%)	149 (70%)	136 (66%)
≥ 2 decrease in CCS class	65 (32%)	87 (42%)	63 (30%)	70 (34%)

marginally significant ($p = 0.045$). In addition, the time to angina was significantly different among the groups (Figure 7, $p = 0.004$). Compared with angiography, the cardiac MRI group had a significantly higher proportion of patients with angina during exercise ($p = 0.011$), and the time to angina was significantly shorter ($p = 0.001$). In addition, although the stress echo group did not have a greater proportion of patients with angina compared with the angiography group, the time to angina was marginally significantly shorter ($p = 0.031$).

Six months post-treatment by treatment group

As Appendix 3 and Figure 8 show, at 6 months post-treatment, as might be expected, there were no significant differences between the groups in total exercise time for the patients assigned to MM, although the cardiac MRI group had shorter mean exercise time by 34 seconds. However, the revascularised patients who were originally allocated to stress echo had significantly shorter exercise time than those allocated to angiography and the mean difference (2.15 minutes for CABG

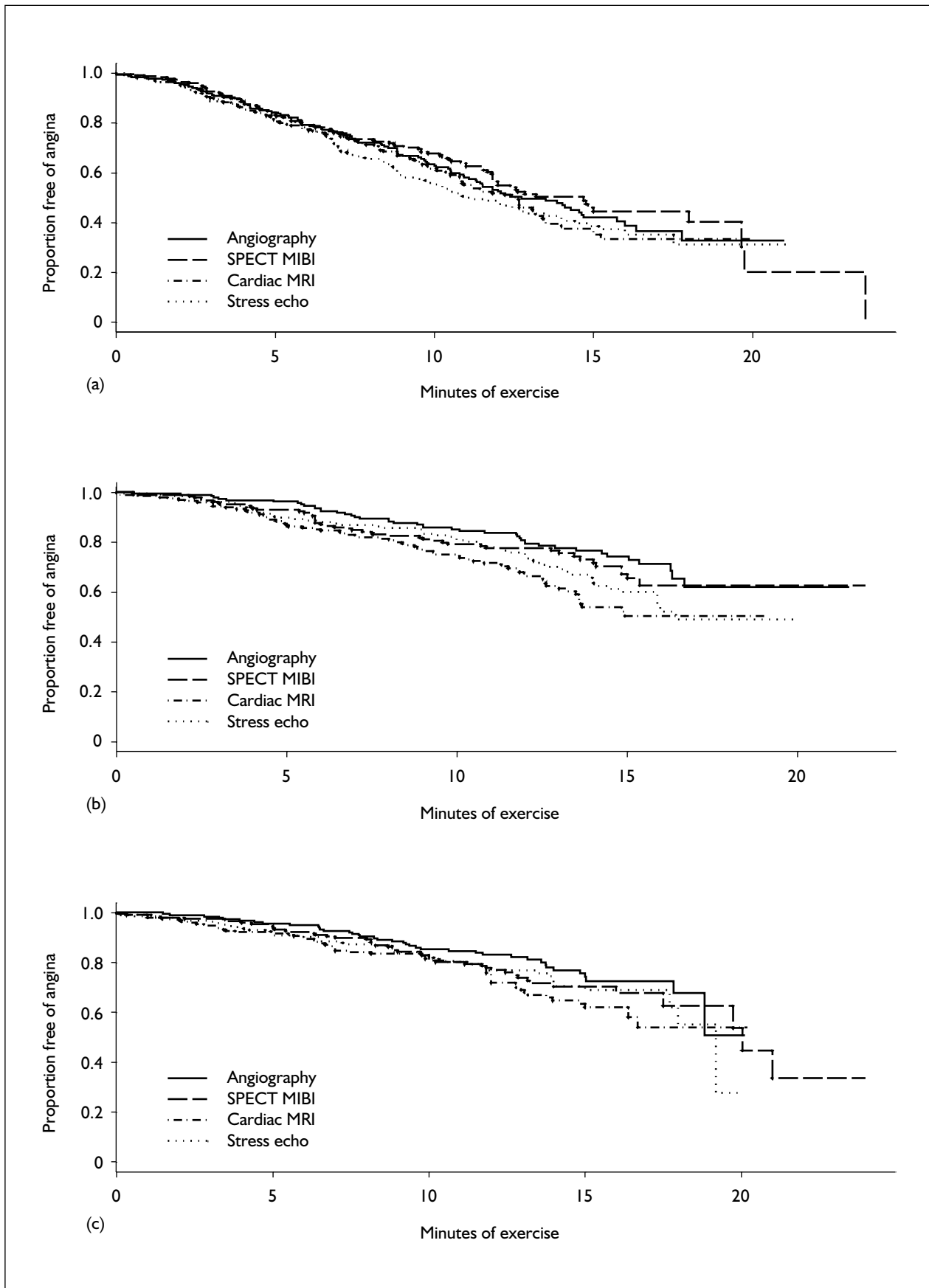


FIGURE 7 Time to angina during modified Bruce protocol treadmill exercise test at (a) baseline, (b) 6 months post-treatment and (c) 18 months post-randomisation

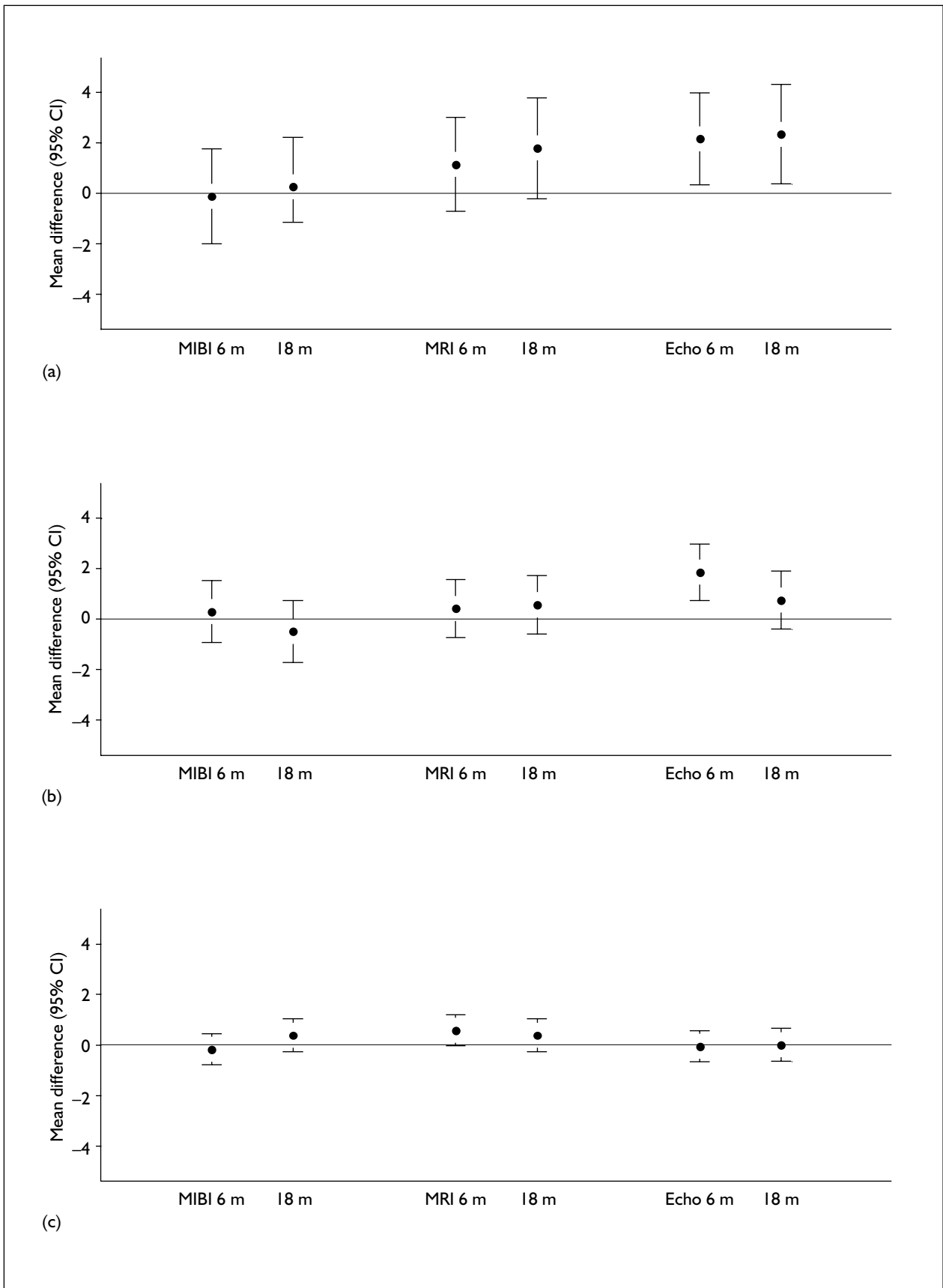


FIGURE 8 Difference in mean total exercise time (95% CI) between functional test groups and angiography group by treatment group. (a) CABG; (b) percutaneous coronary intervention (PCI); (c) MM. Differences within ± 1 minute were defined a priori as not clinically significant. Values above zero favour angiography and values below zero favour the functional test.

and 1.85 minutes for PCI) was both statistically and clinically significant. Although not statistically significant, CABG patients who had been allocated to cardiac MRI stopped the exercise test an average of 1.13 minutes earlier than those allocated to angiography (Appendix 3 and Figure 8).

Few patients who had CABG continued to have angina during exercise at the 6 months post-treatment test (one angiography, three cardiac MRI, one stress echo). There were slightly more PCI patients who had angina during exercise at 6 months but there was no significant variation among the groups (22% angiography, 18% SPECT, 26% cardiac MRI, 27% stress echo; $p = 0.759$). However, for patients who were managed medically, there was some evidence of variation among the groups in the proportion who had angina (27% angiography, 33% SPECT, 42% cardiac MRI, 36% stress echo; $p = 0.060$). Specifically, the cardiac MRI group were more likely to have angina during exercise at 6 months post-treatment than the angiography group ($p = 0.009$) and this was also reflected in the time to angina plots (Figures 9–11).

Secondary outcomes

CCS class

CCS angina class at baseline and the two follow-up assessments is shown in Appendix 4 and Figure 12. As expected, all groups have a significant improvement in CCS class (McNemar–Bowker test within each group, all $p < 0.001$) and the extent of improvement was not significantly different across the four groups at either follow-up assessment (Appendix 5 and Figure 13). At least a two-class decrease in CCS class has been used to define a clinically significant improvement in angina (see, for example, Schofield and colleagues¹⁷²) and Table 24 shows the proportion of patients in each group achieving this level of improvement in the four groups. Although there was no significant difference among the groups overall at either assessment, the group allocated to SPECT had a greater proportion of patients achieving this clinically significant improvement in angina at 18 months.

The proportions who had a significant improvement by treatment group are shown in Table 25 and Figure 14. For this analysis the PCI and CABG groups are combined due to small numbers in each cell. The proportion of patients who had a clinically significant decrease in angina

following revascularisation ranged from 44% in the angiography and cardiac MRI groups to 60% in the SPECT group at 6 months post-treatment and from 36% in the angiography post-treatment group to 60% in the SPECT group at 18 months post-randomisation. At both 6 months post-treatment and 18 months post-randomisation there was evidence that patients in the SPECT group who underwent revascularisation were more likely to have a clinically significant reduction in CCS angina class than the other groups. This reached statistical significance at 18 months post-randomisation.

Naturally, for those patients who were managed medically the proportion who had a significant improvement in angina class was lower, ranging from 20 to 26% at 6 months and from 24 to 33% at 18 months. There were no significant differences between the diagnostic test groups.

Survival and cardiac events

During the first 18 months of the study there were 24 deaths (2.7%) and these were evenly distributed among the four groups (Table 26, log-rank test, $p = 0.829$). Thirteen deaths were due to cardiac causes, three to other cardiovascular causes and eight to other causes, mostly malignancies or respiratory conditions (see footnotes to Table 26).

There were 148 non-fatal adverse events in 103 patients (Table 26), mostly patient-reported hospital admissions for chest pain (100 admissions in 78 patients). There was a significant excess of non-fatal events in the group allocated to stress echo [relative rate compared with the angiography group = 1.95 (95% CI: 1.23 to 3.08), $p = 0.012$], mostly admissions for chest pain. However, seven admissions were reported by one patient in this group and there was no significant difference between the groups in the number of patients reporting non-fatal adverse events [relative rate compared with the angiography group = 1.59 (95% CI: 0.90 to 2.79), $p = 0.327$].

Post-hoc subgroup analysis

Patients with previous MI

There were 243 patients who had had a previous MI confirmed by the referring clinician's hospital. In this subgroup the initial test allocations were 63 to angiography, 52 to SPECT, 69 to cardiac MRI and 59 to stress echo. Of the 63 allocated to the angiography group, 51 (81%) were positive, compared with 47 (92%) in 51 patients who completed a SPECT test, 44 (77%) in 57 patients

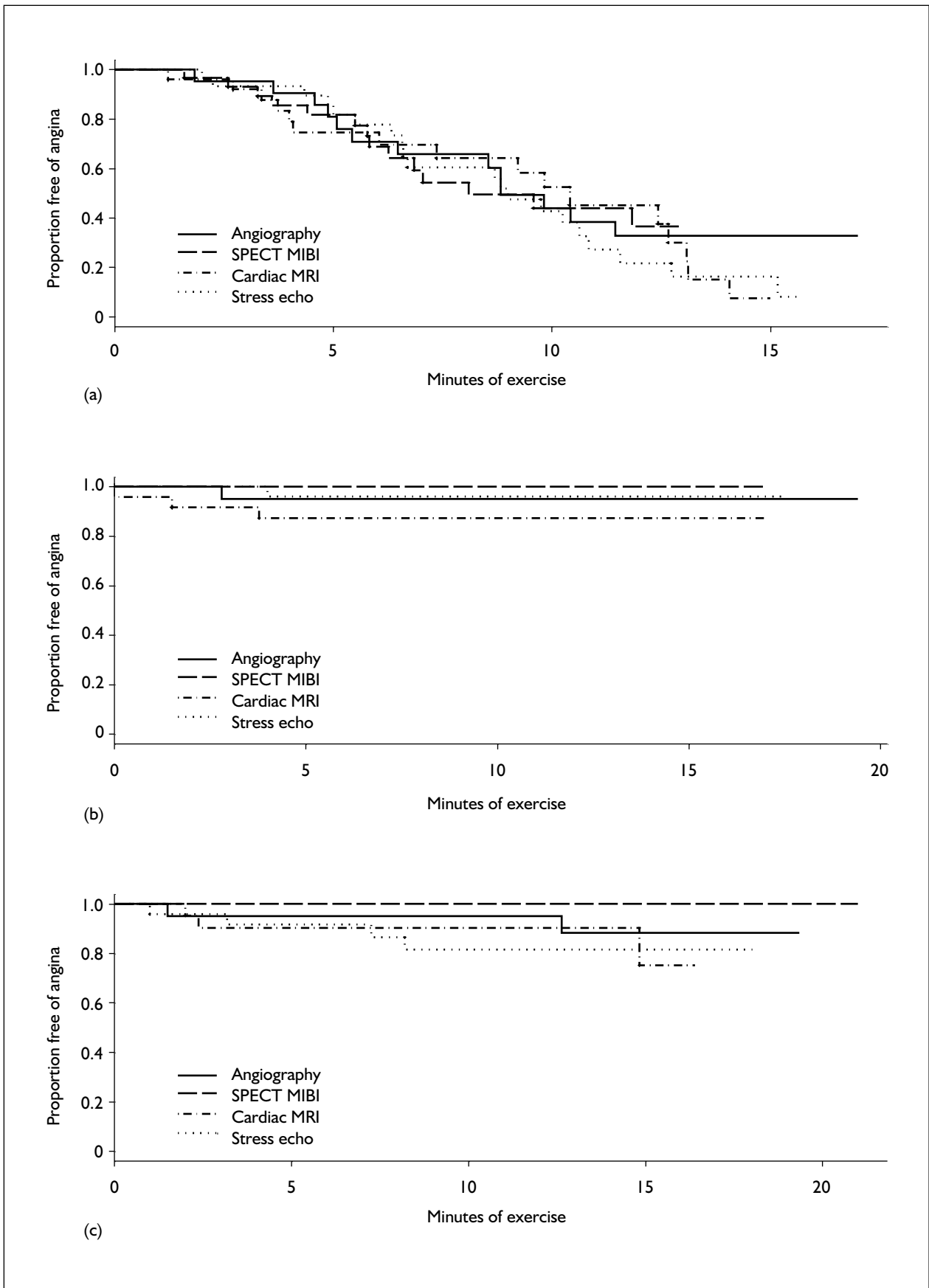


FIGURE 9 Time to angina during exercise test at (a) baseline, (b) 6 months post-treatment and (c) 18 months post-randomisation – CABG patients only

