Magnetic resonance imaging of patients with suspected (non-ischaemic) dilated cardiomyopathies

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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

KEY ISSUES FOR ESC AND MSAC CONSIDERATION

The available evidence on cardiac magnetic resonance (CMR) imaging for dilated cardiomyopathies (DCM) was predominantly concerned with the prediction of cardiac events. CMR using late gadolinium enhancement was a good predictor of cardiac events; and the amount of scarring or inflammation was better than the percentage of normal left ventricular ejection fraction when deciding whether patients should undergo surgery.

One Australian study that scheduled patients for device implantation or surgery according to findings from echocardiography (95%), invasive coronary angiography (51%), and single-photon emission computed tomography (27%) reported that the use of CMR allowed device implantation to be avoided in 29% of patients, and allowed surgery to be avoided in 65% of patients. A small number of patients not initially scheduled for surgery or device implantation had their management amended to a more invasive strategy as a consequence of CMR studies.

A Norwegian study reported that CMR was able to detect the aetiology of DCM in a small proportion of patients (4.5%) who would otherwise have been classified as having idiopathic non-ischaemic DCM.

It could not be ascertained from the evidence base whether using the prognostic information provided by CMR, and changing patient management, will result in improvements in patient health.

MAGNETIC RESONANCE IMAGING OF PATIENTS WITH SUSPECTED (NON-ISCHAEMIC) DILATED CARDIOMYOPATHIES

This contracted assessment examines the available evidence to support the listing of cardiac magnetic resonance (CMR) imaging on the Medicare Benefits Schedule (MBS). This imaging service would be used in the diagnosis and treatment planning of patients who are suspected of having non-ischaemic dilated cardiomyopathies (NIDCM).

The target population comprises:

i) people with heart failure (HF) symptoms in whom echocardiography is inconclusive;

ii) people with HF symptoms and a low to intermediate risk of coronary artery disease (CAD) in whom echocardiography is suggestive of dilated cardiomyopathy (DCM);

iii) asymptomatic first-degree relatives of someone diagnosed with NICDM and in whom echocardiography is inconclusive; or

iv) asymptomatic first-degree relatives of someone diagnosed with NIDCM, with an intermediate to high risk of CAD, and in whom echocardiography is suggestive of DCM that requires further investigation prior to treatment.

Alignment with Agreed Protocol

The clinical management algorithms and PICO[1] criteria specified in the Protocol and ratified by the Protocol Advisory Sub-Committee (PASC) were developed by another assessment group, in

[1] population, intervention, comparator, outcomes

consultation with two clinical experts. During the drafting of the contracted assessment, further advice was sought from these clinical experts to clarify inconsistencies between the clinical management algorithms depicted in the Protocol guiding this contracted assessment and those developed for MSAC assessment no. 1237, *CMR for perfusion and viability imaging in patients with known or suspected coronary artery disease.* After consulting with the clinical experts and the Department of Health, the PASC-ratified clinical management algorithms were amended. This resulted in a slightly different definition of the population (i.e. patients would not be eligible for CMR if they had a high pre-test risk of CAD), clarification that CMR would be used in family members who are found to have DCM after echocardiography, and amendment of the comparators (i.e. 'watchful waiting' was removed and alternative non-invasive imaging modalities were added as comparators).

The use of CMR was not reported in first-degree family members of someone with DCM.

Proposed Medical Service

CMR is a non-invasive imaging technique that is used to: assess the functioning and structures of the heart, confirm previous abnormal findings on an echocardiogram, and determine whether DCM is ischaemic or non-ischaemic. In NIDCM it is used to determine aetiology. Different forms of CMR can be used, including late gadolinium enhancement techniques (LGE-CMR) and stress perfusion techniques (SP-CMR).

Most private and public hospitals within Australia have MRI units. As at March 2015, 351 MRI units were eligible to provide services that are funded under the MBS.

There is no current MBS listing for the use of CMR for cardiomyopathies (CMs), so private patients are required to pay out-of-pocket costs for the service. Public hospitals cover the use of CMR for public patients with suspected CM. CMR scanning was funded for use in research in Australia under a New Technology Grant from the Victorian Policy Advisory Committee on Clinical Practice and Technology.

There is currently another assessment of CMR (Morona et al. unpublished) being considered by MSAC, where CMR is proposed for use in (i) patients presenting with symptoms of stable ischaemic heart disease and an intermediate pre-test probability of CAD; and (ii) patients diagnosed with significant CAD who are being considered for revascularisation.

Proposal for Public Funding

The proposed MBS items (outlined in the PASC-ratified Protocol) are shown in Table 5.

Clinical Management Algorithm(s)

With use of the current testing methods for DCM, there is a small, but serious, risk that some of the more rare aetiologies of NIDCM are not identified and treated appropriately. CMR is an additional imaging tool that would be requested when existing diagnostic methods are inconclusive. CMR can also inform prognostic decisions to rule out the need for investigation of first-degree relatives if the aetiology identified is something other than idiopathic or familial CM.

A different assessment group developed the initial clinical management algorithm, which was presented to, and ratified by, PASC. During the assessment process clinical experts provided further clarification and additional information that led to the algorithms being amended.

Populations and Relevant Comparators

The estimated incidence of DCM in Australia is 1,344 per year. The population proposed for CMR in the current report includes four subgroups of patients suspected of DCM:

i. Patients presenting with HF symptoms in whom echocardiography is inconclusive.

Currently, these patients receive an additional echocardiogram with contrast, or a gated heart pool scan (GHPS), to assess the functioning of the heart. The applicant suggested that CMR would completely replace these tests. In cases where CMR identifies a dilated left ventricle (LV) and systolic dysfunction diagnosing DCM, computed tomography coronary angiography (CTCA), single-photon emission computed tomography (SPECT) and stress echocardiography would also be avoided, as CMR has the ability to determine whether the DCM is ischaemic or non-ischaemic. CMR may also avoid unnecessary invasive coronary angiography (ICA). An evidentiary standard identified in the literature for determining the accuracy of DCM diagnoses was clinical diagnosis.

ii. Patients presenting with HF symptoms and a low to intermediate risk of CAD in whom echocardiography is suggestive of DCM.

The patients in this subgroup currently receive CTCA, pharmacologic (adenosine or dobutamine) SPECT or stress echocardiography to distinguish between the ischaemic and non-ischaemic causes of DCM. Ischaemic patients are referred for more-invasive investigation with ICA, while other patients could receive ICA as an alternative to non-invasive imaging. The clinical experts advised that CMR would partially replace these comparators. The reference standard for determining if a patient has ischaemia or not is ICA. An additional evidentiary standard found in the literature was clinical diagnosis.

If the patient shows signs of DCM, and is suspected of having NIDCM due to being at low risk of CAD, further testing may be needed to determine the aetiology. This testing will usually consist of blood tests, although more-extensive pathology tests, genetic testing, 24-hour electrocardiography (ECG), exercise testing with measurement of peak oxygen uptake, and right-sided cardiac catheterisation with endomyocardial biopsy (EMB) are also done. The advice of the clinical experts was that CMR might replace the use of some of these tests, or be used as an additional test. The reference standard for determining whether the aetiology is inflammatory in nature is EMB. Genetic testing was listed a priori as an alternative reference standard, but no literature was identified that compared CMR against this reference standard.

iii. Asymptomatic first-degree relatives of someone diagnosed with NIDCM, in whom echo is inconclusive.

Investigations currently undertaken in this apparently healthy subgroup, and potentially replaced by CMR, are contrast echocardiography or gated heart pool scans (GHPS). As per population i, if a dilated LV and systolic dysfunction happen to be identified, CMR may replace CTCA and SPECT.

iv. Asymptomatic first-degree relatives of someone diagnosed with NIDCM, with an intermediate to high risk of CAD, in whom echocardiography is suggestive of DCM that requires further investigations prior to treatment.

In this subgroup the current investigations (and comparators) replaced by CMR are CTCA and SPECT. The reference standard is ICA.

Current clinical practice for populations i and ii are shown in Figure 1 and Figure 3, respectively, and the proposed clinical pathways for these subgroups are shown in Figure 2 and Figure 4. The algorithms for first-degree relatives (for which no evidence was identified) are shown in Appendix L.

Key Differences in the Delivery of the Proposed Medical Service and the Main Comparator

One of the main differences between CMR and its comparators (i.e. CTCA, SPECT, ICA or GHPS) is the avoidance of exposure to ionising radiation. Furthermore, CMR is able to replace some (unnecessary) invasive tests (i.e. ICAs) that require local anaesthesia. The advantages and disadvantages of CMR and the comparator imaging techniques are shown in Table 3.

Clinical Claim

The applicant claims that CMR provides important information regarding ventricular morphology and tissue characterisation. This enables more-accurate stratification of patients to distinguish potentially treatable forms of NIDCM from non-treatable causes. If a treatable aetiology is identified, family members would also benefit, by avoiding the need for family screening.

Approach Taken to the Evidence Assessment

A systematic review (SR) of the published and unpublished literature was undertaken. The databases searched were PubMed, Embase and The Cochrane Library, as well as trial registers, grey literature databases and specialty websites (see Appendix B for further details). One researcher culled the citations with the program Rayyan (Elmagarmid et al. 2014), with a second researcher doing duplicate culling of the most relevant 20% of citations as determined by the algorithms within Rayyan. Included studies were critically appraised according to their study design using the AMSTAR checklist (Shea et al. 2007) for SRs and HTAs, QUADAS-2 (Whiting et al. 2011) appraisal tool for test accuracy studies, SIGN 50 (SIGN 2014) checklists for randomised controlled trials (RCTs) and cohort studies, or the NHLBI quality assessment tool for case series studies. Quality appraisal was done at the level of individual outcomes (across studies), as per GRADE methodology (Guyatt et al. 2011).

Due to a lack of direct evidence, a linked evidence approach has been used (Merlin et al. 2013), linking information regarding the diagnostic and predictive accuracy with information on how the test changes management, and investigating the impact that these changes may have on health.

For all sections other than B4 (Prognosis), the available evidence base was limited. To provide sufficient information for decision-making, the inclusion criteria were broadened to include slightly different populations than those specified in the PICO criteria outlined a priori.

CHARACTERISTICS OF THE EVIDENCE BASE

The characteristics of the evidence informing each of the steps of the linked analysis are shown in Table 1. The transferability of results between the linkages could be questioned as the population had to be broadened. For instance, the diagnostic performance studies included patients with HF but it was not clear (due to reporting in the studies) whether these patients had dilated LVs or were suspected of DCM.

Table 1 Key features of the included linked evidence

Type of evidence	Description	Evidence base
Prognostic evidence (section B4.2)	Four SRs of variable quality were included that reported on the prognostic value of cardiac scar tissue identified by CMR in patients with DCM. One good-quality SR compared the prognosis of patients diagnosed with NIDCM with those diagnosed with ICM. Of the 30 included studies (18 were in one or more of the SRs, 12 were identified through literature search), 25 were prospective studies (level II prognostic evidence) (Merlin, Weston & Tooher 2009; NHMRC 2000) and 5 were retrospective cohort studies providing level III-3 evidence (Merlin, Weston & Tooher 2009; NHMRC 2000).	SRs=5 K=30
Diagnostic performance (section B3) and Clinical validity (section B4)	One high-quality level III-1 study was identified that reported on the accuracy of CMR at diagnosing DCM. Eight studies determined the performance of CMR in diagnosing ischaemic or non-ischaemic aetiology, with two different reference standards: ICA (k=6; GRADE ⊕⊕⊙⊙) and clinical diagnosis (k=2; GRADE ⊕⊕⊕⊕). Three studies determined the performance of CMR in determining whether there was an inflammatory aetiology in DCM cases, using EMB as the reference standard (GRADE ⊕⊕⊙⊙). Three of the included studies also compared CMR with one of the identified comparators.	K=12 N=753
Therapeutic efficacy (section B5.1)	One cohort study (GRADE ⊕⊕⊙⊙) was identified that reported on the impact of CMR on patient management in patients suspected of DCM (n=88). Three case series were included on the impact of CMR on the management of a broader population (HF symptoms, unspecified CM).	K=4 N=4,237
Therapeutic effectiveness (section B5.2)	Two studies included in 'therapeutic efficacy' also reported data on health outcomes of patients due to change in management (1 cohort study and a description of case reports at high risk of bias). In addition, 6 SRs (low risk of bias) and 2 HTAs (low and moderate risk of bias) were identified. For more information, see Table 2.	SRs=6 HTAs=2 K=2

CM = cardiomyopathy; CMR = cardiac magnetic resonance (imaging); DCM = dilated cardiomyopathy; EMB = endomyocardial biopsy; HF = heart failure; HTA = health technology assessment; ICA = invasive coronary angiography; ICM = ischaemic cardiomyopathy; K = number of studies; N = number of patients; NIDCM = non-ischaemic dilated cardiomyopathy; SR = systematic review

Results

SAFETY

Test adverse events

The identified SR did not report any adverse events (AEs) from the CMR procedure itself or from the comparator tests. All the non-invasive tests are considered to have a good safety profile, although rare AEs may occur as a consequence of the contrast agents and tracers used in LGE-CMR, contrast echocardiography, SPECT, GHPS and CTCA; and the radiation used in SPECT, GHPS and CTCA. The invasive testing modalities, such as ICA and EMB, have higher rates of complications than the non-invasive imaging techniques. EMBs involve sampling of heart tissue; and ICA involves contrast, radiation and catheterisation through patients' arteries.

AEs from change in management

Evidence from 1 Australian study suggests that the use of CMR will provide clinicians with more information on which to base treatment decisions, and allow patients to be appropriately treated more conservatively (i.e. fewer patients are likely to have cardiac devices implanted or undergo surgery). This would have corresponding safety benefits.

EFFECTIVENESS

Direct effectiveness

No direct evidence was identified concerning how CMR impacts on health outcomes, compared with what would be done in the absence of CMR.

Effectiveness estimated from linked evidence

1. CMR accuracy

In patients presenting with HF and left ventricular (LV) dysfunction, CMR was found in 1 study to diagnose DCM with 83% sensitivity and 93% specificity, compared with all available diagnostic data (i.e. combination of information from clinical diagnosis, echocardiography, CMR, EMB and other diagnostic modalities) (GRADE ⊕⊕⊕⊕).

In the SR, only 3 studies were identified with comparative accuracy data. Two studies compared CMR with ICA, with all available diagnostic data as the reference standard. The larger study (n=120) showed no difference in sensitivity and specificity between the two tests. The smaller study (n=24) showed a lower specificity with ICA (0.45 vs 0.82), although, given the size of the study, this difference was not significantly different. One small study (n=28) compared CTCA and CMR, against the reference standard of ICA, to determine whether patients had NIDCM or ICM. LGE-CMR appeared to have slightly better sensitivity at detecting NIDCM than CTCA (100% vs 90%), whereas CTCA had superior specificity (71% vs 100%). However, given the size of the sample, and the wide confidence interval (CI) surrounding the results, any conclusions on the comparative accuracy would be tentative at best.

Six studies were identified that assessed the accuracy of CMR at distinguishing between NIDCM and ICM. In those studies that restricted the population to those with a dilated LV, the sensitivity at diagnosing NIDCM ranged between 84% and 100%, and specificity between 71% and 100%, using the reference standard of ICA as the benchmark (GRADE ⊕⊕⊙⊙). Compared with an evidentiary standard of all available data, CMR was found to have 85% to 100% sensitivity and 82% to 88% specificity (GRADE ⊕⊕⊕⊕).

Three studies assessed the accuracy of CMR at determining whether DCM was due to an inflammatory cause, compared with the imperfect reference standard of EMB. Sensitivity ranged between 58% and 87%, and specificity 33% and 50% (GRADE ⊕⊕⊙⊙). Compared with 'Lake Louise' criteria in 2 studies (which incorporate LGE-CMR results), CMR showed highly disparate results, with sensitivities ranging between 75% and 85%, and specificities between 7% and 73%. The reason for this heterogeneity could be due to incorporation bias in the studies or the slightly different populations receiving the test.

2. Prognosis

A total of 25 cohort studies were identified from 5 SRs to assess the prognostic value of CMR, with 2 of them comparing CMR with SPECT. It had been suggested that detection of myocardial scarring through LGE-CMR (i.e. LGE+ for scarring) could potentially be used to help assess whether someone should receive an implantable cardioverter defibrillator (ICD) and/or cardiac resynchronisation therapy (CRT). A median of 25% of those who were LGE+ received an ICD/CRT, while a median of

only 10% of those who were LGE– received an ICD/CRT. In patients with an ICD implanted for the primary prevention of sudden cardiac death (SCD), those who were LGE+ were 4.5-times more likely to have an appropriate hospital discharge than those who were LGE–. Similarly, in studies that did not restrict patients to a particular treatment method, those who were LGE+ were 4-times more likely to have an adverse cardiac event, and 3-times more likely to die, than those who were LGE–. However, in children, LGE may be detecting myocardial inflammation rather than fibrotic or scarred myocardium; for children with a recent diagnosis of DCM, those who were LGE+ were 2-times more likely to fully recover LV functioning than those who were LGE–.

Two studies compared the prognostic value of CMR with SPECT, but found contradictory results regarding which modality was superior.

As well as detecting scarring or inflammation using LGE, CMR may also be used to assess left ventricular ejection fraction (LVEF). LVEF determined by CMR was a better predictor of adverse cardiac events than LVEF determined by echocardiography. Treatment guidelines currently use %LVEF as one criterion for determining whether patients should receive an ICD.

