

***Cardiac MRI for
myocardial stress
perfusion and
viability imaging in
patients with known
or suspected
coronary artery
disease***

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Assessment report

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The technical information in this document is used by the Medical Services Advisory Committee (MSAC) to inform its deliberations. MSAC is an independent committee which has been established to provide advice to the Minister for Health on the strength of evidence available on new and existing medical technologies and procedures in terms of their safety, effectiveness and cost effectiveness. This advice will help to inform government decisions about which medical services should attract funding under Medicare.

MSAC's advice does not necessarily reflect the views of all individuals who participated in the MSAC evaluation.

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EXECUTIVE SUMMARY

CARDIAC MRI FOR MYOCARDIAL STRESS PERFUSION AND VIABILITY IMAGING IN PATIENTS WITH KNOWN OR SUSPECTED CORONARY ARTERY DISEASE

MAIN ISSUES FOR MSAC CONSIDERATION

For population 1:

Accuracy and safety:

- SP-CMR & LGE is marginally safer, but less accurate, and less preferred by patients than CTCA. However, CTCA is not listed on the MBS for use in patients with a risk of CAD over 45%, due to lack of cost-effectiveness in intermediate to high-risk patients.
- SP-CMR & LGE appears to have similar accuracy to stress Echo but is not as safe.
- SP-CMR & LGE has similar safety but may be slightly more accurate than SPECT.
- Exercise ECG is very safe but is too inaccurate to be informative.

Change in management:

- Non-invasive imaging may allow 20%–25% of patients suspected of having CAD to avoid having an ICA by ruling out those who are unlikely to be at risk of cardiac events. The only study that compared SP-CMR against the other non-invasive imaging modalities found no significant differences in the way that patients were managed, or fared, between imaging techniques.

For population 2:

Therapeutic effectiveness:

- One good-quality RCT was identified, which showed that when patients with and without viability were randomised to medical therapy or revascularisation, there were no significant differences between treatments in either the viability or non-viability arms. Therefore, regardless of the accuracy of LGE-CMR for ruling out viability using this information to guide whether patients are revascularised or not does not appear to reduce the risk of major adverse cardiac events. Assessment of viability cannot therefore be considered to be effective.

A.1 ALIGNMENT WITH AGREED PICO CONFIRMATION

This contracted assessment of cardiac MRI (magnetic resonance imaging) for myocardial stress perfusion and viability imaging in patients with known or suspected coronary artery disease (CAD) addresses most of the PICO¹ elements that were pre-specified in the Protocol that was ratified by the Protocol Advisory Subcommittee (PASC) or the Medical Services Advisory Committee (MSAC) Executive.

A.2 PROPOSED MEDICAL SERVICE

Cardiac MRI (CMR) uses a standard MRI system, with or without specialised cardiac coils, and specialised software for quantitative analysis. The magnetic field strength used for CMR is usually

¹ population, investigation/Index test, comparators and outcomes

either 1.5 or 3.0 teslas (T) and the images obtained are interpreted by either a qualified cardiologist or radiologist.

Stress perfusion CMR (SP-CMR) detects damaged or ischaemic myocardium, which manifests as perfusion deficits or low signal areas detected during a first-pass perfusion sequence using a gadolinium-based contrast agent (Gotschy et al. 2014). These images are usually compared with perfusion images taken at rest.

Viability imaging via delayed contrast-enhanced CMR, or late gadolinium enhancement (LGE), also uses gadolinium-based contrast agents to define the extent of irreversibly damaged (necrotic or scarred) myocardium (Medical Advisory Secretariat 2010e; Woodard et al. 2006).

CMR for CAD is not currently covered by private health insurance and private patients who utilise CMR services are required to pay the full cost of the procedure.

A.3 PROPOSAL FOR PUBLIC FUNDING

Table ES.1 Proposed Medicare Benefits Schedule (MBS) item descriptor

Category 5 – Diagnostic Imaging Services
<p>MBS [item number to be assigned]</p> <p>NOTE: Benefits are payable for each service included by Subgroup 15 on one occasion only in any 12 month period</p> <p>MAGNETIC RESONANCE IMAGING performed under the professional supervision of an eligible provider at an eligible location where the patient is referred by a specialist or by a consultant physician and where the request for the scan specifically identifies the clinical indication for the scan - scan of the heart for:</p> <ul style="list-style-type: none"> (a) myocardial viability using delayed gadolinium enhancement (Contrast); and (b) stress myocardial perfusion (Contrast); and (c) the request for the scan identifies that the patient presents with: <ul style="list-style-type: none"> (i) symptoms consistent with stable ischaemic heart disease, with an intermediate pre-test probability of coronary artery disease. <p>Fee: \$900 Benefit: 75% = \$675; 85% = \$765</p>
<p>MBS [item number to be assigned]</p> <p>NOTE: Benefits are payable for each service included by Subgroup 15 on one occasion only in any 12 month period</p> <p>MAGNETIC RESONANCE IMAGING performed under the professional supervision of an eligible provider at an eligible location where the patient is referred by a specialist or by a consultant physician and where the request for the scan specifically identifies the clinical indication for the scan - scan of the heart for:</p> <ul style="list-style-type: none"> (a) myocardial viability using delayed gadolinium enhancement (Contrast); and (b) the request for the scan identifies that an adult patient being considered for revascularisation presents with: <ul style="list-style-type: none"> (i) an existing diagnosis of significant CAD, a history of ischaemic heart disease and impaired left ventricular function. <p>Fee: \$700 Benefit: 75% = \$525; 85% = \$595</p>

A.4 POPULATION

CAD is also known as ischaemic heart disease (IHD) and coronary heart disease (CHD). It is the leading cause of a group of heart diseases that include stable angina, unstable angina, myocardial infarction (MI) and sudden coronary death. There are several well-known risk factors for CAD that include high blood pressure, smoking, diabetes, lack of exercise, obesity, high blood cholesterol, poor diet and excessive alcohol.

The use of CMR is proposed in two distinct populations. SP-CMR and LGE would be used to diagnose CAD in patients presenting with symptoms consistent with stable IHD and with an intermediate pre-

test probability (PTP) of CAD (population 1). The PTP would be determined using a clinical decision matrix, which would take into account criteria such as age; gender; family history; risk factors such as hypertension, hypercholesterolaemia, diabetes and smoking; as well as the presence of symptoms such as dyspnoea and chest pain. In population 1 the two tests would be performed consecutively during the same MRI procedure. The rest and stress perfusion (SP) images would be taken first, the order depending on the protocol, followed by the LGE imaging.

LGE would also be used to assess myocardial viability in patients with an existing diagnosis of significant CAD who have a history of IHD and left ventricular dysfunction (LVD), and are being considered for revascularisation (population 2).

In 2010 IHD accounted for the single largest (15%) burden of disease in Australia, based on years of life lost (2014). For a detailed estimate of the potential number of patients eligible for the proposed Medicare Benefits Schedule (MBS) item numbers, see Section A4 of the report.

A.5 COMPARATOR DETAILS

In population 1, where SP-CMR & LGE is proposed as a diagnostic test in patients with an intermediate PTP of having CAD, four comparators were recognised: exercise stress electrocardiography (ECG), exercise or pharmacological stress echocardiography (Echo), exercise or pharmacological stress single-photon emission computed tomography (SPECT), and computed tomography coronary angiography (CTCA). In this population invasive coronary angiography (ICA) is considered to be the reference standard.

In population 2, where LGE-CMR is used as a prognostic test in patients with CAD to determine their eligibility for revascularisation, three comparators were identified: low-dose dobutamine stress Echo, SPECT and computed tomography (CT) perfusion.

For detailed descriptions of the comparators, refer to Section A5 in the report.

A.6 CLINICAL MANAGEMENT ALGORITHM(S)

For clinical management algorithms on how CMR is proposed to be placed relative to the comparators, see Figure 3 and Figure 4 in the report.

A.7 KEY DIFFERENCES IN THE DELIVERY OF THE PROPOSED MEDICAL SERVICE AND THE MAIN COMPARATOR

In population 1 CMR is posed as an alternative investigative test to existing ischaemia stress testing modalities and CTCA. Patients using CMR instead of SPECT or CTCA also avoid exposure to ionising radiation. The advantages and disadvantages identified in the *2013 ESC guidelines on the management of stable coronary artery disease* (Montalescot et al. 2013) are listed in Table 12.

In population 2 the use of CMR for myocardial viability imaging is intended to replace existing methods of viability imaging due to improved safety compared with nuclear imaging technologies; patients will not be exposed to ionising radiation.

A.8 CLINICAL CLAIM

The applicant claims that SP-CMR & LGE has superior diagnostic accuracy compared with existing stress testing modalities, on the basis that it provides more detailed and reliable data with reduced inter- and intra-observer variability (Greenwood et al. 2012). Thus, the use of CMR should:

- i. reduce the test failure rate, leading to earlier diagnosis and management of CAD, or earlier exclusion of CAD;
- ii. allow additional/earlier case detection and management, with fewer false negatives; and
- iii. produce fewer false positives, reducing the need for further invasive testing.

CMR is also posed as an alternative to CTCA for patients with a low to intermediate risk of CAD (15%–45%), thereby avoiding exposure to ionising radiation, although it is possible that CTCA may still be conducted following an equivocal CMR result to confirm the presence of significant CAD.

The use of CMR instead of other imaging modalities is claimed to reduce the need for CTCA, ICA and myocardial biopsy in eligible patients, and reduce downstream costs by reducing the need for layered testing. However, a Health Expert Standing Panel (HESP) member indicated that it would require a major shift in referral patterns to fully replace Echo and nuclear cardiac testing, as they are firmly entrenched in the standard workup of cardiac patients.

In patients with an existing diagnosis of significant CAD and a history of IHD with impaired left ventricular function, and who are being considered for revascularisation procedures, LGE-CMR is proposed to be non-inferior to existing modalities with improved safety. The application also claims that CMR has a significant impact on therapy planning and patients' preferred choice of therapy (Taylor et al. 2013).

APPROACH TAKEN TO THE EVIDENCE ASSESSMENT

A systematic review (SR) of published literature was undertaken on 26 May 2015 to identify relevant studies and SRs published since 1990. Searches were conducted using the databases described in Appendix B. Attempts were also made to source unpublished or grey literature from the additional sources listed in Appendix B. HTA websites listed in Appendix B were also searched. Search terms are described in Table 19 in Section B of the report.

One randomised controlled trial (RCT) providing limited direct evidence for population 1 was identified. This was supplemented by linked evidence. Due to the lack of direct evidence, a linked evidence approach alone was undertaken for population 2.

RESULTS FOR POPULATION 1

Safety

Most adverse events (AEs) associated with non-invasive imaging modalities are attributable to the use of a stressor (Sections B1.6 and B7a). However, the number of serious AEs experienced by patients during ICA far outnumbers those resulting from any non-invasive imaging modality.

The ICA procedure was associated with the highest risk of acute deaths, and the use of a stressor was the most common cause of acute death with non-invasive imaging. Long-term mortality, mostly from cancer or renal failure, is due to the use of radionuclides and contrast agents. The long-term mortality rate is the highest for CTCA and ICA as the procedures use both radionuclides and contrast agents. Conversely, the long-term mortality rate associated with exercise ECG and stress Echo are negligible because radionuclides are not used with these tests, and contrast agents are only rarely used with Echo.

Effectiveness

Direct effectiveness

The pragmatic cost-effectiveness of non-invasive cardiac testing (CECaT) trial compared the effect of initial diagnosis of CAD using SP-CMR, SPECT, stress Echo or ICA on patient management and outcomes. The trial reported that having an initial non-invasive imaging test reduced the number of patients having ICA by 25%, consisting mostly of patients with a negative result. There were no significant differences between imaging modality groups. However, SP-CMR had a successful completion rate of only 78%, compared with 98%, 94% and 90% for the ICA, SPECT and stress Echo groups, respectively. Thus, SP-CMR may not be suitable for use in approximately 20% of the eligible testing population.

There were no clinically or statistically significant differences in morbidity, mortality or quality of life (QoL) between the three non-invasive imaging groups when compared with the ICA group. The only exception was that patients randomised to either SP-CMR or stress Echo did not improve in exercise time as much as patients randomised to either SPECT or ICA.

Effectiveness from linked evidence

1. Accuracy

When the pooled sensitivities for the different non-invasive imaging modalities versus ICA were compared, CTCA was clearly the most sensitive, at 97%. SP-CMR with/without LGE, SPECT and stress Echo had similar sensitivities, ranging from 83% to 88%, and exercise ECG was the least sensitive, at 68%. Thus, one-third of all patients with CAD detectable by ICA would not be diagnosed by exercise ECG (i.e. would be falsely negative) and would not receive any more treatment than for other non-invasive imaging modalities, compared with 12%–17% for SP-CMR with/without LGE, SPECT and stress Echo, and 3% for CTCA.

The specificities of SP-CMR with/without LGE, CTCA and stress Echo were similar, at between 82% and 86%, and both SPECT and exercise ECG were less specific at 77%. Thus, one-quarter of all patients who did not have CAD detectable by ICA would be falsely positive by SPECT and exercise ECG, and may have received unnecessary invasive testing, compared with 14%–18% of patients for SP-CMR with/without LGE, CTCA and stress Echo.

The post-test probability (PoTP) of having CAD after testing positive with CTCA is higher than for other non-invasive imaging modalities, but the PoTPs for stress Echo and SP-CMR with/without LGE are similar (within 10% of CTCA) and are all 2- to 3-fold higher than the PTP in patients with a low-intermediate PTP (15%–45%). The PoTPs of having CAD after testing positive with SPECT and exercise ECG are 15% and 20% lower than for CTCA, respectively.

The PoTPs of having CAD after testing negative are much lower with CTCA than with other modalities, and are 5- to 10-fold lower than the PTP in patients with a high-intermediate PTP (65%–85%). The PoTPs are similar (within 10%) for stress Echo, SP-CMR with/without LGE, and SPECT but are much higher than for CTCA and represent only a 2- to 3-fold decrease from the PTP. In patients with a high-intermediate PTP of 65%–85% tested by exercise ECG, the PoTP of having CAD is only reduced slightly, to 45%–70%.

CTCA is only listed on the MBS for use in patients with a low-intermediate PTP of having CAD (15%–45%). In these patients stress Echo and SP-CMR & LGE are almost as effective at diagnosing patients with CAD as CTCA, when compared with ICA as the reference standard. However, in patients who have a negative test result, CTCA is at least 3-fold more likely to be correct than other non-invasive imaging modalities.

In patients with a high-intermediate PTP (65%–85%) of having CAD, CTCA is the only test that can effectively rule out CAD in the minority of patients who have a negative test result, but it is not listed on the MBS for use in these patients due to lack of cost-effectiveness. In the majority of patients who would have a positive test result, stress Echo and SP-CMR with/without LGE are almost as effective as CTCA in diagnosing CAD.

2. Therapeutic efficacy (change in management)

Due to the lack of comparative evidence regarding how CMR influences management, no statements regarding the comparative therapeutic efficacy can be made.

However, patient acceptance of SP-CMR is questionable. Schonenberger et al. (2007) found that the vast majority of patients preferred CTCA over either SP-CMR or ICA, with both SP-CMR and ICA having similar low rates of preference.

3. Therapeutic effectiveness (health benefit from change in management)

Due to the lack of comparative evidence regarding how SP-CMR influences management, no statements regarding its comparative therapeutic effectiveness can be made. CMR does appear to be good at predicting the prognosis of patients, in regards to their risk of major adverse cardiac events (MACE); however, it is unknown to what extent these findings differ from those in patients having comparative non-invasive imaging modalities such as CTCA, SPECT, stress Echo or exercise ECG.

Summary

On the basis of the benefits and harms reported in the evidence-base (summarised in Table ES.2), it is suggested that SP-CMR with/without LGE has:

- **non-inferior safety** and **inferior effectiveness** relative to **CTCA**
- **inferior safety** and **non-inferior effectiveness** relative to **stress Echo**
- **non-inferior safety** and **non-inferior effectiveness** relative to **SPECT**
- **inferior safety** and **superior effectiveness** relative to **exercise ECG**.

Table ES.2 Balance of clinical benefits and harms of CMR, relative to comparators

Outcomes	Participants (studies)	Quality of evidence	Results	Interpretation	GRADE
CVD-related mortality	N=898 k=1 RCT	Risk of bias: 0 Inconsistency: 0 Indirectness: -1 Imprecision: 0 Publication bias: 0	SP-CMR = 5/226 (2.2%) ICA = 3/222 (1.4%) SPECT = 5/224 (2.2%) Stress Echo = 3/226 (1.3%)	The number of people who died during follow-up was small, so it is possible that any small difference in the risk of death between groups was due to chance.	Moderate ⊕⊕⊕⊖
Non-fatal CVD-related events	N=898 k=1 RCT	Risk of bias: 0 Inconsistency: 0 Indirectness: -1 Imprecision: 0 Publication bias: 0	SP-CMR = 29/226 (12.8%) ICA = 19/222 (8.6%) SPECT = 24/224 (10.7%) Stress Echo = 31/226 (13.7%)	The risk of cardiovascular-related AEs was very similar between groups, with a trend favouring non-invasive imaging over ICA. There was no difference between CMR and SPECT or Echo.	Moderate ⊕⊕⊕⊖
Safety of imaging	No large comparative studies	Risk of bias: -1 Inconsistency: -1 Indirectness: -1 Imprecision: -1 Publication bias: 0	ICA is associated with significantly more AEs and deaths than any of the non-invasive imaging techniques. SP-CMR with/without LGE is associated with slightly fewer deaths than CTCA, but more than stress Echo. SP-CMR is associated with slightly more non-fatal AEs than CTCA and SPECT, and slightly fewer than stress Echo.	Most AEs that occur during non-invasive imaging are due to the stressor used. Most long-term deaths from non-invasive imaging are caused by the use of contrast agents and/or radionuclides. However, any of the non-invasive tests that accurately rule out a patient from needing an ICA is beneficial, given the risk from ICAs.	Very low ⊕⊖⊖⊖
Accuracy (PoTP of	k=16 for SP-CMR	Risk of bias: 0	Stress Echo and SP-CMR with/without LGE	CMR is non-inferior to SPECT and stress Echo	Low

Outcomes	Participant s (studies)	Quality of evidence	Results	Interpretation	GRADE
being positive for CAD, after a negative test result)	k=18 for LGE-CMR k=13 for SPECT k=10 for Echo k=147 for ECG	Inconsistency: -1 Indirectness: -1 Imprecision: 0 Publication bias: 0	are slightly better than SPECT at ruling out the presence of CAD. However, all three modalities were inferior to CTCA in ruling out the presence of CAD in patients with a negative result. Exercise ECG has very poor accuracy.	and superior to exercise ECG, which are funded for patients above 45% risk of having CAD. CMR (and the comparative tests that are funded) are inferior to CTCA.	⊕⊕⊕⊕
Impact on patient management (referral to ICA)	N=898; k=1 RCT	Risk of bias: 0 Inconsistency: 0 Indirectness: -1 Imprecision: 0 Publication bias: 0	SP-CMR = 80% SPECT = 78% Stress Echo = 75%	The non-invasive tests were similar in their ability to rule out patients who did not require an ICA.	Moderate ⊕⊕⊕⊕

^a GRADE Working Group grades of evidence (Guyatt et al. 2011)

⊕⊕⊕⊕ **High quality:** We are very confident that the true effect lies close to that of the estimate of effect

⊕⊕⊕⊕ **Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

⊕⊕⊕⊕ **Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

⊕⊕⊕⊕ **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

AE = adverse events; CAD = coronary artery disease; CMR = cardiac magnetic resonance imaging; CTCA = computed tomography coronary angiography; CVD = cardiovascular disease; ECG = electrocardiogram; Echo = echocardiography; ICA = invasive coronary angiography; k = number of studies; LGE = late gadolinium enhancement; PoTP = post-test probability; RCT = randomised controlled trial; SP-CMR = stress perfusion cardiac magnetic resonance imaging; SPECT = single-photon emission computed tomography

TRANSLATION ISSUES

Translation issues addressed in the assessment of CMR for the diagnosis of CAD are listed in Table ES.3.

Table ES.3 Translation issues addressed in the assessment

Type	Issue
Applicability	<ul style="list-style-type: none"> Which set of accuracy inputs reported in Section Ba should be used in the economic model for CMR? How comparable are the studies used to inform the test parameter inputs of the economic model? Are the studies used to inform the test parameter inputs of the economic model applicable to the proposed MBS population with respect to age and gender distribution? What is the prevalence of CAD in the proposed MBS population?
Extrapolation	None identified
Transformation	None identified
Other	<ul style="list-style-type: none"> How applicable is the evidence for a change in management? i.e. to what extent will the imaging result impact patterns of referral to ICA in Australia?

CAD = coronary artery disease; CMR = cardiac magnetic resonance imaging; ICA = invasive coronary angiography; MBS = Medicare Benefits Schedule

ECONOMIC EVALUATION

The economic model for population 1 will represent comparison of SP-CMR with CTCA, ECG, Echo and SPECT in the population with an intermediate PTP of CAD. There is inadequate data to reliably construct an economic model to generate a full cost-utility analysis. However, a comparative cost analysis of SP-CMR and its comparators, incorporating downstream diagnostic costs and utilising data from the clinical evaluation regarding the accuracy, re-testing and AE rates has been undertaken and the consequences of the different testing strategies is discussed. Additionally, cost-effectiveness analyses with outcomes of interest being (i) incremental cost per correct initial test result (ii) cost per unnecessary ICA avoided and (iii) cost per useful ICA referred are provided.

A summary of the key characteristics of the economic evaluation is given in Table ES.4.

Table ES.4 Summary of the economic evaluation

Perspective	CTCA, stress Echo, SPECT and exercise ECG
Comparators	Cost-consequences and cost-effectiveness analyses
Type of economic evaluation	Systematic review (as presented in Section B)
Sources of evidence	Time to achieve a diagnosis (assumed <1 year – no discounting)
Time horizon	Cost per unnecessary ICA avoided and cost per correct initial test result
Outcomes	Decision-tree analysis
Methods used to generate results	TreeAge Pro
Software packages used	CTCA, stress Echo, SPECT and exercise ECG

CTCA = computed tomography coronary angiography; ECG = electrocardiography; Echo = echocardiography; ICA = invasive coronary angiography; PTP = pre-test probability; SPECT = single-photon emission computed tomography

The time horizon chosen for the economic model is the time to achieve a diagnostic conclusion (based on non-invasive testing or ICA). Since conclusions regarding the long-term health outcome effects of revascularisation post-diagnosis cannot be made with any certainty, the model terminates before this component of the treatment pathway and neither costs nor outcomes associated with post-diagnosis revascularisation are included.

Key structural assumptions of the model are that:

- The implications of a false negative test are uncertain. As per the clinical management algorithm (Figure 3, Section A.6), all patients eligible for testing are assumed to receive optimal medical therapy (OMT), irrespective of CAD diagnosis. Therefore, the implications for a patient with a false negative test would be delayed diagnosis and revascularisation.
- As CMR does appear to reasonably predict patients requiring ICA, and due to the invasive nature of ICA, a reduction in unnecessary ICAs (i.e. ICAs in true CAD0-negative patients) is a patient-relevant outcome that is explored in a secondary cost-effectiveness analysis (CEA).
- A positive result in any non-invasive test is followed by an ICA as part of CAD management. This is consistent with patient management in the CECaT trial, where 93%–98% of patients with positive non-invasive imaging results were referred for ICA (Section B1). Therefore, the implication of a false positive result is that patients undergo ICA unnecessarily to receive the correct negative diagnosis.
- Equivocal/inconclusive/failed test results receive a CTCA.

- As evidence for the accuracy of CTCA, given that a previously equivocal result was not specifically identified in the clinical evaluation, the accuracy of CTCA is assumed to be the same as in patients who were previously untested.
- Change in management resulting from a negative non-invasive test is perfect, with scenario analyses additionally presented with alternative assumptions (see Section Ca.5.1 and Section Ca.5.2).

The limitations of the model's structure are that it does not capture: disutility associated with experiencing AE related to non-invasive testing or ICA; costs or outcomes of long-term AEs associated with testing (e.g. cancer from radiation exposure or nephrotoxicity from gadolinium contrast agent); and the implications of false negative test results. However given that non-invasive imaging results may not necessarily translate into a change in management (with regard to ICA referral), some of these patients may undergo ICA regardless (see Section Ca.5.1).

The absolute costs and outcomes for each of the non-invasive testing strategies are presented in Table ES.5. The incremental costs, outcomes and cost-effectiveness ratios comparing CMR with the comparators are presented in Table ES. 6.

Table ES.5 Absolute results—test results and costs across all comparators

	CMR	CTCA	Stress Echo	SPECT	Exercise ECG
Costs	-	-	-	-	-
Test costs (including treatment of AEs)	\$1,005	\$747	\$459	\$880	\$196
Modelled cost of re-testing	\$83	\$0	\$50	\$30	\$49
Modelled cost of ICA	\$2,165	\$2,319	\$2,172	\$2,308	\$2,017
Total	\$3,252	\$3,065	\$2,681	\$3,217	\$2,262
Testing outcomes	-	-	-	-	-
Total correct diagnoses	75.6%	92.1%	80.7%	76.5%	68.2%
Total incorrect diagnoses	13.3%	8.0%	12.7%	19.5%	25.3%
No result (initial equivocal or failed test)	11.1%	0.0%	6.6%	4.0%	6.6%
<i>Total ICA</i>	<i>46.9%</i>	<i>50.3%</i>	<i>47.1%</i>	<i>50.0%</i>	<i>43.7%</i>
ICA in CAD+	38.8%	43.7%	39.4%	37.6%	31.5%
ICA in CAD-	8.1%	6.6%	7.6%	12.4%	12.3%

AE = adverse event; CAD = coronary artery disease; CMR = stress perfusion cardiac magnetic resonance imaging with late gadolinium enhancement; CTCA = computed tomography coronary angiography; ECG = electrocardiography; Echo = echocardiography; ICA = invasive coronary angiography; SPECT = single-photon emission computed tomography

Table ES. 6 Incremental results and results of the cost-effectiveness analyses, all comparisons

	Increment vs. CTCA	Increment vs. Stress Echo	Increment vs. SPECT	Increment vs. Exercise ECG
Costs				
Test costs (including treatment of AEs)	\$258	\$546	\$125	\$808
Modelled cost of re-testing	\$83	\$33	\$53	\$34
Modelled cost of ICA	-\$154	-\$7	-\$143	\$148
Total	\$187	\$571	\$35	\$990
Testing outcomes				
Total correct diagnoses	-16.5%	-5.1%	-0.9%	7.4%

	Increment vs. CTCA	Increment vs. Stress Echo	Increment vs. SPECT	Increment vs. Exercise ECG
Total incorrect diagnoses	5.4%	0.7%	-6.1%	-11.9%
No result (initial equivocal or failed test)	11.1%	4.4%	7.0%	4.5%
<i>Total ICA</i>	-3.3%	-0.2%	-3.1%	3.2%
ICA in CAD+	-4.8%	-0.6%	1.2%	7.4%
ICA in CAD-	1.5%	0.4%	-4.3%	-4.2%
Incremental cost per correct initial test result	Dominated	Dominated	Dominated	\$13,304
Incremental cost per unnecessary ICA avoided	Dominated	Dominated	\$802	\$23,651
Incremental cost per indicated ICA missed	Dominated	Dominated	\$2,798	\$13,394

AE = adverse event; CAD = coronary artery disease; CMR = stress perfusion cardiac magnetic resonance imaging with late gadolinium enhancement; CTCA = computed tomography coronary angiography; ECG = electrocardiography; Echo = echocardiography; ICA = invasive coronary angiography; SPECT = single-photon emission computed tomography

The modelled results were most sensitive to changes in the accuracy inputs, the proportion of tests requiring re-testing and the cost of CMR.

ESTIMATED EXTENT OF USE AND FINANCIAL IMPLICATIONS

A market-based approach has been used to estimate the financial implications of the introduction of CMR for the diagnosis of CAD. However, as MBS items for the comparator tests are not specific to the population that is proposed to be eligible for CMR, the estimated number of tests has been back-calculated based on the number of ICAs performed in the population who have an intermediate PTP of CAD.

Key assumptions:

- That uptake of CMR for the diagnosis of CAD is low (approximately 10%), because of limited access and low patient acceptability of MRI scanners, due to the high demand in other specialties and indications and the time required to undertake each CMR; and
- That cost offsets for current testing assume that the relative use of the tests across all indications applies to the tests offset by the introduction of CMR.

The financial implications to the MBS resulting from the proposed listing of CMR for the diagnosis of CAD are summarised in Table ES.7.

Table ES.7 Total costs to the MBS associated with CMR for diagnosis of CAD

	2016-17	2017-18	2018-19	2019-20	2020-21
CMR					
Number of services	6,763	6,843	6,924	7,004	7,084
Cost to the MBS	\$5,173,817	\$5,235,202	\$5,296,587	\$5,357,972	\$5,419,357
Tests offset					
Number of services offset	6,763	6,843	6,924	7,004	7,084
Costs offset	\$2,352,761	\$2,380,676	\$2,408,590	\$2,436,505	\$2,464,420
Net cost to the MBS	\$2,821,055	\$2,854,526	\$2,887,997	\$2,921,467	\$2,954,938

CAD = coronary artery disease; CMR = cardiac magnetic resonance imaging; MBS = Medicare Benefits Schedule

RESULTS FOR POPULATION 2

Safety

The number of serious AEs experienced by patients during dobutamine echocardiography (DbE) far outnumbers those resulting from the other three non-invasive imaging modalities due to the use of a stressor. LGE-CMR has similar safety with respect to serious AEs to SPECT, and appears to be safer than CT-DCE; for all three of these modalities the majority of the serious AEs are caused by the contrast agent.

Patients undergoing DbE are more likely to suffer an acute event resulting in death than those having LGE-CMR, SPECT or CT-DCE, mostly due to the use of a stressor. Conversely, patients undergoing DbE are unlikely to die from the long-term effects caused by the radionucleotides or the contrast agents used in LGE-CMR, SPECT and CT-DCE. LGE-CMR has similar safety, with respect to mortality rate, to SPECT, and appears to be safer than CT-DCE. While DbE is the safest imaging modality overall, it has by far the highest acute fatality rate. As patients in population 2 have more advanced disease than those in population 1, long-term safety may be of lesser importance in these patients.

Effectiveness

Direct effectiveness

There was no direct evidence for population 2.

Effectiveness from linked evidence

1. Accuracy

When LGE-CMR using a high cut-off of $\geq 50\%$ hyper-enhancement (HE) was compared with a low cut-off of $\leq 25\%$, the higher cut-off was more sensitive (93% vs 70%) and less specific (45% vs 68%).

LGE-CMR (high cut-off) was slightly more sensitive than DbE and SPECT and should be able to detect 6–14 additional patients, who would have received a false negative result using the other imaging modalities. Conversely, in those without viable myocardium, comparative imaging tests ruled out viability with a higher degree of specificity, with 9–33 fewer false positives per 100 patients with non-viable myocardium.

The concordance between LGE-CMR (high cut-off) and SPECT, DbE and Echo was low to moderate (kappa range 0.23–0.52). This was mostly due to the low estimated specificity of LGE-CMR compared with thallium-SPECT (TI-SPECT) and DbE (41%–54%); half of all patients considered to have non-viable myocardium by TI-SPECT or DbE were considered to have viable myocardium by LGE-CMR.

The negative likelihood ratio (LR⁻) (0.15) for LGE-CMR (using a high cut-off of $\geq 50\%$ HE) suggested that it may be useful to ‘rule out’ patients who would not benefit from revascularisation from having the procedure. Thus, patients who receive a negative test result can be confident that they are unlikely to have a viable myocardium, and would not therefore respond to revascularisation. This corresponds to the negative predictive value (NPV) (calculated using the study prevalence rate of 56%), which was highest for LGE-CMR, at 83%; that is, if 100 patients received a negative test result, only 17 patients would have been misclassified as negative, when they would in fact be likely to respond to revascularisation. Other NPVs were 74% for DbE, 71% for Echo, and 76%–77% for SPECT—that is, 6–12 additional patients would be misclassified as being ruled out for revascularisation using these tests, when they may in fact have viable myocardium.

However, the positive likelihood ratio (LR⁺) (1.7) indicates that patients who receive a positive test result gain no useful information from this test. This is reflected in the positive predictive value (PPV) values, for which LGE-CMR had the lowest at 68%, indicating that one-third of patients assessed as

having viable myocardium were misdiagnosed and would not recover function after revascularisation. DbE had the highest PPV at 82%, and the PPV for SPECT ranged between 71% and 75%.

2. Therapeutic efficacy (change in management)

There were no studies assessing how management of patients may change with LGE-CMR compared with Echo, SPECT or CT-DCE.

There is some Australian evidence available that surgical procedures might be averted for some patients with CAD and LVD who are diagnosed with non-viable myocardium (Taylor et al. 2013).

3. Therapeutic effectiveness (health benefit from change in management)

The increased mortality rate and MACE outcomes seen in observational studies for patients who were classified as viable and received medical treatment, compared with those who were revascularised, were likely confounded by the inclusion of patients who had viable myocardium but were not suitable for revascularisation. Thus, the difference in mortality cannot confidently be attributed to the difference in treatment.

In contrast, the Surgical Treatment for Ischemic Heart Failure (STICH) trial randomised only patients who could tolerate revascularisation to receive either revascularisation plus medical therapy or medical therapy alone. In this trial, patients with viable myocardium who were revascularised did not have significantly better mortality or MACE outcomes than those who received medical therapy alone. Thus, there was no interaction between viability and the likelihood of benefit from revascularisation plus medical therapy, compared with medical therapy alone.

Therefore, although assessment of viability may provide prognostic information, it cannot be considered effective at improving health, as it may not stratify patients to receive appropriate treatment.

Summary





On the basis of the benefits and harms reported in the evidence-base (summarised in Table ES.8), it is suggested that LGE-CMR has:

- **non-inferior safety and superior ability to rule out patients who do not show viability** relative to **DbE and SPECT**
- **superior safety and unknown effectiveness** relative to **CT-DCE**.

However, **strong evidence** suggests that **testing for viability does not reduce the risk of death within 5 years**.

Table ES.8 Balance of clinical benefits and harms of LGE-CMR, relative to Echo, SPECT and CT-DCE

Outcomes	No. of studies	Quality of evidence	Results	Interpretation	GRADE ^a
Therapeutic effectiveness (5-year mortality rate)	k=1 RCT; n=601	Risk of bias: 0 Inconsistency: 0 Indirectness: 0 Imprecision: 0 Publication bias: 0	Viable: Revascularised: 31.2%; Medical: 35.4% Non-viable: Revascularised: 41.5%; Medical: 55.8%	Patients did not differ significantly in their response to medical treatment or revascularisation based on viability status. Using viability status to determine treatment strategy is therefore not beneficial.	High ⊕⊕⊕⊕
Negative predictive	LGE-CMR low cut-off: k=10	Risk of bias: 0	64%	A negative test result from LGE-CMR (high cut-off)	Low

Outcomes	No. of studies	Quality of evidence	Results	Interpretation	GRADE ^a
value	LGE-CMR high cut-off: k=15 DbE: k=33 TI-SPECT: k=40 Tm-SPECT: k=25 Dobutamine Echo: k=12 SPECT (unspecified): k=13	Inconsistency: 0 Indirectness: -1 Imprecision: -1 Publication bias: 0	82% 74% 77% 75% 71% 76%	can be trusted more than a negative result from the comparators. A negative test result from LGE-CMR (low cut-off) can be trusted less than the comparators.	
Positive predictive value	LGE-CMR low cut-off: k=10 LGE-CMR high cut-off: k=15 DbE: k=33 TI-SPECT: k=40 Tm-SPECT: k=25 Dobutamine Echo: k=12 SPECT (unspecified): k=13	Risk of bias: 0 Inconsistency: 0 Indirectness: -1 Imprecision: -1 Publication bias: 0	74% 68% 82% 71% 75% 77% 74%	A positive test result from LGE-CMR (high cut-off) can be trusted less than a positive test result from the comparators. A positive test result from LGE-CMR (low cut-off) can be trusted to a similar degree to other imaging techniques, but less than low-dose stress Echo.	Low 
Safety	No direct comparative studies. Results derived from naïve indirect comparisons	Risk of bias: -1 Inconsistency: -1 Indirectness: -1 Imprecision: -1 Publication bias: 0	LGE-CMR has a reduced risk of serious AEs compared with DbE and CT-DCE, and a similar low rate to SPECT. The risk of acute and long-term mortality from LGE-CMR is less than from CT-DCE, marginally less than from SPECT, and more than from DbE.	Non-invasive imaging techniques have a low risk of harms. The poor quality of evidence makes it difficult to make conclusions on the comparative safety of the tests.	Very low 
Change in management	k=2 before-and-after case series No comparative studies	Risk of bias: 0 Inconsistency: -1 Indirectness: -1 Imprecision: -1 Publication bias: 0	71.5% of patients had a change in management after LGE-CMR (change in invasive procedure in 24.2%). 3/9 CABGs were averted due to non-viability, and overall 13% had a change in surgical	LGE-CMR was found to influence what treatment patients received, but it is unknown how this differs from what they would have received due to the comparators.	Very low 

Outcomes	No. of studies	Quality of evidence	Results	Interpretation	GRADE ^a
			management plan.		

^a GRADE Working Group grades of evidence (Guyatt et al. 2011)

⊕⊕⊕⊕ **High quality:** We are very confident that the true effect lies close to that of the estimate of effect

⊕⊕⊕⊖ **Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

⊕⊕⊖⊖ **Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

⊕⊖⊖⊖ **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

CABG = coronary artery bypass graft; CT-DCE = CT perfusion imaging with delayed contrast enhancement; DbE = SP-CMR = stress perfusion cardiac magnetic resonance imaging; Echo = echocardiography; K = number of studies; LGE-CMR = late gadolinium enhancement with cardiac magnetic resonance imaging; RCT = randomised controlled trial; SPECT = single-photon emission computed tomography; TI-SPECT = thallium-SPECT; Tm-SPECT = thulium SPECT

TRANSLATION ISSUES

Translation issues addressed in the assessment of LGE-CMR for the detection of viable myocardium are listed in Table ES.9.

Table ES.9 Translation issues addressed in the assessment for population 2

Type	Issue
Applicability	<ul style="list-style-type: none"> • Are there relevant differences between the populations included in the studies to inform the test parameters in the economic model and the proposed MBS population? • Is the segmental diagnostic accuracy data reported in the various clinical evaluations valid to inform diagnostic accuracy on a per-patient basis? • Which set of accuracy inputs should be used in the economic evaluation for each of LGE-CMR, SPECT, DbE and CT-DCE tests? • What is the prevalence of viable myocardium in the proposed MBS population? • Do the results of a viability assessment impact on patient relevant health outcomes? • In what proportion are coronary bypass surgery and PCIs (using stents or angioplasty) performed in the proposed MBS population? • What are the intra- and post-operative and/or procedural complications (including mortality) associated with revascularisation procedures CABG and PCI?
Extrapolation	None identified
Transformation	None identified
Other	<ul style="list-style-type: none"> • Does LGE-CMR change clinical management, compared with low-dose dobutamine stress Echo, SPECT or CT-DCE for patients with CAD, a history of IHD with LVD and being considered for revascularisation?

CABG = coronary artery bypass surgery; CAD = coronary artery disease; CT-DCE = computed tomography perfusion imaging with delayed contrast enhancement; DbE = dobutamine echocardiography; IHD = ischaemic heart disease; LGE-CMR = late gadolinium enhancement cardiac magnetic resonance imaging; LVD = left ventricular dysfunction; MBS = Medicare Benefits Schedule; PCI = percutaneous coronary intervention; SPECT = single-photon emission computed tomography

ECONOMIC EVALUATION

Due to the lack of consistent evidence informing health outcomes following revascularisation versus medical management in the population tested (i.e. patients with CAD and LVD), neither a cost-utility,

nor any long-term model could be reliably constructed. Therefore modelled cost-effectiveness analyses examining cost per additional correct diagnosis, cost per additional low benefit (non-viable) revascularisations avoided, and cost per additional appropriate revascularisation performed were undertaken.

A summary of the key characteristics of the economic evaluation is given in Table ES.10.

Table ES.10 Summary of the economic evaluation

Perspective	Australian Health care
Comparator	SPECT, DbE
Type of economic evaluation	Cost-consequence; cost-effectiveness
Sources of evidence	SR
Costs	Australian dollars, 2015 prices
Outcomes	Cost per additional correct diagnosis, cost per incremental unnecessary revascularisation averted and cost per additional appropriate revascularisation performed
Time horizon	30 days
Methods used to generate results	Decision-tree analysis
Software packages used	TreeAge Pro 2015

DbE = low-dose dobutamine echocardiography; SPECT = single-photon emission computed tomography; SR = systematic review

The diagnostic pathway will identify patients with viable and non-viable myocardium. The patients diagnosed with viable myocardium are assumed to be managed by revascularisation and OMT, whereas those diagnosed with non-viable myocardium are assumed to continue their OMT.

Revascularisation is associated with increased risk of mortality and procedure-related complications. A time horizon of 30 days is chosen to capture these health outcomes. All modelled pathways will terminate into survival or death after 30 days, based on the path probabilities related to viability status and treatment received.

Key structural assumptions of the model are that:

- Patients will follow the diagnostic pathways and that those diagnosed with viable myocardium will undergo surgery and those diagnosed with non-viable myocardium will not receive surgical revascularisation. This is a simplification—in clinical practice this decision is complex and based on a patient’s demographics, comorbidities and other factors.
- There will be no alternative confirmatory testing and thus the status or treatment of false positives and false negatives will not change in the diagnostic pathway.
- In the base-case economic analyses, all revascularisations performed are CABG.
- Mortality rates are dependent on the treatment received and not the viability status.

Limitations of the model structure are that:

- It does not capture disutility associated with experiencing AE related to testing strategy or revascularisations.
- Only severe complications and 30-day mortality associated with revascularisation and background 30-day mortality are included in the model; other events are not incorporated.
- It does not capture the costs or outcomes of long-term AEs associated with testing.
- It does not capture the implications of false negative test results (due to a lack of data).

The costs and outcomes for each of the non-invasive testing strategies are presented in Table ES.11. The incremental costs, outcomes and cost-effectiveness ratios comparing LGE-CMR to the comparators are presented in Table ES.12.

Table ES.11 Test results and costs across all comparators

	LGE-CMR	DbE	SPECT
Costs			
Test (including treatment of AEs and specialist referral)	\$788	\$480	\$608
Cost of revascularisation + OMT+ complications	\$35,438	\$25,138	\$29,929
Total	\$36,226	\$25,618	\$30,537
Testing outcomes			
Total correct diagnoses	71.8%	78.5%	74.9%
Unnecessary revascularisations averted	19.8%	34.3%	27.3%
Revascularisations undertaken with correct diagnosis	52.0%	44.2%	47.6%

AE=adverse event; DbE = low-dose dobutamine echocardiography; LGE-CMR = late gadolinium enhancement cardiac magnetic resonance imaging; OMT = optimal medical therapy SPECT=single-photon emission computed tomography

Table ES.12 Incremental results and results of the cost-effectiveness analyses, all comparisons

	Increment vs DbE	Increment vs SPECT
Costs		
Test (including treatment of AEs and specialist referral)	\$308	\$180
Cost of revascularisation + OMT+ complications	\$10,300	\$5,509
Total	\$10,608	\$5,689
Testing outcomes		
Total correct diagnoses	-6.7%	-3.1%
Unnecessary revascularisations averted	-14.5%	-7.5%
Revascularisations undertaken with correct diagnosis	7.8%	4.4%
Incremental cost per correct diagnosis	Dominated	Dominated
Incremental cost per unnecessary revascularisations averted	Dominated	Dominated
Incremental cost per revascularisations undertaken with correct diagnosis	\$136,002	\$129,301

AE = adverse event; DbE = low-dose dobutamine echocardiography; OMT = optimal medical therapy; SPECT = single-photon emission computed tomography

Sensitivity analyses were performed varying the important parameters, and the modelled results were identified to be most sensitive to changes in the accuracy inputs of LGE-CMR.

ESTIMATED EXTENT OF USE AND FINANCIAL IMPLICATIONS

Insufficient epidemiological data was identified to estimate the number of Australian patients with an existing diagnosis of significant CAD and a history of IHD with impaired left ventricular (LV) function, who are being considered for revascularisation. Therefore, a market-based approach was employed to estimate the potential number of services eligible for proposed LGE-CMR for myocardial viability assessment. While comparator testing is currently funded by the MBS, comparator item numbers are not restricted to the eligible population. The estimated number of

tests is therefore based on an assumption that half of these tests are performed for assessing viability, but this approach is also fairly uncertain.

The financial implications to the MBS resulting from the proposed listing of LGE-CMR for the assessment of myocardial viability are summarised in Table ES.13.

Table ES.13 Total costs to the MBS associated with LGE-CMR for the assessment of myocardial viability

	2016–17	2017–18	2018–19	2019–20	2020–21
LGE-CMR					
Number of services	4,444	4,771	5,122	5,499	5,903
Cost to the MBS	\$2,644,130	\$2,838,646	\$3,047,472	\$3,271,660	\$3,512,341
Tests offset					
Number of services offset	4,444	4,771	5,122	5,499	5,903
Costs offset	\$1,914,329	\$2,055,157	\$2,206,345	\$2,368,656	\$2,542,906
Net cost to the MBS	\$729,801	\$783,489	\$841,127	\$903,004	\$969,434

LGE-CMR = late gadolinium enhancement cardiac magnetic resonance imaging; MBS = Medicare Benefits Schedule

CONSUMER IMPACT SUMMARY

The main issues arising from the public consultation period in November 2014 were:

- Patient access:
 - There are currently long waiting times for CMR within public hospitals due to the high demand for MRI from other specialties, such as orthopaedics and neurology;
 - In the private diagnostic imaging environment, access for CMR is extremely limited due to high demand in other areas and the time required to undertake each CMR (45–60 minutes per scan).
- Performing CMR and interpreting CMR scans:
 - Due to the complexity and experience necessary, there is a wide gap in experience/knowledge in performing and reporting CMR to a high level.
- The proposed MBS fee:
 - \$900 for MBS item 1 and \$700 for MBS item 2 are less than the costs of performing the CMR investigation and will require the patient to pay a significant gap. A fee of \$1,100–1,200 would be more appropriate.

OTHER RELEVANT CONSIDERATIONS

International guidelines for the use of CMR indicate that there is still some uncertainty around using this test in this population, as data are still emerging. For all types of non-invasive imaging, recommendations highlight the use of imaging only in cases of genuine clinical uncertainty.

ACRONYMS AND ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
AHTA	Adelaide Health Technology Assessment
CABG	coronary artery bypass graft
CAD	coronary artery disease
CEA	cost-effectiveness analysis
CECaT	Cost-effectiveness of Non-invasive Cardiac Testing (trial)
CHD	coronary heart disease
CI	confidence interval
CMR	cardiac magnetic resonance imaging
CT	computed tomography
CTCA	computed tomography coronary angiography
CT-DCE	CT perfusion imaging with delayed contrast enhancement
CVD	cardiovascular disease
DbE	low-dose dobutamine echocardiography
DS	diameter stenosis
ECG	electrocardiography
Echo	echocardiography
EQ-5D	EuroQoL (questionnaire)
FFR	fractional flow rate
HE	hyper-enhancement
HESP	Health Expert Standing Panel
HR	hazard ratio
HTA	health technology assessment
ICA	invasive coronary angiography
ICER	incremental cost-effectiveness ratio
IHD	ischaemic heart disease
IHPA	Independent Hospital Pricing Authority
LGE	late gadolinium enhancement
LGE-CMR	late gadolinium enhancement cardiac magnetic resonance imaging
LR+	Positive likelihood ratio
LR-	Negative likelihood ratio
LV	left ventricular
LVD	left ventricular dysfunction

Abbreviation	Definition
LVEF	left ventricular ejection fraction
MACE	major adverse cardiovascular events
MBS	Medicare Benefits Schedule
MCS	mental functioning composite scale
MI	myocardial infarction
MM	medical management
MRI	magnetic resonance imaging
MSAC	Medical Services Advisory Committee
NEP	National Efficient Price
NPV	negative predictive value
NRI	net reclassification improvement
OMT	optimal medical therapy
PASC	PICO Confirmation Advisory Sub-Committee of the MSAC
PCI	percutaneous coronary intervention
PCS	physical functioning composite scale
PD	perfusion defect
PICO	population, investigation/Index test, comparators and outcomes
PoTP	post-test probability
PPV	positive predictive value
PTP	pre-test probability
QoL	quality of life
RCT	randomised controlled trial
RR	relative risk
SAQ	Seattle Angina Questionnaire
SF-36	Short Form 36 questionnaire
SPECT	single-photon emission computed tomography
SP-CMR	stress perfusion cardiac magnetic resonance imaging
SR	systematic review
SROC	summary receiver-operator characteristics
TGA	Therapeutic Goods Administration
STICH	Surgical Treatment for Ischemic Heart Failure (trial)
T	tesla

Abbreviation	Definition
TI	thallium-201
TI-SPECT	thallium-SPECT
WMA	wall motion abnormality

SECTION A CONTEXT

This contracted assessment of magnetic resonance imaging (MRI) for myocardial stress perfusion and myocardial viability imaging in patients with known or suspected coronary artery disease (CAD) is intended for the Medical Services Advisory Committee (MSAC). MSAC evaluates new and existing health technologies and procedures for which funding is sought under the Medicare Benefits Schedule (MBS) in terms of their safety, effectiveness and cost-effectiveness, while taking into account other issues such as access and equity. MSAC adopts an evidence-based approach to its assessments, based on reviews of the scientific literature and other information sources, including clinical expertise.

Adelaide Health Technology Assessment (AHTA) has been commissioned by the Australian Government Department of Health to conduct a systematic literature review and economic evaluation of stress perfusion cardiac MRI (SP-CMR) and myocardial viability imaging in patients with known or suspected CAD. This assessment has been undertaken in order to inform MSAC's decision-making regarding whether the proposed medical service should be publicly funded.

Appendix A provides a list of the people involved in the development of this assessment report, including clinical expertise sourced from the Health Expert Standing Panel (HESP). HESP are a pool of experts collated from various medical fields who have been nominated by their associated professional body or by applicants. HESP members are a panel of the MSAC and are engaged to provide practical, professional advice that directly relates to each application and the service being proposed for the MBS. HESP members are not members of either MSAC or its subcommittees. Their role is limited to providing input and guidance to the assessment groups to ensure that the clinical pathway is clinically relevant and takes into account consumer interests. HESP member's advice is used to inform the deliberations that MSAC presents to the Federal Minister for Health.

The proposed use of SP-CMR and myocardial viability imaging in patients with known or suspected CAD in Australian clinical practice was outlined in a PICO Confirmation that was presented to, and accepted by, the PICO Advisory Sub-Committee (PASC). The PICO Confirmation was released for public comment in November 2014 and the protocol was ratified by PASC and finalised in December 2014.

A1 ITEMS IN THE AGREED PICO CONFIRMATION

This contracted assessment of SP-CMR and myocardial viability imaging in patients with known or suspected CAD addresses most of the PICO elements (population, investigation/Index test, comparators and outcomes) that were pre-specified in the PICO Confirmation that was ratified by PASC.

Due to the lack of evidence in patients with an intermediate risk of CAD, the PICO for population 1 was expanded to include studies enrolling patients with known or suspected CAD.

A2 PROPOSED MEDICAL SERVICE

MRI is a sophisticated imaging technique used to investigate a variety of clinical disorders. Cardiac MRI (CMR) uses a standard MRI system, with or without specialised cardiac coils, and specialised software for quantitative analysis. The software may be either incorporated within the scanner or external to the scanner; external software is commonly used in clinical practice as the scanners with incorporated software cannot be used for scanning other patients during analysis. However, CMR is technically more challenging than MRI of other vasculature in the body for several reasons (Hundley et al. 2010). Coronary arteries are small (3–6 mm in diameter) and are in near constant motion due to both the respiratory and cardiac cycles. Imaging is further complicated by signals from the adjacent epicardial fat and myocardium. Nevertheless, CMR offers a non-invasive technique with high intrinsic contrast to visualise changes in the heart that does not expose patients to radiation.

Patients are required to lie as still as possible, in either a prone or supine position, within the MRI machine during the examination. Movement during the procedure will result in poor image quality. The magnetic field strength used for CMR is usually either 1.5 or 3.0 teslas (T) and the images obtained are interpreted by either a qualified cardiologist or radiologist.

SP-CMR imaging involves the visualisation of a gadolinium-based contrast agent as it passes through the myocardium under pharmacologic vasodilation (Gotschy et al. 2014). The pharmacological agents most commonly used are dobutamine, dipyridamole or adenosine infusions. SP-CMR detects damaged or ischaemic myocardium, which manifests as perfusion deficits or low signal areas detected during a first-pass perfusion sequence. Coronary artery stenoses caused by atherosclerotic processes result in a reduction of the resistance of distal perfusion beds in an attempt to normalise myocardial blood flow and maintain oxygen supply (Hundley et al. 2010). These images are usually compared with perfusion images taken at rest. Perfusion defects (PDs) that are identical under stress and at rest are usually considered to be either artefactual or not ischaemic in nature. However, stenoses of less than 70% are not always detectable by SP-CMR (Fihn et al. 2012).

Viability imaging via delayed contrast-enhanced CMR, or late gadolinium enhancement (LGE), also uses gadolinium-based contrast agents to define the extent of irreversibly damaged (necrotic or scarred) myocardium (Medical Advisory Secretariat 2010e; Woodard et al. 2006). Gadolinium-based contrast agents do not penetrate into the intracellular space in healthy myocardium. However, cell death and subsequent rupture of the cell membrane enables gadolinium-based contrast agent to penetrate into the affected myocardium, resulting in an accumulation of the agent. The mechanism of gadolinium-based contrast agent accumulation in scar tissue is thought to be due to larger interstitial spaces between collagen fibres compared with living myocytes (Gotschy et al. 2014). Thus, LGE-CMR can be used to discriminate viable tissue from irreversibly damaged necrotic and scar tissue by measuring the distribution of the contrast agent in the extracellular space 10–20 minutes after administration.

SP-CMR and LGE for detection of myocardial stenoses would be used to diagnose CAD in patients presenting with symptoms consistent with stable ischaemic heart disease (IHD) and with an intermediate pre-test probability (PTP) of CAD (population 1). In this population the two tests would be performed consecutively during the same MRI procedure. The rest and stress perfusion images would be taken first, the order depending on the protocol, followed by the LGE imaging. Examples of SP-CMR plus LGE protocols are given in Figure 1.

HESP feedback suggested that the results of SP-CMR in conjunction with viability imaging would enable a more accurate diagnosis of CAD. When the results of both perfusion and delayed enhancement are considered together, myocardial ischemia would be diagnosed if a myocardial segment shows a perfusion deficit without late enhancement or if the perfusion deficit is larger than the area of delayed enhancement. Myocardial scarring would be diagnosed if an area has a high signal in the delayed enhancement sequence (Cury et al. 2006).

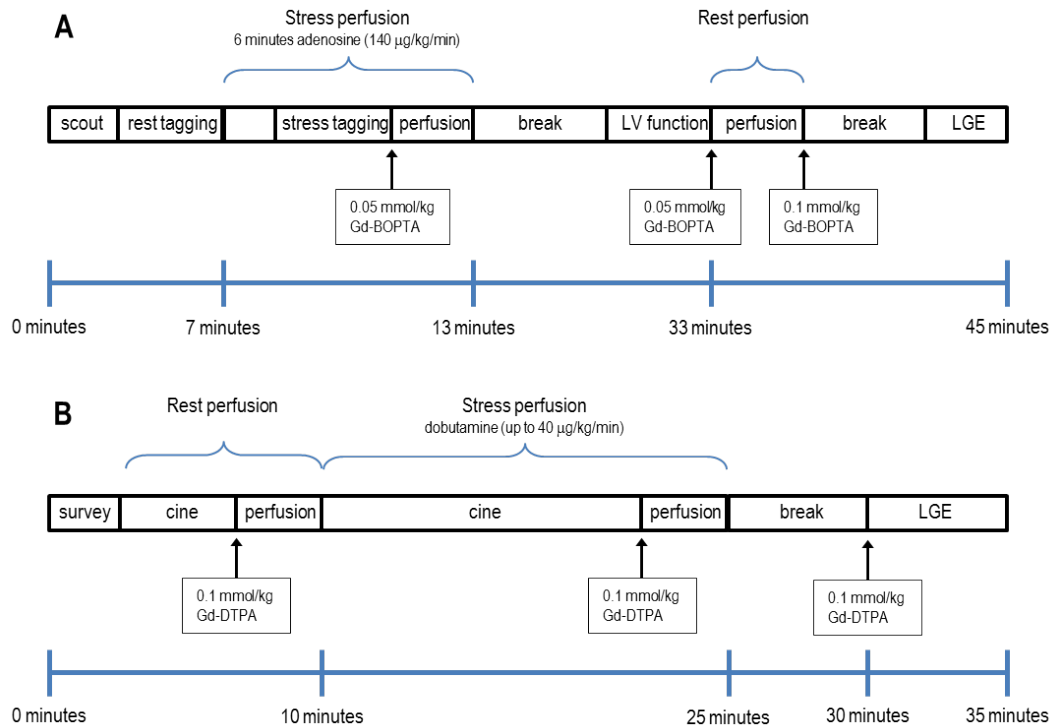


Figure 1 Example time courses of CMR procedures incorporating rest/stress perfusion imaging and delayed enhancement (LGE)

Sources: A. adapted from Thomas et al. (2008); B. adapted from Gebker et al. (2008a)

Gd-BOPTA = gadobenate dimeglumine; Gd-DTPA = gadolinium diethylenetriaminepentaacetic acid; LGE = late gadolinium enhancement

LGE-CMR would also be used to assess myocardial viability in patients with an existing diagnosis of significant CAD who have a history of ischaemic heart disease (IHD) and left ventricular dysfunction (LVD), and are being considered for revascularisation (population 2). The identification and quantification of viable myocardium in patients with CAD being considered for revascularisation is important as this procedure offers limited value in patients with permanent LVD (Medical Advisory Secretariat 2010e).

CMR would be provided as either an inpatient or outpatient service. A CMR study requires approximately 45–60 minutes of image acquisition time plus 15–30 minutes of software analysis time and 15–30 minutes of expert reporting time.

It is intended that specialist referral be required for CMR procedures due to the complexity of the test, specialist understanding of its uses and limitations, and interpretation of image scans. Current legislative requirements stipulate that Medicare-eligible MRI items must be reported on by a trained and credentialed specialist in diagnostic radiology who must be a participant in the Royal Australian and New Zealand College of Radiologist's Quality and Accreditation Program (Health Insurance Regulation 2013 – 2.5.4 – Eligible Providers)². Thus, legislative changes would be required to allow cardiologists to report on CMR scans. It is the intention of the applicant that a radiologist or cardiologist trained in CMR be personally available to attend all CMR examinations.

The applicant suggests that the proposed service is primarily intended to be utilised by cardiologists. The proposed service should not be considered a standard radiological procedure due to the

² Available from < www.comlaw.gov.au/Details/F2013L01979 > (accessed on 7 May 2015)

additional complexity of the test in terms of defining cardiac pathologies, although sufficiently accredited radiologists or cardiologists may also report on CMR images. The applicant recommends that specialist accreditation for radiologists performing CMR procedures should be equivalent to at least level 2 training, as outlined in the guidelines by the Society for Cardiovascular Magnetic Resonance, which are broadly applicable to and consistent with Australian practice. The requirement for a minimum level of training for radiologists performing CMR is also encouraged in the training document for the provision of CMR services by the Cardiac Society of Australia and New Zealand's Imaging Council. However, this will have an impact on the initial availability of CMR services as it is presumed that few Australian radiologists have attained these qualifications to date. The applicant estimates that 20 to 25 sites around Australia currently have the workforce capacity to conduct CMR.

The applicant has suggested that for the initial diagnosis of CAD the proposed medical service would initially be utilised as a single, once-off test for perfusion and viability. In the vast majority of patients, one CMR per 12 month period would be sufficient. However, there would be exceptions to this recommendation, such as patients with new diagnosis of left ventricular (LV) thrombus in the setting of CAD, in which case a follow-up scan (e.g. at 3 or 6 months) would be necessary to determine the success of, and necessity for continuing, anticoagulant treatment.

OTHER INDICATIONS

There are currently four items related to the use of CMR to diagnose heart conditions listed on the MBS. Two relate to the investigation of vascular abnormalities in patients with a previous anaphylactic reaction to an iodinated contrast medium (MBS item numbers 63401 and 63407). The other two relate to the investigation and diagnosis of congenital heart or great vessel defects (MBS item number 63385), and the investigation of heart or great vessel tumours (MBS item number 63388).

CURRENT FUNDING ARRANGEMENTS

There is currently limited funding provided by the Victorian Government to The Alfred Hospital for CMR investigations of CAD. There may be other state-based public hospital arrangements for CMR, but these arrangements are limited to public hospital inpatients. The applicant suggests that CMR for CAD is not currently covered by private health insurance. Private patients who utilise CMR services are therefore required to pay the full cost of the procedure. This is a major factor in current utilisation practices of CMR services beyond the current MBS items.

A3 PROPOSAL FOR PUBLIC FUNDING

The proposed MBS item descriptor is summarised in Table 1.

The applicant has indicated that CMR stress myocardial perfusion imaging is a more complicated technique than myocardial viability imaging, and therefore should attract a higher fee to cover the additional time and resources required to perform the scans. Feedback from HESP indicated that CMR stress myocardial perfusion imaging requires the use of a similar or greater amount of the contrast agent compared with myocardial viability imaging, as well as an infusion of the pharmacological stress agent. These factors are reflected in the proposed fee for each item. The original application requested that new MBS items be made available via specialist referral only. PASC guidance indicates that, as evidence emerges, the first proposed MBS item may need to be revised to allow for GP referral, as CMR may act as a replacement for current GP-ordered tests for CAD.

The applicant recommends that the condition of 'exercise and/or electrocardiogram (ECG) stress testing unfeasible' not be used to limit this population for two reasons. First, there are patients in whom ECG will report a high proportion of false positive results, and in whom CMR is superior

regardless of the feasibility of exercise or ECG stress testing. Second, the MBS items for the comparator tests are not limited in this way.

Table 1 Proposed MBS item descriptor

Category 5 – Diagnostic Imaging Services
<p>MBS [item number to be assigned]</p> <p>NOTE: Benefits are payable for each service included by Subgroup 15 on one occasion only in any 12 month period</p> <p>MAGNETIC RESONANCE IMAGING performed under the professional supervision of an eligible provider at an eligible location where the patient is referred by a specialist or by a consultant physician and where the request for the scan specifically identifies the clinical indication for the scan - scan of the heart for:</p> <ul style="list-style-type: none"> (a) myocardial viability using delayed gadolinium enhancement (Contrast); and (b) stress myocardial perfusion (Contrast); and (c) the request for the scan identifies that the patient presents with: <ul style="list-style-type: none"> (i) symptoms consistent with stable ischaemic heart disease, with an intermediate pre-test probability of coronary artery disease. <p>Fee: \$900 Benefit: 75% = \$675; 85% = \$765</p>
Category 5 – Diagnostic Imaging Services
<p>MBS [item number to be assigned]</p> <p>NOTE: Benefits are payable for each service included by Subgroup 15 on one occasion only in any 12 month period</p> <p>MAGNETIC RESONANCE IMAGING performed under the professional supervision of an eligible provider at an eligible location where the patient is referred by a specialist or by a consultant physician and where the request for the scan specifically identifies the clinical indication for the scan - scan of the heart for:</p> <ul style="list-style-type: none"> (a) myocardial viability using delayed gadolinium enhancement (Contrast); and (b) the request for the scan identifies that an adult patient being considered for revascularisation presents with: <ul style="list-style-type: none"> (i) an existing diagnosis of significant CAD, a history of ischaemic heart disease and impaired left ventricular function. <p>Fee: \$700 Benefit: 75% = \$525; 85% = \$595</p>

The total dose of contrast agent required is dependent on the type of gadolinium used and the weight of the patient. The applicant has suggested that the volume of contrast agent required for myocardial stress perfusion and/or viability testing is greater than for non-cardiac MRI and magnetic resonance angiography applications, which is covered under MBS item number 63491. Therefore, the current MBS item is unlikely to offset the additional cost of the proposed service. In gadolinium-contraindicated patients, the sensitivity for detecting diseases through tissue characterisation and viability would be significantly decreased.

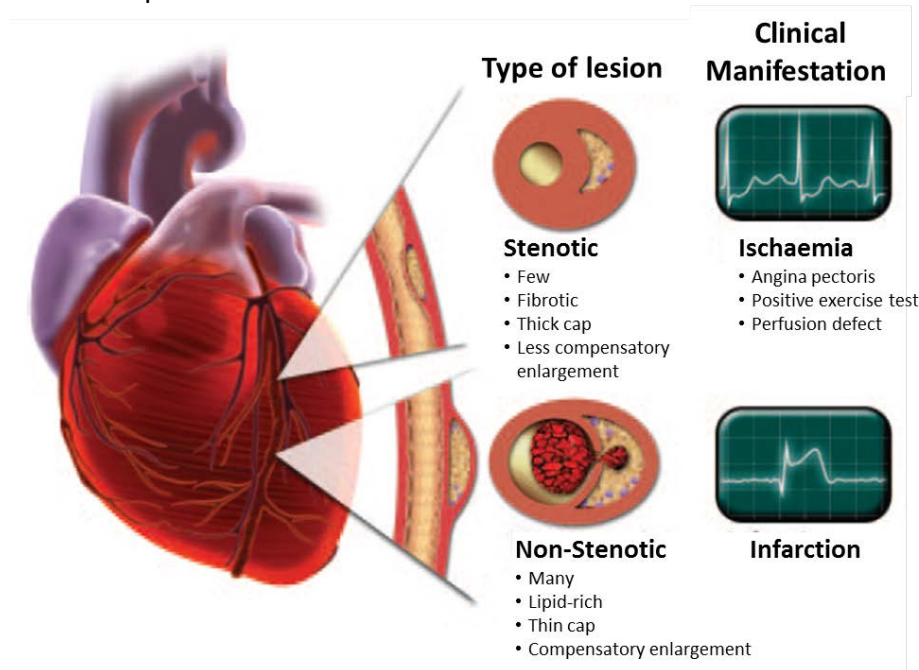
A4 PROPOSED POPULATION

CAD is also known as ischaemic heart disease (IHD) and coronary heart disease (CHD). It is the leading cause of a group of heart diseases that includes stable angina, unstable angina, myocardial infarction (MI) and sudden coronary death. There are several well-known risk factors for CAD that include high blood pressure, smoking, diabetes, lack of exercise, obesity, high blood cholesterol, poor diet and excessive alcohol.

The natural history of CAD is the progression from a mild to a severe stenosis, caused by an atherosclerotic plaque within a coronary artery. The formation of the atherosclerotic plaque is initiated by endothelial dysfunction caused by injury, inflammation and/or oxidative stress (Wexler 2002).

Plaque formation occurs as oxidised low-density lipoprotein is deposited in the intima, producing a local environment prone to thrombogenesis and increased vasoconstriction. These non-stenotic plaques (Figure 2) grow outwards and may cause no symptoms for many years (Libby & Theroux 2005). At some point, degradation of the collagen matrix in the fibrous cap of the plaque leads to platelet adhesion and aggregation, as well as further thrombogenesis, fibroproliferation and vasoconstriction (Wexler 2002). This sequence of events can lead to acute thrombotic occlusion of the lumen and acute coronary syndromes, such as MI, in some patients (Libby & Theroux 2005; Wexler 2002). Ultimately, the fibrous cap is thickened and calcium deposition occurs, leading to a more stable stenotic plaque and the development of symptomatic CAD (Figure 2).

Figure 2 Schematic representation of stenotic and non-stenotic atherosclerotic lesions



Source: Libby & Theroux (2005)

As each non-stenotic plaque progresses, regresses or remains dormant in an independent manner, it is difficult to predict which plaques are likely to progress and acquire characteristics leading to either rupture or rapid luminal obstruction (Stone et al. 2012). By the time the first plaque has progressed to the point of producing stenoses, non-stenotic plaques are usually widely distributed throughout the coronary arteries (Libby & Theroux 2005).

A coronary stenosis first causes a reduction in myocardial perfusion, which limits the blood flow to the myocardium and causes ischemia due to a lack of oxygen. Myocardial ischaemia initially manifests during stress (or exertion) and can progress to ischaemia occurring at rest. A common symptom of myocardial ischaemia is chest pain; shortness of breath may also occur. Sometimes no symptoms may be present prior to an acute ischaemic event such as an MI. This leads to heart muscle damage, which may or may not be reversible. Significant myocardial cell death results in myocardial scarring, which can lead to subsequent heart failure and death.

In population 1, SP-CMR and LGE would be used to diagnose CAD in patients presenting with symptoms consistent with stable IHD and with an intermediate PTP of CAD. The PTP would be determined using a clinical decision matrix, which would take into account criteria such as age; gender; family history; risk factors such as hypertension, hypercholesterolaemia, diabetes and smoking; as well as the presence of symptoms such as dyspnoea and chest pain. The Diamond-Forrester decision matrix for patients with chest pain is a commonly used tool for determining PTP, depending on gender, age and the nature of the pain. The American College of Cardiology Foundation defines an intermediate probability of having CAD as 10%–90% using the original

Diamond-Forrester model (Wolk et al. 2014); whereas an intermediate probability of having CAD is defined as 15%–85% by the European Society of Cardiology (Montalescot et al. 2013) using an updated Diamond-Forrester model (Genders et al. 2011). The differences between the two models are shown in Table 2.

Generally, patients with an intermediate PTP of less than 45% are considered to have a low-intermediate probability of having CAD and those with an intermediate PTP of greater than 65% are considered to have a high-intermediate probability.

Table 2 PTP of having CAD, stratified by age, gender, and nature of chest pain using the original and updated Diamond-Forrester models

Chest pain	Typical		Atypical		Non-anginal	
	original	updated	original	updated	original	updated
Men: age (years)						
30–39	70%	59%	22%	29%	5%	18%
40–49	87%	69%	46%	38%	14%	29%
50–59	92%	77%	59%	49%	22%	37%
60–69	94%	84%	67%	59%	28%	44%
70–79	94%	89%	67%	69%	28%	54%
>80	94%	93%	67%	78%	28%	67%

Women: age (years)	original	updated	original	updated	original	updated
	30–39	26%	28%	4%	10%	1%
40–49	55%	37%	13%	14%	3%	8%
50–59	79%	47%	32%	20%	8%	12%
60–69	91%	58%	54%	28%	19%	17%
70–79	91%	68%	54%	37%	19%	24%
>80	91%	76%	54%	47%	19%	32%

Source: Genders et al. (2011)

CAD = coronary artery disease; PTP = pre-test probability; intermediate PTP (green) defined as: 10–90% in original Diamond-Forrester model, 15–85% in an updated model, low PTP = blue; high PTP = pink.

In population 2, LGE-CMR would be used to assess myocardial ischaemia and determine myocardial viability in patients with an existing diagnosis of significant CAD, who have a history of IHD with LVD and are being considered for revascularisation.

PREVALENCE OF CAD IN AUSTRALIA

In 2010 IHD was the single largest burden of disease in Australia, accounting for 15% based on years of life lost (2014). There are also significant inequalities in the mortality burden of IHD in Australia, according to both remoteness and socioeconomic status, as well as between Aboriginal and Torres Strait Islanders and other Australians.

The prevalence of CAD in Australia is difficult to determine accurately. *The Australian heart disease statistics 2014* (Nichols et al. 2014) reported that, in 2011–12, 1.3% of the Australian population self-reported that they had angina and 2.7% had IHD (Table 3).

Table 3 Prevalence of specific self-reported cardiovascular conditions, by age, in 2011–12

Age group (years)	Angina	Total IHD	Diseases of arteries, arterioles and capillaries
35–44	0.2%	0.6%	0.3%
45–54	0.8%	1.8%	0.5%
55–64	2.0%	4.8%	1.4%
65–74	4.6%	9.7%	3.1%
75–84	7.8%	14.3%	4.4%
85+	14.5%	26.1%	9.5%
All persons aged 2+	1.3%	2.7%	0.9%

Source: Table 2.2 from Nichols et al. (2014)

IHD = ischaemic heart disease

The Australian heart disease statistics 2014 (Nichols et al. 2014) also reported the proportion of men and women, aged between 30 and 65 years, who had angina in 2013 (Table 4). By combining this data with the population data available from the Australian Bureau of Statistics website³, the number of men and women with angina could be estimated. In 2013 there were 11.6 million women and 11.5 million men living in Australia. Of those aged 30–65 years, 106,164 women and 235,555 men had angina (Table 4). The proportion of the population aged over 65 years that had angina in 2013 was not reported, although this would be expected to be considerably higher than in those aged less than 65 years.

Using the updated Diamond-Forrester algorithm (Table 2) to determine the PTP of men and women aged 30–65 years with angina having CAD, only women aged less than 50 years would have a low-intermediate (<45%) PTP and would therefore be eligible for computed tomography coronary angiography (CTCA) testing according to current clinical practice. None of the men would be eligible for CTCA testing, as all have a >45% PTP of having CAD. However, all these patients would be eligible for the proposed SP-CMR & LGE test to diagnose CAD.

Table 4 Number of men and women aged between 30 and 65 years with angina in 2012 and their PTP of having CAD

Age group (years)	% of population	% with angina	Total number with angina	PTP
Women	50.2% = 11.4 million			
30–39	13.6%	1.60%	24,806 women	28%
40–49	14.4%	1.53%	25,116 women	37%
50–59	13.3%	1.88%	28,505 women	47%
60–65	5.7%	4.16%	27,032 women	58%
>65	22.0%	-	-	58%–76%
Men	49.8% = 11.3 million			
30–39	13.6%	3.19%	49,024 men	59%
40–49	14.0%	3.07%	48,567 men	69%

³ Australian Bureau of Statistics. 'Population by age and sex, regions of Australia, 2013'. Available from <www.abs.gov.au> (accessed on 12 August 2015)

Age group (years)	% of population	% with angina	Total number with angina	PTP
50–59	13.1%	6.22%	92,075 men	77%
60–65	5.7%	6.88%	44,314 men	84%
>65	14.1%	-	-	84%–93%

Source: Australian Bureau of Statistics, < www.abs.gov.au>; Table 2.5 from Nichols et al. (2014); PTP was taken from the updated Diamond-Forrester algorithm (Table 2)

CAD = coronary artery disease; PTP = pre-test probability

The number of patients with an existing diagnosis of significant CAD, a history of IHD with LVD and are being considered for revascularisation is even more difficult to ascertain. Using data from *The Australian heart disease statistics 2014* (Nichols et al. 2014) and the Australian Bureau of Statistics website⁴, it was determined that approximately 30% of women and 28% of men aged 30–64 years and with a history of MI in the past 5 years required hospitalisation for IHD in 2012 (Table 5 and Table 6). While the proportion of the population aged 65 years and older that had a history of MI could not be determined, 1.4% of all women and 3.4% of all men aged over 65 years required hospitalisation for IHD in 2012. The number of major procedures performed on coronary arteries in hospitals in 2012 exceeded the number of patients hospitalised for IHD, suggesting that either some of these procedures were performed on patients with other underlying causes of heart disease or some patients required more than one revascularisation procedure. Thus, it is not possible to accurately determine the proportion of patients with known CAD who would undergo an imaging test to determine myocardial viability to guide revascularisation.

Table 5 Number of men and women aged between 30 and 65 years with a history of MI in the past 5 years

Age group (years)	% of population	% with history of MI	Total number
Women	50.2% = 11.4 million		
30–39	13.6%	0.51%	7,907 women
40–49	14.4%	1.04%	17,073 women
50–59	13.3%	0.94%	14,252 women
60–65	5.7%	1.68%	10,917 women
>65	22.0%	-	-
Men	49.8% = 11.3 million		
30–39	13.6%	1.76%	27,048 men
40–49	14.0%	1.98%	31,324 men
50–59	13.1%	3.93%	58,176 men
60–65	5.7%	6.72%	43,284 men
>65	14.1%	-	-

Sources: Australian Bureau of Statistics, < www.abs.gov.au/Ausstats/abs@.nsf/mf/3235.0#PARALINK2>; Table 2.6 and Table 2.7 from Nichols et al. (2014)

MI = myocardial infarction

⁴ Australian Bureau of Statistics. 'Population by age and sex, regions of Australia, 2013'. Available from < www.abs.gov.au/Ausstats/abs@.nsf/mf/3235.0#PARALINK2> (accessed on 27 August 2015)

Table 6 Number of men and women aged 25 years and older that were hospitalised for IHD, and the number of major procedures for CAD performed in hospitals in 2011–12

Age group (years)	Hospitalisations for IHD	Major procedures for CAD
Women		
25–34	165	274
35–44	1,385	1,752
45–54	4,835	6,001
55–64	8,782	12,180
Overall for women aged 30–64	15,167 hospitalisations 29.9% of women with history of MI 0.03% of all women aged 30–64 years	20,207 procedures 40.3% of women with history of MI 0.04% of all women aged 30–64 years
65–74	12,689	17,519
>75	22,714	19,904
Overall for women aged >65	35,403 hospitalisations 1.4% of all women aged >65 years	37,423 procedures 1.5% of all women aged >65 years
Men		
25–34	533	787
35–44	4,037	5,301
45–54	13,626	18,563
55–64	26,115	36,471
Overall for men aged 30–64	44,311 hospitalisations 27.7% of men with history of MI 0.08% of all men aged 30–64 years	61,122 procedures 38.2% of men with history of MI 1.2% of all men aged 30–64 years
65–74	29,623	40,690
>75	29,125	30,444
Overall for men aged >65	58,748 hospitalisations 3.4% of all men aged >65 years	71,134 procedures 45% of all men aged >65 years

Source: Table 2.6 and Table 3.1 from Nichols et al. (2014)

CAD = coronary artery disease; IHD = ischaemic heart disease; MI = myocardial infarction

A5 COMPARATOR DETAILS

PASC considered that there were seven relevant comparators to CMR.

In population 1, where CMR is proposed as a diagnostic test in patients with an intermediate PTP of having CAD, four comparators were recognised: exercise stress ECG, exercise or pharmacological stress echocardiography (Echo), exercise or pharmacological stress single-photon emission computed tomography (SPECT) and CTCA. In this population invasive coronary angiography (ICA) is considered to be the reference standard.

In population 2, where CMR is used as a prognostic test in patients with CAD to determine their eligibility for revascularisation, three comparators were identified: low-dose dobutamine stress Echo (DbE), SPECT and CT perfusion.

A brief description of these imaging techniques and any relevant MBS item numbers are given below.

Exercise ECG

Exercise ECG is a non-invasive test that has been used to assess risk of CAD for over 60 years. Treadmill ECG testing is usually performed with either the Bruce or modified Bruce protocol (Banerjee et al. 2012). In the Bruce protocol the incline and speed of the treadmill are increased every 3 minutes through a total of seven stages. Bicycle testing may be better tolerated than treadmill tests in patients who have orthopaedic or balance problems, as it can occur in the sitting or supine position using a stationary bicycle ergometer (Banerjee et al. 2012). ECG and blood pressure monitoring occur before, during and after the test. An adequate test is performed if the patient can achieve 85% of their maximum heart rate, which is calculated as 220 minus their age in years for men and 210 minus their age for women (Banerjee et al. 2012). Test supervisors must be able to provide CPR if needed. The MBS item descriptor relevant for this comparator is listed in Table 7.

Table 7 MBS item descriptors for exercise ECG

Category 2 – Diagnostic Procedures and Investigations
<p>MBS item number 11712</p> <p>MULTI CHANNEL ECG MONITORING AND RECORDING during exercise (motorised treadmill or cycle ergometer capable of quantifying external workload in watts) or pharmacological stress, involving the continuous attendance of a medical practitioner for not less than 20 minutes, with resting ECG, and with or without continuous blood pressure monitoring and the recording of other parameters, on premises equipped with mechanical respirator and defibrillator</p> <p>Fee: \$152.15 Benefit: 75% = \$114.15; 85% = \$129.35</p>

Stress Echo

Stress Echo images the heart using ultrasound and is one of the most common imaging techniques used to investigate cardiac abnormalities in both community and hospital settings.

In order to diagnosis CAD and assess whether myocardial ischemia is present, images obtained at rest are compared with those obtained during or immediately after stress to detect wall motion abnormalities (WMAs). Stress can be induced using exercise or pharmacological agents such as dobutamine and dipyridamole. However, the interpretation of wall motion contractility and function from stress Echo images is subjective, and 30% of patients have suboptimal stress Echo exams. This leads to inter-observer variability and reduced reproducibility (Medical Advisory Secretariat 2010f).

To overcome this limitation, contrast agents can be used to improve the definition of the LV border and may improve quantification of LV volume and the assessment of LV wall motion. Myocardial contrast Echo can also be used to assess myocardial perfusion (Medical Advisory Secretariat 2010c). Perfusion requires that the echocardiograph is set to a high mechanical index, causing microspheres of the contrast agent to burst. Perfusion is assessed by measuring how quickly the microspheres are replenished within the myocardium. If the microsphere replenishment rate is prolonged, then myocardium perfusion has decreased. Myocardial perfusion assessment with contrast Echo is not routinely used in most Echo laboratories.

Stress Echo can also be used to detect viable myocardium. An improvement of contractility during the infusion of low-dose dobutamine in affected segments indicates the presence of viable myocardium (Medical Advisory Secretariat 2010f). With contrast Echo, microbubbles of the contrast agent act like red blood cells in the vascular space and can be used to assess myocardial viability (Medical Advisory Secretariat 2010c). The MBS item descriptors relevant for this comparator are listed in Table 8.

Table 8 MBS item descriptors for stress Echo

Category 5 – Diagnostic Imaging Services
<p>MBS Item 55116</p> <p>EXERCISE STRESS EchoCARDIOGRAPHY performed in conjunction with item 11712, with two-dimensional recordings</p>

Category 5 – Diagnostic Imaging Services

before exercise (baseline) from at least three acoustic windows and matching recordings from the same windows at, or immediately after, peak exercise, not being a service associated with a service to which an item in Subgroups 1 (with the exception of item 55054) or 3, or another item in this Subgroup applies (with the exception of items 55118 and 55130). Recordings must be made on digital media with equipment permitting display of baseline and matching peak images on the same screen (R)

Bulk bill incentive

Fee: \$261.65 Benefit: 75% = \$196.25; 85% = \$222.45

MBS Item 55117

PHARMACOLOGICAL STRESS EchoCARDIOGRAPHY performed in conjunction with item 11712, with two-dimensional recordings before drug infusion (baseline) from at least three acoustic windows and matching recordings from the same windows at least twice during drug infusion, including a recording at the peak drug dose not being a service associated with a service to which an item in Subgroups 1 (with the exception of item 55054) or 3, or another item in this Subgroup, applies (with the exception of items 55118 and 55130). Recordings must be made on digital media with equipment permitting display of baseline and matching peak images on the same screen (R)

Bulk bill incentive

Fee: \$261.65 Benefit: 75% = \$196.25; 85% = \$222.45

MBS Item 55122

EXERCISE STRESS EchoCARDIOGRAPHY performed in conjunction with item 11712, with two-dimensional recordings before exercise (baseline) from at least three acoustic windows and matching recordings from the same windows at, or immediately after, peak exercise, not being a service associated with a service to which an item in Subgroups 1 (with the exception of items 55026 and 55054) or 3, or another item in this Subgroup applies (with the exception of items 55118, 55125, 55130 and 55131). Recordings must be made on digital media with equipment permitting display of baseline and matching peak images on the same screen (R) (NK)

Bulk bill incentive

Fee: \$130.85 Benefit: 75% = \$98.15; 85% = \$111.25

MBS Item 55123

PHARMACOLOGICAL STRESS EchoCARDIOGRAPHY performed in conjunction with item 11712, with two-dimensional recordings before drug infusion (baseline) from at least three acoustic windows and matching recordings from the same windows at least twice during drug infusion, including a recording at the peak drug dose not being a service associated with a service to which an item in Subgroups 1 (with the exception of items 55026 and 55054) or 3, or another item in this Subgroup, applies (with the exception of items 55118, 55125, 55130 and 55131). Recordings must be made on digital media with equipment permitting display of baseline and matching peak images on the same screen (R) (NK)

Bulk bill incentive

Fee: \$130.85 Benefit: 75% = \$98.15; 85% = \$111.25

SPECT

Cardiac SPECT is a widely used nuclear, non-invasive image acquisition technique for investigating all aspects of detecting and managing CAD including diagnosis, risk assessment/stratification, assessment of myocardial viability and the evaluation of LV function (Medical Advisory Secretariat 2010d).

Cardiac SPECT for the diagnosis of CAD uses an intravenously administered radiopharmaceutical tracer to evaluate regional coronary blood flow, usually at rest and after exercise or pharmacological stress using the positive inotrope dobutamine, or the vasodilators adenosine and dipyridamole (Medical Advisory Secretariat 2010d). After the administration of the tracer, its distribution within the myocardium is imaged using a gamma camera, which rotates around the patient for 10–20 minutes so that multiple 2-dimensional projections are acquired from various angles; 3-dimensional tomographic images are then obtained using computational algorithms to process the raw data (Medical Advisory Secretariat 2010d).

Two radioactive tracers are used. Thallium-201, a potassium analogue, is injected intravenously into the patient; it is taken up by the myocardial cells through regional perfusion and is retained in the cell via the sodium/potassium ATPase pumps (Medical Advisory Secretariat 2010d). Image sets are taken at rest and immediately after stress to identify PDs. Viable tissue is identified if the areas showing PDs exhibit significant fill-in (>10% increase in uptake), or if defects are fixed but the thallium-201 activity is >50% (Medical Advisory Secretariat 2010d). There are two forms of technetium-99m, the second tracer commonly used to target the myocardium: sestamibi and tetrofosmin. Their uptake and retention is dependent on regional perfusion and the integrity of cellular membranes. Viability is defined by segments with tracer activity >50% (Medical Advisory Secretariat 2010d). The MBS item descriptors relevant for this comparator are listed in Table 9.

Table 9 MBS item descriptors for cardiac SPECT

Category 5 – Diagnostic Imaging Services
<p>MBS Item 61302 SINGLE STRESS OR REST MYOCARDIAL PERFUSION STUDY - planar imaging (R) Bulk bill incentive Fee: \$448.85 Benefit: 75% = \$336.65; 85% = \$381.55</p>
<p>MBS Item 61303 SINGLE STRESS OR REST MYOCARDIAL PERFUSION STUDY - with single-photon emission tomography and with planar imaging when undertaken (R) Bulk bill incentive Fee: \$565.30 Benefit: 75% = \$424.00; 85% = \$489.10</p>
<p>MBS Item 61306 COMBINED STRESS AND REST, stress and re-injection or rest and redistribution myocardial perfusion study, including delayed imaging or re-injection protocol on a subsequent occasion - planar imaging (R) Bulk bill incentive Fee: \$709.70 Benefit: 75% = \$532.30; 85% = \$633.50</p>
<p>MBS item number 61307 COMBINED STRESS AND REST, stress and re-injection or rest and redistribution myocardial perfusion study, including delayed imaging or re-injection protocol on a subsequent occasion - with single-photon emission tomography and with planar imaging when undertaken (R) Bulk bill incentive Fee: \$834.90 Benefit: 75% = \$626.20; 85% = \$758.70</p>
<p>MBS Item 61651 SINGLE STRESS OR REST MYOCARDIAL PERFUSION STUDY - planar imaging (R) (NK) Bulk bill incentive Fee: \$224.45 Benefit: 75% = \$168.35; 85% = \$190.80</p>
<p>MBS Item 61652 SINGLE STRESS OR REST MYOCARDIAL PERFUSION STUDY - with single-photon emission tomography and with planar imaging when undertaken (R) (NK) Bulk bill incentive Fee: \$282.65 Benefit: 75% = \$212.00; 85% = \$240.30</p>
<p>MBS Item 61653 COMBINED STRESS AND REST, stress and re-injection or rest and redistribution myocardial perfusion study, including</p>

Category 5 – Diagnostic Imaging Services
<p>delayed imaging or re-injection protocol on a subsequent occasion - planar imaging (R) (NK)</p> <p>Bulk bill incentive</p> <p>Fee: \$354.85 Benefit: 75% = \$266.15; 85% = \$301.65</p>
<p>MBS Item 61654</p> <p>COMBINED STRESS AND REST, stress and re-injection or rest and redistribution myocardial perfusion study, including delayed imaging or re-injection protocol on a subsequent occasion - with single-photon emission tomography and with planar imaging when undertaken (R) (NK)</p> <p>Bulk bill incentive</p> <p>Fee: \$417.45 Benefit: 75% = \$313.10; 85% = \$354.85</p>

CTCA

CTCA is a nuclear cardiac imaging technique that assesses the presence or absence, as well as the extent, of coronary artery stenosis for the diagnosis of CAD (Medical Advisory Secretariat 2010b). It enables a 3-dimensional viewing of the coronary arteries derived from software algorithms of 2-dimensional images. As such, it is a test of cardiac structure and anatomy, and does not assess cardiac function. The visibility of the arteries in CTCA images decreases as they become increasingly calcified. Thus, this procedure works best in populations with PTPs of CAD between 40% and 80% (Medical Advisory Secretariat 2010b).

CTCA requires the addition of an iodinated contrast agent that can be administered only in patients with sufficient renal function to allow for the clearing of the agent from the body. CTCA also requires the patient's heart rate to be <65 beats/minute for single-source CTCA machines and <80 beats/minute for dual-source machines; this often requires administration of beta-blockers. Approximately 10% of patients are considered ineligible for CTCA because their heart rates cannot be decreased to the required levels. Another 10% of patients with an intermediate risk of CAD are ineligible due to additional contraindications, including renal insufficiency and atrial fibrillation. The procedure may take between 1 and 1.5 hours, with about 15 minutes of this time needed for CTCA imaging (Medical Advisory Secretariat 2010b). The MBS item descriptors relevant for this comparator are listed in Table 10.

Table 10 MBS item descriptors for CTCA

Category 5 – Diagnostic Imaging Services
<p>MBS Item 57360</p> <p>COMPUTED TOMOGRAPHY OF THE CORONARY ARTERIES performed on a minimum of a 64 slice (or equivalent) scanner, where the request is made by a specialist or consultant physician, and:</p> <ol style="list-style-type: none"> a) the patient has stable symptoms consistent with coronary ischaemia, is at low to intermediate risk of coronary artery disease and would have been considered for coronary angiography; or b) the patient requires exclusion of coronary artery anomaly or fistula; or c) the patient will be undergoing non-coronary cardiac surgery (R) (K) <p>Bulk bill incentive (Anaes.)</p> <p>Fee: \$700.00 Benefit: 75% = \$525.00; 85% = \$623.80</p>

Category 5 – Diagnostic Imaging Services

MBS Item 57361

COMPUTED TOMOGRAPHY OF THE CORONARY ARTERIES performed on a minimum of a 64 slice (or equivalent) scanner, where the request is made by a specialist or consultant physician, and:

- a) the patient has stable symptoms consistent with coronary ischaemia, is at low to intermediate risk of coronary artery disease and would have been considered for coronary angiography; or
- b) the patient requires exclusion of coronary artery anomaly or fistula; or
- c) the patient will be undergoing non-coronary cardiac surgery (R) (NK)

Bulk bill incentive (Anaes.)

Fee: \$350.00 Benefit: 75% = \$262.50; 85% = \$297.50

CT perfusion imaging with delayed contrast enhancement (CT-DCE)

CT-DCE is an emerging technique for characterising myocardial scars. It follows similar principles to CMR viability imaging (Bettencourt et al. 2013b). In CT-DCE, repeat imaging occurs 6–10 minutes after an iodinated contrast agent, such as iopromide, is administered to determine the steady-state concentration of contrast in the myocardium after the wash-out period. Areas of myocardial scarring retain a higher concentration of contrast compared with healthy myocardium, allowing them to be visualised (Bettencourt et al. 2013b). There are currently no MBS items for CT-DCE.

Invasive coronary angiography (ICA)

ICA is an invasive technique that is performed under local anaesthesia and in sterile conditions. ICA requires insertion of a catheter through an artery in the arm or leg, which is then X-ray guided to the coronary arteries; a radiocontrast agent is then injected into the coronary arteries in order to display the coronary anatomy and possible luminal obstruction (Caluk 2011).

ICA is considered to be the gold standard in the diagnosis of CAD, but is only recommended in stable patients with suspected CAD if non-invasive testing provides inadequate information to determine the likelihood of a cardiac event (Montalescot et al. 2013). The MBS item descriptor relevant for this comparator is listed in Table 11.

Table 11 MBS item descriptors for ICA

		Category 3 – Therapeutic Procedures
MBS Item 38215	Group	T8 - SURGICAL OPERATIONS
	Subgroup	6 - CARDIO-THORACIC
	Subheading	1 - CARDIOLOGY PROCEDURES
SELECTIVE CORONARY ANGIOGRAPHY, placement of catheters and injection of opaque material into the native coronary arteries, not being a service associated with a service to which item 38218, 38220, 38222, 38225, 38228, 38231, 38234, 38237, 38240 or 38246 applies		
Multiple Services Rule (Anaes.)		
Fee: \$354.90 Benefit: 75% = \$266.20; 85% = \$301.70		
(See para T8.53 of explanatory notes to this Category)		

Category 3 – Therapeutic Procedures	
MBS Item 38215	Group T8 - SURGICAL OPERATIONS Subgroup 6 - CARDIO-THORACIC Subheading 1 - CARDIOLOGY PROCEDURES
SELECTIVE CORONARY ANGIOGRAPHY, placement of catheters and injection of opaque material with right or left heart catheterisation or both, or aortography, not being a service associated with a service to which item 38215, 38220, 38222, 38225, 38228, 38231, 38234, 38237, 38240 or 38246 applies	
Multiple Services Rule (Anaes.) Fee: \$532.25 Benefit: 75% = \$399.20; 85% = \$453.85 (See para T8.53 of explanatory notes to this Category)	

A6 CLINICAL MANAGEMENT ALGORITHMS

CLINICAL MANAGEMENT ALGORITHM FOR THE DIAGNOSIS OF CAD

In population 1, CMR is proposed to be an alternative imaging technique to existing stress-testing modalities and CTCA to diagnose CAD in patients presenting with symptoms consistent with stable IHD and with an intermediate PTP. The current clinical algorithm (Figure 3) has been informed by the European Society of Cardiology’s guidelines for the diagnosis of stable CAD (Montalescot et al. 2013). The addition of CMR, as an imaging option, to the current algorithm is shown in red. CMR would be performed following clinical assessment, troponin testing, resting ECG and Echo. However, CTCA or ICA may still need to be conducted to confirm the presence of significant CAD in some patients.

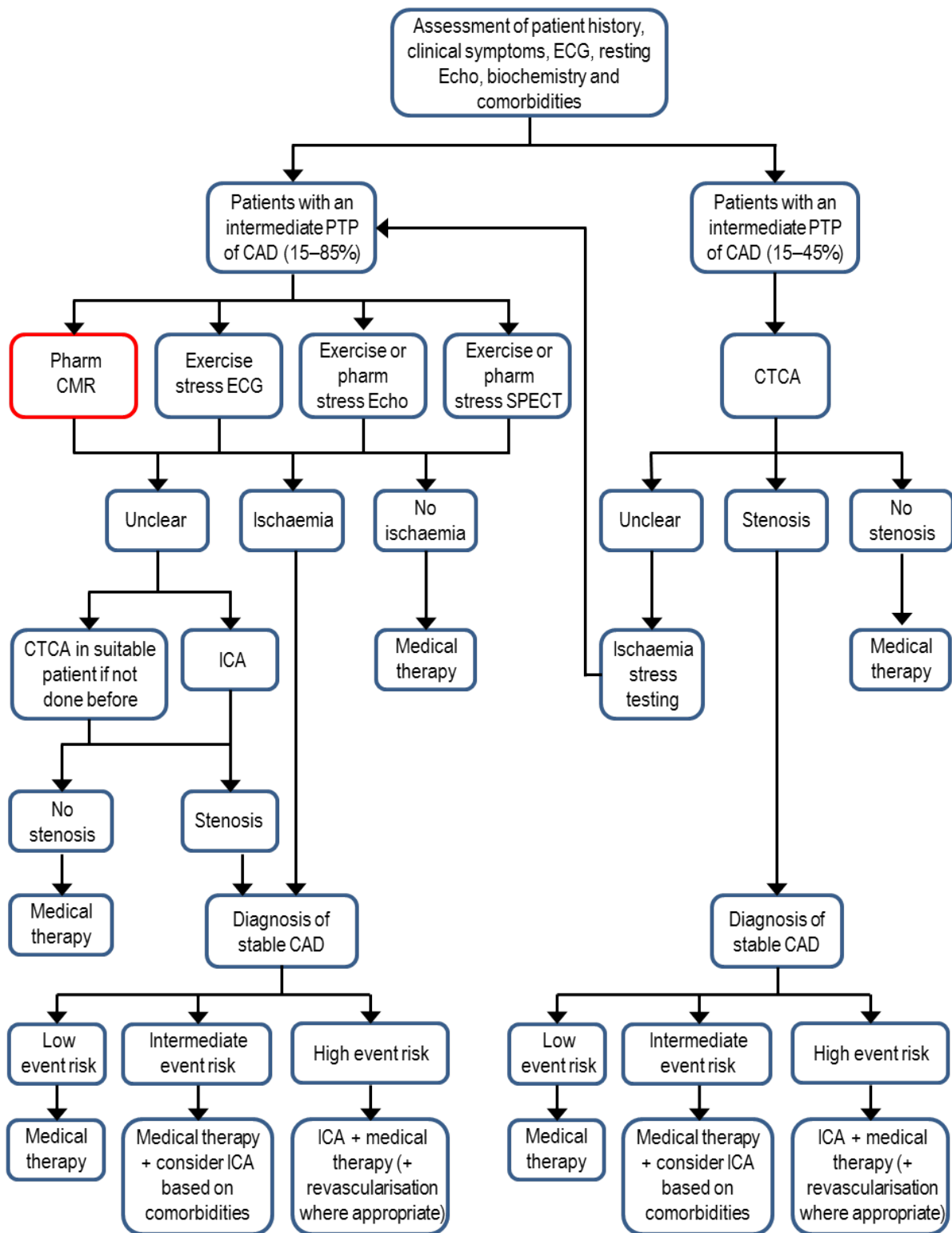


Figure 3 Clinical management algorithm for the diagnosis of patients with suspected ischaemic heart disease who do not have suspected high-risk lesions

The only difference in the current and proposed clinical pathways is the addition of CMR (shown in red box) to the list of imaging modalities available to diagnose eligible patients suspected of having CAD.

CAD = coronary artery disease; CMR = cardiac magnetic resonance imaging; CTCA = computed tomography coronary angiography; ECG = electrocardiography; Echo = echocardiography; ICA = invasive coronary angiography; pharm = pharmacological; PTP = pre-test probability; SPECT = single-photon emission computed tomography

CLINICAL MANAGEMENT ALGORITHM FOR DETERMINING ELIGIBILITY FOR REVASCULARISATION SURGERY

In population 2 the use of CMR for myocardial viability imaging is intended to replace existing viability imaging techniques, including DbE, SPECT and CT-DCE in patients with an existing diagnosis of significant CAD, who have a history of IHD with LVD and are being considered for revascularisation.

The current clinical pathway (Figure 4) for patients in whom surgical revascularisation is contemplated is based on the American College of Cardiology's guidelines for the diagnosis and management of stable IHD (Fihn et al. 2012). The proposed service, representing a change to current practice, is highlighted in red.

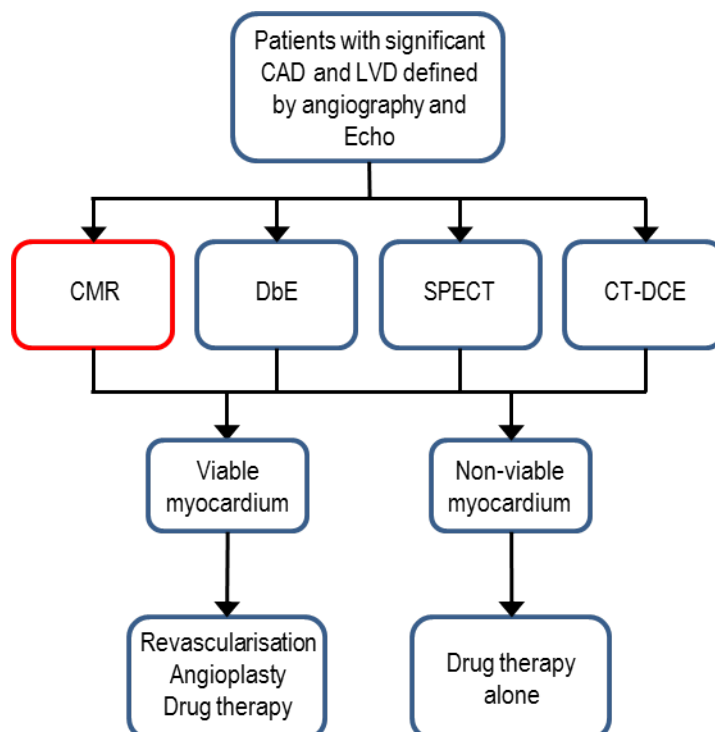


Figure 4 Clinical management algorithm for the use of CMR viability imaging in patients with an existing diagnosis of significant CAD who have a history of IHD and LVD

The only difference in the current and proposed clinical pathways is the addition of CMR (shown in red box) to the list of imaging modalities available to diagnose eligible patients requiring revascularisation procedures.

CAD = coronary artery disease; CMR = cardiac magnetic resonance imaging; CT-DCE = computed tomography perfusion with delayed contrast enhancement; DbE = low-dose dobutamine Echo; Echo = echocardiography; LVD = left ventricular dysfunction; SPECT = single-photon emission computed tomography

Note: The use of 18-fludeoxyglucose positron emission tomography is no longer funded by the MBS; hence, it has been removed as a comparator for this report.

A7 KEY DIFFERENCES IN THE PROPOSED MEDICAL SERVICE AND THE MAIN COMPARATOR

In population 1 SP-CMR & LGE is posed as an alternative investigative test to existing ischaemia stress-testing modalities and CTCA. Patients using SP-CMR & LGE instead of SPECT or CTCA also avoid exposure to ionising radiation. The advantages and disadvantages identified in the *2013 ESC guidelines on the management of stable coronary artery disease* (Montalescot et al. 2013) are listed in Table 12.

In population 2 the use of LGE-CMR for myocardial viability imaging is intended to replace existing methods of viability imaging due to improved safety compared with nuclear imaging technologies; patients will not be exposed to ionising radiation.

Table 12 Advantages and disadvantages of non-invasive stress imaging techniques

Technique	Advantages	Disadvantages
CMR	High soft tissue contrast including precise imaging of myocardial scar No radiation	Limited access in cardiology Contraindications include patients with devices such as pacemakers or claustrophobia that cannot undergo CMR procedures Limited 3D quantification of ischaemia High cost
CTCA	High NPV in patients with low PTP	Radiation exposure Limited availability Assessment limited with extensive coronary calcification or previous stent implantation Image quality limited with arrhythmias and high heart rates that cannot be lowered beyond 60–65/minute Low NPV in patients with high PTP
Echo	Wide access Portability No radiation Low cost	Echo contrast needed in patients with poor ultrasound windows Dependent on operator skills
SPECT	Wide access Extensive data	Radiation exposure
Exercise ECG	Low cost Wide access	Unreliable

Sources: Montalescot et al, (2013); Mordi & Tzemos (2015)

CMR = cardiac magnetic resonance imaging; CTCA = computed tomography coronary angiography; ECG = electrocardiography; Echo = echocardiogram; NPV = negative predictive value; PTP = pre-test probability; SPECT = single-photon emission computed tomography

A8 CLINICAL CLAIM

The applicant claims that CMR has superior diagnostic accuracy compared with existing stress-testing modalities, on the basis that CMR provides more-detailed and reliable data with reduced inter- and intra-observer variability (Greenwood et al. 2012). Thus, the use of CMR should:

- i. reduce the test failure rate, leading to earlier diagnosis and management of CAD, or earlier exclusion of CAD
- ii. allow additional/earlier case detection and management, with fewer false negatives
- iii. produce fewer false positives, reducing the need for further invasive testing.

CMR is also posed as an alternative to CTCA for patients with a low-intermediate risk of CAD (15%–45%), thereby avoiding exposure to ionising radiation. It is possible that CTCA may still be conducted following an equivocal CMR result to confirm the presence of significant CAD.

Thus, the use of CMR instead of other imaging modalities is expected to reduce the need for CTCA, ICA and myocardial biopsy in eligible patients. The use of CMR may also reduce downstream costs by reducing the need for layered testing. However, an HESP member indicated that it would require a major shift in referral patterns to fully replace Echo and nuclear cardiac testing, as they are firmly entrenched in the standard workup of cardiac patients.

In patients with an existing diagnosis of significant CAD and a history of IHD with LVD and who are being considered for revascularisation procedures, CMR is proposed to be non-inferior to existing modalities with improved safety. The application also claims that CMR has a significant impact on therapy planning and patients' preferred choice of therapy (Taylor et al. 2013).

A9 SUMMARY OF THE PICO

The guiding framework of a PICO Confirmation is recommended by MSAC for each assessment. The PICO Confirmation describes current clinical practice and reflects likely future practice with the proposed medical service.

The PICO that were pre-specified to guide the systematic literature review for a direct evidence approach, along with additional criteria for selecting studies for the evidence-base, are presented in Table 13 and Table 14. These criteria were defined a priori to minimise any bias associated with study selection in the systematic literature review.

Table 13 PICO criteria for identifying and selecting studies to determine the safety and effectiveness of CMR in patients suspected of having CAD

Selection criteria	Description
Population	Patients presenting with symptoms consistent with IHD, with an intermediate PTP of CAD
Intervention	CMR gadolinium-based stress perfusion and viability imaging
Comparators	Exercise ECG; exercise or pharmacologic stress Echo; exercise or pharmacologic stress SPECT, or CTCA
Outcomes	<p><u>Effectiveness</u></p> <p><i>Critical outcomes:</i> Cardiac disease specific mortality rate, survival rate, adverse cardiac events over defined period, quality of life scores</p> <p><i>Important outcomes:</i> cardiac hospitalisation</p> <p><i>Outcomes of low importance:</i> regional functional improvement</p> <p><u>Safety</u></p> <p>Adverse reactions to gadolinium contrast medium or stress agent, claustrophobia or discomfort during CMR, physical harms from follow-up testing, other AEs arising from CMR</p> <p><u>Cost-effectiveness</u></p> <p>Cost, cost per quality-adjusted life year or disability-adjusted life year, incremental cost-effectiveness ratio</p>
Systematic review question	What is the safety, effectiveness and cost-effectiveness of CMR gadolinium-based stress perfusion and viability imaging in the diagnosis of CAD in patients presenting with symptoms consistent with IHD, with an intermediate PTP of CAD?

Effectiveness outcomes ranked as critical, important or of low importance as recommended by GRADE.

AE = adverse event; CAD = coronary artery disease; CMR = cardiac magnetic resonance imaging; CTCA = computed tomography coronary angiography; ECG = electrocardiogram; Echo = echocardiogram; IHD = ischaemic heart disease; PTP = pre-test probability; SPECT = single-photon emission computed tomography

Table 14 PICO criteria for identifying and selecting studies to determine the safety and effectiveness of CMR in patients with known CAD

Selection criteria	Description
Population	Patients with an existing diagnosis of significant CAD who have a history of IHD with LVD and are being considered for revascularisation
Intervention	CMR gadolinium-based viability imaging
Comparators	DbE, SPECT using thallium/sestamibi/tetrofosmin, or CT-DCE

Outcomes	<p><u>Effectiveness</u></p> <p><i>Critical outcomes:</i> Cardiac disease specific mortality rate, survival rate, adverse cardiac events over defined period, quality of life scores</p> <p><i>Important outcomes:</i> cardiac hospitalisation</p> <p><i>Outcomes of low importance:</i> regional functional improvement</p> <p><u>Safety</u></p> <p>Adverse reactions to gadolinium contrast medium or stress agent, claustrophobia or discomfort during CMR, physical harms from follow-up testing, other AEs arising from CMR</p> <p><u>Cost-effectiveness</u></p> <p>Cost, cost per quality-adjusted life year or disability-adjusted life year, incremental cost-effectiveness ratio</p>
Systematic review question	What is the safety, effectiveness, and cost-effectiveness of CMR gadolinium-based viability imaging in determining viable myocardium in patients with an existing diagnosis of significant CAD who have a history of IHD with LVD and are being considered for revascularisation?

Effectiveness outcomes ranked as critical, important or of low importance as recommended by GRADE.

AE = adverse event; CAD = coronary artery disease; CMR cardiac magnetic resonance imaging; CT-DCE = computed tomography perfusion imaging with delayed contrast enhancement; DbE = low-dose dobutamine stress echocardiogram; IHD = ischaemic heart disease; LVD = left ventricular dysfunction; SPECT = single-photon emission computed tomography

The PICO that were pre-specified to guide the systematic literature review for a linked evidence approach, along with additional criteria for selecting studies for the evidence-base, are presented in Table 15 to Table 18.

Table 15 PICO criteria for identifying and selecting studies to determine the diagnostic accuracy of CMR in patients suspected of having CAD

Selection criteria	Description
Population	Patients presenting with symptoms consistent with IHD, with an intermediate PTP of CAD
Index test	CMR gadolinium-based stress perfusion and viability imaging
Comparators	Exercise ECG; exercise or pharmacologic stress Echo; exercise or pharmacologic stress SPECT, or CTCA
Reference standard	ICA
Outcomes	Sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, positive predictive value, negative predictive value, SROC curves, unsatisfactory or uninterpretable test results
Systematic review question	What is the diagnostic accuracy of CMR gadolinium-based stress perfusion and viability imaging in the diagnosis of CAD in patients presenting with symptoms consistent with IHD, with an intermediate PTP of CAD?

CAD = coronary artery disease; CMR = cardiac magnetic resonance imaging; CTCA = computed tomography coronary angiography; ECG = electrocardiogram; Echo = echocardiogram; ICA = invasive coronary angiography; IHD = ischaemic heart disease; PTP = pre-test probability; SPECT = single-photon emission computed tomography; SROC = summary receiver-operator characteristics

Table 16 PICO criteria for identifying and selecting studies to determine the diagnostic accuracy of CMR in patients with known CAD

Selection criteria	Description
Population	Adult patients with an existing diagnosis of significant CAD who have a history of IHD with LVD and are being considered for revascularisation
Index test	CMR gadolinium-based viability imaging
Comparators	DbE; SPECT using thallium/sestamibi/tetrofosmin, or CT-DCE

Reference standard	No valid reference test
Outcomes	The assessment of CMR accuracy should be based on the relative effectiveness of revascularisation versus medical management using both health outcomes (e.g. survival, hospitalisation, quality of life) and surrogate outcomes (e.g. global LV function, regional functional improvement) between patients treated with and without viable myocardium
Systematic review question	What is the diagnostic accuracy of CMR gadolinium-based viability imaging in determining viable myocardium in patients with an existing diagnosis of significant CAD who have a history of IHD with LVD and are being considered for revascularisation?

CAD = coronary artery disease; CMR = cardiac magnetic resonance imaging; CT-DCE = computed tomography perfusion imaging with delayed contrast enhancement; DbE = low-dose dobutamine stress echocardiogram; IHD = ischaemic heart disease; LVD = left ventricular dysfunction; SPECT = single-photon emission computed tomography

PASC noted that additional relevant evidence, in the absence of a reference standard, may include the prognostic value of myocardial viability determined by cardiac MRI versus comparator tests. This would include studies that compare the prognosis for CAD patients with and without viable myocardium (measured with CMR and at least one comparator test) who have been treated with revascularisation or medical management.

Table 17 PICO criteria for identifying and selecting studies to determine the impact on patient management of CMR in patients suspected of having CAD

Selection criteria	Description
Population	Patients presenting with symptoms consistent with IHD, with an intermediate PTP of CAD
Intervention	CMR gadolinium-based stress perfusion and viability imaging
Comparators	Exercise ECG; exercise or pharmacologic stress Echo; exercise or pharmacologic stress SPECT, or CTCA
Outcomes	Change in clinical diagnosis, change in treatment pathway, patient compliance/preferences, time to initial diagnosis, time from diagnosis to treatment
Systematic review question	Does CMR gadolinium-based stress perfusion and viability imaging change clinical management, compared with exercise or pharmacologic stress Echo, exercise or pharmacologic stress SPECT, CTCA and ICA for patients with symptoms consistent with IHD, with an intermediate PTP of CAD?

CAD = coronary artery disease; CMR = cardiac magnetic resonance imaging; CTCA = computed tomography coronary angiography; ECG = electrocardiogram; Echo = echocardiogram; IHD = ischaemic heart disease; PTP = pre-test probability; SPECT = single-photon emission computed tomography

Table 18 PICO criteria for identifying and selecting studies to determine the impact on patient management of CMR in patients with known CAD

	Description
Population	Patients with an existing diagnosis of significant CAD who have a history of IHD with LVD and are being considered for revascularisation
Intervention	CMR gadolinium-based viability imaging
Comparators	DbE, SPECT using thallium/sestamibi/tetrofosmin, or CT-DCE
Outcomes	Change in treatment pathway (initiated, ceased, modified, avoided), patient compliance/preference for imaging
Systematic review question	Does CMR gadolinium-based viability imaging change clinical management, compared with DbE, SPECT using thallium/sestamibi/tetrofosmin, or CT-DCE for patients with an existing diagnosis of significant CAD who have a history of IHD with LVD and are being considered for revascularisation?

CAD = coronary artery disease; CMR = cardiac magnetic resonance imaging; CT-DCE = computed tomography perfusion imaging with delayed contrast enhancement; DbE = low-dose dobutamine stress echocardiogram; IHD = ischaemic heart disease; LVD = left ventricular dysfunction; SPECT = single-photon emission computed tomography.

A10 CONSUMER IMPACT STATEMENT

The main issues arising from the public consultation period in November 2014 were:

- Patient access:
 - A Medicare benefit for this procedure does not solve the problems with access to a Medicare-licensed MRI.
 - There are currently long waiting times for CMR within public hospitals due to the high demand for MRI from other specialties, such as orthopaedics and neurology.
 - In the private diagnostic imaging environment, access for CMR is extremely limited due to high demand in other areas and the time required to undertake each CMR (45–60 minutes per scan).
 - Recent changes to the MBS allowing greater access to MRI scans for areas such as breast and Crohn’s disease, and more recently GP access, has meant that Medicare-licensed MRI scanners have no time available for CMR.
 - It was suggested that a separate and limited Medicare MRI licence be initiated to include cardiology item numbers only, to ensure appropriate and timely patient access to CMR and guarantee a superior level of CMR imaging/reporting.
- Performing CMR and interpreting CMR scans:
 - Due to the complexity and experience necessary, there is a wide gap in experience/knowledge in performing and reporting CMR to a high level.

The Royal Australian and New Zealand College of Radiologists (RANZCR) also provided feedback. The main issues raised were:

- The proposed MBS fees of \$900 for MBS item 1 and \$700 for MBS item 2 are below the cost of performing the CMR investigation and will require the patient to pay a significant gap. A fee of \$1,100–1,200 would be more appropriate.
- Ideally, for best practice and quality CMR, the study would be co-reported with both a cardiologist and a radiologist.
- The costing indicates 1.6FTE for technologists, where in fact 1 technologist would perform the scan and another would be required to analyse the data. Therefore, the procedure would require 2 FTE technologists along with helpers and nurses to position the patient, perform pre-scan ECG, cannulate, set up and supervise post-procedure care.
- Nurses will need to observe the patient with stress perfusion post-procedure—this is a requirement, not a maybe scenario as indicated in the costing analysis.

SECTION B CLINICAL EVALUATION

Determination of the clinical effectiveness of an investigative medical service requires either:

- evidence of the effectiveness of CMR from high-quality comparative studies evaluating the use of CMR and subsequent treatment compared with other imaging modalities and treatment (direct evidence). Randomised controlled trials (RCTs) provide the highest quality evidence for this comparison. Or, if this is not available:
- evidence of the treatment effectiveness from high-quality comparative studies evaluating the treatment for CAD, linked with applicable and high-quality evidence of the accuracy of CMR to either diagnose CAD compared with ICA or determine the suitability for revascularisation (linked evidence).

There was insufficient direct evidence identified; thus, this evidence was supplemented by a linked evidence approach.

LITERATURE SOURCES AND SEARCH STRATEGIES

The medical literature was searched on 26 May 2015 to identify relevant studies and systematic reviews (SRs) published since 1990. Searches were conducted using the databases described in Appendix B. Attempts were also made to source unpublished or grey literature from the additional sources listed in Appendix B, and the HTA websites listed in Appendix B were also searched. The search terms are described in Table 19.

Table 19 Search terms used for PubMed

Element of clinical question	Search terms
Population	((“Coronary artery disease” [MeSH] OR “coronary artery disease” OR CAD OR “coronary heart disease” OR CHD) AND (ischaemic OR ischaemia OR stenosis OR stenotic OR “left ventricular” OR LVEF)) OR (“ischaemic heart disease” OR “ischemic heart disease” OR IHD)
Intervention	“Myocardial Perfusion Imaging” [MeSH] OR “magnetic resonance” OR MRI OR CMR
Limits	Publication date from 1990/01/01 to 2015/05/12 NOT (“Other animals” NOT “humans”)

RESULTS OF LITERATURE SEARCH

A PRISMA flowchart (Figure 5) provides a graphic depiction of the results of the literature search and the application of the study selection criteria (listed in Box 1 and Box 2) (Liberati et al. 2009).

Studies were selected by a single reviewer with a random sample equivalent to 20% of the literature being independently assessed by a second reviewer. Disagreements regarding study selection were resolved by a third independent reviewer.

Studies that could not be retrieved or that met the inclusion criteria but were excluded due to insufficient or inadequate data are listed in Appendix L. All other studies that met the inclusion criteria are listed in Appendix C.

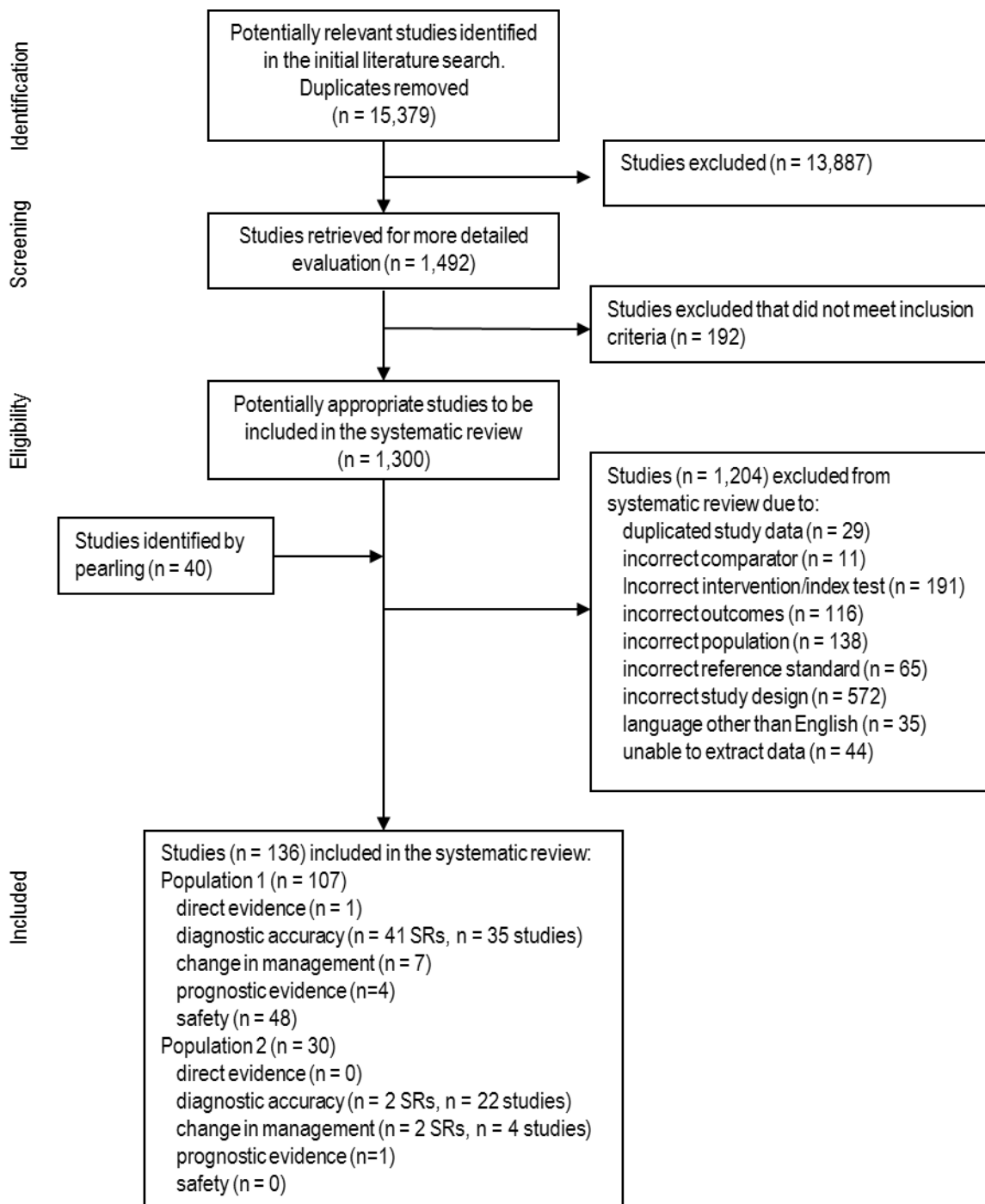


Figure 5 Summary of the process used to identify and select studies for the assessment

A profile of each included study is given in Appendix C, describing the authors, study location, publication year, study design and quality (level of evidence and risk of bias), setting, length of follow-up of patients, study population characteristics, description of the test (and associated interventions), description of the comparator (and associated intervention), description of the reference standard or evidentiary standard, and the relevant outcomes assessed. Those studies that technically met the inclusion criteria but were not included in the results section or meta-analyses are listed in Appendix L.

APPRAISAL OF THE EVIDENCE

Appraisal of the evidence was conducted in four stages:

Stage 1: Appraisal of the risk of bias for different outcomes within individual studies (or SRs) included in the review (Subsections B1.3, B3.3, B4.1.2, B5.1.1)

Stage 2: Appraisal of the precision, size of effect and clinical importance of the results reported in the evidence-base as they relate to the pre-specified primary outcomes for this assessment (Subsections B1.6, B3.6, B4.1.5, B5.1.4, B5.2.4)

Stage 3: Rating of the overall quality of the evidence per outcome, across studies, based on the study limitations (risk of bias), imprecision, inconsistency of results, indirectness of evidence and likelihood of publication bias, which informs the GRADE of the evidence (Evidence profile tables, Appendix G)

Stage 4: Integration of this evidence (across outcomes) for conclusions about the net clinical benefit of the test and associated interventions in the context of Australian clinical practice (Section B.8)

POPULATION 1

B1 DIRECT EVIDENCE (POPULATION 1)

B1.1 LITERATURE SOURCES AND SEARCH STRATEGIES

The literature sources and search strategies are described above (page 66).

B1.2 RESULTS OF LITERATURE SEARCH

No studies were identified that directly compared the effectiveness of SP-CMR with/without LGE with other imaging modalities in the detection of myocardial stenoses in order to diagnose CAD in patients presenting with symptoms consistent with stable IHD and with an intermediate PTP of CAD (population 1). Thus, the PICO criteria were broadened to include studies that enrolled any patients with suspected CAD. One RCT (the Cost-effectiveness of non-invasive cardiac testing (CECaT) trial) was identified that met the broader inclusion criteria (Sharples et al. 2007). This RCT compared the effectiveness of SP-CMR, stress SPECT, stress Echo and ICA in patients with known or suspected CAD who were referred for ICA in order to determine clinical management. The trial was designed to reflect what is likely to happen in a clinical setting and to include all patients for whom the diagnostic strategies could be applied.

Non-comparative level IV evidence (case series with either post-test or pre-test/post-test outcomes) that met the broadened inclusion criteria was also identified to assess the safety of SP-CMR with/without LGE. This evidence included two SRs of level IV studies, which included studies enrolling patients with known or suspected CAD who were tested for carotid artery stenoses using various non-invasive imaging procedures. There were also 48 level IV studies that reported on the safety of SP-CMR: 25 in patients with known or suspected CAD and 23 in patients suspected of having CAD. A full profile of each of these studies is given in Table 142 in Appendix C.

B1.3 RISK OF BIAS ASSESSMENT

The quality of the CECaT trial, which provided direct evidence of the effectiveness of CMR in the diagnosis of CAD, was evaluated using the Downs and Black (1998) checklist(1998). This high quality (overall 20.5/26) RCT was well described (reporting 9/10) with a low risk of bias (internal validity 10.5/13). However, it is uncertain if the results are generalisable to all patients with known or suspected CAD as there were some differences in the baseline characteristics of patients who did and did not enter the trial (external validity 1/3; see Section B1.4). The overall quality of the evidence provided by this RCT for specific outcomes was assessed using GRADE (Guyatt et al. 2011), and the results are presented in Table 175 in Appendix G. As the study population included patients with known or suspected CAD and was broader than the PICO (Table 13 in Section A9), there was some concern about the generalisability of these results to only patients who met the PICO criteria (i.e. had stable IHD and an intermediate PTP of having CAD), Thus, the evidence-base was considered to be of moderate quality (GRADE ⊕⊕⊕○).

The quality of the individual case series reporting on the safety of SP-CMR were assessed using the Institute of Health Economics (IHE) checklist (Moga et al. 2012), and the results are summarised in Table 20. The results for the individual studies are listed in Table 142 in Appendix C. The overall quality of the evidence provided by these case series for specific safety outcomes was assessed using GRADE, and the results are presented in Table 176 and Table 177 in Appendix G. As the evidence-base consists of non-comparative case series, it was considered to be of very low quality (GRADE ⊕○○○).

Table 20 Summary of the overall quality and risk of bias for case series reporting on the safety of SP-CMR

Stress agent	Known or suspected CAD	Suspected CAD
Adenosine	k=8 with a low risk of bias k=9 with a moderate risk of bias	k=12 with a low risk of bias k=6 with a moderate risk of bias
Adenosine or dobutamine	k=1 with a low risk of bias	-
Dobutamine	k=2 with a moderate risk of bias	k=1 with a low risk of bias k=1 with a moderate risk of bias
Dipyridamole	k=2 with a moderate risk of bias k=1 with a high risk of bias	k=3 with a moderate risk of bias
Nicorandil	k=1 with a moderate risk of bias	-
Nitroglycerin	-	k=1 with a moderate risk of bias

CAD = coronary artery disease; k = number of studies; SP-CMR = stress perfusion cardiac magnetic resonance imaging.

B1.4 CHARACTERISTICS OF THE EVIDENCE-BASE

The study profile of the CECaT trial (Sharples et al. 2007) that reports on the effectiveness of SP-CMR compared with SPECT, stress Echo and ICA in diagnosing CAD is provided in Table 141 in Appendix C. The baseline characteristics of the patients in each of the four diagnostic groups are listed in Table 153 in Appendix D.

Briefly, the trial studied 898 patients with established or suspected stable angina who had been referred for ICA in a tertiary referral centre for cardiovascular disease (CVD) in the UK. Patients were randomised to receive an initial SPECT, CP-CMR, stress Echo test (interventions) or initial ICA as planned (control). The four patient groups were well balanced for demographic and disease history characteristics.

The results of the three non-invasive imaging groups were sent on to the patient's cardiologist with a recommendation for ICA if the results were positive for ischaemia. Patients who went on to have ICA, along with those in the control group, received treatment (percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG)) based on the findings of the ICA. As the population consisted of patients with known or suspected CAD (all with angina pain), the target population is broader than that indicated in this assessment.

The study profiles for the SR and the 48 case series that report on the safety of using SP-CMR to diagnose CAD are given in Table 142 in Appendix C. The SR and 24 case series included patients with known or suspected CAD. Of the 24 case series that only included patients suspected of having CAD, only 3 included only patients with a low to intermediate risk of having CAD. Most of the case series excluded patients with known contraindications to CMR (severe claustrophobia, metallic implants / foreign bodies); of the 42 studies that reported exclusion criteria, only 1 did not specify contraindications to CMR. However, only 17/42 specified that patients with contraindications for the gadolinium-based contrast medium (anaphylaxis, estimated glomerular filtration rate 60 ml/min) or at least with renal insufficiency were excluded. Adenosine was the most commonly used stress agent, and 28 out of the 35 adenosine stress studies that reported exclusion criteria (only 1 did not) specifically excluded patients with contraindications to adenosine (second-/third-degree atrioventricular block, obstructive pulmonary disease, dipyridamole use). Only 2 out of 13 studies that used other stress agents specifically excluded contraindications to that drug; however, 5 of these studies did not report any exclusion criteria.

B1.5 OUTCOME MEASURES AND ANALYSIS

The outcomes measured, along with the statistical methods used to analyse the results, in the CECaT trial (Sharples et al. 2007) are listed in Table 21. The statistical analyses were very basic, making no

attempt to calculate relative risks (RRs) or hazard ratios (HRs) for most outcomes. Since not all patients experienced angina during exercise, the time to angina was estimated using Kaplan-Meier curves, with those not having angina censored at the end of their exercise time. Although 2 x 2 data was provided for comparing the accuracy of SP-CMR, SPECT and stress Echo using ICA as the reference standard, the sensitivity, specificity, LRs, PPV and NPV values were not calculated in this study.

To enable comparison of the improvement in angina class, hospitalisation and cardiac-related mortality rates for SP-CMR, SPECT and stress Echo, the RR of having an event compared with ICA was calculated using Stata 13 (StataCorp 2013).

Table 21 Key features of the included evidence from a single RCT comparing SP-CMR, SPECT and stress Echo with ICA

N	Relevant outcomes assessed (i.e. related to outcomes specified in PICO)	Statistical methods	Result used in economic model
	Critical outcomes:		
898	CVD-related mortality rate during 18-month follow-up period	Proportion of patients with events	No
898	Adverse CVD-related events during 18-month follow-up period	Proportion of patients with events	No
898	HRQoL (generic SF-36, disease-specific SAQ and EQ-5D)	Mean difference between functional test groups and ICA group	No
	Important outcomes:		
898	Hospital admission with AEs	Proportion of patients with events	No
	Low importance outcome:		
898	Exercise treadmill time at 6- and 18-month follow-up	Mean difference between functional test groups and ICA group	No
898	Two-class improvement in CCS class of angina at 6- and 18-month follow-up (clinically significant improvement commonly used in angina trials)	% change from baseline	No
	Other relevant outcomes:		
898	Diagnostic accuracy	2 x 2 data presented	No
898	Equivocal and/or failed test results	Proportion of tests	Yes
898	Patients with non-invasive imaging results who received an ICA	Proportion of patients	Yes
898	Patient management decisions Revascularisation rate	Proportion of patients revascularised or medically managed	No

Source: Sharples et al. (2007)

AE = adverse event; CCS = Canadian Cardiovascular Society; CVD = cardiovascular disease; Echo = echocardiogram; HRQoL = health-related quality of life; ICA = invasive coronary angiography; PICO = population, investigation/Index test, comparators and outcomes; RCT = randomised controlled trial; SP-CMR = stress perfusion cardiac magnetic resonance imaging; SPECT = single-photon emission computed tomography

B1.6 RESULTS OF THE SYSTEMATIC LITERATURE REVIEW

IS IT EFFECTIVE?

Summary – What is the effectiveness of SP-CMR imaging in the diagnosis of CAD in patients presenting with symptoms consistent with IHD?

Patient disposition, test completion and management

Of the patients that were randomised to SP-CMR, 11% did not receive that test, 4% could not complete the CMR and 7% had equivocal results, giving a successful completion rate of 78%, compared with 98%, 94% and 90% successful tests for the ICA, SPECT and stress Echo groups, respectively.

Of the patients randomised to non-invasive imaging, 80%, 78% and 75% of those that had SP-CMR, SPECT and stress Echo, respectively, were referred on for an ICA. Thus, 20%–25% of patients undergoing non-invasive imaging did not require further diagnostic tests. There were no significant differences between groups for the proportion of patients who received surgery (CABG or PCI) and the proportion that were medically managed.

Critical outcomes:

Cardiac disease specific mortality rates

The effect of the different diagnostic tests on mortality rates could not be determined due to the very broad 95% confidence intervals (CIs), which can be attributed to the small number of patients who died in each group.

Quality of life scores

There were no statistically or clinically relevant differences between the four groups for any of the QoL measures used in this trial.

Important outcomes:

Cardiac hospitalisation

There were no statistically significant differences between groups in the number of patients who were hospitalised, although there was a trend favouring non-invasive imaging groups over ICA. SP-CMR offers no benefits in the reduction of CVD-related hospitalisations compared with SPECT or stress Echo.

Outcomes of low importance:

Total exercise time at 6 months post-treatment and 18 months post-randomisation

The difference in exercise time between SP-CMR and ICA was statistically significant, favouring ICA at both 6- and 18-month follow-ups; however, the difference was not clinically significant. There were no differences between the other groups and ICA. The SP-CMR group also had a significantly higher proportion of patients with angina during exercise compared with the ICA group, and the time to angina was significantly shorter.

Change in Canadian Cardiovascular Society (CCS) class

Patients requiring a CABG/PCI procedure who were diagnosed using SPECT were more likely to have a clinically significant improvement in angina than those diagnosed with SP-CMR, stress Echo or ICA. Patients who were medically managed and diagnosed with ICA were more likely to have a clinically significant improvement in angina than those diagnosed with non-invasive imaging modalities.

Overall conclusion:

Having an initial non-invasive imaging test reduced the number of patients having ICA by 25%, consisting mostly of those with a negative result. There were no clinically or statistically significant differences in morbidity, mortality or QoL between the three non-invasive imaging groups when compared with the ICA group. The only exception was that patients randomised to either SP-CMR or stress Echo did not improve in exercise time as much as those randomised to either SPECT or ICA.

The *a priori* primary outcome for the CECaT trial was exercise time at 18 months post-randomisation. This outcome is a measure of functional improvement and as such was of low importance for this report. However, the authors also reported on clinical outcomes that are of more importance, including mortality rates, adverse events (AEs) requiring hospitalisation and health-related quality of life.

PATIENT DISPOSITION AND TEST COMPLETION RATE

Figure 6 shows the progress of patients through the trial. The proportion of patients with missing data or lost to follow-up is similar in all groups. However, there were differences in the number of patients who received the test to which they were randomised and in the number who had a successful test. Completion rates for the initial test to which patients were randomised varied from 98% for ICA and SPECT and 96% for stress Echo, to 89% for SP-CMR.

Of those patients who actually completed the allocated test, equivocal results were found for 8% (15/191) of SP-CMR patients, 4% (9/220) of SPECT patients, 3% (7/210) of stress Echo patients and no ICA patients. These equivocal result rates were all significantly higher than ICA ($p < 0.02$) but there was no statistical difference among the three imaging tests ($p = 0.09$). For the purposes of clinical management, all equivocal tests were treated as positive and patients were referred for ICA.

There were similar losses to follow-up in each group at both 6 months and 18 months.