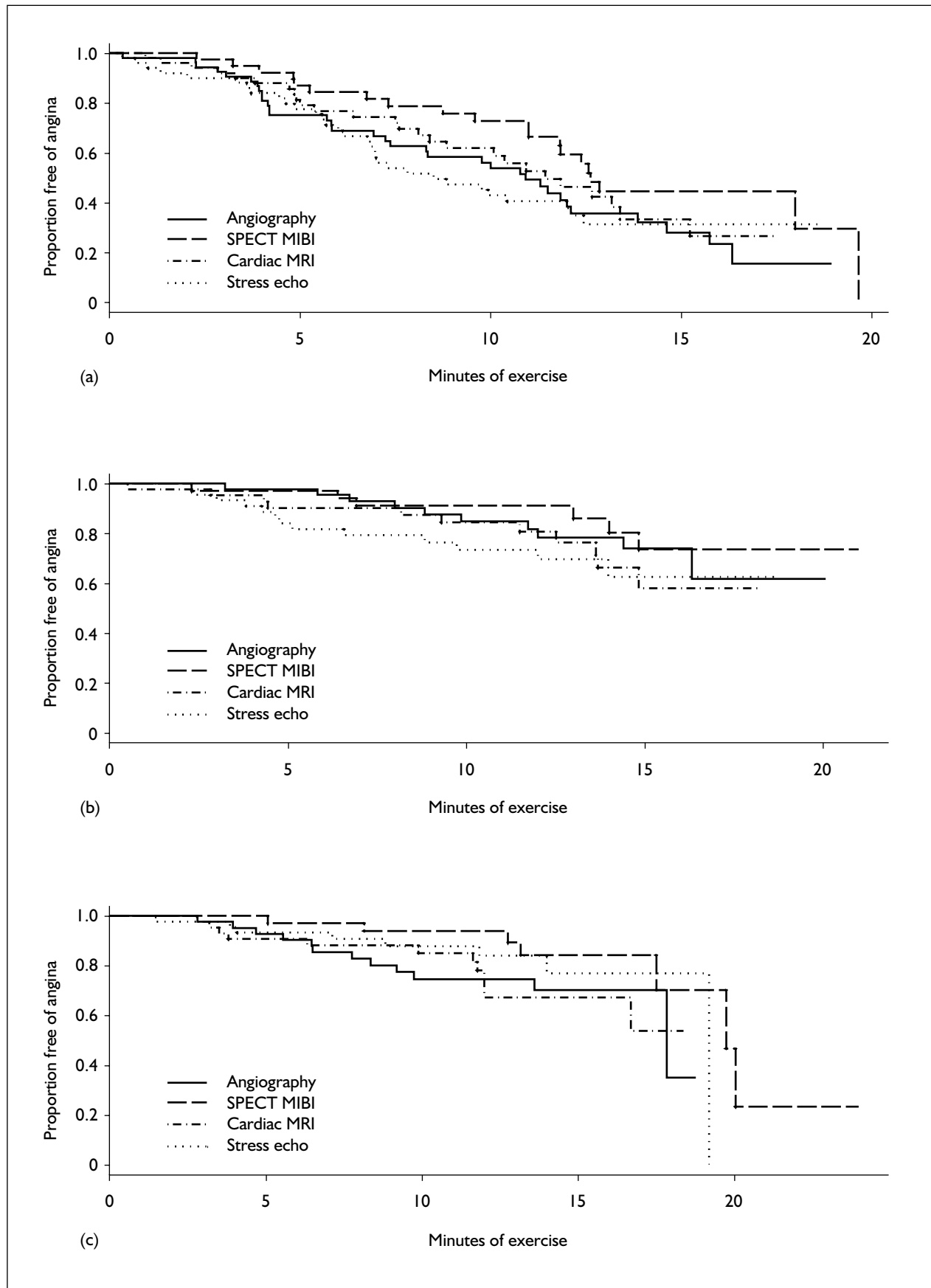


FIGURE 10 Time to angina during exercise test at (a) baseline, (b) 6 months post-treatment and (c) 18 months post-randomisation – PCI patients only

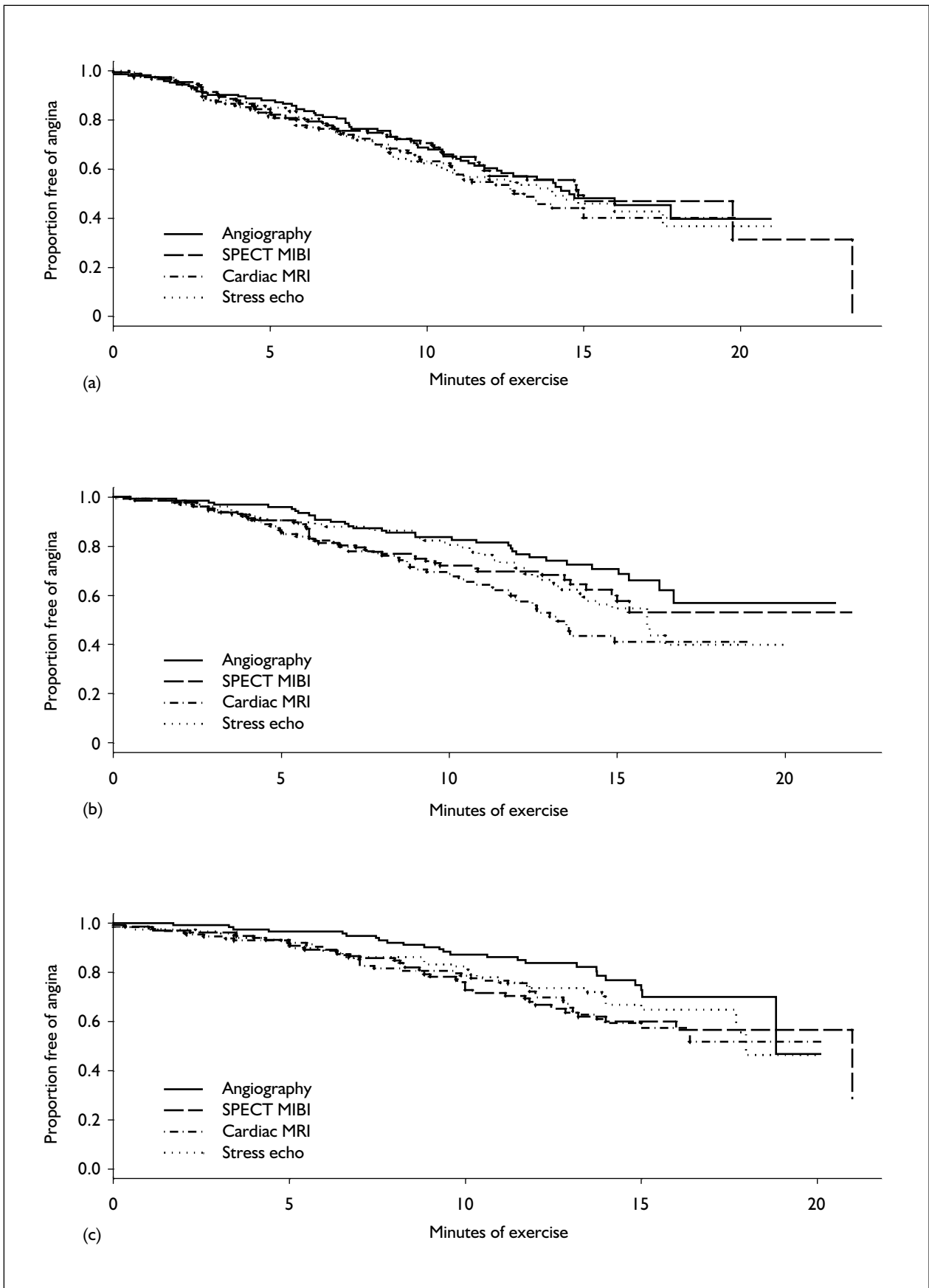


FIGURE 11 Time to angina during exercise test at (a) baseline, (b) 6 months post-treatment and (c) 18 months post-randomisation – MM patients only

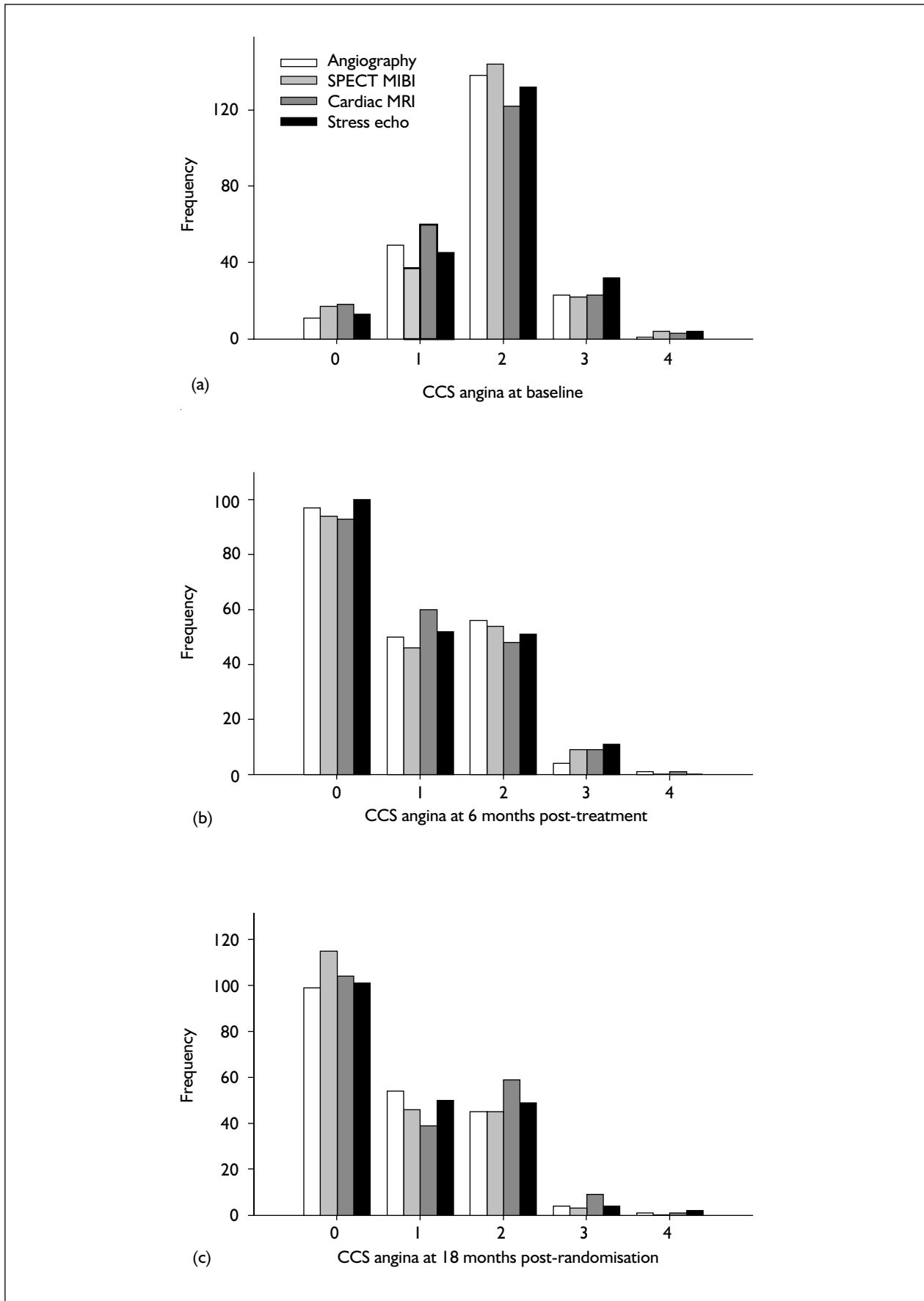


FIGURE 12 CCS angina classification at (a) baseline, (b) 6 months post-treatment and (c) 18 months post-randomisation

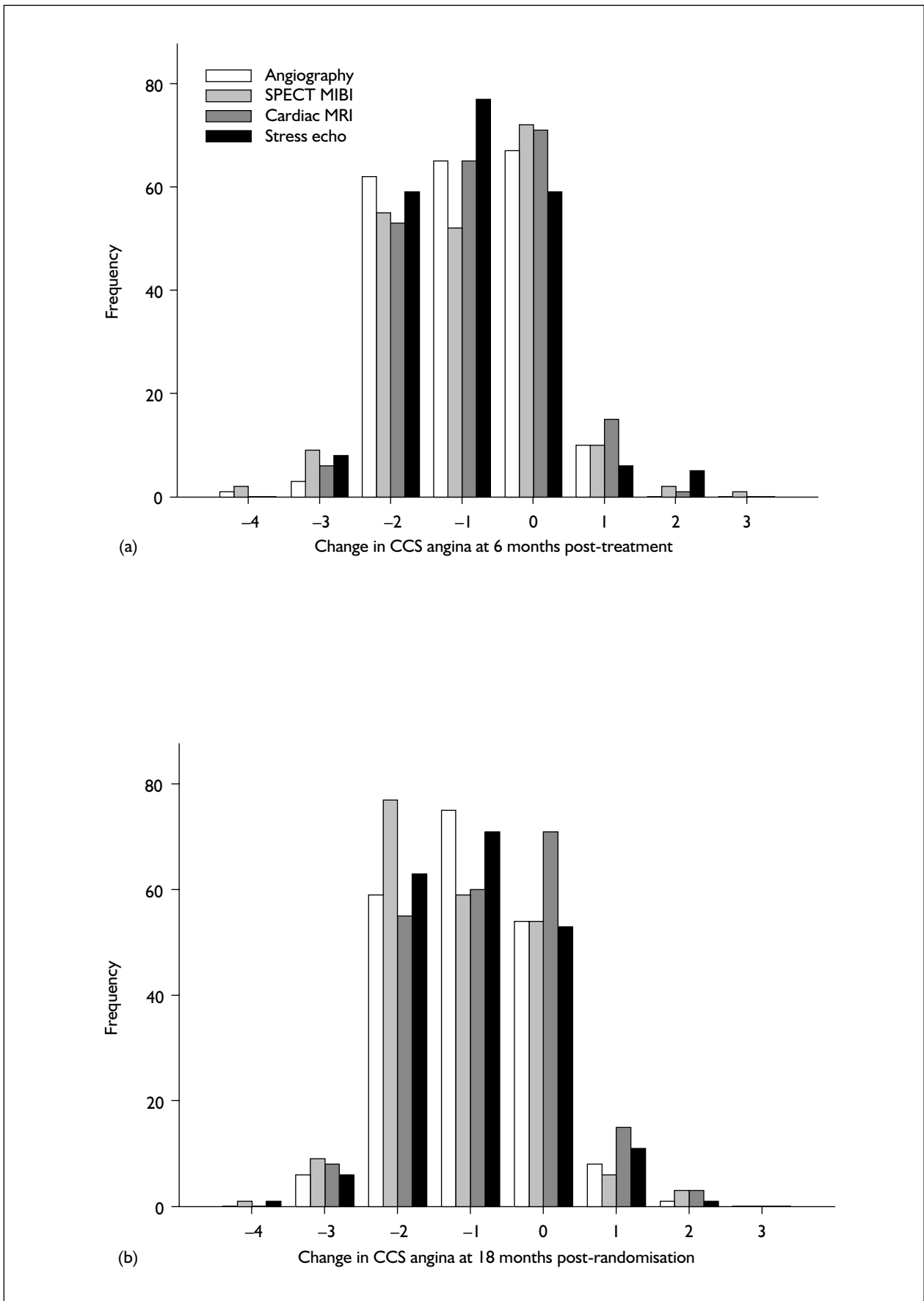


FIGURE 13 Change from baseline in CCS angina class at (a) 6 months post-treatment and (b) 18 months post-randomisation

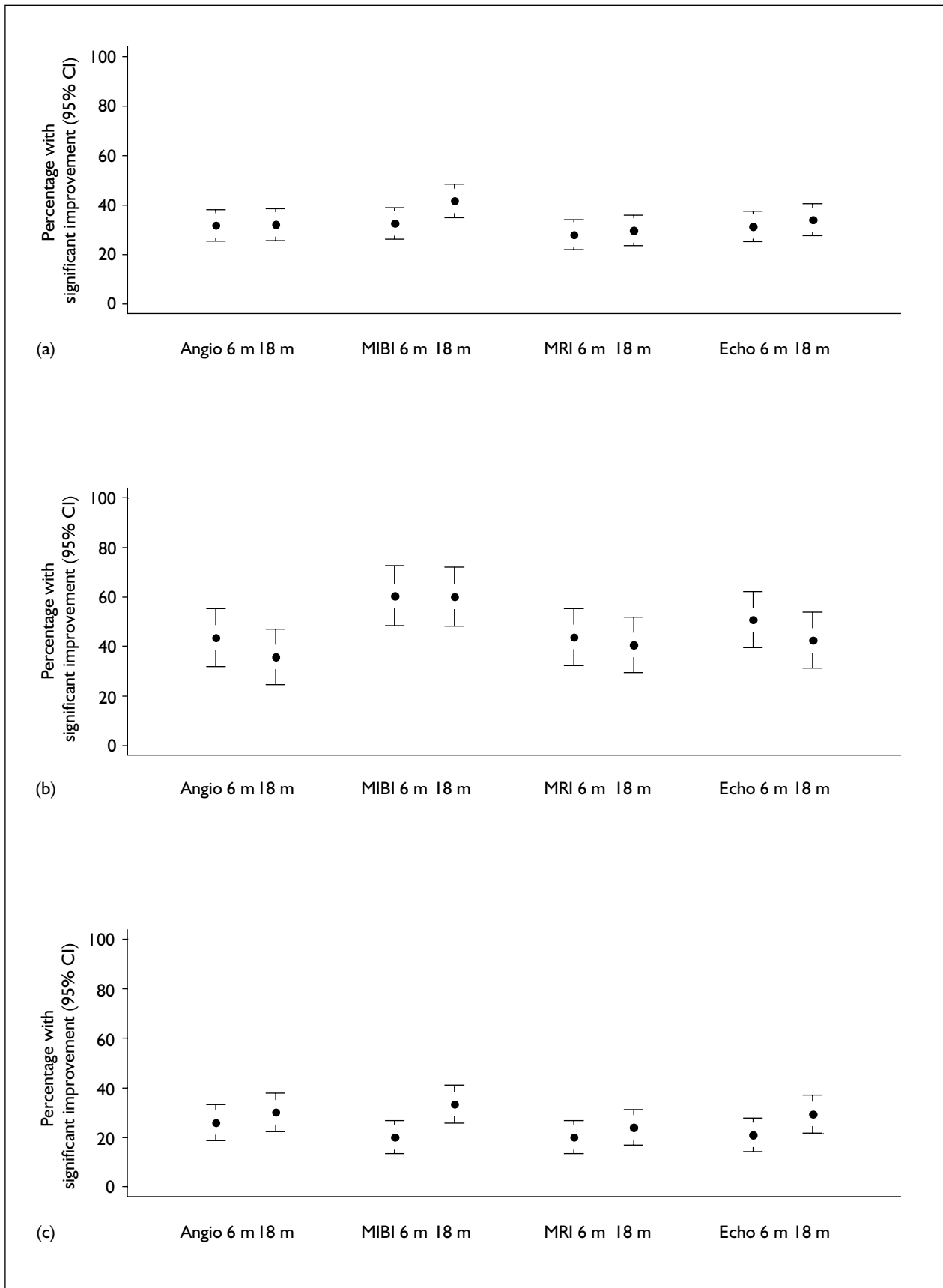


FIGURE 14 At least two-class decrease from baseline in CCS angina class at 6 months post-treatment and 18 months post-randomisation and by treatment group. (a) All patients; (b) revascularised patients only; (c) MM patients only. CABG and PCI groups have been combined due to the small numbers in each group.