3. Therapeutic efficacy (change in management)

Only 4 studies were identified that reported on the ability of CMR to influence patient management decisions. Three studies were before-and-after case series, describing treatment plans or diagnoses prior to CMR and after CMR. One was considered a cohort study that assessed patients with idiopathic NIDCM using a range of further tests, to determine the relative value of each test.

The most relevant study was by Taylor, AJ et al. (2013), performed in Australia, that followed a series of patients with CMs (90% of which were NIDCM) who had received investigations as per current practice (including echocardiography in 95%, ICA in 51%, and SPECT GHPS in 27%), and had existing treatment strategies defined (i.e. device implantation or surgery). CMR was then used, and the number of cases with changed management plans was recorded. In the majority of cases, the change was due to CMR determining that the patient's LVEF functioning was higher than previously assessed. Of the 72 patients who were scheduled for cardiac device implantation (ICD, CRT, ICD and CRT or pacemaker), 21 patients had the implantations averted. In 20/375 patients who were not previously scheduled to receive a device, a device was implanted subsequent to CMR. Of the 20 patients with surgical plans prior to CMR, 13 patients had their surgery averted. In the group of patients without a surgical plan, 7/427 subsequently underwent valve or cardiac surgery. The author explained that in the absence of CMR, clinicians tend to err on the side of caution, but with the additional information gained through CMR, are able to feel more confident in the ability of the patient to have good outcomes through optimal medical treatment alone[2]. This study shows that if CMR is listed on the MBS for assessing patients with DCM, it is likely to have a large impact on those patients who would otherwise undergo a more invasive treatment approach, with a smaller impact on those who are classified by other tests as not requiring surgery or device implantation.

One study assessed the impact of a suite of further tests (CMR, further blood tests, endomyocardial biopsy, exercise testing, 24-hour ECG and genetic testing) in patients who would otherwise be classified as having idiopathic NIDCM on the basis of clinical tests, ECG, echocardiogram and ICA (Broch et al. 2015). A total of 88/102 patients were able to undergo CMR; of these, 2 were identified as having non-compaction CM, and 2 as having systemic inflammatory disease. One of these was identified through EMB as having sarcoidosis, and the other as having Wegener's granulomatosis.

[2] Personal communication, A. Taylor, via a phone call on 3 March 2016

EMBs identified the aetiology in 2/97 cases (one with cardiac sarcoidosis, one with non-familial transthyretin amyloidosis). Genetic testing identified possible disease-causing mutations in 10/102 patients. Further blood tests identified 16/102 patients with viruses, while exercise testing and 24-hour ECG were considered to yield no new aetiologies. While this study does demonstrate that CMR may be useful in detecting rare aetiologies in patients who would otherwise be classified as idiopathic, it also shows that it cannot replace other tests.

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

The prognostic data suggest that using CMR to stratify patients to appropriate treatments, as occurred in the Australian study by Taylor, AJ et al. (2013), is likely to result in superior or at least non-inferior treatment outcomes compared with not using CMR. Taylor, AJ et al. (2013) reported that health outcomes (New York Heart Association (NYHA) classification, mortality, and rate of major AEs) after 12 months were not significantly different between those who had their surgical or device plans avoided due to the additional information provided by CMR and those who proceeded with having surgery or device implantation.

There is a clear logic that using CMR to detect treatable aetiologies of DCM should result in superior health outcomes for those few patients who have their DCM aetiology correctly identified. Corticosteroids were shown in a Cochrane Review to improve LVEF scores in patients with viral myocarditis after 1–3 months of treatment (GRADE ⊕⊕⊕⊙), although mortality was not affected. The literature on cardiac sarcoidosis was very limited, but suggested a trend towards favouring corticosteroids for maintaining or improving LVEF (GRADE ⊕⊙⊙⊙). No systematic reviews were identified for assessing the effectiveness of strategies specific for Wegener's granulomatosis, LV non-compaction or haemochromatosis.

Distinguishing correctly between NIDCM and ICM would be beneficial for patients, as although ICDs appear to have similar effectiveness within both subgroups, revascularisation has been found to be effective in those with ICM (Windecker et al. 2014), but is unlikely to be of benefit in those with NIDCM. A small number of patients who have ICM would likely be falsely classified by LGE-CMR as NIDCM, due to having LGE– findings. These patients have a better prognosis and are less likely to require coronary revascularisation than those with scarring or inflammation detected by LGE-CMR.

Summary

The accuracy of CMR was considered using three different concepts. It was proposed as a means to diagnose DCM, distinguish between ischaemic and non-ischaemic DCM, and determine the aetiology of NIDCM in those diagnosed with idiopathic DCM. CMR was also proposed to predict health outcomes and influence patient management. Overall, it is clear that CMR provides information that is useful for determining a patient's prognosis, and could potentially be helpful at deciding which treatments patients should receive. There is no direct evidence available to demonstrate that CMR benefits the health of patients, but a linked evidence approach suggests that it is likely to do so. A brief summary of findings is shown in Table 2 and a detailed interpretation of the clinical evidence can be found in section B8.

Table 2 Summary of findings for the linked evidence comparison of CMR for DCM

Section in report	Outcomes	Participants (studies)	Results	Interpretation	Quality of evidence using GRADE
B2. Direct evidence	Safety of CMR and comparative	K=0	No studies were identified on the harms of CMR or comparative imaging techniques for	The non-invasive imaging techniques have good safety profiles. Invasive testing such as EMB and	N/A

Section in report	Outcomes	Participants (studies)	Results	Interpretation	Quality of evidence using GRADE
	tests		the population with DCM.	ICA have higher rates of complications.	
B3. Diagnostic performance	Accuracy of CMR for diagnosing DCM	N=136 K=1 diagnostic accuracy study	Sensitivity = 0.83 (0.71, 0.92) Specificity = 0.93 (0.85, 0.97)	CMR is reasonably good at identifying DCM, when compared with clinical diagnosis and EMB. However, these findings were in studies that included patients other than those with an inconclusive echocardiogram.	Moderate ⊕⊕⊕⊙
	Accuracy of CMR at distinguishing ICM from NIDCM	K=8 diagnostic accuracy studies (K=6 vs ICA, K=2 vs clinical diagnosis)	Sensitivity = 0.68–1.00 Specificity = 0.71–1.00	A high proportion of those patients with NIDCM may avoid ICD insertion if imaged with CMR.	Low ⊕⊕⊙⊙ to High ⊕⊕⊕⊕
B3. Diagnostic performance; B4.2. Prognosis or predisposition	Accuracy of CMR vs CTCA, SPECT, or stress echo or contrast echo	K=1 diagnostic accuracy study; 2 prognostic studies	Only very limited evidence compared with CTCA Contradictory evidence compared with SPECT No evidence compared with stress or contrast echocardiography.	Conclusions on the comparative accuracy or prognostic benefit of CMR vs alternative non-imaging techniques cannot be made.	Very low ⊕⊙⊙⊙
B5.1. Therapeutic efficacy	Diagnostic yield of CMR in those classified as having idiopathic DCM	N=102 K=1 comparative diagnostic yield study	CMR identified aetiologies in 4/102 patients. 3/4 aetiologies were not identified by any other further test. 1/4 patients were also identified by EMB.	CMR provides unique information, identifying a small number of cases who would otherwise be classified as having idiopathic NIDCM. None of the other tests could be replaced by CMR, as each reported unique aetiologies.	Very low ⊕⊙⊙⊙
B4.2. Prognosis or predisposition	LGE-CMR for determining prognosis in those with NIDCM	K=30 prospective or retrospective cohort studies	All-cause mortality RR = 2.47 (95%CI 1.63, 3.74) Cardiac deaths RR = 3.21 (95%CI 1.79, 5.76) Any cardiac event RR = 3.71 (95%CI 2.29, 6.04)	Those with signs of scarring or inflammation on LGE-CMR had worse cardiac outcomes than those without signs, and were more likely to have an ICD implanted and to have an appropriate ICD shock.	Low ⊕⊕⊙⊙ to Moderate ⊕⊕⊕⊙
B5.1. Therapeutic efficacy	Effect of CMR on device implantation	N=488 K=1 cohort	In those patients scheduled for devices, 21/72 (29.2%) avoided	CMR is effective at reducing the proportion of patients who receive devices or	Moderate ⊕⊕⊕⊙

Section in report	Outcomes	Participants (studies)	Results	Interpretation	Quality of evidence using GRADE
	and surgery for NIDCM	study	implantation following CMR imaging. In those not scheduled for devices, 20/375 (5.3%) had one implanted after CMR imaging. In those scheduled for surgery, 13/20 (65%) avoided surgery after CMR. In those not scheduled for surgery, 7/427 (1.6%) underwent surgery after CMR.	surgery for treatment of CM, compared with what is done currently in Australia. Only a small proportion of patients who would otherwise not receive devices or surgery had their treatment plan amended following investigation with CMR. Appropriate avoidance of invasive therapies would result in superior safety outcomes.	
B5.2. Therapeutic effectiveness	Effectiveness of corticosteroids for myocarditis	N=719 K=8 RCTs	Mean LVEF difference = 7.36% (95%CI 4.94, 9.79), favouring corticosteroids over no corticosteroids after 1–3 months No significant difference in mortality	Treatment specific for myocarditis may improve cardiovascular functioning, compared with general treatment for HF symptoms.	Moderate ⊕⊕⊕⊙
	Effectiveness of revascular-isation for ICM	N=93,553 K=100 RCTs	CABG reduces the risk of death, myocardial infarction and subsequent revascularisation, compared with medical treatment alone. There were no data specific to patients who were negative for scarring or inflammation using LGE-CMR.	Correct identification of ICM is likely to reduce patient cardiac deaths and other outcomes. However, the impact of an incorrect diagnosis of NIDCM in those who are LGE– is unknown.	Low ⊕⊕⊙⊙

CABG = coronary artery bypass grafting; CI = confidence interval; CM = cardiomyopathy; CMR = cardiac magnetic resonance (imaging); DCM = dilated cardiomyopathy; CTCA = computed tomography coronary angiography; Echo = echocardiography; EMB = endomyocardial biopsy; HF = heart failure; ICA = invasive coronary angiography; ICD = implantable cardioverter defibrillator; ICM = ischaemic cardiomyopathy; K = number of studies; LGE-CMR = late gadolinium enhancement cardiac magnetic resonance (imaging); LVEF = left ventricular ejection fraction; N = number of patients; NIDCM = non-ischaemic dilated cardiomyopathy; RCT = randomised controlled trial; RR = relative risk; SPECT = single-photon emission computed tomography

In patients having a CMR after an indeterminate result from echocardiography (population i), CMR is safe but of uncertain effectiveness.

Based on a linked evidence approach (summarised above), in patients with a low risk of CAD (population iiA), the addition of CMR to further blood tests is safe and effective for determining the aetiology of NIDCM. This benefits a small number of patients with rare DCM aetiologies, and rules

out the need for familial screening in these cases. CMR also has the capacity to accurately target a significant number of patients to different treatments than would have been received on the basis of current tests alone; however, the impact of these changes in management on patient health are uncertain.

In patients with an intermediate risk of CAD (population iiB), CMR has uncertain effectiveness compared with CTCA, SPECT and stress echocardiography for determining ischaemia. It is effective at triaging NIDCM patients to an ICA.

Translation Issues

Discussion on the selection of the most applicable evidence to the Australian setting has been described in the economic analysis section on inputs; no additional evidence translations were required.

Economic Evaluation

The limited and fragmented nature of the clinical evidence did not enable construction of a single economic model to generate an overall cost-effectiveness estimate for the proposed MBS listing. Rather, individual economic analyses for each of the various patient subpopulations and between the relevant comparators were performed, to the extent that available data allowed. The following analyses were undertaken:

- In population i: patients with inconclusive echocardiogram results—a **cost comparison analysis of CMR vs contrast echocardiography or GHPS.**
- In population ii: patients diagnosed with DCM on echocardiogram and requiring further diagnostic clarification, the population was further divided into two subgroups:
    - subpopulation iiA: patients with a low risk of CAD (or where CAD has been ruled out—a (limited) **cost-effectiveness analysis of CMR as an additional diagnostic test.** A description of the costs of additional diagnostic tests undertaken when attempting to identify the aetiology of DCM is presented in Appendix L; however, these tests are not considered to be the main comparators with CMR as it is not generally anticipated that CMR will replace these
    - subpopulation iiB: patients with an intermediate risk of CAD, where the next investigation is to rule out CAD—a (limited) **cost-effectiveness analysis of CMR vs ICA**, and a **cost comparison analysis of CMR vs SPECT, CTCA or stress echocardiography.**

No reliable economic analyses were possible for subpopulations iii and iv, described in the listing as encompassing asymptomatic family members of patients with NIDCM.

The total cost associated with each use of CMR in the economic analysis is $1,106, which includes the cost of the listing, $855.20 (including patient co-payments), the cost of referrals for testing (where applicable) and the cost for treating AEs related to the testing methodology.

In patients with inconclusive echocardiography (i.e. population i), a lack of reliable evidence on clinical outcomes restricted the quantitative analysis to a comparison of costs. Including costs associated with the testing procedure, and with AEs associated with the testing and test follow-up, **the additional cost of CMR over GHPS is approximately $688 per person, and over contrast echocardiography approximately $960 per person**. CMR remained more expensive than either of these comparators in all sensitivity analyses. It is important to note that this cost analysis does not account for the fact that CMR can provide greater diagnostic clarification than either of these

alternatives (section B.8). There are also differences between these tests in terms of the health outcomes associated with side effects, patient acceptability and accessibility (section D.5.(i)).

In patients with a dilated LV and low risk of CAD (or known NIDCM) requiring further diagnostic clarification (i.e. population iiA), it is anticipated that CMR, as proposed, would generally be conducted in addition to the other investigations available, to enable greater diagnostic clarity and more appropriate management. While no data on health outcomes were identified, Australian data on change in management following CMR (vs planned management without CMR) were available, enabling a limited cost-effectiveness analysis. Assuming that addition of CMR (vs no CMR) was 100% accurate and provided for more-appropriate management, the base-case results of the analysis suggest that, after 6 months, **CMR would cost an additional $3,158 per additional patient appropriately managed** (or inappropriate management avoided). This means that for every $100,000 of *additional* net expenditure associated with the proposed listing in this subpopulation, 358 patients would have undergone additional CMR testing. In the 6 months after CMR imaging in these patients, 15.9 additional appropriate device implantations and 5.6 appropriate surgeries would be undertaken, and 16.7 inappropriate device implantations and 8.8 inappropriate surgeries would be avoided. The uncertainty around the accuracy of CMR contributes to uncertainty in this analysis. It is assumed that CMR is 100% accurate in the base-case, but if the sensitivity of CMR is less than 88% relative to the alternative of 'all diagnostic reference data', then the use of CMR would become less effective and more costly than not using it.

In patients with an intermediate risk of CAD (i.e. population iiB), the likely comparators are different as there is a need to identify whether or not ischaemia is present. Currently, without CMR being available, patients could receive an immediate ICA to categorically identify ischaemia (or not), and in some cases non-invasive tests (e.g. CTCA, SPECT and stress echocardiography) may be used before triaging to ICA (if ischaemia appears likely).

A limited cost-effectiveness analysis of CMR used as a triage test for ICA (i.e. where immediate ICA is the comparator) was undertaken. The analysis incorporated diagnostic accuracy estimates; prevalence estimates; and costs of CMR, ICA and AEs associated with ICA. It was assumed that CMR directed a change in patient management, as per a previously identified economic analysis (see section D.5.ii(A)), but there was no strong comparative evidence demonstrating this. The accuracy and prevalence inputs were uncertain and, as there was no evidence on health outcomes, the model could only estimate 'inappropriate ICAs avoided' as an outcome. Primarily because of the high relative cost of ICA, and the choice of outcome (i.e. simply reflecting a preference to avoid invasive testing, rather than overall health outcomes), **the base-case model found that use of CMR to triage patients for ICA was both more effective (in terms of avoiding unnecessary ICAs) and less costly (i.e. dominant) than immediate ICA** (see section D.4.ii(B)). Although inputs were uncertain, this conclusion held across all plausible sensitivity analyses conducted.

Some patients in population iiB would receive an alternative non-invasive comparator (e.g. CTCA, SPECT or stress echocardiography) rather than ICA, and so an economic comparison with these tests was also relevant. As there was little reliable and comparative evidence on diagnostic accuracy, change in management or health outcomes for CMR relative to these comparators, the analysis was again limited to a cost comparison. **CMR testing is associated with an incremental cost of $388 compared with SPECT, $230 compared with CTCA, and $504 compared with stress echocardiography.** It remained more costly in all sensitivity analyses. It is important to note that this cost analysis does not account for the fact that CMR can provide greater diagnostic clarification than any of the alternative tests (see section B.8); and there are differences between these tests on the health outcomes associated with side effects, and patient acceptability and accessibility (see section D.5.ii(B)).

Overall, given the large gaps in comparative clinical outcome data and the identification of incremental cost estimates in opposite directions across different patient groups, it is not possible to form a generalised conclusion of the cost-effectiveness of CMR as per the proposed listing. Rather, only limited conclusions can be drawn for the specific patient groups and circumstances described.

Estimated Extent of Use and Financial Implications

Estimations of the extent of use and financial implications of CMR are highly uncertain. A combination of epidemiological and market share approaches, with numerous assumptions, were required to estimate the financial impact. Based on a reported incidence rate for *primary* DCM, the ratio of ischaemic to non-ischaemic causes of DCM, estimated rates of eligible family members per index case and uptake rates, the following estimates of CMR usage and its directly associated costs were projected (Table 3).

