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Abstract

Systematic review and modelling of the cost-effectiveness of cardiac magnetic resonance imaging compared with current existing testing pathways in ischaemic cardiomyopathy

Fiona Campbell,[1] Praveen Thokala,[1] Lesley C Uttley,[1] Anthea Sutton,[1] Alex J Sutton,[2] Abdallah Al-Mohammad[3] and Steven M Thomas[1,3]*

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Background: Cardiac magnetic resonance imaging (CMR) is increasingly used to assess patients for myocardial viability prior to revascularisation. This is important to ensure that only those likely to benefit are subjected to the risk of revascularisation.

Objectives: To assess current evidence on the accuracy and cost-effectiveness of CMR to test patients prior to revascularisation in ischaemic cardiomyopathy; to develop an economic model to assess cost-effectiveness for different imaging strategies; and to identify areas for further primary research.

Data sources: Databases searched were: MEDLINE including MEDLINE In-Process & Other Non-Indexed Citations Initial searches were conducted in March 2011 in the following databases with dates: MEDLINE including MEDLINE In-Process & Other Non-Indexed Citations via Ovid (1946 to March 2011); Bioscience Information Service (BIOSIS) Previews via Web of Science (1969 to March 2011); EMBASE via Ovid (1974 to March 2011); Cochrane Database of Systematic Reviews via The Cochrane Library (1996 to March 2011); Cochrane Central Register of Controlled Trials via The Cochrane Library 1998 to March 2011; Database of Abstracts of Reviews of Effects via The Cochrane Library (1994 to March 2011); NHS Economic Evaluation Database via The Cochrane Library (1968 to March 2011); Health Technology Assessment Database via The Cochrane Library (1989 to March 2011); and the Science Citation Index via Web of Science (1900 to March 2011). Additional searches were conducted from October to November 2011 in the following databases with dates: MEDLINE including MEDLINE In-Process & Other Non-Indexed Citations via Ovid (1946 to November 2011); BIOSIS Previews via Web of Science (1969 to October 2011); EMBASE via Ovid (1974 to November 2011); Cochrane Database of Systematic Reviews via The Cochrane Library (1996 to November 2011); Cochrane Central Register of Controlled Trials via The Cochrane Library (1998 to November 2011); Database of Abstracts of Reviews of Effects via The Cochrane Library (1994 to November 2011); NHS Economic Evaluation Database via The Cochrane Library (1968 to November 2011); Health Technology Assessment Database via The Cochrane Library (1989 to November 2011); and the Science Citation Index via Web of Science (1900 to October 2011). Electronic databases were searched March–November 2011.

Review methods: The systematic review selected studies that assessed the clinical effectiveness and cost-effectiveness of CMR to establish the role of CMR in viability assessment compared with other imaging techniques: stress echocardiography, single-photon emission computed tomography (SPECT) and positron emission tomography (PET). Studies had to have an appropriate reference standard and contain

accuracy data or sufficient details so that accuracy data could be calculated. Data were extracted by two reviewers and discrepancies resolved by discussion. Quality of studies was assessed using the QUADAS II tool (University of Bristol, Bristol, UK). A rigorous diagnostic accuracy systematic review assessed clinical and cost-effectiveness of CMR in viability assessment. A health economic model estimated costs and quality-adjusted life-years (QALYs) accrued by diagnostic pathways for identifying patients with viable myocardium in ischaemic cardiomyopathy with a view to revascularisation. The pathways involved CMR, stress echocardiography, SPECT, PET alone or in combination. Strategies of no testing and revascularisation were included to determine the most cost-effective strategy.

Results: Twenty-four studies met the inclusion criteria. All were prospective. Participant numbers ranged from 8 to 52. The mean left ventricular ejection fraction in studies reporting this outcome was 24–62%. CMR approaches included stress CMR and late gadolinium-enhanced cardiovascular magnetic resonance imaging (CE CMR). Recovery following revascularisation was the reference standard. Twelve studies assessed diagnostic accuracy of stress CMR and 14 studies assessed CE CMR. A bivariate regression model was used to calculate the sensitivity and specificity of CMR. Summary sensitivity and specificity for stress CMR was 82.2% [95% confidence interval (CI) 73.2% to 88.7%] and 87.1% (95% CI 80.4% to 91.7%) and for CE CMR was 95.5% (95% CI 94.1% to 96.7%) and 53% (95% CI 40.4% to 65.2%) respectively. The sensitivity and specificity of PET, SPECT and stress echocardiography were calculated using data from 10 studies and systematic reviews. The sensitivity of PET was 94.7% (95% CI 90.3% to 97.2%), of SPECT was 85.1% (95% CI 78.1% to 90.2%) and of stress echocardiography was 77.6% (95% CI 70.7% to 83.3%). The specificity of PET was 68.8% (95% CI 50% to 82.9%), of SPECT was 62.1% (95% CI 52.7% to 70.7%) and of stress echocardiography was 69.6% (95% CI 62.4% to 75.9%). All currently used diagnostic strategies were cost-effective compared with no testing at current National Institute for Health and Care Excellence thresholds. If the annual mortality rates for non-viable patients were assumed to be higher for revascularised patients, then testing with CE CMR was most cost-effective at a threshold of £20,000/QALY. The proportion of model runs in which each strategy was most cost-effective, at a threshold of £20,000/QALY, was 40% for CE CMR, 42% for PET and 16.5% for revascularising everyone. The expected value of perfect information at £20,000/QALY was £620 per patient. If all patients (viable or not) gained benefit from revascularisation, then it was most cost-effective to revascularise all patients.

Limitations: Definitions and techniques assessing viability were highly variable, making data extraction and comparisons difficult. Lack of evidence meant assumptions were made in the model leading to uncertainty; differing scenarios were generated around key assumptions.

Conclusions: All the diagnostic pathways are a cost-effective use of NHS resources. Given the uncertainty in the mortality rates, the cost-effectiveness analysis was performed using a set of scenarios. The cost-effectiveness analyses suggest that CE CMR and revascularising everyone were the optimal strategies. Future research should look at implementation costs for this type of imaging service, provide guidance on consistent reporting of diagnostic testing data for viability assessment, and focus on the impact of revascularisation or best medical therapy in this group of high-risk patients.

Funding: The National Institute of Health Technology Assessment programme.

Contents

List of tables

List of figures

Glossary

Clinical terms

Coronary artery disease A condition in which an atheromatous plaque builds up inside the coronary artery, leading to narrowing of the arteries, which may be sufficient to restrict blood flow and cause myocardial ischaemia.

Gadolinium-enhanced cardiovascular magnetic resonance imaging A technique that can visualise both transmural and subendocardial scarring caused by previous myocardial infarction. Enables accurate in vivo visualisation of the transmural distribution of myocardial scarring.

Ischaemia Insufficient blood supply for the needs of a part of the body, in this case the heart muscle, as a result of blockage or narrowing of the blood vessels supplying that part.

Left ventricular dysfunction A common form of heart disease that occurs when the left ventricle starts to lose its ability to pump blood. This impairment of the functioning of the left ventricle is described as left ventricular dysfunction. Systolic dysfunction reflected in a low ejection fraction (< 50%) is a major cause of left ventricular dysfunction. Left ventricular dysfunction is an important determinant of overall outcome for those who are to undergo revascularisation. Improvement in the contraction of dysfunctional myocardium and in function after revascularisation is considered the gold standard for viability.

Left ventricular ejection fraction The calculated proportion of the volume of blood in the ventricle at the end of diastole that is ejected during systole and is expressed as a percentage.

Myocardial hibernation Hibernating myocardium describes a state of persistently impaired myocardial contraction at rest as a result of reduced coronary blood flow. The contraction of the hibernating myocardial segments can be partially or completely restored to normal if the myocardial oxygen supply/demand relationship is favourably altered, either by improving blood flow and/or reducing demand.

Stress echocardiography for the detection of myocardial viability and hibernation This technique for detecting myocardial hibernation requires pharmacological stress usually with an inotrope (dobutamine) or a vasodilator (typically, dipyridamole). Viability on stress echocardiography is determined by the presence of stress-induced contractile reserve. With increasing doses of dobutamine, viable tissue exhibits a biphasic response with improved contractility at low doses (5–0 μg/kg per minute) and regression to abnormal wall motion at higher doses (≥ 15 μg/kg per minute). Dipyridamole leads to transiently increased coronary flow, which leads to improved contractility in viable myocardium.

Viability assessment An assessment of the myocardial muscle to ascertain whether the muscle has undergone necrosis and scarring (non-viable), is viable and functioning normally, or viable and potentially hibernating (in which case revascularisation may result in improved muscle function).

Diagnostic accuracy terms

False negative A test result which indicates that a person does not have the disease when that person actually does have the disease.

False positive A test result which indicates that a person does have the disease when that person actually does not have the disease.

Index test New diagnostic test under examination.

Reference standard Established test(s) against which the accuracy of a new test for detecting a particular condition can be evaluated.

Sensitivity (true-positive rate) The proportion of individuals with the target condition who are correctly identified by the index test.

Specificity (true-negative rate) The proportion of individuals free of the target condition who are correctly identified by the index test.

True negative A person or segment without the disease correctly identified as negative by the index test.

True positive A person or segment with the disease correctly identified as positive by the index test.

List of abbreviations

BIOSIS	Bioscience Information Service
CABG	coronary artery bypass graft
CAD	coronary artery disease
CE CMR	late gadolinium-enhanced cardiac magnetic resonance imaging
CEAC	cost-effectiveness acceptability curve
CI	confidence interval
CMR	cardiac magnetic resonance imaging
DARE	Database of Abstracts of Reviews of Effects
DOR	diagnostic odds ratio
EDWT	end-diastolic wall thickness
EVPI	expected value of perfect information
HES	Hospital Episode Statistics
HF	heart failure
HRQoL	health-related quality of life
HTA	Health Technology Assessment
ICER	incremental cost-effectiveness ratio
ICP	Institute of Clinical Positron Emission Tomography
LR–	negative likelihood ratio
LR+	positive likelihood ratio
LV	left ventricular
LVEF	left ventricular ejection fraction
LYG	life-years gained
MI	myocardial infarction
MR	magnetic resonance
NHS EED	NHS Economic Evaluation Database
NICE	National Institute of Health and Care Excellence
NMB	net monetary benefit
NYHA	New York Heart Association
PCI	percutaneous coronary intervention
PET	positron emission tomography
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement
PSA	probabilistic sensitivity analysis
QALY	quality-adjusted life-year
QoL	quality of life
QUADAS	quality assessment of diagnostic accuracy studies tool
SCI	Science Citation Index
SPECT	single-photon emission computed tomography
STICH	Surgical Treatment for IsChemic Heart failure trial
Stress CMR	stress cardiac magnetic resonance imaging
SWT	systolic wall thickness
WTP	willingness to pay

Plain English summary

More than 700,000 patients over the age of 45 years in the UK have heart failure (HF) (a poorly functioning heart causing shortness of breath and inability to exercise). When assessing these patients the challenge is to identify those with narrow arteries of the heart who will benefit from having the blood supply restored. Cardiac magnetic resonance imaging (CMR) can be used as an alternative to other imaging tests to assess if heart muscle is likely to benefit from restored blood supply.

This review looked at the evidence from clinical trials of the accuracy of CMR to identify those patients with HF likely to benefit from surgery or balloon and stent treatment. Twenty-four studies on CMR showed that CMR is an accurate way to look for this. These results were compared with the results for other imaging tests that can also be used. The results were then used in a computer model to assess if the use of CMR in these patients would be good value for money, that is, is it cost-effective compared with the other tests. All the methods of testing were good value for money. In the model some assumptions had to be made and, depending on these, it was either best to test patients using one method of CMR, contrast enhanced (CE) CMR or to treat all patients regardless of the imaging test results. More research is required to help make this type of study easier to perform and the results more robust.

Scientific summary

Background

Patients with coronary artery disease (CAD) can present with myocardial infarction (MI), while others may develop heart failure (HF), either primarily or following MI. Some patients with HF, as a result of CAD, have poor left ventricular contraction because of ischaemia, and some will have irreversibly damaged heart muscle that has been scarred by infarction, and will not benefit from revascularisation. Others will have heart muscle that is not scarred but functioning poorly because of ischaemia, which may respond to revascularisation with improved function, and are labelled as viable and potentially hibernating.
The aim of viability assessment is to identify those patients in whom revascularisation is worthwhile, targeting those with viable and hibernating myocardium and avoiding intervention on those with scarred non-viable myocardium.

Assessment for viability can be done using a variety of techniques: stress echocardiography, single-photon emission computed tomography (SPECT), positron emission tomography (PET) and cardiac magnetic resonance imaging (CMR).

Objectives

This report aimed to assess the current evidence on the clinical accuracy and cost-effectiveness of the use of CMR in viability assessment for patients being considered for revascularisation to treat ischaemic cardiomyopathy, develop an economic model to assess cost-effectiveness for different imaging strategies and to identify areas for further primary research.

Data sources

Initial searches were conducted in March 2011 in the following databases with dates: MEDLINE including MEDLINE In-Process & Other Non-Indexed Citations via Ovid (1946 to March 2011); Bioscience Information Service (BIOSIS) Previews via Web of Science (1969 to March 2011); EMBASE via Ovid (1974 to March 2011); Cochrane Database of Systematic Reviews via The Cochrane Library (1996 to March 2011); Cochrane Central Register of Controlled Trials via The Cochrane Library 1998 to March 2011; Database of Abstracts of Reviews of Effects via The Cochrane Library (1994 to March 2011); NHS Economic Evaluation Database via The Cochrane Library (1968 to March 2011); Health Technology Assessment Database via The Cochrane Library (1989 to March 2011); and the Science Citation Index via Web of Science (1900 to March 2011). Additional searches were conducted from October to November 2011 in the following databases with dates: MEDLINE including MEDLINE In-Process & Other Non-Indexed Citations via Ovid (1946 to November 2011); BIOSIS Previews via Web of Science (1969 to October 2011); EMBASE via Ovid (1974 to November 2011); Cochrane Database of Systematic Reviews via The Cochrane Library (1996 to November 2011); Cochrane Central Register of Controlled Trials via The Cochrane Library (1998 to November 2011); Database of Abstracts of Reviews of Effects via The Cochrane Library (1994 to November 2011); NHS Economic Evaluation Database via The Cochrane Library (1968 to November 2011); Health Technology Assessment Database via The Cochrane Library (1989 to November 2011); and the Science Citation Index via Web of Science (1900 to October 2011). Relevant conference proceedings were searched via the Web of Science Conference proceedings citation index. The review team also contacted experts in the field and scrutinised the bibliographies of retrieved papers to identify relevant evidence. Searches were conducted from March to November 2011.

Review methods

A systematic review was performed according to the recommendation of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement. We assessed the clinical effectiveness and cost-effectiveness of CMR to establish the role of CMR in viability assessment compared with other imaging techniques (stress echocardiography, SPECT and PET).

The population considered comprised adults with CAD and left ventricular (LV) dysfunction who were potential candidates for revascularisation, to improve LV function. Studies had to have an appropriate reference standard, contain accuracy data (sensitivity, specificity, positive and negative predictive values) or sufficient details so that accuracy data could be calculated. Outcomes included accuracy data derived using different reference standards, with differing thresholds for determining viability. Criteria to define presence or absence of viable myocardium included improvement in wall motion, improvement in regional and global LV function, improvement in clinical symptoms, and reverse LV remodelling.

Data were extracted by two reviewers and discrepancies resolved by discussion. Quality of studies was assessed using the QUADAS II (quality assessment of diagnostic accuracy studies; University of Bristol, Bristol, UK) tool. The data extracted were synthesised and subjected to sensitivity analysis using STATA (2006 release 9.0; Stata Corporation, College Station, TX, USA).

A health economic model was constructed to compare diagnostic pathways for patients with ischaemic cardiomyopathy from an NHS perspective. The model was developed to estimate the costs and quality-adjusted life-years (QALYs) accrued by each potential diagnostic pathway for identifying patients with viable myocardium with a view to revascularisation. The pathways involved using stress echocardiography, late gadolinium-enhanced cardiac magnetic resonance imaging (CE CMR), stress cardiac magnetic resonance imaging (stress CMR), SPECT, PET to identify patients for revascularisation. A no-testing strategy and a revascularise everyone strategy were also included. Costs and benefits were discounted at an annual discount rate of 3.5%. The aim was to determine the optimal strategy in terms of cost-effectiveness.

The Markov model assigned each patient with a yearly probability of death, and, in each year, the patients who were alive had a risk of HF-related hospitalisations. The risks of death were estimated based on their subgroup and age using the data from different scenarios. The effect of the revascularisation on mortality was assumed to last a period of 5 years and, after this, the data from the general population were used. Each patient alive accumulated costs and QALYs every year based on his or her hospitalisation and subgroup. The model used a 40-year time horizon and the economic perspective of the model was the NHS in England and Wales. Scenario analyses were also performed using different mortality rates.

Cost-effectiveness of the different interventions was estimated using both the incremental cost-effectiveness ratio (ICER) and net monetary benefit (NMB) approach. This allows the relative value of different interventions to be compared. The ICER measures the relative value of two strategies, calculating the additional cost to accrue one additional QALY compared with the alternative. The NMB is defined as the QALYs multiplied by a value for the QALYs (e.g. £20,000) minus the costs of obtaining them. Uncertainty around the parameters used in the model (i.e. sensitivity and specificity estimates, mortality risks, hospitalisation rates, costs and utilities) were incorporated in the modelling by performing probabilistic sensitivity analysis, whereby the model is rerun (10,000 times), each time with a different value.

Another measure of uncertainty is the overall expected value of perfect information (EVPI). This estimates how often making the decision based on current evidence could be wrong and also how many QALYs (and costs) would be lost by choosing the strategy that is expected to be most cost-effective given current evidence, when in fact one of the other strategies is truly the most cost-effective. The interpretation of this number is that if one could fund research to eliminate the uncertainty in mortality risks for different patient

groups (e.g. by a large or infinitely large clinical trial) then the value of eliminating the uncertainty via such research would be expected to be the population EVPI.

Results

Twenty-four studies met the inclusion criteria. All of the studies were conducted prospectively and 16 studies reported that patients were recruited consecutively. The included studies were small, with the number of participants ranging from 8 to 52, with a greater proportion of males included. The mean left ventricular ejection fraction ranged from 24% to 62% in the included studies reporting this outcome. CMR approaches included stress CMR and CE CMR. Recovery following revascularisation was used as the reference standard in all the included studies. Twelve studies assessed diagnostic accuracy of stress CMR with sensitivity ranging from 50% to 99%, while specificity ranged from 65% to 100%. Fourteen studies evaluated the accuracy of CE CMR to detect myocardial viability with sensitivity ranging from 86% to 99%, while specificity ranged from 24% to 94%. A bivariate regression model was used to calculate the sensitivity and specificity of both CMR approaches. Summary sensitivity and specificity for stress CMR was 82.2% [95% confidence interval (CI) 73.2% to 88.7%] and 87.1% (95% CI 80.4% to 91.7%) respectively. Summary sensitivity and specificity for CE CMR were 95.5% (95% CI 94.1% to 96.7%) and 53% (95% CI 40.4% to 65.2%) respectively. The sensitivity and specificity of PET, SPECT and echocardiography were also calculated using data from 10 studies and previous published systematic reviews. The sensitivity of PET was 94.7% (95% CI 90.3% to 97.2%), of SPECT was 85.1% (95% CI 78.1% to 90.2%) and of echocardiography was 77.6% (95% CI 70.7% to 83.3%). The specificity of PET was 68.8% (95% CI 50% to 82.9%), of SPECT was 62.1% (95% CI 52.7 to 70.7%) and of echocardiography was 69.6% (95% CI 62.4% to 75.9%). If the annual mortality rates for non-viable patients are assumed to be higher for revascularised patients than for patients on medical therapy, then testing with CE CMR, to correctly identify patients most likely to benefit from revascularisation, was the most cost-effective approach at a threshold of £20,000/QALY, but there is uncertainty involved in suggesting it as the most cost-effective strategy. The proportion of models runs in which CE CMR was the most cost-effective strategy (at £20,000 per QALY threshold) was 40%, with PET at 42% and revascularising everyone at 16.5%. The EVPI at the threshold of £20,000/QALY is £620 per patient.

If it was assumed that all patients (viable or not) gained benefit from revascularisation, then it was most cost-effective to revascularise all patients. Revascularising everyone was cost-effective in 95.2% of the proportion of models runs with CE CMR and PET cost-effective in 3.6% and 1.1% of the runs respectively. This reduction in uncertainty is also reflected in the EVPI of only £28 per patient.

Conclusions

All the diagnostic pathways were a cost-effective use of NHS resources irrespective of the diagnostic pathway used at current National Institute for Health and Care Excellence thresholds, provided their costs and diagnostic accuracy are similar to those reported in this analysis. In terms of determining the most cost-effective strategy, diagnostic parameters and mortality rates of the different subgroups are the key drivers in the model. Two different scenarios relating the mortality rates were analysed in the model, this approach was taken to address the uncertainty in the mortality evidence. For decision-makers deciding which of these presented results are most representative of their setting, the key questions relate to the effect of revascularising non-viable patients. If one believes patients that are revascularised have lower mortality rates, even if they do not have viability, then revascularising everyone is the most cost-effective strategy. If one believes that there is no benefit for revascularising non-viable patients, then CE CMR is the most cost-effective strategy at a threshold of £20,000/QALY, but there is uncertainty involved in suggesting it as the most cost-effective strategy.

Implementation costs (such as set-up costs, staff training costs, costs for running of diagnostic services) were often missing from the studies in the review. Future studies should provide greater detail of the costs of reconfiguration and link more clearly with the financial impact (e.g. cost variation with scale and over time) on provider organisations. Wider adaptation of diagnostic imaging pathways in the NHS can be facilitated by providing financial impact data along with the cost-effectiveness information.

Consensus on reporting of diagnostic testing data in this clinical area would facilitate comparison of trial data and data synthesis in the future. Further research using universally agreed methodology of assessment of viability to answer both the question of testing viability and the impact of revascularisation or best medical therapy in this group of high-risk patients while remaining a priority, may be difficult to achieve in clinical practice.

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The National Institute for Health Research Health Technology Assessment programme.

Chapter 1 Background

In the UK, it is estimated from age-specific incidence rates that there are 38,000 new cases of heart failure (HF) in men each year and about 30,000 in women, giving an overall new case incidence of 68,000. This incidence rises steeply in the elderly, and with changing demographics incidence is likely to increase in the next few decades. In terms of prevalence, it is estimated that in 2006 there were 393,000 men over 45 years old with established HF and 314,000 women, giving a total prevalence of over 700,000.[1] Among these patients, coronary artery disease (CAD) is the major aetiological factor for left ventricular (LV) systolic dysfunction leading to HF. Regional LV dysfunction in patients with CAD is an irreversible phenomenon in the presence of scarred tissue, but it could be reversible in case of stunned or hibernating myocardium.

A common cause of HF is myocardial infarction (MI). There is increasing success in treating MI with reduced mortality,[2] but inevitably this means that more patients survive with severe morbidity post MI. The prognosis for patients post MI is related to the extent of myocardial necrosis, preserved viability, LV dysfunction and degree of stress-induced ischaemia.[2]

Viable myocardium is defined as myocardial segments with reduced function at rest, but potentially recoverable either spontaneously (stunned) or with revascularisation when perfusion is reduced (hibernating myocardium).[3] The clinical challenge is to identify those patients with CAD and HF with viable myocardium who have the potential to recover if revascularised and to ensure that these patients are appropriately treated with surgical or catheter-based coronary intervention, and that those with non-viable myocardium in the target area for revascularisation are not subjected to unnecessary intervention.

This is particularly important as patients with this condition, often referred to as ischaemic cardiomyopathy, which is characterised by extensive CAD and diminished LV function, have 5-year survival rates ranging from 50% to 60%.[4] Survival decreases as LV ejection fraction (LVEF) decreases, the extent of CAD increases and patient age increases.[5] LV dysfunction in patients with ischaemic cardiomyopathy is usually the result of either myocardial necrosis and scarring or myocardial hibernation.[4] Recognising the presence of viable and hibernating myocardium allows targeted revascularisation to potentially improve LV function, functional capacity and prognosis, though this may only be relevant for patients with severe LV systolic dysfunction (< 35%).[3,6] Therefore, patients post MI who have poor LV function and symptoms of HF (ischaemic cardiomyopathy) should be assessed with viability studies. The treatment options are then medical therapy, revascularisation or heart transplantation. For most patients, however, the choice is between offering medical therapy alone or with revascularisation. Revascularisation procedures are associated with an increased risk of perioperative complications so it is important to select appropriate patients for this intervention. Using positron emission tomography (PET) to detect markers of hibernating myocardium, the prevalence of the phenomenon in patients with severe LV systolic dysfunction has been found to be about 55%.[7] Of those revascularised, between 55% and 60% will show evidence of recovery in function in the hibernating myocardium.[8]

The recently published Surgical Treatment for IsChemic Heart failure (STICH) trial[9] has questioned the prognostic value of assessing myocardial viability. The trial did not demonstrate any advantage in terms of survival in the patients evaluated for myocardial viability undergoing revascularisation [coronary artery bypass graft (CABG)] plus medical therapy compared with medial therapy alone. Diffuse severe disease may mean that there is no feasible means to achieve revascularisation, and in such cases assessment for viable myocardium may not be useful. However, there is no convincing evidence that the assessment of myocardial viability should not be included in the work-up of the chronic HF patient.[10]

There are four main imaging methods available to assess for hibernating myocardium:[11]

1. Positron emission tomography scanning examining the uptake of a number of tracers can be used to assess perfusion and metabolism in order to demonstrate perfusion–metabolism mismatch, which is the hallmark of hibernating myocardium. PET offers assessment of anaerobic and aerobic metabolism (including glucose use, fatty acid uptake and oxygen consumption). Other PET applications include assessment of contractile function and neuronal activity.
2. Single-photon emission computed tomography (SPECT) techniques, using thallium-201- or technetium-99m-labelled tracers, are in clinical practice probably the most commonly used techniques to assess patients for viable myocardium across the NHS.
3. Echocardiography, which usually means stress echocardiography, is used to produce a dual response to stress (augmentation followed by reduction of contraction) in an abnormal LV segment as an indication of hibernating myocardium. More recent techniques include myocardial contrast echocardiography and tissue Doppler imaging.
4. Cardiac magnetic resonance imaging (CMR). Two main techniques are available: dobutamine stress cardiac magnetic resonance imaging (stress CMR), which is analogous to stress echocardiography imaging; and the more recently described and more widely used delayed enhancement CMR technique, which allows assessment of the distribution of myocardial scar and viable tissue alongside an assessment of regional myocardial function.

With such a range of techniques available to assess patients with ischaemic cardiomyopathy for viable myocardium, the technique chosen is often dictated by local availability of equipment and expertise. It is generally accepted that PET scanning is the most accurate technique, but it is mainly used as a research tool and is not readily available to all patients. Studies to assess the accuracy of all imaging techniques to detect viable myocardium have been based on evidence of functional improvement of LV function either globally or in defined segments following surgery, and on this basis the sensitivity and specificity of each imaging technique to predict functional improvement have been calculated.[12–14]

Cardiac magnetic resonance imaging, particularly late gadolinium-enhanced CMR (CE CMR), is a relatively new technique used to assess patients for viable myocardium.[15–17] There are a number of papers comparing CMR with other techniques in this clinical area, and a more wide-ranging technology assessment of the role of functional CMR in assessing myocardial perfusion was performed in Canada.[11,15,18,19] Four previous reviews[14,20–22] have explored the diagnostic accuracy of CMR in determining myocardial viability. Three reviews[14,20,22] included only a limited number of studies. Romero *et al.*'s[21] recent well-conducted review excluded data from abstracts and also those studies that used doses of dobutamine for stress CMR greater than 10 µg/kg per minute. No previous studies have reported the cost-effectiveness of CMR in this or other clinical areas.

Most magnetic resonance (MR) scanners being installed within the NHS have the capability to perform CMR for assessment of viability and perfusion in planning revascularisation in patients with ischaemic cardiomyopathy. However, capacity issues mean that access to scanners and scan time remains problematic. The use of MR scanners to perform CMR results in an opportunity cost to other groups of patients who may benefit from MR imaging, or results in a need to provide additional scanners to allow CMR to be performed. As demand for CMR is growing, it is timely to assess whether or not investigating these patients in this way is cost-effective in the NHS.

On a broader front, there are other areas within cardiology when CMR is being used because it produces images of high spatial and temporal resolution in multiple planes. It is a safe method involving no radiation exposure that can assess cardiac structure and, with cine imaging and flow assessment, it can assess ventricular function and volumes, valve function, as well as quantify intracardiac shunts. Perfusion imaging can make an assessment of myocardial ischaemia, often alongside viability imaging. In a number of patient groups, notably patients with congenital heart disease, valvular heart disease and other cardiomyopathies, it complements echocardiography in patient assessment, and in these clinical areas its use is likely to expand. This work on ischaemic cardiomyopathy could act as an introduction to a programme of research into the wider uses of CMR and its cost-effectiveness in the NHS, and form a template for further study of how this technology should be introduced and utilised.

Chapter 2 Assessment of diagnostic accuracy

Review methods

This systematic review was carried out according to the recommendation of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.

Identification of studies

The PRISMA flow diagram shown in *Figure 1* provides a summary of the study identification process.

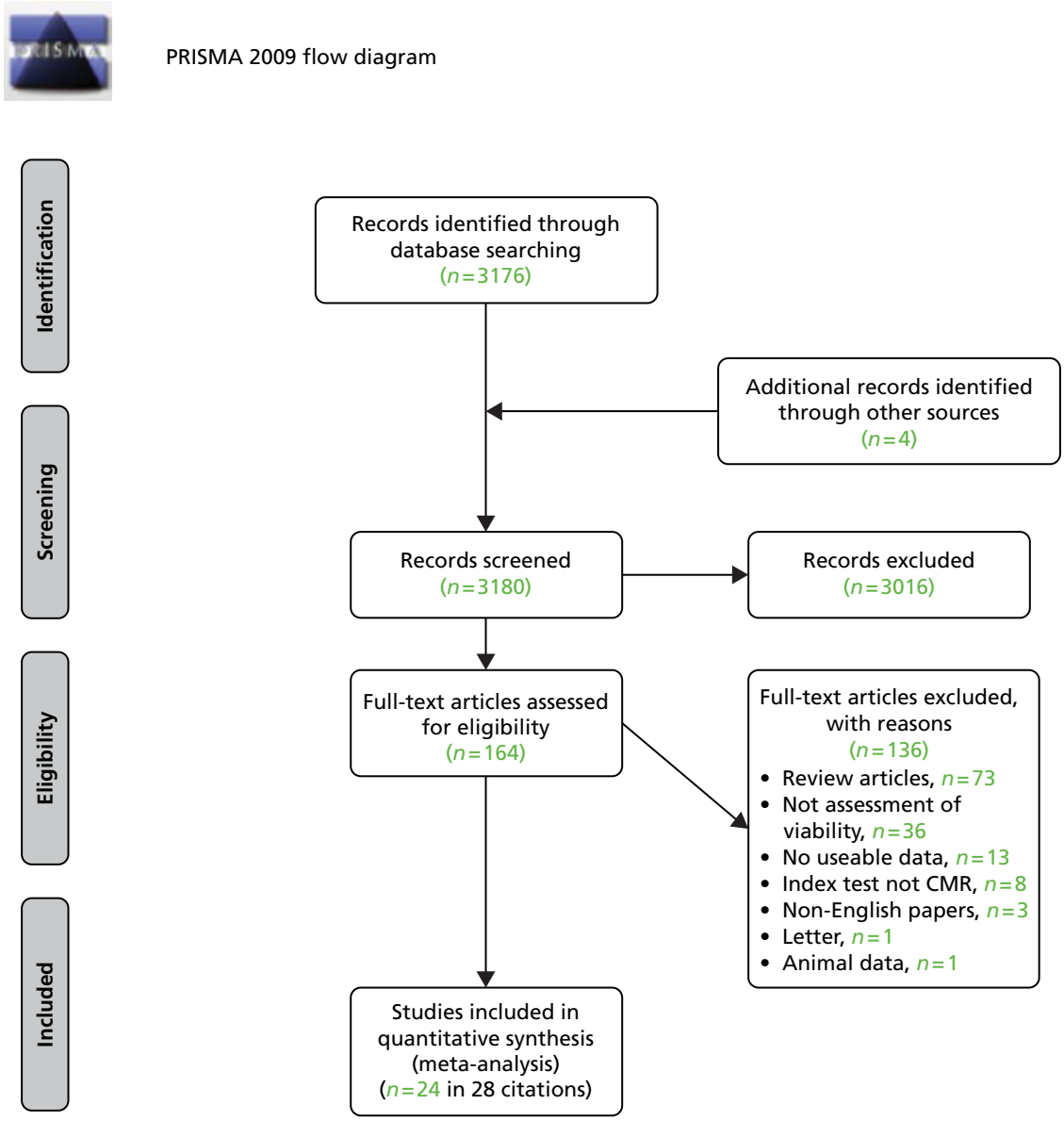


FIGURE 1 The PRISMA flow diagram of included studies.

Search strategy

The search aimed to systematically identify all literature relating to the diagnostic accuracy of cardiac magnetic imaging in detecting viable myocardium in patients with CAD. The searches were conducted between March and November 2011. Initial searches were conducted in March 2011 in the following databases with dates: MEDLINE including MEDLINE In-Process & Other Non-Indexed Citations via Ovid (1946 to March 2011); Bioscience Information Service (BIOSIS) Previews via Web of Science (1969 to March 2011); EMBASE via Ovid (1974 to March 2011); Cochrane Database of Systematic Reviews via The Cochrane Library (1996 to March 2011); Cochrane Central Register of Controlled Trials via The Cochrane Library 1998 to March 2011; Database of Abstracts of Reviews of Effects via The Cochrane Library (1994 to March 2011); NHS Economic Evaluation Database via The Cochrane Library (1968 to March 2011); Health Technology Assessment Database via The Cochrane Library (1989 to March 2011); and the Science Citation Index via Web of Science (1900 to March 2011). Additional searches were conducted from October to November 2011 in the following databases with dates: MEDLINE including MEDLINE In-Process & Other Non-Indexed Citations via Ovid (1946 to November 2011); BIOSIS Previews via Web of Science (1969 to October 2011); EMBASE via Ovid (1974 to November 2011); Cochrane Database of Systematic Reviews via The Cochrane Library (1996 to November 2011); Cochrane Central Register of Controlled Trials via The Cochrane Library (1998 to November 2011); Database of Abstracts of Reviews of Effects via The Cochrane Library (1994 to November 2011); NHS Economic Evaluation Database via The Cochrane Library (1968 to November 2011); Health Technology Assessment Database via The Cochrane Library (1989 to November 2011); and the Science Citation Index via Web of Science (1900 to October 2011). Relevant conference proceedings were searched via the Web of Science Conference proceedings citation index. The review team also contacted experts in the field and scrutinised the bibliographies of retrieved papers to identify relevant evidence. This yielded two additional papers not identified in the electronic searches. Previous review articles and systematic reviews were retrieved and bibliographies searched for further studies that may not have been identified in the search of electronic databases.

Search terms

Searches on electronic databases were conducted between March 2011 and November 2011.
A comprehensive search strategy was constructed using terms (thesaurus and free text) relating to the condition (cardiomyopathy, myocardial ischaemia) and CMR. A number of methodological filters (The InterTASC Information Specialists' Sub-Group Search Filter Resource)[23] were applied to the search to retrieve diagnostic studies, prognostic studies, systematic reviews, randomised controlled trials, guidelines and economic evaluations. No language or date limitations were applied.

Additional specific searches were conducted on the following topics identified from the included studies from the initial search:

- myocardial revascularisation and MR imaging
- diagnosis of MI, coronary disease, coronary artery disease and MR imaging
- comparative study publication type combined with the initial search terms
- magnetic resonance imaging (MRI) and myocardial salvage.

Search terms included:

- cardiomyopath$, isch$, imaging, Magnetic resonance imaging, cardiac disease, radionuclide imaging, echocardiography, viability assessment, perfusion scanning, positron emission tomography, single-photon emission computed tomography.
- imaging pathway, imaging guideline$, plus such terms as
- cohort studies, longitudinal studies, follow-up studies, time factors, long term, sequela$, prognosis, and
- diagnostic terms such as specificity and sensitivity, false positive$, false negative$, true positive$, true negative$.

The MEDLINE search strategies are included in *Appendix 1*.

Inclusion and exclusion criteria

Study design

Diagnostic accuracy studies were included if they had an appropriate reference standard, and if they contained accuracy data (sensitivity, specificity, positive and negative predictive values) or sufficient details so that accuracy data could be calculated. They could have been prospective or retrospective in design. It included reporting results that compared the functional outcome of individuals with and without viable myocardium who received CMR.

Population

The population comprised adults with CAD and LV dysfunction and considered potential candidates for revascularisation by percutaneous coronary intervention (PCI) or CABG.

Index tests

Studies testing any type of CMR to assess for viability were included.

Reference standard

Any evaluation technique to establish the presence of viable myocardium was considered eligible.

Outcomes

The studies contained accuracy data that were derived using different reference standards with differing thresholds for determining viability. The follow-up criteria for defining the presence or absence of viable myocardium included improvement in wall motion, improvement in regional and global LV function, improvement in clinical symptoms and reverse LV remodelling.

Studies excluded from the review

Studies were excluded if they reported acute ischaemic syndromes or were editorials, letters, case reports, technical reports, systematic reviews or meta-analyses.

Study selection

Studies were selected for inclusion through a two-stage process according to the above inclusion/exclusion criteria. All titles and abstracts were examined for inclusion by two reviewers (FC and LU). Discrepancies were resolved by discussion and drew on additional expertise (SMT) where uncertainty remained. Full manuscripts of selected citations were retrieved and assessed by two reviewers using the inclusion/exclusion criteria.

Data extraction strategy

Data were extracted by two reviewers using a standardised data extraction form which had initially been piloted and redesigned in discussion with clinical experts. Discrepancies were resolved by discussion. Where multiple publications of the same study were identified, data were extracted and reported as a single study.

Critical appraisal strategy

The quality of each study was assessed using the QUADAS II (quality assessment of diagnostic accuracy studies) tool.[24] The following factors were considered: methods of patient selection, the conduct and interpretation of the index test and reference standard. This included the extent to which interpretation of the tests might have been biased by knowledge of the results of other tests or the patient characteristics. In addition, the flow of patients through the study and the number of excluded patients from the analysis and the timing of the follow-up assessment. Where available, these data were extracted and their impact on biasing sensitivity and specificity was considered.

Data synthesis

Meta-analyses were performed to estimate a summary measure of sensitivity and specificity for CMR. The statistical software STATA (2006 release 9.0; Stata Corporation, College Station, TX, USA) was used for this analysis.