TABLE 25 Significant improvement in CCS angina class (>2 decrease in CCS class)

	Angiography (n = 222)	SPECT (n = 224)	Cardiac MRI (n = 226)	Stress echo (n = 226)
PCI/CABG patients 6 months post-treatment (p = 0.175)				
<2 decrease in CCS class	39 (56%)	25 (40%)	40 (56%)	37 (49%)
≥2 decrease in CCS class	30 (44%)	38 (60%)	31 (44%)	38 (51%)
PCI/CABG patients 18 months post-randomisation (p = 0.028)				
<2 decrease in CCS class	45 (64%)	26 (40%)	44 (59%)	42 (57%)
≥2 decrease in CCS class	25 (36%)	39 (60%)	30 (41%)	31 (43%)
MM patients 6 months post-treatment (p = 0.577)				
<2 decrease in CCS class	103 (74%)	112 (80%)	112 (80%)	110 (79%)
≥2 decrease in CCS class	36 (26%)	28 (20%)	28 (20%)	29 (21%)
MM patients 18 months post-randomisation (p = 0.376)				
<2 decrease in CCS class	93 (70%)	96 (67%)	105 (76%)	94 (71%)
≥2 decrease in CCS class	40 (30%)	48 (33%)	33 (24%)	39 (29%)

TABLE 26 Number of adverse events (number of patients with adverse event)

	Angiography (n = 222)	SPECT (n = 224)	Cardiac MRI (n = 226)	Stress echo (n = 226)
Admission for chest pain	18 (14)	22 (19)	25 (21)	35 (24)
Admission for acute MI	0 (0)	2 (2)	3 (3)	6 (6)
Unplanned PCI	5 (4)	1 (1)	5 (5)	8 (5)
Unplanned CABG	3 (3)	1 (1)	1 (1)	4 (4)
Other non-fatal events ^a	1 (1)	5 (5)	2 (2)	1 (1)
Total non-fatal events	27 (19)	31 (24)	36 (29)	54 (31)
Deaths				
Cardiac	3	5	4	1
Other cardiovascular	0	0	1	2
Other ^b	2	0	3	3
Total deaths	5	5	8	6
Total non-fatal + fatal events	32 (24)	36 (29)	44 (36)	60 (37)
Total follow up (years)	315.6	318.4	327.0	321.2

^a Other non-fatal events were CVA post-angiography, observed overnight (angio); post-CABG wound infection, admission for breathlessness, admission for ICD implant, admission for suspected MI found to be muscular pain, seen in A&E with chest pain (SPECT); admission for fluid over the heart, admission for blurred vision following angiography (MRI); transient ischaemic attack (stress echo).

^b Other deaths were: bowel cancer, unknown (angio); lung cancer, small cell lung cancer, pancreatic cancer (MRI); pneumonia, respiratory failure, road traffic accident (stress echo).

who completed a cardiac MRI and 39 (74%) in 53 patients who completed a stress echo test ($p = 0.090$). Overall there was no significant variation among these groups in the primary outcome of total exercise time during the modified Bruce treadmill test ($p = 0.118$). When we compare each individual functional test group against angiography, the mean difference in total exercise time between the angiography and SPECT groups was small at -0.23 minutes (95% CI: -1.47 to 1.02). However, the mean exercise time was over

1 minute lower for both the cardiac MRI group [mean difference -1.06 minutes (95% CI: -2.24 to 0.11)] and the stress echo group [mean difference -1.25 minutes (95% CI: -2.47 to -0.03)]. These differences were defined *a priori* as clinically significant.

In the subgroup with no previous history of MI, 159 were allocated to angiography, 172 to SPECT, 157 to cardiac MRI and 167 to stress echo. Of the 155 patients who completed an angiogram

69 (45%) were positive, compared with 74 (44%) of 169 patients who completed a SPECT test, 46 (34%) of 134 patients who completed a cardiac MRI and 64 (41%) of patients who completed a stress echo test ($p = 0.284$). In this subgroup there

was less variation among the groups in total exercise time ($p = 0.806$). Comparing the mean total exercise time for each functional test group with angiography, the 95% CIs of the differences all lay within ± 1 minute.

Chapter 5

Results: health-related quality of life

Compliance

All patients were asked to complete quality of life questionnaires at baseline, 6 months post-treatment and 18 months post-randomisation. At baseline questionnaires were completed by the 898 patients who attended the hospital for the baseline research clinic. At 6 months post-treatment questionnaires were completed by the 788 patients who attended the hospital for exercise testing and 50 patients who agreed to complete these questionnaires and return them by post. This represents a compliance rate of 93% of randomised patients. Corresponding numbers at 18 months were 773 for exercise testing and questionnaires, and 58 for questionnaires only, 93% compliance.

Seattle Angina Questionnaire

The SAQ is disease specific and, therefore, should be the most sensitive quality of life instrument used. Item non-response for the SAQ ranged from 6 (0.2%) to 27 (1.1%) of 2560 questionnaires returned. For the Exertional Capacity Scale (ECS) there were 212 (8.3%) missing. For this scale a high missing rate is to be expected since the items of this scale record information on activities such as jogging, climbing stairs, lifting and strenuous sports, which people in this age group often avoid for reasons other than angina, for example arthritis. The scale is not defined if there are more than four of nine missing items. For the other four scales the maximum number missing was 27 (1.1%). For all five SAQ scales the missing values were evenly distributed among the four groups.

Scores for the five dimensions of the SAQ are summarised in Appendix 6. With one exception all groups improved their SAQ scores in all dimensions at both 6 months post-treatment and 18 months post-randomisation. The treatment satisfaction score did not change significantly for the angiography group at 6 months post-treatment. However, treatment satisfaction was fairly high at baseline, and changed less than other SAQ scores in all groups. The difference between the functional test groups and angiography is summarised in Appendix 7 and *Figure 15*. There were no significant differences

between the groups at either assessment, and the CIs were within ± 10 points. A difference in scores of 10 can be interpreted as a clinically important difference¹⁷⁴ and this falls outside the range of all CIs in this study.

Appendix 8 shows the differences in SAQ scores between the functional tests and angiography group at 6- and 18-month follow-ups, adjusted for baseline, by treatment subgroups. There was some evidence that the SPECT and stress echo groups had better mean anginal frequency score at 6 months after CABG and that the SPECT group had worse exertional capacity and anginal symptom mean scores at 6 months after medical management. In addition, the SPECT subgroup had better exertional capacity score at 18 months in the PCI and medical management subgroups. However, given the number of statistical tests implicit in this analysis and the marginal results found, it is unlikely that these results have any clinical significance.

Short Form with 36 Items

Of the 2563 SF-36 questionnaires completed, item non-response ranged from two (0.08%) to 10 (0.4%). After imputing missing values where appropriate and combining items into the eight scales, there were at most 13 (0.5%) cases where the scale could not be calculated.

Although the SF-36 has eight dimensions, they can be combined into two composite scales, one representing physical functioning (PCS) and one mental functioning (MCS). We concentrate on these two composite scores here. The scales were missing in 32 (1.2%) of 2563 cases and these were evenly distributed among the four groups. For a general population these scales are centred at 50 and have an SD of 10. Analysis of the eight scales demonstrated no significant differences between any functional test group and angiography at any assessment (data not shown).

Appendix 9 summarises the composite scores at baseline and the two follow-up assessments. At baseline all groups had significantly lower mean PCS than 50, the mean for the general population

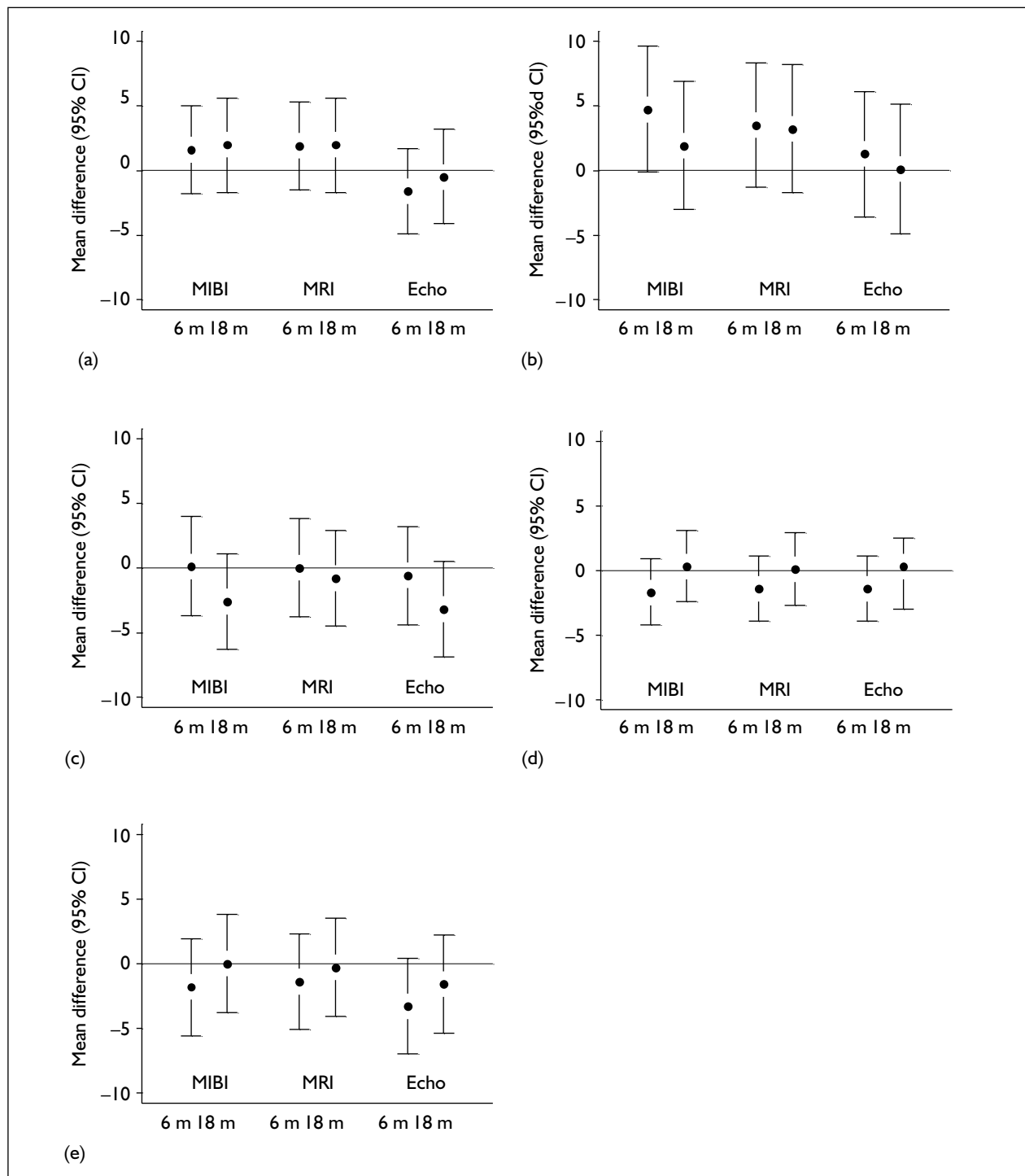


FIGURE 15 Difference in mean SAQ scores (95% CI) between functional test groups and angiography group adjusted for baseline. (a) Exertional capacity; (b) anginal capacity; (c) anginal frequency; (d) treatment satisfaction; (e) disease perception. Values above zero favour angiography and values below zero favour the functional test.

($p < 0.001$). Although all groups had improved PCS at both 6- and 18-month assessment ($p < 0.001$), they were still significantly impaired compared with the general population ($p < 0.001$ for all groups and both follow-ups). Differences between these groups and angiography are summarised in *Table 27* and *Figure 16*. There

were no significant differences between the groups and CIs were within ± 3.8 points. A difference of 5 points has been advocated as the minimum 'clinically and socially relevant' difference for individual scales of the SF-36, although this has not been validated for the composite scales.¹⁸⁷

TABLE 27 Mean difference between function test groups and controls (95% CI) in SF-36 physical and mental component scores, adjusted for baseline^a

	SPECT	Cardiac MRI	Stress echo	p-Value
6 months				
PCS	-0.5 (-2.5 to 1.5)	0.9 (-1.1 to 2.8)	0.0 (-2.0 to 1.9)	0.587
MCS	-0.3 (-2.3 to 1.6)	0.8 (-1.2 to 2.7)	0.1 (-1.9 to 2.0)	0.728
18 months				
PCS	0.8 (-1.4 to 3.0)	1.6 (-0.6 to 3.8)	-0.5 (-2.8 to 1.7)	0.255
MCS	0.3 (-1.9 to 2.4)	1.3 (-0.8 to 3.5)	-1.1 (-3.2 to 1.1)	0.199

^a Positive values favour angiography.

TABLE 28 Mean (SD) EuroQoL EQ-5D

	Angiography (n = 222)	SPECT (n = 224)	Cardiac MRI (n = 226)	Stress echo (n = 226)
Baseline	0.76 (0.23)	0.78 (0.19)	0.75 (0.23)	0.77 (0.22)
6 months post-treatment	0.78 (0.24)	0.81 (0.19)	0.80 (0.22)	0.81 (0.20)
18 months post-randomisation	0.78 (0.25)	0.80 (0.20)	0.77 (0.27)	0.82 (0.21)

At baseline the mean MCS score was much closer to 50 for all groups, and was only marginally significantly lower than 50 in the angiography and cardiac MRI groups ($p = 0.025$ and 0.026 , Appendix 9). All groups improved their MCS significantly by approximately 3–5 points ($p < 0.01$ for all groups, Appendix 9). There were no significant differences between the groups at either 6 months after treatment or 18 months after randomisation and CIs were within ± 3.8 points (Table 27 and Figure 16).

Appendix 10 shows these results by treatment subgroup. The cardiac MRI patients who had PCI had a significantly worse MCS at 6 months and PCS at 18 months compared with the angiography + PCI group. Again, multiple tests and marginal results suggest that this is unlikely to be of clinical significance.

EuroQoL EQ-5D

Of the 2552 EuroQoL questionnaires returned, seven (0.3%) were blank and one (0.04%) was only partially completed. Hence the EQ-5D could not be calculated for eight (0.3%) cases.

The mean and SD of the EQ-5D utility measure is summarised in Table 28. This measure represents

the value that the population attributes to life in a given health state and was recorded in order to estimate quality-adjusted survival for use in the economic analysis. The average EQ-5D score is 0.79 for a population with similar characteristics to patients in this study; that is, mean age 61–62 years and 70% male.¹⁸⁸ At baseline the values for the study patients are slightly lower than the population average but there is improvement in all groups to about the population average.

Table 29 summarises the difference in EQ-5D between the functional test groups and the angiography group, both unadjusted and adjusted for baseline EQ-5D. Adjusted comparisons are plotted in Figure 17. There was very little difference between the groups in mean EQ-5D and no differences were significant. When adjusted for baseline, all CIs lay within ± 0.07 . Any change in EQ-5D of less than 0.05 has been described as ‘descriptively irrelevant’^{189,190} and we can rule out a decrease of 0.05 compared with angiography for all three functional tests (upper limit of CIs < 0.05 , Table 29 and Figure 17).

Appendix 11 shows EQ-5D results by treatment subgroup and there were no significant differences between the functional tests and angiography in any subgroup.