Table 3 Number of CMR tests for suspected DCM (by subpopulation) and total costs

	2016–17	2017–18	2018–19	2019–20	2020–21
Population i: expected uptake	640	651	662	672	683
Population ii: expected uptake	3,338	3,395	3,451	3,507	3,562
Populations iii and iv: expected uptake	108	109	111	113	115
Total projected number of CMR tests for DCM	4,086	4,155	4,224	4,292	4,360
Cost of CMR and associated items to the MBS [a]	$3,125,411	$3,178,692	$3,231,539	$3,283,585	$3,335,423
Cost of CMR and associated items to patients [b]	$299,310	$304,412	$309,473	$314,458	$319,422
Total cost of CMR	$3,424,721	$3,483,104	$3,541,012	$3,598,043	$3,654,845

[a] $765 per service

[b] $73.26 per service

CMR = cardiac magnetic resonance (imaging); DCM = dilated cardiomyopathy; MBS = Medicare Benefits Schedule
Population i: symptomatic patients with indeterminate echocardiogram results; population ii: patients requiring further diagnostic clarification of DCM; populations iii and iv: familial cases eligible for CMR

Calculation of cost offsets is complex given the range of comparators across the different populations for this assessment of CMR. Overall, some cost offset is assumed for approximately 84% of CMRs (i.e. CMR is anticipated to replace an alternative test), based on assumptions around existing and anticipated clinical management within the population subgroups and estimated test uptake rates within the populations. The offsets are apportioned across: GHPS (15%), contrast echocardiography (3.8%), ICA (43%), CTCA (28%), stress echocardiography (5.5%) and SPECT (4.1%), based on existing market share estimates. The net financial impact to the MBS, patient and other health budgets is then calculated. The net impact on the MBS budget is presented in Table 4.

Table 4 Total costs to the MBS associated with CMR for suspected DCM

	2016–17	2017–18	2018–19	2019–20	2020–21
Number of proposed CMR services	4,086	4,155	4,224	4,292	4,360
CMR cost to the MBS	$3,125,411	$3,178,692	$3,231,539	$3,283,585	$3,335,423
Number of services offset	3,413	3,472	3,529	3,586	3,643
Costs offset	$1,573,853	$1,600,683	$1,627,295	$1,653,504	$1,679,608
Net cost to the MBS	$1,551,558	$1,578,008	$1,604,243	$1,630,081	$1,655,815

CMR = cardiac magnetic resonance (imaging); DCM = dilated cardiomyopathy; MBS = Medicare Benefits Schedule

The estimates of net cost are highly uncertain. They are directly sensitive to any changes in the estimates of the incidence of DCM, and the assumptions associated with estimating cost offsets.

Consumer Impact Summary

The key points raised in the public consultation period were:

(i) Patient access to CMR services may be difficult and lead to inequity, even after MBS listing; and (ii) MBS listing will decrease pressure on public hospital CMR services if private providers are able to provide subsidised CMRs.

Other Relevant Considerations

ETHICAL CONSIDERATIONS

One of the ethical issues associated with managing CMs in patients is the dilemma of the timing of ICD deactivation in end-of-life care. Deactivation is important as ICD shock is painful and distressing for the dying patient, and emotionally distressing for family members. The ability to reduce inappropriate ICD treatment would therefore benefit patients and families more than would be immediately apparent.

LVEF MEASUREMENT

LVEF is a critical measurement for identification of a dilated LV and impaired ventricular function in both the current and proposed clinical pathways for patients presenting with HF symptoms, and %LVEF informs decision-making regarding CRT or ICD implantation. Currently, LVEF assessment is performed using echocardiography. LVEF measurements by echocardiography were compared with measurements by CMR (k=4). Overall, there was a lower mean LVEF when measured by CMR.

ACRONYMS AND ABBREVIATIONS

AE	adverse event
AHTA	Adelaide Health Technology Assessment
AICD	automated implantable cardioverter defibrillator
AIHW	Australian Institute of Health and Welfare
AMI	acute myocardial infarction
ARVC	arrhythmogenic right ventricular cardiomyopathy
ATP	anti-tachycardia pacing
CA	cost analysis
CABG	coronary artery bypass graft
CAD	coronary artery disease
CAGS	coronary artery graft surgery
CEA	cost-effectiveness analysis
cEcho	contrast echocardiography
CHF	congestive heart failure
CI	confidence interval
CM	cardiomyopathy
CMR	cardiac magnetic resonance (imaging)
CRT	cardiac resynchronisation therapy
CRT-D	cardiac resynchronisation therapy with defibrillator
CT	computed tomography
CTCA	computed tomography coronary angiography
DCM	dilated cardiomyopathy
DS	diameter stenosis
ECG	electrocardiography
Echo	echocardiography
EGE	early gadolinium enhancement
EMB	endomyocardial biopsy
Gd	gadolinium

Gd-DTPA	gadolinium-diethylenetriamine pentaacetic acid
GHPS	gated heart pool scan(ning)
HCM	hypertrophic cardiomyopathy
HF	heart failure
HR	hazard ratio
HRQoL	health-related quality of life
HTA	health technology assessment
ICA	invasive coronary angiography
ICD	implantable cardioverter defibrillator
ICER	incremental cost-effectiveness ratio
ICM	ischaemic cardiomyopathy
IHD	ischaemic heart disease
IQR	interquartile range
IVIG	intravenous immunoglobulin
LGE	late gadolinium enhancement
LGE-CMR	late gadolinium enhancement cardiac magnetic resonance (imaging)
LR	likelihood ratio
LV	left ventricular / left ventricle
LVEF	left ventricular ejection fraction
LVNC	left ventricular non-compaction
MACE	major adverse cardiac events
MBS	Medicare Benefits Schedule
MI	myocardial infarction
MRI	magnetic resonance imaging
MSAC	Medical Services Advisory Committee
NEP	National Efficient Price
NHMRC	National Health and Medical Research Council
NIDCM	non-ischaemic dilated cardiomyopathy
NPV	negative predictive value

NR	not reported
NYHA	New York Heart Association
OMT	optimal medical treatment
OR	odds ratio
PASC	Protocol Advisory Sub-Committee of the MSAC
PCI	percutaneous coronary intervention
PCR	polymerase chain reaction
PHI	private health insurer/insurance
PICO	population, investigation / index test, comparator and outcomes
PPV	positive predictive value
PTP	pre-test probability
QALY	quality adjusted life year
RCT	randomised controlled trial
SCD	sudden cardiac death
SIGN	Scottish Intercollegiate Guidelines Network (quality assessment tool)
SP-CMR	stress perfusion cardiac magnetic resonance (imaging)
SPECT	single-photon emission computed tomography
SR	systematic review
SROC	summary receiver operating characteristic
VA	ventricular arrhythmia
VF	ventricular fibrillation
VT	ventricular tachycardia

SECTION A CONTEXT

This contracted assessment of cardiac magnetic resonance (CMR) imaging for the diagnosis of dilated cardiomyopathy (DCM) 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 CMR for DCM. 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 Australian clinical experts. The clinical experts were able to provide practical, professional advice that directly related to the application and the service being proposed for the MBS. Their role was limited to providing input and guidance to the assessment groups to ensure that the pathway is clinically relevant and takes into account consumer interests.

The proposed use of CMR in Australian clinical practice was outlined in a Protocol that was presented to, and accepted by, the Protocol Advisory Sub-Committee (PASC). The Protocol was released for public comment in March 2015.

A1 ITEMS IN THE AGREED PROTOCOL

This contracted assessment of CMR for DCM addresses most of the PICO (population, investigation / index test, comparator and outcomes) elements that were pre-specified in the Protocol that was ratified by PASC.

As no evidence was found regarding first-degree family members of DCM patients (one of the proposed populations), no results regarding this group were reported from section B onwards. The clinical management algorithms as presented in the Protocol were modified during the assessment period (after the final Protocol was received) following telephone conversations with clinical experts and personnel from the Australian Government Department of Health.

A2 PROPOSED MEDICAL SERVICE

Cardiac magnetic resonance imaging

CMR is used for the non-invasive assessment of the function and structure of the heart. It uses a standard magnetic resonance imaging (MRI) system, with or without specialised cardiac coils, using magnetic fields and radiofrequency signals to image cardiac tissues.

CMR provides an assessment of left ventricular (LV) functioning using fast cine techniques (steady state free precession) (Lombardi et al. 2010). Generally, the functional measurement is used to confirm previous abnormal findings on echocardiography, whereas the assessment of the structure, or myocardial texture, is unique to CMR and provides the ability to determine the aetiology of DCM (Lombardi et al. 2010). Myocardium is characterised using T1, T2 and T2* relaxation times and delayed contrast enhancement. It has the ability to show different areas of the heart and vascular structure and function (e.g. myocardial viability, tissue characterisation and scar assessment)

without using ionising radiation. It can be used to differentiate between cardiomyopathies (CMs) of varying aetiology. The presence and distribution pattern of late gadolinium enhancement (LGE) on CMR is important in differentiating ischaemic heart disease (IHD) from other forms of CM (Pinamonti & Sinagra 2014).

The majority of MRI scanners use 1.5T as the magnetic field strength for CMR; however, 1.0T and 3.0T are also used. Higher fields allow for images with higher spatial resolution, but also increase the chance of imaging artefacts that may obscure the image (Hundley et al. 2010).

CM means 'heart muscle disease' and the term is often reserved for severe myocardial disease leading to heart failure (HF) or sudden death. Diseases such as coronary artery disease (CAD), hypertension or heart valve abnormalities are usually excluded from the term 'cardiomyopathy'. There are different types of CM and they are usually classified according to their predominant pathophysiological (e.g. dilated, hypertrophic or restrictive CM) or aetiological/pathological features (e.g. alcoholic CM). CMR can assist with identifying and diagnosing CMs when other diagnostic methods (e.g. echocardiography) are inconclusive. The information derived from CMR can reveal the underlying aetiology of HF.

Dilated cardiomyopathy

Dilated cardiomyopathy (DCM) refers to a variety of different myocardial disorders characterised by dilated ventricles and depressed myocardial contractility due to abnormal loading conditions (e.g. hypertension, valvular disease) or significant IHD (Bozkurt & Mann 2007; Elliott et al. 2008). DCM is the third most common cause of HF (Pinamonti & Sinagra 2014) and it is estimated that approximately one-third of patients enrolled in most multicentre randomised controlled trials (RCTs) in HF have non-ischaemic DCM (NIDCM) (Bozkurt & Mann 2007). The most common causes of DCM are idiopathic, cardiotoxic drugs, alcohol abuse, infective agents (viral, bacterial, mycobacterial, fungal), familial, autoimmune disorders, and miscellaneous (metabolic, nutritional, acquired, inflammatory non-infectious). Idiopathic DCM refers to those cases in which the aetiologic cause is unknown, and this is usually around 60% of DCM cases (Pinamonti & Sinagra 2014).

Advanced non-invasive imaging techniques, such as computed tomography (CT), CMR and nuclear imaging, can be useful for diagnosing challenging cases in which echocardiography does not provide an adequate diagnosis. CMR is currently being used in clinical practice in Europe, UK and USA (Bruder et al. 2013), but in Australia its use is restricted due to lack of MBS listing.

MBS listing would allow for the use of CMR for people with HF symptoms suspected of having NIDCM.

A3 PROPOSAL FOR PUBLIC FUNDING

The proposed MBS item descriptor is summarised in Table 5.

Table 5

Proposed MBS item descriptor for the investigation of suspected DCM

Category 5 – Diagnostic Imaging Services
MBS [item number (Note: this will be assigned by the Department if listed on the MBS)]
NOTE: Benefits are payable for each service included by Subgroup ## on one occasion only in any 12-month period
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 cardiovascular system for:
(a) assessment of myocardial structure and function, including tissue characterisation; and
(b) the request for the scan identifies that the patient presents with:
heart failure symptoms, in whom echocardiography is inconclusive or suggests a dilated cardiomyopathy, and in whom further diagnostic clarification is required; or
a family history of non-ischaemic dilated cardiomyopathy in a first-degree relative in whom echocardiography is inconclusive.
(Contrast)
Fee: $855.20 Benefit: 75% = $641.40 85% = $726.90

A4 PROPOSED POPULATION

The proposed population for this report includes the following subgroups of patients suspected of having DCM (for more details see section A2):

i. patients presenting with HF symptoms in whom echocardiography is inconclusive.
ii. patients presenting with HF symptoms in whom echocardiography suggests a dilated CM, and who have a low or intermediate risk of CAD
iii. people with a family history of NIDCM in a first-degree relative, and in whom echocardiography is inconclusive.
iv. people with a family history of NIDCM, and in whom echocardiography suggests a DCM that requires further investigations prior to treatment, due to an intermediate or high risk of CAD.

The estimated incidence of DCM is 7 per 100,000, which would be around 1,344 patients in Australia (based on the projected Australian population aged 18 years and older in 2016–17) (Rakar et al. 1997; Taylor, MR, Carniel & Mestroni 2006). However, PASC suggested that this is likely to provide an upper estimate of the probable utilisation of CMR for the investigation of suspected DCM. According to data by the Australian Institute of Health and Welfare (AIHW), there were 2,118 Australian hospital separations in 2013–14 with DCM as the principal diagnosis. It is recognised that the number of hospital separations is not an ideal indication for prevalence, as only patients with a severe form of DCM will be hospitalised, and there is the possibility of having more than one hospital separation per patient. At least 25% of patients in Western populations have evidence of familial DCM with predominantly autosomal dominant inheritance (Elliott et al. 2008), although according to other sources it can be as high as 30–48% (Pinamonti & Sinagra 2014). Males are more frequently affected than females (with a ratio of approximately 3:1), and symptoms appear more frequently in the age group 40–60 years, although paediatric onset of DCM is not rare (Pinamonti & Sinagra 2014).

In this population CMR may help identify the aetiology of the disease (e.g. whether it is ischaemic or non-ischaemic) through tissue characterisation with late gadolinium enhancement (LGE), as LGE is able to demonstrate different patterns of myocardial scarring for different aetiologies. Specific investigations such as LGE-CMR enable a more precise diagnosis and prognosis following an inconclusive result through first-level exams (e.g. echocardiography and ECG), and increase the ability to choose the correct treatment in selected cases.

A5 COMPARATOR DETAILS

The main comparator is the current practice most likely to be replaced or added to by CMR. In this case it is those tests used to investigate patients with HF symptoms in whom an echocardiography result is unclear or suggests a dilated LV and systolic dysfunction, and in whom further diagnostic clarification is required.

These tests include:

1. Gated heart pool scan (GHPS) (MBS item 61313)

GHPS or single-photon emission computed tomography (SPECT) uses tomography imaging and radiolabelled red blood cells to evaluate the ventricular contractile function. As well as a radiolabel, the patient must be administered with a preparation medicine (usually stannous pyrophosphate) that prepares the red cells for labelling. Gating is achieved through the timing of scans with the heart beat rhythm, and ECG monitoring is conducted at the same time to enable the timing (RANZCR 2015). GHPS is done when patients present with HF symptoms and the echocardiography result is indeterminate (in the absence of CMR).

2. Stress echocardiography (MBS items 55116, 55117, 55122, 55123)

Stress echocardiography 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. This test may be done when a patient presents with a dilated LV and systolic dysfunction on echocardiography, and an ischaemic aetiology is suspected (in the absence of CMR). Stress is induced using exercise or pharmacological agents (e.g. dobutamine, dipyridamole). Stress echocardiography images are subjective, which leads to inter-observer variability and reduced reproducibility in interpreting wall motion contractility and function (Medical Advisory Secretariat 2010b). Therefore, myocardial contrast echocardiography is also used to assess perfusion (Medical Advisory Secretariat 2010a).

3. Contrast echocardiography

For contrast echocardiography an intravenously administered non-ionising contrast agent, typically containing micro-bubbles, is used to assist ultrasound visualisation. The agent used for conventional contrast echocardiography is agitated saline, which is prepared by hand agitation of a mixture of air and saline, and administered by injection through a small lumen catheter. Indications for contrast echocardiography evaluation include assessment of LV systolic function and LV structure, and recognition of regional wall motion abnormalities. The technique can also be used for assessment of myocardial perfusion in ischaemic disease (Senior et al. 2009; Stewart 2003). For MSAC assessment no. 1393, contrast echocardiography would be done when patients present with HF symptoms and the echocardiography result is indeterminate (in the absence of CMR).

4. Invasive coronary angiography (ICA) (MBS items 38215, 38218)

ICA is an invasive technique and will be done when ischaemia (or CAD) is suspected. It is performed under local anaesthesia and in sterile conditions. A catheter is inserted through an artery in the arm or leg, and X-rays are used to guide the catheter to the coronary arteries. To determine whether luminal obstruction is present, a radiocontrast agent is injected into the coronary arteries to show the coronary anatomy (Caluk 2011). ICA is used in stable patients who have an intermediate or high risk of having CAD. Those at high risk would receive an ICA regardless of MBS-listing of CMR. However, it is expected that with LGE-CMR on the MBS, fewer ICAs will need to be performed in the group at intermediate risk, as CMR could diagnose non-ischaemia and therefore avoid unnecessary ICAs. ICA is also classified as a reference standard for diagnostic performance in determining the ischaemic aetiology of DCM.

5. Computed tomography coronary angiography (CTCA) (MBS Items 57360, 57361)

CTCA also enables the diagnosis of ischaemic or non-ischaemic causes of DCM. It uses intravenous contrast to visualise the lumen of the coronary arteries, therefore avoiding the use of invasive testing such as ICA. CTCA is primarily indicated for patients with a low to intermediate pre-test probability (15–45%) of CAD (Paech & Weston 2011), and is not recommended for patients with obesity, high calcium scores (Agatston score >400), high resting heart rate (>65 beats per minute) or difficulty holding their breath.