Sensitivity analysis was performed to explore causes of potential bias and heterogeneity in the meta-analyses. The study data were grouped into stress CMR and CE CMR and analysed separately. Thirteen studies exploring the diagnostic accuracy of CMR with recovery following revascularisation also compared other diagnostic tests within the same study. This included five studies exploring SPECT, four studies exploring PET and three studying echocardiography. These data were used within the cost-effectiveness review to provide more up-to-date measures of diagnostic accuracy for these alternative and commonly used diagnostic tests. In addition, the data obtained from these studies exploring the clinical effectiveness of other tests were pooled with the results of the most recent diagnostic accuracy review.[22]

Chapter 3 Results of the diagnostic accuracy review

Description of included studies

Published literature indicates that the journey to determining which imaging modality is superior for detecting viability is ongoing. Some studies perform head-to-head comparisons between imaging techniques, while some studies compare predicted viability from a single test before revascularisation with improvement of heart function post revascularisation. CMR is known to have clinical utility for cardiovascular imaging at various points in the patient pathway between being diagnosed with CAD, being assessed for viability and being followed up after revascularisation. Despite a body of research examining the relative benefits of CMR, the studies are not easily comparable. There are several reasons for this:

1. There are different types of cardiac MR imaging (delayed enhancement, stress).
2. There are different ways of detecting viability for each type of CMR, which serve as the study outcomes (e.g. wall motion, hyperenhancement).
3. Studies vary in the thresholds for detecting viable myocardium. Therefore, sensitivity and specificity values can vary as a result of the subjectivity of each study's cut-off value.
4. The thresholds and techniques for determining the reference standard may also vary.
5. A major limitation for detailed myocardial phenotyping in clinical investigation is the lack of a true gold standard for defining viability. Histopathological verification of viability in patients is impossible. Thus, the ideal methodology to assess myocardial viability would provide accurate non-invasive measurements of perfusion, metabolism, and cellular membrane integrity in addition to systolic and diastolic function, with sufficient spatial and temporal resolution for a detailed reconstruction of the entire LV as it contracts and relates in three-dimensional space. Increasingly, attempts at assessing multiple aspects of viable myocardium are being made with the various technologies.[25]
6. Imaging technology is evolving so that most clinical trials cannot be completed before a technique becomes obsolete or superseded upon publication. For example, studies in the late 1990s published data using 0.2- or 0.95-tesla-strength magnets, while the majority of papers in the last decade use 1.5-tesla-strength magnets. The lower magnet strength used in earlier studies of CMR may account for lower sensitivity and specificity scores for viability detection. However, 3.0-tesla-strength magnet scanners are now available and increasingly being used for CMR, although there is few published data on cardiac viability assessment using 3.0-tesla-strength magnet scanners. It may, therefore, take considerable time for the merits of this new CMR technology to become apparent.
7. The sensitivity and specificity values for some studies are calculated and reported by segment and others are reported by patients with evidence of ventricular recovery.

Included studies

The search strategy generated 3176 references and four further papers were found through bibliography searching. Therefore, a total of 3180 papers were screened, of which 194 full-text papers were retrieved for further consideration and 28 were identified which met the inclusion criteria. A total of 136 studies were excluded from the review: 123 did not meet the inclusion criteria and 13 did not report sufficient data to be included in the review (see *Figure 1*). A full list of those papers excluded following retrieval is listed in *Appendix 2* and reasons given for their exclusion.

Twenty-four studies (28 citations) met the inclusion criteria.[15–17,25–49] *Table 1* lists the reports for studies with multiple citations. Ten of the included studies were conducted in Germany,[16,27–29,32,37,38,40,48,49] five in the USA,[15,35,39,41,44] four in the UK[31,36,43,47] and one each in the Czech Republic,[46] Belgium,[17] the Netherlands,[30] Finland[34] and Japan.[25]

Quality of diagnostic accuracy studies

The quality of the included studies was evaluated using the QUADAS II tool[23] and a number of potential sources of bias were identified in patient selection, conduct of the index test and reference standard, and in timing and follow-up (*Figure 2*).

TABLE 1 Primary reports for each study

Study citation referred to in review	Other citations reporting the same data
Schmidt 2004[40]	Baer 1998[26]
Kuhl 2006[16]	Kuhl 2006[33]
Schvartzman 2003[41]	Schvartzman 2001[42]
Skala 2011[46]	Skala 2009[45]

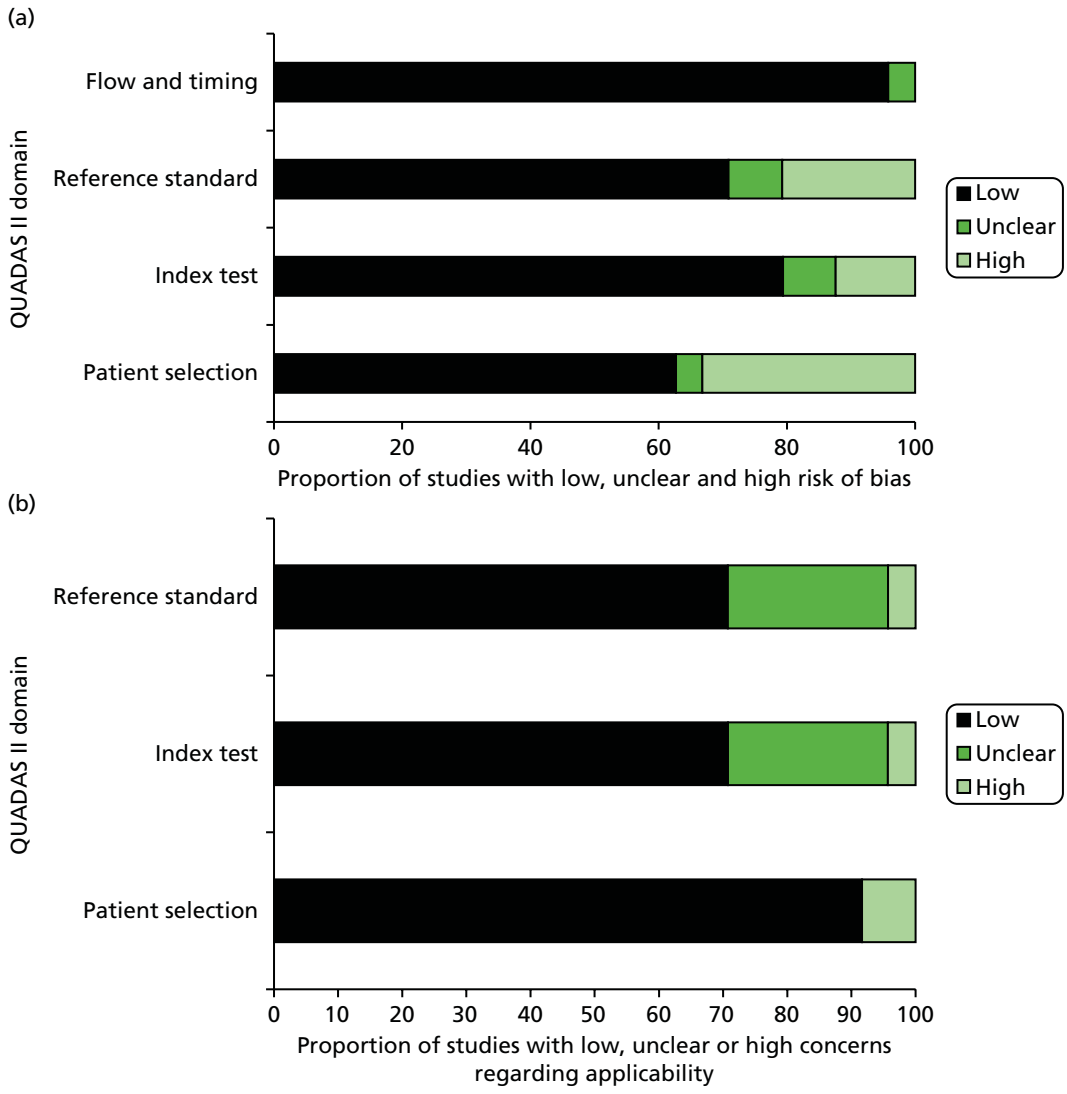


FIGURE 2 Graphs showing proportion of studies in QUADAS II domains.

All of the studies were conducted prospectively and in secondary or tertiary care settings. In most studies patients were recruited following a referral for further assessment and treatment of CAD. In 16 of the studies, the patients were recruited consecutively and the studies were, therefore, considered to be at low risk of bias regarding patient selection (*Table 2*). Eight studies did not report whether or not recruitment occurred consecutively. This may have led to an underestimation or overestimation of test accuracy by investigating a selected population, through inclusion or exclusion of those patients who may be 'difficult to diagnose' or, alternatively, have features highly suggestive of viable myocardium.[24]

TABLE 2 Quality assessment of included studies

	Risk of bias				Applicability concerns		
Study	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Baer 1998[27]	☺	☺	☺	☺	☺	☺	☺
Baer 2000[28]	☺	☺	☺	☺	☺	☺	☺
Becker 2008[29]	☺	☺	☺	☺	☺	☹	☹
Bondarenko 2007[30]	☺	☺	?	☺	☺	☺	☺
Gunning 1998[31]	☺	☺	☺	☺	☺	☺	☺
Gutberlet 2005[32]	☺	☺	?	☺	☺	☹	☹
Hunold 2002[49]	?	☺	☺	?	☺	☺	☺
Kim 2000[15]	☺	☺	☺	☺	☺	☺	☺
Kuhl 2006[16]	☺	☺	☺	☺	☺	?	?
Lauerma 2000[34]	☺	☺	☺	☺	☺	☹	☹
Martinez 2000[35]		☹	☹	☺	?	☺	☺
Pegg 2010[36]	☺	☺	☺	☺	☺	☹	☹
Sandstede 1999[37]	?	?	?	☺	☺	☺	☺
Sandstede 2000[38]	?	?	?	☺		☺	☺
Sayad 1998[39]		☹	☹	☺	☺	☺	☺
Schmidt 2004[40]	☺	☺	?	☺	☺	☺	☺
Schvartzman 2003[41]	☺	☺	☺	☺	☺	☹	☹
Selvanayagam 2004[43]	☺	☺	☺	☺	☺	☺	☺
Sharma 2009[44]	☺	☺	☺	☺	☺	☺	☺
Skala 2011[46]	☺	☺	☺	☺	☺	☹	☹
Trent 2000[47]	?	☺	☺	☺	☺	☺	☺
Van Hoe 2004[17]	☺	☺	☺	☺	☺	☺	☺
Wellnhofer 2004[48]	?	☺	☺	☺	☺	☺	☺
Wu 2007[25]	?	☺	☺	☺	☺	☺	☺

☹, high risk; ☺, low risk; ?, unclear risk.

Blinding to prevent bias in the interpretation of the index and reference standard could include a number of components: blinding of assessors analysing the results of the index test and reference standard to the interpretations of the other assessor(s), blinding to the patients' identity and their clinical characteristics, blinding to the results of the other tests that may have been undertaken alongside the index text and blinding to the results of the reference standard results or index test results. Only three studies blinded all these aspects of the study.[15–17] Seven studies[15,25,31,44,47–49] used more than one experienced observer to assess segmental viability and these assessments were conducted blind and consensus reached if discrepancies in interpretation arose. In a further seven studies,[16,29,32,36,41,43,46] only one assessor was used, but he or she was blind to the other test results and/or clinical information regarding the patient. Seven studies[17,27,28,30,37,38,40] used more than one assessor, but did not describe efforts to blind the assessors to the results of other tests or to details of the patient's clinical condition. Three studies[34,35,39] used only one assessor and did not describe details of blinding the assessor to information that might bias their interpretation of the test results.

All of the included studies were within-patient comparisons, so both the index test and the reference standard were carried out on the same patient. This will have reduced interpatient variability and added strength to the research design.

Studies differed in the length of time between revascularisation and the assessment of recovery. There is some indication that recovery of myocardial function can occur up to 6–12 months after revascularisation. Therefore, studies with a very short follow-up point may underestimate the accuracy of a study.[22,51] Follow-up periods varied from 17 days to 9 months (*Tables 3 and 4*).

Fifteen studies[15–17,25,28–31,35,36,43,44,46–48] did not include all of the recruited patients in the final analysis. The reasons for their exclusion were given, and included death, serious postoperative morbidity, withdrawal from the study, segmental images hard to read and loss to follow-up.

In considering the applicability of each included study in addressing the study question, there were a number of concerns. Three studies[35,39,44] included very small numbers of participants in the analysis ($n = 10$,[35] $n = 10$[39] and $n = 8$[44]), creating uncertainty in the reliability of the findings. One study[31] included a population that had a greater severity of CAD at baseline than the other studies.

Characteristics of participants

The included studies were generally small, with the number of participants ranging from 8 to 52. The total number of participants included in the analyses was 668 across the 24 studies. The profile of the participants across all the studies was homogeneous in terms of age, with a mean age of 62.3 years. The proportion of men in most of the studies was significantly greater than the proportion of women, with the proportion of men ranging from 72.4% to 100%. The Van Hoe *et al.*[17] study had a comparatively lower proportion of men (56% of participants were male). In three studies the sex of patients was not reported.[36,43,49] *Tables 5–7* provide a summary of patient characteristics.

Eighteen studies reported the mean baseline LVEF of the included participants,[15,17,25,27–32,35,36,40,41,43,44,46,47,53] which ranged from LVEF 24% to 62%. All of the studies included patients with chronic CAD, but excluded patients who had experienced a very recent MI or who had an unstable coronary condition. Studies described the extent of vessel disease at baseline in the included patients. The prevalence of three-vessel disease ranged from 21%[25] to 100%.[31] There was, therefore, a greater diversity in baseline levels of disease severity. Four studies[39,41,43,49] did not provide data regarding baseline characteristics, so describing the cohort of included patients accurately is not possible.

Description of index tests

The CMR approach in all of the included studies was either the assessment of contractile reserve (dobutamine stress CMR) or the evaluation of cellular integrity (late gadolinium-enhanced CMR).

The studies evaluating the diagnostic accuracy of stress CMR to detect hibernating myocardium tended to be published earlier than those evaluating late gadolinium-enhanced CMR with the studies of stress CMR published between 1996 and 2005 and of CE CMR between 2000 and 2011. Ten studies evaluated stress CMR[17,27,28,31,34,35,37,39,40,47] and 12 evaluated CE CMR.[15,16,25,29,30,36,38,41,43–46,49] Two studies[32,48] explored the diagnostic accuracy of both CE CMR and stress CMR, but there were insufficient data reported to use the data from the Van Hoe and Vanderheyden[17] study in the analysis of CE CMR. The publication by Kim *et al.*[15] appeared to influence the shift in research investigation from stress CMR to CE CMR. This study was the first to demonstrate a progressive loss of functional recovery with increasing transmural extent of myocardial injury predicted regional functional recovery on a segmental level.

Late gadolinium-enhanced magnetic resonance imaging allows the direct visualisation of the transmural extent of scar at high spatial resolution. This capability of CE CMR to assess the extent of scar in the ventricular wall was considered a valuable advance on the existing stress CMR and other CMR techniques. In this review, we have evaluated stress CMR and CE CMR separately.

The studies used different segmental models to interpret LV segmentation and interpretation of wall motion abnormality. This included an 8-, 9-, 12-, 16-, 17-, 28- and 56-segmental model. The 16-segmental model was used most often and was used in seven of the included studies.[17,29,30,35,36,41,48] The 17-segmental model was recommended in 2002 by the American Heart Association Writing Group on Myocardial Segmentation and Registration for Cardiac imaging.[54] This model was used in three of the more recent studies.[16,25,46] It is unclear if the different segment models used will have influenced the results of this review, and in what way.

TABLE 3 Summary of tests and reference standard: stress CMR

Study details				Test details				
Reference	No. of patients (in analysis)	Country	Follow-up (months)	Segments	Segmental model	Dobutamine dose (μg/kg per minute)	Threshold for viability	Technique to assess LVEF recovery
Baer 1998[27]	43	Germany	4–6	431	8	10	SWT ≥ 2 mm, EDWT ≥ 5 mm	CA
Baer 2000[28]	60 (52)	Germany	4.9	532	28	5–10	SWT ≥ 2 mm EDWT, ≥ 5 mm	CMR
Gunning 1998[31]	30 (23)	UK	3–6	145	9	15	SWT ≥ 2 mm	CMR CA
Gutbertlet 2005[32]	20 (20)	Germany	6	240	12	5–10	SWT ≥ 2 mm, EDWT > 6 mm	CMR
Lauerma 2000[34]	10	Finland	6	86	8	5	SWT ≥ 2 mm	CMR
Martinez 2000[35]	12 (10)	USA	4–6	87	16	Nitroglycerin 0.4 mg	SWT ≥ 2 mm	CMR
Sandstede 1999[37]	27 (25)	Germany	3	207	8	10	Any increase in SWT	CMR
Sayad 1998[39]	10	USA	1–2	26	NR	5–10	SWT increased by > 2 times the SD of measurement technique	CMR
Schmidt 2004[40]	40	Germany	4–6	NR	NR	10	SWT ≥ 2 mm, EDWT ≥ 5 mm	CMR CA
Trent 2000[47]	40 (32)	UK	3–6	346	NR	15	SWT improvement by one grade	CMR
Van Hoe 2004[17]	26 (18)	Belgium	9 (SD 2)	117	16	10	Any increase in SWT	CMR
Wellnhofer 2004[48]	29	Germany	3	288	16	5–10	SWT improvement by one grade	CMR

CA, coronary angiography; EDWT, end-diastolic wall thickness; NR, not reported; SD, standard deviation; SWT, systolic wall thickness.

Positive result		Negative result		Diagnostic accuracy			
True positive	False positive	False negative	True negative	Sensitivity	Specificity	Positive predictive value	Negative predictive value
24	1	3	15	89	94	96	83
24	2	4	22	86	92	92	85
41	41	41	51	50	81	79	56
204	2	2	32	88	89	97	56
43	0	14	29	75	100	100	67
63	8	2	14	97	64	89	88
65	10	41	91	61	90	87	43
25	1	3	14	89	93	96	82
24	2	1	15	96	87	92	93
81	69	25	163	76	70	54	87
56	8	16	37	78	82	88	70
94	14	30	150	76	91	87	83

TABLE 4 Summary of tests and reference standard: CE CMR

Study details				Test details				
Reference	No. of patients (in analysis)	Country	Follow-up (months)	Segments	Segmental model	Gadolinium dose, time after administration (minutes)	Hyper-enhancement (SD above normal intensity)	Technique to assess LVEF
Becker 2008[29]	53	Germany	9	463	16	0.2 mmol/kg, 15	≥ 3	Echocardiography. Increase in resting function by at least one grade
Bondarenko 2007[30]	45 (50)	The Netherlands	3	322	16	0.2 mmol/kg, 10–15	> 5	CMR. Increase in segmental wall thickening of ≥ 1.5 mm
Gutbertlet 2005[32]	20 (20)	Germany	6	240	12	0.4 mmol/kg, 10–12	> 2	CMR wall motion scoring
Hunold 2002[49]	12	Germany	5–6	406	8	0.2 mmol/kg, 8–15	NR	CMR recovery of formally dysfunctional segments
Kim 2000[15]	50 (41)	USA	79 days	804	12	0.2 mmol/kg, NR	> 6	CMR
Kuhl 2006[16]	36 (29)	Germany	6	187	17	0.2 mmol/kg, 15–20	≥ 3	CMR improvement in wall motion score by ≥ 1
Pegg 2010[36]	50 (33)	UK	6	958	16	0.1 mmol/kg, 6	> 2	CMR improvement in regional contraction was defined by an improvement of ≥ 1 functional grade
Sandstede 2000[38]	12	Germany	3	73	8	0.05 mmol/kg, 15	NR	CMR wall motion
Schvartzman 2003[41]	29	USA	6 weeks	207	16	0.2 mmol/kg, 20–30	NR	Echocardiography. Increase in resting function by at least one grade
Selvanayagam 2004[43]	60 (52)	UK	6	612	56	0.125 mmol/kg, 10	> 2	CMR improved systolic contractility
Sharma 2009[44]	40 (8)	USA	5	97		0.15 mmol/kg, 2–5	NR	CMR improved post-vascularisation contractile function: ≥ 15% SWT
Skala 2011[46]	53 (37)[b]	Czech Republic	24	580	17	10 ml, 10	NR	CMR LVEF improvement ≥ 5%
Wellnhofer 2004[48]	29	Germany	3	288	16	0.2 mmol/kg, NR	NR	CMR improvement in wall motion score by ≥ 1
Wu 2007[25]	29 (27)	Japan	17 days	252	17	0.15 µmol/kg, 15	NR	CMR improvement in segmental wall motion

NR, not reported; SD, standard deviation; SWT, systolic wall thickness.

a Based on the percentage extent of hyperenhancement, a hyperenhancement category was determined for each segment related to the 5-point scale proposed by Kim *et al.*:[52] 0% hyperenhancement (category 1), 1–25% hyperenhancement (category 2), 26–50% hyperenhancement (category 3), 51–75% hyperenhancement (category 4) and 76–100% hyperenhancement (category 5).

b Analysis by patient.

	Positive result		Negative result		Diagnostic accuracy			
Cut off for viability[a]	True positive	False positive	False negative	True negative	Sensitivity	Specificity	Positive predictive value	Negative predictive value
< 25%	189	175	38	61	83	26	75	62
< 50%	215	36	12	100	95	42	61	89
< 25%	64	84	21	153	75	65	43	88
< 50%	79	145	6	92	93	38	35	94
< 50%	198	2	2	30	99	94	99	94
< 50%	143	72	7	184	95	72	67	96
< 25%	365	147	60	232	86	61	71	79
< 50%	411	211	14	168	97	44	66	92
≤ 50%	94	27	2	64	98	70	78	97
< 25%	297	126	435	100	41	44	22	19
< 50%	381	228	16	332	96	59	63	95
NR	39	8	1	25	97	76	83	96
< 25%	82	57	19	49	81	46	75	72
< 50%	95	79	6	27	94	25	55	82
< 25%	266	96	77	173	78	64	73	70
< 50%	326	192	17	77	95	29	63	82
< 50%	52	32	3	10	95	24	62	77
< 50%	13	5	2	17	87	77	72	90
< 25%	93	12	31	152	75	93	89	83
< 50%	111	79	13	52	90	52	58	80
< 50%	142	54	12	44	92	45	72	79

TABLE 5 Description of participants: stress CMR

Study	*n* (in analysis)	% male	Mean age (years) (SD)	Medical characteristics, vessel disease (one/two/three)	Mean LVEF % (SD)	Revascularisation	Inclusion criteria	Exclusion criteria
Baer 1998[27]	43	93	58 (9)	One-vessel disease, $n = 13$ Two-vessel disease, $n = 16$ Three-vessel disease, $n = 14$	42 (10)	CABG/PCI	Previous MI (> 4 months since the ischaemic event) and regional LV akinesia or dyskinesia	Unstable angina, congestive HF, atrial fibrillation or a history of sustained ventricular tachycardia. Patients with > 70% diameter restenosis of the infarct-related vessel or > 70% diameter stenosis of the infarct-related bypass graft at follow-up angiography were excluded from the study because recurrent hibernation could not be ruled out
Baer 2000[28]	65 (52)	92	58 (8.8)	75% multivessel disease	41 (10)	CABG/PCI	CAD, infarct age > 4 months. Persisting or dyskinetic infarct region. Severe stenosis of the infarct-related coronary artery, implicating a reduction in resting flow or repetitive ischaemic episodes in the infarct region	Unstable angina. Congestive HF, atrial fibrillation, a permanent pacemaker, a history of multiple MIs or a history of sustained ventricular tachycardia
Gunning 1998[31]	30 (23)	90	61	Three-vessel disease, $n = 30$	24 (8.3)	CABG	LVEF ≤ 35% dyspnoea as a dominant symptom	Significant valve disease; uncontrolled atrial fibrillation; permanent pacemaker; previous coronary bypass
Lauerma 2000[34]	10	80	69	Multivessel disease	NR	CABG	Multivessel CAD and regional wall motion abnormality	NR
Martinez 2000[35]	12 (10)	100	NR	NR	38 (5)	CABG/PCI	Referred for revascularisation; LVEF < 45%	Atrial fibrillation; MI within last 3 weeks
Schmidt 2004[40]	40	93	57	One-vessel disease, $n = 11$ Two-vessel disease, $n = 16$ Three-vessel disease, $n = 13$	42 (10)	CABG/PCI	Previous MI (≥ 4 months since the event)	Instable angina, decompensated left HF, atrial fibrillation, tachycardia or diabetes

Study	*n* (in analysis)	% male	Mean age (years) (SD)	Medical characteristics, vessel disease (one/two/three)	Mean LVEF % (SD)	Revascularisation	Inclusion criteria	Exclusion criteria
Sandstede 1999[37]	27 (25)	88	58	NR	NR	CABG/PCI	Regional LV wall motion abnormalities and associated coronary artery stenosis detected by left ventriculography and coronary angiography	Had a pacemaker, or history of metal fragments, implants or vascular clips, sever arrhythmias, unstable angina pectoris or claustrophobia
Sayad 1998[39]	10	70	NR	NR	NR	CABG/PCI	Segmental wall abnormalities at rest on ventrigulography or echocardiography	Pacemakers, intracranial clips, claustrophobia, atrial fibrillation, ventricular tachycardia, previous CABG, unstable angina, left main disease (> 50%), MI within 3 weeks of procedure or contraindications to dobutamine
Trent 2000[47]	40 (25)	100	60	NR	54 (14.5)	CABG	CAD	NR
Van Hoe 2004[17]	26 (18)	56	63	One-vessel disease, 17% Two-vessel disease, 56% Three-vessel disease, 28%	52 (16)	CABG/PCI	Clinical suspicion of ischaemic heart disease (with or without MI on ECG)	Unstable angina, recent MI (< 7 days old), congestive HF, ventricular arrhythmias, atrial fibrillation or any contraindication for MRI or coronary angiography

ECG, electrocardiogram; MRI, magnetic resonance imaging; NR, not reported; SD, standard deviation.

TABLE 6 Description of participants: CE CMR

Study	*n* (in analysis)	% male	Mean age, years (SD)	Medical characteristics, vessel disease (one/two/three)	Mean LVEF % (SD)	Revascularisation	Inclusion criteria	Exclusion criteria
Becker 2008[29]	55 (53)	83	59	Number of diseased vessels: for those with functional recovery: mean 1.2 (SD 0.3). For those with no functional recovery: 1.1 (SD 0.3)	Baseline LVEF < 40%: for those that had functional recovery, 6 (29%) For those who had no functional recovery, 9 (28%)	CABG/PCI	Patients with LV dysfunction and had to be in sinus rhythm	Patients with non-ischaemic cardiomyopathy or acute coronary syndromes
Bondarenko 2007[30]	50 (45)	84	62	One-vessel disease, 9% Two-vessel disease, 13% Three-vessel disease, 28%	39	CABG	Patients with known CAD and regional wall motion abnormalities without CMR contraindications, who were scheduled to undergo surgical or percutaneous revascularisation	One patient was excluded because coronary artery bypass surgery was accompanied by LV aneurysmectomy
Hunold 2002[49]	12	NR	NR	NR	NR	CABG	NR	NR
Kim 2000[15]	50 (41)	88	63 (11)	NR	43 (13)	CABG/PCI	Scheduled to undergo revascularisation, had abnormalities in regional wall motion	Unstable angina or contraindications to CMR
Kuhl 2006[16]	36 (29)	72	66	Previous MI, 83%; diabetes, 34%; hypertension, 76%; hypercholesterolaemia, 66%; nicotine abuse, 62%; elevated serum creatinine 24%	32 (10)	CABG/PCI	Chronic ischaemic heart disease, regional wall abnormalities and EF < 50%	Severe cardiovascular disease, CPD, kidney disease or peripheral vascular disease impeding revascularisation, pacemaker or defibrillator

Study	*n* (in analysis)	% male	Mean age, years (SD)	Medical characteristics, vessel disease (one/two/three)	Mean LVEF % (SD)	Revascularisation	Inclusion criteria	Exclusion criteria
Pegg 2010[36]	50 (33)	NR	66 (8)	Three-vessel disease, 100%	38 (11)	CABG	Patients with impaired LV function accepted for surgery were recruited if they consented and had no contraindications to CMR or gadolinium contrast. Included patients who needed both elective admissions and patients with recent unstable coronary syndromes requiring inpatient revascularisation	Patients with class IVb angina were excluded
Sandstede 2000[38]	12	83	61 (9)	CAD with hypokinetic or akinetic myocardial regions	NR	CABG/PCI	Hypokinetic or akinetic myocardial regions and associated CAD	MR contraindication
Schvartzman 2003[41]	29	79	62	NR	28	CABG	CAD and wall abnormalities; hypokinetic or akinetic myocardial regions revealed by angiography	History of MI < 8 weeks before either diagnostic imaging or CABG; LV ejection fraction ≥ 50% by echocardiography or CMR, unstable angina and CMR contraindications
Selvanayagam 2004[43]	60 (52)	NR	NR	NR	62 (11)	CABG	Undergoing multivessel CABG	> 75 years, severe pre-existing LV dysfunction, involvement in other clinical trials, MR contraindications, baseline creatinine > 200 µmol/l
Sharma 2009[44]	40 (8)	100	59	From data on 36 patients: One-vessel disease, 10% Two-vessel disease, 20% Three-vessel disease, 60%	26 (8.1)	CABG	Showing symptoms of cardiac failure for more than 3 months	MI, unstable angina pectoris for at least 6 weeks, valvular disease or contraindications to MR

continued

TABLE 6 Description of participants: CE CMR (*continued*)

Study	*n* (in analysis)	% male	Mean age, years (SD)	Medical characteristics, vessel disease (one/two/three)	Mean LVEF % (SD)	Revascularisation	Inclusion criteria	Exclusion criteria
Skala 2011[46]	53 (37)	87	66 (37)	Two-vessel disease, 37% Three-vessel disease, 63%	34.9 (4)	CABG	Stable LVD	MI within the last 6 months; acute coronary syndromes or acute MI; significant valvular disease; chronic atrial fibrillation; contraindications to CMR
Wu 2007[25]	29 (27)	83	66 (10)	Multivessel disease	37 (14)	CABG	Chronic CAD, undergoing surgical revascularisation	Atrial fibrillation, recent (< 6 weeks) MI, unstable angina pectoris, or interventions in the period between different examinations

CPD, chronic pulmonary disease; EF, ejection fraction; LVD, left ventricular dysfunction; NR, not reported; SD, standard deviation.

TABLE 7 Description of participants: stress CMR and CE CMR

Study	*n*	% male	Mean age, years (SD)	Medical characteristics, vessel disease (one/two/three)	Mean LVEF, % (SD)	Revascularisation	Inclusion criteria	Exclusion criteria
Gutbertlet 2005[32]	20	95	63	Diabetes, 50%; hypertension, 60%; hypercholesterolaemia, 65%	28.6 (8.7)	CABG	NR	NR
Wellnhofer 2004[48]	29	93	68 (7)	NR	NR	CABG/PTCA	CAD with stable angina. Ejection fraction <45. At least two adjacent segments with wall motion abnormalities at rest. No infarction within the last 2 months	Contraindications for CMR

NR, not reported; SD, standard deviation.

Stress cardiac magnetic resonance imaging

Twelve studies explored the diagnostic accuracy of stress CMR to identify hibernating myocardium.[17,27,28,31,32,34,35,37,39,40,47,48]

Eleven studies[17,27,28,31,32,34,37,39,40,47,48] used dobutamine to induce cardiac stress and facilitate measurement of contractile reserve. The dose of dobutamine used ranged from 5 to 15 µg/kg per minute, with most studies using between 5 and 10 µg/kg per minute. Two studies[31,47] used the higher dose of 15 µg/kg per minute. One used nitroglycerin (0.4 mg).[35]

The threshold for viability was established in the following way. Systolic wall thickness [SWT (wall motion)] was measured by CMR during rest and stress. Segmental wall thickening was first analysed at rest using a qualitative scoring system with the following scale: 0 = dyskinetic, 1 = akinetic, 2 = severely hypokinetic, 3 = hypokinetic, 4 = normal.

Those segments that were labelled as akinetic or dyskinetic, but which showed SWT of at least 2 mm during dobutamine stress, were classified as viable; otherwise, they were considered to be non-viable. Two studies[17,37] used any change in SWT in akinetic or dyskinetic segments as the threshold for viability. Two studies[47,48] used increase in one grade (see scoring system above) to determine viability. One study[39] used increase in SWT by more than two times the standard deviation of the measurement technique as the threshold for viability. Five studies[27,28,32,40,47] also used a measure of end-diastolic wall thickness (EDWT) in order to identify hibernating myocardium. The cut-off used for EDWT was 5.5–6.0 mm for each study.

Each study performed the second CMR or coronary angiography between 1 and 9 months after revascularisation. The most common follow-up period was approximately 5 months after revascularisation. Differences in timing of the second evaluation were for protocol reasons rather than because it was necessary in clinical practice; the differences in timing may have had some influence on the results, but what this would be is unknown.

The reference standard 'recovery of contractile function' following revascularisation was assessed quantitatively using a 2-mm segmental improvement in SWT from pre- to post-revascularisation CMR at rest in most of the studies. Five studies[17,37,39,47,48] did not define a threshold for SWT, but considered segments that had improved or those that had improved by a grade or a standard deviation of the measurement technique as viable. One study[27] assessed LVEF recovery using coronary angiography. Some studies[27,28,37,40] also included an assessment of viability of myocardial regions, containing multiple segments. A region was defined as viable if ≥ 50% of the affected segments had improved.

Late gadolinium-enhanced cardiac magnetic resonance imaging

Fourteen studies[15,16,25,29,30,32,36,38,41,43,44,46,48,49] evaluated the accuracy of CE CMR to detect myocardial viability. In all of these studies segmental LV recovery following revascularisation served as the reference standard. Two studies[32,48] evaluated stress CMR and CE CMR and sufficient data were reported or provided by authors to enable their inclusion in both meta-analyses.

All of the included CE CMR studies used gadolinium-based contrast agents. There were some differences in technique used, with some variation in dose of gadolinium and in the duration of time between administration of agent and collection of images. The dosage of gadolinium ranged from 0.05 to 0.4 mmol/kg. The most commonly used dosage was 0.2 mmol/kg. Images were obtained 2–30 minutes after administration, most commonly at 15 minutes.

Viability is determined by the extent of hyperenhancement and a hyperenhancement category established for each segment related to the 5-point scale proposed by Kim *et al.*:[52] 0% hyperenhancement (category 1), 1–25% hyperenhancement (category 2), 26–50% hyperenhancement (category 3), 51–75% hyperenhancement (category 4), and 76–100% hyperenhancement (category 5).

The threshold for determining viable myocardium was reported as 50% of LV wall hyperenhancement, with segments with more than 50% hyperenhancement considered non-viable. Seven studies[15,29,30,36,41,43,44] also reported the results at 25% of LV wall hyperenhancement. The results for both the 25% and 50% thresholds are presented in *Table 7*.

The follow-up assessment of LV function occurred between 19 days and 2 years after revascularisation in the included studies. Most of the studies undertook follow-up assessment 6 months after revascularisation, but the variation in the studies may influence heterogeneity in the analysis. There is a suggestion that segmental recovery of viable myocardium may take several months and early assessment of recovery may miss later recovery.

The reference standard, 'recovery following revascularisation', was assessed using CMR (echocardiography was used in two studies)[27,41] to examine segmental wall thickening and make comparisons with preoperative wall motion scores. Recovered segments were those in which there was an increase in segmental wall thickening compared with preoperative segmental functioning by one grade or score,[16,29,32,36,41,48] by any improvement in segmental wall motion,[25,38,43] 15% improvement in contractile function,[44] $\geq$ 5% improvement in LVEF[46] or increased wall thickening of > 1.5 mm.[30]

Diagnostic accuracy for detection of viable myocardium

Meta-analysis of diagnostic parameters

Bivariate random-effects regression analyses were performed in STATA/IC 12.0 (2012; Stata Corporation, College Station, TX, USA) using the program 'metandi' to generate pooled accuracy estimates of sensitivity, specificity, positive likelihood ratios (LR+), negative likelihood ratios (LR–) and diagnostic odds ratios (DORs).

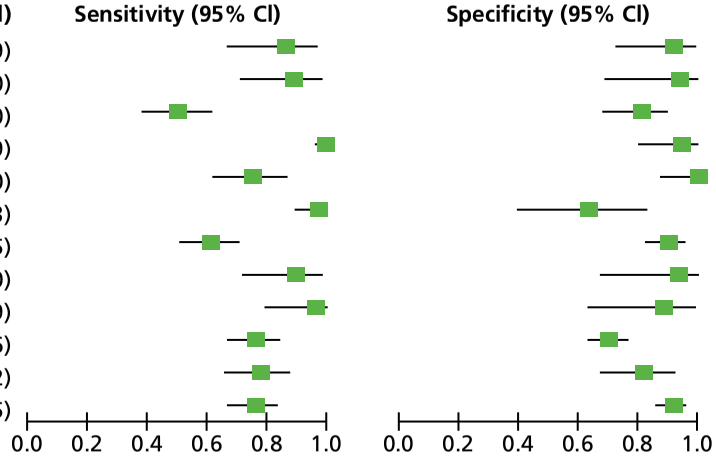
As described by Harbord *et al.*,[55] the bivariate regression method assumes that the sensitivity values from individual studies (after logit transformation) within a meta-analysis are approximately normally distributed around a mean value with a certain amount of variability around this mean. This is a random-effects approach. This variation in underlying sensitivity estimates between studies can be related to undetected differences in study population, differences in implicit threshold (cut-off) or unnoticed variations in the index test protocol. These considerations also apply to specificity estimates. The potential presence of a (negative) correlation between sensitivity and specificity within studies is addressed by explicitly incorporating this correlation into the analysis. The combination of two normally distributed outcomes, the logit-transformed sensitivity and specificity values, while acknowledging the possible correlation between them, leads to the bivariate normal distribution. The bivariate approach overcomes the problems associated with simple pooling (i.e. weighted average) of sensitivity and specificity estimates.

Heterogeneity is usually a concern with meta-analyses and refers to a high degree of variability in accuracy estimates across studies. Heterogeneity could be a result of differences in thresholds, the prevalence of drug resistance, the populations studied, assay methods or reference standard tests. The reasons for the heterogeneity were investigated by pre-specified subgroup (stratified) analysis. In the subgroup analysis, the data were stratified according to the type of CMR tested (CE CMR vs. stress CMR) to determine if accuracy varied across subgroups.

Stress cardiac magnetic resonance imaging

Data from 12 studies[17,27,28,31,32,34,35,37,39,40,47,48] were used in the meta-analysis evaluating the diagnostic accuracy of stress CMR with recovery following revascularisation as the reference standard.
The threshold for determining viability was SWT of 2 mm during cardiac stress in akinetic or dyskinetic myocardial segments.

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Baer 2000[28]	24	2	4	22	0.86 (0.67 to 0.96)	0.92 (0.73 to 0.99)
Baer 1998[27]	24	1	3	15	0.89 (0.71 to 0.98)	0.94 (0.70 to 1.00)
Gunning 1998[31]	41	12	41	51	0.50 (0.39 to 0.61)	0.81 (0.69 to 0.90)
Gutbertlet 2005[32]	204	2	2	32	0.99 (0.97 to 1.00)	0.94 (0.80 to 0.99)
Lauerma 2000[34]	43	0	14	29	0.75 (0.62 to 0.86)	1.00 (0.88 to 1.00)
Martinez 2000[35]	63	8	2	14	0.97 (0.89 to 1.00)	0.64 (0.41 to 0.83)
Sandstede 1999[37]	65	10	41	91	0.61 (0.51 to 0.71)	0.90 (0.83 to 0.95)
Sayad 1998[39]	25	1	3	14	0.89 (0.72 to 0.98)	0.93 (0.68 to 1.00)
Schmidt 2004[40]	24	2	1	15	0.96 (0.80 to 1.00)	0.88 (0.64 to 0.99)
Trent 2000[47]	81	69	25	163	0.76 (0.67 to 0.84)	0.70 (0.64 to 0.76)
Van Hoe 2004[17]	56	8	16	37	0.78 (0.66 to 0.87)	0.82 (0.68 to 0.92)
Wellnhofer 2004[48]	94	14	30	150	0.76 (0.67 to 0.83)	0.91 (0.86 to 0.95)



	Sensitivity		Specificity	
Pooled weight	**82.2**	**(73.2 to 88.7)**	**87.1**	**(80.4 to 91.7)**

FIGURE 3 Mean weighted sensitivity and specificity for stress CMR. FN, false negative; FP, false positive; TN, true negative; TP, true positive.