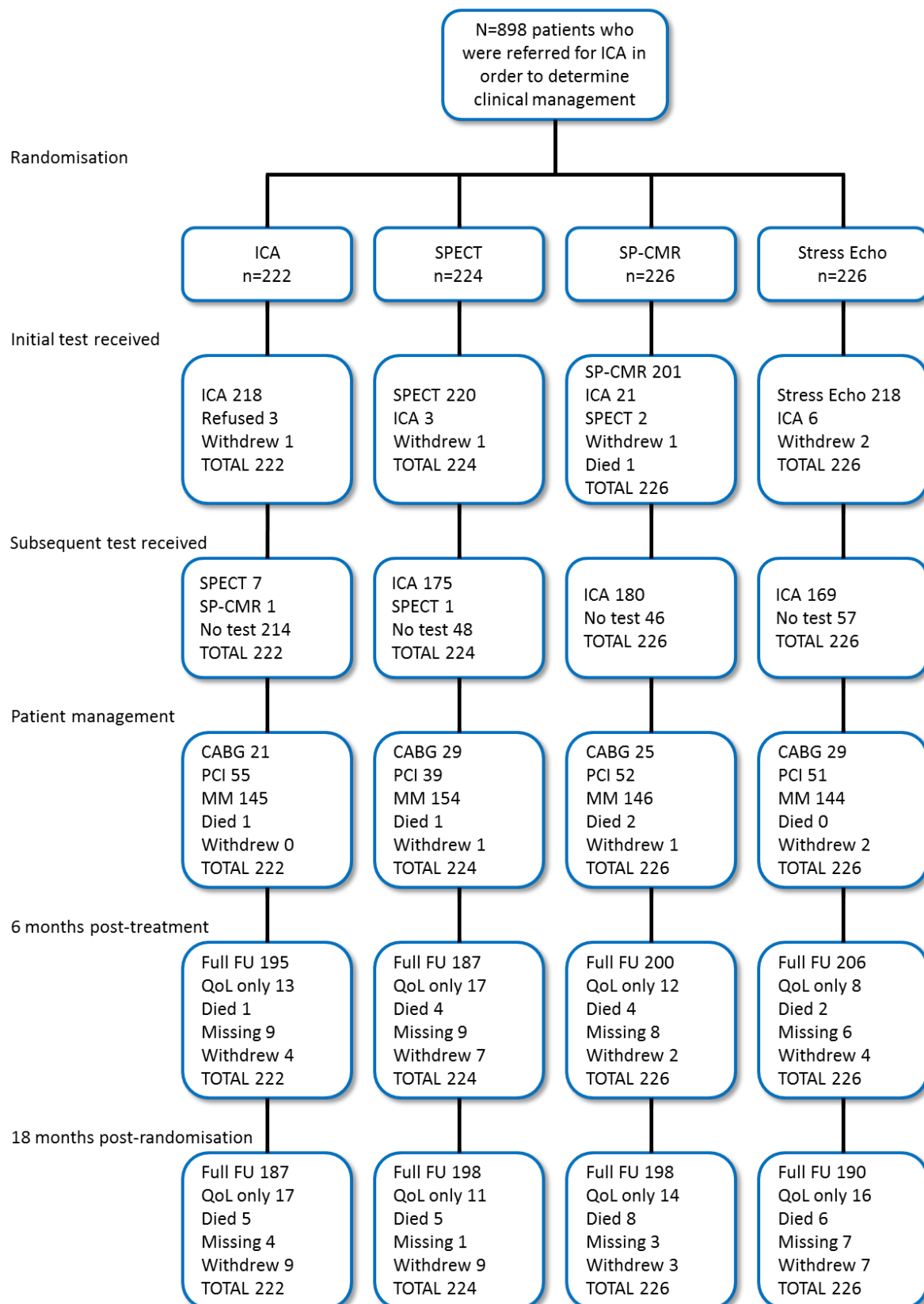


Figure 6 Flow of patients through the trial period

Source: Sharples et al. (2007)

CABG = coronary artery bypass graft; Echo = echocardiogram; FU = follow-up; ICA = invasive coronary angiography; MM = medical management; PCI = percutaneous coronary intervention, QoL = quality of life; SP-CMR = stress perfusion cardiac magnetic resonance imaging; SPECT = single-photon emission computed tomography

PATIENT MANAGEMENT

Table 22 summarises patient management decisions on the basis of the initial and subsequent diagnostic tests. However, the decision for surgery (CABG/PCI) was made on the basis of the ICA result; patients with positive non-invasive imaging results who did not have CAD confirmed by ICA were all medically managed. Four patients died before management was decided. Of the patients randomised to non-invasive imaging, 80%, 78% and 75% of those that had SP-CMR, SPECT and stress Echo, respectively, were referred on for an ICA. Thus, between 20% and 25% of patients undergoing non-invasive imaging were deemed to not require further diagnostic tests.

Most of those not referred for an ICA had negative non-invasive imaging test results; only 58%, 51% and 49% of patients were referred after receiving a negative SP-CMR, SPECT and stress Echo result, respectively. However, 52%, 31% and 48% of SP-CMR, SPECT and stress Echo negative patients, respectively, had positive angiograms. For patients who had a positive non-invasive imaging test, the diagnosis was confirmed by ICA (50% stenosis in the left anterior descending coronary artery or 70% stenosis in any other major vessel) in 89%, 83% and 84% of SP-CMR, SPECT and stress Echo patients, respectively.

Table 22 Patient management according to non-invasive imaging and ICA test results

	CABG	PCI	MM	Died
SP-CMR group				
Initial SP-CMR result positive (n=90)				
ICA result: Positive (n=74)	20	29	25	
Negative (n=9)			9	
Declined (n=1)			1	
Not referred (n=6)			5	1
Initial SP-CMR result negative (n=86)				
ICA result: Positive (n=26)	1	15	10	
Negative (n=24)			24	
Not referred (n=36)			36	
Initial SP-CMR result equivocal (n=15)				
ICA result: Positive (n=7)	1	2	4	
Negative (n=7)			7	
Not referred (n=1)			1	
Initial SP-CMR test failed (n=10)				
ICA result: Positive (n=7)	1	2	4	
Negative (n=3)			3	
Initial SP-CMR test not done (n=25)				
ICA result: Positive (n=9)	2	4	3	
Negative (n=12)			12	
Not referred (n=4)			3	1

	CABG	PCI	MM	Died
SPECT group				
Initial SPECT result positive (n=121)				
ICA result: Positive (n=96)	26	29	41	
Negative (n=20)			20	
Declined (n=1)			1	
Not referred (n=4)			3	1
Initial SPECT result negative (n=90)				
ICA result: Positive (n=14)	1	8	5	
Negative (n=31)			31	
Declined (n=1)			1	
Not referred (n=44)			44	
Initial SPECT result equivocal (n=9)				
ICA result: Positive (n=2)	1	1		
Negative (n=7)			7	
Initial SPECT test not done (n=4)				
ICA result: Positive (n=2)	1	1		
Negative (n=1)			1	
Not referred (n=1)			1	
Stress Echo group				
Initial stress Echo result positive (n=103)				
ICA result: Positive (n=85)	24	36	25	
Negative (n=15)			15	
Equivocal (n=1)			1	
Not referred (n=2)			2	
Initial stress Echo result negative (n=100)				
ICA result: Positive (n=23)	2	12	9	
Negative (n=25)			25	
Declined (n=1)			1	
Not referred (n=51)			51	
Initial stress Echo result equivocal (n=7)				
ICA result: Positive (n=3)	1	2		
Negative (n=2)			2	
Not referred (n=2)			2	
Initial stress Echo test failed (n=8)				
ICA result: Positive (n=4)	1		3	
Negative (n=3)			3	
Not referred (n=1)			1	

		CABG	PCI	MM	Died
Initial SP-CMR test not done (n=8)					
ICA result:	Positive (n=3)	1	1	1	
	Negative (n=3)			3	
	Not referred (n=2)			2	1

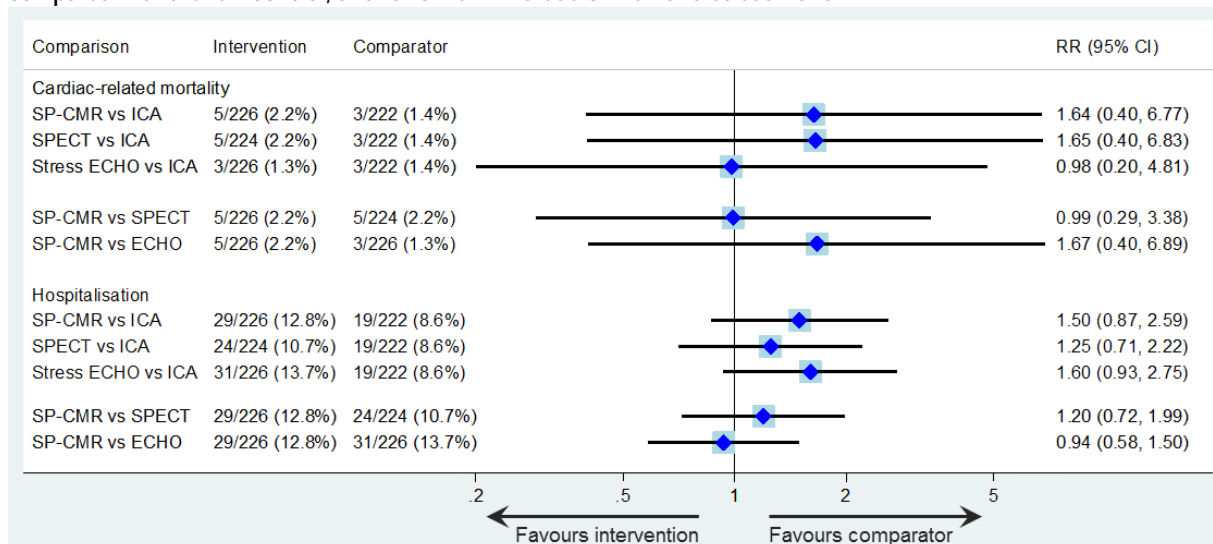
CABG = coronary artery bypass graft; Echo = echocardiogram; ICA = invasive coronary angiography; MM = medical management; PCI = percutaneous coronary intervention; SP-CMR = stress perfusion cardiac magnetic resonance imaging; SPECT = single-photon emission computed tomography

CVD-RELATED MORBIDITY AND MORTALITY RATES

The number of patients who were hospitalised or died during the 18-month follow-up period were recorded for each group (Table 154 in Appendix D); there were 24 deaths evenly distributed among the four groups (log-rank test $p=0.829$). Eight of these were non-cardiac-related deaths, mostly due to malignancies or respiratory conditions. Non-fatal events occurred in as few as 8.6% of patients in the ICA group and as many as 13.7% of patients in the stress Echo group. The most common non-fatal event was hospital admissions for chest pain.

The number of patients who were hospitalised or died from cardiac-related events during the 18-month follow-up period were compared between groups (Figure 7). There were no statistically significant differences between the groups in the proportion of patients hospitalised, although there was a trend favouring ICA over non-invasive imaging groups, as less patients were hospitalised in the ICA group. There was a similar trend favouring SPECT over SP-CMR. The effect of different diagnostic tests on mortality rates could not be determined due to the very broad 95% CIs, which can be attributed to the small number of patients who died.

Figure 7 RR of cardiac-related mortality and of being hospitalised after SP-CMR, SPECT and stress Echo compared with the ICA control, and for SP-CMR versus SPECT and stress Echo



CI = confidence interval; ECHO = echocardiogram; ICA = invasive coronary angiography; RR = relative risk; SP-CMR = stress perfusion cardiac magnetic resonance imaging; SPECT = single-photon emission computed tomography

HEALTH-RELATED QUALITY OF LIFE

All patients were asked to complete three quality of life (QoL) questionnaires at baseline, 6-months post-treatment and 18-months post-randomisation. The generic Short Form 36 (SF-36) has eight dimensions, but they were combined into two composite scales representing physical functioning (PCS) and mental functioning (MCS). The Seattle Angina Questionnaire (SAQ) is disease-specific and the authors reported that it was the most sensitive of the three QoL instruments used. The EuroQoL

EQ-5D measures the value that the population attributes to life in a given health state and was used to estimate quality-adjusted survival.

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

Using the SF36, all groups had improved PCS at both 6- and 18-month assessments, but there were no significant differences between the PCS scores for the intervention and control groups and their CIs were within 3.8 points (Table 155 in Appendix D). A difference of 5 points is considered to be 'clinically and socially relevant'. All groups significantly improved their MCS scores by approximately 3–5 points ($p < 0.01$ for all groups) but there were no clinically relevant differences between the groups at either follow-up period.

The SAQ can be divided into 5 dimensions or scales: anginal frequency, anginal stability, disease perception, exertional capacity, and treatment satisfaction. With one exception all groups significantly improved their SAQ scores in all dimensions at both follow-up periods; the treatment satisfaction score did not change significantly for the ICA group at 6-months post-treatment (Table 156 in Appendix D). However, there were no significant or clinically relevant (at least 10 points) differences between the groups at either assessment.

There was very little difference between the groups in the mean EQ-5D score and no differences were significant (Table 157 in Appendix D). When adjusted for baseline, all CIs lay within 0.07. Any change in EQ-5D of less than 0.05 has been described as 'descriptively irrelevant'.

In summary, there were no statistically or clinically relevant differences between the four groups for any of the QoL measures used in this trial. Thus, there is no benefit to the patient's QoL when using SP-CMR to diagnose CAD and identify obstructive stenoses when compared with SPECT, stress Echo or ICA.

TOTAL EXERCISE TIME USING A MODIFIED BRUCE PROTOCOL TREADMILL TEST

The primary *a priori* outcome for this trial was the total exercise time using a modified Bruce protocol treadmill test at 18-months post-randomisation. Although 773 patients completed the exercise test, it was completed according to the protocol in only 771 cases, and results from these patients were reported. Clinical significance was defined *a priori* as the CI for mean difference from ICA lying within 1 minute. Exercise tests were also performed at 6-month follow-up.

The differences between SP-CMR and ICA were statistically significant, favouring ICA at both 6- and 18-month follow-ups, and there was also a significant difference favouring ICA over stress Echo at 6-month follow-up (Table 23). However, the differences were not clinically significant and the CIs were very wide.

Table 23 Total exercise time (minutes) for non-invasive imaging compared with ICA

Comparison	Intervention	Control	Mean difference (95%CI) ^a	p-value
Mean (SD) at baseline				NR
SP-CMR vs ICA	10.43 (4.43)	11.29 (4.56)	NR	
SPECT vs ICA	10.46 (4.41)	11.29 (4.56)	NR	
Stress Echo vs ICA	10.89 (4.36)	11.29 (4.56)	NR	

Comparison	Intervention	Control	Mean difference (95%CI) ^a	p-value
Mean (SD) at 6-month FU				0.010
SP-CMR vs ICA	10.87 (4.33)	12.26 (4.16)	0.62 (0.08 to 1.16), p <0.01	
SPECT vs ICA	11.67 (3.98)	12.26 (4.16)	-0.06 (-0.61 to 0.48)	
Stress Echo vs ICA	11.30 (4.48)	12.26 (4.16)	0.63 (0.09 to 1.16), p <0.01	
Mean (SD) at 18-month FU				0.165
SP-CMR vs ICA	11.24 (4.40)	12.36 (4.09)	0.58 (0.01 to 1.14), p <0.01	
SPECT vs ICA	11.61 (4.29)	12.36 (4.09)	0.14 (-0.42 to 0.71)	
Stress Echo vs ICA	11.67 (4.05)	12.36 (4.09)	0.44 (-0.13 to 1.01)	

^a Adjusted for baseline, positive values favour ICA.

CI = confidence interval; Echo = echocardiogram; FU = follow-up; ICA = invasive coronary angiography; NR = not reported; SD = standard deviation; SP-CMR = stress perfusion cardiac magnetic resonance imaging; SPECT = single-photon emission computed tomography

At both baseline and the 18-month follow-up point, there was no significant difference between the four groups in the proportion of people experiencing angina during exercise testing (Table 158 in Appendix D). However, there were some statistically significant differences at 6-months post-treatment, with the proportion of patients who had angina during exercise testing ranging from 23% for the ICA group to 35% for the SP-CMR group. In addition, the time to angina was significantly different among the four groups (p=0.004).

Exercise times were also compared between patients who did or did not have a revascularisation procedure (Table 159 in Appendix D). There were no significant differences in total exercise time at either follow-up point between SP-CMR and ICA or SPECT and ICA in patients who had or had not undergone revascularisation; however, revascularised patients who were assigned to stress Echo had both statistically and clinically significantly shorter exercise time than those allocated to ICA at both 6-month (both CABG and PCI patients) and 18-month follow-ups (CABG only).

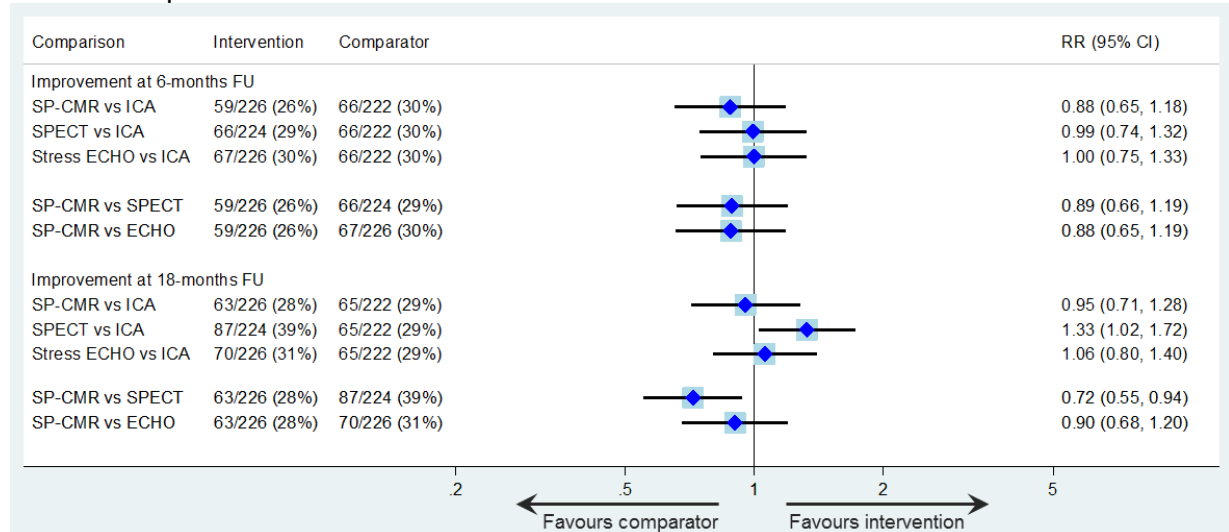
In summary, the difference in exercise time between SP-CMR and ICA was statistically significant, favouring ICA at both 6- and 18-month follow-ups. The SP-CMR group also had a significantly higher proportion of patients with angina during exercise compared with the ICA group, and the time to angina was significantly shorter. However, when revascularised and medically managed patients were analysed separately, CABG patients who had been allocated to SP-CMR stopped the exercise test on average more than 1 minute earlier than those allocated to ICA at both 6- and 18-month follow-ups, although this was not statistically significant. Patients allocated to the stress Echo groups also had some outcomes that were inferior to ICA. Thus, diagnosis of obstructive stenoses using SPECT and ICA appear to result in greater improvements in the ability to exercise compared with patients diagnosed by either SP-CMR or ICA.

CHANGE IN CANADIAN CARDIOVASCULAR SOCIETY (CCS) CLASS

Overall, all groups had a significant improvement in CCS class (McNemar-Bowker test within each group, all p <0.001). At least a two-class improvement in CCS score has been frequently used in trials of angina treatments to define a clinically significant improvement. When the proportion of patients experiencing a clinically significant improvement in each of the non-invasive imaging groups was compared with the ICA control group, there were no significant differences, with the exception of SPECT versus ICA after 18-months post-randomisation; the SPECT group had a significantly greater proportion of patients achieving clinically significant improvement in angina than the ICA group (Figure 8).

Among patients who were revascularised, clinically significant improvement in CCS class was more likely in the non-invasive groups, although this was only statistically significant for SPECT at both follow-up time points (Figure 43 in Appendix D). In the patients who were medically managed, the results tended to favour ICA but there were no statistically significant differences.

Figure 8 RR of improving in CCS angina class (≥ 2 class decrease from baseline) for SP-CMR, SPECT and stress Echo compared with the ICA control, and for SP-CMR versus SPECT and stress Echo, at 6-month and 18-month follow-ups



CCS = Canadian Cardiovascular Society; CI = confidence interval; ECHO = echocardiogram; FU = follow-up; ICA = invasive coronary angiography; SP-CMR = stress perfusion cardiac magnetic resonance imaging; RR = relative risk; SPECT = single-photon emission computed tomography.

IS IT SAFE?

Summary – What is the safety of SP-CMR imaging in the diagnosis of CAD in patients presenting with symptoms consistent with IHD?

Even though most studies excluded patients with known contraindications for MRI (such as claustrophobia), 1% of patients suffered from unknown claustrophobia and could not complete the test. In addition, 3 patients were not able to have the test because they were too large to fit in the MRI machine. Only 4 studies reported on AEs associated with the gadolinium-based contrast agent; 37 (0.3%) patients had mild allergic reactions after it was injected.

Most AEs were attributable to the use of a stressor. By far the greatest number of AEs were observed when adenosine was used as the stressor compared with dobutamine, dipyridamole and nicorandil. Overall, 33% of patients had mild AEs, such as breathlessness, flushing, headache, chest pain or transient AV block, after adenosine administration; and 9% had serious AEs, such as severe angina pectoris, anaphylaxis, bronchospasm or serious ventricular arrhythmias. In comparison, only 1.2% of patients experienced serious AEs, such as sustained ventricular tachycardia, ventricular fibrillation, severe hypotension, or severe hypertension when dobutamine was used as the stressor. Only 1 patient had a serious AE when dipyridamole was used as the stressor; the patient complained of anterior chest pain during the injection of the agent and administration was suspended at 80% of dose. No AEs were reported when nicorandil was used as the stressor.

Limited non-comparative level IV evidence (case series with either post-test or pre-test/post-test outcomes) was identified in the literature search to assess the safety of CMR. One SR of level IV studies reported on the safety of non-invasive imaging modalities in women (Dolor et al. 2012). An additional 48 level IV studies reported on the safety of SP-CMR, 25 in patients with known or suspected CAD and 23 in patients with suspected CAD. The majority of the studies (35/48) used adenosine as the stress agent, 1 used either adenosine or dobutamine, 4 dobutamine, 6 dipyridamole, 1 nitroglycerin and 1 nicorandil. The characteristics of the included studies are summarised in Table 142 in Appendix C and the extracted safety data is reported in Table 160 and Table 161 in Appendix E.

The overall quality of the evidence provided by the level IV studies in assessing the safety of SP-CMR with/without LGE was assessed using GRADE (Guyatt et al. 2011), and the results are presented in Table 176 and Table 177 in Appendix G. As the evidence-base consisted of non-comparative data, it was considered to be of very low quality for all outcomes (GRADE ⊕○○○).

The evidence-base involves mostly patients suspected of having CAD and the testing is conducted in settings applicable for use of SP-CMR in Australia.

ADVERSE EVENTS ARISING FROM CMR PROCEDURE

The AEs that were reported in the 48 case series identified by the literature search were categorised according to the cause of the AE (Table 24). Some AEs were specific to CMR, such as to the MRI procedure itself or the contrast agent used. Other AEs were not specific to CMR; these were related to catheterisation or the stress agent used and would also occur with other procedures that used these agents.

Even though most studies excluded patients with known contraindications for MRI, such as claustrophobia, 1% of patients from 48 studies still suffered from claustrophobia and could not complete the test. In addition, 3 patients were not able to have the test because they were too large to fit in the MRI machine. Only 4 studies reported on AEs associated with the gadolinium-based contrast agent; 37 (0.3%) patients had mild allergic reactions after it was injected.

Four different stress agents were used in the included studies. By far the greatest number of AEs were observed when adenosine was used as the stressor. The AEs experienced by the patients in these studies are outlined in Table 24.

Table 24 AEs reported in case series that were directly related to the SP-CMR procedure or the stress agent used

Procedure	AEs in patients with known and suspected CAD	AEs in patients with suspected CAD	Overall AEs
CMR	11/4,043 (0.3%; k=24) had claustrophobia	44/1,658 (2.7%; k=23) had claustrophobia 9/1,658 (0.5%; k=23) were uncomfortable 1 patient had anxiety 1 patient had discomfort 7 patients refused 2 nd CMR scan 3/1,658 (0.2%) were too large for scanner	55/5,701 (1.0%) k=47
Gadolinium-based contrast agent	37/11,002 (0.3%; k=3) had mild allergic reactions to contrast	0/61 (0%; k=1) had any AEs	37/11,063 (0.3%) k=4
Catheterisation	2/4,043 (0.05%; k=24) developed haematomas or bruising at the site of the intravenous line	3/1,658 (0.2%; k=23) patients could not be catheterised 1 patient refused IV line 2 patients had inaccessible veins	
Adenosine stress	273/967 (29%; k=6) had mild AEs 25/967 (3%; k=6) had moderate AEs 16/2,241 (0.7%; k=21) had serious AEs	83/110 (75%; k=2) had mild AEs 15/1,079 (1%; k=14) had serious AEs	356/1,077 (33%) k=8 31/3,320 (9.3%) k=35
Dobutamine stress	15/1,520 (1%; k=2) had serious AEs	5/139 (4%; k=2) had serious AEs	20/1,659 (1.2%) k=4
Adenosine or dobutamine stress	559/10,228 (5%; k=1) had mild AEs 0/10,228 (k=1) had moderate AEs 7/10,228 (0.07%; k=1) had serious AEs: 4 patients during adenosine stress 3 patients during dobutamine stress	-	
Dipyridamole stress	1/230 (0.4%; k=3) had serious AEs	0/80 (0%; k=2) had serious AEs	1/310 (0.3%) k=5
Nicorandil stress	0/50 (0%; k=1) had any AEs	-	

AE = adverse event; CAD = coronary artery disease; CMR = cardiac magnetic resonance imaging; IV = intravenous; k = number of studies; SP-CMR = stress perfusion cardiac magnetic resonance imaging

SAFETY OF SP-CMR, STRESS ECHO, SPECT AND CTCA IN WOMEN COMPARED WITH MEN

Dolor et al. (2012) reported on the safety of various imaging modalities in women compared with men. The authors identified 13 studies with safety data on the risks to women undergoing non-invasive procedures, of which 7 reported on the differences in AEs and risk between men and women. The authors concluded that the available evidence was not sufficient to conclude whether safety concerns, risks or radiation exposure associated with different non-invasive imaging modalities differed significantly between women and men.

B2 LINKED EVIDENCE APPROACH (POPULATION 1)

B2.1 BASIS FOR LINKED EVIDENCE

Due to the limited amount of direct evidence identified, a linked evidence approach was also taken.

B2.2 STEPS FOR LINKED ANALYSIS

To construct a linked evidence analysis, different evidence components are required:

- consideration of the diagnostic performance and clinical validity of the investigative medical service (Sections B3a and B4a);
- consideration of the clinical utility of the investigative medical service in terms of impact of positive versus negative test results on patient management, the contribution and clinical importance of false negatives versus false positives, and the direct impact of each therapeutic model service option on health outcomes (Section B5a); and
- consideration of the relative safety of performing the investigative service, both the immediate safety issues of directly performing the test and 'flow on' safety issues that arise as a result of conducting the investigative service (Section B7a);
- conclusions linking these steps are made in Section B8a.

B3A DIAGNOSTIC PERFORMANCE (POPULATION 1)

B3A.1 REFERENCE STANDARD

ICA is considered to be the gold standard in the diagnosis of CAD, but it is only recommended in stable patients with suspected CAD if non-invasive testing provides inadequate information to determine the likelihood of a cardiac event (Montalescot et al. 2013).

ICA was performed using standard techniques, such as the Judkins technique, and the severity of coronary stenoses was determined quantitatively. Significant CAD was defined as $\geq 50\%$ diameter stenosis (DS) and severe CAD was defined as $\geq 70\%$ DS. Several studies used fractional flow reserve (FFR) as the reference standard; this is performed during ICA on stenoses with a visual diameter of $\geq 30\%$ using a wire that can simultaneously measure pressure and flow. The cut-off for diagnosing CAD using FFR was either <0.75 or <0.8 , with the former being more-severe disease.

B3A.2 RESULTS OF LITERATURE SEARCH

The details of the literature sources and search strategies are provided at the beginning of Section B.

The CECaT trial, which provided the direct evidence discussed in Section B1, also reported on the diagnostic accuracy of SP-CMR compared with SPECT and stress Echo, using ICA as the reference standard in patients with known or suspected CAD.

In addition to the RCT, 10 SRs were identified that compared the diagnostic accuracy of SP-CMR with ICA. However, all these SRs included studies that enrolled patients with both known and suspected CAD. Thus, 36 diagnostic accuracy studies that enrolled only patients suspected of having CAD were also included to inform on the diagnostic accuracy of SP-CMR with/without LGE compared with ICA.

To compare SP-CMR with CTCA, SPECT, stress Echo and/or exercise ECG, 29 SRs were identified that compared these modalities with ICA. These studies were identified by searching the PubMed Health database for relevant reviews published since 2007 using the comparator and CAD as search terms. Only 2 SRs were identified that investigated the accuracy of exercise ECG compared with ICA. One of these SRs (Banerjee et al. 2012) did not report the sensitivity and specificity of the test and was excluded. However, two additional SRs were identified from the reference lists that were published in 1989 and 1999 (Gianrossi et al. 1989; Kwok et al. 1999). Most of the SRs included studies that enrolled patients with both suspected and known CAD; only 7 included only studies enrolling patients with suspected CAD. A full profile of each included study is given in Appendix C.

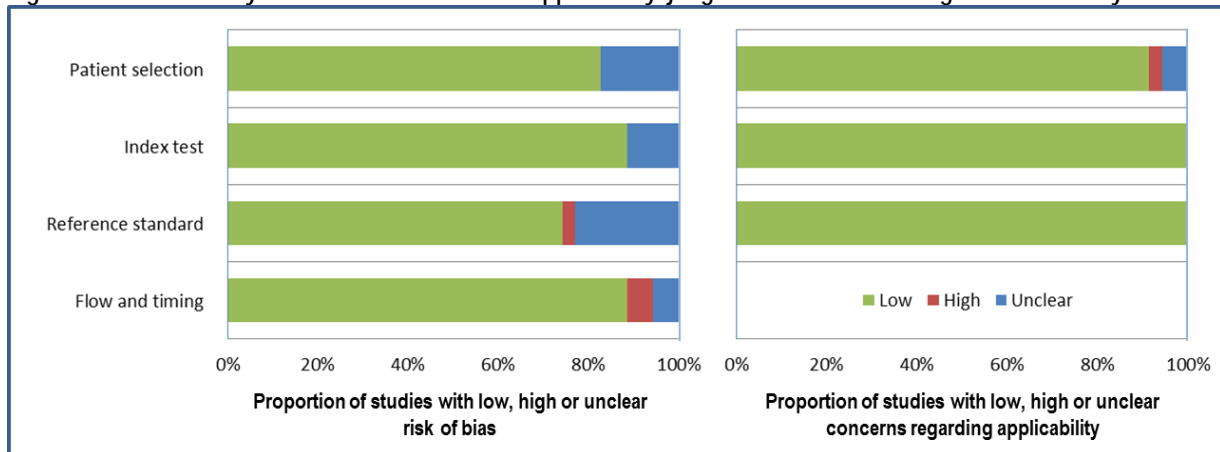
B3A.3 RISK OF BIAS ASSESSMENT

The quality of the diagnostic evidence provided in the CECaT trial was assessed using QUADAS-2 (Whiting et al. 2011). The study had a high risk of bias and high applicability issues with respect to patient selection, as patients with known or suspected CAD were enrolled. The risk of bias for this study is listed in Table 172 in Appendix F.

The risk of bias for the 35 studies that reported on the diagnostic accuracy of SP-CMR compared with ICA was evaluated using QUADAS-2 (Whiting et al. 2011) and a summary of the risk of bias is given in Figure 9. The risk of bias for each of the individual studies is listed in Table 172 in Appendix F. individual studies that had at least two domains with 😊 (indicating a low risk of bias) and no domains with ☹️ (indicating a high risk of bias) out of the four risk of bias domains were defined as having a low risk of bias; studies with three or four domains with ? (indicating that risk of bias could not be determined) were considered to have an unclear risk of bias and studies with at least two domains with ☹️ were defined as having a high risk of bias. Overall, 31 studies had a low risk of bias, 3 studies an unclear risk, 1 had some risk and 1 study had a high risk. Three studies had applicability issues with respect to the patients included in the study. The retrospective study by Husser et al. (2009) included patients suspected of having CAD, but 27% had had a previous MI, and 16% and 11%

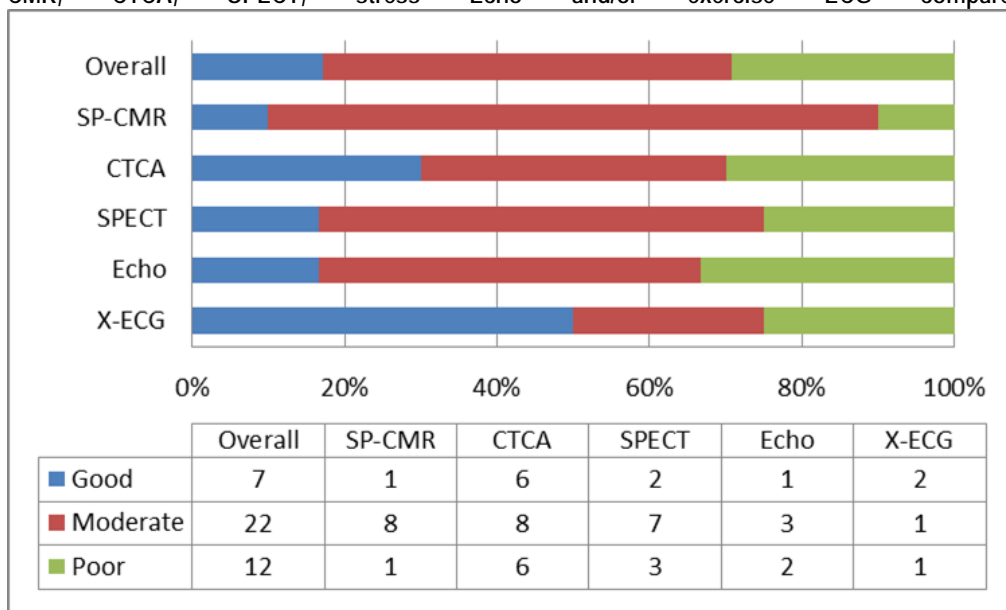
had had a PCI or CABG, respectively. These patients were likely to have a higher PTP of having CAD compared with the patients included in the other studies. The applicability of the patient population could not be evaluated for two studies, as the patient characteristics were not described (Regenfus et al. 2003; Sakuma et al. 2005).

Figure 9 Summary of the risk of bias and applicability judgments for the 36 diagnostic accuracy studies



The AMSTAR checklist (Shea et al. 2007) was used to assess the risk of bias for the 41 SRs that reported on the diagnostic accuracy of SP-CMR (n=10), CTCA (n=21), SPECT (n=12), stress Echo (n=6) and/or exercise ECG (n=4) compared with ICA. SRs that scored 0–3/11 were considered to be of poor quality with a high risk of bias, those that scored 4–6/11 were of moderate quality with an intermediate risk of bias, and a score of 7–11/11 was considered to be a good-quality SR with a low risk of bias. A summary of quality of the SRs reporting on each comparator is given in Figure 10, and the quality score plus the risk of bias for the individual SRs are listed in Table 143 in Appendix C. Overall, only 7 (17%) SRs were of good quality with a low risk of bias, 22 (54%) were of moderate quality with an intermediate risk of bias, and the remaining 12 (29%) were of poor quality with a high risk of bias. There were sufficient SRs of good or moderate quality to enable indirect comparisons between the different imaging modalities using ICA as the reference standard.

Figure 10 The proportion of good-, moderate- and poor-quality SRs reporting on the diagnostic accuracy of SP-CMR, CTCA, SPECT, stress Echo and/or exercise ECG compared with ICA.



CTCA = computed tomography coronary angiography; Echo = echocardiography; ICA = invasive coronary angiography; SP-CMR = stress perfusion cardiac magnetic resonance imaging; SPECT = single-photon emission computed tomography; SR = systematic review; X-ECG = exercise electrocardiogram

B3A.4 CHARACTERISTICS OF THE EVIDENCE-BASE

SRS OF DIAGNOSTIC ACCURACY STUDIES COMPARING SP-CMR WITH ICA

The 10 SRs that compared the accuracy of SP-CMR with the ICA reference standard were published between 2007 and 2014 and most included patients with both known and suspected CAD. One SR included only studies that reported on women suspected of having CAD, and two SRs performed a meta-analysis on the subgroup of included studies that enrolled only patients suspected of having CAD. Each SR included between 4 and 30 studies out of a total of 65 in their meta-analyses. Of these 65 studies, 22 met our inclusion criteria and were included in our meta-analysis. A list of all 65 studies and in which SRs they were included is given in Table 188 in Appendix K.

SRS OF DIAGNOSTIC ACCURACY STUDIES COMPARING CTCA WITH ICA

The accuracy of CTCA compared with ICA was assessed in 21 SRs published between 2007 and 2014. Of these, 7 included only patients suspected of having CAD, and 1 included only studies reporting on women. The number of studies included in the meta-analysis varied from 5 to 45 and the prevalence of CAD varied from 39% to 72% in the 15 SRs that reported the prevalence or provided data to enable its calculation.

SRS OF DIAGNOSTIC ACCURACY STUDIES COMPARING SPECT WITH ICA

The 12 SRs that compared the accuracy of SPECT with ICA were published between 2007 and 2014 and included between 6 and 103 studies, most included studies enrolling patients with known or suspected CAD. Three SRs reported on specific patient populations; 1 included 14 studies reporting on women (Dolor et al. 2012), 1 included 6 studies that investigated the use of both SP-CMR and SPECT compared with ICA in the same patients (Chen et al. 2014), and a third included 13 studies that excluded patients with known CAD (Zhou et al. 2014). These 3 SRs had the lowest CAD prevalence rates (41%–44%) compared with 50%–70% in 4 of the 9 remaining SRs for which the prevalence rate could be determined. They also had the lowest pooled sensitivity values (81%, 70% and 77%, respectively) compared with 82%–89% for the other 9 SRs.

SRS OF DIAGNOSTIC ACCURACY STUDIES COMPARING ECHO WITH ICA

Six SRs published between 2007 and 2013 compared the accuracy of Echo compared with ICA and included between 10 and 15 studies, except 1 SR that reanalysed the data from 226 studies included in 11 SRs (Heijenbrok-Kal, Fleischmann & Hunink 2007). Two SRs included only studies reporting on the accuracy of Echo versus ICA in women (Dolor et al. 2012; Geleijnse et al. 2007), 1 of which also had a separate analysis in men (Geleijnse et al. 2007). All SRs included studies that defined an ICA cut-off of at least 50% DS for the diagnosis of significant CAD, and only 1 performed separate meta-analyses for ICA cut-offs of 50% and 70% DS.

The prevalence of CAD was lowest in the two meta-analyses on women (41% and 43%) and highest in the meta-analysis on men (73%). In the remaining 2 SRs for which the prevalence rate could be determined, 48% and 66% of included patients had CAD.

SRS OF DIAGNOSTIC ACCURACY STUDIES COMPARING EXERCISE ECG WITH ICA

Four SRs published between 1989 and 2012 assessed the accuracy of exercise ECG compared with ICA. The commonly cited SR by Gianrossi et al. (1989) included 147 studies but did not report the prevalence rate. The SRs by Dolor et al. (2012) and Kwok et al. (1999) included 29 and 19 studies, respectively, that enrolled only women and reported a prevalence of CAD of 38%–41%.

STUDIES REPORTING THE DIAGNOSTIC ACCURACY OF SP-CMR WITH/WITHOUT LGE COMPARED WITH ICA

The study profile of the CECaT trial (Sharples et al. 2007) and characteristics of the enrolled patients have been discussed in Section B1.4. This study used SP-CMR without LGE.

We identified 35 diagnostic accuracy studies that met our inclusion criteria and included only patients suspected of having CAD; 22 studies were included in at least 1 SR comparing SP-CMR with ICA, 9 studies published between 2003 and 2013 had not been included in any of the SRs, and 4 studies were published after the most recent SR. All these studies used ICA as the reference standard although the cut-offs varied, but only 19 studies included LGE in the CMR protocol (Table 143 in Appendix C).

The patient populations also varied between studies. Seven studies reported on patients with an intermediate PTP of having CAD, 6 studies reported on patients with chest pain and 2 studies included only women. The study by Klem et al. (2008) included only women suspected of having CAD, but a proportion of the women were also included in the earlier mixed-gender study by Klem et al. (2006). Thus, the data from Klem et al. (2008) has only been included for subgroup analysis of accuracy in women.

The mean prevalence of CAD in studies enrolling patients suspected of having CAD was 55% (range 13%–79%; k=20) for an ICA cut-off of $\geq 50\%$ DS and 46% (range 14%–72%; k=14) for $\geq 70\%$ DS. In the studies enrolling patients with chest pain, the mean prevalence of CAD was 47% (range 13%–73%; k=4) for $\geq 50\%$ DS and 52% (range 32%–72%; k=4) for $\geq 70\%$ DS. Counterintuitively, in studies enrolling only patients with an intermediate PTP of having CAD, the mean prevalence was lower (30%, range 28%–60%; k=3) in studies using an ICA cut-off of $\geq 50\%$ DS than in those studies using a more stringent cut-off of $\geq 70\%$ DS (41%, range 38%–51%; k=3). However, this is likely to be due to the small number of studies in these comparisons.

Seven studies had high prevalence rates above 60%, 5 used an ICA cut-off of 50% DS and two used 70% DS. The reason for the higher rate could not be determined in 2 studies (Antonio et al. 2007; Arnold et al. 2010). The other 5 studies included patients likely to have an increased risk of having CAD due to: previous PCI or MI (Cheng et al. 2007; Husser et al. 2009), NYHA class III heart failure (Schwitter et al. 2001), an intermediate to high risk for a cardiovascular event according to the PROCAM (Assmann, Cullen & Schulte 2002) or Framingham (Wilson et al. 1998) risk scores (Walcher et al. 2013), myocardial ischaemia diagnosed by exercise ECG and/or perfusion SPECT (Bernhardt et al. 2007).

On average 35% of the patients were women (range 8–100%) and studies with fewer women tended towards higher CAD prevalence rates. The 9 studies that included at least 40% women had a lower mean prevalence rate (41%; range 13%–73%), compared with 18 studies that included less than 40% women (54%; range 31%–79%).

B3A.5 OUTCOME MEASURES AND ANALYSIS

To assess the diagnostic accuracy of SP-CMR with/without LGE, studies were only included if they provided data that could be extracted into a classic 2 x 2 table (Table 25), in which the results of the index test or the comparator were cross-classified against the results of the reference standard (Armitage, Berry & Matthews 2002; Deeks 2001), and Bayes' Theorem was applied:

Table 25 Diagnostic accuracy 2 x 2 table for SP-CMR with/without LGE compared with the ICA reference standard

		Reference standard (ICA)		
		Disease +	Disease -	
Index test (SP-CMR)	Test +	true positive	false positive	Total test positive
	Test -	false negative	true negative	Total test negative
		Total with stenosis	Total without stenosis	

ICA = invasive coronary angiography; LGE = late gadolinium enhancement; SP-CMR = stress perfusion cardiac magnetic resonance imaging

PRIMARY MEASURES

Test sensitivity was calculated as the proportion of people with stenoses either $\geq 50\%$ or $\geq 70\%$ diameter (as determined by the reference standard) who had a PD detected by SP-CMR with/without LGE:

Sensitivity (true positive rate) = number with true positive result / total with MTB or NTM infections

Test specificity was calculated as the proportion of people without stenoses (as determined by the reference standard) who did not have a PD detectable by SP-CMR with/without LGE:

Specificity (true negative rate) = number with true negative result / total without MTB or NTM infections

The 95%CI was calculated by exact binomial methods.

Positive and negative likelihood ratios (LR+ and LR-) were also reported. These ratios measure the probability of the test result being true in patients with stenoses compared with those without.

LR+ = sensitivity / 1 - specificity

LR- = 1 - sensitivity / specificity

An LR of 1 means that the test does not provide any useful diagnostic information, whereas LR+ >5 and LR- <0.2 can suggest strong diagnostic ability (MSAC 2005).

SUMMARY MEASURES

Diagnostic test accuracy meta-analysis was undertaken to assess the accuracy of SP-CMR with/without LGE compared with ICA in the diagnosis of CAD using Stata version 13 (StataCorp 2013). Only studies that provided raw (2 x 2) data were included. Summary receiver-operator characteristic (SROC) curves, forest plots and LR scattergrams were generated using the 'midas' command in Stata, which requires a minimum of 4 studies for analysis and calculates summary operating sensitivity and specificity (with confidence and prediction contours in SROC space). Heterogeneity was calculated using the formula $I^2 = 100\% \times (Q - df)/Q$, where Q is Cochran's heterogeneity statistic and df is the degrees of freedom (Higgins et al. 2003). Summary estimates for sensitivity, specificity, LR+ and LR- were also calculated. CIs were computed assuming asymptotic normality after a log transformation for variance parameters and for LR+ and LR-. The post-test probability (PoTP) of having CAD was derived from the PTP and the LRs using the following formula:

$$PoTP = ([PTP / (1 - PTP)] \times LR) / [1 + ([PTP / (1 - PTP)] \times LR)]$$

Subgroup analyses were performed according to ICA cut-off and population subgroups.

B3A.6 RESULTS OF THE SYSTEMATIC LITERATURE REVIEW

IS IT ACCURATE?

Summary – What is the diagnostic accuracy of CMR gadolinium-based stress perfusion and viability imaging in the diagnosis of CAD in patients presenting with symptoms consistent with IHD, with an intermediate PTP of CAD?

Diagnostic accuracy of SP-CMR, SPECT and stress Echo compared with ICA in the CECaT trial

In the CECaT trial SP-CMR was found to be less sensitive and more specific than both SPECT and stress Echo when ICA was used as the reference standard, but the differences were not statistically significant. However, as the proportion of patients who did not have an ICA and were misclassified as true negative could not be determined, the interpretation of the specificity of these tests compared with ICA in this trial was limited.

Diagnostic accuracy of SP-CMR with/without LGE versus ICA

When the accuracy of SP-CMR versus ICA was compared with SP-CMR & LGE versus ICA, there was a slight increase in specificity and a corresponding decrease in sensitivity. These differences were not statistically significant even though the 95% CIs were much narrower when SP-CMR and LGE were combined compared with SP-CMR alone.

There was no difference in the pooled sensitivities and specificities of SP-CMR with/without LGE versus ICA in patients suspected of having CAD compared with patients with chest pain and/or an intermediate PTP of having CAD. However, the sensitivities of these tests were 5%–8% lower when testing only women compared with mixed populations with a mean of 35%–40% being women.

Comparison of SP-CMR with/without LGE, CTCA, SPECT, stress Echo and exercise ECG using ICA as the reference standard

When the pooled sensitivities for the different tests were compared, CTCA was clearly the most sensitive, at 97%. This indicated that only 3% of patients with CAD detectable by ICA would not be diagnosed by CTCA and would not have received further treatment. SP-CMR with/without LGE, SPECT and stress Echo all had similar sensitivities, ranging from 83% to 88%. For these tests 12%–15% of all patients with CAD detectable by ICA would be falsely negative and miss out on potentially beneficial treatment. Exercise ECG was the least sensitive, at 68%. For this test 32% of patients with CAD detectable by ICA would be falsely negative.

The specificities of SP-CMR with/without LGE, CTCA and stress Echo were similar, at between 82% and 86%. This indicates that 14%–18% of patients diagnosed with CAD using the imaging modalities would be misdiagnosed and potentially receive unnecessary invasive treatment. Both SPECT and exercise ECG were less specific, at 77%, with 33% of patients with no CAD being falsely positive and receiving unnecessary treatment.

B3A.6.1 THE CECAT TRIAL

The RCT by Sharples et al. (2007) reported on the diagnostic accuracy of SP-CMR, SPECT and stress Echo compared with ICA in patients with known or suspected CAD. The overall quality of the evidence provided by this trial in assessing the diagnostic accuracy of SP-CMR, SPECT and stress Echo compared with ICA was assessed using GRADE (Guyatt et al. 2011), and the results are presented in Table 178 in Appendix G. There was a serious risk of bias according to the QUADAS-2 checklist (Whiting et al. 2011) for this outcome as not all patients received the reference standard. There was also indirectness due to the inclusion of patients with known CAD in the trial, resulting in the trial population being less applicable to the target population in this assessment. Hence, the evidence-base was considered to be of very low quality for this outcome (GRADE ⊕○○○).

The trial was designed to be pragmatic and reflect the 'real world' situation. Patients were randomised to the first test but any subsequent testing and patient management was left to the discretion of the clinician. Hence, not all patients received both the initial test and the reference

standard. Nearly all patients with positive non-invasive imaging tests were referred for further testing with ICA (93%–98%, depending on test), compared with only 42%–52% of patients with negative non-invasive imaging results. It is likely that the clinicians only referred the patients they considered most likely to have an incorrect non-invasive imaging result. Thus, the proportion of negative tests that were false could be overestimated in this trial. Conversely, if all negative imaging test results (i.e. those that were not confirmed by ICA) are included in the analysis as true negatives, the proportion of false negatives may be underestimated.

The RCT reported the number of equivocal test results and the number of tests not done or not completed (Table 26). Of patients who received both SP-CMR and ICA, 9.5% were equivocal, which was a higher proportion than for SPECT (5.3%) and stress Echo (3.3%). Additionally, 15.5% of all patients allocated to the SP-CMR group did not complete the test, either because it failed or the patient refused or could not undergo the test. This was 9 times higher than for SPECT (1.8%) and more than twice as high as for stress Echo (7.0%).

Table 26 Non-invasive imaging test results compared with ICA in patients from the CECaT trial

Initial test		ICA positive	ICA negative	ICA equivocal	Referred and not done	Not referred / died
SP-CMR N=226	Positive	74	9	0	1	6
	Negative	26	24	0	0	36
	Equivocal	7	7	0	0	1
	Failed / not done	16	15	0	0	4
	Total	123	55	0	1	47
SPECT N=224	Positive	96	20	0	1	4
	Negative	14	31	0	1	44
	Equivocal	2	7	0	0	0
	Failed / not done	2	1	0	0	1
	Total	114	59	0	2	49
Stress Echo N=226	Positive	85	15	1	0	2
	Negative	23	25	0	0	52
	Equivocal	3	2	0	0	2
	Failed / not done	7	6	0	0	3
	Total	118	48	1	0	59

CECaT = Cost-effectiveness of Non-invasive Cardiac Testing (trial); Echo = echocardiography; ICA = invasive coronary angiography; SP-CMR = stress perfusion cardiac magnetic resonance imaging; SPECT = single-photon emission computed tomography.

The sensitivity and specificity were calculated for all patients who had both tests, and the accuracy of SP-CMR was compared with SPECT and stress Echo (Figure 11). SP-CMR was found to be less sensitive and more specific than both SPECT and stress Echo when ICA was used as the reference standard, but the differences were not statistically significant.

An additional analysis included patients with equivocal results (considered positive in the analysis) and/or those who were not referred for ICA. Patients who were not referred for an ICA were included as either true positives or true negatives, according to their non-invasive imaging result. The inclusion of these patients had little effect on the sensitivity of the non-invasive imaging test. However, the specificity was affected by the increase in the false positive rate due to patients with equivocal imaging results being found to not have CAD by ICA. There was also a considerable effect on the specificity when patients who had negative imaging tests and did not have an ICA were

included as true negatives. Thus, it is not possible to determine the true specificity of these tests compared with ICA in this trial, due to the study protocol.

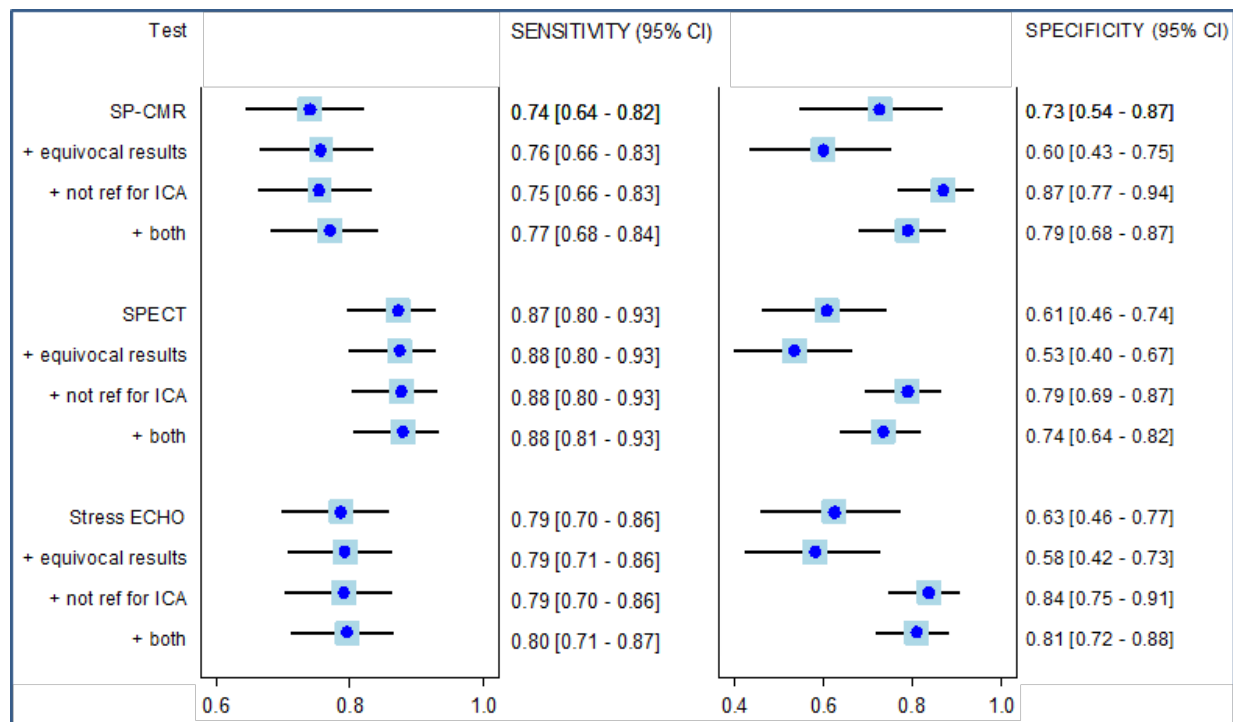


Figure 11 Forest plot showing the sensitivity and specificity of SP-CMR, SPECT and stress Echo versus ICA

+ equivocal results = patients with non-invasive imaging equivocal results included as test positive and those with equivocal ICA results included as test negative; + not ref for ICA = patients not referred for ICA included as either TPs or TNs, according to the non-invasive imaging result; + both = included both patients with equivocal results and patients not referred for ICA; CI = confidence interval; ECHO = echocardiography; ICA = invasive coronary angiography; SP-CMR = stress perfusion cardiac magnetic resonance imaging; SPECT = single-photon emission computed tomography

B3A.6.2 DIAGNOSTIC ACCURACY OF STUDIES ENROLLING ONLY PATIENTS SUSPECTED OF HAVING CAD

Thirty-five studies investigated the diagnostic accuracy of SP-CMR with/without LGE compared with ICA in patients suspected of having CAD, and the 2 x 2 data extracted from these studies is given in Table 162 in Appendix E. Twenty-eight studies reported the results at the patient level, and of these 5 also reported the results at the coronary artery or segment level. The remaining 7 studies only reported results at a coronary artery or segment level.

Although there was some variation in the studies, most (n=32) used quantitative ICA as the reference standard, while 3 studies reported accuracy outcomes using FFR as the reference standard (Groothuis et al. 2013; Kirschbaum et al. 2011; Pereira et al. 2013).

There were 5 different stress agents used, by far the most common being adenosine (24 out of the 35 studies; Table 143 in Appendix C). Twenty-six studies included LGE in the CMR protocol but the LGE results were analysed separately from the SP-CMR results in 4 of these studies and not used in the analysis in 2 studies. Twenty studies combined the SP-CMR and LGE results (SP-CMR & LGE), but three different approaches were taken to analyse the data; the details can be found in Table 143 in Appendix C.

The proposed medical service is for the use of both SP-CMR and LGE to diagnose CAD in patients with symptoms and an intermediate risk of having CAD. However, as the published SRs only compared SP-CMR with ICA, and many of the included studies did not use LGE, separate meta-analyses have been conducted to determine the diagnostic accuracy of SP-CMR with/without LGE, and for LGE alone, compared with ICA. Subgroup analyses were performed according to ICA cut-off

value, as well as for patients with chest pain and/or with intermediate PTP of having CAD, and for women compared with men and/or mixed populations.

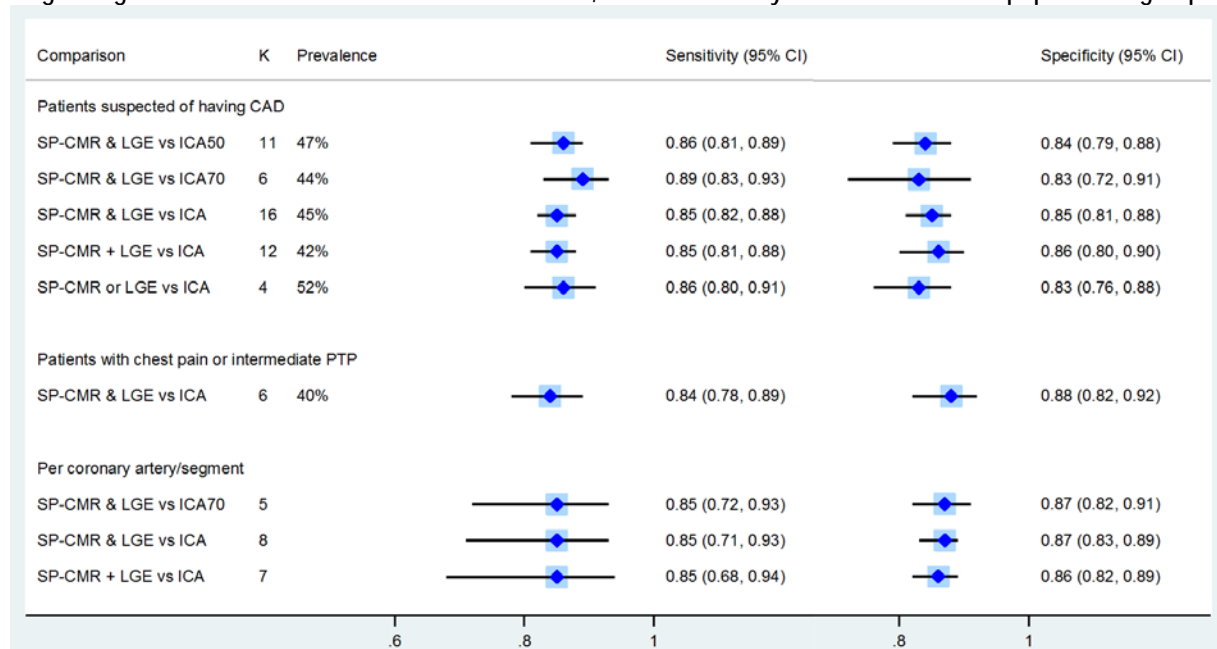
Diagnostic accuracy of SP-CMR & LGE compared with ICA

Overall, 16 studies reported on the diagnostic accuracy of SP-CMR & LGE (the proposed medical service) compared with ICA at the patient level and 8 studies reported accuracy at the coronary artery / segment level. Forest plots showing the sensitivity and specificity for each individual study are shown in Figure 44 and Figure 45 in Appendix H.

The overall quality of the evidence provided by these studies in assessing the diagnostic accuracy of SP-CMR & LGE compared with ICA was assessed using GRADE (Guyatt et al. 2011), and the results are presented in Table 179, Table 180 and Table 183 in Appendix G. For most comparisons there were no overall inconsistencies or publication bias (Figure 60 in Appendix J); hence, the evidence-base was considered to be of high quality (GRADE ⊕⊕⊕⊕). However, for the pooled specificity of SP-CMR & LGE versus ICA 70% DS at the patient level, there was substantial heterogeneity, introducing inconsistency and lowering the quality of evidence to moderate (GRADE ⊕⊕⊕○; Table 179). Similarly, 4 of the 6 comparisons at the coronary artery / segment level were downgraded to moderate due to the substantial heterogeneity between studies (Table 180).

When studies were grouped according to the ICA cut-off used, 11 studies used a cut-off of 50% DS to diagnose significant CAD and 6 used a cut-off of 70% DS to diagnose severe CAD. Three studies reported accuracy data for both cut-off values. Meta-analysis showed that the pooled sensitivity and specificity did not differ significantly according to the ICA cut-off (Figure 12). However, the pooled sensitivity was 3% higher with the higher ICA cut-off value (70% DS). When the sensitivity and specificity for the two cut-offs was directly compared in the 4 studies reporting both, the average difference in sensitivity was larger, at 11%, but still did not reach statistical significance in any study (Figure 46 in Appendix H).

Figure 12 Forest plot showing the sensitivity and specificity of SP-CMR & LGE compared with ICA in diagnosing CAD for different ICA cut-off values, different analysis methods and population groups



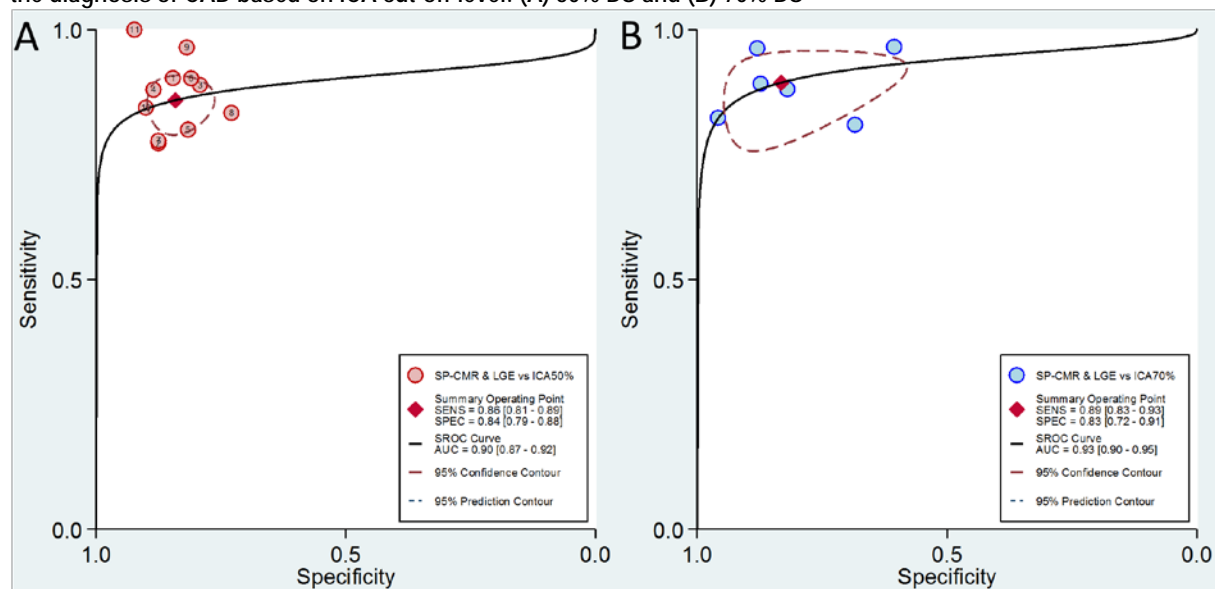
CAD = coronary artery disease; CI = confidence interval; DS = diameter stenoses; ICA = invasive coronary angiography; ICA50 = an ICA cut-off of 50% DS; ICA70 = ICA cut-off of 70% DS; K = number of studies; LGE = late gadolinium enhancement; ; PTP = pre-test probability; SP-CMR = stress perfusion cardiac magnetic resonance imaging; SP-CMR & LGE = combined analysis of SP-CMR and LGE to diagnose CAD; SP-CMR + LGE = integration of perfusion and LGE results to detect ischaemia. SP-CMR or LGE = either perfusion or LGE defects scored positive

The method used to combine the SP-CMR and LGE imaging results had little effect on either the pooled sensitivity or pooled specificity of the test compared with ICA (Figure 12). Similarly, there was no difference when the pooled sensitivity and specificity values for studies enrolling only patients with chest pain and/or an intermediate PTP of having CAD were compared with those enrolling any patient suspected of having CAD (Figure 12).

Meta-analysis of studies reporting at the coronary artery or segment level did not show any differences in the pooled sensitivity and specificity values compared with those reporting at the patient level (Figure 12). However, the 95% CIs for the pooled sensitivities were very wide, suggesting greater variation in the sensitivities reported for individual studies.

The SROC curve, which depicts the relative trade-off between true-positive and false-positive results, indicated that SP-CMR & LGE imaging performs well in predicting the presence of CAD, with an AUC of 0.90 (95%CI 0.87, 0.92) for an ICA cut-off of 50% DS, and 0.93 (95%CI 0.90, 0.95) for an ICA cut-off of 70% DS. The SROC curves showed no threshold effect (Figure 13).

Figure 13 SROC curve for studies investigating the sensitivity and specificity of SP-CMR & LGE versus ICA in the diagnosis of CAD based on ICA cut-off level: (A) 50% DS and (B) 70% DS



AUC = area under the curve; CAD = coronary artery disease; DS = diameter stenoses; ICA = invasive coronary angiography; LGE = late gadolinium enhancement; SP-CMR = stress perfusion cardiac magnetic resonance imaging; SROC = summary receiver-operator characteristics

Diagnostic accuracy of SP-CMR compared with ICA

Overall, 18 studies reported on the diagnostic accuracy of SP-CMR compared with ICA at the patient level, and the sensitivity and specificity of each individual study is shown in Figure 47 in Appendix H. In addition, 6 studies reported accuracy at the coronary artery / segment level. However, a meta-analysis of these 6 studies could not be performed as 3 studies used myocardial perfusion reserve with 3 different cut-offs to define CAD. A forest plot showing the sensitivity and specificity of these 6 studies is shown in Figure 48 in Appendix H.

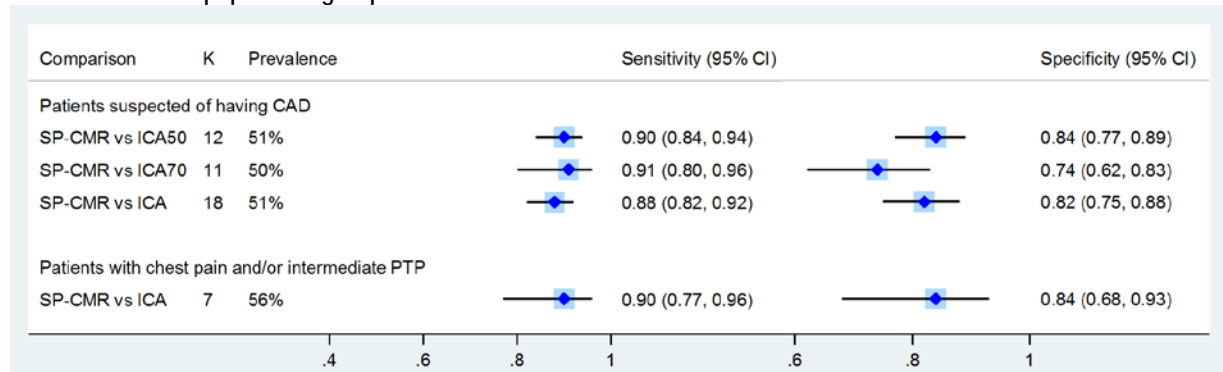
The overall quality of the evidence provided by these studies in assessing the diagnostic accuracy of SP-CMR compared with ICA was assessed using GRADE (Guyatt et al. 2011), and the results are presented in Table 181 and Table 183 in Appendix G. Although there was no publication bias (Figure 61 in Appendix J), there was substantial heterogeneity, introducing inconsistency in all the comparisons; hence, the evidence-base was downgraded to moderate (GRADE ⊕⊕⊕⊙).

When studies were grouped according to the ICA cut-off used, 12 studies used a cut-off of 50% DS to diagnose significant CAD and 11 a cut-off of 70% DS to diagnose severe CAD. Five studies reported

accuracy data for both cut-off values. Meta-analysis showed that the pooled sensitivity did not differ significantly according to the ICA cut-off (Figure 14). When the pooled sensitivity for the two cut-offs was directly compared in the 5 studies reporting both, the average difference was 7% (ranging from 1% to 17%; Figure 49 in Appendix H). Meta-analysis showed that the pooled specificity was 8%–10% lower with the higher ICA cut-off value of 70% DS than for an ICA cut-off of 50% DS, but this was not statistically significantly (Figure 14).

There was no difference when the pooled sensitivity and specificity values for studies enrolling only patients with chest pain and/or an intermediate PTP of having CAD were compared with those enrolling any patient suspected of having CAD (Figure 14).

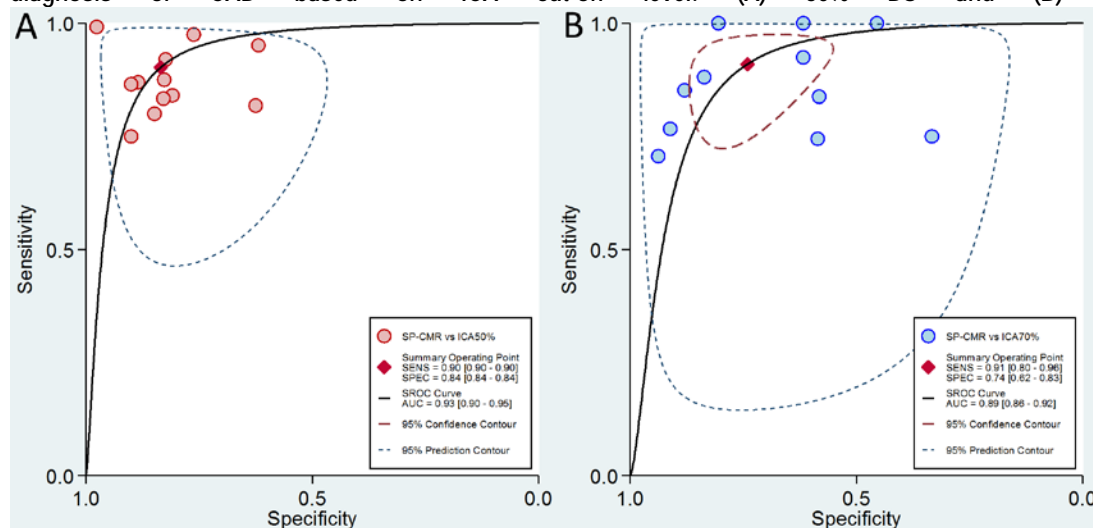
Figure 14 Forest plot showing the sensitivity and specificity of SP-CMR compared with ICA for different ICA cut-off values and population groups



CAD = coronary artery disease; CI = confidence interval; DS = diameter stenoses; ICA = invasive coronary angiography; ICA50 = an ICA cutoff of 50% DS; ICA70 = ICA cut-off of 70% DS; K = number of studies; PTP = pre-test probability; SP-CMR = stress perfusion cardiac magnetic resonance imaging

The SROC curves indicated that SP-CMR imaging performs well in predicting the presence of CAD, with an AUC of 0.93 (95%CI 0.90, 0.95) for an ICA cut-off of 50% DS, and 0.89 (95%CI 0.86, 0.92) for and ICA cut-off of 70% DS. The SROC curves showed no threshold effect (Figure 15).

Figure 15 SROC curve for studies investigating the sensitivity and specificity of SP-CMR versus ICA in the diagnosis of CAD based on ICA cut-off level: (A) 50% DS and (B) 70% DS



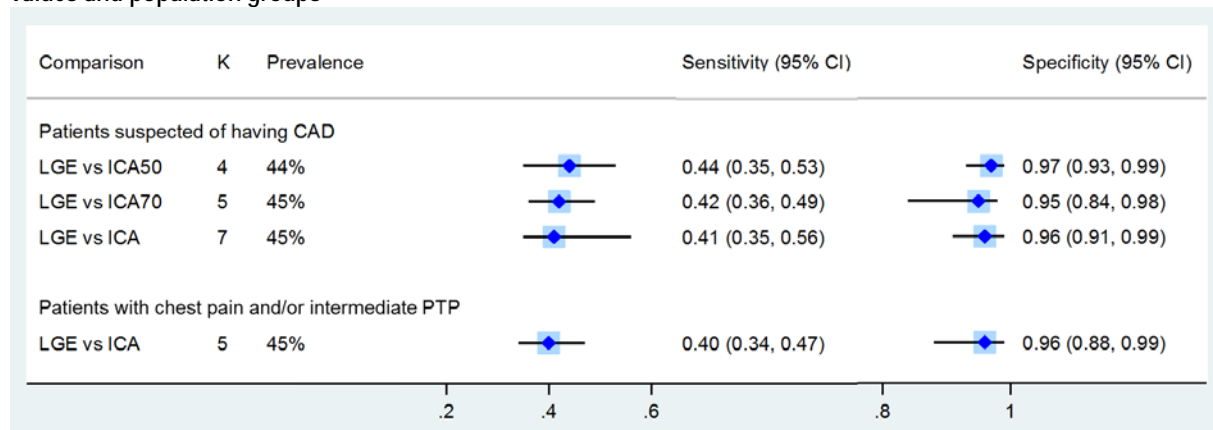
AUC = area under the curve; CAD = coronary artery disease; DS = diameter stenoses; ICA = invasive coronary angiography; SP-CMR = stress perfusion cardiac magnetic resonance imaging; SROC = summary receiver-operator characteristics

Diagnostic accuracy of LGE compared with ICA

Overall, 7 studies reported on the diagnostic accuracy of LGE compared with ICA at the patient level, and the sensitivity and specificity of each individual study is shown in Figure 50 in Appendix H. The overall quality of the evidence provided by these studies in assessing the diagnostic accuracy of LGE compared with ICA was assessed using GRADE (Guyatt et al. 2011), and the results are presented in Table 182 and Table 183 in Appendix G. There was no apparent publication bias although there were too few studies to be certain ($p=0.60$). For all pooled sensitivity comparisons there were no overall inconsistencies and the evidence-base was considered to be of high quality (GRADE ⊕⊕⊕⊕; Table 143). However, for the pooled specificity there was substantial heterogeneity for three of the four comparisons, introducing inconsistency and lowering the quality of evidence to moderate (GRADE ⊕⊕⊕⊙).

When studies were grouped according to the ICA cut-off used, 4 studies used a cut-off of 50% DS to diagnose significant CAD and 5 used a cut-off of 70% DS to diagnose severe CAD. Two studies reported accuracy data for both cut-off values. Meta-analysis showed that the pooled sensitivity did not differ by more than 4% according to the ICA cut-off, and specificity did not differ by more than 2% (Figure 16). When the sensitivity for the two cut-offs was directly compared in the two studies reporting both, the difference was 4% and 8% (Figure 51 in Appendix H). There was no difference when the pooled sensitivity and specificity values for studies enrolling only patients with chest pain and/or an intermediate PTP of having CAD were compared with those enrolling any patient suspected of having CAD (Figure 16).

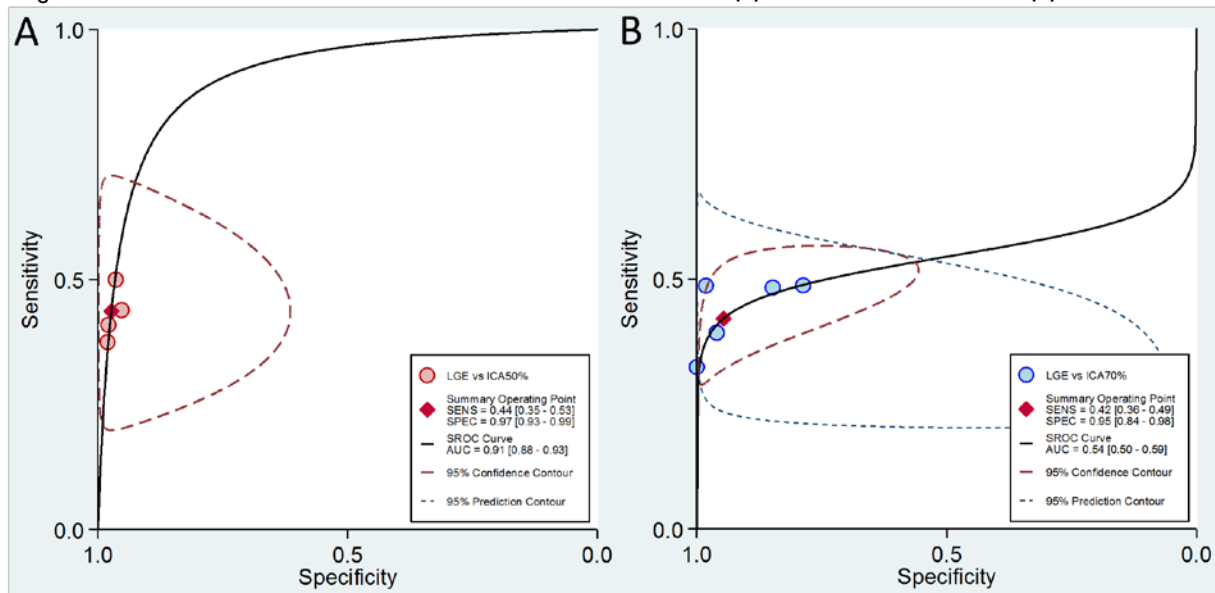
Figure 16 Forest plot showing the sensitivity and specificity of LGE compared with ICA for different ICA cut-off values and population groups



CAD = coronary artery disease; CI = confidence interval; DS = diameter stenoses; ICA = invasive coronary angiography; ICA50 = an ICA cut-off of 50% DS; ICA70 = ICA cut-off of 70% DS; K = number of studies; LGE = late gadolinium enhancement

As expected, the SROC curves indicated that LGE imaging performs poorly when compared with ICA with a 70% DS cut-off in predicting the presence of CAD, with an AUC of 0.54 (95%CI 0.50, 0.59). The AUC for LGE compared with an ICA cut-off of 50% DS was 0.89 (95%CI 0.86, 0.92) and suggests that the test performs much better with a lower ICA cut-off; this is due to the limited number of studies showing a highly level of specificity for LGE compared with ICA using a 50% DS cut-off value. The SROC curves showed a threshold effect; when using a more stringent ICA cut-off to diagnose disease, LGE becomes less specific (Figure 17).

Figure 17 SROC curve for studies investigating the sensitivity and specificity of LGE versus ICA in the diagnosis of CAD based on ICA cut-off level: (A) 50% DS and (B) 70% DS



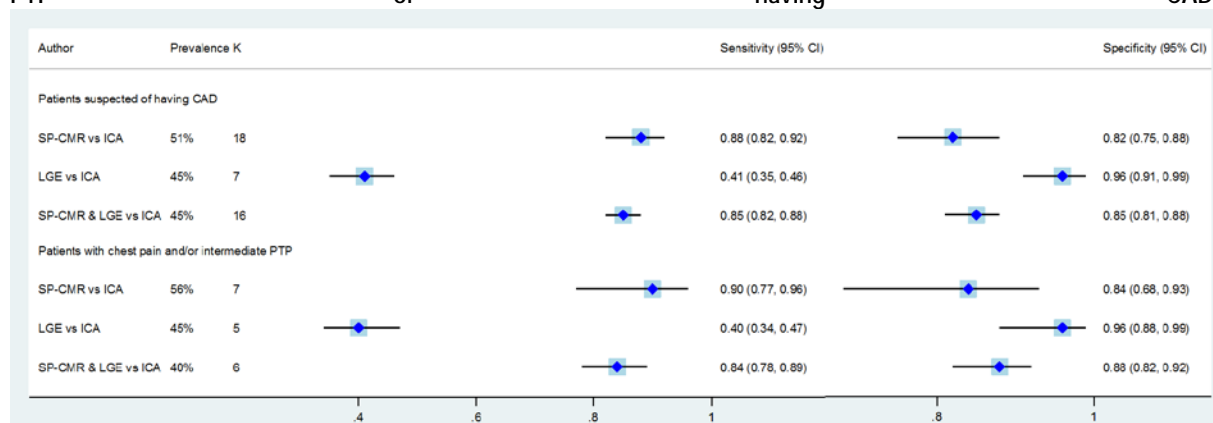
AUC = area under the curve; CAD = coronary artery disease; DS = diameter stenoses; ICA = invasive coronary angiography; LGE = late gadolinium enhancement; SROC = summary receiver-operator characteristics

Comparison of the accuracy of SP-CMR, LGE, and SP-CMR & LGE versus ICA in patients suspected of having CAD

LGE is used to differentiate viable and non-viable myocardium. Hence, it is not surprising that LGE alone performs poorly in the diagnosis of CAD; the presence of non-viable myocardium would not be expected in most patients with an intermediate risk of having CAD. The PDs detectable by SP-CMR would be expected to precede any irreversible changes to the myocardium. However, this test is highly specific as the most likely cause of non-viable myocardium in these patients would be CAD. Thus, when the accuracy of SP-CMR versus ICA is compared with SP-CMR & LGE versus ICA, there is a slight increase in specificity and a corresponding decrease in sensitivity (Figure 18). The differences in sensitivity and specificity were not statistically significant but the 95% CIs were much narrower when SP-CMR and LGE were combined compared with SP-CMR alone.

There was no difference in the pooled sensitivities and specificities of these CMR tests versus ICA in patients suspected of having CAD compared with patients with chest pain and/or an intermediate PTP of having CAD (Figure 18).

Figure 18 Forest plot showing the sensitivity and specificity of SP-CMR, LGE, and SP-CMR & LGE versus ICA in the diagnosis of CAD in patients suspected of having CAD and in patients with chest pain and/or an intermediate PTP of having CAD



CAD = coronary artery disease; CI = confidence interval; ICA = invasive coronary angiography; K = number of studies; LGE = late gadolinium enhancement; PTP = pre-test probability; SP-CMR = stress perfusion cardiac magnetic resonance imaging

The pooled sensitivity and specificity values for SP-CMR with/without LGE vs ICA in patients suspected of having CAD, as shown in Figure 18, were used for comparing the accuracy of SP-CMR with other non-invasive imaging modalities in diagnosing CAD in Section B4. As the proposed MBS listing is for the use of both SP-CMR and LGE to diagnose CAD, SP-CMR & LGE was considered to be the index test and SP-CMR alone was included as a comparator.

Diagnostic accuracy of SP-CMR, LGE, and SP-CMR & LGE versus ICA in women compared with men

The prevalence of CAD is lower in women than in men (see Section A4), and the SRs that report on the accuracy of various non-invasive imaging techniques compared with ICA in women mostly reported that the test has decreased sensitivity when compared with testing in men. To further investigate if SP-CMR with/without LGE and LGE alone is a useful diagnostic tool in women, its accuracy versus ICA in women was compared with that in men and in mixed populations.

Figure 52 (Appendix H) shows that the sensitivity of all three CMR-based tests are 5%–8% lower when testing only women compared with mixed populations with a mean of 35%–40% women. Only two studies reported outcomes for only men (Greenwood et al. 2014; Merkle et al. 2010). Both reported on SP-CMR versus ICA in men and women separately; in both these studies SP-CMR had lower sensitivity in men compared with women. The reason for this anomaly was not determined. Greenwood et al. (2014) also reported on the accuracy of LGE compared with ICA in men and women, with opposite results; LGE had lower sensitivity in women than in men.

B3A.6.3 DIAGNOSTIC ACCURACY OF SP-CMR WITH/WITHOUT LGE COMPARED WITH CTCA, SPECT, STRESS ECHO AND EXERCISE ECG USING ICA AS THE REFERENCE STANDARD

A total of 41 SRs reported on the diagnostic accuracy of SP-CMR (n=10), CTCA (n=21), SPECT (n=12), stress Echo (n=6) and/or exercise ECG (n=4) compared with ICA. The study characteristics are listed in Table 144 in Appendix C. As there was a large degree of overlap between the studies included in the different SRs, an overall summary measure of the pooled values would not be valid. To compare the accuracy of SP-CMR with/without LGE and the comparators using ICA as the common reference standard, the most recent SR of each comparator considered to be comparable to the meta-analyses conducted in Section B3.6.2 was chosen using the following criteria:

- The SR must be of moderate or good quality and report either the mean or total prevalence of CAD, as determined by ICA, for all the studies included in the meta-analysis.

- The population should be as similar as possible to that included in the meta-analysis in section B3.6.2 (i.e. include mostly patients with suspected CAD).
- The prevalence of CAD must be within 10% of the 45% CAD prevalence rate calculated for the meta-analysis for SP-CMR & LGE vs ICA in patients suspected of having CAD in Section B3.6.2.
- The SR does not have an extreme value for the pooled sensitivity or specificity compared with other SRs.
- There was no other difference in the PICO that could affect the pooled values.

If more than one SR met these criteria, the SR with either the most included studies or of better quality was selected.

SRs comparing SP-CMR with ICA

Ten SRs compared the diagnostic accuracy of SP-CMR with ICA, 9 at the patient level and 6 at the coronary artery / segment level. The SRs did not consider LGE in combination with SP-CMR. A summary of the meta-analyses reported in these SRs is given in Table 163 in Appendix E. A forest plot comparing the pooled sensitivity and specificity values from the meta-analyses for SP-CMR with/without LGE versus ICA conducted in Section B3a.6.2 with those from the SRS is shown in Figure 55 in Appendix H.

Overall, at the patient level, the pooled sensitivities and specificities reported in the SRs for SP-CMR compared with ICA were very similar to the pooled values determined for SP-CMR versus ICA in Section B3.6.2.

SRs comparing CTCA with ICA

Twenty-one SRs reported on the accuracy of CTCA compared with ICA; summaries of the meta-analyses reported in these SRs are given in Table 164 in Appendix E, and a forest plot of the pooled sensitivity and specificity values is shown in Figure 56 in Appendix I.

Based on the criteria listed above, the SR by den Dekker et al. (2012) was considered to provide the most appropriate pooled estimates to compare the accuracy of SP-CMR with/without LGE with CTCA, using ICA as a common reference standard (Figure 56). This moderate-quality SR included 21 studies enrolling only patients suspected of CAD, and reported an overall prevalence rate of 39%.

SRs comparing SPECT with ICA

Twelve SRs reported on the accuracy of SPECT compared with ICA, and summaries of the meta-analyses reported in these SRs are given in Table 165 in Appendix E. A forest plot of the pooled sensitivity and specificity values is shown in Figure 57 in Appendix I.

To compare the accuracy of SP-CMR with/without LGE and SPECT using ICA as the common reference standard, the SR by de Jong et al. (2012) was considered to provide the most appropriate pooled estimates (Figure 57). This moderate-quality SR included 13 studies enrolling patients with known or suspected CAD, and reported an overall prevalence rate of 39%.

SRs comparing stress Echo with ICA

Six SRs reported on the accuracy of stress Echo compared with ICA, and summaries of the meta-analyses reported in these SRs are given in Table 166 in Appendix E. A forest plot of the pooled sensitivity and specificity values is shown in Figure 58 in Appendix I.

To compare the accuracy of SP-CMR with/without LGE and SPECT using ICA as the common reference standard, the SR by the Medical Advisory Secretariat (2010c) was considered to provide the most appropriate pooled estimates (Figure 57). This moderate-quality SR included 10 studies enrolling patients with known or suspected CAD and reported an overall prevalence rate of 48%.

However, it should be noted that the pooled sensitivity and specificity values are both high compared with the remaining 3 moderate or good quality SRs. These 3 SRs were not suitable due to an unknown or high CAD prevalence rate in two, and a population consisting of only women in the third.

SRs comparing exercise ECG with ICA

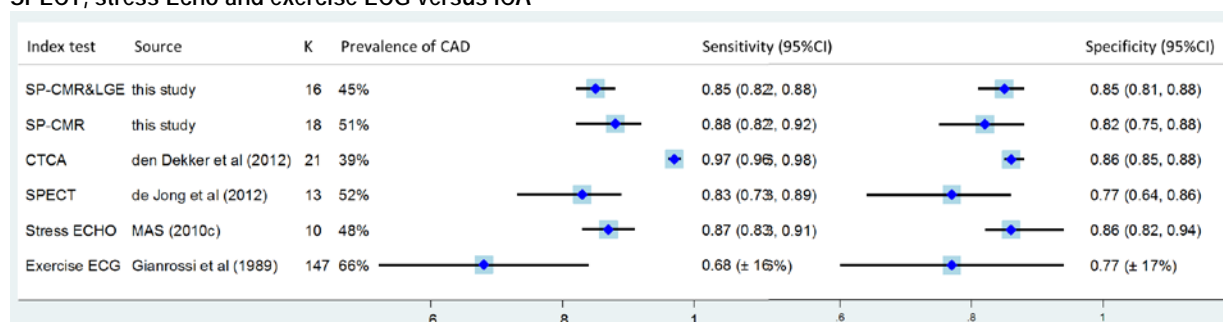
Four SRs reported on the accuracy of exercise ECG compared with ICA, and summaries of the meta-analyses reported in these SRs are given in Table 167 in Appendix E. A forest plot of the pooled sensitivity and specificity values is shown in Figure 59 in Appendix I. None of these SR met our criteria for being comparable to the meta-analyses conducted in Section B3.6.2; two of the SRs included only women, 1 had a high CAD prevalence rate of 66% and the remaining study did not report the prevalence of CAD. The SR conducted by Gianrossi et al. (1989) is often quoted in the literature as the source for determining the accuracy of exercise ECG; hence, the mean sensitivity and specificity of exercise ECG compared with ICA reported in this study were used for further analysis.

Comparison of SP-CMR, CTCA, SPECT, stress Echo and exercise ECG using ICA as the reference standard

The pooled sensitivities and specificities for all non-invasive imaging tests compared with ICA are depicted as a forest plot in Figure 19. When the pooled sensitivities for the different tests were compared, CTCA was clearly the most sensitive, at 97%. This indicated that only 3% of patients with CAD detectable by ICA would not be diagnosed by CTCA and would not receive further treatment. SP-CMR with/without LGE, SPECT and stress Echo all had similar sensitivities, ranging from 83% to 88%. For these tests 12%–15% of all patients with CAD detectable by ICA would be falsely negative and miss out on potentially beneficial treatment. Exercise ECG was the least sensitive, at 68%. For this test 32% of patients with CAD detectable by ICA would be falsely negative.

The specificities of SP-CMR with/without LGE, CTCA and stress Echo were similar, at between 82% and 86%. This indicates that 14%–18% of patients diagnosed with CAD using the imaging modalities would be misdiagnosed and potentially receive unnecessary invasive treatment. Both SPECT and exercise ECG were less specific at 77%, with 23% of patients with no CAD being falsely positive and receiving unnecessary treatment.

Figure 19 Forest plot comparing pooled sensitivities and specificities of SP-CMR with/without LGE, CTCA, SPECT, stress Echo and exercise ECG versus ICA



CAD = coronary artery disease; CI = confidence interval; CTCA = computed tomography coronary angiography; ECG = electrocardiogram; ECHO = echocardiography; ICA = invasive coronary angiography; K = number of studies; LGE = late gadolinium enhancement; SP-CMR = stress perfusion cardiac magnetic resonance imaging; SPECT = single-photon emission computed tomography

B3A.7 EXTENDED ASSESSMENT OF RELIABILITY EVIDENCE

As SP-CMR scans are evaluated subjectively, it is important to assess the degree of variability likely to occur between readers. Eleven of the 35 studies that reported on the diagnostic accuracy of SP-CMR with/without LGE provided data on the interobserver agreement or variability between observers or readers (Table 27). Six studies reported the agreement for SP-CMR as kappa values, and the median value was 0.83 (range 0.56–0.88), and 1 study reported a kappa of 0.84 for LGE. Two studies reported that the observers agreed in 82%–83% of cases when interpreting SP-CMR and LGE scans, and 1 study reported that only 8% of SP-CMR scans required a third reader to resolve disagreements. Two studies reported the interobserver variability for SP-CMR, with a mean difference between observers of 6%–8%. These results indicate that there is a high level of interobserver agreement when interpreting SP-CMR and/or LGE scans.

Table 27 Interobserver agreement for SP-CMR and/or LGE

Study	Population	Test	Interobserver agreement or variability
Becker et al. (2015)	N=424 women with suspected CAD	SP-CMR	Interobserver agreement: kappa = 0.88 (95%CI 0.83, 0.92)
Bernhardt et al. (2007)	N=317 patients who had angina	SP-CMR	Interobserver agreement: kappa = 0.88 (95%CI 0.83, 0.92)
Pereira et al. (2013)	N=80 patients with suspected CAD	SP-CMR	Interobserver agreement: kappa = 0.56
Stolzmann et al. (2011)	N=60 patients with an intermediate PTP for CAD	SP-CMR and LGE	Interobserver agreement for: SP-CMR: kappa = 0.73 LGE: kappa = 0.84
Regenfus et al. (2003)	N=61 patients	SP-CMR	Interobserver agreement: kappa = 0.85
Groothuis et al. (2013)	N=50 patients with low or intermediate PTP for CAD	SP-CMR	Intraobserver agreement: kappa = 0.81+0.09
Arnold et al. (2010)	N=65 patients with exertional chest pain	SP-CMR + LGE	Interobserver agreement: 82% (95%CI 75%, 87%)
Watkins et al. (2009)	N=103 patients with suspected angina	SP-CMR + LGE	Both observers agreed on the pattern of CAD in 83.2% of scans
Klem et al. (2006)	N=100 patients with suspected CAD	SP-CMR	Only 8% of SP-CMR scans required a third reader to resolve disagreements
Al-Saadi et al. (2000)	N=40 patients with new chest pain or progressive symptoms	SP-CMR MPR ≤1.5	Interobserver variability of the upslope: correlation coefficient = 0.96 Relative difference = 8.3 ± 9.9%
Schwitzer et al. (2001)	N=48 patients with suspected CAD	SP-CMR	Interobserver variability of slope _{endo} : mean difference = 5.6% (95%CI -15.3, 26.5) and slope _{trans} : mean difference = 4.7% (95%CI -14.7, 24.1)

CAD = coronary artery disease; CI = confidence interval; LGE = late gadolinium enhancement; PTP = pre-test probability; SP-CMR = stress perfusion cardiac magnetic resonance imaging

In Section B1.6 it was noted that in the CECaT trial 15.5% of all patients allocated to the SP-CMR group did not complete the test, compared with only 1.8% for SPECT and 7.0% for stress Echo. The reasons for this were further investigated. Seventeen of the 35 diagnostic accuracy studies reported on the number of unsuccessful SP-CMR tests undertaken (Table 168 in Appendix E). The median proportion of SP-CMR tests that failed or were not conducted was 7.5% (range 2.1–17.5%). SP-CMR

failed due to technical problems or poor image quality in only a small number of these patients. In the majority of cases, repeating the SP-CMR scans would not be possible (e.g. patient refusal, claustrophobia, too large for scanner) and alternative tests would need to be undertaken in order to diagnose the presence of CAD.

Thus, the higher non-completion rate for SP-CMR compared with SPECT or stress Echo seen in the CECaT trial may be due to patient acceptability and suitability issues.

B3A.8 CONCORDANCE ANALYSIS

As a reference standard was available to enable the diagnostic accuracy of SP-CMR & LGE and its comparators to be determined in Section B3a.6, measures of agreement between SP-CMR and the comparators were not evaluated.

B3A.9 INTERPRETATION OF EVIDENCE ON DIAGNOSTIC PERFORMANCE

B3A.9.1 COMPARISON OF SP-CMR WITH SPECT AND STRESS ECHO IN THE CECAT TRIAL

In the CECaT trial SP-CMR was found to be less sensitive and more specific than both SPECT and stress Echo when ICA was used as the reference standard, but the differences were not statistically significant. However, as the proportion of patients who did not have an ICA and were misclassified as true negative could not be determined, the interpretation of the specificity of these tests compared with ICA in this trial was limited. It should be noted that SP-CMR had a much higher non-completion rate than SPECT or stress Echo, and the results discussed in Section B2a.7 suggest that this may be due to patient acceptability and suitability issues.

B3A.9.2 DIAGNOSTIC ACCURACY OF SP-CMR AND SP-CMR & LGE VERSUS ICA

Meta-analyses were conducted to compare the accuracy of SP-CMR versus ICA against SP-CMR & LGE versus ICA. When LGE was combined with SP-CMR there was a slight increase in specificity and a corresponding decrease in sensitivity. These differences were not statistically significant but the 95% CIs were much narrower for the SP-CMR & LGE pooled results.

There was no difference in the pooled sensitivities and specificities of SP-CMR with/without LGE versus ICA in patients suspected of having CAD compared with patients with chest pain and/or an intermediate PTP of having CAD. However, the sensitivity of these tests was 5%–8% lower when testing only women compared with mixed populations with 35%–40% women.

B3A.9.3 COMPARISON OF SP-CMR, CTCA, SPECT, STRESS ECHO AND EXERCISE ECG

When the pooled sensitivities for the different tests were compared, CTCA was clearly the most sensitive, at 97%. SP-CMR with/without LGE, SPECT and stress Echo had similar sensitivities, ranging from 83% to 88%, and exercise ECG was the least sensitive, at 68%. Thus, one-third of all patients with CAD detectable by ICA would not be diagnosed by exercise ECG (would be falsely negative), and would not receive any more treatment than for other non-invasive imaging modalities, compared with 12%-17% for SP-CMR with/without LGE, SPECT and stress Echo and 3% for CTCA.

The specificity of SP-CMR with/without LGE, CTCA and stress Echo were similar, at between 82% and 86%, and both SPECT and exercise ECG were less specific, at 77%. Thus, one-quarter of all patients who did not have CAD detectable by ICA would be falsely positive by SPECT and exercise ECG and may have received unnecessary invasive testing, compared with 14-18% of patients for SP-CMR with/without LGE, CTCA and stress Echo.

B3A.9.4 RELIABILITY OF SP-CMR WITH/WITHOUT LGE

Although there was a high level of interobserver agreement when interpreting SP-CMR and/or LGE scans, there was also a median 7.5% (range 2.1%–17.5%) of SP-CMR tests that failed or were not conducted, mostly due to patient acceptability or suitability issues.

B4A CLINICAL VALIDITY (POPULATION 1)

B4A.1 MEASURES OF CLINICAL VALIDITY

B4A.1.1 TO B4A.1.4

Please refer to sections B3a.1 to B3a.5 above. The studies that provide data to inform on clinical validity are the same as those that provide diagnostic performance data in Section B3.

B4A.1.5 RESULTS OF THE SYSTEMATIC LITERATURE REVIEW

IS IT ACCURATE IN THE TARGET POPULATION?

Summary – What is the clinical validity of CMR gadolinium-based stress perfusion and viability imaging in the diagnosis of CAD in patients presenting with symptoms consistent with IHD, with an intermediate PTP of CAD?

Comparison of the PTP and PoTP for SP-CMR, SPECT and stress Echo in the CECaT trial

Patients with a positive test result and similar PTPs had similar PoTPs with all three non-invasive imaging tests. Conversely, patients with a high PTP of having CAD who tested negative had a higher PoTP of having CAD if tested using SP-CMR or stress Echo than if tested using SPECT. Thus, SPECT was better at ruling out the presence of disease in patients with a negative test result than either SP-CMR or stress Echo in this trial.

The PoTP of having CAD after testing with SP-CMR with/without LGE, CTCA, SPECT, stress Echo and exercise ECG

The PoTP of having CAD after testing positive with CTCA is the highest, but the PoTPs for stress Echo and SP-CMR with/without LGE are similar (within 10% of CTCA), and all are at least 2- to 3-fold higher than the PTP in patients with a low-intermediate PTP (15–45%). The PoTPs are 15% and 20% lower for SPECT and exercise ECG, respectively, than for CTCA.

The PoTPs of having CAD after testing negative are much lower with CTCA than with other modalities, and are 5- to 10-fold lower than the PTP in patients with a high-intermediate PTP (65%–85%). The PoTPs are similar (within 10%) for stress Echo, SP-CMR with/without LGE and SPECT, but are much higher than for CTCA and represent only a 2- to 3-fold decrease from the PTP. In patients with a high-intermediate PTP of 65%–85%, the PoTP of having CAD after testing by exercise ECG only reduced to 45%–70%.

CTCA is only listed on the MBS for use in patients with a low-intermediate PTP of having CAD (15%–45%). In these patients stress Echo and SP-CMR & LGE are almost as effective at diagnosing patients with CAD as CTCA, when compared with ICA as the reference standard. However, in patients who have a negative test result, CTCA is at least 3-fold more likely to be correct than other non-invasive imaging modality.

In patients with a high-intermediate PTP (65%–85%) of having CAD, CTCA is the only test that can effectively rule out CAD in the minority of patients who have a negative test result. In the majority of patients who would have a positive test result, stress Echo and SP-CMR with/without LGE are almost as effective as CTCA in diagnosing CAD.

Overall summary

The results of the CECaT trial (Section B4a.1.5.1) differed from the findings in Section B4a.1.5.2.

The CECaT trial found that SPECT was better at ruling out the presence of disease in patients with a negative test result than either SP-CMR or stress Echo. The comparison conducted in Section B4.1.5.2, using sensitivity and specificity values reported in SRs, found stress Echo and SP-CMR with/without LGE to be slightly better than SPECT at ruling out the presence of CAD. However, all three modalities were inferior to CTCA in ruling out the presence of CAD in patients with a negative result.

B4A.1.5.1 THE CECAT TRIAL

The pragmatic RCT by Sharples et al. (2007), as discussed in Section B.3, provides very low-quality diagnostic evidence (GRADE ⊕⊖⊖⊖). The PPV and NPV for patients with a PTP at the extreme ends of the intermediate range (15% and 85%), and at the study prevalence, were calculated using the positive and negative LRs (Table 28).

The differences in the LR+ and the PPV, when SP-CMR was compared with either SPECT or stress Echo were small (Table 28). The LR+ values are all low, at <2, and this represents a less than 2-fold increase in the PoTP of having CAD. The PPV indicated that only one-quarter of all patients with a PTP of 15% who have a positive non-invasive imaging test result would actually have CAD when tested with ICA. On the other hand, 9 out of 10 positive patients with a PTP of 85% would be positive by ICA.

The differences in LR- and NPV between SP-CMR and stress Echo were also small, but the comparison of the LR- and NPV values for SP-CMR and SPECT showed a greater difference in patients with higher PTP values. Thus, of patients with a 15% PTP and a negative test result using SP-CMR, stress Echo or SPECT, only 3%, 4% or 6%, respectively, would be diagnosed with CAD by ICA. Of patients with an 85% PTP and a negative non-invasive imaging test result, 70% tested using SP-CMR or stress Echo would have CAD detectable by ICA, compared with 57% for those tested using SPECT.

These results suggest that patients with a positive test result and similar PTPs will have similar PoTPs (= PPV) with all three non-invasive imaging tests. Conversely, patients with a high PTP of having CAD who test negative will have a higher PoTP (= 1 – NPV) of having CAD if tested using SP-CMR or stress Echo than if tested using SPECT. Thus, SPECT was better at ruling out the presence of disease in patients with a negative test result than either SP-CMR or stress Echo in this trial.

Table 28 PPV and NPV of SP-CMR (index test) and comparators SPECT and stress Echo, using ICA as the reference standard

Sharples et al. (2007)	Result	Intervention (95%CI)	Comparator (95%CI)	Difference	
SP-CMR versus SPECT	Sensitivity	75.7% (66.5, 83.5)	87.5% (79.9, 93.0)	-11.8%	
	Specificity	60.0% (43.3, 75.1)	53.5% (39.9, 66.7)	+6.5%	
	LR+	1.89 (1.28, 2.81)	1.88 (1.41, 2.50)	+0.01	
	LR-	0.40 (0.27, 0.62)	0.23 (0.14, 0.40)	+0.17	
Study prevalence of CAD: 69% overall	PPV: PTP	15%	25.0% (17.5, 37.2)	24.9% (19.0, 33.0)	+0.1%
		69%	80.8% (72.3, 88.2)	80.7% (74.7, 86.1)	+0.1%
		85%	91.5% (86.9, 95.0)	91.4% (88.3, 94.1)	+0.1%
73% for SP-CMR 66% for SPECT	NPV: PTP	15%	93.3% (88.0, 96.3)	96.0% (91.8, 98.2)	-2.7%
		69%	52.6% (36.7, 67.2)	65.8% (47.1, 81.1)	-13.2%
		85%	30.4% (18.6, 44.5)	43.0% (25.9, 62.7)	-12.6%

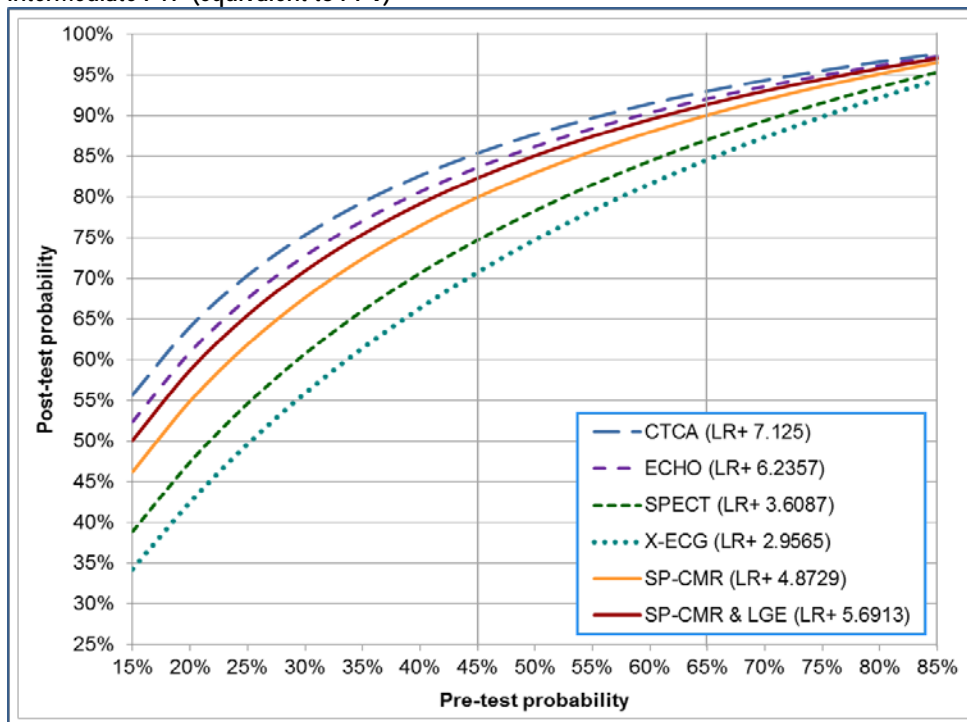
Sharples et al. (2007)	Result	Intervention (95%CI)	Comparator (95%CI)	Difference	
SP-CMR versus stress Echo	Sensitivity	75.7% (66.5, 83.5)	80.0% (71.5, 86.9)	-4.3%	
	Specificity	60.0% (43.3, 75.1)	54.4% (39.0, 69.1)	+5.6%	
	LR+	1.89 (1.28, 2.81)	1.75 (1.26, 2.43)	+0.14	
	LR-	0.40 (0.27, 0.62)	0.37 (0.23, 0.58)	+0.03	
Study prevalence of CAD: 72% overall	PPV:	PTP 15%	25.0% (17.5, 37.2)	23.6% (17.1, 33.2)	+1.4%
		72%	83.0% (75.1, 89.6)	81.9% (75.1, 87.9)	+1.1%
		85%	91.5% (86.9, 95.0)	90.9% (86.9, 94.1)	+0.6%
73% for SP-CMR 71% for Echo	NPV:	PTP 15%	93.3% (88.0, 96.3)	93.9% (88.6, 96.8)	-0.6%
		72%	49.0% (33.5, 63.9)	51.4% (34.7, 67.2)	-2.4%
		85%	30.4% (18.6, 44.5)	32.4% (19.5, 48.2)	-2.0%

CAD = coronary artery disease; Echo = echocardiography; ICA = invasive coronary angiography; LR+ = positive likelihood ratio; LR- = negative likelihood ratio; NPV = negative predictive value; PPV = positive predictive value; PTP = pre-test probability; SP-CMR = stress perfusion cardiac magnetic resonance imaging; SPECT = single-photon emission computed tomography.

B4A.1.5.2 COMPARISON OF PoTP OF HAVING CAD AFTER TESTING WITH SP-CMR, CTCA, SPECT, STRESS ECHO AND EXERCISE ECG

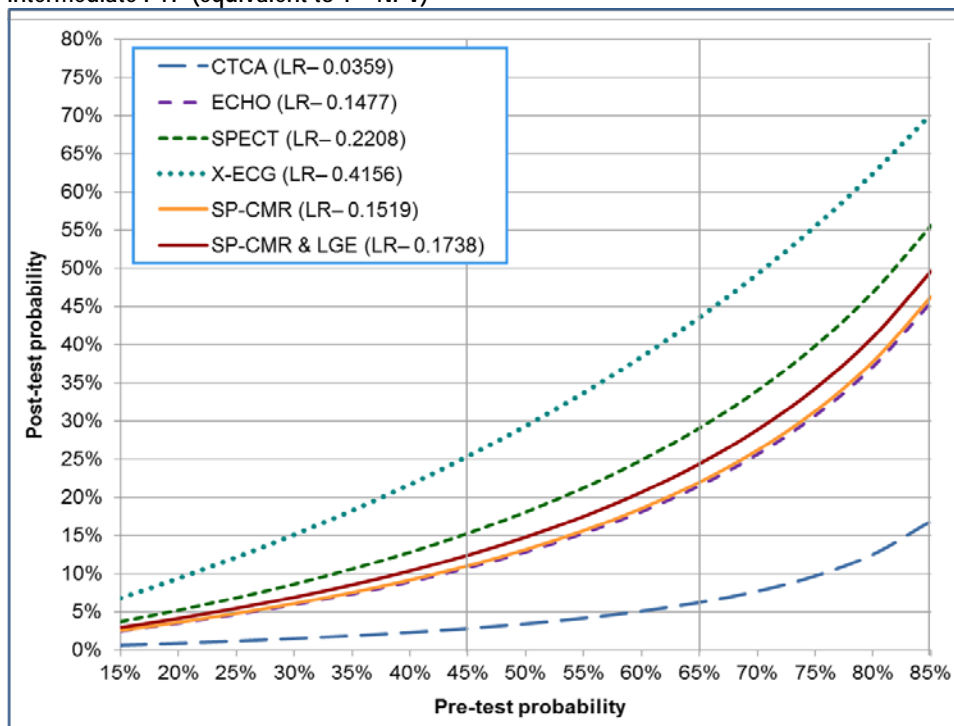
The pooled sensitivities and specificities for all non-invasive imaging modalities compared with ICA, as determined in Section B3, were used to calculate the LRs. The LRs were then used to calculate the PoTP of having CAD (determined by ICA) with either a positive or negative non-invasive imaging result for different PTPs ranging from 15% to 85%. The PoTP values were plotted against the PTP values on the graphs shown in Figure 20 and Figure 21.

Figure 20 PoTP of having CAD after receiving a positive non-invasive imaging test result in patients with an intermediate PTP (equivalent to PPV)



CTCA = computed tomography coronary angiography; ECHO = echocardiography; LGE = late gadolinium enhancement; LR+ = positive likelihood ratio; SP-CMR = stress perfusion cardiac magnetic resonance imaging; SPECT = single-photon emission computed tomography; X-ECG = exercise electrocardiogram

Figure 21 PoTP of having CAD after receiving a negative non-invasive imaging test result in patients with an intermediate PTP (equivalent to 1 - NPV)



CTCA = computed tomography coronary angiography; Echo = echocardiography; LGE = late gadolinium enhancement; LR- = negative likelihood ratio; SP-CMR = stress perfusion cardiac magnetic resonance imaging; SPECT = single-photon emission computed tomography; X-ECG = exercise electrocardiogram

Figure 20 shows that patients with a positive test result that have a PTP of having CAD of:

- 15% have a:
 - 3-fold increase in PoTP to 46%–55% using CTCA, stress Echo or SP-CMR with/without LGE
 - 2-fold increase in PoTP to 34%–39% using SPECT or exercise ECG

This is no better than chance for any testing modality, so the usefulness of a positive result to the clinician is doubtful.

- 45% have a:
 - 2-fold increase in PoTP to 80%–85% using CTCA, stress Echo or SP-CMR with/without LGE
 - smaller increase to a PoTP of 70%–75% using SPECT or exercise ECG
- 65% have a:
 - PoTP of 90%–93% using CTCA, stress Echo or SP-CMR with/without LGE
 - PoTP of 85%–87% using SPECT or exercise ECG
- 85% have a:
 - PoTP of at least 94% regardless of the imaging modality used

These patients are highly likely to have CAD so the usefulness of this result is doubtful.

It is clear from Figure 21 that CTCA performs much better than any other non-invasive imaging test in reducing the PoTP of having CAD detectable by ICA. Patients with a negative test result that have a PTP of having CAD of:

- 15% have a:
 - 15-fold reduction in PoTP to <1% using CTCA
 - 3-fold reduction in PoTP to <4% using stress Echo or SP-CMR with/without LGE or SPECT
 - 2-fold reduction in PoTP to 7% using exercise ECG
- 45% have a:
 - 10-fold reduction in PoTP to 3% using CTCA
 - 3-fold reduction in PoTP to 10%–15% using Echo, SP-CMR with/without LGE, and SPECT
 - 2-fold reduction in PoTP to 25% using exercise ECG
- 65% have a:
 - 10-fold reduction in PoTP to 6% using CTCA
 - 2- to 3-fold reduction in PoTP to 20%–30% using Echo, SP-CMR with/without LGE, and SPECT
 - the PoTP of 45% using exercise ECG is no better than chance, so its usefulness to the clinician is doubtful
- 85% have a:
 - 5-fold reduction in PoTP of 17% using CTCA
 - 2-fold reduction in PoTP to 45–55% using Echo, SP-CMR with/without LGE or SPECT, which is no better than chance so its usefulness to the clinician is doubtful
 - the PoTP of 70% using exercise ECG is not much different from the PTP, so it provides no useful information.

It should be noted that CTCA is only listed on the MBS for use in patients with a low-intermediate PTP of having CAD (15%–45%). In these patients stress Echo and SP-CMR & LGE are almost as effective at diagnosing patients with CAD as CTCA, when compared with ICA as the reference standard (Figure 20). However, the majority of these patients would have a negative test result, and CTCA is at least 3-fold more likely to correctly eliminate the presence of CAD than any other non-invasive imaging modality.

In patients with a high-intermediate PTP (65%–85%) of having CAD, CTCA is the only test that can effectively rule out CAD in the minority of patients with a negative test result (Figure 21). In the majority of patients who would have a positive test result, stress Echo and SP-CMR with/without LGE are almost as effective as CTCA in diagnosing CAD.

B4A.2 PROGNOSIS OR PREDISPOSITION

The studies that provided prognostic data were identified from the literature search described in Section B even though there was no prognostic question defined *a priori*.

B4A.2.1 RISK OF BIAS ASSESSMENT

One SR reported on the ability of SP-CMR to assess the prognosis of patients with suspected or known CAD and the quality of this SR was assessed using the AMSTAR checklist (Shea et al. 2007). Three non-comparative case series reported on the incremental prognostic value of CMR and the quality of these studies was assessed using a checklist by IHE (Moga et al. 2012). The results of the quality appraisal are listed in Table 145 in Appendix C.

B4A.2.2 CHARACTERISTICS OF THE EVIDENCE-BASE

The 3 case series (level IV evidence) that presented results for risk reclassification included patients in a hospital specialist imaging division (Abbasi et al. 2014), outpatient clinic (Bingham & Hachamovitch 2011), and attending general and specialist hospital cardiology services (Shah et al. 2013), all in the USA. Therefore, the results of these studies would be applicable to the Australian healthcare system with few caveats. The patient populations included in the SR were broader than the PICO, including those with known CAD as well as those with suspected CAD, although the weighted mean proportion of patients with CAD was only 42% and the weighted mean left ventricular ejection fraction (LVEF) was within the normal range at $61 \pm 12\%$. Study details are provided in Table 145 in Appendix C. The key outcomes were not used in the economic model.

B4A.2.3 OUTCOME MEASURES AND ANALYSIS

Meta-analyses were performed by Lipinski et al. (2013) to determine whether clinical variables such as a positive SP-CMR or LGE were associated with combined cardiovascular outcome, cardiovascular death or non-fatal MI. Binary outcomes from individual studies were combined using a random-effects model, to compute odds ratios.

The incremental prognostic value of SP-CMR was assessed in 3 case series using net reclassification improvement (NRI) analyses. The NRI is a statistic to measure the improvement in predictive performance that is gained by adding an additional marker to a set of baseline predictors. In this scenario, risk of major adverse cardiovascular events (MACE) was determined using baseline factors such as clinical risk and LV factors, and the additional predictive benefit of SP-CMR was examined. Pre-test risk was defined by the annualised probability of MACE estimated by a multivariate clinical risk model. Post-test risk was defined by the annualised probability of MACE combining the multivariate clinical risk model with SP-CMR findings (inducible ischaemia in Shah et al. (2013)). Those who were reclassified to a higher risk group were considered to have moved upward, and those who were reclassified as being in a lower risk group were considered to have moved downwards. The NRI was calculated by pooling all those who were reclassified upwards and calculating their risk of MACE using a Kaplan-Meier estimate; and performing the same calculation for all downward reclassified patients. Three studies assessed the benefit of SP-CMR, while 1 also examined the benefit of LGE-CMR.

B4A.2.4 PROGNOSTIC VALUE OF SP-CMR

DOES IT PREDICT HEALTH OUTCOMES?

Summary – Does CMR gadolinium-based stress perfusion and viability imaging predict health outcomes, compared with exercise or dobutamine stress echo, exercise or pharmacologic (adenosine or dobutamine) SPECT, CTCA and ICA for patients with symptoms consistent with IHD, with an intermediate PTP of CAD?

Summary – Does CMR gadolinium-based stress perfusion and viability imaging predict health outcomes, compared with exercise or dobutamine stress echo, exercise or pharmacologic (adenosine or dobutamine) SPECT, CTCA and ICA for patients with symptoms consistent with IHD, with an intermediate PTP of CAD?

Patients with positive stress CMR results (PDs and/or inducible WMAs) had a significantly higher incidence of MACE than those with a negative stress CMR result. Patients with LGE had significantly higher odds of cardiovascular death or MACE. The authors concluded that the prognostic risk assessment with stress CMR seemed comparable to that published for other stress-testing modalities for assessing prognostic risk.

One good-quality SR was identified that included only peer-reviewed studies in adults with a follow-up of at least 6 months, and provided summary statistics for the prognostic value of stress CMR for predicting health outcomes (Lipinski et al. 2013). A total of 19 studies that assessed the prognosis of 11,636 patients with known or suspected CAD using stress CMR were included. In 14 studies a vasodilator was used as the stress agent, while in 4 studies dobutamine was used, and 1 study used a combination of the two. The mean follow-up was 32 months (range 9–71 months) and the weighted mean LVEF was within the normal range ($61 \pm 12\%$). Fourteen studies defined a positive SP-CMR as having a reversible PD in at least 1 segment, while 5 studies defined a positive stress CMR as being a new or worsening stress-induced WMA. Although 19 studies were included in the review, some did not have any events during the follow-up period and were not incorporated into the meta-analyses.

Table 29 Ability of CMR to predict health outcomes

No. of studies	Predictive factor	Outcome measure	Odds ratio (95%CI)
k=16	Positive stress CMR	Cardiovascular death and non-fatal MI	6.5 (4.41, 9.58)
k=8	Positive stress CMR	Cardiovascular death	6.96 (4.13, 11.74)
k=8	Positive stress CMR	Non-fatal MI	9.05 (3.29, 24.91)
k=7	LGE	Cardiovascular death and non-fatal MI	3.82 (2.56, 5.71)
k=3	LGE	Cardiovascular death	2.71 (1.66, 4.41)
k=2	LGE	Non-fatal MI	3.29 (0.55, 19.76)

Source: Lipinski et al. (2013)

CI = confidence interval; CMR = cardiac magnetic resonance imaging; k = number of studies; LGE = late gadolinium enhancement; MI = myocardial infarction

The results of the SR (Table 29) show that stress CMR may be a useful tool for determining the prognosis of patients with suspected or known CAD. Patients with positive stress CMR (PD and/or inducible WMA) had a significantly higher incidence of MACE (cardiovascular death and non-fatal MI) than those with a negative stress CMR. Patients with LGE also had significantly higher odds for both cardiovascular death and MACE (Lipinski et al. 2013). The authors concluded that stress CMR seems comparable with other stress-testing modalities for assessing prognostic risk, although the SR did not include other testing modalities.

Incremental prognostic value of SP-CMR (over pre-imaging information)

Shah et al. (2013) used the presence of inducible ischaemia in a multivariate clinical risk model for risk reclassification across American College of Cardiology / American Heart Association practice guideline categories. For those in the intermediate risk category, the use of SP-CMR reclassified the majority of patients into either a low-risk (65.7%) or high-risk (25.8%) category. Patients were then followed up to determine whether health outcomes corresponded with the risk category determined by the clinical model alone or with the addition of inducible ischaemia identified by SP-CMR. Although there was no evidence that the risk categorisation was used to determine who

required further investigations or revascularisation, there was evidence that the categories assigned post-test did reflect the risk of MACE to a higher degree than the clinical model alone (Table 30). Patients with more severe ischaemia scores were more likely to have MACE than those with low ischaemia scores. Patients with more severe ischaemia were more likely to receive CMR-related revascularisation within 90 days after SP-CMR ($p < 0.0001$). The authors reported that revascularisation moderated the effect between the ischaemia score and MACE.

Table 30 MACE after reclassification after CMR stress perfusion

Study Location	Risk classification prior to stress perfusion	N patients (%)	Post-test low risk	Post-test intermediate risk	Post-test high risk
Shah et al. (2013) USA	Pre-test low risk (<1% risk per year)	337/740 (46)	311/337 (92.3%)	23/337 (6.8%)	3/337 (0.9%)
	Annualised rate of MACE		0.4%	1.6%	0%
	Intermediate (1–3% risk per year)	213/740 (29)	140/213 (65.7%)	18/213 (8.5%)	55/213 (25.8%)
	Annualised rate of MACE		0.3%	0%	4.9%
	High (>3% risk per year)	190/740 (26)	11/190 (5.8%)	60/190 (31.6%)	119/190 (62.6%)
	Annualised rate of MACE		0%	2.1%	14.3%

CMR = cardiac magnetic resonance imaging; MACE = major adverse coronary event (coronary death or non-fatal MI); MI = myocardial infarction

Three case series assessed the NRI of SP-CMR and one of LGE-CMR (Table 31). The predictive ability of SP-CMR is relevant if its use influences clinical practice, through having the patient cross a clinically meaning threshold. In the studies included it is unclear whether the cut-offs chosen relate to cut-offs for initiating a different type of treatment.

Among those patients who experienced MACE, Bingham & Hachamovitch (2011) reported that 2% of patients had been incorrectly down-classified, and no patients had been correctly up-classified, whereas Abbasi et al. (2014) and Shah et al. (2013) reported that 12% and 4% of patients, respectively, were correctly up-classified by SP-CMR. Conversely, the 3 studies reported that, in those who did not experience events, 6%–19% of patients were correctly down-classified.

Table 31 Net reclassification improvement after CMR

Study/Location	Outcome	N patients (%)	Results
Abbasi et al. (2014) USA	NRI across all risk categories	304 (100)	0.29 (95%CI 0.0,0.44)
	NRI for patients at intermediate risk pre-CMR	117 (38)	0.68 (95%CI 0.07,1.29)
	Continuous NRI across all risk categories	304 (100)	0.58 (95%CI 0.22,0.95); $p = 0.007$
	NRI with addition of SP-CMR among patients who experienced MACE	45	0.12 (95%CI NR)
	NRI with addition of SP-CMR among patients who did not experience MACE	252	0.17 (95%CI NR)

Study/Location	Outcome	N patients (%)	Results
Bingham & Hachamovitch (2011) USA	NRI with addition of: SP-CMR LGE among patients who experienced MACE	101 (11)	-0.02 (95%CI NR)
		101 (11)	-0.02 (95%CI NR)
	NRI with addition of: SP-CMR LGE among patients without MACE	807 (89)	0.06 (95%CI NR)
		807 (89)	0.11 (95%CI NR)
	Patients correctly reclassified overall by addition of: SP-CMR LGE	NR (3.5)	0.04(95%CI NR)
		NR (8.9)	0.09 (95%CI NR)
Shah et al. (2013) USA	Categorical NRI, overall	740 (100%)	0.23 (95%CI 0.063, 0.391)
	Categorical NRI for patients <i>with</i> MACE	92 (12.4%)	0.04 (95%CI NR)
	Categorical NRI for patients <i>without</i> MACE	648 (87.6%)	0.19 (95%CI NR)
	Continuous NRI	-	1.11 (95%CI 0.81, 1.39)

CMR = cardiac magnetic resonance imaging; LGE = late gadolinium enhancement; MACE = major adverse cardiac event; NR = not reported; NRI = net reclassification improvement; SP-CMR = stress perfusion CMR.

B5A CLINICAL UTILITY (POPULATION 1)

B5A.1 IMPACT ON CLINICAL MANAGEMENT (THERAPEUTIC EFFICACY)

B5A.1.1 RISK OF BIAS ASSESSMENT

Seven studies were included for the assessment of the impact of SP-CMR on clinical management among population 1 (Table 146 in Appendix C). Of these, 6 studies were case series and the risk of bias was determined for these studies using the IHE checklist (Moga et al. 2012). Five case series were considered to have a low risk of bias, and 1 had a moderate risk of bias. The remaining study was a within-patient cross-over study (Schonenberger et al. 2007), which was assessed using the Downs and Black (1998) checklist and was considered to have a low risk of bias. The risk of bias assessment for each study is presented in Table 146 in Appendix C. The main flaw with the studies identified is that, with the exception of the study by Schonenberger et al. (2007), none included a relevant comparator. The documentation of clinical management that occurs after SP-CMR therefore does not inform the research question regarding how the clinical management is *impacted* by SP-CMR. Without comparative imaging, the degree to which SP-CMR influenced the subsequent management of patients is also highly uncertain.

B5A.1.2 CHARACTERISTICS OF THE EVIDENCE-BASE

See Table 146 in Appendix C for details on the individual studies included in the evidence-base. Two of these studies (Abbasi et al. 2014; Bingham & Hachamovitch 2011) included for impact on patient management exactly matched the proposed MBS population, being patients presenting with symptoms consistent with IHD, and with an intermediate PTP of CAD. The remaining studies did not specify the PTP but described the populations as patients presenting with chest pain or other symptoms providing a basis for clinical suspicion of CAD/myocardial ischaemia. They appear likely to be relevant to the target population.

B5A.1.3 OUTCOME MEASURES AND ANALYSIS

See Table 146 in Appendix C for details on the outcomes measured in the included studies, along with the statistical methods used to analyse the results. All the outcome measures for therapeutic efficacy (the clinical management that follows SP-CMR) have little clinical importance by themselves in non-comparative studies. They only have an impact if the clinical management is different to what patients would have received if imaged through other means, or not at all, and the management in itself is beneficial.

Studies included for impact on clinical management reported on six different outcome categories: risk reclassification, change in clinical diagnosis, change in therapeutic decision, additional diagnostic procedures avoided, CMR-related revascularisation and patient acceptance/preference for diagnostic procedure (Table 32). For five of these categories the outcomes were reported as a proportion, which was appropriate. For patient acceptance/preference the outcome was reported as a mean \pm standard deviation across five acceptance domains on patient acceptance, using a 5-point Likert scale that included: a) preparation and information prior to the test; b) degree of concern prior to the test; c) comfort during the test; d) degree of helplessness and c) overall satisfaction.

Table 32 Key features of included evidence for the impact of CMR on patient management

Trial/Study	Key outcome(s)	Clinical importance
Abbasi et al. (2014)	Risk reclassification for MACE	Low
Bingham & Hachamovitch (2011)	Early referral to revascularisation; cardiovascular risk reclassification	Moderate Low

Bodi et al. (2012)	Rate of CMR-directed revascularisation	Moderate
Bodi et al. (2009)	Rate of CMR-directed revascularisation	Moderate
Bruder et al. (2013)	Change in clinical diagnosis; therapeutic consequences; additional diagnostic procedures avoided due to CMR results	Moderate
Schonenberger et al. (2007)	Patient acceptability and preference	Moderate
Shah et al. (2013)	Risk reclassification	Low

CMR = cardiac magnetic resonance imaging; MACE = major adverse cardiac events

B5A.1.4 RESULTS OF THE SYSTEMATIC LITERATURE REVIEW

DOES IT IMPACT ON CLINICAL MANAGEMENT?

Summary – Does CMR gadolinium-based stress perfusion and viability imaging change clinical management, compared with exercise or dobutamine stress echo, exercise or pharmacologic (adenosine or dobutamine) SPECT, CTCA and ICA for patients with symptoms consistent with IHD, with an intermediate PTP of CAD?

Due to the lack of comparative evidence regarding how SP-CMR influences management, no statements regarding the comparative therapeutic efficacy can be made.

Before-and-after case series provided evidence that SP-CMR does change the risk classification of a proportion of patients (particularly those in the 'intermediate risk' category), and this may assist in selecting those patients who should have further invasive testing and/or revascularisation. Furthermore, patients reclassified as having a low risk of cardiac AEs may avoid the need for invasive testing or procedures. However, it is unknown to what extent these findings are different to the number of patients reclassified after having comparative non-invasive imaging modalities such as CTCA, SPECT, stress Echo or ECG.

One cross-over trial compared patient acceptance and preference between CMR, CTCA and ICA. The vast majority of patients preferred CTCA, with similar low rates of preference for CMR and ICA.

A total of 7 studies were included for the assessment of impact on clinical management (Table 146 in Appendix C). The outcomes reported in these studies are presented here according to six main categories: a) risk reclassification; b) change in clinical diagnosis; c) change in therapy/patient management; d) additional diagnostic procedures avoided; e) CMR-related revascularisation and f) patient acceptance/preference.

Risk reclassification

The 3 case series (level IV evidence) that presented results for risk reclassification included patients in a hospital specialist imaging division (Abbasi et al. 2014), outpatient clinic (Bingham & Hachamovitch 2011), and attending general and specialist hospital cardiology services (Shah et al. 2013), all in the USA. Therefore, the results of these studies would be applicable to the Australian healthcare system with few caveats. Given the study design, the quality of the evidence is considered very low (GRADE ⊕⊖⊖⊖).

The results from the 3 case series (level IV evidence) that presented data for risk reclassification are summarised in Table 33 and Table 34 below. In all 3 studies, patients were categorised at baseline for their risk of MACE. Patients were then imaged using CMR and the data on SP-CMR with/without LGE-CMR was used to revise the risk categories. None of the studies undertook any comparison of CMR, with the valid comparators for this assessment specified *a priori*; however, these data do provide a basis on which to *infer* changes to the management of patients that would occur in Australian clinical practice based on changes to patient risk profile resulting from SP-CMR with/without LGE. According to the clinical pathway presented in the research protocol, low-,

intermediate- and high-event risk patients are respectively managed with optimal medical therapy alone (OMT), OMT with or without ICA, depending on comorbidities, and OMT with ICA, followed by revascularisation where appropriate. In all 3 studies there were a large proportion of patients in the intermediate group who were recategorised, and the majority (18%–65.7%) were reclassified as low risk, allowing the patients to avoid unnecessary ICAs on the basis of SP-CMR results. Some ‘intermediate risk’ patients (16%–25.8%) were reclassified as high risk, suggesting that they may be in need of urgent referral to ICA given their post-CMR high-event risk classification. However, whether or not this reclassification results in the avoidance of ICA in favour of OMT is likely to depend on individual patient comorbidity profiles, while taking into account patient preferences informed by appropriate disclosure of the risks and benefits of the two clinical management options (Abbasi et al. 2014).

Table 33 Risk reclassification after SP-CMR

Study Location	Risk classification prior to stress perfusion	N patients (%)	Reclassified as low risk	Reclassified as intermediate risk	Reclassified as high risk
Abbasi et al. (2014) USA	Low ($\leq 5\%$ risk)	26/304 (9)	N/A	4/26 (15%)	1/26 (4%)
	Intermediate (5%–10% risk)	117/304 (38)	21/117 (18%)	N/A	19/117 (16%)
	High (>10% risk)	161/304 (53)	0/304	43/161 (27%)	N/A
Bingham & Hachamovitch (2011) USA	Low risk (0%–1.5%)	130/931 (14)	N/A	9/130 (6.9%)	2/130 (1.5%)
	Intermediate risk (1.5%–2.0%) ^a	59/931 (6)	35/59 (59.3%)	N/A	11/59 (18.6%)
	High risk (>2.0%)	742/931 (82)	7/742 (0.9%)	31/742 (4.1%)	N/A
Shah et al. (2013) USA	Low (<1% risk per year)	337/740 (46)	N/A	23/337 (6.8%)	3/337 (0.9%)
	Intermediate (1%–3% per year)	213/740 (29)	140/213 (65.7%)	N/A	55/213 (25.8%)
	High (>3% risk per year)	190/740 (26)	11/190 (5.8%)	60/190 (31.6%)	N/A

^a As reported in the study paper; the assessment group note that the classification categories 0–1.5% and 1.5% are not mutually exclusive—it would appear that in the original study, 33 patients have been counted in both the 0–1.5% and 1.5–2.0% risk categories when the authors reported on the number of patients reclassified. No addendum and no comments have been made available since publication of the original paper. The authors were contacted in an attempt to clarify, but no response was received.

N/A = not applicable; SP-CMR = stress perfusion cardiac magnetic resonance imaging

Table 34 Risk reclassification after LGE-CMR

Study Location	Risk classification prior to LGE-CMR	N patients (%)	Reclassified as low risk	Reclassified as intermediate risk	Reclassified as high risk
Bingham & Hachamovitch (2011) USA	Low risk (0–1.5%)	117/931 (13)	N/A	0/117	0/117
	Intermediate risk (1.5%–2.0%)	90/931 (10)	0/90	N/A	20/90
	High risk (>2.0%)	701/931 (77)	0/701	43/701	N/A

LGE-CMR = cardiac magnetic resonance imaging with late gadolinium enhancement; N/A = not applicable

The reclassification data reported by the 3 case series, interpreted within the framework provided by the clinical pathway shown in the research protocol, suggest that SP-CMR may result in treatment decisions for patients with suspected CAD that differ from pre-CMR clinical assessment of risk, but it is unknown to what extent management would change if patients had been tested with an alternative non-invasive imaging modality.

Change in clinical diagnosis

The study by Bruder et al. (2013) analysed data collected by the EuroCMR registry, comprising a variety of outcomes for patients undergoing routine CMR in 57 European centres (in 15 countries), and presented results for evidence of a change in clinical diagnosis.

Of the 9,508 patients with suspected CAD/ischaemia who were followed, CMR findings led to a completely new diagnosis not previously suspected in 8.1% of cases. Given the comparable standards of healthcare in Australia and the EU, it would seem reasonable to conclude that these findings have a good degree of applicability in our system; however, it is unclear what the consequences of the findings would be, especially without details of which conditions the different diagnoses included nor any indication of diagnostic findings for any other method applicable for the diagnosis/treatment work-up of patients suspected of CAD. Given the study design, the quality of the evidence is considered very low (GRADE ⊕⊖⊖⊖).

Change in therapy/patient management

The large multicentre study by Bruder et al. (2013) found that for a large proportion of patients, the results of CMR led to a change in patient management, compared with what they would have undergone, based on the information available prior to CMR (prior tests not specified; Table 35). Overall, 71.4% of patients experienced an impact on their management as a result of SP-CMR (GRADE ⊕⊖⊖⊖).

Table 35 Change in therapy/management

Outcome	Results
For patients with suspected CAD/ischaemia only (n=9,508):	
Therapeutic consequences	
Change in medication	24.3%
Invasive procedure	23.1%
Hospital discharge	14.3%
Hospital admission	1.5%
Overall impact on patient management (new diagnosis and/or therapeutic consequence)	71.4%

Source: Bruder et al. (2013)

CAD = coronary artery disease

Additional diagnostic procedures

Bruder et al. (2013) also reported on the impact that SP-CMR had on avoiding the need for further diagnostic procedures (Table 36). The number of patients who received SP-CMR for suspected or known CAD and therefore avoided the need for an ICA, SPECT/PET or CTCA procedure is reported in Table 36 (GRADE ⊕⊖⊖⊖).