6. Exercise or pharmacologic (adenosine or dobutamine) single-photon emission computed tomography (SPECT) (MBS Items 61302, 61303, 61306, 61307, 61651, 61652, 61653, 61654)

SPECT can be used to rule out ischaemic causes of DCM. It utilises radiopharmaceutical tracers (e.g. technetium-99m or thallium-201) to visualise regional myocardial blood flow and perfusion. (Montalescot et al. 2013). Tracer uptake during rest (baseline) is compared with uptake during peak stress (pharmacological or exercise), showing which regional areas are affected by myocardial ischaemia.

7. Further tests

In the absence of CMR, those with a low risk of CAD would receive 'further testing'. The form this would take would depend on whether there is a particular aetiology of NIDCM suspected or not. Clinical advice is that this testing would predominantly involve further blood tests, with a very small number of endomyocardial biopsies (EMBs) being performed. In the literature, investigations used include more-extensive pathology tests for viruses, genetic testing, ambulatory 24-hour ECG, exercise testing with measurement of peak oxygen uptake and right-sided cardiac catheterisation EMB (Broch et al. 2015). The clinical management algorithms in section A6 (Figure 1 and Figure 3) illustrate current practice in absence of CMR.

The MBS item descriptors for the relevant comparators are shown in Appendix F Relevant MBS Items for the Comparators.

A6 CLINICAL MANAGEMENT ALGORITHMS

The clinical management algorithms developed by another assessment group and presented to and ratified by PASC are available from the MSAC website[3]. During the process of performing this contracted assessment, further clarification was sought from clinical experts, and the algorithms were amended. Figure 1 and Figure 3 show current clinical practice of respectively: (i) patients presenting with HF symptoms with an indeterminate result on echocardiography, and (ii) patients presenting with HF in whom echocardiography suggests a DCM. Figure 2 and Figure 4 show the proposed algorithms for these patient groups if LGE-CMR was to be listed on the MBS. CMR is shown as an adjunct diagnostic tool to clinical examination, chest X-ray and echocardiography. It would be requested when the existing tools do not give adequate information, to further clarify the diagnosis and in some cases also inform prognosis and the investigation of first-degree relatives (as shown in Figure 47 and Figure 49 (current), and Figure 48 and Figure 50 (proposed) in Appendix I PICO Criteria and Clinical Management Algorithms for Populations iii and iv.

CMR would have the ability to distinguish between symptoms of acute myocarditis, post-myocarditis fibrosis and ischaemic damage due to CAD, and to identify an idiopathic or familial pattern of fibrosis. This knowledge could inform patient management and possibly avoid unnecessary ICA.

[3] MSAC.gov.au

Figure 1 Current clinical pathway for the diagnosis of patients with HF symptoms in whom echocardiography is inconclusive

CABG = coronary artery bypass graft; CAD = coronary artery disease; CRT = cardiac resynchronisation therapy; CTCA = computed tomography coronary angiography; DCM = dilated cardiomyopathy; Echo = echocardiography; HF = heart failure; ICA = invasive coronary angiography; ICD = implantable cardioverter defibrillator; LV = left ventricular / left ventricle; PCI = percutaneous coronary intervention; SPECT = single-photon emission computed tomography

Figure 2 Proposed clinical pathway for the diagnosis of patients with HF symptoms, in whom echocardiography is inconclusiv

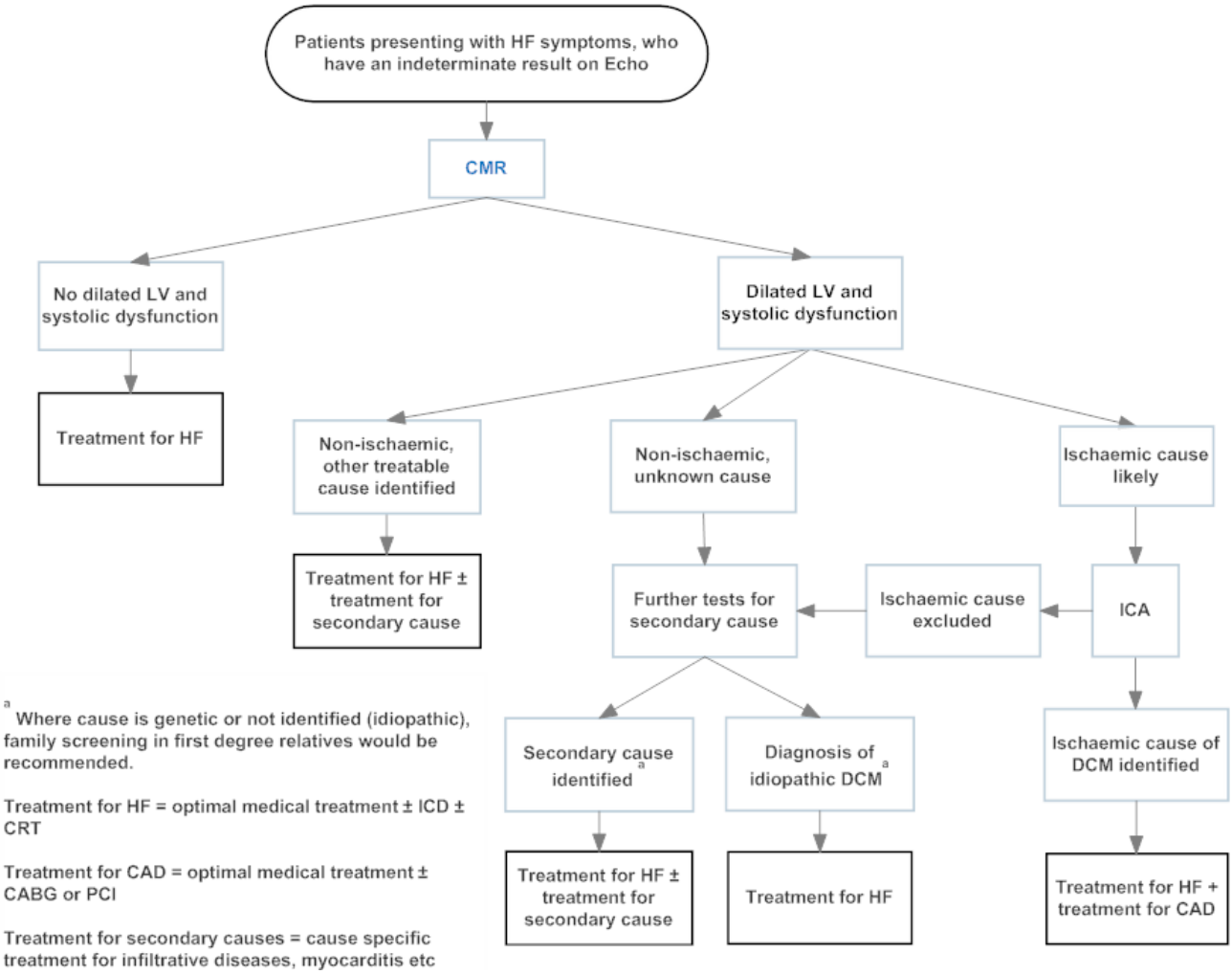
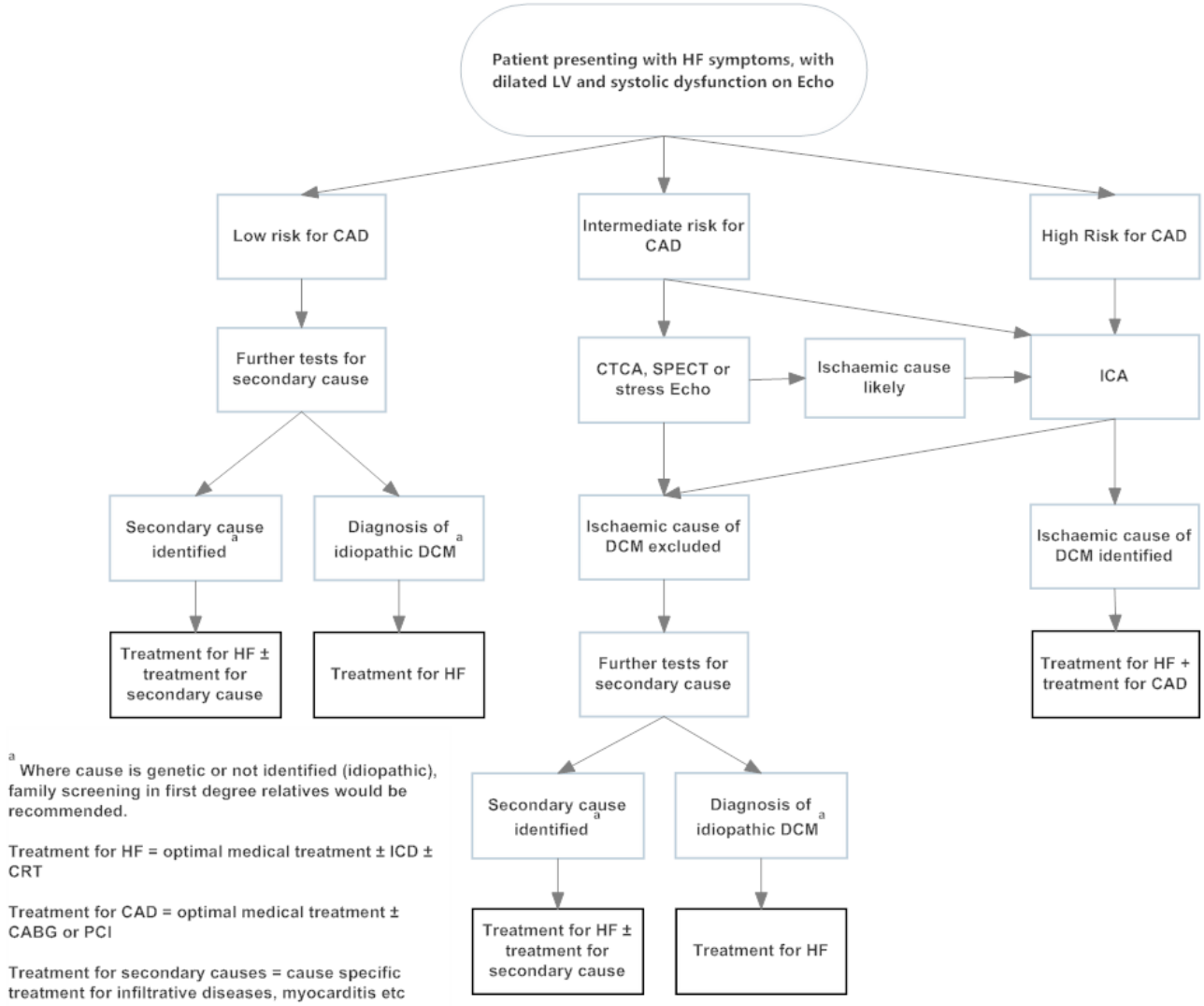
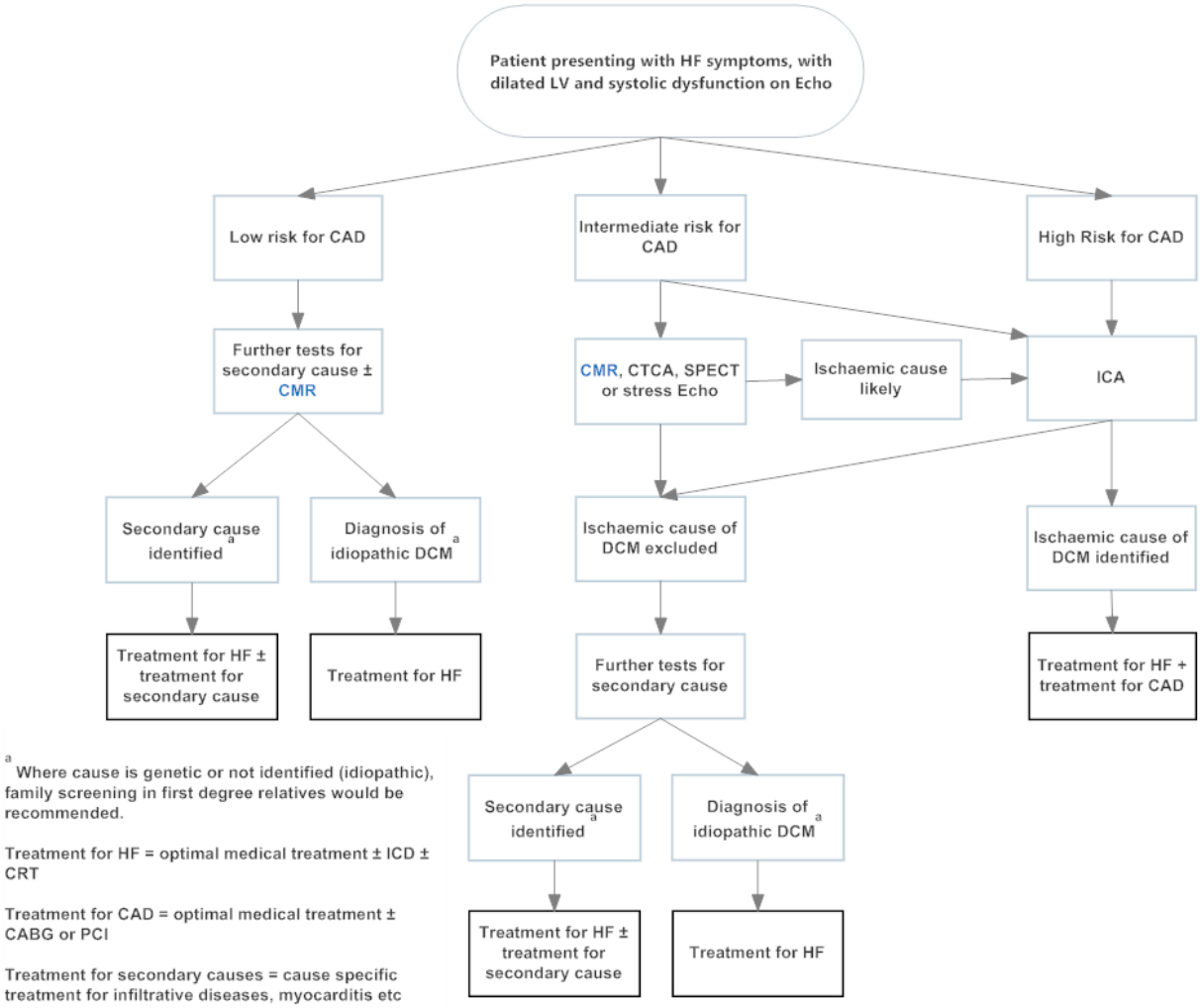


Figure 3 Current clinical pathway for the diagnosis of patients with HF symptoms, in whom echocardiography suggests a DCM



CABG = coronary artery bypass graft; CAD = coronary artery disease; CRT = cardiac resynchronisation therapy; CTCA = computed tomography coronary angiography; DCM = dilated cardiomyopathy; Echo = echocardiography; HF = heart failure; ICA = invasive coronary angiography; ICD = implantable cardioverter defibrillator; LV = left ventricular / left ventricle; PCI = percutaneous coronary intervention; SPECT = single-photon emission computed tomography

Figure 4 Proposed clinical pathway for the diagnosis of patients with HF symptoms, in whom echocardiography suggests a DCM



CABG = coronary artery bypass graft; CAD = coronary artery disease; CRT = cardiac resynchronisation therapy; CTCA = computed tomography coronary angiography; DCM = dilated cardiomyopathy; Echo = echocardiography; HF = heart failure; ICA = invasive coronary angiography; ICD = implantable cardioverter defibrillator; LV = left ventricular / left ventricle; PCI = percutaneous coronary intervention; SPECT = single-photon emission computed tomography

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

In patients suspected of DCM (or patients with a family history of DCM) with an indeterminate result on echocardiography, CMR is posed as a replacement test to the existing GHPS or contrast echocardiography. For patients showing a dilated LV and impaired left ventricular ejection fraction (LVEF) with an intermediate risk of CAD (or high risk in asymptomatic patients), CMR would be an alternative to CTCA, stress Echo and SPECT. Furthermore, it is likely that CMR will replace some (unnecessary) ICAs. Using CMR instead of CTCA, SPECT, ICA or GHPS would avoid exposure to ionising radiation. Identified advantages and disadvantages of the comparators are shown in Table 6.

Table 6 Advantages and disadvantages of 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
GHPS	No specific contraindications Less operator dependent and therefore more reproducible than other scans	Radiation exposure May be less accurate for measurement of cardiac chamber sizes, and less informative regarding valves than Echo Not widely available, and indications are not yet well defined
Stress Echo	No radiation Wide access Low cost	Dependent on operator skills Exercise stress Echo cannot be done in patients who cannot walk a reasonable workload Echo contrast needed in patients with poor ultrasound windows
cEcho	No radiation Low cost Superior visualisation compared with Echo Suitable for quantification of perfusion	Administration of contrast agents contraindicated for patients with known or suspected intracardiac shunting of significant degree, or known hypersensitivity to the agent
ICA	High sensitivity and specificity in diagnosing CAD (reference standard) Possibility for immediate intervention after CAD diagnosis	Invasive test requiring local anaesthesia Radiation exposure Radiocontrast needed; administration of contrast agents contraindicated for patients with known hypersensitivity to the agent Small risk of serious complications
CTCA	High patient acceptability High NPV in patients with low PTP of ischaemia	Radiation exposure Limited availability Image quality limited with arrhythmias and high heart rates that cannot be lowered beyond 60–65/minute
SPECT	Wide access	Radiation exposure

Technique	Advantages	Disadvantages
	Extensive data	

Sources: Montalescot et al. (2013); Mordi & Tzemos (2015); Morona et al. unpublished

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

A8 CLINICAL CLAIM

The applicant claims that CMR in patients with suspected DCM provides important information regarding ventricular morphology and tissue characterisation. It would provide more-accurate information than echocardiography in the assessment of LV structure and function. CMR may also help identify the aetiology of DCM through tissue characterisation with LGE. CMR has the potential to distinguish between treatable (e.g. myocarditis, sarcoidosis, amyloidosis) and non-treatable causes of DCM; therefore, if identified early, this could lead to reversing the DCM and avoiding the need for family screening.