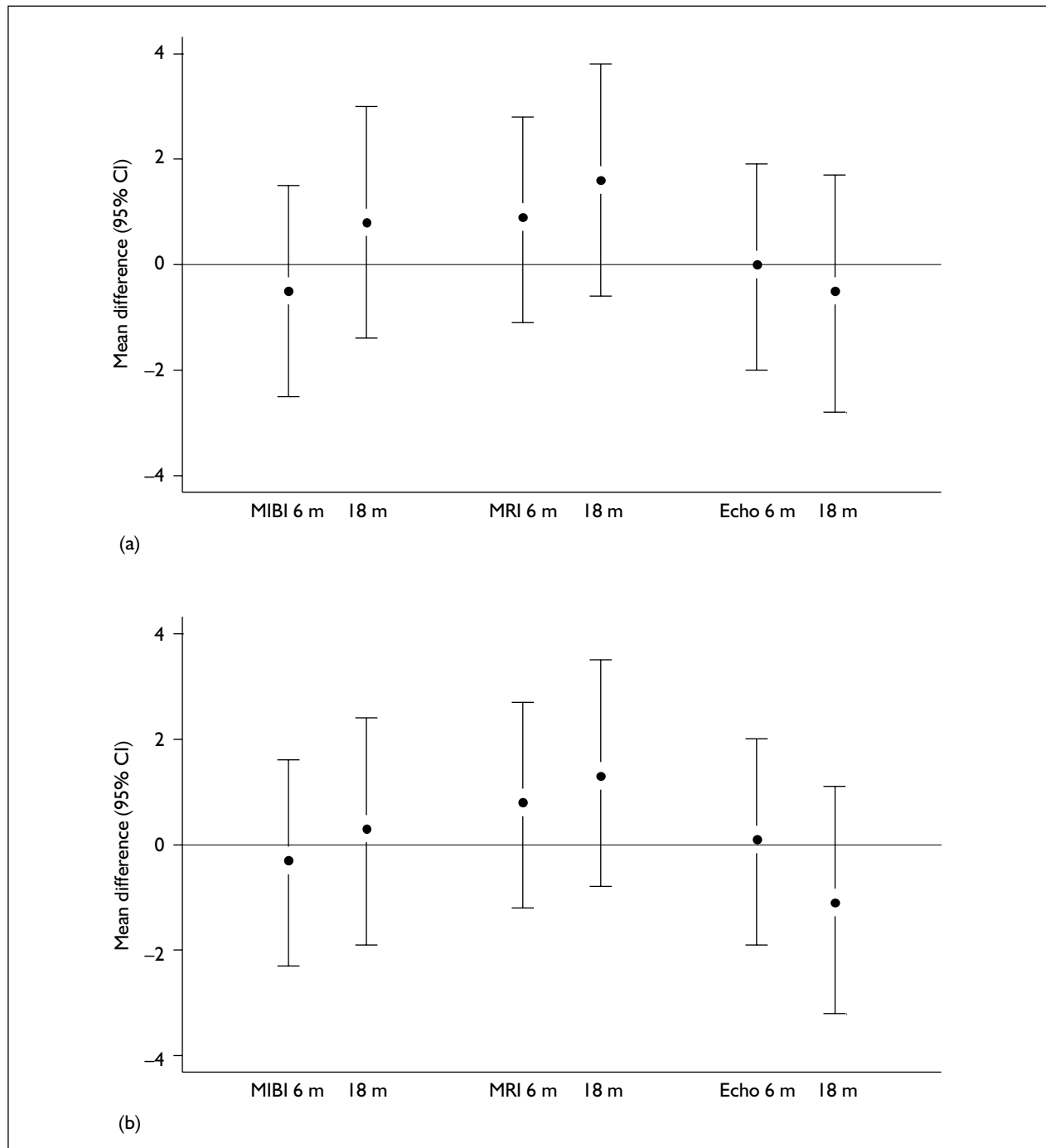


FIGURE 16 Difference in mean SF-36 physical and mental component scores (95% CI) between functional test groups and angiography group adjusted for baseline. (a) PCS; (b) MCS. Values above zero favour angiography and values below zero favour the functional test.

SF-6D utilities

As explained in Chapter 2, SF-6D utilities were derived from the SF-36 in order to investigate the sensitivity of cost-effectiveness results to the choice

of utility measure. The mean and SD of the SF-6D utility measure is summarised in *Table 30*. *Table 31* summarises the difference in SF-6D between the functional test groups and the angiography group, both unadjusted and adjusted for differences in

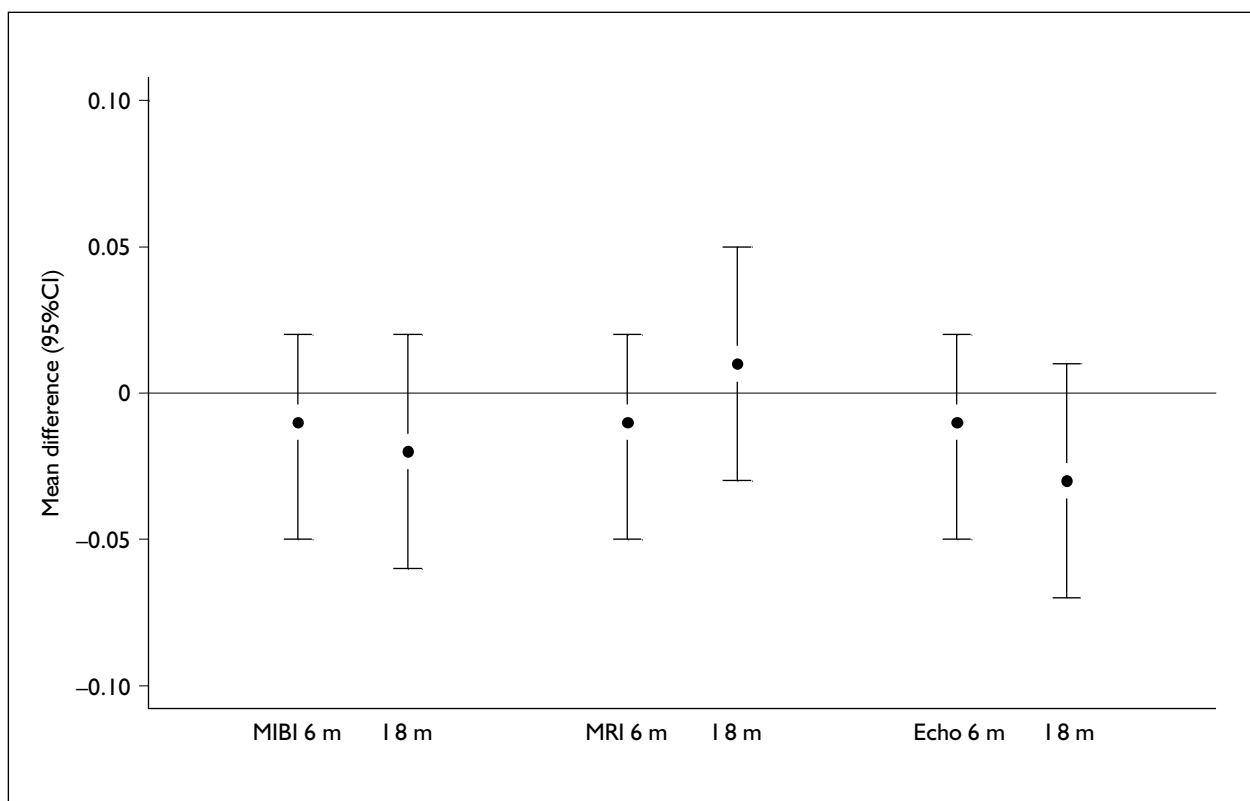


FIGURE 17 Difference in mean EQ-5D (95% CI) between functional test groups and angiography group adjusted for baseline. Values above zero favour angiography and values below zero favour the functional test.

TABLE 29 Mean difference between function test groups and controls (95% CI) in EuroQoL EQ-5D^a

	SPECT	Cardiac MRI	Stress echo	p-Value
Unadjusted				
6 months	-0.03 (-0.07 to 0.01)	-0.02 (-0.06 to 0.03)	-0.03 (-0.07 to 0.01)	0.487
18 months	-0.02 (-0.07 to 0.02)	0.01 (-0.04 to 0.05)	-0.04 (-0.09 to 0.01)	0.134
Adjusted for baseline				
6 months	-0.01 (-0.05 to 0.02)	-0.01 (-0.05 to 0.02)	-0.01 (-0.05 to 0.02)	0.835
18 months	-0.02 (-0.06 to 0.02)	0.01 (-0.03 to 0.05)	-0.03 (-0.07 to 0.01)	0.262

^a Positive values favour angiography.

TABLE 30 Mean (SD) SF-6D

	Angiography (n = 222)	SPECT (n = 224)	Cardiac MRI (n = 226)	Stress echo (n = 226)
Baseline	0.65 (0.07)	0.64 (0.08)	0.64 (0.08)	0.65 (0.07)
6 months post-treatment	0.65 (0.07)	0.64 (0.07)	0.64 (0.07)	0.64 (0.07)
18 months post-randomisation	0.63 (0.07)	0.64 (0.06)	0.63 (0.07)	0.63 (0.07)

baseline SF-6D. Similarly to the results for the EQ-5D utilities, there was very little difference between the groups in mean SF-6D utilities and no differences from the angiography group were significant. When adjusted for baseline, all CIs lay within ± 0.03 . One study concluded that a

difference of 0.041 was medically important for the SF-6D,¹⁹¹ and another found a difference of 0.033 to be clinically significant when combining information from seven studies.¹⁹² A decrease of 0.03 compared with angiography can be ruled out for all three functional tests.

TABLE 31 Mean difference between function test groups and controls (95% CI) in SF-6D^a

	SPECT	Cardiac MRI	Stress echo	p-Value
Unadjusted				
6 months	0.010 (-0.006 to 0.022)	0.014 (-0.001 to 0.027)	0.012 (-0.001 to 0.025)	0.118
18 months	-0.003 (-0.016 to 0.008)	0.003 (-0.011 to 0.017)	-0.003 (-0.016 to 0.010)	0.634
Adjusted for baseline				
6 months	0.008 (-0.007 to 0.020)	0.012 (-0.003 to 0.025)	0.012 (-0.001 to 0.025)	0.164
18 months	0.005 (-0.017 to 0.007)	0.002 (-0.012 to 0.016)	-0.003 (-0.007 to 0.016)	0.645

^a Positive values favour angiography.

Chapter 6

Results: resource use and cost-effectiveness

Resource use results

Total costs

The total mean costs, using Papworth or national tariffs for the base case, are presented for the whole 18-month follow-up period in *Table 32* and split into two periods in *Table 33*: (1) from randomisation to treatment and (2) from treatment to 18 months post-randomisation.

Treatment refers to the date when patients were allocated to one of the three treatment strategies: CABG, PCI or MM.

Cost breakdowns

Figure 18 presents a breakdown of the mean total costs over 18 months for the four test groups. Tables presenting the detailed resource use and cost components for the four test groups along with their 95% CIs can be found in Appendices 12–15.

There is similarity across the four test groups in the overall resource use, as reflected in the mean total costs in *Table 32*. Angiography was the most expensive of the four initial diagnostic tests but the strategy of initial angiography was least costly. There were some cost savings in the functional test groups since only 75–80% of these patients underwent subsequent angiography. The higher

overall mean total cost for the stress echo group was due to a higher number of admissions and interventions as a result of cardiac-related adverse events such as hospital admission for chest pain or acute MI. This excess cost was largely attributable to one or two patients who had a particularly difficult clinical course.

Cost-effectiveness summaries

Table 34 presents summaries of the total costs and effects across the four diagnostic groups over the 18-month follow-up period and cost-effectiveness comparisons of the three imaging tests compared with angiography. *Figures 19* and *20* show bootstrapped estimates of the joint distribution of cost difference and QALY difference and CEACs for each functional test compared with angiography.

For this base case analysis, the results suggest that there is little to choose between the four diagnostic groups in mean costs. Indeed, there was no statistically significant difference in costs between the SPECT and cardiac MRI groups and the angiography group. In all cases there is substantial probability around the values of zero difference in costs and zero difference in QALYs giving little evidence of lower QALYs or higher costs associated with functional tests. Any extra cost for patients in these three groups was largely due to patients who underwent confirmatory angiography following positive test results. There was a significant difference in costs between stress echo and angiography. This was mainly due to more hospital admissions as a result of adverse events; in particular one patient had seven admissions for chest pain in addition to both PCI and CABG surgery.

TABLE 32 Total costs up to 18-months post-randomisation

Test group	Total cost (mean) (£)	95% CI (£)
Angiography (n = 220)	3630	3196 to 4154
SPECT (n = 223)	4045	3494 to 4590
Cardiac MRI (n = 224)	4056	3575 to 4550
Stress echo (n = 224)	4452	3817 to 5223

TABLE 33 Total costs for (1) randomisation to treatment and (2) treatment to 18 months post-randomisation

Test group	Mean total cost (£)	
	Randomisation to treatment (95% CI)	Treatment to 18 months post-randomisation (95% CI)
Angiography	747 (709 to 784)	2904 (2469 to 3339)
SPECT	813 (676 to 949)	3254 (2777 to 3731)
Cardiac MRI	949 (837 to 1061)	3117 (2665 to 3569)
Stress echo	793 (714 to 872)	3682 (3035 to 4329)

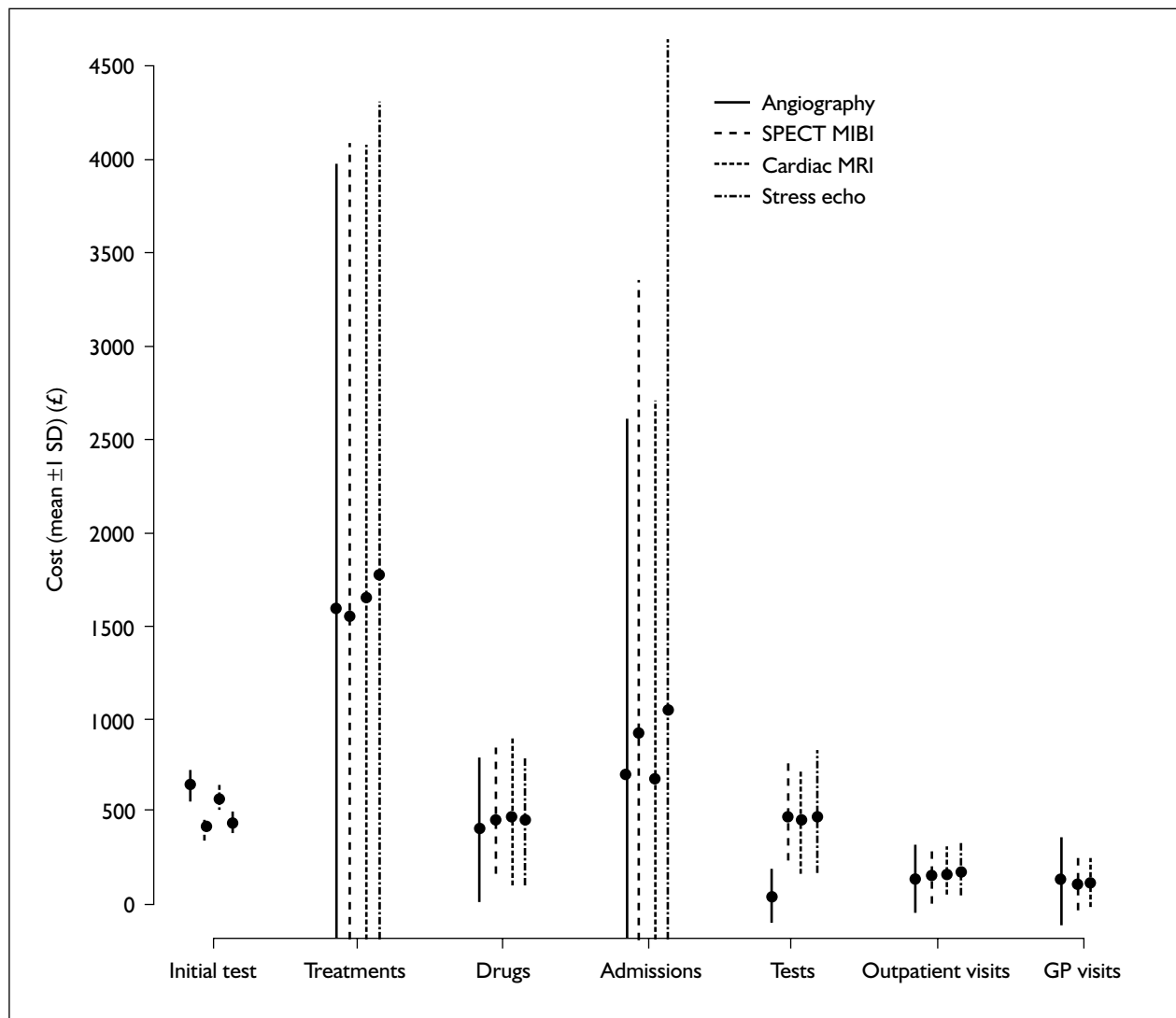


FIGURE 18 Mean total cost per patient (± 1 SD) for different resource use components

Similarly, the results for the QALY estimates did not show any statistically significant differences between the four diagnostic groups. As *Table 34* and *Figure 19* show, there was very little difference in overall quality-adjusted survival between the groups. Similarly, there were no significant differences in EQ-5D utilities between the four groups up to 18 months post-randomisation. Based on this analysis, the strategy of going straight to angiography is cheaper but (marginally) less effective than SPECT, cardiac MRI and stress echo. Although the non-invasive tests are slightly more effective in *Table 34*, the benefit is so close to zero in all three cases that the ICERs are unstable. For example, slight differences in assumptions about the QALY calculations can change the effect from a small benefit to a small loss, with very large implications for the ICER. In addition, the CIs around the

ICERs are so wide as to be effectively uninformative. Although the CEACs (*Figure 20*) suggest that SPECT and stress echo are more likely to be cost-effective at a threshold of £30,000 for a QALY, in this case a simple cost-minimisation approach may be more appropriate and this would clearly favour the angiography strategy.