Table 36 Additional diagnostic procedures avoided due to stress CMR

Study	Diagnostic test avoided due to CMR	N patients (%)
Bruder et al. (2013)	ICA	4,555/10,113 (45)
15 countries	SPECT/PET	3,946/10,113 (39)
	CTCA	2,202/10,113 (22)

Source: Bruder et al. (2013)

CMR = cardiac magnetic resonance imaging; CTCA = computed tomography coronary angiography; ICA = invasive coronary angiography; PET = positron emission tomography; SPECT = single-photon emission computed tomography

Bodi et al. (2012; 2009) also reported rates of ICA following SP-CMR. Patients who had inducible WMAs were most likely to be referred for ICA, followed by those with PDs and then those with LGE (Table 37). A small number of patients without any evidence of ischaemia were still referred for ICA subsequent to SP-CMR (GRADE ⊕⊙⊙⊙). Due to the lack of comparative non-invasive imaging, the impact of SP-CMR, relative to the comparators, cannot be determined.

Table 37 Frequency of ICAs subsequent to CMR

Study	CMR result	ICA after CMR / N patients (%)
Bodi et al. (2012) Spain	No ischaemia	58/901 (6%)
	PD only, without LGE or inducible WMA	122/219 (56%)
	LGE without inducible WMA regardless of PD	139/409 (34%)
	Inducible WMA regardless of PD and LGE	131/193 (68%)
	Total	450/1722 (26%)
Bodi et al. (2009) Spain	No ischaemia	39/354 (11%)
	PD only, without LGE or inducible WMA	99/181 (55%)
	Simultaneous PD and WMA	54/66 (82%)
	Total	192/601 (32%)

Source: Bodi et al. (2012); Bodi et al. (2009)

CMR = cardiac magnetic resonance imaging; ICA = invasive coronary angiography; LGE = late gadolinium enhancement; PD = perfusion defect; WMA = wall motion abnormality

CMR-related revascularisation

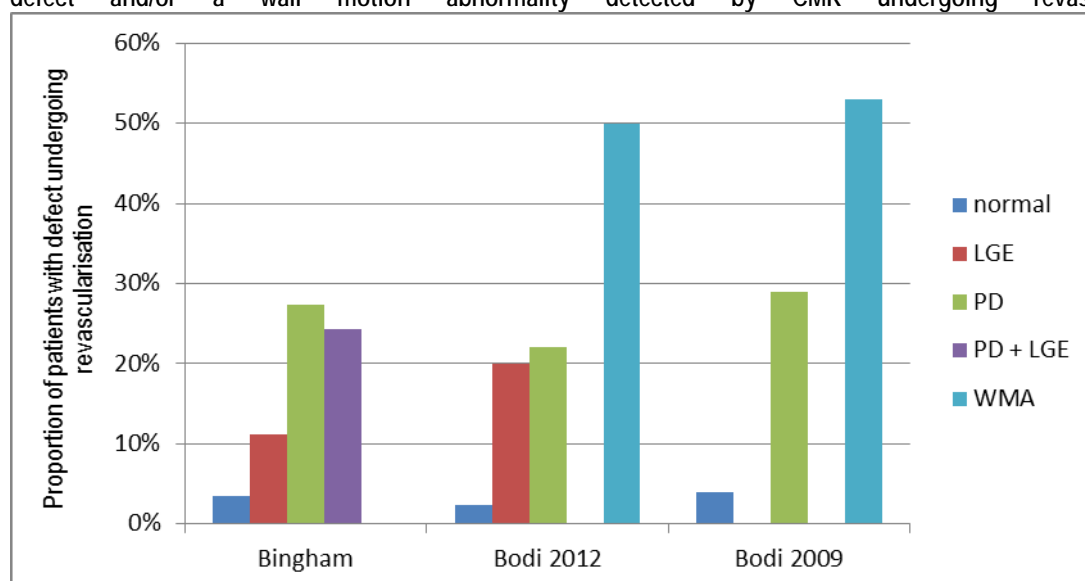
Three studies reported on the frequency of revascularisation as a result of CMR findings, 1 case series in the United States (Bingham & Hachamovitch 2011) and 2 case series from Spain (Bodi et al. 2012; 2009). The results of these studies can be considered applicable to the Australian healthcare system, and are presented in Table 169 (GRADE ⊕⊙⊙⊙). All 3 studies found significant differences in the frequency of referral to early revascularisation across the patient groups compared (Table 169 in Appendix E).

Bingham & Hachamovitch (2011) reported that among patients found to have normal perfusion on CMR, evidence of LGE led to nearly three times as many referrals to revascularisation compared with without LGE ($p < 0.01$). Among patients found to have abnormal perfusion, the number of revascularisation referrals was equivocal regardless of whether LGE was evident (no significant difference reported). Among patients with LGE, those with abnormal perfusion were referred for revascularisation more than twice as frequently as those with normal perfusion status ($p < 0.01$). Among patients for whom LGE was not evident, those with abnormal perfusion were referred much more frequently than those with normal perfusion (27.3% versus 3.5%, respectively; $p < 0.01$). For all patients included in the study, those for whom LGE was used were referred for revascularisation more than three times as frequently as those without LGE ($p < 0.01$). The differences found between the comparisons suggest that specific findings on CMR may have a role in discriminating between patients who require referral to revascularisation and those for whom revascularisation may be avoided or delayed.

Bodi et al. (2012; 2009) presented data on the frequency of patients who underwent ICA, revascularisation by angioplasty and revascularisation by surgery following CMR findings, stratified according to different categories as determined by CMR. Patients who had inducible WMA were most likely to undergo revascularisation subsequent to CMR (GRADE ⊕⊙⊙⊙).

These results are summarised in Figure 22.

Figure 22 The proportion of patients with a normal CMR result, non-viable myocardium (LGE), a perfusion defect and/or a wall motion abnormality detected by CMR undergoing revascularisation



LGE = late gadolinium enhancement; PD = perfusion defect; WMA = wall motion abnormality

Patient acceptance and preference

One study in Germany reported on patient acceptance and preference for patients who underwent CMR, CTCA and ICA (Schonenberger et al. 2007). The study used a within-patient cross-over design (level II evidence), with patients receiving all three tests. As shown by the results in Table 38, it was found that for the comparison between CMR, CTCA and ICA, there were no statistically significant differences in how patients perceived their preparation and information received prior to testing, although patients were less concerned prior to CMR and CTCA compared with ICA ($p < 0.001$). Patients were slightly more comfortable during CTCA compared with CMR ($p < 0.001$), and rated their degree of helplessness in the CTCA procedure to be slightly less than the that during ICA ($p < 0.001$). Overall, the vast majority of patients preferred CTCA to either CMR or ICA ($p < 0.01$). Patient satisfaction did not significantly differ between ICA and CMR. Surprisingly, preference for procedure did not differ between patients who underwent revascularisation compared with those who did not, and patient willingness to undergo the procedures did not significantly differ between CMR, CTCA or ICA (GRADE ⊕○○○).

Table 38 Patient acceptance and preference

Outcome	CMR	CTCA	ICA	Comparison
Patient acceptance (mean ±SD)				
Preparation and information prior to the test*	1.35 ± 0.64	1.27 ± 0.52	1.48 ± 0.72	-
Degree of concern prior to the test**	1.64 ± 0.93	1.51 ± 0.85	2.75 ± 1.23	$p < 0.001$ compared with ICA ^c
Comfort during the test ^a	1.75 ± 0.81	1.49 ± 0.64	1.54 ± 0.68	$p < 0.001$ compared with CMR ^c
Degree of helplessness ^b	1.39 ± 0.89	1.19 ± 0.48	1.52 ± 0.86	$p < 0.001$ compared with ICA ^c
Overall satisfaction ^a	1.58 ± 0.89	1.32 ± 0.51	1.46 ± 0.61	-
Preferred test, N (%)	18 (16%)	80 (72%)	13 (12%)	Preference for CTCA was significantly higher than for CMR and ICA ($p < 0.001$)
Willing to undergo tests again	93/111 (83.8)	106/111 (93.7)	101/111 (91.0)	Differences NS

Source: Schonenberger et al. (2007)

^a Evaluated on a 5-point Likert scale, range: 1=very good to 5=poor

^b Evaluated on a 5-point Likert scale, range 1=none to 5=very high

^c Using Wilcoxon's test for paired samples

CMR = cardiac magnetic resonance imaging; CTCA = computed tomography coronary angiography; ICA = invasive coronary angiography; NS = not significant; SD = standard deviation

B5A.2 THERAPEUTIC EFFECTIVENESS (INCLUDING IMPACT OF EFFECT MODIFICATION)

The therapeutic effectiveness of SP-CMR is based on whether patients are able to have their condition managed in a way that improves their health, relative to the management strategy they would have undergone had SP-CMR not been used. In Australia the population of interest would currently receive the comparators (i.e. exercise ECG, stress Echo, SPECT or CTCA). The therapeutic effectiveness should therefore assess what impact CMR has on health compared with those imaging modalities. Unfortunately, the studies included in this section do not compare CMR against other imaging techniques and are only able to assess the benefit of the management strategies used, after CMR has been used, comparing management strategies for different risk profiles—that is, by providing a comparison of health outcomes, which may be inferred to show how patients benefit from having their treatment guided by CMR (as compared with no imaging).

B5A.2.1 RISK OF BIAS ASSESSMENT

Three studies, two by the same research group, provided information on the non-comparative effectiveness of CMR imaging (Bodi et al. 2012; 2009; Shah et al. 2013). The studies compare the difference in rate of MACE, based on the interaction between stratification by CMR and treatment received. Unfortunately, all 3 of these studies are retrospective and highly subject to selection bias, which threatens the internal validity of the comparisons.

These studies provided information to possibly inform the assessment of the therapeutic effectiveness of CMR. They were considered to be cohort studies, as they compared the effectiveness of revascularisation in those identified as having different risk profiles, based on CMR. These studies were assessed using a modified Downs and Black (1998) checklist; two were considered to be at a moderate risk of bias and one had a high risk of bias (Table 147 in Appendix C). As they were cohort studies rather than randomised studies, there was no discussion of blinding, and it is unclear to what extent the outcomes are due to confounding factors rather than the independent predictors of interest (CMR findings).

B5A.2.2 CHARACTERISTICS OF THE EVIDENCE-BASE

See Table 147 in Appendix C for details on the individual studies included in the evidence-base. The studies are considered to be applicable to the target population; enrolled patients are being investigated with stress CMR for ischaemic chest pain. The reasons for imaging were inconclusive exercise test results, altered baseline ECG, inability to exercise, evaluation of intermediate coronary lesions or as the first choice in patient work-up (Bodi et al. 2012). The mean LVEF from patients in this study was 62 ± 13 , suggesting that the clinical spectrum of the patients is similar enough to the target population to be applicable.

B5A.2.3 OUTCOME MEASURES AND ANALYSIS

See Table 147 in Appendix C for details on the outcomes measured in the included studies, along with the statistical methods used to analyse the results. A summary of the key outcomes is presented in Table 39.

The outcome measure used to determine therapeutic effectiveness is the rate of MACE between treatment strategies for patients with different risk profiles (i.e. cardiac death, non-fatal MIs or admission for unstable angina). This outcome is considered to be of high clinical importance, and to

have a low risk of being influenced by potential sources of bias such as lack of blinding of patients or outcome assessors. The rates of MACE were assessed by multivariate Cox proportional hazards model, adjusted for baseline and CMR variables.

Table 39 Key features of included evidence comparing health outcomes for revascularisation versus no revascularisation in patients stratified by CMR

Trial/Study	Key outcome(s)	Clinical importance
Bodi et al. (2012)	MACE (cardiac mortality or non-fatal MI or unstable angina)	High
Bodi et al. (2009)	MACE (cardiac mortality or non-fatal MI or unstable angina)	High
Shah et al. (2013)	MACE (cardiac mortality or acute, non-fatal MI)	High

CMR = cardiac magnetic resonance imaging; MACE = major adverse cardiac events; MI = myocardial infarction

B5A.2.4 RESULTS OF THE SYSTEMATIC LITERATURE REVIEW

DOES THE CHANGE IN MANAGEMENT IMPROVE HEALTH OUTCOMES?

Summary – Is any resulting change in management from SP-CMR therapeutically effective?

Due to the lack of comparative evidence regarding how SP-CMR influences management, no statements regarding the comparative therapeutic effectiveness can be made. However, SP-CMR does appear to be good at predicting the prognosis of patients in regards to their risk of MACE. It may therefore be concluded that SP-CMR could rule out patients that do not require an ICA.

Stress-CMR appears to be able to identify a large group of patients with good prognosis who do not require ICA or revascularisation. It also appears to be able to identify a small subgroup of patients with PDs and inducible WMAs for whom revascularisation is associated with a significantly reduced risk of cardiac death or non-fatal MIs. However, there is a strong risk that patients may have been allocated to treatments in such a manner that, within this subgroup, those with better prognosis due to clinical characteristics received revascularisation, whereas those with poorer prognosis remained on medical therapy alone. Conclusions regarding the effectiveness of treatment cannot therefore be made with any certainty. There was not a significant difference in major events between treatment strategies in patients with PDs or LGE in the absence of WMAs. The two studies that contributed to these findings were prospective cohort studies, and the risk of selection bias cannot be ruled out.

Two studies, deriving data from one or two university hospitals in Spain, provided information on the possible clinical utility of SP-CMR for patients with ischaemic chest pain (Bodi et al. 2012; 2009). Patients who had no evidence of ischaemia were much more likely to receive medical therapy than revascularisation. The patients who received revascularisation had a higher rate of MACE during follow-up but, given the likelihood that the patients who received revascularisation would have different baseline characteristics than those who received medical therapy, conclusions should not be made on the efficacy of one treatment over the other in this patient group.

No significant differences were found in the subgroups identified with PDs (but no WMAs) or those with LGE (but no WMAs) between groups who received revascularisation or medical therapy alone (Figure 23). In patient groups with WMAs, those who received revascularisation had lower rates of MACE. However, due to the study design, it is unknown whether the difference is due to confounding factors such as baseline differences in the patients allocated to revascularisation rather than medical therapy alone, or whether there is truly a difference in treatment effect in this subgroup.

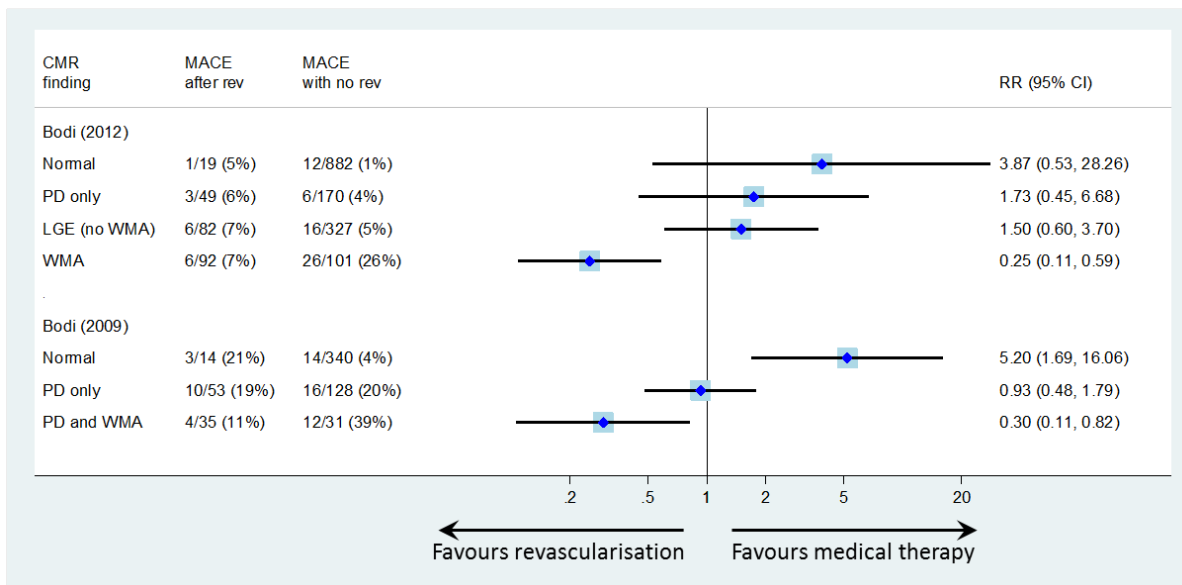


Figure 23 Effect of CMR-related revascularisation

CMR = cardiac magnetic resonance imaging; LGE = late gadolinium enhancement; MACE = major adverse coronary events, defined as cardiac death or non-fatal myocardial infarction; PD = perfusion defect; RR = relative risk; WMA = wall motion abnormality

Assessed by multivariate Cox proportional hazards model, adjusted for a propensity score for undergoing CMR-related revascularisation obtained from a stepwise logistic regression model, including baseline and CMR variables

Shah et al. (2013) also assessed the interaction between ischaemia, revascularisation, and rates of MACE (Table 40). They reported that in those who underwent early revascularisation, the average ischaemia score was 4.9 ± 4.2 , and in those who did not, it was 0.8 ± 2.3 . The interaction between early revascularisation and degree of ischaemia was significant when entered into a multivariate clinical model ($p=0.02$). Those with a greater degree of ischaemia had an increased hazard of MACE if they did not undergo revascularisation, while degree of ischaemia was not a significant predictor of MACE if the patient underwent revascularisation.

Table 40 Comparison of extent of ischaemia in patients who underwent early revascularisation compared with those who did not

Trial/Study	Population	Comparison	HR for MACE (95%CI)
Shah et al. (2013)	Did not undergo revascularisation	Greater vs lesser extent of ischaemia	1.18 (1.12, 1.24), $p < 0.0001$
	Underwent revascularisation	Greater vs lesser extent of ischaemia	1.06 (0.95, 1.18), $p = 0.30$

CI = confidence interval; HR = hazard ratio; MACE = major adverse cardiac events

B6A IMPACT OF REPEAT TESTING/MONITORING (POPULATION 1)

Not applicable.

B7A EXTENDED ASSESSMENT OF COMPARATIVE HARMS (POPULATION 1)

The risks from imaging are small, so determining the rates of AEs is difficult, as they are often too rare to be detected in trials. This section provides an overview of potential safety concerns associated with CMR and the comparative tests in population 1. A review of the literature identified five studies that provided evidence of the short-term and long-term AEs associated with SP-CMR, CTCA, SPECT, stress Echo, exercise ECG and ICA. A summary of the main contributors to AEs and the estimated risk is provided in Table 41. The tests are discussed first, followed by a discussion of the different components associated with AEs.

Table 41 Summary of potential safety concerns and estimated risk of AEs or death for population 1

Test / overall serious AE and mortality rate	Radiation dose	Stressors	Contrast agents and tracers	Other
SP-CMR with/without LGE Serious AEs: 2–19/10,000 scans Mortality: 7–8/10,000 patients	0	<u>Dobutamine</u> ; serious AEs: 18/10,000 tests Death: 1.4/10,000 patients <u>Dipyridamole</u> ; serious AEs: 7.7/10,000 tests Death: 4/100,000 patients <u>Adenosine</u> ; serious AEs: 1.4/10,000 tests Death: 0.1/10,000 patients	Gadolinium Serious AEs: 0.48/10,000 doses Long-term death rate: 6.6/10,000 doses	Claustrophobia Magnetism Serious AEs: 0.2/10,000 scans
Stress Echo Serious AEs: 5–21/10,000 scans Mortality: 1–2/10,000 patients	0	<u>Exercise</u> ; serious AEs: 1.5/10,000 tests Death: 0.1/10,000 patients <u>Dipyridamole</u> ; serious AEs: 7.7/10,000 tests Death: 0.4/10,000 patients <u>Dobutamine</u> ; serious AEs: 18/10,000 tests Death: 1.4/10,000 patients	Microspheres of contrast (not common) Serious AEs: 3/10,000 scans Long-term death rate: 0.1/10,000 patients	Heat from ultrasound
SPECT Serious AEs: 2–18/10,000 scans Mortality: 8–9/10,000 patients	15.6 mSv Additional fatal cancers: 7.8/10,000 patients	<u>Exercise</u> ; serious AEs: 1.5/10,000 tests Death: 0.1/10,000 patients <u>Dipyridamole</u> ; serious AEs: 7.7/10,000 tests Death: 0.4/10,000 patients <u>Adenosine</u> ; serious AEs: 1.4/10,000 tests Death: 0.1/10,000 patients <u>Dobutamine</u> ; serious AEs: 18/10,000 tests Death: 1.4/10,000 patients	Radiotracers (Tc99 sestamibi or Myoview or thallium-201) Serious AEs: 0.06/10,000 scans	-

Test / overall serious AE and mortality rate	Radiation dose	Stressors	Contrast agents and tracers	Other
Exercise ECG Serious AEs: 1.5/10,000 tests Mortality: 0.1/10,000 patients	0	Exercise; serious AEs: 1.5/10,000 tests Death: 0.1/10,000 patients	0	Electrode site
CTCA Serious AEs: 4/10,000 scans Mortality: 8–14/10,000 patients	3–14 mSv Additional fatal cancers: 1.5–7/10,000 patients	-	Iodinated contrast agent Serious AEs: 4/10,000 scans Long-term death rate: 7/10,000 patients	-
ICA Serious AEs: 100–200/10,000 procedures Mortality: 19/10,000 patients	7.0 mSv Additional fatal cancers: 3.5/10,000 patients	-	Iodinated contrast agent Serious AEs: 4/10,000 scans Long-term death rate: 7/10,000 patients	Catheterisation through artery Serious AEs: 100-200/10,000 procedures Acute death rate: 8/10,000 procedures

Sources: Einstein et al. (2012); Knuuti et al. (2014); Varga et al. (2006)

The overall serious AE and mortality rates were calculated assuming that where more than one stressor is used with a procedure, the overall risk was equivalent to their mean; 10 mSv = 5 fatal cancers /10,000 patients (Knuuti et al. 2014).

AE = adverse event; CMR = cardiac magnetic resonance imaging; CTCA = computed tomography coronary angiography; ECG = electrocardiogram; Echo = echocardiography; ICA = invasive coronary angiography; LGE = late gadolinium enhancement; SP-CMR = stress perfusion cardiac magnetic resonance imaging; SPECT = single-photon emission computed tomography

CARDIAC MAGNETIC RESONANCE IMAGING

One benefit of CMR is that it does not require the use of any radiation. However, there are other AEs that may occur—radiofrequency energy may be responsible for tissue heating (Knuuti et al. 2014), and some metallic devices such as pacemaker leads may induce local heating as well as arrhythmias. Knuuti et al. (2014) estimated the risk of accidents to be 0.07/10,000 examinations, and serious AEs (including burns and arrhythmias) occur in 0.2/10,000 examinations.

ECG

Exercise ECG is generally quite safe, not being associated with any radiation dose or contrast agent. There is a small risk due to the heart's response to exercise (walking on a treadmill or riding a stationary bicycle), which is associated with AEs in 1.2–8.6 cases per 10,000 tests, depending on the population (Knuuti et al. 2014).

ECHO

There is no evidence that the ultrasound itself used in Echo has caused any AEs with the doses used in diagnostic imaging. Knuuti et al. (2014), based on post-marketing surveillance with a perflutren lipid microsphere, estimated the risk of serious AEs due to contrast agents used with echocardiography to be 3/10,000 and the risk of death as 0.1/10,000.

SPECT

Radionuclide imaging (SPECT or PET) uses radiotracers (99mTc-sestamibi/-tetrofosmin) which have very good safety profiles. No serious AEs have been identified due to the radiotracers, which are a much lower dose than ordinary diagnostic contrast media. Knuuti et al. (2014) estimated the risk of serious AEs from the radiotracers to be 0.06/10,000 studies.

CTCA

Multislice CTCA uses both radiation and contrast media, which may be associated with AEs. The major concern is contrast-induced nephropathy, which is of particular concern in patients with reduced renal function (creatinine clearance <60) (Salerno & Beller 2009). Radiation and contrast media are discussed below.

ICA

Considered the gold standard for investigations in population 1, ICA may cause serious complications (Knuuti et al. 2014). Based on a rapid review of the literature, the risk of diagnostic cardiac catheterisations is estimated to be 8 deaths / 10,000 procedures, and 177 AEs / 10,000 procedures, contributing to an overall major complication rate of 1%–2% (Knuuti et al. 2014). Being invasive, ICA is associated with a greater risk of acute death than non-invasive imaging, due to the procedure itself.

RADIATION RISK

There are two types of effects from radiation, deterministic and stochastic. Deterministic effects are tissue reactions, where injury to cells is caused by radiation above a threshold dose, with the severity of effect often increasing with the dose. Examples of deterministic effects are skin and hair changes, cardiovascular disease and cataracts (Einstein 2012). However, deterministic effects do not occur at the radiation doses used for diagnostic imaging procedures.

The major concern related to diagnostic imaging tests is with stochastic effects, and is due to the likelihood of an effect happening rather than the severity of an effect. With stochastic effects, the risk is from radiation-induced mutations rather than cell-death—mutations cause malignancies and heritable diseases in offspring (Einstein 2012). Malignancies occur after a latency period which varies from 2 years with non-chronic lymphocytic leukaemia, to at least 5–10 years for most solid tumours (Einstein 2012).

Determining the risk due to radiation is difficult, as no prospective trials have been performed using the doses applied in diagnostic procedures. Extrapolations have been performed, using epidemiological studies from atom bomb survivors, nuclear industry workers and children exposed to x-rays *in utero* (Einstein 2012). The results show that there are statistically significant increases in cancer risk associated with radiation doses consistent with those given through cardiac imaging (Einstein 2012). Radiation doses are estimated in Table 41.

Data from a large Canadian cohort of 82,861 patients who had had an acute MI showed that, per 10 mSv increase in radiation from cardiac procedures, there was an adjusted hazard ratio (controlled for age, sex and radiation exposure from non-cardiac procedures) for cancer of 1.03 (95%CI 1.02, 1.04), with a mean follow-up of 5 years (Eisenberg et al. 2011). That is, for every 10 mSv of low-dose radiation, there was a 3% increase in cancer within 5 years. The estimated risk by the International Commission on Radiological Protection is that 10 mSv would translate to 5 additional fatal cancers / 10,000 patients (Knuuti et al. 2014).

STRESSORS

Knuuti et al. (2014) assessed the risks of different forms of cardiac imaging through a narrative literature review, and found that dynamic exercise is associated with AEs in 1.2–8.6 cases per 10,000 tests, depending on the population. Serious AEs from dipyridamole and adenosine occur at a similar rate to exercise, although minor AEs are more common. Dobutamine is associated with a higher rate of complications than other stressors, and 1 meta-analysis of 335 tests had 1 severe AE.

The International Stress Echo Complication Registry included information from 71 centres in 17 countries, assessing the safety of stress echocardiography (Varga et al. 2006). This included 18 university hospitals, 41 community hospitals and 12 tertiary care centres. Treadmill or bicycle exercise echocardiography was used in 26,295 examinations, and 4 patients (1 per 6,574 examinations) experienced life-threatening AEs (Varga et al. 2006). Dobutamine was used in 35,103 examinations (either low-dose protocol for viability testing or standard large-dose protocol for ischaemia testing, with co-administration of atropine if required), and was associated with 63 life-threatening AEs (Varga et al. 2006), resulting in an event rate of 1 per 557 patients. Dipyridamole infusions were performed in 24,599 patients (with atropine if required), with 19 patients (rate of 1 in 1,294 patients) experiencing life-threatening AEs (Varga et al. 2006).

In total, the rate of fatal events was 1 in 14,332 tests (across all stressors). All patients who died had had a recent or previous MI. The majority of patients who died had received dobutamine (fatal event rate of 1 in 7,021), and 1 person had received dipyridamole (fatal event rate of 1 in 24 599), with no patients dying from exercise stress Echo (Varga et al. 2006). It is estimated that the safety data on exercise and pharmacological stressors from echocardiography can be transferred to other imaging modalities such as CMR, ECG and SPECT.

CONTRAST AGENTS

Gadolinium

Rare acute allergy-like reactions may occur with the use of intravenous gadolinium-based contrast agents in 0.3–0.2% of patients (Knuuti et al. 2014). Most reactions were mild but 33 life-threatening reactions occurred after 687,000 doses, very few of which were fatal. Knuuti et al. (2014) estimated the risk of acute fatal events to be 1/1,000,000 studies, and acute severe AEs to be 4.8/100,000 studies. Using the rate of long-term nephrotic toxicity from CT contrast studies, gadolinium is estimated to be associated with a long-term death rate of 6.6/10,000, and a nephrogenic systemic fibrosis rate of 0.33/10,000 (Knuuti et al. 2014). However, it should be noted that nephrotic systemic fibrosis has never been seen in patients with normal kidney function.

SP-CMR & LGE uses two doses of gadolinium compared with only one dose for SP-CMR. As no safety data is available to determine the effect of increasing the amount of gadolinium used per CMR procedure, it has been assumed that the risk is the same for both SP-CMR and SP-CMR & LGE.

Iodinated contrast agents

CTCA and ICA require injection of an iodinated contrast agent. This is associated with local effects (extravasation), acute or delayed reactions, and contrast-induced nephropathy (Knuuti et al. 2014). Extravasation occurs in approximately 0.2% of procedures and may lead to severe damage such as compartment syndrome. Severe reactions occur in 0.04% of patients, including pulmonary oedema, severe hypotension and loss of consciousness. Nephropathy is rare in patients without a history or symptoms of renal disease but is a serious risk in those with kidney failure, contributing to an additional 14.0%–15.8% mortality in those with pre-existing kidney conditions. Knuuti et al. (2014) estimated that the rate of death due to acute general reactions was 0.06/10,000 procedures, and 6.6/10,000 for intravenous and 7.6/10,000 for intra-arterial administration.

Tracers for radionuclide imaging

The radiotracers for SPECT have a very low rate of AEs: 2–6/1,000,000 injections for 99mTc-sestamibi/-tetrofosmin and even lower for thallium-201 (Knuuti et al. 2014). The overall risk of death was estimated to be negligible, and the rate of serious AEs was 0.06/10,000 studies.

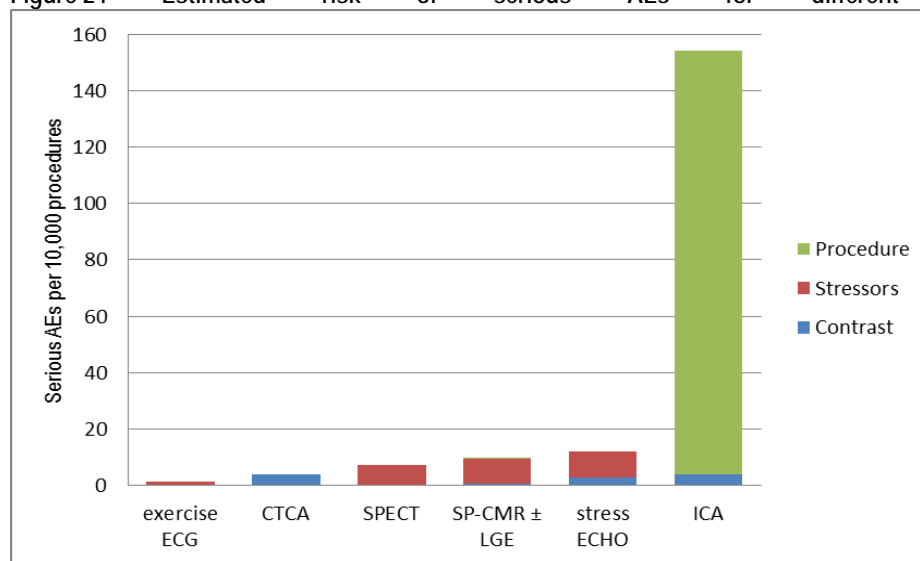
Microspheres of contrast

Contrast may be used for Echo to improve imaging of the endocardial border of the LV and to evaluate myocardial perfusion. Based on post-marketing documentation with a perflutren lipid microsphere, Knuuti et al. (2014) estimated the risk of serious AEs to be 3/10,000 and the risk of death to be 0.1/10,000 due to Echo-contrast administration.

SUMMARY OF COMPARATIVE HARMS

Figure 24 compares the number of serious AEs associated with each procedure discussed above, including the use of contrast and stressors. Where different stressors with different AE rates are used, the mean of all stressors associated with that procedure was used. The number of serious AEs experienced by patients during ICA procedures far outnumbers those resulting from any non-invasive imaging modality. SP-CMR has similar safety with respect to serious AEs to SPECT and stress Echo, and for all three modalities the majority of the serious AEs are caused by the stressor. Exercise ECG and CTCA have less-serious AEs than other non-invasive imaging modalities.

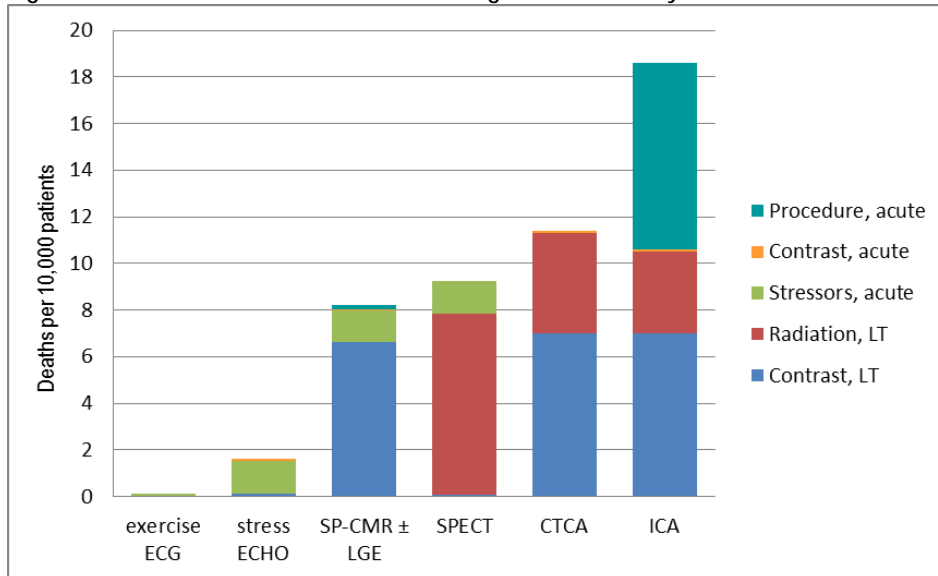
Figure 24 Estimated risk of serious AEs for different imaging procedures



AE = adverse event; CTCA = computed tomography coronary angiography; ECG = electrocardiogram; ECHO = echocardiography; ICA = invasive coronary angiography; LGE = late gadolinium enhancement; SP-CMR = stress perfusion cardiac magnetic resonance imaging; SPECT = single-photon emission computed tomography

Figure 25 compares the acute and long-term mortality rates due to the non-invasive imaging modalities and ICA. The ICA procedure and the use of a stressor are the most common causes of acute deaths, whereas long-term mortality is due to the use of radionuclides and contrast agents, mostly due to cancer or renal disease. The mortality rate from cancer due to radiation exposure for CTCA was calculated using the median exposure level (8.5 mSv). The long-term mortality rate is highest for CTCA and ICA as the procedures use both radionuclides and contrast agents. Conversely, the long-term mortality rate associated with exercise ECG and stress Echo are negligible because radionuclides are not used and contrast agents are only rarely used with Echo.

Figure 25 Estimated acute and long-term mortality rates for different imaging procedures



CTCA = computed tomography coronary angiography; ECG = electrocardiogram; ECHO = echocardiography; ICA = invasive coronary angiography; LGE = late gadolinium enhancement; LT = long-term; SP-CMR = stress perfusion cardiac magnetic resonance imaging; SPECT = single-photon emission computed tomography

B8A INTERPRETATION OF THE CLINICAL EVIDENCE (POPULATION 1)

For population 1 the effectiveness of CMR was assessed through the use of both direct evidence, comparing SP-CMR with stress Echo, SPECT and ICA (but not CTCA), as well as some components of linked evidence, assessing the accuracy of the different non-invasive tests against the reference standard, ICA. The only comparative evidence on the therapeutic efficacy of SP-CMR came from the direct evidence (CECaT trial).

Direct evidence

In the CECaT trial there were no clinically or statistically significant differences in morbidity, mortality or QoL between the three non-invasive imaging groups when compared with the ICA group.

Diagnostic accuracy

When the accuracy of the different non-invasive imaging modalities versus ICA was compared, CTCA was clearly the most accurate. SP-CMR with/without LGE and stress Echo were also effective in diagnosing patients with CAD. Both SPECT and exercise ECG were less accurate than SP-CMR. However, the only non-invasive test confidently able to identify patients with a high-intermediate PTP (65–85%) who do not have CAD is CTCA, but CTCA is not listed on the MBS for use in these patients due to the lack of cost-effectiveness.

Management

SP-CMR had a much lower completion rate than ICA, SPECT and stress Echo, and may not be suitable for use in up to one-fifth of the eligible testing population for various reasons, including claustrophobia, renal disease and patient acceptance—in one study the vast majority of patients preferred CTCA over either SP-CMR or ICA.

Non-invasive imaging may allow 20%–25% of patients suspected of having CAD to avoid having an ICA by ruling out those who are unlikely to be at risk of cardiac events, but the proportion of patients avoiding an ICA did not differ significantly between SP-CMR and other non-invasive imaging modalities.

Safety

The number of serious AEs experienced by patients during ICA procedures far outnumbers those resulting from any non-invasive imaging modality. For SP-CMR, SPECT and stress Echo the majority of the serious AEs were caused by the stressor. Exercise ECG and CTCA had fewer serious AEs than other non-invasive imaging modalities.

The mortality rate associated with each procedure was directly related to the use of stressors, radionucleotides and contrast agents. The ICA procedure and the use of a stressor were the most common causes of acute deaths, whereas long-term mortality was due to the use of radionucleotides and contrast agents, mostly due to cancer or renal disease.

Overall summary

On the basis of the benefits and harms reported in the evidence-base (summarised in Table 42) it is suggested that SP-CMR with/without LGE has:

- **non-inferior safety** and **inferior effectiveness** relative to **CTCA**;
- **inferior safety** and **non-inferior effectiveness** relative to **stress Echo**;
- **non-inferior safety** and **non-inferior effectiveness** relative to **SPECT**; and
- **inferior safety** and **superior effectiveness** relative to **exercise ECG**.

Table 42 Balance of clinical benefits and harms of CMR, relative to stress Echo, SPECT and CTCA

Outcomes	Participants Studies	Quality of evidence	Results	Interpretation	GRADE
CVD-related mortality	N=898 k=1 RCT	Risk of bias: 0 Inconsistency: 0 Indirectness: -1 Imprecision: 0 Publication bias: 0	SP-CMR = 5/226 (2.2%) ICA = 3/222 (1.4%) SPECT = 5/224 (2.2%) Stress Echo = 3/226 (1.3%)	The number of people who died during follow-up was small, so it is possible that any small difference in the risk of death between groups was due to chance.	Moderate ⊕⊕⊕⊖
Non-fatal CVD-related events	N=898 k=1 RCT	Risk of bias: 0 Inconsistency: 0 Indirectness: -1 Imprecision: 0 Publication bias: 0	SP-CMR = 29/226 (12.8%) ICA = 19/222 (8.6%) SPECT = 24/224 (10.7%) Stress Echo = 31/226 (13.7%)	The risk of cardiovascular-related AEs was very similar between groups, with a trend favouring the non-invasive imaging over ICA. There was no difference between CMR and SPECT or Echo.	Moderate ⊕⊕⊕⊖
Safety of imaging	No large comparative studies	Risk of bias: -1 Inconsistency: -1 Indirectness: -1 Imprecision: -1 Publication bias: 0	ICA is associated with significantly more AEs and deaths than any of the non-invasive imaging techniques. SP-CMR with/without LGE is associated with slightly fewer deaths than CTCA, but more than stress Echo. SP-CMR is associated with slightly more non-fatal AEs than CTCA and SPECT, and slightly fewer than stress Echo.	Most AEs that occur during non-invasive imaging are due to the stressor used. Most long-term deaths from non-invasive imaging are caused by the use of contrast agents and/or radionucleotides. However, any of the non-invasive tests that accurately rule out a patient from needing an ICA is beneficial, given the risk from ICAs.	Very low ⊕⊖⊖⊖
Accuracy (PoTP of being positive for CAD, after negative test result)	k=16 for SP-CMR k=18 for LGE-CMR k=13 for SPECT k=10 for Echo k=147 for ECG	Risk of bias: 0 Inconsistency: -1 Indirectness: -1 Imprecision: 0 Publication bias: 0	Stress Echo and SP-CMR with/without LGE are slightly better than SPECT at ruling out the presence of CAD. However, all three modalities were inferior to CTCA in ruling out the presence of CAD in patients with a negative result. Exercise ECG has very poor accuracy.	CMR is non-inferior to the other non-invasive tests funded for patients above 45% risk of having CAD. CMR (and the comparative tests that are funded) are inferior to CTCA.	Low ⊕⊕⊖⊖
Impact on patient management (referral to ICA)	N=898 k=1 RCT	Risk of bias: 0 Inconsistency: 0 Indirectness: -1 Imprecision: 0 Publication bias: 0	SP-CMR = 80% SPECT = 78% Stress Echo = 75%	The non-invasive tests were similar in their ability to rule out patients who did not require an ICA.	Moderate ⊕⊕⊕⊖

GRADE Working Group grades of evidence (Guyatt et al. 2011)

⊕⊕⊕⊕ **High quality:** We are very confident that the true effect lies close to that of the estimate of effect.

⊕⊕⊕⊖ **Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

⊕⊕⊖⊖ **Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

⊕⊖⊖⊖ **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

AE = adverse event; CAD = coronary artery disease; CMR = cardiac magnetic resonance imaging; CTCA = computed tomography coronary angiography; CVD = cardiovascular disease; ECG = electrocardiogram; Echo = echocardiography; ICA = invasive coronary angiography; k = number of studies; LGE = late gadolinium enhancement; PoTP = post-test probability; RCT = randomised controlled trial; SP-CMR = stress perfusion cardiac magnetic resonance imaging; SPECT = single-photon emission computed tomography

SECTION CA TRANSLATION ISSUES (POPULATION 1)

C1A OVERVIEW

The economic model for population 1 will represent the comparison of SP-CMR with CTCA, ECG, Echo and SPECT in the population with an intermediate PTP of CAD. There is inadequate data to reliably construct an economic model to generate a full cost–utility analysis. However, a comparative cost analysis of SP-CMR and its comparators, incorporating downstream diagnostic costs and utilising data from the clinical evaluation regarding the accuracy, re-testing and adverse event rates was undertaken, and the consequences of the different testing strategies are discussed. Additionally, cost-effectiveness analyses with outcomes of interest being (i) incremental cost per correct initial test result, (ii) cost per unnecessary ICA avoided and (iii) cost per useful ICA referred are provided.

Translation issues to be discussed in Section Ca are presented in Table 43.

Table 43 Translation issues addressed in the assessment

Type	Issue
Applicability	<ul style="list-style-type: none"> Which set of accuracy inputs reported in Section Ba should be used in the economic model for CMR? How comparable are the studies used to inform the test parameter inputs of the economic model? Are the studies used to inform the test parameter inputs of the economic model applicable to the proposed MBS population with respect to age and gender distribution? What is the prevalence of CAD in the proposed MBS population?
Extrapolation	None identified
Transformation	None identified
Other	<ul style="list-style-type: none"> How applicable is the evidence for a change in management? That is, to what extent will the imaging result impact patterns of referral to ICA in Australia?

CAD = coronary artery disease; CMR = cardiac magnetic resonance imaging; ICA = invasive coronary angiography; MBS = Medicare Benefits Schedule

C2A APPLICABILITY TRANSLATION ISSUES

C2A.1 CMR ACCURACY DATA TO BE USED IN THE ECONOMIC EVALUATION

Table 44 Applicability of CMR accuracy inputs to the proposed MBS setting

Component	Investigation
Issue/question	Which CMR accuracy inputs should be used in the economic evaluation?
Data	Studies included in clinical evaluation of CMR (Section B) and the proposed MBS item descriptor
Method (focused analytical plan)	To compare proposed MBS item descriptor to determine which set of accuracy inputs are most applicable for use in the economic evaluation

CMR = cardiac magnetic resonance imaging; MBS = Medicare Benefits Schedule

The proposed MBS item descriptor states that the scan of the heart be performed for myocardial viability using delayed gadolinium enhancement and stress myocardial perfusion in patients that present with symptoms consistent with stable IHD and with an intermediate PTP of CAD.

Therefore, the accuracy inputs most applicable to the economic model are for stress perfusion CMR with late gadolinium enhancement (SP-CMR & LGE). The use of late gadolinium enhancement appears to trade off slight improvements in specificity for slightly reduced sensitivity (no significant difference) (Figure 18, Section B3a.6.2); however, the LGE is associated with an additional dose of

gadolinium contrast, which may be associated with a higher safety risk compared with the gadolinium dose used in SP-CMR alone (this has not been quantified in the literature).

C2A.2 COMPARABILITY OF THE STUDIES USED TO INFORM THE TEST PARAMETER INPUTS OF THE MODEL

Table 45 Comparability of studies used to inform test accuracy inputs in the economic model

Component	Investigation
Issue/question	How comparable are the studies included to inform the test parameters in the economic model?
Data	Studies included in clinical evaluation of CMR and its comparators (Section B)
Method (focused analytical plan)	To compare the prevalence of CAD, mean age or the population and gender distribution across the studies included in the clinical evaluation

CAD = coronary artery disease; CMR = stress perfusion cardiac magnetic resonance imaging with late gadolinium enhancement

The data used in the economic model to represent the proposed service is that relating to SP-CMR & LGE (Section C2a.1). For each comparator, the data used was selected from an SR based on criteria outlined in Section B3a.6.3.

The average age (or median for CTCA studies), proportion of males and prevalence of CAD across the SRs selected are presented in Table 46. The average age across the populations studied appeared consistent (where reported). The SPECT SR appeared to have a lower proportion of males across the included studies, and the prevalence of CAD in the exercise ECG review was higher than in the others. The effect of these differences on the relative accuracy of the testing strategies is unclear. Unadjusted accuracy estimates will be used in the economic evaluation.

Table 46 Selected characteristics of studies used to inform accuracy inputs to the economic model

	CMR	CTCA (den Dekker et al. 2012)	SPECT (de Jong et al. 2012)	Stress Echo (MAS 2010c)	Exercise ECG (Gianrossi et al. 1989)
No. studies	16	21	13	10	147
No. patients	1,090	4,504	1,323	677	24,074
Age (years)	Mean: 60 ± 9.5	Median: 62 (IQR: 59–63)	Mean: 59 ± 9	Mean: 59 ± 10	NR
Proportion male	65%	67%	53%	71%	NR
Prevalence of CAD	45%	39%	52%	48%	66%

CAD = coronary artery disease; CMR = stress perfusion cardiac magnetic resonance imaging with late gadolinium enhancement; CTCA = computed tomography coronary angiography; ECG = electrocardiography; Echo = echocardiography; MAS = Medical Advisory Secretariat; NR = not reported; SPECT = single-photon emission computed tomography

C2A.3 APPLICABILITY OF THE STUDIES USED TO INFORM THE TEST PARAMETER INPUTS OF THE ECONOMIC MODEL TO THE PROPOSED MBS POPULATION

Table 47 Applicability of clinical evidence to the proposed MBS population

Component	Investigation
Issue/question	Are the studies included in the clinical evaluation to inform the test parameters in the economic model applicable to the proposed MBS population?
Data	Demographical (age, gender) data for MBS items 57360 (CTCA), 55116 (Echo), 61307 (SPECT) and 11712 (exercise ECG), July 2014 to June 2015 Pre-modelling study Section C2a.2

Method (focused analytical plan)	To compare the mean age or the population and gender distribution across the studies included in the clinical evaluation to the demographics of the proposed MBS population
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CTCA = computed tomography coronary angiography; ECG = electrocardiography; Echo = echocardiography; MBS = Medicare Benefits Schedule; SPECT = single-photon emission computed tomography

None of the comparators are restricted for use in the population in which CMR is proposed for; the Echo, SPECT and ECG populations may be broader than the proposed population and the CTCA population may be narrower (as use is restricted to those with a low to intermediate risk of PTP). As no trials were identified that were conducted in the Australian setting, MBS utilisation data for the comparators may be the best available evidence to support the applicability of the evidence to the proposed population.

Utilisation data for the year July 2014 to June 2015 is presented in Table 48. The average age across the utilisation groups was reasonably consistent with characteristics of the patients in the SRs, with the exception of the population that utilised SPECT. The proportion of males was also slightly lower than observed in the SRs. As the effect of these differences is unknown, unadjusted estimates will be used in the economic evaluation.

It should be noted that the CTCA item descriptor restricts use to be performed on a minimum of a 64-slice (or equivalent) scanner. The accuracy data used in the economic evaluation will reflect this.

Table 48 Demographics of patients who utilised the comparators

	MBS item 57360 (CTCA)	MBS item 55116 (stress Echo)	MBS item 61307 (SPECT)	MBS item 11712 (exercise ECG)
Total services July 2014 – June 2015	44,974	243,163	74,831	464,040
Mean age (years)	61	61	68	62
% males	53%	58%	53%	58%

CTCA = computed tomography coronary angiography; ECG = electrocardiography; Echo = echocardiography; MBS = Medicare Benefits Schedule; SPECT = single-photon emission computed tomography

C2A.4 PREVALENCE OF CAD IN THE PROPOSED MBS POPULATION

Table 49 Prevalence of CAD in the proposed population

Component	Investigation
Issue/question	What is the prevalence of CAD in the proposed MBS population?
Data	Studies included in clinical evaluation of CMR and its comparators (Section Ba)
Method (focused analytical plan)	Ranges of prevalence estimates of CAD in the studies included in the clinical evaluation of diagnostic accuracy will be investigated

CAD = coronary artery disease; CMR = stress perfusion cardiac magnetic resonance imaging; MBS = Medicare Benefits Schedule

The prevalence of CAD in the tested population is likely to be an important driver of the cost-effectiveness of the proposed service and it is unclear what the prevalence might be in the proposed MBS population, as studies conducted in the Australian setting were not identified during the evaluation.

In the studies of SP-CMR & LGE, the prevalence of CAD was observed to be 45% (Figure 12, Section B3a.6.2). SRs of CTCA observed prevalence estimates in the ranges 39%–72% (Figure 56, Appendix I); SPECT 41%–70% (Figure 57, Appendix I); Echo 41%–73% (Figure 58, Appendix I); and ECG 38%–66% (Figure 59, Appendix I).

Given the wide range of prevalence estimates observed in the clinical evidence (in populations suspected of CAD), the base-case economic model will use the prevalence of CAD based on that

observed in the meta-analysis of studies for SP-CMR & LGE (45%). Analyses will additionally be presented across the range of intermediate PTPs (15–85%) to determine the effect of prevalence on the cost and cost-effectiveness of CMR relative to its comparators.

The same prevalence estimate will also be used for the comparison to CTCA. While the clinical management algorithm presented in Figure 3, Section A.6, is consistent with the current MBS item descriptor for CTCA (i.e. restricted to patients with low to intermediate PTP of CAD), subgroup analyses of CMR studies observed similar prevalences of CAD in the low-intermediate (40%) (Figure 12, SP-CMR & LGE versus ICA in patients with chest pain or intermediate PTP) and intermediate (45%) populations.

Given that there is a high degree of uncertainty regarding the true prevalence of CAD in the proposed population and that the accuracy of CMR testing did not appear to differ substantially across the subgroups, CTCA will be modelled across the entire intermediate population. This is supported by HESP input, which suggests that CTCA is the preferred non-invasive methodology and is consistent with the conclusion that in patients with a high-intermediate PTP of CAD, CTCA is the only test that can effectively rule out CAD in the minority of patients with a negative test result (Section B4a.1.5.2). As the MBS item descriptor for CTCA does not define what ‘low to intermediate’ PTP is, and given the superior sensitivity of the test, leakage into the broader intermediate population may be a reasonable assumption.

C3A EXTRAPOLATION TRANSLATION ISSUES

The time horizon of the economic analyses does not extend beyond the diagnostic pathways for which data is available; therefore, no extrapolation is required.

C4A TRANSFORMATION ISSUES

None were identified.

C5A ANY OTHER TRANSLATION ISSUES

C5A.1 CHANGE IN MANAGEMENT EVIDENCE FOR REFERRAL TO ICA WITH NEGATIVE IMAGING RESULTS

Table 50 Incorporating change in management into the economic model

Component	Investigation
Issue/question	How should change in management with testing be included in the model structure?
Data	CECaT study (Sharples et al. 2007)
Method (focused analytical plan)	Compare actual management in the CECaT trial given the results of non-invasive testing to the clinical management algorithm pathways. Differences will be clarified with HESP member input.

CECaT = Cost-effectiveness of Non-invasive Cardiac Testing (trial); HESP = Health Expert Standing Panel

The purpose of testing is to identify patients, using non-invasive methods, who should and should not be referred for further invasive testing for CAD as part of disease confirmation and management. Therefore, if there is a change in management with non-invasive testing, patients with negative test results should not be referred for further testing.

In the trial of direct evidence (CECaT, Sharples et al. 2007), referral to ICA after results of non-invasive testing (CMR, SPECT and Echo) was made on the basis of clinician discretion. While the majority of positive imaging results were referred, so too were approximately half of the negative imaging results. Of the initial negative results that were referred for ICA, the proportion found to be positive with each test was 30% (14/46) with SPECT, 47% (23/49) with Echo and 52% (26/50) with CMR.

The referral rates to ICA after a negative non-invasive test result observed in the trial may be applicable to the proposed Australian setting, as clinical (HESP) input suggests that if there is a high

suspicion of CAD (on the basis of other factors), ICA could be conducted after an initial negative scan.

The CECaT study (Sharples et al. 2007), however, may have had a higher prevalence of CAD (approximately 70%, Table 28, Section B4a.1.5) than other studies included in the clinical evaluation, and so there is uncertainty regarding the applicability of the high referral rate for ICA with a negative result to the proposed population. In Section D, scenario analyses will be conducted assuming different levels in change in management following non-invasive testing. The base-case will assume 100% change in management (i.e. testing determines referral to ICA, so negative test results are not referred for ICA), and two scenario analyses will additionally be considered:

- A proportion of patients with negative test results will be referred for ICA—the same proportion for true negatives and false negatives, as per the rates of all negatives referred to ICA in the CECaT trial (Sharples et al. 2007); and
- As clinical judgement determines referral to ICA, a third scenario will assume that all false negatives will be referred, along with some proportion of true negatives, as per true negatives referred for ICA in CECaT (Sharples et al. 2007).

As CTCA was not included as a comparator in the CECaT trial (Sharples et al. 2007), change in management following testing using CTCA will have to be assumed. Given the superior sensitivity of CTCA to all other non-invasive imaging tests, and similar (or better) specificity, the NPV of CTCA is higher than the other tests. Therefore, it may not be reasonable to assume the same proportion of negative tests will be referred for ICA as the other non-invasive strategies, as a negative test result is more likely to be a true negative (Table 51).

Table 51 Comparison of NPV and negative likelihood ratios

Test	Sensitivity	Specificity	NPV ^a	Negative likelihood ratio
CMR	85%	85%	87.4%	0.18
CTCA	97%	86%	97.3%	0.03
Stress Echo	87%	86%	89.0%	0.15
SPECT	83%	77%	84.7%	0.22
Exercise ECG	68%	77%	74.6%	0.42

Source: Figure 19, Section B3a.6.3 and Figure 21, Section B.4a.1.5.2.

^a assuming prevalence of 45%, as per Section Ca.2.4

CMR = stress perfusion cardiac magnetic resonance with late gadolinium enhancement; CTCA = computed tomography coronary angiography; ECG = electrocardiography; Echo = echocardiography; NPV = negative predictive value; SPECT = single-photon emission computed tomography

In the change in management scenarios proposed, it will therefore be assumed that there will be perfect change in management following a CTCA test. However, to test this assumption, two additional analyses will be presented that assume that the proportion of negative CTCA tests to be referred for ICA is the same as for the other non-invasive strategies (see Appendix M).

C6A RELATIONSHIP OF EACH PRE-MODELLING STUDY TO THE ECONOMIC EVALUATION

A summary of the pre-modelling studies to the economic evaluation is presented in Table 52.

Table 52 Summary of results of pre-modelling studies and their uses in the economic evaluation

Section	Pre-modelling study	Results used in Section D	Cross-reference	Results used in Section D6	Cross-reference
Applicability					
	CMR accuracy	As per Section B3a.6.3	Section D4a.2	95%CI from Section B3a.6.3	Section D6a
	Study comparability	As per Section B3a.6.3	Section D2a	95%CI from Section B3a.6.3	Section D6a
	Applicability to proposed MBS population	As per Section B3a.6.3	Section D2a	Not tested	-
	Prevalence of CAD in the proposed MBS population	As per Section B3a.6.3; and scenario analyses (15%–85%)	Section D4a.1	Not tested	-
Other					
	Change in management	Three scenario analyses	Section D4a.4	Not tested	-

CAD = coronary artery disease; CI = confidence interval; CMR = cardiac magnetic resonance imaging; MBS = Medicare Benefits Schedule

SECTION DA ECONOMIC EVALUATION (POPULATION 1)

D1A OVERVIEW

The clinical evaluation suggests that CMR has:

- inferior effectiveness (in terms of sensitivity) and non-inferior safety (acute and long-term) compared with CTCA
- non-inferior effectiveness, non-inferior acute safety and inferior long-term safety compared with stress Echo
- non-inferior effectiveness and non-inferior safety (acute and long-term) compared with SPECT
- superior effectiveness (in terms of sensitivity) and inferior safety compared with exercise ECG.

Table 53 sets out the framework that was used to classify the clinical evidence in Section B so that a decision could be made about the type of economic analysis to undertake in this Section.

Table 53 Classification of comparative effectiveness and safety of the proposed therapeutic medical service compared with its main comparator, and guide to the suitable type of economic evaluation

Comparative safety	Comparative effectiveness			
	Inferior	Uncertain ^a	Non-inferior ^b	Superior
Inferior	Health forgone: need other supportive factors	Health forgone: possibly need other supportive factors	Health forgone: need other supportive factors	? Likely CUA
Uncertain ^a	Health forgone possible: need other supportive factors	?	?	? Likely CEA/CUA
Non-inferior ^b	Health forgone: need other supportive factors	?	CMA	CEA/CUA
Superior	? Likely CUA	? Likely CEA/CUA	CEA/CUA	CEA/CUA

^a 'Uncertainty' covers concepts such as inadequate minimisation of important sources of bias, lack of statistical significance in an underpowered trial, detecting clinically unimportant therapeutic differences, inconsistent results across trials, and trade-offs within the comparative effectiveness and/or comparative safety considerations.

^b An adequate assessment of 'non-inferiority' is the preferred basis for demonstrating equivalence.

CEA = cost-effectiveness analysis; CMA = cost-minimisation analysis; CUA = cost-utility analysis; ? = reflects uncertainties and any identified health trade-offs in the economic evaluation, as a minimum in a cost-consequences analysis

Given a lack of evidence of health outcome differences associated with the alternative testing methods, it was decided that a modelled cost analysis, comparing CMR with CTCA, stress Echo, SPECT and exercise ECG, would be the most appropriate economic evaluation. To further characterise the economic differences, secondary cost-effectiveness analyses (CEA) will also be presented with the outcomes (i) incremental cost per correct initial test result, (ii) cost per unnecessary ICA avoided and (iii) cost per useful ICA referred. However, the lack of applicable and consistent evidence prevents reliable further economic evaluation of the long-term clinical implications or utility associated with these outcomes.

D2A POPULATIONS AND SETTINGS

The population who enter the model are patients with symptoms consistent with stable IHD who have an intermediate PTP of CAD (consistent with the proposed MBS descriptor as detailed in Sections A.2 and A.4). Demographic characteristics of the patients (e.g. age, gender) are not explicitly defined in the model as the analyses do not estimate health outcomes (e.g. survival and/or procedural risks).⁵

The setting is the Australian healthcare system, with the proposed and comparator services available on either an outpatient or an in-hospital basis. This is consistent with the setting for the majority of comparator tests and for current CMR services (MBS data for number of tests conducted in hospital and out of hospital for items 57360, 11712, 55116, 55117, 61307, 63385, 63388, 63391, 63401 and 63404, 2009–10 to 2014–15).

The comparability and applicability of studies included in the clinical evaluation to the economic evaluation is described in Section Ca. The clinical evidence presented in Section B3a.6.3 was considered applicable to the proposed setting; however, accuracy inputs for CTCA in the model will reflect the accuracy using a 64-slice (minimum) scanner, to be consistent with the current CTCA MBS item descriptor.

D3A STRUCTURE AND RATIONALE OF THE ECONOMIC EVALUATION

A summary of the key characteristics of the economic evaluation is given in Table 54.

Table 54 Summary of the economic evaluation

Perspective	CTCA, stress Echo, SPECT and exercise ECG
Comparators	Cost-consequences and cost-effectiveness analyses
Type of economic evaluation	SR (as presented in Section B)
Sources of evidence	Time to achieve a diagnosis (assumed <1 year – no discounting)
Time horizon	Cost per unnecessary ICA avoided and cost per correct initial test result
Outcomes	Decision tree analysis
Methods used to generate results	TreeAge Pro
Software packages used	CTCA, stress Echo, SPECT and exercise ECG

CTCA = computed tomography coronary angiography; ECG = electrocardiography; Echo = echocardiography; ICA = invasive coronary angiography; SPECT = single-photon emission computed tomography; SR = systematic review

LITERATURE REVIEW

A literature search was conducted in May 2015 and updated in November 2015 to identify published cost-effectiveness analyses of the proposed service. The search terms used are presented in Table 189, Appendix M.

A brief summary of each of the studies identified is presented in Table 55.

⁵ Use of the test parameters identified in the clinical studies is consistent with either of two assumptions:

1. The modelled population has the characteristics of the study patients, as detailed in Section C.2a.3; or
2. The test parameters around accuracy are reasonably independent of demographic characteristics.

Table 55 Summary of identified economic analyses of CMR for the diagnosis of CAD

Study	Setting	Results
Thom et al. (2014)	<p>Trial-based CUA conducted in the UK setting, n=898 patients referred for non-urgent ICA were randomised to stress SPECT, stress CMR, stress Echo or ICA.</p> <p>On the basis of the test results, ICA was recommended only when the imaging test was positive; however, management was left to clinical judgement, with 49–58% of negative imaging results actually being referred for ICA.</p> <p>Outcomes were survival up to a minimum of 2 years post-treatment and quality-adjusted survival.</p> <p>The economic evaluation did not model diagnostic accuracy but, as the evidence is direct, the implication for false positives and false negatives is inherent in the data. However, given that change in management was not solely determined on the basis of the test result, and that half of the negative results were referred for ICA, the effect of false negatives on the cost-effectiveness is reduced.</p>	<p>CMR is dominated by SPECT and is less costly and less effective than stress Echo.</p>
MAS (2010a)	<p>Decision-tree CEA in the Canadian context with outcomes cost per accurate diagnosis and cost per true positive diagnosis of CAD presented in two patient populations: (i) outpatients with stable chest pain; and (ii) inpatients presenting with acute, unstable chest pain.</p> <p>The time horizon was the time required to determine an accurate or true positive diagnosis of CAD.</p>	<p>In stable patients, CTCA dominated CMR, and CMR was found to have ICERs comparable with stress Echo and SPECT, ranging between \$6,000 and \$9,000 Canadian dollars</p>
Walker et al. (2013)	<p>Hybrid decision-tree Markov model CUA, in the UK (National Health Service) setting. A 50-year time horizon was used.</p> <p>60-year-old males enter the model with Grade 2 angina symptoms. Relevant strategies modelled included: exercise treadmill test (Strategy 2), CMR (Strategy 5) and SPECT (Strategy 6). Models the long-term implications of false negative results and false positive results undergoing ICA to confirm diagnosis (i.e. no long-term implications). The effect of radiation exposure is additionally captured in the model structure.</p>	<p>CMR (Strategy 5) is more effective and more costly than SPECT (Strategy 6), with an ICER of approx. £9,000 in the base-case population.</p> <p>Results for Strategy 2 were not reported, as this strategy was dominated or extendedly dominated by the other strategies.</p>
Iwata et al. (2013)	<p>Decision-tree CEA in the Japanese context – outcome measured in terms of incremental cost of true positive diagnosis. Implications for false positives were not considered in the modelling.</p>	<p>CMR dominated SPECT when diagnostic costs only were included. When treatment costs were additionally considered, the ICER increased to approx. 5000 Japanese Yen.</p>
Boldt et al. (2013)	<p>Compared the cost-effectiveness (not incremental cost-effectiveness) of CMR with SPECT and ICA using CUA and CEA. The CEA outcome was cost per correct CAD diagnosis.</p> <p>The model used a 10-year time horizon and positive and inconclusive tests were referred for ICA. Complications due to testing were assumed to reduce QoL by 0.1.</p> <p>Further model assumptions include that a correct CAD diagnosis increases the QALYs gained over the 10-year time horizon by 3 years, and that false negative tests lose an average of 5 QALYs due to risk of MI and death from undetected CAD.</p>	<p>In patients with low to intermediate CAD prevalence, CMR was considered the most cost-effective strategy. With high CAD prevalence, ICA was considered the most cost-effective strategy; however, CMR was considered more cost-effective than SPECT</p>

Study	Setting	Results
Genders et al. (2015)	<p>Hybrid decision-tree (to model diagnostic outcomes) Markov model (to model lifetime prognosis) CUA in the UK (healthcare), US (societal) and Netherlands (societal) perspectives.</p> <p>The modelled population included 60-year-old patients (separates males and females) with stable chest pain and low to intermediate probability of CAD. A number of combinations of diagnostic strategies were compared in which ICA was conducted conservatively or intensively (i.e. all positive results confirmed by ICA). The benefit of testing was to identify CAD and initiate OMT with/without revascularisation, as opposed to risk factor management.</p> <p>The model considered radiation exposure and implications for patients with false positives that would not be confirmed with ICA (patients are assumed to receive OMT for their remaining life span, adding a small disutility for taking unnecessary medication, with no effect on the rate of MACEs) and false negatives (who are re-evaluated and have correct diagnosis within the first year).</p>	Of the scenarios in the UK setting with one test (with/without intensive ICA), CMR is dominated by Echo, CTCA and SPECT.

CAD = coronary artery disease; CEA = cost-effectiveness analysis; CMR = cardiac magnetic resonance imaging; CTCA = computed tomography coronary angiography; CUA = cost-utility analysis; ECG = electrocardiography; Echo = echocardiography; ICA = invasive coronary angiography; ICER = incremental cost-effectiveness ratio; MACE = major adverse cardiac event; OMT = optimal medical therapy; QALY = quality-adjusted life year; QoL = quality of life; SPECT = single-photon emission computed tomography

The types of economic evaluations presented, comparators used, and outcomes and assumptions employed varied substantially across the identified literature. Studies that compared CMR with CTCA (k=2) (MAS 2010a; Genders et al. 2015) both concluded that CMR was dominated (less effective and more costly); in studies that compared CMR with SPECT (k=6), 4 concluded that CMR was more costly and more effective than SPECT, while 2 concluded that CMR was dominated. Three studies compared CMR with Echo and reached different conclusions.

The modelled long-term cost-utility analyses (CUAs) identified (Walker et al. 2013; Genders et al. 2015) assumed that patients with negative results would receive no medical treatment, and so the implication of false negatives was forgone medical therapy rather than only forgone revascularisation, as is the case in the proposed eligible population.

As no studies were identified in the Australian setting and no study considered all the relevant comparators, an economic evaluation was conducted to determine the cost-effectiveness of the proposed MBS service.

STRUCTURE OF THE ECONOMIC EVALUATION

The economic model presented is a decision-tree analysis, built in TreeAge Pro. The time horizon chosen for the economic model is the time to achieve a diagnostic conclusion (based on non-invasive testing or ICA). Since conclusions regarding the long-term health outcome effects of revascularisation post-diagnosis cannot be made with any certainty (see Section B.5a.2.4), the model terminates before this component of the treatment pathway, and neither costs nor outcomes associated with post-diagnosis revascularisation are included.

Patients with an intermediate PTP of having CAD enter the economic model. In the intervention arm, patients receive SP-CMR testing for the diagnosis of CAD. Four control arms are additionally modelled, one each for CTCA, stress Echo, SPECT and exercise ECG.

If testing results in a conclusive result (i.e. the test does not fail, nor is equivocal), patients with a positive result will receive an ICA as part of CAD management and to confirm the initial diagnosis. Patients with an initial false positive result will have their diagnosis corrected at this time.

In the base-case analysis a negative result is assumed to achieve perfect change in management; that is, that all patients with negative results not receive a referral for ICA. As described in Section C5a.1, this assumption may not be reasonable (as per the CECaT trial (Sharples et al. 2007)), and so scenario analyses are presented assuming that some patients with a negative result will receive an ICA to confirm the diagnosis, resolving some or all initial false negative test results.

If testing results in an equivocal outcome or fails, patients are assumed to receive CTCA testing (this assumption is based on clinician advice). Given the high sensitivity of CTCA, it is assumed that change in management (i.e. no further ICA testing) will always occur following a negative CTCA test result, with alternate scenarios presented to test this assumption.

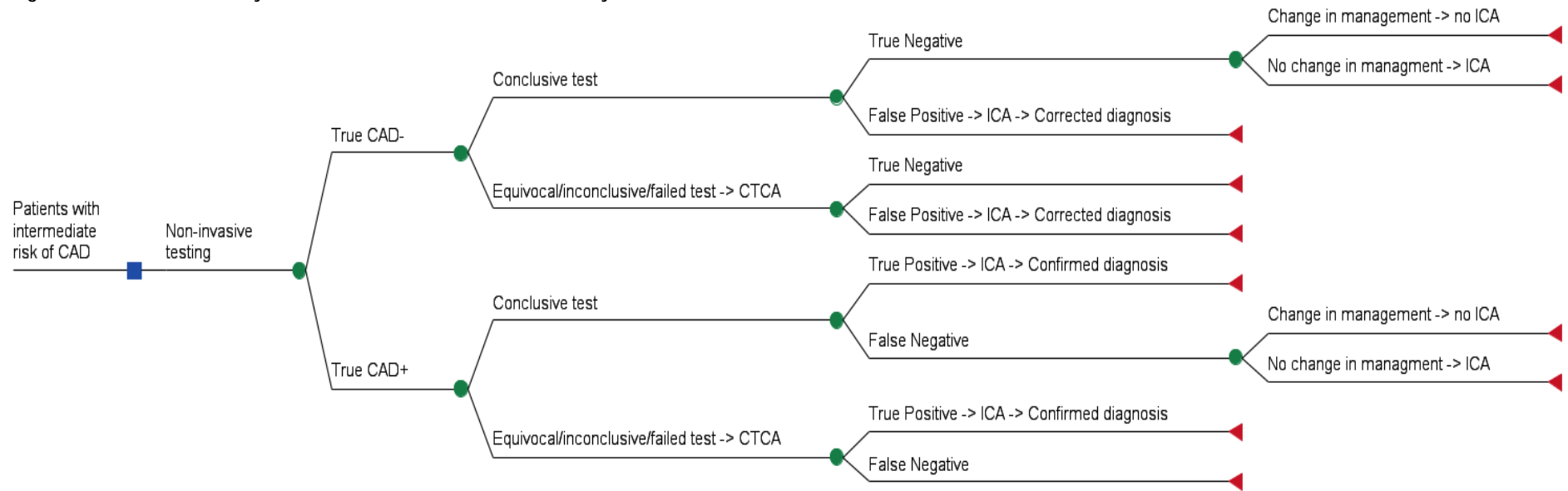
The primary analysis presented is a modelled cost analysis comprising description of the consequences of testing with respect to implications for false negative, false positive and initial equivocal or failed results; the reduction in health outcomes due to immediate AEs related to testing; and the long-term safety concerns.

Two secondary CEAs will also be presented. In the CEA with outcome cost per unnecessary ICA avoided, model terminal points that result in an ICA being performed in a true negative patient are given a score of 1, while all other terminal points are given a score of 0. Therefore, smaller effectiveness outputs correspond with fewer unnecessary ICAs being performed.

In the CEA with outcome cost per correct initial test result, model terminal points that stem from correct (i.e. true positive or true negative) initial testing are given a score of 1. Terminal points that stem from equivocal or failed testing or incorrect testing results (i.e. false negatives or false positives) are given a score of 0. Higher effectiveness output corresponds to greater test accuracy, with regards to sensitivity and specificity, and fewer repeat tests.

The structure of the cost analysis is shown in Figure 26. The structures for the secondary CEAs have the same decision-tree structure, with allocation of outcomes based on accurate results and necessary/unnecessary ICAs, as presented in Figure 64 and Figure 65, Appendix M.

Figure 26 Decision analytic structure of the base-case cost analysis



Note: The model structure for each non-invasive test modelled is the same. Differences modelled include test-specific parameters such as test accuracy, re-testing rate and test costs.

CAD = coronary artery disease; CTCA = computed tomography coronary angiography; ICA = invasive coronary angiography.

Assumptions incorporated into the model structure are that:

- The implications of a false negative test are uncertain. As per the clinical management algorithm (Figure 3, Section A.6), all patients eligible for testing are assumed to receive OMT irrespective of CAD diagnosis. Therefore, the implications for a patient with a false negative test would be delayed revascularisation.
- As CMR does appear to reasonably predict patients requiring ICA, and due to the invasive nature of ICA, a reduction in unnecessary ICAs (i.e. ICAs in true CAD negative patients) is a patient-relevant outcome that is explored in a secondary CEA.
- A positive result in any non-invasive test is followed by an ICA as part of CAD management. This is consistent with patient management in the CECaT trial, where 93%–98% of patients with positive non-invasive imaging results were referred for ICA (Section B1). Therefore, the implication of a false positive result is that patients undergo ICA unnecessarily to receive the correct negative diagnosis.
- Equivocal/inconclusive/failed test results receive a CTCA.
- As evidence for the accuracy of CTCA given that a previously equivocal result was not specifically identified in the clinical evaluation, the accuracy of CTCA is assumed to be the same as in patients who were previously untested.
- Change in management resulting from a negative non-invasive test is perfect, with scenario analyses additionally presented with alternative assumptions (see Section Ca.5.1 and Section Ca.5.2).

The limitations of the model's structure are that it does not capture: disutility associated with experiencing AE related to non-invasive testing or ICA; costs or outcomes of long-term AEs associated with testing (e.g. cancer from radiation exposure or nephrotoxicity from gadolinium contrast agent); and the implications of false negative test results. However, given that non-invasive imaging results may not necessarily translate into a change in management (with regard to ICA referral), some of these patients may undergo ICA regardless (see Section Ca.5.1).

These will be qualitatively described as 'consequences' as part of the base-case modelled cost analysis.

D4A INPUTS TO THE ECONOMIC EVALUATION

D4A.1 EPIDEMIOLOGICAL PARAMETERS

Prevalence of CAD

As per Section C2a.4 and Section C2a.5, the prevalence of CAD used in the base-case economic model is 45%, based on the prevalence observed in studies of CMR included in the meta-analysis for diagnostic accuracy. Scenario analyses will additionally be presented across the range of intermediate PTPs (15–85%) to determine the effect of prevalence on the cost and cost-effectiveness of CMR, relative to its comparators.

D4A.2 TEST-RELATED PARAMETERS

Test accuracy

Test accuracy data used in the economic model for CMR and each comparator are sensitivity and specificity. The values used are presented in Table 56. Justification for the selection of the studies used to inform these data is presented in Section C2a.1 and Section C2a.2. Sensitivity analyses are conducted using the 95% CIs presented.

Table 56 Test accuracy inputs used in the economic model

Test	Source	Sensitivity [95%CI]	Specificity [95%CI]	Section C cross-ref
CMR	Section B3a.6.3	85% [82, 88]	85% [81, 88]	Section C2a.1
CTCA	den Dekker et al. (2012) (Section B3a.6.3)	97% [96, 98]	86% [85, 88]	Section C2a.2
SPECT	de Jong et al. (2012) (Section B3a.6.3)	83% [73, 89]	77% [64, 86]	Section C2a.2
Stress Echo	MAS (2010c) (Section B3a.6.3)	87% [83, 91]	86% [82, 94]	Section C2a.2
Exercise ECG	Gianrossi et al. (1989) (Section B3a.6.3)	68% ± 16%	77% ± 17%	Section C2a.2

CMR = stress perfusion cardiac magnetic resonance with late gadolinium enhancement; CTCA = computed tomography coronary angiography; ECG = electrocardiography; Echo = echocardiography; SPECT = single-photon emission computed tomography

Equivocal/failed test rates

The trial of direct evidence reported the number of CMR, SPECT and stress Echo tests that had an equivocal or failed result. These are assumed to be associated with repeat testing with an alternative strategy, as the majority of these patients in the trial were referred for ICA (92%, 45/49). The estimates used in the base-case model for these tests are presented in Table 57.

Table 57 Equivocal or failed test rates used in the economic model

Test	Source	Base-case estimate	Sensitivity analyses
CMR	CECaT (Sharples et al. 2007)	25/226 (11%)	3%, 17.5%
SPECT	CECaT (Sharples et al. 2007)	9/224 (4%)	4%, 11%
Stress Echo	CECaT (Sharples et al. 2007)	15/226 (7%)	4%, 11%
CTCA	Maffei et al. (2011)	0/1500 (0%)	5%
Exercise ECG	Nielsen et al. (2013)	18/274 (7%)	20%

CECaT = Cost-effectiveness of Non-invasive Cardiac Testing (trial); CMR = stress perfusion cardiac magnetic resonance with late gadolinium enhancement; CTCA = computed tomography coronary angiography; ECG = electrocardiography; Echo = echocardiography; SPECT = single-photon emission computed tomography

Sensitivity analyses are conducted around these parameters. For CMR the alternative estimates are derived from the range of tests that are not completed successfully (3.0%–17.5%, Table 168, Appendix E); for stress Echo and SPECT, the range used was that observed in the CECaT trial.

As the CECaT trial (Sharples et al. 2007) did not use CTCA or exercise ECG testing, studies included in the SRs that informed the accuracy inputs were searched. The largest study included in the den Dekker et al. (2012) SR, Maffei et al. (2011), enrolled 1,500 consecutive patients. Results were available for all patients (i.e. no equivocal or failed tests), and were consistent with other large studies included in the same SR (Marano et al. 2009; Meijs et al. 2009). Sensitivity analysis assuming an upper limit of 5% was conducted.

Nielsen et al. (2013) reported that 7% of exercise ECG tests had an equivocal result. An upper limit of 20% is used in sensitivity analysis based on Rogers et al. (2013).

As per Section D3a, equivocal non-invasive, non-CTCA tests are assumed to be referred to CTCA, as clinical input suggests that it is the preferred testing methodology.

Adverse event rates

Adverse health outcomes associated with testing-related AEs are not captured in the cost analysis or the limited CEAs; however, many of the associated costs of test-related AEs are incorporated. Those considered in the economic model include:

- allergic reactions to gadolinium contrast agent, associated with CMR
- AEs to iodinated contrast agent, associated with CTCA
- adverse reactions to microspheres, associated with stress Echo
- AEs related to exercise or pharmacological stressors, associated with exercise ECG, CMR, SPECT and stress Echo.

The rates used in the economic model are presented in Table 58 and are based on those reported in Table 41, Section B7a. For pharmacological stressors, event rates have been reported by stress type. As the relative use of stress agents in Australia is unknown, an average estimate was used. Sensitivity analysis was conducted around this estimate assuming the lowest and highest pharmacological event rates.

As stress Echo can use either exercise or pharmacological stress, the event rates are weighted by the number of pharmacological Echo MBS services as a proportion of all Echo services, July 2014 to June 2015 (MBS items 55116, 55117) (3.5%). The same weighting is assumed to apply to SPECT. This differs to values presented in Figure 22, in Section B7a, as the estimates used were averages with no weighting by stressor utilisation. The unweighted average was used in sensitivity analyses for the upper limit of these parameters.

Table 58 Proportion of AEs related to non-invasive testing strategies

	AE rate	Source	Sensitivity analysis	Source
CMR				
Pharmacological stress	0.09%	Average AE rate for pharmacological stressors (Table 41, Section B7a)	0.014%, 0.18%	Assuming AEs related to adenosine (lower) and dobutamine (upper)
Gadolinium contrast	0.005%	Table 41, Section B7a	0.011%	Severe AEs in suspected CAD (Bruder et al. 2015)
SPECT				
Exercise or pharmacological stress	0.018%	Weighted ^a AEs for exercise and pharmacological stressors, (Table 41, Section B7a)	0.015%, 0.072%	Assuming AEs related to adenosine in weighted (lower) and average of all stressors (i.e. not weighted) (upper)
Stress ECHO				
Exercise or pharmacological stress	0.018%	Weighted ^a AEs for exercise and pharmacological stressors, (Table 41, Section B7a)	0.015%, 0.072%	Assuming AEs related to adenosine in weighted (lower) and average of all stressors (i.e. not weighted) (upper)
Microspheres	0.03%	Table 41, Section B7a	-	-
CTCA				
Iodinated contrast	0.04%	Table 41, Section B7a	-	-
Exercise ECG				
Exercise stress	0.015%	AE rate for exercise stress (Table 41, Section B7a)	-	-

	AE rate	Source	Sensitivity analysis	Source
ICA				
Iodinated contrast	0.04%	Table 41, Section B7a	-	-
Procedural events	1.77%	Section B7a	1%, 2%	Table 41, Section B7a

a Weighted by the number of pharmacological ECHOs as a proportion of all ECHOs (MBS items 55116, 55117)

AE = adverse event; CAD = coronary artery event; CMR = stress perfusion cardiac magnetic resonance imaging with late gadolinium enhancement; CTCA = computed tomography coronary angiography; ECG = electrocardiography; Echo = echocardiography; ICA = invasive coronary angiogram; SPECT = single-photon emission computed tomography

While SPECT does use radiotracers, these are associated with a very low rate of serious AEs and are not included in the modelling. Other rare serious AEs related to CMR reported in Section B7a are also not included in the economic model.

Rates of AEs (with upper and lower estimates) associated with ICA are also presented in Table 58. These have been derived directly from Section B7a.

D4A.3 HEALTH CARE RESOURCE ITEMS

Test costs

The test costs used in the economic model are presented in Table 59. In the base-case model, test costs are based on the proposed and current MBS item Schedule fee. Sensitivity analyses are conducted using the average provider fee (which takes into account bulk billing and patient contributions above the Schedule fee) for each of the current tests, and based on the fee proposed by RANZCR in feedback to the protocol.

Table 59 Non-invasive test costs used in the economic model

Test	Base-case	Source	Sensitivity analyses	Source
CMR	\$900.00	Proposed MBS item	\$1,200.00	RANZCR protocol feedback (see Section A10)
SPECT	\$834.90	MBS item 61307	\$802.66	Average provider fee for MBS item 61307, July 2009 – June 2015
Stress Echo	\$261.65	MBS items 55116	\$260.72	Average provider fee for MBS item 55116, July 2009 – June 2015
CTCA	\$700.00	MBS item 57360	\$692.90	Average provider fee for MBS item 57360, July 2011 – June 2015
Exercise ECG	\$152.15	MBS item 11712	\$151.16	Average provider fee for MBS item 11712, July 2009 – June 2015

CMR = stress perfusion cardiac magnetic resonance imaging with late gadolinium enhancement; CTCA = computed tomography coronary angiography; ECG = electrocardiography; Echo = echocardiography; MBS = Medicare Benefits Schedule; RANZCR = Royal Australian and New Zealand College of Radiologists; SPECT = single-photon emission computed tomography

Costs associated with testing

Costs associated with testing include the cost of associated professional attendances, and the cost of stressors and contrast agents. It is assumed that the cost of the iodinated contrast agent used in CTCA and ICA and the microsphere contrast used in stress Echo are included in the service fee.

The Schedule fee for each diagnostic imaging service is assumed to cover both the diagnostic imaging procedure and the reading and reporting on that procedure by the provider (Department of

Health 2015). Therefore, each test is assumed to incur the cost of one professional attendance by the referring doctor to review imaging results (MBS item 105, \$43).

The cost of the gadolinium contrast agent used in CMR is based on the MBS item for gadolinium contrast (MBS item 63491, \$44.90); and the cost of the pharmacological stressor (\$10) is based on the patient fee charged for pharmacological stress Echo conducted at SA Heart Clinic⁶. However, as SPECT and stress Echo can use exercise or pharmacological stress, the cost of the stressor is weighted by the number of pharmacological Echo MBS services, July 2014 to June 2015 (MBS item 55117) as a proportion of all Echo services in that period (MBS items 55116 and 55117) (3.5%). The weighted cost of the stressor is \$0.35.

Costs associated with treating AEs related to testing

The AEs considered in the economic model are reported in Section D4a.2. The cost of treating AEs related to testing are presented in Table 60 and are based on the National Efficient Price (NEP) for the AR-DRG code (Independent Hospital Pricing Authority (IHPA) 2015a) most relevant to the event. The International Stress Echo Complication Registry study (Varga et al. 2006) reports that the most common AEs due to stressors are arrhythmias and MIs. Thus, the NEP for AR-DRG code F76A—Arrhythmia, Cardiac Arrest and Conduction Disorders—is used in the analysis

Table 60 Cost of treating AEs related to testing

AE	Treatment cost	Source
Gadolinium reaction	\$1,104	National Efficient Price (IHPA 2015a) for AR-DRG X61Z (Allergic reactions)
Iodinated contrast AE	\$8,850	National Efficient Price (IHPA 2015a) for AR-DRG E64A (Pulmonary oedema)
Microspheres reaction	\$1,104	National Efficient Price (IHPA 2015a) for AR-DRG X61Z (Allergic reactions)
Stressors AEs	\$7,370	National Efficient Price (IHPA 2015a) for AR-DRG F76A (Arrhythmia, Cardiac Arrest and Conduction Disorders)

AE = adverse event; AR-DRG = Australian Refined Diagnosis Related Groups

The weighted cost of treating AEs related to each method of testing is presented in Table 61.

Table 61 Modelled cost of treating AEs related to non-invasive testing strategies

	AE rate	Cost of treating AE	Weighted cost of treating AE
CMR (total)			\$6.71
Pharmacological stress	0.09%	\$7,370	\$6.66
Gadolinium contrast	0.005%	\$1,104	\$0.05
SPECT (total)			\$1.30
Exercise or pharmacological stress	0.018%	\$7,370	\$1.30
Stress Echo (total)			\$1.63
Exercise or pharmacological stress	0.018%	\$7,370	\$1.30
Microspheres	0.03%	\$1,104	\$0.33
CTCA (total)			\$3.54

⁶Available from <[SA Heart Cardiology patient charges for dobutamine stress Echo](#)> (accessed 15 December 2015).

	AE rate	Cost of treating AE	Weighted cost of treating AE
Iodinated contrast	0.04%	\$8,850	\$3.54
Exercise ECG (total)			\$1.11
Exercise stress	0.015%	\$7,370	\$1.11

AE = adverse event; CMR = stress perfusion cardiac magnetic resonance imaging with late gadolinium enhancement; CTCA = computed tomography coronary angiography; ECG = electrocardiography; Echo = echocardiography; SPECT = single-photon emission computed tomography

ICA costs (including costs to treat AEs)

The modelled cost of ICA is based on the National Efficient Price for AR-DRGs F42B (Circulatory disorders, not admitted for AMI with invasive cardiac investigations, no complications, overnight stay) and F42C (same day), weighted by the respective number of hospital separations (IHPA 2014). The treatment of AEs related to ICAs is assumed to be the difference between the National Efficient price for AR-DRG F42A (with complications) and the weighted ICA cost (above).

A summary of the costs used in the economic model related to ICA is presented in Table 62.

Table 62 Summary of ICA costs related to testing used in the economic model

	Cost	Source
ICA	\$4,475	NEP (IHPA 2015a) for AR-DRG F42B and F42C, weighted by hospital separations (IHPA 2014)
AEs related to ICAs	\$7,726	NEP (IHPA 2015a) for AR-DRG F42A minus cost of ICA without complications
Proportion ICA AEs	1.81%	Table 58
Weighted cost of treating AE	\$139.85	Cost of treating AE × proportion of AEs experienced
Total ICA cost	\$4,615	Sum ICA cost and cost of AEs

AE = adverse event; AR-DRG = Australian Refined Diagnosis Related Groups; ICA = invasive coronary angiogram; NEP = National Efficient Price

D4A.4 OTHER

Change in management

As described in Section C5a.1, several change in management scenarios are presented in the economic evaluation. The base-case analysis assumes perfect (i.e. 100%) change in management, and two alternative scenarios that assume varying levels of imperfect change in management are also presented (see Section C5a.1).

D4A.5 SUMMARY OF INPUTS TO THE ECONOMIC EVALUATION

A summary table of test costs including contrast agents, stressors and the cost of treating related AEs is presented in Table 63.

Table 63 Summary of costs related to non-invasive testing used in the economic model

Test	Test cost	Contrast	Stressors	AEs	Consultation	Total
CMR	\$900.00	\$44.90	\$10.00	\$6.71	\$43	\$1,005
SPECT	\$834.90	-	\$0.35	\$1.30	\$43	\$880
Stress Echo	\$413.80 ^a	-	\$0.35	\$1.63	\$43	\$459
CTCA	\$700.00	-	-	\$3.54	\$43	\$747

Test	Test cost	Contrast	Stressors	AEs	Consultation	Total
Exercise ECG	\$152.15	-	-	\$1.11	\$43	\$196

a Includes associated cost of MBS item 11712

AE = adverse event; CMR = stress perfusion cardiac magnetic resonance imaging with late gadolinium enhancement; CTCA = computed tomography coronary angiography; ECG = electrocardiography; Echo = echocardiography; SPECT = single-photon emission computed tomography

A summary of the inputs incorporated in the economic model is presented in Table 190, Appendix M.

D5A RESULTS OF THE ECONOMIC EVALUATION

Decision-tree analyses (with structure as per Section D3a; and inputs, including diagnostic accuracy, prevalence, AE rates and costs, as per Section D4a) were conducted comparing CMR with each comparator, such that total costs, including downstream costs, in each arm could be compared.

Cost-effectiveness analyses are presented for the outcomes of: cost per correct initial test result, cost per unnecessary ICA avoided and cost per 'useful ICA'. Due to the invasive nature of ICAs and directly associated AEs, cost per 'unnecessary ICA avoided' is a patient-relevant outcome. However, as the health implications following an ICA are undetermined, it is more difficult to interpret the value of this outcome.

In all outcome analyses the base-case (Scenario 1) assumes that patients with positive results (from either test) are referred for ICA, and those with negative results (from either test) are not; i.e. there is 'perfect change in management'.

However, as described in Section C5a.1, this assumption may not be reasonable. When reporting for the outcomes 'cost per correct initial test result' or 'cost per unnecessary ICA avoided', two alternative scenarios are presented:

- In scenario 2, following CMR, Echo, SPECT or exercise ECG testing and a negative test result, it is assumed that 53% of patients still receive referral to ICA, due to treating doctors remaining concerned. (The remaining 47% of patients with negative results are appropriately diverted from receiving ICA). This is assumed to apply equally to true negatives and false negatives (see Section C5a.1).
- Scenario 3 also assumes that, following CMR, Echo, SPECT or exercise ECG testing, some patients with a negative result will still be referred for ICA; however, it is assumed that clinical judgement effectively includes all false negative patients for referral (i.e. 0% change in management in false negatives) and, additionally, 38% of true negatives are also referred (i.e. 62% of true negatives are appropriately diverted from receiving ICA) (see Section C5a.1).

In both scenarios CTCA is assumed to have perfect change in management (i.e. positive results referred for ICA and negative results diverted from ICA), given its superior sensitivity (see Section C5a.1). This assumption is tested in Appendix M.

The base-case prevalence of CAD in the tested population is assumed to be 45%. Given the uncertainty around this parameter, sensitivity analyses exploring a range of prevalence estimates are presented in Section D6a.

D5A.1 COMPARISON OF CMR TO CTCA

The results of the economic evaluation for the comparison of CMR with CTCA are presented in Table 64.

Table 64 Results of cost and CEAs, comparison of CMR with CTCA

	CMR	CTCA	Increment
Costs			
Test costs (Table 63)	\$1,005	\$747	\$258
Modelled cost of re-testing	\$83	\$0	\$83
Modelled cost of ICA	\$2,165	\$2,319	-\$154
Total	\$3,252	\$3,065	\$187
Testing outcomes			
Total correct diagnoses	75.6%	92.1%	-16.5%
Total incorrect diagnoses	13.3%	8.0%	5.4%
No result (initial equivocal or failed test)	11.1%	0.0%	11.1%
<i>Total ICAs performed</i>	<i>46.9%</i>	<i>50.3%</i>	<i>-3.3%</i>
ICA in CAD+	38.8%	43.7%	-4.8%
ICA in CAD-	8.1%	6.6%	1.5%
Incremental cost per correct initial test result			Dominated
Incremental cost per unnecessary ICA avoided			Dominated
Incremental cost per useful ICA			Dominated

CAD = coronary artery disease; CMR = stress perfusion cardiac magnetic resonance with late gadolinium enhancement; CTCA = computed tomography coronary angiography; ICA = invasive coronary angiography

Modelled costs

CMR is associated with an incremental cost of \$187 in the base-case analysis. This is driven by the cost of CMR testing and re-testing due to failed or equivocal results. A cost offset is observed due to a reduction in the proportion of patients in whom an ICA is performed. The reduction in ICA costs, however, is due to a decreased number of true positives (as the rate of ICAs missed is increased), as opposed to a reduction in false positives.

Modelled outcomes

Compared with CTCA, CMR is associated with a reduction in the proportion of correct diagnoses and increases in the proportion of tests that require re-testing. This is due to its decreased sensitivity (CMR 85%, CTCA 97%) and the proportion of equivocal or failed tests that require re-testing (CMR 11%, CTCA 0%).

While the AE profiles of the testing strategies vary, long-term mortality from the contrast agents (gadolinium used in CMR and iodinated contrast in CTCA) is observed to be approximately similar (Section B7a). However, CTCA is additionally associated with risks of radiation exposure.

While the model costs re-testing and associated AEs, the long-term safety implications of CTCA testing have not been quantified.

Cost per correct initial test result

Given the decrease in true positives and true negative tests associated with CMR testing and an increase in costs, compared with CTCA, CMR is dominated with respect to this outcome (i.e. it is more costly and less effective).

Cost per unnecessary ICA avoided

Due to the invasive nature of ICAs and associated AEs, the cost per ‘unnecessary ICA avoided’ is a patient-relevant outcome. The base-case analysis (Scenario 1) assumes perfect change in management, where the two alternative scenarios presented assume that some patients will be referred to ICA despite a negative test result—in Scenario 2 this is independent of true CAD status, and in Scenario 3 this assumes that clinical judgement identifies true CAD status—as described in D5a above. The modelled outcomes, in terms of the proportion of ICAs performed and missed for the additional scenarios, are presented in Table 191, Appendix M.

The results of the base-case and additional scenarios are presented in Table 65.

Table 65 Cost per unnecessary ICA avoided, base-case and scenario analyses, comparison of CMR with CTCA

	CMR unnecessary ICAs	CTCA unnecessary ICAs	Incremental outcome	Incremental cost	ICER per unnecessary ICA avoided
Base-case	8.1%	6.6%	-1.5%	\$187	Dominated
Scenario 2	29.9%	6.6%	-23.3%	\$1,340	Dominated
Scenario 3	23.8%	6.6%	-17.2%	\$1,191	Dominated

CMR = stress perfusion cardiac magnetic resonance with late gadolinium enhancement CTCA = computed tomography coronary angiography; ICA = invasive coronary angiogram; ICER = incremental cost-effectiveness ratio

In all scenarios explored, CMR is associated with more unnecessary ICAs and higher costs. Thus, CMR is dominated by CTCA for this outcome (i.e. it is more costly and less effective).

Cost per useful ICA

CMR is associated with an increase in the proportion of ICAs missed in patients who have CAD. As all patients that enter the model should receive medical management for risk factor modification, the implication of false negative results and therefore fewer ‘useful ICAs’ is considered most likely to be delayed revascularisation; however, there is potential for quality of life impacts, cardiac events and death to be associated with delayed diagnosis and treatment. As per Section B.5a.2.4, conclusions regarding the effectiveness of revascularisation cannot be made with any certainty, and so health outcomes associated with this difference have not been quantified in the economic modelling. However, a CEA of the incremental cost per ‘useful’ ICA is presented (Table 64). CMR is also dominated in this outcome (i.e. associated with fewer useful ICAs when compared with CTCA and greater cost).

Compared with CTCA, CMR is less effective (i.e. fewer correct test results, more unnecessary ICAs, more false negatives and higher re-testing rate) and typically more costly—except when the prevalence of CAD in the tested population is at the upper limit. The primary driver of the increase in costs is the cost of CMR testing.

Sensitivity analyses around the base-case analysis will explore the uncertainty surrounding these conclusions further (see Section D6a.1).

D5A.2 COMPARISON OF CMR WITH STRESS ECHO

The results of the economic evaluation for the comparison of CMR with stress Echo are presented in Table 66.

Table 66 Results of CEAs, comparison of CMR with stress Echo

	CMR	Stress Echo	Increment
Costs			
Test costs (Table 63)	\$1,005	\$459	\$546
Modelled cost of re-testing	\$83	\$50	\$33
Modelled cost of ICA	\$2,165	\$2,172	-\$7
Total	\$3,252	\$2,681	\$571
Testing outcomes			
Total correct diagnoses	75.6%	80.7%	-5.1%
Total incorrect diagnoses	13.3%	12.7%	0.7%
No result (initial equivocal or failed test)	11.1%	6.6%	4.4%
<i>Total ICAs performed</i>	<i>46.9%</i>	<i>47.1%</i>	<i>-0.2%</i>
ICA in CAD+	38.8%	39.4%	-0.6%
ICA in CAD-	8.1%	7.6%	0.4%
Incremental cost per correct initial test result			Dominated
Incremental cost per unnecessary ICA avoided			Dominated
Incremental cost per useful ICA			Dominated

CAD = coronary artery disease; CMR = stress perfusion cardiac magnetic resonance with late gadolinium enhancement
Echo = echocardiography ICA = invasive coronary angiography

Modelled costs

CMR is associated with an incremental cost of \$571 in the base-case analysis. This is predominantly driven by the cost of CMR testing.

Modelled outcomes

Compared with Echo, CMR is associated with a reduction in the proportion of true positive and true negative tests, and an increase in the proportion of tests that require re-testing. While the accuracy estimates for CMR and Echo are similar, the point estimates for Echo used in the modelling are both slightly higher than for CMR.

The implications associated with a decrease in true positives and true negatives, and increases in the proportion of tests requiring re-testing, have been previously discussed in the context of the comparison of CMR with CTCA, and apply equally to the comparison of CMR with Echo.

While acute AE rates for CMR and stress Echo are similar, in the long run, as stress Echo does not use contrast agents or radiation, CMR may be associated with inferior safety.

Cost per correct initial test result

Given the decrease in true positive and true negative tests associated with CMR testing and an increase in costs, compared with Echo, CMR is dominated (i.e. it is less effective and more costly).

Cost per unnecessary ICA avoided

Given the increase in ICAs in CAD-negative patients associated with CMR testing, and the increase in costs, CMR is dominated (i.e. it is more costly and less effective) when compared with stress Echo in the base-case analysis (Table 67).

The results of the additional scenarios are also presented in Table 67. The modelled outcomes, in terms of the proportion of ICAs performed and missed, are presented in Table 193, Appendix M. In both of the alternative scenarios, in which change in management is imperfect, CMR is associated with a reduction in unnecessary ICAs being performed. The incremental cost per avoided (unnecessary) ICA was observed to be \$57,000 in Scenario 2 and in excess of \$100,000 in Scenario 3.

Table 67 Cost per unnecessary ICA avoided, base-case and scenario analyses, comparison of CMR with stress Echo

	CMR unnecessary ICAs	Echo unnecessary ICAs	Incremental outcome	Incremental cost	ICER per unnecessary ICA avoided
Base-case	8.1%	7.6%	-0.4%	\$571	Dominated
Scenario 2	29.9%	30.8%	0.9%	\$522	\$56,981
Scenario 3	23.8%	24.4%	0.5%	\$551	\$102,369

CMR = stress perfusion cardiac magnetic resonance with late gadolinium enhancement; Echo = echocardiography; ICA = invasive coronary angiogram; ICER = incremental cost-effectiveness ratio

Cost per useful ICA

CMR is associated with a slight reduction in useful ICAs in patients who have CAD when compared with stress Echo and is associated with a greater cost; therefore, CMR is dominated.

Compared with stress Echo, CMR is observed to be more costly (i.e. driven primarily by test cost) and is associated with fewer correct test results, a higher re-test rate and slightly more unnecessary ICAs and false negative results. In all scenarios explored around the base-case analysis (which assumes perfect change in management), CMR was dominated by stress Echo. When this assumption was relaxed, however, and imperfect change in management of testing was modelled, CMR was associated with improved outcomes in terms of reduction in unnecessary ICAs.

Sensitivity analyses around the base-case analysis will explore the uncertainty surrounding these conclusions further (see Section D6a.2).

D5A.3 COMPARISON OF CMR WITH SPECT

The results of the economic evaluation for the comparison of CMR with SPECT are presented in Table 68.

Table 68 Results of CEAs, comparison of CMR with SPECT

	CMR	SPECT	Increment
Costs			
Test costs (Table 63)	\$1,005	\$880	\$125
Modelled cost of re-testing	\$83	\$30	\$53
Modelled cost of ICA	\$2,165	\$2,308	-\$143
Total	\$3,252	\$3,217	\$35
Testing outcomes			
Total correct diagnoses	75.6%	76.5%	-0.9%
Total incorrect diagnoses	13.3%	19.5%	-6.1%
No result (initial equivocal or failed test)	11.1%	4.0%	7.0%
<i>Total ICA performed</i>	<i>46.9%</i>	<i>50.0%</i>	<i>-3.1%</i>
ICA in CAD+	38.8%	37.6%	1.2%
ICA in CAD-	8.1%	12.4%	-4.3%

	CMR	SPECT	Increment
Incremental cost per correct initial test result			Dominated
Incremental cost per unnecessary ICA avoided			\$802
Incremental cost per useful ICA			\$2,798

CAD = coronary artery disease; CEA = cost-effectiveness analysis; CMR = stress perfusion cardiac magnetic resonance with late gadolinium enhancement; ICA = invasive coronary angiography; SPECT = single-photon emission computed tomography

Modelled costs

CMR is associated with an incremental cost of \$35 in the base-case analysis. This is driven by the cost of CMR testing and re-testing due to failed or equivocal results. A cost offset is observed due to a reduction in the proportion of patients in whom an ICA is performed because of the reduction in false positives.

Modelled outcomes

Compared with SPECT, CMR is associated with a reduction in the false positive rate due to better specificity associated with CMR testing (85%, compared with SPECT: 77%). This is associated with a reduction in unnecessary ICAs being performed. However, CMR is also associated with an increase in the proportion of tests that require re-testing.

Cost per correct initial test result

When compared with SPECT, CMR is associated with a decrease in false positive test results. Due to the higher proportion of tests that require re-testing in the CMR arm, the net effect is fewer correct test results. Given the increase in costs associated with CMR, it is dominated by SPECT in the base-case analysis.

Cost per unnecessary ICA avoided

As for the comparison with stress Echo, three scenarios are considered for the comparison of CMR with SPECT for the outcome of unnecessary ICAs avoided, applying different assumptions around the change in management with negative test results.

Given the decrease in ICAs in CAD-negative patients associated with CMR testing, and the slight increase in costs, CMR is associated with an incremental cost of \$802 per unnecessary ICA avoided when compared with SPECT in the base-case analysis.

The results of the additional scenarios are presented in Table 69. The modelled outcomes, in terms of the proportion of ICAs performed and missed, are presented in Table 194, Appendix M. While the incremental reduction in unnecessary ICAs was observed to be somewhat smaller in the alternative scenarios, relatively larger reductions in cost were also observed, resulting in more favourable ICERs: \$646 in Scenario 2 and a dominant (i.e. less costly, more effective) ICER in Scenario 3.

Table 69 Cost per unnecessary ICA avoided, base-case and scenario analyses, comparison of CMR with SPECT

	CMR unnecessary ICAs	SPECT unnecessary ICAs	Incremental outcome	Incremental cost	ICER per unnecessary ICA avoided
Base-case	8.1%	12.4%	4.3%	\$35	\$802
Scenario 2	29.9%	33.8%	3.9%	\$25	\$646
Scenario 3	23.8%	27.8%	4.0%	-\$11	Dominant

CMR = stress perfusion cardiac magnetic resonance with late gadolinium enhancement; ICA = invasive coronary angiogram; ICER = incremental cost-effectiveness ratio; SPECT = single-photon emission computed tomography

Cost per useful ICA

Compared with SPECT, CMR is associated with a small increase in useful ICAs referred. Given the small incremental cost associated with CMR, the incremental cost per useful ICA referred is \$2,798 in the base-case analysis, which assumes perfect change in management.

Conclusions regarding the cost-effectiveness of CMR compared with SPECT differ depending on the outcome of the CEA. For the outcome of cost per correct initial test result, the differences in both the outcomes and costs are small, and slight variations in assumptions can have substantial effects on the conclusions of cost-effectiveness. For the outcome of cost per unnecessary ICA avoided, the difference in outcomes is more consistent across the scenarios tested, favouring CMR. For both analyses CMR is more effective and less costly than (i.e. is dominant to) SPECT at lower estimates of prevalence.

Sensitivity analyses around the base-case analysis will explore the uncertainty surrounding these conclusions further (see Section D6a.3).

D5A.4 COMPARISON OF CMR WITH EXERCISE ECG

The results of the economic evaluation for the comparison of CMR with exercise ECG are presented in Table 70.

Table 70 Results of CEAs, comparison of CMR with exercise ECG

	CMR	Exercise ECG	Increment
Costs			
Test costs (Table 63)	\$1,005	\$196	\$808
Modelled cost of re-testing	\$83	\$49	\$34
Modelled cost of ICA	\$2,165	\$2,017	\$148
Total	\$3,252	\$2,262	\$990
Testing outcomes			
Total correct diagnoses	75.6%	68.2%	7.4%
Total incorrect diagnoses	13.3%	25.3%	-11.9%
No result (initial equivocal or failed test)	11.1%	6.6%	4.5%
<i>Total ICAs performed</i>	<i>46.9%</i>	<i>43.7%</i>	<i>3.2%</i>
ICA in CAD+	38.8%	31.5%	7.4%
ICA in CAD-	8.1%	12.3%	-4.2%
Incremental cost per correct initial test result			\$13,304
Incremental cost per unnecessary ICA avoided			\$23,651
Incremental cost per reduction in missed ICAs			\$13,394

CAD = coronary artery disease; CMR = stress perfusion cardiac magnetic resonance with late gadolinium enhancement; ECG = electrocardiography; ICA = invasive coronary angiography.

Modelled costs

CMR is associated with an incremental cost of \$990 in the base-case analysis. This is driven primarily by the difference between the test costs; however, CMR is associated with increased re-testing and ICA costs due to a higher proportion of patients requiring re-testing and better targeting of ICA use (in true positives, as opposed to false positives).

Modelled outcomes

Compared with exercise ECG, CMR is associated with an increase in the proportion of true positive and true negative tests. This is due to the improved sensitivity and specificity of CMR (85% and 85%) compared with exercise ECG (68% and 77%). This leads to substantially reduced numbers of false negative and false positive results.

Cost per correct initial test result

Given the improved test performance and higher costs associated with CMR, compared with exercise ECG, CMR has an incremental cost per correct initial test result of \$13,304.

Cost per unnecessary ICA avoided

As for the comparisons with stress ECHO and SPECT, three scenarios are considered for the comparison of CMR with exercise ECG for the outcome of unnecessary ICAs avoided, applying different assumptions around the change in management with negative test results.

Given the decrease in ICAs in CAD-negative patients associated with CMR testing and increase in costs, CMR is associated with an incremental cost of \$23,651 per unnecessary ICA avoided when compared with exercise ECG in the base-case analysis.

The results of the additional scenarios are presented in Table 71. The modelled outcomes, in terms of the proportion of ICAs performed and missed, are presented in Table 195, Appendix M. In both of the alternative scenarios where imperfect change in management is considered, both the incremental outcomes and costs reduce. In Scenario 2 the decrease in outcomes is larger relative to the decrease in costs, leading to an increase in the ICER per unnecessary ICA avoided to \$27,420. However, in Scenario 3 the opposite applies, with a reduction in the ICER to \$19,900.

Table 71 Cost per unnecessary ICA avoided, base-case and scenario analyses, comparison of CMR with exercise ECG

	CMR unnecessary ICAs	ECG unnecessary ICAs	Incremental outcome	Incremental cost	ICER per unnecessary ICA avoided
Base-case	8.1%	12.3%	4.2%	\$990	\$23,651
Scenario 2	29.9%	33.0%	3.1%	\$858	\$27,420
Scenario 3	23.8%	27.3%	3.4%	\$681	\$19,900

CMR = stress perfusion cardiac magnetic resonance with late gadolinium enhancement; ECG = electrocardiography; ICA = invasive coronary angiogram; ICER = incremental cost-effectiveness ratio

Cost per useful ICA

Compared with exercise ECG, CMR is associated with an increase in useful ICA referred. The incremental cost per reduction in missed ICAs is \$13,394.

Compared with exercise ECG, CMR is observed to be more costly, driven primarily by test cost, and is consistently associated with more correct test results, fewer false negative results and a reduction in unnecessary ICAs. While the ICER for cost per correct initial test result appeared to be stable (approx. \$13,000) around varying scenarios of prevalence estimates, more variation was observed around the ICER for cost per unnecessary ICA avoided (ranging from \$10,000 to \$125,000).

Sensitivity analyses around the base-case analysis will explore the uncertainty surrounding these conclusions further (see Section D6a.4).

D6A SENSITIVITY ANALYSES

The results of all sensitivity analyses conducted are presented in tabular form in Appendix M. The analyses that most influence the economic comparisons are summarised and presented in graphical form below.

D6A.1 COMPARISON OF CMR WITH CTCA

Alternative prevalence analyses

For the outcomes of ICER per correct test result and ICER per unnecessary ICA avoided, sensitivity analyses were performed around the estimated prevalence of CAD used in the modelling (Table 72).

Table 72 Prevalence analyses, comparison of CMR with CTCA

Prevalence	Incremental cost	Incremental correct test result	ICER per correct test result	Incremental avoided ICA	ICER per avoided ICA
15%	\$371	-13.8%	Dominated	-2.3%	Dominated
25%	\$310	-14.7%	Dominated	-2.0%	Dominated
35%	\$248	-15.6%	Dominated	-1.7%	Dominated
45% (base-case)	\$187	-16.5%	Dominated	-1.5%	Dominated
55%	\$125	-17.4%	Dominated	-1.2%	Dominated
65%	\$64	-18.3%	Dominated	-0.9%	Dominated
75%	\$2	-19.2%	Dominated	-0.7%	Dominated
85%	-\$60	-20.1%	\$297 (SW-Q)	-0.4%	\$14,871 (SW-Q)

CTCA = computed tomography coronary angiography; ICA = invasive coronary angiogram; ICER = incremental cost-effectiveness ratio; SW-Q = south-west quadrant, intervention is less costly and less effective than comparator

An increase in prevalence is associated with a decrease in the incremental costs, a decrease in the proportion of correct test results and an increase in avoided unnecessary ICAs. However, the conclusion of poor cost-effectiveness (i.e. CMR is dominated by CTCA) does not change for either analysis, except at the upper limit of prevalence (85%), where CMR remains less effective than CTCA but is also at less cost (i.e. south-west quadrant of the cost-effectiveness plane).

Additional sensitivity analyses are presented in Table 196 and Table 197, Appendix M. Tornado analyses presenting the variables that have the most effect on the model are presented in Figure 27:

- All sensitivity analyses in all scenarios conducted resulted in a similar conclusion to the base-case; that is, that CMR is dominated by CTCA.
- The analyses were most sensitive to increases in the cost of CMR, changes in the accuracy inputs and the proportion of tests requiring re-testing, although none of the adjustments to these variables changed the conclusion that CMR is not cost-effective in comparison with CTCA for this indication.

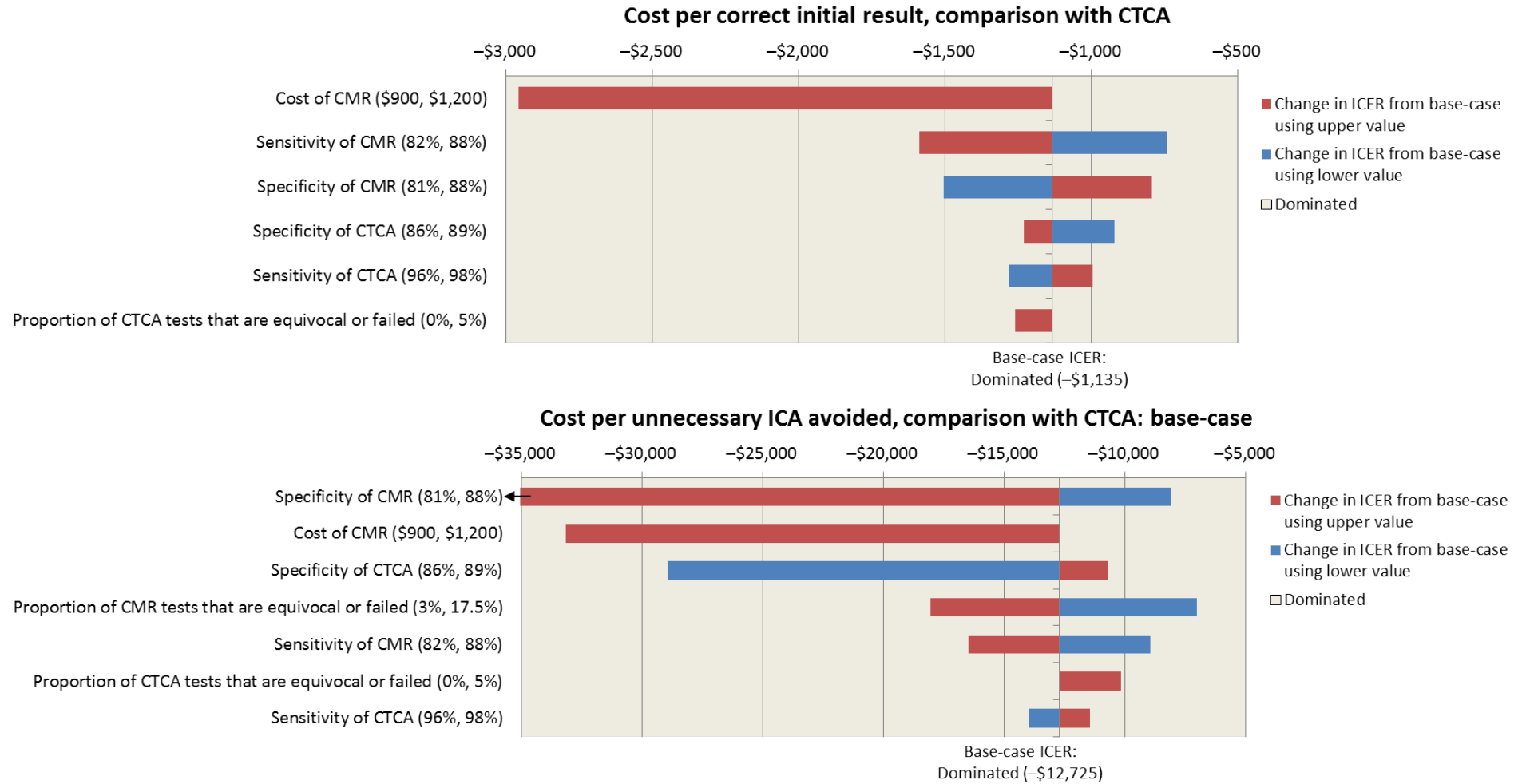


Figure 27 Tornado sensitivity analyses, comparison with CTCA

CMR = cardiac magnetic resonance imaging; CTCA = computed tomography coronary angiography; ICA = invasive coronary angiography; ICER = incremental cost-effectiveness ratio

D6A.2 COMPARISON OF CMR WITH STRESS ECHO

Alternative prevalence analyses

For the outcomes of ICER per correct test result and ICER per unnecessary ICA avoided, sensitivity analyses were performed around the estimated prevalence of CAD used in the modelling (Table 198, Appendix M). Increases in the prevalence were observed to result in slight reductions in both the incremental cost of CMR compared with stress Echo and the proportion of correct test results, with slight increases in the proportion of avoided unnecessary ICAs. However, at all estimates, CMR continued to be more costly and less effective, and so the conclusions of the CEAs do not change: CMR is dominated by Echo.

Additional sensitivity analyses are presented in Table 199 and Table 200, Appendix M. Tornado analyses presenting the variables that have the most effect on the model are presented in Figure 28:

- Sensitivity analyses were generally consistent with the results of the base-case analyses (i.e. CMR dominated by Echo). This conclusion changed when the proportion of failed CMR tests reduced and with changes in the specificities of the tests.
- The scenarios of sensitivity analyses around the alternative cost per unnecessary ICA avoided (which had ICERs of \$57,000 and \$100,000, respectively) were again most sensitive to changes in the specificity and the proportion of failed tests.

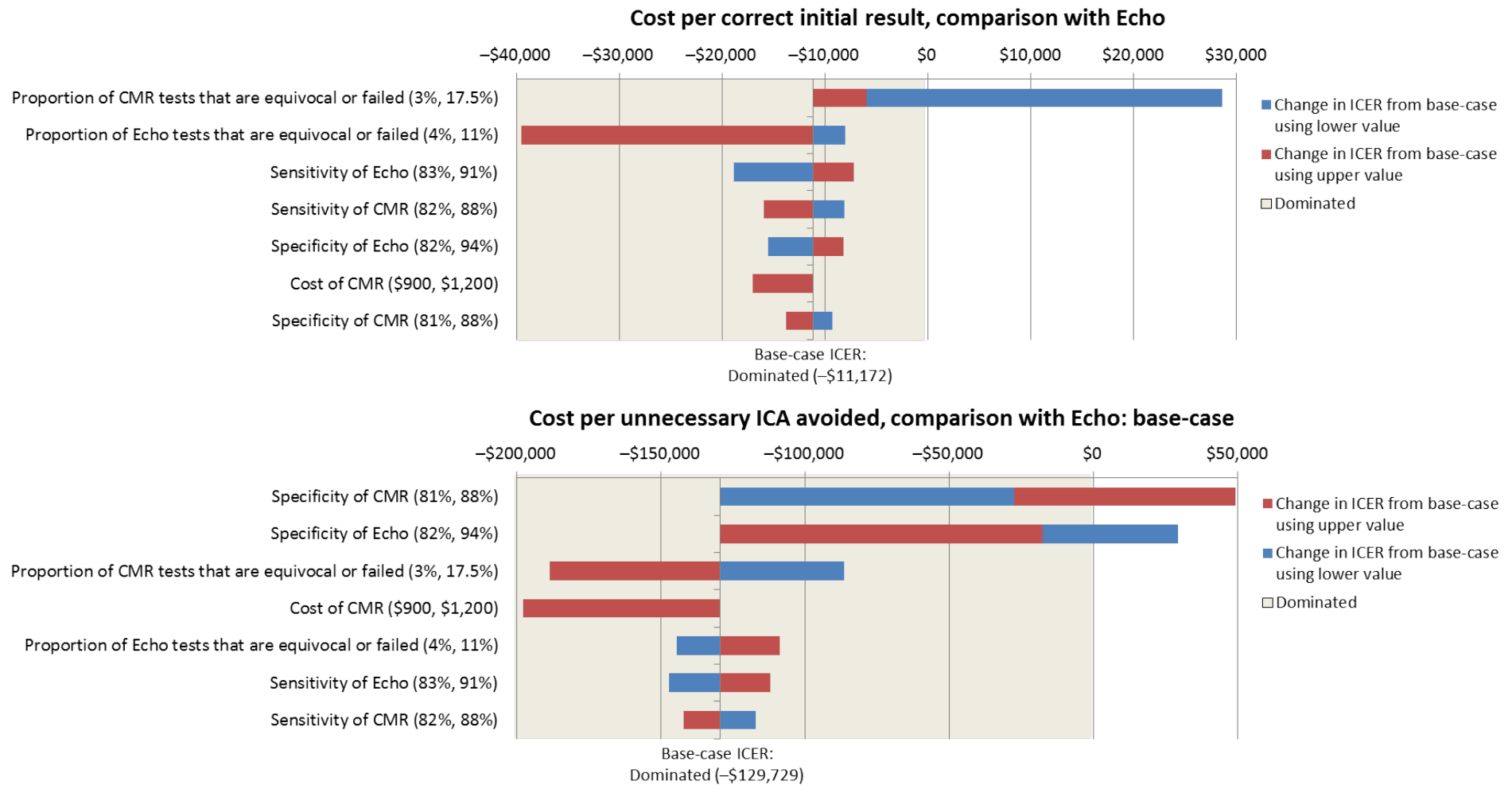


Figure 28 Tornado sensitivity analyses, comparison with stress Echo

CMR = cardiac magnetic resonance imaging; Echo = echocardiography; ICA = invasive coronary angiography; ICER = incremental cost-effectiveness ratio

D6A.3 COMPARISON OF CMR WITH SPECT

Alternative prevalence analyses

For the outcomes of ICER per correct test result and ICER per unnecessary ICA avoided, sensitivity analyses were performed around the estimated prevalence of CAD used in the modelling (Table 73). Increases in the prevalence were observed to increase the incremental costs and decrease the proportion of correct results and the proportion of patients who avoid unnecessary ICA.

The conclusions of cost-effectiveness for the cost per correct initial test result outcome vastly change depending on the prevalence estimate used – from CMR being dominant to SPECT at 15% prevalence of CAD, to being less costly and less effective than SPECT when the prevalence is 35%, and being dominated by SPECT when the prevalence is 45% and above.

For the outcome of cost per unnecessary ICA avoided, as the prevalence increases, the cost-effectiveness of CMR compared with SPECT decreases, from being dominant to SPECT at low estimates of prevalence, to having incremental cost per avoided (unnecessary) ICA of \$20,000 at the highest estimate of prevalence.

Table 73 Prevalence analyses, comparison of CMR with SPECT

Prevalence	Incremental cost	Incremental correct test result	ICER per correct test result	Incremental avoided ICA	ICER per avoided ICA
15%	-\$113	0.8%	Dominant	6.7%	Dominant
25%	-\$64	0.3%	Dominant	5.9%	Dominant
35%	-\$14	-0.3%	\$4,425 (SW-Q)	5.1%	Dominant
45% (base-case)	\$35	-0.9%	Dominated	4.3%	\$802
55%	\$84	-1.5%	Dominated	3.6%	\$2,365
65%	\$133	-2.1%	Dominated	2.8%	\$4,822
75%	\$182	-2.6%	Dominated	2.0%	\$9,243
85%	\$231	-3.2%	Dominated	1.2%	\$19,560

ICA = invasive coronary angiogram; ICER = incremental cost-effectiveness ratio; SPECT = single-photon emission computed tomography; SW-Q = south-west quadrant, intervention is less costly and less effective than comparator

Additional sensitivity analyses are presented in Table 201 and Table 202, Appendix M. Graphical analyses presenting the variables that have the most effect on the model are presented in Figure 29 and Figure 30:

- Sensitivity analyses around base-case cost per correct initial test result observed highly variable results, with subsequent ICERs ranging across all four quadrants of the CE plane. For the outcome of cost per unnecessary ICA avoided (base-case ICER: \$802), CMR was found to be dominant compared with SPECT, with changes to accuracy and rates of re-testing; however, CMR was dominated by SPECT when the specificity of SPECT was better than CMR. The scenarios of alternative costs per unnecessary ICA avoided were most sensitive to changes in accuracy and proportion of re-testing.

Cost per correct initial result, comparison with SPECT

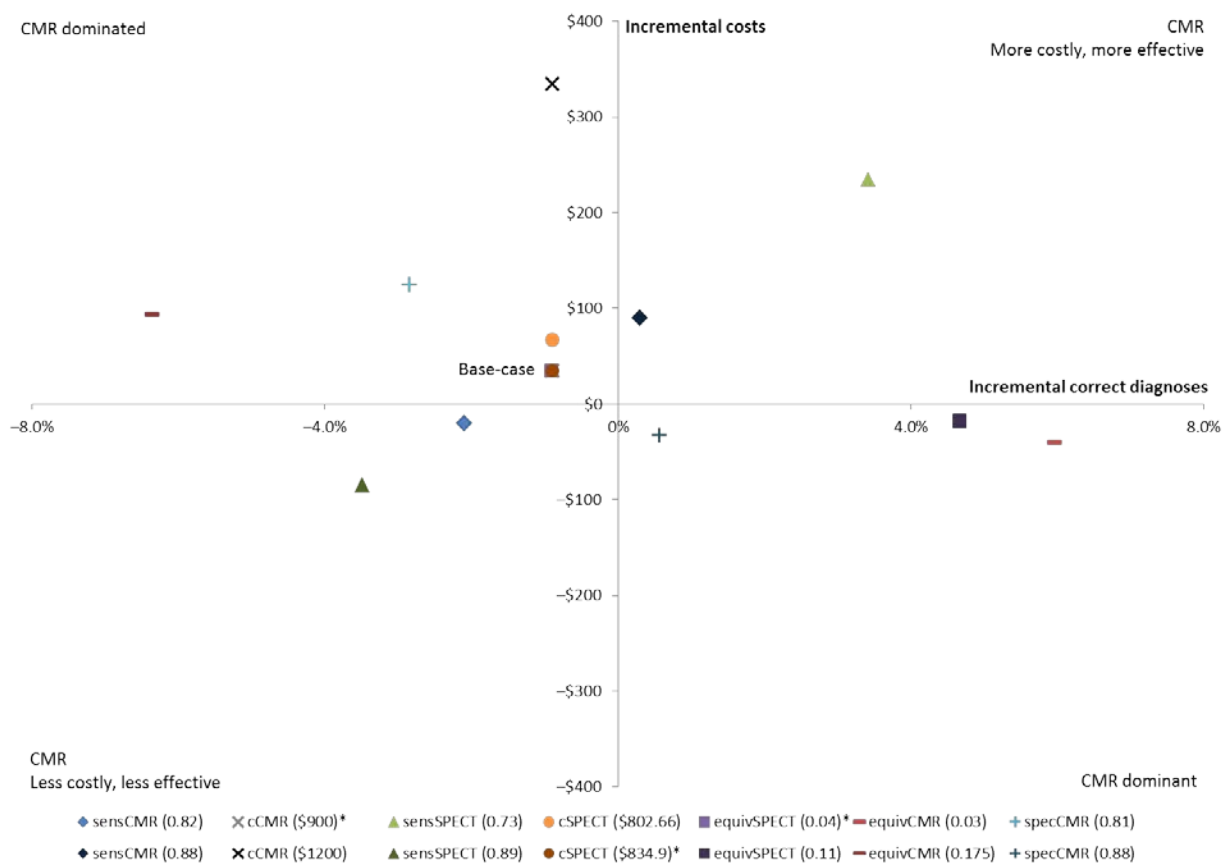


Figure 29 Cost per correct initial test result sensitivity analyses, comparison of CMR with SPECT

* Denotes value used in the base-case analysis

CMR = cardiac magnetic resonance imaging; SPECT = single-photon emission computed tomography

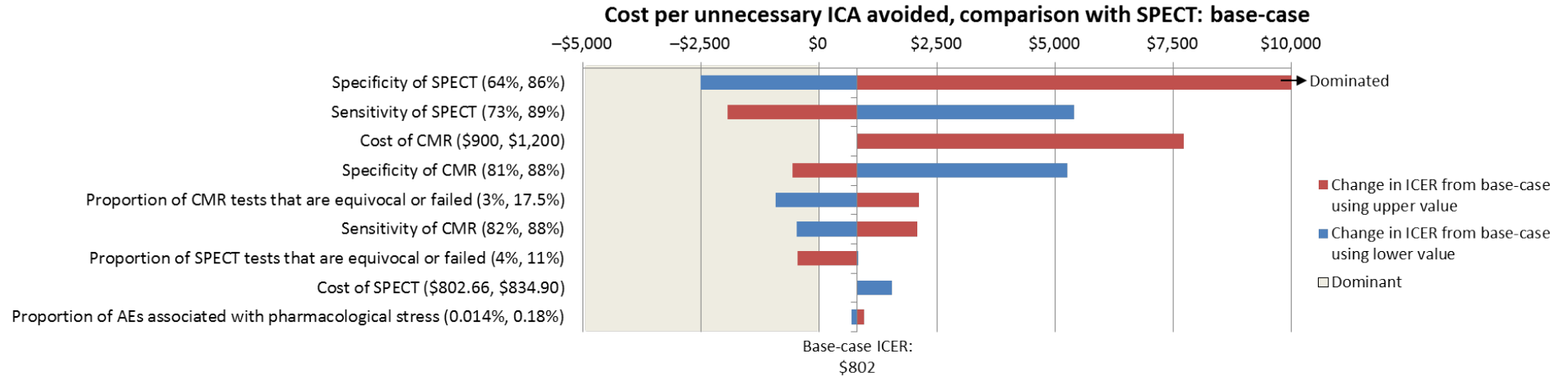


Figure 30 Cost per unnecessary ICA avoided tornado sensitivity analysis, comparison of CMR with SPECT

CMR = cardiac magnetic resonance imaging; ICA = invasive coronary angiography; ICER = incremental cost-effectiveness ratio; SPECT = single-photon emission computed tomography

D6A.4 COMPARISON OF CMR WITH EXERCISE ECG

Alternative prevalence analyses

For the outcomes of ICER per correct test result and ICER per unnecessary ICA avoided, sensitivity analyses were performed around the estimated prevalence of CAD used in the modelling (Table 74). Increases in the prevalence were observed to increase the incremental costs and the proportion of correct results, and decrease the proportion of patients who avoid unnecessary ICA.

The conclusions of cost-effectiveness for the cost per correct initial test result outcome did not change, with an approximate \$100 difference in the ICER at the lower and upper prevalence estimates. For the outcome of cost per unnecessary ICA avoided, as the prevalence increases the cost-effectiveness of CMR compared with exercise ECG decreases, from having incremental cost per avoided (unnecessary) ICA of \$10,000 at the lowest estimate of prevalence to exceeding \$100,000 with the highest.

Table 74 Prevalence analyses, comparison of CMR with exercise ECG

Prevalence	Incremental cost	Incremental correct test result	ICER per correct test result	Incremental avoided ICA	ICER per avoided ICA
15%	\$657	4.9%	\$13,364	6.5%	\$10,159
25%	\$768	5.8%	\$13,338	5.7%	\$13,457
35%	\$879	6.6%	\$13,319	4.9%	\$17,770
45% (base-case)	\$990	7.4%	\$13,304	4.2%	\$23,651
55%	\$1,101	8.3%	\$13,293	3.4%	\$32,145
65%	\$1,212	9.1%	\$13,283	2.7%	\$45,494
75%	\$1,322	10.0%	\$13,275	1.9%	\$69,521
85%	\$1,433	10.8%	\$13,268	1.1%	\$125,584

ECG = electrocardiography; ICS = invasive coronary angiogram; ICER = incremental cost-effectiveness ratio

Additional sensitivity analyses are presented in Table 203 and Table 204, Appendix M. Tornado analyses presenting the variables that have the most effect on the model are presented in Figure 31:

- The base-case analyses were most sensitive to changes in the accuracy—CMR was dominated by ECG when ECG had improved specificity in all scenarios tested. The analyses were also sensitive to changes in the rates of re-testing.

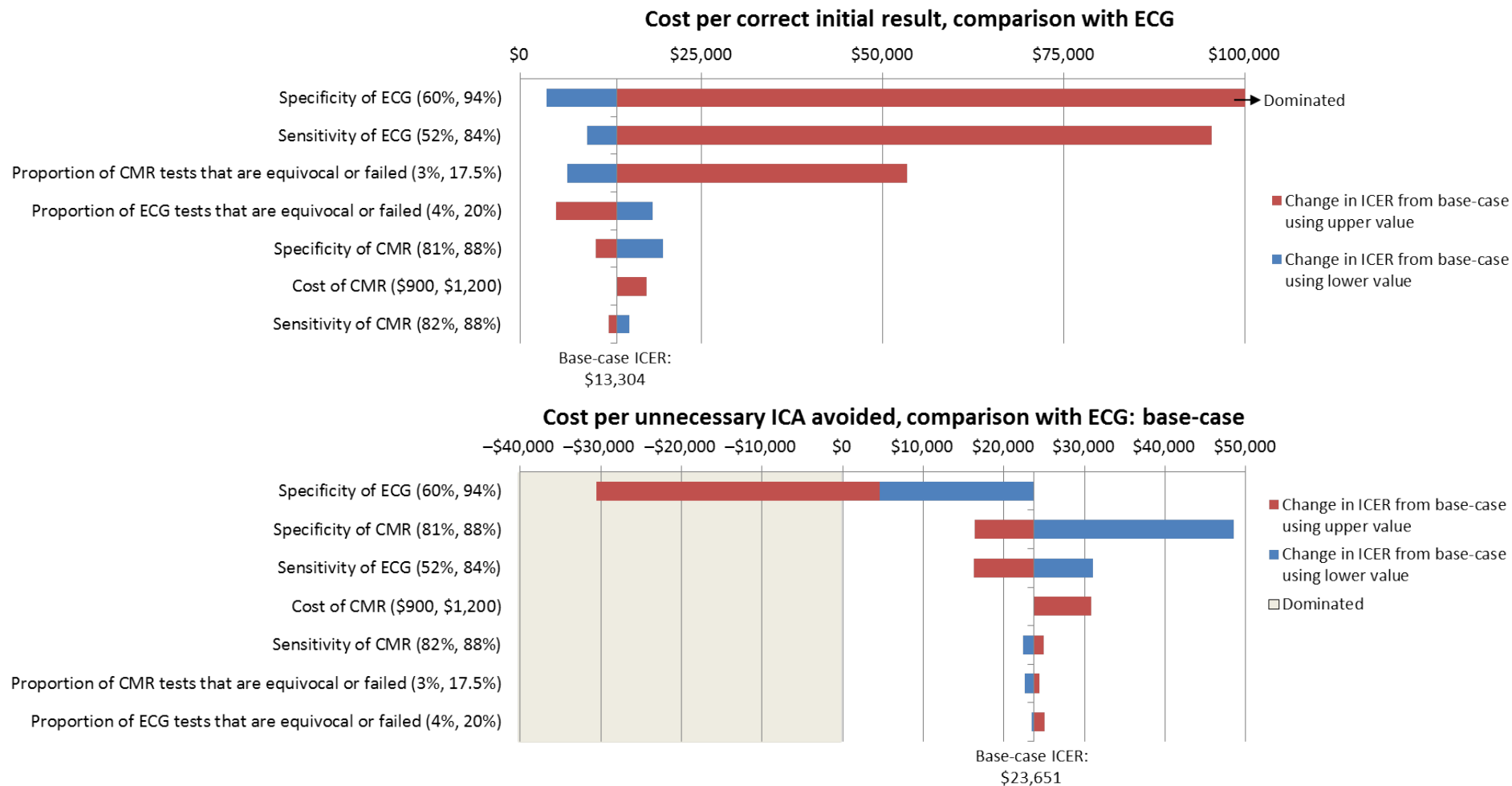


Figure 31 Tornado sensitivity analyses, comparison of CMR with ECG

CMR = cardiac magnetic resonance imaging; ECG = echocardiography; ICA = invasive coronary angiography; ICER = incremental cost-effectiveness ratio

SECTION EA FINANCIAL IMPLICATIONS (POPULATION 1)

A market-based approach has been used to estimate the financial implications of the introduction of CMR for the diagnosis of CAD. However, as MBS items for the comparator tests are not specific to the population that is proposed to be eligible for CMR, the estimated number of tests has been back-calculated based on the number of ICAs performed in the population who have an intermediate PTP of CAD.