According to the Protocol, the proposed benefits of CMR in patients suspected of DCM include:

1. increased diagnostic sensitivity compared with the current non-invasive techniques of investigating and differentiating DCM
2. increased safety compared with ICA, myocardial perfusion scans or CTCA, including the avoidance of ionising tests (radiation) and subsequent cancers
3. potential change in patient management in more than 50% of patients. This may be due to increased diagnostic sensitivity, leading to a change in diagnosis and treatment pathway. In around one in seven patients from the Euro CMR registry, CMR resulted in a different final diagnosis (Bruder et al. 2013).
4. potential avoidance of ICA or CTCA.

A9 SUMMARY OF THE PICO

The guiding framework of a Protocol is recommended by MSAC for each assessment. The Protocol describes current clinical practice and reflects likely future practice with the proposed medical service. PICO criteria were developed for the populations with symptoms and for asymptomatic family members. However, there were no studies identified addressing the PICO criteria for family members; the PICO criteria for family members are shown in Appendix I.

Direct evidence

The PICO that were specified to guide the systematic literature review for direct evidence of safety, effectiveness and cost-effectiveness are presented in Box 1 and Box 2.

Box 1 Criteria for identifying and selecting studies to determine the safety of CMR in patients with suspected DCM

Selection criteria	Description (population i)	Description (population ii)
Population	Patients presenting with HF symptoms, in whom Echo is inconclusive	Patients presenting with HF symptoms, in whom Echo suggests a DCM and who have low or intermediate risk of CAD
Intervention	CMR	CMR
Comparators	- contrast Echo - GHPS - CTCA - SPECT - Stress Echo - ICA	- CTCA - SPECT - Stress Echo - ICA - Further tests (e.g. genetic testing, further blood tests, EMB)
Outcomes	Safety: - Gadolinium contrast adverse reaction - Claustrophobia - Physical harms from follow-up testing - Other adverse events arising from CMR or comparative tests	Safety: - Gadolinium contrast adverse reaction - Claustrophobia - Physical harms from follow-up testing - Other adverse events arising from CMR or comparative tests
Systematic review question	What is the safety of CMR compared with cEcho, CTCA, SPECT, stress Echo, ICA and GHPS in patients with HF symptoms in whom Echo is inconclusive?	What is the safety of CMR compared with SPECT, CTCA, stress Echo, ICA and further testing in patients with HF symptoms in whom Echo suggests a DCM, and who have a low or intermediate risk of CAD?

CAD = coronary artery disease; CMR = cardiac magnetic resonance (imaging); CTCA = computed tomography coronary angiography; DCM = dilated cardiomyopathy; Echo = echocardiography; EMB = endomyocardial biopsy; GHPS = gated heart pool scan; HF = heart failure; ICA = invasive coronary angiography; SPECT = single-photon emission computed tomography

Box 2 Criteria for identifying and selecting studies to determine the direct effectiveness of CMR in patients with suspected DCM

Selection criteria	Description (population i)	Description (population ii)
Population	Patients presenting with HF symptoms, in whom Echo is inconclusive	Patients presenting with HF symptoms, in whom Echo suggests a DCM and who have low or intermediate risk of CAD
Intervention	CMR	CMR
Comparators	- cEcho - GHPS - CTCA - SPECT - Stress Echo - ICA	- CTCA - SPECT - Stress Echo - ICA - Further tests (e.g. genetic testing, further blood tests, EMB)
Outcomes	Health outcomes:	Health outcomes:

	- Cardiac disease-specific mortality - Survival - Cardiac hospitalisation - Adverse cardiac event over defined period - Quality of life scores Cost-effectiveness: - Cost - Cost per quality adjusted life year (QALY) or disability adjusted life year (DALY) - Incremental cost-effectiveness ratio (ICER)	- Cardiac disease-specific mortality - Survival - Cardiac hospitalisation - Adverse cardiac event over defined period - Quality of life scores Cost-effectiveness: - Cost - Cost per quality adjusted life year (QALY) or disability adjusted life year (DALY) - Incremental cost-effectiveness ratio (ICER)
Systematic review question	What is the effectiveness and cost-effectiveness of CMR compared with cEcho, GHPS, CTCA, SPECT, stress Echo and ICA in patients with HF symptoms in whom Echo is inconclusive?	What is the effectiveness and cost-effectiveness of CMR compared with SPECT, CTCA, stress Echo, ICA and further testing in patients with HF symptoms in whom Echo suggests a DCM, and who have a low or intermediate risk of CAD?

CAD = coronary artery disease; CMR = cardiac magnetic resonance (imaging); CTCA = computed tomography coronary angiography; DALY = disability adjusted life year; DCM = dilated cardiomyopathy; Echo = echocardiography; EMB = endomyocardial biopsy; GHPS = gated heart pool scan; HF = heart failure; ICA = invasive coronary angiography; ICER = incremental cost-effectiveness ratio; QALY = quality adjusted life year; SPECT = single-photon emission computed tomography

The PICO that were specified to guide the systematic literature review for a linked evidence approach are presented in Box 3 to Box 6.

Diagnostic performance

Box 3 Criteria for identifying and selecting studies to determine the accuracy of CMR in patients with patients with suspected DCM

Selection criteria	Description (population i)	Description (population ii)
Population	Patients presenting with HF symptoms, in whom Echo is inconclusive	Patients presenting with HF symptoms, in whom Echo suggests a DCM and who have low or intermediate risk of CAD
Prior tests	Clinical examination, ECG, Echo	Clinical examination, ECG, Echo
Index test	CMR	CMR
Comparators	- cEcho - GHPS - CTCA - SPECT - Stress Echo - ICA	- CTCA - SPECT - Stress Echo - ICA - Further tests (e.g. genetic testing, further blood tests, EMB)
Reference standard	- ICA	- ICA

	- Clinical diagnosis [a] - EMB - Genetic testing	- EMB - Genetic testing
Outcomes	Sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, positive predictive value, negative predictive value, SROC curves, unsatisfactory or uninterpretable test results	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 compared with cEcho, GHPS, CTCA, SPECT, stress Echo and ICA in patients with HF symptoms in whom Echo is inconclusive?	What is the diagnostic accuracy of CMR compared with SPECT, CTCA, stress Echo, ICA and further testing in patients with HF symptoms in whom Echo suggests a DCM, and who have a low or intermediate risk of CAD?

[a] Diagnosis based on a review of all available diagnostic data: information from medical history, laboratory tests, ICA, biopsy, CMR, Echo etc. by treating cardiologists (Assomull, RG et al. 2011; de Melo et al. 2013)

CAD = coronary artery disease; CMR = cardiac magnetic resonance (imaging); CTCA = computed tomography coronary angiography; DCM = dilated cardiomyopathy; ECG = electrocardiogram; Echo = echocardiography; EMB = endomyocardial biopsy; GHPS = gated heart pool scan; HF = heart failure; ICA = invasive coronary angiography; SPECT = single-photon emission computed tomography; SROC = summary receiving operating characteristic

Prognostic value

Box 4 Criteria for identifying and selecting studies to determine the prognostic value of CMR in patients with suspected DCM

Selection criteria	Description (population i)	Description (population ii)
Population	Patients presenting with HF symptoms, in whom Echo is inconclusive	Patients presenting with HF symptoms, in whom Echo suggests a DCM and who have low or intermediate risk of CAD
Prior tests	Clinical examination, ECG, Echo	Clinical examination, ECG, Echo, CMR
Index test	CMR	CMR
Comparators	- cEcho - GHPS - CTCA - SPECT - Stress Echo - ICA	- CTCA - SPECT - Stress Echo - ICA - Further tests (e.g. genetic testing, further blood tests, EMB)
Outcomes	Hazard ratio, relative risk, mortality rates	Hazard ratio, relative risk, mortality rates
Systematic review question	What is the prognostic value of CMR compared with cEcho, GHPS, CTCA, SPECT, stress Echo and ICA in patients with HF symptoms in whom Echo is inconclusive?	What is the prognostic value of CMR compared with SPECT, CTCA, stress Echo, ICA and further testing in patients with HF symptoms in whom Echo suggests a DCM and who have a low or intermediate risk of CAD?

CAD = coronary artery disease; CMR = cardiac magnetic resonance (imaging); CTCA = computed tomography coronary angiography; DCM = dilated cardiomyopathy; ECG = electrocardiogram; Echo = echocardiography; EMB = endomyocardial biopsy; GHPS = gated heart pool scan; HF = heart failure; ICA = invasive coronary angiography; SPECT = single-photon emission computed tomography

Therapeutic efficacy

Box 5 Criteria for identifying and selecting studies to determine the therapeutic efficacy (change in management) of CMR in patients with suspected DCM

Selection criteria	Description (population i)	Description (population ii)
Population	Patients presenting with HF symptoms, in whom Echo is inconclusive	Patients presenting with HF symptoms, in whom Echo suggests a DCM and who have low or intermediate risk of CAD
Prior tests	Clinical examination, ECG, Echo	Clinical examination, ECG, Echo
Index test	CMR	CMR
Comparators	- cEcho - GHPS - CTCA - SPECT - Stress Echo - ICA	- CTCA - SPECT - Stress Echo - ICA - Further tests (e.g. genetic testing, further blood tests, EMB)
Outcomes	Change in clinical diagnosis, change in treatment pathway (initiated, ceased, modified, avoided), patient compliance, time to initial diagnosis, time from diagnosis to treatment, rates of reintervention	Change in clinical diagnosis, change in treatment pathway (initiated, ceased, modified, avoided), patient compliance, time to initial diagnosis, time from diagnosis to treatment, rates of reintervention
Systematic review question	Is there a change in management from CMR compared with cEcho, GHPS, CTCA, SPECT, stress Echo and ICA in patients with HF symptoms in whom Echo is inconclusive?	Is there a change in management from CMR compared with SPECT, CTCA, stress Echo, ICA and further testing in patients with HF symptoms in whom Echo suggests a DCM and who have a low or intermediate risk of CAD?

CAD = coronary artery disease; CMR = cardiac magnetic resonance (imaging); CTCA = computed tomography coronary angiography; DCM = dilated cardiomyopathy; ECG = electrocardiogram; Echo = echocardiography; EMB = endomyocardial biopsy; GHPS = gated heart pool scan; HF = heart failure; ICA = invasive coronary angiography; SPECT = single-photon emission computed tomography

Therapeutic effectiveness

One potential change in management, expected a priori, was treatment differences due to the distinction between ischaemic and non-ischaemic DCM (see Box 6). Other changes in management (i.e. treatment effectiveness for rare aetiologies such as myocarditis and sarcoidosis), as determined from the literature, were investigated ad hoc without pre-defined criteria.

Box 6 Criteria for identifying and selecting studies to determine the therapeutic effectiveness of the change in patient management subsequent to CMR in patients with NIDCM

Selection criteria	Description
Population	Patients classified (correctly or incorrectly) as having NIDCM
Intervention	Optimal medical therapy ± ICD implantation
Comparators	Revascularisation and/or optimal medical therapy or monitoring
Outcomes	Cardiac disease-specific mortality, survival, cardiac hospitalisation, adverse cardiac event

	over defined period, quality of life scores
Systematic review question	Does optimal medical therapy and/or ICD implantation lead to better health outcomes in patients with NIDCM, compared with revascularisation and/or optimal medical therapy or monitoring?

DCM = dilated cardiomyopathy; ICD = implantable cardioverter defibrillator; NIDCM = non-ischaemic dilated cardiomyopathy

A10 CONSUMER IMPACT STATEMENT

Some key points/issues received during the public consultation period of the development of the Protocol were:

- Access to CMR can be difficult. There can be long waiting periods for CMR within public hospitals due to demand for MRI from other specialties (e.g. orthopaedics and neurology). Recent changes to the MBS allow greater access to MRI for other areas, and recent changes allowing general practitioner access has meant that Medicare-licensed MRI scanners have limited time available for CMR. Therefore, even after MBS listing of CMR for DCM, patient access to the service may be difficult and lead to inequity.
- It is expected that MBS listing of CMR will significantly reduce the costs paid by patients, improve the commercial viability for providers of CMR, and decrease pressure on public hospital CMR services if private providers are able to provide a subsidised CMR service.

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 ICA, GHPS, stress echocardiography or contrast echocardiography, SPECT or CTCA, and treatment (direct evidence). 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 treatment for NIDCM, linked with applicable and high-quality evidence of the accuracy of CMR for diagnostic clarification of DCM compared with ICA, GHPS, stress- or contrast echocardiography, SPECT or CTCA. This is called 'linked evidence'.

As there was not sufficient direct evidence available to assess CMR for DCM, the evidence was supplemented by a linked evidence approach.

LITERATURE SOURCES AND SEARCH STRATEGIES

The medical literature was searched on 21 December 2015 to identify relevant studies and systematic reviews (SRs) published during the period 1990 to 21 December 2015. Searches were conducted of the databases and sources described in Appendix B. Attempts were also made to source unpublished or grey literature, and the HTA websites listed in Appendix B were also searched. Search terms, described in Table 7, included a broad range of CMs, which were divided into groups based on population in the culling stages of the assessment. Eligible studies including patients suspected of DCM (and their family members), and CM in general in the absence of eligible data on DCM, were included in this assessment report.

A separate (non-systematic) search was done for the last step of the linked analysis—the therapeutic effectiveness. Furthermore, a search was conducted in Pubmed, Cochrane Library and PubMed Health to aim to find SRs or clinical guidelines on the diagnostic accuracy of comparators in the patient population, and Embase and Pubmed were searched specifically for diagnostic performance studies on LGE-CMR (as shown in section B3.2).

Table 7 Search terms used for CMR for cardiomyopathies (Pubmed/medline platform)

Element of clinical question	Search terms
Population	("Cardiomyopathy, Dilated" [MeSH] OR "Cardiomyopathy, Hypertrophic" [MeSH] OR "Cardiomyopathy, Hypertrophic, Familial" [MeSH] OR "Cardiomyopathy, Restrictive" [MeSH] OR "Arrhythmogenic Right Ventricular Dysplasia" [MeSH] OR "Endocardial Fibroelastosis" [MeSH] OR "Isolated Noncompaction of the Ventricular Myocardium" [MeSH] OR cardiomyopathy OR Takotsubo) OR (("Death, Sudden, Cardiac" [MeSH] OR "sudden cardiac death") NOT ("Channelopathies" [MeSH] OR "Arrhythmias, Cardiac" [MeSH] OR channelopathy OR arrhythmia))
Intervention	"Magnetic Resonance Angiography" [MeSH] OR "cardiac magnetic resonance" OR "cardiac MRI" OR "coronary magnetic resonance" OR "coronary MRI"
Comparator (if applicable)	-
Outcomes (if applicable)	-
Limits	-

MeSH = Medical Subject Heading, based on a Medline/PubMed platform

RESULTS OF LITERATURE SEARCH

PRISMA flowcharts provide a graphic depiction of the results of the literature searches and the application of the study selection criteria (listed in section A9) (Liberati et al. 2009). Separate PRISMA flowcharts show the flow of studies for the different steps in the linked analysis (diagnostic performance, clinical validity, clinical utility etc). For the different PRISMA flowcharts, see section B3.2 for diagnostic performance (Figure 5), section B4.2.1 for prognosis (Figure 16) and section B5.1.1.2 for therapeutic efficacy (Figure 24).

Studies were selected by a single reviewer, with a random sample (20%) receiving independent assessment by a second reviewer. Disagreements regarding study selection were resolved by a third independent reviewer.

In general, studies were excluded if they did not address the research question, did not provide information on the pre-specified target population, did not address one of the pre-specified outcomes and/or provided inadequate data on these outcomes, were in a language other than English and a lower level of evidence (than the studies in English), did not have the appropriate study design, or were conference abstracts.

Studies that could not be retrieved or that met the inclusion criteria but contained insufficient or inadequate data for inclusion are listed as excluded studies in Appendix E. All other studies that met the inclusion criteria are listed in Appendix C.

A profile of each included study is given in Appendix C. This study profile describes the author(s), study ID, publication year, study design and quality (level of evidence and risk of bias), study location, 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 relevant outcomes assessed.

APPRAISAL OF THE EVIDENCE

Appraisal of the evidence was conducted in four stages:

Stage 1: Appraisal of the risk of bias within individual studies (or SRs) included in the review (see 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 (see 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 the likelihood of publication bias, which informs the GRADE of the evidence (see evidence profile tables, Appendix D).

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 (see section B8).

B1 DIRECT EVIDENCE

B1.1 LITERATURE SOURCES AND SEARCH STRATEGIES

The literature sources and search strategies are described above (page 52).