Sensitivity analysis

Using QALYs based on SF-6D utilities

The results of the QALY estimates based on SF-6D utilities are presented in *Table 35* and the mean QALY differences between functional test groups and angiography are shown in *Table 36*. Overall, the QALY estimates were lower compared with estimates based on the EQ-5D (approximately 0.95 versus 1.15). This is mainly because the

TABLE 34 Cost-effectiveness summaries for 18 months post-randomisation

Parameter	Mean	Median	SD	95% CI for mean
Costs (£)				
Angiography	3,630	1,593	3,405	3,196 to 4,154
SPECT MIBI	4,045	1,876	4,136	3,494 to 4,590
Cardiac MRI	4,056	2,139	3,825	3,575 to 4,550
Stress echo	4,452	2,107	5,383	3,817 to 5,223
Cost comparisons (£)				
SPECT MIBI – angiography	415	420	5,357	–310 to 1,084
Cardiac MRI – angiography	426	427	5,122	–247 to 1,088
Stress echo – angiography	821	817	6,370	10 to 1,715
Life years (£)				
Angiography	1.46	1.49	0.21	0.58 to 1.74
SPECT MIBI	1.48	1.50	0.17	1.28 to 1.69
Cardiac MRI	1.48	1.50	0.18	0.90 to 1.71
Stress echo	1.48	1.50	0.21	0.67 to 1.82
QALYs (£)				
Angiography	1.13	1.20	0.34	1.08 to 1.17
SPECT MIBI	1.17	1.19	0.27	1.13 to 1.20
Cardiac MRI	1.14	1.20	0.31	1.10 to 1.18
Stress echo	1.17	1.22	0.29	1.13 to 1.20
QALY comparisons (£)				
SPECT MIBI – angiography	0.0362	0.0349	0.433	–0.092 to 0.080
Cardiac MRI – angiography	0.00956	0.0085	0.464	–0.055 to 0.074
Stress echo – angiography	0.0371	0.0365	0.446	–0.024 to 0.095
Cost per QALYs gained (£)				
SPECT MIBI – angiography	11,463	8,568	162,299	–99,480 to 120,130
Cardiac MRI – angiography	44,573	5,481	1,245,321	–80,543 to 282,058
Stress echo – angiography	22,157	16,748	484,426	–253,083 to 213,286

SF-6D is lower and less sensitive to within- and between-patient differences than the EQ-5D. In common with QALY estimates based on EQ-5D utilities, no significant differences were detected between the three non-invasive test groups and angiography. In contrast to the base case analysis, the three non-invasive test groups had slightly lower mean QALYs over 18 months compared with angiography, although again the differences were minimal.

Alternative cost estimates for the initial imaging tests

In order to investigate the sensitivity of the total cost estimates to the unit costs of the initial imaging tests, alternative estimates for these unit costs were used. Alternative unit costs were taken from the latest NHS reference cost estimates (2005–6) and are presented in *Table 37*. The cost of angiography was based on the HRG cost of £1083 including one overnight stay in hospital. Therefore, for day-case angiography patients, the cost of one bed-day in a cardiac ward was subtracted from the total HRG cost. The cost of cardiac MRI was based on the band F1 MRI cost

of £307 and the cost of £902 for the SPECT was based on band L Radionuclide (Isotope) Test costs. The total cost for these three tests also included the cost of an exercise stress test (£81) from the NHS Reference Costs. Unfortunately, no alternative UK estimates for the unit cost of stress echo were available, so the same Papworth unit costs were used. The mean total costs and cost differences for this scenario are presented in *Tables 38* and *39*.

The results indicated that the total costs for all four test groups increased, with the SPECT group having the largest increase in total costs from the base case analysis (approximately £900). The higher total costs in both the angiography and SPECT groups reflect the higher initial test cost estimates used, suggesting that a comparison of the total costs for the four imaging test groups is sensitive to the costs of the initial tests. However, the total costs for the cardiac MRI and stress echo groups also increased, although to a lesser extent, despite the lower or equivalent initial test costs that were used. This resulted from the higher cost of the confirmatory angiograms carried out. The

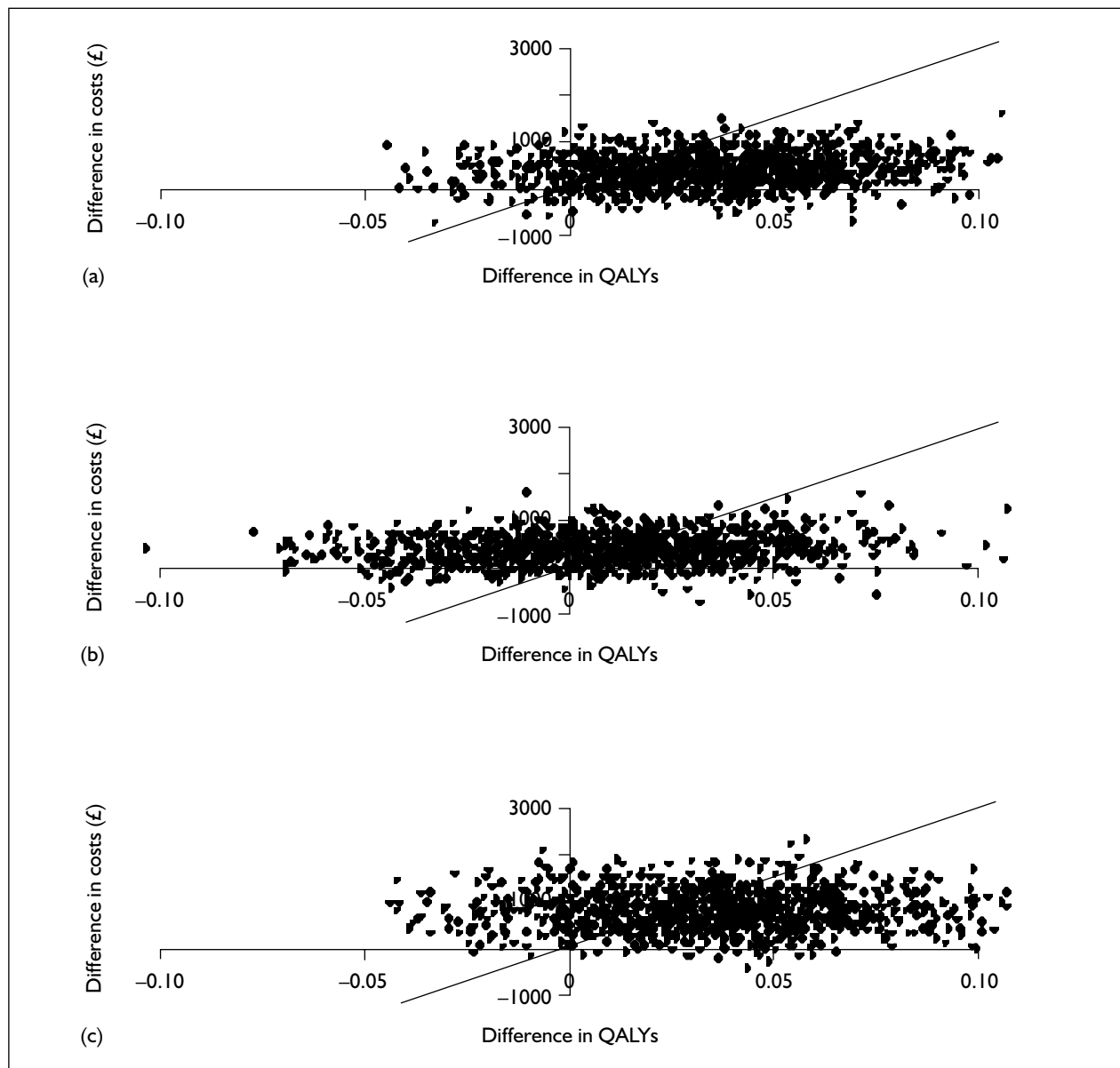


FIGURE 19 Bootstrapped samples from the joint distribution of the difference in costs and the difference in QALYs for each functional test against angiography (with an illustrative line for an ICER of £30,000 per QALY). (a) SPECT MIBI; (b) cardiac MRI; (c) stress echo. Positive values indicate that the functional tests cost more and have greater QALYs.

overall impact on the cost comparison with the angiography group indicated that the SPECT group had higher mean costs over 18 months whereas the cardiac MRI and stress echo groups both had lower costs during this period compared with the base case analysis. As a result, the SPECT

strategy cost significantly more than angiography alone.

Removing costs of confirmatory angiography

As explained earlier in this chapter, some of the extra costs incurred in the imaging test groups compared with the angiography group were explained by the large number of patients who underwent confirmatory angiography despite negative initial test results. Approximately 20% of the patients in each of the three imaging test groups had confirmatory angiography following a negative test result. In clinical practice, patients who have a negative initial

TABLE 35 Mean QALYs based on SF-6D utilities

	Mean	Median	SD	95% CI
Angiography	0.95	0.96	0.10	0.94 to 0.97
SPECT	0.94	0.95	0.12	0.92 to 0.95
Cardiac MRI	0.94	0.95	0.11	0.92 to 0.96
Stress echo	0.94	0.95	0.10	0.93 to 0.96

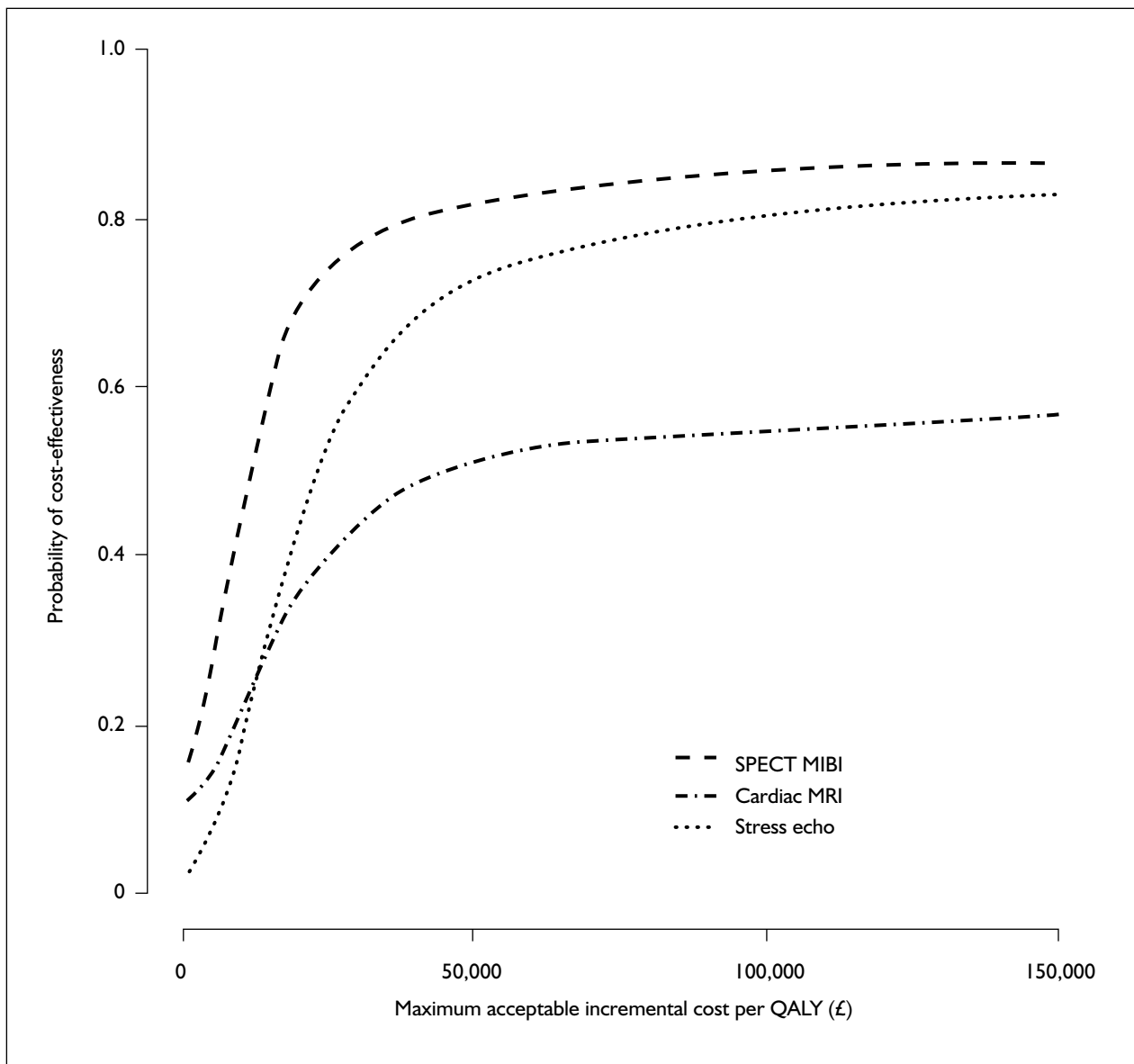


FIGURE 20 CEACs for the three imaging test groups

TABLE 36 QALY comparisons based on SF-6D utilities

	Mean	Median	SD	95% CI
SPECT – angiography	-0.014	-0.0014	0.16	-0.036 to 0.0091
Cardiac MRI – angiography	-0.015	-0.0015	0.15	-0.035 to 0.0055
Stress echo – angiography	-0.0095	-0.0096	0.14	-0.029 to 0.011

imaging test result would not necessarily proceed to confirmatory angiography. Therefore, in this scenario, the costs of confirmatory angiography were removed for all patients who had negative test results in the three non-invasive test groups. The total mean costs and mean cost differences for this scenario are presented in *Tables 40* and *41*. As the results show, the

mean total costs for the three non-invasive test groups decreased by approximately £100–200 in comparison with the base case analysis. In terms of the cost comparisons with the angiography group, the cost differences decreased by approximately £100–200 for all three groups and these differences were not significantly greater than zero.

Removing the cost ‘outliers’ from the cost analysis

In this case, a small number of high-cost patients in the stress echo patient group had a large influence on the mean of the total costs. Another scenario was to explore the impact of removing the ‘outliers’ in the cost distributions on the mean

TABLE 37 Unit costs of initial diagnostic test based on national estimates

Diagnostic test	Average unit cost (£)
Angiography (day case)	1032
Angiography (overnight)	1113
SPECT	983
MR perfusion imaging	388
Stress echo	435 ^a

^a Cost of stress echo based on Papworth unit cost.

total costs and cost differences between the four groups. The Winsorized mean method was used. This involves reordering the total patient-specific costs for each group and removing the k smallest values and replacing with the $k + 1$ th smallest value and replacing the k largest values with the $k + 1$ th largest value. For this scenario, the bottom and top 2.5% of the cost distributions were removed using this method and the results for the mean total costs and cost differences for the four groups are presented in *Tables 42 and 43*. As a result, in the three cost comparisons, the CIs and SDs became much smaller. Overall, the mean cost comparisons for the SPECT and cardiac MRI groups with the angiography group were relatively unchanged whereas the cost differences with the stress echo group fell by approximately £300. This confirms the large impact of the cost ‘outliers’ in the stress echo group on the overall results of the base case analysis.

TABLE 38 Mean total costs (based on alternative imaging test costs) (£)

	Mean	Median	SD	95% CI
Angiography	4067	1970	3442	3601 to 4592
SPECT	4935	2861	4176	4385 to 5486
Cardiac MRI	4234	2323	3893	3738 to 4750
Stress echo	4780	2470	5509	4095 to 5551

TABLE 39 Mean total cost differences (based on alternative imaging test costs) (£)

	Mean	Median	SD	95% CI
SPECT – angiography	868	841	5412	146 to 1,579
Cardiac MRI – angiography	167	144	5197	–489 to 830
Stress echo – angiography	713	687	6496	–126 to 1628

TABLE 40 Mean total costs with costs of confirmatory angiography removed (£)

	Mean	Median	SD	95% CI
Angiography	3630	1593	3405	3174 to 4154
SPECT	3891	1876	3979	3364 to 4428
Cardiac MRI	3903	2139	3663	3430 to 4388
Stress echo	4274	2107	5233	3624 to 5005

TABLE 41 Mean cost comparisons (costs of confirmatory angiography removed) (£)

	Mean	Median	SD	95% CI
SPECT – angiography	261	233	5237	–439 to 975
Cardiac MRI – angiography	273	251	5002	–353 to 920
Stress echo – angiography	644	617	6243	–162 to 1538

TABLE 42 Mean total costs with cost 'outliers' removed (£)

	Mean	Median	SD	95% CI
Angiography	3640	1612	3382	3191 to 4086
SPECT	4080	2338	3457	3754 to 4676
Cardiac MRI	4128	2480	3346	3405 to 4399
Stress echo	4150	2445	3401	3786 to 4673

TABLE 43 Mean cost differences with cost 'outliers' removed (£)

	Mean	Median	SD	95% CI
SPECT – angiography	441	563	4837	–78 to 1190
Cardiac MRI – angiography	488	249	4758	–381 to 954
Stress echo – angiography	510	563	4797	–39 to 1190

TABLE 44 Mean total costs for interventionists subgroup (£)

	Mean	Median	SD	95% CI
Angiography	4116	4526	3495	3344 to 4912
SPECT	4292	2232	4024	3465 to 5093
Cardiac MRI	4873	2641	4395	3971 to 5719
Stress echo	4934	2244	6646	3759 to 6329

TABLE 45 Mean cost differences for the interventionists subgroup (£)

	Mean	Median	SD	95% CI
SPECT – angiography	176	164	5329	–972 to 1260
Cardiac MRI – angiography	757	762	5616	–428 to 1921
Stress echo – angiography	818	814	7509	–568 to 2430

TABLE 46 Mean total costs for the non-interventionists subgroup (£)

	Mean	Median	SD	95% CI
Angiography	3394	1541	3347	2858 to 4035
SPECT	3858	1773	4224	3156 to 4665
Cardiac MRI	3476	1945	3258	2955 to 4033
Stress echo	4077	1992	4135	3377 to 4841

TABLE 47 Mean cost differences for the non-interventionists subgroup (£)

	Mean	Median	SD	95% CI
SPECT – angiography	464	449	5390	–473 to 1408
Cardiac MRI – angiography	82	71	4671	–689 to 927
Stress echo – angiography	683	647	5320	–247 to –1653

Comparison of interventionists and non-interventionists

There was considerable variation between clinicians in the rate of referral for angiography following a negative functional test. In a *post hoc* subgroup analysis, clinicians were divided into interventional cardiologists and non-interventional

cardiologists according to their clinical practice outside of the trial. Results for the interventionists are given in *Tables 44* and *45*. This subgroup was much more likely to refer patients with negative functional tests for angiography and was more likely to intervene in the event of a positive test. Thus, all four groups had higher mean costs.

Conversely, non-interventionists in all four groups had lower mean costs (*Tables 46 and 47*).

There were no significant differences between interventionists and non-interventionists in QALYs. The mean differences (non-interventionists – interventionists) in QALYs were 0.02, –0.02, 0.06 and 0.05 for the angiography, SPECT, cardiac MRI and stress echo groups, respectively, with all CIs overlapping zero.