E1A JUSTIFICATION OF THE SELECTION OF SOURCES OF DATA

The sources for data used in the financial analysis are presented in Table 75.

Table 75 Data sources used in the financial analysis

Data	Source
Number of ICAs performed in Australian public and private hospitals	Round 12 ^a , 13 ^b , 14 ^c , 16 ^d and 17 ^e Public Hospital costing data and Round 12 ^a and 13 ^b Private Hospital costing data. These data are projected to estimate the number of ICAs performed through to 2020–21
Number of ICAs performed in patients with an intermediate PTP of CAD	MSAC application 1105 report (based on Advisory Panel estimates). This data, in conjunction with the ICA separations data for 2007–08 (Department of Health 2012a) is used to estimate the proportion of ICAs performed in the population with an intermediate PTP of CAD.
Proportion of tests that lead to a referral to ICA	Estimated from Section D5a This data is used to estimate the number of tests performed in patients with an intermediate PTP of CAD
Cost of CMR to the MBS	85% of the proposed Schedule fee, assuming that tests are performed in an outpatient setting, consistent with the setting for the majority of comparator tests and for current CMR services (MBS data for items 57360, 11712, 55116, 55117, 61307 63385, 63388, 63391, 63401 and 63404, 2009–10 to 2014–15)
Patient co-payment for CMR service	MBS data for current CMR services (MBS items 63385, 63388, 63391, 63401, and 63404) for the weighted average contribution per service for out of hospital billed patients, 2009–10 to 2014–15
Bulk-billing rate for CMR service	MBS data for current CMR services (MBS items 63385, 63388, 63391, 63401, and 63404) for the weighted average bulk-billing rate, 2009–10 to 2014–15
CMR uptake rate	Assumed, with consideration of feedback to the protocol suggesting that CMR for diagnosis of CAD has very limited access due to high demand for MRI in other indications and the time required to undertake each CMR
Market share of current testing	Base-case: assumes proportions based on the total use of each method of testing (for all indications), 2014–15 Scenario analyses: <ul style="list-style-type: none"> assuming that 50% of current tests are being performed using CTCA, with the remaining market shared between exercise ECG, stress Echo and SPECT, based on relative use of testing (for all indications), 2014–15 assuming CMR will only share the market with ECG and SPECT (whose share is based on the relative use of these tests, 2014–15)
Cost of current tests to the MBS	MBS data for items 57360, 11712, 55116, 55117 and 61307 for the weighted average MBS benefit paid per service, 2009–10 to 2014–15 (from 2011–12 for MBS item 57360)
Patient co-payment for current tests	MBS data for items 57360, 11712, 55116, 55117 and 61307 for the weighted average patient contribution per service (across all patients, and so intrinsic in

Data	Source
	this data are the bulk billing rates for the tests), 2009–10 to 2014–15 (from 2011–12 for MBS item 57360)

^a Department of Health (2012a)

^b Department of Health (2012b)

^c Department of Health (2012c)

^d IHPA (2014)

^e IHPA (2015b)

CAD = coronary artery disease; CMR = cardiac magnetic resonance imaging; CTCA = computed tomography coronary angiography; ECG = electrocardiography; Echo = echocardiography; ICA = invasive coronary angiography; MBS = Medicare Benefits Schedule; MSAC = Medical Services Advisory Committee; PTP = pre-test probability; SPECT = single-photon emission computed tomography

E2A USE AND COSTS OF CMR FOR DIAGNOSIS OF CAD

Epidemiological data for the population to be tested could not be identified during the evaluation, so a market-based approach was employed to estimate the potential number of services eligible for proposed CMR for CAD. While comparator testing is currently funded by the MBS, comparator item numbers are not restricted to the eligible population. The estimated number of tests is therefore back-calculated from the number of ICAs performed in the population with an intermediate PTP of CAD, assuming that non-invasive testing was conducted prior.

The following steps are taken and are explained in more detail below:

- Project the number of ICAs performed during the period 2016–17 to 2020–21.
- Estimate the proportion of ICAs conducted in patients with an intermediate PTP of CAD.
- Estimate the number of non-invasive tests that would have been performed prior to ICA.
- Estimate the uptake of CMR.
- Estimate the cost of CMR testing for diagnosis of CAD, disaggregated by payer (i.e. MBS, patient).

PROJECTION OF THE NUMBER OF ICAs PERFORMED DURING THE PERIOD 2016–17 TO 2020–21

To project the number of ICAs performed during 2016–17 to 2020–21, recent data for the number of diagnostic ICAs performed (F42A, F42B and F42C) were extracted from the National Hospital Costing Data Collection, 2007–08 to 2012–13 (Table 76).

Table 76 Observed number of ICAs performed, 2007–08 to 2012–13

	Source	2007–08	2008–09	2009–10	2010–11	2011–12	2012–13
Public	Round 12 ^a , 13 ^b , 14 ^c , 16 ^d and 17 ^e Hospital Costing Data	27,696	28,212	29,328	NR	29,901	29,763
Private	Round 12 ^a and 13 ^b Hospital Costing Data	37,749	38,400	NR	NR	NR	NR
Total		65,445	66,612	-	-	-	-

^a Department of Health (2012a) F42A, F42B and F42C separations

^b Department of Health (2012b) F42A, F42B and F42C separations

^c Department of Health (2012c) F42A, F42B and F42C separations

^d IHPA (2014) F42A, F42B and F42C separations

^e IHPA (2015b) F42A, F42B and F42C separations

NR = not reported

While data for the public setting were projected from the observed data, as only two data points were reported in the private setting, the rate of growth in the public setting was assumed to apply to the private setting. The observed and projected estimates are presented in Figure 66, Appendix N, and the projected number of tests during 2016–17 to 2020–21 is presented in Table 77.

ESTIMATION OF THE PROPORTION OF ICAs CONDUCTED IN PATIENTS WITH AN INTERMEDIATE PTP OF CAD

In the MSAC assessment of CTCA for diagnosis of CAD (2007), it was assumed that 30,000 ICAs were being performed in patients with an intermediate PTP of CAD per year. This represents approximately 46% (30,000/65,445) of tests performed in 2007–08 (the year of MSAC assessment). This proportion is assumed to remain consistent across the projected estimates. Sensitivity analyses are performed assuming lower (25%) and higher (75%) proportions.

ESTIMATION OF THE NUMBER OF NON-INVASIVE TESTS THAT WOULD HAVE BEEN PERFORMED PRIOR TO ICA

Approximately 50% of non-invasive tests are assumed to result in an ICA being performed. This is consistent with results reported in the economic evaluation ('Total ICAs' reported in Table 64, Table 66, Table 68 and Table 70) presented in Section D5a. A sensitivity analysis using an upper estimate of 75% is used, which is consistent with the total number of ICAs conducted in the varying scenario analyses conducted in Section D (see Appendix M).

UPTAKE OF CMR

Feedback to the protocol suggested that there would likely be very limited access to CMR for diagnosis of CAD due to the high demand for other specialties and indications. Furthermore, due to the time required to undertake each CMR (in a confined space), patient acceptability may also be low. Therefore, it is likely that, even prior to the consideration of the clinical evidence and economic evaluation, uptake of CMR would be small. In the base-case analysis an uptake estimate of 10% is assumed, with upper estimates of 20%–30% and a lower estimate of 5% tested in sensitivity analyses.

The estimated number of services eligible and utilised with the introduction of CMR for the diagnosis of CAD is presented in Table 77.

Table 77 Estimation of the number of CMR tests performed

	2016–17	2017–18	2018–19	2019–20	2020–21
Projected number of ICAs	73,769	74,644	75,520	76,395	77,270
Proportion of ICAs in intermediate PTP of CAD	45.8%	45.8%	45.8%	45.8%	45.8%
No. of ICAs in intermediate PTP of CAD	33,816	34,217	34,618	35,019	35,421
Proportion of non-invasive tests that lead to ICA	50%	50%	50%	50%	50%
No. of non-invasive tests performed	67,632	68,434	69,236	70,039	70,841
Uptake of CMR	10%	10%	10%	10%	10%
Total no. of CMR tests	6,763	6,843	6,924	7,004	7,084

CAD = coronary artery disease; CMR = cardiac magnetic resonance imaging; ICA = invasive coronary angiography; PTP = pre-test probability

ESTIMATED COST OF CMR TESTING

The proposed item fee for CMR is \$900. As the majority of comparator tests and current CMR services are conducted in the out-of-hospital setting (MBS data for the number of tests conducted in hospital and out of hospital for items 57360, 11712, 55116, 55117, 61307, 63385, 63388, 63391,

63401 and 63404, 2009–10 to 2014–15), the estimated benefit paid by the MBS is assumed to be 85%.

The proportion of patients bulk billed (67.3%) and the patient contribution (\$213.36; including the gap and out-of-pocket costs) are assumed based on data for current CMR services (MBS items 63385, 63388, 63391, 63401 and 63404). Therefore, the estimated patient contribution per test is \$69.74⁷. Both estimates are tested in sensitivity analyses, assuming the highest and lowest bulk billing rates for the comparator tests, and varying the the patient contribution, should the patient be billed \$1,200 for the service (based on RANZCR protocol feedback, see Section A10) (i.e. patient contribution = \$435).

The total cost of CMR testing is reported in Table 78, disaggregated by payer (i.e. the MBS and the patient). The average total cost of CMR testing per year is estimated to be \$5.5–6.0 million per year.

Table 78 Total cost of CMR testing for the diagnosis of CAD

	2016–17	2017–18	2018–19	2019–20	2020–21
Total no. of CMR tests (Table 77)	6,763	6,843	6,924	7,004	7,084
Cost per service to the MBS	\$765.00	\$765.00	\$765.00	\$765.00	\$765.00
Cost per service to the patient	\$69.74	\$69.74	\$69.74	\$69.74	\$69.74
Cost of CMR services to the MBS	\$5,173,817	\$5,235,202	\$5,296,587	\$5,357,972	\$5,419,357
Cost of CMR services to patients	\$471,644	\$477,240	\$482,836	\$488,432	\$494,028
Total cost of CMR	\$5,645,461	\$5,712,442	\$5,779,423	\$5,846,404	\$5,913,385

CAD = coronary artery disease; CMR = cardiac magnetic resonance imaging; ICA = invasive coronary angiography; MBS = Medical Benefits Schedule

E3A CHANGES IN USE AND COST OF OTHER MEDICAL SERVICES

ESTIMATED MARKET SHARE OF CURRENT TESTING

The relative use of each of the comparator tests in the diagnosis of CAD is unknown. In the base-case analysis it is assumed that the relative use of the tests across all indications applies to the tests offset by the introduction of CMR. These data are based on MBS statistics for items 57360, 11712, 55116, 55117 and 61307 in 2014–15. As exercise ECG is conducted with stress Echo (and is specifically listed in the stress Echo item descriptors), the number of exercise ECGs that are performed with stress Echo are excluded from the analyses.

The numbers of services for each of the tests reported in 2014–15, and their relative weights, are presented in Table 79.

Table 79 Comparator services, 2014–15

Test	Source	Services	Weight
Exercise ECG	MBS item 11712 ^a , 2014–15 services	212,084	36.3%
Stress Echo	MBS item 55116 and 55117, 2014–15 services	251,956	43.2%
CTCA	MBS item 57360, 2014–15 services	44,974	7.7%
SPECT	MBS item 61307, 2014–15 services	74,831	12.8%

⁷ \$213.36 × (1 – 67.3%) (Note: Figures are not exact due to rounding)

^a Excludes those performed with stress Echo

CTCA = computed tomography coronary angiography; ECG = electrocardiography; Echo = echocardiography; MBS = Medicare Benefits Schedule; SPECT = single-photon emission computed tomography

HESP member feedback suggested that CTCA may currently be the preferred method for diagnosis of CAD. However, the current item number for CTCA is restricted for use in patients with low to intermediate PTP of CAD. Leakage of the use of CTCA to the broader intermediate population may be reasonable, given its superior accuracy compared with the other non-invasive testing methods. An alternative scenario will be presented assuming that 50% of tests offset by CMR would have been performed by CTCA, and that the share of the other comparators is according to their relative use.

A further alternative scenario is presented assuming that CMR will only share the market with exercise ECG and SPECT, given the dominance of CTCA and stress Echo over CMR, as observed in Section Da.

The estimated numbers of each test performed that are offset with the introduction of CMR for the diagnosis of CAD are presented in Table 80.

Table 80 Estimation of the number of comparator tests offset

	2016–17	2017–18	2018–19	2019–20	2020–21
Number of tests offset (Table 77)	6,763	6,843	6,924	7,004	7,084
Market share					
Exercise ECG	36.3%	36.3%	36.3%	36.3%	36.3%
Stress Echo	43.2%	43.2%	43.2%	43.2%	43.2%
CTCA	7.7%	7.7%	7.7%	7.7%	7.7%
SPECT	12.8%	12.8%	12.8%	12.8%	12.8%
Number of each test offset					
Exercise ECG	2,457	2,486	2,515	2,544	2,573
Stress Echo	2,919	2,953	2,988	3,022	3,057
CTCA	521	527	533	540	546
SPECT	867	877	887	898	908

CTCA = computed tomography coronary angiography; ECG = electrocardiography; Echo = echocardiography; SPECT = single-photon emission computed tomography

Estimated costs offset

The estimated costs per service to the MBS and to the patient used in the financial model are presented in Table 81. These are based on the average MBS benefit and patient contribution paid per service, 2009–10 to 2014–15 (weighted by the number of tests performed each year) for each of the comparator tests (items 11712 for exercise ECG, 55116 and 55117 for stress Echo, 57360 for CTCA and 61307 for SPECT).

Table 81 Estimated cost per comparator service

	Exercise ECG	Stress Echo	CTCA	SPECT
Average cost per service to the MBS	\$127.65	\$350.95	\$650.66	\$779.73
Average cost per service to the patient	\$23.51	\$61.30	\$42.24	\$22.93

CTCA = computed tomography coronary angiography; ECG = electrocardiography; Echo = echocardiography; MBS = Medicare Benefits Schedule; SPECT = single-photon emission computed tomography

Therefore, the cost offsets with the introduction of CMR for diagnosis of CAD is presented in Table 82.

Table 82 Total cost offsets by CMR testing for diagnosis of CAD

	2016-17	2017-18	2018-19	2019-20	2020-21
<i>Number tests offset</i>					
Exercise ECG	2,457	2,486	2,515	2,544	2,573
Stress Echo	2,919	2,953	2,988	3,022	3,057
CTCA	521	527	533	540	546
SPECT	867	877	887	898	908
<i>MBS cost offset</i>					
Exercise ECG	\$313,599	\$317,319	\$321,040	\$324,761	\$328,482
Stress Echo	\$1,024,295	\$1,036,448	\$1,048,601	\$1,060,754	\$1,072,907
CTCA	\$338,976	\$342,998	\$347,020	\$351,042	\$355,064
SPECT	\$675,891	\$683,910	\$691,930	\$699,949	\$707,968
Total offsets to the MBS	\$2,352,761	\$2,380,676	\$2,408,590	\$2,436,505	\$2,464,420
<i>Patient cost offset</i>					
Exercise ECG	\$57,752	\$58,437	\$59,122	\$59,807	\$60,493
Stress Echo	\$178,900	\$181,023	\$183,145	\$185,268	\$187,390
CTCA	\$22,005	\$22,266	\$22,527	\$22,788	\$23,049
SPECT	\$19,880	\$20,116	\$20,352	\$20,588	\$20,824
Total offsets to patients	\$278,537	\$281,841	\$285,146	\$288,451	\$291,756
Total cost offsets	\$2,631,298	\$2,662,517	\$2,693,737	\$2,724,956	\$2,756,175

CTCA = computed tomography coronary angiography; ECG = electrocardiography; Echo = echocardiography; MBS = Medical Benefits Schedule; SPECT = single-photon emission computed tomography

E4A FINANCIAL IMPLICATIONS FOR THE MBS

The financial implications to the MBS resulting from the proposed listing of CMR for the diagnosis of CAD are summarised in Table 83.

Table 83 Total costs to the MBS associated with CMR for diagnosis of CAD

	2016-17	2017-18	2018-19	2019-20	2020-21
CMR					
Number of services	6,763	6,843	6,924	7,004	7,084
Cost to the MBS	\$5,173,817	\$5,235,202	\$5,296,587	\$5,357,972	\$5,419,357
Tests offset					
Number of services offset	6,763	6,843	6,924	7,004	7,084
Costs offset	\$2,352,761	\$2,380,676	\$2,408,590	\$2,436,505	\$2,464,420
Net cost to the MBS	\$2,821,055	\$2,854,526	\$2,887,997	\$2,921,467	\$2,954,938

CAD = coronary artery disease; CMR = cardiac magnetic resonance imaging; MBS = Medicare Benefits Schedule

E5A FINANCIAL IMPLICATIONS FOR GOVERNMENT HEALTH BUDGETS

No financial implications to other health budgets are anticipated with the listing of CMR for diagnosis of CAD; however, the implications to patients are reported in Table 84.

Table 84 Total costs to patients associated with CMR for diagnosis of CAD

	2016–17	2017–18	2018–19	2019–20	2020–21
CMR					
Number of services	6,763	6,843	6,924	7,004	7,084
Cost to patients	\$471,644	\$477,240	\$482,836	\$488,432	\$494,028
Tests offset					
Number of services offset	6,763	6,843	6,924	7,004	7,084
Costs offset	\$278,537	\$281,841	\$285,146	\$288,451	\$291,756
Net cost to patients	\$193,107	\$195,399	\$197,690	\$199,981	\$202,272

CAD = coronary artery disease; CMR = cardiac magnetic resonance imaging

The results of the alternative market-share scenarios considered are presented in Table 85.

Table 85 Market-share scenario analyses

	2016–17	2017–18	2018–19	2019–20	2020–21
Base-case					
Net cost of CMR to the MBS	\$2,821,055	\$2,854,526	\$2,887,997	\$2,921,467	\$2,954,938
Net cost of CMR to patients	\$193,107	\$195,399	\$197,690	\$199,981	\$202,272
<i>CTCA 50% share</i>					
Net cost of CMR to the MBS	\$1,882,622	\$1,904,959	\$1,927,295	\$1,949,632	\$1,971,968
Net cost of CMR to patients	\$189,842	\$192,095	\$194,347	\$196,599	\$198,852
<i>Only ECG and SPECT offset</i>					
Net cost of CMR to the MBS	\$3,160,298	\$3,197,794	\$3,235,289	\$3,272,785	\$3,310,281
Net cost of CMR to patients	\$313,670	\$317,392	\$321,113	\$324,835	\$328,557

CMR = cardiac magnetic resonance imaging; CTCA = computed tomography coronary angiography; ECG = electrocardiography; MBS = Medicare Benefits Schedule; SPECT = single-photon emission computed tomography

E6A IDENTIFICATION, ESTIMATION AND REDUCTION OF UNCERTAINTY

Sensitivity analyses around inputs to the financial model are presented in Table 86. Additional sensitivity analyses are presented in Table 205, Appendix N.

Table 86 Sensitivity analysis of financial implications of listing CMR for CAD

	2016–17	2017–18	2018–19	2019–20	2020–21
Base-case					
Net cost of CMR to the MBS	\$2,821,055	\$2,854,526	\$2,887,997	\$2,921,467	\$2,954,938
Net cost of CMR to patients	\$193,107	\$195,399	\$197,690	\$199,981	\$202,272
<i>Proportion of ICAs with intermediate PTP: 25% (base-case: 46%)</i>					
Net cost of CMR to the MBS	\$1,538,533	\$1,556,787	\$1,575,041	\$1,593,295	\$1,611,549
Net cost of CMR to patients	\$105,316	\$106,566	\$107,815	\$109,065	\$110,314

	2016-17	2017-18	2018-19	2019-20	2020-21
<i>Proportion of ICAs with intermediate PTP: 75% (base-case: 46%)</i>					
Net cost of CMR to the MBS	\$4,615,599	\$4,670,361	\$4,725,124	\$4,779,886	\$4,834,648
Net cost of CMR to patients	\$315,948	\$319,697	\$323,445	\$327,194	\$330,942
<i>Proportion of tests that go on for ICA: 75% (base-case: 50%)</i>					
Net cost of CMR to the MBS	\$1,880,704	\$1,903,017	\$1,925,331	\$1,947,645	\$1,969,959
Net cost of CMR to patients	\$128,738	\$130,266	\$131,793	\$133,321	\$134,848
<i>CMR accessibility and uptake: 30% (base-case: 10%)</i>					
Net cost of CMR to the MBS	\$8,463,166	\$8,563,578	\$8,663,990	\$8,764,402	\$8,864,814
Net cost of CMR to patients	\$579,322	\$586,196	\$593,069	\$599,943	\$606,816

CAD = coronary artery disease; CMR = cardiac magnetic resonance imaging; ICA = invasive coronary angiography; MBS = Medicare Benefits Schedule; PTP = pre-test probability

POPULATION 2

There was no direct evidence on the effectiveness of LGE-CMR in assessing myocardial ischaemia and determining myocardial viability in patients with an existing diagnosis of significant CAD who have a history of IHD with LVD and are being considered for revascularisation (population 2).

In the absence of direct evidence, only a linked evidence approach was taken.

To construct a linked evidence analysis, the following evidence requirements had to be met:

- consideration of the diagnostic performance and clinical validity of LGE-CMR (Sections B3b and B4b);
- consideration of the clinical utility of LGE-CMR in terms of impact of positive versus negative test results on patient management, the contribution and clinical importance of false negatives versus false positives, and the direct impact of each therapeutic model service option on health outcomes (Section B5b); and
- conclusions linking these steps (Section B8b).

B3B DIAGNOSTIC PERFORMANCE (POPULATION 2)

B3B.1 REFERENCE STANDARD

There was no valid reference standard for detecting viable myocardium in the protocol ratified by PASC. However, a review by Camici, Prasad & Rimoldi (2008) stated that there is general consensus (supported by at least 7 studies) that the changes in LVEF after revascularisation linearly correlate with the number of viable segments in the patient. Indeed, the studies that provided accuracy data used regional functional improvement of myocardial segments, as a predictor for LV function, as the reference standard. Thus, to assess the accuracy of LGE-CMR, regional functional improvement was used as the evidentiary standard in this report.

B3B.2 RESULTS OF THE LITERATURE SEARCH

The details of the literature sources and search strategies are provided in Section B1.1.

Nineteen studies were identified that investigated the diagnostic accuracy of LGE-CMR and provided 2 x 2 data. One SR was identified that conducted a meta-analysis comparing LGE-CMR with the evidentiary standard (Campbell et al. 2014).

To compare LGE-CMR with DbE and SPECT, the PubMed Health database was searched for relevant SRs published since 2007 using the comparator and CAD as search terms. Only 2 SRs were identified that investigated the diagnostic accuracy of Echo and SPECT compared with regional functional improvement of myocardial segments (Campbell et al. 2014; Schinkel et al. 2007). No studies were identified that investigated the sensitivity and specificity of CT perfusion imaging with delayed contrast enhancement.

B3B.3 RISK OF BIAS ASSESSMENT

Diagnostic accuracy and concordance studies were assessed using the QUADAS 2 tool (Whiting et al. 2011), and the risk of bias for each of the individual studies is listed in Table 173 and Table 174 in Appendix F. The risk of bias was evaluated as described in Section B3a.3. Overall, 18 studies had a low risk of bias and 1 study had an unclear risk of bias. All 4 studies providing concordance data had a low risk of bias.

The AMSTAR checklist (Shea et al. 2007) was used to assess the quality of the 2 SRs that reported on the diagnostic accuracy of LGE-CMR, SPECT and Echo compared with regional functional improvement, and the results are reported in Table 148 in Appendix C. The risk of bias was determined as described in Section B3a.3.

B3B.4 CHARACTERISTICS OF THE EVIDENCE-BASE

See Table 148 in Appendix C for details on the 19 studies included in the evidence-base. The studies generally matched the proposed target population (i.e. patients with CAD being considered for revascularisation). Different segmental models to interpret LV segmentation were used in the studies, with models varying between 8 and 56 segments per patient. Most common was the 16-segmental model (8 studies), followed by the 17-segmental model (5 studies). There was one 8-segmental study, two 12-segmental studies, one 24-segmental study and one 56-segmental study. It is not known if the different segmental models influenced the study results. Different dosages of gadolinium-based contrast were used in the included studies, varying from 0.01 to 0.2 mmol/kg body weight, and images were obtained 2–30 minutes after the administration of the contrast agent. The impact of the method of administration of contrast on the study results is unknown. Seventeen of the 19 studies were included in the meta-analyses. The remaining 2 studies did not report the cut-off values used for viability and therefore it was not known in which meta-analysis subgroup they should have been included.

The study profiles of the two SRs comparing LGE-CMR, Echo and SPECT with the evidentiary standard are shown in Table 150 in Appendix C.

B3B.5 OUTCOME MEASURES AND ANALYSIS

To assess the diagnostic accuracy of LGE-CMR compared with segmental functional recovery as the evidentiary standard, studies were only included if they provided data that could be extracted into a classic 2 x 2 table. Diagnostic accuracy outcome measures and meta-analysis were calculated as described in Section B3a.5.

Meta-analyses were undertaken for two subgroups: cut-off value for viability $\leq 25\%$ hyper-enhancement (HE) and cut-off value for viability $\geq 50\%$ HE. The studies where the cut-off value was not reported were not included in the meta-analyses (Gerber et al. 2002; Sandstede et al. 2000). Some studies reported data for both cut-off at 25% HE and cut-off at 50% or 75% HE, and were therefore included in both meta-analyses.

B3B.6 RESULTS OF THE SYSTEMATIC LITERATURE REVIEW

IS IT ACCURATE?

Summary – What is the diagnostic accuracy of LGE-CMR viability imaging in determining viable myocardium in patients with an existing diagnosis of significant CAD, who have a history of IHD with LVD and are being considered for revascularisation?

When pooled sensitivities of LGE-CMR, Echo and SPECT were compared, LGE-CMR (high cut-off) was the most sensitive, at 93%. This indicates that only 7% of patients with a viable myocardium would be misdiagnosed as not being viable. LGE-CMR (low cut-off) had the lowest pooled sensitivity, at 72%. The pooled sensitivity of DbE was 79% and 83%–87% for SPECT.

When pooled specificities of LGE-CMR, Echo and SPECT were compared, LGE-CMR (high cut-off) was the least specific, at 45%. A very high proportion of patients would therefore receive a false positive test, being classified as having a viable myocardium, when they would be unlikely to benefit from revascularisation. The pooled specificity was highest for DbE (78%), and was between 54% and 65% for LGE-CMR (low cut-off) and SPECT.

The concordance between LGE-CMR (high cut-off) and SPECT was low to moderate (kappa range 0.32–0.52). This was mostly due to the low estimated specificity of LGE-CMR compared with thallium-SPECT (TI-SPECT) (50%–54%); half of all patients considered to have non-viable myocardium by TI-SPECT were considered to have viable myocardium by LGE-CMR.

The concordance between LGE-CMR (high cut-off) and DbE or Echo was very low (kappa = 0.24). Again, this was mostly due to the low estimated specificity of LGE-CMR compared with DbE (41%–45%), and to the low estimated sensitivity of LGE-CMR compared with Echo (58%). This indicates that 42% of patients with viable myocardium detected by Echo would not be detected by LGE-CMR.

No evidence was identified on the accuracy of CT-DCE.

B3B.6.1 ACCURACY OF LGE-CMR FOR DETERMINING VIABILITY

The accuracy of LGE-CMR in patients with an existing diagnosis of significant CAD who have a history of IHD with LVD and are being considered for revascularisation (population 2) was assessed in two subgroups: studies using a cut-off value of $\leq 25\%$ HE (low cut-off group; k=10) and studies using cut-off value of $\geq 50\%$ HE (high cut-off group; k=15). None of the included studies used a cut-off value between 25% HE and 50% HE. All included studies compared LGE-CMR with the evidentiary standard: regional functional improvement of myocardial segments at follow-up. A summary of the diagnostic accuracy data is shown in Table 170 in Appendix E.

Fifteen studies were included in the meta-analysis of the high cut-off group (Figure 53 in Appendix H). Thirteen studies used a cut-off value of 50% HE and only 2 studies used 75% HE (Becker et al. 2011; Van Hoe & Vanderheyden 2004). The overall quality of the evidence provided by these studies in assessing the diagnostic accuracy of detecting viable myocardium compared with regional functional improvement was assessed using GRADE (Guyatt et al. 2011), and the results are presented in Table 184 in Appendix G. There was considerable heterogeneity (above 95%) in both the sensitivity and specificity, introducing inconsistency and lowering the quality of evidence to very low (GRADE ⊕⊖⊖⊖). A high level of heterogeneity can be expected in meta-analyses of diagnostic test accuracy⁸. However, the use of different segmental models, types and amounts of the gadolinium-based contrast agents and follow-up periods probably all contributed to the high level of heterogeneity. Using Deeks' funnel plot asymmetry test, no significant publication bias was identified (Figure 62 in Appendix J; k=15, p=0.42).

The pooled sensitivity (93%; 95%CI 90, 96) and specificity (45%; 95%CI 30, 61) of the high cut-off group are shown in Figure 32. When the analysis was restricted to the 13 studies that used 50% HE as a cut-off, the pooled sensitivity and specificity were almost the same (94%; 95%CI 91, 96 and 46%; 95%CI 36, 57, respectively). Figure 33 shows the SROC curve, which depicts the relationship between true positives and false positives by plotting sensitivity against 1 – specificity, and suggests a high level of predicting segmental recovery in viable segments among all studies, with an AUC of 0.88 (95%CI 0.85, 0.91).

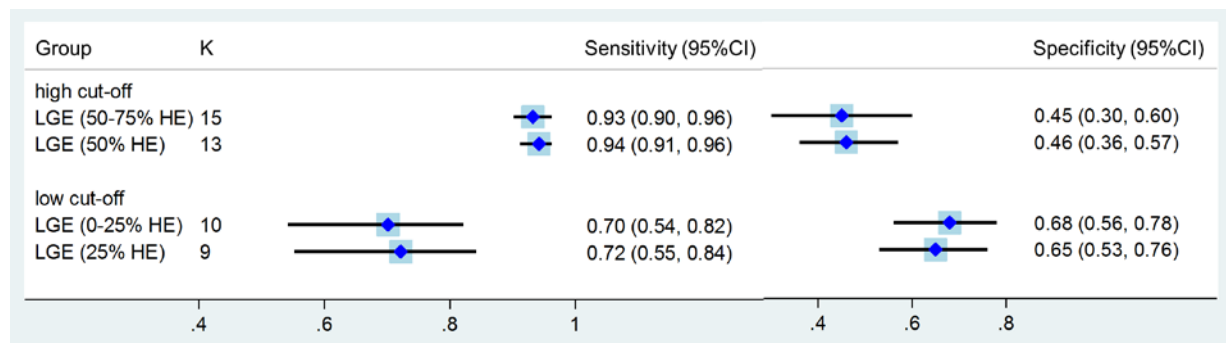


Figure 32 Pooled sensitivity and specificity of LGE-CMR for different HE cut-offs, with recovery of regional function after revascularisation as the reference standard

CI = confidence interval; HE = hyper-enhancement; K = number of studies; LGE = late gadolinium enhancement

Ten studies were included in the meta-analysis of the low cut-off group, and the overall quality of the evidence provided by these studies in assessing the diagnostic accuracy of detecting viable myocardium compared with regional functional improvement was assessed using GRADE (Guyatt et al. 2011). As for the high cut-off group, there was considerable heterogeneity in both sensitivity and specificity, introducing inconsistency and lowering the quality of evidence to very low (GRADE ⊕⊖⊖⊖; Table 184 in Appendix G). Using Deeks' funnel plot asymmetry test, no significant publication bias was identified (Figure 63 in Appendix J; k=10, p=0.43).

The pooled sensitivity and specificity values for these studies were 70% (95%CI 54, 82) and 68% (95%CI 56, 78), respectively (Figure 54 in Appendix H). The study by Glaveckaite et al. (2014) had a cut-off value of 0%, whereas all the other studies had a cut-off value of 25%. When Glaveckaite et al. (2014) was excluded from the meta-analysis, the pooled sensitivity (72%; 95%CI 55, 84) and

⁸ Source: Macaskill P, Gatsonis C, Deeks JJ, Harbord RM, Takwoingi Y. Chapter 10: Analysing and Presenting Results. In: Deeks JJ, Bossuyt PM, Gatsonis C (editors), Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy Version 1.0. The Cochrane Collaboration, 2010. Available from: <http://srdta.cochrane.org/>.

specificity (65%; 95%CI 0.53, 0.76) values did not differ significantly. Heterogeneity for sensitivity and specificity was also considerable in the low cut-off group, at 96% (95%CI 94.6, 97.5). Figure 34 shows the SROC curve with an AUC of 0.74 (95%CI 0.70, 0.78). A score about 0.7 is generally considered good.

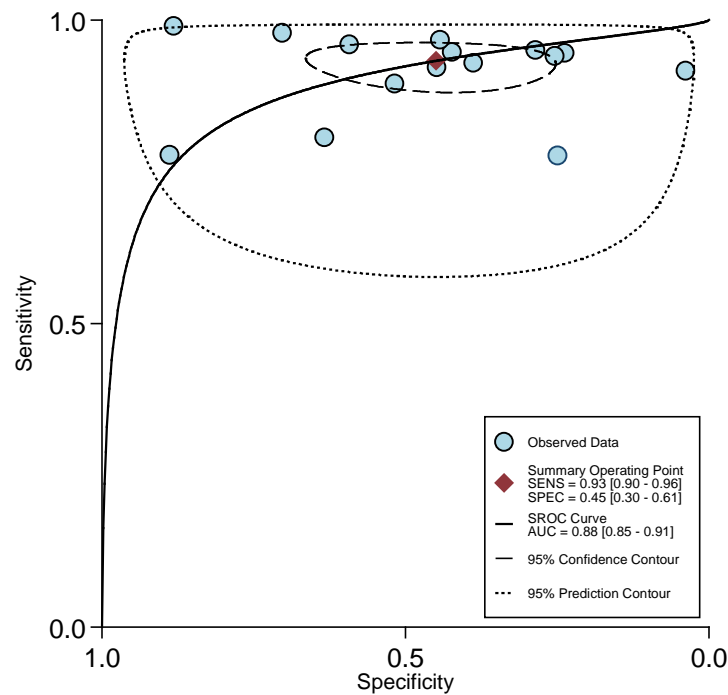


Figure 33 SROC curve with prediction and confidence contours (high cut-off group)

AUC = area under the curve; SROC = summary receiver-operator curve

The two studies that did not report a cut-off value for viability and were not included in the meta-analysis (Gerber et al. 2002; Sandstede et al. 2000), reported high specificities when compared with the meta-analyses: 82% (95%CI 76, 87) and 76% (95%CI 58, 89), respectively. The study by Sandstede et al. (2000) also had a high sensitivity: 98% (95%CI 87, 100; n=73), whereas Gerber et al. (2002) reported a sensitivity of only 64% (95%CI 56, 71; n=389).

The SR by Campbell et al. (2014) conducted a similar meta-analysis of LGE-CMR versus regional functional improvement, using a threshold of 50% HE for determining viability. Fourteen studies were included in this National Institute of Health Research (NIHR) report, 12 of which were also included in the meta-analysis for the high cut-off group described above, and the pooled sensitivity and specificity were similar (Figure 35). The level of heterogeneity between studies was not reported.

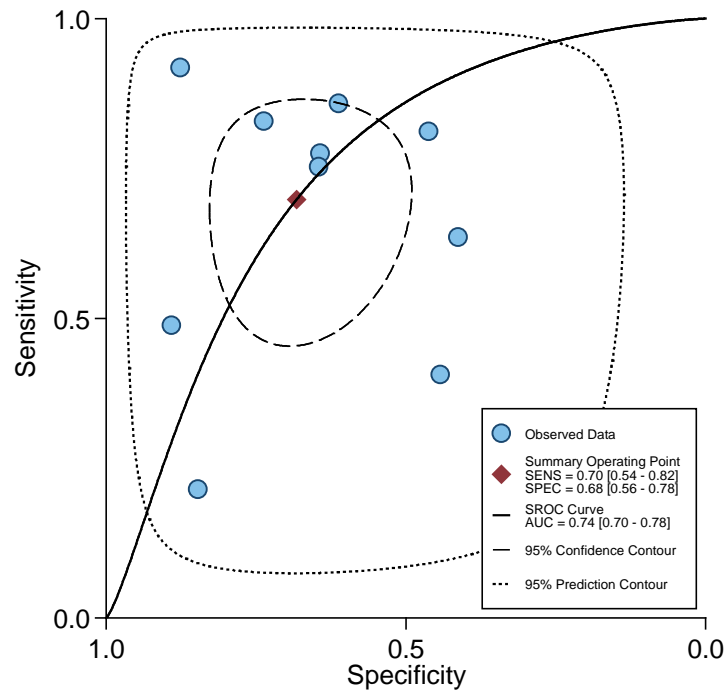


Figure 34 SROC curve with prediction and confidence contours (low cut-off group)

AUC = area under the curve; SROC = summary receiver-operator curve

B3B.6.2 ACCURACY OF ECHO AND SPECT COMPARED WITH REGIONAL FUNCTIONAL IMPROVEMENT

Two SRs (Campbell et al. 2014; Schinkel et al. 2007) investigated the sensitivity and specificity of two comparators specified *a priori*, low-dose dobutamine stress Echo (DbE) and SPECT using thallium/sestamibi/tetrofosmin, compared with the evidentiary standard. The use of the evidentiary standard allows comparison of the accuracy of DbE, SPECT and LGE-CMR. Schinkel et al. (2007) reported detailed comparator data, whereas Campbell et al. (2014) did not provide subgroup data for DbE or SPECT. Campbell et al. (2014) included the studies included in the SR by Schinkel et al. (2007) that were published after 2000, and pooled this with studies they identified that assessed other tests as well as LGE-CMR.

The comparators (DbE and SPECT) had a lower sensitivity than the high cut-off LGE-CMR group but not compared with the low cut-off LGE-CMR group (Figure 35). Although high cut-off LGE-CMR had the highest sensitivity, the specificity in this group was the lowest. The specificity of the low cut-off LGE-CMR group was similar to DbE and the specificity of SPECT was slightly lower than for DbE.

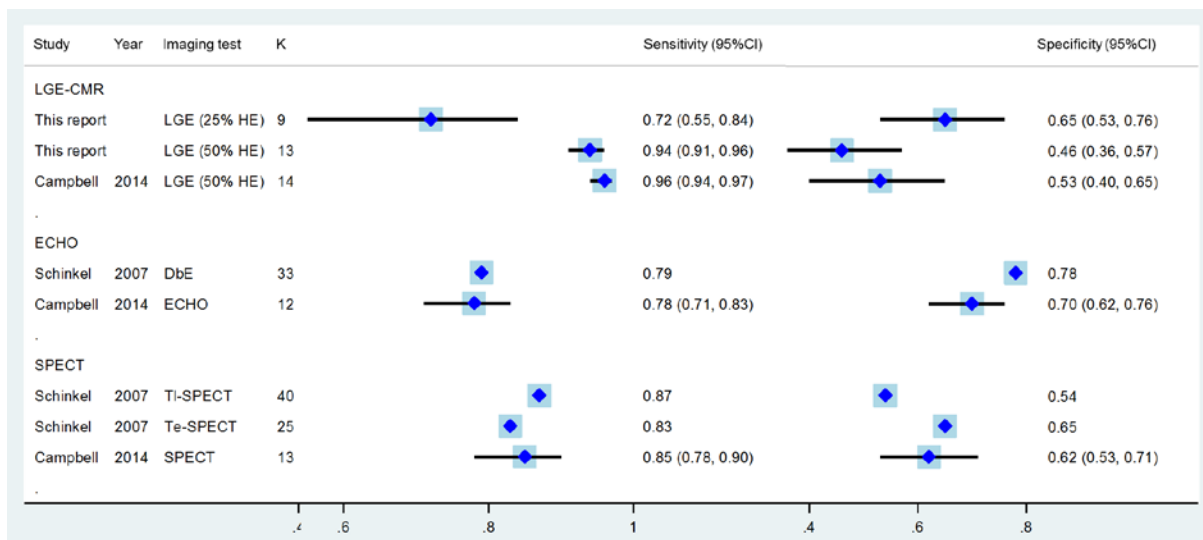


Figure 35 Pooled sensitivity and specificity of LGE-CMR, DbE and SPECT with recovery of regional function after revascularisation as the reference standard

Data of included studies in SR by Campbell et al. (2014) was pooled with the most recent (published in or after 2001) results in the SR by Schinkel et al. (2007). The SR by Campbell et al. (2014) included both high-dose and low-dose dobutamine stress Echo studies and did not report which radioisotopes were used with SPECT.

CI = confidence interval; CMR = cardiac magnetic resonance imaging; DbE = low-dose dobutamine Echo; ECHO = echocardiography; HE = hyper-enhancement; K = number of studies; LGE = late gadolinium enhancement; SPECT = single-photon emission computed tomography; Te = Technetium-99m sestamibi/ tetrofosmin; TI = thallium-201

B3B.7 EXTENDED ASSESSMENT OF RELIABILITY EVIDENCE

No studies were identified investigating reliability evidence.

B3B.8 CONCORDANCE ANALYSIS

Due to the limited volume of accuracy data available, concordance between LGE-CMR and its comparators was also assessed. Studies that directly compared the accuracy of LGE-CMR with one of the listed comparators, and provided either 2 x 2 data or a kappa statistic, were included. In all, 4 studies met the inclusion criteria and compared LGE-CMR with DbE, Echo and/or SPECT for the assessment of the viability of myocardium (Nelson et al. 2004; Schwartzman et al. 2003; Solar et al. 2006; Wu et al. 2007a). One study (Nelson et al. 2004) reported concordance data for 372 segments with abnormal resting function by Echo (n= 60 patients), whereas the others reported data on both normal and abnormal segments. The latter 3 studies enrolled between 29 and 40 patients, and included between 444 and 1360 segments in their analysis (Table 149 in Appendix C).

Three of the studies included patients with LVD who were being assessed prior to revascularisation surgery (Schvartzman et al. 2003; Solar et al. 2006; Wu et al. 2007a), and 1 study investigated viability in patients with LVD following MI (Nelson et al. 2004). The dosage of gadolinium infusion ranged from 0.1 to 0.2 mmol/kg. The studies by Nelson et al. (2004) and Schvartzman et al. (2003) used a 16-segment model for their investigations, whereas in the other studies the model used was not explicitly stated. The studies used similar scoring systems to grade the level of scarring seen by contrast enhancement, but only 3 of the 4 studies reported data that used a cut-off of $\leq 50\%$ HE for viability. The fourth study (Schvartzman et al. 2003) reported the number of hyper-enhanced segments for each of six categories (0=0% to 5=10%).

B3B.8.1 LGE-CMR COMPARED WITH SPECT

Three studies reported data that compared the performance of LGE-CMR with TI-SPECT (Nelson et al. 2004; Solar et al. 2006; Wu et al. 2007a). In one study (Wu et al. 2007a) the TI-SPECT procedure varied between patients in that those who were able underwent exercise stress testing, others

underwent pharmacological stress testing prior to TI-SPECT, and some underwent rest-redistribution TI-SPECT because of their severe heart failure. Wu et al. (2007a) did not report a cut-off value for viability with assessment by TI-SPECT. Another study used a rest-late redistribution protocol for TI-SPECT in all patients and specified a cut-off value of >60% maximum activity for viable segments. Data was only reported for segments classified as abnormal by a two-dimensional echogram (Nelson et al. 2004). In the remaining study TI-SPECT was performed in the supine and prone position with the left arm raised, and segments were classified as non-viable if TI activity was observed at <50%.

The estimated sensitivity and specificity of LGE-CMR compared with TI-SPECT, and the level of agreement between tests, are shown in Table 87. While 82%–93% of patients with viable myocardium detected by TI-SPECT also had viable myocardium detectable by LGE-CMR, half of all patients considered to have non-viable myocardium by TI-SPECT were considered to have viable myocardium by LGE-CMR. Kappa statistics for the 3 studies showed poor to moderate agreement between LGE-CMR and TI-SPECT for the diagnosis of viable cardiac segments. This disagreement is largely driven by the discrepancy among diagnoses in patients with a negative TI-SPECT result.

Table 87 Estimated accuracy of TI-SPECT compared with LGE-CMR

Study	Index test (cut-off ^a)	Comparator (cut-off ^b)	Estimated sensitivity (95%CI)	Estimated specificity (95%CI)	Concordance	Kappa (95%CI)
Nelson et al. (2004)	LGE-CMR (50%)	TI-SPECT (60%)	82% (76, 87)	50% (43, 57)	65.3%	0.32 (0.22, 0.41)
Solar et al. (2006)	LGE-CMR (50%)	TI-SPECT (50%)	91% (89, 92)	50% (44, 56)	82.5%	0.43 (0.36, 0.50)
Wu et al. (2007a)	LGE-CMR (50%)	TI-SPECT (NR)	93% (90, 95)	54% (47, 61)	80.5%	0.51 (0.43, 0.58)

^a Cut-off for gadolinium enhancement above which segments are considered non-viable

^b Cut-off for TI uptake above which segments are considered viable

LGE-CMR = late gadolinium enhancement cardiac magnetic resonance imaging; NR = not reported; TI-SPECT = thallium-201 single-photon emission tomography

B3B.8.2 LGE-CMR COMPARED WITH DbE AND ECHO

Three studies reported concordance data for assessment of segment viability by LGE-CMR compared with Echo, 2 of which used DbE to assist imaging (Nelson et al. 2004; Wu et al. 2007a) and 1 did not report use of any stressor (Schvartzman et al. 2003). Nelson et al. (2004) reported that segments were considered viable if they were dysfunctional at rest and had augmented function at low-dose (5–10 µg/kg per minute). In the other studies segment viability was based on detected contractile reserve (cut-off point not reported) (Wu et al. 2007a) and by level of systolic function grade (graded from 1 = normal to 4 = dyskinesia) (Schvartzman et al. 2003). From the latter study, raw data is presented for Grade 1 segments (i.e. normal: absence of any hypokinesia), compared with myocardial scar Grade 0 (i.e. no scar) by LGE-CMR.

The estimated sensitivity and specificity of LGE-CMR compared with DbE and Echo, and level of agreement between tests, are shown in Table 88. When LGE-CMR was compared with DbE, 82%–95% of patients with viable myocardium detected by DbE were also detected by LGE-CMR, whereas only 58% of patients with viable myocardium detected by Echo (without the use of dobutamine) were also detected by LGE-CMR. Conversely, 55%–59% of patients with non-viable myocardium according to DbE results were considered to have viable myocardium by LGE-CMR, and only 22% of those considered non-viable by Echo (without the use of dobutamine) were considered viable by LGE-CMR. The kappa values reflected poor agreement between DbE or Echo and LGE-CMR in all three studies (kappa<0.40).

Table 88 Estimated accuracy of DbE and Echo compared with LGE-CMR

Study	Index test (cut-off ^a)	Comparator (cut-off)	Estimated sensitivity (95%CI)	Estimated specificity (95%CI)	Concordance	Kappa (95%CI)
Nelson et al. (2004)	LGE-CMR (50%)	DbE (viable if dysfunctional at rest and augmented function at low-dose)	82% (74, 88)	45% (38, 52)	59.1%	0.23 (0.14, 0.32)
Wu et al. (2007a)	LGE-CMR (50%)	DbE (NR)	95% (88, 98)	41% (29, 54)	68.8%	0.39 (0.23, 0.54)
Schwartzman et al. (2003)	LGE-CMR (50%)	Echo (viable: no hypokinesia; non-viable: any level of hypokinesia)	58% (45, 70)	78% (73, 83)	78.6%	0.31 (0.19, 0.44)

^a Cut-off for gadolinium enhancement above which segments are considered non-viable

DbE = dobutamine echocardiography; Echo = echocardiography; LGE-CMR = late gadolinium enhancement cardiac magnetic resonance imaging; NR = not reported

B3b.9 INTERPRETATION OF EVIDENCE ON DIAGNOSTIC PERFORMANCE

Overall, LGE-CMR (using a high cut-off of $\geq 50\%$ HE) appears to have similar accuracy to DbE or SPECT, with a slightly higher sensitivity to the other tests but a corresponding lower specificity. For every 100 patients with viable myocardium, LGE-CMR is expected to be able to detect 6–14 additional patients, who would have received a false negative result using other imaging modalities. Conversely, in those without viable myocardium, LGE-CMR is expected to falsely classify a very large proportion of patients (55%) as being viable. The comparative imaging tests (DbE and SPECT) ruled out viability with a higher degree of specificity, with 9–33 fewer false positives per 100 patients with non-viable myocardium.

The concordance between LGE-CMR (high cut-off) and SPECT was low to moderate (kappa range 0.32–0.52). This was mostly due to the low estimated specificity of LGE-CMR compared with TI-SPECT (50%–54%); half of all patients considered to have non-viable myocardium by TI-SPECT were considered to have viable myocardium by LGE-CMR.

The concordance between LGE-CMR (high cut-off) and DbE or Echo was very low (kappa = 0.24). Again, this was mostly due to the low estimated specificity of LGE-CMR compared with DbE (41%–45%), and to the low estimated sensitivity of LGE-CMR compared with Echo (58%). This indicates that 42% of patients with viable myocardium detected by Echo would not be detected by LGE-CMR.

B4B CLINICAL VALIDITY (POPULATION 2)

B4B.1 MEASURES OF CLINICAL VALIDITY

The clinical validity of a test depends on the prevalence (or PTP) of the outcome of interest (in this case, recovery of LV function). The key measures used are positive and negative predictive values (PPV and NPV), which are the probabilities of recovery or absence of recovery in a tested individual. The PPV and NPV are dependent on the prevalence of recovery in the study population. The likelihood ratio (LR) is the likelihood that a given test result (e.g. viable) would be expected in a patient with the outcome (e.g. recovery of LV function) compared with the likelihood that the same result would be expected in a patient without the outcome.

Information regarding the improvement rate of patients with significant CAD and LVD, considered for revascularisation, was lacking. In the absence of useful Australasian data, the assumption was made that the PTP of the study samples was representative of the target population. Therefore, the segmental data included in the accuracy studies was used to estimate the PTP of recovery. The rate of segmental improvement in wall motion in our target population varied from 26.4% to 76.5% (median 54.5%), and from 26.4% to 85.8% (median 56.0%) in low and high cut-off accuracy studies, respectively. This corresponds with the SR by Campbell et al. (2014), which states that, of those patients with LVD who were revascularised, between 55% and 60% will show evidence of recovery in function in the hibernating myocardium. Based on this information, 56% (median recovery in the high cut-off group) was chosen as the prevalence of recovery for this report. The accuracy data in Section B3.4 (sensitivity and specificity) were used with the prevalence data to derive the NPV and PPV.

B.4B.1.1 TO B.4B.1.4

The studies that provide data to inform on clinical validity are the same as those that provide diagnostic performance data in Section B3b. Thus, see Sections B3b.1 to B3b.5 for a description of the risk of bias, the characteristics of the evidence-base, outcome measures and analysis of these studies.

B4B.1.5 RESULTS OF THE SYSTEMATIC LITERATURE REVIEW

IS IT ACCURATE?

Summary – What is the clinical validity of CMR gadolinium-based viability imaging in determining viable myocardium in patients with an existing diagnosis of significant CAD, who have a history of IHD with LVD and are being considered for revascularisation?

The LRs for LGE-CMR suggested that it is useful as a rule-out test when a high cut-off of $\geq 50\%$ is used, but not as a rule-in test. Thus, patients who receive a negative test result can be confident that they are unlikely to have a viable myocardium and would not respond to revascularisation. However, those who receive a positive test may or may not respond to revascularisation.

NPV and PPV were calculated using the median prevalence of recovery (56%) derived from Section B4b.1.

The LGE-CMR high cut-off group had the lowest PPV, at 68%, indicating that 32 out of 100 patients assessed as having viable myocardium were misdiagnosed and would not recover function after revascularisation. DbE had the highest PPV, at 82%, and the PPV for the LGE-CMR low cut-off groups and SPECT ranged between 71% and 75%.

The NPV was highest for LGE-CMR (high cut-off), at 83%; if 100 patients received a negative test result, 17 would have been misclassified as negative, when they would be likely to respond to revascularisation. The NPVs were 74% for DbE, 71% for Echo, and 76%–77% for SPECT; thus, 6–12 additional patients would be misclassified as being ruled out for revascularisation, when they may in fact have viable myocardium, using these tests.

Summary – What is the clinical validity of CMR gadolinium-based viability imaging in determining viable myocardium in patients with an existing diagnosis of significant CAD, who have a history of IHD with LVD and are being considered for revascularisation?

An SR found that the presence of LGE predicted the risk of mortality (HR 4.77; 95%CI 2.07, 7.46) and MACE (HR 3.90; 95%CI 2.69, 5.11) in univariate analyses, although it was not clear what treatment patients received between LGE-CMR and follow-up. No comparison was done on the accuracy of LGE-CMR in predicting health outcomes compared with the other imaging techniques.

The LRs were calculated for LGE-CMR in both the low cut-off group (k=10, red dots) and the high cut-off group (k=15, blue dots), as shown in Figure 36 and Table 89. LR scattergrams plot LR+ against LR–, where the likelihood of correctly identifying recovery increases along the x-axis and the likelihood of correctly eliminating the presence of ‘recovery’ decreases along the y-axis. The summary LR+ and LR– values for both groups fall within the lower right quadrant of the scattergram. This represents LR values inconclusive for correctly confirming or excluding post-revascularisation recovery (LR+ <10 and LR– >0.1). However, as the LR– value for the high cut-off group lies in the 0.1–0.2 range, it is still a strong indicator that a negative test result is likely to lead to no recovery after revascularisation. So, the test may still be useful for exclusion (false negative rate = 7%). This could be a tool for excluding non-viable patients from revascularisation, as it is an invasive procedure and the likelihood of recovery is low.

The SR by Campbell et al. (2014) also reported pooled LRs for LGE-CMR: 2.03 (95%CI 1.53, 2.69) and 0.08 (95%CI 0.05, 0.13) for LR+ and LR–, respectively. These ratios are slightly better than those for the high cut-off group in this report and would be located in the lower left quadrant of the scattergram (exclusion only); however, there is no statistically significant difference between the results by Campbell et al. (2014) and the results in Figure 36.

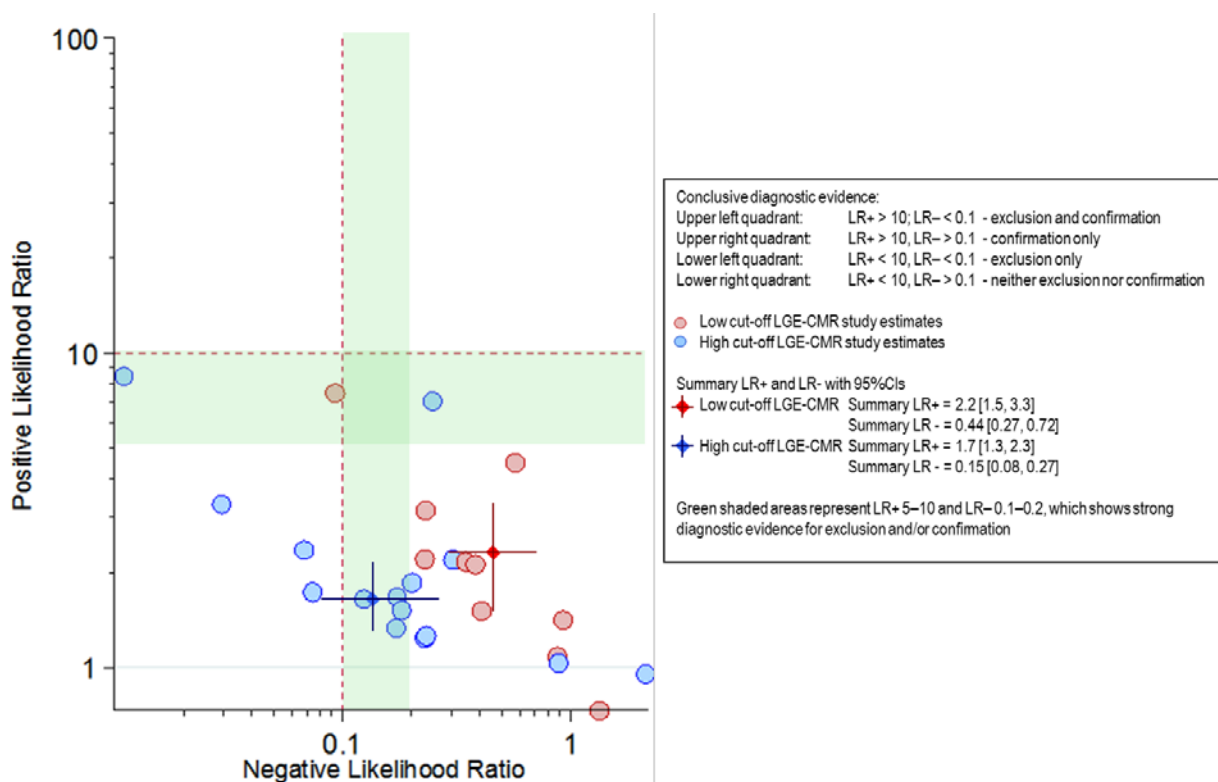


Figure 36 Likelihood ratio scattergram for the prediction of recovery by LGE-CMR in the low and high cut-off groups

CI = confidence interval; LGE-CMR = late gadolinium enhancement cardiac magnetic resonance imaging; LR– = negative likelihood ratio; LR+ = positive likelihood ratio

The NPV and PPV for LGE-CMR and the comparators were calculated using the LR_s and the segmental median prevalence of recovery of 56.0%, as determined in section B4.1 (Table 89). DbE had the highest PPV, indicating that 18 out of 100 patients assessed to have viable myocardium were misdiagnosed and would not recover function after revascularisation. The LGE-CMR high cut-off group had the lowest PPV, with 32 out of 100 patients assessed as having viable myocardium being misdiagnosed. The PPV for the LGE-CMR low cut-off groups and SPECT ranged between 71% and 75%.

The LGE-CMR high cut-off group had the highest NPV, indicating that 83 out of 100 patients with a non-viable test result were correctly classified and would not have benefited from revascularisation due to a lack of functional improvement. On the other hand, the LGE-CMR low cut-off group had the lowest NPV of 64%, indicating that 36 out of 100 patients with a non-viable test result were misdiagnosed and would have experienced functional recovery after revascularisation. The NPV for DbE and SPECT were similar and ranged between 71% and 77%.

Table 89 Likelihood ratios and predictive values for LGE-CMR and comparators, with segmental recovery in wall motion as the evidentiary standard

SR / meta-analysis	Intervention	Number of studies	LR+ (95%CI)	LR- (95%CI)	PPV	NPV
Section B3.4	LGE-CMR, low cut-off group	k=10	2.2 (1.5, 3.3)	0.44 (0.27, 0.72)	74%	64%
Section B3.4	LGE-CMR, high cut-off group	k=15	1.7 (1.3, 2.3)	0.15 (0.08, 0.27)	68%	83%
Schinkel et al. (2007)	DbE	k=33 N=1,121 patients	3.59	0.27	82%	74%
	TI-SPECT	k=40 N=1,119 patients	1.89	0.24	71%	77%
Schinkel et al. (2007)	Technetium-99m sestamibi/tetrofosmin SPECT	k=25 N=721 patients	2.37	0.26	75%	75%
Campbell et al. (2014) ^a	Echo (both high-dose and low-dose dobutamine stress)	k=12	2.55	0.32	77%	71%
	SPECT (NR which radioisotopes were used)	k=13	2.25	0.24	74%	76%

^a PPV and NPV were calculated using pooled sensitivity and specificity from the SRs and a prevalence of 56%.

Echo = echocardiography; LGE-CMR = late gadolinium enhancement cardiac magnetic resonance imaging; LR₋ = negative likelihood ratio; LR₊ = positive likelihood ratio; NPV = negative predictive value; PPV = positive predictive value; SPECT = single-photon emission computed tomography; SR = systematic review; TI-SPECT = thallium-SPECT

B4B.2 PROGNOSIS OR PREDISPOSITION

For population 2, LGE-CMR is proposed for determining the viability of the myocardium as a predictive tool as to whether or not patients will respond to treatment. Research questions were therefore developed *a priori* to assess whether LGE-CMR is accurate and benefits patients when used for this purpose. The reference standard for assessing the accuracy of LGE-CMR for determining viability was whether patients responded to revascularisation. All studies included therefore focused on patients who received revascularisation.

Outside the scope of the research questions explicitly outlined *a priori* was whether LGE-CMR provides prognostic information. One good-quality SR conducted by the Centre for Reviews and

Dissemination at the University of York assessed whether LGE-CMR predicted mortality and MACE in patients with CAD (Zemrak & Petersen 2011).

Zemrak and Petersen (2011) included 21 studies that enrolled male and female adults suspected of having CAD, with known CAD, with a previous or acute MI, or with a previous PCI or CABG. The main outcome assessed was mortality (i.e. cardiac or all-cause), and the secondary outcome was MACE (i.e. death, non-fatal MI, new or worsening heart failure or LVD, unstable angina, ventricular tachycardia or fibrillation, and stroke). The number of patients with available follow-up data varied from 61 to 1,148, and follow-up periods ranged from 6 months to 58 months.

Zemrak and Petersen (2011) reported that presence of LGE (as a dichotomous variable), or an extra 1% or 1 gram of LGE (as a continuous variable), were associated with a higher probability of dying during the follow-up period, and of having a MACE (Table 90). Per extra gram or 1% of LGE, there was an estimated mean random effect size of 4% increase in likelihood of death.

Table 90 Ability of CMR-LGE to predict health outcomes (mortality and MACE)

No. of studies	Predictive factor	Outcome measure	Hazard ratio (95%CI)
k=4	Presence of LGE	Mortality	4.77 (2.07, 7.46)
k=5	LGE size (in grams or per cent)	Mortality	1.04 (1.01, 1.06)
k=5	Presence of LGE	MACE	3.90 (2.69, 5.11)
k=8	LGE size (in grams or per cent)	MACE	1.05 (1.03, 1.07)

CI = confidence interval; K = number of studies; LGE = late gadolinium enhancement; LGE-CMR = late gadolinium enhancement cardiovascular magnetic resonance imaging; MACE = major adverse cardiac event

The included studies were not always explicit regarding what treatment patients received between undergoing LGE-CMR and the outcomes assessed. The implications of these results are therefore somewhat limited, however, from this data, it could be hypothesised that LGE-CMR predicts who is likely to respond to treatment overall, rather than just predicting response to revascularisation. This is further explored in Section B5b.2.

B5B CLINICAL UTILITY (POPULATION 2)

Clinical utility refers to how likely the test is to significantly impact on patient management and health outcomes. As the intervention is as accurate as the comparators, and LGE-CMR seems to be as safe or safer (Section B7a), the clinical utility should be assessed. Only if there is a net harm (when the index test is less or as accurate as the comparator and less safe), the clinical utility would not be required.

B5B.1 IMPACT ON CLINICAL MANAGEMENT (THERAPEUTIC EFFICACY)

B5B.1.1 RISK OF BIAS ASSESSMENT

The two included studies informing on the impact of LGE-CMR on clinical management were non-comparative, and were individually assessed for risk of bias using the IHE checklist (Moga et al. 2012) (Table 151 in Appendix C).

B5B.1.2 CHARACTERISTICS OF THE EVIDENCE-BASE

See Table 151 in Appendix C for the details of the characteristics for the two studies included in the evidence-base.

B5B.1.3 OUTCOME MEASURES AND ANALYSIS

Relevant outcomes reported in the two studies were the proportion of patients changing treatment after LGE-CMR and the number of revascularisations averted due to non-viability.

B5B.1.4 RESULTS OF THE SYSTEMATIC LITERATURE REVIEW

DOES IT IMPACT ON CLINICAL MANAGEMENT?

Summary – Does LGE-CMR viability imaging change clinical management, compared with DbE, SPECT using thallium/sestamibi/tetrofosmin or CT-DCE for patients with significant CAD who have a history of IHD with LVD and are being considered for revascularisation?

There were no studies assessing how management of patients may change with LGE-CMR, compared with DbE, SPECT or CT-DCE.

Two before-and-after case series (one conducted in Australia) reported on the impact of LGE-CMR on the management of patients being considered for revascularisation. The data indicates that LGE-CMR may rule out some patients from requiring revascularisation due to the lack of viable myocardium. Given the lack of comparative data, the implications of this are unknown.

A study by Bruder et al. (2013) investigated the impact of CMR on patient management in 27,301 patients from 57 centres in 15 countries. Myocardial viability testing was recorded as primary indication in 14.6% of the scans (n=4,048). However, it was not known if these patients met the PICO for population 2 (e.g. having decreased LVEF and being considered for revascularisation). New diagnoses and therapeutic consequences were reported after CMR viability testing (Table 91). The study stated that 71.5% of patients had a change in management after CMR viability testing; however, most of these changes were for medication. A change in invasive procedure was recorded in 24.2% of patients.

Table 91 Impact of viability CMR testing on patient management

Type of change in management impact	Percentage of patients
Completely new diagnosis not suspected before	5.3%
Therapeutic consequences:	

Type of change in management impact	Percentage of patients
- Change in medication	33.5%
- Invasive procedure	24.2%
- Hospital discharge	6.9%
- Hospital admission	1.9%

Source: Bruder et al. (2013)

An Australian study (Taylor et al. 2013) included all patients referred to the Alfred Hospital, Melbourne, for clinical CMR scanning between July 2007 and 30 June 2009. During this time 732 CMR scans were performed, and in only 92 cases (12%) was a viability CMR study done. It was not known if these patients met the PICO for population 2. Most patients were already receiving medical treatment for CAD at the time of testing and, prior to LGE-CMR, 83 patients also received an Echo, 67 an angiogram, 24 a stress test, 17 a stress ECG, 16 a non-CMR viability study, 7 a SPECT-gated blood pool scan, 6 a stress SPECT and 1 a stress Echo. Surgical plans before LGE-CMR were recorded for 78 patients: 13 were initially considered for cardiac surgery, 9 for CABG and 10 for automated implantable cardioverter-defibrillator implantation. Three CABGs were averted following LGE due to no myocardial viability (33.3%). It was reported that, overall, 89/666 (13%) patients with 6 months follow-up data had a change in their cardiac device or surgical management plan. The assumption was made that for those patients whose management plan changed after CMR testing, this change was due to the CMR results.

In conclusion, limited evidence was found showing that invasive procedures may be averted in Australia following negative viability results on CMR. This was confirmed by a clinical expert (HESP member) in a teleconference with the Department of Health and AHTA (5/11/2015). The HESP member indicated that viability testing is part of the decision-making process; however, other factors (e.g. age, habits, BMI, comorbidities, state of the arteries supplying the area of concern) can also play a role when making the decision whether to revascularise or not.

B5B.2 THERAPEUTIC EFFECTIVENESS (INCLUDING IMPACT OF EFFECT MODIFICATION)

For this step of the linked analysis, we aimed to identify whether a change in patient management would lead to a difference in mortality/health. We investigated whether revascularisation of viable myocardium leads to better health outcomes, compared with medical treatment alone, and whether giving medical therapy alone leads to better health outcomes compared with revascularisation in patients with non-viable myocardium.

B5B.2.1 RISK OF BIAS ASSESSMENT

Bias was assessed using the Downs and Black (1998) checklist for the assessment of randomised and non-randomised studies of healthcare interventions for RCTs and cohort studies. SRs were assessed for bias using the AMSTAR checklist (Shea et al. 2007). Study quality per study is shown in Table 152 in Appendix C, and the risk of bias in Table 92.

B5B.2.2 CHARACTERISTICS OF THE EVIDENCE-BASE

See Table 152 in Appendix C for details on the individual studies included in the evidence-base.

Four studies were identified investigating the effects of the different treatment strategies in groups of patients with viable or non-viable myocardium. Two SRs of poor quality were identified that included non-randomised studies (Allman et al. 2002; Schinkel et al. 2007). The SR by Allman et al. (2002) is outdated, as medical treatment and revascularisation procedures have improved significantly since this review was published. In addition, 1 medium-quality cohort study (Gerber et al. 2012) and 1 high-quality RCT (Bonow et al. 2011) were also included.

For population 2, the target population are those patients with known CAD and LVD, who are being considered for revascularisation. The test should therefore be restricted to those who would be able to tolerate revascularisation based on other clinical factors. It is unclear what proportion of patients in the studies included in the SRs, and in the cohort study by Gerber et al. (2012) met these criteria. In these studies a large proportion of patients received medical therapy despite being classified as having viable myocardium. This is likely due to other factors (e.g. age, habits, BMI, comorbidities, state of the arteries supplying the area of concern). Therefore, the study by Bonow et al. (2011) provided the only evidence that was considered to be directly relevant to the target population, as all patients included in the trial were considered suitable candidates for revascularisation prior to CMR results.

A summary of the trial characteristics of studies providing evidence relating to the health impact from the change in management is provided in Table 92.

Table 92 Key features of the included evidence assessing impact of change in patient management

Trial/Study	Number of studies (k) and/or patients (N)	Design/duration	Risk of bias	Patient population	Key outcome(s)	Result used in economic model
Allman et al. (2002)	k=24 N=3,088	SR	High	Patients with CAD undergoing revascularisation or medical therapy	Survival Annualised mortality rate	Not used
Schinkel et al. (2007)	k=29 N=3,640	SR	High	Patients with chronic CAD undergoing revascularisation or medical therapy	Annualised mortality rate	Not used
Gerber et al. (2012)	N=144	Cohort study	Some	Patients with CAD undergoing revascularisation, PCI or medical therapy alone	3-year overall survival Hazard ratio	Used
Bonow et al. (2011)	N=601	RCT	Low	Patients with CAD <i>amenable to revascularisation</i> and with LVD	Mortality rate Hazard ratio	Used

CAD = coronary artery disease; LVD = left ventricular dysfunction; PCI = percutaneous coronary intervention; RCT = randomised controlled trial; SR = systematic review.

B5B.2.3 OUTCOME MEASURES AND ANALYSIS

See Table 152 in Appendix C for details on the included studies. Outcomes extracted and discussed were mortality rates, annualised mortality rates and hazard ratios.

B5B.2.4 RESULTS OF THE SYSTEMATIC LITERATURE REVIEW

DOES THE CHANGE IN MANAGEMENT IMPROVE HEALTH OUTCOMES?

Summary – Does change in management in patients with viable myocardium (as shown on LGE-CMR) receiving revascularisation, and patients with non-viable myocardium (on LGE-CMR) receiving medical therapy alone, lead to better health outcomes?

Two very different sets of results were identified for the assessment of whether the change in management expected from viability testing (as assessed by LGE-CMR, DbE or SPECT) results in a reduced risk of mortality.

Two SRs of observational studies and 1 cohort study showed that, within the subgroup of patients who were classified as having viable myocardium, those who received revascularisation had a reduced risk of death during follow-up compared with those who received medical treatment alone. The differences in mortality between medical and surgical treatments in the non-viable subgroup were not significant. On the other hand, patients who were classified as viable and received medical treatment alone fared significantly worse than

Summary – Does change in management in patients with viable myocardium (as shown on LGE-CMR) receiving revascularisation, and patients with non-viable myocardium (on LGE-CMR) receiving medical therapy alone, lead to better health outcomes?

those that were revascularised. However, these studies were not restricted to patients being considered for revascularisation, and included patients unsuitable for surgery for various reasons, irrespective of viability status. Therefore, it is likely that patients who had viable myocardium and received medical therapy had worse prognosis at baseline than those who received revascularisation. Thus, the difference in mortality cannot confidently be attributed to the difference in treatment.

One high-quality RCT (the STICH trial), which restricted the population to those who could tolerate revascularisation (CABG), and randomised patients to either revascularisation plus medical therapy or medical therapy alone, provided further evidence. Patients had their viability assessed using dobutamine Echo or SPECT; those classified as having viable myocardium had lower overall mortality during the follow-up period than those with non-viable myocardium (HR 0.64; 95%CI 0.48, 0.86). However, patients with viable myocardium who were revascularised did not have significantly better mortality or MACE outcomes than those who received medical therapy alone. Equally, patients with non-viable myocardium also did not have significant differences in outcomes between treatment groups. Thus, there was no interaction between viability and the likelihood of benefit from revascularisation plus medical therapy, as compared with medical therapy alone.

According to the clinical pathway, patients with viable myocardium would receive revascularisation/angioplasty and/or drug therapy. Patients with non-viable myocardium would receive drug therapy alone. An Australian study (Taylor et al. 2013) confirmed that in some cases, CABG was averted due to non-viability of the myocardium in patients considered for revascularisation. It was investigated whether this change in management—patients with viable myocardium (as shown on LGE-CMR) receiving revascularisation and patients with non-viable myocardium (on LGE-CMR) receiving medical therapy alone—leads to better survival in those patients.

A poor-quality SR by Allman et al. (2002) performed a meta-analysis of 24 studies (3,088 patients) in 1999. The pooled annual mortality rates were reported; the rate was as low as 3.2% in patients with viable myocardium undergoing revascularisation but this was 16% among ‘viable’ patients receiving only medical therapy, representing a relative reduction of 79.6% in risk of death for revascularised patients. A second SR and the cohort study showed similar results. In the SR patients with viable myocardium had annual mortality rates of 3.5% and 12.2% in the revascularisation group and medically treated group, respectively (Schinkel et al. 2007). The cohort study reported that patients with viable myocardium had a 4.56 higher risk of death when staying on medical therapy or when revascularisation was incomplete, compared with complete revascularisation (Gerber et al. 2012). This difference was not observed in patients with non-viable myocardium, where annualised mortality rates in the SRs were 7.7% and 8.5% for revascularisation and 6.2% and 9.6% for medical therapy.

As the cohort study and the studies included in the SRs were observational (non-randomised), it is not known whether the differences in mortality rates are due to the treatment (i.e. revascularisation vs. medical treatment) or to patient differences (e.g. patients with viable myocardium who do not undergo revascularisation might be older, have comorbidities or other reasons why revascularisation is not recommended). The group that did not undergo revascularisation might have had a higher risk of death at baseline. Randomised trial data is necessary to decide whether revascularisation was responsible for the observed decrease in mortality in patients with viable myocardium.

One RCT investigated if there was an association between myocardial viability, treatment and outcome (Bonow et al. 2011). Patients with angiographic documentation of CAD amenable to revascularisation and with LVD were randomly assigned to either CABG with medical therapy or to medical therapy alone. Among 601 patients, 487 and 114 were found to have viable and non-viable

myocardium, respectively. During the follow-up period (median 5.1 years), 51% of patients with non-viable myocardium (56% of those randomised to medical therapy and 42% of those randomised to CABG) and 37% with viable myocardium (35% of those randomised to medical therapy and 31% of those randomised to CABG) died. Overall, rates of death were lower in patients with viable myocardium: the hazard ratio among patients with viable myocardium was 0.64 (95%CI 0.48, 0.86; p=0.003). However, when the study adjusted for other significant baseline prognostic variables in a multivariable model, the viability status was no longer significantly associated with death (p=0.21). There was also no significant interaction between myocardial viability and randomised treatment (i.e. revascularisation vs. medical therapy) with respect to death (p=0.53).

Mortality rates and hazard ratios as presented in the included studies are shown in Table 93. Annualised mortality rates per study are shown in Figure 37. Bonow et al. (2011) provides the most reliable data, as this is the only randomised study and the only one of high quality.

Table 93 Mortality rates per viability status group and treatment method

Study and study type	Study population	Mortality rate revascularisation	Mortality rate medical therapy	Hazard ratio, death [95%CI]
Allman et al. (2002) SR	k=24 studies N=3,088 patients 35% revascularisation, 65% medical therapy	Annual mortality rate V: 3.2% NV: 7.7%	Annual mortality rate V: 16% NV: 6.2%	NR
Schinkel et al. (2007) SR	k=29 studies N=3,640 patients	Annual mortality rate V: 3.53% NV: 8.45%	Annual mortality rate V: 12.16% NV: 9.59%	NR
Gerber et al. (2012) Prospective cohort	N=144 patients, 86 revascularisation, 46 medical therapy, 12 incomplete PCI	3-year follow-up V: 12% NV: 29%	3 year follow-up V: 52% NV: 33%	V: 4.56 [1.93, 10.8] ^a NV: 0.71 [0.18, 2.8] ^a
Bonow et al. (2011) RCT (STICH trial)	N=601 patients, 298 CABG and medical therapy 303 medical therapy alone.	5-year follow-up V: 31.2% NV: 41.5%	5-year follow-up V: 35.4% NV: 55.8%	V: 0.86 [0.64, 1.16] ^b NV: 0.70 [0.41, 1.18] ^b

^a A score >1 means revascularisation is better, a score <1 means medical therapy is better.

^b A score >1 means medical therapy is better, a score <1 means CABG is better.

CABG = coronary artery bypass graft; k = number of studies; N = number of patients; NR = not reported; NV = non-viable myocardium; PCI = percutaneous coronary intervention; RCT = randomised controlled trial; SR = systematic review; V = viable myocardium

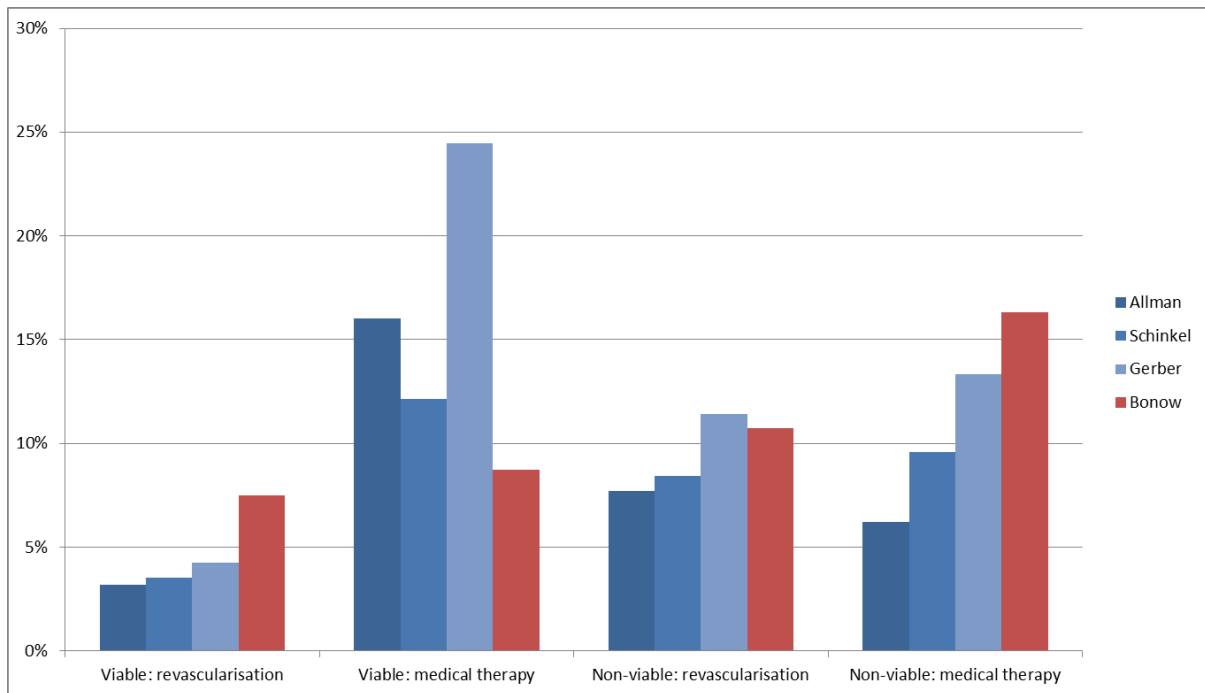


Figure 37 Annualised mortality rates per study in patients who were revascularised or received medical therapy, and according to the presence of viable or non-viable myocardium

Allman = Allman et al. (2002); Schinkel = Schinkel et al. (2007); Gerber = Gerber et al. (2012); Bonow = Bonow et al. (2011)

B6B IMPACT OF REPEAT TESTING/MONITORING (POPULATION 2)

This section is not applicable to LGE-CMR as it is not used as a monitoring test in the target population.

B7B EXTENDED ASSESSMENT OF COMPARATIVE HARMS (POPULATION 2)

As for population 1, the risks associated with non-invasive viability imaging in population 2 are small. A summary of the main contributors to AEs and the estimated risk in population 2 is provided in Table 94. As no data was identified that was specific for population 2, see Section B7a for a discussion about these AEs.

Table 94 Summary of potential safety concerns related to population 2

Test / overall mortality rate	Radiation dose	Stressors	Contrast agents and tracers	Other
LGE-CMR Serious AEs: 0.7/10,000 scans Mortality: 7/10,000 patients	0	-	Gadolinium Serious AEs: 0.48/10,000 doses Long-term death rate: 6.6/10,000 doses	Claustrophobia Magnetism Serious AEs: 0.2/10,000 scans
DbE Serious AEs: 21/10,000 scans Mortality: 1/10,000 patients	0	Low-dose dobutamine Serious AEs: 18/10,000 tests Death: 1.4/10,000 patients	Microspheres of contrast (not common) Serious AEs: 3/10,000 scans Long-term death rate: 0.1/10,000 patients	Heat from ultrasound
SPECT Serious AEs: 0.06/10,000 scans Mortality: 8/10,000 patients	15.6 mSv Additional fatal cancers: 7.8/10,000 patients	-	Radiotracers (Tc99 sestamibi or Myoview or thallium-201) Serious AEs: 0.06/10,000 scans	-
CT-DCE Serious AEs: 4/10,000 scans Mortality: 12/10,000 patients	10 mSv Additional fatal cancers: 5/10,000 patients	-	Iodinated contrast agent Serious AEs: 4/10,000 scans Long-term death rate: 7/10,000 patients	-

Sources: Einstein et al. (2012); FDA website: 'What are the Radiation Risks from CT?'; Knuuti et al. (2014); Varga et al. (2006)

AE = adverse event; CT-DCE = computed tomography perfusion with delayed contrast enhancement; DbE = low-dose dobutamine echocardiography; LGE-CMR = late gadolinium enhancement cardiac magnetic resonance imaging; SPECT= single-photon emission computed tomography

DbE uses one-quarter of the amount of dobutamine stressor used by normal stress Echo. However, as there is no safety data available for this lower dose, and the patients in population 2 generally have more advanced disease, the AE and mortality rates were assumed to be equal for both tests.

Figure 38 compares the number of serious AEs associated with each procedure discussed above, including the use of contrast and stressors. The number of serious AEs experienced by patients during DbE far outnumbers those resulting from the other three non-invasive imaging modalities

⁹ Available from <[visit FDA website](#)> (accessed on 20 October 2015)

due to the use of a stressor. LGE-CMR has similar safety with respect to serious AEs to SPECT and appears to be safer than CT-DCE; for all three of these modalities the majority of the serious AEs are caused by the contrast agent.

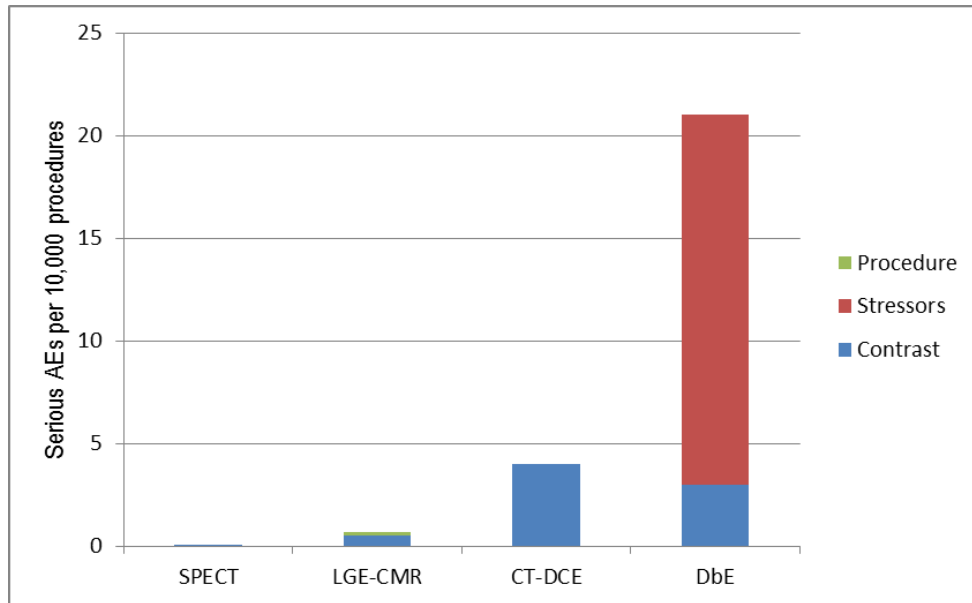


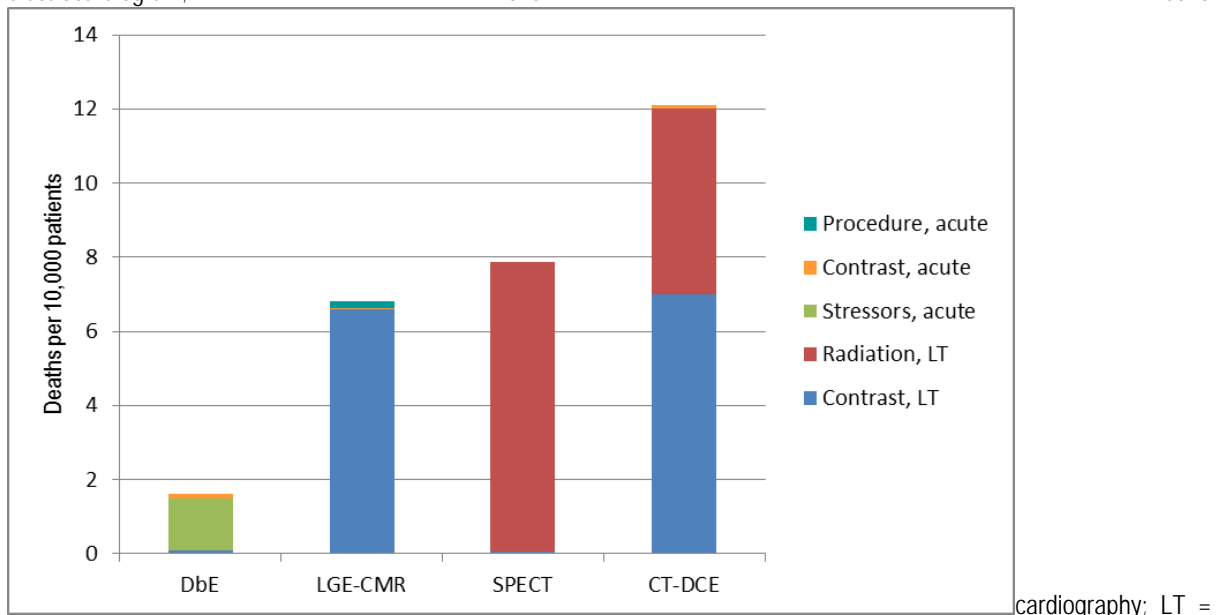
Figure 38 Estimated risk of serious AEs for different imaging procedures

AE = adverse event; CT-DCE = computed tomography perfusion with delayed contrast enhancement; DbE = low-dose dobutamine echocardiography; LGE-CMR = late gadolinium enhancement cardiovascular magnetic resonance imaging; SPECT = single-photon emission computed tomography

Figure 39 compares the acute and long-term mortality due to the non-invasive imaging modalities. Patients undergoing DbE are more likely to suffer an acute event resulting in death than those having LGE-CMR, SPECT or CT-DCE, mostly due to the use of a stressor. Conversely, patients undergoing DbE are unlikely to die from long-term effects caused by the radionuclides or the contrast agents used in LGE-CMR, SPECT and CT-DCE. LGE-CMR has similar safety, with respect to mortality rate, to SPECT, and appears to be safer than CT-DCE. While DbE is the safest imaging modality overall, it has by far the highest acute fatality rate. As patients in population 2 have more advanced disease than those in population 1, long-term safety may be of lesser importance in these patients.

Figure 39 Estimated acute and long-term mortality rates rates for different imaging procedures

CT-DCE = computed tomography perfusion with delayed contrast enhancement; DbE = low-dose dobutamine echocardiography; LGE-CMR = late gadolinium enhancement cardiovascular magnetic resonance imaging; ECG = electrocardiogram; Echo =



long-term; SPECT = single-photon emission computed tomography

B8B INTERPRETATION OF THE CLINICAL EVIDENCE (POPULATION 2)

Diagnostic accuracy

LGE-CMR using a high cut-off of $\geq 50\%$ HE was slightly more sensitive, but less specific, than DbE and SPECT when compared with the evidentiary standard of regional functional improvement. Conversely, LGE-CMR using a low cut-off of $\leq 25\%$ HE was less sensitive and more specific. The concordance between tests was low to moderate, mostly due to half of all patients considered to have non-viable myocardium by TI-SPECT or DbE being considered to have viable myocardium by LGE-CMR ($\geq 50\%$ HE).

LGE-CMR, using a high cut-off of $\geq 50\%$ HE, may be useful to 'rule-out' patients who would not benefit from revascularisation. The NPV indicated that if 100 patients receive a negative LGE-CMR test result, 17 of these patients would have been misclassified as negative, when they would be likely to respond to revascularisation. Testing using DbE or SPECT would result in an additional 6–12 patients being misclassified and ruled out for revascularisation. However, a positive test result is less useful, as the PPV suggests that one-third of patients assessed as having viable myocardium by LGE-CMR were misdiagnosed and would not recover function after revascularisation. For DbE and SPECT one-fifth and one-quarter of patients with a positive test result would have been misdiagnosed, respectively.

Safety

The number of serious AEs and acute events resulting in death experienced by patients during DbE far outnumbers those resulting from the other three non-invasive imaging modalities due to the use of a stressor. CT-DCE, LGE-CMR and SPECT have higher long-term mortality rates due to the use of radionuclides and/or the contrast agents. However, as patients in population 2 have more advanced disease than those in population 1, long-term safety may be of lesser importance in these patients.

Therapeutic effectiveness

There is some Australian evidence available that surgical procedures might be averted due to non-viability in patients with CAD and LVD who are able to undergo revascularisation (Taylor et al. 2013). There is also evidence to suggest that LGE-CMR is prognostic and can predict who is likely to respond to treatment (medical or surgical) rather than just predicting response to revascularisation. However, there was no evidence that revascularisation would lead to better survival compared with medical therapy. Patients with viable myocardium who were randomised to revascularisation did not have significantly better mortality or MACE outcomes than those who were randomised to receive medical therapy alone. Therefore, using LGE-CMR results to guide whether patients are revascularised or not does not appear to reduce the risk of MACE, and assessment of viability cannot be considered to be effective.

Overall summary


On the basis of the benefits and harms reported in the evidence-base (summarised in Table 95), it is suggested that LGE-CMR has:

- **non-inferior safety** and **superior ability to rule out patients who do not show viability** relative to **DbE and SPECT**; and
- **superior safety** and **unknown effectiveness** relative to **CT-DCE**.

However, strong evidence suggests that **testing for viability does not reduce the risk of death within 5 years**.


Table 95 Balance of clinical benefits and harms of LGE-CMR relative to Echo, SPECT and CT-DCE


Outcomes	No. of studies	Quality of evidence	Results	Interpretation	GRADE ^a
Therapeutic effectiveness (5-year mortality rate)	k=1 RCT; N=601	Risk of bias: 0 Inconsistency: 0 Indirectness: 0 Imprecision: 0 Publication bias: 0	<u>Viable:</u> Revascularised: 31.2%; Medical: 35.4% <u>Non-viable:</u> Revascularised: 41.5%; Medical: 55.8%	Patients did not differ significantly in their response to medical treatment or revascularisation, based on viability status. Using viability status to determine treatment strategy is therefore not beneficial.	High ⊕⊕⊕⊕
Negative predictive value	LGE-CMR low cut-off: k=10 LGE-CMR high cut-off: k=15 DbE: k=33 TI-SPECT: k=40 Tm-SPECT: k=25 Echo (high- and low-dose): k=12 SPECT (unspecified) k=13	Risk of bias: 0 Inconsistency: 0 Indirectness: -1 Imprecision: -1 Publication bias: 0	64% 82% 74% 77% 75% 71% 76%	A negative test result from LGE-CMR (high cut-off) can be trusted more than a negative result from the comparators. A negative test result from LGE-CMR (low-cut-off) can be trusted less than the comparators.	Low ⊕⊕⊖⊖
Positive predictive value	LGE-CMR low cut-off: k=10 LGE-CMR high cut-off: k=15 DbE: k=33 TI-SPECT: k=40 Tm-SPECT: k=25 Echo (high- and low-dose): k=12 SPECT (unspecified) k=13	Risk of bias: 0 Inconsistency: 0 Indirectness: -1 Imprecision: -1 Publication bias: 0	74% 68% 82% 71% 75% 77% 74%	A positive test result from LGE-CMR (high cut-off) can be trusted less than a positive test result from the comparators. A positive test result from LGE-CMR (low cut-off) can be trusted to a similar degree to other imaging techniques, but less than DbE.	Low ⊕⊕⊖⊖
Safety	No direct comparative studies. Results derived from naïve indirect comparisons.	Risk of bias: -- Inconsistency: -1 Indirectness: -1 Imprecision: -1 Publication bias: 0	LGE-CMR has a reduced risk of serious AEs compared with DbE and CT-DCE, and a similar low rate to SPECT. Risk of acute and long-term mortality from LGE-CMR is less than CT-DCE, marginally less than SPECT, and more than DbE.	Non-invasive imaging techniques have a low risk of harms. The poor quality of evidence makes it difficult to make conclusions on the comparative safety of the tests.	Very low ⊕⊖⊖⊖


Outcomes	No. of studies	Quality of evidence	Results	Interpretation	GRADE ^a
Change in management	k=2 before-and-after case series No comparative studies	Risk of bias: 0 Inconsistency: -1 Indirectness: -1 Imprecision: -1 Publication bias: 0	71.5% of patients had a change in management after LGE-CMR (change in invasive procedure in 24.2%). 3/9 CABGs were averted due to non-viability, and overall 13% had a change in surgical management plan.	LGE-CMR was found to influence what treatment patients received, but it is unknown how this differs from what they would have received due to the comparators.	Very low 

^a GRADE Working Group grades of evidence (Guyatt et al. 2011)

 **High quality:** We are very confident that the true effect lies close to that of the estimate of effect.

 **Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

 **Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

 **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

AE = adverse event; CABG = coronary artery bypass; CT-DCE = computed tomography perfusion with delayed contrast enhancement; DbE = low-dose dobutamine Echo; Echo = echocardiography; k = number of studies; LGE-CMR = late gadolinium enhancement with cardiac magnetic resonance imaging; RCT = randomised controlled trial; SPECT = single-photon emission computed tomography; Tl = thallium-201; Tm = technetium-99m

SECTION CB TRANSLATION ISSUES (POPULATION 2)

C1B OVERVIEW

Economic analysis is performed to assess the cost-effectiveness of assessing myocardium viability using LGE-CMR in comparison with SPECT and low-dose DbE in patients presented with significant CAD, and history of IHD and LVD who are being considered for revascularisation. No evidence was found regarding the diagnostic performance of CT perfusion with delayed contrast enhancement; thus this is not included as a comparator in the economic model. The outcomes of interest are; cost per correct diagnosis and cost per unnecessary revascularisations avoided. Data required for the model (i.e. accuracy, re-testing and AE rates associated with intervention, comparator tests and revascularisation procedures) are primarily sourced from the clinical evaluation (Section B), with use of additional relevant studies where required.

Translation issues to be presented in Section C, related to population 2, include:

- Are there relevant differences between the populations included in the studies to inform the test parameters in the economic model and the proposed MBS population?
- Is the segmental accuracy data reported in the clinical evaluation comparable and valid to inform the diagnostic accuracy for LGE-CMR and comparators on a per patient basis?
- Of the various sets of accuracy inputs identified for LGE-CMR, SPECT, DbE and CT-DCE, which should be used in the economic evaluation?
- What is the prevalence of viable myocardium in the target population?
- What impact does viability assessment have on the patient relevant health outcomes?
- Does LGE-CMR change clinical management, compared with DbE, SPECT or CT-DCE for patients with CAD, history of IHD with LVD and are being considered for revascularisation?
- In what proportion are CABG surgery and PCIs (using stents or angioplasty) performed in the proposed MBS population?
- What are the procedural complications (including mortality) associated with revascularisation procedures CABG and PCI?

C2B APPLICABILITY TRANSLATION ISSUES

C2B.1 COMPARISON OF THE POPULATIONS INCLUDED IN THE CLINICAL STUDIES AND THE AUSTRALIAN POPULATION

Table 96 Applicability of the studies used to inform test accuracy inputs in the economic model

Component	Investigation
Issue/question	Are there relevant differences between the populations included in the studies to inform the test parameters in the economic mode and the proposed MBS population?
Data	Assessment of the differences between patient characteristics in studies included in the clinical evaluation of LGE-CMR and its comparators (Section B) and those of the target population.
Method (focused analytical plan)	To compare demographics (mean age of the population and gender distribution), the prevalence of viable myocardium, and the type of revascularisations performed across the studies included in the clinical evaluation to those of the target population; Search for studies reporting patient characteristics in Australia

LGE-CMR = late gadolinium enhancement cardiac magnetic resonance imaging; MBS = Medicare Benefits Schedule

The data used for LGE-CMR in the economic model is derived from the studies included in the meta-analyses in Section B.3b. For the comparators DbE and SPECT, data were selected from two SRs by Schinkel et al. (2007) and Campbell et al. (2014). Schinkel et al. (2007) reported detailed comparator data by pooling results of their previous SR (Bax et al. 2001) and the relevant studies published after that. In comparison, Campbell et al. (2014) did not provide subgroup data for Echo or SPECT. Campbell et al. (2014) reported on the studies included in the SR by Schinkel et al. (2007) that were published after 2000, and pooled this with studies that assessed intervention and comparator tests.

The studies included in the clinical evaluation generally matched the proposed target population (i.e. patients with CAD being considered for revascularisation), but varied in the inclusion criteria of threshold for LVEF. The average age, proportion of males, method of revascularisation and median of prevalence of recovery are presented in Table 97. Where reported, the data across the populations appeared consistent. LGE-CMR studies appeared to have patients older in age and have a lower proportion of males compared with patient populations across SPECT and DbE.

Table 97 Selected characteristics of the study populations and the Australian population ^a

	LGE-CMR ^b	DbE ^c	SPECT ^c	Australian data ^d
Number of studies	17	65	30	-
Number of patients	715	1833	1106	-
Mean (SD) age (years)	62 (9)	56 (9)	57 (8)	65
Proportion male (%)	78	85	88	66%–73%

Source: Section B.3b and Schinkel et al. (2007) for LGE-CMR, and Bax et al. (2001), Campbell et al. (2014) and Schinkel et al. (2007) for DbE and SPECT

^a Data reported in the table are pooled (weighted) average for all parameters, where reported.

^b Section B.3b

^c Bax et al. (2001); Schinkel et al. (2007)

^d ANZSCTS registry; Chan et al. (2015)

ANZSCTS = The Australian and New Zealand Society of Cardiac and Thoracic Surgeons; DbE = low-dose dobutamine echocardiography; LGE-CMR = late gadolinium enhancement cardiac magnetic resonance imaging; SD = standard deviation; SPECT = single-photon emission computed tomography

There is a paucity of Australian data related to the proposed population. Most estimates in the literature are derived from data reported in those patients with chronic heart failure with reduced LVEF (HFrEF). There are limitations in using this data as chronic heart failure is one of the advanced prognoses in patients with CAD and ischemic LVD, and its prevalence increases with age. As Australian data specific to the target population could not be found, the epidemiological profiles of these patients were assessed based on reports of data from the Australian and New Zealand Society of Cardiac and Thoracic Surgeons (ANZSCTS) registry (Tran et al. 2012) and a report conducted by Mary MacKillop Institute for Health Research (Chan et al. 2015).

Reports of data from the ANZSCTS registry for the 2010–11 financial year included all cardiac surgeries performed in six Victorian hospitals from 1 July 2010 to 30 June 2011 (Tran et al. 2012). In the group of patients who underwent cardiac surgery in 2010–11, the average age was 65 years and approximately 73% were male. Chan et al. (2015) reported the contemporary burden and profile of heart failure in Australia. The study reported a prevalence of around 480,000 cases of HFrEF in Australians aged 45 years or older, out of which 66% were men. The average age of patients was 65 years.

This limited available evidence indicates that Australian patients may generally be older and include more females than the study populations; however, the implications of these variations is uncertain.

C2B.2 COMPARABILITY OF THE STUDIES USED TO INFORM THE DIAGNOSTIC ACCURACY INPUTS IN THE MODEL

Table 98 Comparability of the studies used to inform the diagnostic accuracy inputs in the model

Component	Investigation
Issue/question	Is the segmental diagnostic accuracy data reported in the various clinical evaluations valid to inform diagnostic accuracy on a per patient basis?
Data	Studies included in clinical evaluation of LGE-CMR (Section B) and studies included in the SRs reporting test accuracy inputs for DbE and SPECT Additional evidence from Camici, Prasad & Rimoldi (2008) and Pegg et al. (2010)
Method (focused analytical plan)	To assess the inclusion criteria—criteria used for viability, characteristics of the tests, and reference standard used in the studies included in the evidence-base

DbE = low-dose dobutamine echocardiography; LGE-CMR = late gadolinium enhancement cardiac magnetic resonance imaging; SPECT = single-photon emission computed tomography; SR = systematic review

A key issue when applying the data on diagnostic accuracy identified in Section B.3 to the economic model is whether the accuracy data on a segment level can be translated to a patient level. The sensitivity and specificity values in the studies included in clinical evaluation are calculated and reported on a per segment basis and, therefore, provide information on the ability of these imaging techniques to determine viability within particular myocardial segments, but not for detecting the presence or absence of viable myocardium on a per patient basis. However, ‘per patient’ accuracy is the parameter required to model costs and cost-effectiveness on a population basis.

Furthermore, the studies used to assess diagnostic accuracy were heterogeneous with respect to inclusion criteria, thresholds for viability, types and dosage of contrasts (CMR) or micro-tracers (SPECT) used in the imaging, and the reference standard used. This raised a number of issues:

- a) Different segmental models to interpret LV segmentation were used in the accuracy studies, with models varying between 8 and 56 segments per patient (discussed in Section B3b.4). It is uncertain if the differences in the segment models are relevant to the results.
- b) Different dosages of gadolinium-based contrast were used, varying from 0.01 to 0.2 mmol/kg body weight, and images were obtained 2–30 minutes after the administration of the contrast agent. The impacts of the dose and method of administration of contrast on the study results are unknown.
- c) There is no valid reference test for determining myocardial viability. All included studies used regional functional improvement of myocardial segments at follow-up as the imperfect surrogate of viability.

The key concern regarding translation of segmental accuracy to patient-level accuracy is discussed in a review by Camici et al. (2008). This states that there is a general consensus (supported by at least 7 studies) that the changes in LVEF after revascularisation are linearly correlated with the number of viable segments in the patient (Camici, Prasad & Rimoldi 2008). Similarly, a non-randomised trial by Pegg et al. (2010) reported that the number of viable plus normal segments is a predictor of functional recovery after revascularisation (Pegg et al. 2010).

Although highly uncertain, for modelling purposes it is assumed that the patient-level diagnostic accuracy for CMR is represented by the segmental diagnostic accuracy reported in Section B.3b. Also, it is assumed that the different segmental models and dosages of contrast agent used have no impact on the diagnostic accuracy of LGE-CMR.

C2b.3 DIAGNOSTIC ACCURACY OF LGE-CMR AND EACH COMPARATOR TO BE USED IN THE ECONOMIC EVALUATION

Table 99 Diagnostic accuracy of the LGE-CMR and comparators to be used in the economic evaluation

Component	Investigation
Issue/question	Which set of accuracy inputs should be used in the economic evaluation for each of LGE-CMR, SPECT, DbE and CT-DCE tests?
Data	Accuracy data reported in clinical evaluation of LGE-CMR (Section B.3b.5) Studies included in clinical assessment of SPECT and DbE (Section B) and clinical management algorithm (Section A)
Method (focused analytical plan)	Identify the set of accuracy inputs most appropriate to LGE-CMR based on the general threshold used in the literature. Compare the description of comparator tests included in the clinical management algorithm to determine which set of accuracy inputs are most applicable for use in the economic evaluation.

CT-DCE = computed tomography perfusion imaging with delayed contrast enhancement; DbE = low-dose dobutamine echocardiography; LGE-CMR = late gadolinium enhancement cardiac magnetic resonance imaging; SPECT = single-photon emission computed tomography

The accuracy of LGE-CMR is assessed in two subgroups in Section B.3b.5: studies using a threshold of $\leq 25\%$ HE (low cut-off group) and studies using a threshold of $\geq 50\%$ HE (high cut-off group). The pooled sensitivity of the high cut-off group is 0.93 (95%CI 0.90, 0.96) and the pooled specificity is 0.45 (95%CI 0.30, 0.61). For the low cut-off group, the pooled sensitivity is 0.72 (95%CI 0.55, 0.84) and the pooled specificity is 0.65 (95%CI 0.53, 0.76).

Most studies in the literature reported results based on high cut-offs ($\geq 50\%$ HE). Therefore, sensitivity and specificity derived using high cut-offs will be used in the base-case model and the results based on accuracy data derived from low cut-offs will be presented in scenario analyses.

No studies were identified comparing the accuracy of LGE-CMR and CT-DCE. Consequently, CT-DCE is not included as a comparator in the economic evaluation.

Two SRs were identified in the clinical assessment that provided meta-analysed results for the diagnostic accuracy of the comparator tests SPECT and DbE (Campbell et al. 2014; Schinkel et al. 2007). The results of these studies are summarised in Table 100.

The accuracy data reported in the study by Schinkel et al. (2007) is categorised depending on the radioisotopes used for SPECT and the dosage of dobutamine (high or low dose) used in the echocardiography. The accuracy data provided in the review by Campbell et al. (2014) does not have any categorisation for the comparator tests. In the clinical algorithm presented in Section A of the assessment, low-dose dobutamine Echo was specified as the comparator, but the radioisotope used in the SPECT testing was not specified. As such, the accuracy data for SPECT is sourced from the study by Campbell et al. (2014) and the DbE accuracy is taken from the review by Schinkel et al. (2007). The accuracy data reported in these two studies vary considerably and thus will be tested in the sensitivity analyses.

Table 100 summarises the diagnostic accuracy inputs used in the base-case and scenario analyses for LGE-CMR, DbE and SPECT.

Table 100 Diagnostic accuracy inputs used in the economic evaluation

Test	Sensitivity	Specificity	Source	Values tested in sensitivity analyses [95%CI] sensitivity, [95%CI] specificity	Source
LGE-CMR (high cut-off): Scenario 1	0.93	0.45	Meta-analyses, Section B.3b	[0.90, 0.96], [0.30, 0.61]	Meta-analyses, Section B.3b
LGE-CMR (low cut-off): Scenario 2	0.70	0.68	Meta-analyses, Section B.3b	[0.54, 0.82], [0.56, 0.78]	Meta-analyses, Section B.3b
DbE	0.79	0.78	SR, Schinkel et al. (2007)	[0.71, 0.83], [0.62, 0.76]	SR, Campbell et al. (2014)
SPECT	0.85	0.62	SR, Campbell et al. (2014)	[0.78, 0.90], [0.53, 0.70]	SR, Campbell et al. (2014)
CT-DCE	-	-	Not found	-	-

CI = confidence interval; CT-DCE = computed tomography perfusion imaging with delayed contrast enhancement; DbE = low-dose dobutamine echocardiography; LGE-CMR = late gadolinium enhancement cardiac magnetic resonance imaging; SPECT= single-photon emission computed tomography; SR = systematic review

C2B.4 PREVALENCE OF VIABLE MYOCARDIUM IN THE PROPOSED MBS POPULATION

Table 101 Prevalence of viable myocardium in the proposed population

Component	Investigation
Issue/question	What is the prevalence of viable myocardium in the proposed MBS population?
Data	Studies included in clinical evaluation of LGE-CMR and its comparators (Section B)
Method (focused analytical plan)	Ranges of prevalence estimates of myocardium viability in the included studies

LGE-CMR = late gadolinium enhancement cardiac magnetic resonance imaging; MBS = Medicare Benefits Schedule

Evidence related to the true prevalence of viable myocardium in the proposed MBS population is lacking. In the absence of relevant Australian data, the rate of recovery (i.e. segmental improvement in wall motion) in the study samples was assumed to be representative of the prevalence of viability in the target population. The prevalence of recovery varied from 26.4% to 85.8% (median 56%), 22% to 91% (median 54%) and 16% to 82% (median 54%) in LGE-CMR, SPECT and DbE accuracy studies, respectively (see Table 102). Section B.3b concludes that the prevalence of myocardial viability in the trials is reasonably estimated at 56% and this value is used in the base-case of the economic model.

Table 102 Prevalence of recovery and ratio of CABG to PCI identified in studies included in SRs ^a

	LGE-CMR ^b	DbE ^c	SPECT ^c	Australian data
Median (range) prevalence of recovery (%)	56 (26–86)	54 (16–82)	54 (22–91)	No data identified (assumed to be 56%)
Ratio of CABG:PCI (%)	66:34	66:34	69:31	39:61 obtained using the number of hospital separations (2011-12) reported in National Hospital Cost Report

Source: Section B.3b and Schinkel et al. (2007) for LGE-CMR, Bax et al. (2001), Campbell et al. (2014) and Schinkel et al. (2007) for DbE and SPECT, and IHPA (2014)

^a Data reported in the table is pooled (weighted) average for all parameters, where reported.

^b Section B.3b

c Bax et al. (2001); Schinkel et al. (2007)

CABG = coronary artery bypass graft; DbE = low-dose dobutamine echocardiography; LGE-CMR = late gadolinium enhancement cardiac magnetic resonance imaging; PCI = percutaneous coronary intervention; NR = not reported; SPECT = single-photon emission computed tomography

As the results of the CEAs may be sensitive to the prevalence of viable myocardium in the population tested, and the estimate is relatively uncertain (i.e. the range of estimates is wide), scenario analyses are presented for prevalence estimates ranging from 15% to 95%.

C2B.5 VIABILITY ASSESSMENT TO PROGNOSTIC IMPLICATIONS

Table 103 Prognostic implications of LGE-CMR testing

Component	Investigation
Issue/question	Do the results of a viability assessment impact on patient-relevant health outcomes?
Data	Clinical assessment in Section B.5b
Method (focused analytical plan)	Analyse evidence presented in Section B.5b to determine prognostic implications of testing in this population

LGE-CMR = late gadolinium enhancement cardiac magnetic resonance imaging

PASC and MSAC have a preference that economic analyses consider patient-relevant health outcomes. To determine what patient-relevant outcomes may be affected with the use of CMR to determine myocardial viability requires identification of how patient management will be affected based on test-result status and the long-term implications of subsequent treatment.

It is suggested that LGE-CMR could be useful for excluding patients with non-viable myocardium from invasive revascularisation procedures from which they are unlikely to benefit. The clinical evaluation assessed the correlation between a patient's myocardial viability status and improved outcomes following revascularisation; however, the benefits of revascularisation compared with medical therapy alone were unable to be clearly identified in the available evidence, even in patients with viable myocardium. There was no significant interaction between treatments with respect to mortality rate when patients were randomised (see Section B.5b.2).

Due to the lack of evidence regarding long-term prognostic implications of the diagnostic test, a long-term model extrapolating the benefit of testing will not be able to be adequately populated with evidence. Therefore, the economic analyses are over a short time horizon of 30 days, capturing only the immediate quantifiable outcomes (i.e. post-operative complications and mortality) associated with revascularisation on the basis of the diagnostic test result.

C2B.6 PROPORTION OF CABG AND PCI PERFORMED IN THE PROPOSED MBS POPULATION

Table 104 Proportion of CABG and PCI performed in the proposed MBS population

Component	Investigation
Issue/question	In what proportion are coronary bypass surgery and PCIs (using stents or angioplasty) performed in the proposed MBS population?
Data	Assessment of average number of procedures performed in the included studies Literature and guidelines search
Method (focused analytical plan)	Determine the proportion of revascularisation methods used in the included studies and compare them with the type of procedures performed in the proposed MBS population

CABG = coronary bypass surgery; MBS = Medicare Benefits Schedule; PCI = percutaneous coronary interventions

Assuming that test results guide revascularisation, it is necessary to characterise the revascularisation procedures that would be used in the Australian setting to be able to subsequently estimate the associated costs and relevant outcomes. The current American Heart Association (AHA)

guidelines state that revascularisation in patients with CAD and LV dysfunction is directed by a number of clinical variables, including coronary disease complexity, patient comorbidities, severity of LV dysfunction, patient preferences and local expertise. Revascularisation can be performed either surgically (coronary artery bypass graft; CABG) or percutaneously (percutaneous coronary intervention; PCI). No Australian guidelines stating the optimum revascularisation strategy in the target population were identified but the (AHA guidelines describe CABG as reasonable treatment (class IIa, level B) in patients with moderate LV dysfunction (LVEF, 35%–50%) and it may also be considered (class IIb, level B) for patients with LVEF <35% without significant left main disease (Hillis et al. 2011). There is insufficient data to make a recommendation regarding the role of PCI in patients with LV dysfunction. Considering that the target population includes patients with significant CAD and severe LV dysfunction, in the base-case economic analyses it is assumed that CABG will be performed as a revascularisation procedure in all patients.

As health resource utilisation and treatment complications vary substantially between the PCI and CABG treatments, alternative assumptions with mixed utilisation of CABG and PCI are explored in scenario analyses, as shown in Table 105.

Table 102 identified the ratio of CABG:PCI revascularisations across the studies in the SR. On average, 66% of revascularisations performed were CABGs in LGE-CMR and DbE study populations, compared with 69% in the SPECT studies. Also presented is the only available Australian estimate, a ratio of 39%:61% (CABG:PCI), based on the number of hospital separations (2011–12) reported in the National Hospital Cost Report relating to CABG and PCI, respectively; however, this is based on an unrestricted population, not the target population.

Table 105 Summary of alternative scenario assumptions for the proportion of revascularisation procedures utilising CABG and PCI

Scenario analysis	Revascularisations using CABG	Revascularisations using PCI	Source
Scenario 1 (base-case)	100%	0%	AHA (Hillis et al. 2011)
Scenario 3	66%	34%	Table 102
Scenario 4	39%	61%	Table 102

AHA = American Heart Association; CABG = coronary bypass surgery; PCI = percutaneous coronary interventions

C2B.7 INTRA- AND POST-OPERATIVE COMPLICATIONS AND MORTALITY ASSOCIATED WITH REVASCULARISATION

Table 106 Procedural complications (intra- and post-operative) associated with revascularisation

Component	Investigation
Issue/question	What are the intra and post-operative and/or procedural complications (including mortality) associated with revascularisation procedures CABG and PCI?
Data	Data reported in the literature, data from relevant clinical trials
Method (focused analytical plan)	Analyse data reported in the clinical trials and other published research to identify the mortality associated with the revascularisation procedures (CABG and PCI) and background risk of mortality in the target population

CABG = coronary bypass surgery; PCI = percutaneous coronary interventions

There is limited evidence available regarding post-operative complications due to CABG or PCI in the target population, as patients with severe CAD and LVEF ≤35% are under-represented in many studies. One randomised trial (STICH trial) was identified that studied the rate of mortality and cardiac events in patients with significant CAD and LVEF ≤35% who were considered for revascularisation (Wrobel et al. 2015). Patients were randomised to receive CABG plus medical

therapy (n=1,460) or medical therapy alone (n=2,136). Of the patients randomised to and receiving CABG, 24% developed a severe complication within 30 days. Overall mortality observed at 30 days for this group of patients was 5.1%, whereas for patients receiving medical therapy alone it was 1.1% (Panza et al. 2014). PCI was considered as a downstream medical procedure and not a comparative treatment in both trial arms.

The 30-day post-operative mortality risk associated with CABG in the STICH trial (Wrobel et al. 2015) was consistent with observational data reported in studies by Nagendran et al. (2013) and Kunadian et al. (2011). A summary of additional observational data on mortality rates associated with revascularisation and heart failure is provided in Appendix O.

Therefore, in the economic model, the 30-day overall mortality associated with CABG is assumed to be 5.1% with a post-operative complication rate of 24%, and the background 30-day mortality in the medical therapy arm is estimated to be 1.1% (all values from the STICH RCT). For the scenario analyses including PCI, an estimated post-operative mortality associated with PCI is 7%, based on an observational study by Nagendran et al. (2013) (see Appendix O). As no data related to procedural complications of PCI in the target population was available, a weighted number of separations for PCI with complications (AR-DRGs F15A and F16A) and PCI without complications (AR-DRGs F15B and F16B) was used. Of the PCI separations, 25% had severe complications (IHPA 2014). Therefore, the PCI procedural risk is assumed to be 25% in the economic model.

As the target population may be considered at high risk of mortality post-revascularisation, and the assumed rate may impact decision making in this population, an upper limit of a plausible mortality rate of 10% is tested in a sensitivity analysis, based on the findings of an inpatient mortality rate around 9% in an Australian study by Chan et al. (2015) (detailed in Appendix O).

C3B EXTRAPOLATION TRANSLATION ISSUES

None were identified.

C4B TRANSFORMATION ISSUES

None were identified.

C5B ANY OTHER TRANSLATION ISSUES

C5B.1 CHANGE IN MANAGEMENT FOLLOWING LGE-CMR TESTING IN THE PROPOSED MBS POPULATION

Table 107 Change in management following LGE-CMR testing in the proposed MBS population

Component	Investigation
Issue/question	Does LGE-CMR change clinical management compared with low-dose dobutamine stress Echo, SPECT or CT-DCE for patients with CAD and a history of IHD and LVD who are being considered for revascularisation?
Data	Clinical assessment in Section B.5b
Method (focused analytical plan)	Analyse evidence presented in clinical evaluation to determine change in management due to testing in the proposed population.

CAD = coronary artery disease; CT-DCE = computed tomography perfusion imaging with delayed contrast enhancement; DbE = low-dose dobutamine echocardiography; IHD = ischaemic heart disease; LGE-CMR = late gadolinium enhancement cardiac magnetic resonance imaging; LVD = left ventricular dysfunction; MBS = Medicare Benefits Schedule; SPECT = single-photon emission computed tomography

The clinical evaluation did not identify any comparative studies assessing how management of patients may change with LGE-CMR, compared with Echo, SPECT or CT-DCE. In one single-arm Australian study (Taylor et al. 2013) (detailed in Section B5b.1.4), three out of nine planned CABGs (33.3%) were averted following LGE-CMR due to a finding of non-viability of myocardium. This

suggests that invasive procedures may be averted in Australia following negative viability results on CMR. This was confirmed by a clinical expert¹⁰ who indicated that viability testing is part of the decision-making process; however, other factors including age, lifestyle, BMI, comorbidities and state of the arteries supplying the area of concern can also play a role when making the decision whether or not to perform revascularisation.

The economic analyses assume that diagnostic testing will result in perfect change of management; that is, all patients assessed with myocardium viability will be managed by revascularisation and medical therapy, whereas patients with non-viability will be managed by medical therapy alone.

C6B RELATIONSHIP OF EACH PRE-MODELLING STUDY TO THE ECONOMIC EVALUATION

Table 108 provides a summary from Sub-sections C2, C3, C4 and C5 and their uses in response to Section D.

Table 108 Summary of results of pre-modelling studies and their uses in the economic evaluation

Section	Pre-modelling study	Results used in Section D	Cross-reference	Results used in Subsection D.6	Cross-reference
C.2b.3	Determination of diagnostic accuracy for: <u>LGE-CMR</u> : High threshold: Scenario 1 Low threshold: Scenario 2 <u>DbE</u> <u>SPECT</u>	Sensitivity: 0.93 Specificity: 0.45 Sensitivity: 0.70 Specificity:0.68 Sensitivity: 0.79 Specificity:0.78 Sensitivity:0.85 Specificity:0.62	Section D.4b.2	95%CI [0.90, 0.96] 95%CI [0.30, 0.61] 95%CI [0.71, 0.83] 95%CI [0.62, 0.76] 95%CI [0.78, 0.90] 95%CI [0.53, 0.70]	Section D.6b
C.2b.4	Identification of the prevalence of myocardium viability	56%	Section D.4b.1	Prevalence scenarios: 15%–95%	Section D.4b.1
C.2b.6	Determination of the proportion of revascularisations using CABG (Scenario 1)	100%	Section D.4b.3	Scenario analyses Scenario 3: 66% Scenario 4: 39%	Section D.4b.3
C.2b.7	Determination of AEs and mortality associated with revascularisation and medical management	CABG AEs: 23.7% 30-day mortality: 5.1% Medical management: 30-day mortality: 1.1%	Section D.4b.3	CABG 30-day mortality: 1%–10%	Section D.4b.3
C.5b.1	Change in management	100%	-	-	-

¹⁰ HESP member advice in a telecommunication with the Department of Health and AHTA on 5 November 2015.

AE = adverse event; CABG = coronary bypass surgery; CT-DCE = computed tomography perfusion imaging with delayed contrast enhancement; DbE = low-dose dobutamine echocardiography; LGE-CMR = late gadolinium enhancement cardiac magnetic resonance imaging; SPECT = single-photon emission computed tomography

SECTION DB ECONOMIC EVALUATION (POPULATION 2)

D1B OVERVIEW

The clinical evidence profile in the clinical assessment suggested that, relative to the comparators, LGE-CMR has non-inferior safety and superior ability to predict non-recovery. CMR viability testing has a prognostic value in predicting recovery independent of treatment. Therefore, LGE-CMR could be useful for excluding patients with non-viable myocardium from revascularisation procedures, since these are invasive, with risk, and the likelihood of recovery is low.

Given the lack of consistent evidence informing health outcomes following revascularisation vs medical management in the population tested, neither a cost–utility nor any long-term model would be reliable. Therefore, modelled cost-effectiveness analyses examining cost per additional correct diagnosis, cost per additional low benefit (non-viable) revascularisations avoided, and cost per additional appropriate revascularisation performed were undertaken.

D2B POPULATIONS AND SETTINGS

The MBS item descriptor specifies that the request for myocardial viability scan using delayed gadolinium enhancement is restricted to an adult patient presenting with an existing diagnosis of significant CAD who has a history of IHD and impaired LV function.

The setting is the Australian healthcare system, with the proposed and comparator services available on an outpatient or inpatient basis.

The comparability and applicability of studies included in the clinical evaluation to the economic evaluation are described in Section C.2b.1 and Section C.2b.2.

D3B STRUCTURE AND RATIONALE OF THE ECONOMIC EVALUATION

A summary of the key characteristics of the economic evaluation is given in Table 109.

Table 109 Summary of the economic evaluation

Perspective	Australian healthcare
Comparator	SPECT, DbE
Types of economic evaluation	Cost-consequence; cost-effectiveness
Sources of evidence	SR
Costs	Australian dollars, 2015 prices
Outcomes	Cost per additional correct diagnosis, cost per incremental unnecessary revascularisation averted and cost per additional appropriate revascularisation performed
Time horizon	30 days
Methods used to generate results	Decision-tree analysis
Software packages used	TreeAge Pro 2015

DbE = low-dose dobutamine echocardiography; SPECT= single-photon emission computed tomography

LITERATURE REVIEW

A literature search was conducted in May 2015 to identify published cost-effectiveness analyses of the proposed service. The search terms used are presented in Table 206, Appendix P.

One Health Technology Assessment report was identified as being relevant to this assessment. A brief summary of this study is provided in Table 110. No studies were conducted in the Australian setting.

Table 110 Economic evaluations identified that investigate CMR for viability assessment

Study	Setting	Outcome measures / results
Campbell (2014)	Compared the cost-effectiveness of LGE-CMR, no testing, Echo, stress CMR, SPECT, PET and revascularising everyone strategies in patients with ischaemic cardiomyopathy to identify patients with viable myocardium	A decision analytic model was presented 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. Lifetime horizon (40 years) was chosen with NHS perspective

Echo = echocardiography; LGE-CMR = late gadolinium enhancement cardiac magnetic resonance imaging; NHS = National Health Service; PET = positron emission tomography; SPECT=single-photon emission computed tomography

In this review Campbell et al. (2014) analysed the incremental cost-utility ratios of six different testing strategies with no testing using Monte Carlo Markov simulations. A lifetime horizon of 40 years was chosen. Based on clinical expert opinion, the analysis assumed that viable patients correctly diagnosed and having revascularisation will have lower hospitalisation rates compared with viable patients on medical therapy or non-viable patients on any treatment. Different scenarios were presented based on the varied mortality rates identified from the SRs by Schinkel et al. (2007) and Allman et al. (2002). Both SRs presented annual mortality rates depending on the viability status and treatment received, and differed in the mortality rates depicted for non-viable and revascularised patients. All diagnostic strategies were found to be cost-effective compared with no testing at the NICE threshold. The results were found to be driven by the diagnostic parameters and the mortality rates chosen.

An approach similar to the above study is not considered appropriate in the present assessment for two reasons. First, the hospitalisation rates assumed for the truly viable patients who are revascularised are based on clinical expert opinion, and no evidence was found supporting this. Second, the evidence for mortality rates in the above study was derived from the SRs which included studies from one to two decades ago; and the medications and surgical procedures have improved and advanced substantially. More recent studies (Bonow et al. 2011; Gerber et al. 2012) did not find any difference in survival depending on the viability status and treatment received, as discussed in Section B.5b.2.

STRUCTURE OF THE ECONOMIC EVALUATION

Patients with existing significant CAD, history of IHD and impaired LV function considered for revascularisation enter the model. The intervention arm of the model includes viability assessment of myocardium using an LGE-CMR test. The comparator arms include models for SPECT and DbE.

The diagnostic pathway will identify patients with viable and non-viable myocardium. Patients diagnosed with viable myocardium are assumed to be managed by revascularisation and optimal medical therapy (OMT), whereas patients diagnosed with non-viable myocardium are assumed to continue their OMT.

The probability of correct viability assessment is determined by the overall accuracy of the diagnostic pathway. The patients are classified into four groups, based on their true status and the diagnosis:

1. True positives: diagnosed correctly as viable and revascularised
2. False negative: diagnosed incorrectly as non-viable and not revascularised
3. False positive: diagnosed incorrectly as viable and revascularised (unnecessary revascularisation)
4. True negatives: diagnosed correctly as non-viable and not revascularised.

Revascularisation is associated with increased risk of mortality and procedure-related complications. The time horizon of 30 days is chosen to capture these health outcomes. All modelled pathways will terminate into survival or death after 30 days based on the path probabilities related to viability status and the treatment received. The implications of a false positive result include unnecessary revascularisation and associated complications and increased costs, and a false negative result implies a missed opportunity of suggested treatment (i.e. revascularisation).

Figure 40 shows the decision analytic structure of the base-case cost analysis. The structures for the secondary CEAs have the same decision-tree structure, with allocation of outcomes based on correct diagnoses and necessary/unnecessary revascularisations performed, as shown in Figure 67 and Figure 68, Appendix P.

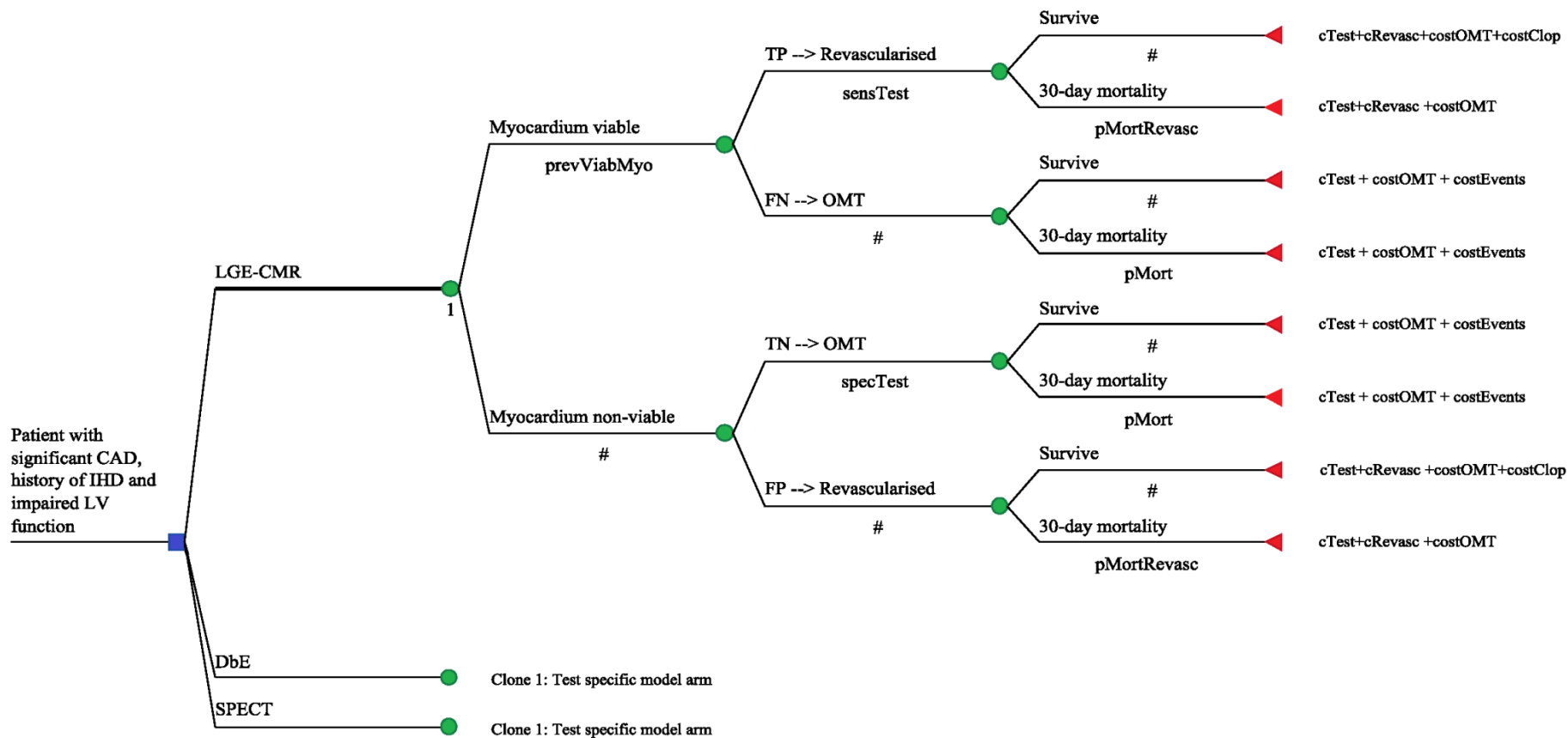


Figure 40 Decision analytic structure of the base-case cost consequences analysis in population 2

Note: where Test is denoted, the parameter is specific to the model arm, so sensTest in the LGE-CMR arm relates to the sensitivity of LGE-CMR

CAD = coronary artery disease; costClop = cost of clopidogrel for 30 days treatment; costEvents = cost associated with cardiac events; costOMT = cost of optimal medical therapy; costRevasc = cost associated with revascularisation; cTest = cost associated with testing; DbE = low-dose dobutamine echocardiography; FN = false negative; FP = false positive; IHD = ischaemic heart disease; LGE-CMR = late gadolinium enhancement cardiac magnetic resonance imaging; LV = left ventricular; pMort = background risk of 30 day mortality in the population; pMortRevasc = risk of 30 day mortality associated with revascularisation; prevViabMyo = prevalence of myocardial viability; sensTest = sensitivity of the Test; SPECT=single-photon emission computed tomography; specTest = specificity of the Test; TN=true negative; TP=true positive

Assumptions incorporated into the model structure are that:

- It is assumed that patients will follow the diagnostic pathways and will undergo surgery when diagnosed with viable myocardium; those diagnosed with non-viable myocardium will not receive surgical revascularisation. This is a simplification; in clinical practice this decision is complex and based on the patient's demographics, comorbidities and other factors.
- It is assumed in the model that there will be no alternative confirmatory testing and thus the status or treatment of false positives and false negatives will not change in the diagnostic pathway.
- It is assumed in the base-case economic analyses that all revascularisations performed are CABG.
- Mortality rates are assumed to be dependent on the treatment received and not the viability status.

Limitations of the model structure are that:

- It does not capture disutility associated with experiencing AE related to testing strategy or revascularisations.
- Only severe complications and 30-day mortality associated with revascularisation and background 30-day mortality are included in the model; other events are not incorporated.
- It does not capture the costs or outcomes of long-term AEs associated with testing.
- It does not capture the implications of false negative test results (due to a lack of data).

Model outcomes

In an attempt to describe the cost-effectiveness of testing in the proposed population, the following outcomes are reported, as incremental costs and outcomes between LGE-CMR and the comparators:

- additional cost per additional correct diagnosis (includes both true positives and true negatives)
- additional cost per incremental unnecessary revascularisation averted due to correct diagnosis of non-viability (i.e. true negatives)
- additional cost per additional appropriate revascularisation performed (in true positives).

The summary of the decision-tree final outcome states in the economic evaluation is provided in Table 207, Appendix P.

D4B INPUTS TO THE ECONOMIC EVALUATION

D4B.1 EPIDEMIOLOGICAL PARAMETERS

Prevalence of viable myocardium

As discussed in Section C.2b.5, the prevalence of myocardium viability used in the base-case economic model is 56%, based on the median of prevalence of recovery observed in studies of LGE-CMR included in the meta-analyses for diagnostic accuracy. The true estimate of prevalence of viability is highly uncertain in this population; therefore, additional scenario analyses will be presented across the range of prevalence of recovery (15%–95%) observed in the studies included in the SRs and meta-analyses to determine the impact of prevalence on cost and cost-effectiveness of CMR, relative to its comparator.

D4b.2 TEST RELATED PARAMETERS

Test accuracy

Test accuracy data used in the economic model for LGE-CMR and each comparator are sensitivity and specificity. The values used are presented in Table 111. Justification for the selection of the studies used to inform these data is presented in Section C.2b.3 and Section C.2b.4. Sensitivity analyses are conducted using the 95%CI presented.

Table 111 Test accuracy inputs used in the economic model

Test	Sensitivity [95%CI]	Specificity [95%CI]	Source
LGE-CMR (high cut-off)	0.93 [0.90, 0.96]	0.45 [0.30, 0.61]	Section C.2b.3
LGE-CMR (low cut-off)	0.70 [0.54, 0.82]	0.68 [0.56, 0.78]	Section C.2b.3
DbE	0.79 [0.71, 0.83]	0.78 [0.62, 0.76]	Section C.2b.4
SPECT	0.85 [0.78, 0.90]	0.62 [0.53, 0.71]	Section C.2b.4

CI = confidence interval; DbE = low-dose dobutamine echocardiography; LGE-CMR = late gadolinium enhancement cardiac magnetic resonance imaging; SPECT= single-photon emission computed tomography

Adverse event rates

The AEs considered in the model include:

- allergic reactions to gadolinium contrast agent, associated with CMR
- adverse reaction to microspheres and the pharmacological stressor dobutamine, associated with DbE.

The rates used in the economic model are presented in Table 112 and are based on those reported in Table 94, Section B7b.

Table 112 Proportion of AEs related to non-invasive testing strategies

	AE rate	Source
LGE-CMR		
Gadolinium contrast	0.005%	Table 94, Section B7b
DbE		
Stressor (dobutamine)	0.018%	Table 94, Section B7b
Microspheres	0.03%	Table 94, Section B7b
SPECT		
Radiotracers	0.001%	Table 94, Section B7b

AE = adverse event; DbE = low-dose dobutamine echocardiography; LGE-CMR = late gadolinium enhancement cardiac magnetic resonance imaging; SPECT = single-photon emission computed tomography

Other long-term or rare severe AEs related to all tests reported in Section B7b are not included in the economic analyses.