B1.2 RESULTS OF LITERATURE SEARCH

No studies were identified that directly compared the effectiveness of LGE-CMR with other comparator tests in asymptomatic individuals with a family history of NIDCM or in patients presenting with HF symptoms, in whom echocardiography is inconclusive or suggests a DCM and in whom diagnostic clarification is required. Therefore, a linked analysis approach was chosen and in some cases the populations were broadened to allow for patients suspected of CM to be included (irrespective of a dilated LV).

As there were no studies included on direct effectiveness or safety, effectiveness results are shown in the following linked sections: B3 (diagnostic performance), B4 (clinical validity) and B5 (clinical utility). Safety results are presented in section B7 (extended assessment of comparative harms).

B2 LINKED EVIDENCE APPROACH

B2.1 BASIS FOR LINKED EVIDENCE

Due to the absence of direct evidence, a linked evidence approach was taken.

B2.2 STEPS FOR LINKED ANALYSIS

To construct a linked evidence analysis, the following evidence requirements are needed.

- consideration of the diagnostic performance and clinical validity of the investigative medical service (sections B3 and B4);
- 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 B5); and
- consideration of the relative safety of performing the investigative service, both the immediate safety issues of directly performing the test and the 'flow on' safety issues that arise as a result of conducting the investigative service (section B7).

Conclusions linking the different steps of the linked evidence approach can be found in section B8.

B3 DIAGNOSTIC PERFORMANCE

The PICO criteria for the first step of the linked analysis (diagnostic performance) are shown in Box 5.

B3.1 REFERENCE STANDARD

To determine whether DCM has an ischaemic or non-ischaemic cause, ICA is often used. However, as it is an invasive test, it is only recommended in stable patients and only if non-invasive tests provide inadequate information, or if there is a suspicion that the patient may have ischaemia. The identification of ischaemic disease often relies on the demonstration of (coronary) lesions on ICA, and ICA is currently seen as the reference standard to determine ischaemia. However, as shown in Figure 2, ICA is also a comparator, as LGE-CMR could potentially avoid ICA in some patients.

Myocardial inflammation mediated by acute or chronic viral infection, direct toxic injury or autoimmune response is another important cause of DCM (Voigt et al. 2011). To investigate whether myocardial inflammation (myocarditis) is the cause of DCM symptoms, EMB is a widely accepted method and is currently considered the reference standard. Although it can be safely performed by experienced operators, it is an invasive test and life-threatening complications can still occur (Cooper et al. 2007).

The third reference standard that was identified during the literature search was a final diagnosis based on a review of all the available diagnostic data (e.g. information from medical history, laboratory tests, ICA, EMB, CMR and echocardiography by treating cardiologists) (Assomull et al. 2011; de Melo et al. 2013). This was considered to be the 'gold standard'.

Studies using genetic testing as a reference standard in the patient population were not identified.

B3.2 LITERATURE SOURCES AND SEARCH STRATEGIES

In addition to the general broad literature search as described in section B (page 52), a separate search on diagnostic accuracy studies was conducted on 29 February 2016. The search terms used to search Embase and PubMed are shown in Table 8.

Table 8 Search terms used in diagnostic accuracy search

Element of clinical question	Search terms
Population	("heart failure" OR dilated cardiomyopathy))
Intervention	(((“Magnetic Resonance Angiography” [MeSH] OR “cardiac magnetic resonance” OR “cardiac MRI" OR “coronary magnetic resonance” OR “coronary MRI” OR CMR))
Comparator (if applicable)	-
Outcomes (if applicable)	(accuracy OR sensitivity OR specificity OR positive predictive value OR false positive OR false negative)
Limits	-

MeSH = Medical Subject Heading, based on a Medline/PubMed platform

Due to the lack of comparative diagnostic performance data, a second separate search was conducted in PubMed, the Cochrane Library and PubMed Health, with the aim of identifying SRs on the diagnostic accuracy of comparator tests and conducting an indirect comparison. The search terms used were “Diagnos*”, “cardiomyopathy” and “heart failure”. The search terms were kept broad as searching for the intervention yielded no results. The limits applied to the search were “systematic reviews”, “meta analyses” and “clinical guidelines”.

B3.2.1 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 section A9) (Liberati et al. 2009).

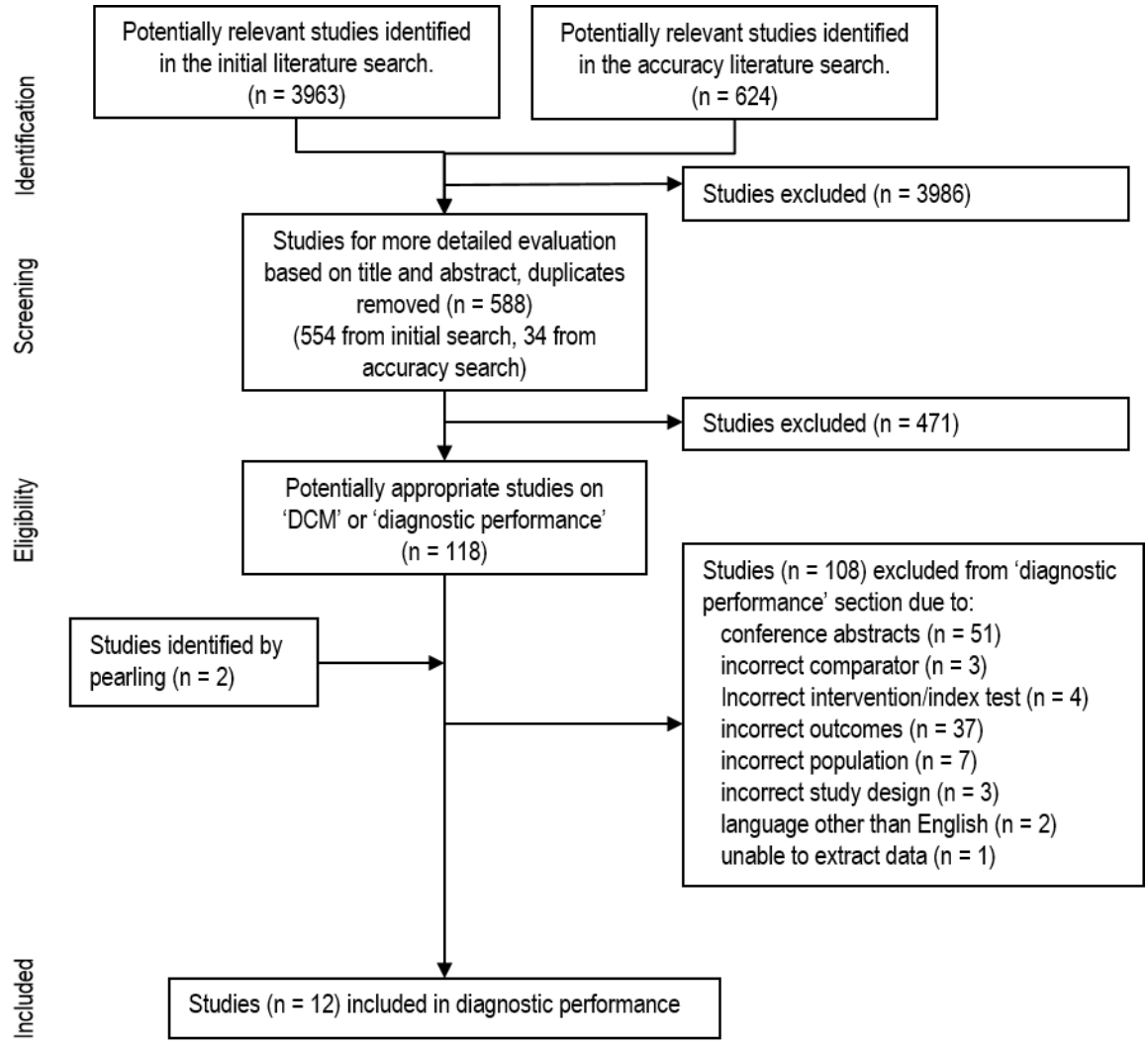


Figure 5 Summary of the process used to identify and select studies for the assessment of diagnostic performance of CMR for patients suspected of DCM

CMR = cardiac magnetic resonance (imaging); DCM = dilated cardiomyopathy

A summary of the characteristics of accuracy studies is shown in Table 7. A full profile of each included study is given in Appendix C. Those studies that technically met the inclusion criteria but were not included in the results section or meta-analyses are listed in Appendix E.

No studies were identified that compared the diagnostic performance of LGE-CMR with other comparator tests in asymptomatic individuals with a family history of DCM. Furthermore, no SRs, meta-analyses or clinical guidelines were identified to allow for an indirect comparison of the selected comparators with LGE-CMR.

Twelve studies met the inclusion criteria for diagnostic performance (in patients with HF / suspected of DCM). Coronary angiography, 'available diagnostic data' and EMB were used as the reference standards in 6, 3 and 3 studies, respectively, with CMR as the index test. Of the studies with 'available diagnostic data' as the reference standard, 1 study included EMB as a comparator to CMR

(Yoshida, Ishibashi-Ueda et al. 2013), and 2 studies included ICA as a comparator to CMR (Assomull et al. 2011; de Melo et al. 2013). CTCA was included as a comparator with CMR in a study that used ICA as the reference standard (Hamilton-Craig et al. 2012). The key outcomes in all studies were sensitivity and specificity.

Table 9 Key features of the included evidence of diagnostic accuracy of LGE-CMR

Trial/Study	N	Level of evidence	Risk of bias	Patient population	Purpose of test	Reference standard
Assomull et al. (2011)	120	II	Low	HF patients with reduced and dilated LV	Determining whether DCM is ischaemic or non-ischaemic	Clinical data
Bohnen et al. (2015)	31	II	Medium	HF patients with reduced LVEF	Determining whether CM has an inflammatory cause	EMB
Casolo et al. (2006)	60	II	Low	HF patients with LV dysfunction and dilation	Determining whether DCM is ischaemic or non-ischaemic	ICA
de Melo et al. (2013)	24	III-1	Unclear	HF patients with DCM	Determining whether DCM is ischaemic or non-ischaemic	Clinical data
Hamilton-Craig et al. (2011)	28	II	Low	Patients suspected of DCM referred for ICA	Determining whether DCM is ischaemic or non-ischaemic	ICA
McCrohonet al. (2003)	90	III-3	Unclear	63 DCM patients, 27 CAD patients and 15 control subjects	Determining whether there was ischaemia	ICA
Mor-Avi et al. (2008)	16	III-1	Low	Patients suspected of CM referred for ICA	Determining whether CM is ischaemic or non-ischaemic	ICA
Sramko et al. (2013)	42	II	Low	HF patients with DCM	Determining whether DCM has an inflammatory cause	EMB
Valle-Munoz et al. (2009)	100	II	Low	HF patients with LV dysfunction suspected of DCM	Determining whether DCM is ischaemic or non-ischaemic	ICA
Voigt et al. (2011)	23	II	Low	HF patients with NIDCM	Determining whether DCM has an inflammatory cause	EMB
Won et al. (2015)	83	II	Low	HF patients with LV dysfunction	Determining whether CM is ischaemic or non-ischaemic	ICA

Trial/Study	N	Level of evidence	Risk of bias	Patient population	Purpose of test	Reference standard
Yoshida, Ishibashi-Ueda et al. (2013)	136	III-1	Low	HF patients with LV hypertrophy or dysfunction	Diagnosing DCM (negative result = other CM, hypertensive heart disease or other)	Clinical data

I = SR of level II studies

II = study of test accuracy with an independent, blinded comparison with a valid reference standard, among consecutive patients with a defined clinical presentation

III-1 = study of test accuracy with an independent blinded comparison with a valid reference standard, among non-consecutive persons with a defined clinical presentation

III-2 = comparison with reference standard that does not meet the criteria for level II and III-1 evidence

III-3 = diagnostic case-control study

IV = study of diagnostic yield (no reference standard)

CAD = coronary artery disease; CM = cardiomyopathy; DCM = dilated cardiomyopathy; ECG = electrocardiogram; EMB = endomyocardial biopsy; HF = heart failure; ICA = invasive coronary angiography; LGE-CMR = late gadolinium enhancement; LV = left ventricular / left ventricle; LVEF = left ventricular ejection fraction: SR = systematic review

B3.3 Risk of Bias Assessment

The risk of bias for the 12 studies identified in the literature searches was assessed using the QUADAS-2 tool (Whiting et al. 2011). A summary of the risk of bias and the concerns regarding applicability are shown in Figure 6. The risk of bias for each of the available studies is listed in Table 10. 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, 8 out of 12 studies had a low risk of bias, 1 had a high risk of bias and 2 had an unclear risk of bias. Four studies did not specify whether the patient population had dilated LVs or included patients with varying types of CM.

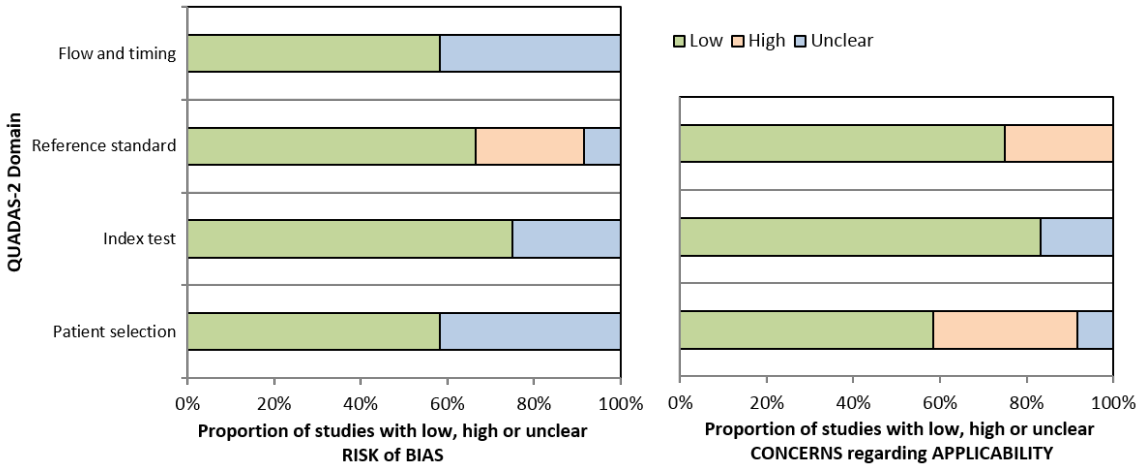


Figure 6 Summary of the risk of bias and applicability judgments for the 12 diagnostic accuracy studies

Table 10 Tabular presentation for QUADAS-2 results

	Risk of bias				Applica-bility concerns		
Study	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Assomull et al. (2011)	☺	?	☺	☺	☺	☺	☺
Bohnen et al. (2015)	?	☺	☹	☺	☹	?	☹
Casolo et al. (2006)	☺	☺	☺	☺	☺	☺	☺
de Melo et al. (2013)	?	?	?	?	☺	?	☺
Hamilton-Craig et al. (2011)	☺	☺	☺	☺	☺	☺	☺
McCrohon et al. (2003)	?	?	☺	?	?	☺	☺
Mor-Avi et al. (2008)	?	☺	☺	☺	☹	☺	☺
Sramko et al. (2013)	☺	☺	☹	☺	☺	☺	☹
Valle-Munoz et al. (2009)	☺	☺	☺	?	☺	☺	☺
Voigt et al. (2011)	☺	☺	☹	☺	☺	☺	☹
Won et al. (2015)	?	☺	☺	?	☹	☺	☺
Yoshida, Ishibashi-Ueda, et al. (2013)	☺	☺	☺	?	☹	☺	☺

☺ Low risk ☹ High risk ? Unclear risk

B3.4 CHARACTERISTICS OF THE EVIDENCE BASE

See Appendix C for details on the individual studies included in the evidence base.

The only study aimed at determining the diagnostic accuracy of LGE-CMR to diagnose DCM included patients with HF and LV dysfunction, which matches the proposed population as shown in Figure 1 and Figure 2.

In the included studies (k=7) where the aim was to determine whether (dilated) CM had an ischaemic or non-ischaemic cause, 2 studies included patients with HF symptoms; however, these studies did not report whether the patients had dilated LVs or were suspected of DCM (Mor-Avi et al. 2008; Won et al. 2015). One study was a case-control study and included both patients (63 DCM patients and 27 CAD patients) and control subjects with normal LV function (McCrohon et al. 2003). Four studies included patients with HF and LV dilation and dysfunction, referred for further investigation (Assomull et al. 2011; Casolo et al. 2006; Hamilton-Craig et al. 2012; Valle-Munoz et al. 2009). The study by Hamilton-Craig et al. (2011) was the only study based in Australia (n=28).

Of the 4 studies aimed at determining whether DCM had an inflammatory cause, only 1 did not report whether patients had dilated LVs. The other studies included patients with diagnosed DCM and a history of HF.

B3.5 OUTCOME MEASURES AND ANALYSIS

To assess the diagnostic accuracy of the proposed test, studies were included only if they provided data that could be extracted into a classic 2x2 table (Table 11), or if the data could be calculated from the sensitivity and specificity provided, in which case the results of the index test or the comparator were cross-classified against the results of the reference standard (Armitage et al. 2002; Deeks 2001), and Bayes' Theorem was applied:

Table 11 Diagnostic accuracy data extraction

		Reference standard (ICA, myocardial biopsy or available diagnostic data)		
		Disease +	*Disease –*	
LGE-CMR	*Test +*	true positive	false positive	Total test positive
or comparator	*Test –*	false negative	true negative	Total test negative
		Total with disease	Total without disease	

ICA = invasive coronary angiography; LGE-CMR = late gadolinium enhancement cardiac magnetic resonance (imaging)

The 2x2 data extraction tables for diagnostic performance are available upon request. Disease+ was defined as patients having either NIDCM or, in studies with EMB as the reference standard, inflammatory lesions or active myocarditis. A negative result indicated the diagnosis of CAD, ICM or other heart disease. In studies with EMB as the reference standard, no inflammatory lesions or the absence of myocarditis was seen as a true negative. 'Clinical data' was used to diagnose varying aetiologies or conditions, for example the type of CM or whether DCM had an ischaemic cause.