The mean weighted sensitivity and specificity for stress CMR are provided in *Figure 3*. Gunning *et al.*[31] had a lower sensitivity [50%, 95% confidence interval (CI) 39% to 61%]. The patients in this study had the lowest mean LVEF (24%) and all participants had three-vessel CAD. This may have resulted in reduced sensitivity of the test. It has been suggested that the more profound ultrastructural changes and loss of contractile protein in areas of dysfunctional but viable myocardium may reduce the chance of eliciting a dobutamine-stimulated contraction reserve.[28,31]

Late gadolinium-enhanced cardiac magnetic resonance imaging

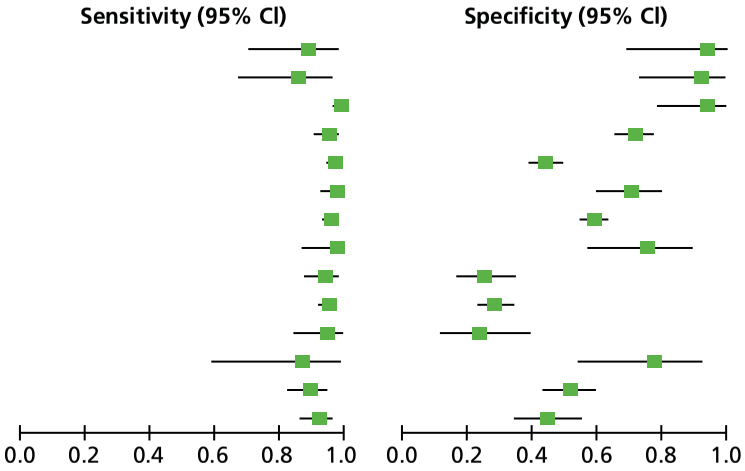
Data from 14 studies were used in the meta-analysis evaluating the diagnostic accuracy of CE CMR with recovery following revascularisation as the reference standard.[15,16,25,29,30,32,36,38,41,43,44,46,48,49] The threshold for determining viability was $\leq 50\%$ of LV wall hyperenhancement.

The mean weighted sensitivity and specificity for CE CMR, with recovery following revascularisation as the reference standard, are provided in *Figure 4*. Specificity was lower in the studies of Sharma *et al.*,[44] Schvartzman *et al.*[41] and Selvanayagam *et al.*[41,43,44] (24%, 25% and 29% respectively). The range for the remaining studies was 44–94%.

Characteristics of these three studies may have influenced the accuracy of the findings. Schvartzman *et al.*[25] had a very short follow-up between initial CMR and follow-up CMR to determine recovery following revascularisation (6 weeks). Only one other study[25] had a shorter follow-up (17 days), and it also had a lower specificity (60%). The study by Sharma *et al.*[44] was one of the smallest studies, with only eight patients and 97 segments included in the analysis.

There may be a number of reasons for the low specificity of CE CMR. The reduced accuracy of CMR in identifying the non-viable myocardium may be a consequence of seeking to diagnose myocardial viability in segments without full-thickness hyperenhancement. The cut-off of 50% wall thickness hyperenhancement to differentiate viable from non-viable myocardium will have meant that the included segments may have incorporated those segments with partial enhancement. It has also been suggested that different degrees of wall motion abnormalities have a major impact on myocardial recovery, with segments showing akinesia demonstrating the best recovery.[21] The lack of the ability to show contractile recruitability with stress (which makes stress echocardiography and stress CMR specific) is another reason why CE CMR may have a lower specificity.

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Becker 2008[29]	24	1	3	15	0.89 (0.71 to 0.98)	0.94 (0.70 to 1.00)
Bondarenko 2007[30]	24	2	4	22	0.86 (0.67 to 0.96)	0.92 (0.73 to 0.99)
Gutbertlet 2005[32]	198	2	2	30	0.99 (0.96 to 1.00)	0.94 (0.79 to 0.99)
Hunold 2002[49]	143	72	7	184	0.95 (0.91 to 0.98)	0.72 (0.66 to 0.77)
Kim 2000[15]	411	211	14	168	0.97 (0.95 to 0.98)	0.44 (0.39 to 0.49)
Kuhl 2006[16]	94	27	2	64	0.98 (0.93 to 1.00)	0.70 (0.60 to 0.79)
Pegg 2010[36]	381	228	16	332	0.96 (0.94 to 0.98)	0.59 (0.55 to 0.63)
Sandstede 2000[38]	39	8	1	25	0.97 (0.87 to 1.00)	0.76 (0.58 to 0.89)
Schvartzman 2003[41]	95	79	6	27	0.94 (0.88 to 0.98)	0.25 (0.18 to 0.35)
Selvanayagam 2004[43]	326	192	17	77	0.95 (0.92 to 0.97)	0.29 (0.23 to 0.34)
Sharma 2009[44]	52	32	3	10	0.95 (0.85 to 0.99)	0.24 (0.12 to 0.39)
Skala 2011[46]	13	5	2	17	0.87 (0.60 to 0.98)	0.77 (0.55 to 0.92)
Wellnhofer 2004[48]	111	79	13	85	0.90 (0.83 to 0.94)	0.52 (0.44 to 0.60)
Wu 2007[25]	142	54	12	44	0.92 (0.87 to 0.96)	0.45 (0.35 to 0.55)



	Sensitivity		Specificity	
Pooled weight	**95.5**	**(94.1 to 96.7)**	**53.0**	**(40.4 to 65.2)**

FIGURE 4 Late gadolinium-enhanced CMR with recovery following revascularisation as the reference standard. FN, false negative; FP, false positive; TN, true negative; TP, true positive.

Pooled summary estimates of diagnostic parameters for different tests

Ten studies[16,25,28,31,32,35,40,44,46,49] also tested other index tests as well as CE CMR and/or stress CMR. These included PET,[40,49] SPECT[16,25,31,32,44,46] and echocardiography,[28,35] with recovery of LV function following revascularisation as the reference standard. These data were pooled with the results from a previously published systematic review[22] in order to estimate the diagnostic accuracy of other tests compared with CMR. We also undertook a sensitivity analysis, testing the effect of Schmidt *et al.*[40] on the results. This was because of uncertainty that some of the patients may also have been in included in another study[28] and, therefore, included twice in the meta-analysis. There was a non-significant difference in the pooled estimate with the exclusion of Schmidt *et al.*[40] *Table 8* shows the estimated pooled summary estimates of diagnostic parameters for different tests.

TABLE 8 Pooled summary estimates of diagnostic parameters for different tests

Test	Number of studies	Sensitivity (95% CI)	Specificity (95% CI)	Pooled LR+ (95% CI)	Pooled LR– (95% CI)	Pooled DOR (95% CI)
CE CMR	14	95.5 (94.1 to 96.7)	53.0 (40.4 to 65.2)	2.03 (1.53 to 2.69)	0.08 (0.05 to 0.13)	24.33 (11.6 to 51.1)
Stress CMR	12	82.2 (73.2 to 88.7)	87.1 (80.4 to 91.7)	6.35 (4.12 to 9.80)	0.20 (0.13 to 0.31)	31.2 (15.7 to 61.9)
Stress CMR[a]	11	80.6 (71.4 to 87.4)	87.0 (79.9 to 91.9)	6.21 (3.94 to 9.80)	0.22 (0.15 to 0.33)	27.9 (14.1 to 55.5)
SPECT	13	85.1 (78.1 to 90.2)	62.1 (52.7 to 70.7)	2.25 (1.74 to 2.89)	0.24 (0.15 to 0.37)	9.41 (5.05 to 17.5)
PET	4	94.7 (90.3 to 97.2)	68.8 (50.0 to 82.9)	3.04 (1.80 to 5.12)	0.07 (0.05 to 0.13)	39.9 (21.1 to 75.6)
Echocardiography	12	77.6 (70.7 to 83.3)	69.6 (62.4 to 75.9)	2.55 (2.06 to 3.16)	0.32 (0.24 to 0.41)	7.96 (5.31 to 11.9)

a Excluding Schmidt *et al.*[40]

Chapter 4 Assessment of cost-effectiveness

This chapter details the methods and results of the health economic model, which has been developed to compare different strategies for diagnostic pathways for patients with ischaemic cardiomyopathy. It includes a brief review of existing economic evaluations and a detailed explanation of the methods and results of a de novo economic model. *Review of cost-effectiveness evidence* presents the results of the systematic review of economic literature. *Independent economic assessment methods* presents the modelling approach adopted to estimate the cost-effectiveness of different diagnostic pathways. The results of the analysis are presented in *Results of the independent economic assessment* and the discussion of the results is presented in *Discussion of the cost-effectiveness results*.

Review of cost-effectiveness evidence

The objective of this review was to identify and evaluate studies exploring the cost-effectiveness of CMR for patients with ischaemic cardiomyopathy.

Identification of studies

Search strategy

Studies were identified by searching the following electronic databases:

- MEDLINE(R) In-Process & Other Non-Indexed Citations and MEDLINE(R) (Ovid) 1948 to August 2012
- EMBASE (Ovid) 1980 to August 2012
- SCI Expanded (Web of Science) 1899 to August 2012
- Conference Proceedings Index – Science (Web of Science) 1990 to August 2012
- NHS EED (Wiley Interscience) 1995 to August 2012
- HTA database (Wiley Interscience) 1995 to August 2012
- DARE (Wiley Interscience) 1995 to August 2012
- PsycINFO (Ovid) 1806 to August 2012
- BIOSIS Previews (Web of Science) 1982 to August 2012
- Allied and Complementary Medicine (AMED) database (Ovid) 1985 to August 2012
- Health Economic Evaluations Database (HEED; OHE-IFPHA) 1967 to August 2012.

Sensitive keyword strategies using free text and, where available, thesaurus terms using Boolean operators and database-specific syntax were developed to search the electronic databases. Synonyms relating to the condition (e.g. viable myocardium) were combined with sensitive economic evaluations (where applicable) or quality-of-life (QoL) search filters aimed at restricting results to economic and cost-related studies (used in the searches of MEDLINE, BIOSIS Previews and EMBASE).

To identify additional published, unpublished and ongoing studies, grey literature was also searched. The reference lists of all relevant studies (including existing systematic reviews) were hand-searched and a citation search of relevant articles (using the Web of SCI Expanded) was undertaken to identify articles that cite the relevant articles.

All identified citations from the electronic searches and other resources were imported into and managed using the Reference Manager bibliographic software (version 12.0; Thomson Reuters, Philadelphia, PA, USA).

Inclusion and exclusion criteria

Studies were selected for inclusion according to predetermined inclusion and exclusion criteria. Studies were included if they reported an economic evaluation of diagnostic pathways for patients with

ischaemic cardiomyopathy and estimated the benefits in terms of life-years gained (LYGs) or quality-adjusted life-years (QALYs).

Studies that performed economic evaluations alongside trials were excluded if they did not extrapolate the outcomes beyond the trial duration, as these economic analyses are only valid for the trials under consideration. Studies that were considered to be methodologically unsound, which were not reported in sufficient detail to extract costs and outcome estimates (including abstracts) or which did not report an estimate of cost-effectiveness (e.g. costing studies) were also excluded. Papers not published in the English language were also excluded.

The inclusion of potentially relevant articles was undertaken using a two-step process. First, all titles were examined for inclusion by one reviewer (PT) and any citations that clearly did not meet the inclusion criteria were excluded. Second, all abstracts and full-text articles were examined independently by two reviewers (PT and ST). Any disagreements in the selection process were resolved through discussion.

Quality assessment strategy

The methodological quality of each included study was assessed using a combination of key components of the Drummond and Jefferson checklist for economic evaluations,[56,57] together with the Eddy checklist for mathematical models used in technology assessments.[58] The use of the checklist ensured a consistent approach to assessing the quality of each economic evaluation.

Results of cost-effectiveness review

The electronic database literature searches identified 351 potentially relevant publications, of which two met the inclusion criteria. However, the grey literature identified two additional relevant publications on economic evaluations of PET for myocardial viability. Even though these studies were not identified in the initial database search, they provide valuable insight into modelling cost-effectiveness of diagnostic imaging techniques for myocardial viability. A flow chart describing the process of identifying relevant literature can be found in *Figure 5*. The details of these relevant studies including an assessment of methodological quality are provided below.

Dussault *et al.*[59]

Dussault *et al.*[59] performed an exploratory analysis of the potential impact of PET on the detection of viable myocardium in a hypothetical cohort of male patients with a LVEF < 30%, as part of their HTA of PET (AÉTMIS). The model compared PET with clinical decision as a second-line viability test in case of first-line equivocal SPECT thallium scans. Expert clinicians at Hôpital Laval in Québec were consulted for the purpose of developing decision trees and determining the explicit probabilities for the variables. For each strategy, the proportion of surviving individuals and the overall costs were estimated using a 5-year time horizon and a health-care system perspective. Costs of viability tests, medical services and reimbursement of professional services were included as costs, while patients' mean probability of survival at 5 years was used as a measure of clinical effectiveness. Monte Carlo analysis, used to estimate the mean and incremental cost and efficacy intervals to compare the PET option with the no-PET option, suggested that the PET strategy was cost-effective.

Comments

The sources of data used in the analysis were predominantly expert opinion, owing to the lack of published data, which has implications on the robustness of the findings. The model did not estimate QALYs as the measure of clinical effectiveness and the authors report that, for the sake of simplicity, the costs and consequences have not been discounted. Also, the analysis used PET as a second-line viability test rather than as the only test. Thus, these cost-effectiveness analysis results are not applicable to the current decision problem.

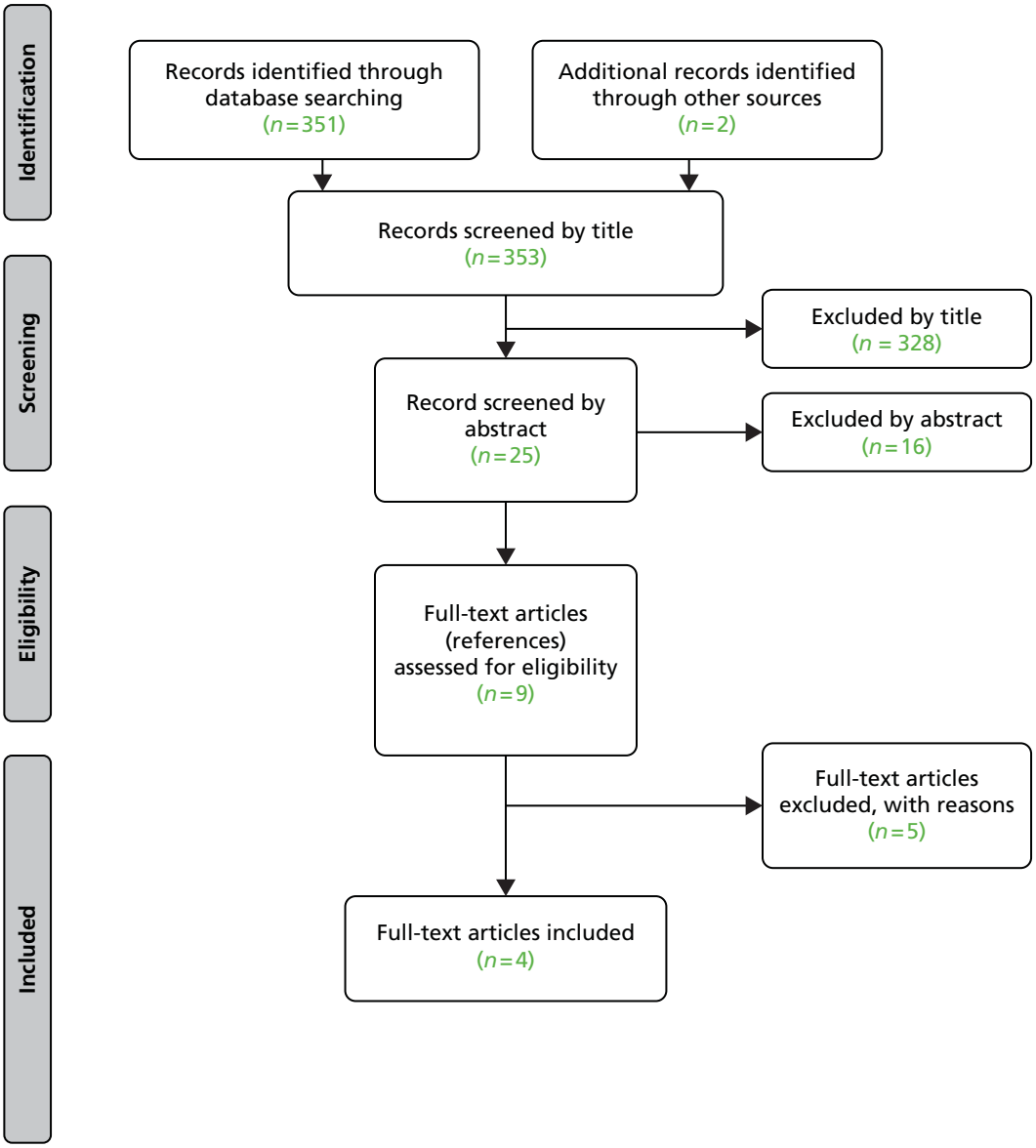


FIGURE 5 Study flow chart: cost-effectiveness.

Miles *et al.*[60]

Miles *et al.*[60] estimate the cost implications of PET for myocardial viability from an Australian perspective. Their estimation of costs is based on the Institute of Clinical PET (ICP) Cardiology Task Force's decision tree analysis and analysis by Beanlands *et al.*[61] The analysis based on ICP decision tree model, assuming a prevalence of viable myocardium of 0.71 and specificity for PET of 0.74, indicate that the PET strategy would produce cost savings of US$300.24 per patient compared with a strategy based on coronary angiography. Sensitivity analyses indicate that PET would remain cost-effective for values of prevalence of up to 0.76 or values for specificity of PET as low as 0.63. The authors also report that analysis based on data from Beanlands *et al.*[61] ($n = 87$) on patient management indicate a cost saving of US$2069.65 per patient examined with PET.

Comments

Miles *et al.*[60] used previous models to estimate the costs of PET imaging for assessing myocardial viability and concluded that a PET strategy would be cost saving. However, the analysis was based on data from studies reported in 1994 and 1997 which might no longer be relevant. Furthermore, the analysis did not include impact on clinical effectiveness and the cost-effectiveness results are not reported.

Jacklin *et al.*[62]

Jacklin *et al.*[62] conducted an economic analysis of PET for selecting patients with hibernating myocardium for revascularisation in the UK. The model compared three management strategies: (1) CABG surgery for all patients, (2) medical therapy for all patients and (3) a PET-guided strategy. The prevalence of significant hibernating myocardium was estimated at 50%, while the sensitivity and specificity of PET were both estimated as 80%. Costs and survival data were estimated from Guy's and St. Thomas' Hospitals while the prevalence of hibernating myocardium and PET diagnostic characteristics were estimated from the literature. A decision-analysis model was developed to estimate the costs and outcomes (measured as LYGs) of treating 1000 hypothetical patients using the model for three different strategies. The model used a 1-year time horizon and reported that medical therapy had the lowest cost, PET was the most cost-effective option (with £77,186 per LYGs compared with medical therapy) while CABG was the most expensive and least beneficial of the strategies. One-way sensitivity analysis performed to understand the impact of individual parameters produced similar results.

Comments

The sources of clinical data were non-randomised cohort studies and this is likely to limit the conclusions. The model used LYGs as the measure of effectiveness and did not take QoL into account to perform cost–utility analysis. Furthermore, the model used only a 1-year time horizon, which does not take the full lifetime of the costs and outcomes into account. Therefore, the validity of findings from this study is still uncertain.

The Medical Advisory Secretariat Health Technology Assessment report[63]

The Medical Advisory Secretariat HTA report[63] developed an economic model to compare the cost-effectiveness of myocardial viability assessment using three different strategies: (1) SPECT and clinical decision, (2) PET only and (3) SPECT followed by PET when SPECT results are equivocal. For each strategy, the probability of a positive test and the probability of an individual surviving 5 years were estimated, often using expert opinion. Costs from health system perspective, i.e. costs of diagnostic tests, treatment costs and other hospital services costs, were considered. For each strategy, Monte Carlo analyses were used to estimate the mean cost and the probability of survival at 5 years. Incremental costs and clinical effectiveness analysis concluded that PET alone or SPECT plus PET would probably result in lower cost and better 5-year survival than SPECT alone. Sensitivity analyses were also performed to understand the impact of key model parameters on the results.

Comments

As the sources of data used in the analysis were predominantly expert opinion, there is uncertainty in the robustness of the findings. Again, the analysis did not estimate QALYs and, thus, the cost-effectiveness analysis results are not applicable to the current decision problem.

Cost-effectiveness review summary

Although four cost-effectiveness analyses studies were identified via the literature searches, there are a number of limitations associated with generalising the findings of these included studies.

None of the studies identified performed cost–utility analysis, the preferred approach for estimating cost-effectiveness in UK. Three studies[59,62,63] reported incremental cost per life-year gained, while one study[60] reported only the cost savings.

None of the studies compared all the relevant diagnostic strategies. Two studies[59,63] compared PET with SPECT (including PET as a second-line viability test), while the two other studies[60,62] compared PET with medical therapy and CABG. In addition, the diagnostic accuracy of these strategies was elicited using expert opinion because of a lack of evidence. Given the current decision problem is to identify the optimal diagnostic pathway, the cost-effectiveness analysis needs to include all potential diagnostic strategies.

The analysis reported by Jacklin *et al.*[62] was based on a single non-randomised cohort study, while the other studies[59,60,63] included data from expert opinion. This was because of a lack of published data on the impact of viability assessment and revascularisation on the long-term clinical outcomes of patients. This scarcity of data about patient outcomes (such as survival, hospitalisation and QoL) is a significant barrier in estimating the cost-effectiveness of diagnostic pathways for myocardial viability assessment. Although there have been studies recently that provide this information, assumptions would need to be made about their long-term effects beyond the trial duration.

The appropriate time horizon of the model for estimating the cost-effectiveness is not clear. One study used a 1-year time horizon,[62] two studies[59,63] used a 5-year horizon and the time horizon was unclear in the other study.[60] Choosing the time horizon is a key issue, especially when assumptions need to be made about the extrapolation of patient outcomes.

However, despite the differences in the data used, all four studies used a similar modelling approach. The studies used a cohort model, the proportion of patients with viable myocardium modelled using prevalence, and the patients identified by the diagnostic strategies as viable undergoing revascularisation. The costs and outcomes (usually measured as survival or LYGs) were then estimated for the different strategies to estimate the cost-effectiveness.

A de novo economic model was developed based on these studies using the diagnostic accuracy data from meta-analysis, patient outcomes and UK cost data from literature as detailed in *Independent economic assessment methods*.

Independent economic assessment methods

This section details the methods and assumptions of the de novo economic model constructed to evaluate the cost-effectiveness of several potential diagnostic pathways for identifying patients with viable myocardium.

Objectives

The objectives of the cost-effectiveness analysis were to:

1. estimate the cost-effectiveness of diagnostic pathways for assessing patients with ischaemic cardiomyopathy to identify patients with viable myocardium with a view to revascularisation, in terms of the cost per QALY gained by each strategy
2. identify the optimal diagnostic imaging pathway for investigating patients with ischaemic cardiomyopathy (to identify patients with viable myocardium) and estimate the impact of CMR in terms of cost-effectiveness with reference to the National Institute for Health and Care Excellence (NICE) threshold for willingness to pay per QALY gained
3. identify the critical areas of uncertainty in these imaging pathways where future research would produce most benefit and recommend specific primary research designs to address the uncertainty.

The costs and benefits of diagnostic testing

The aim of these diagnostic pathways is to assess patients with ischaemic cardiomyopathy in order to identify those with viable myocardium with a view to revascularisation. The clinical challenge is to identify patients with viable myocardium who have the potential to recover if revascularised and to ensure that these patients are appropriately treated with surgical or catheter-based coronary intervention, and that those with non-viable myocardium in the target area for revascularisation are not subjected to unnecessary intervention.

The main benefits of diagnostic testing relate to identification and treatment of patients with potential for revascularisation using either PCI or CABG. The main disadvantages are the risks associated with adverse events of unnecessary revascularisation. The direct costs of diagnostic management include the costs of diagnostic testing, the costs of investigation and the subsequent costs of providing treatment (revascularisation or medical therapy). The suboptimal nature of the diagnostic tests (i.e. sensitivities and specificities below 100%) means that some patients with viable myocardium will not receive revascularisation and, similarly, some patients without viable myocardium will receive revascularisation, probably unnecessarily, based on the potential lack of benefit from revascularisation, its costs and its risk of mortality. A de novo economic model was built to analyse the effect of different diagnostic management pathways on these costs and benefits.

The decision-analysis model structure

A de novo economic model was developed using Microsoft Excel software (2007; Microsoft Corporation, Redmond, WA, USA) to explore the costs and health outcomes associated with different diagnostic pathways. The economic perspective of the model is the NHS in England and Wales with the structure of the model shown in *Figure 6*.

The different diagnostic pathways were applied to a hypothetical cohort of patients with ischaemic cardiomyopathy. It was assumed that the diagnostic pathway would identify patients with viable myocardium and that the probability of successful identification of viable myocardium and non-viable myocardium was determined by the overall accuracy of the diagnostic pathway. It was assumed that patients diagnosed with viable myocardium would be managed promptly by revascularisation and that the patients diagnosed with non-viable myocardium would be on medical therapy. The model assigned each patient a risk of death and rehospitalisation depending upon whether or not the patient was truly viable and whether or not the patient had received revascularisation. Each patient then accrued lifetime QALYs. Health-care costs were also accrued through measuring diagnostic costs and treatment costs, depending on the pathway and the patient's treatment status. Details of these are outlined below.

Model structure: A decision-analytic model was developed to estimate the costs and health outcomes associated with different diagnostic pathways to identify viable myocardium in a hypothetical cohort of patients with ischaemic cardiomyopathy. The model took a lifetime horizon and the economic perspective of the model was the NHS in England and Wales.

Population: The population comprised patients with ischaemic cardiomyopathy, characterised by extensive CAD and reduced LVEF, including both those with viable myocardium and non-viable myocardium.

Diagnostic pathways: There are five main imaging methods available to assess for viable myocardium: (1) echocardiography, (2) PET, (3) SPECT, (4) CE CMR and (5) stress CMR. Pathways including combinations (i.e. more than one) of these tests were not evaluated as they are not clinically relevant in UK.

Patient management: Patients diagnosed with non-viable myocardium were assumed to be on medical therapy, while the patients diagnosed with viable myocardium were assumed to receive revascularisation.

Time horizon: A lifetime time horizon of 40 years was used. Patients progressed through the model until they either died or reached the end of the 40-year time horizon.

Discount rate: Both the costs and QALYs were discounted at an annual discount rate of 3.5%, as recommended by NICE.

The key modelling methods together with the evidence sources and assumptions used to populate the model are discussed in detail in *Prevalence of viable myocardium, Selection of pathways, Sensitivity and specificity of diagnostic pathways in the model* and *Patient management after diagnosis*.

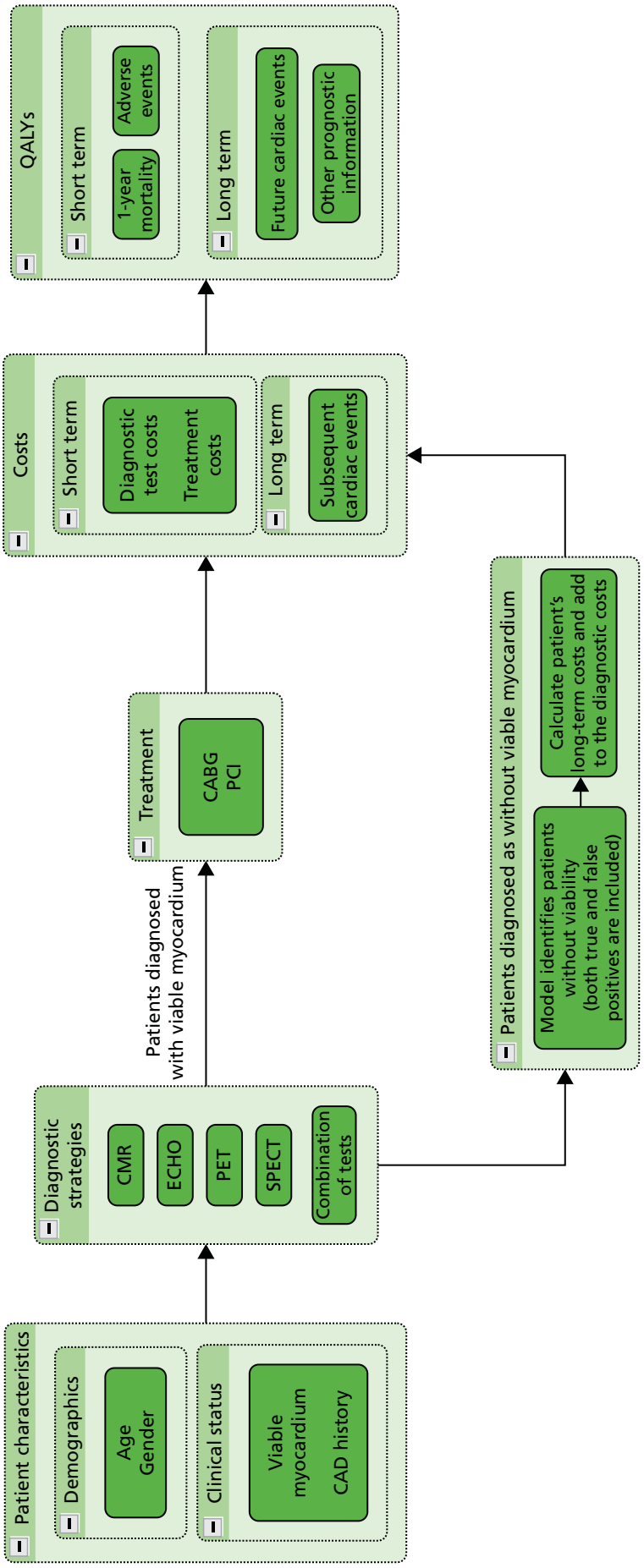


FIGURE 6 Structure of the cost-effectiveness model.

Prevalence of viable myocardium

In a study reported by Al-Mohammad *et al.*,[7,8] the prevalence of viable myocardium in patients with ischaemic heart disease was around 45–55% and the prevalence of LVEF was 30%. These values are similar to those reported in other studies.[64,65] In the economic model, the prevalence of viable myocardium is assumed to be 50% (95% CI 45% to 55%).

Selection of pathways

There are five main imaging methods available to assess for viable myocardium: (1) echocardiography, (2) PET, (3) SPECT, (4) stress CMR and (5) CE CMR. With such a range of techniques available to assess patients for viable myocardium, the choice of diagnostic imaging pathway is often dictated by a number of factors.

Individual hospitals may have access to different types of imaging tests and relevant expertise, with some hospitals being equipped to deliver only one modality while others may have a choice of several. Furthermore, there may be differences in the availability of some tests and, therefore, the choice of which diagnostic pathway to use may depend on the balance of accuracy, availability and cost. For these reasons it was felt important to model all the imaging tests. This would allow decision-makers to identify the pathway that most closely resembled their local setting, and to see how changing to another pathway may affect their costs and QALYs.

The diagnostic pathways were chosen to include all the real-life pathways in clinical practice, i.e. to incorporate the variation of different hospital protocols, regionally and internationally. Pathways including two or more tests are not considered for evaluation in the economic model as, although there might be instances where more than one test is used to assess viability, they are not used regularly in clinical practice.

The single-test pathways include the five main imaging methods (echocardiography, PET, SPECT, stress CMR and CE CMR). Two hypothetical strategies, a 'discharge everyone without testing or revascularisation' strategy and a 'revascularise everyone' strategy are also analysed.

After extensive discussions with the clinical expert group, the following pathways were chosen to be included in the primary analysis:

1. discharge all patients home without testing or treatment
2. echocardiography
3. stress CMR
4. CE CMR
5. SPECT
6. PET
7. treat all patients without testing.

It should be noted that, in clinical practice, the imaging pathways are much more complex with a lot of subjective clinical judgement based on individual patient's situation. Multiple diagnostic tests are often used to detect the presence of viable myocardium; however, the clinical decision-making rules behind the use of multiple tests are complex and subject to variation. Therefore, for the purposes of this evaluation, the single diagnostic test pathways provided above are assumed to be representative of the protocols followed in most hospitals, both in the UK and elsewhere.

The results of multiple test pathways are not included in the analysis for a number of reasons. First, it is not clear what proportion of patients would be subjected to multiple tests and there tend to be local variations in the diagnostic pathways used. Second, these multiple test pathways can be represented as either (1) reinforcement of positive diagnosis, i.e. the second test is performed only if the first test indicated viable myocardium, or (2) confirmation of negative result, i.e. second test is performed only

if the first test indicated non-viability. It is not clear whether or not the decision to offer the patient revascularisation will be based on the result from the second test in case of non-concordance between tests. In order to estimate the combined diagnostic accuracy of combination of tests, the correlation between the result of the initial test and the secondary test needs to be estimated. There are no data on the correlation between tests and, in the absence of evidence, postulating correlation factors might lead to bias. Furthermore, during probabilistic sensitivity analysis (PSA), the sensitivities and specificities of the combined tests need to be estimated from the samples of joint distributions of the diagnostic parameters for each test to preserve the correlation. Given all these limitations in the evidence base and the relative scarcity in the use of multiple diagnostic tests in UK, the analysis was limited to pathways with single diagnostic tests.

Sensitivity and specificity of diagnostic pathways in the model

The methodology used for determining the sensitivity and specificity of each non-invasive imaging test is given in *Chapter 3, Diagnostic accuracy for detection of viable myocardium*.

Table 9 shows the estimates of sensitivity and specificity for each test strategy and the sources for these estimates. The meta-analysis data were selected because the point estimates of sensitivity and specificity varied in the expected manner when different test types (a different variation of the test for viable myocardium) were used. The mean values of the posterior distributions for sensitivity and specificity were used in the deterministic analysis.

Patient management after diagnosis

It was assumed that, after the diagnostic pathway had been applied, the subsequent progress of each patient would depend on whether or not the patient had viable myocardium, and, if viable myocardium was identified, whether or not the patient was revascularised. The patients can be classified into four groups, as shown in *Figure 7*, based on their true status and the diagnosis as:

(a) viable and revascularised, i.e. diagnosed correctly as viable
(b) viable but not revascularised, i.e. diagnosed wrongly as non-viable
(c) non-viable and revascularised, i.e. wrongly diagnosed as viable
(d) non-viable and not revascularised, i.e. diagnosed correctly as non-viable.

It was assumed that patients diagnosed with non-viable myocardium would be on medical therapy and that the patients diagnosed with viable myocardium would be managed promptly by revascularisation, returning to medical therapy after the revascularisation. Although there are multiple variants of medical therapy and two main variants of revascularisation, they are represented in the model as single entities.

TABLE 9 Estimates of sensitivity and specificity for the diagnostic tests

Strategy	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	Source
Discharge everyone without testing or revascularisation	0	1	Theoretical
Echocardiography	77.6 (70.7 to 83.3)	69.6 (62.5 to 75.9)	Meta-analysis
Stress CMR	82.2 (73.2 to 88.7)	87.1 (80.4 to 91.7)	Meta-analysis
CE CMR	95.5 (94.1 to 96.7)	53.0 (40.4 to 65.2)	Meta-analysis
SPECT	85.1 (78.1 to 90.2)	62.1 (52.7 to 70.7)	Meta-analysis
PET	94.7 (90.3 to 97.2)	68.8 (50.1 to 82.9)	Meta-analysis
Revascularise everyone	1	0	Theoretical

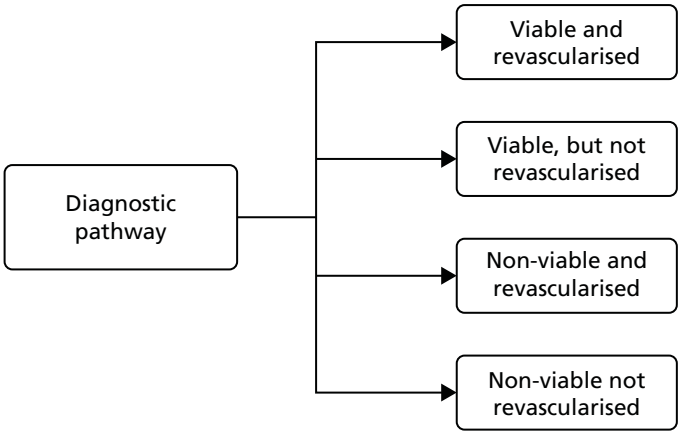


FIGURE 7 Patient groups after diagnosis.

The clinical systematic review identified considerable heterogeneity among included studies for medical therapy after diagnosis. Clear descriptions of the medical therapy were not always provided in the studies identified in the systematic review, which made it difficult to estimate costs. This lack of detail also meant that the outcomes estimated (see *Chapter 3, Diagnostic accuracy for detection of viable myocardium*) were a conglomeration of estimates from heterogeneous studies and this has implications for the robustness of the analysis of cost-effectiveness. In the economic model, medical therapy was assumed to be the same in non-revascularised patients and the revascularised patients (as they will be put on medical therapy after revascularisation), i.e. it was assumed in the model that the medical therapy costs were the same in both groups and, therefore, these costs were not included in the model.

Revascularisation procedures can be broadly classified into surgical or catheter-based coronary interventions (CABG and PCI, respectively), with the choice of revascularisation procedure in clinical practice depending upon patient characteristics notwithstanding other practical issues and constraints such as ease and availability, etc. Despite some known differences between PCI and CABG[66] (e.g. incidence of 30-day major adverse events is higher for CABG whereas PCI is less invasive and has shorter hospital length of stay), there is still debate on which is better, with randomised trials comparing PCI with CABG showing conflicting data about the incidence of short- and long-term complications.[66,67] Furthermore, data on outcomes after revascularisation were captured from a mixture of studies that used PCI, CABG or both, which made it difficult to tease out their individual clinical effectiveness. Therefore, revascularisation is treated in the economic model as a single treatment and its outcomes were estimated by pooling the results from all the studies, irrespective of whether they used PCI, CABG or both (see *Outcomes)*. The cost of the revascularisation procedure is estimated as the weighted average cost of PCIs and CABGs using data on the numbers of procedures performed in UK in the last year, as detailed in *Costs*. According to the NHS information centre, Hospital Episode Statistics (HES) for England, in 2010–11 there were 19,743 inpatient admissions for CABG procedures and 67,908 inpatient admissions for PCI procedures.

Outcomes

It should be noted that the outcomes after revascularisation are assumed to be the same in the economic model irrespective of the diagnostic pathway used to assess the viability. Although there were some studies that report data of outcomes separately for the individual imaging techniques, these data could not be extrapolated for different tests without causing bias as the clinical effectiveness of imaging tests is already incorporated in the model by using the diagnostic accuracy, it was deemed that incorporating a separate additional effect of the type of test on outcomes might lead to double counting. As described earlier, the outcomes after revascularisation in the model are also assumed to be the same for both PCI and CABG, as revascularisation is treated as a single treatment.