D4b.3 HEALTH CARE RESOURCE ITEMS

Test costs

The test costs used in the economic model are presented in Table 113. For LGE-CMR the proposed MBS item Schedule fee of \$700 is used. For the comparators the test costs are based on current MBS item Schedule fees. Sensitivity analyses are conducted using the average provider fee, which takes

into account bulk billing and patient contributions above the Schedule fee, for each of the current tests.

Costs associated with testing

As discussed in Section D.4a.3, costs associated with testing include the cost of associated professional attendances, and the cost of stressors and contrast agents. It is assumed that the cost of microsphere contrast used in DbE and microtracers used in SPECT are included in the service fee.

The Schedule fee for each diagnostic imaging service is assumed to cover both the diagnostic imaging procedure, and reading and reporting on that procedure by the provider (Medicare Benefits Schedule 2015). Therefore, each test is assumed to incur the cost of consultation by the referring doctor to review imaging results.

DbE is performed in conjunction with exercise ECG. Therefore, the cost of DbE testing will include the cost of stressor, the cost of exercise ECG and the fee for professional attendance, in addition to the cost of DbE imaging. LGE-CMR will include the cost of imaging, gadolinium contrast and a consultation fee. There are no stressors used in SPECT in population 2. Therefore, the cost of SPECT will include the cost associated with imaging and the fee for consultation. Table 113 summarises the costs associated with testing used in the economic model.

Table 113 Costs associated with testing used in the economic model

Item	Base-case	Source	Sensitivity analyses	Source
<i>Test</i>				
LGE-CMR	\$700.00	Proposed MBS item	\$1,100–\$1,200	Section A.10 (applicant's suggestion)
DbE	\$261.65	MBS items 55117	\$270.45	Average provider fee for MBS item 55117, July 2009 – June 2015
SPECT	\$565.30	MBS item 61303	\$536.05	Average provider fee for MBS item 61303, July 2009 – June 2015
<i>Other</i>				
Exercise ECG	\$152.15	MBS item 11712	\$151.16	Average provider fee for MBS item 11712, July 2009 – June 2015
Stressor	\$10.00	Patient fee charged for pharmacological stress Echo at SA Heart Clinic ¹¹	-	-
Gadolinium contrast	\$44.90	MBS item 63491	-	-
Consultation	\$43.00	MBS item 105	-	-

DbE = low-dose dobutamine echocardiography; ECG = electrocardiography; Echo = echocardiography; LGE-CMR = late gadolinium enhancement cardiac magnetic resonance imaging; MBS = Medicare Benefits Schedule; SPECT = single-photon emission computed tomography

¹¹ Available from <<http://www.saheart.com.au/services/diagnostic-tests/dobutamine-stress-echocardiogram.html>> (accessed on 16 October 2015)

Costs associated with treating AEs related to testing

The AEs considered in the economic model are reported in Table 112. The costs of treating AEs related to testing are based on the NEP for the AR-DRG code (IHPA 2015a) most relevant to the event and are presented in Table 60, Section D.4a.3.

The weighted cost of treating AEs associated with each testing strategy is presented in Table 114.

Table 114 Weighted cost of treating AEs related to testing strategies

	AE rate	Cost of treating AE	Weighted cost of treating AE
LGE-CMR (total)			\$0.05
Gadolinium contrast	0.005%	\$1,104	\$0.05
DbE (total)			\$14.71
Stressor (dobutamine)	0.18%	\$1,104	\$13.27
Microspheres	0.03%	\$7,370	\$0.33
SPECT (total)			\$0.01
Radiotracers	0.001%	\$1,104	\$0.01

AE = adverse event; DbE = low-dose dobutamine echocardiography; LGE-CMR = late gadolinium enhancement cardiac magnetic resonance imaging; SPECT = single-photon emission computed tomography

The cost associated with treating AEs related to radiotracers in SPECT testing is very low (\$0.01) and is not included in the economic model.

A summary table of test costs including contrast agents, stressors, consultation and the cost of treating related AEs is presented in Table 115.

Table 115 Summary of costs related to testing used in the economic model

Test	Test cost	Contrast	Stressors	AEs	Consultation	Total
LGE-CMR	\$700.00	\$44.90	-	\$0.05	\$43	\$788
DbE	\$413.80 ^a	-	\$10.00	\$14.71	\$43	\$480
SPECT	\$565.30	-	-	-	\$43	\$608

^a Includes associated cost of MBS item 11712 (exercise electrocardiography)

AE = adverse event; DbE = low-dose dobutamine echocardiography; LGE-CMR = late gadolinium enhancement cardiac magnetic resonance imaging; SPECT = single-photon emission computed tomography

Cost of optimal medical treatment

Patients with significant CAD, IHD and impaired LV have severe disease and are often managed for their lifetime with guideline-directed medical therapy. This usually includes a treatment management plan including several concomitant medicines targeting various symptoms of the disease and existing comorbidities. One study predicted that the mean (SD) annual cost of treating cardiovascular disease per patient in Australia was \$2,424 (\$1,844) in 2010. This equates to \$2,644 (\$2,011) or an average cost per 30 days of \$217¹² in 2015 Australian dollars (AUD)¹³. To validate this estimate, costs of the medications prescribed in general for managing this patient population were

¹² Cost per 30 days is derived as (\$2,644/365)*30, which equates to \$217.

¹³ Costs were reported in 2010 AUD and are converted to 2015 AUD using the Consumer Price Index Inflation Calculator. <[visit ABS calculator](#)> (accessed on 25 November 2015).

summed up and an estimate of \$206 per 30 days was obtained. Details and costs of medicines as recommended by the Australian Heart Foundation (National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand 2012) are described in Attachment P. At estimated average doses these were costed as totalling approximately \$212 per month, which is consistent with the adjusted estimates by Hirst et al. (2011). Therefore, the adjusted Hirst estimate is considered appropriate, and the cost of OMT per 30 days is assumed to be \$217 in the base-case. Since the SD is quite high, the cost of OMT will be tested in the range \$52– \$383 in the sensitivity analyses.

Revascularisation costs (including costs to treat complications)

The modelled cost of CABG is based on the NEP for AR-DRGs F05B and F06B (Coronary bypass, with or without invasive cardiac investigation), weighted by the respective number of hospital separations (2011–12) (IHPA 2014). The treatment of complications related to CABG is assumed to be different between the weighted cost of AR-DRGs F05A and F06A (CABG with complications) and the weighted CABG cost (above).

The modelled cost of PCI (used in the sensitivity analysis) is based on the NEP for AR-DRGs F15B and F16B (Interventional coronary procedures, not admitted for AMI, no complications, with or without stent implant), weighted by the respective number of hospital separations (2011–12) (IHPA 2014). The treatment of complications related to CABG is assumed to be the difference between the weighted cost of AR-DRGs F15A and F16A (CABG with complications) and the weighted cost of CABG without complications.

As discussed in Section C.2b.6, the base-case economic analyses assume that all revascularisation procedures performed are CABG; therefore, only costs associated with CABG are included. In the scenario analyses, the weighted cost of CABG and PCI will be used, based on the proportion of the respective procedures performed and the associated complications.

Table 116 presents the summarised results of the costs used in the economic model related to revascularisation.

Table 116 Summary of revascularisation costs related to testing used in the economic model

	Cost	Source
CABG		
CABG (without complications)	\$43,678	NEP (IHPA 2015a) for AR-DRGs F05B and F06B, weighted by hospital separations (2011–12)
CABG (with complications)	\$54,076	NEP (IHPA 2015a) for AR-DRGs F05A and F06A, weighted by hospital separations (2011–12)
Cost of treating complications related to CABG	\$10,398	Cost of CABG with complications minus cost of CABG without complications
Proportion of complications with CABG	23.7%	Section C.2b.7
Weighted cost of treating complications with CABG	\$2,464	Cost of treating complications × proportion of complications experienced
Total CABG cost	\$46,142	Sum of cost of CABG (without complications) and weighted cost of treating complications
PCI		
PCI (without complications)	\$9,419	NEP (IHPA 2015a) for AR-DRGs F15B and F16B, weighted by hospital separations (2011–12)
PCI (with complications)	\$19,019	NEP (IHPA 2015a) for AR-DRGs F15A and F16A, weighted by hospital separations (2011–12)

	Cost	Source
Cost of treating complications related to PCI	\$9,600	Cost of PCI with complications minus cost of PCI without complications
Proportion of complications with PCI	24%	Section C.2b.7
Weighted cost of treating complications with PCI	\$2,304	Cost of treating complications × proportion of complications experienced
ICA	\$4,475	NEP (IHPA 2015a) for AR-DRG F42B and F42C, weighted by hospital separations (2011–12)
Total PCI cost	\$16,198	Sum of cost of PCI (without complications), ICA (without complications) and weighted cost of treating complications

Source: IHPA (2014) and National Efficient Price Determination 2015-16 (IHPA 2015a).

AE = adverse event; AR-DRG = Australian Refined Diagnosis Related Groups; CABG = coronary bypass grafting; ICA = invasive coronary angiography; NEP = National Efficient Price; PCI = percutaneous coronary intervention

D4b.4 SUMMARY OF INPUTS TO THE ECONOMIC EVALUATION

A summary of the inputs incorporated in the economic model is presented in Table 209, Appendix P.

D5B RESULTS OF THE ECONOMIC EVALUATION

The model identifies several health outcomes, including revascularisations performed after correct diagnosis, revascularisations performed after incorrect diagnosis, procedure-related deaths due to both correct and unnecessary revascularisations, revascularisations averted after incorrect diagnosis, and deaths. The cost-effectiveness results reported are: cost per correct diagnosis, cost per unnecessary revascularisation, and cost per correct revascularisation

The base-case analysis (Scenario 1) assume that diagnostic accuracy for LGE-CMR is based on a high cut-off of HE, the prevalence of myocardium viability is 56% and all the revascularisations performed are CABG. Additional alternative scenario analyses are presented as summarised below:

- Scenario 2: assumes that diagnostic accuracy estimates are based on a lower cut-off of HE
- Scenario 3: Changing the proportion of revascularisations where CABG is performed to 66% (with PCI accounting for the remainder).
- Additional scenario analyses that change the ratio of revascularisations (CABG:PCI) to 39:61 (Scenario 4), and explore the entire range of prevalence estimates (15%–95%) in the population with CAD and LVD, are presented in Appendix O.

The results are presented in two comparison sets, LGE-CMR vs DbE and LGE-CMR vs SPECT, and report:

- disaggregated costs
- disaggregated outcomes
- incremental cost-effectiveness ratios (ICERs) for additional correct diagnosis, unnecessary revascularisations averted, and revascularisations with correct diagnosis.

D5b.1 COMPARISON OF LGE-CMR WITH DbE

Modelled costs

Figure 40 shows the type of costs included in each terminal node for each modelled arm. Table 117 presents a summary of modelled costs for LGE-CMR and DbE disaggregated by the costs associated with testing and the costs associated with treatment and related complications.

LGE-CMR testing is associated with an incremental cost of \$308 compared with DbE. As can be observed from Table 117, the treatment costs (including complications) accounted for the largest cost incurred per diagnosis in each modelled arm: \$35,438 in LGE-CMR group (97.8%) and \$25,138 in DbE group (98.1%).

Based on all costs incurred in either arm of the economic model, LGE-CMR testing compared with DbE testing resulted in an incremental cost of \$10,608 per diagnosis.

Table 117 Modelled cost analysis, comparison of LGE-CMR with DbE

Cost	LGE-CMR	DbE	Incremental cost
Test costs (including AEs related to testing)	\$788	\$480	\$308
Cost of revascularisation + OMT+ complications	\$35,438	\$25,138	\$10,300
Total cost per diagnosis	\$36,226	\$25,618	\$10,608

AE = adverse event; DbE = low-dose dobutamine echocardiography; LGE-CMR = late gadolinium enhancement cardiac magnetic resonance imaging; OMT = optimal medical therapy.

Modelled outcomes and incremental effects

The probability at each decision-tree terminal of each testing arm is derived from a composite of the prevalence of myocardium viability, diagnostic accuracy of the test, treatment chosen based on the test results, and complications associated with the treatment in the tested population.

The outcomes and incremental effects for comparison of LGE-CMR and DbE, as derived from the decision-tree analyses, are presented in Table 118. All outcomes are considered clinically relevant.

Table 118 Base-case modelled outcome and incremental effects, LGE-CMR compared with DbE

Outcomes	LGE-CMR	DbE	Incremental effectiveness	Nature of effect
Total correct diagnoses:	71.8%	78.5%	-6.7%	Harm
True positives (revascularisations with correct diagnosis)	52.0%	44.2%	7.8%	Benefit
True negatives (unnecessary revascularisations averted)	19.8%	34.3%	-14.5%	Harm
Total incorrect diagnoses:	28.1%	21.4%	6.7%	Harm
False positives	24.2%	9.7%	14.5%	Harm
False negatives	3.9%	11.7%	-7.8%	Benefit
Total revascularisations performed:	76.2%	53.9%	22.3%	
Unnecessary	24.2%	9.7%	14.5%	Harm
Revascularisations missed	3.9%	11.7%	-7.8%	Benefit
Total procedure-related deaths	3.8%	2.7%	1.1%	
Correct diagnosis	2.6%	2.2%	0.4%	Harm
Incorrect diagnosis	1.2%	0.5%	0.7%	
Deaths	0.2%	0.5%	-0.3%	Harm

DbE = low-dose dobutamine echocardiography; LGE-CMR = late gadolinium enhancement cardiac magnetic resonance imaging

LGE-CMR detects 7.8% more true positives than DbE, but the overall number of correct diagnoses are 6.7% lower than DbE due to the lower specificity of the test. There are higher numbers of

revascularisations and procedure-related deaths, but fewer revascularisations missed or averted, in LGE-CMR group compared with DbE.

The incremental effectiveness is derived by subtracting the outcomes of the DbE strategy from the outcomes of the LGE-CMR strategy. Overall, LGE-CMR testing is associated with limited benefits related to fewer revascularisations missed (due to false negative results), and a higher number of total revascularisations performed due to detection of patients with truly viable myocardium.

Incremental cost-effectiveness

The ICERs are calculated by dividing the differences in the costs per diagnosis of LGE-CMR and DbE by the differences in the number of outcomes of interest observed in each test. Incremental effect is considered beneficial in the intervention arm when the incremental outcome is positive for the outcomes measured as benefit, and when the incremental outcome is negative for the outcomes measured as harm, as described in Table 118. Therefore, for LGE-CMR to be beneficial in comparison with DbE, the incremental outcomes of correct diagnosis, and revascularisations undertaken with correct diagnosis, should be positive; whereas the incremental outcomes of unnecessary revascularisations averted should be negative.

The incremental costs per correct diagnosis, per unnecessary revascularisation averted, and per revascularisation undertaken with correct diagnosis are derived as discussed above. The incremental cost per revascularisation undertaken with correct diagnosis was observed to be \$136,002 in the base-case analysis. However, LGE-CMR was dominated by DbE for all other outcomes. Table 119 presents summary of the ICERs for the base-case analyses. Results for each outcome measure assessed are discussed further in detail.

Table 119 Incremental cost-effectiveness ratios, base-case analyses

Clinically relevant outcomes	Incremental outcomes (%)	ICER (\$ / outcome)
<i>Incremental cost</i>		<i>\$10,608</i>
Correct diagnosis	-6.7	Dominated
Unnecessary revascularisations averted	-14.5	Dominated
Revascularisations undertaken with correct diagnosis	7.8	\$136,002 / additional revascularisation undertaken with correct diagnosis

Dominated = intervention is more costly and less effective than comparator; ICER = incremental cost-effectiveness ratio

Cost per correct diagnosis

When the overall number of correct diagnoses (true positives plus true negatives) is accounted for, 6.7% higher correct results are obtained with DbE compared with LGE-CMR in the base-case model. This is expected as, although LGE-CMR is more sensitive relative to DbE (93% vs 79%, respectively), the specificity of the test is lower (45% vs 78%). LGE-CMR is dominated, that is more costly and less effective compared with DbE.

Scenario analyses as described previously in Section D.5b were performed for estimates of the diagnostic accuracy of LGE-CMR using a lower threshold of the proportion of CABGs performed (66:34, CABG:PCI). The results of additional scenario analyses varying the prevalence of myocardium viability in the range 15%–95% and ratio of CABG:PCI performed to be 39:61 are presented in Table 210, Appendix P.

Table 120 presents a summary of the results obtained for each scenario. LGE-CMR is dominated (i.e. less effective and more costly) in both scenarios 2 and 3, where the accuracy inputs for LGE-CMR and proportion of CABGs are varied.

Table 120 Incremental cost per correct diagnosis, scenario analyses

Scenario	LGE-CMR correct diagnoses	DbE correct diagnoses	Increment in correct diagnoses	Incremental cost	ICER per correct diagnosis
Scenario 1 (base-case)	71.8%	78.5%	-6.7%	\$10,608	Dominated
Scenario 2 (LGE-CMR accuracy based on lower threshold)	69.1%	78.5%	-9.4%	\$13	Dominated
Scenario 3 (CABG:PCI, 66:34)	71.9%	78.5%	-6.6%	\$8,332	Dominated

CABG = coronary bypass grafting; DbE = low-dose dobutamine echocardiography; dominated = intervention is more costly and less effective than comparator; ICER = incremental cost-effectiveness ratio; LGE-CMR = late gadolinium enhancement cardiac magnetic resonance imaging; PCI = percutaneous coronary intervention.

Cost per unnecessary revascularisation averted

Due to the invasive nature of revascularisations and high rates of associated complications, the cost per unnecessary revascularisation averted may be considered a relevant outcome. LGE-CMR is associated with more unnecessary revascularisations (due to the increase in false positive results) than DbE. Being less effective and more costly, LGE-CMR is dominated by DbE in the base-case analysis for this ICER measure.

When analyses are performed for scenarios 2 and 3, and other additional (scenario 4) and prevalence scenarios presented in Table 211, Appendix P, the results of the comparison remain unchanged. LGE-CMR is associated with increased costs and increased numbers of unnecessary revascularisations due to more false positive diagnoses compared with DbE and is, therefore, dominated in all scenarios (Table 121).

Table 121 Incremental cost per unnecessary revascularisation averted in comparison with DbE, scenario analyses

Scenario	LGE-CMR (unnecessary revascularisations averted)	DbE (unnecessary revascularisations averted)	Increment in unnecessary revascularisations averted	Incremental cost	ICER per unnecessary revascularisation averted
Scenario 1 (base-case)	19.8%	34.3%	-14.5%	\$10,608	Dominated
Scenario 2 (LGE-CMR accuracy based on a lower threshold)	29.9%	34.3%	-4.4%	29.9%	Dominated
Scenario 3 (CABG:PCI, 66:34)	19.8%	34.3%	-14.5%	19.8%	Dominated

CABG = coronary artery bypass graft; DbE = low-dose dobutamine echocardiography; Dominated = intervention is more costly and less effective than comparator; ICER = incremental cost-effectiveness ratio; LGE-CMR = late gadolinium enhancement cardiac magnetic resonance imaging; PCI = percutaneous coronary intervention

Cost per revascularisation with correct diagnosis

LGE-CMR results in an increased number of true positives compared with DbE. Therefore, a higher number of revascularisations is performed in patients with true myocardium viability in the LGE-CMR

group than DbE group. The incremental cost per correct revascularisation received was observed to be \$136,002 in the base-case analysis.

Summary results for all pre-specified scenario analyses are presented in Table 122 and additionally in Table 212, Appendix P. Being lower in sensitivity (70% vs 79%) and specificity (68% vs 78%) and higher in cost compared with DbE, LGE-CMR is dominated in the scenario 2 analysis (where LGE-CMR accuracy is based on a lower threshold of HE). The rest of the scenarios use a diagnostic accuracy of LGE-CMR based on a high cut-off of HE similar to the base-case.

Table 122 Incremental cost per revascularisation undertaken with correct diagnosis in comparison with DbE, scenario analyses

Scenario	LGE-CMR (correct revascularisation)	DbE (correct revascularisation)	Increment in (correct revascularisation)	Incremental cost	ICER per correct revascularisation received
Scenario 1 (base-case)	52.0%	44.2%	7.8%	\$10,608	\$136,002
Scenario 2 (LGE-CMR accuracy based on a lower threshold)	39.2%	44.2%	-5.0%	\$13	Dominated
Scenario 3 (CABG:PCI, 66:34)	52.1%	44.2%	7.8%	\$8,332	\$106,271

CABG = coronary artery bypass graft; DbE = low-dose dobutamine echocardiography; Dominated = intervention is more costly and less effective than comparator; ICER = incremental cost-effectiveness ratio; LGE-CMR = late gadolinium enhancement cardiac magnetic resonance imaging; PCI = percutaneous coronary intervention

D5B.2 COMPARISON OF CMR WITH SPECT

Modelled costs

Table 123 presents a summary of modelled costs for LGE-CMR and SPECT disaggregated by the costs associated with testing and the costs associated with treatment and related complications.

LGE-CMR testing is associated with an incremental cost of \$180 compared with SPECT. As can be observed from Table 123, the treatment costs (including complications) accounted for the largest cost incurred per diagnosis in each modelled arm: \$35,438 in the LGE-CMR group (97.8%) and \$29,929 in the SPECT group (98%).

Based on all costs incurred in either arm of the economic model, LGE-CMR testing compared with SPECT testing resulted in an incremental cost of \$5,689 per diagnosis.

Table 123 Modelled cost analysis, comparison of LGE-CMR with SPECT

Cost	LGE-CMR	SPECT	Incremental cost
Test (including all costs, as per Table 115)	\$788	\$608	\$180
Cost of revascularisation + OMT+ complications	\$35,438	\$29,929	\$5,509
Total	\$36,226	\$30,537	\$5,689

LGE-CMR = late gadolinium enhancement cardiac magnetic resonance imaging; OMT = optimal medical therapy; SPECT=single-photon emission computed tomography

Modelled outcomes and incremental effects

The outcomes and incremental effects for comparison of LGE-CMR and SPECT, as derived from the decision-tree analyses, are presented in Table 124.

Table 124 Base-case modelled outcome and incremental effects of LGE- CMR testing, comparison with SPECT

Outcomes	LGE-CMR	SPECT	Incremental effectiveness	Nature of effect
Total correct diagnoses:	71.8%	74.9%	-3.1%	Harm
True positives (revascularisations with correct diagnosis)	52.0%	47.6%	4.4%	Benefit
True negatives (unnecessary revascularisations averted)	19.8%	27.3%	-7.5%	Harm
Total incorrect diagnoses:	28.1%	25.1%	3.0%	Harm
False positives	24.2%	16.7%	7.5%	Harm
False negatives	3.9%	8.4%	-4.5%	Benefit
Total revascularisations performed:	76.2%	64.3%	11.9%	
Unnecessary	24.2%	16.7%	7.5%	Harm
Revascularisations missed	3.9%	8.4%	-4.5%	Benefit
Total procedure-related deaths	3.8%	3.2%	0.6%	
Correct diagnosis	2.6%	2.4%	0.2%	Harm
Incorrect diagnosis	1.2%	0.8%	0.4%	
Deaths	0.2%	0.4%	-0.2%	Harm

LGE-CMR = late gadolinium enhancement cardiac magnetic resonance imaging; SPECT=single-photon emission computed tomography

LGE-CMR detects 4.4% more true positives than SPECT, but the overall number of correct diagnoses is 3.1% lower than SPECT due to the lower specificity of the test. There is a higher number of correct revascularisations performed, but fewer revascularisations are missed or averted in the LGE-CMR group than the SPECT group. Overall, LGE-CMR testing is associated with limited benefits related to fewer revascularisations missed (due to false negative results), and a higher number of total revascularisations performed due to detection of patients with a truly viable myocardium.

Incremental cost-effectiveness

The ICERs are calculated by dividing the differences in the costs per diagnosis of LGE-CMR and SPECT by the differences in the number of outcomes of interest observed in each test. The incremental effect is considered beneficial in the intervention arm when the incremental outcome is positive for the outcomes measured as benefits, and when the incremental outcome is negative for the outcomes measured as harms, as described in Table 124. Therefore, for LGE-CMR to be beneficial in comparison with SPECT, the incremental outcomes of correct diagnosis, and revascularisations undertaken with correct diagnosis, should be positive; whereas the incremental outcomes of unnecessary revascularisations averted should be negative.

The incremental costs per correct diagnosis, per unnecessary revascularisation averted, and per revascularisation undertaken with correct diagnosis are derived as discussed above. The incremental cost per revascularisation undertaken with correct diagnosis was observed to be \$129,301 in the base-case analysis. However, LGE-CMR was dominated by SPECT for all other outcomes. Table 125 presents summary of the ICERs for the base-case analyses. Results for each outcome measure assessed are discussed further in detail.

Table 125 ICERs for base-case analyses, comparison with SPECT

Clinically relevant outcomes	Incremental outcomes (%)	ICER (\$ / outcome)
------------------------------	--------------------------	---------------------

Clinically relevant outcomes	Incremental outcomes (%)	ICER (\$ / outcome)
Incremental cost		\$5,689
Correct diagnosis	-3.1%	Dominated
Unnecessary revascularisations averted	-7.5%	Dominated
Revascularisations undertaken with correct diagnosis	4.4%	\$129,301

Dominated = intervention is more costly and less effective than comparator; ICER = incremental cost-effectiveness ratio; SPECT=single-photon emission computed tomography

Cost per correct diagnosis

When the overall number of correct diagnoses (true positives plus true negatives) is accounted for, SPECT testing is associated with 3.1% higher correct diagnoses compared with LGE-CMR in the base-case model. This is expected as, although LGE-CMR is more sensitive relative to SPECT (93% vs 85%, respectively), the specificity of the test is lower (45% vs 62%). LGE-CMR is dominated, that is more costly and less effective, compared with SPECT.

Scenario analyses as described previously in Section D.5b were performed for the estimates of diagnostic accuracy of LGE-CMR using a lower threshold (scenario 2), a ratio of CABG:PCI (scenario 3 and 4) and varying the prevalence of myocardium viability in the range 15%–95%. Table 126 presents a summary of results obtained for scenario 1 to 3. Results for additional scenario analyses are presented in Table 213, Appendix P.

LGE-CMR is dominated (i.e. less effective and more costly) by SPECT in scenario 3 (CABG:PCI, 66:34). However, in scenario 1 where the accuracy of LGE-CMR is based on a low cut-off (sensitivity: 70% vs 85%; and specificity: 68% vs. 62% for LGE-CMR vs SPECT), LGE-CMR appears to be less effective and less costly (south-west quadrant of the cost-effectiveness plane).

Table 126 Incremental cost per correct diagnosis, scenario analyses

Scenario	LGE-CMR correct diagnoses	SPECT correct diagnoses	Increment in correct diagnoses	Incremental cost	ICER per correct diagnosis
Scenario 1 (base-case)	71.8%	74.9%	-3.1%	\$5,689	Dominated
Scenario 2 (LGE-CMR accuracy based on a lower threshold)	69.1%	74.9%	-5.8%	-\$4,906	\$84,589 (SW-Q)
Scenario 3 (CABG:PCI, 66:34)	71.9%	74.9%	-3.0%	\$4,472	Dominated

CABG = coronary bypass grafting; Dominated = intervention is more costly and less effective than comparator; ICER = incremental cost-effectiveness ratio; LGE-CMR = late gadolinium enhancement cardiac magnetic resonance imaging; PCI = percutaneous coronary intervention; SPECT = single-photon emission computed tomography; SW-Q = south-west quadrant, intervention is less costly and less effective than comparator

Cost per unnecessary revascularisation averted

LGE-CMR is associated with increased costs and an increase in the number of unnecessary revascularisations due to more false positive diagnoses compared with SPECT. Being less effective and more costly, LGE-CMR is dominated by SPECT in the base-case analysis for this ICER measure.

When additional scenario analyses are conducted (Table 127), the results of the comparison remain unchanged (i.e. LGE-CMR is dominated by SPECT) except in scenario 2 (where LGE-CMR accuracy inputs are based on a low cut-off), where LGE-CMR is dominant (i.e. more effective and less costly than SPECT). This is primarily because, with the low cut-off, LGE-CMR has better specificity than

SPECT (68% vs 62%) and thus fewer false positive results. The conclusions of cost-effectiveness do not change in other additional scenario analyses, and results are presented in Table 214, Appendix P.

Table 127 Incremental cost per unnecessary revascularisation in comparison with SPECT, scenario analyses

Scenario	LGE-CMR (unnecessary revascularisations averted)	DbE (unnecessary revascularisations averted)	Increment in (unnecessary revascularisations averted)	Incremental cost	ICER per unnecessary revascularisation averted
Scenario 1 (base-case)	19.8%	27.3%	-7.5%	\$5,689	Dominated
Scenario 2 (LGE-CMR accuracy based on a lower threshold)	29.9%	27.3%	2.6%	-\$4,906	Dominant
Scenario 3 (CABG:PCI, 66:34)	19.8%	27.3%	-7.5%	\$4,472	Dominated

CABG = coronary bypass grafting; DbE = low-dose dobutamine echocardiography; Dominant = intervention is less costly and more effective than the comparator (i.e. south-east quadrant); Dominated = intervention is more costly and less effective than comparator; ICER = incremental cost-effectiveness ratio; LGE-CMR = late gadolinium enhancement cardiac magnetic resonance imaging; PCI = percutaneous coronary intervention; SPECT=single-photon emission computed tomography; unnec revasc = unnecessary revascularisations

Cost per additional correct revascularisation received

LGE-CMR results in a small increase (4.4%) in the number of true positives compared with SPECT. Therefore, a higher number of revascularisations is performed in patients with correct diagnoses of myocardium viability in the LGE-CMR group than in the SPECT group. The incremental cost per correct revascularisation received was observed to be \$129,301 in the base-case analysis (Table 125).

In the scenario analyses LGE-CMR appears to be less effective and less costly when the diagnostic accuracy inputs used are based on a low cut-off (scenario 2), but remain more costly and more effective compared with SPECT for all other scenarios, where the proportion of CABG or prevalence is changed in the model (Table 128 and Table 215, Appendix P). This indicates that the comparison results are sensitive to the diagnostic accuracy of the tests used.

Table 128 Incremental cost per revascularisation undertaken with correct diagnosis in comparison with SPECT, scenario analyses

Scenario	LGE-CMR (revascularisation undertaken with correct diagnosis)	SPECT (revascularisation undertaken with correct diagnosis)	Increment in (revascularisation undertaken with correct diagnosis)	Incremental cost	ICER per revascularisation undertaken with correct diagnosis
Scenario 1 (base-case)	52.0%	47.6%	4.4%	\$5,689	\$129,301
Scenario 2 (LGE-CMR accuracy based on a lower threshold)	39.2%	47.6%	-8.4%	-\$4,906	\$58,406 (SW-Q)
Scenario 3 (CABG:PCI, 66:34)	52.1%	47.6%	4.5%	\$4,472	\$99,813

CABG = coronary bypass grafting; ICER = incremental cost-effectiveness ratio; LGE-CMR = late gadolinium enhancement cardiac magnetic resonance imaging; PCI = percutaneous coronary intervention; SPECT = single-photon emission computed tomography; SW-Q=south-west quadrant, intervention is less costly and less effective than comparator

D5B.3 SUMMARY OF THE RESULTS

Table 129 presents the analyses of additional cost, benefits and harms per 100 diagnoses in the proposed population obtained with LGE-CMR compared with DbE and SPECT (base-case model):

Table 129 Analyses of associated benefits and harms per 100 diagnoses with LGE-CMR testing, in comparison with DbE and SPECT

LGE-CMR versus DbE (per 100 diagnoses)	LGE-CMR versus SPECT (per 100 diagnoses)
Incremental cost \$1,060,813	\$586,926
Benefits	
7.8 additional revascularisations received after correct diagnosis	4.4 additional revascularisations received after correct diagnosis
Harms	
6.7 additional incorrect diagnoses	3.1 additional incorrect diagnoses
14.5 additional inappropriate revascularisations received (increased false positives)	7.5 additional inappropriate revascularisations received (increased false positives)

DbE = low-dose dobutamine echocardiography; LGE-CMR = late gadolinium enhancement cardiac magnetic resonance imaging; SPECT = single-photon emission computed tomography

In summary, LGE-CMR testing in this population results in very limited cost-effectiveness due to the lower overall diagnostic accuracy compared with DbE and SPECT.

D6B SENSITIVITY ANALYSES

Univariate sensitivity analyses on all important variables were conducted using the 95% CIs of point estimates or the range specified in Section D.4b. The diagnostic accuracy of the test will impact the differences in health outcomes of interest and are therefore tested, along with the costs of the tests.

D6B.1 COMPARISON OF LGE-CMR WITH DbE

The impact of varying costs of DbE and the mortality rate associated with revascularisation were negligible for all outcomes and, thus, not presented here. Variations in ICER with changes in other parameters tested, for all health outcomes assessed, are shown in the tornado diagrams comparing LGE-CMR with DbE in Figure 41.

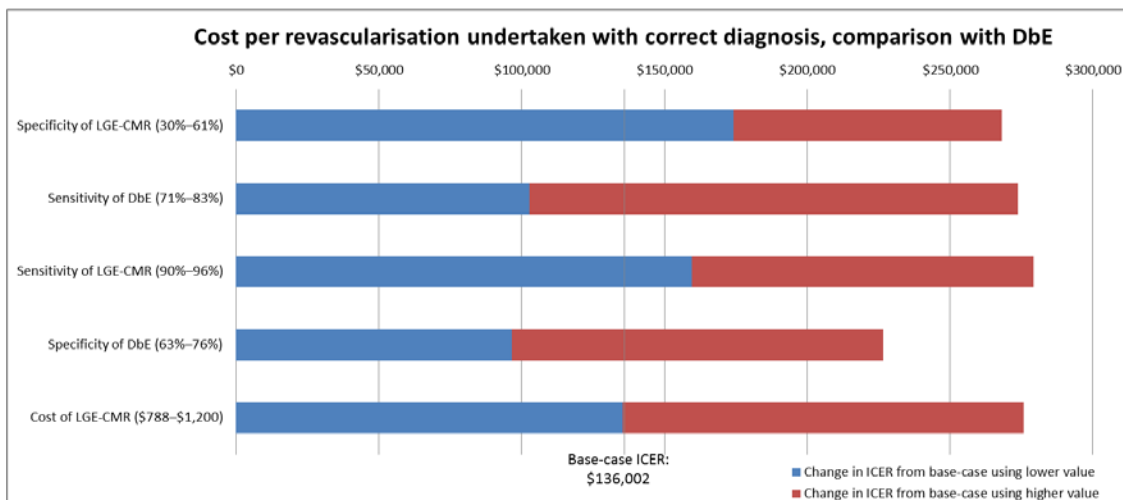
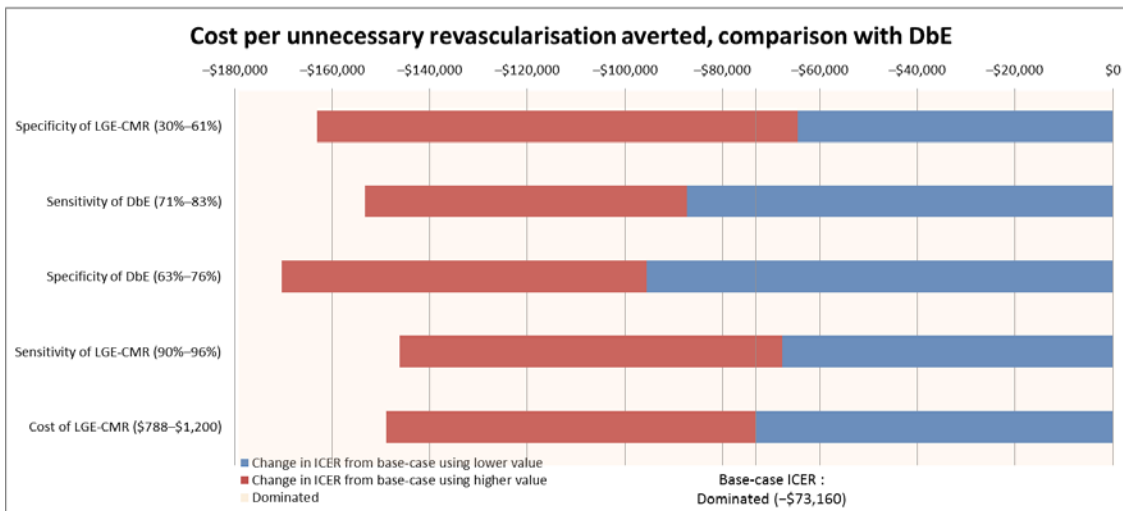
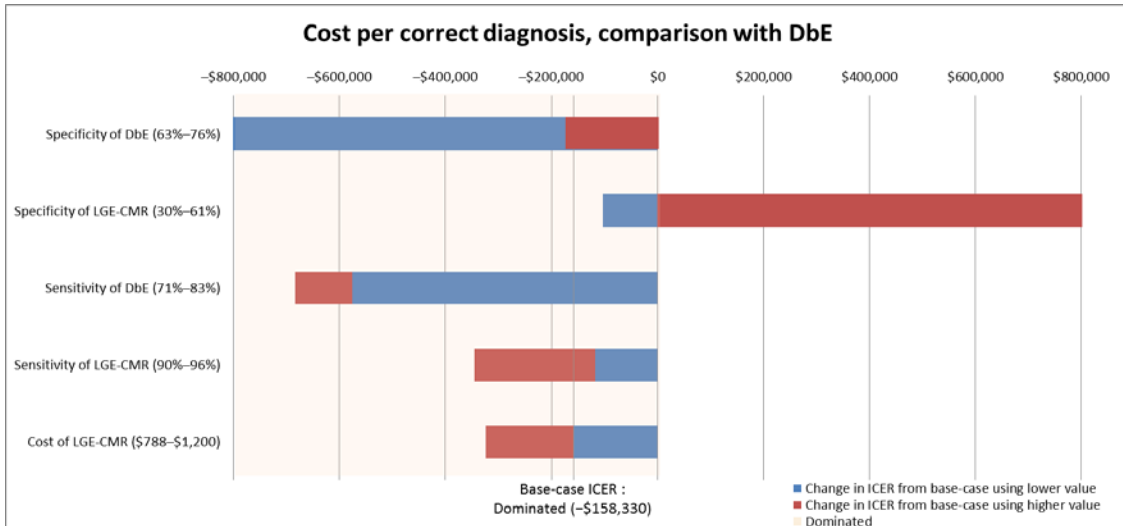


Figure 41 Tornado sensitivity analyses, comparison with DbE

DbE = low-dose dobutamine echocardiography; ICER = incremental cost-effectiveness ratio; LGE-CMR = late gadolinium enhancement cardiac magnetic resonance imaging

Summary of results of sensitivity analyses

Cost per correct diagnosis: LGE-CMR is dominated by DbE in all one-way sensitivity analyses, except where the specificity of LGE-CMR is increased to 61%.

Cost per unnecessary revascularisation averted: LGE-CMR results in a higher number of unnecessary revascularisations due to a higher number of false positive test results. The direction of this outcome remained unchanged in all sensitivity analyses.

Cost per revascularisation undertaken with correct diagnosis: Due to the higher sensitivity of LGE-CMR compared with DbE, a higher number of correct revascularisations is recorded in the tested population. Reducing the sensitivity or specificity decreases the value of ICERs obtained; and increasing the specificity of LGE-CMR decreases the value of ICER. However, the conclusions of cost-effectiveness for the outcome do not change.

D6B.2 COMPARISON OF CMR WITH SPECT

The impact of varying the costs of SPECT and the mortality rate associated with revascularisation were negligible and, thus, not presented here. Variations in ICER with changes in other parameters tested, for all health outcomes assessed, are shown in the tornado diagrams comparing LGE-CMR with SPECT in Figure 42.

Summary of results of the sensitivity analyses

Cost per correct diagnosis: When comparing LGE-CMR with SPECT, the ICERs are affected when the specificity or sensitivity of SPECT is decreased or when the specificity of LGE-CMR is increased. In all other scenarios SPECT dominates LGE-CMR.

Cost per unnecessary revascularisation averted: The conclusions of cost-effectiveness for the outcome do not change in all sensitivity analyses; that is, LGE-CMR is dominated by SPECT irrespective of the variations in tested parameters.

Cost per revascularisation undertaken with correct diagnosis: The conclusions of cost-effectiveness for the outcome do not change with the variations in parameter value, but reducing the sensitivity or specificity, or increasing the cost of the comparator, decreases the value of ICERs obtained; and an increase in the specificity of LGE-CMR decreases the value of ICER.

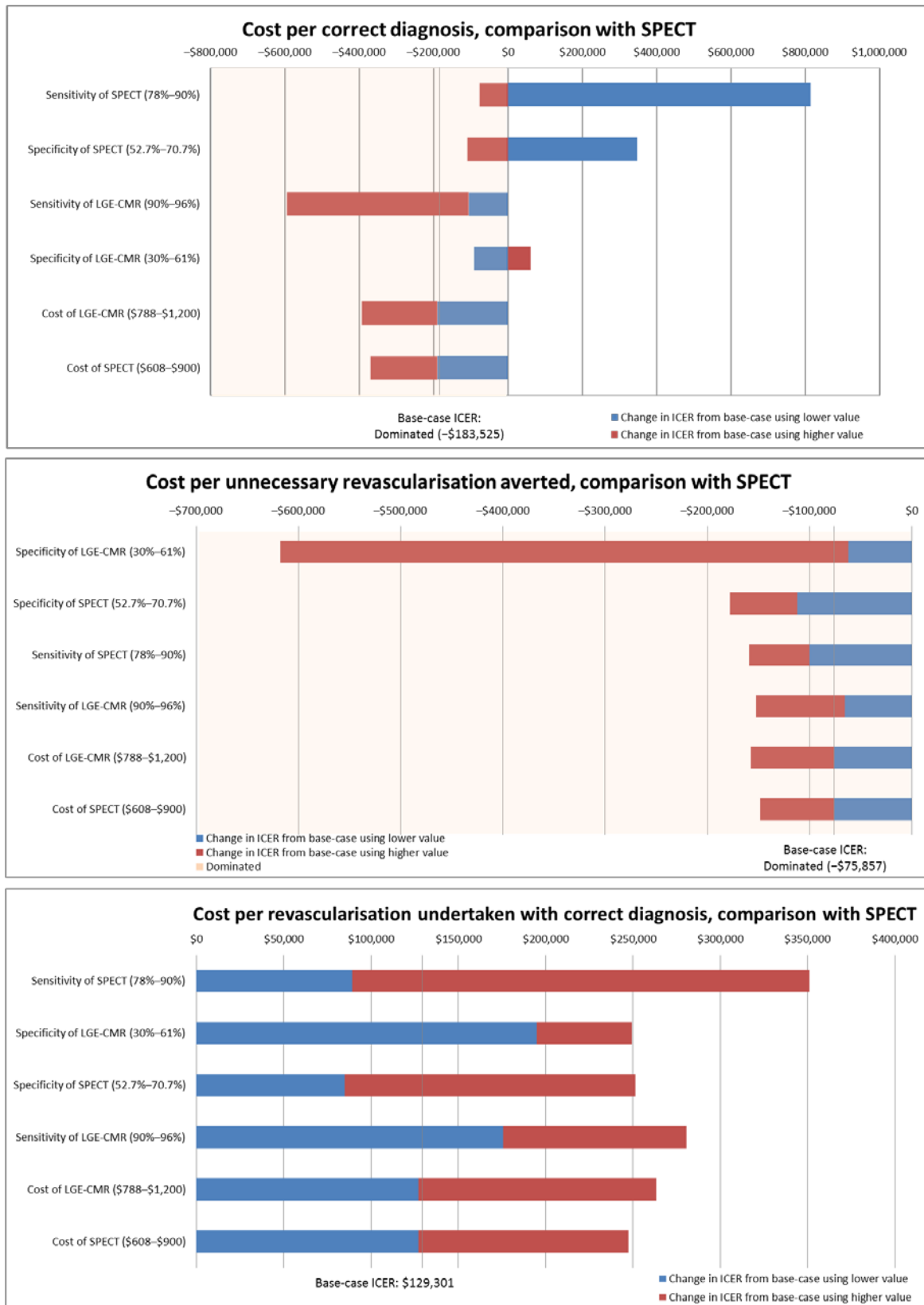


Figure 42 Tornado sensitivity analyses, comparison with SPECT

ICER = incremental cost-effectiveness ratio; LGE-CMR = late gadolinium enhancement cardiac magnetic resonance imaging; SPECT= single-photon emission computed tomography

SECTION EB FINANCIAL IMPLICATIONS

A market-based approach has been used to estimate the utilisation and financial estimates of the introduction of LGE-CMR testing for myocardial viability assessment.

E1B JUSTIFICATION OF THE SELECTION OF SOURCES OF DATA

The sources for data used in the financial analysis are presented in Table 130.

Table 130 Data sources used in the financial analysis

Data	Source
Number of myocardium viability scans performed in Australia	Assumed 50% of the total services for MBS items 55117 and 61303
Cost of CMR to the MBS	85% of the proposed Schedule fee, assuming that tests are performed in an outpatient setting, consistent with the setting for the majority of comparator tests and for current CMR services (MBS data for items 55117, 61303, 63385, 63388, 63391, 63401 and 63404, 2009–10 to 2014–15)
Patient co-payment for CMR service	MBS data for current CMR services (MBS items 63385, 63388, 63391, 63401 and 63404) for the weighted average contribution per service for out-of-hospital billed patients, 2009–10 to 2014–15
LGE-CMR uptake rate	Assumed 50%, based on the clinical expert advice ^a
Cost of current tests to the MBS	MBS data for items 55117 and 61303 for the weighted average MBS benefit paid per service, 2009–10 to 2014–15
Patient co-payment for current tests	MBS data for items 55117 and 61303 for the weighted average patient contribution per service (across all patients, and so intrinsic in this data are the bulk billing rates for the tests), 2009–10 to 2014–15
Market share of current testing	Assumed weight of all tests based on relative use of testing (for all indications), 2014–15

^a Based on a personal communication with HESP member on 9 December 2015

CMR = cardiac magnetic resonance imaging; LGE-CMR = late gadolinium enhancement cardiac magnetic resonance imaging; MBS = Medicare Benefits Schedule

E2B USE AND COSTS OF CMR FOR ASSESSMENT OF MYOCARDIUM VIABILITY

Insufficient epidemiological data was identified to estimate the number of Australian patients with an existing diagnosis of significant CAD and a history of IHD with impaired LV function who are being considered for revascularisation. Therefore, a market-based approach was employed to estimate the potential number of services eligible for proposed LGE-CMR for myocardial viability assessment. While comparator testing is currently funded by the MBS, comparator item numbers are not restricted to the eligible population. The estimated number of tests is therefore based on an assumption that half of these tests are performed for assessing viability, but this approach is also fairly uncertain.

PROJECTION OF THE NUMBER OF VIABILITY TESTS PERFORMED, 2016–17 TO 2020–21

To project the number of myocardial viability scans performed during 2016–17 to 2020–21, MBS item statistics for items 55117 and 61303 were extracted for the years 2010–11 to 2014–15 (Table 131).

Table 131 Number of comparator services performed, 2010–11 to 2014–15

Test	2010–11	2011–12	2012–13	2013–14	2014–15
DbE (MBS item 55117)	6,498	7,281	7,907	8,352	8,793

Test	2010–11	2011–12	2012–13	2013–14	2014–15
SPECT (MBS item 61303)	4,317	5,582	5,789	6,561	6,630
Total	10,815	12,863	13,696	14,913	15,423

DbE = low-dose dobutamine echocardiography; MBS = Medicare Benefits Schedule; SPECT= single-photon emission computed tomography

An average increase of 7.4% per year is observed in the number of services utilised for the comparators in the past 5 years. Since comparator testing is not restricted to the eligible population, it is assumed in the financial analyses that only half (50%) of these services are performed for myocardial viability assessment. Although arbitrary, this estimate falls in the range specified in the MSAC report (Ref 35f) for PET scanning for myocardial viability assessment in 2010, in which, based on a clinical expert opinion, an estimate of 3,000–5,000 scans a year for myocardial viability testing in Australia was suggested. Based on these assumptions, the projected number of myocardial viability scans performed in 2016–17 to 2020–21 is presented in Table 132.

Uptake of CMR

The results of clinical and economic evaluations suggested that LGE-CMR testing has limited benefit compared with either DbE or SPECT in the tested population. Also, feedback to MSAC protocol 1237¹⁴ suggested that there would likely be limited availability of access to CMR for time-intensive cardiac tests due to high demand in other specialties. Based on these results and feedback, it is likely that LGE-CMR testing would have limited substitution for the current comparators, DbE and SPECT, in the target population, and the uptake may be small. However, feedback from HESP members¹⁵ suggested that if LGE-CMR is listed on the MBS, the uptake may be relatively strong (around 50%) provided that there is sufficient technical or clinical expertise available to provide the service. Therefore, in the base-case analysis, an uptake estimate of 50% is assumed, with lower estimates of 10%–30% tested in sensitivity analyses.

The estimated number of services eligible and utilised with the introduction of CMR for the assessment of myocardium viability is presented in Table 132.

Table 132 Estimation of the number of LGE-CMR tests performed

	2016–17	2017–18	2018–19	2019–20	2020–21
Projected number of scans for myocardial viability testing	8,888	9,542	10,244	10,997	11,806
Uptake of LGE-CMR	50%	50%	50%	50%	50%
Total no. LGE-CMR tests	4,444	4,771	5,122	5,499	5,903

LGE-CMR = late gadolinium enhancement cardiac magnetic resonance imaging

Estimated cost of LGE-CMR testing

The proposed item fee for CMR is \$700. As the majority of comparator tests and current CMR services are conducted in the out-of-hospital setting (MBS data for number of tests conducted in hospital and out of hospital for items 55117, 61303, 63385, 63388, 63391, 63401 and 63404, 2009–10 to 2014–15), the estimated benefit paid by the MBS is assumed to be 85%.

¹⁴ MSAC Protocol 1237. Final protocol to guide the assessment of cardiac magnetic resonance imaging of patients with known or suspected coronary artery disease, December 2014.

¹⁵ Personal communication with the HESP members, received on 9 December 2015.

As described in Section E.2b, the proportion of patients bulk billed (67.3%) and the patient contribution (\$213.36;(including the gap and out-of-pocket costs) are assumed to be based on data for current CMR services (MBS items 63385, 63388, 63391, 63401 and 63404). The estimated patient contribution per test is \$69.74. Both estimates are tested in sensitivity analyses, assuming the highest and lowest bulk billing rates for the comparator tests, and that the patient contribution should \$1,100 for the service (based on RANZCR protocol feedback, see Section A10) (i.e. patient contribution = \$505).

The total cost of LGE-CMR testing is reported in Table 133 disaggregated by payer (i.e. the MBS and the patient). The average total cost of CMR testing per year is estimated to be \$2.9–\$3.9 million.

Table 133 Total cost of LGE-CMR testing for the assessment of myocardial viability

	2016–17	2017–18	2018–19	2019–20	2020–21
Total number LGE-CMR tests (Table 132)	4,444	4,771	5,122	5,499	5,903
Cost per service to the MBS	\$595.00	\$595.00	\$595.00	\$595.00	\$595.00
Cost per service to the patient	\$69.74	\$69.74	\$69.74	\$69.74	\$69.74
Cost of LGE-CMR services to the MBS	\$2,644,130	\$2,838,646	\$3,047,472	\$3,271,660	\$3,512,341
Cost of LGE-CMR services to patients	\$309,907	\$332,705	\$357,180	\$383,457	\$411,666
Total cost of LGE-CMR	\$2,954,036	\$3,171,351	\$3,404,652	\$3,655,117	\$3,924,006

LGE-CMR = late gadolinium enhancement cardiac magnetic resonance imaging; MBS = Medicare Benefits Schedule

E3B CHANGES IN USE AND COST OF OTHER MEDICAL SERVICES

ESTIMATED MARKET SHARE OF CURRENT TESTING

No data was found to estimate the relative use of each of the comparator tests in the assessment of myocardial viability. In the base-case financial analysis, the relative usage of the comparators is based on the weighted proportion of MBS item statistics for items 55117 and 61303 in 2014–15. The number of services for each of the tests reported in 2014–15, and their relative weight, is presented in Table 134.

Table 134 Comparator services, 2014–15

Test	Source	Services	Weight
DbE	MBS item 55117, 2014–15 services	8,793	57%
SPECT	MBS item 61303, 2014–15 services	6,630	43%

DbE = low-dose dobutamine echocardiography; MBS = Medicare Benefits Schedule; SPECT = single-photon emission computed tomography

Feedback was also sought from the HESP members regarding the number of viability scans and their relative usage in the Australian population; however, there was no consensus of opinion¹⁶, and two ratios for relative usage were therefore tested in sensitivity analyses (Section E.6b)—10:90 and 90:10 for DbE:SPECT.

¹⁶ According to one HESP member, it is difficult to estimate the relative usage of the comparator tests as the practice varies widely, and some of the tests currently being performed for viability are not covered under MBS; and also less than 5% of the SPECT or other nuclear cardiac scans are performed in Australia. In contrast, other HESP members suggested that relatively fewer DbEs (around 10%) are performed for viability assessment than SPECT. (Personal communication with the HESP members, received on 9 December 2015.)

It is assumed that the relative use of the tests across all indications applies to the tests offset by the introduction of LGE-CMR. The estimated numbers of each type of test performed that are offset by the introduction of LGE-CMR for the assessment of myocardial viability are presented in Table 135.

Table 135 Estimation of number of comparator tests offset

	2016-17	2017-18	2018-19	2019-20	2020-21
Number tests offset	4,444	4,771	5,122	5,499	5,903
Market share					
DbE	57%	57%	57%	57%	57%
SPECT	43%	43%	43%	43%	43%
Number of each test offset					
DbE	2,533	2,719	2,919	3,134	3,365
SPECT	1,911	2,051	2,202	2,364	2,538

DbE = low-dose dobutamine echocardiography; SPECT=single-photon emission computed tomography.

ESTIMATED COSTS OFFSET

The estimated costs per service to the MBS and to the patient used in the financial model are presented in Table 136. These are based on the average MBS benefit and patient contribution paid per service, 2009-10 to 2014-15 (weighted by number of tests performed each year) for each of the comparator tests (items 55117 for pharmacological stress Echo and 61303 for SPECT).

Table 136 Estimated cost per comparator service

	DbE ^a	SPECT
Average cost per service to the MBS	\$360.05	\$524.52
Average cost per service to the patient	\$61.55	\$11.52

^a Cost per DbE service includes costs per service of exercise electrocardiography, MBS item 11712.

DbE = low-dose dobutamine echocardiography; MBS = Medicare Benefits Schedule; SPECT = single-photon emission computed tomography

Therefore, the costs offset with the introduction of LGE-CMR for the assessment of myocardial viability is presented in Table 137.

Table 137 Total cost offsets by LGE-CMR testing for the assessment of myocardial viability

	2016-17	2017-18	2018-19	2019-20	2020-21
<i>Number tests offset</i>					
DbE	2,533	2,719	2,919	3,134	3,365
SPECT	1,911	2,051	2,202	2,364	2,538
<i>MBS cost offset</i>					
DbE	\$912,025	\$979,118	\$1,051,147	\$1,128,475	\$1,211,492
SPECT	\$1,002,304	\$1,076,039	\$1,155,198	\$1,240,180	\$1,331,415
Total offsets to the MBS	\$1,914,329	\$2,055,157	\$2,206,345	\$2,368,656	\$2,542,906
<i>Patient cost offset</i>					
DbE	\$155,919	\$167,389	\$179,703	\$192,923	\$207,115
SPECT	\$22,016	\$23,636	\$25,374	\$27,241	\$29,245
Total offsets to patients	\$177,935	\$191,025	\$205,078	\$220,164	\$236,361

	2016-17	2017-18	2018-19	2019-20	2020-21
Total cost offsets	\$2,092,264	\$2,246,182	\$2,411,423	\$2,588,820	\$2,779,267

DbE = low-dose dobutamine echocardiography; LGE-CMR = late gadolinium enhancement cardiac magnetic resonance imaging; MBS=Medicare Benefits Schedule; SPECT=single-photon emission computed tomography.

E4B FINANCIAL IMPLICATIONS FOR THE MBS

The financial implications to the MBS resulting from the proposed listing of LGE-CMR for the assessment of myocardial viability are summarised in Table 138.

Table 138 Total costs to the MBS associated with LGE-CMR for the assessment of myocardial viability

	2016-17	2017-18	2018-19	2019-20	2020-21
LGE-CMR					
Number of services	4,444	4,771	5,122	5,499	5,903
Cost to the MBS	\$2,644,130	\$2,838,646	\$3,047,472	\$3,271,660	\$3,512,341
Tests offset					
Number of services offset	4,444	4,771	5,122	5,499	5,903
Costs offset	\$1,914,329	\$2,055,157	\$2,206,345	\$2,368,656	\$2,542,906
Net cost to the MBS	\$729,801	\$783,489	\$841,127	\$903,004	\$969,434

LGE-CMR = late gadolinium enhancement cardiac magnetic resonance imaging; MBS = Medicare Benefits Schedule

E5B FINANCIAL IMPLICATIONS FOR GOVERNMENT HEALTH BUDGETS

No financial implications to other health budgets are anticipated with the listing of LGE-CMR for the assessment of myocardial viability; however, the implications to patients are reported in Table 139.

Table 139 Total costs to patients associated with LGE-CMR testing for the assessment of myocardial viability

	2016-17	2017-18	2018-19	2019-20	2020-21
LGE-CMR					
Number of services	4,444	4,771	5,122	5,499	5,903
Cost to patients	\$309,907	\$332,705	\$357,180	\$383,457	\$411,666
Tests offset					
Number of services offset	4,444	4,771	5,122	5,499	5,903
Costs offset	\$177,935	\$191,025	\$205,078	\$220,164	\$236,361
Net cost to patients	\$131,972	\$141,680	\$152,103	\$163,292	\$175,305

LGE-CMR = late gadolinium enhancement cardiac magnetic resonance imaging; MBS = Medicare Benefits Schedule.

E6B IDENTIFICATION, ESTIMATION AND REDUCTION OF UNCERTAINTY

Sensitivity analyses around the main inputs to the financial model are presented in Table 140. Results of additional sensitivity analyses are provided in Table 216, Appendix Q.

Table 140 Sensitivity analysis of financial implications of listing LGE-CMR for the assessment of myocardial viability

	2016-17	2017-18	2018-19	2019-20	2020-21
Base-case					
Net cost of LGE-CMR to the MBS	\$729,801	\$783,489	\$841,127	\$903,004	\$969,434
Net cost of LGE-CMR to patients	\$131,972	\$141,680	\$152,103	\$163,292	\$175,305

	2016–17	2017–18	2018–19	2019–20	2020–21
Base-case					
Net cost of LGE-CMR to the MBS	\$729,801	\$783,489	\$841,127	\$903,004	\$969,434
Net cost of LGE-CMR to patients	\$131,972	\$141,680	\$152,103	\$163,292	\$175,305
<i>LGE-CMR accessibility and uptake: 20% (base-case: 50%)</i>					
Net cost of LGE-CMR to the MBS	\$291,920	\$313,396	\$336,451	\$361,202	\$387,774
Net cost of LGE-CMR to patients	\$52,789	\$56,672	\$60,841	\$65,317	\$70,122
<i>LGE-CMR accessibility and uptake: 30% (base-case: 10%)</i>					
Net cost of LGE-CMR to the MBS	\$437,881	\$470,093	\$504,676	\$541,803	\$581,661
Net cost of LGE-CMR to patients	\$79,183	\$85,008	\$91,262	\$97,975	\$105,183
<i>Current DbE and SPECT relative usage 10:90 (base-case: 57:43)</i>					
Net cost of LGE-CMR to the MBS	\$386,280	\$414,697	\$445,204	\$477,956	\$513,117
Net cost of LGE-CMR to patients	\$236,472	\$253,868	\$272,544	\$292,594	\$314,119
<i>Current DbE and SPECT relative usage 90:10 (base-case: 57:43)</i>					
Net cost of LGE-CMR to the MBS	\$970,997	\$1,042,428	\$1,119,115	\$1,201,443	\$1,289,827
Net cost of LGE-CMR to patients	\$58,599	\$62,910	\$67,538	\$72,506	\$77,840

DbE = low-dose dobutamine echocardiography; LGE-CMR = late gadolinium enhancement cardiac magnetic resonance imaging; MBS = Medicare Benefits Schedule; SPECT = single-photon emission computed tomography

SECTION F OTHER RELEVANT CONSIDERATIONS

Although there are no Australian guidelines for the use of imaging in the diagnosis of CAD, there are international guidelines that are relevant. The recommendations of these guidelines highlight the uncertainty of using CMR (and other imaging modalities) in the diagnosis of CAD.

The UK National Institute for Health and Care Excellence (NICE) has produced evidence-based guidelines for patients presenting with acute chest pain, and makes recommendations about non-invasive functional imaging (including the comparators) in certain patient groups (National Institute of Health and Care Excellence 2010). The recommendations state that non-invasive imaging should only be undertaken in patients with chest pain:

- in whom stable angina cannot be diagnosed or excluded after clinical assessment and resting 12-lead ECG, and who have an estimated likelihood of CAD of 61%–90% and in whom coronary revascularisation is not being considered, is not clinically appropriate or not acceptable to the patient; or
- in whom stable angina cannot be diagnosed or excluded after clinical assessment alone and who have an estimated likelihood of CAD of 30%–60%.

The guidelines do not distinguish between different types of non-invasive imaging, focusing on the need for imaging only where there is genuine uncertainty about a CAD diagnosis after clinical assessment.

Extensive evidence-based American guidelines produced in 2012 by a group including the American College of Physicians, American College of Cardiology Foundation and the American Heart Association concluded that ‘data were still emerging’ for the use of a test in diagnosing CAD, and they also noted that the test was costly, with limited availability (Qaseem et al. 2012). The recommendation was that non-invasive imaging with pharmacologic stress should not be used in patients who have an interpretable ECG, at least moderate physical functioning or no disabling comorbidity.

The American College of Radiology also produced guidelines, the ACR Appropriateness Criteria® for chest pain suggestive of acute coronary syndrome, in 2014. These evidence-based guidelines concluded that there is ‘limited experience in the clinical setting and lack of availability’ (Mammen et al. 2014).

Appendix A Clinical Experts and Assessment Group

HEALTH EXPERT STANDING PANEL (HESP)

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Expertise or affiliation

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Noted conflicts of interest

There were no conflicts of interest.

APPENDIX B SEARCH STRATEGIES

BIBLIOGRAPHIC DATABASES

Electronic database	Period covered
Cochrane Library – including, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, the Cochrane Central Register of Controlled Trials (CENTRAL), the Health Technology Assessment Database, the NHS Economic Evaluation Database	1990–6/2014
Current Contents	1990–6/2014
Embase	1990–6/2014
PubMed	1990–6/2014
Web of Science – including Science Citation Index Expanded and Conference Proceedings Citation Index- Science	1990–6/2014
Cinahl	1990–6/2014
Econlit	1990–6/2014
Scopus	1990–6/2014

ADDITIONAL SOURCES OF LITERATURE (INCLUDING WEBSITES)

Source	Location
Internet	
NHMRC- National Health and Medical Research Council (Australia)	www.nhmrc.gov.au/
US Department of Health and Human Services (reports and publications)	www.hhs.gov/
New York Academy of Medicine Grey Literature Report	www.greylit.org/
Trip database	www.tripdatabase.com
Current Controlled Trials metaRegister	http://controlled-trials.com/
National Library of Medicine Health Services/Technology Assessment Text	http://text.nlm.nih.gov/
U.K. National Research Register	www.nihr.ac.uk/Pages/NRRArchive.aspx
Google Scholar	http://scholar.google.com/
Australian and New Zealand Clinical Trials Registry	www.anzctr.org.au
World Health Organization	www.who.int/en/
Pearling	
All included articles will have their reference lists searched for additional relevant source material	

HTA WEBSITES

INTERNATIONAL

International Network of Agencies for Health Technology Assessment www.inahta.org/

AUSTRALIA

Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP-S) www.surgeons.org/for-health-professionals/audits-and-surgical-research/asernip-s/

Centre for Clinical Effectiveness, Monash University www.monashhealth.org/page/Health_Professionals/CCE/

Centre for Health Economics, Monash University www.buseco.monash.edu.au/centres/che/

AUSTRIA

Institute of Technology Assessment / HTA unit www.oeaw.ac.at/ita

CANADA

Institut National d'Excellence en Santé et en Services Sociaux (INESSS) www.inesss.qc.ca/en/publications/publications/

Alberta Heritage Foundation for Medical Research (AHFMR) www.ahfmr.ab.ca/publications.html

Alberta Institute of Health Economics www.ihe.ca/

The Canadian Agency for Drugs And Technologies in Health (CADTH) www.cadth.ca/index.php/en/

The Canadian Association for Health Services and Policy Research (CAHSPR) www.cahspr.ca/

Centre for Health Economics and Policy Analysis (CHEPA), McMaster University www.chepa.org

Health Utilities Index (HUI), McMaster University www.hiip.mcmaster.ca/hug/index.htm

Centre for Health Services and Policy Research (CHSPR), University of British Columbia

Institute for Clinical and Evaluative Studies (ICES) www.ices.on.ca

Saskatchewan Health Quality Council (Canada) www.hqc.sk.ca

DENMARK

Danish National Institute Of Public Health www.si-folkesundhed.dk/?lang=en

FINLAND

Finnish National Institute for Health and Welfare www.thl.fi/en/web/thlfi-en/

FRANCE

L'Agence Nationale d'Accréditation et d'Evaluation en Santé (ANAES) www.anaes.fr/

GERMANY

German Institute for Medical Documentation and Information (DIMDI) / HTA www.dimdi.de/static/en/index.html

Institute for Quality and Efficiency in Health Care (IQWiG) www.iqwig.de

THE NETHERLANDS

Health Council of the Netherlands Gezondheidsraad www.gezondheidsraad.nl/en/

Institute for Medical Technology Assessment www.imta.nl/

(Netherlands)

NEW ZEALAND

www.otago.ac.nz/christchurch/research/nzhta/

New Zealand Health Technology Assessment (NZHTA)

NORWAY

www.kunnskapssenteret.no

Norwegian Knowledge Centre for the Health Services

SPAIN

Agencia de Evaluación de Tecnologías Sanitarias, Instituto de Salud "Carlos III"/Health Technology Assessment Agency (AETS)

www.isciii.es/

Andalusian Agency for Health Technology Assessment (Spain)

www.juntadeandalucia.es/

Catalan Agency for Health Technology Assessment (CAHTA)

www.gencat.cat

SWEDEN

Center for Medical Technology Assessment, Linköping University

www.cmt.liu.se/?l=en&sc=true

Swedish Council on Technology Assessment in Health Care (SBU)

www.sbu.se/en/

SWITZERLAND

Swiss Network on Health Technology Assessment (SNHTA)

www.snhta.ch/

UNITED KINGDOM

National institute for Health Research, Health Technology Assessment Programme

www.hta.ac.uk/

NHS Quality Improvement Scotland

www.nhshealthquality.org/

National Institute for Clinical Excellence (NICE)

www.nice.org.uk/

The European International Network on New and Changing Health Technologies

www.euroscan.bham.ac.uk/

University of York NHS Centre for Reviews and Dissemination (NHS CRD)

www.york.ac.uk/inst/crd/

UNITED STATES

Agency for Healthcare Research and Quality (AHRQ)

www.ahrq.gov/clinic/techix.htm

Harvard School of Public Health

www.hsph.harvard.edu/

Institute for Clinical and Economic Review (ICER)

www.icer-review.org/

Institute for Clinical Systems Improvement (ICSI)

www.icsi.org

Minnesota Department of Health (US)

www.health.state.mn.us/

National Information Centre of Health Services Research and Health Care Technology (US)

www.nlm.nih.gov/nichsr/nichsr.html

Oregon Health Resources Commission (US)

www.oregon.gov/oha/OHPR/HRC/Pages/index.aspx

Office of Health Technology Assessment Archive (US)

<http://ota.fas.org/>

U.S. Blue Cross/ Blue Shield Association Technology Evaluation Center (Tec)

www.bcbs.com/blueresources/tec/

Veteran's Affairs Research and Development Technology Assessment Program (US)

www.research.va.gov/default.cfm

	Description
Index test	<p>SP-CMR (n=226)</p> <p><u>Scanner</u>: 1.5-T scanner with a high-performance cardiac gradient insert and a 4-channel phased array surface coil</p> <p><u>Perfusion sequence</u>: first-pass saturation recovery prepared hybrid fast gradient echo/echoplanar sequence</p> <p><u>Image acquisition</u>: during breath-holds</p> <p><u>Stress agent</u>: adenosine</p> <p><u>Contrast agent</u>: gadolinium-DTPA</p> <p><u>LGE</u>: No</p> <p><u>Sequence</u>: stress/rest</p> <p>Reports were either positive (i.e. showing reversible ischaemia with or without WMA or thinning) or negative.</p>

	Description
Comparators	<p>SPECT (n=224)</p> <p>Rest and stress SPECT imaging using 400–MBq ^{99m}Tc MIBI was performed within 4 weeks of randomisation using a 2-day protocol for rest and stress studies in order to optimise the radioactive dose administered.</p> <p>Adenosine stress was used routinely in all patients except those with contraindications such as asthma, in which case dobutamine was infused instead. Examinations were reported as positive if showing reversible ischaemia in at least 1 segment of a 20–segment model, or negative.</p> <p>Dobutamine stress Echo (n=226)</p> <p>Performed using a standard staged protocol of increasing doses of dobutamine infusion in stages of 3 minutes' duration. Imaging was performed with standard views acquired using tissue harmonic imaging on a 3.5-MHz ultrasound probe in the last 1 minute of each 3-minute stage. If necessary, 300–600 µg of atropine were added at peak stress to achieve 90% of target heart rate. Intravenous ultrasound contrast medium (microspheres) was used to delineate the LV endocardial border.</p> <p>Reports were either positive for ischaemia if they showed stress-related deterioration in contractility in functional or hibernating myocardial segments (i.e. in segments that were not akinetic or dyskinetic throughout) or negative.</p>
Reference standard	<p>ICA n=222</p> <p>Patients were assigned to PCI or CABG (performed within 6 months of ICA) or to medical therapy according to standard practice.</p> <p>ICA was performed and reported as per standard techniques from the right femoral artery approach using the Seldinger technique. A minimum of five views of the left and three views of the right coronary system were taken. LV ICA was performed in the majority of cases.</p> <p>Extent of disease was determined by the performing cardiologist, who recorded percentage DS by visual assessment on a standard clinical template.</p>
Patient management	<p>The results were sent to the referring cardiologist with a strong recommendation to proceed with ICA only when the stress imaging test was 'positive' for reversible ischaemia. The cardiologist's decision, however, was final and they were at liberty to proceed with ICA if they considered it clinically indicated. If ICA was considered necessary, it was performed within 3 months of the baseline research clinic.</p> <p>Revascularisation was decided on the basis of ICA, using the same criteria as for the comparator. For those patients who did not require revascularisation, medical therapy was at the discretion of the referring clinician and depended on the history and symptoms of the patient.</p>

^a NHMRC hierarchy of evidence (NHMRC 2000)

CABG = coronary artery bypass graft; CAD = coronary artery disease; CCS = Canadian Cardiovascular Society; CMR = coronary magnetic resonance imaging; CVD = cardiovascular disease; DS = diameter stenosis; ECG = electrocardiogram; Echo = echocardiography; EET = exercise ECG test; ICA = invasive coronary angiography; LGE = late gadolinium enhancement; LV = left ventricular; MI = myocardial infarction; PCI = percutaneous coronary intervention; RCT = randomised controlled trial; SP-CMR = stress perfusion cardiac magnetic resonance imaging; SPECT = single-photon emission computed tomography; T = tesla; WMA = wall motion abnormality

Table 142 Study profiles of included studies that reported on the safety of CMR (population 1)

Study Country	Study design Quality appraisal ^a	Study population	Inclusion/exclusion criteria	Intervention
Al-Saadi et al. (2000) Germany	Level IV A case series with either post-test or pre-/post-test outcomes Moderate risk of bias (IHE 6.5/12)	N=40 patients with suspected single-vessel or double-vessel disease who were referred for a ICA because of new chest pain or progressive symptoms Mean age: 59 ± 11 years n=8 women (20%) Mean LVEF: 56 ± 10%	Exclusion criteria: <18 years old or had a history of MI; unstable angina; haemodynamic-relevant valvular disease; ventricular extrasystole Low class ≥III ; atrial fibrillation; ejection fraction <30%; blood pressure >160/95 or <100/70 mm Hg; obstructive pulmonary disease; claustrophobia; or contraindications such as incompatible metal implants	Dipyridamole SP-CMR
Al-Saadi et al. (2002) Germany	Level IV A case series with either post-test or pre-/post-test outcomes Moderate risk of bias (IHE 6/12)	N=27 patients with suspected or proven single or double CAD admitted for ICA Mean age: 56 ± 9 years n=7 women (26%) Mean LVEF: 61 ± 9%	Exclusion criteria: History of prior MI; unstable angina; triple vessel disease; haemodynamic-relevant valvular disease; ventricular extrasystole ≥ Lown III; atrial fibrillation; LVEF <40%; blood pressure >160/95 or <100/70 mm Hg; known claustrophobia; or a contraindication for an CMR examination such as incompatible metallic implants	Dobutamine SP-CMR
Arnold et al. (2010) UK	Level IV A case series with either post-test or pre-/post-test outcomes Low risk of bias (IHE 8/12)	N=65 patients who had been referred to the regional tertiary centre for elective diagnostic angiography as part of routine clinical care for further investigation of exertional chest pain Mean age: 64 ± 9 years n=22/62 women (35%) Mean LVEF: 62 ± 12% CAD risk factors: hypertension 53% hypercholesterolaemia 57% smoker 10% diabetes 18% family history 36%	Exclusion criteria: Recent MI (within 7 days) and contraindications to CMR (severe claustrophobia metallic implants / foreign bodies); adenosine (2nd- or 3rd-degree AV block; obstructive pulmonary disease; dipyridamole use); gadolinium (anaphylaxis, estimated glomerular filtration rate 60 mL/minute) and sulphur hexafluoride (previous allergic reaction)	Adenosine SP-CMR + LGE

Study Country	Study design Quality appraisal ^a	Study population	Inclusion/exclusion criteria	Intervention
Beanlands et al. (2007) Canada	SR of level IV studies High risk of bias (AMSTAR 2/11)	Searches were divided into 4 categories: CAD and/or ischemia detection and diagnosis CAD prognostication Myocardial viability detection Myocardial viability prognostication	Search period: Up to June 2005 Databases searched: Medline, EMBASE, Cochrane library, and other evidence-based medicine Web sites, such as that of the Agency for Healthcare Research and Quality. Inclusion criteria: A systematic search of the literature, using validated British Medical Journal filters for diagnosis and prognosis, was used to identify the best evidence for use of CTCA and CMR. Exclusion criteria: None reported	Dobutamine stress CMR k = 11 CTCA 16-slice: k = 19 64-slice: k = 4
Bernhardt et al. (2012) Germany	Level IV A case series with either post-test or pre-/post-test outcomes Moderate risk of bias (IHE 6/12)	N=34 patients with stable angina and suspected or known CAD referred for ICA Mean age: 62 ± 11 years n=8/34 women (24%) PROCAM score 42.7 ± 8.8 CAD risk factors: hypertension 79% hypercholesterolaemia 53% smoker 47% diabetes 15%	Exclusion criteria: Not reported	Adenosine SP-CMR
Bettencourt et al. (2013a) Portugal	Level IV A case series with either post-test or pre-/post-test outcomes Low risk of bias	N=113/176 consecutive patients referred by general physicians to the hospital outpatient cardiology clinic due to clinical suspicion of CAD with an intermediate or high PTP for CAD according to the modified Diamond-Forrester score	Inclusion criteria: Age >40 years, symptoms compatible with CAD and ≥2 risk factors and/or a positive/ inconclusive treadmill test Exclusion criteria: Unstable clinical status; previous MI, CABG or PCI; valvular heart	Adenosine SP-CMR + LGE

Study Country	Study design Quality appraisal ^a	Study population	Inclusion/exclusion criteria	Intervention
	(IHE 8/12)	Mean age: 62 ± 8 years n=35/103 women (34%) 66% had intermediate or high PTP for CAD using the modified Diamond-Forrester score CAD risk factors: hypertension 73% hypercholesterolaemia 80% smoker 14% diabetes 39% family history 20%	disease; pregnancy; atrial fibrillation; renal insufficiency (creatinine clearance ≤60 mL/minute); and standard contraindications to CMR, adenosine and gadolinium	
Bruder et al. (2013) Europe	Level IV: A case series with either post-test or pre-/post-test outcomes Low risk of bias (IHE 8/12)	N=27,301 consecutive patients undergoing CMR according to the ACCF/ACR/SCCT/SCMR/ASNC/NASCI/SCAI/SIR 2006 consensus appropriateness criteria for CMR imaging from 57 participating centres Mean age: 60 years (range 47–70) Women: 35% Primary indication of suspected CAD or ischaemia in known CAD: 34.2%	Exclusion criteria: Not reported	CMR used according to the ACCF/ACR/SCCT/SCMR/ASNC/NASCI/SCAI/SIR 2006 consensus appropriateness criteria
Bunce et al. (2004) UK	Level IV: A case series with either post-test or pre-/post-test outcomes Moderate risk of bias (IHE 6.5/12)	N=35 consecutive patients undergoing diagnostic ICA for the investigation of angina Mean age: 56 ± 12 years (range 34–81) n=8/35 women (23%) Mean LVEF: 61 ± 12% CAD risk factors: hypertension 34% smoker 46%	Exclusion criteria: An inability or unwillingness to give informed consent; unstable angina or recent MI; the presence of an implanted permanent pacemaker, defibrillator or intracranial clips; significant claustrophobia; bronchial asthma; or previous CABG surgery	Adenosine SP-CMR

Study Country	Study design Quality appraisal ^a	Study population	Inclusion/exclusion criteria	Intervention
		diabetes 9% family history 37%		
Cheng et al. (2007) UK	Level IV A case series with either post-test or pre-/post-test outcomes Low risk of bias (IHE 8/12)	N=65 consecutive patients with suspected CAD who were awaiting diagnostic ICA as part of routine clinical care Mean age: 64 ± 8 years n=15/61 women (25%) Mean LVEF: 68 ± 9% Previous MI: 15% Previous PCI: 20% Mean Canadian Cardiovascular Society Score: 1.7 ± 0.7 CAD risk factors: hypertension 57% hypercholesterolaemia 77% smoker 20% diabetes 16% family history 41%	Exclusion criteria: Medically unstable; MI in the preceding 2 weeks; any contraindications to CMR (e.g. metallic implants such as pacemakers, defibrillators, cerebral aneurysm clips, ocular metallic deposits, severe claustrophobia) or to adenosine (2nd- or 3rd-degree AV block, history of asthma)	Adenosine SP-CMR
Costa et al. (2007) USA	Level IV A case series with either post-test or pre-/post-test outcomes Moderate risk of bias (IHE 7.5/12)	N=37 consecutive patients with suspected CAD who underwent ICA, FFR, and CMR assessments Mean age: 65 ± 11 years n=14/30 women (47%) Mean LVEF: 57 ± 13% CAD risk factors: hypertension 80% hyperlipidaemia 57% smoker 20% diabetes 23%	Exclusion criteria: MI within 14 days of either procedure; high-degree AV block; hypotension (systolic blood pressure <90 mm Hg); severe chronic obstructive pulmonary disease; decompensated congestive heart failure (NYHA functional class III or IV); a ferromagnetic metallic implant; claustrophobia; pregnant or lactating	Adenosine SP-CMR ICA + FFR
Dolor et al.	SR of level IV studies	Non-invasive technologies to diagnose	Search period:	Stress perfusion CMR

Study Country	Study design Quality appraisal ^a	Study population	Inclusion/exclusion criteria	Intervention
(2012) USA	Low risk of bias (AMSTAR 7/11)	CAD in women with symptoms suspicious for CAD	<p>Published in English from January 1, 2000, through September 12 2011</p> <p>Databases searched: PubMed, EMBASE, the Cochrane Database of Systematic Reviews, and the Cochrane Central Registry of Controlled Trials.</p> <p>Grey literature databases included Clinicaltrials.gov; metaRegister of Controlled Trials; ClinicalStudyResults.org; WHO: International Clinical Trials Registry Platform Search Portal; CSA Conference Papers Index; and Scopus.</p> <p>Inclusion criteria: RCTs prospective or retrospective observational studies with original data or related methodology paper of an included article</p> <p>Exclusion criteria: Editorials, Letters to the editor, case series, review articles and studies that were not peer reviewed; studies where all patients were known to have CAD or were asymptomatic, studies with outcomes not related to diagnostic accuracy for detecting CAD or with vessel-based outcomes, non-English studies</p>	<p>k = 6</p> <p>Exercise ECG: k = 41</p> <p>Stress Echo with or without a contrast agent: k = 22</p> <p>Stress SPECT: k = 30</p> <p>CTCA: k = 8</p>
Ebersberger et al. (2013) USA	<p>Level IV</p> <p>A case series with either post-test or pre-/post-test outcomes</p> <p>Moderate risk of bias (IHE 6.5/12)</p>	<p>N=120 patients with suspected or known CAD who underwent SP-CMR and ICA plus FFR measurements in intermediate lesions</p> <p>Mean age: 63 ± 14 years n=45 women (39%)</p> <p>CAD risk factors: hypertension 60% hypercholesterolaemia 54% smoker 53% diabetes 30%</p>	<p>Exclusion criteria: Contraindications to CMR due to claustrophobia or metallic implants; obstructive pulmonary disease; AV block grade I; MI within previous 7 days; acute coronary syndrome; NYHA class IV heart failure; and kidney disease with a GFR of <45 mL/minute</p>	<p>3-Tesla adenosine myocardial perfusion CMR + LGE</p>

Study Country	Study design Quality appraisal ^a	Study population	Inclusion/exclusion criteria	Intervention
		family history 27%		
Falcao et al. (2013) Brazil	Level IV A case series with either post-test or pre-/post-test outcomes Moderate risk of bias (IHE 6.5/12)	N=57 consecutive patients with suspected CAD who were scheduled for ICA and underwent dobutamine stress Echo and CMR using the same protocol Mean age: 59 ± 8 years n=22/42 women (53%) Mean LVEF: 63 ± 6% CAD risk factors: hypertension 83% hypercholesterolaemia 66% smoker 5% diabetes 40%	Exclusion criteria: Clinical history of previous MI or CABG surgery; abnormal LVEF (<55%) or regional systolic function; unstable angina pectoris; atrial flutter or fibrillation; significant valvular disease; incompatible metallic implants; claustrophobia; morbid obesity (>150 kg body weight); severe hypertension (blood pressure >180/110 mm Hg); or contraindications to any drug used in the protocol Patients with intervening events between CMR and ICA were excluded from the analysis	Dobutamine SP-CMR
Gebker et al. (2007) Germany	Level IV A case series with either post-test or pre-/post-test outcomes Low risk of bias (IHE 8/12)	N=43 consecutive patients with known or suspected CAD who were scheduled for clinically-indicated ICA Mean age: 61 ± 8 years n=12/40 women (30%) Suspected CAD: 37/40 (92%) CAD risk factors: hypertension 88% hypercholesterolaemia 72% smoker 48% diabetes 8% family history 22%	Exclusion criteria: Contraindications to CMR imaging (non-compatible biometallic implants or claustrophobia) or adenosine administration (AV block more severe than grade I or asthma); patients with arrhythmia and those who had undergone previous CABG placement	Adenosine SP-CMR + LGE
Giang et al. (2004) Switzerland, Germany and	Level IV A case series with either post-test or pre-/post-test outcomes	N=94 patients with known or suspected CAD who were scheduled for ICA Mean age: 58 ± 9 years n=15/80 women (19%)	Exclusion criteria: Recent MI (<2 weeks prior to enrolment); unstable angina; atrial fibrillation; 2nd- or 3rd-degree AV block; and previous CABG	Adenosine SP-CMR

Study Country	Study design Quality appraisal ^a	Study population	Inclusion/exclusion criteria	Intervention
UK	Moderate risk of bias (IHE 6/12)	<p>Prior PCI: 21%</p> <p>CAD risk factors:</p> <ul style="list-style-type: none"> hypertension 39% hypercholesterolaemia 56% smoker 35% diabetes 15% family history 16% 		
Groothuis et al. (2013) The Netherlands	<p>Level IV</p> <p>A case series with either post-test or pre-/post-test outcomes</p> <p>Low risk of bias (IHE 8/12)</p>	<p>N=198 patients with low or intermediate PTP of having CAD</p> <p>104 patients had no obstructive CAD on CTCA or CMR and did not have ICA and FFR</p> <p>Mean age, 56 ± 10 years n=96 women (50%)</p> <p>PTP according to the combined Diamond/Forrester and CASS scale: low PTP 45% intermediate PTP 33% high PTP 22%</p> <p>CAD risk factors:</p> <ul style="list-style-type: none"> hypertension 38% hyperlipidaemia 20% smoker 27% diabetes 12% family history 41% 	<p>Inclusion criteria:</p> <p>Chest pain and low or intermediate PTP of having CAD according to the Diamond/Forrester and CASS scales.</p> <p>Exclusion criteria:</p> <p>Any prior history of CAD (prior documented myocardial ischaemia, MI, PCI or cardiac surgery), significant arrhythmia, pregnancy, renal insufficiency, known allergy to iodinated contrast material, any absolute contra-indication for CMR (e.g. cerebral clips), claustrophobia, and asthma.</p>	Adenosine SP-CMR + LGE

Study Country	Study design Quality appraisal ^a	Study population	Inclusion/exclusion criteria	Intervention
Heitner et al. (2014) USA	Level IV A case series with either post-test or pre-/post-test outcomes Low risk of bias (IHE 8/12)	N=68 patients who presented with acute chest discomfort and were deemed to have intermediate PTP of CAD. Mean age 55 ± 10 years n=33/60 women (55%) CAD risk factors: hypertension 60% hypercholesterolaemia 37% smoker 17% diabetes 13% family history 35%	Inclusion criteria: Intermediate risk was defined as (a) one or more CAD risk factors in a man older than 40 years or a woman older than 50 years; or (b) two or more risk factors in a man older than 30 years or a woman older than 40 years Risk factors included hypertension, hyperlipidaemia, diabetes mellitus, current smoker, and a family history of MI before age 55 years Exclusion criteria: Atypical chest pain; with a very low or high PTP of having CAD; aortic stenosis with a mean gradient of 40 mm Hg or more; 2nd-degree or higher AV block; pregnancy; haemodynamic or clinical instability; non-cardiac medical problems that could lead to hospital admission; and standard contraindications to MR imaging	Adenosine SP-CMR + LGE
Ishida et al. (2003) Japan	Level IV A case series with either post-test or pre-/post-test outcomes Moderate risk of bias (IHE 6.5/12)	N=104 patients without MI who had undergone both first-pass contrast-enhanced stress CMR imaging and ICA less than 4 weeks apart Mean age 66 ± 12 years n=23/104 women (22%)	Exclusion criteria: Previous MI; abnormal Q wave on ECG; chest pain at rest; abnormal myocardial wall motion on cine CMR images obtained at rest; and/or coronary event between ICA and perfusion CMR imaging	Dipyridamole SP-CMR + LGE
Jogiya et al. (2012) UK	Level IV A case series with either post-test or pre-/post-test outcomes Low risk of bias (IHE 9/12)	N=55 consecutive patients with known or suspected CAD Mean age 64 ± 11 years n=12/53 women (23%) Normal LVEF: 93% CAD risk factors: hypertension 66% dyslipidaemia 83% smoker 9%	Exclusion criteria: Recent (<3 months) ACS, CABG; and contraindications to CMR imaging (including pacemakers and claustrophobia) or adenosine stress testing (e.g. poorly controlled obstructive airway disease and 2nd- or 3rd-degree AV block)	Adenosine SP-CMR + LGE

Study Country	Study design Quality appraisal ^a	Study population	Inclusion/exclusion criteria	Intervention
		diabetes 16% family history 20%		
Kawase et al. (2004) Japan	Level IV A case series with either post-test or pre-/post-test outcomes Moderate risk of bias (IHE 5.5/12)	N=50 consecutive patients who underwent ICA for assessment of CAD Mean age: 67 ± 12 years n=21 women (42%)	Exclusion criteria: A history of acute MI; atrial fibrillation; ventricular extrasystole ≥ Lown III; or contraindications to CMR examination (e.g. claustrophobia, artificial pacemaker)	Nocorandil SP-CMR
Kirschbaum et al. (2011) The Netherlands	Level IV A case series with either post-test or pre-/post-test outcomes Moderate risk of bias (IHE 6/12)	N=50 patients with stable angina and suspected CAD with normal LVEF who were referred for ICA Mean age: 64 ± 10 years n=12 women (24%) Mean LVEF: 64 ± 6% Low PTP 6% Intermediate PTP 68% High PTP 26% CAD risk factors: hypertension 50% hypercholesterolaemia 64% smoker 20% diabetes 18% family history 44%	Exclusion criteria: MI; previous revascularisation; pregnancy; claustrophobia; unstable CAD; renal insufficiency or arrhythmias	Adenosine SP-CMR
Kitagawa et al. (2008) Japan	Level IV A case series with either post-test or pre-/post-test outcomes Moderate risk of bias (IHE 7/12)	N=50 patients with known or suspected CAD who were scheduled for ICA with suspect of current obstructive CA stenosis based on clinical symptom and/or positive stress test Mean age: 65 ± 9 years	Exclusion criteria: Medically unstable; contraindications for adenosine triphosphate stress (i.e. 2nd- or 3rd-degree AV block, sick sinus syndrome, known hypersensitivity to adenosine) or contrast-enhanced CMR; clinical MI by history or medical record; and previously CABG	Adenosine SP-CMR + LGE

Study Country	Study design Quality appraisal ^a	Study population	Inclusion/exclusion criteria	Intervention
		n=14 women (28%) Previous PCI: 8% CAD risk factors: hypertension 52% hyperlipidaemia 58% smoker 42% diabetes 46%		
Klein et al. (2008) Germany	Level IV A case series with either post-test or pre-/post-test outcomes Low risk of bias (IHE 8/12)	N=55 consecutive patients with suspected CAD who were referred for ICA Mean age: 60 ± 10 years n=19/54 women (35%) Mean LVEF: 59 ± 9% CAD risk factors: hypertension 69% hypercholesterolaemia 76% smoker 33% diabetes 22% family history 31%	Exclusion criteria: Known MI; atrial fibrillation; unstable angina; AV block >1st-degree; obstructive lung disease; claustrophobia or other contraindications for CMR	Adenosine SP-CMR + LGE
Klem et al. (2008) USA and Germany	Level IV A case series with either post-test or pre-/post-test outcomes Low risk of bias (IHE 9/12)	N=100 consecutive women with chest pain or other symptoms suggestive of CAD who were not included in the Klem et al. (2006) study Mean age: 63 ± 11.1 years Angina according to Rose chest pain questionnaire: 50% CAD risk factors: hypertension 68% hyperlipidaemia 57% smoker 31% diabetes 22%	Inclusion criteria: Women who referred to the Duke University Medical Center in Durham NC, USA, and to Robert-Bosch-Krankenhaus Hospital in Stuttgart, Germany Exclusion criteria: Patients with known CAD including those with prior MI or revascularisation procedures; and contraindications to CMR (e.g. pacemaker) or adenosine (e.g. high-grade AV-block)	Adenosine SP-CMR + LGE

Study Country	Study design Quality appraisal ^a	Study population	Inclusion/exclusion criteria	Intervention
		family history 53%		
Klem et al. (2006) USA	Level IV A case series with either post-test or pre-/post-test outcomes Low risk of bias (IHE 8/12)	N=100 consecutive patients with suspected CAD scheduled for ICA Mean age: 58 ± 11.5 years n=47/92 women (51%) Angina according to Rose chest pain questionnaire: 34% CAD risk factors: hypertension 64% hypercholesterolaemia 54% smoker 39% diabetes 23% family history 52%	Exclusion criteria: Patients with known CAD including those with prior MI or revascularisation procedures; and contraindications to CMR (e.g. pacemaker) or adenosine (e.g. high-grade AV-block)	Adenosine SP-CMR + LGE
Korosoglou et al. (2010) Germany	Level IV: A case series with either post-test or pre-/post-test outcomes Some risk of bias (IHE 7.5/12)	N=1,493 consecutive patients with suspected or known CAD underwent dobutamine SP-CMR Mean age: 65 ± 13 years n=383 women (26%) CAD risk factors: hypertension 71% hyperlipidaemia 53% smoker 18% diabetes 19% family history 22%	Exclusion criteria: Non-sinus rhythm; unstable angina; severe arterial hypertension (200/120 mm Hg), moderate or severe valvular disease; and general contraindications to CMR (e.g. implanted pacemakers or defibrillators)	Dobutamine SP-CMR, using a standard protocol in a 1.5-T magnetic resonance scanner

Study Country	Study design Quality appraisal ^a	Study population	Inclusion/exclusion criteria	Intervention
Lockie et al. (2011) UK	Level IV A case series with either post-test or pre-/post-test outcomes Low risk of bias (IHE 8/12)	N=44 patients with known or suspected CAD Mean age: 57 ± 10 years n=9 women (21%) Previous PCI: 19% CAD risk factors: smoker 21% diabetes 19% family history 26%	Exclusion criteria: Contraindications for CMR or gadolinium-contrast agents; previous MI, CABG, ACS; impaired LVEF (<40%); and obstructive pulmonary disease	Adenosine SP-CMR + LGE
Ma et al. (2012) China	Level IV A case series with either post-test or pre-/post-test outcomes Low risk of bias (IHE 8/12)	N=50 consecutive patients with suspected CAD who were scheduled for primary diagnostic ICA Mean age: 56 ± 16 years n=22/50 women (44%) n=28/50 men (56%) CAD risk factors: hypertension 36% hypercholesterolaemia 54% smoker 46% diabetes 18% family history 32%	Exclusion criteria: Medical instability; known CAD; any contraindications to CMR (i.e. metallic implants such as pacemakers, defibrillators, cerebral aneurysm clips, ocular metallic deposits; severe claustrophobia); or contraindications to adenosine (e.g., 2nd- or 3rd- degree AV block, history of asthma); and renal insufficiency	Adenosine SP-CMR + LGE
Merkle et al. (2010) Germany	Level IV A case series with either post-test or pre-/post-test outcomes Low risk of bias (IHE 8/12)	N=256 consecutive patients with known or suspected CAD and a time interval of less than 4 weeks between CMR and ICA n=32/73 women (44%) Mean age: 63.4 ± 11.7 years CAD risk factors: hypertension 78% hypercholesterolaemia 71% smoker 16%	Exclusion criteria: Acute MI; previous CABG; severe claustrophobia; CMR-incompatible implants; a heart rate not well controlled; and pulmonary disease requiring treatment with methyl xanthine derivatives.	Adenosine SP-CMR

Study Country	Study design Quality appraisal ^a	Study population	Inclusion/exclusion criteria	Intervention
		diabetes 19% n=41/73 men (56%) Mean age: 60.9 ± 10.3 years CAD risk factors: hypertension 69% hypercholesterolaemia 83% smoker 36% diabetes 21%		
Merkle et al. (2007) Germany	Level IV A case series with either post-test or pre-/post-test outcomes Low risk of bias (IHE 8/12)	N=228 consecutive patients referred for known or primary diagnosis of CAD and with a time interval of less than 4 weeks between the CMR and ICA Mean age: 61.2 ± 11.2 years n=48/228 women (21%) CAD risk factors: hypertension 69% hyperlipidaemia 80% smoker 32% diabetes 20%	Exclusion criteria: Acute MI; previous CABG; severe claustrophobia; CMR-incompatible implants; a heart rate not well controlled; and pulmonary disease requiring treatment with methyl xanthine derivatives.	Adenosine SP-CMR
Meyer et al. (2008) Germany and USA	Level IV A case series with either post-test or pre-/post-test outcomes Moderate risk of bias (IHE 6/12)	N=60 patients with suspected occlusive CAD based on clinical findings and/or abnormal stress ECG testing Mean age: 59 ± 10 years n=22 women (37%) Previous MI: 23% Previous revascularisation: 18% CAD risk factors: hypertension 65% hypercholesterolaemia 55% smoker 57% diabetes 23%	Exclusion criteria: An established contraindication for CMR or adenosine stress testing	Adenosine SP-CMR + LGE

Study Country	Study design Quality appraisal ^a	Study population	Inclusion/exclusion criteria	Intervention
		family history 43%		
Mordi et al. (2014) UK	Level IV A case series with either post-test or pre-/post-test outcomes Low risk of bias (IHE 8.5/12)	N=82 consecutive patients with LBBB and an intermediate PTP for CAD with typical features of angina (exertional chest pain or dyspnoea) who were referred for testing Mean age: 56.5 ± 7.8 years n=29 women (35%) CAD risk factors: hypertension 46% hyperlipidaemia 48% smoker 40% diabetes 23% family history 45%	Exclusion criteria: Previous history of established CAD; renal impairment; metallic implants incompatible with CMR; uncontrolled arterial hypertension; atrial fibrillation with uncontrolled ventricular response; and prior adverse reaction to dobutamine	Dobutamine SP-CMR + LGE
Motwani et al. (2012) UK	Level IV A case series with either post-test or pre-/post-test outcomes Low risk of bias (IHE 8/12)	N=111 consecutive patients with suspected CAD who were scheduled to undergo diagnostic ICA Mean age: 61 ± 7 years n=26 women (26%) Mean LVEF: 58 ± 9% Median PTP: 51% (IQR 31–65) CAD risk factors: hypertension 67% hypercholesterolaemia 65% smoker 42% diabetes 18% family history 37%	Exclusion criteria: Contraindications to CMR, adenosine or gadolinium contrast agents; a history of recent (within 6 months) MI or unstable angina; or poorly controlled arrhythmias	Adenosine SP-CMR + LGE

Study Country	Study design Quality appraisal ^a	Study population	Inclusion/exclusion criteria	Intervention
Nagel et al. (2003) Germany	Level IV A case series with either post-test or pre-/post-test outcomes Low risk of bias (IHE 8/12)	N=90 consecutive patients with moderate PTP for CAD who were scheduled for a primary diagnostic ICA Mean age, 63 ± 8 years n=17 women (19%)	Exclusion criteria: MI <7 days previously, unstable angina pectoris; arterial hypertension (>160/140 mm Hg); diabetes mellitus; LVEF <50%; atrial flutter or fibrillation; sick sinus rhythm; SA- or AV block >I; ventricular premature beats (≥ Lown-III); relevant obstructive pulmonary disease or valvular disease ≥II; or contraindications to CMR examination (e.g. incompatible metallic implants, claustrophobia)	Adenosine SP-CMR
Okuda et al. (2005) Japan	Level IV A case series with either post-test or pre-/post-test outcomes Low risk of bias (IHE 8.5/12)	N=33 patients admitted to hospital for assessment of IHD Mean age, 60 years (range 31–77) n=4 women (12%) Previous PCI: 45%	Exclusion criteria: Not reported	Dipyridamole SP-CMR + LGE
Pereira et al. (2013) Portugal	Level IV A case series with either post-test or pre-/post-test outcomes Moderate risk of bias (IHE 7.5/12)	N=121 consecutive patients referred by general physicians due to clinical suspicion of CAD Mean age, 61 ± 8 years n=26 women (32%) PTP: low 12% intermediate 62% high 25% CAD risk factors: hypertension 72% hyperlipidaemia 76% smoker 10% diabetes 44% family history 20%	Inclusion criteria: Age >40 years, symptoms compatible with CAD and at least 1 cardiovascular risk factor Exclusion criteria: Previous MI; previous PCI or CABG; unstable CAD; valvular heart disease; pregnancy; renal insufficiency and standard contraindications to CMR, contrast media, adenosine and gadolinium	Adenosine SP-CMR + LGE

Study Country	Study design Quality appraisal ^a	Study population	Inclusion/exclusion criteria	Intervention
Pilz et al. (2006) Germany	Level IV A case series with either post-test or pre-/post-test outcomes Moderate risk of bias (IHE 6.5/12)	N=176 consecutive patients referred with known or suspected CAD who underwent additional CMR imaging prior to ICA Mean age, 62 ± 12 years n=64 women (37%) Known CAD 52% Previous revascularisation 37% CAD risk factors: hypertension 61% hypercholesterolaemia 64% smoker 31% diabetes 27%	Exclusion criteria: Contraindications to CMR imaging in general; known severe heart valve stenosis; obstructive respiratory disease; and the inability to obtain written informed consent	Adenosine SP-CMR + LGE
Pingitore et al. (2008) Italy	Level IV A case series with either post-test or pre-/post-test outcomes Moderate risk of bias (IHE 6.5/12)	N= 93 patients with known or suspected CAD Mean age, 61 ± 6 years n=28 women (30%) LVEF 66 ±5% Previous revascularisation 13% CAD risk factors: hypertension 74% hypercholesterolaemia 69% smoker 54% diabetes 27% family history 53%	Inclusion criteria: A history of chest pain (typical or atypical); normal LVEF, without regional or global WMAs at rest; no previous or acute MI; the provision of informed consent; and having been scheduled for ICA Exclusion criteria: Contraindications to CMR; previous or recent MI; baseline WMAs; and inability or refusal to give informed consent.	Dipyridamole SP-CMR
Plein et al. (2008a) UK and Switzerland	Level IV A case series with either post-test or pre-/post-test outcomes Low risk of bias (IHE 9/12)	N= 51 patients with known or suspected CAD Mean age, 59 ± 10 years n=12 women (24%) Previous PCI 8% CAD risk factors:	Exclusion criteria: Contraindications to CMR (e.g. incompatible metallic implants, claustrophobia) or adenosine infusion (e.g. asthma, AV block); MI within 7 days, unstable angina pectoris; and NYHA Class 4 heart failure	Adenosine SP-CMR + LGE

Study Country	Study design Quality appraisal ^a	Study population	Inclusion/exclusion criteria	Intervention
		hypertension 68% hypercholesterolaemia 70% smoker 57% diabetes 14%		
Plein et al. (2005) UK	Level IV A case series with either post-test or pre-/post-test outcomes Moderate risk of bias (IHE 6.5/12)	N=92 patients who were suspected of having or known to have CAD and were scheduled to undergo conventional ICA owing to clinical referral Mean age, 58 ± 11 years n=24 women (26%) Previous MI 21% CAD risk factors: hypertension 33% hypercholesterolaemia 59% smoker 38% diabetes 9% family history 43%	Exclusion criteria: Obstructive airway disease; cardiac arrhythmias; and contraindications to cardiac CMR	Adenosine SP-CMR
Regenfus et al. (2003) Germany	Level IV A case series with either post-test or pre-/post-test outcomes Moderate risk of bias (IHE 6/12)	N=427 CA segments from 61 patients referred for diagnostic ICA due to clinically suspected CAD Mean age, 63 ± 6 years n=9 women (15%)	Exclusion criteria: Patients with arrhythmias; in unstable clinical condition; or with contraindications to CMR imaging (e. g. cardiac pacemakers, other ferromagnetic implants or claustrophobia)	Nitroglycerin SP-CMR
Sakuma et al. (2005) Japan	Level IV A case series with either post-test or pre-/post-test outcomes Moderate risk of bias (IHE 5/12)	N=40 patients with suspected CAD Mean age, 64.6 ± 9.0 years n=12 women (30%)	Inclusion criteria: Underwent stress first-pass contrast-enhanced CMR, stress thallium-201 SPECT and ICA within 4 weeks Exclusion criteria: Previous MI; abnormal Q-wave on ECG; chest pain at rest; abnormal myocardial wall motion; severe arrhythmia; and coronary	Dipyridamole SP-CMR + LGE

Study Country	Study design Quality appraisal ^a	Study population	Inclusion/exclusion criteria	Intervention
			event between the imaging studies	
Schwitzer et al. (2008) Europe and USA	Level IV: A case series with either post-test or pre-/post-test outcomes Low risk of bias (IHE 9.5/12)	N=241 patients from 18 centres who were scheduled for a conventional ICA and/or SPECT examination for clinical reasons Mean age, 60 ± 10 years n=63 women (27%) Previous MI 39% Previous PCI 31% CAD risk factors: hypertension 69%	Exclusion criteria: Acute MI (<1 week prior to study enrolment); a history of CABG surgery; unstable angina pectoris; decompensated heart failure; any interventions on CAs in the time period between ICA, SPECT and perfusion-CMR examinations; arrhythmias (considered to compromise quality of CMR imaging such as atrial fibrillation or frequent ectopic beats of >20/minute); any contraindications for adenosine (e.g. second or third AV block, sick sinus syndrome, symptomatic bradycardia, severe bronchial asthma or chronic obstructive pulmonary disease), CM (known allergy) or CMR examination (implanted electronic devices, metallic foreign bodies in the eye, severe claustrophobia, and others according to local regulations and manufacturer's recommendations)	Adenosine SP-CMR
Schwitzer et al. (2013) Europe and USA	Level IV: A case series with either post-test or pre-/post-test outcomes Low risk of bias (IHE 10/12)	N=533 patients from 33 centres who were scheduled for a conventional ICA and/or SPECT examination for clinical reasons Mean age, 60 ± 10 years n=138 women (27%) Previous MI 27% Previous PCI 33% History of heart failure 21% CAD risk factors: hypertension 70% hypercholesterolaemia 69% diabetes 18%	Exclusion criteria: Acute MI (<2 weeks prior to study enrolment), a history of CABG surgery; unstable angina pectoris; decompensated heart failure; any interventions on CAs in the time period between ICA, SPECT, and CMR examinations; arrhythmias (considered to compromise quality of CMR imaging such as atrial fibrillation or frequent ectopic beats of >20/minute); any contraindications for adenosine (e.g. second or third AV block, sick sinus syndrome, symptomatic bradycardia, severe bronchial asthma or chronic obstructive pulmonary disease), contrast media (known allergy) or CMR examination (e.g. implanted electronic devices, metallic foreign bodies in the eye, severe claustrophobia, and others according to local regulations and manufacturer's recommendations)	Adenosine SP-CMR + LGE

Study Country	Study design Quality appraisal ^a	Study population	Inclusion/exclusion criteria	Intervention
Thiele et al. (2004) Germany and UK	Level IV A case series with either post-test or pre-/post-test outcomes Moderate risk of bias (IHE 7/12)	N=32 patients with suspected or known CAD within a mean of 45 ± 31 days after tetrofosmin SPECT perfusion Mean age, 64 ± 8 years n=11 women (34%) Previous MI 25% CAD risk factors: hypertension 66% hypercholesterolaemia 75% smoker 25% diabetes 32%	Exclusion criteria: Haemodynamically unstable; had contraindications to CMR examination such as implanted pacemakers, metallic cerebral clips or reasons for inadequate image quality such as high-grade ventricular extrasystole ≥ Lown III, atrial flutter or fibrillation; or contraindications to adenosine-infusion such as asthma or treatment with oral dipyridamole	Adenosine SP-CMR
Thomas et al. (2008) Germany	Level IV A case series with either post-test or pre-/post-test outcomes Moderate risk of bias (IHE 7.5/12)	N=60 patients with or without prior CAD diagnosis who were suspected of having significant occlusive CAD Mean age, 64 ± 8 years n=11 women (34%) Known CAD 65% CAD risk factors: hypertension 73% hypercholesterolaemia 73% smoker 38% diabetes 23%	Inclusion criteria: Patients >18 years of age who were referred to MR Department for non-invasive adenosine stress testing Exclusion criteria: Contraindications to adenosine medication, such as a history of MI <3 days prior; severe arterial hypertension, asthma or severe obstructive pulmonary disease or AV block >IIa; general contraindications to CMR such as severe claustrophobia or metal implants / coils in the brain	Adenosine SP-CMR + LGE
Walcher et al. (2013) Germany	Level IV A case series with either post-test or pre-/post-test outcomes Low risk of bias (IHE 8/12)	N=57 consecutive patients with suspected CAD and intermediate to high risk for a cardiovascular event according to the PROCAM or Framingham risk score Mean age, 62 ± 10 years n=15 women (29%) Mean LVEF: 68 ± 10% Mean PROCAM risk score: 44 ± 8	Exclusion criteria: Medically unstable; recent history of MI within 30 days; previous CABG or prosthetic valve surgery; and contraindications for CMR, adenosine infusion or gadolinium-based contrast agents	Adenosine SP-CMR + LGE

Study Country	Study design Quality appraisal ^a	Study population	Inclusion/exclusion criteria	Intervention
		Mean Framingham risk score: 15 ± 3 CAD risk factors: hypertension 79% hypercholesterolaemia 58% smoker 33% diabetes 19% family history 48%		
Watkins et al. (2009) Ireland	Level IV A case series with either post-test or pre-/post-test outcomes Moderate risk of bias (IHE 7/12)	N=103 patients who had been referred to a single cardiologist for investigation of suspected angina that was suspected to be CAD after assessment Mean age, 60 ± 9 years n=26 women (26%) Mean LVEF: 68 ± 7% Previous MI: 24% CAD risk factors: hypertension 62% hypercholesterolaemia 78% smoker 18% diabetes 16% family history 52%	Exclusion criteria: MI with evidence of ongoing myocardial ischemia in the preceding 48 hours; previous CABG; pregnancy; atrial fibrillation; and standard contraindications to CMR, adenosine, and gadolinium	Adenosine SP-CMR + LGE
Wolff et al. (2004) USA	Level IV A case series with either post-test or pre-/post-test outcomes Moderate risk of bias (IHE 7.5/12)	N=99 patients who had known or suspected CAD and were scheduled for ICA as part of their clinical care Mean age, 57 ± 9 years n=13 women (13%)	Exclusion criteria: Medically unstable; an MI <2 weeks earlier; any contraindication to CMR (e.g. pacemaker, internal defibrillator); a known allergy or contraindication to any paramagnetic or iodinated contrast agent; a contraindication to adenosine (e.g. asthma, heart block); or had ingested agents within 24 hours of the study that could potentiate (e.g. dipyridamole) or antagonise (e.g. caffeine, methylxanthines) the effects of adenosine; previous CABG	Adenosine SP-CMR

^a Quality appraisal of SRs was conducted using the AMSTAR checklist (Shea et al. 2007) and the level IV case series were appraised using the IHE checklist (Moga et al. 2012).

ACS = acute coronary syndrome; AV block = atrioventricular block; CA = coronary artery; CABG = coronary artery bypass graft, CAD = coronary artery disease; CASS = composite autonomic severity score; CMR = cardiac magnetic resonance imaging; CTCA = computed tomography coronary angiography; ECG = electrocardiogram; Echo = echocardiography; FFR = fractional flow rate; GFR = glomerular filtration rate; ICA = invasive coronary angiography; IHD = ischaemic heart disease; IHE = Institute of Health Economics; LBBB = left bundle branch block; LGE = late gadolinium enhancement; LVEF = left ventricular ejection fraction; MI = myocardial infarction; MR = magnetic resonance; NYHA = New York Heart Association; PROCAM score = scoring scheme for calculating the risk of acute coronary events based on the 10-year follow-up of the Prospective Cardiovascular Munster (PROCAM) study; PCI = percutaneous coronary intervention, PTP = pre-test probability; RCT = randomised controlled trial; SP-CMR = stress perfusion CMR; SPECT = single-photon emission computed tomography; SR = systematic review; WMA = wall motion abnormalities.

Table 143 Study profiles of included studies reporting on diagnostic accuracy in patients suspected of having CAD (population 1)

Study Country	Study design Quality appraisal ^a	Study population	Inclusion/exclusion criteria	Intervention (SP CMR with/without LGE)	Reference standard (ICA)
Al-Saadi et al. (2000) Germany	Level III-1: A comparison against independent, blinded reference standard among non-consecutive patients Quality: low risk of bias Patient selection ? Index test 😊 Reference standard 😊 Flow and timing 😊	N=40 patients with suspected single-vessel or double-vessel disease, who were referred for a ICA because of new chest pain or progressive symptoms Mean age: 59 ± 11 years n=8 women (20%) Mean LVEF: 56 ± 10%	Exclusion criteria: <18 years of age or had a history of MI; unstable angina; haemodynamic relevant valvular disease; ventricular extrasystole Low class ≥III; atrial fibrillation; ejection fraction <30%; blood pressure >160/95 or <100/70 mm Hg; obstructive pulmonary disease; claustrophobia; or contraindications such as incompatible metal implants	Scanner: 1.5-T whole-body scanner with the use of a 5-element, phased-array cardiac surface coil Perfusion sequence: First-pass ECG-triggered, T1-weighted, inversion recovery single-shot turbo gradient echo Image acquisition: During breath-holds Stress agent: Dipyridamole Contrast agent: Gadolinium DTPA LGE: No Sequence: Rest/stress	After the CMR examination, all patients underwent left-sided cardiac catheterisation and biplane selective ICA by the Judkins technique. The angiograms were quantitatively assessed with the QANSAD-QCA system (ARRI).
Antonio et al. (2007) Portugal	Level III-2 A comparison with reference standard (not blinded or blinding not known) Quality: unclear risk of bias Patient selection 😊 Index test ?	N=30 consecutive patients with suspected CAD Mean age: 58.5 ± 12.6 years n=4 women (13%) Mean LVEF: 61 ± 13%	Exclusion criteria: NR	Scanner: 1.5-T scanner Perfusion sequence: Fast imaging with steady-state free precession Image acquisition: NR Stress agent: Adenosine Contrast agent: Gadodiamide LGE: Yes (15-minute delay) Sequence: Stress/rest/LGE	ICA was performed in 18 patients.

Study Country	Study design Quality appraisal ^a	Study population	Inclusion/exclusion criteria	Intervention (SP CMR with/without LGE)	Reference standard (ICA)
	Reference standard ? Flow and timing ?			Image analysis: LGE images not used to diagnose CAD	
Arnold et al. (2010) UK	Level II: A comparison against independent, blinded reference standard among consecutive patients Quality: low risk of bias Patient selection 😊 Index test 😊 Reference standard 😊 Flow and timing 😊	N=65 patients who had been referred to the regional tertiary centre for elective diagnostic angiography as part of routine clinical care for further investigation of exertional chest pain Mean age: 64 ± 9 years n=22/62 women (35%) Mean LVEF: 62 ± 12% CAD risk factors: hypertension 53% hypercholesterolaemia 57% smoker 10% diabetes 18% family history 36%	Exclusion criteria: Recent MI (within 7 days); and contraindications to CMR (severe claustrophobia, metallic implants / foreign bodies), adenosine (2nd- or 3rd-degree AV block, obstructive pulmonary disease, dipyridamole use), gadolinium (anaphylaxis, estimated glomerular filtration rate 60 mL/minute) and sulphur hexafluoride (previous allergic reaction)	Scanner: 3.0-T scanner using anterior and posterior phased-array coils Perfusion sequence: First-pass ECG-gated T1-weighted fast gradient echo Image acquisition: During breath-holds Stress agent: Adenosine Contrast agent: Gadodiamide LGE: Yes (5-minute delay) Sequence: Stress/rest/LGE Image analysis: Perfusion + LGE algorithm to detect ischaemia	All patients underwent CA using standard techniques.
Becker et al. (2015) Germany	Level II: A comparison against independent, blinded reference standard among consecutive patients Quality: low risk of bias Patient selection 😊 Index test ? Reference standard 😊 Flow and timing 😊	N=424 postmenopausal women with symptoms suggestive of CAD Mean age: 61 ± 7 years Cardiovascular risk was determined using the Reynolds Risk Score Mean risk: 13 ± 3% n=365 low to intermediate risk: 9 ± 2% n=59 intermediate to high risk: 17 ± 3% CAD risk factors: hypertension 66% hyperlipidaemia 52% smoker 26% diabetes 23%	Inclusion criteria: Postmenopausal women with symptoms suggestive of CAD (typical or atypical chest pain, prolonged discomfort or shortness of breath) who were referred to the University Hospital Aachen between 2005 and 2008 Exclusion criteria: Women with known CAD, ACS, valvular heart disease, significant arrhythmia or contraindications to either CMR or dobutamine administration	Scanner: 1.5-T whole-body scanner using a 5-element cardiac synergy coil Perfusion sequence: Not described Image acquisition: During breath-holds Stress agent: Dobutamine Contrast agent: NR LGE: No Sequence: NR	ICA was performed using standard techniques. The severity of CA stenosis was determined quantitatively using the software QuantCor.

Study Country	Study design Quality appraisal ^a	Study population	Inclusion/exclusion criteria	Intervention (SP CMR with/without LGE)	Reference standard (ICA)
		family history 43%			
Bernhardt et al. (2007) Germany	Level II: A comparison against independent, blinded reference standard among consecutive patients Quality: low risk of bias Patient selection 😊 Index test 😊 Reference standard 😊 Flow and timing 😊	N=317 consecutive patients scheduled for ICA who had angina without previously diagnosed CHD and myocardial ischemia diagnosed by exercise ECG and/or PD as seen in thallium-201 perfusion SPECT Mean age: 63.7 ± 12.2 years n=129 women (41%) CAD risk factors: hypertension 58% hypercholesterolaemia 52% smoker 32% diabetes 20%	Exclusion criteria: An internal pacemaker or defibrillator; contraindications for adenosine infusion; or inability to give written informed consent	Scanner: 1.5-T whole-body scanner using a 4-element phased array surface coil Perfusion sequence: First-pass using a hybrid gradient echo/echo-planar pulse Image acquisition: During breath-holds Stress agent: Adenosine Contrast agent: Gadolinium-based contrast agent (Omniscan) LGE: No Sequence: Stress	Cardiac catheterisations were performed by experienced consultant cardiologists as recommended by the ACC and AHA.
Bettencourt et al. (2013a) Portugal	Level II: A comparison against independent, blinded reference standard among consecutive patients Quality: low risk of bias Patient selection 😊 Index test 😊 Reference standard 😊 Flow and timing 😊	N=113/176 consecutive patients referred by general physicians to the hospital outpatient cardiology clinic due to clinical suspicion of CAD with an intermediate or high PTP for CAD according to the modified Diamond-Forrester score Mean age: 62 ± 8 years n=35/103 women (34%) 66% had intermediate or high PTP for CAD using the modified Diamond-Forrester score CAD risk factors: hypertension 73% hypercholesterolaemia 80% smoker 14% diabetes 39%	Inclusion criteria: Age >40 years; symptoms compatible with CAD and ≥2 risk factors; and/or a positive/inconclusive treadmill test Exclusion criteria: Unstable clinical status; previous MI; previous CABG; previous PCI; valvular heart disease; pregnancy; atrial fibrillation; renal insufficiency (creatinine clearance ≤60 mL/minute); and standard contraindications to CMR, adenosine and gadolinium	Scanner: 1.5-T scanner with a 6-channel anterior chest coil combined with a 6-channel spinal coil within the gantry table Perfusion sequence: First-pass of contrast, using a gradient echo pulse Image acquisition: During breath-holds Stress agent: Adenosine Contrast agent: Gadobutrol LGE: Yes (≥10 minutes delay) Sequence: Stress/rest/LGE Image analysis: Either perfusion or LGE defects scored positive	ICA was performed according to standard techniques by experienced cardiologists. A pressure wire was used to determine FFR in all major patent epicardial CAs with a visually estimated SD above 40%.

Study Country	Study design Quality appraisal ^a	Study population	Inclusion/exclusion criteria	Intervention (SP CMR with/without LGE)	Reference standard (ICA)
		family history 20%			
Cheng et al. (2007) UK	Level III-2 A comparison with reference standard (not blinded or blinding not known) Quality: low risk of bias Patient selection 😊 Index test 😊 Reference standard ? Flow and timing 😊	N=65 consecutive patients with suspected CAD who were awaiting diagnostic ICA as part of routine clinical care Mean age: 64 ± 8 years n=15/61 women (25%) Mean LVEF: 68 ± 9% Previous MI: 15% Previous PCI: 20% Mean Canadian Cardiovascular Society Score: 1.7 ± 0.7 CAD risk factors: hypertension 57% hypercholesterolaemia 77% smoker 20% diabetes 16% family history 41%	Exclusion criteria: Medically unstable; MI in the preceding 2 weeks; any contraindications to CMR (metallic implants such as pacemakers, defibrillators, cerebral aneurysm clips or ocular metallic deposits, and severe claustrophobia) or to adenosine (2nd- or 3rd-degree AV block, history of asthma)	Scanner: 3.0-T scanner with anterior phased-array surface coil and posterior phased-array surface coil Perfusion sequence: First-pass of contrast, using a T1-weighted fast-gradient echo (turbo fast low-angle shot) Image acquisition: During breath-holds Stress agent: Adenosine Contrast agent: Gadolinium-based contrast agent (Gadodiamide) LGE: No Sequence: Stress/rest	ICA using standard techniques
Costa et al. (2007) USA	Level II: A comparison against independent, blinded reference standard among consecutive patients Quality: low risk of bias Patient selection 😊 Index test 😊 Reference standard 😊 Flow and timing 😊	N=37 consecutive patients with suspected CAD who underwent ICA, FFR and CMR assessments Mean age: 65 ± 11 years n=14/30 women (47%) Mean LVEF: 57 ± 13% CAD risk factors: hypertension 80% hyperlipidaemia 57% smoker 20% diabetes 23%	Exclusion criteria: MI within 14 days of either procedure; high-degree AV block; hypotension (systolic blood pressure <90 mm Hg); severe chronic obstructive pulmonary disease; decompensated congestive heart failure (NYHA functional class III or IV); a ferromagnetic metallic implant; claustrophobia; or were pregnant or lactating	Scanner: 1.5-T scanner using a 6-channel body coil Perfusion sequence: First-pass single-shot gradient echo with saturation-recovery magnetisation preparation for T1 weighting and linear k-spacing Image acquisition: During breath-holds Stress agent: Adenosine Contrast agent: Gadolinium-DPTA LGE: No Sequence: Stress/rest	Guiding catheters (6-F) without side holes were used. Cine angiographies were performed in at least 2 orthogonal projections after 100–200 g intracoronary nitroglycerin infusion. Intracoronary pressure was measured using a 0.014-inch pressure guide wire across the target stenosis. FFR was calculated after

Study Country	Study design Quality appraisal ^a	Study population	Inclusion/exclusion criteria	Intervention (SP CMR with/without LGE)	Reference standard (ICA)
					intravenous adenosine at 140 g/kg/minute for at least 2 minutes.
Cury et al. (2006) Brazil	Level III-1: A comparison against independent, blinded reference standard among non-consecutive patients Quality: low risk of bias Patient selection ? Index test 😊 Reference standard 😊 Flow and timing 😊	N=33 patients suspected of having CAD Mean age: 63 ± 5.3 years n=9/47 women (19%) Mean LVEF: 55 ± 8% Previous CABG: 21%	Exclusion criteria: Haemodynamic instability; ACS; severe hypertension; atrial fibrillation; known severe aortic stenosis; and asthma	Scanner: 1.5-T scanner and a 4-element phased-array cardiac coil Perfusion sequence: First-pass hybrid gradient echo-planar imaging pulse Image acquisition: During breath-holds Stress agent: Dipyridamole Contrast agent: Gadopentetate dimeglumine LGE: Yes (10-minute delay) Sequence: Stress/rest/LGE Image analysis: Integration of perfusion + LGE results to detect ischaemia	ICA was performed using the Judkins technique via a transfemoral approach by two interventional cardiologists with 7 and 15 years of experience.
de Mello et al. (2012) Brazil	Level III-1: A comparison against independent, blinded reference standard among non-consecutive patients Quality: low risk of bias Patient selection ? Index test 😊 Reference standard 😊 Flow and timing 😊	N=38 patients with symptoms suspected to be CAD, or any prior abnormal non-invasive stress test, and had undergone both CMR and ICA for CAD detection Mean age: 60.4 ± 10.5 years n=15/54 women (28%) Mean LVEF: 62 ± 15% CAD risk factors: hypertension 41% hypercholesterolaemia 63% smoker 35% diabetes 26%	Exclusion criteria: >60 days between CMR and ICA; any intervention associated with ICA if performed before CMR	Scanner: 1.5-T scanner with a 4-element phased-array cardiac coil Perfusion sequence: First-pass Image acquisition: During breath-holds Stress agent: Dipyridamole Contrast agent: Gadolinium-based contrast (gadoversetamide) LGE: Yes (10-minute delay) Sequence: Stress/rest/LGE Image analysis: Integration of perfusion + LGE results to detect ischaemia	The ICA was performed by standard technique via a transfemoral or radial approach.

Study Country	Study design Quality appraisal ^a	Study population	Inclusion/exclusion criteria	Intervention (SP CMR with/without LGE)	Reference standard (ICA)
Falcao et al. (2013) Brazil	Level II: A comparison against independent, blinded reference standard among consecutive patients Quality: low risk of bias Patient selection 😊 Index test 😊 Reference standard 😊 Flow and timing 😊	N=57 consecutive patients with suspected CAD who were scheduled for ICA and underwent dobutamine stress Echo and CMR using the same protocol Mean age: 59 ± 8 years n=22/42 women (53%) Mean LVEF: 63 ± 6% CAD risk factors: hypertension 83% hypercholesterolaemia 66% smoker 5% diabetes 40%	Exclusion criteria: Clinical history of previous MI or CABG surgery; abnormal LVEF (<55%) or regional systolic function; unstable angina pectoris; atrial flutter or fibrillation; significant valvular disease; incompatible metallic implants; claustrophobia; morbid obesity (>150 kg body weight); severe hypertension (blood pressure >180/110 mm Hg); or contraindications to any drug used in the protocol Patients with intervening events between CMR, real-time contrast Echo and ICA were excluded from the analysis.	Scanner: 1.5-T scanner with high performance gradients Perfusion sequence: First-pass segmented k-space steady-state free precession gradient echo Image acquisition: During breath-holds Stress agent: Dobutamine Contrast agent: Gadolinium-based contrast (Dotarem) LGE: Yes Sequence: Rest/stress/LGE Image analysis: LGE images not used to diagnose CAD	Quantitative ICA measurements were made by an experienced interventional cardiologist.
Greenwood et al. (2014) UK	Level II: A comparison against independent, blinded reference standard among consecutive patients Quality: low risk of bias Patient selection 😊 Index test 😊 Reference standard 😊 Flow and timing 😊	N=752 consecutive patients with suspected angina pectoris n=235 women had CMR and ICA results available Mean age: 60.5 ± 9.4 years Previous MI or ACS: 6% Previous PCI: 7% CAD risk factors: hypertension 52% smoker 59% diabetes 13% n=393 men had CMR and ICA results available	Inclusion criteria: At least one major cardiovascular risk factor and judged to have stable angina needing investigation by a cardiologist; and had complete data from both CMR and ICA with no interim cardiovascular events Exclusion criteria: Previous CABG surgery; crescendo angina or ACS; contraindication to CMR (e.g. pacemaker) or adenosine infusion (e.g. reversible airways disease,	Scanner: 1.5-T Philips Intera CV scanner Perfusion sequence: First-pass T1-weighted saturation-recovery, single-shot k-space gradient echo pulse Image acquisition: During breath-holds Stress agent: Adenosine Contrast agent: Dimeglumine gadopentetate LGE: Yes Sequence: Stress/rest/LGE Image analysis: Perfusion and LGE	Clinically significant CHD was defined as 70% or more stenosis of a first order CA measuring 2 mm or greater in diameter, or left main stem stenosis 50% or more as measured by quantitative ICA with use of QCAPlus software.

Study Country	Study design Quality appraisal ^a	Study population	Inclusion/exclusion criteria	Intervention (SP CMR with/without LGE)	Reference standard (ICA)
		Mean age: 59.5 ± 9.5 years Previous MI: 9% Previous PCI: 5% CAD risk factors: hypertension 49% smoker 42% diabetes 13%	AV block); pregnancy; inability to lie supine; and a glomerular filtration rate of 30 mL/minute per 1.73 m ² or less	analysed separately	
Groothuis et al. (2013) The Netherlands	Level III-1: A comparison against independent, blinded reference standard among non-consecutive patients Quality: some risk of bias Patient selection 😊 Index test 😊 Reference standard 😊 Flow and timing 😞	N=192 patients with low or intermediate PTP of having CAD 104 patients had no obstructive CAD on CTCA or CMR and did not have ICA and FFR Mean age, 56 ± 10 years n=96 women (50%) PTP according to the combined Diamond/Forrester and CASS scale: low PTP 45% intermediate PTP 33% high PTP 22% CAD risk factors: hypertension 38% hyperlipidaemia 20% smoker 27% diabetes 12% family history 41%	Inclusion criteria: Chest pain and low or intermediate PTP of having CAD according to the Diamond-Forrester and CASS scales Exclusion criteria: Any prior history of CAD (prior documented myocardial ischaemia, MI, PCI or cardiac surgery); significant arrhythmia; pregnancy; renal insufficiency; known allergy to iodinated contrast material; any absolute contraindication for CMR (e.g. cerebral clips); claustrophobia; and asthma	Scanner: 1.5-T whole-body scanner Perfusion sequence: First-pass dynamic single-shot saturation recovery gradient-echo-planar pulse Image acquisition: Using TSENSE Stress agent: Adenosine Contrast agent: Gadolinium-based contrast agent (Magnevist) LGE: Yes Sequence: Stress/rest/LGE Image analysis: Integration of perfusion + LGE results to detect ischaemia	ICA was performed according to standard clinical protocols. During the procedure the cardiologist performed direct visual assessment of the CAs. In case of intermediate lesions (30%–70% visually assessed DS), FFR was measured using a 0.014-inch pressure guide wire.
Heitner et al. (2014) USA	Level III-1: A comparison against independent, blinded reference standard among non-consecutive	N=68 patients who presented with acute chest discomfort and were deemed to have intermediate PTP of CAD Mean age 55 ± 10 years	Inclusion criteria: Intermediate risk was defined as (a) one or more CAD risk factors in a man older than 40 years or a woman older than 50 years; or (b) two or more risk factors in a man	Scanner: 1.5-T scanner and phased-array receiver coils Perfusion sequence: First-pass saturation recovery gradient-echo Image acquisition: During breath-holds	The reference standard for the presence of significant CAD was pre-specified and was a composite endpoint based on ICA findings and cardiac

Study Country	Study design Quality appraisal ^a	Study population	Inclusion/exclusion criteria	Intervention (SP CMR with/without LGE)	Reference standard (ICA)
	<p>patients</p> <p>Quality: high risk of bias</p> <p>Patient selection 😊</p> <p>Index test 😊</p> <p>Reference standard 😞</p> <p>Flow and timing 😞</p>	<p>n=33/60 women (55%)</p> <p>CAD risk factors: hypertension 60% hypercholesterolaemia 37% smoker 17% diabetes 13% family history 35%</p>	<p>older than 30 years or a woman older than 40 years.</p> <p>Risk factors included hypertension, hyperlipidaemia, diabetes mellitus, current smoker, and a family history of MI before age 55 years.</p> <p>Exclusion criteria:</p> <p>Atypical chest pain; those with a very low or high PTP of having CAD; aortic stenosis with a mean gradient of 40 mm Hg or more; 2nd-degree or higher AV block; pregnancy; haemodynamic or clinical instability; non-cardiac medical problems that could lead to hospital admission; and standard contraindications to CMR imaging.</p>	<p>Stress agent: Adenosine</p> <p>Contrast agent: Gadolinium</p> <p>LGE: Yes (5-minute delay)</p> <p>Sequence: Stress/rest/LGE</p> <p>Image analysis: Perfusion + LGE algorithm to detect ischaemia</p>	<p>events during follow-up.</p>
Husser et al. (2009) Spain	<p>Level III-1:</p> <p>A comparison against independent, blinded reference standard among non-consecutive patients</p> <p>Quality: low risk of bias</p> <p>Patient selection 😊</p> <p>Index test 😊</p> <p>Reference standard 😊</p> <p>Flow and timing 😊</p>	<p>N=166 patients with chest pain of possible coronary origin who underwent dipyridamole stress CMR and ICA within 3 months</p> <p>Mean age 65 ± 11 years n=51 women (31%) Mean LVEF: 60 ± 13% Previous MI: 27% Previous PCI: 16%</p> <p>CAD risk factors: hypertension 66% hypercholesterolaemia 54% smoker 21%</p>	<p>Inclusion criteria:</p> <p>Retrospective selection of women who underwent both CMR and ICA within 3 months</p> <p>Exclusion criteria:</p> <p>Patients who had undergone a coronary revascularisation; had had an MI within 3 months before the CMR study; or any contraindication for dipyridamole</p>	<p>Scanner: 1.5-T scanner with a phased-array body surface coil</p> <p>Perfusion sequence: First-pass with a notched saturation pulse</p> <p>Image acquisition: During breath-holds</p> <p>Stress agent: Dipyridamole</p> <p>Contrast agent: Gadopentetate dimeglumine</p> <p>LGE: Yes (10-minute delay)</p> <p>Sequence: Rest/stress/LGE</p> <p>Image analysis: Perfusion and LGE</p>	<p>Angiographic data was evaluated by an experienced cardiologist on a standard digital imaging system</p>

Study Country	Study design Quality appraisal ^a	Study population	Inclusion/exclusion criteria	Intervention (SP CMR with/without LGE)	Reference standard (ICA)
		diabetes 39%		analysed separately	
Kirschbaum et al. (2011) The Netherlands	Level II: A comparison against independent, blinded reference standard among consecutive patients Quality: unclear risk of bias Patient selection 😊 Index test ? Reference standard ? Flow and timing ?	N=75 vessels from 50 patients with stable angina and suspected CAD with normal LVEF who were referred for ICA Mean age: 64 ± 10 years n=12 women (24%) Mean LVEF: 64 ± 6% low PTP 6% intermediate PTP 68% high PTP 26% CAD risk factors: hypertension 50% hypercholesterolaemia 64% smoker 20% diabetes 18% family history 44%	Exclusion criteria: MI; previous revascularisation; pregnancy; claustrophobia; unstable CAD; renal insufficiency; or arrhythmias	Scanner: 1.5-T scanner Perfusion sequence: First-pass Image acquisition: During breath-holds Stress agent: Adenosine Contrast agent: Gadolinium diethyltriaminepentaacetic acid LGE: No Sequence: Rest/stress	ICA was part of routine clinical management, and FFR functional assessment was performed for stenosis of visually >30% diameter using a wire that can simultaneously measure pressure and flow.
Klein et al. (2008) Germany	Level II: A comparison against independent, blinded reference standard among consecutive patients Quality: low risk of bias Patient selection 😊 Index test 😊 Reference standard 😊 Flow and timing 😊	N=55 consecutive patients with suspected CAD who were referred for ICA Mean age: 60 ± 10 years n=19/54 women (35%) Mean LVEF: 59 ± 9% CAD risk factors: hypertension 69% hypercholesterolaemia 76% smoker 33% diabetes 22% family history 31%	Exclusion criteria: Known MI; atrial fibrillation; unstable angina; AV block >1st-degree; obstructive lung disease; claustrophobia; or other contraindications for CMR	Scanner: 1.5-T scanner with a 5–element cardiac synergy coil Perfusion sequence: First-pass Image acquisition: Breathing motion was compensated for using a cranio-caudal navigator technique Stress agent: Adenosine Contrast agent: Gd-BOPTA LGE: Yes (10-minute delay) Sequence: Stress/rest/LGE Image analysis: Either perfusion or	All ICAs were performed within 24 hours after CMR examination. Two experienced interventional cardiologists blinded to the results of the CMR examinations visually evaluated the angiograms.