Primary measures

Test sensitivity was calculated as below and showed the proportion of patients with either NIDCM or myocarditis as determined by the reference standard, who had a 'positive test' on LGE-CMR (indicating either NIDCM or myocarditis / inflammatory lesions):

> Sensitivity (true positive rate) = number with true positive result on LGE-CMR / total with NIDCM or inflammatory lesions

Test specificity was calculated as the proportion of people without NIDCM or myocarditis / inflammatory lesions (but ICM or other heart disease) as determined by the reference standard, who had a 'negative test' on LGE-CMR (indicating either ICM or absence of myocarditis / inflammatory lesions):

> Specificity (true negative rate) = number with true negative result / total without NIDCM or inflammatory lesions

The 95%CI was calculated by exact binomial methods.

Positive and negative likelihood ratios (LR+ and LR–, respectively) were also reported (in section B4). These ratios measure the probability of the test result being true in patients with NIDCM or myocarditis and 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 2005a).

Summary measures

Due to differences in patient populations and reference standards, diagnostic test accuracy meta-analysis could not be undertaken. The 'midas' command in Stata version 14 (StataCorp 2014) was used to generate forest plots to show the sensitivity and specificity of LGE-CMR in the different studies. The results were narratively summarised and subdivided according to the purpose of the tests (e.g. diagnosing CMR, determining whether the cause of DCM was ischaemic or inflammatory, or other).

B3.6 RESULTS OF THE SYSTEMATIC LITERATURE REVIEW

Is it accurate?

Summary – What is the diagnostic accuracy of CMR in patients with HF symptoms in whom echocardiography is inconclusive or suggests a DCM, and in whom further diagnostic clarification is required, compared with ICA, SPECT, CTCA, , or contrast- or stress echocardiography?

Twelve studies were identified on diagnostic performance of LGE-CMR in the eligible patient population. Three test purposes for LGE-CMR in patients with HF symptoms were identified in the accuracy studies: (1) diagnosing DCM, (2) identifying whether DCM was of non-ischaemic or ischaemic aetiology, and (3) identifying whether DCM had an inflammatory aetiology.

Diagnosing DCM

One Japanese study provided diagnostic accuracy evidence on LGE-CMR to diagnose DCM in patients with CM, with clinical diagnosis as the reference standard (GRADE ⊕⊕⊕⊕). The study included 136 patients, and sensitivity and specificity of 0.83 (95%CI 0.71, 0.92) and 0.93 (95%CI 0.85, 0.97), respectively, were reported.

Determining non-ischaemic or ischaemic aetiology of DCM

Eight studies were included for determining the accuracy of LGE-CMR to determine whether DCM had a non-ischaemic or ischaemic aetiology using two different reference standards: ICA (k=6; GRADE ⊕⊕⊙⊙) and clinical diagnosis (k=2; GRADE ⊕⊕⊕⊕). The sensitivity ranged from 0.68 to 1.00 and the specificity from 0.71 to 1.00 in the different studies. An SROC curve showed excellent test performance for determining non-ischaemic aetiology when all studies were combined, indicating that some patients could potentially avoid ICA with LGE-CMR.

Determining inflammatory aetiology of DCM

Three studies investigated the diagnostic accuracy of LGE-CMR with the purpose of determining whether there was an inflammatory aetiology in patients with DCM, using EMB as the reference standard (GRADE ⊕⊕⊙⊙). The sensitivities ranged from 0.58 to 0.87 and the specificities from 0.33 to 0.50. LGE-CMR was less sensitive and less specific compared with the reference standard when used for this purpose than for the two purposes discussed above. Furthermore, when EMB was used for the purpose of diagnosing DCM and was compared with clinical diagnosis as a reference standard, it performed poorly at identifying patients who did not have DCM, raising questions about the quality of the reference standard.

Reference standards and comparators

ICA was compared with clinical diagnosis to determine the quality of the reference standard. The sensitivities were excellent in the two included studies, although the specificities varied.

CTCA, ICA, GHPS, stress and contrast echocardiography, and SPECT were identified as the comparators for LGE-CMR. Data regarding the diagnostic performance of LGE-CMR against the main comparators was lacking. Only 2 studies compared ICA with LGE-CMR, and 1 small study (n=28) comparing the accuracy of CTCA and LGE-CMR using ICA as the reference standard in determining non-ischaemic aetiology was identified. The results showed that CTCA and LGE-CMR are both highly sensitive, but the overlapping wide 95%CIs surrounding the disparate specificity values suggest that any conclusions regarding the comparative specificity of the two tests should be tentative. No difference in diagnostic performance was observed between ICA and LGE-CMR in diagnosing NIDCM.

An additional broader search for SRs on the diagnostic performance of comparator tests in the eligible patient populations to enable an indirect comparison could not identify any additional evidence.

B3.6.1 Diagnostic accuracy of LGE-CMR in diagnosing DCM

One study was identified that included patients with HF and LV dysfunction and aimed to diagnose the type of CM (Yoshida, Ishibashi-Ueda et al. 2013). This level III-1 study compared CMR with EMB,

with clinical diagnosis as the reference standard. Clinical data used in the diagnosis was defined as the results from any method that could be used to diagnose HF including echocardiography, CMR and EMB. This included the collection of a patient's medical history, laboratory tests, scintigraphy and coronary angiography. The final diagnosis was made prior to patient discharge by an expert team of cardiologists using all the available data, including the results of EMB, CMR and other diagnostic modalities. A diagnosis of DCM was considered a positive result. The overall quality of the evidence provided by this study in assessing the diagnostic accuracy of LGE-CMR compared with clinical diagnosis was assessed using GRADE (Guyatt et al. 2011), and was graded as high quality (⊕⊕⊕⊕).

When CMR was used to diagnose DCM, sensitivity and specificity of 0.83 and 0.93, respectively, were reported (Yoshida, Ishibashi-Ueda et al. 2013) (Table 12).

Table 12 Sensitivity and specificity of LGE-CMR in diagnosing DCM when available diagnostic data is used as the reference standard

Author	N	Population	Purpose of test	Sensitivity (95%CI)	Specificity (95%CI)
Yoshida, Ishibashi-Ueda et al. (2013)	136	HF patients with LV hypertrophy or dysfunction	Diagnosing DCM (negative result = other CM, hypertensive heart disease or other)	0.83 (0.71, 0.92)	0.93 (0.85, 0.97)

CI = confidence interval; CM = cardiomyopathy; DCM = dilated cardiomyopathy; HF = heart failure; LGE-CMR = late gadolinium enhancement cardiac magnetic resonance (imaging); LV = left ventricular

B3.6.2 Diagnostic accuracy of LGE-CMR in determining the aetiology of NIDCM in patients with a low risk of CAD

DIAGNOSTIC ACCURACY OF LGE-CMR COMPARED WITH EMB AS REFERENCE STANDARD

Three studies were included that investigated the diagnostic accuracy of LGE-CMR compared with EMB in patients with HF symptoms and impaired LVEF (Bohnen et al. 2015; Sramko et al. 2013; Voigt et al. 2011). Patients underwent EMB and LGE-CMR to determine whether inflammation was the cause of CM symptoms. The study by Bohnen et al. (2015), which had a medium risk of bias, did not report whether patients had dilated LVs. The remaining studies were of low risk of bias and included patients with diagnosed DCM and a history of HF to determine the cause of the disease.

The overall quality of the evidence provided by these studies in assessing the diagnostic accuracy of LGE-CMR compared with EMB was assessed using GRADE (Guyatt et al. 2011), and the results are presented in Table 13. The evidence base for this section was graded as being of low (⊕⊕⊙⊙) quality.

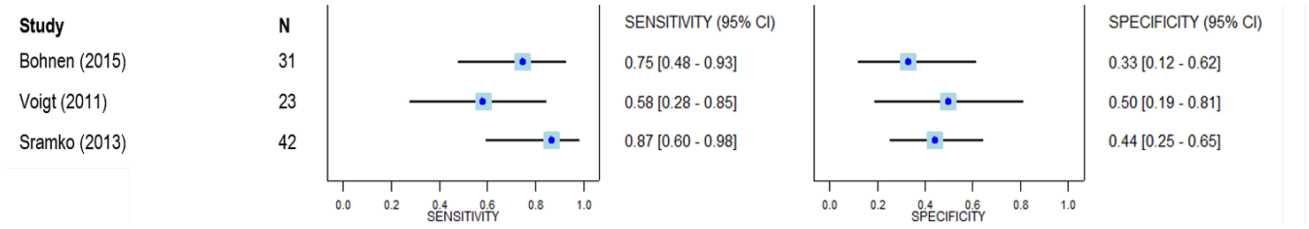


Figure 7 Forest plot showing the sensitivity and specificity of LGE-CMR compared with EMB in diagnosing inflammation

Figure 7 shows the sensitivity and specificity of LGE-CMR for the detection of inflammation, with EMB as the reference standard. The presence of LGE was used in all 3 studies to determine

inflammation. Active myocarditis was defined by ongoing inflammation on EMB (Bohnen et al. 2015). Due to the lack of available studies and the differences in study population, no meta-analysis was conducted. The sensitivity of LGE-CMR varied from 0.58 (95%CI 0.28, 0.85) to 0.87 (95%CI 0.60, 0.98), and the specificity was low, varying from 0.33 (95%CI 0.12, 0.62) to 0.50 (95%CI 0.19, 0.81).

DIAGNOSTIC ACCURACY OF LGE-CMR 'LAKE LOUISE CRITERIA' COMPARED WITH EMB AS REFERENCE STANDARD

In addition to the 'presence of LGE', the 'Lake Louise criteria' were also used to define inflammation in 2 studies (Bohnen et al. 2015; Voigt et al. 2011). The International Consensus Group on Cardiovascular Magnetic Resonance in Myocarditis developed recommendations for the diagnosis of myocardial inflammation (i.e. the 'Lake Louise criteria' (LL)) (Voigt et al. 2011). This includes a comprehensive CMR protocol, which involves assessment of global myocardial oedema, global relative enhancement (e.g. myocardial hyperaemia), and LGE with non-ischaemic regional distribution. For LL to be positive for inflammation, ≥2 of the 3 tissue-based criteria have to be positive. The sensitivity and specificity of CMR using the LL criteria are shown in Figure 8, with EMB as the reference standard. The specificity varied significantly between the 2 studies, from 0.07 (95%CI 0.00, 0.32) to 0.73 (95%CI 0.39, 0.94), whereas the 95%CIs for the sensitivity were overlapping, with 0.88 (95%CI 0.62, 0.98) in Bohnen et al. (2015) and 0.75 (95%CI 0.43, 0.95) in Voigt et al. (2011). The study by Bohnen et al. (2015) was of medium risk of bias and it was not known whether these patients had dilated LVs as well as HF symptoms. The study by Voigt et al. (2011) was of low risk of bias and included patients with DCM. It is not known whether this would have caused the difference in specificity.

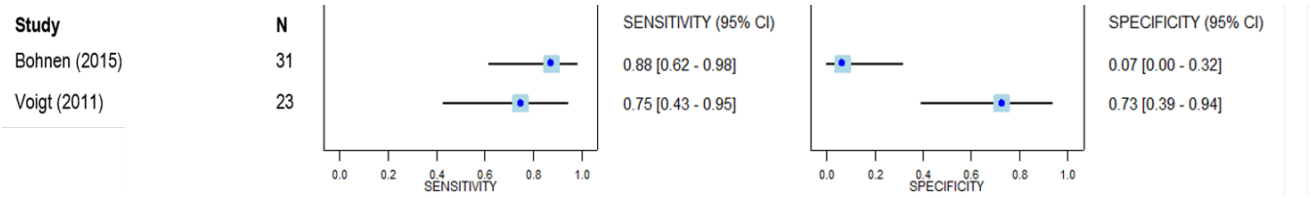


Figure 8 Forest plot showing the sensitivity and specificity of the 'Lake Louise criteria' measured with CMR compared with EMB in diagnosing inflammation

DIAGNOSTIC ACCURACY OF EMB COMPARED WITH CLINICAL DIAGNOSIS AS REFERENCE STANDARD

One study, which included 136 patients who were admitted for the management of HF, compared the accuracy of EMB with available diagnostic data in diagnosing DCM (Yoshida, Ishibashi-Ueda et al. 2013). The sensitivity and specificity of EMB in diagnosing DCM were 0.89 (95%CI 0.77, 0.96) and 0.71 (95%CI 0.58, 0.79), respectively. This study also assessed the accuracy of LGE-CMR compared with clinical diagnosis. Its sensitivity was similar (0.83; 95%CI 0.71, 0.92); however, the specificity of LGE-CMR was significantly higher than for EMB when they were compared with clinical diagnosis (0.93, 95%CI 0.84, 0.98 vs 0.71, 95%CI 0.58, 0.79). The superior performance of LGE-CMR raises questions about the suitability of EMB as a reference standard. Thus, the proportion of patients that do not have DCM who are correctly identified would be higher with LGE-CMR compared with EMB. However, this study does not inform on the accuracy of LGE-CMR and EMB when used to determine whether DCM has an inflammatory cause or not.

B3.6.3 Diagnostic accuracy of LGE-CMR in diagnosing whether DCM has a non-ischaemic or ischaemic cause in patients with an intermediate risk of CAD

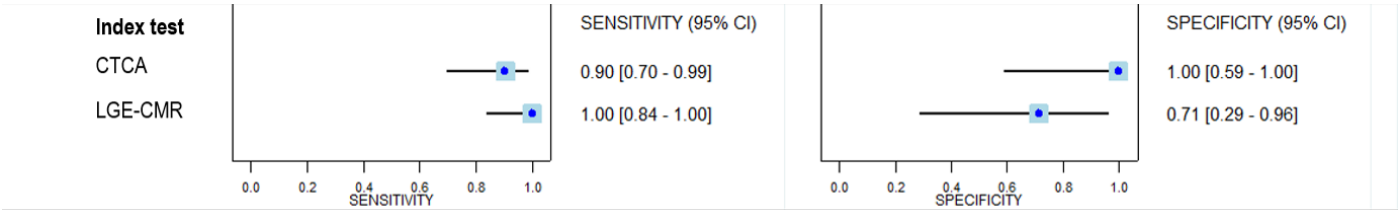
DIAGNOSTIC ACCURACY OF LGE-CMR COMPARED WITH CTCA AND ICA

CTCA, SPECT, GHPS, contrast- and stress echocardiography, and ICA were identified as the comparators for LGE-CMR, as shown in the proposed clinical pathways (Figure 2 and Figure 4). One small study that included 28 patients suspected of DCM compared the accuracy of CTCA and LGE-

CMR using ICA as the reference standard (Hamilton-Craig et al. 2012), and 2 studies were identified comparing ICA and LGE-CMR with available diagnostic data as the reference standard. When a separate search was conducted for SRs on the diagnostic performance of comparator tests in the eligible patient population to obtain more diagnostic information on the comparators, no SRs were identified (see section B3.2).

No studies that were included for diagnostic performance compared LGE-CMR and SPECT with a common reference standard.

Figure 9 shows that both CTCA and LGE-CMR are both highly sensitive when ICA was used as the reference standard. The specificity appeared to be much higher for CTCA than for LGE-CMR (1.00, 95%CI 0.59, 1.00 vs 0.71. 95%CI 0.29, 0.96, respectively), but the wide CIs overlapped. The lack of significance was most likely due to the small size of the study. Consequently, any conclusions regarding the comparative accuracy of the 2 tests should be tentative.



Data extracted from Hamilton-Craig et al. (2011; N=28). Reference standard is ICA

Figure 9 Forest plot showing the sensitivity and specificity of CTCA and LGE-CMR compared with ICA in diagnosing whether HF symptoms are of ischaemic aetiology (true positive = non-ischaemic DCM)

Figure 10 shows the sensitivity and specificity of ICA and LGE-CMR with available diagnostic data as the reference standard. These studies were also included in section B3.6.4, comparing ICA with available diagnostic data. It is shown that, in the larger study, there is no difference in sensitivity and specificity between ICA and LGE-CMR. The smaller study shows a lower specificity with ICA, although this difference is not statistically significant, and is possibly due to the small sample size.