Survival

A rapid review was conducted to estimate the effect of treatment on survival of patients and three review studies were found. This section provides a discussion of the evidence available for survival and describes the survival parameters used in the economic model.

Allman *et al.*[6] performed a meta-analysis of 24 studies (in 1999), with the mean age, LVEF and New York Heart Association (NYHA) functional class of 3088 patients (2228 men) reported as 61 years, 32.8% and 2.8 respectively. The follow-up was 87.7% complete over 25 months [Standard deviation (SD) 10 months]. For patients with defined myocardial viability, annual mortality rate was 16% among medically treated patients but only 3.2% among revascularised patients, representing a 79.6% relative reduction in risk of death for revascularised patients. For patients without viability, revascularisation was associated with slightly higher annual mortality than medical therapy (7.7% with revascularisation vs. 6.2% for medical therapy).

Camici *et al.*[68] synthesised the results from 20 studies (2217 patients) that were published between 1998 and 2006 to assess viability in patients with LV dysfunction caused by CAD. The pooled analysis by Camici *et al.*[68] also reported similar results with survival benefit in patients with ischaemic cardiomyopathy who underwent revascularisation compared with patients with viable myocardium treated medically (10.64% in medically treated patients but only 3.71% in revascularised patients). However, the authors report that revascularisation also reduced the mortality rate in non-viable patients (8.45% with revascularisation vs. 11.69% for medical therapy).

Schinkel *et al.*[22] performed a pooled analysis of 29 studies (3640 patients) and reported the annual mortality rates for revascularised and non-revascularised patients, with and without viable myocardium. For patients with defined myocardial viability, annual mortality rate was reported as 12.16% in medically treated patients but only 3.53% in revascularised patients, suggesting that patients with viable myocardium who undergo revascularisation have the best prognosis. However, the authors report that revascularisation also reduced the mortality rate in non-viable patients (8.45% with revascularisation vs. 9.59% for medical therapy).

More recently randomised control trials (RCTs) – PARR 2,[69] HEART[70] and STICH[71] – have reported no benefit of viability testing, but these trials are subject to a number of limitations, as described here. PET and Recovery Following Revascularisation (PARR 2)[69] compared optional viability testing using PET ($n = 218$) with standard care ($n = 212$) in Canada and reported no significant differences in outcomes. HEART[70] (Heart Failure Revascularisation Trial) was an unblinded UK clinical study that aimed to randomise 800 patients but was stopped early because of problems with recruiting and funding. Of the 138 patients enrolled, 69 were randomised to a strategy of revascularisation, but only 45 ultimately underwent a procedure and there were no differences in mortality. STICH,[71] a multicentre, non-blinded, randomised study of 601 patients conducted at 127 clinical sites in 26 countries, with a median follow-up of 5.1 years, compared optional viability testing using SPECT, echocardiography or both. The results suggested that viability status is not linked to mortality. Furthermore, these studies have significant weaknesses, as outlined elsewhere,[10] and, based on the recommendation from the clinical expert group, the conclusions from these studies were deemed as not applicable to the research question under consideration.

Comparison of the results from the evidence

For patients with viable myocardium, results from all three meta-analysis studies were in agreement in suggesting that patients with viable myocardium will have improved survival after revascularisation. In the absence of viable myocardium, all three studies report that no clear-cut differences are observed between treatments, with Allman *et al.*[6] reporting slightly higher mortality among revascularised patients, while Camici *et al.*[68] and Schinkel *et al.*[22] report slightly lower mortality rate among patients on medical therapy.

However, Camici *et al.*[68] observed that the annual mortality rate in patients treated medically appears to be similar regardless of the presence of viability, which is different from what was reported by Allman *et al.*[6] and Schinkel *et al.*[22] (for patients treated medically, both report higher annual mortality rate among non-viable patients than in viable patients). Camici *et al.*[68] argue that it could be a reflection of the optimisation, by twenty-first century standards, of patient management because they have included only the studies published between 1998 and 2006 whereas Allman *et al.*[6] and Schinkel *et al.*[22] have also included older studies (where patient management might not have been optimal). Data from the study by Schinkel *et al.*[22] were used in the economic model, since this is the most recent study containing the largest cohort of patients that is relevant to the current research question.

Mortality rates used in the model

According to the clinical expert group, the mortality of patients with HF because of LV systolic dysfunction is relatively high in the first 2 years after diagnosis and then falls to an attrition rate that is more or less constant. In addition, in the subgroups in which revascularisation takes place, there is a short period of 2 months after surgical revascularisation when the mortality rate is higher than those patients who did not receive surgical revascularisation. However, for the modelling purposes it was difficult to know whether the patients underwent the revascularisation at an early stage of their illness or not, besides all the studies accept the presence of an initial downwards dip in the surgically treated patients' survival curve. Thus, pragmatically, it was assumed that the survival/mortality rates are constant over time until death and scenario analyses were performed using different time horizons (5 years and lifetime) to understand the impact of this assumption.

In the economic model, survival data were incorporated into the model as constant annual mortality rates for revascularised patients and non-revascularised patients, both with and without viability, i.e. the patients have different mortality rates dependent upon whether or not they received treatment appropriately. The economic model used evidence from the Schinkel *et al.*[22] review conducted in 2006 which suggested that identification of viable myocardium can predict which patients will have improved survival after revascularisation. The annual mortality rates based on Schinkel *et al.*[22] are presented in *Table 10*.

However, the clinicians felt that the mortality rates presented in *Table 10* are counterintuitive as they suggest that patients who are revascularised have lower mortality rates, even if they do not have viability. They commented that this is contrary to common belief that revascularising patients with non-viable myocardium is unnecessary and may result in poor prognosis. Thus, scenario analysis was performed using the annual mortality rates from Allman *et al.*[6] and the annual mortality rates for this scenario are presented in *Table 11*.

TABLE 10 Annual mortality of patient subgroups based on Schinkel *et al.*[22]

Schinkel *et al.*[22]	Viability present (%)	Viability absent (%)
Revascularised patients	3.53	8.45
Non-revascularised patients	12.16	9.59

TABLE 11 Annual mortality of patient subgroups based on Allman *et al.*[6]

Allman *et al.*[6]	Viability present (%)	Viability absent (%)
Revascularised patients	3.2	7.7
Non-revascularised patients	16.0	6.2

Hospitalisations

There is insufficient evidence to model the hospitalisation rates for the four patient groups, i.e. viable and revascularised, viable but not revascularised, non-viable and revascularised, and non-viable and not revascularised. Moroi *et al.*[72] reported that there is no difference in hospitalisation rate between the revascularised and non-revascularised patients with stable ischaemic heart disease. Also, according to the clinical expert group, the hospitalisation rate is constant except for two periods: in the first 3 months after discharging the patient from an acute event and in the last 3–6 months of the life of patients who do not die suddenly. However, for the purposes of the model, it was assumed that the hospitalisation rate is constant because revascularisation takes place when the HF status and therapy are stable (therefore less likely to have a high readmission rate), and that the patients in NYHA stage IV are excluded from revascularisation.

The mean numbers of annual HF-related hospitalisations were estimated from the meta-analysis reported by Klersy *et al.*[73] and are presented in *Table 12*. Klersy *et al.*[73] reviewed 17 trials from different countries which included 2089 patients and reported an annual incidence of HF hospitalisation of 42.1%.

This annual hospitalisation rate was deemed sensible by the clinical expert group for an average non-revascularised patient with ischaemic cardiomyopathy. However, the clinical expert group reported that the main reason for revascularisation of patients with viable myocardium is to reduce the number of hospitalisations through improvement of the LV contraction. In the economic model, hospitalisation rate was assumed to be the same for three patient groups (viable but not revascularised, non-viable and revascularised, non-viable and not revascularised) while the annual hospitalisation rate for revascularised viable patients was assumed to be approximately one-third the hospitalisation rate of other patient subgroups, as suggested by the clinical expert group. *Table 12* shows the parameters used in the model.

Health-related quality of life

This section provides a discussion of the evidence available on the effect caused by revascularisation for viable patients and non-viable patients on their health-related quality of life (HRQoL), the impact caused by hospital readmission for HF and the impact caused by hospital readmission for other causes. It was assumed that the survivors accrued QALYs according to their age and sex and whether or not they were revascularised. The lifetime QALYs were then estimated based on patients' life expectancy and their corresponding annual utilities, depending upon their hospitalisation status.

In the studies identified in the review, there was no direct quantified evidence on the extent to which revascularisation improves HRQoL of the patients. However, Schinkel *et al.*[22] reported the improvement in symptoms using NYHA class for the patient subgroups, as shown in *Table 13*. This improvement in NYHA

TABLE 12 Annual risk of HF hospitalisations per patient in usual care

	Source	Estimate	95% CI
Viable and revascularised	Expert opinion	0.140	0.11 to 0.16
All other patients[a]	Klersy *et al.*[73]	0.421	0.4 to 0.5

a i.e viable but not revascularised, non-viable and revascularised, non-viable not revascularied.

TABLE 13 Mean NYHA class (correlated to HRQoL) of patient groups

	Viability present	Viability absent	Source
Revascularised patients	1.6 ± 0.5	2.8 ± 0.6	Schinkel *et al.*[22]
Non-revascularised patients	2.9 ± 0.5	2.9 ± 0.7	Schinkel *et al.*[22]

class was converted into utility values for revascularised and non-revascularised patients (both with and without viability) in the economic model.

Gohler *et al.*[74] performed regression analysis of QoL data of 1395 patients (mean age of 64 years) against their NYHA classes and reported that the utilities associated with NYHA classes I–IV as reported in *Table 14*. It should be noted that the utilities reported are based on analysis of patients with HF after acute MI and not for patient population in the current study, i.e. patients with ischaemic cardiomyopathy. However, it was assumed that the NYHA class is an independent measure of HF disease progression and one that is relevant for all HF patients.

Assuming that the data in *Table 14* are applicable to the population in the economic model, the utility values can be estimated for the different patient groups from the NYHA class, assuming a linear relationship between the utility values and NYHA class. The deterministic utility values estimated for the different patient groups are reported in *Table 15*. For the PSA, the uncertainty in the utility values were represented by sampling independently from *Tables 13* and *14* (i.e. mean NYHA classes of patient groups and the utility values for each NYHA class) and estimating the utility samples for the different patient groups by assuming a linear relationship between the utility values and NYHA class.

A disutility was incorporated for every HF-related hospitalisation based on a study by Yao *et al.*,[75] who estimated the disutility to be equivalent to the utility of one health state lower in terms of NYHA class. Any HF-related hospitalisation was assumed to result in a disutility of 0.1 for a whole month, i.e. approximately 0.01. Within the PSA, the disutility was represented using a triangular distribution (range –0.08 to 0.11; mode –0.1). Evidence on the disutility caused by rehospitalisation for other causes (not directly HF-related) was limited. In the absence of evidence, we assumed no disutility was caused by rehospitalisation for other causes.

TABLE 14 Utility values according to NYHA class

	Utility	95% CI
NYHA class I	0.855	0.845 to 0.864
NYHA class II	0.771	0.761 to 0.781
NYHA class III	0.673	0.665 to 0.690
NYHA class IV	0.532	0.480 to 0.584

TABLE 15 Mean utility of patient groups

	Viability present	Viability absent	Source
Revascularised patients	0.8046	0.6926	Schinkel *et al.*[22]
Non-revascularised patients	0.6828	0.6828	Schinkel *et al.*[22]

Treatment effectiveness

In the model, the treatment effectiveness on survival and QoL was assumed to last only 5 years, based on the length of follow-up of studies included in Schinkel *et al.*[22]

This meant that the annual mortality rates and the utility values (shown in *Tables 10–15*) are valid for only the first 5 years after the time horizon. After the 5-year treatment effectiveness period, the parameters for the general population are used.

For survival parameters, the annual mortality rate beyond the 5-year period is estimated by adding the age-specific annual mortality rate to the disease-specific mortality rate (estimated based on patient subgroup). The age-specific annual mortality rates are estimated from life expectancy tables assuming an 85% : 15% male to female ratio.

Furthermore, the utility values are also capped at age-specific general population utilities in order to ensure that the patient utilities do not exceed the average population utility in their age group. The age-specific utilities are estimated from a study by Ara *et al.*[22,76] assuming an 85% : 15% male to female ratio.

Risks associated with the treatment procedures

The interventions also carried risks to patient health, and these were estimated as a probability of death each time the procedure was performed. The HES data showed that there were 67,908 PCIs compared with 19,743 CABGs, resulting in a PCI to CABG ratio of 3.44. As revascularisation is represented as one procedure (i.e. not distinguishing between PCI or CABG), the mortality risk for a single revascularisation procedure was estimated as a weighted average of the mortality of PCI and CABG with their corresponding proportions. The overall mortality used in the model is as shown in *Table 16*.

Risks associated with the diagnostic tests

Some of the investigations also carried risks to patient health. These can be modelled by estimating a QALY loss that was applied each time the investigation was performed.

1. risk of death or MI induced by stress echocardiography
2. risk of developing death, MI or radiation-related malignancy as a consequence of SPECT
3. risk of developing death, MI or radiation-related malignancy as a consequence of PET.

However, given the lack of evidence on the adverse events of the diagnostic tests and the suggestion from the expert clinical group that they are negligible, the model analyses were performed assuming that there are no risks associated with the diagnostic tests.

Costs

The costs included in the model are:

1. diagnostic testing costs
2. treatments administered
3. subsequent cardiac hospitalisations.

TABLE 16 Mortality rates associated with each revascularisation procedure

	Mortality rates	Source	Distribution
PCI mortality	0.1%	BCIS	Beta distribution
CABG mortality	1–2%	SCTS	Beta distribution
Overall mortality	0.52%	BCIS, SCTS, HES data	Beta distribution

BCIS, British Cardiovascular Intervention Society; SCTS, Society for Cardiothoracic Surgery.

We assumed that patients would incur costs whenever a diagnostic test was performed, and the costs of diagnostic tests were estimated from literature, as shown in *Table 17*. The cost of treatment for revascularisation was estimated as shown in *Table 18*.

The mean inpatient admission cost for HF-related hospitalisations was calculated as shown in *Table 19* from the weighted average of the costs for the health-related group 'Heart Failure or Shock' (EB03I) based on the data obtained from the NHS Reference Costs for 2011.[77]

As there was no evidence on the annual costs of survivors (e.g. beyond hospitalisations), it was assumed that these costs were the same across both arms.

Summary of modelling input parameters

The Markov model assigned each patient a yearly probability of death, and in each year the patients who are alive were at risk of HF-related hospitalisations. The risks of death were estimated based on the patients' subgroup and age using the data from different scenarios described in *Mortality rates used in the model*. The effect of the revascularisation was assumed to last a period of 5 years, and after this the data from general population were also used. Each patient alive accumulated costs and QALYs every year based on their hospitalisation and subgroup. The model used a 40-year time horizon and the economic perspective of the model was the NHS in England and Wales. Scenario analyses were also performed using different mortality rates. The summary of the model parameters is provided in *Table 20*.

TABLE 17 Cost estimates of diagnostic testing used in the model

	Estimate (£)	95% CI (£)	Source
Echocardiography	425	400 to 450	HTA: CECaT trial
Stress CMR	600	500 to 700	HTA: CECaT trial
CE CMR	500	400 to 600	HTA: CECaT trial
SPECT	1000	900 to 1100	NICE guidance HTA: CECaT trial
PET	1200	1000 to 1500	Jacklin *et al.*[62] DH 2005

CeCaT, Cost-Effectiveness of non-invasive Cardiac Testing; DH, Department of Health.

TABLE 18 Cost estimates of revascularisation used in the model

	Estimate (£)	95% CI (£)	Source
CABG	7959	6500 to 10,000	NHS reference costs
PCI	2610	1500 to 3000	NHS reference costs
Overall cost	3815	2625 to 4575	NHS reference costs, HES data

TABLE 19 Costs of hospitalisation per patient

	Average cost (lower and upper quartile)
HF hospitalisation costs[a]	£1413.59 (£1157.10, £1809.95)

a Heart failure or shock (EB031), non-elective inpatient (long stay) including excess bed-days.[77]

TABLE 20 Summary of model parameters

Parameter	Central estimate	Distribution	Source
Prevalence	0.5	Normal (0.5, 0.03)	Al-Mohammad *et al.*[7,8]
Diagnostic accuracy (sensitivity and specificity)			
Echocardiography	(0.776, 0.696)	Sampled values	Meta-analysis
Stress CMR	(0.822, 0.871)	Sampled values	Meta-analysis
CE CMR	(0.955, 0.530)	Sampled values	Meta-analysis
SPECT	(0.851, 0.621)	Sampled values	Meta-analysis
PET	(0.947, 0.688)	Sampled values	Meta-analysis
***Annual mortality for the different patient subgroups using data from Schinkel* et al.[22]**			
Viable and revascularised	0.0353	Normal (0.0353, 0.0071)	Schinkel *et al.*[22]
Non-viable and revascularised	0.0845	Normal (0.0845, 0.0092)	Schinkel *et al.*[22]
Viable and on medical therapy	0.1216	Normal (0.1216, 0.0087)	Schinkel *et al.*[22]
Non-viable and on medical therapy	0.0959	Normal (0.0959, 0.0074)	Schinkel *et al.*[22]
***Annual mortality for the different patient subgroups using data from Allman* et al.[6]**			
Viable and revascularised	0.032	Normal (0.032, 0.006)	Allman *et al.*[6]
Non-viable and revascularised	0.16	Normal (0.16, 0.0087)	Allman *et al.*[6]
Viable and on medical therapy	0.077	Normal (0.077, 0.008)	Allman *et al.*[6]
Non-viable and on medical therapy	0.062	Normal (0.062, 0.006)	Allman *et al.*[6]
Hospitalisation rates for different patient subgroups			
Viable and revascularised	0.14	Normal (0.14, 0.01)	Expert opinion, Klersy *et al.*[73]
Non-viable and revascularised	0.421	Normal (0.421, 0.03)	Klersy *et al.*[73]
Viable and on medical therapy	0.421	Normal (0.421, 0.03)	Klersy *et al.*[73]
Non-viable and on medical therapy	0.421	Normal (0.421, 0.03)	Klersy *et al.*[73]
HRQoL for patient different subgroups			
Viable and revascularised	0.8046	Sampled values	Gohler *et al.*,[74] Schinkel *et al.*[22]
Non-viable and revascularised	0.6926	Sampled values	Gohler *et al.*,[74] Schinkel *et al.*[22]
Viable and on medical therapy	0.6828	Sampled values	Gohler *et al.*,[74] Schinkel *et al.*[22]
Non-viable and on medical therapy	0.6828	Sampled values	Gohler *et al.*,[74] Schinkel *et al.*[22]

continued

TABLE 20 Summary of model parameters (*continued*)

Parameter	Central estimate	Distribution	Source
Costs of diagnostic tests			
Echocardiography	£425	Triangular (400, 425, 450)	Expert opinion, HTA: CECaT trial
Stress CMR	£600	Triangular (500, 600, 700)	Expert opinion, HTA: CECaT trial
CE CMR	£500	Triangular (400, 500, 600)	Expert opinion, HTA: CECaT trial
SPECT	£1000	Triangular (900, 1000, 1100)	Expert opinion, HTA: CECaT trial
PET	£1200	Triangular (1000, 1200, 1500)	Jacklin *et al.*,[62] DH 2005
Hospitalisation costs and disutility			
Hospitalisation costs	£1413	Normal (£1413, £125)	NHS reference costs
QALY loss	–0.01	Triangular (–0.008, –0.01, –0.011)	Expert opinion, Yao *et al.*[75]
Revascularisation costs and perioperative mortality			
Hospitalisation costs	£3815	Triangular (£2625, £3815, £4575)	NHS reference costs, HES data
Risk of death for viable patients	0.005	Normal (0.005, 0.0003)	Expert opinion
Risk of death for non-viable patients	0.01	Normal (0.01, 0.0005)	Expert opinion

DH, Department of Health.

Methods to estimate cost-effectiveness

Cost-effectiveness of the different interventions was estimated using both the incremental cost-effectiveness ratio (ICER) and net monetary benefit (NMB) approach. Uncertainty was incorporated in the modelling by performing PSA. A description of these terms and approaches is provided in this section.

Definitions of cost-effectiveness terms

The ICER measures the relative value of two strategies and is calculated as the mean incremental costs divided by the mean incremental benefits, i.e. the additional cost required using the strategy to accrue one additional QALY compared with the next most effective alternative. A strategy is dominated when another strategy accrues more QALYs for less cost. Extended dominance occurs when a combination of two alternative strategies can produce the same QALYs as a chosen strategy but at a lower cost. Strategies that are neither dominated nor extendedly dominated constitute the cost-effectiveness frontier, and the ICER is reported for these strategies compared with the next least effective strategy. However, as there are multiple possible strategies, ICERs need to be calculated between different pairs, comparing each strategy against the next most effective strategy.

The willingness-to-pay (WTP) threshold is the amount of money the decision-maker is willing to pay to gain one additional QALY. The usual threshold for decision-making at NICE is considered to be around £20,000 per QALY,[78] so if the ICER exceeds £20,000 per QALY then the strategy is unlikely to be considered cost-effective.

The NMB is defined as the QALYs multiplied by a value for the QALYs (e.g. £20,000) minus the costs of obtaining them, i.e. NMB = QALYs × λ – cost, where λ is the WTP threshold. The net benefit approach is simpler to calculate and gives equivalent findings (but requires an explicit assumption regarding the value of λ).

Uncertainty analysis

The results presented in *Results of independent economic assessment* include the effects of accounting for uncertainty in the model parameters, i.e. essentially the CIs surrounding the diagnostic accuracy, costs, utilities and risks (for mortality and HF hospitalisations). PSA is undertaken where the model is rerun (10,000 times) each time with a different value for the sensitivity and specificity estimates, mortality risks, hospitalisation rates, costs and utilities which are sampled from the probability distributions.

The cost-effectiveness acceptability curve (CEAC) shows the proportion of model runs for which each strategy is cost-effective over a range of potential WTP thresholds (i.e. λ). Another measure of uncertainty is the overall expected value of perfect information (EVPI). This calculation is done based on the theory that the decision-maker will choose the most cost-effective option but could acquire additional evidence to reduce the uncertainties in the decision, e.g. knowing exactly what the mortality and hospitalisation risks are for each patient group rather than having evidence based on current best estimates and CIs. In the EVPI calculation, it can be estimated how often making the decision based on current evidence could be wrong and also how many QALYs (and costs) would be lost by choosing the strategy that is expected to be most cost-effective given current evidence when in fact one of the other strategies is truly the most cost-effective. Valuing the QALYs lost by making a 'wrong' decision to choose a strategy based on current evidence by using the WTP threshold, one can estimate a monetary value for this possible loss on each of the occasions when another strategy would be optimal, i.e. the net benefit lost. This can be multiplied by the number of patients per year and the expected lifetime of the decision to estimate the population EVPI. The interpretation of this number is that if one could fund research to eliminate the uncertainty in mortality risks for different patient groups (e.g. by a large or infinitely large clinical trial) then the value of eliminating the uncertainty via such research would be expected to be the population EVPI.

Results of the independent economic assessment

This section details the results of the cost-effectiveness analyses estimated for a cohort of 10,000 patients as mean values of 10,000 PSA runs, each PSA run with a different estimate for the prevalence, diagnostic parameters, hospitalisation rates, costs and utilities sampled from the probability distributions reported in *Table 20*.

Results are presented using different mortality parameters as summarised in *Tables 10* and *11*. The cost-effectiveness for both of these scenarios was performed for all the diagnostic pathways reported in *Cost-effectiveness results for scenario using data from Allman* et al.[6] and *Cost-effectiveness results for scenario using data from Schinkel* et al.[22]

This approach was taken to address the uncertainty in the mortality evidence. For decision-makers who need to decide which of these presented results are most representative of their setting, the key questions relate to the effect of revascularising non-viable patients. If the mortality rates presented in *Table 10* are correct (i.e. patients who are revascularised have lower mortality rates, even if they do not have viability), then the results from that scenario might be considered more relevant. However, if the mortality rates presented in *Table 11* are correct (i.e. the annual mortality rates for revascularised patients with non-viable myocardium are higher than for patients with non-viable myocardium on medical therapy), then the results from this scenario might be considered more relevant.

In each case, the expected estimates of cost-effectiveness and the uncertainty around them are presented, along with the probability that each of the strategies on the cost-effectiveness frontier is the most cost-effective. The EVPI, a measure of how valuable it would be to eliminate all the existing uncertainty evidence, is also provided for each scenario.

Diagnostic performance of different pathways

Table 21 shows the mean values of sensitivity and specificity of all the pathways tested in the model, estimated from the meta-analysis.

The mean numbers of patients in different subgroups after the diagnostic pathway are shown in *Table 22*. These patient numbers are estimated using an initial cohort size of 10,000 patients with a mean prevalence of viable myocardium of 0.5, i.e. 5000 patients out of a total of 10,000 patients are viable, with the remainder of the 5000 patients non-viable. The higher the sensitivity of the pathway, the higher the proportion of 5000 patients with viable myocardium detected to be revascularised and, consequently, the lower the number of patients with viable myocardium on medical therapy. Similarly, the higher the specificity, the higher the number of patients with non-viable myocardium detected correctly (and not revascularised unnecessarily) and the lower the number of revascularised patients with non-viable myocardium.

As presented earlier, the revascularisation procedure carries a risk of perioperative mortality. The mean value of this risk of death in the model is 0.5% for patients with viable myocardium and 1% for patients who do not have viable myocardium. The mean values of total number of deaths for each diagnostic pathway are also presented in *Table 22*.

Although the performance of the diagnostic pathways in terms of sensitivity and specificity is the same in both scenarios tested, the cost-effectiveness estimates are different because of the effect of different mortality assumptions (which affect the total costs and total QALYs). Therefore, cost-effectiveness for each of these scenarios is presented separately below and the users can decide which scenario is most relevant for them.

TABLE 21 Overall sensitivity and specificity of diagnostic pathways

Intervention	Sensitivity (95% CI)	Specificity (95% CI)
No testing	0.000	1.000
Echocardiography	77.6 (70.7 to 83.3)	69.6 (62.4 to 75.9)
Stress CMR	82.2 (73.2 to 88.7)	87.1 (80.4 to 91.7)
CE CMR	95.5 (94.1 to 96.7)	53.0 (40.4 to 65.2)
SPECT	85.1 (78.1 to 90.2)	62.1 (52.7 to 70.7)
PET	94.7 (90.3 to 97.2)	68.8 (50.0 to 82.9)
Revascularise all	1.000	0.000

TABLE 22 Patient subgroups immediately after different diagnostic pathways

Intervention	Number viable and revascularised	Number non-viable and revascularised	Number viable and on medical	Number non-viable and on medical	Number of deaths because of revascularisation
No testing	0	0	5000	5000	0.0
Echocardiography	3880	1520	1120	3480	34.6
Stress CMR	4110	645	890	4355	27
CE CMR	4775	2350	225	2650	47.3
SPECT	4255	1895	745	3105	40.2
PET	4735	1560	265	3440	39.3
Revascularise all	5000	5000	0	0	75.0

Cost-effectiveness results for scenario using data from Allman et al.[6]

This section presents the cost-effectiveness results using the mortality rates presented in *Table 11*. If the annual mortality rates for non-viable patients are higher for revascularised patients than for patients on medical therapy, then the results from this scenario might be considered more relevant.

In this scenario, no testing, the stress CMR, CE CMR and PET pathways are on the cost-effectiveness frontier, as shown in *Table 23*. Stress CMR is cost-effective with a mean ICER of £1073.8 per QALY compared with the no testing strategy, and CE CMR has an ICER of £2906.5 per QALY compared with stress CMR. Both strategies are cost-effective assuming a threshold of £20,000 per QALY. Echocardiography and SPECT are dominated by stress CMR and CE CMR respectively. In addition, PET is not cost-effective at a threshold of £20,000 per QALY as it has an ICER of £21,299 per QALY compared with CE CMR. Furthermore, the strategy of revascularising everyone is dominated by PET. Thus, CE CMR is estimated to be the most cost-effective option at a threshold of £20,000/QALY. This is because CE CMR has good sensitivity with a reasonable specificity and also costs less, resulting in it being the best strategy in terms of cost-effectiveness. The higher ICER for PET can be attributed to its high costs even though it has better sensitivity and specificity than CE CMR.

Furthermore, it should be noted that, compared with no testing, all the diagnostic pathways are cost-effective at the current NICE threshold. This suggests that all current services for diagnosing viable myocardium are a cost-effective use of NHS resources irrespective of the diagnostic pathway used, provided their costs and diagnostic accuracy are similar to those reported in this analysis.

Another presentation of these same results is to calculate the net benefit of each strategy. This approach takes away the need to calculate the ICERs and simplifies the interpretation for decision makers as the strategy with the highest expected incremental monetary net benefit is the most cost-effective. Since the model is rerun 10,000 times each time with different values for the sensitivity, specificity, costs and utilities sampled from the probability distributions, in some of the sampled model runs, it could turn out that one diagnostic pathway is better than others because of the overlap in their CIs. For example, there is a chance

TABLE 23 Incremental cost-effectiveness ratios for the diagnostic pathways on the cost-effectiveness frontier

Test	Costs (£)	QALYs	ICER
No testing	37,301,604.28	40,195.52	–
Echocardiography	58,128,798.55	57,726.28	Dominated by stress CMR
Stress CMR	57,813,941.19	59,298.41	1073.8/QALY
CE CMR	64,224,494.74	61,503.98	2906.5/QALY
SPECT	66,189,474.51	59,249.63	Dominated by CE CMR
PET	68,938,873.64	61,725.31	21,299/QALY
Revascularise everyone	68,277,954.54	60,969.28	Dominated by PET

that in truth, the cost effectiveness of PET could be better than CE CMR. The CEAC in *Figure 8* shows the proportion of model runs for which each strategy is cost-effective over a range of potential WTP thresholds. The proportion of models runs in which CE CMR was the most cost-effective strategy (at £20,000 per QALY threshold) was 40%, with PET at 42% and revascularising everyone at 16.5%, as shown in *Figure 8*.

A CEAC in which the best strategy is not cost-effective all the time indicates that there is uncertainty as to which strategy is the optimal in terms of NMB. This uncertainty can also be measured as overall EVPI, which is defined as the maximum investment a decision-maker would be willing to pay to eliminate all parameter uncertainty from the decision problem. The EVPI at the threshold of £20,000 per QALY in this case is £620 per patient for whom the decision is made, as shown in *Figure 9*. The population EVPI per annum can be estimated by multiplying the EVPI per patient with the annual incidence of patients with ischaemic cardiomyopathy in England and Wales.

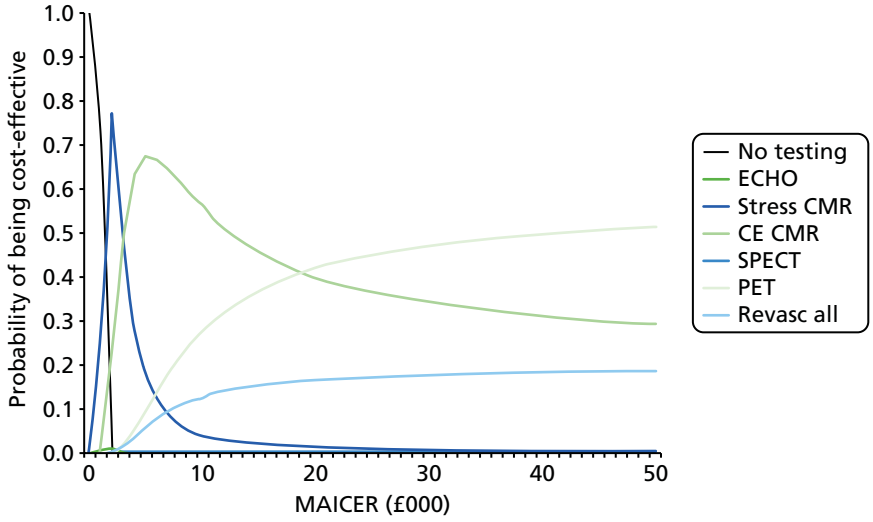


FIGURE 8 Cost-effectiveness acceptability curve for scenario using data from Allman *et al.*[6] MAICER, maximum acceptable incremental cost-effectiveness ratio.

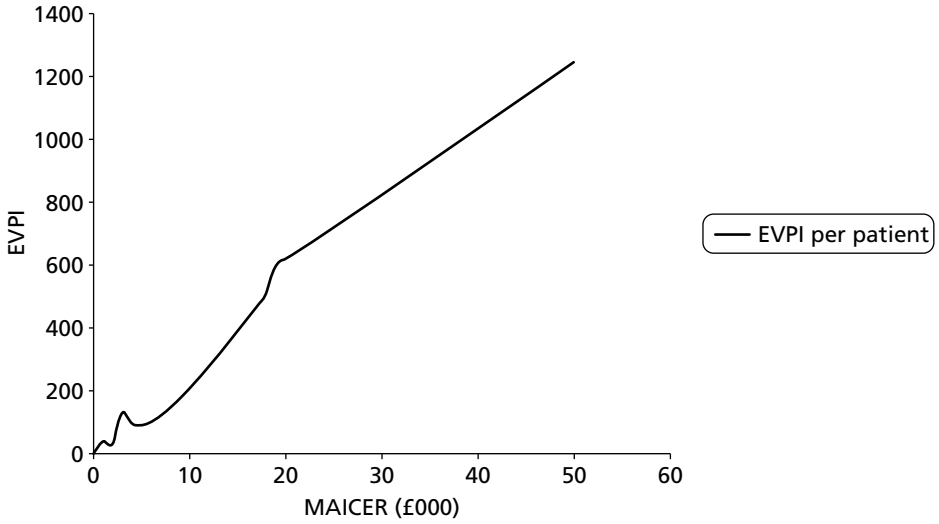


FIGURE 9 Expected value of perfect information per patient for scenario using data from Allman *et al.*[6] MAICER, maximum acceptable incremental cost-effectiveness ratio.

Cost-effectiveness results for scenario using data from Schinkel et al.[22]

The analyses were also performed using mortality rates presented in *Table 10*, based on the data from Schinkel *et al.*[22] If patients who are revascularised have lower mortality rates, even if they do not have viability, then the results from this scenario might be considered more relevant.

The strategies that are on the cost-effectiveness frontier are the no testing, stress CMR, CE CMR and revascularise everyone pathways, and the ICERs calculated for these strategies are as shown in *Table 24*. In this scenario, revascularising everyone is estimated to be the most cost-effective option with an ICER of £3612 per QALY. This is because all patients get benefit from revascularisation (including the non-viable patients); therefore, revascularising everyone is the best strategy in terms of cost-effectiveness.

All the diagnostic pathways are cost-effective at the current NICE threshold when compared with no testing. This suggests that all the current services for diagnosing viable myocardium are a cost-effective use of NHS resources in this scenario as well, provided their costs and diagnostic accuracy are similar to those reported in this analysis.

Revascularising everyone was the most cost-effective strategy (at £20,000 per QALY threshold) and is cost-effective in 95.2% of the model runs, with CE CMR and PET being cost-effective in 3.6% and 1.1% of the runs respectively (*Figure 10*). The decrease in uncertainty compared with the scenario using data from Allman *et al.*[6] can be attributed to the fact that all patients receive benefit from revascularisation (including the non-viable patients) in the current scenario (i.e. using data from Schinkel *et al.*[22]), thus revascularising everyone is the best strategy in terms of cost-effectiveness. In contrast, in the scenario using Allman *et al.*[6], the benefits of revascularisation are only from the patients in the viable myocardium group (rather than everyone as in scenario 1). This reduction in uncertainty is also reflected in the EVPI of only £28 per patient, as seen in *Figure 11*.

TABLE 24 Incremental cost-effectiveness ratios for the diagnostic pathways on the cost-effectiveness frontier

Test	Costs (£)	QALYs	ICER
No testing	35,364,889.9	38,011.57	–
Echocardiography	54,812,088.5	53,339.42	Dominated by stress CMR
Stress CMR	53,675,251.2	53,927.02	£1150.5/QALY
CE CMR	60,963,216.6	57,040.69	£2340.6/QALY
SPECT	62,923,997.1	54,866.92	Dominated by CE CMR
PET	65,100,350.7	56,612.86	Dominated by CE CMR
Revascularise everyone	66,940,003.9	58,695.24	£3612.3/QALY

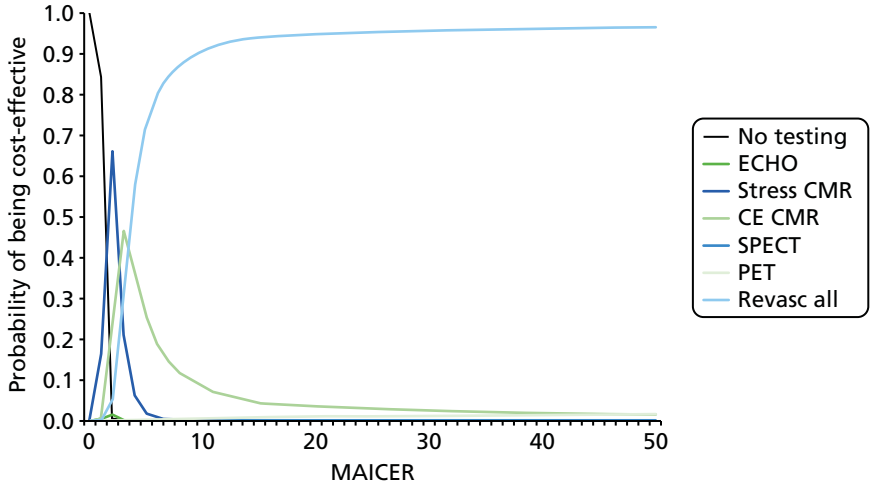


FIGURE 10 Cost-effectiveness acceptability curve for scenario using data from Schinkel *et al.*[22] MAICER, maximum acceptable incremental cost-effectiveness ratio.

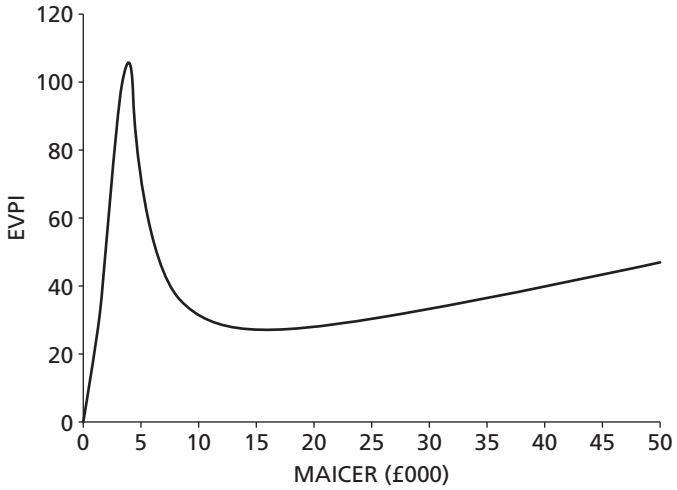


FIGURE 11 Expected value of perfect information per patient for scenario 3. MAICER, maximum acceptable incremental cost-effectiveness ratio.