Study Country	Study design Quality appraisal ^a	Study population	Inclusion/exclusion criteria	Intervention (SP CMR with/without LGE)	Reference standard (ICA)
				LGE defects scored positive	
Klem et al. (2008) USA and Germany	Level II: A comparison against independent, blinded reference standard among consecutive patients Quality: low risk of bias Patient selection 😊 Index test 😊 Reference standard 😊 Flow and timing 😊	N=147 consecutive women with chest pain or other symptoms suggestive of CAD who were referred to the Duke University Medical Center in Durham NC, USA; and to Robert-Bosch-Krankenhaus Hospital in Stuttgart, Germany Mean age: 63 ± 11.1 years Angina according to Rose chest pain questionnaire: 50% CAD risk factors: hypertension 68% hyperlipidaemia 57% smoker 31% diabetes 22% family history 53%	Exclusion criteria: Patients with known CAD including those with prior MI or revascularisation procedures; and contraindications to CMR (e.g. pacemaker) or adenosine (e.g. high-grade AV-block).	Scanner: 1.5-T scanner with a phased-array receiver coil Perfusion sequence: First-pass with a saturation-recovery, single-shot, gradient-echo Image acquisition: Echo-planar hybrid or parallel imaging Stress agent: Adenosine Contrast agent: Gadoversetamide or gadodiamide LGE: Yes (10-minute delay) Sequence: Stress/rest/LGE Image analysis: Perfusion + LGE algorithm to detect ischaemia	ICA was performed by standard techniques and analysed, masked to identity, clinical information and CMR results.
Klem et al. (2006) USA	Level II: A comparison against independent, blinded reference standard among consecutive patients Quality: low risk of bias Patient selection 😊 Index test 😊 Reference standard 😊 Flow and timing 😊	N=100 consecutive patients with suspected CAD scheduled for ICA Mean age: 58 ± 11.5 years n=47/92 women (51%) Angina according to Rose chest pain questionnaire: 34% CAD risk factors: hypertension 64% hypercholesterolaemia 54% smoker 39% diabetes 23% family history 52%	Exclusion criteria: Patients with known CAD including those with prior MI or revascularisation procedures; and contraindications to CMR (e.g. pacemaker) or adenosine (e.g. high-grade AV-block)	Scanner: 1.5-T scanner with a phased-array receiver coil Perfusion sequence: First-pass Image acquisition: During breath-holds Stress agent: Adenosine Contrast agent: Gadoversetamide LGE: Yes (5-minute delay) Sequence: Stress/rest/LGE Image analysis: Perfusion + LGE algorithm to detect ischaemia	ICA was performed by standard techniques and interpreted, masked to identity, clinical information and the CMR results by the consensus of two experienced cardiologists.
Ma et al.	Level II:	N=50 consecutive patients with	Exclusion criteria:	Scanner: 3.0-T whole-body scanner	ICA was performed in all

Study Country	Study design Quality appraisal ^a	Study population	Inclusion/exclusion criteria	Intervention (SP CMR with/without LGE)	Reference standard (ICA)
(2012) China	<p>A comparison against independent, blinded reference standard among consecutive patients</p> <p>Quality: low risk of bias</p> <p>Patient selection 😊</p> <p>Index test 😊</p> <p>Reference standard 😊</p> <p>Flow and timing 😊</p>	<p>suspected CAD who were scheduled for primary diagnostic ICA</p> <p>Mean age: 56 ± 16 years n=22/50 women (44%) n=28/50 men (56%)</p> <p>CAD risk factors: hypertension 36% hypercholesterolaemia 54% smoker 46% diabetes 18% family history 32%</p>	<p>Medical instability; known CAD; any contraindications to CMR (i.e. metallic implants such as pacemakers, defibrillators, cerebral aneurysm clips, ocular metallic deposits, and severe claustrophobia); contraindications to adenosine (e.g. 2nd- or 3rd-degree AV block, history of asthma); and renal insufficiency</p>	<p>using a 12–element matrix coil</p> <p>Perfusion sequence: First-pass using a modified radial-sampled fast low-angled shot</p> <p>Image acquisition: During breath-holds with CG-HYPR processing</p> <p>Stress agent: Adenosine</p> <p>Contrast agent: Gadolinium contrast material (Magnevist)</p> <p>LGE: Yes (10-minute delay)</p> <p>Sequence: Stress/rest/LGE</p> <p>Image analysis: Integration of perfusion + LGE results to detect ischaemia</p>	<p>patients and quantitatively evaluated by two independent blinded cardiologists in consensus.</p>
Merkle et al. (2010) Germany	<p>Level III-2</p> <p>A comparison with reference standard (not blinded or blinding not known)</p> <p>Quality: low risk of bias</p> <p>Patient selection 😊</p> <p>Index test 😊</p> <p>Reference standard ?</p> <p>Flow and timing 😊</p>	<p>N=73/256 consecutive patients with suspected CAD and a time interval of less than 4 weeks between CMR and ICA</p> <p>n=32/73 women (44%) Mean age: 63.4 ± 11.7 years</p> <p>CAD risk factors: hypertension 78% hypercholesterolaemia 71% smoker 16% diabetes 19%</p> <p>n=41/73 men (56%) Mean age: 60.9 ± 10.3 years</p> <p>CAD risk factors: hypertension 69% hypercholesterolaemia 83%</p>	<p>Exclusion criteria: Acute MI; previous CABG; severe claustrophobia; MR-incompatible implants; a heart rate not well controlled; and pulmonary disease requiring treatment with methyl xanthine derivatives</p>	<p>Scanner: 1.5-T whole-body scanner using a five-element, phase-array cardiac coil</p> <p>Perfusion sequence: First-pass</p> <p>Image acquisition: During breath-holds</p> <p>Stress agent: Adenosine</p> <p>Contrast agent: Gadolinium-DTPA</p> <p>LGE: Yes (15-minute delay)</p> <p>Sequence: Stress/rest/LGE</p> <p>Image analysis: Perfusion (regions of LGE excluded from analysis)</p>	<p>ICA was performed via the femoral approach using a standard Judkins technique. CAs were visualised in multiple projections after intracoronary administration of glycerol nitrate.</p>

Study Country	Study design Quality appraisal ^a	Study population	Inclusion/exclusion criteria	Intervention (SP CMR with/without LGE)	Reference standard (ICA)
		smoker 36% diabetes 21%			
Merkle et al. (2007) Germany	Level III-2 A comparison with reference standard (not blinded or blinding not known) Quality: low risk of bias Patient selection 😊 Index test 😊 Reference standard ? Flow and timing 😊	N=59/228 consecutive patients referred for primary diagnosis of CAD and with a time interval of less than 4 weeks between CMR and ICA Mean age: 61.2 ± 11.2 years n=48/228 women (21%) CAD risk factors: hypertension 69% hyperlipidaemia 80% smoker 32% diabetes 20%	Exclusion criteria: Acute MI; previous CABG; severe claustrophobia; CMR-incompatible implants; a heart rate not well controlled; and pulmonary disease requiring treatment with methyl xanthine derivatives	Scanner: 1.5-T whole-body scanner using a 5–element, phase-array cardiac coil Perfusion sequence: First-pass Image acquisition: During breath-holds Stress agent: Adenosine Contrast agent: Gadolinium-DTPA LGE: Yes (15-minute delay) Sequence: Stress/rest/LGE Image analysis: Perfusion (regions of LGE excluded from analysis)	ICA was performed via the femoral approach using a standard Judkins technique. CAs were visualised in multiple projections after intracoronary administration of glycerol nitrate.
Meyer et al. (2008) Germany and USA	Level III-2 A comparison with reference standard (not blinded or blinding not known) Quality: low risk of bias Patient selection ? Index test 😊 Reference standard ? Flow and timing 😊	N=60 patients with suspected occlusive CAD based on clinical findings and/or abnormal stress ECG testing Mean age: 59 ± 10 years n=22 women (37%) Previous MI: 23% Previous revascularisation: 18% CAD risk factors: hypertension 65% hypercholesterolaemia 55% smoker 57% diabetes 23% family history 43%	Exclusion criteria: An established contraindication for CMR or adenosine stress testing.	Scanner: 3.0-T whole-body cardiac imaging system Perfusion sequence: First-pass saturation recovery gradient echo Image acquisition: During breath-holds Stress agent: Adenosine Contrast agent: Gadobutrol LGE: Yes (15-minute delay) Sequence: Stress/rest/LGE Image analysis: Either perfusion or LGE defects scored positive	Conventional ICA was performed at different institutions by experienced interventional cardiologists in multiple projections using standard techniques within 28 days after the CMR study
Mordi et al. (2014)	Level II: A comparison against	N=82 consecutive patients with LBBB and an intermediate PTP for CAD with	Exclusion criteria: Previous history of established	Scanner: 1.5-T scanner using an 8–element cardiac phased-array receiver	ICA was performed in all 82 patients. An

Study Country	Study design Quality appraisal ^a	Study population	Inclusion/exclusion criteria	Intervention (SP CMR with/without LGE)	Reference standard (ICA)
UK	independent, blinded reference standard among consecutive patients Quality: low risk of bias Patient selection 😊 Index test 😊 Reference standard 😊 Flow and timing 😊	typical features of angina (exertional chest pain or dyspnoea) who were referred for testing Mean age: 56.5 ± 7.8 years n=29 women (35%) CAD risk factors: hypertension 46% hyperlipidaemia 48% smoker 40% diabetes 23% family history 45%	CAD; renal impairment; metallic implants incompatible with CMR; uncontrolled arterial hypertension; atrial fibrillation with uncontrolled ventricular response; and prior adverse reaction to dobutamine	coil Perfusion sequence: First-pass ECG triggered TurboFLASH Image acquisition: During breath-holds Stress agent: Dobutamine Contrast agent: Gadolinium-DOTA LGE: Yes (10-minute delay) Sequence: Stress/rest/LGE Image analysis: Either perfusion or LGE defects scored positive	experienced investigator blinded to echocardiographic and CMR findings assessed the presence of CA stenosis.
Motwani et al. (2012) UK	Level II: A comparison against independent, blinded reference standard among consecutive patients Quality: low risk of bias Patient selection 😊 Index test 😊 Reference standard 😊 Flow and timing 😊	N=111 consecutive patients with suspected CAD who were scheduled to undergo diagnostic ICA Mean age: 61 ± 7 years n=26 women (26%) Mean LVEF: 58 ± 9% Median PTP: 51% (IQR 31–65) CAD risk factors: hypertension 67% hypercholesterolaemia 65% smoker 42% diabetes 18% family history 37%	Exclusion criteria: Contraindications to CMR, adenosine or gadolinium contrast agents; a history of recent (within 6 months) MI or unstable angina; or poorly controlled arrhythmias	Scanner: 1.5-T scanner using a 5-element cardiac phased-array receiver coil Perfusion sequence: First-pass perfusion saturation recovery gradient echo pulse accelerated with k-t BLAST Image acquisition: During breath-holds Stress agent: Adenosine Contrast agent: Dimeglumine gadopentetate LGE: Yes (not reported) Sequence: Stress/rest/LGE Image analysis: Integration of perfusion + LGE results to detect ischaemia	Quantitative ICA was performed (QCAPlus; Sanders Data Systems, Palo Alto, CA) on all x-ray angiography images by an experienced observer blinded to clinical and CMR data.
Nagel et al. (2003)	Level II: A comparison against independent, blinded	N=90 consecutive patients with moderate PTP for CAD who were scheduled for a primary diagnostic ICA	Exclusion criteria: MI <7 days; unstable angina pectoris; arterial hypertension	Scanner: 1.5-T scanner using a 5-element phased-array cardiac coil Perfusion sequence: First-pass single	Biplane ICA using the Judkins technique was performed. Two

Study Country	Study design Quality appraisal ^a	Study population	Inclusion/exclusion criteria	Intervention (SP CMR with/without LGE)	Reference standard (ICA)
Germany	reference standard among consecutive patients Quality: low risk of bias Patient selection 😊 Index test 😊 Reference standard 😊 Flow and timing 😊	Mean age, 63 ± 8 years n=17 women (19%)	(>160/140 mm Hg); diabetes mellitus; LVEF <50%; atrial flutter or fibrillation; sick sinus rhythm; sinoatrial or AV block >I; ventricular premature beats (≥Low-II); relevant obstructive pulmonary disease or valvular disease ≥II; or contraindications to CMR examination (e.g. incompatible metallic implants, claustrophobia)	shot segmented k-space turbo-gradient echo/echo-planar imaging hybrid technique Image acquisition: During breath-holds Stress agent: Adenosine Contrast agent: Gadolinium-DTPA LGE: No Sequence: Rest/stress	experienced blinded observers visually assessed the angiograms.
Pereira et al. (2013) Portugal	Level II: A comparison against independent, blinded reference standard among consecutive patients Quality: low risk of bias Patient selection 😊 Index test 😊 Reference standard 😊 Flow and timing 😊	N=121 consecutive patients referred by general physicians due to clinical suspicion of CAD Mean age, 61 ± 8 years n=26 women (32%) low PTP 12% intermediate PTP 62% high PTP 25% CAD risk factors: hypertension 72% hyperlipidaemia 76% smoker 10% diabetes 44% family history 20%	Inclusion criteria: Age >40 years; symptoms compatible with CAD and at least one cardiovascular risk factor Exclusion criteria: Previous MI; previous PCI or CABG; unstable CAD; valvular heart disease; pregnancy; renal insufficiency; and standard contraindications to CMR, contrast media, adenosine and gadolinium	Scanner: 1.5-T scanner with a 6-channel anterior chest coil and spinal coils within the gantry table Perfusion sequence: First-pass with a gradient echo pulse Image acquisition: During breath-holds Stress agent: Adenosine Contrast agent: Gadobutrol LGE: Yes (10-minute delay) Sequence: Stress/rest/LGE Image analysis: Either perfusion or LGE defects scored positive	All ICAs were performed according to standard techniques. When stenosis >40% was visually perceived, FFR was assessed using a pressure wire under steady-state hyperaemia obtained with an adenosine infusion.
Regenfus et al. (2003) Germany	Level III-1: A comparison against independent, blinded reference standard among non-consecutive patients	N=427 CA segments from 61 patients referred for diagnostic ICA due to clinically suspected CAD Mean age, 63 ± 6 years n=9 women (15%)	Exclusion criteria: Arrhythmias; in unstable clinical condition; or with contraindications to CMR imaging (e.g. cardiac pacemakers, other ferromagnetic implants, claustrophobia)	Scanner: 1.5-T scanner with a circular polarised body array coil Perfusion sequence: First-pass using a turbo FLASH Image acquisition: During breath-holds Stress agent: Nitroglycerin	ICA was performed within 3 days of CMR imaging. Angiograms were documented in digitised format and evaluated by visual assessment by two cardiologists.

Study Country	Study design Quality appraisal ^a	Study population	Inclusion/exclusion criteria	Intervention (SP CMR with/without LGE)	Reference standard (ICA)
	Quality: low risk of bias Patient selection 😊 Index test 😊 Reference standard 😊 Flow and timing 😊			Contrast agent: Gadopentetate dimeglumine LGE: No Sequence: Stress/rest Image analysis: Original source imaging	
Sakuma et al. (2005) Japan	Level III-2 A comparison with reference standard (not blinded or blinding not known) Quality: unclear risk of bias Patient selection ? Index test ? Reference standard ? Flow and timing 😊	N=40 patients with suspected CAD Mean age, 64.6 ± 9.0 years n=12 women (30%)	Inclusion criteria: Underwent stress first-pass contrast-enhanced CMR, stress thallium-201 SPECT and ICA within 4 weeks Exclusion criteria: Previous MI; abnormal Q-wave on ECG; chest pain at rest; abnormal myocardial wall motion; severe arrhythmia; and coronary event between the imaging studies	Scanner: 1.5-T scanner with a body array coil Perfusion sequence: First-pass saturation-recovery turbo FLASH Image acquisition: During breath-holds Stress agent: Dipyridamole Contrast agent: Gadopentetate dimeglumine LGE: Yes (15-minute delay) Sequence: Rest/stress/LGE Image analysis: Integration of perfusion + LGE results to detect ischaemia	ICA was performed by cardiologists as a diagnostic procedure. Stenosis of 70% or more of the luminal diameter on ICA was used as the reference standard.
Schwitzer et al. (2001) Switzerland	Level III-1: A comparison against independent, blinded reference standard among non-consecutive patients Quality: low risk of bias Patient selection ? Index test 😊	N=48 patients with suspected CAD who were referred for ICA n=37 with CAD Mean age, 61 ± 10 years 3/37 women (8%) Mean LVEF: 67 ± 7% NYHA class III 24% CAD risk factors: hypertension 62% hypercholesterolaemia 57%	Exclusion criteria: Unstable angina; atrial fibrillation; valvular heart disease; a history of revascularisation; or previous MI as indicated by history, Q waves in the resting 12-lead ECG, or WMAs at rest (by echocardiography or CMR)	Scanner: 1.5-T scanner with a 4-element phased-array radiofrequency coil Perfusion sequence: First-pass using a hybrid echo-planar pulse sequence Image acquisition: During breath-holds Stress agent: Dipyridamole Contrast agent: Gadolinium diethylenetriaminepentaacetic acid	Not described

Study Country	Study design Quality appraisal ^a	Study population	Inclusion/exclusion criteria	Intervention (SP CMR with/without LGE)	Reference standard (ICA)
	Reference standard 😊 Flow and timing 😊	<p>smoker 43% diabetes 19% family history 26%</p> <p>n=10 without CAD</p> <p>Mean age, 50 ± 12 years 5/10 women (50%) Mean LVEF: 73 ± 4</p> <p>CAD risk factors: hypertension 60% hypercholesterolaemia 100% smoker 80% diabetes 0% family history 50%</p>		<p>bismethylamide</p> <p>LGE: No</p> <p>Sequence: Stress</p>	
Stolzmann et al. (2011) Switzerland	<p>Level II: A comparison against independent, blinded reference standard among consecutive patients</p> <p>Quality: low risk of bias</p> <p>Patient selection 😊</p> <p>Index test 😊</p> <p>Reference standard 😊</p> <p>Flow and timing 😊</p>	<p>N=60 consecutive patients referred to CA who all had an intermediate risk of having CAD based on the Diamond and Forrester criteria</p> <p>Mean age, 64 ± 10 years n=8 women (13%)</p> <p>CAD risk factors: hypertension 77% hyperlipidaemia 72% smoker 33% diabetes 15% family history 18%</p>	<p>Exclusion criteria: Contraindications for adenosine (e.g. 2nd or 3rd AV block, sick sinus syndrome, symptomatic bradycardia, severe asthma or obstructive pulmonary disease) or to CMR (e.g. implanted electronic devices, metallic foreign bodies in the eye, severe claustrophobia, and others according to local regulations and manufacturer's recommendations)</p>	<p>Scanner: 1.5-T scanner with cardiac phased-array receiver coils</p> <p>Perfusion sequence: First-pass with a saturation recovery gradient echo pulse</p> <p>Image acquisition: During breath-holds</p> <p>Stress agent: Adenosine</p> <p>Contrast agent: Gadobutrolum</p> <p>LGE: Yes (10-minute delay)</p> <p>Sequence: Stress/rest/LGE</p> <p>Image analysis: Either perfusion or LGE defects scored positive</p>	<p>Angiograms were obtained in at least two orthogonal projections according to standard techniques. Coronary angiograms of the target vessels were evaluated by consensus of two readers.</p>
Takase et al. (2004) Japan	<p>Level III-2</p> <p>A comparison with reference standard (not blinded or blinding not)</p>	<p>N=57 consecutive patients with suspected CAD</p> <p>Mean age, 66 ± 10 years n=17 women (17%)</p>	<p>Inclusion criteria: Referred to the National Defense Medical College Hospital and who agreed to undergo the dipyridamole stress perfusion</p>	<p>Scanner: 1.5-T scanner with a phased array cardiac coil</p> <p>Perfusion sequence: First-pass</p> <p>Image acquisition: During breath-holds</p>	<p>ICA was performed using the standard Judkins technique and the presence of significant stenosis (>50%) was</p>

Study Country	Study design Quality appraisal ^a	Study population	Inclusion/exclusion criteria	Intervention (SP CMR with/without LGE)	Reference standard (ICA)
	known) Quality: low risk of bias Patient selection 😊 Index test 😊 Reference standard ? Flow and timing 😊	CAD risk factors: hypertension 47% hyperlipidaemia 39% smoker 67% diabetes 39% family history 74%	CMR None of the subjects had suffered an MI within 3 months or underwent coronary revascularisation procedures within 6 months prior to the start of the study, nor had any suffered from uncontrolled moderate-to-severe systemic hypertension (>160/90 mm Hg).	Stress agent: Dipyridamole Contrast agent: Gadolinium LGE: Yes (delay not reported) Sequence: Stress/rest/LGE Image analysis: Either perfusion or LGE defects scored positive	determined within 1 month of performing a dipyridamole stress perfusion CMR study.
Van Werkhoven et al. (2010) The Netherlands	Level II: A comparison against independent, blinded reference standard among consecutive patients Quality: low risk of bias Patient selection 😊 Index test 😊 Reference standard 😊 Flow and timing 😊	N=53 consecutive patients referred for ICA because of chest pain suspected to be CAD Mean age, 57 ± 9 years n=28 women (40%) PTP according to the Diamond and Forrester method, with a risk threshold of <13.4% for low risk, >87.2% for high risk: low PTP 3% intermediate PTP 83% high PTP 11% CAD risk factors: hypertension 57% hypercholesterolaemia 55% smoker 30% diabetes 15% family history 43%	Exclusion criteria: Cardiac arrhythmias; renal insufficiency; known hypersensitivity to iodine contrast media (for CTCA); pregnancy; cardiac pacemakers or intracranial aneurysm clips; claustrophobia; a cardiac event (e.g. revascularisation, worsening angina or MI) occurred in the period between the three examinations	Scanner: 1.5-T scanner using a multichannel surface coil array Perfusion sequence: First-pass Image acquisition: During breath-holds Stress agent: Adenosine Contrast agent: Adolinium-DOTA LGE: Yes (15-minute delay) Sequence: Stress/LGE Image analysis: Integration of perfusion + LGE results to detect ischaemia	Conventional ICA was performed according to standard techniques. Analysis of the most severe lesion was performed for each CA by an observer blinded to the CTCA and CMR results using an offline software program.
Walcher et al. (2013) Germany	Level II: A comparison against independent, blinded	N=57 consecutive patients with suspected CAD and intermediate to high risk for a cardiovascular event according to the PROCAM or	Exclusion criteria: Medically unstable; recent history of MI (within 30 days); previously	Scanner: 1.5- and 3.0-T scanner using a 32-channel phased-array surface coil Perfusion sequence: First-pass using	All ICAs were performed in concordance to the recommendations of the ACC and AHA. In case of

Study Country	Study design Quality appraisal ^a	Study population	Inclusion/exclusion criteria	Intervention (SP CMR with/without LGE)	Reference standard (ICA)
	reference standard among consecutive patients Quality: low risk of bias Patient selection 😊 Index test 😊 Reference standard 😊 Flow and timing 😊	Framingham risk score Mean age, 62.3 ± 10.2 years n=15 women (29%) Mean LVEF: 68 ± 10% Mean PROCAM risk score: 44 ± 8 Mean Framingham risk score: 15 ± 3 CAD risk factors: hypertension 79% hypercholesterolaemia 58% smoker 33% diabetes 19% family history 48%	undergone CABG or prosthetic valve surgery; contraindications for CMR, adenosine infusion or gadolinium-based contrast agents	a spoiled gradient-echo Image acquisition: During breath-holds Stress agent: Adenosine Contrast agent: Gadolinium-based contrast agent (Dotarem) LGE: Yes (10-minute delay) Sequence: Stress/rest/LGE Image analysis: Perfusion + LGE algorithm to detect ischaemia	CA stenosis quantitative analysis was performed.
Watkins et al. (2009) Ireland	Level III-1: A comparison against independent, blinded reference standard among non-consecutive patients Quality: low risk of bias Patient selection 😊 Index test 😊 Reference standard 😊 Flow and timing 😊	N=103 patients who had been referred to a single cardiologist for investigation of suspected angina that was suspected to be CAD after assessment Mean age, 60 ± 9 years n=26 women (26%) Mean LVEF: 68 ± 7% Previous MI: 24% CAD risk factors: hypertension 62% hypercholesterolaemia 78% smoker 18% diabetes 16% family history 52%	Exclusion criteria: MI with evidence of ongoing myocardial ischemia in the preceding 48 hours; previous CABG; pregnancy; atrial fibrillation; standard contraindications to CMR, adenosine and gadolinium	Scanner: 1.5-T scanner using a 6-channel anterior chest coil and spinal coils Perfusion sequence: First-pass with a Turbo-FLASH Image acquisition: During breath-holds Stress agent: Adenosine Contrast agent: Gadolinium diethylenetriaminepentaacetic acid bismethylamide LGE: Yes (20-minute delay) Sequence: Stress/LGE/rest Image analysis: Integration of perfusion + LGE results to detect ischaemia	After the acquisition of the diagnostic ICA images, FFR was measured at steady-state hyperaemia, induced by adenosine, in all major patent epicardial CAs.

^a Quality appraisal of diagnostic accuracy studies was conducted using the QUADAS-2 checklist (Whiting et al. 2011)

ACC = American College of Cardiology; ACS = acute coronary syndrome; AHA = American Heart Association; AV block = atrioventricular block; CA = coronary artery; CABG = coronary artery bypass graft; CAD = coronary artery disease; CASS = composite autonomic severity score; CHD = coronary heart disease; CMR = cardiac magnetic resonance imaging; CTCA = computed

tomography coronary angiography; DOTA = 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid; DTPA = diethylenetriaminepentaacetic acid; ECG = electrocardiogram; Echo = echocardiography; FFR = fractional flow rate; ICA = invasive coronary angiography; LBBB = left bundle branch block; LGE = late gadolinium enhancement; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NR = not reported; NYHA = New York Heart Association; PCI = percutaneous coronary intervention, PD = perfusion defect; PROCAM score = scoring scheme for calculating the risk of acute coronary events based on the 10-year follow-up of the Prospective Cardiovascular Munster (PROCAM) study; PTP = pre-test probability; SD = stenosis diameter; SP-CMR = stress perfusion cardiac magnetic resonance imaging; SPECT = single-photon emission computed tomography; T = tesla; WMA = wall motion abnormality

Table 144 Study profiles of included SRs on diagnostic accuracy of the index test or comparators compared with the reference standard (population 1)

Study Country	Quality appraisal ^a	Review aim/question Population	Inclusion/exclusion criteria	Intervention Number of studies included in MA	Reference standard
Abdulla et al. (2007) Denmark	27% (3/11) Poor quality with a high risk of bias	To evaluate the diagnostic accuracy of 64-slice multidetector CTCA compared with the reference standard conventional ICA Patients with known or suspected CAD Patient analysis for CMR and CTCA; segment analysis for CTCA	Search period: Until the end of April 2007 Databases searched: PubMed, EMBASE, and Cochrane Library Inclusion criteria: Studies that included patients with proven or suspected CAD using 64-slice CTCA compared with ICA, and provided absolute numbers of diagnostic accuracy tests using 2 x 2 tables Exclusion criteria: Studies not providing relevant data on diagnostic accuracy	64-slice CTCA: k=27	ICA: DS cut-off at 50% or above
Al Moudi et al. (2011) Australia	18% (2/11) Poor quality with a high risk of bias	To investigate the diagnostic value of SPECT, PET and PET/CT in the diagnosis of CAD, based on an SR Adult patients with CAD or suspected of having CAD Analysis at patient level	Search period: Between 1985 and September 2010 Databases searched: PubMed/Medline and ScienceDirect Inclusion criteria: Studies that included patients who underwent MPI rest/stress test while ICA was used as the reference standard, and at least 10 patients were included, diagnosis of CAD was based on >50% stenosis Exclusion criteria: Review articles or case study reports; animal or phantom studies; studies dealing	SPECT: k=15	ICA: DS cut-off at 50%

Study Country	Quality appraisal ^a	Review aim/question Population	Inclusion/exclusion criteria	Intervention Number of studies included in MA	Reference standard
			with MPI without addressing the diagnostic accuracy of coronary artery stenosis or occlusion, and studies including patients treated with coronary stents or bypass grafts		
Beanlands et al. (2007) Canada	18% (2/11) Poor quality with a high risk of bias	To define Canadian recommendations for the clinical use of advanced imaging modalities Searches were divided into 4 categories: CAD and/or ischemia detection and diagnosis; CAD prognostication; myocardial viability detection; and viability prognostication Analysis at patient and segment level	Search period: Up to June 2005 Databases searched: Medline, EMBASE, Cochrane library, and other evidence-based medicine Web sites, such as that of the Agency for Healthcare Research and Quality Inclusion criteria: A systematic search of the literature, using validated British Medical Journal filters for diagnosis and prognosis, was used to identify the best evidence for use of CTCA and CMR. Exclusion criteria: None reported	Multidetector CTCA 16-slice: k=19 64slice: k=4 Dobutamine SP-CMR: k=11 PET: k=14	ICA: DS cut-off at 50% or above
Chen et al. (2014) China	55% (6/11) Moderate quality with a moderate risk of bias	To use direct comparative studies or RCTs to compare the accuracy of CMR and SPECT for the detection of obstructive CAD Adult patients with CAD or suspected of having CAD Analysis at patient and coronary artery level	Search period: Publication date no later than June 2013 Databases searched: PubMed, EMBASE, Web of Science and the Cochrane Library Inclusion criteria: Direct comparative studies or randomised controlled trials. The data reported in the primary studies were sufficient for the calculation of true-positive, false-positive, true-negative or false-negative values. Exclusion criteria: Review articles, letters, comments, case reports and unpublished articles were excluded.	Both SP-CMR and SPECT evaluated in the same patient population: k=6	ICA: DS cut-off at 50% or above

Study Country	Quality appraisal ^a	Review aim/question Population	Inclusion/exclusion criteria	Intervention Number of studies included in MA	Reference standard
			<p>Non-English and non-Chinese articles for which a full-text translation or evaluation could not be obtained.</p> <p>Studies with fewer than 20 patients; and if multiple reports were published for the same study population (the most detailed or recent publication was chosen)</p>		
de Jong et al. (2012) The Netherlands	55% (6/11) Moderate quality with a moderate risk of bias	<p>To determine and compare the diagnostic performance of stress myocardial perfusion imaging for the diagnosis of CAD, using conventional ICA as the reference standard</p> <p>Known or suspected adult CAD patients</p> <p>Analysis at patient level</p>	<p>Search period: January 2000 and May 2011</p> <p>Databases searched: Medline and EMBASE</p> <p>Inclusion criteria: English-language studies with a prospective study design that evaluated stress perfusion imaging tests in the diagnosis of CAD Absolute numbers of true positives, false positives, true negatives and false negatives were available at the patient level or could be derived adequately.</p> <p>Exclusion criteria: Review or meta-analysis studies; patients who had (suspected) ACS; normal healthy volunteers or asymptomatic patients were included; less than 30 patients were included; (potentially) overlapping study populations were reported; very specific patient populations (e.g. only patients with a heart transplant, LBBB or aortic stenosis) were studied; the study focused on in-stent or graft stenosis after PCI or CABG</p>	<p>SP-CMR: k=20 Contrast-enhanced Echo: k=10 SPECT: k=13</p> <p>Used as a measure of haemodynamically significant myocardial ischaemia</p>	ICA: DS cut-off at 50% or above
den Dekker et al. (2012) The Netherlands and Belgium	55% (6/11) Moderate quality with a moderate risk of bias	<p>An SR and meta-analysis to assess sensitivity and specificity of CTCA for significant stenosis at different degrees of coronary calcification</p> <p>Adult patients suspected of</p>	<p>Search period: January 2001 and June 2011</p> <p>Databases searched: PubMed and EMBASE</p> <p>Inclusion criteria: English-language studies that addressed diagnostic accuracy of CTCA according to</p>	≥16-slice CTCA by multidetector and dual source for significant stenosis (≥50%);k=21	ICA: DS cut-off at 50%

Study Country	Quality appraisal ^a	Review aim/question Population	Inclusion/exclusion criteria	Intervention Number of studies included in MA	Reference standard
		having CAD Analysis at patient and segment level	calcium score categories Exclusion criteria: Laboratory or phantom studies; concerned a review or case report; included examinations of stented or bypassed CAs; or used <16-slice CTCA		
Desai and Jha (2013) USA	45% (5/11) Moderate quality with a moderate risk of bias	To determine the test characteristics of SP-CMR in the diagnosis of flow-limiting obstructive CAD using FFR at ICA as the reference standard Patients with known or suspected CAD Analysis at patient and coronary artery level	Search period: January 2000 to August 2012 Databases searched: Medline, PubMed, Cochrane Database and EMBASE Inclusion criteria: The use of a magnet of strength of at least 1.5-T; provision of sensitivity and specificity and NPV and PPV or information enabling such calculation; stable CAD Exclusion criteria: Studies with less than 20 patients; overlapping or duplicate data; that used phantoms; on patients with suspected ACS; and published in non-English journals	SP-CMR: in women: k=12 in men: k=8	FFR: diagnostic cut-off at 0.75 or above
Dolor et al. (2012) USA	64% (7/11) Good quality with low risk of bias	What is the accuracy of one non-invasive technology (NIT) in diagnosing obstructive and non-obstructive CAD when compared with another NIT or with ICA in women with symptoms suspicious for CAD? Adult women who presented symptoms suspicious for CAD	Search period: Published in English from 1 January 2000 to 12 September 2011 Databases searched: PubMed, EMBASE, the Cochrane Database of Systematic Reviews and the Cochrane Central Registry of Controlled Trials Grey literature databases included Clinicaltrials.gov; metaRegister of Controlled Trials; ClinicalStudyResults.org; WHO: International Clinical Trials Registry Platform Search Portal; CSA Conference Papers Index; and Scopus. Inclusion criteria: RCTs; prospective or retrospective observational studies with original data; related methodology paper of an included article	Exercise ECG: k=41 Exercise/stress Echo with or without a contrast agent: k=22 Exercise/stress SPECT: k=30 SP-CMR: k=6 CTCA: k=8	ICA: DS cut-off at 50% or above

Study Country	Quality appraisal ^a	Review aim/question Population	Inclusion/exclusion criteria	Intervention Number of studies included in MA	Reference standard
		Analysis at patient level	Exclusion criteria: Editorials; letters to the editor; case series; review articles; studies that were not peer reviewed; studies where all patients were known to have CAD or were asymptomatic; studies with outcomes not related to diagnostic accuracy for detecting CAD or with vessel-based outcomes; non-English studies		
Geleijnse et al. (2007) The Netherlands	9% (1/11) Poor quality with a high risk of bias	To determine the diagnostic accuracy of dobutamine stress Echo in women Women with known or suspected CAD Analysis at patient level	Search period: Published through to June 2006 Databases searched: Medline Inclusion criteria: Studies of diagnostic dobutamine stress Echo in women Exclusion criteria: None reported	Dobutamine stress Echo: k=14	ICA: DS cut-off at 50% or above
Gianrossi et al. (1989) USA	36% (4/11) Moderate quality with a moderate risk of bias	To evaluate the variability in the reported diagnostic accuracy of the exercise electrocardiogram Patients with known or suspected CAD Analysis at patient level	Search period: 1967 to 1987 Databases searched: The Bibliography Retrieval Service and Medlars were used to search the National Library of Medicine database. The bibliographies of three major textbooks on the subject and of review articles published between 1984 and 1987 and retrieved from the search were also scanned. Inclusion criteria: Reports published after 1967 on the diagnostic accuracy of the exercise ECG when compared with ICA Exclusion criteria: Studies with less than 50 patients	Exercise ECG: k=147	ICA: DS cut-off at 50%

Study Country	Quality appraisal ^a	Review aim/question Population	Inclusion/exclusion criteria	Intervention Number of studies included in MA	Reference standard
Gopalakrishnan et al. (2008) USA	9% (1/11) Poor quality with a high risk of bias	To determine the diagnostic accuracy of newer versions of multislice CT in detecting CAD in comparison with conventional ICA Unselected patients being tested for CAD Analysis at patient and segment level	Search period: Published from 2002 to August 2006 Databases searched: PubMed Inclusion criteria: Studies in English; included unselected patients or patients with native vessels Exclusion criteria: Studies with less than 25 patients; or involving CTCA with less than 16 detectors	16-slice, 40-slice, and 64-slice CTCA: k=22	ICA: DS cut-off at 50%
Guo et al. (2011) China	45% (5/11) Moderate quality with a moderate risk of bias	To evaluate the diagnostic accuracy of the first-generation dual-source CTCA in the diagnosis of CAD Patients with known or suspected CAD Analysis at patient, vessel and segment level	Search period: Published from January 2005 to January 2010 Databases searched: PubMed, EMBASE, the Cochrane central register of controlled trials (CENTRAL) and Chinese biomedical literature database Inclusion criteria: Studies that included adult patients with suspected/known CAD; the data were obtained using the first generation dual-source CTCA; the reference was ICA; the diagnostic criteria for CA stenosis based on ICA were clearly stated (lumen reduction $\geq 50\%$ as significant stenosis); the numbers of true positives, false positives, false negatives and true negatives could be easily extracted Exclusion criteria: Studies that were not peer reviewed (e.g. abstracts from meetings); and that focused on second-generation dual-source CTCA or on single-source CT	Dual-source CTCA: k=24	ICA: DS cut-off at 50%
Hacioglu et al. (2010) USA	9% (1/11) Poor quality with	To analyse the available evidence from the studies comparing the diagnostic and prognostic performance	Search period: Not stated Databases searched:	SPECT MPI: k=8	ICA: DS cut-off at 50% or above

Study Country	Quality appraisal ^a	Review aim/question Population	Inclusion/exclusion criteria	Intervention Number of studies included in MA	Reference standard
	a high risk of bias	of the CACS and CTCA versus MPI, in terms of strengths and limitations, providing further hypothetical and methodological insight about the specific areas requiring further clarification by well-designed research trials Patients with known or suspected CAD Analysis at patient level	PubMed Inclusion criteria: Studies comparing the diagnostic and prognostic performance of CACS or CTCA versus MPI in the diagnosis and prognostication of symptomatic patients with known or suspected CAD Exclusion criteria: Studies focusing only on asymptomatic patients		
Hamon et al. (2010) France	45% (5/11) Moderate quality with a moderate risk of bias	Evaluation of the diagnostic accuracy of stress perfusion CMR for the diagnosis of significant obstructive CAD Patients with known or suspected CAD Analysis at patient and coronary artery level	Search period: Published before July 2009 Databases searched: Medline, Cochrane Library and BioMed Central Inclusion criteria: The absolute numbers of true positives, false positives, true negatives and false negatives were reported or could be derived Exclusion criteria: Studies performed with a 0.5- or 1-T scanner; if included less than 10 patients; if only abstracts from scientific meetings were published	SP-CMR as a diagnostic test for significant obstructive CAD: k=26	ICA: DS cut-off at 50%
Heijenbrok-Kal et al. (2007) The Netherlands and USA	27% (3/11) Poor quality with a high risk	To compare the diagnostic performance of stress Echo, stress SPECT, and electron-beam CTCA	Search period: January 1990 to December 2006 Databases searched:	Exercise Echo: k=55 Stress Echo: k=226 Exercise SPECT: k=48	ICA: DS cut-off at 50% or above

Study Country	Quality appraisal ^a	Review aim/question Population	Inclusion/exclusion criteria	Intervention Number of studies included in MA	Reference standard
	of bias	Pooled meta-analyses of studies included in 11 SRs Analysis at patient level	PubMed and the Cochrane Library Inclusion criteria: Meta-analyses on the diagnostic performance of non-invasive imaging tests for the diagnosis of CAD with ICA as the reference standard; the absolute numbers of true positives, false negatives, true negatives and false positives of the source studies were available or derivable from the meta-analyses, or from the authors Exclusion criteria: Meta-analyses published before 1990	Stress SPECT: k=103	
Iskandar et al. (2013) USA	64% (7/11) Good quality with low risk of bias	To perform an SR and bivariate meta-analysis to compare the diagnostic accuracy of SPECT MPI between men and women Patients with known or suspected CAD Analysis at patient level	Search period: From inception to January 2012 Databases searched: Medline and EMBASE, bibliographies of review articles and relevant chapters of central cardiology textbooks Inclusion criteria: English-language literature; prospective studies that provided patient level; gender-specific true and false positives and negatives of at least 20 patients Exclusion criteria: Studies that explicitly stated they were retrospective or reported data of <20 patients of one gender; in case of overlapping publication of study cohorts, only largest study was included	SPECT MPI: In women: k=17 In men: k=13	ICA: DS cut-off at 50%
Jaarsma et al. (2012) The Netherlands and UK	36% (4/11) Moderate quality with a moderate risk of bias	To determine the diagnostic accuracy of the most commonly used non-invasive myocardial perfusion imaging modalities, for the diagnosis of obstructive CAD	Search period: January 1990 to February 2010 Databases searched: PubMed Inclusion criteria:	Stress perfusion: SPECT: k=105 SP-CMR: k=27	ICA: DS cut-off at 50% or above

Study Country	Quality appraisal ^a	Review aim/question Population	Inclusion/exclusion criteria	Intervention Number of studies included in MA	Reference standard
		<p>Patients who were referred for suspected or known CAD</p> <p>Analysis at patient and coronary artery level</p>	<p>English literature; a perfusion imaging modality was included in the meta-analysis if >10 studies reporting patient-based results of diagnostic accuracy</p> <p>Studies that reported cases in absolute numbers of true positive, false positive, true negative and false negative results, or if these data were derivable</p> <p>Different articles by the same author or research group were included for analysis only when it was obvious that different patient samples were used</p> <p>Exclusion criteria:</p> <p>Studies conducted with: phantom-only models; animals; normal healthy volunteers only; or included <10 patients</p>		
<p>Janne d'Othee et al. (2008)</p> <p>USA</p>	<p>18% (2/11)</p> <p>Poor quality with a high risk of bias</p>	<p>To perform an SR of diagnostic accuracy of contrast-enhanced CTCA</p> <p>Patients with known or suspected CAD</p> <p>Analysis at patient and segment level</p>	<p>Search period:</p> <p>1 January 1990 to 1 March 2006</p> <p>Databases searched:</p> <p>Medline and EMBASE</p> <p>Inclusion criteria:</p> <p>Studies that used contrast-enhanced CTCA as a diagnostic test; evaluated native CAs; used ICA as a reference standard independently of CTCA findings; reported raw data (i.e. numbers that allowed recalculation of 2 × 2 contingency tables); and were published in peer-reviewed journals</p> <p>Exclusion criteria:</p> <p>Animal, autopsy and phantom studies as well as human studies on CABG and/or stent placement</p>	<p>Contrast-enhanced multidetector CTCA: k=28</p>	<p>ICA: DS cut-off at 50% or above</p>
<p>Jiang et al. (2014)</p> <p>China</p>	<p>55% (6/11)</p> <p>Moderate quality with a moderate risk of bias</p>	<p>To perform a meta-analysis to compare the diagnostic performance of single-source 64-section CTCA versus dual-source CTCA for diagnosis of CAD</p>	<p>Search period:</p> <p>Published until June 2013</p> <p>Databases searched:</p> <p>The Cochrane Library, MEDLINE and EMBASE</p>	<p>Single-source 64-slice CTCA: k=24</p> <p>Dual-source CTCA: k=18</p>	<p>ICA: DS cut-off at 50%</p>

Study Country	Quality appraisal ^a	Review aim/question Population	Inclusion/exclusion criteria	Intervention Number of studies included in MA	Reference standard
		Patients with known or suspected CAD Analysis at patient and segment level	Inclusion criteria: Studies that reported significant CAD defined as 50% reduction in luminal diameter by using ICA as the reference standard; single-source 64-section CTCA or dual-source CTCA was used; results reported in absolute numbers of true positives, false positives, true negatives and false negatives or sufficiently detailed data for deriving these numbers Exclusion criteria: Studies that included patients who had undergone CABG surgery; patients who had undergone PCI for stent patency assessment; a subset of patients who underwent prior heart transplantation; fewer than 30 enrolled patients		
Kwok et al. (1999) USA	18% (2/11) Poor quality with a high risk of bias	To determine the accuracy of the exercise ECG, exercise thallium and exercise Echo for the diagnosis of CAD in women Women with known or suspected CAD Analysis at patient level	Search period: January 1966 to December 1995 Databases searched: Medline Inclusion criteria: Studies with data on ≥50 women who underwent at least one of the exercise tests and ICA; data presented in a manner that allowed calculation of sensitivity and specificity of tests separately for women Exclusion criteria: Non-English language studies; abstracts and studies where exercise tests were done for post-MI risk stratification or post-angioplasty evaluation	Exercise ECG: k=19	ICA: DS cut-off at 50% or above
Lapado et al. (2013) USA	36% (4/11) Moderate quality with a moderate risk of bias	To evaluate the potential impact of referral bias on diagnostic effectiveness and clinical decision-making Patients with and without	Search period: January 1990 to November 2012 Databases searched: PubMed and EMBASE Inclusion criteria:	Exercise Echo: k=15 Exercise SPECT MPI: k=30 Performed to detect or evaluate CAD	ICA: DS cut-off at 50% or above

Study Country	Quality appraisal ^a	Review aim/question Population	Inclusion/exclusion criteria	Intervention Number of studies included in MA	Reference standard
		previously known CAD DA studies identified from previously published meta-analyses Analysis at patient level	English-language articles reporting cardiac catheterisation referral rates after normal or abnormal exercise MPI and Echo; studies enrolling patients with a history of MI or revascularisation included if they comprised <15% of the study population Exclusion criteria: Enrolled only patients with history of MI or revascularisation; enrolled patients with unstable coronary syndromes; majority of patients underwent pharmacological stress testing		
Li et al. (2014) China	45% (5/11) Moderate quality with a moderate risk of bias	To systematically analyse the performance of CMR perfusion to diagnose CAD with FFR as the reference standard Patients with known or suspected CAD Analysis at patient and coronary artery level	Search period: Not reported Databases searched: PubMed and EMBASE Inclusion criteria: English-language studies evaluating the accuracy of CMR perfusion with FFR as the reference standard; reported results in absolute numbers of true-positive, false-positive, true-negative and false-negative results, or sufficiently detailed data were provided to derive these numbers Exclusion criteria: Included patients with a history of CABG or PCI; retrospective studies; with duplicate or overlapping data	CMR perfusion: k=8	FFR: diagnostic cut-off at 0.75 or above
Mc Ardle et al. (2012) Canada	45% (5/11) Moderate quality with a moderate risk of bias	To evaluate the accuracy of rubidium (Rb)-82 PET for the diagnosis of obstructive CAD in comparison with SPECT Patients with known or suspected CAD Analysis at patient level	Search period: Updated previous searches for PET (up to 2006) and SPECT (up to 2009) Included studies published after January 2005 for PET and after January 2008 for SPECT and up to 14 March 2012 Databases searched: Ovid Medline, Medline In-Process and Other Non-indexed Citations, Ovid HealthSTAR, EMBASE and the Cochrane Library	Technetium (Tc)-99m SPECT with both ECG-gating and AC with either CT or transmission sources as an imaging modality: k=8	ICA: DS cut-off at 50% or above

Study Country	Quality appraisal ^a	Review aim/question Population	Inclusion/exclusion criteria	Intervention Number of studies included in MA	Reference standard
			<p>Inclusion criteria:</p> <p>Prospective, observational and retrospective studies, and case series published in peer-reviewed journals; involving humans using either PET, or technetium (Tc)-99m SPECT where ICA was used as a reference standard for diagnosis of obstructive CAD</p> <p>Studies where data was available to calculate true positives, true negatives, false positives and false negatives, and where accuracy data was reported on a per-patient basis</p> <p>Exclusion criteria:</p> <p>Abstracts and trials involving patients with non-IHD</p>		
Medical Advisory Secretariat (2010a) Canada	36% (4/11) Moderate quality with a moderate risk of bias	<p>What is the diagnostic accuracy of CMR in the diagnosis of patients with known or suspected CAD compared with ICA?</p> <p>Patients with suspected or known CAD</p> <p>Analysis at patient level</p>	<p>Search period:</p> <p>Update of Nandalur et al. (2007)</p> <p>1 January 2005 to 9 October 2008</p> <p>Databases searched:</p> <p>OVID Medline, Medline In-Process and Other Non-Indexed Citations, EMBASE, Cinahl, the Cochrane Library and INAHTA</p> <p>Inclusion criteria:</p> <p>HTAs, SRs, RCTs and observational studies with ≥20 adult patients with suspected or known CAD enrolled, and results by patient</p> <p>Exclusion criteria:</p> <p>Non-English studies and grey literature; studies with patients with recent MI; non-IHD; special populations (e.g. women, diabetics)</p>	<p>SP-CMR: k=23</p> <p>CMR wall motion analysis: k=13</p>	ICA: DS cut-off at 50%
Medical Advisory Secretariat (2010b) Canada	45% (5/11) Moderate quality with a moderate	To determine the accuracy of 64-slice CTCA compared with ICA in the diagnosis of CAD in stable (non-emergent) symptomatic	<p>Search period:</p> <p>1 January 2004 to 20 July 2009</p> <p>Included 5 studies identified in the HTA by Van Brabandt et al. (2008)</p>	64-slice CTCA: k=10	ICA: DS cut-off at 50%

Study Country	Quality appraisal ^a	Review aim/question Population	Inclusion/exclusion criteria	Intervention Number of studies included in MA	Reference standard
	risk of bias	patients Patients with suspected or known CAD Analysis at patient level	Databases searched: OVID Medline, Medline In-Process and Other Non-Indexed Citations, EMBASE, Cinahl, the Cochrane Library and INAHTA Inclusion criteria: English- or French-language HTAs, English-language SRs, RCTs and non-randomised clinical trials and observational studies with symptomatic adult patients at intermediate PTP of CAD Exclusion criteria: Non-English studies; studies with paediatric patients; patients with low or high PTP of CAD or non-IHD		
Medical Advisory Secretariat (2010c) Canada	36% (4/11) Moderate quality with a moderate risk of bias	To compare Echo performed with microsphere contrast agents to Echo performed without contrast and to SPECT Patients with suspected or known CAD Analysis at patient level	Search period: 1 January 2004 until 30 June 2009 Databases searched: OVID Medline, Medline In-Process and Other Non-Indexed Citations, EMBASE, the Cochrane Library and INAHTA Inclusion criteria: HTAs, SRs, RCTs and observational studies with ≥ 20 adult patients for the diagnosis of CAD Exclusion criteria: Non-systematic reviews, case reports and grey literature (e.g. conference abstracts)	Stress contrast Echo: k=10	ICA: DS cut-off at 50% or above
Medical Advisory Secretariat (2010d) Canada	36% (4/11) Moderate quality with a moderate	What is the diagnostic accuracy of SPECT for the diagnosis of CAD compared with the reference standard of ICA?	Search period: Update of SR by Heijenbrok-Kal et al. (2007) 1 January 2002 to 30 October 2009 Databases searched:	Stress SPECT: vs $\geq 50\%$ DS: k=51 vs $\geq 70\%$ DS: k=12	ICA: DS cut-off at 50% or above

Study Country	Quality appraisal ^a	Review aim/question Population	Inclusion/exclusion criteria	Intervention Number of studies included in MA	Reference standard
	risk of bias	Patients with suspected or known CAD Analysis at patient level	OVID Medline, Medline In-Process and Other Non-Indexed Citations, EMBASE, the Cochrane Library and INAHTA Inclusion criteria: SRs, RCTs and observational studies with ≥ 20 adult patients for the diagnosis of CAD; with data available to calculate true positives, false positives, false negatives and true negatives on a patient level Exclusion criteria: Non-systematic reviews, case reports and grey literature (e.g. conference abstracts); studies using planar imaging only, conducted in patients with non-IHD; and those conducted exclusively among special populations (e.g. patients with LBBB, diabetics, minority populations)		
Menke and Kowalski (2015) Germany	64% (7/11) Good quality with low risk of bias	To meta-analyse diagnostic accuracy, test yield and utility of CTCA in CAD by an intention-to-diagnose approach with inclusion of unevaluable results Patients with suspected or known CAD Analysis at patient level	Search period: January 2005 to March 2013 Databases searched: PubMed, Scopus, BIOSIS and Web of Science Inclusion criteria: Prospective study that included patients with suspected or known CAD; the reference standard was performed in all patients; assessed $\geq 50\%$ coronary stenosis on the patient level in at least 20 patients; 3x2 count data could be reconstructed for CCTA (positive, negative or unevaluable) versus ICA (positive or negative) at the patient level and, optionally, also on the segment level Exclusion criteria: None reported	16–40 row CTCA: k=7 64–320 row CTCA: k=22	ICA: DS cut-off at 50%
Mowatt et al. (2008) UK	73% (8/11) Good quality with	To assess the clinical effectiveness and cost-effectiveness, in different patient groups, of the use of 64-slice or higher CTCA,	Search period: 2002 to November 2006 Databases searched:	≥ 64 -slice CTCA: k=41	ICA: DS cut-off at 50% or above

Study Country	Quality appraisal ^a	Review aim/question Population	Inclusion/exclusion criteria	Intervention Number of studies included in MA	Reference standard
	a low risk of bias	instead of ICA, for diagnosing people with suspected CAD and assessing people with known CAD Patients with suspected or known CAD Analysis at patient and segment level	Medline, EMBASE, BIOSIS, Science Citation Index, Medline In-Process, The Cochrane Library, DARE, HTA Database and Health Management Information Consortium, recent conference proceedings and reference lists of all included studies Inclusion criteria: RCTs or prospective/retrospective non-randomised comparative studies or case series that used 64-slice or higher multislice CTCA compared with ICA or long-term follow-up as the reference standard in adults undergoing CTCA for the detection of CAD; reported cases in absolute numbers of true-positive, false-positive, true-negative and false-negative results or stated data adequate to derive this information Exclusion criteria: None reported		
Nandalur et al. (2007) USA	55% (6/11) Moderate quality with a moderate risk of bias	To conduct an evidence-based evaluation of stress CMR in the diagnosis of CAD Patients with suspected or known CAD Analysis at coronary artery level (patient-level data included in SR by Medical Advisory Secretariat (2010a))	Only include vessel-level data as patient level data was updated by Medical Advisory Secretariat (2010a) Search period: January 1990 to January 2007 Databases searched: Medline and EMBASE Inclusion criteria: Studies that used stress CMR as a diagnostic test for obstructive CAD, with $\geq 50\%$ DS selected as the threshold for significant CAD, using catheter-based X-ray angiography as the reference standard; reported cases in absolute numbers of true-positive, false-positive, true-negative and false-negative results or stated data adequate to derive this information. Studies were eligible regardless of whether they were referred for suspected or known CAD and regardless of technique used for stress CMR. Exclusion criteria:	SP-CMR: k=16	ICA: DS cut-off at 50% or above

Study Country	Quality appraisal ^a	Review aim/question Population	Inclusion/exclusion criteria	Intervention Number of studies included in MA	Reference standard
			Meeting abstracts; studies performed in phantom-only models or animals; studies that used normal healthy volunteers or included <10 patients		
Nielsen et al. (2014) Denmark	64% (7/11) Good quality with low risk of bias	To systematically review and perform a meta-analysis of the diagnostic accuracy and post-test outcomes of conventional exercise ECG and SPECT compared with CTCA Patients with suspected stable CAD Analysis at patient level	Search period: January 2002 and February 2013 Databases searched: PubMed, EMBASE and Cochrane Library Inclusion criteria: Studies that reported the diagnostic accuracy of CTCA compared with exercise ECG and/or SPECT. with ICA as a reference standard, and results were reported so that a 2 x 2 table of results could be constructed Exclusion criteria: Studies that did not fully report relevant data, and studies using systems older than 16-slice CTCA	≥16-slice CTCA: k=7 Exercise ECG: k=7 SPECT meta-analysis excluded from this SR as ICA not performed on all patients in included studies	ICA: DS cut-off at 50% or above
Ollendorf et al. (2011) USA	45% (5/11) Moderate quality with a moderate risk of bias	Focus targeted at the use of CTCA to evaluate patients at low-to-intermediate CAD risk for (a) acute chest pain of unknown origin in an emergency department setting; and (b) stable chest pain symptoms in an outpatient setting Patients with suspected CAD Analysis at patient level	Search period: January 2005 (the first year of published studies from 64-slice scanners) to February 2010 Databases searched: Medline, EMBASE and The Cochrane Library Inclusion criteria: Studies that used ICA as the reference standard in all or a random sample of patients; reported results at the patient level or whose results could be used to construct per-patient findings; estimation of degree of stenosis was determined by visual inspection alone; and evaluated accuracy in native CAs only Exclusion criteria: Studies that did not include blinded review of both CTCA and ICA; had an elapsed time between CTCA and ICA >3 months	64-slice CTCA: k=42	ICA: DS cut-off at 50% or above

Study Country	Quality appraisal ^a	Review aim/question Population	Inclusion/exclusion criteria	Intervention Number of studies included in MA	Reference standard
Paech and Weston (2011) Australia	27% (3/11) Poor quality with a high risk of bias	To summarise recent evidence pertaining to the clinical effectiveness of 64-slice CTCA in patients with suspected CAD Patients with suspected CAD Analysis at patient, segment and vessel level	Search period: Based on a previous HTA of the clinical effectiveness and cost-effectiveness of 64-slice or higher CTCA as an alternative to ICA in the investigation of CAD with an end search date end of December 2006 Searched for studies published December 2006 to March 2009 Databases searched: EMBASE, Medline, the Cochrane library and HTA databases Inclusion criteria: English-language studies that compared the diagnostic accuracy of CTCA with ICA in patients with suspected CAD Exclusion criteria: Prognostic studies; technical studies (e.g. image quality); assessment studies; post-revascularisation studies; conference abstracts Studies that used the wrong intervention (i.e. not 64-slice or higher CTCA); did not report diagnostic performance results relating to the identified outcome of interest ($\geq 50\%$ stenosis); or had fewer than 50 study participants receiving both CTCA and reference standard	64-slice CTCA: k=18	ICA: DS cut-off at 50%
Salavati et al. (2012) Germany, Iran and USA	55% (6/11) Moderate quality with a moderate risk of bias	To perform an SR of diagnostic accuracy of dual-source CTCA in the diagnosis of CAD Patients with suspected or known CAD Analysis at patient and segment level	Search period: English-, German- and French-language literature published between 1 January 2005 and 1 March 2011 Databases searched: Medline, EMBASE, ISI Web of Science, BIOSIS, Cochrane Controlled Trials Register, Cochrane Database of Systematic Reviews and Databases of Abstracts of Reviews of Effectiveness and Health Technology Assessment Inclusion criteria: Studies that included consecutive patients who underwent both dual-source CTCA as the index test and ICA as the reference standard; enrolled patients with	Dual-source CTCA: k=25	ICA: DS cut-off at 50%

Study Country	Quality appraisal ^a	Review aim/question Population	Inclusion/exclusion criteria	Intervention Number of studies included in MA	Reference standard
			<p>suspected or known CAD; significant CAD was defined as $\geq 50\%$; reduction in luminal diameter on both CTCA and ICA was considered a positive test result; results were regarded positive if CTCA was able to detect at ≥ 1 significant stenosis at the respective level; and sufficient data were reported to construct a 2 x 2 table of test performance</p> <p>Exclusion criteria:</p> <p>Studies that used imaging modalities other than ICA as the reference standard; the entire study group did not receive the reference standard; retrieval of raw data of accuracy estimates was not possible; duplicate inclusion of patients from other studies; assessment of in-stent restenosis; patients had received a heart transplant; animal studies; in-vitro studies; and review articles, meeting abstracts, case reports, editorials and letters</p>		
Schuetz et al. (2010) Germany	55% (6/11) Moderate quality with a moderate risk of bias	To compare CT and CMR for ruling out clinically significant CAD in adults with suspected or known CAD Patients with suspected or known CAD Analysis at patient level (suspected CAD subgroup)	<p>Search period:</p> <p>From inception to 2 June 2009</p> <p>Databases searched:</p> <p>PubMed, EMBASE, and ISI Web of Science</p> <p>Inclusion criteria:</p> <p>Studies that compared CTCA or CMR with ICA as the reference standard; had a prospective design; used state-of-the-art CT scanners (12 simultaneous detector rows) and CMR approaches (3-dimensional sequence); used diameter reduction of $\geq 50\%$ as the cut-off criterion for clinically significant CA stenoses for all patients; provided absolute numbers for 2 x 2 data at the patient level; and were published in English or German</p> <p>Exclusion criteria:</p> <p>Studies that explicitly stated that they were retrospective or reported populations that potentially overlapped with other studies</p>	<p>≥ 12-slice CTCA: k=89 for known and suspected CAD k=45 for suspected CAD</p> <p>CMR: excluded as not perfusion</p>	ICA: DS cut-off at 50% or above
Schuijf et al. (2006)	9% (1/11)	To evaluate the accuracies of MRI and MSCT in the	<p>Search period:</p> <p>January 1990 to January 2005</p>	<p>16-slice CTCA: k=11 CMR: not perfusion</p>	ICA: DS cut-off at 50%

Study Country	Quality appraisal ^a	Review aim/question Population	Inclusion/exclusion criteria	Intervention Number of studies included in MA	Reference standard
Belgium	Poor quality with a high risk of bias	detection of CAD Patients with suspected or known CAD Analysis at segment level	Databases searched: Medline plus a manual search of cardiology and radiology journals Inclusion criteria: Studies that performed a head-to-head comparison between non-invasive angiography and either CMR or CTCA and ICA in patients with known or suspected CAD Exclusion criteria: Abstracts, reviews and articles written in language other than English; studies with duplicated data or with insufficient data to calculate sensitivity and specificity on a segmental basis		
Stein et al. (2008) USA	18% (2/11) Poor quality with a high risk of bias	To assess the accuracy of 64-slice CTCA for the diagnosis of CAD Patients suspected of having CAD or a worsening of known CAD Analysis at patient and segment level	Search period: Up to 28 November 2007 Databases searched: Medline, OLDMEDLINE, OVID and the Cochrane Library database Inclusion criteria: Studies using 64-slice CTCA compared with a reference standard of ICA or intravascular ultrasound (IVUS) Studies that were performed prospectively; sensitivity and specificity of CTCA were reported or calculable from the data; criteria for selection of patients were stated; readers of 64-slice CTCA were blinded to the results of reference standard; the decision to perform the reference diagnostic test was made independently of the results of 64-slice CT; the severity of CA stenoses was stated in sufficient detail to perform analysis of significant (50%) or severe (70%) stenoses Exclusion criteria: Abstracts, case reports, letters, comments, reviews, animal studies, in-vitro studies, case series with ≤ 10 patients, retrospective studies and studies of electron-beam CT; those limited to methods, plaque characterisation or minor vessel wall	64-slice CTCA: k=23	ICA: DS cut-off at 50% or above

Study Country	Quality appraisal ^a	Review aim/question Population	Inclusion/exclusion criteria	Intervention Number of studies included in MA	Reference standard
			abnormalities		
Sun and Ng (2012) Australia	64% (7/11) Good quality with low risk of bias	To perform an SR and meta-analysis of the diagnostic value of prospective ECG-gating CTCA compared with ICA in the diagnosis of CAD Patients with suspected or known CAD Analysis at patient, vessel and segment level	Search period: January 2008 to December 2011 Databases searched: Medline, PubMed, EMBASE and the Cochrane Library databases Inclusion criteria: Studies that included at least 10 patients with suspected or known CAD for evaluation of CAD, with >50% lumen stenosis defined as the cut-off criterion; assessment of diagnostic value of prospective ECG-gating 64- or more-slice CTCA in CAD must be addressed at either patient-based, vessel-based or segment-based analysis when compared with ICA in terms of sensitivity, specificity, PPV and (NPV; the absolute number of true-positive, true-negative, false-positive and false-negative results were available or could be derived from available data; the effective dose of prospective ECG-gating protocols was reported in each study Exclusion criteria: Studies with patients after treatment of CABG or PCI; potential duplication or overlapping data	ECG-gating using ≥64-slice CTCA: k=14	ICA: DS cut-off at 50%
Van Brabandt et al. (2008) Belgium	36% (4/11) Moderate quality with a moderate risk of bias	HTA summarising the current evidence supporting the use of multislice CTCA as a diagnostic aid in patients suspected for CAD Patients with suspected CAD Analysis at patient level	Search period: Studies published after those included in the SR by Abdulla et al. (2007) 1 January 2007 to 10 March 2008 Databases searched: Medline (through PubMed), EMBASE and SUMSearch Inclusion criteria: SRs and diagnostic studies that enrolled at least 30 patients with proven or suspected CAD, using 64-(or higher)slice CTCA compared with ICA as the reference to identify significant stenosis; that provided per-patient data on native	64-slice CTCA: k=9	ICA: DS cut-off at 50%

Study Country	Quality appraisal ^a	Review aim/question Population	Inclusion/exclusion criteria	Intervention Number of studies included in MA	Reference standard
			CAs Exclusion criteria: None reported		
von Ballmoos et al. (2011) USA	82% (9/11) Good quality with low risk of bias	To summarise current evidence about the ability of low-dose CTCA to rule out CAD in symptomatic adults Patients with suspected CAD Analysis at patient, vessel and segment level	Search period: From inception to 31 October 2010 Databases searched: Medline, EMBASE, BIOSIS, Cinahl, the Cochrane Library, ISI Web of Knowledge, Faculty of 1000 and abstract databases (CAB Abstracts and Zetoc), without language restrictions Inclusion criteria: Primary reason for referral was clinical suspicion of symptomatic CAD Exclusion criteria: Studies that evaluated CTCA as a possible screening tool for asymptomatic patients	Multidetector row CT scanner with at least 64 detectors patient level: k=13 segment level: k=13 vessel level: k=12	ICA: DS cut-off at 50% or above
Zhou et al. (2014) China	55% (6/11) Moderate quality with a moderate risk of bias	To illustrate the accuracy of myocardial perfusion SPECT to diagnose functional stenotic CAD, with FFR as reference standard Patients with suspected CAD Analysis at patient level	Search period: Not reported Databases searched: PubMed, EMBASE and Cochrane Library Inclusion criteria: Studies where the true positives, false positives, true negatives and false negatives were available, could be calculated or could be obtained by contacting the authors Exclusion criteria: Studies that enrolled patients undergoing PCI or CABG, or had prior heart transplants	Perfusion SPECT: k=13	FFR: diagnostic cut-off at 0.75 or above

^a The AMSTAR checklist (Shea et al. 2007) was used to appraise the quality of the SRs

ACS = acute coronary syndrome; CA = coronary artery; CABG = coronary artery bypass graft; CACS = coronary artery calcium score; CAD = coronary artery disease; CMR = cardiac magnetic resonance imaging; CTCA = computed tomography coronary angiography; DS = diameter stenosis; ECG = electrocardiogram; Echo = echocardiography; FFR = fractional flow rate; HTA = health technology assessment; ICA = invasive coronary angiography; MPI = myocardial perfusion imaging; NPV = negative predictive value; PCI = percutaneous coronary intervention; PET = positron emission tomography; PET/CT = positron emission tomography / computed tomography; PPV = positive predictive value; PTP = pre-test probability; RCT = randomised controlled trial; SP-CMR = stress perfusion CMR; SPECT = single-photon emission computed tomography; SR = systematic review; T = tesla

Table 145 Study profiles of included studies for the prognostic value of SP-CMR with/without LGE (population 1)

Study	Study design / Quality appraisal	Study population	Inclusion/exclusion criteria/	Intervention	Key outcomes
Abbasi et al. (2014) USA	Level IV: CS Quality: (IHE 9/12) Low risk of bias	N=346 patients with suspected ischaemia, or symptoms suspicious of CAD Mean age: 55.1±14.8 years Male: 60.7%	Inclusion criteria: Patients >18 years of age and referred for assessment of symptoms suspicious of CAD Exclusion criteria: Severe renal dysfunction (glomerular filtration rate <30 mL/minute), acute coronary syndromes, pregnancy or absolute contraindication to CMR	MRI machine: 3.0-T scanner with 16-element coil Stress agent: Regadenoson Protocol for CMR: Vasodilator MPI, ventricular function and LGE imaging Follow-up: Median 1.9 years	NRI due to inducible ischaemia result
Bingham & Hachamovitch (2011) USA	Level IV: CS Quality: (IHE 8.5/12) Moderate risk of bias	N=908 patients with suspected coronary stenosis and/or ischaemia Age, median = 65 years (25 th , 75 th percentiles: 55, 74) Male: 59%	Inclusion criteria: Referred for stress CMR Exclusion criteria: Moderate to severe valvular disease	MRI machine: 1.5-T scanner Stress agent: Adenosine Protocol for CMR: Adenosine stress perfusion, myocardial delayed enhancement, LV volumes and function, and aortic blood flow Follow-up: Median (25 th , 75 th percentiles): 948 days (639, 1,263)	NRI due to inducible ischaemia result
Lipinski et al. (2013) Locations not stated	Level II: SR Quality: (AMSTAR 9/11) Low risk of bias	k=19 included studies that enrolled patients with known or suspected CAD	Search period: From inception to October 2012 Databases searched: Cochrane CENTRAL, meta-Register of Controlled Trials, and PubMed Inclusion criteria: Studies assessing for myocardial ischemia with stress CMR, with 6 months of prognostic follow-	SP-CMR with/without LGE Follow-up: >6 months	Prognostic value of SP-CMR and LGE

Study	Study design / Quality appraisal	Study population	Inclusion/exclusion criteria/	Intervention	Key outcomes
			up data including cardiac death and/or MI Exclusion criteria: Study populations composed of patients with cardiomyopathy or acute MI within the past 14 days		
Shah et al. (2013) USA	Level IV: CS Quality: (IHE 10/12) Low risk of bias	N=815 patients with suspected myocardial ischaemia in patients with suspected or known CAD Mean age: 56 ± 14 years Male: 60%	Inclusion criteria: Patients >18 years of age with clinical suspicion of myocardial ischaemia Exclusion criteria: Absolute contraindication to CMR (e.g. metallic hazards, pregnancy, severe renal dysfunction) or contraindications to vasodilator stress testing	MRI machine: 1.5-T scanner for 381 patients (47%) enrolled pre-2006 3.0-T scanner used post-2006 for 434 patients (53%) Stress agent: Adenosine (n=396); regadenoson (n=389); dipyridamole (n=30) Protocol for CMR: Stress and rest MPI, ventricular function and LGE Follow-up: 8 years	NRI due to inducible ischaemia result Risk reclassification

CAD = coronary artery disease; CMR = cardiac magnetic resonance imaging; CS = case series; LGE = late gadolinium enhancement; MI = myocardial infarction; MPI = myocardial perfusion imaging; MRI = magnetic resonance imaging; NRI = net reclassification improvement; SP-CMR = stress perfusion cardiac magnetic resonance imaging; T = tesla

Table 146 Study profiles of included studies for impact on clinical management (population 1)

Study	Study design / Quality appraisal	Study population	Inclusion/exclusion criteria/ objectives	Intervention	Comparator	Outcomes assessed for change in management
Abbasi et al. (2014) USA	Level IV: CS Quality: 9/12 Low risk of bias	N=346 patients referred for assessment of symptoms suggesting CAD Mean age: 55.1±14.8 years Male: 60.7% Ethnicity: NR	Inclusion criteria: Patients >18 years of age and showing symptoms suggesting CAD Exclusion criteria: Severe renal dysfunction (glomerular filtration rate <30 mL/minute); acute coronary syndromes; pregnancy; absolute	Setting: Hospital (specialist imaging division) / medical school MRI machine: 3.0-T scanner with 16-element coil Stress agent: Regadenoson Protocol for CMR: Protocol consisted of vasodilator MPI, ventricular function and LGE imaging Follow-up: Median 1.9 years	NA	Reclassification of risk for MACE by addition of inducible ischaemia ^a ('Model') across pre-CMR clinical risk categories ('Model 1') NRI across all risk categories NRI for patients at intermediate risk pre-

Study	Study design / Quality appraisal	Study population	Inclusion/exclusion criteria/ objectives	Intervention	Comparator	Outcomes assessed for change in management
			<p>contraindication to CMR</p> <p>Objective:</p> <p>To determine whether the addition of regadenoson stress CMR to a clinical risk model can be used for reclassification of cardiovascular risk</p>			<p>CMR</p> <p>Continuous NRI</p>
<p>Bingham & Hachamovitch (2011)</p> <p>USA</p>	<p>Level IV: CS</p> <p>Quality: 8.5/12</p> <p>Moderate risk of bias</p>	<p>N=932 patients referred to stress CMR of whom 908 (98%) were included in the final analysis</p> <p>Age, median (25th, 75th percentiles): 65 years (55, 74)</p> <p>Male: 59%</p> <p>Ethnicity: NR</p>	<p>Inclusion criteria:</p> <p>Referred for stress CMR</p> <p>Exclusion criteria:</p> <p>Moderate to severe valvular disease</p> <p>Objective:</p> <p>To assess the incremental prognostic power of myocardial viability, vasodilator stress perfusion, and ventricular wall motion and volumes over patient clinical and historical data alone for the prediction of adverse cardiac events</p>	<p>Setting: Outpatient clinic</p> <p>MRI machine: 1.5-T scanner</p> <p>Stress agent: Adenosine</p> <p>Protocol for CMR: Adenosine stress perfusion, myocardial delayed enhancement, LV volumes and function and aortic blood flow</p> <p>Follow-up: Median (25th, 75th percentiles): 948 days (639, 1,263)</p>	NA	<p>Early referral to revascularisation</p> <p>Cardiovascular risk reclassification with the addition of LGE and stress perfusion models to model of baseline patient characteristics</p>

Study	Study design / Quality appraisal	Study population	Inclusion/exclusion criteria/ objectives	Intervention	Comparator	Outcomes assessed for change in management
Bodi et al. (2009) Spain	Level IV: CS Quality: 10/12 Low risk of bias	N=601 registry patients with chest pain of possible coronary origin and known or suspected CAD Mean age: 64 ± 11 years Male: 60% Ethnicity: NR	Inclusion criteria: Patients who underwent CMR between January 2003 and January 2007 Exclusion criteria: History of MI or coronary revascularisation in past 3 months, clinical instability, asthma or contraindications to CMR	Setting: One university hospital, Spain MRI machine: 1.5-T scanner Stress agent: Dipyridamole Protocol for CMR: WMAs at rest, hyperaemia PDs, LGE and inducible WMAs were analysed Follow-up: Mean (range) / median: 640 ± 360 (182–1,603) / 553 days	NA	Rate of ICA following SP-CMR according to the findings (WMA, PD and LGE) Rate of CMR-directed revascularisation
Bodi et al. (2012) Spain	Level IV: CS Quality: 10.5/12 Low risk of bias	N=1,797 registry patients with chest pain of possible coronary origin of whom 1,722 comprised the final study group Mean age: 64 ± 11 years Male: 62% Ethnicity: NR	Inclusion criteria: Underwent dipyridamole CMR Exclusion criteria: Acute coronary syndromes or any contraindication to dipyridamole CMR Objective: To evaluate dipyridamole CMR in the prediction of MACE	Setting: Two university hospitals MRI machine: 1.5-T scanner Stress agent: Dipyridamole Protocol for CMR: WMAs at rest, hyperaemia PDs, LGE and inducible WMAs were analysed Follow-up: Mean (range) / median: 55 ± 45 (24–78) / 44 weeks	NA	Rate of ICA following SP-CMR according to the findings (WMA, PD and LGE) Rate of CMR-directed revascularisation
Bruder et al. (2013) Europe	Level IV: CS Quality: 10.5/12 Low risk of bias	N=27,301 patients undergoing CMR (27,781 scans), of whom 34.2% were indicated for risk stratification in suspected CAD/ischaemia Mean age (range): 60 (47–70) years	Inclusion criteria: Patients who underwent CMR between April 2007 and June 2012 at participating European sites (n=57 centres) Exclusion criteria: Not explicit Objective:	Setting: 57 centres across 15 European countries MRI machine: All procedures in compliance with stress CMR 1-T: 134/27,699 scans (0.5%) 1.5-T: 25,899/27,699 scans (93.6) 3.0-T: 1,636/27,699 scans (5.9) Stress agent: None: 17,158/27,395	NA	Change in clinical diagnosis Therapeutic consequences (change in medication, invasive procedure, hospital discharge, hospital admission) Additional diagnostic procedures avoided due

Study	Study design / Quality appraisal	Study population	Inclusion/exclusion criteria/ objectives	Intervention	Comparator	Outcomes assessed for change in management
		Male: 65% Ethnicity: NR	To evaluate indications, image quality, safety and <i>impact on patient management</i> of clinical routine CMR in a multi-national European setting	scans (62.6%) Adenosine: 8,018/27,395 scans (29.3%) Dobutamine: 2,219/27,395 scans (8.1%) Protocol for CMR: In accordance with standardized stress CMR protocols Follow-up: Mean (IQR): 400 days (367–419); follow-up rate 90%		to results of CMR
Schonenberger et al. (2007) Germany	Level II: Cross-over study Quality: Reporting 9/10 External validity 1/3 Bias 6/7 Confounding 5/6 Total 21/26 Low risk of bias	N=111 patients with suspected CAD Mean age: 63 ± 8 years Male: 75% Ethnicity: NR	Inclusion criteria: No contraindications to CMR Exclusion criteria: Patients with contraindications (e.g. claustrophobia, implanted pacemakers) Objective: To compare the patient acceptability of CMR, CTCA and ICA	Setting: NR MRI machine: 1.5-T scanner with 12-element phased-array coil Stress agent: NR Protocol for CMR: Unclear Follow-up: NR	CTCA, ICA	Patient acceptability and preference
Shah et al. (2013) USA	Level IV: CS Quality: 10/12 Low risk of bias	N=815 patients referred for assessment of myocardial ischaemia, of whom 792 were included in the final analysis; 273/792 (34%) had previous CAD Mean age:	Inclusion criteria: Patients >18 years of age with clinical suspicion of myocardial ischaemia Exclusion criteria: Absolute contraindication to CMR (e.g. metallic hazards, pregnancy, severe renal dysfunction) or contraindications to vasodilator	Setting: General and specialist cardiology services within hospital MRI machine: 1.5-T scanner for 381 patients (47%) enrolled pre-2006 3.0-T scanner used post-2006 for 434 patients (53%) Stress agent: Adenosine (n=396); regadenoson (n=389); dipyridamole	NA	Change in risk classification with addition of inducible ischaemia to the clinical risk model for patients with and without MACE Overall risk reclassification by addition of inducible ischaemia to clinical risk

Study	Study design / Quality appraisal	Study population	Inclusion/exclusion criteria/objectives	Intervention	Comparator	Outcomes assessed for change in management
		56 ± 14 years Male: 60% Ethnicity: NR	stress testing Objective: To test the hypothesis that stress CMR effectively reclassifies patients across ACC/AHA-recommended cardiac risk categories, the basis for clinical management	(n=30) Protocol for CMR: Stress and rest MPI, ventricular function and LGE Follow-up: 8 years		model Categorical NRI Continuous NRI

*Determined according to stress perfusion protocol

ACC = American College of Cardiology; AHA = American Heart Association; CAD = coronary artery disease; CMR = cardiac magnetic resonance imaging; CS = case series; CTCA = computed tomography coronary angiography; ICA = invasive coronary angiography; LGE = late gadolinium enhancement; LV = left ventricular; MACE = major adverse cardiovascular events; MI = myocardial infarction; MPI = myocardial perfusion imaging; MRI = magnetic resonance imaging; NA = not applicable; NR = not reported; NRI = net reclassification improvement; PD = perfusion defect; T = tesla; WMA = wall motion abnormality

Table 147 Study profiles of included studies for impact of change in patient management (population 1)

Study	Study design / Quality appraisal	Study population	Inclusion/exclusion criteria/objectives	Intervention	Key outcomes
Bodi et al. (2009) Spain	Level III-2: Cohort Quality: 18/26 Reporting: 9/10 External validity: 3/3 Bias: 4/7 Confounding: 2/6 Moderate risk of bias	N=601 registry patients with chest pain of possible coronary origin and known or suspected CAD	Inclusion criteria: Patients who underwent CMR between January 2003 and January 2007 Exclusion criteria: History of MI or coronary revascularisation in past 3 months; clinical instability; asthma; or contraindications to CMR	Setting: One university hospital, Spain MRI machine: 1.5-tesla scanner Stress agent: Dipyridamole Protocol for CMR: WMAs at rest, hyperaemia PDs, LGE and inducible WMAs were analysed	Cardiac mortality and nonfatal MI
Bodi et al. (2012) Spain	Level III-2: Cohort Quality: 18/26 Reporting: 9/10 External validity: 3/3	N=1,722 registry patients with chest pain of possible coronary origin, of whom 1,722 comprised the final	Inclusion criteria: Patients who underwent dipyridamole CMR Exclusion criteria: Acute coronary syndromes; any	Setting: Two university hospitals MRI machine: 1.5-T scanner Stress agent: Dipyridamole Protocol for CMR: WMAs at rest,	Cardiac mortality and nonfatal MI

Study	Study design / Quality appraisal/	Study population	Inclusion/exclusion criteria/objectives	Intervention	Key outcomes
	Bias: 4/7 Confounding: 2/6/ Moderate risk of bias	study group Mean age: 64 ± 11 years Male: 62% Ethnicity: NR	contraindication to dipyridamole CMR Objective: To evaluate dipyridamole CMR in the prediction of MACE	hyperaemia PDs, LGE and inducible WMAs were analysed Follow-up: Mean (range) / median: 55 ± 45 (24–78) / 44 weeks	
Shah et al. (2013) USA	Level III-2: Cohort Quality: 12/26 Reporting: 4/10 External validity: 3/3 Bias: 3/7 Confounding: 2/6/ High risk of bias	N=815 patients referred for assessment of myocardial ischaemia, of whom 792 were included in the final analysis; 273/792 (34%) patients had previous CAD Mean age: 56 ± 14 years Male: 60% Ethnicity: NR	Inclusion criteria: Patients >18 years of age with clinical suspicion of myocardial ischaemia Exclusion criteria: Absolute contraindication to CMR (e.g. metallic hazards, pregnancy, severe renal dysfunction); contraindications to vasodilator stress testing Objective: To test the hypothesis that stress CMR effectively reclassifies patients across ACC/AHA-recommended cardiac risk categories, the basis for clinical management	Setting: General and specialist cardiology services within hospital MRI machine: 1.5-T scanner for 381 patients (47%) enrolled pre-2006 3.0-T scanner used post-2006 for 434 patients (53%) Stress agent: Adenosine (n=396); regadenoson (n=389); dipyridamole (n=30) Protocol for CMR: Stress and rest MPI, ventricular function and LGE Follow-up: 8 years	Cardiac mortality and nonfatal MI

ACC = American College of Cardiology; AHA = American Heart Association; CAD = coronary artery disease; CMR = cardiac magnetic resonance imaging; CS = case series; CTCA = computed tomography coronary angiography; ICA = invasive coronary angiography; LGE = late gadolinium enhancement; MACE = major adverse cardiovascular events; MI = myocardial infarction; MPI = myocardial perfusion imaging; MRI = magnetic resonance imaging; NR = not reported; PD = perfusion defect; T = tesla; WMA = wall motion abnormality

Table 148 Study profiles of included studies on diagnostic accuracy in population 2

Study Country	Study design Quality appraisal	Study population	Inclusion/exclusion criteria	Intervention (perfusion CMR with/without LGE)	Reference standard (ICA)
Becker et al. (2008) Germany	Level III-1 A comparison against independent, blinded	N=53 patients with ischemic LVD undergoing revascularisation	Inclusion criteria: Patients with LV dysfunction; in sinus rhythm	Scanner: 1.5-T whole-body scanner with a 5-element phased-array cardiac coil	Functional recovery at follow-up. Segmental functional recovery at follow-up, assessed using echocardiographic images at

Study Country	Study design Quality appraisal	Study population	Inclusion/exclusion criteria	Intervention (perfusion CMR with/without LGE)	Reference standard (ICA)
	reference standard among non-consecutive patients Quality: low risk of bias Patient selection: ? Index test: 😊 Reference standard: 😊 Flow and timing: 😊 Applicability: 😊	Mean age: 59 ± 8 years Male = 75%	Exclusion criteria: Non-ischemic cardiomyopathy; ACS; no revascularisation	Data acquisition: Prospectively ECG-gated gradient echo sequence with inversion pre-pulse Contrast agent: 0.2 mmol/kg body weight Gd-DTPA LGE: 15-minute delay	9 ± 2 months after revascularisation. A segment was considered to demonstrate functional improvement if it improved by at least 1 grade (1 = normokinetic, 2 = hypokinetic, 3 = akinetic, 4 = dyskinetic). Global functional recovery = increase in ejection fraction >5% at follow-up.
Becker et al. (2011) Germany	Level III-1 A comparison against independent, blinded reference standard among non-consecutive patients Quality: low risk of bias Patient selection: ? Index test: 😊 Reference standard: 😊 Flow and timing: 😊 Applicability: 😊	N=132 patients scheduled to undergo revascularisation Mean age: 56 ± 7 years Male = 64%	Inclusion criteria: WMAs; no unstable angina; class IV heart failure; contraindications to CMR; or severe valvular heart disease Exclusion criteria: Insufficient ECG window; refusing revascularisation	Scanner: 1.5-T whole body scanner with a 5-element phased-array cardiac coil Data acquisition: Prospectively ECG-gated gradient echo sequence with inversion pre-pulse Contrast agent: 0.2 mmol/kg body weight Gd-DTPA LGE: 15-minute delay	Functional recovery at follow-up. Segmental functional recovery at follow-up, assessed using echocardiographic images at 8 ± 2 months after revascularisation. A segment was considered to demonstrate functional improvement if it improved by at least 1 grade (1 = normokinetic, 2 = hypokinetic, 3 = akinetic, 4 = dyskinetic). Global functional recovery = increase in ejection fraction >5% at follow-up.
Bondarenko et al. (2007) The Netherlands	Level III-2 A comparison with reference standard (not blinded or blinding not known) Quality: low risk of bias Patient selection: ?	N=45 patients undergoing CABG (n=32) or PCI (n=13) Mean age: 62 ± 9 years Male = 84%	Inclusion criteria: Patients with known CAD and regional wall abnormalities on Echo or LV angiography, scheduled to undergo revascularisation Exclusion criteria:	Scanner: 1.5-T scanner Data acquisition: Prospectively ECG-gated gradient echo sequence with inversion pre-pulse Contrast agent: 0.2 mmol/kg body weight gadolinium-based	Functional improvement at follow-up (3 months after revascularisation) defined as increase in segmental wall thickness of ≥1.5 mm.

Study Country	Study design Quality appraisal	Study population	Inclusion/exclusion criteria	Intervention (perfusion CMR with/without LGE)	Reference standard (ICA)
	Index test: 😊 Reference standard: 😊 Flow and timing: 😊 Applicability: 😊		CMR contraindication	contrast agent LGE: 10–15-minute delay	
Gerber et al. (2002) USA	Level III-2 A comparison with reference standard (not blinded or blinding not known) Quality: low risk of bias Patient selection: ? Index test: 😊 Reference standard: ? Flow and timing: 😊 Applicability: 😊	N=20 patients hospitalised for first AMI. 6 patients were successfully revascularised by direct angioplasty, 12 patients received thrombolysis (8 of whom received angioplasty), 2 patients did not undergo revascularisation. Between baseline and follow-up, 4 patients had CABG Mean age: 61 ± 14 years Male = 65%	Inclusion criteria: AMI diagnosed by acute chest pain, increased creatine phosphokinase levels, characteristic ECG changes, and angiographically demonstrated partial or complete occlusion of the infarct related artery; haemodynamic stability; no contraindication to CMR Exclusion criteria: NR	Scanner: 1.5-T scanner using a phased-array coil wrapped around chest Data acquisition: Inversion-recovery prepared gated fast-gradient echo-pulse sequence Contrast agent: Gadodiamine, 0.1 mmol/kg body weight LGE: 10-minute delay	Recovery of Eulerian circumferential shortening strain, expressed as a fractional change of length of the myocardium between end diastole and systole and was defined as having a negative sign representing shortening (active contraction) and a positive sign representing stretching (passive deformation).
Glaveckaite et al. (2011) Lithuania	Level III-1 A comparison against independent, blinded reference standard among non-consecutive patients Quality: low risk of bias Patient selection: ? Index test: 😊 Reference standard: 😊 Flow and timing: 😊	N=46 patients with LVD (systolic): 3 with previous CABG 35 with 3 vessel disease 3 with 1 vessel disease Mean age: 63 ± 10 years Male = 85%	Inclusion criteria: CAD (>70% DS in one or more epicardial vessels); scheduled for a revascularisation procedure; LVEF ≤45%; at least two adjacent segments with WMAs at rest; no MI or revascularisation within the past 2 months Exclusion criteria: Contraindications to CMR	Scanner: 1.5-T scanner Data acquisition: Inversion recovery gradient-echo sequence triggered to end-diastole Contrast agent: 0.15 mmol/kg body weight Gd-DTPA2 or gadodiamide LGE: 10–15 minute delay	Functional improvement in segmental function at follow up at 6 months. Functional improvement was defined as improvement in wall motion of at least 1 grade, with the exception of improvement from grade 5 to grade 4 compared with baseline. (1=normal, 2=mild hypokinesia, 3=severe hypokinesia, 4=akinesia, 5=dyskinesia)

Study Country	Study design Quality appraisal	Study population	Inclusion/exclusion criteria	Intervention (perfusion CMR with/without LGE)	Reference standard (ICA)
	Applicability: 😊				
Glaveckaite et al. (2014) Lithuania	Level II A comparison against independent, blinded reference standard among consecutive patients Quality: low risk of bias Patient selection: 😊 Index test: 😊 Reference standard: 😊 Flow and timing: 😊 Applicability: 😊	N=42 patients with LVD undergoing surgical (n=32) or percutaneous (n=10) revascularisation Mean age: 65±10 years Male = 93%	Inclusion criteria: CAD (>70% DS in one or more epicardial vessels); scheduled for a revascularisation procedure; LVEF ≤45%; at least two adjacent segments with WMAs at rest; no MI or revascularisation within the past 2 months Exclusion criteria: Contraindications to CMR	Scanner: 1.5-T scanner Data acquisition: Inversion recovery gradient-echo sequence triggered to end-diastole Contrast agent: 0.15 mmol/kg body weight Gd-DTPA2 or gadodiamide LGE: 10–15-minute delay	Functional improvement in segmental function at follow up at 151 ± 27 weeks (35 ± 6 months; median 2.9 years, range 1.5–4.0 years). Functional improvement was defined as improvement in wall motion of at least 1 grade, with the exception of improvement from grade 5 to grade 4 compared with baseline (1 = normal, 2 = mild hypokinesia, 3 = severe hypokinesia, 4 = akinesia, 5 = dyskinesia)
Gutberlet et al. (2005) Germany	Level III-1 A comparison against independent, blinded reference standard among non-consecutive patients Quality: low risk of bias Patient selection: ? Index test: 😊 Reference standard: 😊 Flow and timing: ? Applicability: 😊	N=20 patients with triple-vessel CAD, severely impacted LV function (all patients underwent bypass surgery within 1 week after imaging) Mean age: 63.7 ± 7.3 years Male = 95%	Inclusion criteria: LVEF <45% measured by MRI Exclusion criteria: Contraindications to CMR	Scanner: 1.5-T imager using a thorax phased-array surface coil Data acquisition: T1-weighted 2D gradient echo sequence in breath-hold with an inversion prepulse to null viable myocardium was used. Contrast agent: 0.2 mmol/kg body weight Gd-DTPA LGE: 10–20-minute delay	Functional recovery at follow up (>6 months after surgery). This was examined with CMR and gated SPECT.
Kim et al. (2000) USA	Level II A comparison against independent, blinded	N=50 consecutive patients undergoing revascularisation	Inclusion criteria: Scheduled to undergo revascularisation; abnormalities	Scanner: 1.5-T imager, using a phased-array receiver coil Data acquisition: During	Improved contractility at follow-up (79 ± 36 days after revascularisation). The extent of wall thickening was agreed on by two observers and

Study Country	Study design Quality appraisal	Study population	Inclusion/exclusion criteria	Intervention (perfusion CMR with/without LGE)	Reference standard (ICA)
	reference standard among consecutive patients Quality: low risk of bias Patient selection: 😊 Index test: 😊 Reference standard: 😊 Flow and timing: 😊 Applicability: 😊	Mean age: 63 ± 11 years Male = 88%	in regional wall motion on contrast ventriculography or Echo; no unstable angina, New York Heart Association class IV heart failure; contraindications to CMR; gave informed consent Exclusion criteria: NR	breath-hold Contrast agent: 0.2 mmol/kg body weight gadolinium-based contrast agent LGE: 10–20-minute delay	graded on a five-point scale. 0 = normal, 1 = mild or moderate hypokinesia, 2 = severe hypokinesia, 3 = akinesia, 4 = dyskinesia).
Kuhl et al. (2006) Germany	Level II A comparison against independent, blinded reference standard among consecutive patients Quality: low risk of bias Patient selection: 😊 Index test: 😊 Reference standard: 😊 Flow and timing: 😊 Applicability: 😊	N=29 patients with chronic IHD, regional WMA and LVEF <50% with clinical indication for myocardial viability 15 patients underwent PCI with stent implantation and 14 patients underwent CABG. Mean age: 66 ± 9 years Male = 72%	Inclusion criteria: LVEF <50%; regional WMAs Exclusion criteria: Severe concomitant disease; previous pacemaker or defibrillator implementation; claustrophobia	Scanner: 1.5-T scanner using a 5-element phased array cardiac synergy coil Data acquisition: During breath-hold, segmented inversion-recovery gradient echo pulse sequence triggered to end-diastole Contrast agent: Gadolinium-based, 0.2 mmol/kg LGE: 15-minute delay	Regional functional recovery at follow-up (6 months). 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, as measured on a 5-point scale (1 = normal contractility, 2 = mild to moderate hypokinesia, 3 = severe hypokinesia, 4 = akinesia, 5 = dyskinesia)
Oh et al. (2015) Korea	Level III-1 A comparison against independent, blinded reference standard among non-consecutive patients Quality: low risk of bias Patient selection: ?	N=33 patients with multivessel CAD and a LVEF <35% being considered for CABG Mean age: 62.8 ± 9.7 years Male = 85%	Inclusion criteria: LVEF <35%; presence of LGE in pre-operative CMR; patients who underwent off-pump complete revascularisation for multivessel CAD (after pre-operative CMR); normal sinus rhythm at the time of CMR	Scanner: 1.5-T scanner Data acquisition: Segmented inversion-recovery spoiled gradient echo and phase-sensitive recovery methods Contrast agent: adopenetate dimeglumine, 0.2 mmol/kg	Improvement of segmental wall motion at follow-up (24.1 ± 17.6 months). Segmental wall motion was visually rated on a 5-point scale (0 = normokinesia, 1 = hypokinesia, 2 = akinesia, 3 = dyskinesia, 4 = aneurysm)

Study Country	Study design Quality appraisal	Study population	Inclusion/exclusion criteria	Intervention (perfusion CMR with/without LGE)	Reference standard (ICA)
	Index test: 😊 Reference standard: 😊 Flow and timing: ? Applicability: 😊		Exclusion criteria: Patients with a history of ST-segment elevated MI within 3 months pre-operatively; chronic renal failure; medical history such as malignant disease that limits the possibility of mid-term follow-up	LGE: 10-minute delay	
Pegg et al. (2010) UK	Level III-1 A comparison against independent, blinded reference standard among non-consecutive patients Quality: low risk of bias Patient selection: ? Index test: 😊 Reference standard: 😊 Flow and timing: 😊 Applicability: 😊	N=33 patients with impaired LV function accepted for surgery Mean age: 66 ± 8 years Gender: NR	Inclusion criteria: Impaired LV function; provided consent Exclusion criteria: Contraindications to CMR or gadolinium contrast; class IVb angina; 2 patients were excluded because of death, 1 had a cerebrovascular accident, and 2 had retained pacing wires	Scanner: 1.5-T scanner using prospective gating Data acquisition: T1-weighted segmented inversion-recovery turbo fast low-angle shot (FLASH) sequence Contrast agent: Gadodiamide, 0.1 mmol/kg LGE: 6-minute delay	Visual assessment of regional wall motion score using Argus software was undertaken by two observers, blinded to other data, at follow-up (6 months). Segments were graded according to a 5-point scale (1 = normally contracting and 5 = dyskinetic). Improvement was defined by an improvement of ≥1 functional grade (with exception of improvement from grades 5 to 4).
Regenfus et al. (2012) Germany	Level II A comparison against independent, blinded reference standard among consecutive patients Quality: low risk of bias Patient selection: 😊 Index test: 😊	N=56 patients with chronic IHD and LVD scheduled to undergo myocardial revascularisation (34 underwent CABG and 22 PCI with stent placement) Mean age: 63 ± 12 years Male = 79%	Inclusion criteria: Patients with chronic IHD and LV dysfunction scheduled to undergo myocardial revascularisation Exclusion criteria: Unstable angina; advanced heart failure; contraindications to CMR	Scanner: 1.5-T scanner using a phased-array receiver coil Data acquisition: During breath-hold, segmented inversion-recovery Turbo FLASH sequence Contrast agent: 0.15 mmol/kg body weight Gd-DTPA LGE: 10-minute delay	Improvement in segmental wall motion at follow-up (8 months). Recovery was considered if an improvement of ≥1 grade was observed on cine MRI (0 = normal findings, 1 = mild or moderate hypokinesia, 2 = severe hypokinesia, 3 = akinesia, 4 = dyskinesia)

Study Country	Study design Quality appraisal	Study population	Inclusion/exclusion criteria	Intervention (perfusion CMR with/without LGE)	Reference standard (ICA)
	Reference standard: 😊 Flow and timing: 😊 Applicability: 😊				
Sandstede et al. (2000) Germany	Level III-2 A comparison with reference standard (not blinded or blinding not known) Quality: some risk of bias Patient selection: ? Index test: 😊 Reference standard: ? Flow and timing: ? Applicability: 😊	N=12 patients with hypokinetic or akinetic myocardial regions undergoing revascularisation therapy (2 underwent CABG, 10 PCI; n=6 with stents, n=4 without stents) Mean age: 61 ± 9 years Male = 83%	Inclusion criteria: Patients with hypokinetic or akinetic myocardial regions and associated CAD revealed by left ventriculography and ICA Exclusion criteria: NR	Scanner: 1.5-T scanner using a phased array body coil Data acquisition: During breath-hold Contrast agent: 0.05 mmol/kg body weight Gd-DTPA2 LGE: 15-minute delay	Contractile recovery / mechanical improvement at follow-up (3 months)
Schwartzman et al. (2003) USA	Level II A comparison against independent, blinded reference standard among consecutive patients Quality: low risk of bias Patient selection: 😊 Index test: 😊 Reference standard: 😊 Flow and timing: 😊 Applicability: 😊	N=29 patients with chronic IHD who underwent surgical revascularisation and had resting 2-dimensional Echo for assessment of segmental LV function before and after CABG Mean age: 62 ± 11 years Male = 79%	Inclusion criteria: Chronic IHD; LV dysfunction Exclusion criteria: History of MI <8 weeks before diagnostic imaging or CABG; LV ejection fraction ≥50% by Echo or CMR; unstable angina; CMR contraindications (e.g. implanted defibrillator)	Scanner: 1.5-T scanner using a phased array torso coil Data acquisition: During breath-hold, inversion recovery imaging Contrast agent: Gd-DTPA, 0.2 mmol/kg body weight LGE: 20–30-minute delay	Segmental improvement after revascularisation (interval 188 ± 57 days) defined as increase in resting function by at least 1 grade between pre- and post-CABG Echo. (1 = normal, 2 = mild hypokinesia, 3 = severe hypokinesia, 4 = akinesia or dyskinesia)
Selvanayagam et	Level III-1	N=52 patients undergoing multivessel CABG and early	Inclusion criteria:	Scanner: 1.5-T scanner	Regional wall motion recovery after revascularisation (6 months follow-up).

Study Country	Study design Quality appraisal	Study population	Inclusion/exclusion criteria	Intervention (perfusion CMR with/without LGE)	Reference standard (ICA)
al. (2004) UK	A comparison against independent, blinded reference standard among non-consecutive patients Quality: low risk of bias Patient selection: 😊 Index test: 😊 Reference standard: 😊 Flow and timing: 😊 Applicability: 😊	(day 6) and late (6 months) post-operative cine CMR and delayed-enhancement CMR Mean age: 60 years	Patients undergoing multivessel CABG Exclusion criteria: Age >75 years, severe pre-existing LV dysfunction; involvement in other clinical trials; typical CMR contraindications (e.g. pacemaker, severe claustrophobia); baseline creatinine >22 µmol/L	Data acquisition: inversion recovery segmented gradient echo sequence Contrast agent: Gadodiamide, 0.1 mmol/kg body weight LGE: 10-minute delay	Regional wall motion was graded as 0 = normal, 1 = mild or moderate hypokinesia, 2 = severe hypokinesia, 3 = akinesia and 4 = dyskinesia
Sharma and Katz (2009) USA	Level II A comparison against independent, blinded reference standard among consecutive patients Quality: low risk of bias Patient selection: 😊 Index test: 😊 Reference standard: 😊 Flow and timing: 😊 Applicability: 😊	N=8 patients with significant CAD undergoing revascularisation Mean age: NR Male = 100%	Inclusion criteria: Showing symptoms of cardiac failure for more than 3 months Exclusion criteria: MI, unstable angina for at least 6 weeks; valvular disease; contraindications to CMR	Scanner: 1.5-T scanner using a phased-array coil Data acquisition: Segmented inversion-recovery prepared turbo gradient echo pulse sequence Contrast agent: Gd-DTPA, 0.15 mmol/kg body weight LGE: 2–5-minute delay	In the follow-up (3 months), improved post-vascularisation contractile function was defined as ≥15% systolic wall thickening. In addition, grade 3 served as threshold empirical range of signal enhancement (0 = no HE, 1 = 1%–25% HE, 2 = 26%–50% HE, 3 = 51%–75% HE, 4 = >75% HE).
Van Hoe and Vanderheyden. (2004) Belgium	Level III-2 A comparison with reference standard (not blinded or blinding not known) Quality: low risk of bias	N=18 patients with a clinical suspicion of IHD who underwent myocardial revascularisation	Inclusion criteria: Patients with a clinical suspicion of IHD who underwent myocardial revascularisation Exclusion criteria:	Scanner: 1.5-T scanner with body phased array coils Data acquisition: During breath-hold, inversion recovery snapshot segmented FLASH sequence	Improvement in contractile status after revascularisation at follow-up (9 ± 2 months), measured visually at rest and during stress (dobutamine), and described as normal, hypokinetic, akinetic or dyskinesic.

Study Country	Study design Quality appraisal	Study population	Inclusion/exclusion criteria	Intervention (perfusion CMR with/without LGE)	Reference standard (ICA)
	Patient selection: 😊 Index test: 😊 Reference standard: ? Flow and timing: ? Applicability: 😊	Mean age: 62 ± 8 years Male = 56%	Unstable angina; recent MI (<7 days); congestive heart failure; ventricular arrhythmias; atrial fibrillation; any contraindication for CMR or ICA	Contrast agent: Gd-DTPA2, 0.175 mmol/kg body weight LGE: 30–40-minute delay	
Wellnhofer et al. (2004) Germany	Level III-1 A comparison against independent, blinded reference standard among non-consecutive patients Quality: low risk of bias Patient selection: ? Index test: 😊 Reference standard: 😊 Flow and timing: 😊 Applicability: 😊	N=29 patients: 27 with previous MI 13 with previous CBAG 12 with diabetes 28 with hyperlipidaemia Mean age: 68 ± 7 years Male = 93%	Inclusion criteria: Chronic CAD with stable angina; LVEF <45%; at least 2 adjacent segments with WMA at rest; no MI within the past 2 months; scheduled for revascularisation Exclusion criteria: NR	Scanner: 1.5-T scanner Data acquisition: Inversion recovery turbo gradient echo sequence Contrast agent: Gd-DTPA, 0.2 mmol/kg body weight LGE: 10–15-minute delay	An improvement of wall motion at follow-up (3 months) by at least 1 grade. Wall motion was graded as normokinesia, hypokinesia, akinesia, and dyskinesia.
Wu et al. (2007b) Japan	Level III-1 A comparison against independent, blinded reference standard among non-consecutive patients Quality: low risk of bias Patient selection: ? Index test: 😊 Reference standard: 😊	N=41 patients with chronic CAD and LVD who received CMR for clinical evaluation, of whom 20 (49%) had a history of MI Mean age: 66 ± 10 years Male = 78%	Inclusion criteria: LVEF ≤50%; regional WMAs on resting Echo Exclusion criteria: NR	Scanner: 1.5-T scanner with a 12-element surface-coil array Data acquisition: During breath hold, inversion-recovery segmented gradient-echo sequence Contrast agent: 0.15 μmol/kg body weight of gadodiamine LGE: 15-minute delay	Segmental functional recovery at follow-up (17 ± 7 days after revascularisation). Recovery = an improvement in segmental wall motion by ≥1 grade on cine MRI, evaluated on a 4-point scale (1 = normal, 2 = mild to moderate hypokinesia, 3 = severe hypokinesia, 4 = akinesia or dyskinesia).

Study Country	Study design Quality appraisal	Study population	Inclusion/exclusion criteria	Intervention (perfusion CMR with/without LGE)	Reference standard (ICA)
	Flow and timing: ? Applicability: 😊				

ACS = acute coronary syndrome; AMI = acute myocardial infarction; CABG = coronary artery bypass graft; CAD = coronary artery disease; CMR = coronary magnetic resonance imaging; DS = diameter stenosis; ECG = electrocardiogram; Echo = echocardiography; Gd-DTPA = gadolinium-diethylenetriamine pentaacetic acid; ICA = invasive coronary angiography; IHD = ischaemic heart disease; LGE = late gadolinium enhancement; LVD = left ventricular dysfunction; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NR = not reported; PCI = percutaneous coronary intervention; SPECT = single-photon emission computed tomography; T = tesla; WMA = wall motion abnormality.

Table 149 Study profiles for studies on concordance between LGE-CMR and SPECT or Echo (population 2)

Study Country	Study design Quality appraisal	Study population	Inclusion/exclusion criteria	Intervention (perfusion CMR with/without LGE)	Comparator
Nelson et al. (2004) Australia	Level III-1 A comparison against independent, blinded reference standard among non-consecutive patients Quality: low risk of bias Patient selection: ? Index test: 😊 Comparator: 😊 Flow and timing: ? Applicability: 😊	N=60 patients with LVD after MI Mean age: 61 ± 12 years Male = 83%	Exclusion criteria: Patients with coronary revascularisation; valvular disease of more than moderate severity; end-stage renal failure; any contraindication to DbE or CMR	Scanner: 1.5-T scanner Data acquisition: Using an inversion-recovery segmented gradient Echo sequence Contrast agent: 0.1 mmol/kg body weight gadolinium LGE: Started 5 minutes after	TI-SPECT: Using a rest-late redistribution protocol. Segments with a resting WMA on 2-dimensional Echo were designated as viable if activity was >60% of maximum or showed significant redistribution. DbE: Using a standard Db/atropine protocol. Segments were considered viable if they were dysfunctional at rest and had augmented function at low dose (5–10 µg/kg per minute).
Schwartzman et al. (2003) USA	Level II A comparison against independent, blinded reference standard among consecutive patients Quality: low risk of bias	N=29 patients with chronic IHD who underwent surgical revascularisation and had resting 2-dimensional Echo for assessment of segmental LV function before and after CABG	Inclusion criteria: Chronic IHD; LV dysfunction Exclusion criteria: History of myocardial infarction <8 weeks before diagnostic imaging or CABG; LV ejection fraction ≥50% by Echo or CMR;	Scanner: 1.5-T scanner using a phased array torso coil Data acquisition: During breath-hold, inversion recovery imaging Contrast agent: Gd-DTPA, 0.2 mmol/kg body weight	Echo: Using standard techniques and commercially available equipment.

Study Country	Study design Quality appraisal	Study population	Inclusion/exclusion criteria	Intervention (perfusion CMR with/without LGE)	Comparator
	Patient selection: 😊 Index test: 😊 Comparator: 😊 Flow and timing: 😊 Applicability: 😊	Mean age: 62 ± 11 years Male = 79%	unstable angina; CMR contraindications (e.g. implanted defibrillator)	LGE: 20–30 minutes	
Solar et al. (2006) Czech Republic	Level III-2 A comparison with reference standard (not blinded or blinding not known) Quality: low risk of bias Patient selection: ? Index test: 😊 Comparator: 😊 Flow and timing: ? Applicability: 😊	N=40 patients with LVD (systolic; LVEF <45%) and CAD who were indicated for CABG Mean age: 62 ± 7 years Male = 93%	Exclusion criteria: Significant valvular heart disease; ACS in past 4 months and during follow-up; cardiomyopathy with a suspected non-ischemic origin; contraindication to CMR or TI-SPECT imaging	Scanner: 1.0-T scanner Data acquisition: Inversion recovery Turbo FLASH (fast low-angle shot) sequence Contrast agent: 0.15 mmol/kg body weight gadolinium-based contrast agent LGE: 12–25 minutes	TI-SPECT: A dual-head, digital, rotating gamma camera with infra-red body contouring and general all-purpose collimators was used. IV administration of 80–120 MBq of TI chloride. Activity of <50% was considered non-viable.
Wu, Huang et al. (2007) Taiwan	Level II A comparison against independent, blinded reference standard among consecutive patients Quality: low risk of bias Patient selection: 😊 Index test: 😊 Comparator: 😊	N=40 patients with angiographically significant CAD (>70% DS) and symptoms of heart failure Mean age: 59.4 ± 12.5 years Male = 90%	Exclusion criteria: LVEF <40%; dysfunctional myocardium; recent MI or angina pectoris <6 weeks; valvular disease; contraindications for CMR	Scanner: 1.5-T scanner using a phased-array surface coil on the chest Data acquisition: Segmented inversion-recovery prepared turbo gradient echo technique Contrast agent: 0.15 mmol/kg body weight Gd-DTPA LGE: 10 minutes	TI-SPECT: 8 patients were studied under exercise stress test (TI injection at peak exercise). Simultaneous DbE and TI-SPECT (pharmacological stress) 10 patients (TI injected 1 minute before termination of dobutamine infusion); and dipyridamole for 14 patients (TI injected 3 minutes after completion of infusion). Imaging was 5 minutes after TI infusion. 8 patients

Study Country	Study design Quality appraisal	Study population	Inclusion/exclusion criteria	Intervention (perfusion CMR with/without LGE)	Comparator
	Flow and timing: ? Applicability: 😊				underwent rest-distribution TI SPECT. Dobutamine stress Echo: 10 patients received both TI SPECT and Echo. M-mode and 2D Echo data were used to assess contractile function.

ACS = acute coronary syndrome; CABG = coronary artery bypass graft; CAD = coronary artery disease; CMR = cardiac magnetic resonance imaging; DbE = dobutamine echocardiography; DS = diameter stenosis; Echo = echocardiography; Gd-DTPA = gadolinium-diethylenetriamine pentaacetic acid; IHD = ischaemic heart disease; LGE = late gadolinium enhancement; LV = left ventricular; LVD = left ventricular dysfunction; LVEF = left ventricular ejection fraction; MI = myocardial infarction; SPECT = single-photon emission computed tomography; T = tesla; TI = thallium-201; WMA = wall motion abnormality

Table 150 Study profiles of included SRs on diagnostic accuracy of the comparators compared with the reference standard (population 2)

Study Country	Quality appraisal ^a	Review aim/question Population	Inclusion/exclusion criteria	Intervention Number of studies included in MA	Reference standard
Schinkel et al. (2007) The Netherlands	Quality: 2/11 Poor quality	The aim was to determine and compare the relative merits of the most frequently used techniques for the evaluation of viable myocardium and assessment of patient outcomes. Population: NR	Search period: 1980 to January 2007 Databases search: MEDLINE, manual search of cardiology and nuclear medicine journals, and pearling Inclusion criteria: Prospective studies in patients with chronic CAD who underwent revascularisation; evaluation of one of the selected techniques (dobutamine Echo, SPECT, PET); results allowing assessment of sensitivity, specificity, PPV and NPV of techniques tested Exclusion criteria: Techniques evaluated in patients who did not undergo revascularisation; patients with acute ischemic coronary syndromes; did not allow assessment of sensitivity and specificity to predict improvement of regional LV function after revascularisation	DbE: k=33 N=1121 TI-SPECT: k=40 N=1119 Tm-SPECT: k=25 N=721	Recovery of regional function after revascularisation

Study Country	Quality appraisal ^a	Review aim/question Population	Inclusion/exclusion criteria	Intervention Number of studies included in MA	Reference standard
Campbell et al. (2014) UK	Quality: 8/11 Good quality	The aim was to assess current evidence on the accuracy and cost-effectiveness of CMR to test patients prior to revascularisation in ischemic cardiomyopathy; develop an economic model to assess cost-effectiveness for different imaging strategies; and identify areas for further primary research Population: Adults with CAD and LV dysfunction who were considered potential candidates for revascularisation by PCI or CABG	Search period: Start database – August 2012 Databases searched: MEDLINE In-Process and Other Non-indexed Citations, MEDLINE, EMBASE, SCI Expanded (Web of Science), Conference Proceedings Index – Science (Web of Science), NHS EED (Wiley Interscience), DARE (Wiley Interscience), PsychINFO (Ovid), BIOSIS Previews (Web of Science), Allied and complimentary medicine (AMED) database, Health Economic Evaluations Database, grey literature and pearling Inclusion criteria: Prospective or retrospective studies that had an appropriate reference standard; accuracy data (i.e. sensitivity, specificity, PPV and NPV) or sufficient details so that accuracy data could be calculated. Exclusion criteria: Studies reporting acute ischemic syndromes; editorials; letters; case reports; technical reports; SRs or meta-analyses	LGE-CMR: k=14 Echo: k=12 SPECT: k=13	Recovery of LV function after revascularisation

CABG = coronary artery bypass graft; CAD = coronary artery disease; DbE = low-dose dobutamine stress Echo; Echo = echocardiography; LGE-CMR = late gadolinium enhancement cardiac magnetic resonance imaging; LV = left ventricular; NPV = negative predictive value; NR = not reported; PET = positron emission tomography; PCI = percutaneous coronary intervention; PPV = positive predictive value; SPECT = single-photon emission computed tomography; SR = systematic review; Tm = technetium-99m sestamibi / tetrofosmin; TI = thallium-201

Table 151 Study characteristics change in management studies for population 2

Study	Level and quality appraisal	Study population	Inclusion/exclusion criteria/objectives	Intervention	Comparator	Outcomes assessed for change in management
Bruder et al. (2013) Europe (57 centres in 15)	Level IV: Quality: 11/12 Low risk of bias	N=4,048 patients undergoing CMR for myocardial viability testing	Inclusion criteria: Consecutive patients undergoing CMR according to the ACCF/ACR/SCCT/SCMR/ASNC/NA	CMR imaging: non-stress CMR was done in 17,136 patients, myocardial viability testing was done in 4,048 patients (14.6%)	NA	% of patients with a completely new diagnosis % of patients who had a change in management

Study	Level and quality appraisal	Study population	Inclusion/exclusion criteria/objectives	Intervention	Comparator	Outcomes assessed for change in management
countries) Prospective multicentre (non-comparative) cohort study		Age (viability testing): <45 years: 5.3%, 45–59 years: 17.0%, 60–74 years: 19.2%, >74 years: 22.4% Mean age (IQR): 60 years (range 47–70) Male: 65.5% Ethnicity: NR Follow-up: Mean 400 days (IQR 367–419 days)	SCI/SIR consensus appropriateness criteria for CMR imaging, in centres included in the EuroCMR registry Exclusion criteria: NR Objective: Evaluate indications, image quality, safety and impact on patient management of routine CMR imaging on a European level			Therapeutic consequences: Changes in medication Invasive procedure Hospital discharge Hospital admission
Taylor et al. (2013) Australia Prospective (non-comparative) cohort study	Level IV: Quality: 9.5/12 Low risk of bias	N=92/732 patients referred for CMR for whom viability testing was done Age (viability testing), mean: 55.9 ± 15.0 years Male: 83% Ethnicity: NR Follow-up: 6 months	Inclusion criteria: All patients referred to the Alfred Hospital in Melbourne for clinical CMR scanning Exclusion criteria: Patients undergoing scans for research purposes or non-funded indications Objective: Evaluate the impact of CMR imaging on cardiac device and surgical therapy	Setting: Hospital MRI machine: 1.5-T scanner using a cardiac coil and ECG gating Protocol for LGE-CMR: Inversion recovery gradient echo sequences 10 minutes after intravenous administration of contrast agent (0.2 mmol/kg Gd-DTPA) to demonstrate myocardial delayed enhancement were performed	NA	% of patients who had a change in surgical management plan

CMR = cardiac magnetic resonance imaging; Gd-DTPA = gadolinium diethylenetriaminepentaacetic acid; IQR = inter-quartile range; LGE = late gadolinium enhancement; MRI = magnetic resonance imaging; NR = not reported; NA = not applicable; T = tesla

Table 152 Study characteristics of therapeutic effectiveness studies (population 2)

Study	Study design	Study population	Inclusion/exclusion criteria	Intervention and outcomes
Country	Quality appraisal			

Study Country	Study design Quality appraisal	Study population	Inclusion/exclusion criteria	Intervention and outcomes
Allman et al. (2002) USA SR	Level III-2 Quality: 2/11 Poor quality	k=24 studies N=3,088 patients 35% underwent revascularisation 65% underwent medical therapy Age mean: 61.4 years (range 55–69) Male: 70.1% (range 38%–91%) Ethnicity: NR Follow-up: mean 24.7 months (range 12–47)	Inclusion criteria: NR Exclusion criteria: Studies not reporting deaths or where deaths could not be apportioned to patients with versus without viability were excluded.	Intervention: Revascularisation Comparator: Medical therapy Outcomes: Survival
Bonow et al. (2011) USA RCT	Level III-1 Quality: 23/26 Good quality	N=601 patients undergoing assessment for myocardial viability 298 patients randomised to medical therapy + CABG 303 randomised to medical therapy alone. Mean age: 60.7 ± 9.4 years Male: 87% Ethnicity: NR Follow-up: median 5.1 years	Inclusion criteria: Patients with angiographic documentation of CAD amenable to surgical revascularisation and with LVD (LVEF <35%) Exclusion criteria: Left main coronary artery stenosis of >50%; cardiogenic shock; MI within 3 months; need for aortic valve surgery	Intervention: CABG + medical therapy Comparator: Medical therapy alone Outcomes: Mortality rates; hazard ratios

Study Country	Study design Quality appraisal	Study population	Inclusion/exclusion criteria	Intervention and outcomes
Gerber et al. (2012) Belgium Cohort study	Level III-2 Quality: 18.5/26 Moderate quality	N=144 patients 86 patients underwent complete revascularisation 46 patients had medical therapy alone 12 had incomplete PCI Mean age: 65 ± 11 years Male: 90.3% Ethnicity: NR Follow-up: median 3 years	Inclusion criteria: Consecutive patients undergoing LGE-CMR for assessment of myocardial viability; with CAD and LVEF <35% who satisfied Felker's criteria for ischemic cardiomyopathy. Exclusion criteria: Patients with non-ischemic cardiomyopathy; without cardiac catheterisation within 3 months before CMR; with significant valve disease (grade >2 mitral or aortic insufficiency or significant mitral or aortic stenosis); who had already been revascularised; life expectancy <1 year due to other comorbidities; infarct complications	Intervention: Full revascularisation Comparator: Incomplete PCI or medical therapy alone Outcomes: 3-year overall survival
Schinkel et al. (2007) The Netherlands SR	Level III-2 Quality: 2/11 Poor quality	k=29 studies N=3,640 patients Patient characteristics: NR	Inclusion criteria: Prospective studies in patients with chronic CAD who underwent revascularisation; 1 of the selected techniques(dobutamine Echo, SPECT and PET) evaluated; results allowing assessment of sensitivity, specificity, PPV and NPV of techniques tested Exclusion criteria: Techniques evaluated in patients who did not undergo revascularisation; with acute ischemic coronary syndromes; studies that did not allow assessment of sensitivity and specificity to predict improvement of regional LV function after revascularisation	Intervention: Revascularisation Comparator: Medical therapy Outcomes: Annualised mortality rates

CABG = coronary artery bypass graft; CAD = coronary artery disease; CMR = cardiac magnetic resonance imaging; Echo = echocardiogram; LGE = late gadolinium enhancement; LVD = left ventricular dysfunction; LVEF = left ventricular ejection fraction; NPV = negative predictive value; NR = not reported; PCI = percutaneous coronary intervention; PET = positron emission tomography; PPV = positive predictive value; RCT = randomised controlled trial; SPECT= single-photon emission computed tomography; SR = systematic review

APPENDIX D EXTRACTED DATA FROM CECAT TRIAL

Table 153 Characteristics of patients randomised to each group in the CECaT trial

	ICA (control)	SPECT	SP-CMR	Stress Echo
Mean (SD) age (years)	60.7 (9.1)	62.1 (9.5)	62.2 (9.0)	61.9 (9.9)
Males (%)	149 (67%)	157 (70%)	153 (68%)	160 (71%)
Mean (SD) BMI (kg/m ²)	27.6 (4.2)	27.3 (4.3)	28.0 (4.4)	27.9 (4.2)
Mean (SD) systolic blood pressure (mm Hg)	148.3 (23.4)	152.8 (23.1)	149.2 (21.7)	151.3 (24.0)
Mean (SD) diastolic blood pressure (mm Hg)	84.5 (10.2)	86.3 (9.9)	84.1 (10.0)	84.4 (11.0)
History/risk factors:				
Previous MI (%)	63 (28%)	52 (23%)	69 (31%)	59 (26%)
Previous CVA (%)	10 (5%)	13 (6%)	8 (4%)	12 (5%)
Peripheral VD (%)	20 (9%)	21 (9%)	17 (8%)	18 (8%)
Diabetes (%)	28 (12%)	26 (12%)	32 (14%)	27 (12%)
Family history of CAD	60 (27%)	55 (25%)	63 (28%)	59 (26%)
Smoking history (%):				
Current light (<25 pack-years)	31 (14%)	32 (14%)	20 (9%)	28 (12%)
Heavy current or ex- (≥25 pack-years)	73 (33%)	62 (28%)	78 (35%)	71 (31%)
Treated hyperlipidaemia (%)	164 (74%)	171 (76%)	179 (79%)	179 (79%)
Treated hypertension (%)	117 (53%)	132 (59%)	115 (51%)	129 (57%)
Cardiovascular-related medication:				
Anti-platelets	168 (76%)	167 (75%)	179 (79%)	182 (81%)
Statins	141 (64%)	149 (67%)	164 (73%)	157 (69%)
Beta-blockers	126 (57%)	112 (50%)	126 (56%)	144 (64%)
ACE inhibitors	77 (35%)	71 (32%)	74 (33%)	71 (31%)
Calcium-channel blockers	60 (27%)	70 (31%)	71 (31%)	64 (28%)
Nicorandil/potassium-channel activators	42 (19%)	40 (18%)	36 (16%)	54 (24%)
Nitrates	35 (16%)	35 (16%)	56 (25%)	39 (17%)
Diuretics	38 (17%)	30 (13%)	21 (9%)	33 (15%)
Angiotensin-II receptor antagonists	15 (7%)	10 (4%)	17 (8%)	15 (7%)
Exercise tolerance test				
Mean (SD) total exercise time (minutes)	11.29 (4.56)	10.46 (4.41)	10.43 (4.43)	10.89 (4.36)
Angina during test:				
Mean (SD) time to angina (minutes)	7.61 (4.23)	7.59 (4.68)	7.34 (4.11)	7.03 (3.86)
Mean (SD) total exercise time (minutes)	10.86 (4.38)	9.88 (4.38)	10.23 (4.18)	10.56 (3.86)
ECG changes on exercise test:				
1–2-mm ST depression with symptoms	53 (24%)	43 (19%)	54 (24%)	57 (25%)
2-mm ST depression without symptoms	16 (7%)	24 (11%)	20 (9%)	24 (11%)
ST elevation / no change	153 (69%)	157 (70%)	152 (67%)	145 (64%)

	ICA (control)	SPECT	SP-CMR	Stress Echo
CCS class:				
0	11 (5%)	17 (8%)	18 (8%)	13 (6%)
I	49 (22%)	37 (17%)	60 (27%)	45 (20%)
II	138 (62%)	144 (64%)	122 (54%)	132 (58%)
III	23 (10%)	22 (10%)	23 (10%)	32 (14%)
IV	1 (1%)	4 (2%)	3 (1%)	4 (2%)
Prior risk assessment:				
Low	69 (31%)	69 (31%)	69 (31%)	70 (31%)
High	153 (69%)	155 (69%)	157 (69%)	156 (69%)

ACE = angiotensin converting enzyme; BMI = body mass index; CAD = coronary artery disease; CCS = Canadian Cardiovascular Society; CVA = cerebrovascular accident; ECG = electrocardiography; Echo = echocardiography; ICA = invasive coronary angiography; MI = myocardial infarction; SD = standard deviation; SP-CMR = stress perfusion cardiac magnetic resonance imaging; SPECT = single-photon emission computed tomography; VD = vascular disease

Table 154 Number of patients who had non-fatal AEs requiring hospitalisation or died during the 18-month follow-up period

	ICA (n=222)	SPECT (n=224)	SP-CMR (n=226)	Stress Echo (n=226)
Admission for chest pain	14 (6.3%)	19 (8.5%)	21 (9.3%)	24 (10.6%)
Admission for acute MI	0 (0%)	2 (0.9%)	3 (1.3%)	6 (2.7%)
Unplanned PCI	4 (1.8%)	1 (0.4%)	5 (2.2%)	5 (2.2%)
Unplanned CABG	3 (1.4%)	1 (0.4%)	1 (0.4%)	4 (1.8%)
Other non-fatal events ^a	1 (0.4%)	5 (2.2%)	2 (0.9%)	1 (0.4%)
Total non-fatal events	19 (8.6%)	24 (10.7%)	29 (12.8%)	31 (13.7%)
Deaths Cardiac	3	5	4	1
Other cardiovascular	0	0	1	2
Other ^b	2	0	3	3
All-cause mortality	5 (2.3%)	5 (2.2%)	8 (3.5%)	6 (2.7%)
CVD-related mortality	3 (1.4%)	5 (2.2%)	5 (2.2%)	3 (1.3%)
Total follow-up (years)	315.6	318.4	327.0	321.2

^a Other non-fatal events were CVA post-ICA (observed overnight); post-CABG wound infection, admission for breathlessness, admission for ICD implant, admission for suspected MI found to be muscular pain, seen in an accident and emergency department with chest pain; admission for fluid over the heart, admission for blurred vision following ICA; transient ischaemic attack.

^b Other deaths were various cancers, pneumonia, respiratory failure, road traffic accident and unknown.

AE = adverse event; CABG = coronary artery bypass graft; CVA = cerebrovascular accident; CVD = cardiovascular disease; Echo = echocardiography; ICA = invasive coronary angiography; ICD = implantable cardioverter defibrillator; ICVA = invasive coronary angiography; MI = myocardial infarction; PCI = percutaneous coronary intervention; SP-CMR = stress perfusion cardiac magnetic resonance imaging; SPECT = single-photon emission computed tomography

Table 155 SF-36 physical and mental component scores for non-invasive imaging groups compared with the ICA control group

Comparison	Intervention	Control	Mean difference (95%CI) ^a	p-value
Mean (SD) PCS score at 6 months follow-up				0.587
SP-CMR vs ICA	41.0 (13.7)	42.1 (14.0)	0.9 (-1.1, 2.8)	
SPECT vs ICA	43.3 (13.1)	42.1 (14.0)	-0.5 (-2.5, 1.5)	
Stress Echo vs ICA	43.2 (13.6)	42.1 (14.0)	0.0 (-2.0, 1.9)	
Mean (SD) MCS score at 6 months follow-up				0.728
SP-CMR vs ICA	50.2 (13.2)	51.1 (14.1)	0.8 (-1.2, 2.7)	
SPECT vs ICA	52.3 (12.8)	51.1 (14.1)	-0.3 (-2.3, 1.6)	
Stress Echo vs ICA	52.1 (13.4)	51.1 (14.1)	0.1 (-1.9, 2.0)	
Mean (SD) PCS score at 18 months follow-up				0.255
SP-CMR vs ICA	41.8 (15.0)	43.6 (14.2)	1.6 (-0.6, 3.8)	
SPECT vs ICA	43.2 (14.2)	43.6 (14.2)	0.8 (-1.4, 3.0)	
Stress Echo vs ICA	44.5 (13.6)	43.6 (14.2)	-0.5 (-2.8, 1.7)	
Mean (SD) MCS score at 18 months follow-up				0.199
SP-CMR vs ICA	50.8 (14.5)	52.0 (14.3)	1.3 (-0.8, 3.5)	
SPECT vs ICA	52.2 (13.7)	52.0 (14.3)	0.3 (-1.9, 2.4)	
Stress Echo vs ICA	53.5 (12.6)	52.0 (14.3)	-1.1 (-3.2, 1.1)	

^a Adjusted for baseline; positive values favour ICA

CI = confidence interval; Echo = echocardiogram; ICA = invasive coronary angiography; MCS = mental functioning composite scale; PCS = physical functioning composite scale; SD = standard deviation; SF-36 = 36-Item Short Form Health Survey; SP-CMR = stress perfusion cardiac magnetic resonance imaging; SPECT = single-photon emission computed tomography.