Summary of sensitivity analyses

The various one-way sensitivity analyses together demonstrate that the rank ordering of costs and QALYs and the magnitude of the differences between options are sensitive to reasonable alternative methods of estimation. However, in no case do the 18-month costs of the three non-invasive alternatives fall below those of angiography, and the alternative estimation of QALYs (using the SF-6D) makes all three alternatives less effective (in terms of QALYs) than angiography.

Chapter 7

Discussion, implications and conclusions

Feasibility and patient management

This is one of the first RCTs looking at cost-effectiveness of diagnosis and management of patients presenting with possible CAD using several different diagnostic modalities. All of the tests evaluated showed a satisfactory safety rate, with no serious adverse events with SPECT or MRI scanning. One patient had recurrent ventricular fibrillation (VF) and ventricular tachycardia (VT) during recovery after stress echo but was successfully resuscitated and went on to have coronary artery bypass grafting. Two patients suffered VF or VT arrests during recovery after exercise ECG testing, both of whom were successfully resuscitated.

The 'bottom line' results are summarised in *Table 48*. Our results showed that cardiologists value results of the three functional tests equally. No functional test was shown to be superior in this respect. As may be expected, however, in a study where the patients were initially referred for coronary angiography, the clinician's opinion was more strongly polarised at the highest and lowest risk categories following angiography. This is expected since angiography provides a view of the coronary anatomy and allows judgements on the feasibility and type of revascularisation required. However, as an anatomical test, it does not necessarily establish the relationship between coronary disease and presenting symptoms, and advanced coronary atheroma can be present despite a normal coronary lumen on angiogram.¹⁹³

The trial had been designed for the functional tests to act as 'gateways' to angiography and the clinician's opinion scores reflect this. Indeed, 20–25% of patients receiving a functional test did not go on to have an angiogram, with up to 85% of patients with a negative functional test not having an angiogram. For those patients who did undergo subsequent angiography, positive functional tests were confirmed by positive angiography in 83–89% of patients and there was little to choose between the groups. However, in the patients selected for angiography on clinical criteria, the proportion of negative tests that were followed by a positive angiogram was high, approximately 30% of

negative SPECT scans and half of all negative cardiac MRIs and stress echocardiograms. These figures should be interpreted allowing for the fact that a large number of negative tests were not followed by angiography, and those that were are likely to have been for patients who had more severe anginal symptoms or functional limitation, thus influencing the decision to perform a subsequent angiogram. It is interesting to reflect, however, that only five patients who had angiography following a negative functional test actually proceeded to CABG surgery, implying that non-invasive imaging appeared to be missing only a very small proportion of those requiring intervention. SPECT is the best established of the non-invasive, functional tests and is likely to have had the highest pre-existing level of physician acceptance. This may explain why there were fewer negative SPECTs followed by positive angiograms.

Comparison of SPECT and angiography

The SPECT is the best established of the three functional tests investigated and in this study was most likely to give a definitive test result, and produce outcomes that were no different to those of the angiography group. A systematic review has shown that incorporating SPECT into the diagnostic pathway with selective referral to angiography resulted in a lower rate of normal angiograms compared with direct referral to angiography. A large observational study of 972 patients included 507 patients who had a SPECT scan, the result of which was not disclosed to the clinical team. About 76% of patients with a negative SPECT scan were found to have a normal angiogram (i.e. positive predictive probability). Our results are consistent with this study, although our trial was designed to be pragmatic, reflecting current clinical practice, and not to assess formally sensitivity, specificity and diagnostic accuracy.

In this study, the strategy of SPECT followed by angiography if necessary provided a definitive test result for only marginally fewer patients than the angiography first strategy (*Table 48*). In most outcomes measured, this group had similar results

TABLE 48 CECaT – summary of comparisons

Comparison with angiogram	SPECT	MRI	Echo
Successful test (vs 98%) (%)	94	78	90
Unequivocal test result, of those who completed the test (vs 100%) (%)	96	92	97
Clinician's risk	Less confidence	Less confidence	Less confidence
Referred for subsequent angiogram (%)	78	80	75
Positive test followed by positive angio (%)	83	89	84
Negative test followed by positive angio (%)	31	52	48
No. CABG (vs 10%) (%)	13	11	13
No. PCI (vs 25%) (%)	18	23	23
6 m EET (vs 12.3)	+0.06	-0.62	-0.63
18 m EET (vs 12.4)	-0.14	-0.58	-0.44
6 m EET			
CABG group	+0.13	-1.13	-2.15
PCI group	-0.29	-0.42	-1.85
MM group	+0.18	-0.57	+0.06
6 m angina during EET (vs 23%) (%)	26	35	30 (NB time to angina significant)
18 m angina during EET (vs 21%) (%)	25	29	26
6 m ≥2 CCS class decrease (vs 32%) (%)	33	28	31
18 m ≥2 CCS class decrease (vs 32%) (%)	42	30	34
6 m ≥2 CCS class decrease, revasc group (vs 44%) (%)	60	44	51
MM group (vs 26%) (%)	20	20	21
No. non-fatal adverse event rate (vs 0.09 per patient-year)	0.10	0.11	0.17
Patients with non-fatal adverse events (vs 9%) (%)	11	13	14
Deaths (vs 2%) (%)	2	4	3
6 m EQ-5D (vs 0.78)	+0.01	+0.01	+0.01
18 EQ-5D (vs 0.78)	+0.02	-0.01	+0.03
6 m SF-36			
PCS (vs 42.1)	+0.5	-0.9	0.0
MCS (vs 51.1)	+0.3	-0.8	-0.1
18 m SF-36			
PCS (vs 43.6)	-0.8	-1.6	+0.5
MCS (vs 52.0)	-0.3	-1.3	+1.1
SAQ 6m/18m 5 scales	-	-	-
Costs (vs £3630)	+£415	+£426	+£821
QALYs (vs 1.13)	0.0362	0.00956	0.0371

Dark grey shading, significantly worse; light grey shading, borderline; boxed, significantly better.

to the angiography group and we could rule out clinically significant differences. In addition, at 18 months after randomisation this group had a greater proportion of patients with significant improvement in CCS class compared with angiography patients, and the fact that this was only apparent in the subgroup that had either CABG or PCI may indicate that SPECT scanning results in better identification of patients who are likely to benefit from revascularisation. Thus,

based on this study, the SPECT would be a very acceptable initial diagnostic test, since it would avoid invasive diagnostic testing for a significant number of patients and provide similar outcomes, although it does involve exposure to a relatively high dose of radiation (approximately 8 msv if both stress and rest studies are required).

In a number of studies SPECT tests have been found to be cost-effective in the diagnosis and

management of CAD.^{4,164,194,195} In this study, there was little to choose between the SPECT and angiography groups in cost-effectiveness. This is despite the use of the 2-day protocol in which patients have rest and stress images taken on separate (usually consecutive) days, requiring two outpatient attendances. It should be noted that costs to the patient are not included in this analysis but are likely to be higher for SPECT than other functional tests, since it requires 2 days travelling to the test centre, or an overnight stay, and, for those still employed, at least 2 days off work. This compares with angiography patients, for whom 5% (34/744) required an overnight stay mainly due to their home circumstances. Our current practice is to perform the stress part of the SPECT test on day 1, and cancel the rest test if the stress test is negative. This has reduced the extra time involved, the radiation dose required, and therefore the cost of SPECT, for patients since the CECaT trial.

Comparison of cardiac MRI and angiography

MRI had the largest number of test failures and, in this study, appears to have the least practical use in screening patients with suspected CAD. A large number of patients in our study could not complete the MRI test either because they were too large to fit in the scanner or were claustrophobic (nearly 10% of patients being randomised to the test), resulting in either the scan not being attempted or being aborted. Other studies have reported claustrophobia rates up to 10%.¹⁵⁷⁻¹⁵⁹ However, cardiac MRI has been shown to be a useful test for the diagnosis of CAD with a positive MRI identifying those at risk of MI and cardiac death independent of the presence of conventional risk factors for CAD¹⁹⁶ and compared favourably with alternative imaging techniques.^{57,197} One reason for the large number of test failures in this study may result from the patients' awareness that if they refused the initial test they would be investigated by angiography, possibly resulting in a lower threshold for aborting the examination.

It should also be noted that the high number of negative cardiac MRIs followed by positive angiograms in this study reflects their use in current clinical practice. The generally accepted method for measuring the true sensitivity of a new test against a pre-existing gold standard entails that readers for each test are blind to any clinical information regarding the patient. In this study, angiograms were assessed by clinicians who were

aware of functional test results, and other clinical information. Although clear predetermined reference values were applied to the angiography to define the presence or absence of an abnormal state (50% stenosis in left main stem or 70% stenosis in any other main vessel), we cannot rule out bias attributed to the clinician's access to other clinical information. In addition, the measurement of diameter stenosis was made by visual estimation rather than using quantitative methods. Since the definition of a 'positive' angiogram in the current context may be influenced by the referring clinician's decision to proceed to revascularisation, some patients with a genuine true negative may have been classified as a false negative on the basis of clinical bias towards intervention in borderline patients. Equally, true positives could be wrongly classified as false positives where the angiogram shows intermediate severity lesions (possibly causing ischaemia), but there is a clinical bias towards MM. This latter scenario is important for cardiac MRI since it has the ability to pick up more subtle ischaemia than any other common functional tests because of its superior spatial resolution. These particular biases will exist to an extent for each of the functional tests, but are likely to apply particularly to tests with which the clinician is least familiar, especially if the test actually possesses a higher sensitivity than any currently existing test. Given the very high spatial resolution of MRI, there are good theoretical reasons for believing that this may indeed be the case. This may partly explain the apparently high false negative rate of MRI reported in this study compared with the recent literature. Even in truly blinded conditions, previous work suggests that comparison of MRI perfusion versus angiography may result in an underestimate of diagnostic accuracy for the MRI technique when PET is employed as the universally-regarded gold standard.⁷¹ However, as mentioned above, formal assessment of sensitivity, specificity and diagnostic accuracy was not the aim of the current study.

The cardiac MRI group also had significantly poorer mean exercise time than the angiography group and this was mainly attributable to those patients who had CABG. This deserves careful consideration since all surgical patients in this group also had an angiogram as part of the diagnostic work up. One explanation may be that cardiac MRI over-diagnoses the importance of ischaemia, so that some patients with positive MRIs and borderline angiography may have been referred for CABG on the joint evidence. Without the functional test the cardiologist may have been prepared to take a more conservative management

decision. These borderline cases may be less likely to benefit from CABG than patients who are clearly requiring surgery according to the angiogram.

It is disappointing but perhaps not surprising that stress perfusion MRI appeared less successful than SPECT at guiding selection for beneficial revascularisation. This is particularly so when the imaging attributes of the test (superior spatial resolution and dynamic first-pass coverage) would be expected to mandate otherwise. However, it should be remembered that, unlike the other two functional techniques, perfusion MRI remains in its infancy with rapidly evolving pulse sequence technology that remains to be fully evaluated. The optimum pulse sequence for clinical use together with degree of anatomical and temporal coverage required (for example, three slices per heart beat versus six slices every two heart beats) remain to be determined.

In our study, we employed a form of echo planar imaging which is susceptible to artefact and highly sensitive to off-resonance effects. These difficulties were compounded by the fact that the MRI examinations in this study all took place in a mobile MRI unit with different geographical locations in Britain from day to day. This is likely to have had an effect on the degree of magnetic field uniformity (shim), which in turn can impair image quality.

Finally, it should be appreciated that stress perfusion MRI **in clinical use of this sort** was unusual anywhere in the world at the time of this study. As with any other new imaging modality, a learning curve exists for the physician reporting these studies. The difficulty, in this context, of setting internal 'decision rules' for calling a study positive or negative, should not be underestimated.

Comparison of stress echo and angiography

There were also test failures with stress echo due to obesity and concomitant chronic obstructive pulmonary disease, but the numbers were fewer than with MRI. The high apparent false negative rate for stress echo in this study is consistent with various researchers who have shown it to be more specific but less sensitive than SPECT.¹⁹⁴

In addition to the higher test failure rate, patients in the stress echo group had a significantly shorter total exercise time and time to angina, and a greater number of non-fatal SAEs, leading to

significantly higher costs. As already stated, much of the excess cost was attributable to a small number of patients with particularly difficult clinical courses and this was not considered related to the diagnostic strategy. The poorer exercise time was confined to those who had revascularisation and the reasons may be similar to those described for cardiac MRI above. There are some reasons why stress echo might be expected to be less useful than other functional tests. Whereas SPECT and cardiac MRI are direct measures of perfusion, stress echo is essentially an assessment of wall motion and thickening, and so is a less direct measure of cardiac perfusion. Also, given the level of skill required for its interpretation, it may be best to reserve this test for those who have a contraindication to the SPECT and are unable or unwilling to have cardiac MRI.

Study limitations

As with any research study, there are limitations.

First, this study was carried out in a single specialist cardiothoracic centre which may have a greater proportion of high-risk patients, and a greater proportion of cardiologists with significant experience of high-risk patients than an average DGH. This is reflected in the proportion of patients (69%) with high Pryor risk of significant coronary disease and with known risk factors (*Table 18*). However, all DGHs within the regional health authority refer patients to Papworth, so that the study population should represent all such referrals. Coronary disease prevalence and morbidity are not uniform across the British Isles, tending to be higher in the north and in large conurbations. Papworth hospital has a catchment area of west Norfolk, Suffolk, Cambridgeshire and east Bedfordshire, so that most of the patients come from relatively small cities, towns and villages. We did not collect data that would have allowed us to generate socio-economic deprivation scores and therefore sampling bias cannot be ruled out. However, since patients were randomised to different diagnostic strategies, the various cardiovascular risk factors (for which socio-economic class is a surrogate marker) are equally distributed amongst the groups. Although it has been suggested that post code may be an acceptable method for generating deprivation scores,¹⁹⁸ others have suggested that such area-based methods are relatively crude tools, which fail to account for individual circumstances and may underestimate the effects of deprivation.¹⁹⁹

Second, although we did not collect data relating to ethnicity, our sample population was predominantly white European. The indigenous population of a country tends to have better health than the immigrant population, so that our results may not be wholly transferable to areas with large immigrant Asian or Afro-Caribbean populations. The rate of coronary heart disease is particularly high in south-east Asians, for whom a strategy of initial angiography may well be appropriate. Further studies are required to confirm the most appropriate diagnostic pathway for this patient subgroup.

Third, our population was young overall, with a mean age of 62 years. In part this is due to the trial design; since exercise time at 18 months was the primary outcome measure it was not possible to include patients who could not manage a modified Bruce protocol exercise test. This undoubtedly excluded those with significant peripheral vascular disease, arthritis, lack of balance or frailty from any cause, all of which are more common in elderly patients. Therefore, our results are not necessarily generalisable to these subgroups. However, given the increased risks associated with angiography and coronary intervention in the elderly, further work might focus on the benefits of non-invasive imaging to these patients.

Fourth, it is reasonable to ask what the relevance of our study is to the wider NHS. In particular, we should consider the general availability of the non-invasive imaging modalities that we employed. NICE published the results of its Technology Appraisal 73, *Myocardial perfusion scintigraphy for the diagnosis and management of angina and myocardial infarction*, in 2003 and concluded that there was significant underutilisation of scintigraphy in the UK compared with the rest of Europe and North America. It was suggested that a four-fold increase in activity might be appropriate in Britain. The British Nuclear Cardiology Society survey in 2000 demonstrated that over half of the nuclear medicine departments in British hospitals were involved in myocardial perfusion scintigraphy, suggesting that access for most of the population should be feasible in principle. However, the busiest quartile of centres accounted for nearly 70% of all UK activity, indicating wide variations in geographic availability. Overall use of the technique was low at 1200 SPECT scans per one million people in the population, roughly half the target level set in 1994 to match the European average at that time. Cardiology input to the service was low, with only 35% of studies being

reported by a cardiologist; and crucially, the mean waiting time for scintigraphy was 4 weeks longer than the national service framework target for angiography (12 weeks), a situation in which functional testing is unlikely to flourish.²⁰⁰

Stress echo currently remains an even more patchily distributed service in Britain than perfusion scintigraphy. It has been calculated that the current number of tests performed per year is 165 per million people in the population, far fewer than the 1200 per million nuclear perfusion studies currently taking place. This under-provision appears to relate more to inadequate numbers of trained clinical staff than to a deficiency of echocardiographic equipment. Non-invasive imaging has long been regarded as the 'poor relation' in cardiology, with most trainees expressing a preference for intervention or electrophysiology and implantable device training; and cardiac radiology has only recently revived. There has been a growing recognition, however, that, with the advent of CT and MRI, there will be a need for large numbers of properly trained imaging physicians. One recent opinion article by a group of influential British cardiologists and radiologists has postulated that although a 50% reduction in invasive CA might be achievable, this could require as many as an extra 50,000 coronary CT angiograms and 75,000 stress MRI scans over the next 5–10 years.²⁰¹

Stress MRI is limited to only a few UK centres at the present time and the information from this arm of our study is perhaps least transferable to the 'real' NHS. MRI may have under-performed in this trial for the reasons given previously and is clearly continuing to evolve (and improve). Certainly the British Cardiovascular Society Working Group on non-invasive imaging believes that cardiac MRI could potentially reduce the need for CA by 25% at those centres where it was available.²⁰¹

Since the trial began, other modalities such as EBCT and MDCT have become more generally available and may provide both anatomical and functional information. These were not commonly used for patients with established or suspected coronary disease when this study was designed. Further investigational studies are required to assess their place in the armoury of diagnostic tools.