Discussion of the cost-effectiveness results

All the diagnostic pathways are cost-effective when compared with no testing at the current NICE threshold in both scenarios. This suggests that all the current services for diagnosing viable myocardium are a cost-effective use of NHS resources irrespective of the diagnostic pathway used, provided their costs and diagnostic accuracy are similar to those reported in this analysis. This is because any reduction in mortality leads to gain in QALYs and, as a result of the low costs of diagnostic pathways, all of them are cost-effective at the current NICE threshold.

In terms of determining the most cost-effective strategy, diagnostic parameters and mortality rates of the different subgroups are the key drivers in the model. Two different scenarios relating the mortality rates were analysed in the model; this approach was taken to address the uncertainty in the mortality evidence. For decision-makers who need to decide which of these presented results are most representative of their setting, the key questions relate to the effect of revascularising non-viable patients. If patients who are revascularised have lower mortality rates, even if they do not have viability, then revascularising everyone is the most cost-effective strategy. If there is no benefit of revascularising non-viable patients, then CE CMR is the most cost-effective strategy at a threshold of £20,000/QALY. However, there is uncertainty involved in suggesting it as the most cost-effective strategy.

Chapter 5 Discussion

Discussion of diagnostic accuracy review

Twenty-four diagnostic accuracy studies were included in the systematic review.[15,17,25,27–31,34–41,43,44,46,47,49,53] Ten studies[17,27,28,31,34,35,37,39,40,47] explored the diagnostic accuracy of stress CMR to detect viable myocardium in patients with cardiovascular disease. Twelve studies[15,25,29,30,37,38,41,43,44,46,49,51] explored the diagnostic accuracy of CE CMR, while two[34,38] explored (and reported with sufficient data) both stress CMR and CE CMR to establish their diagnostic accuracy in correctly diagnosing viable myocardium, amenable to revascularisation. In all included studies the reference standard was recovery following revascularisation. The number of included participants was small (from 10 to 65 participants) and the majority of participants were men. The population included patients with cardiovascular disease and impaired LV dysfunction, but all studies excluded patients with very recent MI (< 4 months). More studies were carried out in Germany than in any other country, and dates of publication suggest that earlier work explored stress CMR, with a trend to more recent evaluations of CE CMR. The studies varied in their reporting of the study design. All were prospectively carried out, and the analysis was a within-subject comparison in each study. Few studies adequately blinded analysts, and this may have created a source of bias in the interpretation of the test and reference standard results. Most of the studies reported sensitivities and specificities based on 'per segment' rather than 'per patient' analysis. These have been pooled together in the analyses, potentially not allowing the results to be interpreted with sufficient caution.

Late gadolinium-enhanced CMR was a more sensitive test (95.5%, 95% CI 94.1% to 96.7%) for identifying viable myocardium compared with stress CMR (82.2%, 95% CI 73.2% to 88.7%). Stress CMR, however, had greater specificity than CE CMR (87.1%, 95% CI 80.4% to 91.7% vs. 53%, 95% CI 40.4% to 65.2% respectively). These values were determined for improvement in LV function following revascularisation.

Sensitivity analysis was carried out to explore the impact of very small studies ($n \leq 10$), the impact of population differences at baseline in terms of pre-existing extent of ventricular dysfunction and the potential risk of duplicate publication. None of these additional analyses found a significant difference in the overall pooled results.

Few studies reported adverse effects occurring as a result of either the index test or the follow-up evaluation. A number of studies ($n = 8$) described patients withdrawing from the study before the follow-up assessment, after revascularisation. This may indicate patient discomfort with the procedure.

Limitations and strengths of the review

We conducted extensive literature searches to locate all relevant studies. The methods for identifying diagnostic studies are less robust and, despite efforts to identify all relevant studies, the fact that two included studies were not identified in the electronic searches made us aware that there may be additional studies we have not identified.[79]

Our review is limited by the lack of high-quality, well-reported studies. Most studies that provided data on diagnostic accuracy had small sample sizes (range 8–65) and reported results on a per segment rather than per patient basis. Our review, therefore, provides information on the ability of these techniques to detect viability within particular myocardial segments but not for determining the presence or absence of viable

myocardium on a per patient basis. Analysis by segment also means that the estimates of the 95% CIs for sensitivity and specificity do not account for the clustering of segments within patients.

Our findings are consistent with a recent review carried out by Romero *et al.*[21] Although there were some differences in inclusion and exclusion criteria (they excluded studies using higher doses of dobutamine, i.e. 15 µg/kg per minute, and abstracts), the weighted means were similar in each review. For stress CMR the sensitivity and specificity in the Romero *et al.*[21] review was 81% and 91% respectively. For CE CMR, the sensitivity and specificity was 95% and 51% respectively.

Discussion of cost-effectiveness results

All the diagnostic pathways are cost-effective when compared with no testing at current NICE thresholds in all three scenarios. This suggests that all the current services for diagnosing viable myocardium are a cost-effective use of NHS resources irrespective of the diagnostic pathway used, provided their costs and diagnostic accuracy are similar to those reported in this analysis. This is because any reduction in mortality leads to gain in QALYs and, as a result of the low costs of diagnostic pathways, all of them are cost-effective at the current NICE threshold.

In terms of determining the most cost-effective strategy, diagnostic parameters and mortality rates of the different subgroups are the key drivers in the model. Mortality reduction leads to gaining more QALYs and, as the intervention costs are only a small part of the overall costs, a diagnostic pathway is likely to be cost-effective if it can help save lives. However, the most cost-effective strategy is dependent on the mortality rates after revascularisation for patients with non-viable myocardium. Different scenarios relating the mortality rates were analysed in the model to address the uncertainty in the mortality evidence.

For decision makers who need to decide which of these presented results is most representative of their setting, the key questions relate to the effect of revascularising patients with non-viable myocardium. If patients who are revascularised have lower mortality rates, even if they do not have viability, then revascularising everyone is the most cost-effective strategy. If there is no benefit for revascularising non-viable patients, then CE CMR is the most cost-effective strategy at a threshold of £20,000/QALY, but there is uncertainty involved in suggesting it as the most cost-effective strategy.

Statement of principal findings

The current evidence is difficult to interpret given the variability of the diagnostic criteria used in different studies, and to the conflicting outcomes of the studies that looked at the issues of revascularisation and viability imaging in the literature. We have tried to cover that uncertainty through proposing different scenarios and applying the current evidence base to each of these scenarios. If the presence of viable myocardium is believed to have an impact on the management strategy, then a viability assessment using CE CMR appears to be most cost-effective.

Limitations and strengths of the analysis

Although an extensive literature search was conducted, it is possible that some relevant studies may have been missed. However, the impact of such omissions is likely to have been minimal, as the search included all identifiable publications in the grey literature (including contact with clinical experts in the field).

The data were analysed using a bivariate regression method, assuming that the sensitivity and specificity values from individual studies (after logit transformation) within the meta-analysis are normally distributed. Parameter estimates were estimated using Markov chain Monte Carlo, but do not include uncertainty in the estimate of the between-study standard deviation. The cost-effectiveness analysis has been undertaken assuming that the 95% confidence region represents the best knowledge regarding the relative

uncertainty in the diagnostic parameters. It is a limitation that the sensitivity and specificity values are sampled just from the 95% confidence region rather than from the 95% predictive region, which allows the estimation of the predictive distribution of the effect of each intervention in a new study.

The primary analysis assumed single testing scenarios. The results of multiple test pathways are not included in the analysis for a number of reasons, as outlined in *Chapter 4, Selection of pathways*. However, it is a limitation of the model that the multiple diagnostic tests are not part of the analysis.

The hospitalisation rate is constant except for two periods: in the first 3 months after discharging the patient from an acute event and in the last 3–6 months of the life of the patient who does not die suddenly. However, for the purposes of the model, it was assumed that the hospitalisation rate is constant because revascularisation takes place when the HF status and therapy are stable (thus less likely to have a high readmission rate), and that the patients in stage NYHA IV are excluded from revascularisation according to the clinical expert group.

Any limitations in the evidence base also manifest as limitations of the cost-effectiveness model. One limitation was the assumption of constant mortality rates. The mortality of patients with HF because of LV systolic dysfunction follows a pattern where the mortality is relatively high in the first 2 years after diagnosis and then falls to an attrition rate that is more or less constant. In addition, in the subgroups in which revascularisation takes place, there is a short period of 2 months after surgical revascularisation when the mortality rate is higher than among those patients who did not undergo surgical revascularisation. However, for the study purposes, it was difficult to know whether or not the patients underwent the revascularisation at an early stage of their illness; in any case all the studies accept the presence of an initial downwards dip in the surgically treated patients' survival curve. Thus, pragmatically, it was assumed that the survival/mortality rates are constant. If the studies reported observations at different time points, time-dependent mortality rates can be estimated and used in the cost-effectiveness model. Furthermore, duration of clinical effectiveness after revascularisation can also be identified.

Scenarios for different mortality rates after revascularisation for patients with non-viable myocardium were developed and their cost-effectiveness were estimated. Although the users can decide which of these analyses is most representative of their setting, uncertainties still remain about the assumptions made in the estimation of these mortality rates. This uncertainty in the mortality rates after revascularisation for patients with non-viable myocardium is a limitation, especially given that the aim of any diagnostic pathway is to correctly identify patients with viability; any small difference in mortality patterns can lead to marked changes in the cost-effectiveness. One limitation is that the mortality rates after revascularisation remained the same for the different diagnostic pathways, whereas in reality there might be some correlation between the diagnostic pathways and outcomes after revascularisation in different diagnostic pathways.

Uncertainties

In terms of determining the most cost-effective strategy, diagnostic parameters and mortality rates of the different subgroups are the key drivers in the model. However, there is uncertainty in the mortality evidence, especially in the differences in mortality rates for non-viable patients on medical therapy and after revascularisation. This uncertainty is reflected in different strategies being cost-effective in the different scenarios of mortality rates analysed.

Chapter 6 Conclusions

Implications for service provision

Given the uncertainty in the mortality rates, the cost-effectiveness analysis was performed using a set of scenarios. In general, although the diagnostic accuracy of the pathways varied widely, all the diagnostic pathways are cost-effective when compared with no testing at current NICE threshold in both scenarios. This suggests that all the current services for diagnosing viable and potentially hibernating myocardium are a cost-effective use of NHS resources irrespective of the diagnostic pathway used, provided their costs and diagnostic accuracy are similar to those reported in this analysis. The cost-effectiveness analyses suggest that revascularising everyone and CE CMR were the optimal strategies in most of the scenarios.

Suggested research priorities

To aid robust cost-effectiveness estimations, the mortality rates associated with different patient subgroups need to be reported in detail. In addition, QoL, patient severity status transitions (e.g. NYHA class) and hospitalisations need to be reported with observations at specific time points to enable the estimation of effectiveness of revascularisation over time and also to identify the effectiveness duration of revascularisation.

Implementation costs (such as set-up costs, staff training costs and costs for running of diagnostic services) were often missing from the studies in the review. Future studies should provide greater detail of the costs of reconfiguration and link more clearly with the financial impact (e.g. cost variation with scale and over time) on provider organisations. Wider adaptation of diagnostic imaging pathways in the NHS can be facilitated by providing financial impact data along with the cost-effectiveness information.

Consensus on reporting of diagnostic testing data in this clinical area would facilitate comparison of trial data and data synthesis in the future. Further research using universally agreed methodology of assessment of viability to answer both the question of testing viability and the impact of revascularisation or best medical therapy in this group of high-risk patients while remaining a priority, is understood to be very difficult to achieve in real clinical settings.

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Contributions of authors

Fiona Campbell was the project lead and undertook the diagnostic accuracy review.

Praveen Thokala performed the meta-analyses for the diagnostic accuracy review, undertook the cost-effectiveness review, developed the cost-effectiveness model and wrote the cost-effectiveness section.

Lesley C Uttley helped undertake the diagnostic accuracy review.

Anthea Sutton performed the literature searches.

Alex J Sutton provided statistical advice.

Abdallah Al-Mohammad provided clinical advice and contributed significantly to the design of the cost-effectiveness model and peer reviewing of the final report.

Steven M Thomas conceived and designed the project, providing clinical and methodological expertise.

References

1. Allender S, Peto V, Scarborough P, Boxer A, Rayner M. *Coronary Heart Disease Statistics*. London: British Heart Foundation and Stroke Association; 2006.
2. Miller S, Helber U, Brechtel K, Nagele T, Hahn U, Kramer U, *et al.* MR imaging at rest early after myocardial infarction: detection of preserved function in regions with evidence for ischemic injury and non-transmural myocardial infarction. *Eur Radiol* 2003;**13**:498–506.
3. Marwick TH. The viable myocardium: epidemiology, detection, and clinical implications. *Lancet* 1998;**351**:815–19. http://dx.doi.org/10.1016/S0140-6736(97)08080-X
4. Beller GA. Noninvasive assessment of myocardial viability. *N Engl J Med* 2000;**343**:1488–90. http://dx.doi.org/10.1056/NEJM200011163432011
5. Bart BA, Shaw LK, McCants CB Jr., Fortin DF, Lee KL, Califf RM, *et al.* Clinical determinants of mortality in patients with angiographically diagnosed ischemic or nonischemic cardiomyopathy. *J Am Coll Cardiol* 1997;**30**:1002–8. http://dx.doi.org/10.1016/S0735-1097(97)00235-0
6. Allman KC, Shaw LJ, Hachamovitch R, Udelson JE. Myocardial viability testing and impact of revascularization on prognosis in patients with coronary artery disease and left ventricular dysfunction: a meta-analysis. *J Am Coll Cardiol* 2002;**39**:1151–8. http://dx.doi.org/10.1016/S0735-1097(02)01726-6
7. Al-Mohammad A, Mahy IR, Norton MY, Hillis G, Patel JC, Mikecz P, *et al.* Prevalence of hibernating myocardium in patients with severely impaired ischaemic left ventricles. *Heart* 1998;**80**:559–64.
8. Al-Mohammad A, Walton MS. Prevalence of myocardial viability as detected by positron emission tomography in patients with ischemic cardiomyopathy. *Circulation* 2000;**102**:E31. http://dx.doi.org/10.1161/01.CIR.102.4.e31
9. Velazquez EJ, Lee KL, O'Connor CM, Oh JK, Bonow RO, Pohost GM, *et al.* The rationale and design of the Surgical Treatment for IsChemic heart failure (STICH) trial. *J Thorac Cardiovasc Surg* 2007;**134**:1540–7. http://dx.doi.org/10.1016/j.jtcvs.2007.05.069
10. Cortigiani L, Bigi R, Sicari R. Is viability still viable after the STICH trial? *Eur Heart J* 2013;**13**:219–26. http://dx.doi.org/10.1093/ejechocard/jer237
11. Tomlinson DR, Becher H, Selvanayagam JB. Assessment of myocardial viability: comparison of echocardiography versus cardiac magnetic resonance imaging in the current era. *Heart Lung Circ* 2008;**17**:173–85. http://dx.doi.org/10.1016/j.hlc.2007.10.005
12. Bax JJ, Poldermans D, Elhendy A, Boersma E, Rahimtoola SH. Sensitivity, specificity, and predictive accuracies of various noninvasive techniques for detecting hibernating myocardium. *Curr Probl Cardiol* 2001;**26**:147–86. http://dx.doi.org/10.1067/mcd.2001.109973
13. Bax JJ, Wijns W, Cornel JH, Visser FC, Boersma E, Fioretti PM. Accuracy of currently available techniques for prediction of functional recovery after revascularization in patients with left ventricular dysfunction due to chronic coronary artery disease: comparison of pooled data. *J Am Coll Cardiol* 1997;**30**:1451–60. http://dx.doi.org/10.1016/S0735-1097(97)00352-5
14. Kaandorp TA, Lamb HJ, van der Wall EE, de RA, Bax JJ. Cardiovascular MR to access myocardial viability in chronic ischaemic LV dysfunction. *Heart* 2005;**91**:1359–65. http://dx.doi.org/10.1136/hrt.2003.025353
15. Kim RJ, Wu E, Rafael A, Chen EL, Parker MA, Simonetti O, *et al.* The use of contrast-enhanced magnetic resonance imaging to identify reversible myocardial dysfunction. *N Engl J Med* 2000;**343**:1445–53. http://dx.doi.org/10.1056/NEJM200011163432003

16. Kuhl HP, Lipke CS, Krombach GA, Katoh M, Battenberg TF, Nowak B, *et al.* Assessment of reversible myocardial dysfunction in chronic ischaemic heart disease: comparison of contrast-enhanced cardiovascular magnetic resonance and a combined positron emission tomography-single photon emission computed tomography imaging protocol. *Eur Heart J* 2006;**27**:846–53. http://dx.doi.org/10.1093/eurheartj/ehi747

17. Van Hoe L, Vanderheyden M. Ischemic cardiomyopathy: value of different MRI techniques for prediction of functional recovery after revascularization. *Am J Roentgenol* 2004;**182**:95–100. http://dx.doi.org/10.2214/ajr.182.1.1820095

18. Cowley D CPHD. *Functional diagnostic imaging in the assesment of myocardial viability and perfusion: an evidence-based analysis*. Alberta: Alberta Heritage Foundation for Medical Research (AHRMR), 1999.

19. Schwitter J. Myocardial perfusion imaging by cardiac magnetic resonance. *J Nucl Cardiol* 2006;**13**:841–54. http://dx.doi.org/10.1016/j.nuclcard.2006.09.008

20. Bax JJ, Poldermans D, Elhendy A, Boersma E, van der Wall EE. Assessment of myocardial viability by nuclear imaging techniques. *Curr Cardiol Rep* 2005;**7**:124–9. http://dx.doi.org/10.1007/s11886-005-0024-4

21. Romero J, Xue X, Gonzalez W, Garcia MJ. CMR imaging assessing viability in patients with chronic ventricular dysfunction due to coronary artery disease: a meta-analysis of prospective trials. *JACC Cardiovasc Imag* 2012;**5**:494–508. http://dx.doi.org/10.1016/j.jcmg.2012.02.009

22. Schinkel AF, Bax JJ, Poldermans D, Elhendy A, Ferrari R, Rahimtoola SH. Hibernating myocardium: diagnosis and patient outcomes. *Curr Probl Cardiol* 2007;**32**:375–410. http://dx.doi.org/10.1016/j.cpcardiol.2007.04.001

23. Glanville J, Lefebvre C, Wright K, (n.d.) *The InterTASC Information Specialists' Sub-Group Search Filter Resource*. URL: www.york.ac.uk/inst/crd/intertasc/ (accessed 29 March 2011).

24. Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, *et al.* QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Ann Intern Med* 2011;**155**:529–36. http://dx.doi.org/10.7326/0003-4819-155-8-201110180-00009

25. Wu Y-W, Tadamura E, Kanao S, Yamamuro M, Marui A, Komeda M, *et al.* Myocardial viability by contrast-enhanced cardiovascular magnetic resonance in patients with coronary artery disease: comparison with gated single-photon emission tomography and FDG position emission tomography. *Int J Cardiovasc Imag* 2007;**23**:757–65. http://dx.doi.org/10.1007/s10554-007-9215-y

26. Baer F, Voth E, Schneider C, Theissen P, Crnac J, Schmidt M, *et al.* Dobutamine-magnetic resonance imaging versus 18F-fluorodeoxyglucose positron emission tomography: predictive value for the functional recovery of viable myocardium after successful revascularization. *Eur Heart J* 1998;**19**(Abstract Suppl.):30.

27. Baer FM, Theissen P, Schneider CA, Voth E, Sechtem U, Schicha H, *et al.* Dobutamine magnetic resonance imaging predicts contractile recovery of chronically dysfunctional myocardium after successful revascularization. *J Am Coll Cardiol* 1998;**31**:1040–8. http://dx.doi.org/10.1016/S0735-1097(98)00032-1

28. Baer FM, Theissen P, Crnac J, Schmidt M, Deutsch HJ, Sechtem U, *et al.* Head to head comparison of dobutamine-transoesophageal echocardiography and dobutamine-magnetic resonance imaging for the prediction of left ventricular functional recovery in patients with chronic coronary artery disease. *Eur Heart J* 2000;**21**:981–91. http://dx.doi.org/10.1053/euhj.2000.1946

29. Becker M, Lenzen A, Ocklenburg C, Stempel K, Kuhl H, Neizel M, *et al.* Myocardial deformation imaging based on ultrasonic pixel tracking to identify reversible myocardial dysfunction. *J Am Coll Cardiol* 2008;**51**:1473–81. http://dx.doi.org/10.1016/j.jacc.2007.10.066

30. Bondarenko O, Beek AM, Nijveldt R, McCann GP, van Dockum WG, Hofman MB, *et al.* Functional outcome after revascularization in patients with chronic ischemic heart disease: a quantitative late gadolinium enhancement CMR study evaluating transmural scar extent, wall thickness and periprocedural necrosis. *J Cardiovasc Magn Reson* 2007;**9**:815–21. http://dx.doi.org/10.1080/10976640701547335

31. Gunning MG, Anagnostopoulos C, Knight CJ, Pepper J, Burman ED, Davies G, *et al.* Comparison of Tc-tetrofosmin, and dobutamine magnetic resonance imaging for identifying hibernating myocardium. *Circulation* 1998;**98**:1869–74. http://dx.doi.org/10.1161/01.CIR.98.18.1869

32. Gutberlet M, Frohlich M, Mehl S, Amthauer H, Hausmann H, Meyer R, *et al.* Myocardial viability assessment in patients with highly impaired left ventricular function: comparison of delayed enhancement, dobutamine stress MRI, end-diastolic wall thickness, and TI201-SPECT with functional recovery after revascularization. *Eur Radiol* 2005;**15**:872–80. http://dx.doi.org/10.1007/s00330-005-2653-9

33. Kuhl HP, Battenberg T, Katoh M, Heussen N, Rassaf T, Grawe H, *et al.* Prognostic relevance of contrast-enhanced cardiovascular magnetic resonance in patients with ischemic cardiomyopathy. *Circulation* 2006;**114**(Suppl. 18):680.

34. Lauerma K, Niemi P, Hanninen H, Janatuinen T, Voipio-Pulkki LM, Knuuti J, *et al.* Multimodality MR imaging assessment of myocardial viability: combination of first-pass and late contrast enhancement to wall motion dynamics and comparison with FDG PET-initial experience. *Radiology* 2000;**217**:729–36. http://dx.doi.org/10.1148/radiology.217.3.r00dc18729

35. Martinez RR, Bennett J, Eikman EA, Fontanet HL, Sayad DE. Comparison of nitroglycerin magnetic resonance imaging with dobutamine echocardiography for predicting recovery of function after revascularization. *Am J Cardiol* 2000;**85**:1250–2. http://dx.doi.org/10.1016/S0002-9149(00)00739-6

36. Pegg TJ, Selvanayagam JB, Jennifer J, Francis JM, Karamitsos TD, Dall'Armellina E, *et al.* Prediction of global left ventricular functional recovery in patients with heart failure undergoing surgical revascularization, based on late gadolinium enhancement cardiovascular magnetic resonance. *J Cardiovasc Magn Reson* 2010;**12**;56.

37. Sandstede JJ, Bertsch G, Beer M, Kenn W, Werner E, Pabst T, *et al.* Detection of myocardial viability by low-dose dobutamine Cine MR imaging. *Magn Reson Imag* 1999;**17**:1437–43. http://dx.doi.org/10.1016/S0730-725X(99)00095-8

38. Sandstede JJ, Lipke C, Beer M, Harre K, Pabst T, Kenn W, *et al.* Analysis of first-pass and delayed contrast-enhancement patterns of dysfunctional myocardium on MR imaging: use in the prediction of myocardial viability. *Am J Roentgenol* 2000;**174**:1737–40. http://dx.doi.org/10.2214/ajr.174.6.1741737

39. Sayad DE, Willett DL, Hundley WG, Grayburn PA, Peshock RM. Dobutamine magnetic resonance imaging with myocardial tagging quantitatively predicts improvement in regional function after revascularization. *Am J Cardiol* 1998;**82**:1149–51. http://dx.doi.org/10.1016/S0002-9149(98)00579-7

40. Schmidt M, Voth E, Schneider CA, Theissen P, Wagner R, Baer FM, *et al.* F-18-FDG uptake is a reliable predictory of functional recovery of akinetic but viable infarct regions as defined by magnetic resonance imaging before and after revascularization. *Magn Reson Imag* 2004;**22**:229–36. http://dx.doi.org/10.1016/j.mri.2003.07.006

41. Schvartzman PR, Srichai MB, Grimm RA, Obuchowski NA, Hammer DF, McCarthy PM, *et al.* Nonstress delayed-enhancement magnetic resonance imaging of the myocardium predicts improvement of function after revascularization for chronic ischemic heart disease with left ventricular dysfunction. *Am Heart J* 2003;**146**:535–41. http://dx.doi.org/10.1016/S0002-8703(03)00318-1

42. Schvartzman PR, Srichai MB, Brunken RC, Rodriguez L, Obuchowski NA, White RD. Delayed-enhancement (DE) MRI: comparison with dobutamine stress echo (DSE), positron emission tomography (PET), and contraction/perfusion-MRI for determination of myocardial viability. *Circulation* 2001;**104**(Suppl. 17):534.

43. Selvanayagam JB, Kardos A, Francis JM, Wiesmann F, Petersen SE, Taggart DP, *et al.* Value of delayed-enhancement cardiovascular magnetic resonance imaging in predicting myocardial viability after surgical revascularization. *Circulation* 2004;**110**:1535–41. http://dx.doi.org/10.1161/01.CIR.0000142045.22628.74

44. Sharma R, Katz JK. Increased myocardial wall thickening as index of viability assessment: a preliminary report on delayed contrast MRI. *Contrast Media Mol Imag* 2009;**4**:37–41. http://dx.doi.org/10.1002/cmmi.260

45. Skala T, Hutyra M, Vaclavik J, Kaminek M, Horak D, Lukl J. Cardiac magnetic resonance is superior to SPECT in long-term prediction of reverse left ventricular remodeling in patients with ischemic cardiomyopathy undergoing cardiosurgical revascularization. *Eur Heart J* 2009;**30**(Suppl. 1):597–8.

46. Skala T, Hutyra M, Vaclavik J, Kaminek M, Horak D, Novotny J, *et al.* Prediction of long-term reverse left ventricular remodeling after revascularization or medical treatment in patients with ischemic cardiomyopathy: a comparative study between SPECT and MRI. *Int J Cardiovasc Imag* 2011;**27**:343–53. http://dx.doi.org/10.1007/s10554-010-9677-1

47. Trent RJ, Waiter GD, Hillis GS, McKiddie FI, Redpath TW, Walton S. Dobutamine magnetic resonance imaging as a predictor of myocardial functional recovery after revascularisation. *Heart* 2000;**83**:40–6. http://dx.doi.org/10.1136/heart.83.1.40

48. Wellnhofer E, Olariu A, Klein C, Gräfe M, Wahl A, Fleck E, *et al.* Magnetic resonance low-dose dobutamine test is superior to SCAR quantification for the prediction of functional recovery. *Circulation* 2004;**109**:2172–4. http://dx.doi.org/10.1161/01.CIR.0000128862.34201.74

49. Hunold P, Brandt-Mainz K, Knipp S, Neumann T, Debatin JF, Barkhausen J. Cardiac contrast-enhanced MRI and [18F]-FDG-PET in the assessment of myocardial viability: accuracy of the prediction of functional recovery after revascularisation. *Radiology* 2002;**225**:298.

50. Schvartzman PR, Srichai MB, Kasper JM, Obuchowski NA, Grimm RA, White RD. Non-stress delayed-enhancement cardiac MRI predicts recovery of wall motion after coronary revascularization. *Circulation* 2000;**102**(Suppl. 18):535–41.

51. Bax JJ, Visser FC, Poldermans D, Elhendy A, Cornel JH, Boersma E, *et al.* Time course of functional recovery of stunned and hibernating segments after surgical revascularization. *Circulation* 2001;**104**(Suppl. 1):I314–18. http://dx.doi.org/10.1161/hc37t1.094853

52. Kim RJ, Fieno DS, Parrish TB, Harris K, Chen EL, Simonetti O, *et al.* Relationship of MRI delayed contrast enhancement to irreversible injury, infarct age, and contractile function. *Circulation* 1999;**100**:1992–2002. http://dx.doi.org/10.1161/01.CIR.100.19.1992

53. Kuhl HP, Beek AM, van der Weerdt AP, Hofman MB, Visser CA, Lammertsma AA, *et al.* Myocardial viability in chronic ischemic heart disease: comparison of contrast-enhanced magnetic resonance imaging with (18)F-fluorodeoxyglucose positron emission tomography. *J Am Coll Cardiol* 2003;**41**:1341–8.

54. American Heart Association Writing Group on Myocardial Segmentation and Registration for Cardiac Imaging, Cerqueira MD, Weissman NJ, Dilsizian V, Jacobs AK, Kaul S, *et al.* Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart: a statement for healthcare professionals from the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association. *Circulation* 2002;**105**:539–42. http://dx.doi.org/10.1161/hc0402.102975

55. Harbord RM, Deeks JJ, Egger M, Whiting P, Sterne JA. A unification of models for meta-analysis of diagnostic accuracy studies. *Biostatistics* 2007;**8**:239–51. http://dx.doi.org/10.1093/biostatistics/kxl004

56. Drummond MF, Jefferson TO. Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. *BMJ* 1996;**313**:275–83. http://dx.doi.org/10.1136/bmj.313.7052.275

57. Drummond MF, Sculpher MJ, Torrance GW, O'Brien BJ, Stoddart GL. *Methods for the Economic Evaluation of Health Care Programmes*. Oxford University Press, Oxford; 2005.

58. Eddy DM. *Technology Assessment: the Role of Mathematical Modelling. Assessing Medical Technology*. Washington DC: National Academy Press; 1985. pp. 144–54.

59. Dussault F-P, Nguyen VH, Rachet F. *Positron Emission Tomography in Québec*. AÉTMIS 01–3 RE, xviii-270. 2001. Montréal: Agence d'évaluation des technologies et des modes d'intervention en santé (AÉTMIS); 2001. pp. xviii–270.

60. Miles KA. An approach to demonstrating cost-effectiveness of diagnostic imaging modalities in Australia illustrated by positron emission tomography. *Australa Radiol* 2001;**45**:9–18. http://dx.doi.org/10.1046/j.1440-1673.2001.00865.x

61. Beanlands RS, Dekemp RA, Smith S, Johansen H, Ruddy TD. F-18-fluorodeoxyglucose PET imaging alters clinical decision making in patients with impaired ventricular function. *Am J Cardiol* 1997;**79**:1092–5. http://dx.doi.org/10.1016/S0002-9149(97)00054-4

62. Jacklin PB, Barrington SF, Roxburgh JC, Jackson G, Sariklis D, West PA, *et al.* Cost-effectiveness of preoperative positron emission tomography in ischemic heart disease. *Ann Thorac Surg* 2002;**73**:1403–9. http://dx.doi.org/10.1016/S0003-4975(02)03459-8

63. Medical Advisory Secretariat. Positron Emission Tomography for the Assessment of Myocardial Viability: an evidence based analysis. *Ontario Health Technol Assess Series* 2005;**5**(16).

64. Auerbach MA, Schoder H, Hoh C, Gambhir SS, Yaghoubi S, Sayre JW, *et al.* Prevalence of myocardial viability as detected by positron emission tomography in patients with ischemic cardiomyopathy. *Circulation* 1999;**99**:2921–6. http://dx.doi.org/10.1161/01.CIR.99.22.2921

65. Bourantas CV, Nikitin NP, Loh HP, Lukaschuk EI, Sherwi N, de Silva R, *et al.* Prevalence of scarred and dysfunctional myocardium in patients with heart failure of ischaemic origin: a cardiovascular magnetic resonance study. *J Cardiovasc Magn Reson* 2011;**13**:53. http://dx.doi.org/10.1186/1532-429X-13-53

66. Barker AP, Nashef SA. Coronary artery bypass grafting versus percutaneous intervention in heart failure. *Scand J Surg* 2007;**96**:107–10.

67. Buszman P, Szkrobka I, Gruszka A, Parma R, Tendera Z, Lesko B, *et al.* Comparison of effectiveness of coronary artery bypass grafting versus percutaneous coronary intervention in patients with ischemic cardiomyopathy. *Am J Cardiol* 2007;**99**:36–41. http://dx.doi.org/10.1016/j.amjcard.2006.07.056

68. Camici PG, Prasad SK, Rimoldi OE. Stunning, hibernation, and assessment of myocardial viability. *Circulation* 2008;**117**:103–14. http://dx.doi.org/10.1161/CIRCULATIONAHA.107.702993

69. Beanlands RSB, Nichol G, Huszti E, Humen D, Racine N, Freeman M, *et al.* F-18-Fluorodeoxyglucose positron emission tomography imaging-assisted management of patients with severe left ventricular dysfunction and suspected coronary disease: a randomized, controlled trial (PARR-2). *J Am Coll Cardiol* 2007;**50**:2002–12. http://dx.doi.org/10.1016/j.jacc.2007.09.006

70. Cleland JG, Calvert M, Freemantle N, Arrow Y, Ball SG, Bonser RS, *et al.* The Heart Failure Revascularisation Trial (HEART). *Eur J Heart Fail* 2011;**13**:227–33. http://dx.doi.org/10.1093/eurjhf/hfq230

71. Bonow RO, Maurer G, Lee KL, Holly TA, Binkley PF, Desvigne-Nickens P, *et al.* Myocardial viability and survival in ischemic left ventricular dysfunction. *N Engl J Med* 2011;**364**:1617–25. http://dx.doi.org/10.1056/NEJMoa1100358

72. Moroi M, Yamashina A, Tsukamoto K, Nishimura T, ACCESS I. Coronary revascularization does not decrease cardiac events in patients with stable ischemic heart disease but might do in those who showed moderate to severe ischemia. *Int J Cardiol* 2012;**158**:246–52. http://dx.doi.org/10.1016/j.ijcard.2011.01.040

73. Klersy C, De SA, Gabutti G, Raisaro A, Curti M, Regoli F, *et al.* Economic impact of remote patient monitoring: an integrated economic model derived from a meta-analysis of randomized controlled trials in heart failure. *Eur J Heart Fail* 2011;**13**:450–9. http://dx.doi.org/10.1093/eurjhf/hfq232

74. Gohler A, Geisler BP, Manne JM, Kosiborod M, Zhang ZF, Weintraub WS, *et al.* Utility estimates for decision-analytic modeling in chronic heart failure-health states based on New York Heart Association classes and number of rehospitalizations. *Value Health* 2009;**12**:185–7. http://dx.doi.org/10.1111/j.1524-4733.2008.00425.x

75. Yao G, Freemantle N, Flather M, Tharmanathan P, Coats A, Poole-Wilson PA. Long-term cost-effectiveness analysis of nebivolol compared with standard care in elderly patients with heart failure: an individual patient-based simulation model. *Pharmacoeconomics* 2008;**26**:879–89. http://dx.doi.org/10.2165/00019053-200826100-00007

76. Ara R, Brazier JE. Populating an economic model with health state utility values: moving toward better practice. *Value Health* 2010;**13**:509–18. http://dx.doi.org/10.1111/j.1524-4733.2010.00700.x

77. Department of Health. *NHS reference costs 2009–10*. London, UK: Department of Health; 2011.

78. Brazier J, Roberts J, Deverill M. The estimation of a preference-based measure of health from the SF-36. *J Health Econ* 2002;**21**:271–92. http://dx.doi.org/10.1016/S0167-6296(01)00130-8

79. Doust JA, Pietrzak E, Sanders S, Glasziou PP. Identifying studies for systematic reviews of diagnostic tests was difficult due to the poor sensitivity and precision of methodologic filters and the lack of information in the abstract. *J Clin Epidemiol* 2005;**58**:444–9. http://dx.doi.org/10.1016/j.jclinepi.2004.09.011

80. Duncan BH, Ahlberg AW, Levine LG, McGill CC, Mann A, White AP, *et al.* Comparison of electrocardiographic-gated technetium-99m sestamibi single-photon emission computed tomographic imaging and rest-redistribution thallium-201 in the prediction of myocardial viability. *Am J Cardiol* 2000;**85**:680–4. http://dx.doi.org/10.1016/S0002-9149(99)00840-1

81. Leoncini M, Sciagrà R, Maioli M, Bellandi F, Marcucci G, Sestini S, *et al.* Usefulness of dobutamine Tc-99m sestamibi-gated single-photon emission computed tomography for prediction of left ventricular ejection fraction outcome after coronary revascularization for ischemic cardiomyopathy. *Am J Cardiol* 2000;**89**:817–21. http://dx.doi.org/10.1016/S0002-9149(02)02203-8

82. Mabuchi M, Kubo N, Morita K, Makino Y, Matsui Y, Murashita T, *et al.* Prediction of functional recovery after coronary bypass surgery using quantitative gated myocardial perfusion SPECT. *Nucl Med Commun* 2003;**24**:625–31. http://dx.doi.org/10.1097/00006231-200306000-00003

83. Murashita T, Makino Y, Kamikubo Y, Yasuda K, Mabuchi M, Tamaki N. Quantitative gated myocardial perfusion single photon emission computed tomography improves the prediction of regional functional recovery in akinetic areas after coronary bypass surgery: useful tool for evaluation of myocardial viability. *J Thorac Cardiovasc Surg* 2003;**126**:1328–34.