Table 156 SAQ scores for non-invasive imaging groups compared with the ICA control group

Comparison	Intervention	Control	Mean difference (95%CI) ^a	p-value
Mean (SD) ECS score at 6 months follow-up				0.155
SP-CMR vs ICA	77.3 (22.0)	80.2 (19.3)	1.9 (-1.5, 5.3)	
SPECT vs ICA	77.5 (21.3)	80.2 (19.3)	1.6 (-1.8, 5.0)	
Stress Echo vs ICA	81.0 (20.5)	80.2 (19.3)	-1.6 (-4.9, 1.7)	
Mean (SD) ASS score at 6 months follow-up				0.213
SP-CMR vs ICA	63.2 (24.6)	66.6 (24.7)	3.5 (-1.3, 8.3)	
SPECT vs ICA	61.9 (24.1)	66.6 (24.7)	4.7 (-0.1, 9.6)	
Stress Echo vs ICA	65.2 (26.6)	66.6 (24.7)	1.3 (-3.6, 6.1)	
Mean (SD) AFS score at 6 months follow-up				0.982
SP-CMR vs ICA	83.3 (22.1)	83.8 (21.1)	0.0 (-3.8, 3.8)	
SPECT vs ICA	83.5 (21.7)	83.8 (21.1)	0.1 (-3.7, 4.0)	
Stress Echo vs ICA	84.0 (23.1)	83.8 (21.1)	-0.6 (-4.4, 3.2)	
Mean (SD) TSS score at 6 months follow-up				0.544
SP-CMR vs ICA	91.7 (12.5)	90.4 (15.1)	-1.4 (-3.9, 1.1)	
SPECT vs ICA	92.0 (12.7)	90.4 (15.1)	-1.7 (-4.2, 0.9)	
Stress Echo vs ICA	91.6 (14.8)	90.4 (15.1)	-1.4 (-3.9, 1.1)	
Mean (SD) DPS score at 6 months follow-up				0.370
SP-CMR vs ICA	73.3 (22.6)	73.1 (22.5)	-1.4 (-5.1, 2.3)	
SPECT vs ICA	74.8 (20.1)	73.1 (22.5)	-1.8 (-5.6, 1.9)	
Stress Echo vs ICA	75.6 (22.2)	73.1 (22.5)	-3.3 (-7.0, 0.4)	
Mean (SD) ECS score at 18 months follow-up				0.418
SP-CMR vs ICA	78.5 (23.1)	81.7 (19.2)	2.0 (-1.7, 5.6)	
SPECT vs ICA	78.5 (23.0)	81.7 (19.2)	2.0 (-1.7, 5.6)	
Stress Echo vs ICA	81.5 (20.0)	81.7 (19.2)	-0.5 (-4.1, 3.2)	
Mean (SD) ASS score at 18 months follow-up				0.512
SP-CMR vs ICA	61.4 (25.0)	64.6 (25.1)	3.2 (-1.7, 8.2)	
SPECT vs ICA	62.6 (25.1)	64.6 (25.1)	1.9 (-3.0, 6.9)	
Stress Echo vs ICA	64.4 (26.3)	64.6 (25.1)	0.1 (-4.9, 5.1)	
Mean (SD) AFS score at 18 months follow-up				0.297
SP-CMR vs ICA	84.4 (22.3)	84.2 (21.4)	-0.8 (-4.5, 2.9)	
SPECT vs ICA	86.9 (19.4)	84.2 (21.4)	-2.6 (-6.3, 1.1)	
Stress Echo vs ICA	86.8 (21.8)	84.2 (21.4)	-3.2 (-6.9, 0.5)	
Mean (SD) TSS score at 18 months follow-up				0.980
SP-CMR vs ICA	91.3 (14.2)	91.8 (15.0)	0.1 (-2.7, 2.9)	
SPECT vs ICA	91.2 (14.6)	91.8 (15.0)	0.3 (-2.4, 3.1)	
Stress Echo vs ICA	91.9 (16.1)	91.8 (15.0)	0.3 (-3.0, 2.5)	

Comparison	Intervention	Control	Mean difference (95%CI) ^a	p-value
Mean (SD) DPS score at 18 months follow-up				0.820
SP-CMR vs ICA	76.6 (22.0)	77.4 (21.2)	-0.3 (-4.1, 3.5)	
SPECT vs ICA	77.0 (21.9)	77.4 (21.2)	0.0 (-3.8, 3.8)	
Stress Echo vs ICA	78.4 (22.0)	77.4 (21.2)	-1.6 (-5.4, 2.2)	

^a Adjusted for baseline; positive values favour ICA

AFS = Anginal Frequency Scale; ASS = Anginal Stability Scale; CI = confidence interval; DPS = Disease Perception Scale; Echo = echocardiogram; ECS = Exertional Capacity Scale; ICA = invasive coronary angiography; SAQ = Seattle Angina Questionnaire; SD = standard deviation; SP-CMR = stress perfusion cardiac magnetic resonance imaging; SPECT = single-photon emission computed tomography; TSS = Treatment Satisfaction Scale

Table 157 EQ-5D scores for non-invasive imaging groups compared with the ICA control group

Comparison	Intervention	Control	Mean difference (95%CI) ^a	p-value
Mean (SD) score at baseline				NR
SP-CMR vs ICA	0.75 (0.23)	0.76 (0.23)	NR	
SPECT vs ICA	0.78 (0.19)	0.76 (0.23)	NR	
Stress Echo vs ICA	0.77 (0.22)	0.76 (0.23)	NR	
Mean (SD) score at 6 months follow-up				0.835
SP-CMR vs ICA	0.80 (0.22)	0.78 (0.24)	-0.01 (-0.05, 0.02)	
SPECT vs ICA	0.81 (0.19)	0.78 (0.24)	-0.01 (-0.05, 0.02)	
Stress Echo vs ICA	0.81 (0.20)	0.78 (0.24)	-0.01 (-0.05, 0.02)	
Mean (SD) score at 18 months follow-up				0.262
SP-CMR vs ICA	0.77 (0.27)	0.78 (0.25)	0.01 (-0.03, 0.05)	
SPECT vs ICA	0.80 (0.20)	0.78 (0.25)	-0.02 (-0.06, 0.02)	
Stress Echo vs ICA	0.82 (0.21)	0.78 (0.25)	-0.03 (-0.07, 0.01)	

^a Adjusted for baseline; positive values favour ICA

CI = confidence interval; Echo = echocardiogram; ICA = invasive coronary angiography; NR = not reported; SD = standard deviation; SP-CMR = stress perfusion cardiac magnetic resonance imaging; SPECT = single-photon emission computed tomography

Table 158 Number of patients who had angina during exercise test and time to angina

	SP-CMR	SPECT	Stress Echo	ICA
Angina during exercise testing				
Number (%) at baseline	111 (49%)	96 (43%)	117 (52%)	108 (49%)
Number (%) at 6 months follow-up	70 (35%)	48 (26%)	62 (30%)	44 (23%)
p-value (versus ICA)	0.011	NS	NS	-
Number (%) at 18 months follow-up	58 (29%)	49 (25%)	49 (26%)	39 (21%)
p-value (versus ICA)	NS	NS	NS	-

	SP-CMR	SPECT	Stress Echo	ICA
Mean time to angina (minutes)				
Mean (SD) at baseline	7.34 (4.11)	7.59 (4.68)	7.03 (3.86)	7.61 (4.23)
Mean (SD) at 6 months follow-up	7.66 (4.16)	7.47 (4.20)	8.62 (4.56)	8.93 (4.29)
p-value (versus ICA)	0.001	NS	0.031	-
Mean (SD) at 18 months follow-up	8.19 (4.58)	8.83 (4.98)	8.09 (4.93)	9.15 (4.42)
p-value (versus ICA)	NS	NS	NS	-

Echo = echocardiogram; ICA = invasive coronary angiography; NS = not significant; SD = standard deviation; SP-CMR = stress perfusion cardiac magnetic resonance imaging; SPECT = single-photon emission computed tomography

Table 159 Total exercise time (minutes) for non-invasive imaging compared with ICA in patients who did or did not have a revascularisation procedure

Mean difference (95%CI) ^a	6 months follow-up	18 months follow-up
CABG patients		
SP-CMR vs ICA	1.13 (-0.73, 3.00)	1.78 (-0.23, 3.78)
SPECT vs ICA	-0.13 (-2.01, 1.76)	0.25 (-1.71, 2.20)
Stress Echo vs ICA	2.15 (0.33, 3.97), p < 0.05	2.33 (0.36, 4.30), p < 0.05
p-value between all groups	0.038	0.043
PCI patients		
SP-CMR vs ICA	0.42 (-0.73, 1.57)	0.56 (-0.60, 1.72)
SPECT vs ICA	0.29 (-0.93, 1.52)	-0.49 (-1.72, 0.74)
Stress Echo vs ICA	1.85 (0.73, 2.96), p < 0.05	0.75 (-0.41, 1.90)
p-value	0.007	0.184
MM patients		
SP-CMR vs ICA	0.57 (-0.04, 1.18)	0.38 (-0.27, 1.03)
SPECT vs ICA	-0.18 (-0.80, 0.44)	0.38 (-0.27, 1.03)
Stress Echo vs ICA	-0.06 (-0.67, 0.55)	0.00 (-0.66, 0.66)
p-value	0.072	0.455

^a Adjusted for baseline; positive values favour ICA

CABG = Coronary artery bypass graft; CI = confidence interval; Echo = echocardiogram; ICA = invasive coronary angiography; MM = medical management; PCI = percutaneous coronary intervention; SP-CMR = stress perfusion cardiac magnetic resonance imaging; SPECT = single-photon emission computed tomography

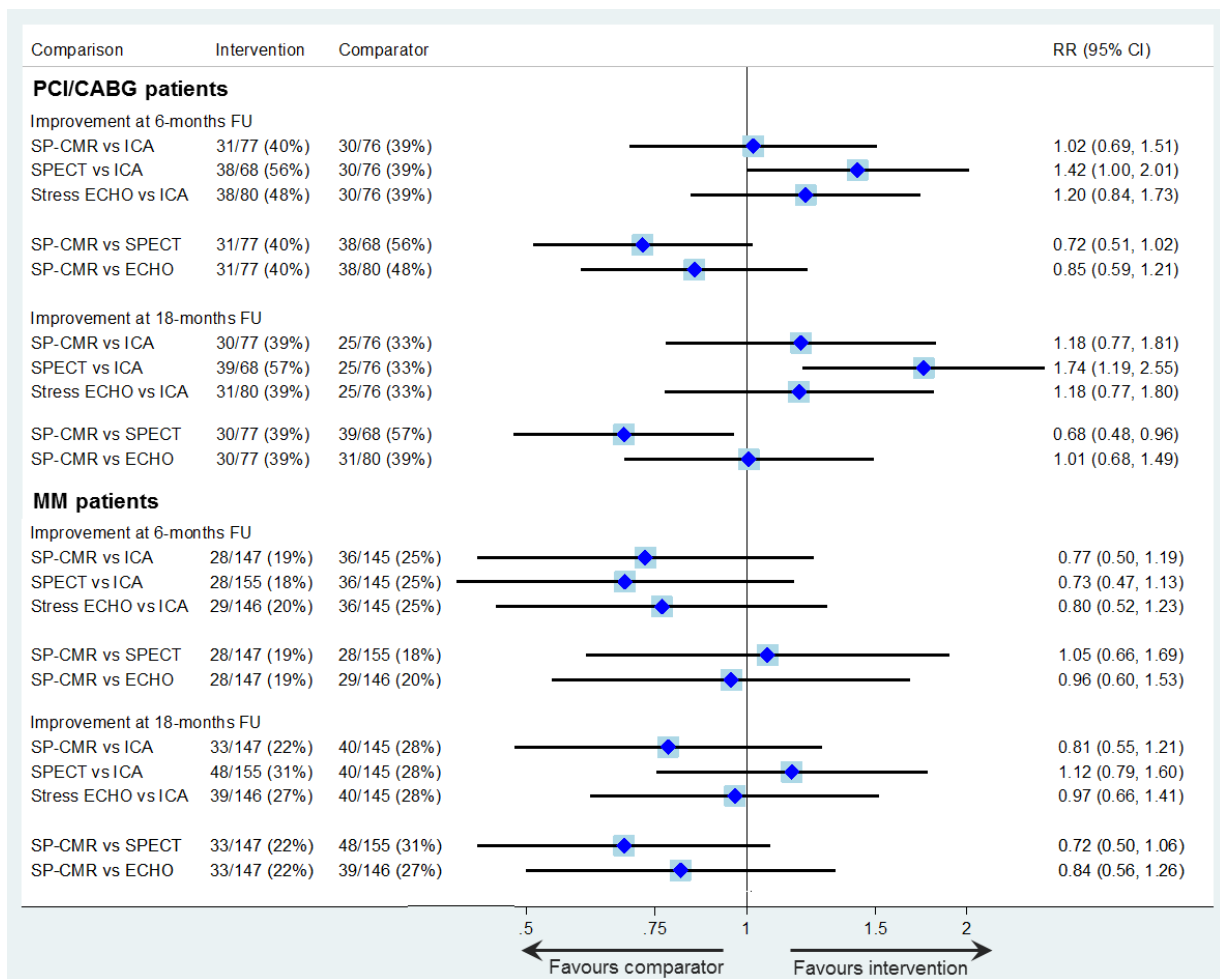


Figure 43 Relative risk of improvement in CCS angina class (≥ 2 class decrease from baseline) after either PCI/CABG or medical management for the non-invasive imaging groups versus the ICA control and for SP-CMR versus other imaging groups

CABG = coronary artery bypass graft; CI = confidence interval; ECHO = echocardiogram; FU = follow-up; ICA = invasive coronary angiography; MM = medical management; PCI = percutaneous coronary intervention; RR = relative risk; SP-CMR = stress perfusion cardiac magnetic resonance imaging; SPECT = single-photon emission computed tomography

APPENDIX E EXTRACTED DATA FROM INCLUDED STUDIES

Table 160 AEs reported in patients with known or suspected CAD undergoing SP-CMR with/without LGE (case series)

Study Country	Evidence level and risk of bias	Population	Intervention	AEs due to MRI procedure	AEs due to stress agent	AEs due to other tests
Adenosine						
Schwitzer et al. (2013) Europe and USA	Level IV: Low risk of bias (IHE 10/12)	N=533 patients from 33 centres who were scheduled for a conventional ICA and/or SPECT examination for clinical reasons (exclusion criteria included contraindications to CMR, contrast medium or stress agent)	SP-CMR + LGE	1 patient had injection site bruising that required treatment. There were no trends for clinically significant changes in vital signs or ECG changes following gadolinium administration.	114 AEs occurred in 74 patients: 91 were mild 23 were moderate 11 required treatment: 4 had angina pectoris (1 serious) 4 had headache 3 had chest pain	-
Schwitzer et al. (2008) Europe and USA	Level IV: Low risk of bias (IHE 9.5/12)	N=241 patients from 18 centres who were scheduled for a conventional ICA and/or SPECT examination for clinical reasons (exclusion criteria included contraindications to CMR, contrast medium or stress agent)	SP-CMR	1 patient developed a haematoma at the site of the intravenous line. There were no trends for clinically significant changes in vital signs or ECG changes following gadolinium administration. No AE resulted in subject withdrawal.	Twenty of 23 AEs were mild and the only severe AE was angina pectoris, which resolved within minutes of stopping adenosine. The most commonly reported mild AEs were angina, chest pain, flushing and hyperpnoea, and were primarily considered to be due to the adenosine administration.	-
Merkle et al. (2010) Germany	Level IV Low risk of bias (IHE 8/12)	N=256 patients with known or suspected CAD (exclusion criteria included contraindications to CMR)	SP-CMR	-	No adverse side effects of adenosine such as anaphylaxis, bronchospasm or serious ventricular arrhythmias were observed during pharmacologic stress.	-
Merkle et al. (2007)	Level IV Low risk of bias	N=228 patients with suspected or known CAD	SP-CMR	-	14 patients had transient AV block grade III.	-

Study Country	Evidence level and risk of bias	Population	Intervention	AEs due to MRI procedure	AEs due to stress agent	AEs due to other tests
Germany	(IHE 8/12)	(exclusion criteria included contraindications to CMR)			105 patients experienced angina pectoris during adenosine stress. No serious adverse side effects of adenosine like anaphylaxis, bronchospasm or serious ventricular arrhythmias occurred during pharmacological stress.	
Jogiya et al. (2012) UK	Level IV Low risk of bias (IHE 9/12)	N=55 consecutive patients with known or suspected CAD. (exclusion criteria included contraindications to CMR or stress agent)	SP-CMR + LGE	1 patient had claustrophobia.	46 patients experienced typical symptoms during adenosine stress.	-
Plein et al. (2008a) UK and Switzerland	Level IV Low risk of bias (IHE 9/12)	N= 51 patients with known or suspected CAD (exclusion criteria included contraindications to CMR or stress agent)	SP-CMR +LGE	-	40 patients experienced side effects during the adenosine infusion (e.g. breathlessness, flushing, headache), but no clinically relevant complications occurred.	-
Lockie et al. (2011) UK	Level IV Low risk of bias (IHE 8/12)	N=44 patients with known or suspected CAD. (exclusion criteria included contraindications to CMR or contrast agent)	SP-CMR +LGE	1 patient had claustrophobia.	42 patients showed mild symptoms consistent with adenosine stress but there were no serious complications.	-
Gebker et al. (2007) Germany	Level IV Low risk of bias (IHE 8/12)	N=43 consecutive patients with known or suspected CAD (exclusion criteria included contraindications to CMR or stress agent)	SP-CMR	-	1 patient could not complete CMR due to bronchospasm during adenosine stress. 31 patients had minimal side effects (e.g. flush and dyspnoea). No serious AEs occurred.	-
Pilz et al. (2006) Germany	Level IV Moderate risk of bias	N=176 consecutive patients referred with known or suspected CAD (exclusion criteria included	SP-CMR + LGE	3 patients had claustrophobia	2 patients had adenosine-induced bronchospasm.	171 patients underwent ICA without major complications.

Study Country	Evidence level and risk of bias	Population	Intervention	AEs due to MRI procedure	AEs due to stress agent	AEs due to other tests
	(IHE 6.5/12)	contraindications to CMR)				
Ebersberger et al. (2013) USA	Level IV Moderate risk of bias (IHE 6.5/12)	N=120 patients with suspected or known CAD (exclusion criteria included contraindications to CMR, contrast medium or stress agent)	SP-CMR + LGE	1 patient had claustrophobia. 3 required surgery prior to CMR.	Intravenous adenosine application at 170 mg/kg/minute was well tolerated by all patients. All showed mild side-effects but none required stopping of the procedure.	ICA was successfully performed in all patients without AEs.
Wolff et al. (2004) USA	Level IV Moderate risk of bias (IHE 7.5/12)	N=99 patients who had known or suspected CAD (exclusion criteria included contraindications to CMR, contrast medium or stress agent)	SP-CMR	1 patient had claustrophobia.	There were no serious AEs recorded. 1 patient had an AV block.	-
Giang et al. (2004) Switzerland, Germany and UK	Level IV Moderate risk of bias (IHE 6/12)	N=94 patients with known or suspected CAD who were scheduled for ICA (exclusion criteria included contraindications to stress agent)	SP-CMR	1 patient had claustrophobia.	No serious AEs were reported.	-
Plein et al. (2005) UK	Level IV Moderate risk of bias (IHE 6.5/12)	N=92 patients who were suspected of having or known to have CAD (exclusion criteria included contraindications to CMR)	SP-CMR	3 patients could not be imaged owing to claustrophobia.	1 patient was unwilling to undergo adenosine infusion. No arrhythmias or other marked AEs were observed during stress.	-
Thomas et al. (2008) Germany	Level IV Moderate risk of bias (IHE 7.5/12)	N=60 patients with or without prior CAD diagnosis who were suspected of having significant occlusive CAD (exclusion criteria included contraindications to CMR or stress agent)	SP-CMR + LGE	-	1 patient developed a second-grade AV block upon completion of the study that resolved spontaneously after cessation of the adenosine infusion. Minor AEs occurred 2–4 minutes after the onset of adenosine infusion: 29 had angina 26 had dyspnoea 11 had headache 13 had nausea.	-

Study Country	Evidence level and risk of bias	Population	Intervention	AEs due to MRI procedure	AEs due to stress agent	AEs due to other tests
Kitagawa et al. (2008) Japan	Level IV Moderate risk of bias (IHE 7/12)	N=50 patients with known or suspected CAD (exclusion criteria included contraindications to CMR, contrast medium or stress agent)	SP-CMR + LGE	-	No serious AE was reported during adenosine stress.	-
Bernhardt et al. (2012) Germany	Level IV Moderate risk of bias (IHE 6/12)	N=34 patients with stable angina and suspected or known CAD referred for ICA	SP-CMR	-	CMR was completed without complications in all patients.	ICA was completed without complications in all patients.
Thiele et al. (2004) Germany and UK	Level IV Moderate risk of bias (IHE 7/12)	N=32 patients with suspected or known CAD (exclusion criteria included contraindications to CMR or stress agent)	SP-CMR	All 32 patients tolerated the imaging procedure and contrast agent well.	All 32 patients tolerated adenosine administration well.	All 32 patients tolerated the tetrofosmin for SPECT well.
Adenosine or dobutamine						
Bruder et al. (2013) 15 European countries	Level IV Low risk of bias (IHE 8/12)	N=10,228 patients on the EuroCMR registry who underwent stress CMR testing for suspected or known CAD	Stress CMR	5% of mild cases were allergic reactions after injection of contrast (e.g. mild urticarial or exanthema).	745 (7.3%) patients had mild complications. 75% of events (e.g. dyspnoea, chest pain, extra systoles) occurred during dobutamine or adenosine infusion. 7 (0.1%) patients had severe complications. 2 had non-sustained VT and 1 had ventricular fibrillation during dobutamine infusion 2 had overt heart failure, 1 had unstable angina and 1 had an anaphylactic shock during adenosine stress.	-
Dobutamine						

Study Country	Evidence level and risk of bias	Population	Intervention	AEs due to MRI procedure	AEs due to stress agent	AEs due to other tests
Korosoglou et al. (2010) Germany	Level IV Moderate risk of bias (IHE 7.5/12)	N=1,493 consecutive patients with suspected or known CAD (exclusion criteria included contraindications to CMR)	SP-CMR	No MIs or fatal complications occurred during imaging.	Severe side effects requiring the termination of the study occurred in 15 (1.0%) patients due to sustained VT (n=3), ventricular fibrillation (n=2), severe hypotension (n=4) and severe hypertension (n=6). The majority of these patients with life-threatening arrhythmias and severe hypotension (7 out of 9) had severely impaired resting LV function.	-
Al-Saadi et al. (2002) Germany	Level IV Moderate risk of bias (IHE 6/12)	N=27 patients with suspected or proven single or double CAD admitted for ICA (exclusion criteria included contraindications to CMR)	SP-CMR	-	Besides the known minor side effects of dobutamine, no major AEs occurred during the CMR examination.	No major AEs occurred during ICA
Dipyridamole						
Ishida et al. (2003) Japan	Level IV Moderate risk of bias (IHE 4.5/12)	N=104 patients without MI who had undergone SP-CMR and ICA less than 4 weeks apart.	SP-CMR + LGE	-	No patient experienced life-threatening or serious AEs, such as MI, during pharmacologic stress.	-
Pingitore et al. (2008) Italy	Level IV Moderate risk of bias (IHE 6.5/12)	N=93 with known or suspected CAD. (exclusion criteria included contraindications to CMR)	SP-CMR	-	Neither major nor minor limiting AEs occurred during stress testing,	-
Okuda et al. (2005) Japan	Level IV High risk of bias (IHE 4/12)	N=33 patients admitted to hospital for assessment of IHD	SP-CMR + LGE	-	1 patient complained of anterior chest pain during dipyridamole injection, and administration was suspended at 80% of dose.	-
Nicorandil						
Kawase et al. (2004)	Level IV Moderate risk of	N= 50 consecutive patients who underwent ICA for assessment of	SP-CMR	-	No patients exhibited anginal symptoms, arrhythmia or any adverse reactions during	-

Study Country	Evidence level and risk of bias	Population	Intervention	AEs due to MRI procedure	AEs due to stress agent	AEs due to other tests
Japan	bias (IHE 5.5/12)	CAD. (exclusion criteria included contraindications to CMR)			nicorandil stress.	

AE = adverse event; AV block = atrioventricular block; CAD = coronary artery disease; CMR = cardiac magnetic resonance imaging; ECG = electrocardiogram; ICA = invasive coronary angiography; IHD = ischaemic heart disease; IHE = Institute of Health Economics; LGE = late gadolinium enhancement; LV = left ventricular; MI = myocardial infarction; SP-CMR = stress perfusion CMR; SPECT = single-photon emission computed tomography; VT = ventricular tachycardia

Table 161 AEs reported in patients suspected of having CAD undergoing SP-CMR with/without LGE (case series)

Study Country	Evidence level and risk of bias	Population	Intervention	AEs due to MRI procedure	AEs due to stress agent	AEs due to other tests
Adenosine						
Groothuis et al. (2013) The Netherlands	Level IV Low risk of bias (IHE 8/12)	N=198 patients with suspected CAD (exclusion criteria included contraindications to CMR, contrast medium or stress agent)	SP-CMR + LGE	3 patients had unknown prior claustrophobia.	2 patients had transient adenosine-induced third-degree AV block that disappeared after stopping the adenosine administration. 1 patient had transient supraventricular tachycardia.	10 patients had persistent heart rates >65 bpm after the administration of metoprolol orally and intravenously, so CTCA was not performed.
Bettencourt et al. (2013a) Portugal	Level IV Low risk of bias (IHE 8/12)	N=113 patients with clinical suspicion of CAD (exclusion criteria included contraindications to CMR, contrast medium or stress agent)	SP-CMR + LGE	3 patients had claustrophobia. 1 patients refused catheter.	108 patients completed the CMR without AEs.	-
Motwani et al. (2012) UK	Level IV Low risk of bias (IHE 8/12)	N=111 patients with suspected CAD (exclusion criteria included contraindications to CMR, contrast medium or stress agent)	SP-CMR + LGE	3 patients were claustrophobic. 2 patients refused second CMR scan.	-	-
Klem et al. (2006)	Level IV Low risk of bias	N=100 patients with suspected CAD	SP-CMR + LGE	1 patient was too large for CMR scanner.	1 patient had adenosine-induced dyspnoea, which quickly resolved after	-

Study Country	Evidence level and risk of bias	Population	Intervention	AEs due to MRI procedure	AEs due to stress agent	AEs due to other tests
USA	(IHE 8/12)	(exclusion criteria included contraindications to CMR or stress agent)		In 1 patient intravenous access could not be obtained.	stopping adenosine.	
Klem et al. (2008) USA and Germany	Level IV Low risk of bias (IHE 9/12)	N=100 women with symptoms suggestive of CAD who were not included in the Klem et al. (2006) study (exclusion criteria included contraindications to CMR or stress agent)	SP-CMR + LGE	1 patient had discomfort during CMR and discontinued. In 2 patients intravenous access could not be obtained.	1 patient had severe adenosine-induced dyspnoea, which quickly resolved after stopping adenosine.	-
Nagel et al. (2003) Germany	Level IV Low risk of bias (IHE 8/12)	N=90 patients with moderate PTP for CAD (exclusion criteria included contraindications to CMR or stress agent)	SP-CMR	3 patients had claustrophobia. 1 patient was too obese (>150 kg) for scan.	Most patients had minimal side effects (e.g. flush, warmth, headache). 6 patients had angina (1 with severe symptoms). 1 patient had breathing difficulties. 1 patient had AV block III that resolved within 30 seconds after stopping the adenosine infusion.	-
Heitner et al. (2014) USA	Level IV Low risk of bias (IHE 8/12)	N=68 patients with acute chest discomfort and an intermediate PTP of CAD (exclusion criteria included contraindications to CMR or stress agent)	SP-CMR + LGE	1 patient had claustrophobia. 2 patients had body circumference too large to fit in CMR scanner.	There were no AEs or complications associated with adenosine administration.	-
Arnold et al. (2010) UK	Level IV Low risk of bias (IHE 8/12)	N=65 patients for investigation of exertional chest pain (exclusion criteria included contraindications to CMR, contrast medium or stress agent)	SP-CMR + LGE	2 patients had claustrophobia.	No significant AEs occurred during the scan.	-
Cheng et al.	Level IV	N=65 patients with suspected	SP-CMR	2 patients had	1 patient had adenosine intolerance.	1 patient had ICA

Study Country	Evidence level and risk of bias	Population	Intervention	AEs due to MRI procedure	AEs due to stress agent	AEs due to other tests
(2007) UK	Low risk of bias (IHE 8/12)	CAD (exclusion criteria included contraindications to CMR or stress agent)		claustrophobia.		cancelled for clinical reasons.
Walcher et al. (2013) Germany	Level IV Low risk of bias (IHE 8/12)	N=57 patients with suspected CAD (exclusion criteria included contraindications to CMR, contrast medium or stress agent)	SP-CMR + LGE	2 patients were claustrophobic. 3 patients refused a second CMR scan.	-	-
Klein et al. (2008) Germany	Level IV Low risk of bias (IHE 8/12)	N=55 patients with suspected CAD (exclusion criteria included contraindications to CMR or stress agent)	SP-CMR + LGE	-	1 patient had severe dyspnoea during adenosine.	-
Ma et al. (2012) China	Level IV Low risk of bias (IHE 8/12)	N=50 patients with suspected CAD (exclusion criteria included contraindications to CMR, contrast medium or stress agent)	SP-CMR + LGE	-	45 patients experienced mild AEs during adenosine stress (e.g. breathlessness, flushing, headache), but no clinically relevant complications occurred.	-
Pereira et al. (2013) Portugal	Level IV Moderate risk of bias (IHE 7.5/12)	N=121 patients with suspected CAD (exclusion criteria included contraindications to CMR, contrast medium or stress agent)	SP-CMR + LGE	4 patients had unknown claustrophobia.	-	4 patients refused catheterisation so ICA was not performed.
Watkins et al. (2009) Ireland	Level IV Moderate risk of bias (IHE 7/12)	N=103 patients with suspected angina (exclusion criteria included contraindications to CMR, contrast medium or stress agent)	SP-CMR + LGE	3 patients felt claustrophobic. 1 patient suffered anxiety.	-	-

Study Country	Evidence level and risk of bias	Population	Intervention	AEs due to MRI procedure	AEs due to stress agent	AEs due to other tests
Meyer et al. (2008) Germany and USA	Level IV Moderate risk of bias (IHE 6/12)	N=60 patients with suspected occlusive CAD (exclusion criteria included contraindications to CMR or stress agent)	SP-CMR +LGE	-	38 patients had mild side effects such as headache, flushing, warmth or mild dyspnoea, which resolved within 5 minutes after stopping the adenosine infusion.	-
Kirschbaum et al. (2011) The Netherlands	Level IV Moderate risk of bias (IHE 6/12)	N=50 patients with stable angina and suspected CAD with normal LVEF (exclusion criteria included contraindications to CMR or contrast medium)	SP-CMR	-	No serious AEs occurred.	-
Costa et al. (2007) USA	Level IV Moderate risk of bias (IHE 7.5/12)	N=37 patients with suspected CAD (exclusion criteria included contraindications to CMR or stress agent)	SP-CMR ICA + FFR	-	No patients had serious AEs during CMR.	1 patient had wire-induced coronary spasm during FFR measurements.
Bunce et al. (2004) UK	Level IV: Moderate risk of bias (IHE 6.5/12)	N=35 consecutive patients undergoing diagnostic ICA for the investigation of angina (exclusion criteria included contraindications to CMR or stress agent)	SP-CMR	-	CMR was well tolerated with no AEs.	-
Dobutamine						
Mordi et al. (2014) UK	Level IV Low risk of bias (IHE 8.5/12)	N=82 patients with LBBB and an intermediate PTP for CAD and typical features of angina (exclusion criteria included contraindications to CMR, contrast medium or stress agent)	SP-CMR + LGE	-	There were no major AEs.	-
Falcao et al.	Level IV	N=57 patients with suspected	SP-CMR	2 patients had	1 patient had sustained ventricular	-

Study Country	Evidence level and risk of bias	Population	Intervention	AEs due to MRI procedure	AEs due to stress agent	AEs due to other tests
(2013) Brazil	Moderate risk of bias (IHE 6.5/12)	CAD (exclusion criteria included morbid obesity and contraindications to CMR or contrast medium)		claustrophobia. 2 patients refused to undergo CMR.	tachycardia, and 2 had hypertension resulting in interruption of the stress test. 2 patients had intolerable side-effects, cause not reported.	
Dipyridamole						
Al-Saadi et al. (2000) Germany	Level IV Moderate risk of bias (IHE 7.5/12)	N=40 patients referred for ICA because of new chest pain or progressive symptoms (exclusion criteria included contraindications to CMR)	SP-CMR	3 patients had claustrophobia. ECG triggering was insufficient because of frequent premature ventricular complexes in 2 patients, and 1 patient developed atrial fibrillation at the beginning of the CMR scan.	Neither the dipyridamole infusion nor the placement of the central venous catheter caused any serious AEs requiring active treatment; however, the usual side effects of dipyridamole were observed.	-
Sakuma et al. (2005) Japan	Level IV Moderate risk of bias (IHE 5/12)	N=40 patients with suspected CAD	SP-CMR + LGE	-	No patient experienced life-threatening or serious adverse reactions during pharmacologic stress.	-
Nitroglycerin						
Regenfus et al. (2003) Germany	Level IV Moderate risk of bias (IHE 6/12)	N=61 patients with clinically suspected CAD (exclusion criteria included contraindications to CMR or stress agent)	SP-CMR	None of the patients experienced nausea or any other adverse reaction to the contrast agent.	-	-

AE = adverse event; AV block = atrioventricular block; CAD = coronary artery disease; CMR = cardiac magnetic resonance imaging; CTCA = computed tomography coronary angiography; ECG = electrocardiogram; FFR = fractional flow rate; ICA = invasive coronary angiography; IHE = Institute of Health Economics; LBBB = left bundle branch block; LGE = late gadolinium enhancement; PTP = pre-test probability; SP-CMR = stress perfusion CMR

Table 162 Diagnostic accuracy data for SP-CMR compared with ICA in patients suspected of having CAD

Study Country	Evidence level Risk of bias	Population	Index test	Reference test	Prevalence of CAD	True positives	False positives	False negatives	True negatives	Uninterpretable or no results interobserver agreement
Greenwood et al. (2014) UK	Level II Low risk of bias	N=628 patients n=235 women n=393 men with suspected angina pectoris	SP-CMR n=517 n=229 women n=288 men LGE n=627 n=235 women n=392 men	ICA ≥70% DS	39% 23% 49%	187 43 144 97 18 79	43 19 14 15 4 11	57 10 47 150 35 115	340 157 183 365 178 187	CMR not done: 65/752 SPECT not done: 67/752 ICA not done: 23/752
Becker et al. (2015) Germany	Level II Low risk of bias	N=424 women with suspected CAD	SP-CMR	ICA ≥50% DS	73%	132	51	25	216	Interobserver agreement for CMR: kappa = 0.88 (95%CI 0.83, 0.92)
Bernhardt et al. (2007) Germany	Level II Low risk of bias	N=317 patients who had angina	SP-CMR	ICA ≥70% DS ICA ≥50% DS	56% 73%	176 230	54 2	0 2	87 83	Interobserver agreement for CMR: kappa = 0.92
Klem et al. (2008) USA and Germany	Level II Low risk of bias	N=136/147 women with symptoms suggestive of CAD Overlap with Klem et al. (2006)	SP-CMR SP-CMR + LGE SP-CMR + LGE	ICA ≥70% DS ICA ≥50% DS	27% 34%	29 31 32	44 12 11	8 6 14	55 87 79	Incomplete CMR test: 11/147 scanner operator error: 1/147 patient discomfort: 1/147 adenosine-induced dyspnoea: 1/147 non-CMR related issues: 8/147
Bettencourt et al. (2013a) Portugal	Level II Low risk of bias	N=103/113 patients with clinical suspicion of CAD N=309 vessels	SP-CMR SP-CMR or LGE SP-CMR SP-CMR or LGE SP-CMR SP-CMR or LGE	Per patient: FFR <0.80 ICA ≥70% DS Per segment: FFR <0.80	41%	 39 39 37 37 58 60	 8 9 10 11 18 21	 3 3 5 5 11 9	 53 52 51 50 222 219	No CMR results due to: Claustrophobia: 3/113 patients ECG synchronisation failure: 1/113 Refusal of catheter: 1/113 5/113 patients did not undergo FFR as per protocol.

Study Country	Evidence level Risk of bias	Population	Index test	Reference test	Prevalence of CAD	True positives	False positives	False negatives	True negatives	Uninterpretable or no results interobserver agreement
			SP-CMR SP-CMR or LGE	ICA $\geq 70\%$ DS		51 53	25 28	14 12	219 216	
Motwani et al. (2012) UK	Level II Low risk of bias	N=100/111 patients with suspected CAD	SP-CMR + LGE	ICA $\geq 50\%$ DS	30%	25	19	5	51	CMR could not be completed: 8/111 (3 patients were claustrophobic, 2 declined and 3 encountered technical problems). ICA was cancelled for clinical reasons unrelated to the CMR findings: 3/111
Pereira et al. (2013) Portugal	Level II Low risk of bias	N=80/121 patients with suspected CAD N=50 patients with an intermediate PTP for CAD	SP-CMR + LGE	ICA $\geq 90\%$ DS or FFR ≤ 0.80	46% 38%	30 15	18 2	7 4	25 29	CMR not performed: 13/121 (4 due to claustrophobia) ICA not performed: 4/121 (refusal) Treadmill exercise tolerance testing not performed: 24/121 Interobserver agreement for CMR: kappa = 0.56. Both observers agreed on the exact pattern of perfusion in 57 (71.2%) scans
Klem et al. (2006) USA	Level II Low risk of bias	N=92/100 patients with suspected CAD	SP-CMR LGE viability SP-CMR + LGE SP-CMR LGE viability SP-CMR + LGE	ICA $\geq 70\%$ DS ICA $\geq 50\%$ DS	40% 48%	31 18 33 36 18 34	23 1 7 18 1 6	6 19 4 8 26 10	32 54 48 30 47 42	Incomplete CMR test: 8/100: scanner/operator error: 3/100 patient too large: 1/100 adenosine-induced dyspnoea: 1/100 non-CMR related issues: 3/100 Interobserver variability was not tested (readers not independent), but only 8% of SP-

Study Country	Evidence level Risk of bias	Population	Index test	Reference test	Prevalence of CAD	True positives	False positives	False negatives	True negatives	Uninterpretable or no results interobserver agreement
										CMR scans required a third reader to resolve disagreements.
Nagel et al. (2003) Germany	Level II Low risk of bias	N=84/90 patients with moderate PTP for CAD	SP-CMR	ICA \geq 75% DS	51%	32	17	11	24	CMR could not be completed in 6/90: claustrophobia: 3/6 obesity (>150 kg): 1/6 patient heart problems 2/6
Mordi et al. (2014) UK	Level II Low risk of bias	N=82 patients with LBBB and an intermediate PTP for CAD and typical features of angina	SP-CMR LGE viability SP-CMR + LGE	ICA \geq 70% DS	41%	24 11 28	3 0 2	10 23 6	45 48 46	-
Arnold et al. (2010) UK	Level II Low risk of bias	N=62/65 patients for investigation of exertional chest pain	SP-CMR LGE viability SP-CMR + LGE SP-CMR LGE viability SP-CMR+ LGE	ICA \geq 50% DS ICA \geq 70% DS	66% 47%	39 18 37 29 14 28	8 1 4 18 5 13	2 23 4 0 15 1	13 20 17 15 28 20	No CMR results due to: Claustrophobia 2/65 patients Withdrawn consent: 1/65 patients Interobserver agreement for CMR: 82% (95%CI 75%, 87%) Interobserver agreement for ICA: 96% (95%CI 92%, 98%)
Stolzmann et al. (2011) Switzerland	Level II Low risk of bias	N=60 patients with an intermediate PTP for CAD	SP-CMR or LGE	ICA \geq 50% DS	60%	28	3	8	21	Interobserver agreement for the assessment of perfusion abnormalities: kappa = 0.73; and for LGE: kappa = 0.84
Klein et al. (2008) Germany	Level II Low risk of bias	N=54/55 patients with suspected CAD	SP-CMR LGE viability SP-CMR or LGE	ICA \geq 50% DS (n=49) (n=54) (n=51)	49%	20 13 22	3 1 3	3 13 3	23 27 23	SP-CMR not performed: 3/54 SP-CMR technical failure: 2/54 LGE images were obtained from all patients.
Van	Level II	N=53 patients with chest	SP-CMR + LGE	ICA \geq 50% DS						-

Study Country	Evidence level Risk of bias	Population	Index test	Reference test	Prevalence of CAD	True positives	False positives	False negatives	True negatives	Uninterpretable or no results interobserver agreement
Werkhoven et al. (2010) The Netherlands	Low risk of bias	pain, 83% had intermediate PTP N=159 coronary territories		Per patient Per artery	28%	12 13	3 12	7 17	31 117	
Walcher et al. (2013) Germany	Level II Low risk of bias	N=52/57 patients with suspected CAD	SP-CMR SP-CMR + LGE	ICA Scanner ≥50% 1.5-T 3.0-T ≥70% 1.5-T 3.0-T ≥50% 1.5-T 3.0-T ≥70% 1.5-T 3.0-T	62% 52%	21 24 21 23 24 27 24 26	5 2 5 3 5 2 5 3	11 8 6 4 8 5 3 1	15 18 20 22 15 18 20 22	CMR at both field strengths could not be completed for 5 patients: n=2 were claustrophobic n=3 refused second CMR scan. 34 (4.1 %) segments at 1.5 T and 39 (4.7 %) at 3 T could not be analysed due to artefacts or poor image quality.
Ma et al. (2012) China	Level II Low risk of bias	N=50 patients with suspected CAD	SP-CMR + LGE	ICA ≥50% DS Per patient Per artery	56%	27 62	4 10	1 1	18 77	All image acquisitions were successful.
Costa et al. (2007) USA	Level II Low risk of bias	N=30/37 patients with suspected CAD N=44 segments for FFR N=108 segments for ICA	SP-CMR MPR ≤2.04 MPR ≤1.85	Per segment FFR <0.75 ICA ≥50% DS ICA ≥70% DS	NR	13 40 13	13 31 47	1 7 1	17 30 47	Wire-induced coronary spasm during FFR measurements: 1/37 patients Inadequate CMR image quality: 6/37
Husser et al. (2009) Spain	Level III-1 Low risk of bias	N=166 patients with chest pain of possible coronary origin	SP-CMR LGE viability	ICA ≥70% DS	72%	110 58	18 10	9 61	29 37	Stress CMR data and angiographic data of all 166 patients were evaluated.
Watkins et al. (2009) Ireland	Level III-1 Low risk of bias	N=101/103 patients with suspected angina N=302 segments	SP-CMR + LGE	Per artery ICA ≥70% DS (n=300)	NR	72	50	2	178	2 patients (2%) were excluded because of delays between the CMR and the ICA. Both observers agreed on the

Study Country	Evidence level Risk of bias	Population	Index test	Reference test	Prevalence of CAD	True positives	False positives	False negatives	True negatives	Uninterpretable or no results interobserver agreement
				FFR <0.75 FFR ≤0.80		110 118	11 3	11 26	168 153	pattern of CAD in 84 (83.2%) scans.
Regenfus et al. (2003) Germany	Level III-1 Low risk of bias	N=61 patients N=427 segments	SP-CMR	Per segment ICA ≥50% DS	NR	58	25	10	235	99 segments could not be evaluated. Cohen Interobserver agreement for CMR: kappa = 0.85 Interobserver agreement for ICA: kappa = 0.95
Schwitzer et al. (2001) Switzerland	Level III-1 Low risk of bias	N=47/48 patients with suspected CAD	SP-CMR	ICA ≥50% DS	79%	32	1	5	9	One CMR result was excluded from analysis for technical reasons. Intraobserver variability of slope _{endo} : mean difference = -0.3% (95%CI -18.3, 17.7); and slope _{trans} : mean difference = -2.5% (95%CI -14.3, 19.4) Interobserver variability of slope _{endo} : mean difference = 5.6% (95%CI -15.3, 26.5); and slope _{trans} : mean difference = 4.7% (95%CI -14.7, 24.1)
de Mello et al. (2012) Brazil	Level III-1 Low risk of bias	N=38 patients with suspected CAD N=114 segments	SP-CMR + LGE	Per artery ICA ≥70% DS	NR	41	8	6	59	-
Al-Saadi et al. (2000) Germany	Level III-1 Low risk of bias	N=34/40 patients referred for ICA because of new chest pain or progressive symptoms	SP-CMR MPR ≤1.5	Per segment ICA ≥75% DS	NR	54	7	6	35	No CMR results due to: Claustrophobia: 3/40 patients ECG triggering insufficient: 3/40 In 19/648 evaluated segments,

Study Country	Evidence level Risk of bias	Population	Index test	Reference test	Prevalence of CAD	True positives	False positives	False negatives	True negatives	Uninterpretable or no results interobserver agreement
		N=102 segments								curve fitting was not possible because of artefacts or noise: Interobserver variability: $r = 0.96$ intraobserver variability: $r = 0.99$
Cury et al. (2006) Brazil	Level III-1 Low risk of bias	N=32/33 patients suspected of having CAD N=96 coronary territories	SP-CMR SP-CMR + LGE	Per artery ICA $\geq 70\%$ DS	NR	19 20	9 6	8 7	60 63	Poor-quality CMR images: 1/33 patients
Groothuis et al. (2013) The Netherlands	Level III-1 Some risk of bias	N=88/192 patients with low or intermediate PTP of having CAD	SP-CMR + LGE	FFR ≤ 0.75	30%	22	11	4	51	8/210 patients had no or incomplete CMR unknown prior claustrophobia: 3/210 Intraobserver agreement for CMR: kappa = 0.78 + 0.09 Interobserver agreement for CMR: kappa = 0.81 + 0.09
Heitner et al. (2014) USA	Level III-1 High risk of bias	N=60/68 patients with acute chest discomfort and an intermediate PTP of CAD	SP-CMR LGE viability SP-CMR + LGE	ICA $\geq 50\%$ DS + clinical follow-up	13%	7 3 8	5 9 4	1 5 0	47 43 48	Withdrew consent before imaging: 5/68 Could not undergo CMR due to: large body circumference: 2/68 claustrophobia: 1/68
Merkle et al. (2010) Germany	Level III-2 Low risk of bias	N=73 patients with suspected CAD	SP-CMR n=32 women n=41 men	ICA $\geq 50\%$ DS	27%	16 5 11	8 1 7	4 1 3	45 25 20	-
Cheng et al. (2007) UK	Level III-2 Low risk of bias	N=61/65 patients with suspected CAD	SP-CMR	ICA $\geq 50\%$ DS	66%	39	5	1	16	No CMR results due to: Claustrophobia: 2/65 patients Adenosine intolerance: 1/65 ICA was cancelled for 1/65 patients.

Study Country	Evidence level Risk of bias	Population	Index test	Reference test	Prevalence of CAD	True positives	False positives	False negatives	True negatives	Uninterpretable or no results interobserver agreement
Meyer et al. (2008) Germany and USA	Level III-2 Low risk of bias	N=60 patients with suspected occlusive CAD N=180 vessels	SP-CMR or LGE	ICA \geq 50% DS Per patient Per segment	60%	32 47	5 16	4 15	19 102	-
Merkle et al. (2007) Germany	Level III-2 Low risk of bias	N=59 patients with suspected CAD	SP-CMR	ICA \geq 70% DS ICA \geq 50% DS	22% 31%	13 15	9 7	0 3	37 34	An increase in heart rate >10% during adenosine infusion was achieved in 204/228 (89.5%) patients. Transient AV block grade III occurred in 14/228 patients (6.1%) and resulted in trigger dropouts. All patients included in ITT analysis
Takase et al. (2004) Japan	Level III-2 Low risk of bias	N=57 patients with suspected CAD	SP-CMR or LGE	ICA \geq 50% DS	54%	28	4	3	22	-
Falcao et al. (2013) Brazil	Level III-2 Low risk of bias	N=42/57 patients with suspected CAD	SP-CMR	ICA \geq 50% DS	60%	23	3	2	14	10/57 patients did not undergo CMR 2/57 had claustrophobia 2/57 had inadequate CMR images 1/57 patients had PCI.
Kirschbaum et al. (2011) The Netherlands	Level III-2 Unclear risk of bias	N=75 vessels from patients with stable angina and suspected CAD with normal LVEF	SP-CMR	Per artery FFR <0.8	NR	27 31 31 31	14 17 19 25	5 1 1 1	29 26 24 18	-

Study Country	Evidence level Risk of bias	Population	Index test	Reference test	Prevalence of CAD	True positives	False positives	False negatives	True negatives	Uninterpretable or no results interobserver agreement
Sakuma et al. (2005) Japan	Level III-2 Unclear risk of bias	N=40 patients with suspected CAD N=120 arteries	SP-CMR + LGE	ICA ≥70% DS Per patient Per artery	53%	17 23	6 11	4 10	13 76	-
Antonio et al. (2007) Portugal	Level III-2 Unclear risk of bias	N=18/30 patients with suspected CAD	SP-CMR	ICA ≥70% DS	67%	9	4	3	2	ICA was not performed: 12/30

AV = atrioventricular; CAD = coronary artery disease; CMR = cardiac magnetic resonance imaging; DS = diameter stenosis; ECG = electrocardiogram; FFR = fractional flow rate; ICA = invasive coronary angiography; ITT = intention-to-treat; LBBB = left bundle branch block; LGE = late gadolinium enhancement; LVEF = left ventricular ejection fraction; MPR = myocardial perfusion reserve; PCI = percutaneous coronary intervention; PTP = pre-test probability; SP-CMR = stress perfusion CMR; SPECT = single-photon emission computed tomography; T = tesla

Table 163 Diagnostic accuracy reported in SRs of SP-CMR compared with ICA and FFR in patients with suspected or known CAD

SR Quality	Comparison	Prevalence of CAD	Number of studies	Sensitivity per patient	Specificity per patient	Number of studies	Sensitivity per segment/vessel	Specificity per segment/vessel
Chen et al. (2014) Moderate	SP-CMR vs ICA ≥50%–75% DS	44%	6	79% [72, 84] I ² = 75.0%	75% [65, 83] I ² = 75.0%	5	80% [73, 85] I ² = 20.9%	87% [81, 91] I ² = 20.9%
Li et al. (2014) Moderate	SP-CMR vs FFR <0.75–0.80	45%	8	90% [86, 93] I ² = 0%	87% [82, 90] I ² = 0%	9	Artery-based 89% [83, 92]; I ² = 18.3%	86% [77, 92]; I ² = 86.6%
Desai and Jha (2013) Moderate	SP-CMR vs FFR <0.75–0.80	66%	4	89% [84, 93] I ² = 78.6%	85% [77, 91] I ² = 78.6%	11	88% [84, 91] I ² = 75.1%	89% [87, 90] I ² = 89.9%
de Jong et al. (2012) Moderate	SP-CMR in suspected CAD vs ICA ≥50% DS vs ICA ≥70% DS	54%	30 (all) 4 18 12	91% [88, 93] 90% [78, 96] 89% [86, 92] 91% [87, 94]	80% [76, 83] 86% [74, 83] 79% [73, 84] 82% [75, 87]	- - - -	- - - -	- - - -
Jaarsma et al. (2012)	SP-CMR in suspected CAD	59%	27 (all) 18	89% [88, 91] 89% [86, 91]	76% [73, 78] 74% [71, 77]	17	Artery-based 84% [81, 86]	83% [81, 86]

SR Quality	Comparison	Prevalence of CAD	Number of studies	Sensitivity per patient	Specificity per patient	Number of studies	Sensitivity per segment/vessel	Specificity per segment/vessel
Moderate	vs ICA \geq 50% DS vs ICA \geq 70% DS		12 15	88% [86, 90] 90% [87, 92]	79% [71, 77] 78% [74, 82]			
Dolor et al. (2012) Good	SP-CMR Suspected CAD-women vs ICA \geq 50%–75% DS	27%	6 (all) 5	78% [61, 89] 72% [55, 85]	84% [74, 90] 84% [69, 93]	- -	- -	- -
Medical Advisory Secretariat (2010a) Moderate	SP-CMR vs ICA \geq 50% DS	62%	23	91% [89, 92] $I^2 = 54.6\%$	79% [76, 82] $I^2 = 32.9\%$	- -	- -	- -
Hamon et al. (2010) Moderate	SP CMR vs ICA \geq 50% DS	57%	26	89% [88, 91] $I^2 = 55.0\%$	80% [78, 83] $I^2 = 66.7\%$	17	Artery-based 82% [79, 84]	84% [82, 85]
Beanlands et al. (2007) Poor	Dobutamine SP-CMR vs ICA \geq 50%–75% DS	66%	11	84% (weighted mean) 89% (corrected) ^a	81% (weighted mean)	- -	- -	- -
Nandalur et al. (2007) Moderate	SP-CMR vs ICA \geq 50%–75% DS	NR	-	-	-	16	Artery-based 84% [80, 87]	85% [81, 88]

^a The weighted mean was recalculated due to an error in reporting the data for one of the included studies

CAD = coronary artery disease; DS = diameter stenosis; FFR = fractional flow rate; ICA = invasive coronary angiography; SP-CMR = stress perfusion coronary magnetic resonance.

Table 164 Diagnostic accuracy reported in SRs of CTCA compared with ICA in patients with suspected or known CAD

SR Quality	Comparison	Prevalence of CAD	Number of studies	Sensitivity per patient	Specificity per patient	Number of studies	Sensitivity per coronary artery	Specificity per coronary artery
Menke and Kowalski (2015)	16–40-slice CTCA	55%	7	97% (92, 99) 84% (66, 94) including unevaluable results	87% (76, 94) 70% (54, 83) including unevaluable results	-	-	-

SR Quality	Comparison	Prevalence of CAD	Number of studies	Sensitivity per patient	Specificity per patient	Number of studies	Sensitivity per coronary artery	Specificity per coronary artery
Good	64–320-slice CTCA vs ICA \geq 50% DS		22	98% (97, 99) 96% (93, 98) including unevaluable results	88% (83, 92) 82% (75, 87) including unevaluable results			
Nielsen et al. (2014) Good	\geq 16-slice CTCA vs ICA \geq 50%–70% DS	NR	7	98% [93, 99]	82% [63, 93]	-	-	-
Jiang et al. (2014) Moderate	64-slice CTCA Dual-source CTCA vs ICA \geq 50% DS	56%	24 18	97% [96, 97] 97% [96, 98]	78% [76, 80] 86% [84, 89]	27 19	81% [80, 82] 91% [90, 92]	94% [93, 94] 96% [96, 96]
Sun and Ng (2012) Good	64-slice ECG-gated CTCA vs ICA \geq 50% DS	60%	14	99% [98, 100]	91% [88, 94]	13 12	Vessel-based 95% [93, 96] Segment-based 92% [90, 93]	95% [93, 95] 97% [97, 98]
Salavati et al. (2012) Moderate	Dual-source CTCA vs ICA \geq 50% DS	55%	22	99% [97, 99]	89% [84, 92]	22	94% [92, 96]	97% [96, 98]
den Dekker et al. (2012) Moderate	16-slice CTCA 64-slice CTCA 320-slice CTCA Dual-source CTCA vs ICA \geq 50% DS	39%	3 12 1 5 21 (all)	95% [92, 97] 97% [96, 98] 100% [92, 100] 97% [94, 98] 97% [96, 98]	78% [72, 82] 88% [86, 89] 93% [66, 99] 90% [85, 94] 86% [85, 88]	6 9 1 7 23 (all)	75% [73, 78] 93% [92, 94] 95% [91, 98] 92% [91, 93] 89% [88, 90]	92% [92, 93] 95% [95.2, 95.7] 98% [96, 99] 96% [95, 96] 95% [94.7, 95.1]
Dolor et al. (2012) Good	CTCA Suspected CAD–women Known or suspected vs ICA \geq 50%–75% DS	45%	5 8	93% [69, 99] 94% [81, 98]	77% [54, 91] 87% [68, 96]	-	-	-

SR Quality	Comparison	Prevalence of CAD	Number of studies	Sensitivity per patient	Specificity per patient	Number of studies	Sensitivity per coronary artery	Specificity per coronary artery
von Ballmoos et al. (2011) Good	≥64-slice CTCA vs ICA ≥50%–70% DS	58%	13	100% [98, 100]	89% [85, 92]	12	Vessel-based 97% [95, 98]	93% [89, 96]
						13	Segment-based 91% [86, 95]	96% [94, 97]
Ollendorf et al. (2011) Moderate	64-slice CTCA vs ICA ≥50%–70% DS	50%	42	98% [96, 99]	85% [81, 89]	-	-	-
Guo et al. (2011) Moderate	Dual-source CTCA vs ICA ≥50% DS	NR	NR	99% [98, 99]	87% [84, 90]	NR	Segment-based 92% [90, 93] Vessel-based 96% [94, 97]	96% [96, 96] 93% [91, 94]
Paech and Weston (2011) Poor	64-slice CTCA vs ICA ≥50% DS	60%	18 22	98% [97, 99]	82% [79, 84]	17	Vessel-based 95% [94, 96]	90% [89, 90]
				98% [97, 99] (including equivocal results as positive)	83% [81, 85]		17	Segment-based 91% [90, 92]
Schuetz et al. (2010) Moderate	≥12-slice CTCA vs ICA ≥50%–70% DS	51%	89	All included studies 97% [96, 98]	87% [85, 90]	-	-	-
			45	Suspected CAD only 98% [96, 99]	89% [86, 92]	-	-	-
Medical Advisory Secretariat (2010b) Moderate	64-slice CTCA vs ICA ≥50% DS	58%	10	96% [94, 98]	82% [73, 90]	-	-	-
Mowatt et al. (2008) Good	≥64-slice CTCA vs ICA ≥50%–70% DS	54%	18	99% [97, 99]	89% [83, 94]	17	Segment-based 90% (85, 94)	97% (95, 98)
Stein et al. (2008)	64-slice CTCA	61%	23	98% [96, 98]	88% [85, 89]	21	Segment-based 90% [88, 90]	96% [95, 96]

SR Quality	Comparison	Prevalence of CAD	Number of studies	Sensitivity per patient	Specificity per patient	Number of studies	Sensitivity per coronary artery	Specificity per coronary artery
Poor	vs ICA \geq 50%–70% DS							
Janne d'Othee et al. (2008)	16-slice CTCA	72%	9	99% (86–100)	83% (67–100)	9	95% (all segments)	86% (all segments)
Poor	64-slice CTCA vs ICA \geq 50%–70% DS		5	98% (95–99)	92% (90–98)	5	96% (assessable) 91% (all segments) 96% (assessable)	98% (assessable) 98% (all segments) 97% (assessable)
Gopalakrishnan et al. (2008)	16-slice CTCA	NR	14	91% [86, 95]	78% [68, 85]	27	84% [80, 88]	94% [91, 97]
Poor	40–64-slice CTCA vs ICA \geq 50% DS		8 22 (all)	96% [93, 96] 93% [90, 96]	91% [85, 96] 82% [76, 88]	10 37 (all)	91% [86, 97] 86% [83, 89]	96% [95, 97] 94% [92, 97]
Van Brabandt et al. (2008)	64-slice CTCA vs ICA \geq 50% DS	56%	9	98% [97, 99] (inconclusive results counted as positive)	82% [79, 86]	-	-	-
Abdulla et al. (2007)	64-slice CTCA vs ICA \geq 50%–70% DS	58%	13	98% [96, 99]	91 [88, 94]	19	86% [85, 87]	96% [96, 97]
Beanlands et al. (2007)	16-slice CTCA	70%	10	98% (weighted mean)	86% (weighted mean)	19	87% (weighted mean)	96% (weighted mean)
Poor	64-slice CTCA vs ICA \geq 50%–70% DS		4 13 (all)	97% (weighted mean) 98% (weighted mean)	94% (weighted mean) 88% (weighted mean)	4 13 (all)	91% (weighted mean) 88% (weighted mean)	95% (weighted mean) 96% (weighted mean)
Schuijf et al. (2006)	16-slice CTCA vs ICA \geq 50% DS	65%	-	-	-	11	88% [86, 90] 85% [83, 87] with uninterpretable segments	96% [95, 97] 94% [93, 95] with uninterpretable segments

CAD = coronary artery disease; CTCA = computed tomography coronary angiography; DS = diameter stenosis; ECG = electrocardiogram; ICA = invasive coronary angiography; NR = not reported; SR = systematic review

Table 165 Diagnostic accuracy reported in SRs of SPECT compared with ICA and FFR in patients with suspected or known CAD

SR	Comparison	Prevalence of CAD	Number of studies	Sensitivity per patient	Specificity per patient	Number of studies	Sensitivity per coronary artery	Specificity per coronary artery
Zhou et al. (2014) Moderate	Stress perfusion SPECT vs FFR <0.75–0.80	44%	13	77% [70, 83]; I ² = 59.4%	77% [67, 84]; I ² = 79.8%	-	-	-
Chen et al. (2014) Moderate	SPECT vs ICA ≥50%–75% DS	41%	6	70% [58, 79]; I ² = 83.6%	76% [66, 83]; I ² = 83.6%	5	67% [60, 72], I ² = 0%	80% [75, 84], I ² = 0%
Iskandar et al. (2013) Good	Stress SPECT In women In men Pharm stress SPECT Tech 99m SPECT vs ICA ≥50% DS	NR	17 13 8 10	84% [79, 87] 89% [84, 93] 86% [74, 93] 85% [77, 90]	79% [70, 85] 71% [61, 80] 83% [68, 91] 78% [63, 89]	-	-	-
Lapado et al. (2013) Poor	Perfusion SPECT vs ICA ≥50%–75% DS	NR	30	85% [81, 88]	69% [61, 78]	-	-	-
de Jong et al. (2012) Moderate	Stress perfusion SPECT In suspected CAD vs ICA ≥50% DS vs ICA ≥70% DS	52%	13 (all) 4 8 6	83% [73, 89] 83% [70, 91] 81% [72, 87] 85% [76, 91]	77% [64, 86] 79% [66, 87] 81% [72, 87] 66% [54, 77]	-	-	-
Jaarsma et al. (2012) Moderate	Stress perfusion SPECT In suspected CAD vs ICA ≥50% DS vs ICA ≥70% DS	70%	105 56 88 17	88% [88, 89] 85% [84, 86] 87% [86, 87] 93% [92, 94]	61% [59, 62] 69% [67, 71] 69% [67, 71] 43% [41, 46]	45	Artery-based 69% [68, 70]	79% [78, 80]
Dolor et al. (2012) Good	Stress SPECT Suspected CAD–women	42%	14	81% [76, 86]	78% [69, 84]	-	-	-

SR	Comparison	Prevalence of CAD	Number of studies	Sensitivity per patient	Specificity per patient	Number of studies	Sensitivity per coronary artery	Specificity per coronary artery
	Known or suspected vs ICA \geq 50%–75% DS		30	82% [77, 87]	81% [74, 86]			
Mc Ardle et al. (2012) Moderate	Perfusion SPECT vs ICA \geq 50%–75% DS	50%	8	85% [82, 87]	85% [82, 87]	-	-	-
Al Moudi et al. (2011) Poor	Perfusion SPECT vs ICA \geq 50% DS	NR	15	82% [76, 88]	76% [70, 82]			
Medical Advisory Secretariat (2010d) Moderate	Stress SPECT Pharm stress SPECT Exercise stress SPECT vs ICA \geq 50%–70% DS	65%	63 33 20	87% [85, 89] 86% [82, 89] 86% [82, 90]	70% [66, 75] 76% [70, 82] 68% [59, 76]	- - -	- - -	- - -
Hacioglu et al. (2010) Poor	SPECT MPI vs ICA \geq 50%–75% DS	NR	8	82% (75–94)	67% (36–100)	-	-	-
Heijenbrok-Kal et al. (2007) Poor	Stress SPECT Exercise stress SPECT vs ICA \geq 50%–70% DS	NR	103 48	88% [87, 90] 88% [86, 90]	73% [69, 77] 69% [63, 75]	- -	- -	- -

CAD = coronary artery disease; DS = diameter stenosis; FFR = fractional flow rate; ICA = invasive coronary angiography; MPI = myocardial perfusion imaging; NR = not reported; SPECT = single-photon emission computed tomography; SR = systematic review

Table 166 Diagnostic accuracy reported in SRs of Echo compared with ICA in patients with suspected or known CAD

SR	Comparison	Prevalence of CAD	Number of studies	Sensitivity per patient	Specificity per patient	Number of studies	Sensitivity per coronary artery	Specificity per coronary artery
Lapado et al. (2013)	Stress Echo vs ICA \geq 50%–75% DS	NR	15	84% [80, 89]	77% [69, 86]	-	-	-

SR	Comparison	Prevalence of CAD	Number of studies	Sensitivity per patient	Specificity per patient	Number of studies	Sensitivity per coronary artery	Specificity per coronary artery
Moderate								
de Jong et al. (2012)	Stress contrast Echo	66%	10 (all)	87% [81, 91]	72% [56, 83]	-	-	-
Moderate	In suspected CAD		1	88% [60, 97]	89% [58, 98]			
	vs ICA \geq 50% DS		7	86% [79, 92]	74% [63, 82]			
	vs ICA \geq 70% DS		3	90% [80, 96]	65% [46, 80]			
Dolor et al. (2012)	Stress Echo	43%				-	-	-
Good	Suspected CAD–women		14	79% [74, 83]	83% [74, 89]			
	Known or suspected		22	78% [73, 83]	86% [79, 91]			
	vs ICA \geq 50%–75% DS							
Medical Advisory Secretariat (2010c)	Stress contrast Echo	48%	10	87% [83, 91]	86% [82, 89]	-	-	-
Moderate	Perfusion analysis		6	88% [84, 90]	65% [59, 70]			
	Wall motion analysis		6	69% [65, 73]	79% [72, 85]			
	vs ICA \geq 50%–70% DS							
Heijenbrok-Kal et al. (2007)	Stress Echo	NR	226	79% [78, 81]	87% [86, 89]	-	-	-
Poor	Exercise Echo		55	83% [80, 85]	84% [80, 88]			
	vs ICA \geq 50%–70% DS							
Geleijnse et al. (2007)	Dobutamine Stress Echo	41%	14	72% (weighted mean)	88% (weighted mean)	-	-	-
Poor	in women							
	in men	73%	8	77% (weighted mean)	77% (weighted mean)			
	vs ICA \geq 50%–70% DS							

CAD = coronary artery disease; DS = diameter stenosis; Echo = echocardiography; ICA = invasive coronary angiography; NR = not reported; SR = systematic review

Table 167 Diagnostic accuracy reported in SRs of Exercise ECG compared with ICA in patients with suspected or known CAD

SR	Comparison	Prevalence of CAD	Number of studies	Sensitivity per patient	Specificity per patient	Number of studies	Sensitivity per coronary artery	Specificity per coronary artery
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SR	Comparison	Prevalence of CAD	Number of studies	Sensitivity per patient	Specificity per patient	Number of studies	Sensitivity per coronary artery	Specificity per coronary artery
Nielsen et al. (2014) Good	Exercise ECG vs ICA \geq 50%–70% DS	NR	7	67% [54, 78]	46% [30, 64]	-	-	-
Dolor et al. (2012) Good	Exercise ECG Suspected CAD–women Known or suspected vs ICA \geq 50%–75% DS	41%	29 41	62% [55, 68] 61% [54, 67]	68% [63, 73] 65% [58, 72]	-	-	-
Kwok et al. (1999) Poor	Exercise ECG Suspected CAD–women Known or suspected vs ICA \geq 50%–75% DS	38%	19	61% (54, 68)	70% (64, 75)			
Gianrossi et al. (1989) Moderate	Exercise ECG vs ICA \geq 50% DS	NR	147	Weighted mean: 68 \pm 16% SD	77 \pm 17% SD	-	-	-

CAD = coronary artery disease; DS = diameter stenosis; ECG = electrocardiogram; ICA = invasive coronary angiography; NR = not reported; SD = standard deviation; SR = systematic review

Table 168 Proportion of CMR tests that were not completed (population 1)

Study	Population	Incomplete tests
Klem et al. (2008)	N=147 women with symptoms suggestive of CAD	Incomplete CMR test: 11/147 (7.5%) (scanner operator error in 1 patient, 1 had discomfort, 1 had adenosine-induced dyspnoea, and 8 had non-CMR related issues)
Bettencourt et al. (2013a)	N=113 patients with clinical suspicion of CAD	No CMR results: 5/113 (4.4%) (3 patients were claustrophobic, ECG synchronisation failure in 1, and refusal of catheter in 1)
Motwani et al. (2012)	N=111 patients with suspected CAD	CMR could not be completed: 8/111 (7.2%) (3 patients were claustrophobic, 2 declined, and 3 encountered technical problems).
Pereira et al. (2013)	N=121 patients with suspected CAD	CMR not performed: 13/121 (10.7%)

Study	Population	Incomplete tests
		(4 due to claustrophobia)
Klem et al. (2006)	N=100 patients with suspected CAD	Incomplete CMR test: 8/100 (8.0%) (scanner/operator error for 3 patients, 1 patient was too large, adenosine-induced dyspnoea in 1 patient, and non-CMR related issues in 3 patients)
Nagel et al. (2003)	N=90 patients with moderate PTP for CAD	CMR could not be completed: 6/90 (6.7%) (3 patients were claustrophobic, 1 patient was too large, 2 patients had heart problems)
Arnold et al. (2010)	N=65 patients with exertional chest pain	No CMR results: 3/65 (4.6%) (2 patients were claustrophobic, 1 patient withdrew consent)
Klein et al. (2008)	N=55 patients with suspected CAD	No SP-CMR results: 5/55 (9.1%) (not performed in 3 patients and technical failure with 2 patients) LGE images were obtained from all patients.
Walcher et al. (2013)	N=57 patients with suspected CAD	CMR at both field strengths could not be completed: 5/57 (8.8%) (2 patients were claustrophobic, 3 patients refused second CMR scan) 34 (4.1 %) segments at 1.5-tesla and 39 (4.7 %) at 3-tesla could not be analysed due to artefacts or poor image quality.
Costa et al. (2007)	N=37 patients with suspected CAD	Inadequate CMR image quality: 6/37 (16.2%)
Schwittler et al. (2001)	N=48 patients with suspected CAD	1/48 CMR result excluded from analysis for technical reasons (2.1%)
Al-Saadi et al. (2000)	N=40 patients with new chest pain or progressive symptoms	No CMR results: 6/40 (15.0%) (claustrophobia in 3 patients, ECG triggering was insufficient in 3)
Cury et al. (2006)	N=33 patients suspected of having CAD	Poor-quality CMR images: 1/33 patients (3.0%)
Groothuis et al. (2013)	N=192 patients with low or intermediate PTP	No or incomplete CMR: 8/210 (3.8%) (unknown prior claustrophobia in 3 patients)
Heitner et al. (2014)	N=68 patients with acute chest discomfort and an intermediate PTP	Could/did not undergo CMR: 8/68 (11.8%)

Study	Population	Incomplete tests
		(1 patient was claustrophobic, 2 patients were too large and 5 patients withdrew consent before imaging)
Cheng et al. (2007)	N=65 patients with suspected CAD	No CMR results: 3/65 (4.6%) (2 patients were claustrophobia, 1 patient had adenosine intolerance)
Falcao et al. (2013)	N=57 patients with suspected CAD	Did not undergo CMR: 10/57 (17.5%) (2 patients had claustrophobia, 2 had inadequate CMR images and 1 had PCI)

CAD = coronary artery disease; CMR = cardiac magnetic resonance imaging; ECG = electrocardiogram; LGE = late gadolinium enhancement; PCI = percutaneous coronary intervention; PTP = pre-test probability; SP-CMR = stress perfusion CMR

Table 169 Effect of CMR-related revascularisation (population 1)

Study / Location	Outcome	N patients who underwent revascularisation (%)	Results
Bingham & Hachamovitch (2011) USA	Frequency of referral to early revascularisation after CMR		
	Patients with normal perfusion, with vs without LGE, respectively	11/98 (11.2) vs 18/512 (3.5)	p<0.01
	Patients with abnormal perfusion, with vs without LGE, respectively	59/243 (24.3) vs 15/55 (27.3)	Not significant
	Patients with LGE, with normal vs abnormal perfusion, respectively	11/98 (11.2) vs 59/243 (24.3)	p<0.01
	Patients without LGE, with normal vs abnormal perfusion without, respectively	18/512 (3.5) vs 15/55 (27.3)	p<0.01
	All patients with vs without LGE, respectively	70/341 (20.5) vs 33/567 (5.8)	p<0.01
Bodi et al. (2012) Spain	Patients who had angioplasty following CMR findings:		
	No abnormalities	14/901 (2)	NA
	PD only, without LGE or inducible WMA	43/219 (20)	NA
	LGE without inducible WMA regardless of PD	56/409 (14)	NA
	Inducible WMA regardless of PD and LGE	65/193 (34)	NA
	Total angioplasty	178/1,722 (10)	NA
	Patients who underwent revascularisation by surgery following CMR findings:		
No abnormalities	3/901 (0.3)	NA	
PD only, without LGE or inducible WMA	5/219 (2)	NA	

Study / Location	Outcome	N patients who underwent revascularisation (%)	Results
	LGE without inducible WMA regardless of PD	25/409 (6)	NA
	Inducible WMA regardless of PD and LGE	31/193 (16)	NA
	Total surgery	64/1,722 (4)	NA
Bodi et al. (2009) Spain	Normal	14/354 (4%, all PCI)	NA
	PD only, without LGE or inducible WMA	53/181 (29%, 45 PCI, 9 CABG)	NA
	Simultaneous PD and inducible WMA	35/66 (53%, 26 PCI, 9 CABG)	NA
	Total	102/601 (17%)	

CABG = coronary artery bypass graft; CMR = cardiac magnetic resonance imaging; LGE = late gadolinium enhancement; NA = not applicable; PCI = percutaneous coronary intervention; PD = perfusion defect; SCMR = Society for Cardiovascular Magnetic Resonance Imaging; WMA = wall motion abnormality

Table 170 Diagnostic accuracy of LGE-CMR in patients with an existing diagnosis of CAD and LVD who are being considered for revascularisation

Study Country	Evidence level and risk of bias	Population	Index test	Reference test	True positives (viable)	False positives	False negatives	True negatives	Uninterpretable or no results
Becker et al. (2008) Germany	Level III-1 Low risk of bias	N=463 dysfunctional segments	LGE-CMR cut-offs ^a : 43% HE 25% HE 50% HE.	Functional recovery at follow-up (9 ± 2 months).	<43% HE 161 <25% HE 189 <50% HE 215	20 62 136	66 39 12	216 174 100	In 771 LV segments, echographic image quality allowed visual assessment of segmental function and myocardial deformation imaging at baseline at follow-up (91%); not known why the other 9% failed. 463 segments were dysfunctional (227 showed functional recovery and 236 did not).
Becker et al. (2011) Germany	Level III-1 Low risk of bias	N=1001 segments	LGE-CMR (cut-off 25% or 75% HE)	Segmental functional recovery at follow-up (8 ± 2 months)	<25% HE 149 <75% HE 635	47 296	544 58	261 12	Two of the revascularised patients died, 3 patients had biochemical evidence of MI and 2 patients declined follow-up examinations.
Bondarenko et	Level III-2	N=322 dysfunctional	LGE-CMR (cut-off 25%)	Segmental functional improvement	<25% HE				-

Study Country	Evidence level and risk of bias	Population	Index test	Reference test	True positives (viable)	False positives	False negatives	True negatives	Uninterpretable or no results
al. (2007) The Netherlands	Low risk of bias	segments	or 50% HE)	(3 months after revascularisation)	64 <50% HE 79	84 145	21 6	153 92	
Gerber et al. (2002) USA	Level III-2 Low risk of bias	N=389 dysfunctional segments	LGE-CMR (cut-off NR)	Improved function at follow-up (7 months after MI)	109	40	61	179	-
Glaveckaite et al. (2011) Lithuania	Level III-1 Low risk of bias	N=333 dysfunctional segments	LGE-CMR (cut-off value 50% HE)	Regional functional recovery at follow-up (6 months)	154	52	37	90	-
Glaveckaite et al. (2014) Lithuania	Level II Low risk of bias	N=319 dysfunctional segments	LGE-CMR (cut-off value 0% HE)	Regional functional recovery at follow-up (35 ± 6 months)	102	12	107	98	-
Gutberlet et al. (2005) Germany	Level III-1 Low risk of bias	N=240	LGE-CMR (cut-off value 50% HE)	Functional recovery after revascularisation	204	4	2	30	-
Kim et al. (2000) US	Level II Low risk of bias	N=804 dysfunctional segments	LGE-CMR (cut-off value 25% and 50% HE)	Improvement in regional contractility at follow-up (79 ± 36 days after revascularisation)	<25% HE 365 <50% HE 411	147 211	60 14	232 168	-
Kuhl et al. (2006) Germany	Level II Low risk of bias	N=187 severely dysfunctional segments	LGE-CMR (cut-off value 50% HE) & PET/SPECT	Regional functional recovery after revascularisation	LGE-CMR 94 PET/SPECT 83	27 24	2 13	64 67	-

Study Country	Evidence level and risk of bias	Population	Index test	Reference test	True positives (viable)	False positives	False negatives	True negatives	Uninterpretable or no results
Oh et al. (2015) Korea	Level III-1 Low risk of bias	N=373 dysfunctional segments	LGE-CMR (cut-off value 25% and 50% HE)	Improvement of segmental wall motion at follow-up (24.1 ± 17.6 months)	<25% HE 171 <50% HE 209	61 78	98 60	43 26	-
Pegg et al. (2010) UK	Level III-1 Low risk of bias	N=957 dysfunctional segments	LGE-CMR (cut-off value 25% and 50% HE)	Improved segmental contractility (at 6 months follow-up)	<25% HE 297 <50% HE 381	126 228	435 16	100 332	-
Regenfus et al. (2012) Germany	Level II Low risk of bias	N=350 dysfunctional segments	LGE-CMR (cut-off 25% HE) & SPECT	Regional functional improvement after vascularisation (8 months)	LGE-CMR 158 SPECT 148	22 78	14 24	156 100	-
Sandstede et al. (2000) Germany	Level III-2 Some risk of bias	N=73 segments with WMAs	LGE-CMR (cut-off NR)	Mechanical improvement / contractile recovery	39	8	1	25	-
Schvartzman et al. (2003) US	Level II Low risk of bias	N=207 segments with abnormal contraction before revascularisation	LGE-CMR (cut-off 25% or 50% HE)	Recovery of function after vascularisation	<25% HE 82 <50% HE 95	57 79	19 6	49 27	-
Selvanayagam et al. (2004) UK	Level III-1 Low risk of bias	N=612 dysfunctional segments	LGE-CMR (cut-off 25% or 50% HE)	Regional functional recovery after vascularisation	<25% HE 266	96	77	173	-

Study Country	Evidence level and risk of bias	Population	Index test	Reference test	True positives (viable)	False positives	False negatives	True negatives	Uninterpretable or no results
				(>6 months)	<50% HE 326	192	17	77	
Sharma and Katz (2009) US	Level II Low risk of bias	N=97 dysfunctional segments	LGE-CMR (cut-off 50% HE) & SPECT	Recovery of regional function after 3 months	LGE-CMR 52 SPECT 43	32	3	10	-
Van Hoe and Vanderheyden (2004) Belgium	Level III-2 Low risk of bias	N=117 dysfunctional segments	LGE-CMR (cut-off 75% HE)	Improved contractile function after vascularisation (9 ± 2 months)	56	5	16	40	-
Wellnhofer et al. (2004) Germany	Level III-1 Low risk of bias	N=288 dysfunctional segments	LGE-CMR (cut-off 50% HE)	Improvement of wall motion after revascularisation (3 months follow-up)	111	79	13	85	-
Wu et al. (2007b) Japan	Level III-1 Low risk of bias	N=252 dysfunctional segments	LGE-CMR (cut-off 50% HE) & PET/SPECT	Regional functional recovery after vascularisation (17 ± 7 days)	LGE-CMR 142 PET/SPECT 152	54	12	44	-

^a 0% HE (category 1), 1% to 25% HE (category 2), 26% to 50% HE (category 3), 51% to 75% HE (category 4), and 76% to 100% HE (category 5)

CAD = coronary artery disease; HE = hyper-enhancement; LGE-CMR = late gadolinium enhancement cardiac magnetic resonance imaging; LV = left ventricular; MI = myocardial infarction; PET = positron emission tomography; SPECT = single-photon emission computed tomography

Table 171 Concordance data of LGE-CMR compared with the comparators in patients with an existing diagnosis of CAD and LVD who are being considered for revascularisation

Study Country	Evidence level and risk of bias	Population	Index test (CMR)	Comparator	True positives (viable)	False positives	False negatives	True negatives	Uninterpretable or no results
Nelson et al. (2004) Australia	Level III-1 Low risk of bias	N=372 dysfunctional segments	LGE-CMR cut-off = 50% scarring	TI-SPECT (cut-off = 60% of maximum activity) & DbE (viable if they were dysfunctional at rest and had augmented function at low dose)	<u>SPECT:</u> All: 146 ≤3 months follow-up: 51 >3 months follow-up: 95 <u>DbE:</u> All: 116 ≤3 months follow-up: 54 >3 months follow-up: 62	<u>SPECT:</u> All: 97 ≤3 months follow-up: 38 >3 months follow-up: 59 <u>DbE:</u> All: 127 ≤3 months follow-up: 35 >3 months follow-up: 92	<u>SPECT:</u> All: 32 ≤3 months follow-up: 12 >3 months follow-up: 20 <u>DbE:</u> All: 26 ≤3 months follow-up: 10 >3 months follow-up: 15	<u>SPECT:</u> All: 97 ≤3 months follow-up: 20 >3 months follow-up: 77 <u>DbE:</u> All: 104 ≤3 months follow-up: 22 >3 months follow-up: 82	Concordance Data only reported for abnormal segments
Schvartzman et al. (2003) US	Level II Low risk of bias	N=444 segments	LGE-CMR cut-off = any scarring	Echo (normal vs mild/severe hypokinesia, akinesia or dyskinesia)	Echo: 37	Echo: 67	Echo: 28	Echo: 312	464 segments were assessed prior to CABG, but 104 were excluded from further analysis due to poor visualisation (16) or resection (88)
Solar et al. (2006) Czech Republic	Level III-2 Low risk of bias	N=1,360 segments (40 patients)	LGE-CMR cut-off = 50% HE	TI-SPECT (cut-off = 50% of the maximum activity)	SPECT: 936 DbE: 91	SPECT: 129 DbE: 38	SPECT: 96 DbE: 5	SPECT: 129 DbE: 26	
Wu et al. (2007a) Taiwan	Level II Low risk of bias	N=680 segments with TI-SPECT	LGE-CMR cut-off = 50% HE	TI-SPECT (cut-off not reported) & stress DbE	SPECT: 411 DbE: 91	SPECT: 93 DbE: 38	SPECT: 33 DbE: 5	SPECT: 109 DbE: 26	

Study Country	Evidence level and risk of bias	Population	Index test (CMR)	Comparator	True positives (viable)	False positives	False negatives	True negatives	Uninterpretable or no results
		N=170 stress DbE							

CABG = coronary artery bypass graft; CAD = coronary artery disease; DbE = dobutamine Echo; Echo = echocardiography; HE = hyper-enhancement; LGE-CMR = late gadolinium enhancement cardiac magnetic resonance imaging; LVD = left ventricular dysfunction; SPECT = single-photon emission computed tomography; Tl = thallium-201.

APPENDIX F QUADAS RISK OF BIAS TABLES

Table 172 Risk of bias and applicability judgments for population 1 diagnostic accuracy studies (QUADAS-2)

Study	Risk of bias				Applicability		
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Al-Saadi et al. (2000)	?	☺	☺	☺	☺	☺	☺
Antonio et al. (2007)	☺	?	?	?	☺	☺	☺
Arnold et al. (2010)	☺	☺	☺	☺	☺	☺	☺
Becker et al. (2015)	☺	?	☺	☺	☺	☺	☺
Bernhardt et al. (2007)	☺	☺	☺	☺	☺	☺	☺
Bettencourt et al. (2013a)	☺	☺	☺	☺	☺	☺	☺
Cheng et al. (2007)	☺	☺	?	☺	☺	☺	☺
Costa et al. (2007)	☺	☺	☺	☺	☺	☺	☺
Cury et al. (2006)	?	☺	☺	☺	☺	☺	☺
de Mello et al. (2012)	?	☺	☺	☺	☺	☺	☺
Falcao et al. (2013)	☺	☺	☺	☺	☺	☺	☺
Greenwood et al. (2014)	☺	☺	☺	☺	☺	☺	☺
Groothuis et al. (2013)	☺	☺	☺	☹	☺	☺	☺
Heitner et al. (2014)	☺	☺	☹	☹	☺	☺	☺
Husser et al. (2009)	☺	☺	☺	☺	☹	☺	☺
Kirschbaum et al. (2011)	☺	?	?	?	☺	☺	☺
Klein et al. (2008)	☺	☺	☺	☺	☺	☺	☺
Klem et al. (2008)	☺	☺	☺	☺	☺	☺	☺
Klem et al. (2006)	☺	☺	☺	☺	☺	☺	☺
Ma et al. (2012)	☺	☺	☺	☺	☺	☺	☺
Merkle et al. (2010)	☺	☺	?	☺	☺	☺	☺
Merkle et al. (2007)	☺	☺	?	☺	☺	☺	☺
Meyer et al. (2008)	?	☺	?	☺	☺	☺	☺
Mordi et al. (2014)	☺	☺	☺	☺	☺	☺	☺
Motwani et al. (2012)	☺	☺	☺	☺	☺	☺	☺
Nagel et al. (2003)	☺	☺	☺	☺	☺	☺	☺
Pereira et al. (2013)	☺	☺	☺	☺	☺	☺	☺
Regenfus et al. (2003)	☺	☺	☺	☺	?	☺	☺
Sakuma et al. (2005)	?	?	?	☺	?	☺	☺
Schwitzer et al. (2001)	?	☺	☺	☺	☺	☺	☺
Sharples et al. (2007)	☺	☺	?	☹	☹	☺	☺
Stolzmann et al. (2011)	☺	☺	☺	☺	☺	☺	☺
Takase et al. (2004)	☺	☺	?	☺	☺	☺	☺

Study	Risk of bias				Applicability		
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Van Werkhoven et al. (2010)	😊	😊	😊	😊	😊	😊	😊
Walcher et al. (2013)	😊	😊	😊	😊	😊	😊	😊
Watkins et al. (2009)	😊	😊	😊	😊	😊	😊	😊

😊 = low risk; 😞 = high risk; ? = unclear risk

Table 173 Risk of bias and applicability judgements for population 2 diagnostic accuracy studies (QUADAS-2)

Study	Risk of bias				Applicability		
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Becker et al. (2008)	?	😊	😊	😊	😊	😊	😊
Becker et al. (2011)	?	😊	😊	😊	😊	😊	😊
Bondarenko et al. (2007)	?	😊	😊	😊	😊	😊	😊
Gerber et al. (2002)	?	😊	?	😊	😊	😊	😊
Glaveckaite et al. (2011)	?	😊	😊	😊	😊	😊	😊
Glaveckaite et al. (2014)	😊	😊	😊	😊	😊	😊	😊
Gutberlet et al. (2005)	?	😊	😊	?	😊	😊	😊
Kim et al. (2000)	😊	😊	😊	😊	😊	😊	😊
Kuhl et al. (2006)	😊	😊	😊	😊	😊	😊	😊
Oh et al. (2015)	?	😊	😊	?	😊	😊	😊
Pegg et al. (2010)	?	😊	😊	😊	😊	😊	😊
Regenfus et al. (2012)	😊	😊	😊	😊	😊	😊	😊
Sandstede et al. (2000)	?	😊	?	?	😊	😊	😊
Schwartzman et al. (2003)	😊	😊	😊	😊	😊	😊	😊
Selvanayagam et al. (2004)	😊	😊	😊	😊	😊	😊	😊
Sharma and Katz (2009)	😊	😊	😊	😊	😊	😊	😊
Van Hoe and Vanderheyden (2004)	😊	😊	?	?	😊	😊	😊
Wellnhofer et al. (2004)	?	😊	😊	😊	😊	😊	😊
Wu et al. (2007b)	?	😊	😊	?	😊	😊	😊

😊 = low risk; ? = unclear risk

Table 174 Risk of bias and applicability judgements for population 2 concordance studies (QUADAS-2)

Study	Risk of bias				Applicability		
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Nelson et al. (2004)	?	😊	😊	?	😊	😊	😊
Schwartzman et al. (2003)	😊	😊	😊	😊	😊	😊	😊
Solar et al. (2006)	?	😊	😊	?	😊	😊	😊
Wu et al. (2007a)	😊	😊	😊	?	😊	😊	😊

😊 = low risk; ? = unclear risk

APPENDIX G GRADE EVIDENCE PROFILE TABLES

The GRADE Working Group grades of evidence (Guyatt et al. 2011) presented in the tables below are defined as:

- ⊕⊕⊕⊕ **High quality:** We are very confident that the true effect lies close to that of the estimate of effect.
- ⊕⊕⊕○ **Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- ⊕⊕○○ **Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
- ⊕○○○ **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Table 175 Evidence profile for the effectiveness of SP-CMR compared with SPECT, stress Echo and ICA in patients with known or suspected CAD

Outcome	No. of participants, No. of studies and study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Result	Quality of evidence	Importance
CVD-related mortality	N=898 k=1 RCT	Not serious	Not serious	Serious ^a	Not serious	None	ICA = 3/222 (1.4%) SPECT = 5/224 (2.2%) SP-CMR = 5/226 (2.2%) Stress Echo = 3/226 (1.3%)	Moderate ⊕⊕⊕○	Critical (9/9)
Non-fatal CVD-related events	N=898 k=1 RCT	Not serious	Not serious	Serious ^a	Not serious	None	ICA = 19/222 (8.6%) SPECT = 24/224 (10.7%) SP-CMR = 29/226 (12.8%) Stress Echo = 31/226 (13.7%)	Moderate ⊕⊕⊕○	Critical (7/9)

^a The population is broader than in the PICO

CAD = coronary artery disease; CVD = cardiovascular disease; Echo = echocardiography; ICA = invasive coronary angiography; RCT = randomised controlled trial; SP-CMR = stress perfusion coronary magnetic resonance imaging; SPECT = single-photon emission computed tomography

Table 176 Evidence profile for the safety of SP-CMR in patients with known or suspected CAD

Outcome	No. of participants, No. of studies and study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Result	Quality of evidence	Importance
Gadolinium-based contrast:	N=11,002 k=3 case series	Not serious	Not serious	Very serious ^a	Not serious	None	0 (0%) had serious adverse reactions after injection of contrast.	Very low	Critical (7/9)

Outcome	No. of participants, No. of studies and study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Result	Quality of evidence	Importance
serious AEs								⊕○○○	
Adenosine: serious AEs	N=2,241 k=21 case series	Not serious	Not serious	Very serious ^a	Not serious	None	16 (0.7%) patients had a serious AE during adenosine stress.	Very low ⊕○○○	Critical (7/9)
Dobutamine: serious AEs	N=1,520 k=2 case series	Serious ^b	Not serious	Very serious ^a	Not serious	None	15 (10%) patients had a serious AE during dobutamine stress.	Very low ⊕○○○	Critical (7/9)
Adenosine or dobutamine: serious AEs	N=10,228 k=1 case series	Not serious	Not serious	Very serious ^a	Not serious	None	7 (0.07%) patients had a serious AE during either adenosine or dobutamine stress (3 with dobutamine and 4 with adenosine).	Very low ⊕○○○	Critical (7/9)
Dipyridamole: serious AEs	N=230 k=3 case series	Serious ^c	Not serious	Very serious ^a	Not serious	None	1 (0.4%) patients had a serious AE during dipyridamole stress.	Very low ⊕○○○	Critical (7/9)
Nicorandil: serious AEs	N=50 k=1 case series	Serious ^d	Not serious	Very serious ^a	Not serious	None	No patients exhibited any adverse reactions during nicorandil stress.	Very low ⊕○○○	Critical (7/9)
Adenosine: moderate AEs	N=976 k=6 case series	Not serious	Not serious	Very serious ^a	Not serious	None	25 (3%) patients had a moderate AE during adenosine stress.	Very low ⊕○○○	Important (6/9)
Claustrophobia	N=4,043 k=23 case series	Serious ^e	Not serious	Very serious ^a	Not serious	None	11 (0.3%) patients had unknown claustrophobia.	Very low ⊕○○○	Important (6/9)
Gadolinium-based contrast: mild AEs	N=11,002 k=3 case series	Not serious	Not serious	Very serious ^a	Not serious	None	37 (0.3%) had mild allergic reactions after injection of contrast.	Very low ⊕○○○	Important (4/9)
Adenosine: mild AEs	N=967 k=6 case series	Not serious	Not serious	Very serious ^a	Not serious	None	273 (29%) patients had a mild AE during adenosine stress.	Very low ⊕○○○	Important (4/9)
Adenosine or dobutamine: mild AEs	N=10,228 k=1 case series	Not serious	Not serious	Very serious ^a	Not serious	None	559 (5%) patients had a mild AE during either adenosine or dobutamine stress.	Very low ⊕○○○	Important (4/9)
Catheterisation	N=4,043 k=23 case series	Serious ^e	Not serious	Very serious ^a	Not serious	None	2 (0.05%) patients developed haematomas or bruising at the site of the intravenous line.	Very low ⊕○○○	Not important (3/9)

^a Non-comparative case series data

^b Both studies had a moderate risk of bias

^c 2 studies had moderate and 1 had high risk of bias

^d The study had a moderate risk of bias

^e 8 studies with low, 14 with moderate and 1 with high risk of bias

AE = adverse event; CAD = coronary artery disease; SP-CMR = stress perfusion coronary magnetic resonance imaging

Table 177 Evidence profile for the safety of SP-CMR in patients suspected of having CAD

Outcome	No. of participants, No. of studies and study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Result	Quality of evidence	Importance
Gadolinium-based contrast: any AE	N=61 k=1 case series	Serious ^a	Not serious	Very serious ^b	Not serious	None	No patients experienced any AE to the contrast agent.	Very low ⊕⊖⊖⊖	Critical (7/9)
Adenosine: serious AEs	N=1,079 k=14 case series	Not serious	Not serious	Very serious ^b	Not serious	None	15 (1%) patients had a serious AE during adenosine stress.	Very low ⊕⊖⊖⊖	Critical (7/9)
Dobutamine serious AEs	N=139 k=2 case series	Not serious	Not serious	Very serious ^b	Not serious	None	5 (4%) patients had a serious AE during dobutamine stress.	Very low ⊕⊖⊖⊖	Critical (7/9)
Dipyridamole serious AEs	N=230 k=3 case series	Serious ^c	Not serious	Very serious ^b	Not serious	None	No patient had a serious AE during dipyridamole stress.	Very low ⊕⊖⊖⊖	Critical (7/9)
Claustrophobia	N=5,501 k=24 case series	Not serious	Not serious	Very serious ^b	Not serious	None	11 (0.3%) patients had unknown claustrophobia.	Very low ⊕⊖⊖⊖	Important (6/9)
Adenosine: mild AEs	N=110 k=2 case series	Serious ^a	Not serious	Very serious ^b	Not serious	None	83 (75%) patients had a mild AE during adenosine stress.	Very low ⊕⊖⊖⊖	Important (4/9)

^a Study had a moderate risk of bias

^b Non-comparative case series data

^c All 3 studies had a moderate risk of bias

AE = adverse event; CAD = coronary artery disease; SP-CMR = stress perfusion coronary magnetic resonance imaging

Table 178 Evidence profile for the accuracy of SP-CMR, SPECT and stress Echo compared with ICA in patients with known or suspected CAD

Outcome	No. of participants, No. of studies Study design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Effect per 1,000 patients/year			QoE Importance
							PTP 15%	study prevalence	PTP 85%	
SP-CMR							60%			
True positives	N=106 patients k=1 study Cross-sectional (cohort type accuracy study)	Very serious (QUADAS-2 high risk of bias)	Serious (included patients with known CAD)	Not serious	Serious (7% of +ve patients did not have ICA)	None	115 (102–126)	462 (408–504)	655 (578–714)	Very low ⊕⊖⊖⊖
False negatives							35 (24–48)	138 (96–192)	195 (136–272)	
True negatives	N=69 patients k=1 study Cross-sectional (cohort type accuracy study)	Very serious (QUADAS-2 high risk of bias)	Serious (included patients with known CAD)	Not serious	Very serious (42% of –ve patients did not have ICA)	None	672 (578–739)	316 (272–348)	119 (102–131)	Very low ⊕⊖⊖⊖
False positives							178 (111–272)	84 (52–128)	31 (19–48)	
SPECT							53%			
True positives	N=114 patients k=1 study Cross-sectional (cohort type accuracy study)	Very serious (QUADAS-2 high risk of bias)	Serious (included patients with known CAD)	Not serious	Not serious (3% of +ve patients did not have ICA)	None	132 (122–140)	466 (429–493)	748 (689–791)	Very low ⊕⊖⊖⊖
False negatives							18 (10–28)	64 (37–101)	102 (59–161)	
True negatives	N=95 patients k=1 study Cross-sectional (cohort type accuracy study)	Very serious (QUADAS-2 high risk of bias)	Serious (included patients with known CAD)	Not serious	Very serious (49% of –ve patients did not have ICA)	None	629 (544–697)	348 (301–385)	111 (96–123)	Very low ⊕⊖⊖⊖
False positives							221 (153–306)	122 (85–169)	39 (27–54)	
Stress Echo							54%			
True	N=110 patients	Very serious	Serious	Not serious	Not serious	None	120	432	680	Very low

Outcome	No. of participants, No. of studies Study design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Effect per 1,000 patients/year			QoE Importance
							PTP 15%	study prevalence	PTP 85%	
positives	k=1 study Cross-sectional (cohort type accuracy study)	(QUADAS-2 high risk of bias)	(included patients with known CAD)		(2% of +ve patients did not have ICA)		(107–131)	(383–470)	(603–739)	⊕⊖⊖⊖
False negatives							30 (19–43)	108 (70–157)	170 (111–247)	
	N=92 patients k=1 study Cross-sectional (cohort type accuracy study)	Very serious (QUADAS-2 high risk of bias)	Serious (included patients with known CAD)	Not serious	Very serious (52% of –ve patients did not have ICA)	None	689 (612–748)	373 (331–405)	122 (108–132)	Very low ⊕⊖⊖⊖
							161 (102–238)	87 (55–129)	28 (18–42)	

SP-CMR pooled sensitivity = 77% (95%CI 68, 84) and pooled specificity = 79% (95%CI 68, 87); SPECT pooled sensitivity = 88% (95%CI 81, 93) and pooled specificity = 74% (95%CI 64, 82); stress Echo pooled sensitivity = 80% (95%CI 71, 87) and pooled specificity = 81% (95%CI 72, 88)

CAD = coronary artery disease; Echo = echocardiography; ICA = invasive coronary angiography; PTP = pre-test probability; QoE= quality of evidence; SP-CMR = stress perfusion cardiac magnetic resonance imaging; SPECT = single-photon emission computed tomography.

Table 179 Evidence profile for the accuracy of SP-CMR & LGE compared with ICA in patients suspected of having CAD

Outcome	No. of participants, No. of studies Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Effect per 1,000 patients/year			QoE Importance
							PTP 15%	study prevalence	PTP 85%	
ICA cut-off 50% DS							47%			
True positives	N=326 patients k=11 studies Cross-sectional (cohort type accuracy study)	Not serious	Not serious	Not serious	Not serious	None	129 (122–134)	404 (381–418)	731 (689–757)	High ⊕⊕⊕⊕
False negatives							21 (16–28)	66 (52–89)	119 (93–161)	
True negatives	N=371 patients k=11 studies	Not serious	Not serious	Not serious	Not serious	None	714 (672–748)	445 (419–466)	126 (119–132)	High ⊕⊕⊕⊕

Outcome	No. of participants, No. of studies Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Effect per 1,000 patients/year			QoE Importance
							PTP 15%	study prevalence	PTP 85%	
False positives	Cross-sectional (cohort type accuracy study)						136 (102–178)	85 (64–111)	24 (18–31)	
ICA cut-off 70% DS							44%			
True positives	N=190 patients k=6 studies Cross-sectional (cohort type accuracy study)	Not serious	Not serious	Not serious	Not serious	None	134 (124–140)	392 (365–409)	757 (705–791)	High ⊕⊕⊕⊕
False negatives							16 (10–26)	48 (31–75)	93 (59–145)	
True negatives	N=241 patients k=6 studies Cross-sectional (cohort type accuracy study)	Not serious	Serious (substantial heterogeneity; $I^2 = 60\%–95\%$)	Not serious	Not serious	None	705 (612–774)	465 (403–510)	125 (108–137)	Moderate ⊕⊕⊕⊕
False positives							145 (76–238)	95 (50–157)	25 (13–42)	
All studies							45%			
True positives	N=486 patients k=16 studies Cross-sectional (cohort type accuracy study)	Not serious	Not serious	Not serious	Not serious	None	128 (123–132)	383 (369–396)	722 (697–748)	High ⊕⊕⊕⊕
False negatives							22 (18–27)	67 (54–81)	128 (102–153)	
	N=604 patients k=16 studies Cross-sectional (cohort type accuracy study)	Not serious	Not serious	Not serious	Not serious	None	722 (689–748)	468 (446–484)	128 (122–132)	High ⊕⊕⊕⊕
							128 (102–161)	82 (66–104)	22 (18–28)	

Outcome	No. of participants, No. of studies Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Effect per 1,000 patients/year			QoE Importance
							PTP 15%	study prevalence	PTP 85%	
SP-CMR + LGE – all							42%			
True positives	N=261 patients k=12 studies Cross-sectional (cohort type accuracy study)	Not serious	Not serious	Not serious	Not serious	None	128 (122–132)	357 (340–370)	722 (689–748)	High ⊕⊕⊕⊕
False negatives							22 (18–28)	63 (50–80)	128 (102–161)	
	N=469 patients k=12 studies Cross-sectional (cohort type accuracy study)	Not serious	Not serious	Not serious	Not serious	None	731 (680–765)	499 (464–522)	129 (120–135)	High ⊕⊕⊕⊕
							119 (85–170)	81 (58–116)	21 (15–30)	
SP-CMR or LGE – all							52%			
True positives	N=145 patients k=4 studies Cross-sectional (cohort type accuracy study)	Not serious	Not serious	Not serious	Not serious	None	129 (120–137)	447 (416–473)	731 (680–774)	High ⊕⊕⊕⊕
False negatives							21 (13–30)	73 (47–104)	119 (76–170)	
	N=135 patients k=4 studies Cross-sectional (cohort type accuracy study)	Not serious	Not serious	Not serious	Not serious	None	705 (646–748)	398 (365–422)	125 (114–132)	High ⊕⊕⊕⊕
							145 (102–204)	82 (58–115)	25 (18–36)	

SP-CMR & LGE versus: ICA cut-off 50% DS pooled sensitivity = 86% (95%CI 81, 89) and pooled specificity = 84% (95%CI 79, 88); ICA cut-off 70% DS pooled sensitivity = 89% (95%CI 83, 93) and pooled specificity = 83% (95%CI 72, 91); ICA (all studies) pooled sensitivity = 85% (95%CI 82, 88) and pooled specificity = 85% (95%CI 81, 88); SP-CMR + LGE versus ICA (all studies) pooled sensitivity = 85% (95%CI 81, 88) and pooled specificity = 86% (95%CI 80, 90); SP-CMR or LGE versus ICA (all studies) pooled sensitivity = 56% (95%CI 80, 91) and pooled specificity = 83% (95%CI 76, 88)

CAD = coronary artery disease; DS = diameter stenosis; ICA = invasive coronary angiography; LGE = late gadolinium enhancement; PTP = pre-test probability; QoE= quality of evidence; SP-CMR = stress perfusion cardiac magnetic resonance imaging

Table 180 Evidence profile for the accuracy of SP-CMR & LGE compared with ICA by coronary artery or segment in patients suspected of having CAD

Outcome	No. of participants, No. of studies Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Effect per 1,000 patients/year			QoE Importance
							PTP 15%	study prevalence	PTP 85%	
ICA cut-off 70% DS							44%			
True positives	N=190 patients k=6 studies Cross-sectional (cohort type accuracy study)	Not serious	Serious (substantial heterogeneity; I ² = 60%–95%)	Not serious	Not serious	None	134 (124–140)	392 (365–409)	757 (705–791)	Moderate ⊕⊕⊕⊖
False negatives							16 (10–26)	48 (31–75)	93 (59–145)	
True negatives	N=241 patients k=6 studies Cross-sectional (cohort type accuracy study)	Not serious	Serious (substantial heterogeneity; I ² = 60%–95%)	Not serious	Not serious	None	705 (612–774)	465 (403–510)	125 (108–137)	Moderate ⊕⊕⊕⊖
False positives							145 (76–238)	95 (50–157)	25 (13–42)	
All studies							45%			
True positives	N=486 patients k=16 studies Cross-sectional (cohort type accuracy study)	Not serious	Serious (substantial heterogeneity; I ² = 60%–90%)	Not serious	Not serious	None	128 (123–132)	383 (369–396)	722 (697–748)	Moderate ⊕⊕⊕⊖
False negatives							22 (18–27)	67 (54–81)	128 (102–153)	
	N=604 patients k=16 studies Cross-sectional (cohort type accuracy study)	Not serious	Not serious	Not serious	Not serious	None	722 (689–748)	468 (446–484)	128 (122–132)	High ⊕⊕⊕⊕
							128 (102–161)	82 (66–104)	22 (18–28)	

Outcome	No. of participants, No. of studies Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Effect per 1,000 patients/year			QoE Importance
							PTP 15%	study prevalence	PTP 85%	
SP-CMR + LGE – all							42%			
True positives	N=261 patients k=12 studies Cross-sectional (cohort type accuracy study)	Not serious	Serious (substantial heterogeneity; I ² = 60%–95%)	Not serious	Not serious	None	128 (122–132)	357 (340–370)	722 (689–748)	Moderate ⊕⊕⊕⊖
False negatives							22 (18–28)	63 (50–80)	128 (102–161)	
	N=469 patients k=12 studies Cross-sectional (cohort type accuracy study)	Not serious	Not serious	Not serious	Not serious	None	731 (680–765)	499 (464–522)	129 (120–135)	High ⊕⊕⊕⊕
							119 (85–170)	81 (58–116)	21 (15–30)	

SP-CMR & LGE versus ICA cut-off 70% DS pooled sensitivity = 89% (95%CI 83, 93) and pooled specificity = 83% (95%CI 72, 91); ICA (all studies) pooled sensitivity = 85% (95%CI 82, 88) and pooled specificity = 85% (95%CI 81, 88); SP-CMR + LGE versus ICA (all studies) pooled sensitivity = 85% (95%CI 81, 88) and pooled specificity = 86% (95%CI 80, 90)

CAD = coronary artery disease; DS = diameter stenosis; ICA = invasive coronary angiography; LGE = late gadolinium enhancement; PTP = pre-test probability; QoE= quality of evidence; SP-CMR = stress perfusion cardiac magnetic resonance imaging

Table 181 Evidence profile for the accuracy of SP-CMR compared with ICA in patients suspected of having CAD

Outcome	No. of participants, No. of studies Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Effect per 1,000 patients/year			QoE Importance
							PTP 15%	study prevalence	PTP 85%	
ICA cut-off 50% DS							44%			
True positives	N=677 patients k=12 studies Cross-sectional (cohort type accuracy study)	Not serious	Serious (substantial heterogeneity; I ² = 60%–95%)	Not serious	Not serious	None	135 (126–141)	396 (370–414)	765 (714–799)	Moderate ⊕⊕⊕⊖
False negatives							15 (9–24)	44 (26–70)	85 (51–136)	
True negatives	N=661 patients k=12 studies Cross-sectional (cohort type accuracy study)	Not serious	Serious (substantial heterogeneity; I ² = 60%–95%)	Not serious	Not serious	None	714 (655–757)	470 (431–498)	126 (116–134)	Moderate ⊕⊕⊕⊖
False positives							136 (93–195)	90 (62–129)	24 (16–34)	
ICA cut-off 70% DS							50%			
True positives	N=776 patients k=11 studies Cross-sectional (cohort type accuracy study)	Not serious	Serious (substantial heterogeneity; I ² = 60%–95%)	Not serious	Not serious	None	137 (120–144)	455 (400–480)	774 (680–816)	Moderate ⊕⊕⊕⊖
False negatives							13 (6–30)	45 (20–100)	76 (34–170)	
True negatives	N=876 patients k=11 studies Cross-sectional (cohort type accuracy study)	Not serious	Serious (substantial heterogeneity; I ² = 60%–95%)	Not serious	Not serious	None	629 (527–705)	370 (310–415)	111 (93–125)	Moderate ⊕⊕⊕⊖
False positives							221 (145–323)	130 (85–190)	39 (25–57)	
All studies							51%			
True	N=1,171 patients	Not serious	Serious	Not serious	Not serious	None	132	449	748	Moderate

Outcome	No. of participants, No. of studies Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Effect per 1,000 patients/year			QoE Importance
							PTP 15%	study prevalence	PTP 85%	
positives False negatives	k=18 studies Cross-sectional (cohort type accuracy study)		(substantial heterogeneity; I ² = 60%–95%)				(123–138) 18 (12–27)	(418–469) 61 (41–92)	(679–782) 102 (68–153)	⊕⊕⊕⊕
	N=1,035 patients k=18 studies Cross-sectional (cohort type accuracy study)	Not serious	Serious (substantial heterogeneity; I ² = 60%–95%)	Not serious	Not serious	None	697 (638–748) 153 (102–212)	402 (368–431) 88 (59–122)	123 (113–132) 27 (18–37)	Moderate ⊕⊕⊕⊕

SP-CMR versus: ICA cut-off 50% DS pooled sensitivity = 90% (95%CI 84, 94) and pooled specificity = 84% (95%CI 77, 89); ICA cut-off 70% DS pooled sensitivity = 91% (95%CI 80, 96) and pooled specificity = 74% (95%CI 62, 83); ICA (all studies) pooled sensitivity = 88% (95%CI 82, 92) and pooled specificity = 82% (95%CI 75, 88)

CAD = coronary artery disease; DS = diameter stenosis; ICA = invasive coronary angiography; PTP = pre-test probability; QoE=quality of evidence; SP-CMR = stress perfusion cardiac magnetic resonance imaging

Table 182 Evidence profile for the accuracy of LGE compared with ICA in patients suspected of having CAD

Outcome	No. of participants, No. of studies Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Effect per 1,000 patients/year			QoE Importance
							PTP 15%	study prevalence	PTP 85%	
ICA cut-off 50% DS							44%			
True positives False negatives	N=119 patients k=4 studies Cross-sectional (cohort type accuracy study)	Not serious	Not serious	Not serious	Not serious	None	66 (53–80) 84 (70–97)	194 (154–233) 246 (207–286)	374 (298–451) 476 (399–552)	High ⊕⊕⊕⊕
True negatives	N=149 patients k=4 studies	Not serious	Not serious	Not serious	Not serious	None	825 (791–842)	543 (521–554)	146 (140–149)	High ⊕⊕⊕⊕

Outcome	No. of participants, No. of studies Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Effect per 1,000 patients/year			QoE Importance
							PTP 15%	study prevalence	PTP 85%	
False positives	Cross-sectional (cohort type accuracy study)						25 (8-59)	17 (6-39)	4 (1-10)	
ICA cut-off 70% DS							45%			
True positives	N=466 patients k=5 studies Cross-sectional (cohort type accuracy study)	Not serious	Not serious	Not serious	Not serious	None	63 (54-74)	189 (162-221)	357 (306-417)	High ⊕⊕⊕⊕
False negatives							87 (76-96)	261 (229-288)	493 (433-544)	
True negatives	N=563 patients k=5 studies Cross-sectional (cohort type accuracy study)	Not serious	Serious (substantial heterogeneity; I ² = 60%-95%)	Not serious	Not serious	None	808 (714-833)	523 (462-539)	143 (126-147)	Moderate ⊕⊕⊕⊕
False positives							42 (17-136)	27 (11-88)	7 (3-24)	
All studies							45%			
True positives	N=519 patients k=7 studies Cross-sectional (cohort type accuracy study)	Not serious	Not serious	Not serious	Not serious	None	61 (53-69)	185 (158-207)	349 (298-391)	High ⊕⊕⊕⊕
False negatives							89 (81-97)	265 (243-292)	501 (459-552)	
	N=624 patients k=7 studies Cross-sectional (cohort type accuracy study)	Not serious	Serious (substantial heterogeneity; I ² = 60%-95%)	Not serious	Not serious	None	816 (774-842)	528 (501-545)	144 (137-149)	Moderate ⊕⊕⊕⊕
							34 (8-76)	22 (5-49)	6 (1-13)	

LGE versus: ICA cut-off 50% DS pooled sensitivity = 44% (95%CI 35, 53) and pooled specificity = 97% (95%CI 93, 99); ICA cut-off 70% DS pooled sensitivity = 42% (95%CI 36, 49) and pooled specificity = 95% (95%CI 84, 98); ICA (all studies) pooled sensitivity = 41% (95%CI 35, 46) and pooled specificity = 96% (95%CI 91, 99)

CAD = coronary artery disease; DS = diameter stenosis; ICA = invasive coronary angiography; LGE = late gadolinium enhancement; PTP = pre-test probability; QoE= quality of evidence

Table 183 Evidence profile for the accuracy of SP-CMR & LGE, SP-CMR and LGE compared with ICA in patients with chest pain and/or an intermediate PTP of having CAD

Outcome	No. of participants, No. of studies Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Effect per 1,000 patients/year			QoE Importance
							PTP 15%	study prevalence	PTP 85%	
SP-CMR & LGE							45%			
True positives	N=160 patients k=6 studies Cross-sectional (cohort type accuracy study)	Not serious	Not serious	Not serious	Not serious	None	126 (117-134)	336 (312-356)	714 (663-757)	High ⊕⊕⊕⊕
False negatives							24 (16-33)	64 (44-88)	136 (93-187)	
True negatives	N=245 patients k=6 studies Cross-sectional (cohort type accuracy study)	Not serious	Not serious	Not serious	Not serious	None	748 (697-782)	528 (492-552)	132 (123-138)	High ⊕⊕⊕⊕
False positives							102 (68-153)	72 (48-108)	18 (12-27)	
SP-CMR							51%			
True positives	N=721 patients k=7 studies Cross-sectional (cohort type accuracy study)	Not serious	Serious (substantial heterogeneity; I ² = 60%-95%)	Not serious	Not serious	None	135 (115-144)	504 (431-538)	765 (655-816)	Moderate ⊕⊕⊕⊕
False negatives							15 (6-35)	56 (22-129)	85 (34-195)	
True negatives	N=677 patients k=7 studies Cross-sectional (cohort type accuracy study)	Not serious	Serious (substantial heterogeneity; I ² = 60%-95%)	Not serious	Not serious	None	714 (578-791)	370 (299-409)	126 (102-140)	Moderate ⊕⊕⊕⊕
False							136	70	24	

Outcome	No. of participants, No. of studies Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Effect per 1,000 patients/year			QoE Importance
							PTP 15%	study prevalence	PTP 85%	
positives							(59-272)	(31-141)	(10-48)	
LGE							45%			
True positives	N=449 patients k=5 studies Cross-sectional (cohort type accuracy study)	Not serious	Not serious	Not serious	Not serious	None	61 (53-69)	185 (158-207)	349 (298-391)	High ⊕⊕⊕⊕
False negatives							89 (81-97)	265 (243-292)	501 (459-552)	
	N=548 patients k=5 studies Cross-sectional (cohort type accuracy study)	Not serious	Serious (substantial heterogeneity; I ² = 60%-95%)	Not serious	Not serious	None	816 (774-842)	528 (501-545)	144 (137-149)	Moderate ⊕⊕⊕⊖
							34 (8-76)	22 (5-49)	6 (1-13)	

SP-CMR & LGE pooled sensitivity = 84% (95%CI 78, 89) and pooled specificity = 88% (95%CI 82, 92); SP-CMR pooled sensitivity = 90% (95%CI 77, 96) and pooled specificity = 84% (95%CI 68, 93); LGE pooled sensitivity = 40% (95%CI 34, 47) and pooled specificity = 96% (95%CI 88, 99)

CAD = coronary artery disease; ICA = invasive coronary angiography; LGE = late gadolinium enhancement; PTP = pre-test probability; QoE= quality of evidence; SP-CMR = stress perfusion cardiac magnetic resonance imaging

Table 184 GRADE assessment of body of evidence for diagnostic accuracy of LGE-CMR in patients diagnosed with CAD and LVD to predict segmental recovery

Outcome	No. of participants, No. of studies Study design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Effect per 1000 patients/year		QoE Importance
							PTP: 56%		
LGE-CMR (high cut-off)							56%		
True positives	N=3,438 segments k=15 studies Cross-sectional (cohort type accuracy study)	Not serious	Not serious	Very serious (considerable heterogeneity; I ² = >95%)	Not serious	None	521 (504-538)		Low ⊕⊕⊖⊖
False									

Outcome	No. of participants, No. of studies Study design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Effect per 1000 patients/year PTP: 56%	QoE Importance
negatives							39 (22–56)	
True negatives	N=2,815 segments k=15 studies Cross-sectional (cohort type accuracy study)	Not serious	Not serious	Very serious (considerable heterogeneity; $I^2 = >95\%$)	Not serious	None	198 (132–268)	Low ⊕⊕⊖⊖
False positives							242 (172–308)	
LGE-CMR (low cut-off)								
True positives	N=3,257 segments k=10 Cross-sectional (cohort type accuracy study)	Not serious	Not serious	Very serious (considerable heterogeneity; $I^2 = >95\%$)	Not serious	None	382 (294–447)	Low ⊕⊕⊖⊖
False negatives							163 (98–251)	
True negatives	N=2,153 segments k=10 Cross-sectional (cohort type accuracy study)	Not serious	Not serious	Very serious (considerable heterogeneity; $I^2 = >95\%$)	Not serious	None	309 (255–355)	Low ⊕⊕⊖⊖
False positives							146 (100–200)	

LGE-CMR (low cut-off) pooled sensitivity = 70% (95%CI 54, 82) and pooled specificity = 68% (95%CI 56, 78); LGE-CMR (high cut-off) pooled sensitivity = 93% (95%CI 90, 96) and pooled specificity = 45% (95%CI 30, 61)

CAD = coronary artery disease; LGE-CMR = late gadolinium enhancement cardiac magnetic resonance imaging; LVD = left ventricular dysfunction; PTP = pre-test probability; QoE= quality of evidence

Table 185 GRADE assessment of body of evidence for change in management after SP-CMR in patients suspected of having CAD

Outcome	No. of participants, No. of studies and study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Result	Quality of evidence	Importance
Risk reclassification	N=1,275 k=3 case series	Not serious	Not serious	Not serious	Not serious	none	Mostly patients in the intermediate group were recategorised. 18%–65.7% were reclassified as low risk. 16%–25.8% were reclassified as high risk.	Very low ⊕⊖⊖⊖	Low importance
Change in clinical diagnosis	N=27,301 k=1 case series	Not serious	Not serious	Not serious	Not serious	none	CMR findings led to a completely new diagnosis not previously suspected in 8.1% of cases	Very low ⊕⊖⊖⊖	Important
Change in therapy/clinical management	N=27,301 k=1 case series	Not serious	Not serious	Not serious	Not serious	none	Overall impact on patient management (new diagnosis and/ or therapeutic consequence) = 71.4%	Very low ⊕⊖⊖⊖	Important
Diagnostic tests avoided	N=27,301 k=1 case series	Not serious	Not serious	Not serious	Not serious	none	ICA 4,555/10,113 (45%) SPECT/PET 3,946/10,113 (39%) CTCA 2,202/10,113 (22%)	Very low ⊕⊖⊖⊖	Important
Frequency of ICA after SP-CMR	N=2,398 k=2 case series	Not serious	Not serious	Not serious	Not serious	none	No ischaemia 6-11% PD only 55-56%) LGE, no WMA 34% WMA ± PD or LGE 68% PD + WMA 82%	Very low ⊕⊖⊖⊖	Important
CMR-related revascularisation	N=3,330 k=3 case series	Not serious	Not serious	Not serious	Not serious	none	No ischaemia 2-4% LGE only 11-20% PD only 22-29%) LGE + PD 24%	Very low ⊕⊖⊖⊖	Important

Outcome	No. of participants, No. of studies and study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Result	Quality of evidence	Importance
							WMA 50–53%		
Preferred test	N=111 k=1 non-randomised cross-over trial	Not serious	Not serious	Not serious	Not serious	none	Preferred test: CMR 16% CTCA 72% ICA 12% Willing to undergo tests again: CMR 84% CTCA 94% ICA 91%	High ⊕⊕⊕⊕	Important

CAD = coronary artery disease; CMR = cardiac magnetic resonance imaging; CTCA = computed tomography coronary angiography; ICA = invasive coronary angiography; LGE = late gadolinium enhancement; PD = perfusion defect; PET = positron emission tomography; SP-CMR = stress perfusion CMR; SPECT= single-photon emission computed tomography; WMA = wall motion abnormality

Table 186 GRADE assessment of body of evidence for change in management after LGE-CMR in patients diagnosed with CAD and LVD

Outcome	No. of participants, No. of studies and study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Result	Quality of evidence	Importance
% change in management	N=4,140 k=2 cohort studies	Not serious	Serious ^a	Serious ^b	Not serious	none	71.5% of patients had a change in management after LGE-CMR in 1 study (change in invasive procedure in 24.2%), and the second study reported that 3/9 CABGs were averted due to non-viability, and overall 13% had a change in surgical management plan.	Very low ⊕⊖⊖⊖	Important

^a Bruder et al. (2013) also recorded change in medication etc.; this leads to a much higher percentage change compared with the other study, which only recorded change in invasive procedures

^b Patients may differ from population of interest

CABG = coronary artery bypass graft; CAD = coronary artery disease; LGE-CMR = cardiac magnetic resonance imaging with late gadolinium enhancement; LVD = left ventricular dysfunction

Table 187 GRADE assessment of body of evidence for change in health outcomes (revascularisation vs medical therapy alone) in patients diagnosed with CAD and LVD

Outcome	No. of participants, No. of studies and study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Revascularisation (N deaths)	Medical treatment	Relative effect: HR (95%CI)	Absolute effect	Quality of evidence	Importance
Mortality rate	N=601 k=1 RCT	Not serious	Not serious	Not serious	Not serious	None	98/298 (32.9%)	119/303 (39.3%)	<u>Viable:</u> 0.86 [0.64–1.16] <u>Non-viable:</u> 0.70 [0.41–1.18]	<u>Viable:</u> 41 fewer per 1,000 (from 44 more to 110 fewer) <u>Non-viable:</u> 122 fewer per 1,000 (from 60 more to 271 fewer)	High ⊕⊕⊕⊕	Critical

CAD = coronary artery disease; CI = confidence interval; HR = hazard ratio; LVD = left ventricular dysfunction; RCT = randomised controlled trial

APPENDIX H FOREST PLOTS SHOWING SENSITIVITY AND SPECIFICITY OF INDIVIDUAL STUDIES (POPULATIONS 1 AND 2)

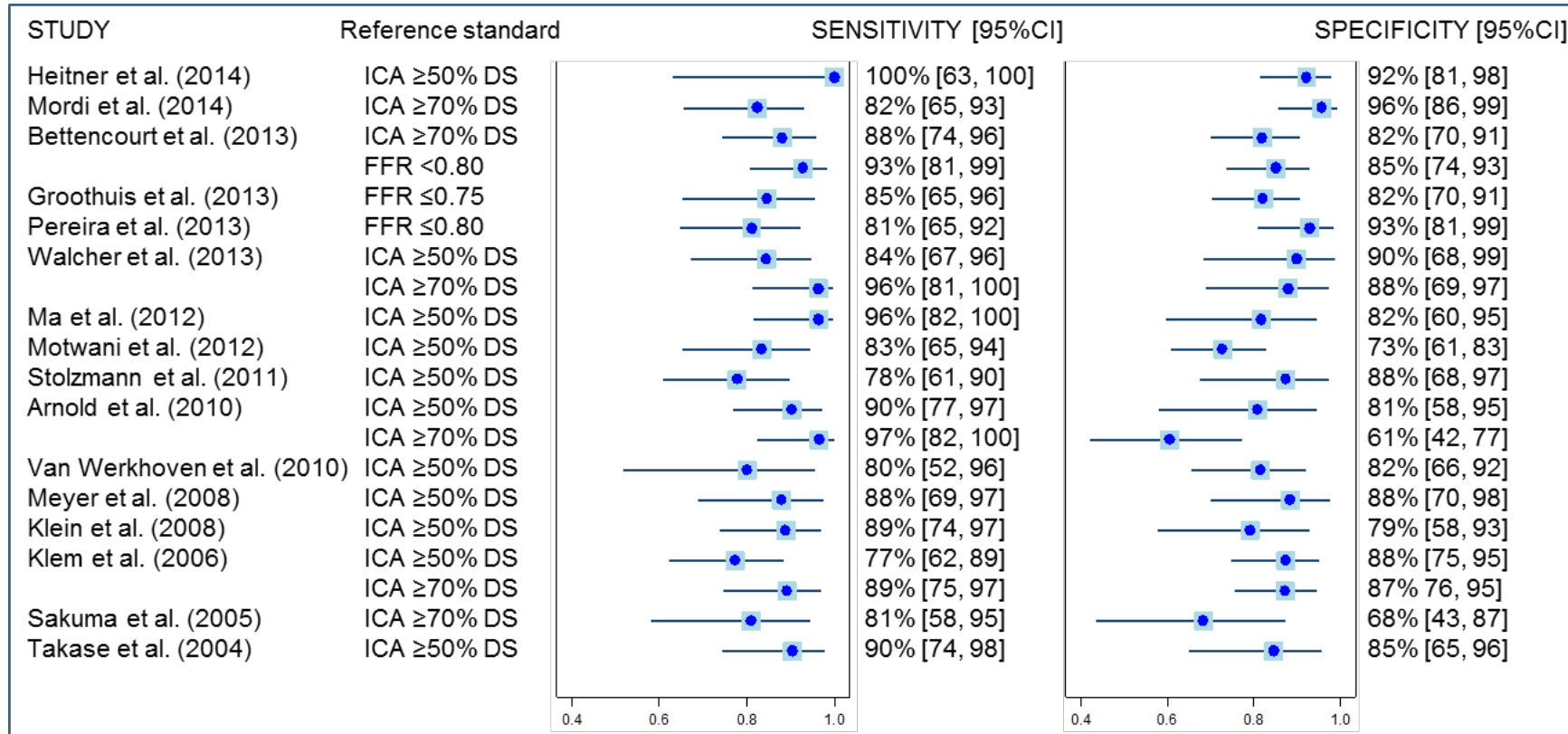


Figure 44 Forest plot showing sensitivity and specificity of SP-CMR & LGE compared with ICA at the patient level for individual studies that enrolled patients suspected of having CAD

CAD = coronary artery disease; CI = confidence interval; DS = diameter stenosis; FFR = fractional flow reserve; ICA = invasive coronary angiography; LGE = late gadolinium enhancement; SP-CMR = stress perfusion cardiac magnetic resonance imaging

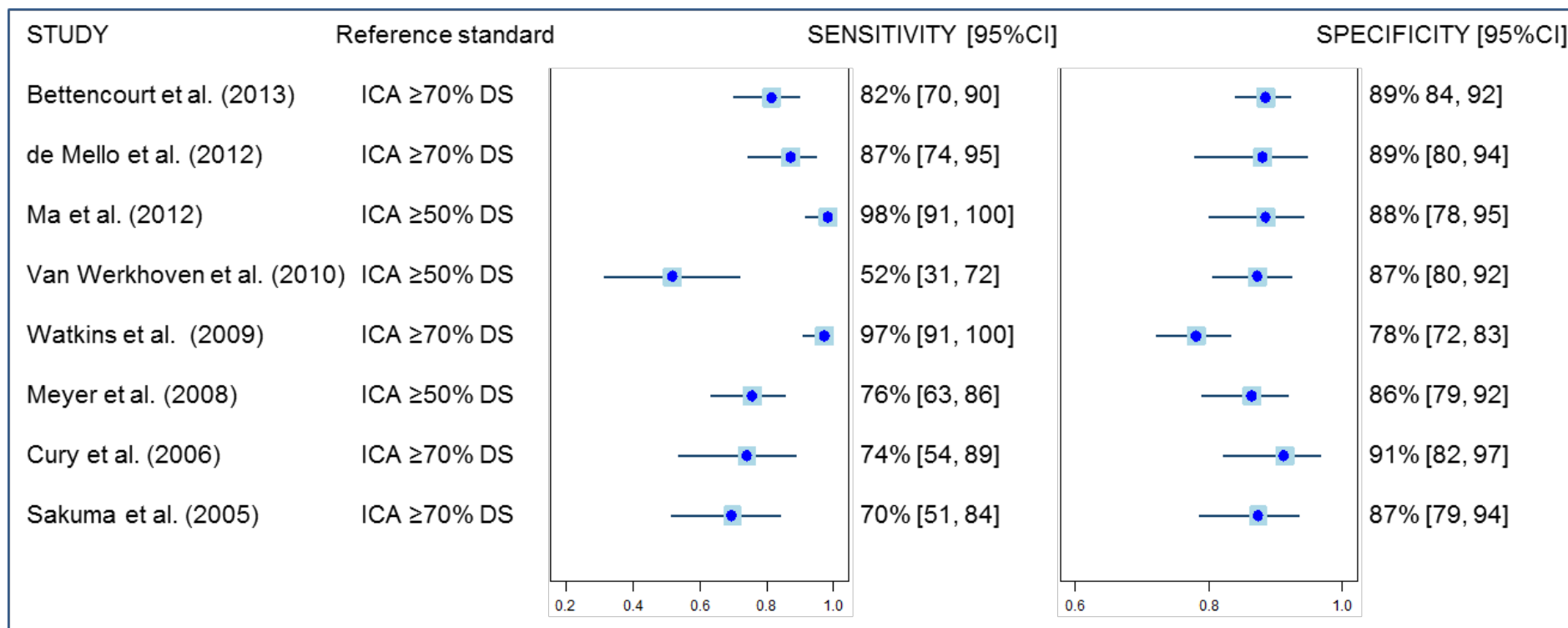


Figure 45 Forest plot showing sensitivity and specificity of SP-CMR & LGE compared with ICA at the coronary artery / segment level for individual studies that enrolled patients suspected of having CAD

CAD = coronary artery disease; CI = confidence interval; DS = diameter stenosis; ICA = invasive coronary angiography; LGE = late gadolinium enhancement; SP-CMR = stress perfusion cardiac magnetic resonance imaging

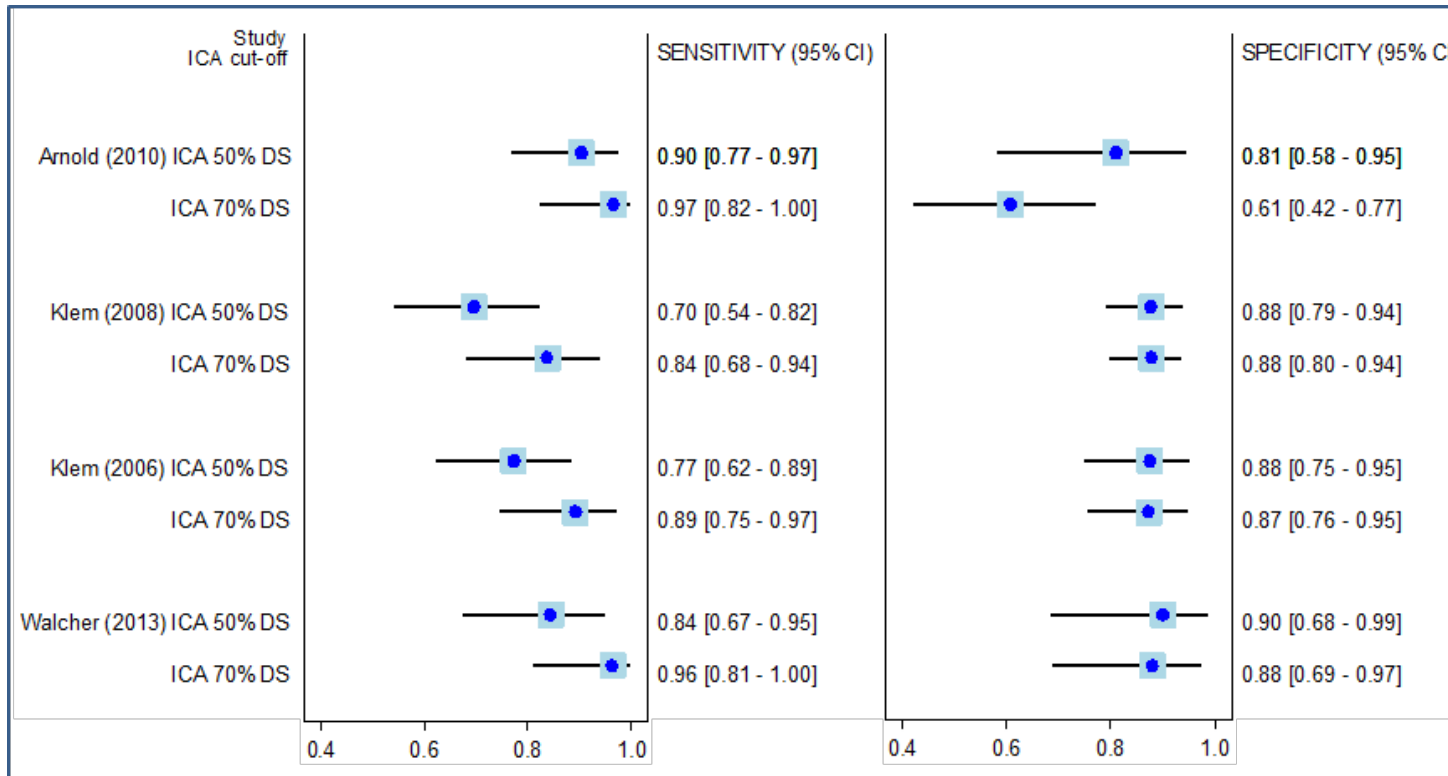


Figure 46 Forest plot showing sensitivity and specificity of SP-CMR & LGE compared with ICA in studies that used both ICA 50% DS and 70% DS cut-off values to diagnose CAD

CAD = coronary artery disease; CI = confidence interval; DS = diameter stenosis; ICA = invasive coronary angiography; LGE = late gadolinium enhancement; SP-CMR = stress perfusion cardiac magnetic resonance imaging.

The study by Arnold et al. (2010) showed a non-significant difference in specificity of 20%, favouring the lower cut-off value (Figure 46); this was due to the relatively large number of patients with stenoses of between 50% and 70% who had PDs detectable by SP-CMR and/or LGE in that study (Table 162). The remaining 3 studies only showed a 0%–2% difference in specificity between cut-offs.

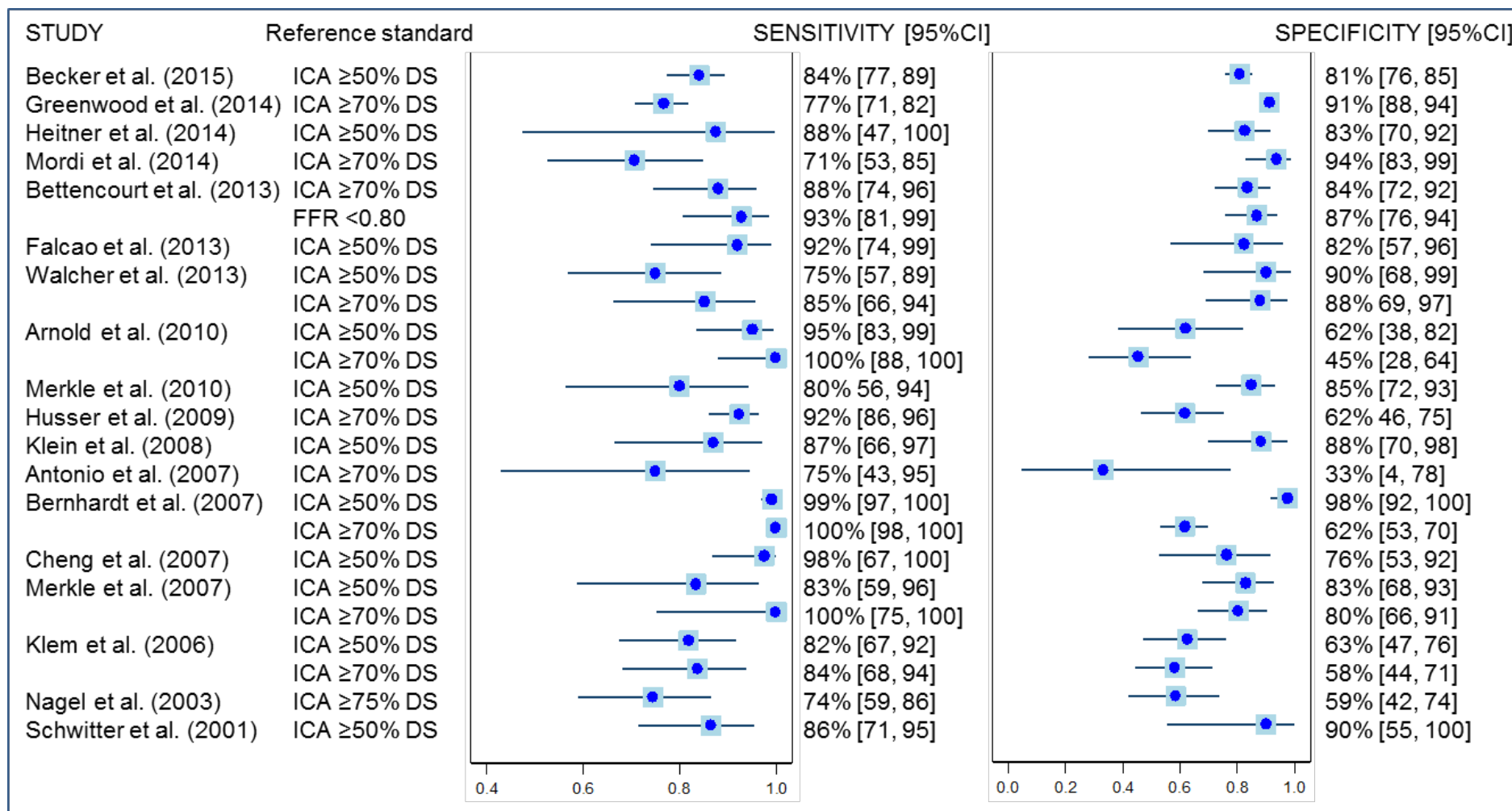


Figure 47 Forest plot showing sensitivity and specificity of SP-CMR compared with ICA at the patient level for individual studies that enrolled patients suspected of having CAD

CAD = coronary artery disease; CI = confidence interval; DS = diameter stenosis; FFR = fractional flow reserve; ICA = invasive coronary angiography; SP-CMR = stress perfusion cardiac magnetic resonance imaging

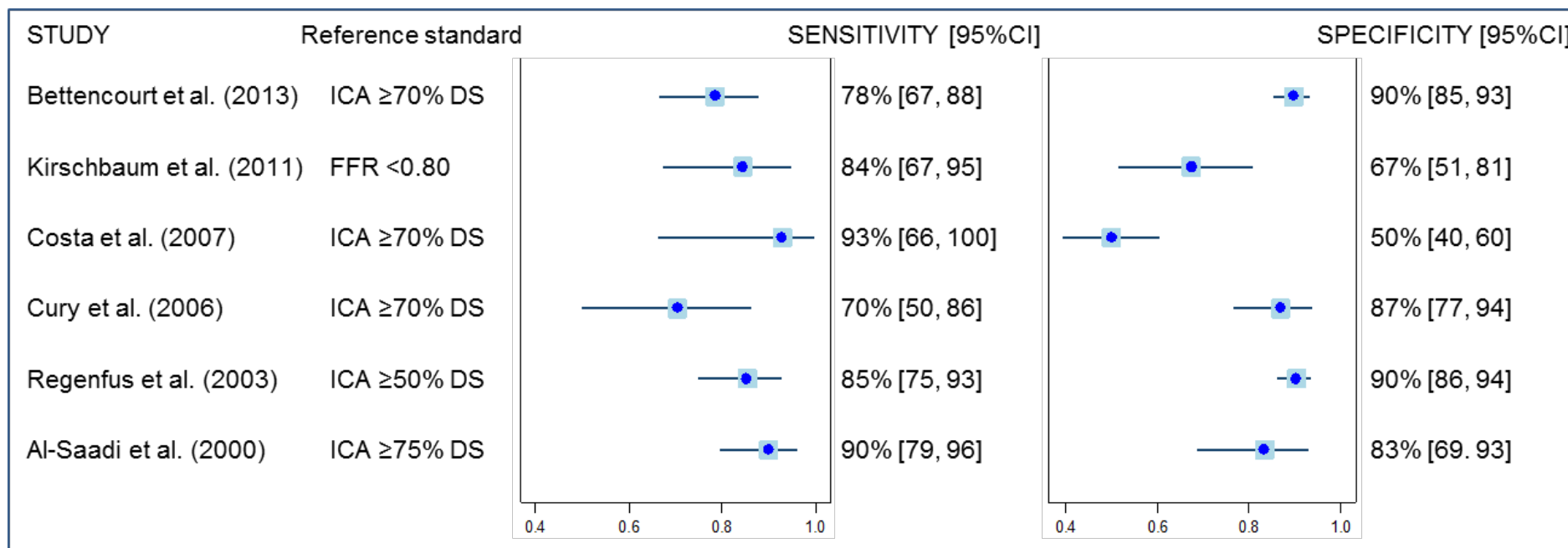


Figure 48 Forest plot showing sensitivity and specificity of SP-CMR compared with ICA at the coronary artery / segment level for individual studies that enrolled patients suspected of having CAD

CAD = coronary artery disease; CI = confidence interval; DS = diameter stenosis; FFR = fractional flow reserve; ICA = invasive coronary angiography; SP-CMR = stress perfusion cardiac magnetic resonance imaging

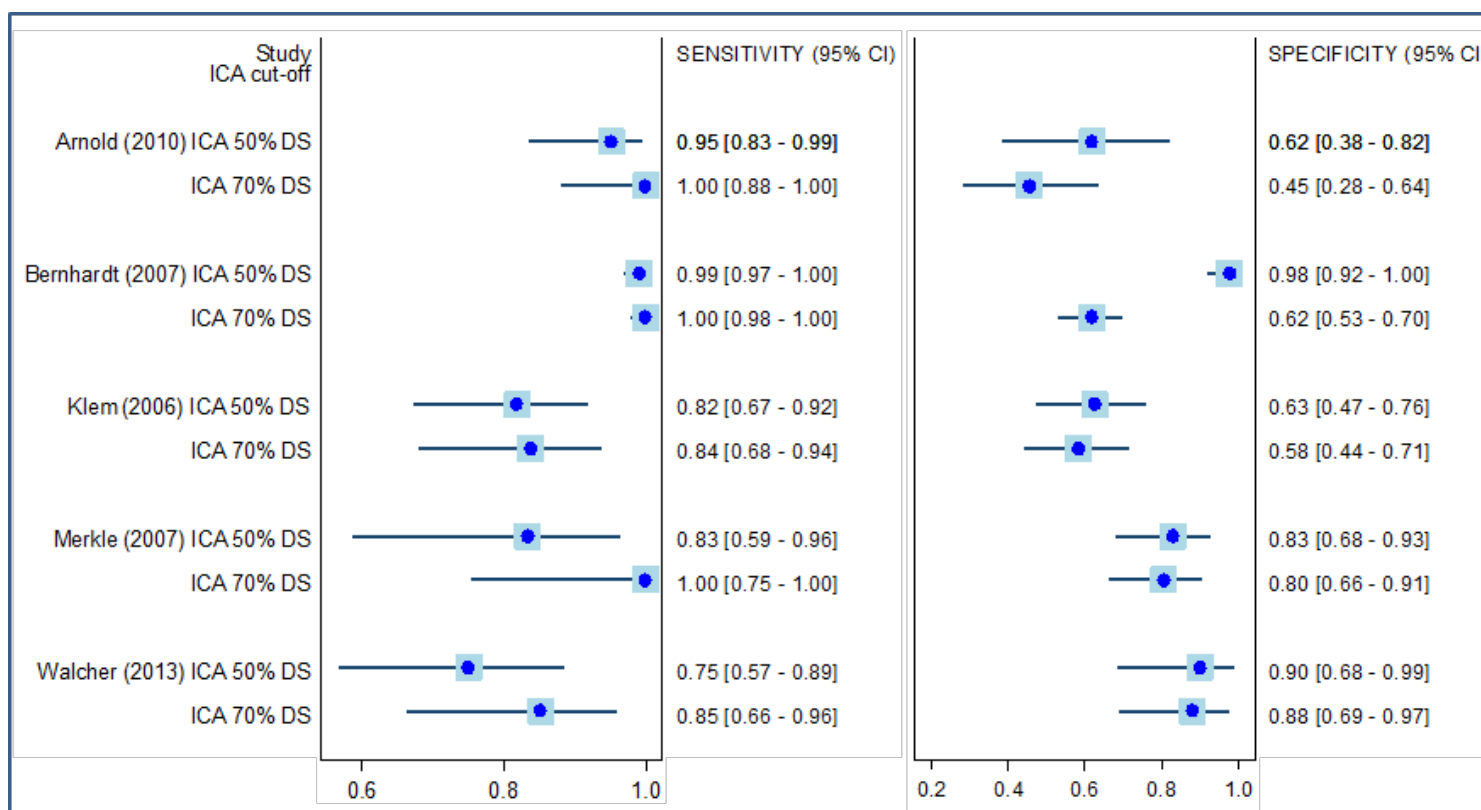


Figure 49 Forest plot showing sensitivity and specificity of SP-CMR compared with ICA in studies that used both ICA 50% DS and 70% DS cut-off values to diagnose CAD

CAD = coronary artery disease; CI = confidence interval; DS = diameter stenosis; ICA = invasive coronary angiography; SP-CMR = stress perfusion cardiac magnetic resonance imaging

Two studies showed differences in sensitivity greater than 5% (Merkle et al. 2007; Walcher et al. 2013); both of these studies had a relatively high proportion of false negatives using an ICA cut-off of 50% DS, suggesting that patients with stenoses of between 50% and 70% were not readily detected by SP-CMR in those studies. The difference in specificity between different cut-offs (36%) reached statistical significance in the study by Bernhardt et al. (2007). The study by Arnold et al. (2010) showed a non-significant increase in specificity for the lower cut-off value by 17%. Both these studies had relatively large numbers of patients with stenoses of between 50% and 70% who had PDs detectable by SP-CMR compared with the other 3 studies (Table 162 in Appendix E).