The most significant limitation of our study relates to breach of trial protocol. Almost half of the patients with negative functional tests were sent on for CA by the referring physicians in full knowledge of the fact that the trial protocol

default position would have been for the patients to have been managed medically and outcomes monitored. This lack of adherence to the protocol appears to have stemmed more from a difficulty in dissociating from current clinical practice and a reluctance to tolerate uncertainty rather than deliberate perversion or overwhelming clinical justification. Indeed, in some instances the physicians indicated that they were requesting angiography to reassure the patient rather than themselves – whether this represents truth or transference is unknown.

Nevertheless, it is very important to note that the 150 or so additional angiograms that this approach entailed resulted in only six additional CABG operations being performed within the 18-month period with no excess of fatal or non-fatal events. Hence the cost-effectiveness data are likely to have been skewed against non-invasive imaging by virtue of the large number of functional test patients (both positive and negative) who had two tests. It might be argued that this should be accepted at face value – after all, this was designed as an attempt to assess cost-effectiveness in the ‘real world’. Nevertheless, since the study was performed at a tertiary cardiac centre with a high volume of coronary interventional procedures performed every year, it was perhaps inevitable that an increased number of arguably unnecessary catheterisations were performed on study patients. It is feasible that functional testing could have appeared more cost-effective than our data imply in less specialised cardiological settings.

Finally, as already discussed, the trial aimed to be pragmatic and to reflect the strategy of using functional tests as a gateway to angiography in current clinical practice. The test results were considered in conjunction with other information available at the time. Hence it is not possible to formally assess diagnostic accuracy of the functional tests in this context. However, this practice did ensure that current referral practices were not influenced, and inclusion in the trial did not affect waiting times or access to other investigations outside the trial. Also, although this trial is relatively large for an RCT of diagnostic strategies, only 301 (34%) patients had revascularisation (CABG or PCI) following the diagnostic workup, giving limited power to detect effects of different strategies in this subgroup.

Conclusions

In terms of traditional cost-effectiveness, all three non-invasive strategies were slightly more

expensive than angiography with similar QALYs. However, overall the results suggest that functional testing may have a valuable place in the diagnostic pathway for the assessment of chest pain in an outpatient population because of ‘process’ advantages to the patients, clinicians or hospital. All three tests can avoid invasive diagnostic tests in a significant proportion of patients.

These findings are clearly highly relevant in the context of the NICE guidelines on the use of myocardial perfusion scintigraphy issued in 2003.² This study supports the use of nuclear cardiology as a ‘gate-keeper’ investigation in patients with chest pain but also lends support to other non-invasive modalities used in this fashion. Cardiac MRI perfusion remains in evolution but the evidence base for the diagnostic accuracy of this investigation continues to grow. SPECT and stress echo can both be reasonably regarded as mature technologies. The necessary equipment for the latter can be found in almost every DGH in the country, in which case operator experience may be the limiting factor. Early studies suggest that at least 100 stress echocardiograms need to be read before the plateau phase of the learning curve is reached.²⁰² Evidence for a learning curve has also been demonstrated in myocardial scintigraphy, most recently with attenuation correction.²⁰³ Sensitivity and specificity data from multiple studies show that there is little to choose between perfusion scintigraphy and stress echo and our own study confirms that mean costs and effects are similar. We suggest that future guidelines consider incorporating the use of stress echo as a directly equivalent alternative to myocardial perfusion imaging where appropriate expertise exists.

It is more difficult to make formal suggestions regarding stress perfusion MRI as a screening tool at present. Although it appeared less robust than the other two modalities in terms of patient acceptability and was associated with statistically inferior exercise times than angiography, there was little evidence that this translated into worse outcomes or poorer HRQoL or that it was a less cost-effective strategy. The lack of large multi-centre studies of stress MRI perfusion will undoubtedly be remedied within the next 5 years; if these confirm the diagnostic accuracy of the many smaller published studies, we suggest that this too could be included in a non-invasive, gate-keeper algorithm. We suggest that policy makers consider MR perfusion in future evaluations of non-invasive imaging.

Coronary CT is an exciting and rapidly evolving area of cross-sectional cardiac imaging that was not included in this study. This was simply because the technique was insufficiently accurate in 2001 when the trial began. At that time, CT scanners had no more than four detector rows, with early publications demonstrating the relatively low level of diagnostic accuracy (and a high number of segments excluded from analysis), even in highly selected patient populations.^{204–206} Current CT literature based on the results from the 64-slice multi-detector row machines is far more encouraging. It has been suggested that the negative predictive value of a normal study is as high as 95–100% in a number of different studies, with very low numbers of non-assessable segments compared with previous work.^{207–210} With such a high negative predictive value, it seems inevitable that coronary CT will increasingly have a role in the evaluation of patients at low or intermediate risk of CAD such as those with atypical chest pain, equivocal exercise tests and premenopausal women. Indeed, it has been suggested that, more than any other modality, CT may shift the paradigm away from invasive CA.²¹¹

A further advantage of CT is that it allows an assessment of the coronary artery calcium burden, which is pathognomonic of coronary artery atheroma and has been shown to be an independent predictor of coronary events. One criticism which may be levelled at the functional tests we used is that a negative study may correctly rule out inducible ischaemia but it tells the referring physician nothing about the presence of non-flow-limiting disease, which could be targeted appropriately with primary prevention therapy. However, the same criticism may be levelled at angiography with equal validity.²¹²

One recent cost comparison study involving a modelling exercise based on various rates of coronary disease prevalence has suggested that coronary CT is likely to be cost-effective up to a 50% pretest likelihood of disease, equivalent to

invasive angiography at a pretest likelihood of 60% and only inferior as a strategy when the pretest likelihood rises as high as 70%. However, it should be acknowledged that this study simply looked at the effectiveness of establishing a diagnosis of significant coronary disease as defined by conventional catheterisation. Hence it potentially shares the same limitations when attempting to decide whether a visually intermediate stenosis is of functional significance. Furthermore, the study was really one of cost comparison rather than cost-effectiveness, since the model made no attempt to incorporate quality of life measurements or subsequent outcomes.²¹³ Despite this coronary CT remains a strong contender amongst the wide range of investigations with which physicians may choose to investigate chest pain. We would therefore suggest that the research-funding agencies give strong consideration to formal evaluation of the cost-effectiveness of coronary CT versus standard chest pain triage pathways in both the acute and outpatient hospital setting.

Recommendations for future research

Further research, using blinded reassessment of functional test results and angiograms, is required to formally assess accuracy of new tests in diagnosing CAD.

Longer-term cost-effectiveness modelling in patients investigated for CAD should assess whether management decisions based on functional tests such as SPECT MIBI, cardiac MRI and stress echo, have significant impact in the longer term.

Further studies of cardiac MRI and new generation CT are required to define features of scans that have clinical significance in the diagnosis of CAD.



Acknowledgements

The CECaT study group is indebted to the patients who participated in this study and the staff at Papworth Hospital NHS Trust and referral centres in the East Anglia region for their support. The group is also grateful for helpful advice and support from the Trial Steering Group members: Professor Adrian Dixon (Chair), Professor Roger Hall, Professor Andrew Briggs and Ian White. Anne Scott and Donna Griggs provided administrative support to the study and took responsibility for the preparation of the final report.

The CeCAT study group were: Johanna Armstrong, Martin Buxton, Noreen Caine, Richard Coulden, Andrew Crean, Matthew Dyer, Margaret Gillham, Hester Goddard, Kim Goldsmith, Vikki Hughes, Chris Jackson, Evelyn Lee, Roger Patel, Peter Schofield, Linda Sharples, Emer Sonnex, David Stone and Carmen Treacy.

Contributions of the CECaT investigators

Johanna Armstrong was involved in consent, data collection and patient contact. Martin Buxton supervised the review of cost-effectiveness studies and the design, collection and analysis of resource use data, costs and cost-effectiveness. He also contributed to the drafting of the final report. Noreen Caine was jointly responsible for the original proposal and led the design of the HRQoL survey. Richard Coulden was principal investigator for the first 5 years of the study, was jointly responsible for the original proposal and supervised all radiological aspects of the study. Andrew Crean was responsible for patient recruitment during the first 2 years of the study, supervised stress MRI and acted as clinical liaison between patients, trial staff and referring cardiologists and contributed to drafting of the final report. Matthew Dyer was responsible for the analysis of resource use data and the calculation of costs and contributed to the drafting of the final report. Margaret Gillham was involved in the design of data collection forms, consent, data collection and patient contact. Hester Goddard was responsible for coordination of the study and managed data collection and the Clinical Research

Assistants. Kim Goldsmith was responsible for some of the statistical analysis and contributed to the drafting of the report. Vikki Hughes was involved in the design of data collection forms, consent, data collection and patient contact and contributed to the drafting of the report. Chris Jackson completed some of the economic analyses. Evelyn Lee was involved in the design of the study, was responsible for providing the stress echo service and interpreting and reporting the stress echo studies. Roger Patel was responsible for patient recruitment during the last 2 years of the study, supervised stress MRI and acted as general clinical liaison between patients, trial staff and referring cardiologists. Peter Schofield advised on the original proposal and facilitated trial recruitment through his role as Senior Consultant Cardiologist in Coronary Intervention. Linda Sharples was jointly responsible for the original proposal, involved in the design of the study, supervised the statistical analysis, contributed to cost-effectiveness and cost-utility estimation and led the process of integrating the various components into the final draft. Emer Sonnex was responsible for the clinical care of patients undergoing stress perfusion MRI. David Stone was jointly responsible for the original proposal, took over as local principal investigator for the final stages of the study and was the lead cardiologist for the whole of the study. Carmen Treacy was involved in consent, data collection and patient contact.

Contribution of authors

The final report was drafted by Linda Sharples (MRC Programme Leader), Vikki Hughes (Clinical Research Assistant), Andrew Crean (Radiology Specialist Registrar), Matthew Dyer (Research Fellow in Health Economics), Martin Buxton (Professor of Health Economics), Kim Goldsmith (MRC Non-clinical Scientist) and David Stone (Consultant Cardiologist). These authors take responsibility for the content of the final report.

This study was sponsored by Papworth Hospital NHS Foundation Trust. It was approved by Huntingdon Research Ethics Committee on 16 January 2001, reference number H01/619.



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Appendix I

Clinician's risk assessment

	Angiography (n = 222)	SPECT (n = 224)	Cardiac MRI (n = 226)	Stress echo (n = 226)
Baseline risk of CAD	(n = 221)	(n = 220)	(n = 224)	(n = 224)
1 (lowest)	3 (1%)	2 (1%)	3 (1%)	4 (2%)
2	21 (10%)	27 (12%)	18 (8%)	26 (12%)
3	42 (19%)	41 (19%)	43 (19%)	39 (17%)
4	70 (32%)	81 (37%)	74 (33%)	79 (35%)
5 (highest)	85 (38%)	69 (31%)	86 (38%)	76 (34%)
Risk of CAD after initial test	(n = 210)	(n = 217)	(n = 212)	(n = 218)
1 (lowest)	45 (21%)	10 (5%)	14 (7%)	8 (4%)
2	22 (11%)	33 (15%)	34 (16%)	36 (17%)
3	9 (4%)	39 (18%)	28 (13%)	37 (17%)
4	4 (2%)	53 (24%)	57 (27%)	51 (23%)
5 (highest)	130 (62%)	82 (38%)	79 (37%)	86 (39%)
Baseline likelihood of revascularisation	(n = 221)	(n = 219)	(n = 223)	(n = 224)
1 (lowest)	16 (7%)	12 (6%)	15 (7%)	12 (5%)
2	52 (24%)	60 (27%)	44 (20%)	61 (27%)
3	89 (40%)	78 (36%)	104 (46%)	90 (40%)
4	53 (24%)	61 (28%)	53 (24%)	50 (22%)
5 (highest)	11 (5%)	8 (4%)	7 (3%)	11 (5%)
Likelihood of revascularisation after initial test	(n = 210)	(n = 217)	(n = 212)	(n = 217)
1 (lowest)	90 (43%)	33 (15%)	48 (23%)	41 (19%)
2	27 (13%)	53 (24%)	35 (17%)	42 (19%)
3	10 (5%)	77 (36%)	66 (31%)	69 (32%)
4	15 (7%)	45 (21%)	47 (22%)	53 (24%)
5 (highest)	68 (32%)	9 (4%)	16 (8%)	12 (6%)

Appendix 2

Results of exercise testing using the modified Bruce protocol treadmill test

	Angiography (n = 222)	SPECT (n = 224)	Cardiac MRI (n = 226)	Stress echo (n = 226)
Total exercise time (SD) (minutes)				
Baseline	11.29 (4.56)	10.46 (4.41)	10.43 (4.43)	10.89 (4.36)
6 months post-treatment	12.26 (4.16)	11.67 (3.98)	10.87 (4.33)	11.30 (4.48)
18 months post-random	12.36 (4.09)	11.61 (4.29)	11.24 (4.40)	11.67 (4.05)
Angina during ETT				
Baseline	108 (49%)	96 (43%)	111 (49%)	117 (52%)
6 months post-treatment	44 (23%)	48 (26%)	70 (35%)	62 (30%)
18 months post-random	39 (21%)	49 (25%)	58 (29%)	49 (26%)
Mean (SD) time to angina (minutes)^a				
Baseline	7.61 (4.23)	7.59 (4.68)	7.34 (4.11)	7.03 (3.86)
6 months post-treatment	8.93 (4.29)	7.47 (4.20)	7.66 (4.16)	8.62 (4.56)
18 months post-random	9.15 (4.42)	8.83 (4.98)	8.19 (4.58)	8.09 (4.93)
^a Restricted to those patients who experienced angina during exercise testing.				

Appendix 3

Mean difference between functional test groups and controls (95% CI) in exercise test results using the modified Bruce protocol treadmill test, split by treatment group

	SPECT	Cardiac MRI	Stress echo	p-Value
CABG patients total exercise time (minutes)^a				
<i>Unadjusted</i>				
6 months	1.32 (-1.04 to 3.68)	2.08 (-0.28 to 4.44)	2.44 (0.12 to 4.76) ^b	0.181
18 months	1.85 (-0.54 to 4.24)	2.74 (0.24 to 5.23) ^b	2.70 (0.23 to 5.17) ^b	0.113
<i>Adjusted for baseline</i>				
6 months	-0.13 (-2.01 to 1.76)	1.13 (-0.73 to 3.00)	2.15 (0.33 to 3.97) ^b	0.038
18 months	0.25 (-1.71 to 2.20)	1.78 (-0.23 to 3.78)	2.33 (0.36 to 4.30) ^b	0.043
PCI patients total exercise time (minutes)^a				
<i>Unadjusted</i>				
6 months	-0.67 (-2.60 to 1.27)	0.92 (-0.89 to 2.74)	2.22 (0.46 to 3.98) ^b	0.016
18 months	-1.23 (-3.18 to 0.71)	0.71 (-1.11 to 2.54)	1.02 (-0.81 to 2.84)	0.111
<i>Adjusted for baseline</i>				
6 months	0.29 (-0.93 to 1.52)	0.42 (-0.73 to 1.57)	1.85 (0.73 to 2.96) ^b	0.007
18 months	-0.49 (-1.72 to 0.74)	0.56 (-0.60 to 1.72)	0.75 (-0.41 to 1.90)	0.184
MM patients total exercise time (minutes)^a				
<i>Unadjusted</i>				
6 months	0.78 (-0.26 to 1.83)	1.43 (0.39 to 2.47) ^c	0.24 (-0.80 to 1.28)	0.035
18 months	1.14 (0.12 to 2.17) ^b	0.99 (-0.04 to 2.02)	0.20 (-0.85 to 1.25)	0.071
<i>Adjusted for baseline</i>				
6 months	-0.18 (-0.80 to 0.44)	0.57 (-0.04 to 1.18)	-0.06 (-0.67 to 0.55)	0.072
18 months	0.38 (-0.27 to 1.03)	0.38 (-0.27 to 1.03)	0.00 (-0.66 to 0.66)	0.455
^a Positive difference indicates angiography group have longer mean total exercise time.				
^b $p < 0.05$.				
^c $p < 0.01$.				

Appendix 4

CCS angina class

	Angiography (n = 222)	SPECT (n = 224)	Cardiac MRI (n = 226)	Stress echo (n = 226)
Baseline				
0	11 (5%)	17 (8%)	18 (8%)	13 (6%)
I	49 (22%)	37 (17%)	60 (27%)	45 (20%)
II	138 (62%)	144 (64%)	122 (54%)	132 (58%)
III	23 (10%)	22 (10%)	23 (10%)	32 (14%)
IV	1 (1%)	4 (2%)	3 (1%)	4 (2%)
6 months post-treatment				
0	97 (47%)	94 (46%)	93 (44%)	100 (47%)
I	50 (24%)	46 (23%)	60 (28%)	52 (24%)
II	56 (27%)	54 (27%)	48 (23%)	51 (24%)
III	4 (2%)	9 (4%)	9 (4%)	11 (5%)
IV	1 (1%)	0 (0%)	1 (1%)	0 (0%)
18 months post-randomisation				
0	99 (49%)	115 (55%)	104 (49%)	101 (49%)
I	54 (27%)	46 (22%)	39 (18%)	50 (24%)
II	45 (22%)	45 (22%)	59 (28%)	49 (24%)
III	4 (2%)	3 (1%)	9 (4%)	4 (2%)
IV	1 (1%)	0 (0%)	1 (1%)	2 (1%)

Appendix 5

Change from baseline in CCS angina class^a

	Angiography (n = 222)	SPECT (n = 224)	Cardiac MRI (n = 226)	Stress echo (n = 226)
6 months post-treatment (p = 0.418)^b				
-4	1 (1%)	2 (1%)	0 (0%)	0 (0%)
-3	3 (1%)	9 (4%)	6 (3%)	8 (4%)
-2	62 (30%)	55 (27%)	53 (25%)	59 (28%)
-1	65 (31%)	52 (26%)	65 (31%)	77 (36%)
0	67 (32%)	72 (36%)	71 (34%)	59 (28%)
1	10 (5%)	10 (5%)	15 (7%)	6 (3%)
2	0 (0%)	2 (1%)	1 (1%)	5 (2%)
3	0 (0%)	1 (1%)	0 (0%)	0 (0%)
18 months post-randomisation (p = 0.174)^b				
-4	0 (0%)	1 (1%)	0 (0%)	1 (1%)
-3	6 (3%)	9 (4%)	8 (4%)	6 (3%)
-2	59 (29%)	77 (37%)	55 (26%)	63 (31%)
-1	75 (37%)	59 (28%)	60 (28%)	71 (35%)
0	54 (27%)	54 (26%)	71 (34%)	53 (26%)
1	8 (4%)	6 (3%)	15 (7%)	11 (5%)
2	1 (1%)	3 (1%)	3 (1%)	1 (1%)
^a Negative values represent improvement.				
^b For statistical tests, infrequent categories were combined with adjacent categories.				