84. Sciagrà R, Leoncini M, Marcucci G, Dabizzi RP, Pupi A. Technetium-99m sestamibi imaging to predict left ventricular ejection fraction outcome after revascularisation in patients with chronic coronary artery disease and left ventricular dysfunction: comparison between baseline and nitrate-enhanced imaging. *Eur J Nucl Med* 2001;**28**:680–7. http://dx.doi.org/10.1007/s002590100543

85. Leoncini M, Sciagrà R, Bellandi F, Maioli M, Sestini S, Marcucci G, *et al.* Low-dose dobutamine nitrate-enhanced technetium 99m sestamibi gated SPECT versus low-dose dobutamine echocardiography for detecting reversible dysfunction in ischemic cardiomyopathy. *J Nucl Cardiol* 2002;**9**:402–6. http://dx.doi.org/10.1067/mnc.2002.123856

86. González JM, Castell-Conesa J, Candell-Riera J, Rosselló-Urgell J, Spanish Working Group of Nuclear Cardiology. Relevance of 99mTc-MIBI rest uptake, ejection fraction and location of contractile abnormality in predicting myocardial recovery after revascularization. *Nucl Med Commun* 2001;**22**:795–805. http://dx.doi.org/10.1097/00006231-200107000-00011

87. Slart RHJA, Bax JJ, van Veldhuisen DJ, van der Wall EE, Irwan R, Sluiter WJ, *et al.* Prediction of functional recovery after revascularisation in patients with chronic ischaemic left ventricular dysfunction: head-to-head comparison between ^{99m}Tc-sestamibi/^{18}F-FDG DISA SPECT and ^{13}N-ammonia/^{18}F-FDG PET. *Eur J Nucl Med Mol Imag* 2006;**33**:716–23. http://dx.doi.org/10.1007/s00259-005-0016-z

88. Nowak B, Schaefer WM, Koch KC, Kaiser HJ, Block S, Knackstedt C, *et al.* Assessment of myocardial viability in dysfunctional myocardium by resting myocardial blood flow determined with oxygen 15 water PET. *J Nucl Cardiol* 2003;**10**:34–45. http://dx.doi.org/10.1067/mnc.2003.128743

89. Cwajg JM, Cwajg E, Nagueh SF, He ZX, Qureshi U, Olmos LI, *et al.* End-diastolic wall thickness as a predictor of recovery of function in myocardial hibernation: relation to rest-redistribution T1-201 tomography and dobutamine stress echocardiography. *J Am Coll Cardiol* 2000;**35**:1152–61. http://dx.doi.org/10.1016/S0735-1097(00)00525-8

90. Ling LH, Christian TF, Mulvagh SL, Klarich KW, Hauser MF, Nishimura RA, *et al.* Determining myocardial viability in chronic ischemic left ventricular dysfunction: a prospective comparison of rest-redistribution thallium 201 single-photon emission computed tomography, nitroglycerin-dobutamine echocardiography, and intracoronary myocardial contrast echocardiography. *Am Heart J* 2006;**151**:882–9. http://dx.doi.org/10.1016/j.ahj.2005.06.023

91. Zaglavara T, Karvounis HI, Haaverstad R, Pillay TM, Hamilton JR, Hasan A, *et al.* Dobutamine stress echocardiography is highly accurate for the prediction of contractile reserve in the early postoperative period, but may underestimate late recovery in contractile reserve after revascularization of the hibernating myocardium. *J Am Soc Echocardiogr* 2006;**19**:300–6. http://dx.doi.org/10.1016/j.echo.2005.09.020

92. Hanekom L, Jenkins C, Jeffries L, Case C, Mundy J, Hawley C, *et al.* Incremental value of strain rate analysis as an adjunct to wall-motion scoring for assessment of myocardial viability by dobutamine echocardiography: a follow-up study after revascularization. *Circulation* 2005;**112**:3892–900. http://dx.doi.org/10.1161/CIRCULATIONAHA.104.489310

93. Dellegrottaglie S, Perrone-Filardi P, Pace L, Prastaro M, Della Morte AM, Ponticelli MP, *et al.* Prediction of long-term effects of revascularization on regional and global left ventricular function by dobutamine echocardiography and rest Tl-201 imaging alone and in combination in patients with chronic coronary artery disease. *J Nucl Cardiol* 2002;**9**:174–82. http://dx.doi.org/10.1067/mnc.2002.120162

94. Piscione F, Perrone-Filardi P, De Luca G, Prastaro M, Indolfi C, Golino P, *et al.* Low dose dobutamine echocardiography for predicting functional recovery after coronary revascularisation. *Heart* 2001;**86**:679–86. http://dx.doi.org/10.1136/heart.86.6.679

95. Pace L, Filardi PP, Cuocolo A, Prastaro M, Acampa W, Dellegrottaglie S, *et al.* Diagnostic accuracy of low-dose dobutamine echocardiography in predicting post-revascularisation recovery of function in patients with chronic coronary artery disease: relationship to thallium-201 uptake. *Eur J Nucl Med* 2001;**28**:1616–23. http://dx.doi.org/10.1007/s002590100608

96. Piscione F, De Luca G, Perrone-Filardi P, Prastaro M, Pace L, Galasso G, *et al.* Relationship between contractile reserve, Tl-201 uptake, and collateral angiographic circulation in collateral-dependent myocardium: implications regarding the evaluation of myocardial viability. *J Nucl Cardiol* 2003;**10**:17–27. http://dx.doi.org/10.1067/mnc.2003.127012

Appendix 1 Search strategy

MEDLINE search strategies

Initial search

1. Cardiomyopathies/ or Myocardial Ischemia/ or Cardiomyopathy, Dilated/
2. (isch$ adj1 cardiomyopath$).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier]
3. 1 or 2
4. Magnetic Resonance Imaging/ or Magnetic Resonance Imaging, Cine/
5. cardiac magnetic resonance imag$.ti,ab.
6. cardiac magnetic resonance.mp.
7. CMR.ti,ab.
8. or/4-7
9. 3 and 8
10. exp "Sensitivity and Specificity"/
11. sensitivity.tw.
12. specificity.tw.
13. ((pre-test or pretest) adj probability).tw.
14. post-test probability.tw.
15. predictive value$.tw.
16. likelihood ratio$.tw.
17. or/10-16
18. prognosis.sh.
19. diagnosed.tw.
20. cohort:.mp.
21. predictor:.tw.
22. death.tw.
23. exp models, statistical/
24. or/18-23
25. 17 or 24
26. **9 and 25**
27. Meta-Analysis/
28. meta analy$.tw.
29. metaanaly$.tw.
30. meta analysis.pt.
31. (systematic adj (review$1 or overview$1)).tw.
32. exp Review Literature/
33. or/27-32
34. cochrane.ab.
35. embase.ab.
36. (psychlit or psyclit).ab.
37. (psychinfo or psycinfo).ab.
38. (cinahl or cinhal).ab.
39. science citation index.ab.
40. bids.ab.
41. cancerlit.ab.
42. or/34-41
43. reference list$.ab.
44. bibliograph$.ab.

45. hand-search$.ab.
46. relevant journals.ab.
47. manual search$.ab.
48. or/43-47
49. selection criteria.ab.
50. data extraction.ab.
51. 49 or 50
52. review.pt.
53. 51 and 52
54. comment.pt.
55. letter.pt.
56. editorial.pt.
57. animal/
58. human/
59. 57 not (57 and 58)
60. or/54-56,59 (4,524,361)
61. 33 or 42 or 48 or 53 (1,626,552)
62. 61 not 60 (1,479,918)
63. **9 and 62**
64. randomized controlled trial.pt.
65. controlled clinical trial.pt.
66. randomized controlled trials/
67. random allocation/
68. double blind method/
69. single blind method/
70. clinical trial.pt.
71. exp Clinical Trial/
72. (clin$ adj25 trial$).ti,ab.
73. ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.
74. placebos/
75. placebos.ti,ab.
76. random.ti,ab.
77. research design/
78. or/64-77
79. **9 and 78**
80. Practice Guideline/
81. Guideline/
82. Practice Guidelines as Topic/
83. Consensus Development Conference/
84. Guideline Adherence/
85. practice guideline.pt.
86. guideline.pt.
87. consensus development conference.pt.
88. practice guideline$.tw.
89. practice parameter$.tw.
90. recommendation$.tw.
91. guideline$.ti.
92. consensus.ti.
93. or/80-92
94. (comment or letter or editorial or note or erratum or short survey or news or newspaper article or patient education handout or case report or historical article).pt.
95. 93 not 94
96. Animals/

97. 95 not 96
98. 9 and 97
99. Economics/
100. "costs and cost analysis"/
101. Cost allocation/
102. Cost-benefit analysis/
103. Cost control/
104. cost savings/
105. Cost of illness/
106. Cost sharing/
107. "deductibles and coinsurance"/
108. Health care costs/
109. Direct service costs/
110. Drug costs/
111. Employer health costs/
112. Hospital costs/
113. Health expenditures/
114. Capital expenditures/
115. Value of life/
116. exp economics, hospital/
117. exp economics, medical/
118. Economics, nursing/
119. Economics, pharmaceutical/
120. exp "fees and charges"/
121. exp budgets/
122. (low adj cost).mp.
123. (high adj cost).mp.
124. (health?care adj cost$).mp.
125. (fiscal or funding or financial or finance).tw.
126. (cost adj estimate$).mp.
127. (cost adj variable).mp.
128. (unit adj cost$).mp.
129. (economic$ or pharmacoeconomic$ or price$ or pricing).tw.
130. or/99-129
131. 9 and 130

Additional searches

1. *Myocardial Revascularisation/
2. Magnetic Resonance Imaging/
3. magnetic resonance imag$.ti,ab.
4. MRI.ti,ab.
5. or/2-4
6. 1 and 5
7. ri.fs.
8. Myocardial Infarction/
9. Coronary Disease/
10. Coronary Artery Disease/
11. or/2-4
12. 1 and 5
13. di.fs.
14. 6 and 7
15. Magnetic Resonance Imaging/

16. 8 and 9
17. Cardiomyopathies/ or Myocardial Ischemia/ or Cardiomyopathy, Dilated/
18. (isch$ adj1 cardiomyopath$).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier]
19. 1 or 2
20. Magnetic Resonance Imaging/ or Magnetic Resonance Imaging, Cine/
21. cardiac magnetic resonance imag$.ti,ab.
22. cardiac magnetic resonance.mp.
23. CMR.ti,ab.
24. or/4-7
25. 3 and 8
26. comparative study.pt
27. 9 and 10
28. *Magnetic Resonance Imaging/
29. myocardial salvage.ti,ab.
30. 1 and 2

Appendix 2 List of excluded studies

TABLE 25 Full-text articles with reasons for exclusion

Reference	Reason for exclusion
Alfakih K, Sparrow P, Plein S, Sivananthan MU, Walters K, Ridgway JP, *et al.* Delayed enhancement imaging: standardised segmental assessment of myocardial viability in patients with ST-elevation myocardial infarction. *Eur J Radiol* 2008;**66**:42–7	Acute MI
Baer F, Voth E, Larosee K, Theissen P, Crnac J, Schmidt M, *et al.* Predictive value of functional and metabolic parameters of myocardial viability for the post-revascularisation recovery of left-ventricular function: dobutamine-TEE and dobutamine-MRI versus FDG-PET. *Eur Heart J* 1998;**19**:629	Incomplete record
Baer FM, Voth E, Schneider CA, Theissen P, Crnac J, Schmidt M, *et al.* Dobutamine-magnetic resonance imaging is a reliable alternative to positron emission tomography for the prediction of functional recovery of viable myocardium after successful revascularisation. *Circulation* 1998;**98**:I513	Incomplete record
Barmeyer AA, Stork A, Bansmann M, Muellerleile K, Heuer M, Bavastro M, *et al.* Prediction of myocardial recovery by dobutamine magnetic resonance imaging and delayed enhancement early after reperfused acute myocardial infarction. *Eur Radiol* 2008;**18**:110–18	Acute MI
Bauner KU, Muehling O, Theisen D, Hayes C, Wintersperger BJ, Reiser MF, *et al.* Assessment of myocardial viability with 3D MRI at 3 T. *Am J Roentgenol* 2009;**192**:1645–50	Review
Bax JJ, de RA, van der Wall EE. Assessment of myocardial viability by MRI. *J Magn Reson Imag* 1999;**10**:418–22	Review
Bax JJ, Lamb H, Dibbets P, Pelikan H, Boersma E, Viergever EP, *et al.* Comparison of gated single-photon emission computed tomography with magnetic resonance imaging for evaluation of left ventricular function in ischemic cardiomyopathy. *Am J Cardiol* 2000;**86**:1299–305	Not viability assessment
Bax JJ, van der Wall EE. Evaluation of myocardial viability in chronic ischemic cardiomyopathy. *Int J Cardiovasc Imag* 2003;**19**:137–40	Review
Bax JJ. Assessment of myocardial viability in ischemic cardiomyopathy. *Heart Lung Circulat* 2005;**14**:8–13	Review
Bax JJ, Poldermans D, Elhendy A, Boersma E, van der Wall EE. Assessment of myocardial viability by nuclear imaging techniques. *Curr Cardiol Rep* 2005;**7**:124–9	Review
Bax JJ, Poldermans D, Schuijf JD, Scholte AJ, Elhendy A, van der Wall EE. Imaging to differentiate between ischemic and nonischemic cardiomyopathy. *Heart Fail Clin* 2006;**2**:205–14	Review
Beanlands RS, Chow BJ, Dick A, Friedrich MG, Gulenchyn KY, Kiess M, *et al.* CCS/CAR/CANM/CNCS/CanSCMR joint position statement on advanced noninvasive cardiac imaging using positron emission tomography, magnetic resonance imaging and multidetector computed tomographic angiography in the diagnosis and evaluation of ischemic heart disease – executive summary. *Can J Cardiol* 2007;**23**:107–19	Review
Becker M, Altiok E, Lente C, Otten S, Friedman Z, Adam D, *et al.* Layer-specific analysis of myocardial function for accurate prediction of reversible ischaemic dysfunction in intermediate viability defined by contrast-enhanced MRI. *Heart* 2011;**97**:748–56	Deformation imaging (MRI with echocardiography, similar to coregistration)
Becker M, Lenzen M, Stempel K, Franke A, Kelm M, Hoffmann R. The use of myocardial deformation imaging based on ultrasonic pixel tracking to identify reversible myocardial dysfunction. *Circulation* 2007;**116**:501	Review
Beek AM, Bondarenko O, Afsharzada F, van Rossum AC. Quantification of late gadolinium enhanced CMR in viability assessment in chronic ischemic heart disease: a comparison to functional outcome. *J Cardiovasc Magn Reson* 2009;**11**:6	No useable data

continued

TABLE 25 Full-text articles with reasons for exclusion (*continued*)

Reference	Reason for exclusion
Beek AM, van Rossum AC. Use of cardiovascular magnetic resonance imaging in the assessment of left ventricular function, scar and viability in patients with ischaemic cardiomyopathy and chronic myocardial infarction. *Heart* 2010;**96**:1494–501	Review
Beer M, Machann W, Sandstede J, Buchner S, Lipke C, Kostler H, *et al.* Energetic differences between viable and non-viable myocardium in patients with recent myocardial infarction are not an effect of differences in wall thinning – a multivoxel P-31-MR-spectroscopy and MRI study. *Eur Radiol* 2007;**17**:1275–83	Not viability assessment
Beller GA. Noninvasive assessment of myocardial viability. *N Engl J Med* 2000;**343**:1488–90	Review
Beller GA, Budge LP. Viable: yes, no, or somewhere in the middle? *JACC Cardiovasc Imag* 2009;**2**:1069–71	Review
Bello D, Shah DJ, Farah GM, Di LS, Parker M, Johnson MR, *et al.* Gadolinium cardiovascular magnetic resonance predicts reversible myocardial dysfunction and remodeling in patients with heart failure undergoing beta-blocker therapy. *Circulation* 2003;**108**:1945–53	Not viability assessment
Bernhardt P, Spiess J, Levenson B, Pilz G, Hofling B, Hombach V, *et al.* Combined assessment of myocardial perfusion and late gadolinium enhancement in patients after percutaneous coronary intervention or bypass grafts: a multicenter study of an integrated cardiovascular magnetic resonance protocol. *JACC Cardiovasc Imag* 2009;**2**:1292–300	Not viability assessment
Bernhardt P, Engels T, Levenson B, Haase K, Albrecht A, Strohm O. Prediction of necessity for coronary artery revascularisation by adenosine contrast-enhanced magnetic resonance imaging. *Int J Cardiol* 2006;**112**:184–90	Not hibernating myocardium
Bodi V, Sanchis J, Lopez-Lereu MP, Losada A, Nunez J, Pellicer M, *et al.* Usefulness of a comprehensive cardiovascular magnetic resonance imaging assessment for predicting recovery of left ventricular wall motion in the setting of myocardial stunning. *J Am Coll Cardiol* 2005;**46**:1747–52	Acute MI
Bogaert J, Dymarkowski S. Delayed contrast-enhanced MRI: use in myocardial viability assessment and other cardiac pathology. *Eur Radiol* 2005;**15**(Suppl. 2):B52–8	Review
Bondarenko O, Beek AM, Twisk JW, Visser CA, van Rossum AC. Time course of functional recovery after revascularisation of hibernating myocardium: a contrast-enhanced cardiovascular magnetic resonance study. *Eur Heart J* 2008;**29**:2000–5	Not viability assessment
Borreguero LJJ, Ruiz-Salmeron R. Assessment of myocardial viability in patients before revascularisation. *Revista Espanola de Cardiologia* 2003;**56**:721–33	Non-English
Bree D, Wollmuth JR, Cupps BP, Krock MD, Howells A, Rogers J, *et al.* Low-dose dobutamine tissue-tagged magnetic resonance imaging with 3-dimensional strain analysis allows assessment of myocardial viability in patients with ischemic cardiomyopathy. *Circulation* 2006;**114**(Suppl. 1):I33–6	Comparison with healthy volunteers – does not fit into any of the three sections
Carlsson M, Ubachs JF, Hedstrom E, Heiberg E, Jovinge S, Arheden H. Myocardium at risk after acute infarction in humans on cardiac magnetic resonance: quantitative assessment during follow-up and validation with single-photon emission computed tomography. *JACC Cardiovasc Imag* 2009;**2**:569–76	Acute MI
Casolo G, Minneci S, Manta R, Sulla A, Del MJ, Rega L, *et al.* Identification of the ischemic etiology of heart failure by cardiovascular magnetic resonance imaging: diagnostic accuracy of late gadolinium enhancement. *Am Heart J* 2006;**151**:101–8	Not viability assessment
Castro PF, Bourge RC, Foster RE. Evaluation of hibernating myocardium in patients with ischemic heart disease. *Am J Med* 1998;**104**:69–77	Review
Catalan P, Delgado V, Moya JL, Pare C, Munoz M, Caralt T, *et al.* [Assessing myocardial viability by magnetic resonance imaging]. *Revista Espanola de Cardiologia Suplementos* 2006;**6**:49E–56E	Non-English
Chan FP, Williamson EE. MR functional and viability assessment of the heart. *Appl Radiol* 2003;**32**:11–20	Review

TABLE 25 Full-text articles with reasons for exclusion (*continued*)

Reference	Reason for exclusion
Cury RC, Cattani CA, Gabure LA, Racy DJ, de Gois JM, Siebert U, *et al.* Diagnostic performance of stress perfusion and delayed-enhancement MR imaging in patients with coronary artery disease. *Radiology* 2006;**240**:39–45	Not hibernating myocardium
De FM, Julsrud P, Araoz P, De BM, Agnese G, Squarcia U, *et al.* MRI evaluation of myocardial viability. *Radiologia Medica* 2006;**111**:1035–53	Review
de RA, Doornbos J, Rebergen S, Van RP, Pattynama P, Van Der WALL. Cardiovascular applications of magnetic resonance imaging and phosphorus-31 spectroscopy. *Eur J Radiol* 1992;**14**:97–103	Review
Dendale P, Franken PR, Block P, Pratikakis Y, de RA. Contrast enhanced and functional magnetic resonance imaging for the detection of viable myocardium after infarction. *Am Heart J* 1998;**135**:875–80	Review
Eitel I, Fuernau G, Sareban M, Desch S, Gutberlet M, Schuler G, *et al.* Prognostic significance and determinants of myocardial salvage assessed by cardiovascular magnetic resonance imaging. *Circulation* 2009;**120**:S336	Acute MI
Elliott MD, Kim RJ. Late gadolinium cardiovascular magnetic resonance in the assessment of myocardial viability. *Coron Artery Dis* 2005;**16**:365–72	Review
Fedele F, Montesano T, Ferro-Luzzi M, Di CE, Di RP, Scopinaro F, *et al.* Identification of viable myocardium in patients with chronic coronary artery disease and left ventricular dysfunction: role of magnetic resonance imaging. *Am Heart J* 1994;**128**:484–9.	No useable data
Foo TKF, Stanley DW, Castillo E, Rochitte CE, Wang Y, Lima JAC, *et al.* Myocardial viability: breath-hold 3D MR imaging of delayed hyperenhancement with variable sampling in time. *Radiology* 2004;**230**:845–51	Not viability assessment
Gerbaud E, Faury A, Coste P, Erickson M, Corneloup O, Dos SP, *et al.* Comparative analysis of cardiac magnetic resonance viability indexes to predict functional recovery after successful percutaneous coronary intervention in acute myocardial infarction. *Am J Cardiol* 2010;**105**:598–604	Acute MI
Giordano A, Calcagni ML, Verrillo A, Maccafeo S. Myocardial SPECT in the study of ischemic heart disease detection of hibernating myocardium and evaluation of cost/benefit ratio. *Rays* 1999;**24**:73–80	Not CMR
Grover-McKay M. Detection of myocardial viability and infarction using cardiac MRI. *Appl Radiol* 2002;**31**:15–16	Review
Gunning MG, Kaprielian RR, Pepper J, Pennell DJ, Sheppard MN, Severs NJ, *et al.* The histology of viable and hibernating myocardium in relation to imaging characteristics. *J Am Coll Cardiol* 2002;**39**:428–35	Review
Gunning MG, Anagnostopoulos C, Kinight CJ, Pepper J, Burman ED, Davies G, *et al.* Comparison of 201 Tl, 99m Tc-tetrofosmin and dobutamine magnetic resonance imaging for identifying hibernating myocardium. *Circulation* 1998;**98**:1869–74	No useable data
Heasley DC, Bluemke DA. MR evaluation of myocardial viability in chronic ischemic heart disease. *Appl Radiol* 2003;**32**:58–64	Review
Hillenbrand HB, Sandstede J, Lipke C, Kostler H, Pabst T, Werner E, *et al.* Detection of myocardial viability in acute infarction using contrast-enhanced H-1 magnetic resonance imaging. *Magn Reson Materials Phys Biol Med* 2003;**16**:129–34	Acute MI
Hofman HA, Knaapen P, Boellaard R, Bondarenko O, Gotte MJ, van Dockum WG, *et al.* Measurement of left ventricular volumes and function with O-15-labelled carbon monoxide gated positron emission tomography: comparison with magnetic resonance imaging. *J Nucl Cardiol* 2005;**12**:639–44	Not viability assessment
Horn M. 23Na magnetic resonance imaging for the determination of myocardial viability: the status and the challenges. *Curr Vasc Pharmacol* 2004;**2**:329–33	Review
Isbell DC, Kramer CM. Cardiovascular magnetic resonance: structure, function, perfusion, and viability. *J Nucl Cardiol* 2005;**12**:324–36	Review

continued

TABLE 25 Full-text articles with reasons for exclusion (*continued*)

Reference	Reason for exclusion
Isbell DC, Kramer CM. Magnetic resonance for the assessment of myocardial viability. *Curr Opin Cardiol* 2006;**21**:469–72	Review
Jacquier A, Revel D, Croisille P, Gaubert JY, Saeed M. [Mechanisms of delayed myocardial enhancement and value of MR and CT contrast materials in the evaluation of myocardial viability]. *Journal de Radiologie* 2010;**91**:751–7	Review
Kaandorp T, Lamb H, van der Wall E, de Roos A, Bax J. Cardiovascular MR to access myocardial viability in chronic ischaemic LV dysfunction. *Heart* 2005;**91**:1359–65	Review
Kim RJ, Shah DJ. Fundamental concepts in myocardial viability assessment revisited: when knowing how much is "alive" is not enough. *Heart* 2004;**90**:137–40	Review
Klein C, Nekolla SG, Bengel FM, Momose M, Sammer A, Haas F, *et al.* Assessment of myocardial viability with contrast-enhanced magnetic resonance imaging comparison with positron emission tomography. *Circulation* 2002;**105**:162–7	Non-viable analysis
Klein C. Magnetic resonance imaging and positron emission tomography as predictors of heart failure. *Heart Metab* 2009;**42**:15–20	Review
Klow NE, Smith HJ, Gullestad L, Seem E, Endresen K. Outcome of bypass surgery in patients with chronic ischemic left ventricular dysfunction. Predictive value of MR imaging. *Acta Radiol* 1997;**38**:76–82	Not hibernating myocardium
Knuesel PR, Nanz D, Wyss C, Buechi M, Kaufmann PA, von Schulthess GK, *et al.* Characterization of dysfunctional myocardium by positron emission tomography and magnetic resonance: relation to functional outcome after revascularization. The role of magnetic resonance imaging in the diagnosis of coronary artery disease. *Circulation* 2003;**108**:1095–100	Not viability assessment
Kuehl HP, Battenberg T, Katoh M, Heussen N, Rassaf T, Grawe H, *et al.* Prognostic relevance of contrast-enhanced cardiovascular magnetic resonance in patients with ischemic cardiomyopathy. *Circulation* 2006;**114**:680	Not viability assessment
Kuhl HP, Spuentrup E, Wall A, Franke A, Schroder J, Heussen N, *et al.* Assessment of myocardial function with interactive non-breath-hold real-time MR imaging: comparison with echocardiography and breath-hold Cine MR imaging. The role of magnetic resonance imaging in the diagnosis of coronary artery disease. *Radiology* 2004;**231**:198–207	Not viability assessment
Lenge VV, Muthupilla R, Van den Bosch H, Greenwood J, Gerber B, Krittyaphong R, *et al.* Delayed-enhancement MRI can predict recovery of LV function after revascularisation: results from an international multicenter myocardial viability trial. *J Am Coll Cardiol* 2008;**51**:A163	No useable data
Maddahi J. Viability assessment with MRI is superior to FDG-PET for viability: pro. *J Nucl Cardiol* 2010;**17**:292–7	Review
Moon JC, Prasad SK. Cardiovascular magnetic resonance and the evaluation of heart failure. *Curr Cardiol Rep* 2005;**7**:39–44	Review
Murtagh J, Foerster V, Warburton RN, Lentle BC, Wood RJ, Mensinkai S, *et al.* Clinical and cost effectiveness of CT and MRI for selected clinical disorders: results of two systematic reviews. *Ottawa Can Agency Drugs Technol Health* 2006;**15**:1–11	Review
Murtagh J, Warburton RN, Foerster V, Lentle BC, Wood RJ, Mensinkai S, *et al.* CT and MRI for selected clinical disorders: a systematic review of economic evaluations. *Ottawa Can Agency Drugs Technol Health* 2006;**96**:1–32	Review
Muzzarelli S, Ordovas K, Higgins CB. Cardiovascular MRI for the assessment of heart failure: focus on clinical management and prognosis. *J Magn Reson Imag* 2011;**33**:275–86	Review
Nagel E, Schuster A. Shortening without contraction: new insights into hibernating myocardium. *JACC Cardiovasc Imag* 2010;**3**:731–3	Review
Patterson RE, Sigman SR, O'Donnell RE, Eisner RL. Viability assessment with MRI is superior to FDG-PET for viability: con. *J Nucl Cardiol* 2010;**17**:298–309	Review

TABLE 25 Full-text articles with reasons for exclusion (*continued*)

Reference	Reason for exclusion
Peshock RM. Assessing myocardial viability with magnetic resonance imaging. *Am J Cardiac Imag* 1992;**6**:237–43	Review
Poldermans D, Bax JJ, Boersma E, De HS, Eeckhout E, Fowkes G, *et al.* Guidelines for pre-operative cardiac risk assessment and perioperative cardiac management in non-cardiac surgery: the task force for preoperative cardiac risk assessment and perioperative cardiac management in non-cardiac surgery of the European society of Cardiology (ESC) and endorsed by the European society of anaesthesiology (ESA). *Eur J Anaesthesiol* 2010;**27**:92–137	Review
Potter DD, Araoz PA, Mcgee KP, Harmsen WS, Mandrekar JN, Sundt TM. Low-dose dobutamine cardiac magnetic resonance imaging with myocardial strain analysis predicts myocardial recoverability after coronary artery bypass grafting. *J Thorac Cardiovasc Surg* 2008;**135**:1342–7	No useable data
Ragosta M, Beller GA. The noninvasive assessment of myocardial viability. *Clin Cardiol* 1993;**16**:531–8	Review
Ramani K, Judd RM, Holly TA, Parrish TB, Rigolin VH, Parker MA, *et al.* Contrast magnetic resonance imaging in the assessment of myocardial viability in patients with stable coronary artery disease and left ventricular dysfunction. *Circulation* 1998;**98**:2687–94	No useable data
Rerkpattanapipat P. Low-dose dobutamine imagings predicting regional improvement in left ventricular function after revascularisation. *Am J Cardiol* 2000;**86**:1402–3	Letter
Richardson JD, Bertaso A, Wong D, Nelson AJ, Tayeb H, Carbone A, *et al.* Prognostic value of negative adenosine stress perfusion cardiac magnetic resonance with late gadolinium enhancement in intermediate cardiovascular risk patients. *J Am Coll Cardiol* 2011;**57**:E675	Not viability assessment
Rizzello V, Poldermans D, Bax JJ. Assessment of myocardial viability in chronic ischemic heart disease: current status. *Q J Nucl Med Mol Imag* 2005;**49**:81–96	Review
Roes SD, Kaandorp TAM, Marsan NA, Westenberg JJM, Dibbets-Schneider P, Stokkel MP, *et al.* Agreement and disagreement between contrast-enhanced magnetic resonance imaging and nuclear imaging for assessment of myocardial viability. *Eur J Nucl Med Mol Imag* 2009;**36**:594–601	No useable data
Rost C, Schmid M, Daniel W, Flachskampf F. The combined use of wall motion score and circumferential strain improves detection of myocardial viability. *Eur Heart J* 2010;**31**:1064	Not CMR
Ruzsics B, Rosenblum M, Zwerner P, Chiaramida S, Abro J, Vogt S, *et al.* Adenosine stress dual-energy CT of the heart for diagnosing myocardial ischemia and viability compared with cardiac MRI and SPECT: initial experience. *J Am Coll Cardiol* 2009;A262	Not hibernating myocardium
Sachdev V, Aletras AH, Padmanabhan S, Sidenko S, Rao YN, Brenneman CL, *et al.* Myocardial strain decreases with increasing transmurality of infarction: a Doppler echocardiographic and magnetic resonance correlation study. *J Am Soc Echocardiography* 2006;**19**:34–9	Not viability assessment
Sadeghian H, Majd-Ardakani J, Lotfi-Tokaldany M. Assessment of myocardial viability: selection of patients for viability study and revascularisation. *J Tehran Uni Heart Center* 2009;**4**:5–15	Incomplete record
Saeed M, Wendland MF, Watzinger N, Akbari H, Higgins CB. MR contrast media for myocardial viability, microvascular integrity and perfusion. *Eur J Radiol* 2000;**34**:179–95	Review
Samady H, Choi C, Ragosta M, Powers ER, Beller GA, Kramer CM. Electromechanical mapping identifies improvement in function and retention of contractile reserve after revascularisation in ischemic cardiomyopathy. *Circulation* 2004;**110**:2410–16	No useable data
Sanz J, Rius T, Kuschnir P, Bodes RS, Poon M. Assessment of myocardial ischemia and viability using cardiac magnetic resonance. *Curr Cardiol Rep* 2004;**6**:62–9	Review

continued

TABLE 25 Full-text articles with reasons for exclusion (*continued*)

Reference	Reason for exclusion
Sanz J, Poon M. Evaluation of ischemic heart disease with cardiac magnetic resonance and computed tomography. *Exp Rev Cardiovasc Ther* 2004;**2**:601–15	Review
Saraste A, Nekolla S, Schwaiger M. Contrast-enhanced magnetic resonance imaging in the assessment of myocardial infarction and viability. *J Nucl Cardiol* 2008;**15**:105–17	Review
Sawada SG. Positron emission tomography for assessment of viability. *Curr Opin Cardiol* 2006;**21**:464–8	Not CMR
Schaefer WM, Lipke CS, Standke D, Kühl HP, Nowak B, Kaiser HJ, *et al.* Quantification of left ventricular volumes and ejection fraction from gated 99mTc-MIBI SPECT: MRI validation and comparison of the Emory Cardiac Tool Box with QGS and 4D-MSPECT. *J Nucl Med* 2005;**46**:1256–63	Not CMR viability data, only SPECT
Schalla S, Klein C, Paetsch I, Lehmkuhl H, Bornstedt A, Schnackenburg B, *et al.* Real-time MR image acquisition during high-dose dobutamine hydrochloride stress for detecting left ventricular wall-motion abnormalities in patients with coronary arterial disease. *Radiology* 2002;**224**:845–51	Not viability assessment
Schecter SO, Teichholz LE, Klig V, Goldman ME. Ultrasonic tissue characterization: review of a noninvasive technique for assessing myocardial viability. *Echocardiography* 1996;**13**:415–30	Review
Schietinger BJ, Voros S, Isbell DC, Meyer CH, Christopher JM, Kramer CM. Can late gadolinium enhancement by cardiovascular magnetic resonance identify coronary artery disease as the etiology of new onset congestive heart failure? *Int J Cardiovasc Imag* 2007;**23**:595–602	Review
Schinkel AF, Poldermans D, Elhendy A, Bax JJ. Assessment of myocardial viability in patients with heart failure. *J Nucl Med* 2007;**48**:1135–46	Review
Schinkel AF, Bax JJ, Delgado V, Poldermans D, Rahimtoola SH. Clinical relevance of hibernating myocardium in ischemic left ventricular dysfunction. *Am J Med* 2010;**123**:978–86	Review
Schinkel AFL, Bax JJ, Poldermans D, Elhendy A, Ferrari R, Rahimtoola SH. Hibernating myocardium: diagnosis and patient outcomes. *Curr Problems Cardiol* 2007;**32**:375–410	Review
Schwitter J, Nanz D, Kneifel S, Bertschinger K, Büchi M, Knüsel PR, *et al.* Assessment of myocardial perfusion in coronary artery disease by magnetic resonance: a comparison with positron emission tomography and coronary angiography. *Circulation* 2001;**103**:2230–5	Detecting CAD
Schwitter J, Arai AE. Assessment of cardiac ischaemia and viability: role of cardiovascular magnetic resonance. *Eur Heart J* 2011;**32**:799	Review
Selvanayagam JB, Rahimi K, Banning A, Cheng AS, Pegg TJ, Karamitsos TD, *et al.* Prognostic significance of post-revascularisation irreversible myocardial injury detected by cardiovascular magnetic resonance imaging. *Circulation* 2007;**116**:694	Not viability assessment
Selvanayagam JB, Jerosch-Herold M, Porto I, Sheridan D, Cheng AS, Petersen SE, *et al.* Resting myocardial blood flow is impaired in hibernating myocardium – a magnetic resonance study of quantitative perfusion assessment. *Circulation* 2005;**112**:3289–96	Not hibernating myocardium
Senior R. Diagnostic and imaging considerations: role of viability. *Heart Fail Rev* 2006;**11**:125–34	Review
Senthilkumar A, Majmudar MD, Shenoy C, Kim HW, Kim RJ. Identifying the etiology: a systematic approach using delayed-enhancement cardiovascular magnetic resonance. *Heart Fail Clin* 2009;**5**:349–67	Review
Shan K, Constantine G, Sivananthan M, Flamm SD. Role of cardiac magnetic resonance imaging in the assessment of myocardial viability. *Circulation* 2004;**109**:1328–34	Review
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)	Not viability assessment

TABLE 25 Full-text articles with reasons for exclusion (*continued*)

Reference	Reason for exclusion
Slart RH, Bax JJ, van-Veldhuisen DJ, van der Wall EE, Dierckx RA, De BJ, *et al.* Prediction of functional recovery after revascularisation in patients with coronary artery disease and left ventricular dysfunction by gated FDG-PET. *J Nucl Cardiol* 2006;**13**:210–19	Not CMR viability data, only PET
Slart RH, Bax JJ, van Veldhuisen DJ, van der Wall EE, Irwan R, Sluiter WJ, *et al.* Prediction of functional recovery after revascularisation in patients with chronic ischaemic left ventricular dysfunction: head-to-head comparison between ^{99m}Tc-sestamibi/^{18}F-FDG DISA SPECT and ^{13}N-ammonia/^{18}F-FDG PET. *Eur J Nucl Med Mol Imag* 2006;**33**:716–23	Not CMR viability data, only PET and SPECT
Slaughter RE, Mottram PM. What should be the principle imaging test in heart failure-CMR or echocardiography? *JACC Cardiovasc Imag* 2010;**3**:776–82	Review
Soman P, Udelson JE. Prognostic and therapeutic implications of myocardial viability in patients with heart failure. *Curr Cardiol Rep* 2004;**6**:211–16	Review
Soriano CJ, Ridocci F, Estornell J, Perez-Bosca JL, Pomar F, Trigo A, *et al.* Late gadolinium-enhanced cardiovascular magnetic resonance identifies patients with standardized definition of ischemic cardiomyopathy: a single centre experience. *Int J Cardiol* 2007;**116**:167–73	Not viability assessment
Steel K, Broderick R, Gandla V, Larose E, Resnic F, Jerosch-Herold M, *et al.* Complementary prognostic values of stress myocardial perfusion and late gadolinium enhancement imaging by cardiac magnetic resonance in patients with known or suspected coronary artery disease. *Circulation* 2009;**120**:1390–400	No useable data
Stillman AE, Wilke N, Jerosch-Herold M. Myocardial viability. *Radiol Clin North Am* 1999;**37**:361–78	Review
Strzelczyk J, Attili A. Cardiac magnetic resonance evaluation of myocardial viability and ischemia. *Semin Roentgenol* 2008;**43**:193–203	Review
Suranyi P, Kiss P, Brott BC, Simor T, Elgavish A, Ruzsics B, *et al.* Percent infarct mapping: an R_1-map-based CE-MRI method for determining myocardial viability distribution. *Magn Reson Med* 2006;**56**:535–45	Not viability assessment
Tajouri TH, Chareonthaitawee P. Myocardial viability imaging and revascularisation in chronic ischemic left ventricular systolic dysfunction. *Exp Rev Cardiovasc Ther* 2010;**8**:55–63	Review
Takeda K, Matsumiya G, Hamada S, Sakaguchi T, Miyagawa S, Yamauchi T, *et al.* Left ventricular basal myocardial scarring detected by delayed enhancement magnetic resonance imaging predicts outcomes after surgical therapies for patients with ischemic mitral regurgitation and left ventricular dysfunction. *Circulation J* 2010;**75**:148–56	Not viability assessment
Teoh K, Tsim N, Yap J. Preoperative investigations in cardiac surgery in adults. *Surgery* 2008;**26**:477–80	Review
Tomlinson DR, Becher H, Selvanayagam JB. Assessment of myocardial viability: comparison of echocardiography versus cardiac magnetic resonance imaging in the current era. *Heart Lung Circulation* 2008;**17**:173–85	Review
Travin MI, Bergmann SR. Assessment of myocardial viability. *Semin Nucl Med* 2005;**35**:2–16	Review
Tsukiji M, Nguyen P, Narayan G, Hellinger J, Chan F, Herfkens R, *et al.* Peri-infarct ischemia determined by cardiovascular magnetic resonance evaluation of myocardial viability and stress perfusion predicts future cardiovascular events in patients with severe ischemic cardiomyopathy. *J Cardiovasc Magn Reson* 2006;**8**:773–9	No useable data
Ugander M, Cain PA, Perron A, Hedström E, Arheden H. Infarct transmurality and adjacent segmental function as determinants of wall thickening in revascularised chronic ischemic heart disease. *Clin Physiol Funct Imag* 2005;**25**:209–14	Not CMR

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TABLE 25 Full-text articles with reasons for exclusion (*continued*)

Reference	Reason for exclusion
Valle-Munoz A, Estornell-Erill J, Soriano-Navarro CJ, Nadal-Barange M, Martinez-Alzamora N, Pomar-Domingo F, *et al.* Late gadolinium enhancement-cardiovascular magnetic resonance identifies coronary artery disease as the aetiology of left ventricular dysfunction in acute new-onset congestive heart failure. *Eur J Echocardiogr* 2009;**10**:968–74	Acute MI
van der Wall EE, Vliegen HW, de RA, Bruschke AVG. Magnetic resonance techniques for assessment of myocardial viability. *J Cardiovasc Pharmacol* 1996;**28**:S37–S44	Review
van der Wall EE, Bax JJ. Late contrast enhancement by CMR: more than scar? *Int J Cardiovasc Imag* 2008;**24**:609–11	Review
Vliegen HW, de RA, Bruschke AV, van der Wall EE. Magnetic resonance techniques for the assessment of myocardial viability: clinical experience. *Am Heart J* 1995;**129**:809–18	Review
Voehringer M, Mahrholdt H, Yilmaz A, Sechtem U. Significance of late gadolinium enhancement in cardiovascular magnetic resonance imaging (CMR). *Herz* 2007;**32**:129–37	Review
Vogel-Claussen J, Rochitte CE, Wu KC, Kamel IR, Foo TK, Lima JA, *et al.* Delayed enhancement MR imaging: utility in myocardial assessment. *Radiographics* 2006;**26**:795–810	Review
Vymazal J, Weichet J, Balak J. [Ischemic and non-ischemic myocardial injury: differential diagnosis using post-contrast delayed magnetic resonance imaging scans]. *Cor et Vasa* 2008;**50**:470–2	Non-English
Watzinger N, Maier R, Furnau G, Wonisch M, Fruhwald FM, Klein W. [MR assessment of myocardial viability: current solutions and future concepts]. *Journal fur Kardiologie* 2003;**10**:32–5	Review
Weinsaft JW, Klem I, Judd RM. MRI for the assessment of myocardial viability. *Magn Reson Imag Clin North Am* 2007;**15**:505–25	Review
Weinsaft JW, Klem I, Judd RM. MRI for the assessment of myocardial viability. *Cardiol Clin* 2007;**25**:35–56. [Reprint published in *Magn Reson Imag Clin N Am* 2007;**15**:505–25]	Review
Weissman G, Asch FM. Myocardial viability in chronic ischemic cardiomyopathy: similarities and discordance of different diagnostic approaches. *J Cardiovasc Translat Res* 2009;**2**:24–9	Review
Wendland MF, Saeed M, Lund G, Higgins CB. Contrast-enhanced MRI for quantification of myocardial viability. *J Magn Reson Imag* 1999;**10**:694–702	Review
White R. Cardiac surgery: Pre- & post-operative insights from MR & CT. *Circulation* 2006;**114**(Suppl.):II_F	Review
Williams TJ, Manghat NE, McKay-Ferguson A, Ring NJ, Morgan-Hughes GJ, Roobottom CA. Cardiomyopathy: appearances on ECG-gated 64-detector row computed tomography. *Clin Radiol* 2008;**63**:464–74	Review
Zamorano J, Delgado J, Almeria C, Moreno R, Gomez SM, Rodrigo J, *et al.* Reason for discrepancies in identifying myocardial viability by thallium-201 redistribution, magnetic resonance imaging, and dobutamine echocardiography. *Am J Cardiol* 2002;**90**:455–9	Heart transplant
Zhang X. [Progress in the study of radiology in China]. *Chung-Hua i Hsueh Tsa Chih* 1998;**78**:930–1	Review
Zhang Y, Chan A, Lam W, Yu CM, So N, Yip G, *et al.* Postsystolic shortening is consistently prevalent in nonviable myocardium in patients with acute myocardial infarction: comparison with contrast-enhanced magnetic resonance imaging. *J Am Coll Cardiol* 2004;**43**:317A	Acute MI
Wagner A, Mahrholdt H, Holly TA, Elliott MD, Regenfus M, Parker M, *et al.* Contrast-enhanced MRI and routine single photon emission computed tomography (SPECT) perfusion imaging for detection of subendocardial myocardial infarcts: an imaging study. *Lancet* 2003;**362**:374–9	Animal data

MRI, magnetic resonance imaging.