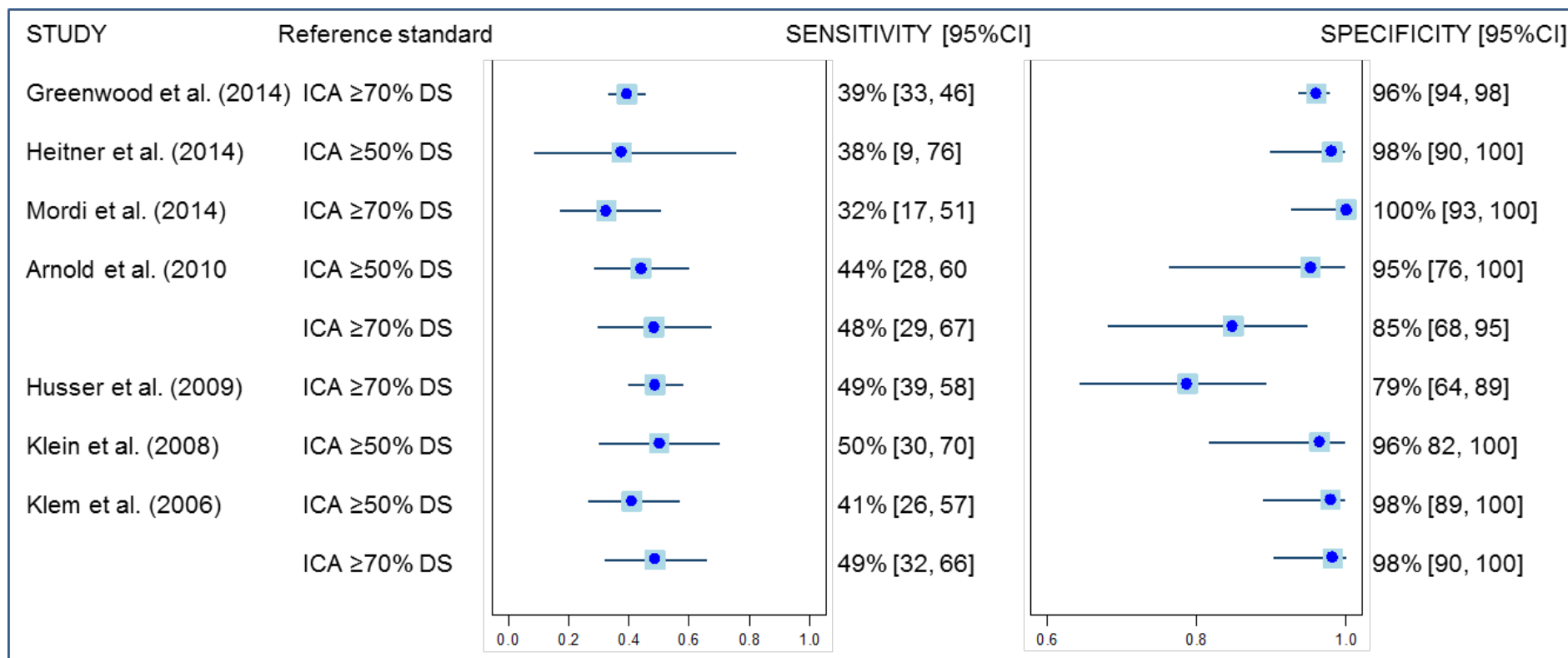


Figure 50 Forest plot showing sensitivity and specificity of LGE compared with ICA at the patient level for individual studies that enrolled patients suspected of having CAD
 CAD = coronary artery disease; CI = confidence interval; DS = diameter stenosis; ICA = invasive coronary angiography; LGE = late gadolinium enhancement

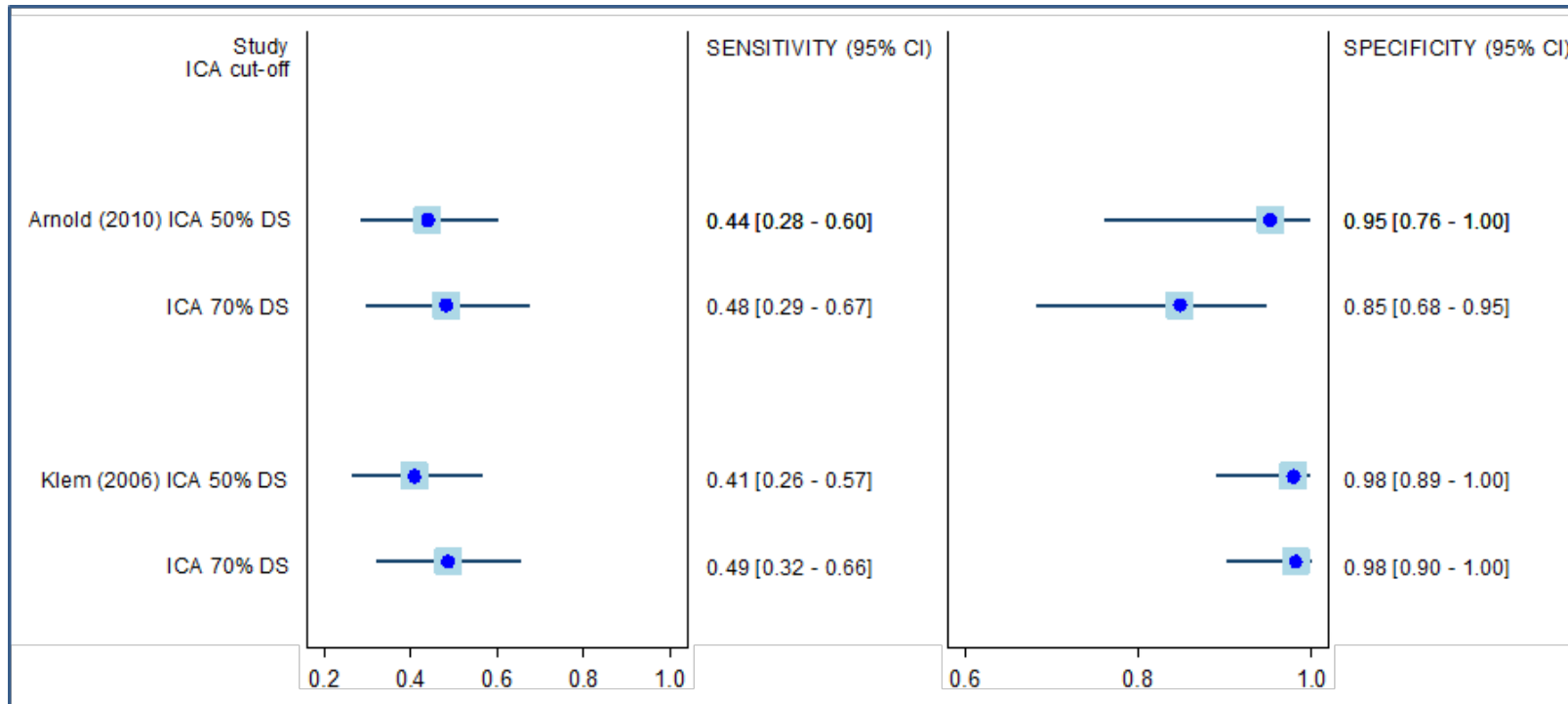


Figure 51 Forest plot showing sensitivity and specificity of LGE compared with ICA in studies that used both ICA 50% DS and 70% DS cut-off values to diagnose CAD
 CAD = coronary artery disease; CI = confidence interval; ICA = invasive coronary angiography; LGE = late gadolinium enhancement.

Direct comparison of the specificity for the two cut-offs showed no difference in 1 study and a difference of 10% in the other. This study had a greater number of false positive patients when using the higher cut-off value.

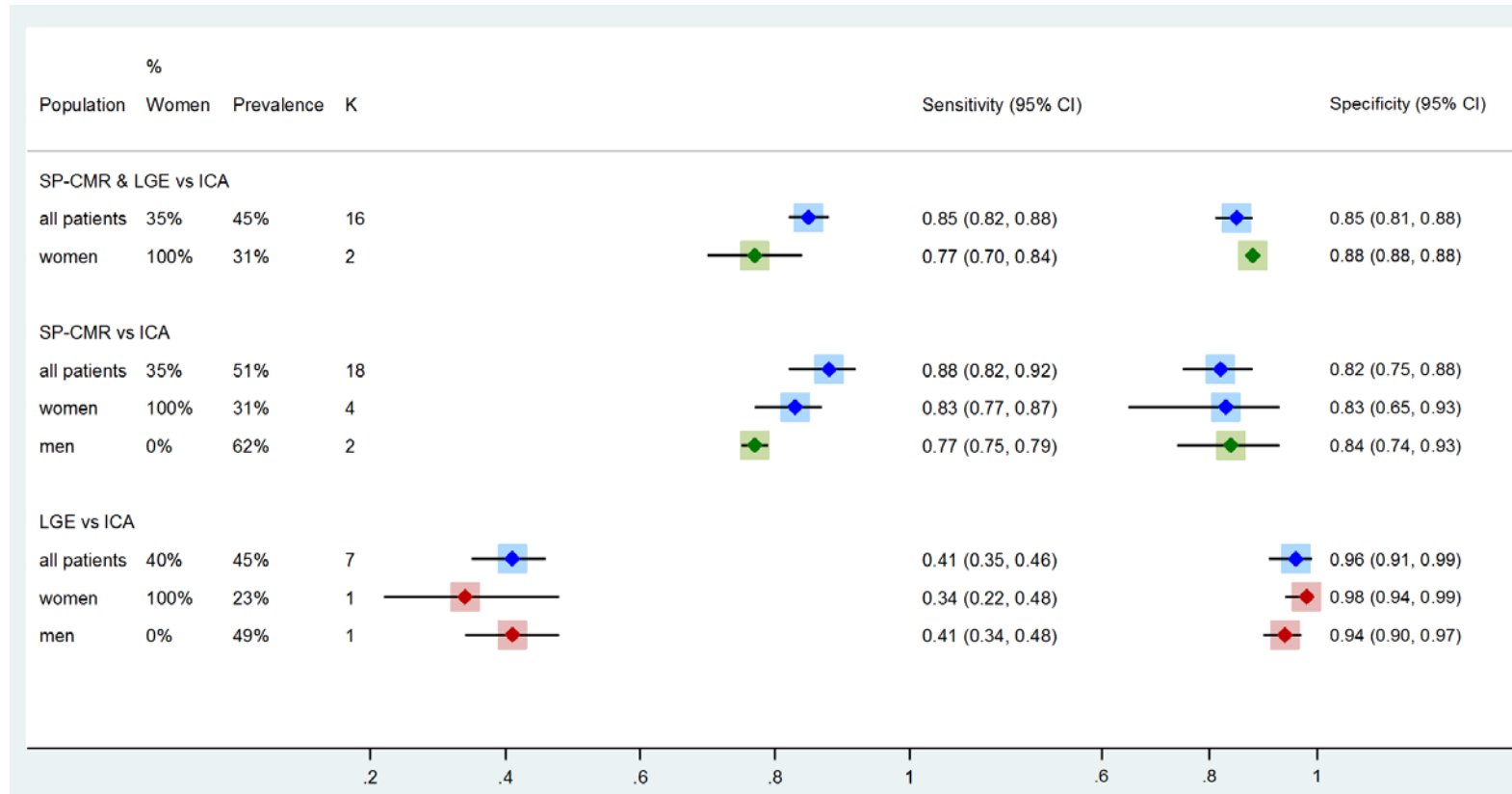


Figure 52 Forest plot showing sensitivity and specificity of SP-CMR, LGE and SP-CMR & LGE versus ICA in the diagnosis of CAD in women compared with men and mixed populations

Pooled estimates are shown in blue; mean and range (when less than 4 studies) are shown in green; and estimates from single studies are shown in red.

CAD = coronary artery disease; CI = confidence interval; ICA = invasive coronary angiography; K = number of studies; LGE = late gadolinium enhancement; SP-CMR = stress perfusion cardiac magnetic resonance imaging

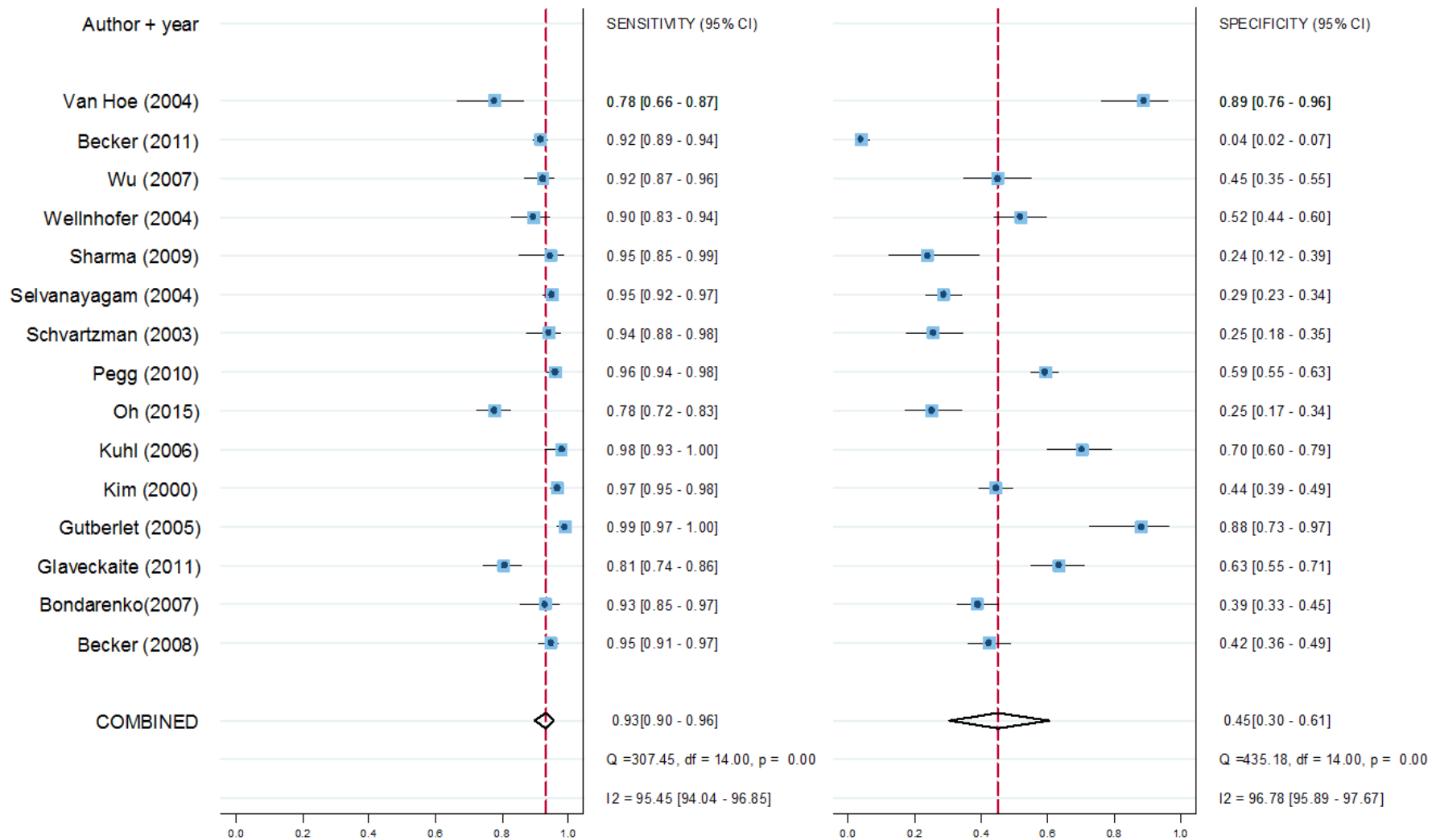


Figure 53 Forest plot showing sensitivity and specificity of LGE-CMR using a high cut-off compared with regional functional recovery in patients with CAD and LVD who are being considered for revascularisation for each included study and pooled values

CAD = coronary artery disease; CI = confidence interval; LGE-CMR = late gadolinium enhancement cardiac magnetic resonance imaging; LVD = left ventricular dysfunction

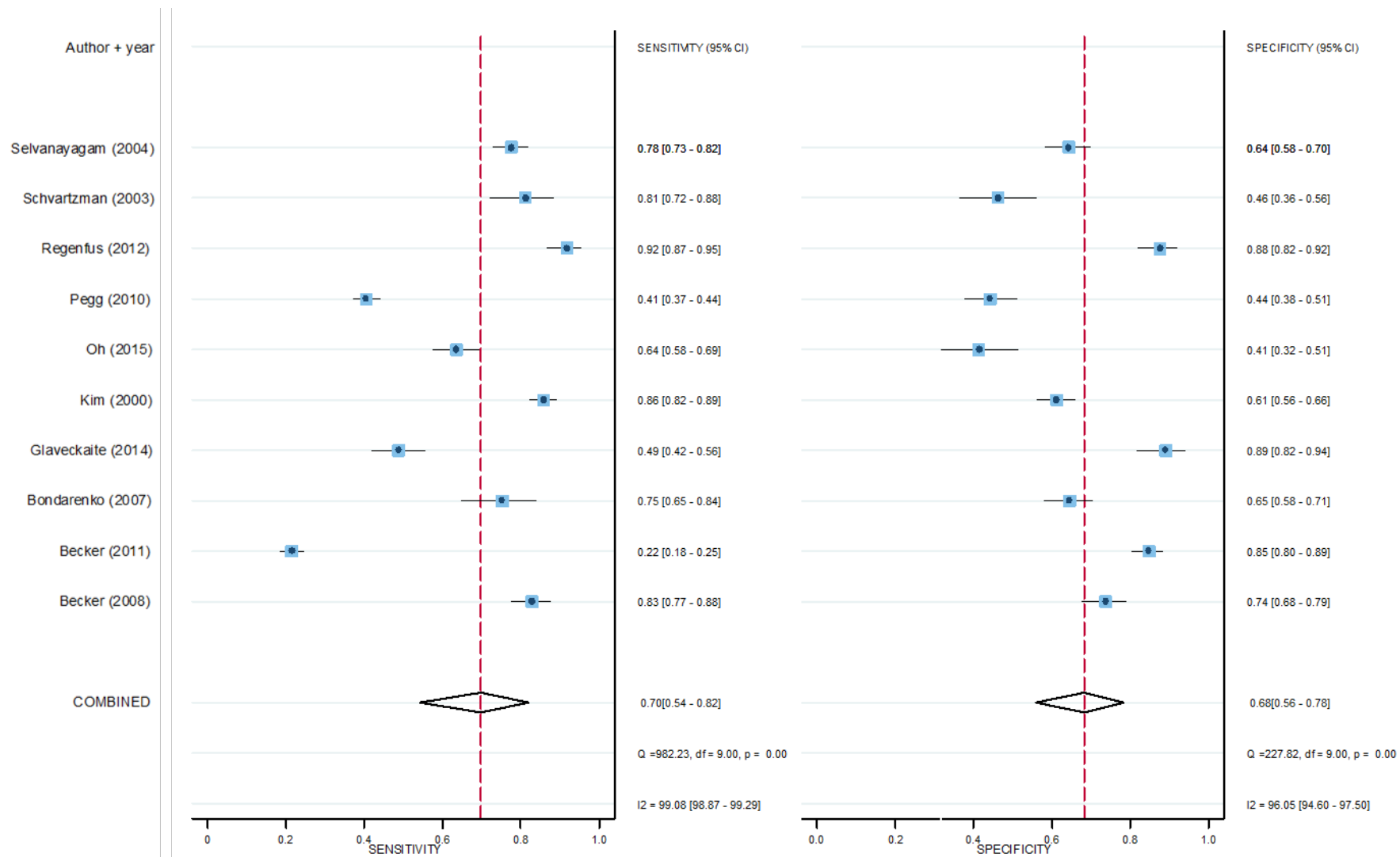


Figure 54 Forest plot showing sensitivity and specificity of LGE-CMR using a low cut-off compared with regional functional recovery in patients with CAD and LVD who are being considered for revascularisation for each included study and the pooled values

CAD = coronary artery disease; CI = confidence interval; LGE-CMR = late gadolinium enhancement cardiac magnetic resonance imaging; LVD = left ventricular dysfunction

APPENDIX I FOREST PLOTS SHOWING POOLED SENSITIVITY AND SPECIFICITY FOR SP-CMR, CTCA, SPECT OR STRESS ECHO COMPARED WITH ICA AS REPORTED IN SRs (POPULATION 1)

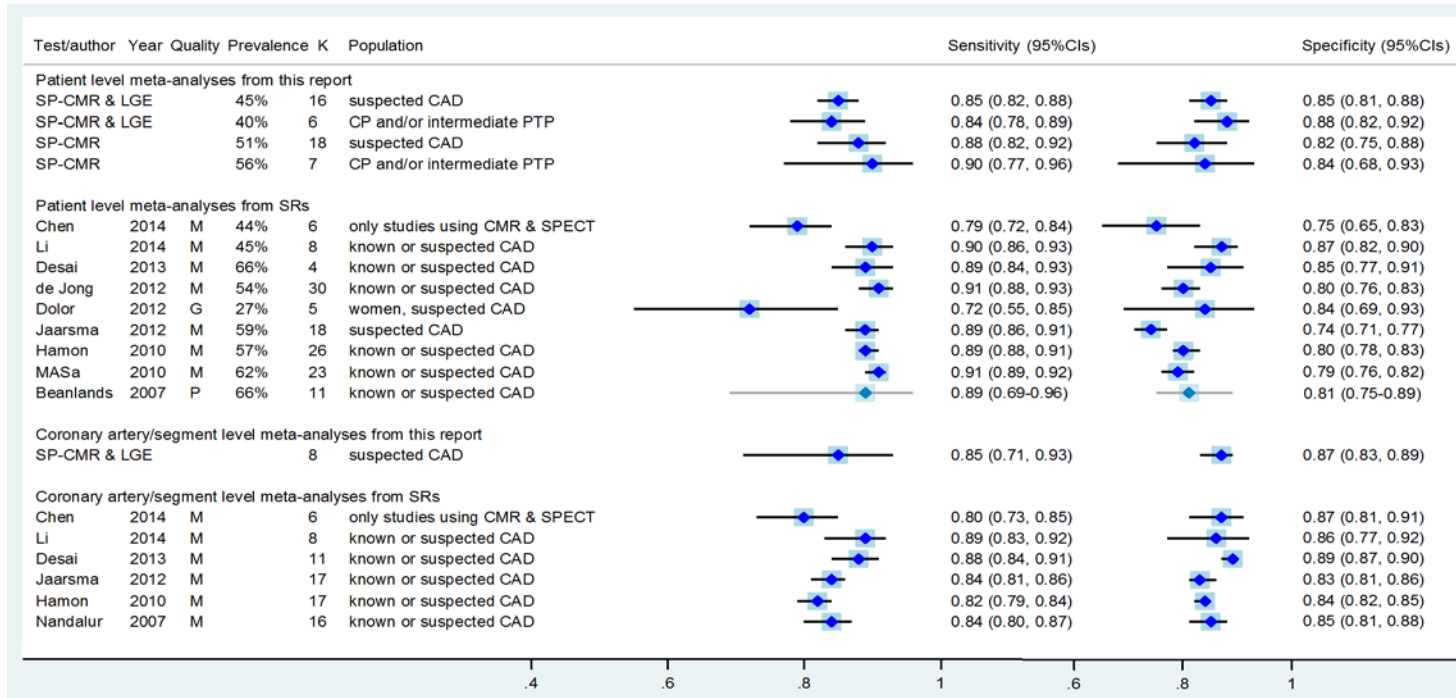


Figure 55 Forest plot showing pooled sensitivities and specificities reported in Section B3.6.2 and by SRs comparing SP-CMR with/without LGE with ICA

Beanlands et al. (2007) reported weighted means (range) for sensitivity and specificity. One poor-quality study is shown in pale blue/grey.

CAD = coronary artery disease; CI = confidence interval; CP = chest pain; ICA = invasive coronary angiography; K = number of studies; LGE = late gadolinium enhancement; PTP = pre-test probability; Quality: G = good, M = moderate, P = poor; SP-CMR = stress perfusion cardiac magnetic resonance imaging; SPECT = single-photon emission computed tomography; SR = systematic review

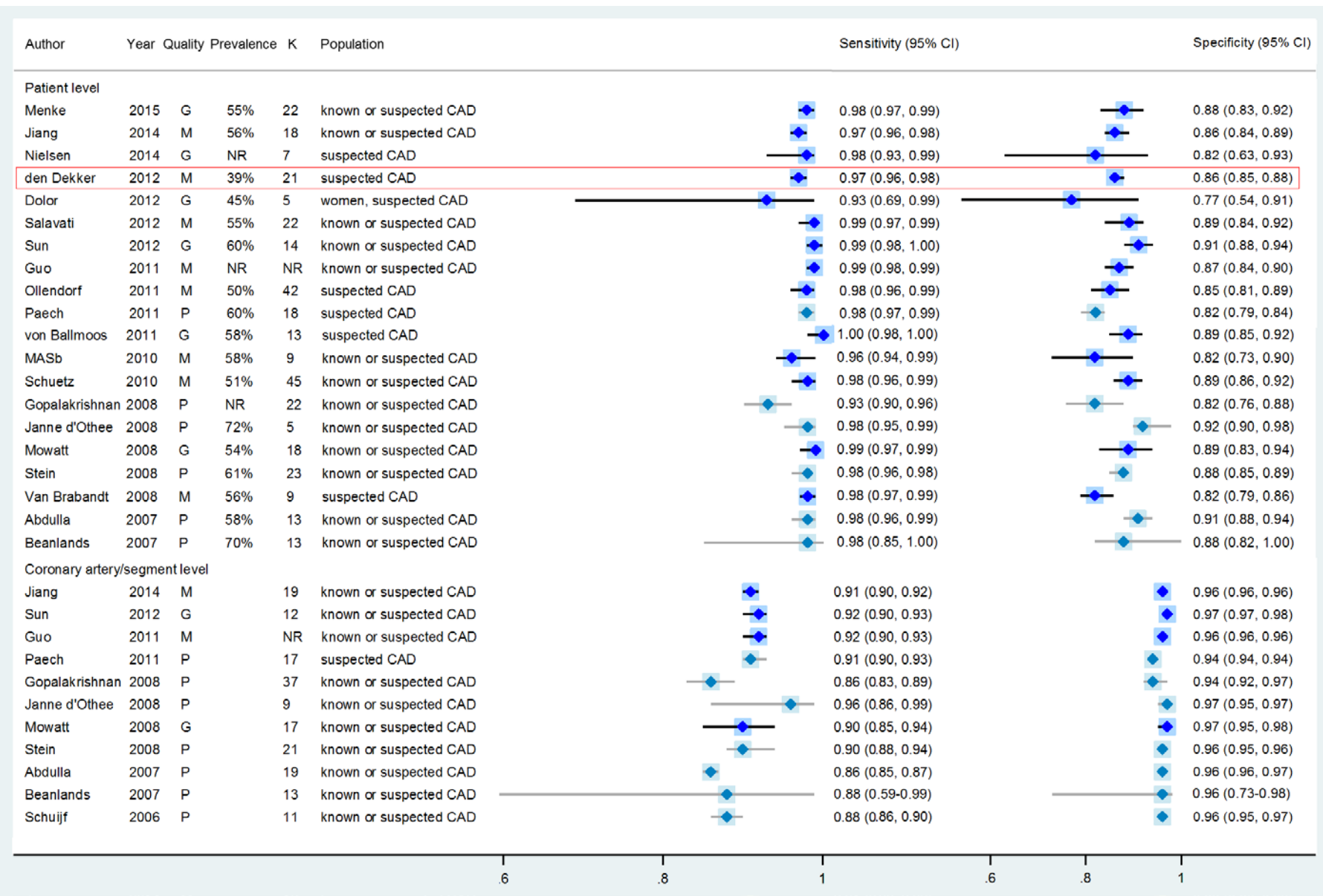


Figure 56 Forest plot showing pooled sensitivities and specificities reported by SRs comparing CTCA with ICA

Based on the selection criteria described in Section B3a.6.3, the SR by den Dekker et al. (2012) was considered to provide the most appropriate pooled estimates to compare the accuracy of SP-CMR with/without LGE with CTCA, using ICA as a common reference standard (boxed in red)

Beanlands et al. (2007) reported weighted means (range) for sensitivity and specificity. Poor-quality studies are shown in pale blue/grey.

CAD = coronary artery disease; CI = confidence interval; CTCA = computed tomography coronary angiography; ICA = invasive coronary angiography; K = number of studies; LGE = late gadolinium enhancement; NR = not reported; Quality: G = good, M = moderate, P = poor; SR = systematic review; SP-CMR = stress perfusion cardiac magnetic resonance imaging; SR = systematic review

All except 2 of the SRs included only studies that used at least 16-slice CTCA or dual-source CTCA. One study did not describe the type of CTCA used in the included studies (Dolor et al. 2012), and 1 study included 3/89 studies that used 12-slice CTCA (Schuetz et al. 2010).

At the patient level the pooled sensitivities were very consistent for most studies (96%–100%), but 2 studies had lower values of 93%. One of these included a small subset of studies that reported outcomes only in women (Dolor et al. 2012). The 95%CIs for both sensitivity and specificity were very broad in this SR compared with the others. The second SR to have a lower pooled sensitivity was a poor-quality study by Gopalakrishnan et al(2008). The poor-quality SR by Beanlands et al. (2007) also had wide 95%CIs. The pooled specificities were over a broader range (82%–92%) for all studies except Dolor et al. (2012), which had a lower pooled specificity value of 77%. At the coronary artery / segment level, the pooled sensitivities were lower than at the patient level, with a broader range (86%–96%) and a corresponding increase in the pooled specificities (range 94%–97%).

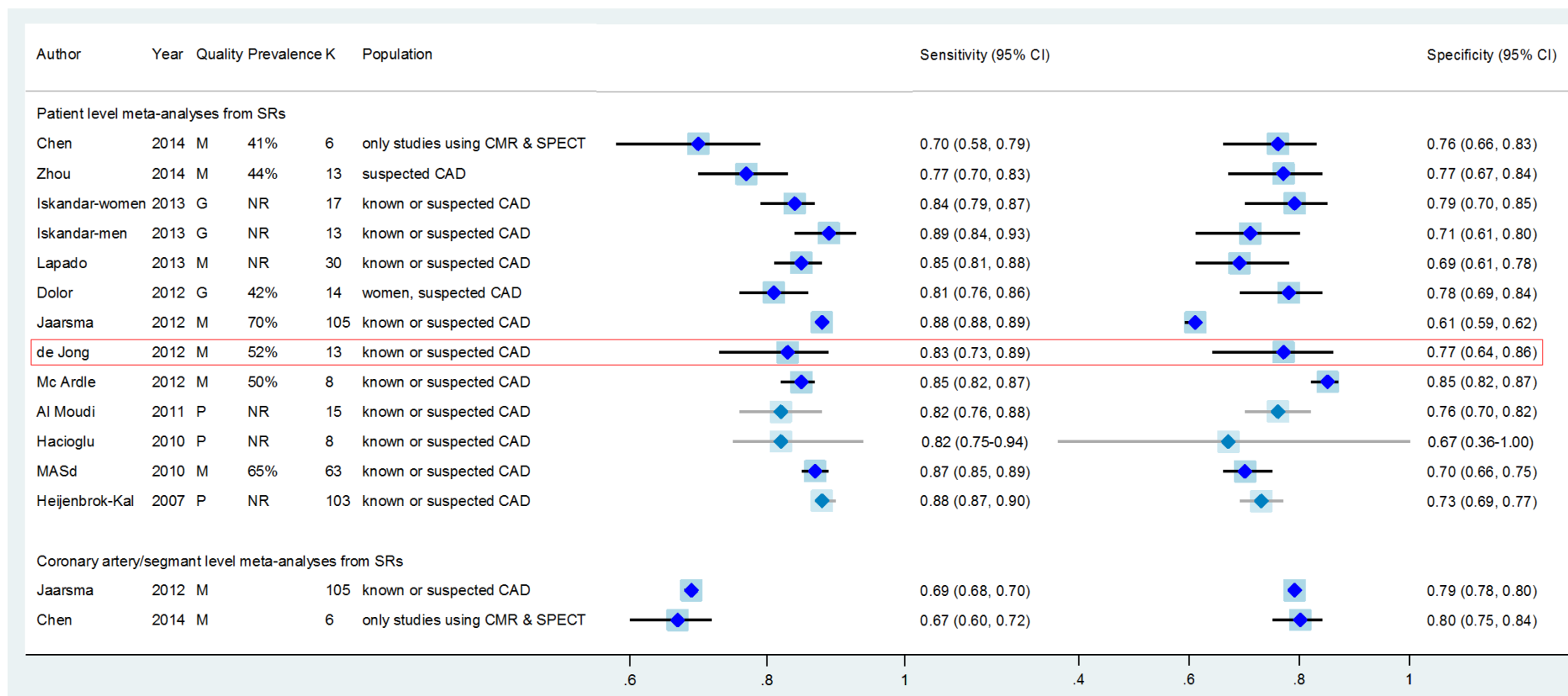


Figure 57 Forest plot showing pooled sensitivities and specificities reported by SRs comparing SPECT with ICA

Hacioglu et al. (2010) reported weighted means (range) for sensitivity and specificity. Poor-quality studies are shown in pale blue/grey.

CAD = coronary artery disease; CI = confidence interval; CMR = cardiac magnetic resonance imaging; ICA = invasive coronary angiography; K = number of studies; NR = not reported; Quality: G = good, M = moderate, P = poor; SPECT = single-photon emission computed tomography; SR = systematic review

At the patient level the pooled sensitivities were between 81% and 89% in all but the 2 SRs published in 2014. One of these SRs only included studies that compared both SP-CMR and SPECT with ICA (Chen et al. 2014), and the other used ICA with FFR as the reference standard (Zhou et al. 2014). Only 2 SRs reported pooled values at the coronary artery / segment level, and the pooled sensitivities were lower than at the patient level.

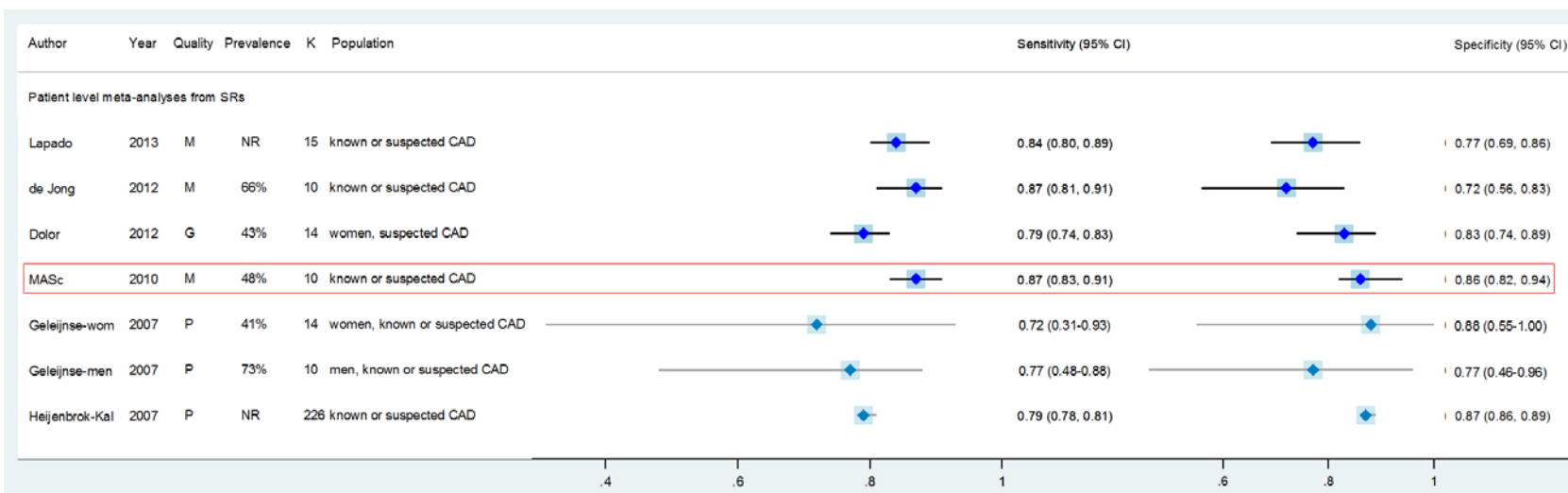


Figure 58 Forest plot showing pooled sensitivities and specificities reported by SRs comparing stress Echo with ICA

Geleijnse et al. (2007) reported weighted means (range) for sensitivity and specificity. Poor-quality studies are shown in pale blue/grey.

CAD = coronary artery disease; CI = confidence interval; Echo = echocardiography; ICA = invasive coronary angiography; K = number of studies; NR = not reported; Quality: G = good, M = moderate, P = poor; SR = systematic review

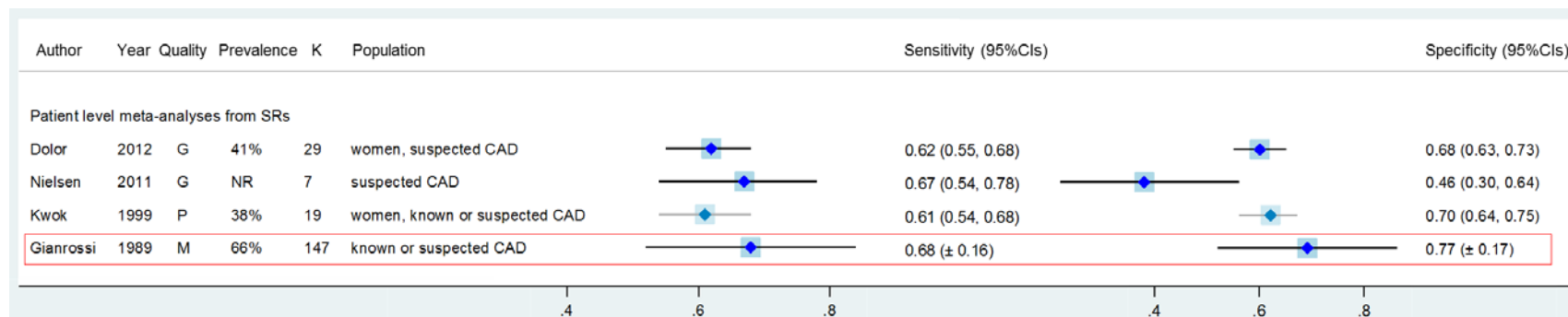


Figure 59 Forest plot showing pooled sensitivities and specificities reported by SRs comparing exercise ECG with ICA

Gianrossi et al. (1989) reported weighted means (range) for sensitivity and specificity. One poor-quality study is shown in pale blue/grey.

CAD = coronary artery disease; CI = confidence interval; ECG = electrocardiogram; ICA = invasive coronary angiography; K = number of studies; Quality: NR = not reported; G = good, M = moderate, P = poor; NR = not reported; SR = systematic review

APPENDIX J PUBLICATION BIAS

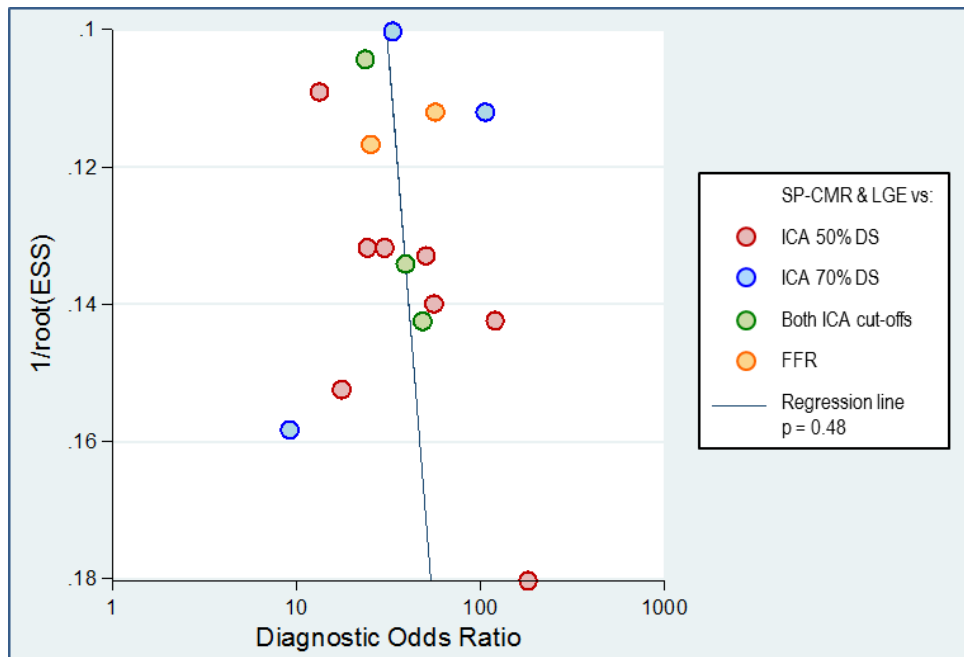


Figure 60 Deek's funnel plot asymmetry test to assess publication bias for diagnostic accuracy of SP-CMR & LGE compared with ICA

The p-value of the regression line for ICA 70% DS cut-off was $p = 0.72$, and for ICA 50% DS the cut-off was $p = 0.80$.

DS = diameter stenosis; ESS = effective sample size; FFR = fractional flow reserve; ICA = invasive coronary angiography; LGE = late gadolinium enhancement; SP-CMR = stress perfusion cardiac magnetic resonance imaging

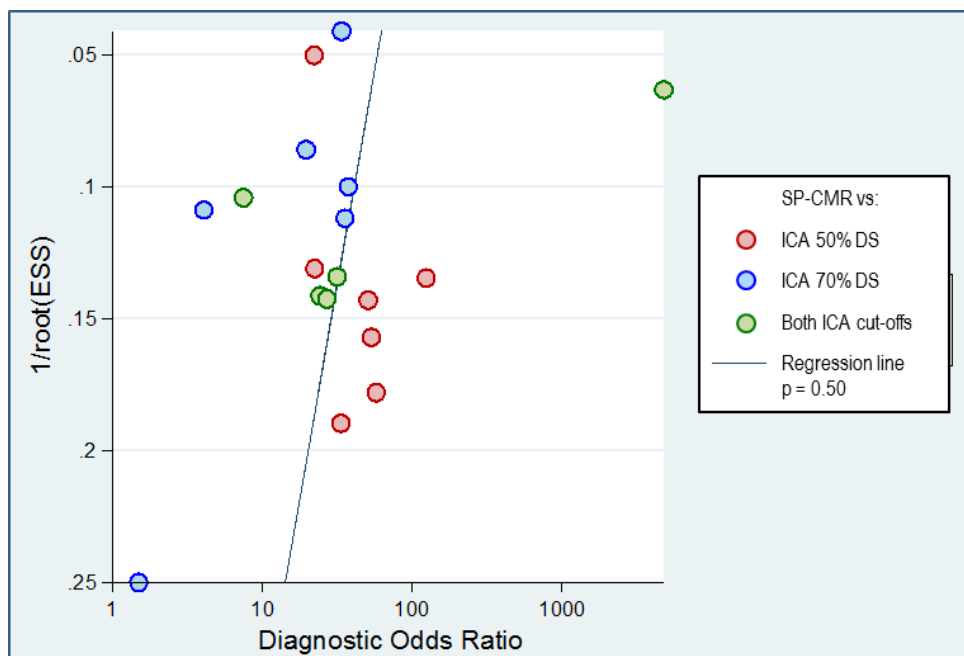


Figure 61 Deek's funnel plot asymmetry test to assess publication bias for diagnostic accuracy of SP-CMR compared with ICA

The p-value of the regression line for ICA 70% DS cut-off was $p = 0.29$, and for ICA 50% DS the cut-off was $p = 0.47$.

DS = diameter stenosis; ESS = effective sample size; ICA = invasive coronary angiography; SP-CMR = stress perfusion cardiac magnetic resonance imaging

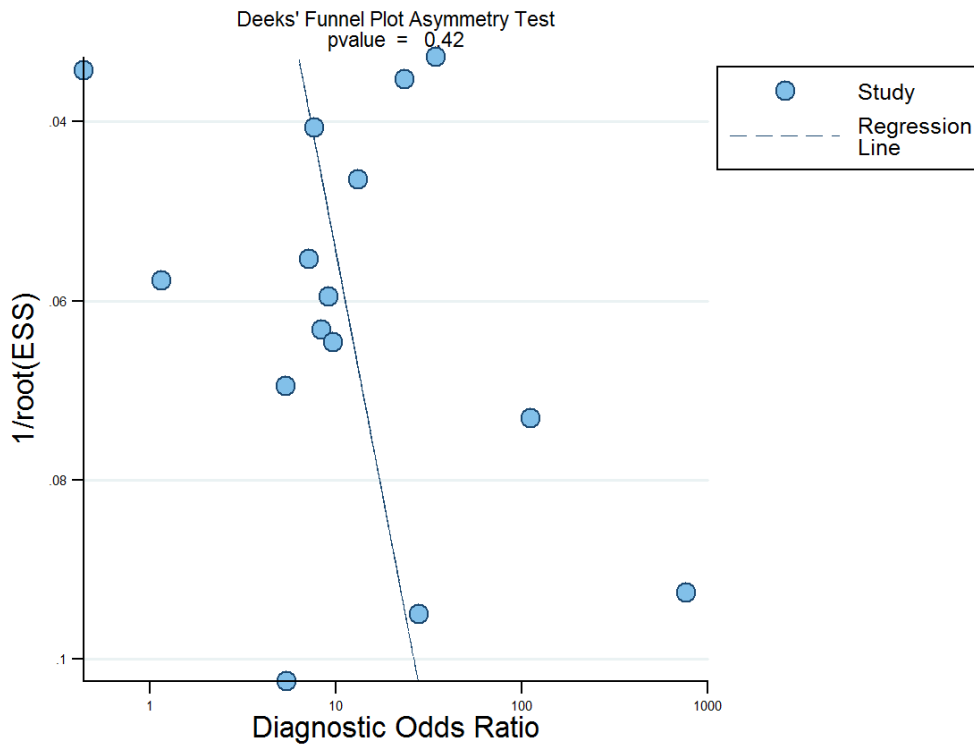


Figure 62 Deek's funnel plot asymmetry test to assess publication bias for diagnostic accuracy of LGE-CMR using a high cut-off compared with regional functional recovery

ESS = effective sample size; LGE-CMR = late gadolinium enhancement cardiac magnetic resonance imaging

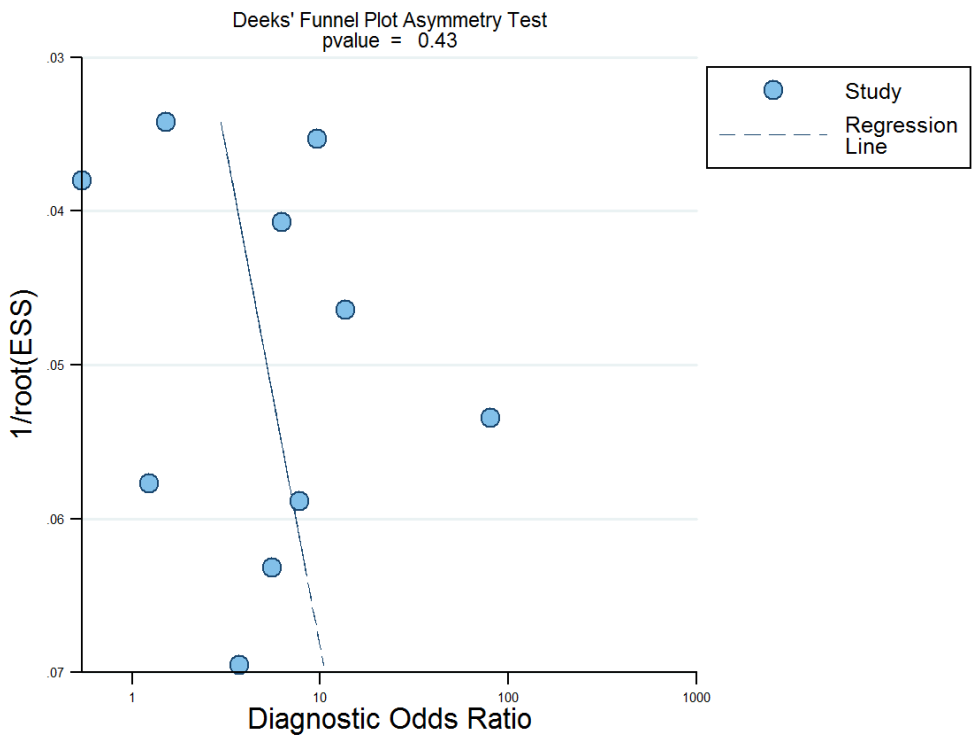


Figure 63 Deek's funnel plot asymmetry test to assess publication bias for diagnostic accuracy of LGE-CMR using a low cut-off compared with regional functional recovery

ESS = effective sample size; LGE-CMR = late gadolinium enhancement cardiac magnetic resonance imaging

APPENDIX K STUDIES INCLUDED IN META-ANALYSES COMPARING THE ACCURACY OF SP-CMR WITH ICA

Table 188 List of studies included in the meta-analyses performed in various SRs and/or in this report

Study	Beanlands et al. 2007	Nandalur et al. 2007	MAS 2010a	Hamon et al. 2010	Jaarsma et al. 2012	de Jong et al. 2012	Dolor et al. 2010	Desai et al. 2013	Chen et al. 2014	Li et al. 2014	This study	Reason for exclusion from this report
Reference standard	ICA	ICA	ICA	ICA	ICA	ICA	ICA	FFR	ICA	FFR	ICA or FFR	
Al-Saadi et al. (2000)	✓	✓	✓	✓	✓	-	-	-	-	-	✓	
Panting et al. (2001)		✓	✓	-					✓			Included patients with known CAD
Schwitzer et al. (2001)	✓	✓	✓	✓	-	-	-	-	-	-	✓	
Al-Saadi et al. (2002)	✓	✓	✓		✓							Included patients with known CAD
Doyle et al. (2003)	-	✓	✓	✓	✓	✓	✓		✓	-		Not stress CMR
Ishida et al. (2003)		✓	✓	✓	✓				✓			Included patients with known CAD
Nagel et al. (2003)	✓	✓	✓	✓	✓	✓	-	-	-	-	✓	
Regenfus et al. (2003)	-	-	-	-	-	-	-	-	-	-	✓	
Bunce et al. (2004)		✓	✓	✓	✓							Included patients with known CAD
Giang et al. (2004)	✓	✓	✓	✓	✓	✓						Included patients with known CAD
Kawase et al. (2004)	✓	✓	✓	✓	-	✓						Included patients with known CAD
Paetsch et al. (2004)	✓	✓	✓	✓	✓	✓						Included patients with known CAD
Plein et al. (2004)	✓	✓	✓	✓	✓							Included patients with known CAD
Takase et al. (2004)	-	✓	✓	✓	✓	✓	-	-	-	-	✓	
Thiele et al. (2004)		✓	✓	✓	✓				✓			Included patients with known CAD
Wolff et al. (2004)	✓				✓							Included patients with known CAD
Okuda et al. (2005)		✓	✓	✓	✓				✓			Included patients with known CAD

Study	Beanlands et al. 2007	Nandalur et al. 2007	MAS 2010a	Hamon et al. 2010	Jaarsma et al. 2012	de Jong et al. 2012	Dolor et al. 2010	Desai et al. 2013	Chen et al. 2014	Li et al. 2014	This study	Reason for exclusion from this report
Reference standard	ICA	ICA	ICA	ICA	ICA	ICA	ICA	FFR	ICA	FFR	ICA or FFR	
Plein et al. (2005)	✓	✓	✓	✓	✓	✓						Included patients with known CAD
Sakuma et al. (2005)	-	✓	✓	✓	✓	-	-	-	✓	-	✓	
Cury et al. (2006)	-	✓	✓	✓	✓	✓	-	-	-	-	✓	
Klem et al. (2006)	-	✓	✓	✓	✓	✓	-	-	-	-	✓	
Pilz et al. (2006)		✓	✓	✓	✓	✓						Included patients with known CAD
Rieber et al. (2006)		✓	✓	✓				✓		✓		Included patients with known CAD
Antonio et al. (2007)	-	-	-	-	-	-	-	-	-	-	✓	
Bernhardt et al. (2007)											✓	
Cheng et al. (2007)			✓	✓	✓	✓					✓	
Costa et al. (2007)				✓	✓			✓		✓	✓	
Gebker et al. (2007)			✓		✓	✓						Included patients with known CAD
Kuhl et al. (2007)				✓	✓			✓		✓		Included patients with known CAD
Merkle et al. (2007)			✓	✓		✓					✓	
Sharples et al. (2007)									✓			Included patients with known CAD
Gebker et al. (2008a)					✓							Included patients with known CAD
Gebker et al. (2008b)			✓	✓		✓						Included patients with known CAD
Kitagawa et al. (2008)					✓	✓						Included patients with known CAD
Klein et al. (2008)			✓	✓	✓	✓					✓	
Klem et al. (2008)				✓	✓		✓				✓	
Meyer et al. (2008)			✓	✓	✓	✓					✓	
Pingitore et al. (2008)						✓						Included patients with known CAD

Study	Beanlands et al. 2007	Nandalur et al. 2007	MAS 2010a	Hamon et al. 2010	Jaarsma et al. 2012	de Jong et al. 2012	Dolor et al. 2010	Desai et al. 2013	Chen et al. 2014	Li et al. 2014	This study	Reason for exclusion from this report
Reference standard	ICA	ICA	ICA	ICA	ICA	ICA	ICA	FFR	ICA	FFR	ICA or FFR	
Plein et al. (2008a)						✓						Included patients with known CAD
Plein et al. (2008b)						✓						Included patients with known CAD
Schwitter et al. (2008)									✓			Included patients with known CAD
Thomas et al. (2008)			✓	✓	✓							Included patients with known CAD
Husser et al. (2009)			✓								✓	
Krittayaphong et al. (2009)					✓	✓						Included patients with known CAD
Langer et al. (2009)							✓					Not contrast CMR
Watkins et al. (2009)								✓		✓	✓	
Arnold et al. (2010)						✓					✓	
Donati et al. (2010)						✓						Included patients with known CAD
Gebker et al. (2010)							✓					Included patients with known CAD
Klumpp et al. (2010)					✓	✓						Included patients with known CAD
Merkle et al. (2010)					✓		✓				✓	
Schuchlenz et al. (2010)								✓				Conference abstract
Van Werkhoven et al. (2010)											✓	
Coehlo-Filino et al. (2011)							✓					Included patients with known CAD
Ebersberger et al. (2011)								✓				Included patients with known CAD
Kirschbaum et al. (2011)								✓		✓	✓	
Lockie et al. (2011)								✓		✓		Included patients with known CAD
Stolzmann et al. (2011)						✓					✓	
Bernhardt et al. (2012)								✓		✓		Included patients with known CAD

Study	Beanlands et al. 2007	Nandalur et al. 2007	MAS 2010a	Hamon et al. 2010	Jaarsma et al. 2012	de Jong et al. 2012	Dolor et al. 2010	Desai et al. 2013	Chen et al. 2014	Li et al. 2014	This study	Reason for exclusion from this report
Reference standard	ICA	ICA	ICA	ICA	ICA	ICA	ICA	FFR	ICA	FFR	ICA or FFR	
de Mello et al. (2012)											✓	
Gebker et al. (2012)						✓						Included patients with known CAD
Greenwood et al. (2012)									✓			Duplicate data
Huber et al. (2012)								✓		✓		Could not extract data
Jogiya et al. (2012)								✓		✓		Included patients with known CAD
Ma et al. (2012)											✓	
Manka et al. (2012)								✓		✓		Included patients with known CAD
Motwani et al. (2012)											✓	
Bettencourt et al. (2013a)										✓	✓	
Ebersberger et al. (2013)										✓		Included patients with known CAD
Falcao et al. (2013)											✓	
Groothuis et al. (2013)										✓	✓	
Pereira et al. (2013)											✓	
Schwiter et al. (2013)									✓			Included patients with known CAD
Walcher et al. (2013)											✓	
Greenwood et al. (2014)											✓	
Heitner et al. (2014)											✓	
Mordi et al. (2014)											✓	
Becker et al. (2015)											✓	

Studies highlighted in light and dark green have been included in this report. Those in darker green have been included in this report but are not in any of the listed SRs.

CAD = coronary artery disease; CMR = cardiac magnetic resonance imaging; FFR = fractional flow reserve; ICA = invasive coronary angiography; SR = systematic review

APPENDIX L EXCLUDED STUDIES

Studies that met the PICO criteria to assess the safety, effectiveness and cost-effectiveness of SP-CMR & LGE in the diagnosis of CAD in patients presenting with symptoms consistent with IHD and with an intermediate PTP of CAD; and of LGE-CMR in determining viable myocardium in patients with an existing diagnosis of significant CAD who have a history of IHD with LVD and are being considered for revascularisation, but were excluded for the reasons listed below.

COULD NOT RETRIEVE ARTICLE ON TIME

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APPENDIX M ATTACHMENT TO THE ECONOMIC EVALUATION (POPULATION 1)

LITERATURE REVIEW

Table 189 Economic literature search terms

Search	Query	PubMed	CRD
#1	"Coronary artery disease" [MeSH] OR "coronary artery disease" OR CAD OR "coronary heart disease" OR CHD OR ischaemic OR ischaemia OR stenosis OR stenotic OR "Ventricular function, left" [MeSH] OR "left ventricular" OR LVEF OR "ischaemic heart disease" OR "ischemic heart disease" OR IHD	665,467	3,997
#2	"Myocardial Perfusion Imaging" [MeSH] OR "magnetic resonance" OR MRI OR CMR	599,878	1,297
#3	"economics"[MeSH Terms] OR "costs and cost analysis"[MeSH Terms] OR "cost allocation"[MeSH Terms] OR "cost benefit analysis"[MeSH Terms] OR "cost control"[MeSH Terms] OR "cost savings"[MeSH Terms] OR "cost of illness"[MeSH Terms] OR "health care costs"[MeSH Terms] OR "drug costs"[MeSH Terms] OR "health expenditures"[MeSH Terms] OR "economics, medical"[MeSH Terms] OR "economics, pharmaceutical"[MeSH Terms] OR "fees and charges"[MeSH Terms] OR "budgets"[MeSH Terms] OR "high cost"[All Fields] OR "low cost"[All Fields] OR "cost utility"[All Fields] OR "fiscal"[All Fields] OR "economics"[All Fields] OR "funding"[All Fields] OR "financial"[All Fields] OR finance[All Fields] OR "healthcare cost"[All Fields] OR "health care cost"[All Fields] OR "cost estimate"[All Fields] OR "cost variable"[All Fields] OR "unit cost"[All Fields] OR "economic"[All Fields] OR "pharmaceutical economics"[All Fields] OR "pharmacoeconomic"[All Fields] OR "commerce"[MeSH Terms] OR "commerce"[All Fields] OR "price"[All Fields] OR (("costs"[All Fields] OR "cost"[All Fields]) AND "analysis"[All Fields]) OR "costs and cost analysis"[All Fields] OR "pricing"[All Fields]	921,427	25,291
#4	#1 AND #2 AND #3	472	79

After duplicate removal, 513 studies were identified, 6 of which were relevant to the proposed service: 1 study was a trial-based economic evaluation based on the study included for direct evidence, presented in Section B1 of the clinical evaluation of Population 1, and the remaining 5 studies were modelled economic evaluations.

STRUCTURE OF THE ECONOMIC EVALUATION

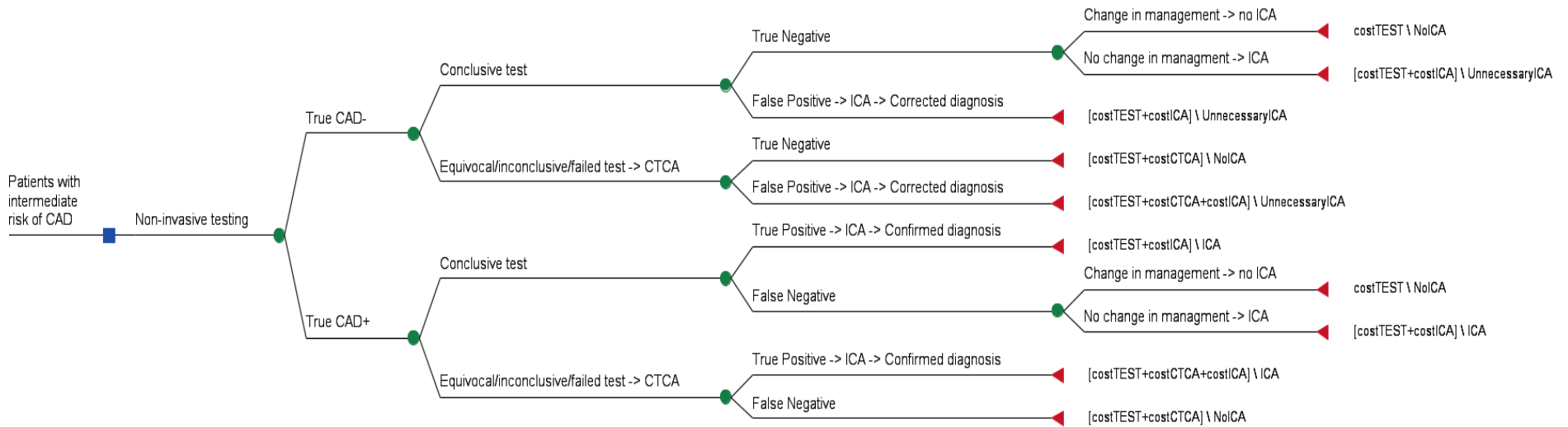


Figure 64 Decision analytic structure of the cost per unnecessary ICA avoided analysis

Note: the model structure for each non-invasive test modelled is the same. Differences modelled include test-specific parameters such as test accuracy, re-testing rate and test costs. For this CEA the outcome 'UnnecessaryICA' is equal to 1 and the outcomes 'NoICA' and 'ICA' are equal to 0.

CAD = coronary artery disease; CTCA = computed tomography coronary angiography; ICA = invasive coronary angiography; TEST = non-invasive test

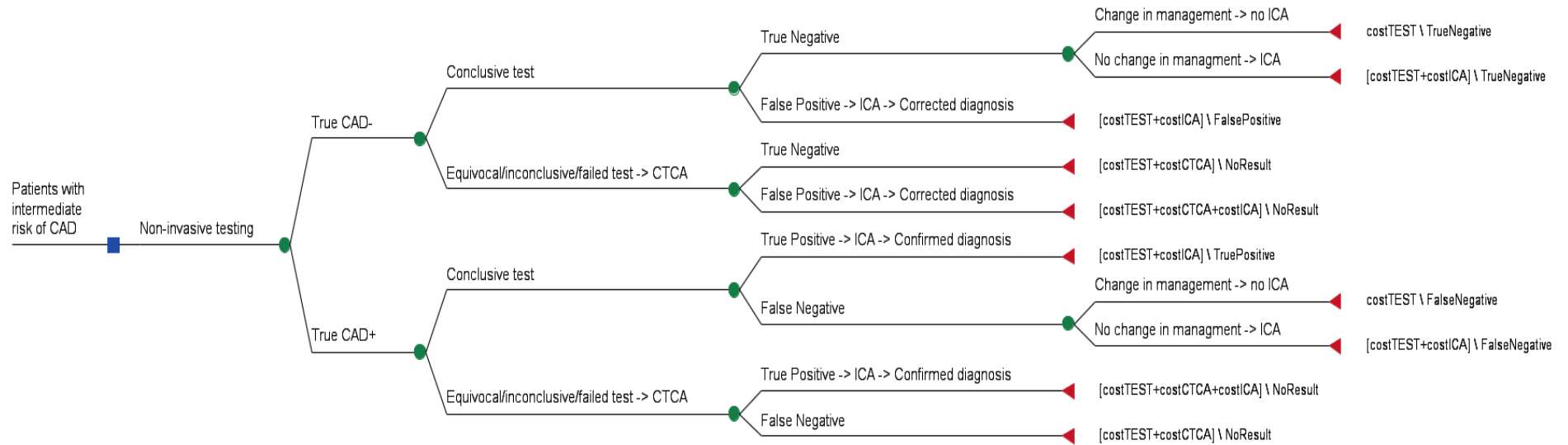


Figure 65 Decision analytic structure of the cost per correct initial test result analysis

Note: the model structure for each non-invasive test modelled is the same. Differences modelled include test-specific parameters such as test accuracy, re-testing rate and test costs. For this CEA the outcomes 'TrueNegative' and 'TruePositive' are equal to 1 and the outcomes 'FalseNegative', 'FalsePositive' and 'NoResult' are equal to 0.

CAD = coronary artery disease; CTCA = computed tomography coronary angiography; ICA = invasive coronary angiography; TEST = non-invasive test

INPUTS TO THE ECONOMIC EVALUATION

Table 190 Summary of inputs to the economic model

Parameter	Estimate	Source	Sensitivity analysis	Source
Epidemiological				
Prevalence	45%	Systematic review and meta-analysis of studies that used SP-CMR (Section B3a.6.2)	Scenario analyses: 15%–85%	Defined by the intermediate PTP of CAD range
Test parameters				
<i>CMR</i>				
Sensitivity	85%	Systematic review and meta-analysis of studies that used SP-CMR (Section B3a.6.3)	82%, 88%	95%CI of point estimate
Specificity	85%	Systematic review and meta-analysis of studies that used SP-CMR (Section B3a.6.3)	81%, 88%	95%CI of point estimate
Equivocal/fail rate	11%	CECaT (Sharples et al. 2007) proportion of equivocal and failed tests, SP-CMR group	3%, 17.5%	Table 168, Appendix E
AEs – gadolinium	0.005%	Section B7a	0.011%	Bruder et al. (2015)
AEs – stressors	0.09%	Section B7a	0.014%, 0.18%	Assuming AEs related to adenosine (lower) and dobutamine (upper) (Section B7a)
<i>CTCA</i>				
Sensitivity	97%	den Dekker et al. (2012) [64 slice]	96%, 98%	95%CI of point estimate
Specificity	88%	den Dekker et al. (2012) [64 slice]	86%, 89%	95%CI of point estimate
Equivocal/fail rate	0%	Maffei et al. (2011)	5%	Assumption
AEs – contrast	0.04%	Section B7a	0%	Assume only self-limiting AEs
<i>Stress Echo</i>				
Sensitivity	87%	MAS (2010c)	93%, 91%	95%CI of point estimate
Specificity	86%	MAS (2010c)	82%, 94%	95%CI of point estimate
Equivocal/fail rate	7%	CECaT (Sharples et al. 2007) proportion of equivocal and failed tests, stress Echo group	4%, 11%	Range of equivocal and failed tests in CECaT (Sharples et al. 2007)
AEs- stressor	0.018%	Section B7a—weighted AEs exercise and pharmacological stressors	0.015%, 0.072%	Assuming AEs related to adenosine in weighted (lower) and average of all stressors (i.e. not weighted) (upper) (Section B7a)
AEs microspheres	0.03%	Section B7a	-	-
<i>SPECT</i>				
Sensitivity	83%	de Jong et al. (2012)	73%, 89%	95%CI of point estimate

Parameter	Estimate	Source	Sensitivity analysis	Source
Specificity	77%	de Jong et al. (2012)	64%, 86%	95%CI of point estimate
Equivocal/fail rate	4%	CECaT (Sharples et al. 2007) proportion of equivocal and failed tests, SPECT group	4%, 11%	Range of equivocal and failed tests in CECaT (Sharples et al. 2007)
AEs – stressor	0.018%	Section B7a—weighted AEs exercise and pharmacological stressors	0.015%, 0.072%	Assuming AEs related to adenosine in weighted (lower) and average of all stressors (i.e. not weighted) (upper) (Section B7a)
<i>Exercise ECG</i>				
Sensitivity	68%	Gianrossi et al. (1989)	52%, 84%	± 1 SD of the point estimate
Specificity	77%	Gianrossi et al. (1989)	60%, 94%	± 1 SD of the point estimate
Equivocal/fail rate	7%	Nielsen et al. (2013)	20%	Rogers et al. (2013)
AEs – ex-stressor	0.015%	Section B7a—AEs exercise stressor	-	-
<i>ICA</i>				
AEs – contrast	0.04%	Section B7a	0%	Assume only self-limiting AEs
AEs – procedure	1.77%	Section B7a	1%, 2%	Section B7a
Test costs				
CMR ¹	\$900	Proposed MBS item number	\$1,200	RANZCR protocol feedback (see Section A10)
CTCA ¹	\$700	MBS item 57360	\$693	Average provider fee for MBS item 57360, July 2011 – June 2015
Stress Echo ^a	\$414	MBS items 55116 and 11712	\$261	Average provider fee for MBS item 55116, July 2009 – June 2015
SPECT ^a	\$835	MBS item 61307	\$803	Average provider fee for MBS item 61307, July 2009 – June 2015
Exercise ECG ^a	\$152	MBS item 11712	\$151	Average provider fee for MBS item 11712, July 2009 – June 2015
ICA	\$4,420	NEP (IHPA 2015a) for AR-DRG F42B and F42C, weighted by hospital separations (IHPA 2014)	-	-
Associated costs				
Specialist consult	\$43	MBS item 105 for review of results by referring doctor	-	-
Gadolinium contrast agent	\$45	MBS item 63491 for contrast agent used with SP-CMR	-	-
Pharmacological stress agent	\$10	Cost to patient for dobutamine stress agent at SA Heart Clinic ^b	-	-
AE treatment cost				
Gadolinium reaction	\$3,535	NEP (IHPA 2015a) for AR-DRG X61Z	-	-

Parameter	Estimate	Source	Sensitivity analysis	Source
Iodinated contrast AE	\$8,850	NEP (IHPA 2015a) for AR-DRG E64A	-	-
Microspheres reaction	\$1,104	NEP (IHPA 2015a) for AR-DRG X61Z	-	-
AE related to stressors	\$7,370	NEP (IHPA 2015a) for AR-DRG F76A	-	-
ICA procedure AE	\$7,781	NEP (IHPA 2015a) for AR-DRG F42A minus cost of ICA without complications	-	-

^a The Schedule fee for each diagnostic imaging service is assumed to cover both the diagnostic imaging procedure and the reading and reporting on that procedure by the diagnostic imaging service provider; results will be sent to referring doctor for management.

^b [SA Heart Cardiology patient charges for dobutamine stress Echo](#)

AE = adverse event; AR-DRG = Australian Refined Diagnosis Related Groups; CAD = coronary artery disease; CECaT = Cost-effectiveness of Non-invasive Cardiac Testing (trial); CTCA = computed tomography coronary angiography; ECG = electrocardiography; Echo = echocardiography; ICA = invasive coronary angiography; MBS = Medicare Benefits Schedule; NEP = National Efficient Price; PTP = pre-test probability; RANZCR = Royal Australian and New Zealand College of Radiologists; SD = standard deviation; SP-CMR = stress perfusion cardiac magnetic resonance imaging; SPECT = single-photon emission computed tomography

RESULTS OF THE ECONOMIC EVALUATION

The modelled results from testing under each change in management scenario, by comparison, are presented below. As the alternative scenarios do not affect whether the non-invasive test is initially correct or not, these have not been presented.

Table 191 Modelled outcome of testing, comparison of CMR with CTCA (alternative scenarios)

	CMR	CTCA	Difference
Scenario 2			
Total ICA	71.9%	50.3%	21.7%
ICA in CAD+	42.0%	43.7%	-1.6%
ICA in CAD-	29.9%	6.6%	23.3%
ICA missed	3.0%	1.4%	1.6%
Scenario 3			
Total ICA	68.7%	50.3%	18.4%
ICA in CAD+	44.9%	43.7%	1.2%
ICA in CAD-	23.8%	6.6%	17.2%
ICA missed	0.1%	1.4%	-1.2%
Scenario 4			
Total ICA	74.8%	76.4%	-1.6%
ICA in CAD+	42.1%	44.4%	-2.3%
ICA in CAD-	32.7%	32.0%	0.7%
ICA missed	2.9%	0.6%	2.3%

	CMR	CTCA	Difference
Scenario 5			
Total ICA	70.9%	70.0%	0.9%
ICA in CAD+	45.0%	45.0%	0.0%
ICA in CAD-	25.9%	25.0%	0.9%
ICA missed	0.0%	0.0%	0.0%

CAD = coronary artery disease; CMR = stress perfusion cardiac magnetic resonance with late gadolinium enhancement; CTCA = computed tomography coronary angiography; ICA = invasive coronary angiography

Table 192 Cost per unnecessary ICA, additional scenario analyses for the comparison of CMR with CTCA

	CMR unnecessary ICAs	CTCA unnecessary ICAs	Incremental avoided ICA	Incremental cost	ICER per avoided ICA
Base-case	8.1%	6.6%	-1.5%	\$187	Dominated
Scenario 4	32.7%	32.0%	-0.7%	\$268	Dominated
Scenario 5	25.9%	25.0%	-0.9%	\$383	Dominated

CMR = stress perfusion cardiac magnetic resonance with late gadolinium enhancement CTCA = computed tomography coronary angiography; ICA = invasive coronary angiography; ICER = incremental cost-effectiveness ratio

Table 193 Modelled outcome of testing, comparison of CMR with stress Echo (alternative scenarios)

	CMR	Stress Echo	Difference
Scenario 2			
Total ICA	71.9%	73.1%	-1.2%
ICA in CAD+	42.0%	42.3%	-0.3%
ICA in CAD-	29.9%	30.8%	-0.9%
ICA missed	3.0%	2.7%	0.3%
Scenario 3			
Total ICA	68.7%	69.3%	-0.6%
ICA in CAD+	44.9%	44.9%	-0.1%
ICA in CAD-	23.8%	24.4%	-0.5%
ICA missed	0.1%	0.1%	0.1%

CAD = coronary artery disease; CMR = stress perfusion cardiac magnetic resonance with late gadolinium enhancement; CTCA = computed tomography coronary angiography; Echo = echocardiography; ICA = invasive coronary angiography

Table 194 Modelled outcome of testing, comparison of CMR with SPECT (alternative scenarios)

	CMR	SPECT	Difference
Scenario 2			
Total ICA	71.9%	75.2%	-3.3%
ICA in CAD+	42.0%	41.5%	0.5%
ICA in CAD-	29.9%	33.8%	-3.9%
ICA missed	3.0%	3.5%	-0.5%

	CMR	SPECT	Difference
Scenario 3			
Total ICA	68.7%	72.8%	-4.1%
ICA in CAD+	44.9%	44.9%	-0.1%
ICA in CAD-	23.8%	27.8%	-4.0%
ICA missed	0.1%	0.1%	0.1%

CAD = coronary artery disease; CMR = stress perfusion cardiac magnetic resonance with late gadolinium enhancement; CTCA = computed tomography coronary angiography; ICA = invasive coronary angiography; SPECT = single-photon emission computed tomography

Table 195 Modelled outcome of testing, comparison of CMR with exercise ECG (alternative scenarios)

	CMR	Exercise ECG	Difference
Scenario 2			
Total ICA	71.9%	71.6%	0.3%
ICA in CAD+	42.0%	38.5%	3.5%
ICA in CAD-	29.9%	33.0%	-3.1%
ICA missed	3.0%	6.5%	-3.5%
Scenario 3			
Total ICA	68.7%	72.2%	-3.5%
ICA in CAD+	44.9%	44.9%	-0.1%
ICA in CAD-	23.8%	27.3%	-3.4%
ICA missed	0.1%	0.1%	0.1%

CAD = coronary artery disease; CMR = stress perfusion cardiac magnetic resonance with late gadolinium enhancement; CTCA = computed tomography coronary angiography; ECG = electrocardiography; ICA = invasive coronary angiography

RESULTS OF SENSITIVITY ANALYSES

Comparison of CMR with CTCA

Table 196 Sensitivity analyses, cost per correct initial test result, comparison of CMR with CTCA

Variable	Lower value ICER	Upper value ICER
Base-case	Dominated (-\$1,135)	
Sensitivity of CMR (82%, 88%)	Dominated (-\$744)	Dominated (-\$1,588)
Specificity of CMR (81%, 88%)	Dominated (-\$1,505)	Dominated (-\$794)
Specificity of CTCA (86%, 89%)	Dominated (-\$922)	Dominated (-\$1,231)
Sensitivity of CTCA (96%, 98%)	Dominated (-\$1,282)	Dominated (-\$996)
Proportion of CTCA tests that are equivocal or failed (0%, 5%)	Dominated (-\$1,135)	Dominated (-\$1,261)
Proportion of AEs associated with pharm stress (0.014%, 0.18%)	Dominated (-\$1,101)	Dominated (-\$1,175)
Proportion of CMR tests that are equivocal or failed (3.0%, 17.5%)	Dominated (-\$1,173)	Dominated (-\$1,122)
Cost of CTCA (\$693, \$700)	Dominated (-\$1,173)	Dominated (-\$1,135)
Proportion of AEs with contrast (0%, 0.04%)	Dominated (-\$1,155)	Dominated (-\$1,135)

Variable	Lower value ICER	Upper value ICER
Base-case	Dominated (-\$1,135)	
Proportion of AEs associated with ICA procedure (1%, 2%)	Dominated (-\$1,147)	Dominated (-\$1,131)
Proportion of AEs with gadolinium (0.005%, 0.01%)	Dominated (-\$1,135)	Dominated (-\$1,135)

AE = adverse event; CMR = cardiac magnetic resonance imaging; CTCA = computed tomography coronary angiography; ICA = invasive coronary angiography; ICER = incremental cost-effectiveness ratio; pharm = pharmacological

Table 197 Sensitivity analyses, cost per unnecessary ICA avoided, comparison of CMR with CTCA

Variable	Lower value ICER	Upper value ICER
Base-case	Dominated (-\$12,725)	
Specificity of CMR (81%, 88%)	Dominated (-\$8,091)	Dominated
Specificity of CTCA (86%, 89%)	Dominated (-\$28,946)	Dominated (-\$10,698)
Proportion of CMR tests that are equivocal or failed (3.0%, 17.5%)	Dominated (-\$7,035)	Dominated (-\$18,068)
Sensitivity of CMR (82%, 88%)	Dominated (-\$8,950)	Dominated (-\$16,501)
Proportion of CTCA tests that are equivocal or failed (0%, 5%)	Dominated (-\$12,725)	Dominated (-\$10,182)
Sensitivity of CTCA (96%, 98%)	Dominated (-\$13,984)	Dominated (-\$11,467)
Proportion of AEs associated with pharm stress (0.014%, 0.18%)	Dominated (-\$12,342)	Dominated (-\$13,176)
Cost of CTCA (\$693, \$700)	Dominated (-\$13,156)	Dominated (-\$12,725)
Proportion of AEs with contrast (0%, 0.04%)	Dominated (-\$12,947)	Dominated (-\$12,725)
Proportion of AEs associated with ICA procedure (1%, 2%)	Dominated (-\$12,860)	Dominated (-\$12,685)
Proportion of AEs with gadolinium (0.005%, 0.01%)	Dominated (-\$12,725)	Dominated (-\$12,730)

AE = adverse event; CMR = cardiac magnetic resonance imaging; CTCA = computed tomography coronary angiography; ICA = invasive coronary angiography; ICER = incremental cost-effectiveness ratio; pharm = pharmacological

Comparison of CMR to stress Echo

Table 198 Prevalence analyses, comparison of CMR with Echo

Prevalence	Incremental cost	Incremental correct test result	ICER per correct test result	Incremental avoided ICA	ICER per avoided ICA
15%	\$601	-4.8%	Dominated	-0.7%	Dominated
25%	\$591	-4.9%	Dominated	-0.6%	Dominated
35%	\$581	-5.0%	Dominated	-0.5%	Dominated
45% (base-case)	\$571	-5.1%	Dominated	-0.4%	Dominated
55%	\$562	-5.2%	Dominated	-0.4%	Dominated
65%	\$552	-5.3%	Dominated	-0.3%	Dominated
75%	\$542	-5.4%	Dominated	-0.2%	Dominated
85%	\$532	-5.5%	Dominated	-0.1%	Dominated

CMR = cardiac magnetic resonance imaging; Echo = echocardiography; ICA = invasive coronary angiography; ICER = incremental cost-effectiveness ratio

Table 199 Sensitivity analyses, cost per correct initial test result, comparison of CMR with stress Echo

Variable	Lower value ICER	Upper value ICER
Base-case	Dominated (-\$11,172)	
Proportion of CMR tests that are equivocal or failed (3.0%, 17.5%)	\$28,616	Dominated (-\$5,957)
Proportion of Echo tests that are equivocal or failed (4%, 11%)	Dominated (-\$8,050)	Dominated (-\$39,610)
Sensitivity of Echo (83%, 91%)	Dominated (-\$18,897)	Dominated (-\$7,268)
Sensitivity of CMR (82%, 88%)	Dominated (-\$8,171)	Dominated (-\$16,015)
Specificity of Echo (82%, 94%)	Dominated (-\$15,573)	Dominated (-\$8,251)
Specificity of CMR (81%, 88%)	Dominated (-\$9,358)	Dominated (-\$13,811)
Proportion of AEs associated with pharm stress (0.014%, 0.18%)	Dominated (-\$11,066)	Dominated (-\$11,297)
Proportion of AEs weighted by stress type (0.015%, 0.072%)	Dominated (-\$11,176)	Dominated (-\$11,095)
Cost of Echo (\$260.72, \$261.65)	Dominated (-\$11,190)	Dominated (-\$11,172)
Proportion of AEs associated with ICA procedure (1%, 2%)	Dominated (-\$11,174)	Dominated (-\$11,172)
Proportion of AEs with gadolinium (0.005%, 0.01%)	Dominated (-\$11,172)	Dominated (-\$11,174)

AE = adverse event; CMR = cardiac magnetic resonance imaging; Echo = echocardiography; ICER = incremental cost-effectiveness ratio; pharm = pharmacological

Table 200 Sensitivity analyses, cost per unnecessary ICA avoided, comparison of CMR with stress Echo

Variable	Lower value ICER	Upper value ICER
Base-case	Dominated (-\$129,729)	
Specificity of CMR (81%, 88%)	Dominated (-\$27,605)	\$49,048
Specificity of Echo (82%, 94%)	\$29,542	Dominated (-\$16,731)
Proportion of CMR tests that are equivocal or failed (3.0%, 17.5%)	Dominated (-\$86,713)	Dominated (-\$188,670)
Proportion of Echo tests that are equivocal or failed (4%, 11%)	Dominated (-\$144,665)	Dominated (-\$108,915)
Sensitivity of Echo (83%, 91%)	Dominated (-\$147,336)	Dominated (-\$112,123)
Sensitivity of CMR (82%, 88%)	Dominated (-\$117,151)	Dominated (-\$142,308)
Proportion of AEs associated with pharm stress (0.014%, 0.18%)	Dominated (-\$128,497)	Dominated (-\$131,177)
Proportion of AEs weighted by stress type (0.015%, 0.072%)	Dominated (-\$129,773)	Dominated (-\$128,828)
Cost of Echo (\$260.72, \$261.65)	Dominated (-\$129,940)	Dominated (-\$129,729)
Proportion of AEs associated with ICA procedure (1%, 2%)	Dominated (-\$129,751)	Dominated (-\$129,723)
Proportion of AEs with gadolinium (0.005%, 0.01%)	Dominated (-\$129,729)	Dominated (-\$129,744)

AE = adverse event; CMR = cardiac magnetic resonance imaging; Echo = echocardiography; ICA = invasive coronary angiography; ICER = incremental cost-effectiveness ratio; pharm = pharmacological

Comparison of CMR with SPECT

Table 201 Sensitivity analyses, cost per correct initial test result, comparison of CMR with SPECT

Variable	Lower value ICER	Upper value ICER
Base-case	Dominated (-\$3,866)	
Sensitivity of CMR (82%, 88%)	SW-Q (\$980)	\$30,049

Variable	Lower value ICER	Upper value ICER
Base-case	Dominated (-\$3,866)	
Sensitivity of SPECT (73%, 89%)	\$6,848	SW-Q (\$2,428)
Cost of SPECT (\$802.66, \$834.90)	Dominated (-\$7,446)	Dominated (-\$3,866)
Proportion of SPECT tests that are equivocal or failed (4%, 11%)	Dominated (-\$3,821)	Dominant (-\$388)
Proportion of CMR tests that are equivocal or failed (3.0%, 17.5%)	Dominant (-\$661)	Dominated (-\$1,475)
Specificity of CMR (81%, 88%)	Dominated (-\$4,379)	Dominant (-\$5,804)
Proportion of AEs associated with pharm stress (0.014%, 0.18%)	Dominated (-\$3,263)	Dominated (-\$4,574)
Proportion of AEs weighted by stress type (0.015%, 0.072%)	Dominated (-\$3,888)	Dominated (-\$3,425)
Proportion of AEs associated with ICA procedure (1%, 2%)	Dominated (-\$4,071)	Dominated (-\$3,805)
Specificity of SPECT (64%, 86%)	Dominated (-\$4,728)	Dominated (-\$4,496)
Proportion of AEs with gadolinium (0.005%, 0.01%)	Dominated (-\$3,866)	Dominated (-\$3,873)

AE = adverse event; CMR = cardiac magnetic resonance imaging; ICA = invasive coronary angiography; ICER = incremental cost-effectiveness ratio; pharm = pharmacological; SPECT = single-photon emission computed tomography; SW-Q = south-west quadrant, intervention is less costly and less effective than comparator

Table 202 Sensitivity analyses, cost per unnecessary ICA avoided, comparison of CMR with SPECT

Variable	Lower value ICER	Upper value ICER
Base-case	\$802	
Specificity of SPECT (64%, 86%)	Dominant (-\$2,516)	Dominated (-\$61,715)
Sensitivity of SPECT (73%, 89%)	\$5,395	Dominant (-\$1,954)
Specificity of CMR (81%, 88%)	\$5,250	Dominant (-\$567)
Proportion of CMR tests that are equivocal or failed (3.0%, 17.5%)	Dominant (-\$935)	\$2,115
Sensitivity of CMR (82%, 88%)	Dominant (-\$475)	\$2,079
Proportion of SPECT tests that are equivocal or failed (4%, 11%)	\$805	Dominant (-\$463)
Cost of SPECT (\$802.66, \$834.90)	\$1,545	\$802
Proportion of AEs associated with pharm stress (0.014%, 0.18%)	\$677	\$949
Proportion of AEs weighted by stress type (0.015%, 0.072%)	\$807	\$711
Proportion of AEs associated with ICA procedure (1%, 2%)	\$845	\$790
Proportion of AEs with gadolinium (0.005%, 0.01%)	\$802	\$804

AE = adverse event; CMR = cardiac magnetic resonance imaging; ICA = invasive coronary angiography; ICER = incremental cost-effectiveness ratio; pharm = pharmacological; SPECT = single-photon emission computed tomography; SW-Q = south-west quadrant, intervention is less costly and less effective than comparator

Comparison of CMR with exercise ECG

Table 203 Sensitivity analyses, cost per correct initial test result, comparison of CMR with exercise ECG

Variable	Lower value ICER	Upper value ICER
Base-case	\$13,304	
Specificity of ECG (60%, 94%)	\$3,627	Dominated (-\$107,472)
Sensitivity of ECG (52%, 84%)	\$9,178	\$95,325

Variable	Lower value ICER	Upper value ICER
Base-case		\$13,304
Proportion of CMR tests that are equivocal or failed (3.0%, 17.5%)	\$6,407	\$53,321
Proportion of ECG tests that are equivocal or failed (4%, 20%)	\$18,279	\$4,909
Specificity of CMR (81%, 88%)	\$19,699	\$10,352
Sensitivity of CMR (82%, 88%)	\$14,977	\$12,097
Proportion of AEs associated with pharm stress (0.014%, 0.18%)	\$13,229	\$13,393
Proportion of AEs associated with ICA procedure (1%, 2%)	\$13,279	\$13,312
Cost of ECG (\$151.16, \$152.15)	\$13,318	\$13,304
Proportion of AEs with gadolinium (0.005%, 0.01%)	\$13,304	\$13,305

AE = adverse event; CMR = cardiac magnetic resonance imaging; ECG = electrocardiography; ICA = invasive coronary angiography; ICER = incremental cost-effectiveness ratio; pharm = pharmacological

Table 204 Sensitivity analyses, cost per unnecessary ICA avoided, comparison of CMR with exercise ECG

Variable	Lower value ICER	Upper value ICER
Base-case		\$23,651
Specificity of ECG (60%, 94%)	\$4,540	Dominated (-\$30,609)
Specificity of CMR (81%, 88%)	\$48,469	\$16,313
Sensitivity of ECG (52%, 84%)	\$31,068	\$16,233
Sensitivity of CMR (82%, 88%)	\$22,327	\$24,975
Proportion of CMR tests that are equivocal or failed (3.0%, 17.5%)	\$22,597	\$24,445
Proportion of ECG tests that are equivocal or failed (4%, 20%)	\$23,437	\$25,089
Proportion of AEs associated with pharm stress (0.014%, 0.18%)	\$23,516	\$23,809
Proportion of AEs associated with ICA procedure (1%, 2%)	\$23,605	\$23,664
Cost of ECG (\$151.16, \$152.15)	\$23,674	\$23,651
Proportion of AEs with gadolinium (0.005%, 0.01%)	\$23,651	\$23,652

AE = adverse event; CMR = cardiac magnetic resonance imaging; ECG = electrocardiography; ICA = invasive coronary angiography; ICER = incremental cost-effectiveness ratio; pharm = pharmacological

APPENDIX N ATTACHMENT TO THE FINANCIAL IMPLICATION ANALYSIS (POPULATION 1)

USE AND COST OF CMR FOR DIAGNOSIS OF CAD

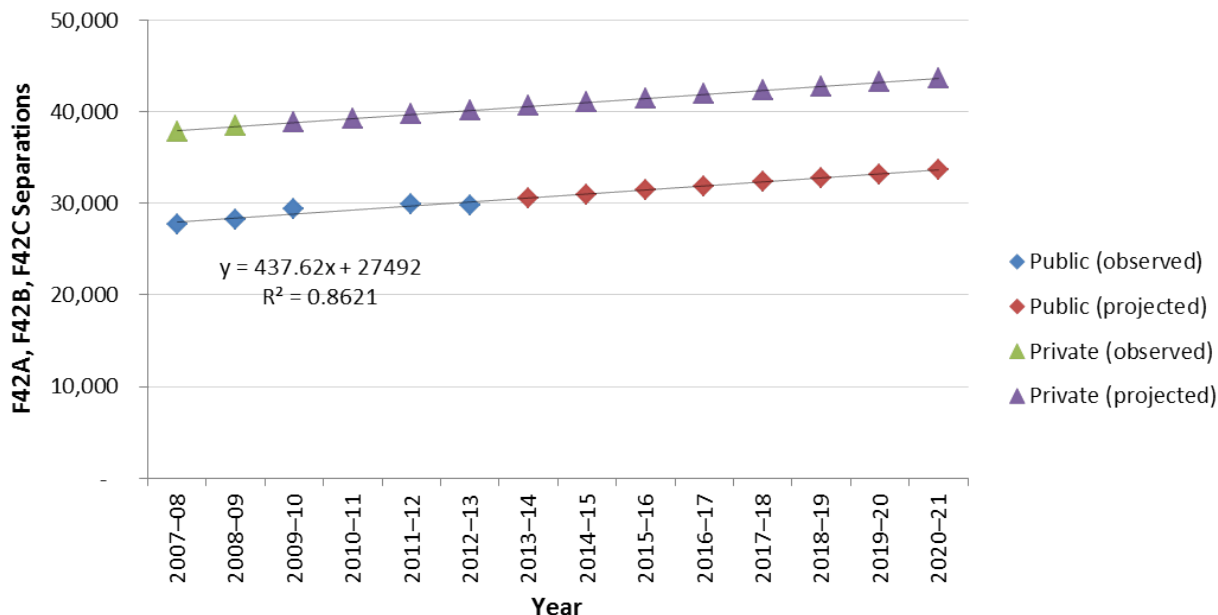


Figure 66 Observed and projected number of ICAs performed

CAD = coronary artery disease; CMR = cardiac magnetic resonance imaging; ICA = invasive coronary angiography

SENSITIVITY ANALYSES

Table 205 Results of additional sensitivity analyses

	2016-17	2017-18	2018-19	2019-20	2020-21
Base-case					
Net cost of CMR to the MBS	\$2,821,055	\$2,854,526	\$2,887,997	\$2,921,467	\$2,954,938
Net cost of CMR to patients	\$193,107	\$195,399	\$197,690	\$199,981	\$202,272
<i>Proportion of CMR tests bulk billed: 59.2% (base-case: 67.3%)</i>					
Net cost of CMR to the MBS	\$2,821,055	\$2,854,526	\$2,887,997	\$2,921,467	\$2,954,938
Net cost of CMR to patients	\$310,331	\$314,012	\$317,694	\$321,376	\$325,058
<i>Proportion of CMR tests bulk billed: 87.3% (base-case: 67.3%)</i>					
Net cost of CMR to the MBS	\$2,821,055	\$2,854,526	\$2,887,997	\$2,921,467	\$2,954,938
Net cost of CMR to patients	-\$95,027	-\$96,155	-\$97,282	-\$98,410	-\$99,537

	2016–17	2017–18	2018–19	2019–20	2020–21
Base-case					
Net cost of CMR to the MBS	\$2,821,055	\$2,854,526	\$2,887,997	\$2,921,467	\$2,954,938
Net cost of CMR to patients	\$193,107	\$195,399	\$197,690	\$199,981	\$202,272
<i>CMR co-payment for billed patients: \$435 (base case: \$213.36)</i>					
Net cost of CMR to the MBS	\$2,821,055	\$2,854,526	\$2,887,997	\$2,921,467	\$2,954,938
Net cost of CMR to patients	\$683,038	\$691,142	\$699,246	\$707,350	\$715,454
<i>CMR accessibility and uptake: 5% (base case: 10%)</i>					
Net cost of CMR to the MBS	\$1,410,528	\$1,427,263	\$1,443,998	\$1,460,734	\$1,477,469
Net cost of CMR to patients	\$96,554	\$97,699	\$98,845	\$99,990	\$101,136
<i>CMR accessibility and uptake: 20% (base case: 10%)</i>					
Net cost of CMR to the MBS	\$5,642,111	\$5,709,052	\$5,775,993	\$5,842,935	\$5,909,876
Net cost of CMR to patients	\$386,215	\$390,797	\$395,380	\$399,962	\$404,544

CMR = cardiac magnetic resonance imaging; MBS = Medicare Benefits Schedule

APPENDIX O ADDITIONAL INFORMATION RELATING TO THE APPLICABILITY ISSUES (POPULATION 2)

SUMMARY OF ADDITIONAL OBSERVATIONAL DATA ON MORTALITY RATES ASSOCIATED WITH REVASCULARISATION

Kunadian, Zaman & Qiu (2011) performed a meta-analysis of 26 observational studies (n=4,119) to determine the operative mortality and long-term outcomes among patients undergoing CABG for severe CAD and LVD. In this analysis the study populations were, on average, 64 years of age and 82% male. A weighted estimate of overall 30-day mortality was 5.31%.

These authors also performed a meta-analysis of 13 observational studies (n=2,202) utilising PCI among patients with LVD (LVEF \leq 40%) and reported an in-hospital mortality of 1.8% (Kunadian et al. 2012). The mean age was 65 years and 80% patients were males.

Nagendran et al. (2013) utilised data from the Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease (APPROACH) to identify 2,925 patients with CAD and LVD undergoing CABG (n=1,326) or PCI (n=1,599) between 1995 and 2008 to report survival at 30 days; 1 year; and 5, 10 and 15 years. The unadjusted estimated survival at 30 days was 95% and 93% in CABG and PCI patients, respectively.

As no relevant Australian data was found for the target population, Australian mortality rates were assessed in the broader patient population with chronic heart failure. A recent report by Chan et al. (Chan et al. 2015) estimated a 9% inpatient case fatality rate associated with incident heart failure admissions. As not all patients in the target population will have disease as severe as above, this may be an overestimate.

APPENDIX P ADDITIONAL INFORMATION RELATING TO ECONOMIC EVALUATION (POPULATION 2)

LITERATURE REVIEW

Table 206 Literature search to identify economic evaluations conducted for LGE-CMR used for viability assessment

Search	Query	PubMed	CRD
#1	((“Coronary artery disease” [MeSH] OR “coronary artery disease” OR CAD OR “coronary heart disease” OR CHD OR ischaemic OR ischaemia OR stenosis OR stenotic OR “Ventricular function, left” [MeSH] OR “left ventricular” OR LVEF OR “ischaemic heart disease” OR “ischemic heart disease” OR IHD) AND (myocardial revascularization[MeSH Terms] OR “myocardium viability” OR “viable myocardium” OR “myocardial infarction” OR “LV dysfunction” OR ‘ventricular dysfunction’ OR “functional myocardium” OR “Heart Failure/diagnosis” [MeSH] OR “Myocardial Infarction/diagnosis” [MeSH] OR “Myocardium/cytology” [MeSH]))	99,498	1,425
#2	“Magnetic Resonance Imaging” [MeSH] OR “Time-Lapse Imaging” [MeSH] OR “Cardiac Imaging Techniques” [MeSH] OR “viability imaging” OR “magnetic resonance” OR MRI OR CMR OR “cardiac MRI” OR “cardiac MR” OR “coronary MR” OR “contrast-enhanced MR” OR “contrast-enhanced imaging” OR “contrast-enhanced viability imaging” OR “myocardial infarction/radionuclide imaging”[MeSH] OR “Gadolinium DTPA” [MeSH] OR CE-MRI OR DE-MRI OR “delayed enhanced MRI” OR “delayed enhanced imaging”	734,512	1,775
#3	(“economics”[MeSH Terms] OR “costs and cost analysis”[MeSH Terms] OR “cost allocation”[MeSH Terms] OR “cost benefit analysis”[MeSH Terms] OR “cost control”[MeSH Terms] OR “cost savings”[MeSH Terms] OR “cost of illness”[MeSH Terms] OR “health care costs”[MeSH Terms] OR “drug costs”[MeSH Terms] OR “health expenditures”[MeSH Terms] OR “economics, medical”[MeSH Terms] OR “economics, pharmaceutical”[MeSH Terms] OR “fees and charges”[MeSH Terms] OR “budgets”[MeSH Terms] OR “high cost”[All Fields] OR “low cost”[All Fields] OR “cost utility”[All Fields] OR “economics”[All Fields] OR “financial”[All Fields] OR finance[All Fields]) OR (“healthcare cost”[All Fields] OR “health care cost”[All Fields]) OR “cost estimate”[All Fields] OR “unit cost”[All Fields] OR (“economics, pharmaceutical”[MeSH Terms] OR (“economics”[All Fields] AND “pharmaceutical”[All Fields]) OR “pharmaceutical economics”[All Fields] OR “pharmacoeconomic”[All Fields]) OR (“commerce”[MeSH Terms] OR “commerce”[All Fields] OR “price”[All Fields]) OR (“costs”[All Fields] AND “cost”[All Fields] AND “analysis”[All Fields]) OR “costs and cost analysis”[All Fields] OR “pricing”[All Fields]) OR (cost-effectiveness OR “cost effectiveness” OR “economic evaluation”)	870,697	24,773
#4	#1 AND #2 AND #3	351	75

After removing duplicates and articles in languages other than English, a total of 367 studies were identified.

MODEL OUTCOMES

The decision-trees (presented in Figure 67 and Figure 68) culminate in different categories according to the chosen outcome measure. These are referred to as ‘outcome states’ and are summarised in Table 207.

Table 207 Summary of decision-tree final outcome states in the economic evaluation

Outcome state	Inference
<i>Effect 1</i>	<i>Revascularisations performed</i>
Correct revascularisation	Revascularisations performed after correct diagnosis of viability (in tp)
Revascularisation missed	Revascularisation missed due to false negative results
No revascularisation	Revascularisations averted due to true status of non-viability
Unnecessary revascularisations	Revascularisations performed in non-viable patients due to incorrect diagnosis
Procedure-related deaths	Post-operative deaths associated with revascularisation (in tp and fp)
Deaths	Background mortality in the target population
<i>Effect 2</i>	<i>Correct diagnosis</i>
tp	True positives
tn	True negatives
fp	False positives
fn	False negatives

fn = false negative; fp = False positive; tn = true negative; tp = true positive

ADDITIONAL INFORMATION ON COST OF OPTIMAL MEDICAL THERAPY IN AUSTRALIA FOR POPULATION 2

The National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand (2012) recommend the following medicines in patient management plans for secondary prevention of CHD.

- All patients with stable angina should be treated with aspirin (75–150 mg tab per day) and a statin (40 mg simvastatin recommended per day), unless contraindicated.
- ACE inhibitors (e.g. enalapril maleate 10 mg/day) are recommended for patients with co-existing conditions that would benefit from this treatment (e.g. hypertension, diabetes, heart failure, asymptomatic LVD or previous MI).
- Anti-anginal medication short-acting nitrates (glyceril trinitrites) are recommended for all patients, unless contraindicated.
- Beta receptor blockers (e.g. non-selective: propranolol; selective: atenolol or metoprolol) are recommended for all patients post-MI, unless contraindicated, and continued indefinitely, especially in patients with either significant myocardial necrosis, LVSD, persistent evidence of ischemia or ventricular arrhythmia.
- Calcium channel receptor blockers (e.g. dihydropyridine: amlodipine, nifedipine; phenylalkylamine derivative: verapamil; benzothiazepine derivative: diltiazem) are appropriate when beta-blockers are contraindicated or not tolerated.
- A long-acting nitrate (e.g. isosorbide mononitrate, nicorandil) can be used if a beta-blocker or calcium channel blocker is not tolerated or contraindicated.

- Aldosterone antagonists (e.g. epleronone) may be used early (3–14 days) post-MI in patients with LVSD and symptoms of heart failure.
- Clopidogrel is recommended for patients undergoing revascularisation.

Table 208 provides PBS-listed costs of some of the medicines prescribed for CHD.

Table 208 PBS-listed costs of some of the medicines prescribed in CHD

PBS item no.	Name, form and strength, and pack size	Dose	Max. price	Price per 30 days
8202Q	Aspirin, 100 mg tablet, 112	100 mg/day	\$17.12	\$4.59
9483D	Ezetimibe 10 mg + Simvastatin 40 mg tablet, 30	1 tab/day	\$37.70	\$37.70
8171C	Glyceryl trinitrate 400 microgram/actuation spray, 200 actuations	2 x sprays on episode of angina	\$27.78	\$2.32
1081X	Atenolol 50 mg tablet, 30	50 mg/day	\$17.00	\$17.00
1694E	Nifedipine 10 mg tablet, 60	10 mg twice daily	\$21.45	\$21.45
1558B	Isosorbide mononitrate 60 mg tablet: modified release, 30 tablets	60 mg/day	\$19.32	\$19.32
10012Y	Ivabradine 5 mg tablet, 56	5 mg twice daily	\$37.70	\$40.39
8228C	Nicorandil 10 mg tablet, 60	10 mg twice daily	\$29.84	\$29.84
1368B	Enalapril maleate 10 mg tablet, 30	10 mg day	\$19.88	\$19.88
1486F	Hydrochlorothiazide 50 mg + amiloride hydrochloride 5 mg tablet, 50	1/day	\$22.03	\$13.22
10169F	Clopidogrel 75 mg tablet, 28	75 mg/day	\$6.10	\$6.54
			Total	\$212.24

CHD = chronic heart disease; PBS = Pharmaceutical Benefit Schedule

There is no reliable data on the uptake of drugs in this patient population. A study by Chan et al. (2015) suggested that around 800,000 Australian adults aged ≥ 45 years are prescribed the combination of drugs typically used to treat heart failure and its associated comorbidity hypertension.

SUMMARY OF INPUTS TO THE ECONOMIC EVALUATION

Table 209 Summary of inputs incorporated in the economic model

Parameter	Estimate	Source	Sensitivity analysis	Source
Epidemiological parameters				
Prevalence	56%	Systematic review and meta-analysis of studies that used LGE-CMR	Scenario analyses: 15%–95%	Section C.2b.5
Test parameters				
<i>LGE-CMR (high cut-off)</i>				
Sensitivity	93%	Systematic review and meta-analysis of studies	90%, 96%	95%CI of point estimate

Parameter	Estimate	Source	Sensitivity analysis	Source
		that used LGE-CMR		
Specificity	45%	Systematic review and meta-analysis of studies that used LGE-CMR	30%, 61%	95%CI of point estimate
AEs – gadolinium	0.005%	Section B.7a	-	-
<i>LGE-CMR (low cut-off)</i>				
Sensitivity	70%	Systematic review and meta-analysis of studies that used LGE-CMR	54%, 82%	95%CI of point estimate
Specificity	68%	Systematic review and meta-analysis of studies that used LGE-CMR	56%, 78%	95%CI of point estimate
<i>DbE</i>				
Sensitivity	79%	Schinkel et al. (2007)	[0.71, 0.83]	95%CI of point estimate (Campbell et al. 2014)
Specificity	78%	Schinkel et al. (2007)	[0.62, 0.76]	95%CI of point estimate (Campbell et al. 2014)
AEs – stressor	0.18%	Section B.7b	-	-
AEs – microspheres	0.03%	Section B.7b	-	-
<i>SPECT</i>				
Sensitivity	85%	Campbell et al. (2014)	78%, 90%	95%CI of point estimate
Specificity	62%	Campbell et al. (2014)	53%, 71%	95%CI of point estimate
Test costs				
LGE-CMR	\$700	Proposed MBS item number	\$1,100–\$1,200	Section A.10
DbE	\$414 ^a	MBS items 55116 and 11712	\$422 ^a	Average provider fee for MBS item 55117, July 2009 – June 2015
SPECT	\$565	MBS item 61307	\$536	Average provider fee for MBS item 61303, July 2009 – June 2015
Associated testing costs				
Specialist consult	\$43	MBS item 105 for review of results by referring doctor	-	-
Gadolinium contrast agent	\$45	MBS item 63491 for contrast agent used with CMR	-	-
Pharmacological stress agent	\$10.00	Cost to patient for dobutamine stress agent at SA Heart Clinic ^b	-	-
Cost of AE treatment				

Parameter	Estimate	Source	Sensitivity analysis	Source
Gadolinium reaction	\$3,535	NEP (IHPA 2015a) for AR-DRG X61Z	-	-
Microspheres reaction	\$1,104	NEP (IHPA 2015a) for AR-DRG X61Z	-	-
AE related to stressors	\$7,370	NEP (IHPA 2015a) for AR-DRG F76A	-	-
OMT				
Cost of OMT	\$217.31	Hirst et al. (2011)	\$52–\$383	Section D.4b.2
Cost of clopidogrel	\$6.54	30-day price for PBS item no 10169F	-	-
Background event rates				
30-day mortality	1.1%	Panza et al. (2014)	-	
Cost of treating cardiac events	\$81.06	1.1% × cost of AR-DRG F76A	-	-
Revascularisation				
<i>CABG</i>				
Proportion of CABG performed	100%	Section C.2b.6	66% and 39%	Section C.2b.6
Cost	\$9,419	NEP (IHPA 2015a) for AR-DRGs F15B and F16B, weighted by hospital separations (2011–12)	-	-
Costs associated with CABG complications	\$10,398	Cost of CABG with complications minus cost of CABG without complications (Table 62)	-	-
AEs – severe complications	23.7%	Section C.2b.7	-	-
AEs – 30-day mortality	5.1%	Section C.2b.7	-	-
<i>PCI</i>				
Cost of PCI (without complications)	\$9,419	NEP (IHPA 2015a) for AR-DRGs F15B and F16B, weighted by hospital separations (2011–12)	-	-
Costs associated with PCI complications	\$9,600	Cost of PCI with complications minus cost of PCI without complications (Table 62)	-	-
AEs – severe complications	24%	Section C.2b.7	-	-
AEs – 30-day mortality	7%	Section C.2b.7	1%–10%	Section C.2b.6

^a Includes associated cost of MBS item 11712 (exercise electrocardiography)

^b Source: www.saheart.com.au/services/diagnostic-tests/dobutamine-stress-echocardiogram.html

AE = adverse event; AR-DRG = Australian Refined Diagnosis Related Groups; CABG = coronary artery bypass graft; CI = confidence interval; DbE = low-dose dobutamine echocardiography; LGE-CMR = late gadolinium enhancement cardiac magnetic resonance imaging; MBS = Medicare Benefits Schedule; OMT = optimal medical therapy; PBS = Pharmaceutical Benefit Schedule; PCI = percutaneous coronary intervention; SPECT = single-photon emission computed tomography

DECISION ANALYTIC STRUCTURE SHOWING DIFFERENT OUTCOMES

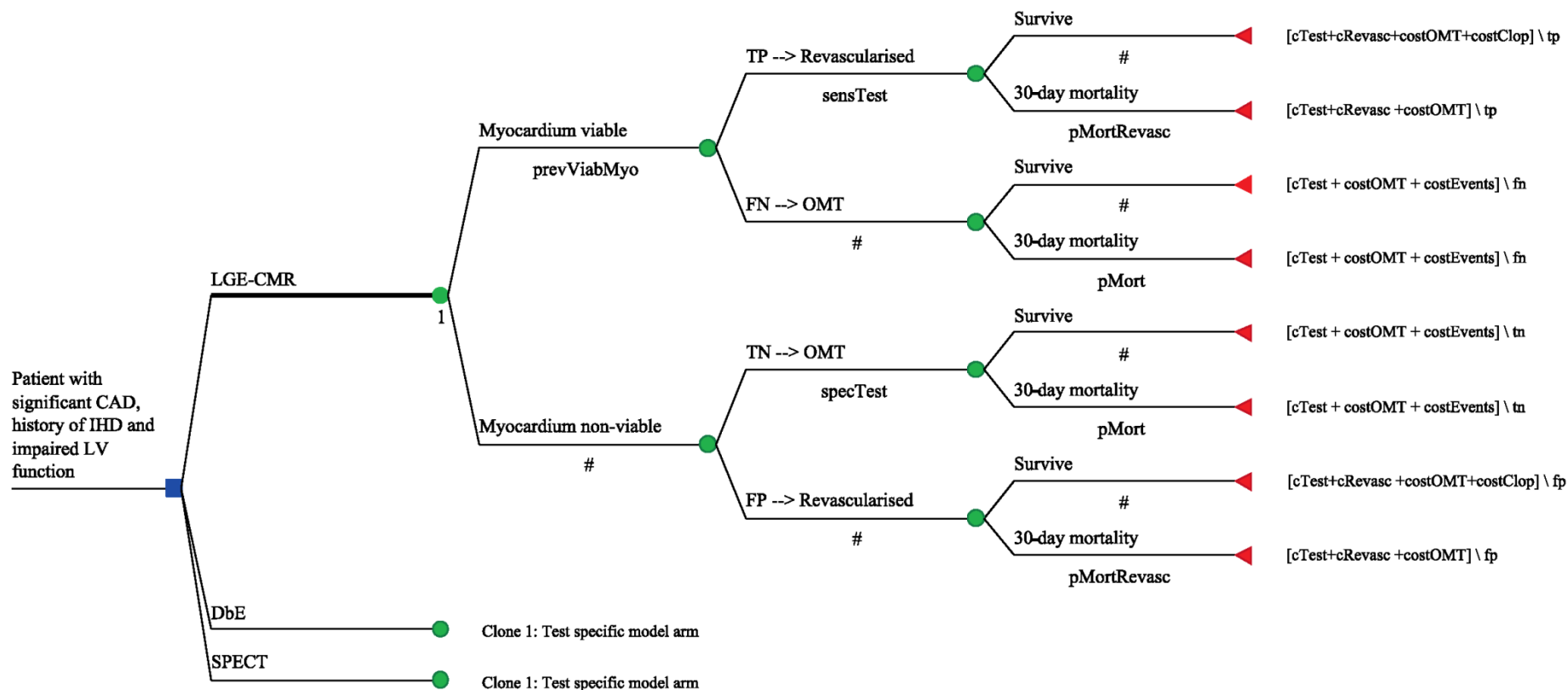


Figure 67 Decision analytic structure of cost per correct diagnosis analysis, population 2

Note: where 'Test' is denoted, the parameter is specific to the model arm, so 'sensTest' in the LGE-CMR arm relates to the sensitivity of LGE-CMR. For this CEA the outcomes 'tp' and 'tn' are set to 1 and the outcomes 'fn' and 'fp' are set to 0.

CAD = coronary artery disease; costCABG = cost associated with revascularisation; costClop = cost of clopidogrel for 30 days; costEvents = cost associated with cardiac events; costOMT = cost of optimal medical therapy; cTest = cost associated with testing; DbE = low-dose dobutamine echocardiography; FN/fn = false negative; FP/fp = false positive; IHD = ischaemic heart disease; LGE-CMR = late gadolinium enhancement cardiac magnetic resonance imaging; LV = left ventricular; pMort = background risk of 30-day mortality in the population; pMortCABG = risk of 30-day mortality associated with CABG; prevViabMyo = prevalence of myocardial viability; sensTest = sensitivity of the Test; SPECT = single-photon emission computed tomography; specTest = specificity of the Test; TN/tn = true negative; TP/tp = true positive

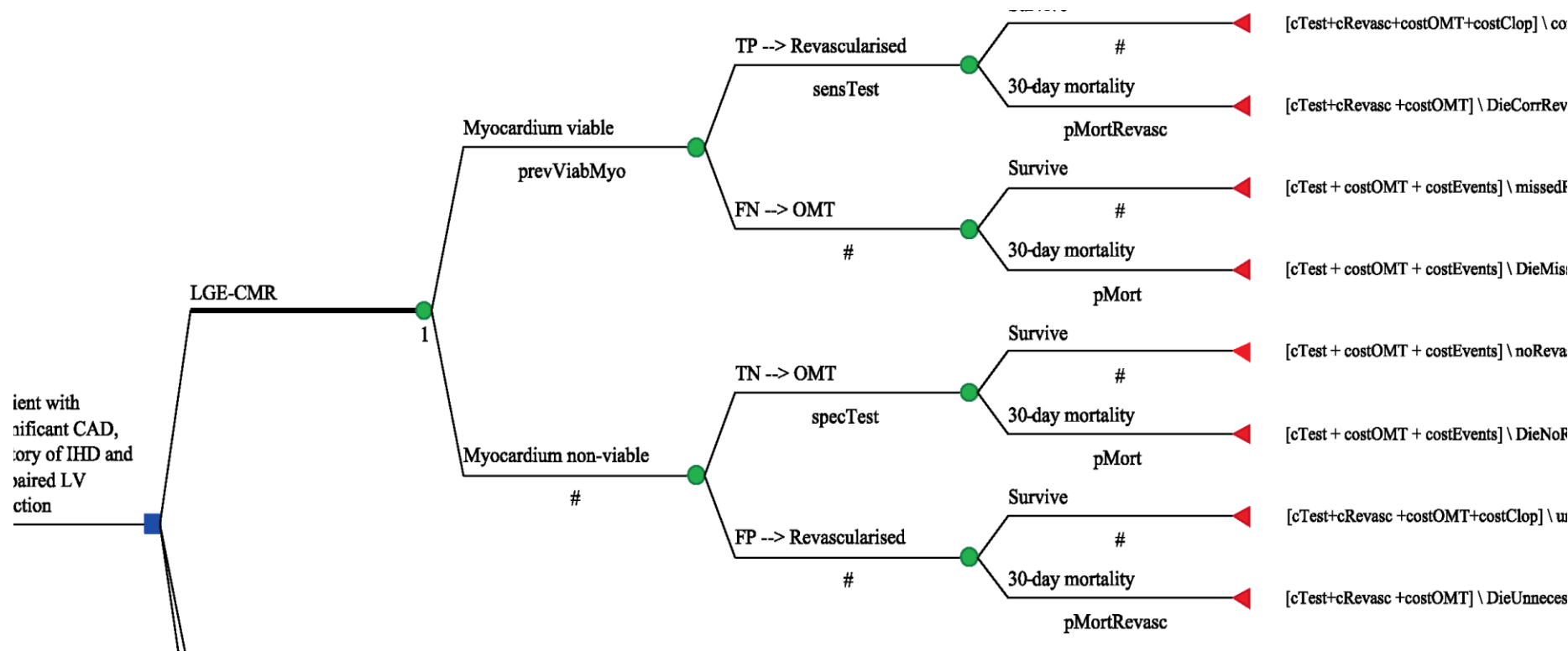


Figure 68 Decision analytic structure of cost per unnecessary revascularisation avoided analysis, population 2

Note: where 'Test' is denoted, the parameter is specific to the model arm, so 'sensTest' in the LGE-CMR arm relates to the sensitivity of LGE-CMR. For this CEA the outcomes 'unnecessaryRevasc' and 'DieUnnecessaryRevasc' are equal to 1; and all other outcomes are set to 0.

CAD = coronary artery disease; CEA = cost-effectiveness analysis; corrRevasc = revascularisations performed after correct diagnosis; costClop = cost of clopidogrel for 30 days; costEvents = cost associated with cardiac events; costOMT = cost of optimal medical therapy; costRevasc = cost associated with revascularisation; cTest = cost associated with testing; DbE = low-dose dobutamine echocardiography; DieCorrRevasc = deaths due to revascularisation in true positives; DieMissedRevasc = deaths in false negatives; DieNoRevasc = deaths in true negatives; DieUnnecessaryRevasc = deaths due to unnecessary revascularisations; FN = false negative; FP = false positive; IHD = ischaemic heart disease; LV = left ventricular; LGE-CMR = late gadolinium enhancement cardiac magnetic resonance imaging; missedRevasc = revascularisation missed due to incorrect diagnosis; noRevasc = no revascularisations performed in true negatives; pMort = background risk of 30-day mortality in the population; pMortRevasc = risk of 30-day mortality associated with revascularisation; prevViabMyo = prevalence of myocardial

viability; sensTest = sensitivity of the Test; SPECT = single-photon emission computed tomography; specTest = specificity of the Test; TN = true negative; TP = true positive; unnecessaryRevasc = unnecessary revascularisations performed due to incorrect diagnosis

ADDITIONAL RESULTS OF THE ECONOMIC MODEL

Comparison of LGE-CMR with DbE

Additional scenario analyses varying prevalence of myocardial viability (15–95%) and ratio of CABG:PCI (39:61) are presented below.

Cost per correct diagnosis

LGE-CMR is observed to be less effective at correctly identifying viability than DbE when the prevalence is below 75%. Increases in the prevalence are observed to escalate the comparative effectiveness of CMR, with a prevalence of 75% or more resulting in LGE-CMR being more effective.

Increases in prevalence are also associated with a decrease in incremental costs; however, these do not change the conclusion of cost-effectiveness, where LGE-CMR is dominated by DbE in all scenarios except when prevalence is 75% or more, where LGE-CMR is more costly and more effective than DbE; ICERs ranging from \$62,000 to \$398,000 (Table 210).

LGE-CMR is dominated (i.e. less effective and more costly) in scenario 3, where the ratio CABG:PCI is varied from the base-case (100:1 to 39:61).

Table 210 Incremental cost per correct diagnosis, additional scenario analyses

Scenario	LGE-CMR correct diagnoses	DbE correct diagnoses	Increment in correct diagnoses	Incremental cost	ICER per correct diagnosis
Scenario 1 (base-case)	71.8%	78.5%	-6.7%	\$10,608	Dominated
Scenario 4 (CABG:PCI, 39:61)	71.9%	74.9%	-3.0%	\$3,218	Dominated
<i>Prevalence scenarios</i>					
15%	52.2%	78.2%	-26.0%	\$14,197	Dominated
25%	57.0%	78.3%	-21.3%	\$13,321	Dominated
35%	61.8%	78.4%	-16.6%	\$12,446	Dominated
45%	66.6%	78.5%	-11.9%	\$11,571	Dominated
55%	71.4%	78.6%	-7.2%	\$10,696	Dominated
65%	76.2%	78.7%	-2.5%	\$9,820	Dominated
75%	81.0%	78.8%	2.3%	\$8,945	\$397,561
85%	85.8%	78.9%	7.0%	\$8,070	\$116,113
95%	90.6%	79.0%	11.7%	\$7,195	\$61,756

DbE = low-dose dobutamine echocardiography; Dominated = intervention is more costly and less effective than comparator; ICER = incremental cost-effectiveness ratio; LGE-CMR = late gadolinium enhancement cardiac magnetic resonance imaging

Cost per unnecessary revascularisation averted

The results of the comparison remain unchanged in additional scenario analyses (Table 211). LGE-CMR is associated with increased costs and an increased number of unnecessary revascularisations due to more false positive diagnoses compared with DbE and is, therefore, dominated in all scenarios.

Table 211 Incremental cost per unnecessary revascularisation averted in comparison with DbE, additional scenario analyses

Scenario	LGE-CMR (unnecessary revascularisations averted)	DbE (unnecessary revascularisations averted)	Increment in (unnecessary revascularisations averted)	Incremental cost	ICER per unnecessary revascularisation averted
Scenario 1 (base-case)	19.8%	34.3%	-14.5%	\$10,608	Dominated
Scenario 4 (CABG:PCI, 39:61)	19.8%	34.3%	-14.5%	\$5,988	Dominated
<i>Prevalence scenarios</i>					
15%	38.3%	66.3%	-28.1%	\$14,197	Dominated
25%	33.8%	58.5%	-24.8%	\$13,321	Dominated
35%	29.3%	50.7%	-21.5%	\$12,446	Dominated
45%	24.8%	42.9%	-18.2%	\$11,571	Dominated
55%	20.3%	35.1%	-14.9%	\$10,696	Dominated
65%	15.8%	27.3%	-11.6%	\$9,820	Dominated
75%	11.3%	19.5%	-8.3%	\$8,945	Dominated
85%	6.8%	11.7%	-5.0%	\$8,070	Dominated
95%	2.3%	3.9%	-1.7%	\$7,195	Dominated

CABG = coronary artery bypass graft; DbE = low-dose dobutamine echocardiography; Dominated = intervention is more costly and less effective than comparator; ICER = incremental cost-effectiveness ratio; LGE-CMR = late gadolinium enhancement cardiac magnetic resonance imaging; PCI = percutaneous coronary intervention

Cost per revascularisation undertaken with correct diagnosis

With increased prevalence, LGE-CMR is associated with an increased number of true positives, and therefore an increased number of revascularisations with correct diagnosis, and a decrease in cost in comparison with DbE. The ICERs drop from \$676,000 to \$54,000, when the prevalence increases from 15% to 95% (Table 212).

Table 212 Incremental cost per revascularisation undertaken with correct diagnosis comparison with DbE, additional scenario analyses

Scenario	LGE-CMR (correct revascularisations)	DbE (correct revascularisations)	Increment in (correct revascularisations)	Incremental cost	ICER per correct revascularisation received
Scenario 1 (base-case)	52.0%	44.2%	7.8%	\$10,608	\$136,002
Scenario 4 (CABG:PCI, 39:61)	52.1%	44.2%	7.8%	\$5,988	\$76,380
<i>Prevalence scenarios</i>					
15%	14.0%	11.9%	2.1%	\$14,197	\$676,036
25%	23.3%	19.8%	3.5%	\$13,321	\$380,614

Scenario	LGE-CMR (correct revascularisations)	DbE (correct revascularisations)	Increment in (correct revascularisations)	Incremental cost	ICER per correct revascularisation received
35%	32.6%	27.7%	4.9%	\$12,446	\$254,004
45%	41.9%	35.6%	6.3%	\$11,571	\$183,666
55%	51.2%	43.5%	7.7%	\$10,696	\$138,905
65%	60.5%	51.4%	9.1%	\$9,820	\$107,916
75%	69.8%	59.3%	10.5%	\$8,945	\$85,192
85%	79.1%	67.2%	11.9%	\$8,070	\$67,814
95%	88.4%	75.1%	13.3%	\$7,195	\$54,095

CABG = coronary artery bypass graft; DbE = low-dose dobutamine echocardiography; ICER = incremental cost-effectiveness ratio; LGE-CMR = late gadolinium enhancement cardiac magnetic resonance imaging; PCI = percutaneous coronary intervention

COMPARISON OF CMR WITH SPECT

Additional scenario analyses varying the prevalence of myocardial viability (15%–95%) and the ratio CABG:PCI (39:61) are presented below.

Cost per correct diagnosis

LGE-CMR is observed to be less effective at correctly identifying viability than SPECT, when the prevalence is below 75%—the results are similar to the comparison of LGE-CMR with DbE. Increases in the prevalence are observed to escalate the comparative effectiveness of LGE-CMR, with a prevalence of 75% or higher resulting in LGE-CMR being more effective.

Increases in prevalence are also associated with a decrease in the incremental costs; however, these do not change the conclusion of cost-effectiveness, where LGE-CMR is dominated by SPECT in all scenarios except when prevalence is 75% or more, where LGE-CMR is more costly and more effective than SPECT; ICERs ranging from \$60,000 to \$280,000 (Table 213).

LGE-CMR is dominated (i.e. less effective and more costly) by SPECT in scenario 4, where the ratio CABG:PCI is 39:61.

Table 213 Incremental cost per correct diagnosis, additional scenario analyses

Scenario	LGE-CMR correct diagnoses	SPECT correct diagnoses	Increment in correct diagnoses	Incremental cost	ICER per correct diagnosis
Scenario 1 (base- case)	71.8%	74.9%	–3.1%	\$5,689	Dominated
Scenario 4 (CABG:PCI, 39:61)	71.9%	74.9%	–3.0%	\$3,218	Dominated
<i>Prevalence scenarios</i>					
15%	52.2%	65.5%	–13.3%	\$7,389	Dominated
25%	57.0%	67.8%	–10.8%	\$6,975	Dominated
35%	61.8%	70.1%	–8.3%	\$6,560	Dominated
45%	66.6%	72.4%	–5.8%	\$6,145	Dominated
55%	71.4%	74.7%	–3.3%	\$5,731	Dominated

Scenario	LGE-CMR correct diagnoses	SPECT correct diagnoses	Increment in correct diagnoses	Incremental cost	ICER per correct diagnosis
65%	76.2%	77.0%	-0.8%	\$5,316	Dominated
75%	81.0%	79.3%	1.8%	\$4,902	\$280,087
85%	85.8%	81.6%	4.3%	\$4,487	\$105,575
95%	90.6%	83.9%	6.8%	\$4,072	\$60,331

CABG = coronary artery bypass graft; Dominated = intervention is more costly and less effective than comparator; ICER = incremental cost-effectiveness ratio; LGE-CMR = late gadolinium enhancement cardiac magnetic resonance imaging; PCI = percutaneous coronary intervention; SPECT = single-photon emission computed tomography

Cost per unnecessary revascularisation averted

The results of the LGE-CMR and SPECT comparison remain unchanged in additional scenario analyses (Table 214); that is, LGE-CMR is dominated by SPECT.

Table 214 Incremental cost per unnecessary revascularisation averted in comparison with SPECT, additional scenario analyses

Scenario	LGE-CMR (unnecessary revascularisations averted)	DbE (unnecessary revascularisations averted)	Increment in (unnecessary revascularisations averted)	Incremental cost	ICER per unnecessary revascularisation averted
Scenario 1 (base-case)	19.8%	27.3%	-7.5%	\$5,689	Dominated
Scenario 4 (CABG:PCI, 39:61)	19.8%	27.3%	-7.5%	\$3,218	Dominated
<i>Prevalence scenarios</i>					
15%	38.3%	52.7%	-14.5%	\$7,389	Dominated
25%	33.8%	46.5%	-12.8%	\$6,975	Dominated
35%	29.3%	40.3%	-11.1%	\$6,560	Dominated
45%	24.8%	34.1%	-9.4%	\$6,145	Dominated
55%	20.3%	27.9%	-7.7%	\$5,731	Dominated
65%	15.8%	21.7%	-6.0%	\$5,316	Dominated
75%	11.3%	15.5%	-4.3%	\$4,902	Dominated
85%	6.8%	9.3%	-2.6%	\$4,487	Dominated
95%	2.3%	3.1%	-0.9%	\$4,072	Dominated

CABG = coronary artery bypass graft; DbE = low-dose dobutamine echocardiography; ICER = incremental cost-effectiveness ratio; LGE-CMR = late gadolinium enhancement cardiac magnetic resonance imaging; PCI = percutaneous coronary intervention; SPECT = single-photon emission computed tomography

Cost per revascularisation undertaken with correct diagnosis

Table 215 Incremental cost per revascularisation undertaken with correct diagnosis in comparison with SPECT, additional scenario analyses

Scenario	LGE-CMR (revascularisations undertaken with correct diagnosis)	SPECT (revascularisations undertaken with correct diagnosis)	Increment in (revascularisations undertaken with correct diagnosis)	Incremental cost	ICER per revascularisation undertaken with correct diagnosis
Scenario 1 (base-case)	52.0%	47.6%	4.4%	\$5,689	\$129,301
Scenario 4 (CABG:PCI, 39:61)	52.1%	47.6%	4.5%	\$3,218	\$71,833
<i>Prevalence scenarios</i>					
15%	14.0%	12.8%	1.2%	\$7,389	\$615,761
25%	23.3%	21.3%	2.0%	\$6,975	\$348,727
35%	32.6%	29.8%	2.8%	\$6,560	\$234,283
45%	41.9%	38.3%	3.6%	\$6,145	\$170,704
55%	51.2%	46.8%	4.4%	\$5,731	\$130,244
65%	60.5%	55.3%	5.2%	\$5,316	\$102,233
75%	69.8%	63.8%	6.0%	\$4,902	\$81,692
85%	79.1%	72.3%	6.8%	\$4,487	\$65,984
95%	88.4%	80.8%	7.6%	\$4,072	\$53,583

CABG = coronary artery bypass graft; ICER = incremental cost-effectiveness ratio; LGE-CMR = late gadolinium enhancement cardiac magnetic resonance imaging; PCI = percutaneous coronary intervention; SPECT = single-photon emission computed tomography

APPENDIX Q ATTACHMENT TO THE FINANCIAL IMPLICATION ANALYSIS (POPULATION 2)

SENSITIVITY ANALYSES

Table 216 Results of additional sensitivity analyses

	2016-17	2017-18	2018-19	2019-20	2020-21
Base-case					
Net cost of LGE-CMR to the MBS	\$729,801	\$783,489	\$841,127	\$903,004	\$969,434
Net cost of LGE-CMR to patients	\$131,972	\$141,680	\$152,103	\$163,292	\$175,305
<i>Proportion LGE-CMR tests bulk billed: 62.1% (base-case: 67.3%)</i>					
Net cost of LGE-CMR to the MBS	\$729,801	\$783,489	\$841,127	\$903,004	\$969,434
Net cost of LGE-CMR to patients	\$181,006	\$194,322	\$208,618	\$223,965	\$240,441
<i>Proportion LGE-CMR tests bulk billed: 91.4% (base-case: 67.3%)</i>					
Net cost of LGE-CMR to the MBS	\$729,801	\$783,489	\$841,127	\$903,004	\$969,434
Net cost of LGE-CMR to patients	-\$96,803	-\$103,924	-\$111,569	-\$119,777	-\$128,588
<i>Average LGE-CMR co-payment for billed patients: \$505 (base-case: \$213.36)</i>					
Net cost of LGE-CMR to the MBS	\$729,801	\$783,489	\$841,127	\$903,004	\$969,434
Net cost of LGE-CMR to patients	\$555,567	\$596,437	\$640,315	\$687,420	\$737,990
<i>LGE-CMR accessibility and uptake: 10% (base-case: 50%)</i>					
Net cost of LGE-CMR to the MBS	\$145,960	\$156,698	\$168,225	\$180,601	\$193,887
Net cost of LGE-CMR to patients	\$26,394	\$28,336	\$30,421	\$32,658	\$35,061
<i>LGE-CMR accessibility and uptake: 30% (base-case: 10%)</i>					
Net cost of LGE-CMR to the MBS	\$437,881	\$470,093	\$504,676	\$541,803	\$581,661
Net cost of LGE-CMR to patients	\$79,183	\$85,008	\$91,262	\$97,975	\$105,183

LGE-CMR = late gadolinium enhancement cardiac magnetic resonance imaging; MBS = Medicare Benefits Schedule

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