Appendix 6

Mean (SD) SAQ scores

	Angiography (n = 222)	SPECT (n = 224)	Cardiac MRI (n = 226)	Stress echo (n = 226)
Baseline				
Exertional capacity	75.1 (20.4)	72.6 (21.2)	72.8 (21.1)	73.2 (21.5)
Anginal stability	52.5 (21.8)	52.2 (22.5)	53.0 (21.6)	50.0 (20.4)
Anginal frequency	67.4 (24.1)	67.8 (23.9)	66.9 (25.5)	65.4 (25.8)
Treatment satisfaction	88.9 (14.7)	88.8 (15.2)	88.9 (13.3)	87.5 (15.5)
Disease perception	60.5 (23.1)	59.8 (22.5)	57.5 (23.3)	57.1 (25.4)
6 months post-treatment				
Exertional capacity	80.2 (19.3)	77.5 (21.3)	77.3 (22.0)	81.0 (20.5)
Anginal stability	66.6 (24.7)	61.9 (24.1)	63.2 (24.6)	65.2 (26.6)
Anginal frequency	83.8 (21.1)	83.5 (21.7)	83.3 (22.1)	84.0 (23.1)
Treatment satisfaction	90.4 (15.1)	92.0 (12.7)	91.7 (12.5)	91.6 (14.8)
Disease perception	73.1 (22.5)	74.8 (20.1)	73.3 (22.6)	75.6 (22.2)
18 months post-randomisation				
Exertional capacity	81.7 (19.2)	78.5 (23.0)	78.5 (23.1)	81.5 (20.0)
Anginal stability	64.6 (25.1)	62.6 (25.1)	61.4 (25.0)	64.4 (26.3)
Anginal frequency	84.2 (21.4)	86.9 (19.4)	84.4 (22.3)	86.8 (21.8)
Treatment satisfaction	91.8 (15.0)	91.2 (14.6)	91.3 (14.2)	91.9 (16.1)
Disease perception	77.4 (21.2)	77.0 (21.9)	76.6 (22.0)	78.4 (22.0)

Appendix 7

Mean difference between functional test groups and controls (95% CI) in SAQ scores^a

	SPECT	Cardiac MRI	Stress echo	p-Value
6 months				
ECS	1.6 (-1.8 to 5.0)	1.9 (-1.5 to 5.3)	-1.6 (-4.9 to 1.7)	0.155
ASS	4.7 (-0.1 to 9.6)	3.5 (-1.3 to 8.3)	1.3 (-3.6 to 6.1)	0.213
AFS	0.1 (-3.7 to 4.0)	0.0 (-3.8 to 3.8)	-0.6 (-4.4 to 3.2)	0.982
TSS	-1.7 (-4.2 to 0.9)	-1.4 (-3.9 to 1.1)	-1.4 (-3.9 to 1.1)	0.544
DPS	-1.8 (-5.6 to 1.9)	-1.4 (-5.1 to 2.3)	-3.3 (-7.0 to 0.4)	0.370
18 months				
ECS	2.0 (-1.7 to 5.6)	2.0 (-1.7 to 5.6)	-0.5 (-4.1 to 3.2)	0.418
ASS	1.9 (-3.0 to 6.9)	3.2 (-1.7 to 8.2)	0.1 (-4.9 to 5.1)	0.512
AFS	-2.6 (-6.3 to 1.1)	-0.8 (-4.5 to 2.9)	-3.2 (-6.9 to 0.5)	0.297
TSS	0.3 (-2.4 to 3.1)	0.1 (-2.7 to 2.9)	0.3 (-3.0 to 2.5)	0.980
DPS	0.0 (-3.8 to 3.8)	-0.3 (-4.1 to 3.5)	-1.6 (-5.4 to 2.2)	0.820

AFS, Anginal Frequency Scale; ASS, Anginal Stability Scale; DPS, Disease Perception Scale; ECS, Exertional Capacity Scale; TSS, Treatment Satisfaction Scale.

^a Positive values favour angiography.

Appendix 8

Mean difference between functional test groups and controls (95% CI) in SAQ scores, adjusted for baseline,^a by treatment group

	SPECT	Cardiac MRI	Stress echo	p-Value
6 months				
CABG ECS	-4.7 (-11.9 to 2.5)	-7.6 (-15.3 to 0.1)	-7.1 (-14.4 to 0.1)	0.164
CABG ASS	0.4 (-15.8 to 16.6)	7.1 (-9.0 to 23.2)	-3.0 (-18.9 to 12.9)	0.601
CABG AFS	-6.5 (-12.1 to -0.9) ^b	-3.8 (-9.5 to 1.9)	-5.7 (-11.3 to -0.1) ^b	0.110
CABG TSS	-3.2 (-7.1 to 0.8)	-1.5 (-5.6 to 2.6)	-1.8 (-5.9 to 2.2)	0.467
CABG DPS	-6.0 (-14.0 to 2.1)	-2.8 (-11.1 to 5.5)	-3.0 (-11.2 to 5.2)	0.534
PCI ECS	-2.0 (-9.5 to 5.5)	4.7 (-2.3 to 11.7)	1.6 (-5.4 to 8.7)	0.339
PCI ASS	-1.4 (-12.7 to 9.8)	0.7 (-9.8 to 11.2)	1.8 (-8.7 to 12.2)	0.955
PCI AFS	-1.4 (-10.9 to 8.0)	3.7 (-5.0 to 12.5)	1.9 (-6.9 to 10.7)	0.718
PCI TSS	-1.7 (-6.4 to 2.9)	-1.0 (-5.4 to 3.3)	1.6 (-2.7 to 5.9)	0.489
PCI DPS	-1.1 (-9.5 to 7.4)	5.5 (-2.5 to 13.3)	0.9 (-7.0 to 8.7)	0.416
MM ECS	4.2 (0.3 to 8.0) ^b	1.9 (-2.0 to 5.8)	-1.2 (-5.0 to 2.7)	0.036
MM ASS	7.7 (2.0 to 13.4) ^b	4.1 (-1.6 to 9.8)	2.3 (-3.4 to 8.0)	0.057
MM AFS	3.5 (-0.9 to 7.8)	0.1 (-4.2 to 4.5)	0.0 (-4.3 to 4.4)	0.323
MM TSS	-1.4 (-4.7 to 2.0)	-1.5 (-4.8 to 1.8)	-2.2 (-5.6 to 1.1)	0.616
MM DPS	-0.6 (-4.9 to 3.8)	-2.9 (-7.3 to 1.4)	-3.8 (-8.1 to 0.6)	0.258
18 months				
CABG ECS	-6.7 (-15.7 to 2.4)	-1.9 (-11.1 to 7.4)	-2.3 (-11.3 to 6.7)	0.504
CABG ASS	3.6 (-11.7 to 18.8)	15.0 (-0.2 to 30.2)	14.6 (-0.4 to 29.6)	0.097
CABG AFS	-6.2 (-14.3 to 2.0)	0.1 (-7.3 to 9.2)	-2.7 (-10.8 to 5.5)	0.269
CABG TSS	0.2 (-5.9 to 6.3)	0.1 (-6.3 to 6.4)	3.3 (-3.0 to 9.6)	0.657
CABG DPS	-0.8 (-9.8 to 8.2)	5.5 (-3.8 to 14.8)	5.3 (-3.9 to 14.5)	0.323
PCI ECS	-9.5 (-17.2 to -1.9) ^b	-2.2 (-9.0 to 4.6)	-4.8 (-11.8 to 2.2)	0.091
PCI ASS	4.2 (-7.2 to 15.5)	1.3 (-9.0 to 11.6)	-5.7 (-16.0 to 4.7)	0.349
PCI AFS	-2.5 (-11.7 to 6.7)	-4.1 (-12.4 to 4.3)	-7.4 (-15.9 to 1.2)	0.392
PCI TSS	2.0 (-3.1 to 7.1)	1.7 (-2.9 to 6.3)	-0.5 (-5.2 to 4.2)	0.679
PCI DPS	-3.1 (-12.5 to 6.2)	-4.4 (-12.9 to 4.0)	-4.2 (-12.9 to 4.5)	0.720
MM ECS	7.2 (2.8 to 11.7) ^b	4.3 (-0.3 to 8.8)	1.9 (-2.6 to 6.5)	0.011
MM ASS	1.9 (-4.0 to 7.8)	2.6 (-3.4 to 8.5)	0.2 (-5.8 to 6.2)	0.790
MM AFS	-0.7 (-5.1 to 3.7)	0.6 (-3.8 to 5.0)	-1.3 (-5.7 to 3.2)	0.855
MM TSS	-0.2 (-3.9 to 3.5)	-0.4 (-4.1 to 3.3)	-0.8 (-4.5 to 3.0)	0.980
MM DPS	2.2 (-2.2 to 6.7)	0.8 (-3.8 to 5.2)	-1.0 (-5.6 to 3.5)	0.532

^a Positive values favour angiography.
^b $p < 0.05$.

Appendix 9

Mean (SD) SF-36 physical and mental component scores

	Angiography (n = 222)	SPECT (n = 224)	Cardiac MRI (n = 226)	Stress echo (n = 226)
Baseline				
PCS	37.6 (14.1)	38.4 (12.7)	37.6 (13.1)	38.1 (14.2)
MCS	47.8 (14.8)	48.7 (12.2)	48.0 (13.2)	48.4 (14.2)
6 months post-treatment				
PCS	42.1 (14.0)	43.3 (13.1)	41.0 (13.7)	43.2 (13.6)
MCS	51.1 (14.1)	52.3 (12.8)	50.2 (13.2)	52.1 (13.4)
18 months post-randomisation				
PCS	43.6 (14.2)	43.2 (14.2)	41.8 (15.0)	44.5 (13.6)
MCS	52.0 (14.3)	52.2 (13.7)	50.8 (14.5)	53.5 (12.6)

Appendix 10

Mean difference between functional test groups and controls (95% CI) in SF-36 physical and mental component scores, adjusted for baseline,^a by treatment group

	SPECT	Cardiac MRI	Stress echo	p-Value
6 months				
CABG PCS	-1.5 (-6.6 to 3.6)	0.5 (-4.7 to 5.8)	-1.7 (-6.8 to 3.4)	0.751
CABG MCS	-0.4 (-5.2 to 4.3)	1.0 (-3.9 to 5.9)	0.2 (-4.6 to 5.0)	0.933
PCI PCS	-0.8 (-5.6 to 4.0)	3.3 (-1.1 to 7.8)	2.4 (-1.9 to 6.7)	0.260
PCI MCS	-0.1 (-4.8 to 4.6)	4.8 (0.5 to 9.2) ^b	3.5 (-0.8 to 7.7)	0.067
MM PCS	0.1 (-2.2 to 2.4)	0.4 (-1.9 to 2.7)	-0.2 (-2.5 to 2.1)	0.968
MM MCS	-0.1 (-2.4 to 2.3)	-0.3 (-2.6 to 2.1)	-0.7 (-3.1 to 1.6)	0.920
18 months				
CABG PCS	-1.9 (-7.9 to 4.1)	0.7 (-5.6 to 7.1)	-0.4 (-6.7 to 5.9)	0.842
CABG MCS	-1.7 (-7.9 to 4.5)	1.9 (-4.6 to 8.4)	0.2 (-6.3 to 6.6)	0.711
PCI PCS	0.3 (-4.9 to 5.5)	5.1 (0.4 to 9.7) ^b	-0.1 (-4.8 to 4.5)	0.091
PCI MCS	-0.7 (-5.5 to 4.1)	4.0 (-0.3 to 8.3)	-0.9 (-5.2 to 3.5)	0.106
MM PCS	1.4 (-1.3 to 4.0)	0.4 (-2.2 to 3.2)	-0.5 (-3.3 to 2.2)	0.547
MM MCS	0.8 (-1.8 to 3.5)	0.3 (-2.4 to 2.9)	-1.2 (-3.9 to 1.5)	0.514
^a Positive values favour angiography.				
^b $p < 0.05$.				

Appendix II

Mean difference between functional test groups and controls (95% CI) in EuroQoL EQ-5D,^a adjusted for baseline, by treatment group

	SPECT	Cardiac MRI	Stress echo	p-Value
6 months				
CABG	-0.05 (-0.13 to 0.03)	-0.01 (-0.09 to 0.07)	-0.03 (-0.11 to 0.05)	0.598
PCI	0.01 (-0.07 to 0.08)	0.03 (-0.04 to 0.10)	0.05 (-0.02 to 0.12)	0.535
MM	-0.01 (-0.06 to 0.03)	-0.03 (-0.07 to 0.02)	-0.03 (-0.07 to 0.02)	0.637
18 months				
CABG	0.03 (-0.08 to 0.14)	0.09 (-0.03 to 0.20)	0.01 (-0.11 to 0.12)	0.380
PCI	-0.05 (-0.13 to 0.03)	0.01 (-0.06 to 0.09)	-0.03 (-0.11 to 0.04)	0.370
MM	-0.01 (-0.06 to 0.04)	0.00 (-0.05 to 0.05)	-0.03 (-0.08 to 0.02)	0.703

^a Positive values favour angiography.

Appendix 12

Angiography resource use and cost components

Resource use component	Total cost: randomisation to treatment: mean (95% CI) (£)	Total cost: treatment to 18 months post-randomisation: mean (95% CI) (£)	Total cost: mean (95% CI) (£)
Initial test	640 (630 to 649)	NA	640 (630 to 649)
Treatments (CABG/PCI) ^a	NA	1585 (1268 to 1902)	1585 (1268 to 1902)
Drugs	36 (24 to 48)	365 (318 to 412)	401 (350 to 452)
Admissions	46 (20 to 71)	657 (404 to 909)	702 (449 to 956)
Tests	4 (-0 to 8)	50 (33 to 68)	54 (36 to 72)
Visits	14 (7 to 21)	125 (105 to 146)	139 (116 to 163)
GP visits	8 (6 to 9)	122 (93 to 151)	129 (99 to 159)

NA, not applicable.
^a Includes MIM patients who incur no 'treatment' costs.

Appendix 13

SPECT resource use and cost components

Resource use component	Total cost: randomisation to treatment: mean (95% CI) (£)	Total cost: treatment to 18 months post-randomisation: mean (95% CI) (£)	Total cost: mean (95% CI) (£)
Initial test	411 (404 to 418)	NA	411 (404 to 418)
Treatments (CABG/PCI) ^a	NA	1543 (1209 to 1878)	1543 (1209 to 1878)
Drugs	63 (46 to 81)	394 (346 to 443)	458 (403 to 513)
Admissions	138 (27 to 249)	780 (471 to 1089)	918 (589 to 1247)
Tests	172 (127 to 216)	296 (255 to 337)	468 (422 to 513)
Visits	20 (10 to 30)	142 (124 to 161)	162 (139 to 185)
GP visits	9 (7 to 12)	98 (77 to 119)	107 (85 to 130)

NA, not applicable.
^a Includes MIM patients who incur no 'treatment' costs.

Appendix 14

Cardiac MRI resource use and cost components

Resource use component	Total cost: randomisation to treatment: mean (95% CI) (£)	Total cost: treatment to 18 months post-randomisation: mean (95% CI) (£)	Total cost: mean (95% CI) (£)
Initial test	572 (567 to 577)	NA	572 (567 to 577)
Treatments (CABG/PCI) ^a	NA	1620 (1295 to 1945)	1620 (1295 to 1945)
Drugs	52 (38 to 67)	414 (363 to 465)	466 (412 to 521)
Admissions	118 (32 to 205)	564 (314 to 814)	682 (416 to 949)
Tests	181 (143 to 219)	265 (226 to 304)	446 (403 to 489)
Visits	16 (10 to 23)	145 (126 to 164)	161 (140 to 183)
GP visits	9 (7 to 11)	109 (88 to 131)	118 (95 to 142)

NA, not applicable.
^a Includes MM patients who incur no 'treatment' costs.

Appendix 15

Stress echo resource use and cost components

Resource use component	Total cost: randomisation to treatment: mean (95% CI) (£)	Total cost: treatment to 18 months post-randomisation: mean (95% CI) (£)	Total cost: mean (95% CI) (£)
Initial test	441 (436 to 447)	NA	441 (436 to 447)
Treatments (CABG/PCI) ^a	NA	1765 (1427 to 2103)	1765 (1427 to 2103)
Drugs	50 (37 to 62)	409 (360 to 459)	459 (405 to 513)
Admissions	79 (30 to 127)	964 (513 to 1415)	1043 (561 to 1525)
Tests	197 (161 to 233)	276 (230 to 323)	474 (426 to 521)
Visits	16 (9 to 23)	151 (130 to 173)	167 (144 to 191)
GP visits	10 (7 to 12)	116 (86 to 146)	126 (94 to 158)

NA, not applicable.
^a Includes MM patients who incur no 'treatment' costs.



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Feedback

The HTA Programme and the authors would like to know your views about this report.

The Correspondence Page on the HTA website (<http://www.hta.ac.uk>) is a convenient way to publish your comments. If you prefer, you can send your comments to the address below, telling us whether you would like us to transfer them to the website.

We look forward to hearing from you.