Appendix 3 Summary of included studies

Paper, study design	Participants, country, *n* (in final analysis), % male, clinical features, inclusion/exclusion criteria	Index test	Reference standard	Outcomes
Stress CMR *Baer 1998*[27]				
Purpose: to compare the predictive value of quantitatively assessed dobutamine-induced SWT and preserved DWT for the recovery of LV wall thickening (SWT), as assessed by MRI Study design: prospective. 122 consecutive patients with CAD between June 1993 and December 1996 who were referred for assessment of residual myocardial viability. A subgroup had successful catheter-based interventional therapy ($n = 22$) or patent bypass grafts ($n = 21$) and were followed up 4–6 months later. These 43 patients were included	Country: Germany $n = 43$ Percentage male: 93% Mean age: 58 years (SD 9 years) Clinical features • Vessel disease • Mean LVEF: 41.7% (10.3%) Inclusion criteria: previous MI (> 4 months since the ischaemic event) and regional LV akinesia or dyskinesia Exclusion criteria: unstable angina, congestive HF, atrial fibrillation or a history of sustained ventricular tachycardia	Low dose dobutamine stress (10 µg/kg per minute) Defined as viable if: (1) dobutamine induced SWT was ≥ 2 mm; or (2) the mean DWT was ≥ 5.5 mm The entire infarct region was graded viable if ≥ 50% of segments fulfilled morphologic or functional MRI viability criteria Viable: dysfunctional SWT < 2 mm DWT: end-diastolic wall thickness SWT: dobutamine-induced systolic wall thickening	4–6 months after revascularisation Indication of successful revascularisation: improvement of LV function after revascularisation was defined as SWT ≥ 2 mm. Functional recovery of the infarct region after successful revascularisation was defined as SWT ≥ 2 mm in ≥ 50% of the pre-revascularised dysfunctional infarct region-related segments	1832 MRI segments 48 segments excluded because of inadequate image quality for wall thickening analysis 1353 segments had SWT ≥ 2 mm at rest 431 segments were graded as dysfunctional (SWT < 2 mm) 407 segments successfully revascularised 24 segments belonged to non-revascularised or unsuccessfully revascularised regions. The study focuses on the 407 chronically akinetic or dyskinetic segments Analysis by patient ($n = 43$)

Test	TP	FP	FN	TN	Sn	Sp
SWT	24	3	1	15	89	94
DWT	25	2	7	9	93	56

Paper, study design	Participants, country, *n* (in final analysis), % male, clinical features, inclusion/exclusion criteria	Index test	Reference standard	Outcomes
Schmidt 2004[40] *and Baer 1998*[26]				

Purpose: to determine the predictive value of dobutamine induced systolic wall thickening and preserved EDWT
 	
Study design: all patients underwent coronary and LV angiography LVEF F-18 Fluorodeoxyglucose (F-18-FDG)-PET and rest and dobutamine-MRI studies within 10 days without intervening cardiac events before revascularisation. Coronary angiography and rest-MRI studies were repeated 4–6 months after revascularisation
 	
Left ventricular wall motion was visually evaluated from biplane left ventriculography and graded by two independent and experienced observers. In the case of disagreement, a third observer reviewed the study and the majority judgement binding
	Country: Germany
	
	n = 40
	
	Percentage male: 93%
	
	Mean age: 57 years (SD 9 years), range 32–76 years
	
	Clinical features:
	
	• Vessel disease:
	  ○ One-vessel CAD *n* = 11
	  ○ Two-vessel CAD *n* = 16
	  ○ Three-vessel CAD *n* = 13
	• Mean LVEF: 42% (SD 10%)
	
	Inclusion criteria: all had previous MI (infarct age ≥ 4 months), regional a- or dyskinesia by left ventriculography and an infarct related coronary artery with ≥ 80% diameter stenosis
	
	Exclusion criteria: patients with unstable angina, decompensated left HF (NYHA IV), atrial fibrillation, a history of sustained ventricular tachycardia or diabetes were excluded
		Rest and dobutamine MRI. 10 µg dobutamine/kg body weight per minute)
		
		Method of assessing viability:
		
		(1) EDWT was ≥ 5.5 mm, (2) dobutamine-induced wall thickening of ≥ 2 mm could be measured and (3) normalised F-18-FDG uptake was ≥ 50% in ≥ 50% of akinetic segments
		
		DWT: end-diastolic wall thickness
		
		SWT: dobutamine-induced systolic wall thickening ≥ 2 mm
			Method of assessing viability:
			
			Successful revascularisation documented by angiography after 4–6 months
			
			Recovery of regional LV function as the reference standard
				LVEF improved in 29/40 patients
				
				Test / TP / FP / FN / TN / Sn / Sp
				SWT 24 1 2 13 96 87
				DWT 25 0 7 8 100 53
				PET 25 0 4 11 100 73
				
				EDWT: ≥ 5.5 mm
				
				Side effects: none reported
				
				PET was more sensitive, dobutamine MRI had the better specificity. Further comparisons between dobutamine MRI and PET especially in patients with severe LV dysfunction and longer follow-up periods post revascularisation may be helpful to clarify the mismatch between morphological, functional and metabolic viability parameters

Paper, study design	Participants, country, *n* (in final analysis), % male, clinical features, inclusion/exclusion criteria	Index test	Reference standard	Outcomes
Baer 2000[28]				
Purpose: to compare the predictive accuracy of dobutamine-TEE (transoesophageal echocardiography) and dobutamine-MRI for the improvement of LV function Study design: prospective. Patients referred for coronary revascularisation index test analysis done by three experienced examiners, by consensus, blind to patients coronary status and whether it was a pre- or postoperative scan. Delayed enhancement was assessed by one examiner, blind to the other results. Eight not in final analysis	Country: Germany *n* = 65 Percentage male: 92% Mean age: 58 years (SD 8.8 years) Clinical features: • Vessel disease: 75% multivessel disease • Mean LVEF: 41% (SD 10%) Inclusion criteria: CAD, infarct age > 4 months. Persisting a or dyskinetic infarct region. Severe stenosis of the infarct-related coronary artery, implicating a reduction in resting flow or repetitive ischaemic episodes in the infarct region Exclusion criteria: unstable angina, congestive HF, atrial fibrillation, a permanent pacemaker, a history of multiple MIs or a history of sustained ventricular tachycardia	MRI (using 1.5-Tesla superconducting magnet). Dobutamine (5 µg/kg and 10 µg/kg per minute). Imaging time – ranged between 20 and 30 minutes. Cine loops analysed on a visual basis. Wall motion and SWT were assessed semiquantiatively on a segmental basis using a system where a score of 1 indicated normal or hyperkinetic myocardium and a score of 4 indicated dyskinesia TEE study: Dobutamine (5 µg/kg and 10 µg/kg per minute). Control TEE performed 4–6 months after revascularisation. Imaging time – ranged between 20 and 30 minutes. Cine loops analysed on a visual basis Segmental model: 28 segmental model Method of assessing viability: dobutamine-induced wall thickening could be observed. Infarct regions were graded viable if 50% of a or dyskinetic segments showed dobutamine-induced SWT	Reference standard 'contractile recovery after revascularisation' was evaluated quantitatively by measuring end-diastolic and ESWT. Improvement of LV function was defined as SWT at rest ≥ 2 mm. This threshold value was chosen based on a spatial resolution of 1.3 mm of the MR machine. However, this suggests that viable regions with a weak contractile recovery are not detected. Functional recovery of the entire infarct region was defined as systolic wall thickening ≥ 2 mm in ≥ 50% of the dysfunctional segments prior to revascularisation	*n* = 52 in final analysis Analysis by participant Side effects: none

Test	TP	FP	FN	TN	Sn	Sp
SWT	24	4	2	22	86	92
TEE	23	5	4	20	82	83

Paper, study design	Participants, country, *n* (in final analysis), % male, clinical features, inclusion/exclusion criteria	Index test	Reference standard	Outcomes
Lauerma 2000[34]				

Purpose: to determine the effect of the addition of information from first-pass MR imaging and from late enhancement on T1-weighted images to dobutamine stress cine imaging
 	
Ten consecutive patients
	Country: Finland
	
	$n = 10$
	
	Percentage male: 80%
	
	Mean age: 69 years (range 64–71 years)
	
	• Clinical features: NYHA functional classification:
	  ○ Group 1: $n = 1$
	  ○ Group 2: $n = 5$
	  ○ Group 3: $n = 4$
	• Vessel disease: NR
	• Mean LVEF: NR
	• Seven had a previous MI, mean time from last infarction was 16 months (range 3–60 months)
	• Diabetes: $n = 3$
	• Hypertension: $n = 2$
	• Psoriasis: $n = 2$
	• Hypercholesterolaemia: $n = 1$
	• All patients underwent bypass surgery after imaging
	
	Inclusion criteria: multivessel CAD and regional wall motion abnormality
	
	Exclusion criteria: NR
		MRI (multimodal). Dobutamine stress. Gadopentetate dimeglumine (0.05 mmol/kg) was injected intravenously with a rate of 5 ml/second
		
		Segmental model: 8 segmental model
		
		Method of assessing viability: systolic wall thickening < 2 mm that responded to bypass surgery (SWT ≥ 2 mm at rest) were classified as hibernating
		
		FDG PET
			Left ventricular wall thickening was assessed with MR imaging 6 months after bypass surgery and the findings of wall thickening at rest were used as the standard	SWT at rest was normal (≥ 2 mm) in 154 sectors and 86 hypokinetic (< 2mm)
				
				6 months after bypass surgery, 211 sectors had normal SWT. 29 sectors still hypokinetic and labelled as unviable. 57 preoperatively hypokinetic sectors that had recovered were labelled as hibernating
				
				Test TP FP FN TN Sn Sp
				CMR 43 0 14 29 75 100
				
				(data for detecting unviable myocardium for other CMR modalities, unable to extract figures from the paper)

Paper, study design	Participants, country, *n* (in final analysis), % male, clinical features, inclusion/exclusion criteria	Index test	Reference standard	Outcomes
Gunning 1998[31]				
Purpose: to compare the value of low-dose dobutamine cine MRI, stress/redistribution and separate-day rest/redistribution thallium scintigraphy, and stress/rest tetrofosmin imaging in these patients Methods: prospective. Selected from the waiting list for CBGS MR images were analysed by two experienced observers independently and without knowledge of the findings of the other imaging techniques	Country: UK *n* = 30 Male: 27 (90%) Mean age: 61 years (median) range 40–70 years Clinical features: • Vessel disease • Mean LVEF: 24% (SD 8.3%) – for those completing study Inclusion criteria: LV dysfunction, LVEF ≤ 35% and dyspnoea as a dominant symptom. All patients had three-vessel coronary artery disease (defined as > 70% luminal diameter stenosis) and all had suffered previous MI Exclusion criteria: significant valve disease, uncontrolled atrial fibrillation, permanent pacemaker, or previous CABG surgery	Preoperative assessment was performed within 3 months of surgery and postoperative assessment between 3 and 6 months after surgery Cine MRI at rest and during infusion of low-dose dobutamine Segmental model: 9 segment model of the LV was used Method of assessing viability: late rest thallium scintigraphy ≥ 2 and rest motion ≤ 1	Thallium scintigraphy Tetrofosmin scintigraphy Segmental model: 9 Functional recovery was defined as ≥ 1 wall motion grade improvement on postoperative MRI	23 patients with complete imaging data: 207 segments 145 severe hypokinesia ≤ 1 wall motion score 82 improved ≥ 1 wall motion grade **Test** — **TP FP FN TN Sn Sp** CMR (endocardial motion) — 41 12 41 51 50 81 CMR (myocardial thickening) — 37 11 45 52 45 83 SPECT — 62 35 20 28 64 58 Side effects: no cardiac events were reported between preoperative assessment and surgery

Paper, study design	Participants, country, *n* (in final analysis), % male, clinical features, inclusion/exclusion criteria	Index test	Reference standard	Outcomes
Martinez 2000[35]				
Purpose: to determine if the use of nitroglycerin MRI predicts segmental recovery of function after revascularisation and to compare this novel technique with the widely used dobutamine stress echocardiography (DSE) Method: MRI and DSE on same day repeat MRI and echocardiography at 4–6 weeks after revascularisation. No description of blinding	Country: USA $n = 12$ Percentage male: 100% Mean age: range 44–78 years Clinical features: • Vessel disease • Mean LVEF: 38% (SD 5%) Inclusion criteria: referred for coronary revascularisation. Eligible if they had segmental wall motion abnormalities at test with an LVEF of < 45% Exclusion criteria: patients with atrial fibrillation and MI within 3 weeks of the procedure	Sublingual nitroglycerin 0.4 mg was administered as the patient entered the MRI scanner and the same dose was repeated 3 minutes later Segmental model: 16 segments Method of assessing viability: after revascularisation an increase in the ESWT by > 2 times the SD of the measurement technique	DSE – infusion began at 5 µg/kg/minute to a mix of 15 µg/kg/minute at 3-minute intervals Segmental model: 16 segments Method of assessing viability: for DSE the presence of contractile reserve and viability in the abnormal segments was defined as a decrease of wall motion score by 1 with dobutamine or after revascularisation respectively	160 segments available for the analysis 47 segments were normal 87 segments demonstrated abnormal wall motion at rest 26 segments could not be analysed because of poor echocardiography visualisation 71 (of 87) segments demonstrating abnormal wall motion at rest showed contractile reserve with DSE whereas 16 did not 10 (of 16) segments without contractile reserve did not show recovery of function Side effects: 1 MRI – claustrophobia MRI was superior to DSE in identifying segments that improved in function after revascularisation with less false positive results

Test	TP	FP	FN	TN	Sn	Sp
CMR	63	8	2	14	97	64
DSE	57	14	6	10	90	58

<table>
<tr><th>Paper, study design</th><th>Participants, country, n (in final analysis), % male, clinical features, inclusion/exclusion criteria</th><th>Index test</th><th>Reference standard</th><th>Outcomes</th></tr>
<tr><td colspan="5">Schmidt 2004[40]</td></tr>
<tr>
<td>Purpose: to determine the predictive value of dobutamine induced systolic wall thickening and preserved EDWT

All patients underwent coronary and LV angiography LVEF ^{18}F-FDG-PET and rest and dobutamine-MRI studies within 10 days without intervening cardiac events before revascularisation. Coronary angiography and rest-MRI studies were repeated 4–6 months after revascularisation

Left ventricular wall motion was visually evaluated from biplane left ventriculography and graded by two independent and experienced observers. In case of disagreement a third observer reviewed the study and the majority judgement binding</td>
<td>Country: USA

$n = 40$

Percentage male: 93%

Mean age: 57 years (SD 9 years) range 32–76 years

Clinical features:

• Vessel disease:
  ○ One-vessel CAD $n = 11$
  ○ Two-vessel CAD $n = 16$
  ○ Three-vessel CAD $n = 13$

• Mean LVEF: 42% (SD 10%)

Inclusion criteria: all had previous MI (infarct age ≥ 4 months), regional a- or dyskinesia by left ventriculography and an infarct related coronary artery with ≥ 80% diameter stenosis. Patients with unstable angina [Canadian Cardiovascular Society (CCS) IV], decompensated left HF (NYHA IV), atrial fibrillation, a history of sustained ventricular tachycardia or diabetes were excluded

Exclusion criteria: instable angina, decompensated left HF, atrial fibrillation, tachycardia or diabetes</td>
<td>Rest and dobutamine MRI

10 µg dobutamine/kg body weight per minute)

Segmental model: standard 17 segmental model

Method of assessing viability: (1) EDWT was ≥ 5.5 mm, (2) dobutamine induced wall thickening of ≥ 2 mm and (3) normalised F-18-FDG-uptake was ≥ 50% in ≥ 50% of akinetic segments</td>
<td>Method of assessing viability:

Successful revascularisation documented by angiography after 4–6 months

Recovery of regional LV function as the reference standard</td>
<td>LVEF improved in 29/40 patients

<table>
<tr><th>Test</th><th>Sn</th><th>Sp</th><th>+ pv</th><th>– pv</th><th>DA</th></tr>
<tr><td>EDWT</td><td>100</td><td>53</td><td>78</td><td>100</td><td>83</td></tr>
<tr><td>DICR</td><td>96</td><td>87</td><td>92</td><td>93</td><td>93</td></tr>
<tr><td>PET</td><td>100</td><td>73</td><td>86</td><td>100</td><td>90</td></tr>
</table>

EDWT: ≥ 5.5 mm

DICR: dobutamine induced systolic wall thickening ≥ 2 mm

<table>
<tr><th>Test</th><th></th><th>Recovery</th><th></th></tr>
<tr><td></td><td></td><td>+</td><td>–</td></tr>
<tr><td>CMR</td><td>+</td><td>24</td><td>1</td></tr>
<tr><td></td><td>–</td><td>2</td><td>13</td></tr>
</table>

Side effects: none reported

PET was more sensitive, dobutamine MRI had the better specificity. Further comparisons between dobutamine MRI and PET especially in patients with severe LV dysfunction and longer follow-up periods post revascularisation may be helpful to clarify the mismatch between morphological, functional and metabolic viability parameters</td>
</tr>
</table>

Paper, study design	Participants, country, *n* (in final analysis), % male, clinical features, inclusion/exclusion criteria	Index test	Reference standard	Outcomes
Trent 2000[47]				
Study design: Blinding: three independent observers. Interpretation of postoperative resting MR images was performed blinded to the results of the dobutamine study and in a random manner Loss to follow-up: four excluded because of recent unstable symptoms and three produced images of insufficient quality, one as a result of technical reasons	Country: UK *n* = 40 (32 in analysis) Percentage male: 100% Mean age: 60 years Clinical features: • Vessel disease: NR • Mean LVEF: NR Inclusion criteria: previous MI awaiting CABG Exclusion criteria: NR	Stress CMR 0.95 Tesla Siemens Rest and stress images were performed sequentially using a dobutamine infusion mean dose 15 µg/kg per minute (SD 4.9 µg/kg per minute) to induce a 50% increase in mean basal heart rate from 65 beats per minute to 95 beats per minute Method of assessing viability: viability determined on basis of the response to dobutamine. Data then tested against the post-revascularisation results Left ventricular wall thickness (manual and semi-automated measurements). A reduction of > 1 SD below normal was considered reduced	Reference standard: MRI scans assessing segmental recovery. Wall motion and wall thickness Method of assessing viability: unclear	See table Test TP FP FN TN Sn Sp CMR 81 69 33 163 71 70 Side effects: NR

Paper, study design	Participants, country, *n* (in final analysis), % male, clinical features, inclusion/exclusion criteria	Index test	Reference standard	Outcomes
Sandstede 1999[37]				
Study design: prospective clinical study Purpose: to assess the value of dobutamine stress MR imaging in predicting myocardial viability in all patients with wall motion abnormalities Loss to follow-up: two because of haemodynamically significant re-stenosis All images were analysed visually by consensus of two observers	Germany *n* = 27 Percentage male: 88% (22/25) Mean age: 58 years (SD 10 years) range 36–79 years Clinical features: • Vessel disease: NR • Mean LVEF: NR • Previous MI: *n* = 21, mean 23 days (SD 8 days; range 13–49 days) before MRI examination • Four patients showed wall motion abnormalities without MI. All patients had high-grade coronary stenoses requiring revascularisation by percutaneous transluminal coronary angioplasty or CABG Inclusion criteria: regional LV wall motion abnormalities and associated coronary artery stenoses detected by left venticulography and coronary angiography Exclusion criteria: had a pacemaker, history of metal fragments, implants or vascular clips, sever arrhythmias, unstable angina pectoris or claustrophobia	Predicting viability only referred to regions with wall motion abnormalities supplied by the stenosed and later revascularised artery. Remote segments supplied by a different coronary artery were not included into the evaluation MR imaging at rest and during dobutamine stress. Dose: 10 µg/kg per minute Segmental model: 8 segments Myocardial viability was defined as any detectable dobutamine-induced increase of end-systolic wall thickening of one segment by comparison of end-systolic thickness pre-dobutamine and end-systolic thickness post-dobutamine. If a patient showed both viable and non-viable segments, the akinetic myocardial region was defined as viable if ≥ 50% of the affected segments improved	10–14 weeks post intervention patients were re-examined by MR imaging at rest only Restoration of regional function re-examined by MR imaging after revascularisation therapy was used as the criterion of viability Follow-up criterion of viability was an improvement of systolic wall thickening at rest of the major part of one segment after revascularisation compared with the examination at rest before therapy	207 myocardial segments with wall motion abnormalities at rest were analysed Test / TP / FP / FN / TN / Sn / Sp CMR (per segment) 65 10 41 91 61 90 CMR (per patient) 13 0 4 8 76 100

Paper, study design	Participants, country, *n* (in final analysis), % male, clinical features, inclusion/exclusion criteria	Index test	Reference standard	Outcomes
Sayad 1998[39]				
Purpose: to determine if the use of dobutamine CMR quantitatively predicts segmental recovery of myocardial function after revascularisation Study design: unclear if consecutive, patients referred for coronary revascularisation. Blinding unclear	USA $n = 10$ Percentage male: 70% Mean age: NR range 42–71 years Clinical features: • Vessel disease: NR • Mean LVEF: NR Inclusion criteria: segmental wall abnormalities at rest on ventrigulography or echocardiography Exclusion criteria: coronary stents or bypass grafts	Stress CMR. 1.5 tesla Picker Vista HPQ system Dobutamine 5–10 µg/kg per minute Segmental model: 18 segments Viability: dobutamine ESWT increased > 2 times the SD of the measurement technique	Viability after revascularisation demonstrated by: ESWT increased after revascularisation by > 2 times the SD of the measurement technique	Stress CMR Test TP FP FN TN Sn Sp CMR 25 1 3 14 89 93 Side effects: NR

Paper, study design	Participants, country, *n* (in final analysis), % male, clinical features, inclusion/exclusion criteria	Index test	Reference standard	Outcomes
CE CMR *Becker 2008*[29]				

Study design: echocardiographic images obtained before revascularisation and at follow-up were placed in a random order and analysed by two independent observers who were unaware of the patients clinic and the findings of the other imaging modalities
 	
Purpose: to define whether or not the assessment of myocardial viability based on myocardial deformation imaging allows the identification of reversible myocardial dysfunction and to compare its predictive value for segmental and global functional recovery after revascularisation with CE CMR. MR imaging data were assessed by an experienced reader blinded to clinical data and results of the other imaging technique
	Country: Germany
	
	$n = 55$ ($n = 53$ in final analysis)
	
	Percentage male: 83%
	
	Mean age 59 years (SD 8 years)
	
	Clinical features:
	• Vessel disease:
	  ○ Number of diseased vessels:
	  – For those with functional recovery: mean = 1.2 (SD 0.3)
	  – For those with no functional recovery: mean = 1.1 (SD 0.3)
	  ○ Baseline LVEF < 40%:
	  – For those that had functional recovery – $n = 6$ (29%)
	  – For those who had no functional recovery – $n = 9$ (28%)
	
	Inclusion criteria: patients with LV dysfunction and had to be in sinus rhythm
	
	Exclusion criteria: patients with non-ischemic cardiomyopathy or acute coronary syndromes
		Vivid Seven System, with a 2.5 MHz transducer
		
		1.5 tesla whole body scanner
		
		Segmental model: 16 segments
		
		Each myocardial segment was evaluated for the presence of hyperenhancement, defined as an area of signal enhancement ≥ 3 SDs of the signal intensity of the non-enhanced myocardium
		
		Mean interval between imaging studies and revascularisation was 12 days (SD 11 days)
			Revascularisation was defined as a final diameter stenosis less than 30% and a thrombolysis in MI flow grade 3 in all cases
			
			Segmental and global functional recovery was assessed using echocardiographic images before and 9 months (SD 2 months) after revascularisation
			
			Segment was considered to demonstrate functional improvement during follow-up if it improved by at least 1 grade. Global functional recovery was defined as an increase in LVEF > 5% at follow-up
				463 dysfunctional segments, 227 segments recovered, 236 segments were not

SEH	TP	FP	FN	TN	Sn	Sp
0–25%	189	175	38	61	83	26
0–50%	215	136	12	100	95	42

Paper, study design	Participants, country, *n* (in final analysis), % male, clinical features, inclusion/exclusion criteria	Index test	Reference standard	Outcomes
Bondarenko 2007[30]				

Study design: prospective
 	
Purpose: to combine all information from CE CMR to evaluate viability in a group of patients with chronic ischaemic myocardial dysfunction
	Country: the Netherlands
	
	n = 45
	
	Percentage male = 84%
	
	Mean age: 62 years (SD 9 years)
	
	Clinical features:
	• Vessel disease:
	  ○ One-vessel CAD = 9%
	  ○ Two-vessel CAD = 13%
	  ○ Three-vessel CAD = 28%
	• Mean LVEF: NR
	
	Inclusion criteria: patients with known CAD and regional wall motion abnormalities without CMR contraindications, who were scheduled to undergo surgical or percutaneous revascularisation
	
	Exclusion criteria: one patient was excluded because coronary artery bypass surgery was accompanied by LV aneurysmectomy
		Index test: 1.5-tesla scanner, 1 month before revascularisation. Gadolinium-based contrast agent (0.2 mmol/kg)
		
		Segmental model: 16 segment model
		
		Segments with SWT < 3 mm (mean – 2 SDs) were considered dysfunctional
		
		Hyperenhancement [segmental extent of hyperenhancement (SEH)] was defined as signal intensity ≥ 5 SD above the signal intensity of remote myocardium in the same slice
		
		Mean segmental thickness of the non-enhanced, viable rim was calculated as total segmental wall thickness (100% – SEH). A viable rim of ≥ 4.5 mm was considered thick
			3 months after revascularisation. Complete revascularisation defined as revascularisation of all vessels with > 50% diameter stenosis	720 available segments. 644 segments were successfully revascularised. 356 segments were dysfunctional at baseline, of which 322 were revascularised
				
				85 segments showed functional improvement by CE CMR
				
				SEH: 0–25%: TP 64, FP 84, FN 21, TN 153, Sn 75, Sp 65
				SEH: 0–50%: TP 79, FP 145, FN 6, TN 92, Sn 93, Sp 38

Paper, study design	Participants, country, *n* (in final analysis), % male, clinical features, inclusion/exclusion criteria	Index test	Reference standard	Outcomes
Hunold 2002[49] *(abstract)*				
Study design: unclear Purpose: to evaluate contrast enhanced MRI and FDG-PET for the assessment of myocardial viability in CAD and to compare the preoperative prediction of functional recovery with the outcome following CABG Methods: segments were analysed separately in a blinded manner	Country: Germany *n* = 12 Percentage male: NR Mean age: NR Clinical features: • Vessel disease: NR • Mean LVEF: NR Inclusion criteria: CAD Exclusion criteria: NR	Gadolinium late enhancement was classified on a 4-point scale [1 = no enhancement, 2 = subendorcardial late enhancement (LE) of < 50% of wall thickness, 3 = non-transmural LE of > 50%, 4 = transmural LE] Segmental model: based on an 8-segment model	PET scans were performed – FDG uptake was analysed using an analogous scale > 50% minimum and < 50% maximum	Test TP FP FN TN Sn Sp PET 146 136 4 120 97 47 CE CMR 143 72 7 184 95 72 Side effects: NR

Paper, study design	Participants, country, *n* (in final analysis), % male, clinical features, inclusion/exclusion criteria	Index test	Reference standard	Outcomes
Kuhl 2006[33]				
Purpose: to compare CE CMR and a combined nuclear imaging protocol using F-FDG-PET for metabolic imaging and ^{99m}Tc-sestamibi SPECT for perfusion imaging for the prediction of reversible myocardial dysfunction in patients with chronic ischaemic heart disease Prospective consecutive recruitment CMR regional wall motion was assessed visually by consensus interpretation of two experienced observers before revascularisation and at 6 month follow-up	Country: Germany $n = 46$ Percentage male: 89.7% (of 29 completing follow-up) Five excluded for clinical reasons and four excluded because of previous pacemaker or defibrillator implantation and one refused CMR. Three died, three refused to complete the follow-up and one was lost to follow-up. Twenty-nine completed follow-up Mean age: 66 years (SD 9 years) Clinical features: • Vessel disease: NR • Mean LVEF: 32% (SD 10%) • Previous MI: 83% • Diabetes: 34% • Hypertension: 76% • Hypercholesterolaemia: 66% • Nicotine abuse: 62% • Elevated serum creatinine: 24% Inclusion criteria: chronic ischaemic heart disease, regional wall abnormalities and LVEF < 50% Exclusion criteria: severe cardiovascular disease, CPD, kidney disease or peripheral vascular disease impeding revascularisation, pacemaker or defibrillator	Gadolinium based contrast agent Segmental model: 17 segment model Method of assessing viability: cine CMR regional wall motions Each myocardial segment was scored using a 5-point scale 1 = normal contractility, 2 = mild to moderate hypokinesia, 3 = severe hypokinesia, 4 = akinesia and 5 = dyskinesia Evaluation of the contrast-enhanced images was performed separately and independently from the wall motion analysis. Each segment was evaluated for the presence of hyperenhancement, defined as an area of signal enhancement ≥ 3 SD of the signal intensity of non-enhanced myocardium. The total myocardial area and the contrast-enhanced area of each segment were traced manually. The segmental extent of hyperenhancement was calculated Segmental extent of hyperenhancement (SHE) ≤ 50% viable myocardium	F-FDG-PET and perfusion ^{99m}Tc-sestamibi SPECT studies were performed on the same day as CMR Segmental model: standard 17 segment model Method of assessing viability: four different categories of segments were defined. Viability was assumed to be present in segments with normal perfusion by SPECT as well as in segments demonstrating a mismatch pattern (reduced ^{99m}Tc-sestamibi uptake and F-FDG uptake consistent with a non-transmural scar) Revascularisation Improvement of segmental myocardial function was assumed to be present when the difference in wall motion score between baseline and follow-up examination was ≥ 1	For prediction of recovery of regional myocardial function CE CMR, PET and SPECT are comparable for the prediction of regional and global improvement of LV function after revascularisation. However, for segments classified as non-viable, CE CMR was superior to PET/SPECT in predicting lack of functional recovery. This finding may be clinically important, indicating that CE CMR may be especially useful in identifying patients who may not need a coronary revascularisation Side effects: NR

Test	TP	FP	FN	TN	Sn	Sp
CMR	94	27	2	64	97	68
PET/SPECT	83	24	13	67	87	76

DOI: 10.3310/hta18590

Paper, study design	Participants, country, *n* (in final analysis), % male, clinical features, inclusion/exclusion criteria	Index test	Reference standard	Outcomes
Kim 2000[15]				
Purpose: to test the hypothesis that CE MRI can be used to predict whether or not regions of myocardial dysfunction will improve after revascularisation Methods: prospectively enrolled consecutive patients. Mean interval between MRI and revascularisation was 18 days (SD 25 days) In 41 patients MRI was repeated a mean of 79 days (SD 36 days) after revascularisation 41 patients in second MRI – one died, two lost to follow-up, two had pacemaker implanted, four declined to return. 50 patients in the analysis (ITT). Assessors blind to MRI findings and patient identity	Country: USA *n* = 50 Percentage male = 88% Mean age: 63 years (SD 11 years) Clinical features: • Vessel disease: NR • Mean LVEF: 43% Inclusion criteria: ventricular dysfunction and scheduled to undergo revascularisation, had abnormalities in regional wall motion on either contrast ventriculography or echocardiography Exclusion criteria: unstable angina, NYHA class IV HF or contraindications to MRI (e.g. a pacemaker) and gave written informed consent	Index test: gadolinium-based contrast agent at a dose of 0.2 mmol/kg body weight. CE images were acquired in same views as those used for cine MRI Segmental model: left ventricle was divided into 12 circumferential segments Method of assessing viability: < 25% delayed hyperenhancement	Recovery following revascularisation Segmental model: 12 segments Method of assessing viability: improvement in mean wall motion	The likelihood of functional improvement in regions without hyperenhancement was 86% for segments with at least severe hypokinesia and 100% for segments with akinesia of dyskinesia. CE MRI appears to have greater accuracy in segments with the most severe dysfunction. This high level of accuracy, even in patients with severe ventricular dysfunction, may be related to the ability of CE MRI to delineate the transmural extent of viable and non-viable myocardium through the ventricular wall SEH: TP 147, FP 60, FN 232, TN 86, Sn 61, Sp CMR (0–25%) CMR (0–50%) 411, 211, 14, 168, 97, 44 Side effects: NR

Paper, study design	Participants, country, *n* (in final analysis), % male, clinical features, inclusion/exclusion criteria	Index test	Reference standard	Outcomes
Pegg 2010[36]				
Purpose: to explore how the number of viable and number of viable + normal segments predicted recovery of global LV function in patients undergoing CABG Blinding: LV analysis undertaken by one observer blind to regional wall motion score and CE CMR findings. Visual assessment of RWMS was undertaken by two observers working in consensus and blinded to the CE CMR findings. Kappa score for agreement between observers for transmurality grading (0.872)	Country: UK $n = 50$ (data analysis based on $n = 33$) Two died, one cardiovascular accident (CVA), two retained pacing wires, nine significant procedural injury, one cardiac defibrillator, two refused imaging Percentage male: NR Mean age: 66 years (SD 8 years) Clinical features: • Vessel disease: all patients had three-vessel CAD or left main stem disease • Mean LVEF: 38% (SD 11%) • Mean preoperative RWMS was 2.4 (0.7) Inclusion criteria: patients with impaired LV function accepted for surgery were recruited if they consented and had no contraindications to CMR or CE CMR. Included patients who needed both elective admissions and patients with recent unstable coronary syndromes requiring inpatient revascularisation Exclusion criteria: patients with class IVb angina were excluded	All elective patients were assessed with CMR within 4 weeks of their surgery while all urgent in-hospital referrals for CABG underwent their pre-operative CMR assessment the evening before surgery 1.5 tesla MR scanner Segmental mode: 16 segments Segments were graded between 1 (normally contracting) and 5 (dyskinetic) Transmural extent of MI – extent of hyperenhancement into subgroups: 0 (no CE CMR) to 4 (> 74%)	Segments with < 50% CE CMR were considered as 'viable' 6 month follow-up Improvement was defined as improvement in LVEF, improvement in regional contraction was defined by an improvement of ≥ 1 functional grade	1408 segments available for analysis 957 segments (958 in figure 2) dysfunctional before revascularisation SEH: TP 297, FP 126, FN 435, TN 100, Sn 41, Sp 44 (CMR 0–25%) SEH: TP 381, FP 228, FN 16, TN 333, Sn 96, Sp 59 (CMR 0–50%)

Paper, study design	Participants, country, *n* (in final analysis), % male, clinical features, inclusion/exclusion criteria	Index test	Reference standard	Outcomes
Sandstede 2000[38]				
Purpose: to analyse first pass and delayed contrast enhancement patterns of dysfunctional myocardial regions on MR imaging after injection of contrast to predict myocardial viability Study design: unclear on patient recruitment. Interpretation by consensus two experienced observers, regional wall motion was judged as normal, hypokinetic, or akinetic	Country: Germany *n* = 12 Percentage male: 83% Mean age: 61 years (SD 9 years) range 49–79 years Clinical features: • Previous MI 27 days (SD 9 days) before examination 83.3% • Vessel disease: NR • Mean LVEF: NR Inclusion criteria: hypokinetic or akinetic myocardial regions and associated CAD Exclusion criteria: contraindications to CMR	CE CMR Index test: delayed hyperenhancement MRI using a 1.5 tesla MR scanner. Imaged 15 minutes after injection of 0.05 mmol/kg of gadopentetate dimeglumine Delayed hyperenhancement was determined using both qualitative judgements and signal intensity measurements Segmental model: each slice was divided into 8 segments	Reference standard: functional recovery after revascularisation Method of assessing viability: any improvement of SWT after revascularisation of the affected segments served as the criterion of viability 3 months after revascularisation	Unclear how many segments were excluded 73 dysfunctional segments DE CMR SEH: TP 39, FP 8, FN 1, TN 25, Sn 98, Sp 75 Side effects: NR Threshold for defining delayed hyperenhancement

Paper, study design	Participants, country, *n* (in final analysis), % male, clinical features, inclusion/exclusion criteria	Index test	Reference standard	Outcomes
Schvartzman 2003[41]				
Purpose: to assess the use of CE CMR for predicting functional improvement after coronary artery bypass grafting in patients with CAD Study design: consecutive patients with CAD and LV dysfunction < 50% who underwent resting non-stress CE CMR for assessment of myocardial viability. Investigator prospectively analysed the CE CMR images blind to pre-CABG echocardiography and to subsequent evaluation or treatment	Country: USA *n* = 29 Percentage male: 79% Mean age: 62 years (SD 11 years) range 35–78 years Clinical features: • Vessel disease: NR • Mean LVEF: NR Inclusion criteria: CAD and wall abnormalities. Hypokinetic or akinetic myocardial regions revealed by angiography Exclusion criteria: history of MI < 8 weeks before either diagnostic imaging or CABG. LVEF ≥ 50% by echocardiography or MRI, unstable angina and MRI contraindications	1.5-tesla MR scanner Inversion recovery imaging at 20–30 minutes after intravenous gadolinium (0.2 mmol/kg) Prevascularisation MRI and echocardiography were performed within 1 week of each other. Both CE CMR and pre-CABG echocardiography preceded surgery by < 2 weeks Segmental model: 16 segments Method of assessing viability: hyperenhancement from scar relative to nulled signal from viable myocardium was semiquantitatively evaluated in each segment using a six-grade system: 0 = 0% 1 = 1–24% 2 = 25–49% 3 = 50–74% 4 = 75–99%	Reference standard: Two–dimensional echocardiography assessing segmental LV function before and after CABG Motion with thickening 4 grade system; 1 = normal contraction, 2 = mild hypokinesia, 3 = severe hypokinesia, 4 = akinesia or dyskinesia At least 6 weeks were required between revascularisation and post-CABG echocardiography Method of assessing viability: an increase in resting function by at least 1 grade between pre and post CABG echocardiography	464 segments Excluded segments: 22 patients also underwent surgical remodelling for post-MI apical aneurysm. In these patients the LV apical regions (88 segments) were excluded from further analyses 16 segments excluded because of poor endocardial visualisation 207 dysfunctional segments evaluated SEH TP FP FN TN Sn Sp CMR (0–25%) 82 57 19 49 81 46 CMR (0–50%) 95 79 6 27 94 25 Side effects: none described

Paper, study design	Participants, country, *n* (in final analysis), % male, clinical features, inclusion/exclusion criteria	Index test	Reference standard	Outcomes
Selvanayagam 2004[43]				
Purpose: diagnostic study embedded in a larger trial exploring long-term effects of different CABG surgical techniques Study design: patients were already included in a RCT comparing two different CABG techniques Blinding: separate observer blind to the CE CMR finding Loss to follow-up: seven, three because of morbidity and four declined follow-up	Country: UK *n* = 60 (52 in analysis) Percentage male: NR Mean age: NR Clinical features: • Vessel disease: NR • Mean LVEF: NR Inclusion criteria: undergoing CABG Exclusion criteria: age > 75 years, severe pre-existing LV dysfunction, involvement in other clinical trials, typical MRI contraindications (pacemaker, severe claustrophobia) baseline creatinine > 200 µmol/l	CE CMR Regional wall motion graded as 0–4 (normal-dyskinesia). Areas of late gadolinium HE were graded in transmural extent 0–4 (no HE – > 76%) and quantified by the use of computer-assisted planimetry on each of the short-axis images. HE pixels were defined as those with image intensities > 2 SD above the mean of image intensities in a remote myocardial region in the same image Segmental model: 56 segments	Reference standard: Method of assessing viability: 6 month follow-up CMR	2471 segments 612 segments had abnormal function 359 of segments with abnormal function improved by at least one grade at 6 months 291 segments had very severe preoperative dysfunction TP FP FN TN Sn Sp 0–25% 266 96 77 173 78 64 0–50% 326 192 17 77 95 29 Side effects: NR

Paper, study design	Participants, country, *n* (in final analysis), % male, clinical features, inclusion/exclusion criteria	Index test	Reference standard	Outcomes
Sharma 2009[44]				

Purpose: to compare the CE CMR with SPECT to assess myocardial viability
 	
Study design: consecutive, prospective, only 8 revascularised and included. Two blinded radiologists – assume blinding is to reference standard. None of the eight revascularised were lost to follow-up
	Country: USA
	
	n = 40 (8 included in analysis)
	
	Percentage male: 100%
	
	Mean age: 59 years
	
	Clinical features:
	
	• Vessel disease (*n* = 36):
	  ○ One-vessel CAD 10%
	  ○ Two-vessel CAD 20%
	  ○ Three-vessel CAD 60%
	
	• Mean LVEF: 26% (SD 8.1%)
	
	Inclusion: showing symptoms of cardiac failure for more than 3 months
	
	Exclusion: MI within the last 6 months; acute coronary syndromes or acute MI; significant valvular disease; chronic atrial fibrillation; contraindications to MRI
		CE CMR
		
		1.5-tesla scanner. Late galidium (0.15 mmol/kg)
		
		SPECT image acquired 15 minutes and 4 hours after administration of 2–3 mCi TI
		
		Wall thickening on cine MR images was measured as the percentage of SWT. Delayed contrast enhancement in each segment was quantified with in-house MRI analysis
			Revascularisation
			
			Improved post-vascularisation contractile function was defined as ≥ 15% SWT
				Test TP FP FN TN Sn Sp
				SPECT 41 30 14 12 75 29
				CMR 52 32 3 10 95 24
				
				Side effects: none reported

Paper, study design	Participants, country, *n* (in final analysis), % male, clinical features, inclusion/exclusion criteria	Index test	Reference standard	Outcomes
Skala 2011[46]				

Purpose: to evaluate the ability of MRI and SPECT to predict reverse LV remodelling in long-term follow-up after CABG with the aim to find parameters with the highest predictive value
 	
Methods: consecutive patients, prospective. Within 1 week after coronary angiography, the patients underwent MRI and SPECT which were repeated 12 and 24 months after enrolment. CT coronary angiography was performed 24 months after enrolment to evaluate the number of occluded coronary artery bypasses
 	
MRI at baseline and 12 and 24 months of follow-up. All examinations were performed and assessed by one experienced radiologist blinded to patient clinical data
	Country: the Czech Republic
	
	n = 53 (848 segments)
	
	Percentage male: 86.8%
	
	Mean age: 66.4 years (SD 15.9 years)
	
	Clinical features:
	
	• Vessel disease:
	  ○ Two-vessel CAD: 37%
	  ○ Three-vessel CAD: 33%
	
	• 37 underwent revascularisation
	• Mean LVEF: 34.9% (SD 4%)
	
	Inclusion criteria: stable CAD and impaired LV function < 40% all of whom were candidates for CABG
	
	Exclusion criteria: experiencing MI during the 6 months prior to admission. Patients with acute coronary syndromes or any signs of an acute myocardial ischaemia as well as patients with significant valvular disease chronic atrial fibrillation and contraindications to MRI (claustrophobia, implanted pacemaker or implantable cardioverter defibrillator). Redo CABG patients excluded, also during the 24 months of follow-up – those who were readmitted for acute coronary syndrome or had a PCI
		Standard cine sequence (assessment of LV end-diastolic thickness and LVEF) and CE CMR (dose 10 ml)
		
		Segmental model: 17 segments
		
		Method of assessing viability: extent of transmurality of scars, average LV wall width. Late gadolinium enhancement was present in 363 segments
		
		After 24 months patients were divided into responders and non-responders. Responders were those with an LVEF improvement of > 5% at 24 months
			SPECT ^{99m}Tc-sestamibi (MIBI) was injected at rest
			
			Segmental model: 17 segments
			
			Method of assessing viability: myocardial areas with a MIBI uptake below 50% of the maximum value were defined as non-viable
				Gold standard ≥ 5% improvement in LVEF
				
				n = 37 TP FP TN FN Sn Sp
				MRI DEWTR ≥ 50% (1) 86 75
				MRI DEWTR ≥ 75% (2) 71 67
				SPECT, FPD 64 69
				
				(1) Patients with five or less segments with a DE/wall thickness ratio ≥ 50%
				
				(2) In patients with 2 or fewer segments with a DE/wall thickness ratio ≥ 74%
				
				End systolic volume, end diastolic volume, total perfusion defect – not found to be useful parameters in prediction of long term LV reverse remodelling
				
				Test TP FP FN TN Sn Sp
				CMR 13 5 2 17 87 77
				
				Side effects: NR

Paper, study design	Participants, country, *n* (in final analysis), % male, clinical features, inclusion/exclusion criteria	Index test	Reference standard	Outcomes
				Strengths: long 24-month follow-up might have overcome the limitation of previous studies – the late recovery of function in some ventricular segments.
Wu 2007[25]				
Purpose: to test whether or not differences between CE MRI and F-FDG PET/TI SPECT tissue characterisation of myocardium might be related to both the recovery and non-recovery of function and the rate of recovery of function after surgical revascularisation. In addition to test whether or not the combination of MRI and nuclear techniques could be incrementally beneficial for predicting segmental functional recovery Methods: retrospective study Images of CE CMR and PET/SPECT were evaluated by two experienced observers who had no previous knowledge of any patients' clinical data. All cine images and DE on MRI were evaluated independently by two observers who were unaware of other study results. If there was no agreement in the interpretations, the image was re-evaluated by the two physicians until a consensus was reached	Country: Japan *n* = 41 (29 revascularised, data for 27) Percentage male: 78% (51.9% of the revascularised group) Mean age: 66 years (SD 10 years) Clinical features: • Vessel disease: all had multivessel diseases • Mean LVEF: 38% (SD 13%) Inclusion criteria: referred for PET and presented with chronic CAD and NYHA functional class of ≥ II, LVEF of ≤ 50% and regional wall motion abnormalities on resting echocardiography. Patients who had PET, stress or rest T1 SPECT and MRI studies within 2 weeks were enrolled for subsequent analysis Exclusion criteria: atrial fibrillation, recent (< 6 weeks) MI, unstable angina pectoris, or interventions in the period between different examinations	Gadolinium enhanced MRI Segmental model: 17 segments Method of assessing viability: Cine MRI: regional wall motion analyses, evaluated on a four-point scale (kinesis). A summed wall motion score was calculated as the sum of the individual scores of 17 segments in each patient CE MRI: the average segmental transmural extent of DE on MRI was graded visually To compare viability between MRI and nuclear techniques of a myocardial segment, a cut-off value of ≤ 50% DE on CE MRI indicating that viable myocardium was used	F-FDG PET Stress SPECT PET/SPECT regional T1 activity and F-FDG-PET quantification were performed Segments with preserved perfusion (T1 uptake ≥ 50% of maximal activity) on 4-hour SPECT images and segments with decreased perfusion (< 50%) but preserved or increased metabolism (≥ 50%) mismatch patterns were considered viable. Segments with decreased perfusion and metabolism were considered non-viable Segmental model: 17 segments Method of assessing viability	Gold standard: early functional outcome after surgical revascularisation. In patients who had surgical revascularisation an improvement in segmental wall motion by one grade or more on cine MRI was considered significant. An increase of LVEF ≥ 5% was used to define global functional improvement. In addition, a reduction of ≥ 10% in end-diastolic volume and end systemic volume were considered clinically meaningful reverse remodelling Improvement of LVEF (≥ 5%) or reverse LV remodelling [≥ 10% end systolic volume (ESV) and ESV reduction] *n* = 29 were revascularised (data for 27), 252 dysfunctional segments

Test	TP	FP	FN	TN	Sn	Sp
MRI DE (50% cut off)	142	54	12	44	92.2	44.9
PET/SPECT	152	39	2	59	60.2	98.7

<table>
<tr><th>Paper, study design</th><th>Participants, country, n (in final analysis), % male, clinical features, inclusion/exclusion criteria</th><th>Index test</th><th>Reference standard</th><th>Outcomes</th></tr>
<tr><td></td><td></td><td></td><td></td><td>Side effects: NR

Retrospective, non-randomised small study and patient management is based on clinical decisions which could have been sources of selection bias. Patient characteristics and surgical procedures were heterogeneous. Deaths were excluded from analyses which might influence the results. Lacks a longer-term assessment</td></tr>
<tr><td colspan="5">CE CMR and stress CMR
Gutberlet 2005[32]</td></tr>
<tr><td>Purpose: to compare the MRI methods of dobutamine stress, end-diastolic wall thickness, MRI-DE and the scintigraphic method TI-SPECT with functional recovery 6 months after surgery

Methods: all patients underwent bypass surgery within 1 week after imaging, At 6 months after surgery at the earliest, MR imaging and SPECT imaging were repeated to assess myocardial response to revascularisation</td><td>Country: Germany

n = 20 (240 segments)

Male: 95

Mean age: 63.7 years (SD 7.3 years)

Clinical features:

• Diabetes: 50%
• Hypertension: 60%
• Hypercholesterolaemia: 65%
• Vessel disease
• Mean LVEF: 28.6% (SD 8.7%)</td><td>Segmental model:
12 segments

Method of assessing viability: low-dose dobutamine stress. If an akinetic or dyskinetic segment showed hypokinesia with a SWT of at least 2 mm during low-dose dobutamine stress it was considered to be viable, otherwise it was considered non-viable, as was a segment with a mean EDWT < 6 mm</td><td>1. SPECT

Segmental model:
12 segments

Method of assessing viability: the absence of a T1 uptake defect during rest was considered indicative of viability. Thallium defects during rest of more than 50% of the area of the analysed segment were classified as non-viable</td><td>Recovery after revascularisation (as reference standard)

CE CMR (50%)

<table><tr><th>Test</th><th>TP</th><th>FP</th><th>FN</th><th>TN</th><th>Sn</th><th>Sp</th></tr><tr><td></td><td>204</td><td>2</td><td>2</td><td>34</td><td>99</td><td>94</td></tr></table>
MRI wall thickness

<table><tr><th>Test</th><th>TP</th><th>FP</th><th>FN</th><th>TN</th><th>Sn</th><th>Sp</th></tr><tr><td></td><td>216</td><td>20</td><td>9</td><td>11</td><td>96</td><td>35</td></tr></table></td></tr>
</table>

Paper, study design	Participants, country, *n* (in final analysis), % male, clinical features, inclusion/exclusion criteria	Index test	Reference standard	Outcomes
MRI wall motion analysis and measurement of mean EDWT were done by three experienced examiners by consensus; they were unaware of the patient's coronary status and whether it was a pre- or postoperative scan	Inclusion criteria: patients with triple vessel CAD, severely impaired LV function (LVEF < 45% measured by MRI), no contraindications to MRI and the need for CABG surgery Exclusion criteria: NR	CE CMR: transmural extent of hyperenhancement was determined and qualitatively assessed as non-viable if the extent of hyperenhanced tissue was more than 50%. Assessment was made by one author blinded to the rest of the results	2. CE CMR Segmental model: Method of assessing viability: wall motion CE CMR: the transmural extent of hyperenhancement was determined and qualitatively assessed as non-viable if the extent of hyperenhanced tissue was more than 50%	MRI wall motion (dobutamine) Test TP FP FN TN Sn Sp 169 14 25 32 88 90 SPECT Test TP FP FN TN Sn Sp 175 9 31 25 86 68 Side effects: NR
Van Hoe 2004[17]				

Purpose: to compare the value of different MRI techniques for the assessment of myocardial viability
 	
Study design: consecutive, prospective. Two observers, independently analysed the images, if there was a disagreement this was resolved by consensus. Pre and post images in random order. Identifying information removed. 8 lost to follow-up
	Country: Belgium
	
	n = 26 (18 included)
	
	Percentage male: 56%
	
	Mean age: 62 years (SD 8 years)
	
	Clinical features:
	
	• Vessel disease:
	  ○ One-vessel CAD = 17%
	  ○ Two-vessel CAD = 56%
	  ○ Three-vessel CAD = 28%
	
	• Mean LVEF: 52% (SD 16%)
		CE CMR
		
		0.2 mmol/kg gadolinium diethylene triamine peta acetic acid (GD-DTPA). < 25% delayed hyperenhancement
		
		All images were viewed on a computer console
		
		Wall motion at rest and wall motion during dobutamine stress were assessed visually
			Global and segmental cardiac function following revascularisation
			
			Segmental model: 16 segments
			
			Method of assessing viability: NR
				This study investigated the relative contribution of MRI at rest, stress cine MRI, perfusion MRI and delayed contrast enhanced MRI for the assessment of myocardial viability
				
				Findings: CE CMR is adequate to differentiate dysfunctional but viable from non-viable myocardium. Dobutamine stress and perfusion MRI studies offer little or no information

Paper, study design	Participants, country, *n* (in final analysis), % male, clinical features, inclusion/exclusion criteria	Index test	Reference standard	Outcomes
	Inclusion criteria: clinical suspicion of ischaemic heart disease (with or without MI on ECG) Exclusion criteria: unstable angina, recent MI (< 7 days old), congestive HF, ventricular arrhythmias, atrial fibrillation or any contraindication for MRI or coronary angiography	Segmental model: 16 segments Method of assessing viability: 25% delayed hyperenhancement	Follow-up MRI study was performed 9 months (SD 2 months) after the initial study and consisted of an evaluation of baseline contractility using the same cine sequence	Side effects: NR DE CMR SEH TP FP FN TN Sn Sp 0–25% 56 5 16 40 78 89 Stress CMR Test TP FP FN TN Sn Sp 56 8 16 37 78 82
Wellnhofer 2004[48]				
Purpose: prospective blinded within-patient comparison of low dose dobutamine MRI and CE CMR (gadolinium)	Country: Germany *n* = 29	Stress vs. CE CMR Segmental model: 16 segments	Revascularisation – the primary success of revascularisation controlled by a review of all angiograms	288/464 segments with wall motion abnormalities at rest

Paper, study design	Participants, country, *n* (in final analysis), % male, clinical features, inclusion/exclusion criteria	Index test	Reference standard	Outcomes
Methods: stress and CE CMR were performed 1 day before revascularisation and recovery was verified at 3 months after revascularisation Two blinded investigators. Discordant assessments were jointly reviewed	Male: 93.1% Mean age: 68 years (SD 7 years) Clinical features: • Vessel disease • Mean LVEF: 32% (8%) • At least two adjacent segments with wall motion abnormalities at rest. No infarction within the last 2 months. Definite inclusion occurred after coronary revascularisation Inclusion criteria: chronic CAD with stable angina. LVEF < 45% Exclusion criteria: contraindications for CMR	Method of assessing viability: transmurality – assess on a 5 grade scale. 10–15 minutes after GD-DTPA (0.2 mmol/kg) Wall motion was assessed at rest and at end of each dose of dobutamine. Graded as normokinesia, hypokinesia, akinesia and dyskinesia	Method of assessing recovery: an improvement of wall motion at follow-up by at least one grade	CE CMR at 25% predicted 73% of hibernating segments correctly. Stress MRI predicted 85% of hibernating segments correctly CE CMR Side effects: NR DE CMR SEH TP FP FN TN Sn Sp 0–25% 93 12 31 152 75 93 0–50% 111 79 13 85 90 52 Stress CMR Test TP FP FN TN Sn Sp 94 14 30 150 76 91 NB: these data were supplied by author. Insufficient data for stress CMR

+pv, positive predictive value; –pv, negative predictive value; DA, diagnostic accuracy; DE, delayed enhancement; DETWR delayed enhanced wall thickness ratio; DSE, dobutamine stress echocardiography; DWT, diastolic wall thickness; ECG, electrocardiogram; ESWT, end systolic wall thickness; F-18-FDG, F-18 Fluorodeoxyglucose; FN, false negative; FP, false positive; FPD, fixed perfusion defect; HE, hyperenhancement; ITT, intention to treat; MIBI, ^{99m}Tc-sestamibi; MRI, magnetic resonance imaging; NR, not reported; RCT, randomised controlled trial; RWMS, regional wall motion score; SD, standard deviation; SEH, segmental extent of hyperenhancement; Sn, sensitivity; Sp, specificity; TN, true negative; TP, true positive; VD, vessel disease.

Appendix 4 Meta-analyses

Pooled summary estimates of diagnostic parameters for different tests

TABLE 26 Contrast-enhanced cardiovascular magnetic resonance imaging: meta-analysis of diagnostic accuracy

Log-likelihood = −97.790904		Number of studies = 14	
	Coefficient	Standard error	95% CI
Bivariate[a]			
E(logitSe)	3.071154	0.1573777	2.762699 to 3.379608
E(logitSp)	0.1206598	0.260793	−0.3904852 to 0.6318047
Var(logitSe)	0.1734921	0.1398701	0.0357303 to 0.8424072
Var(logitSp)	0.8762317	0.3939162	0.3630406 to 2.114865
Corr(logits)	0.8858773	0.1737588	0.178021 to 0.9949026
Hierarchical summary receiver operating characteristic			
Lambda	4.684499	0.9258158	2.869933 to 6.499064
Theta	2.261762	0.4438836	1.391766 to 3.131758
beta	0.8097493	0.3888251	0.0476661 to 1.571833
s2alpha	1.470594	0.790014	0.5131223 to 4.21468
s2theta	0.022248	0.0352209	0.0009994 to 0.4952583
Summary			
Sn	0.9556871	0.0066648	0.9406265 to 0.9670611
Sp	0.5301284	0.0649615	0.4036005 to 0.6528986
DOR	24.33251	9.217289	11.58103 to 51.12423
LR+	2.033932	0.2901764	1.537792 to 2.690144
LR−	0.0835891	0.0205449	0.0516342 to 0.1353198

Sn, sensitivity; Sp, specificity.
a Covariance between estimates of E(logitSe) and E(logitSp) 0.0253564.

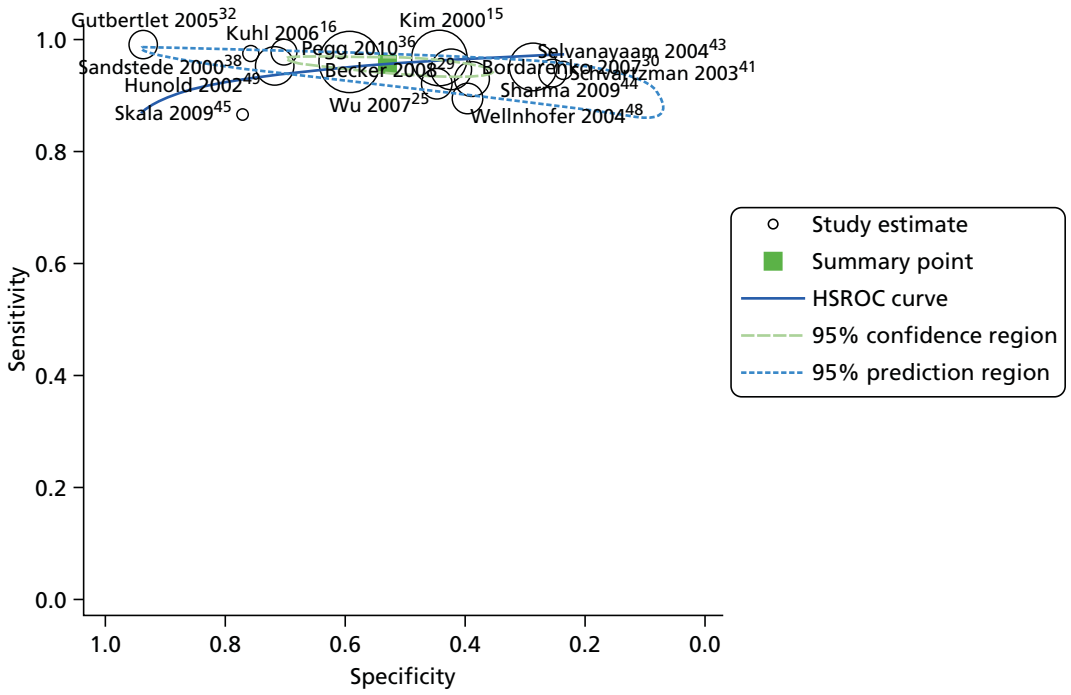

FIGURE 12 Summary receiver operating characteristic plot for meta-analysis of CE CMR studies with revascularisation as gold standard. HSROC, hierarchical summary receiver operating characteristic.

TABLE 27 Stress CMR: meta-analysis of diagnostic accuracy

Log-likelihood = −73.275835		Number of studies = 12	
	Coefficient	Standard error	95% CI
Bivariate[a]			
E(logitSe)	1.532157	0.2683608	1.006179 to 2.058134
E(logitSp)	1.90703	0.2529787	1.411201 to 2.402859
Var(logitSe)	0.6725586	0.3598789	0.2356467 to 1.919548
Var(logitSp)	0.4215842	0.2774576	0.1160599 to 1.531392
Corr(logits)	−0.1461542	0.3871955	−0.7271544 to 0.5568428
Hierarchical summary receiver operating characteristic			
Lambda	3.506532	0.3752162	2.771122 to 4.241942
Theta	−0.3899651	0.3733121	−1.121643 to 0.3417131
Beta	−0.2335348	0.4218122	−1.060271 to 0.5932018
s2alpha	0.9093198	0.5455962	0.280538 to 2.947417
s2theta	0.3051549	0.1716382	0.1013331 to 0.9189445
Summary			
Sn	0.8223216	0.0392099	0.7322717 to 0.8867669
Sp	0.8706851	0.0284835	0.8039553 to 0.9170451
DOR	31.1616	10.93582	15.6639 to 61.99257
LR+	6.359065	1.404779	4.124341 to 9.804645
LR−	0.2040673	0.0448958	0.1325882 to 0.3140811
1/LR−	4.900344	1.078099	3.183891 to 7.542147

Sn, sensitivity; Sp, specificity.
a Covariance between estimates of E(logitSe) and E(logitSp) −0.0064288.

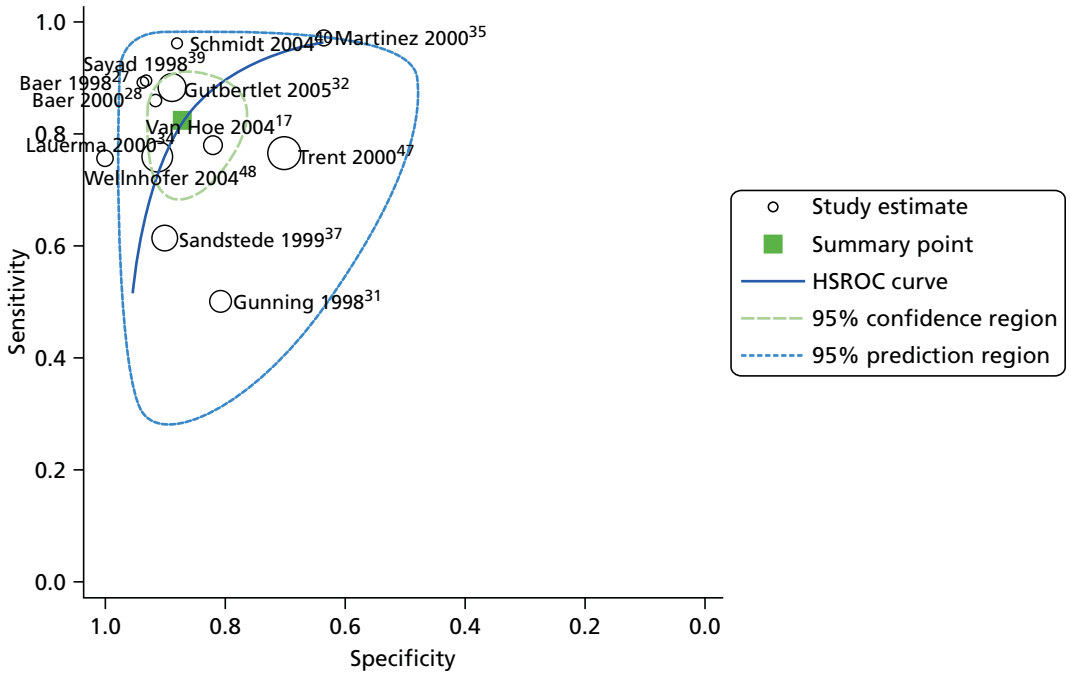

FIGURE 13 Summary receiver operating characteristic plot for meta-analysis of stress CMR studies with revascularisation as gold standard. HSROC, hierarchical summary receiver operating characteristic.

TABLE 28 Single-photon emission tomography: meta-analysis of diagnostic accuracy

Log-likelihood = −87.904668		Number of studies = 13	
	Coefficient	Standard error	95% CI
Bivariate[a]			
E(logitSe)	1.746286	0.2423578	1.271273 to 2.221298
E(logitSp)	0.4954893	0.1971306	0.1091204 to 0.8818582
Var(logitSe)	0.6147793	0.3103291	0.2285854 to 1.653446
Var(logitSp)	0.3874867	0.1879477	0.1497572 to 1.002596
Corr(logits)	0.0406427	0.3223407	−0.5314447 to 0.5872686
Hierarchical summary receiver operating characteristic			
Lambda	2.112061	0.3563283	1.41367 to 2.810451
Theta	0.4999341	0.2354043	0.0385501 to 0.9613181
Beta	−0.2307908	0.3498725	−0.9165284 to 0.4549467
s2alpha	1.015827	0.4800675	0.4023019 to 2.564999
s2theta	0.2341199	0.1123643	0.0913924 to 0.5997454
Summary			
Sn	0.8514837	0.0306484	0.7809606 to 0.9021458
Sp	0.6213987	0.0463774	0.5272531 to 0.7072071
DOR	9.410017	2.985523	5.052764 to 17.52475
LR+	2.249025	0.2896242	1.747344 to 2.894743
LR–	0.2390033	0.0529831	0.154777 to 0.3690636
1/LR–	4.184043	0.9275338	2.70956 to 6.460909

Sn, sensitivity; Sp, specificity.
a Covariance between estimates of E(logitSe) and E(logitSp) 0.0015315.

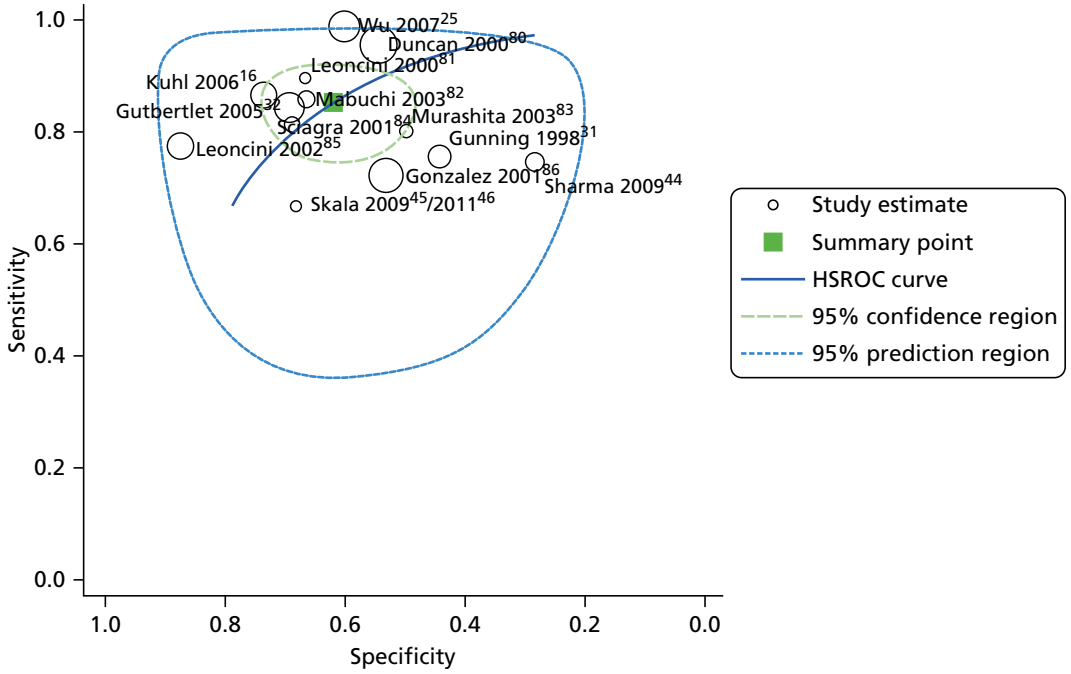

FIGURE 14 Summary receiver operating characteristic plot for meta-analysis of all SPECT studies. HSROC, hierarchical summary receiver operating characteristic.

TABLE 29 Positron emission tomography: meta-analysis of diagnostic accuracy

Log-likelihood = −22.570007		Number of studies = 4	
	Coefficient	Standard error	95% CI
Bivariate[a]			
E(logitSe)	2.89631	0.3367881	2.236218 to 3.556403
E(logitSp)	0.7921053	0.4031167	0.0020111 to 1.582199
Var(logitSe)	0.1832845	0.2193723	0.017552 to 1.913923
Var(logitSp)	0.5335768	0.4157517	0.1158667 to 2.457169
Hierarchical summary receiver operating characteristic			
Lambda	4.38964	0.7667298	2.886877 to 5.892402
Theta	1.588412	0.5916754	0.428749 to 2.748074
Beta	0.5342817	0.5146041	−0.4743239 to 1.542887
s2theta	0.3127241	0.271732	0.0569555 to 1.717065
Summary			
Sn	0.9476637	0.0167037	0.9034551 to 0.9722507
Sp	0.6882832	0.0864885	0.5005028 to 0.8295158
DOR	39.98146	13.00363	21.1355 to 75.63185
LR+	3.040143	0.8110108	1.802276 to 5.128222
LR−	0.0760388	0.0197397	0.0457155 to 0.1264759
1/LR−	13.15117	3.41405	7.906646 to 21.87443

Sn, sensitivity; Sp, specificity.
a Covariance between estimates of E(logitSe) and E(logitSp) −0.0850736.

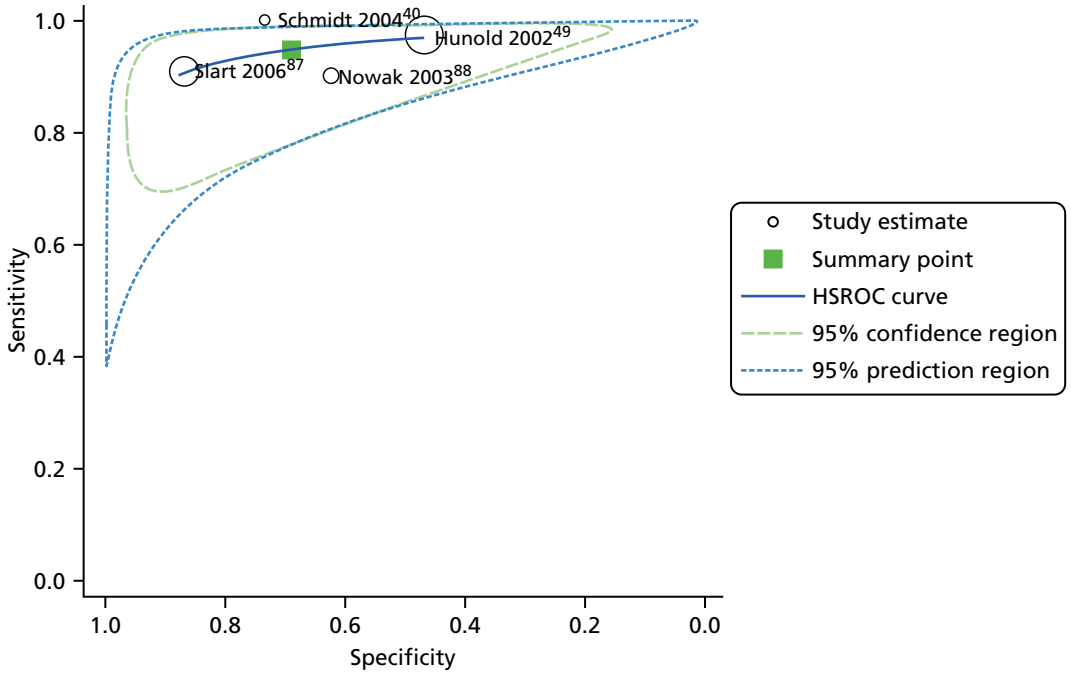

FIGURE 15 Summary receiver operating characteristic plot for meta-analysis of all PET studies. HSROC, hierarchical summary receiver operating characteristic.

TABLE 30 Echocardiography: meta-analysis of diagnostic accuracy

Log-likelihood = −84.232837		Number of studies = 12	
	Coefficient	Standard error	95% CI
Bivariate[a]			
E(logitSe)	1.245713	0.1843334	0.8844259 to 1.607
E(logitSp)	0.8293239	0.1635205	0.5088296 to 1.149818
Var(logitSe)	0.3071516	0.1671668	0.1057031 to 0.8925198
Var(logitSp)	0.2406187	0.1398436	0.0770238 to 0.7516811
Corr(logits)	−0.3819004	0.3387733	−0.8273388 to 0.3584247
Hierarchical summary receiver operating characteristic			
Lambda	2.053474	0.2076613	1.646465 to 2.460482
Theta	0.1452212	0.2350727	−0.3155129 to 0.6059553
Beta	−0.122064	0.382553	−0.8718541 to 0.6277262
s2alpha	0.3360699	0.2105767	0.0984189 to 1.147574
s2theta	0.1878399	0.0968468	0.0683792 to 0.5160025
Summary			
Sn	0.7765568	0.0319849	0.7077385 to 0.8329944
Sp	0.6962119	0.0345847	0.6245321 to 0.7594777
DOR	7.964838	1.648614	5.308718 to 11.9499
LR+	2.556245	0.2785782	2.064615 to 3.164944
LR−	0.3209413	0.0439368	0.2454123 to 0.4197154
1/LR−	3.115835	0.4265571	2.382567 to 4.074776

Sn, sensitivity; Sp, specificity.
a Covariance between estimates of E(logitSe) and E(logitSp) −0.0089372.

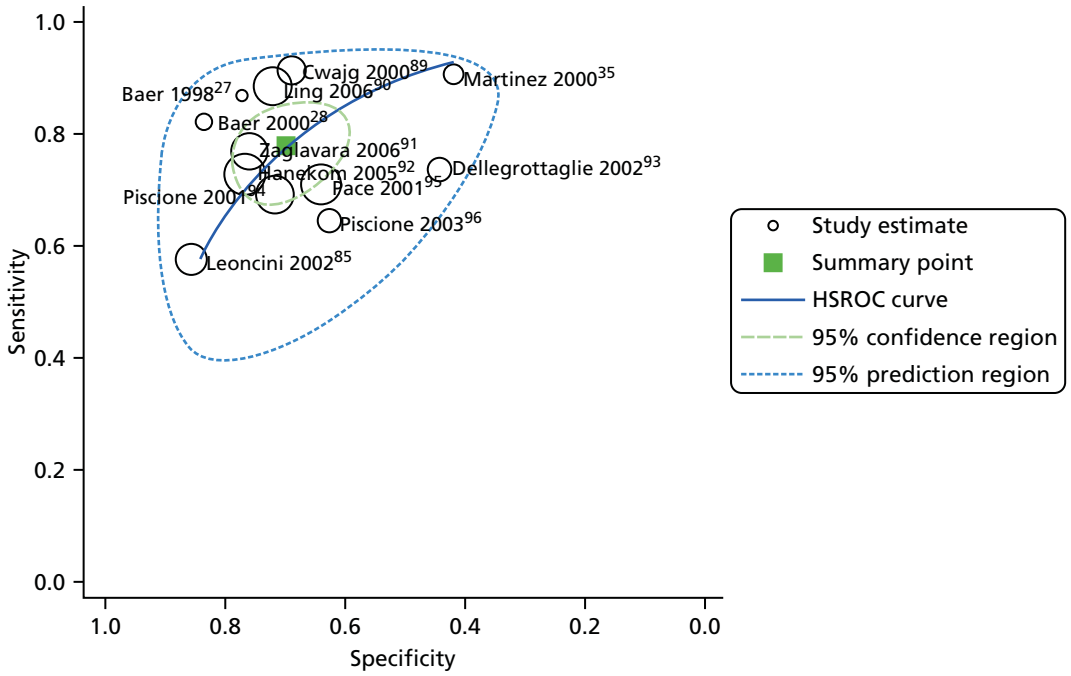

FIGURE 16 Summary receiver operating characteristic plot for meta-analysis of all echocardiographic studies. HSROC, hierarchical summary receiver operating characteristic.

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