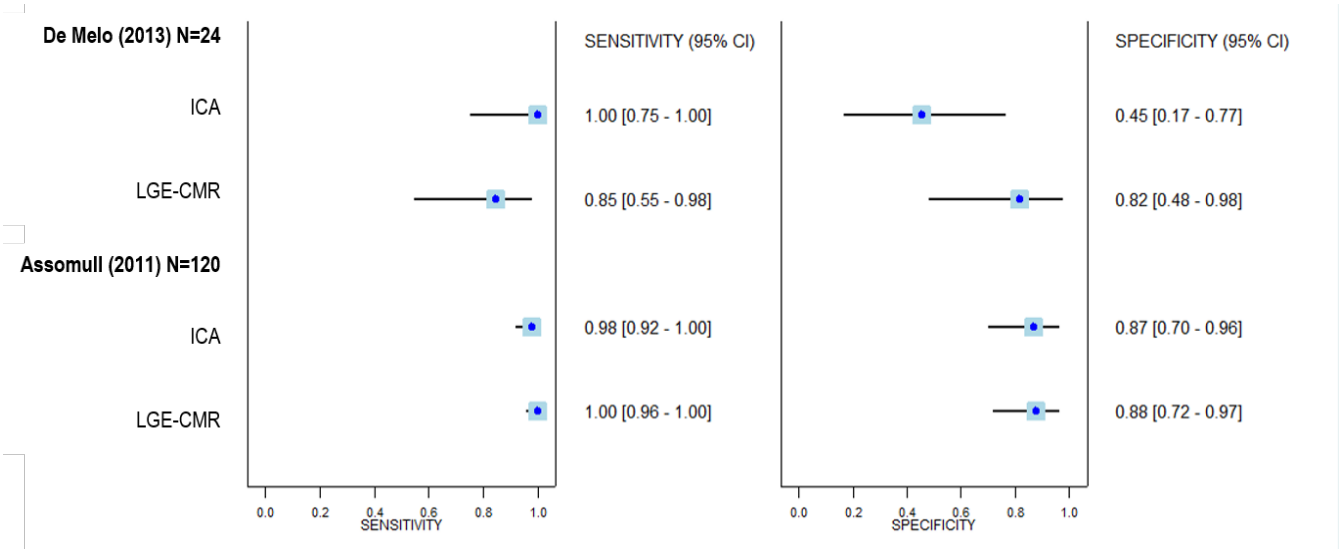


Figure 10 Forest plot showing the sensitivity and specificity of ICA and LGE-CMR compared with available diagnostic data in diagnosing NIDCM

DIAGNOSTIC ACCURACY OF LGE-CMR COMPARED WITH ICA AS REFERENCE STANDARD

Six studies investigated the diagnostic accuracy of LGE-CMR compared with ICA in the eligible patient population, to determine whether the cause of the symptoms was ischaemic or non-ischaemic. The overall quality of the evidence provided by these studies in assessing the diagnostic accuracy of LGE-CMR compared with ICA was assessed using GRADE (Guyatt et al. 2011), and the results are presented in Table 13. The evidence base for this section was graded as low (⊕⊕⊙⊙) quality.

Different cut-off values for ICA were used for diagnosing ischaemia: a cut-off of 50% diameter stenosis (DS) in ≥1 coronary arteries was used in 3 studies (Hamilton-Craig et al. 2012; McCrohon et al. 2003; Mor-Avi et al. 2008), 70% DS in 2 (Valle-Munoz et al. 2009; Won et al. 2015) and 75% DS in 1 (Casolo et al. 2006). Due to the differences in patient population and reference standards used, no meta-analysis was conducted. The sensitivities and specificities of the included studies (based on the 2x2 data extracted) are shown in a forest plot in Figure 11. When excluding studies that did not limit the population to patients with dilated LVs, the sensitivity of LGE-CMR compared with ICA for 'diagnosing non-ischaemic cause' of DCM ranged between 0.84 (95%CI 0.60, 0.97) and 1.00 (95%CI 0.84, 1.00), and the specificity ranged from 0.71 (95%CI 0.29, 0.96) to 1.00 (95%CI 0.87, 1.00). In the 2 studies where the type of CM was not defined, the sensitivity and specificity ranged from 0.68 (95%CI 0.53, 0.81) to 0.78 (95%CI 0.40, 0.97), and from 0.89 (95%CI 0.74, 0.97) to 1.00 (95%CI 0.59, 1.00), respectively.

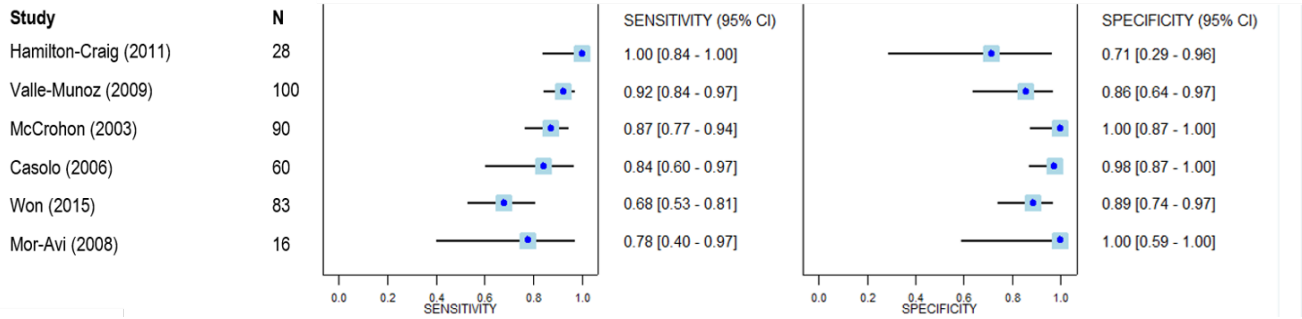


Figure 11 Forest plot showing the sensitivity and specificity of LGE-CMR compared with ICA in diagnosing NIDCM

DIAGNOSTIC ACCURACY OF LGE-CMR COMPARED WITH CLINICAL DIAGNOSIS AS REFERENCE STANDARD

Two studies investigated the diagnostic accuracy of LGE-CMR using available diagnostic data as the reference standard, to determine whether the cause of patients' HF symptoms was ischaemic or non-ischaemic (Assomull et al. 2011; de Melo et al. 2013). The study by de Melo et al. was a level III-1 study, included DCM patients, used ICA as a comparator, and used available diagnostic data specified as 'global analysis of cases by two clinical cardiologists, including all data in clinical history and laboratory tests available in medical records' as the reference standard. The study by Assomull et al. was a level II study and included patients suspected of DCM, where the reference standard was defined as a review of all the available diagnostic data, including tissue characterisation information from LGE-CMR and luminographic data from ICA, reviewed by a separate consensus group of three cardiologists (Assomull et al. 2011). This study, which provided the highest quality evidence with a large patient population (n=120) reported a sensitivity of 1.00 (95%CI 0.96, 1.00) and a specificity of 0.88 (0.72, 0.97) for diagnosing non-ischaemic cause of DCM (Figure 12). The overall quality of this evidence was graded as high (⊕⊕⊕⊕).

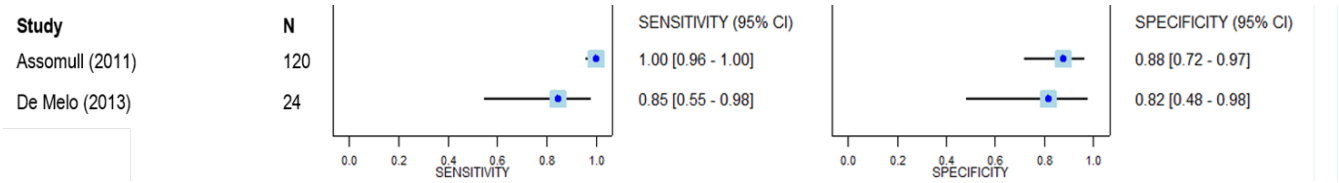


Figure 12 Forest plot showing the sensitivity and specificity of LGE-CMR when available diagnostic data is used as the reference standard

All included studies where LGE-CMR was used to determine non-ischaemic aetiology were combined in a summary receiver operating characteristic curve (SROC) to get an idea of the relative trade-offs between true positives and false positives in these studies (see Figure 13). The light blue dots show the studies with 'available diagnostic data' as the reference standard, whereas the dark blue dots depict the studies with ICA as the reference standard. The figure shows that all studies lie in the upper left corner of the graph and would have a high area under the ROC curve (AUROC) value if they were suitable for meta-analysis, indicating that CMR performs well when compared with the reference standard.

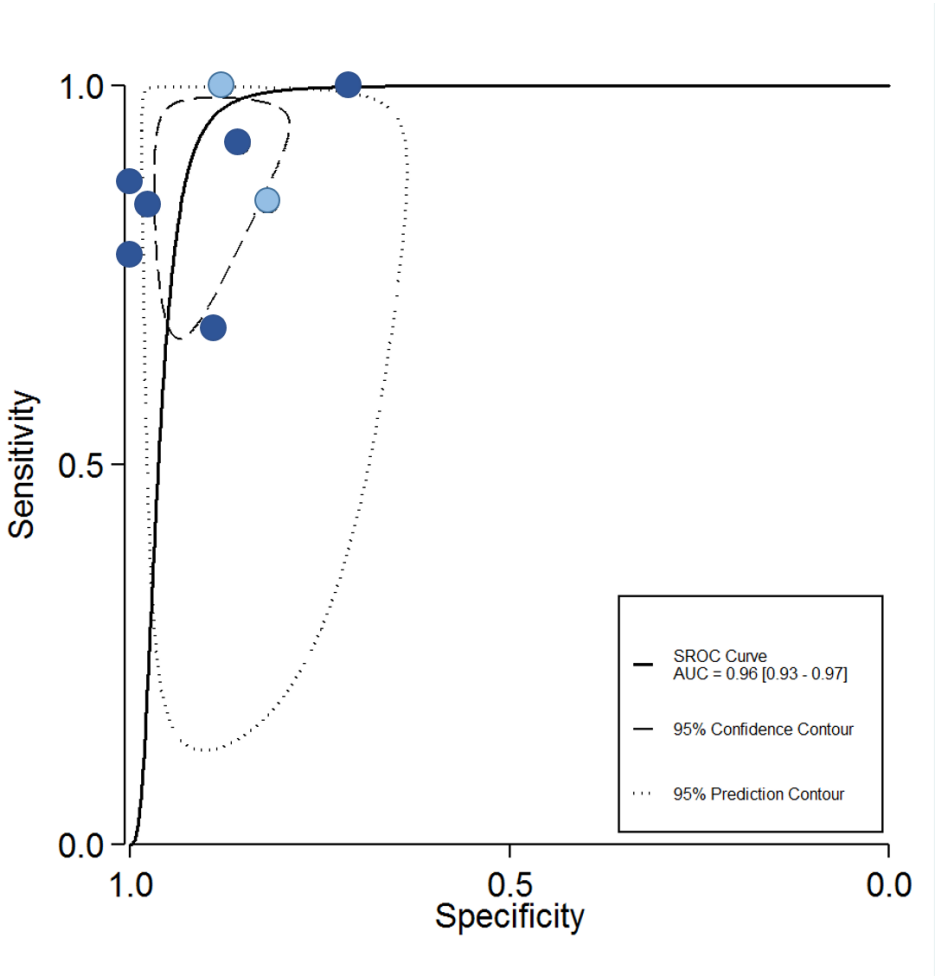


Figure 13 SROC of diagnostic accuracy of LGE-CMR in determining non-ischaemic aetiology

DIAGNOSTIC ACCURACY OF ICA COMPARED WITH CLINICAL DIAGNOSIS AS REFERENCE STANDARD

Two studies compared ICA with clinical diagnosis as the reference standard in patients with or suspected of NIDCM (Assomull et al. 2011; de Melo et al. 2013). The sensitivity of ICA compared with the 'gold standard' of clinical diagnosis defined by the synthesis of all available clinical information

was 1.00 (95%CI 0.75, 1.00) in the small study by de Melo et al. (n=24) and 0.98 (95%CI 0.92, 1.00) in the larger study by Assomull et al., which had 120 included patients (see Figure 14). The larger study reported a specificity of 0.87 (95%CI 0.70, 0.96), whereas the small study only showed a specificity of 0.45 (95%CI 0.17, 0.77). This means that, in the study by de Melo et al. (2013), only 45% of patients with an ischaemic cause of DCM were correctly identified as having ischaemic DCM on ICA.

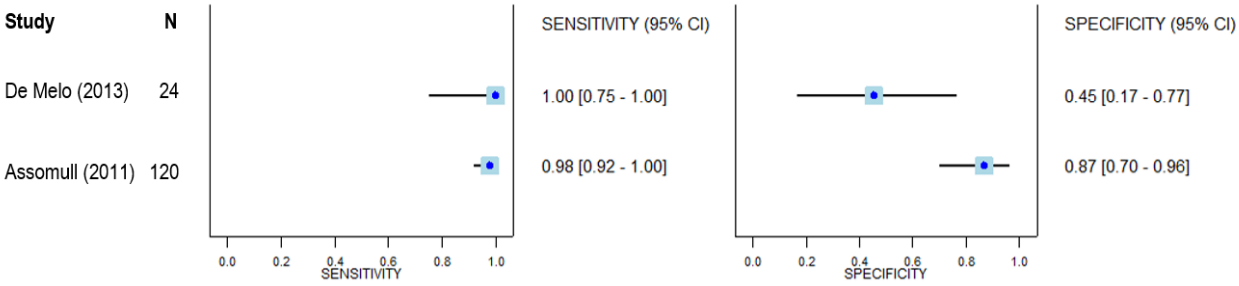


Figure 14 Forest plot showing the sensitivity and specificity of ICA compared with available diagnostic data in diagnosing NIDCM

B3.6.4 Summary of findings

Table 13 shows the summary of findings for the accuracy of LGE-CMR compared with the different reference standards identified when used for the different purposes as outlined in the proposed clinical pathway (see Figure 4). The studies with available diagnostic data as the reference standard were considered to provide high-quality evidence according to GRADE (the complete GRADE evidence profiles are shown in 86 in Appendix D).

Table 13 Summary of findings for the accuracy of LGE-CMR in patients suspected of DCM or patients with DCM and an unknown aetiology

Aim of the test	No. of participants No. of studies	Sensitivity and specificity of LGE-CMR (individual or range from studies)	Reference standard	Quality of evidence [a]
Diagnose DCM	N=136 patients K=1 study	Sensitivity: 0.89 (95%CI 0.77, 0.96) Specificity: 0.70 (95%CI 0.58, 0.79)	Clinical diagnosis	High ⊕⊕⊕⊕
Determine non-ischaemic cause	N=377 K=6 studies	Sensitivity: 0.68–1.00 Specificity: 0.71–1.00	ICA	Low ⊕⊕⊙⊙
	N=144 patients K=2 studies	Sensitivity: 0.85–1.00 Specificity: 0.82–0.88	Clinical diagnosis	High ⊕⊕⊕⊕
Determine inflammatory cause	N=97 patients K=3 studies	Sensitivity: 0.58–0.87 Specificity: 0.33–0.50	Biopsy	Low ⊕⊕⊙⊙

[a] GRADE Working Group grades of evidence (Guyatt et al. 2013):

⊕⊕⊕⊕ 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.

DCM = dilated cardiomyopathy; ICA = invasive coronary angiography; K = number of studies; LGE-CMR = late gadolinium enhancement cardiac magnetic resonance (imaging); N = number of patients

B3.7 EXTENDED ASSESSMENT OF RELIABILITY OF EVIDENCE

The term *reliability* (which is analogous to the concept of *precision*) refers to the amount of agreement between/among different operators or instruments applying the same investigative medical service; that is, a reliable investigative medical service is measuring something consistently. Reliability is sometimes referred to as *reproducibility* or *repeatability*.

No studies were identified that included reproducibility analysis of either LGE-CMR or the main comparators in the patient population.

B3.8 CONCORDANCE ANALYSIS

No studies were identified that examined the concordance between LGE-CMR and one of the comparators in the eligible patient population.

B3.9 INTERPRETATION OF EVIDENCE ON DIAGNOSTIC PERFORMANCE

CTCA, ICA, GHPS, contrast and stress echocardiography, and SPECT were identified as the comparators for LGE-CMR, as shown in the proposed clinical pathways (see Figure 2 and Figure 4). Data regarding the diagnostic performance of LGE-CMR against the main comparators was lacking. Only 1 small study, including 28 patients suspected of DCM, that compared the accuracy of CTCA and LGE-CMR using ICA as the reference standard (Hamilton-Craig et al. 2012) was identified, and only 2 studies compared ICA with LGE-CMR (with clinical diagnosis as the reference standard). An even broader search for SRs on the diagnostic performance of comparator tests in the eligible patient populations to enable an indirect comparison could not identify any suitable studies (see section B3.2).

The included study showed that both CTCA and LGE-CMR are both highly sensitive, but the overlapping wide 95%CIs surrounding the disparate specificity values suggest that any conclusions regarding the comparative specificity of the two tests should be tentative.

When assessing the diagnostic performance of LGE-CMR, three different test purposes were identified. Only 1 study provided evidence for determining the accuracy of using LGE-CMR to diagnose DCM in patients with CM. This study reported a high sensitivity and a questionable specificity when LGE-CMR was compared with clinical diagnosis (see Table 11). Although the study had a low risk of bias, it was conducted in Japan and there are some concerns regarding its applicability to the Australian population.

Eight studies provided evidence for assessing the accuracy of LGE-CMR to determine whether DCM had a non-ischaemic or ischaemic aetiology using two different reference standards: ICA (k=6) and clinical diagnosis (k=2). The sensitivity ranged from 0.68 to 1.00, and the specificity from 0.71 to 1.00, in the different studies. Even though the populations of the included studies varied slightly and different reference standards were used, when the sensitivity and specificity values for each study were plotted on an SROC curve the studies were all in the upper left corner, indicating an excellent test performance for determining non-ischaemic aetiology of DCM. This could potentially result in some patients avoiding an invasive ICA.

Three studies investigated the diagnostic performance of LGE-CMR in determining whether there was an inflammatory aetiology in patients with DCM, using EMB as the reference standard. LGE-CMR was less sensitive and less specific compared with the reference standard when used for this purpose than for the two purposes discussed above. As LGE is also frequently found in DCM patients

without immunohistologically proven myocardial inflammation, the diagnostic performance of LGE-CMR was insufficient for reliable diagnosis of myocardial inflammation in patients with DCM (Voigt et al. 2011). Conversely, when biopsy was used for the purpose of diagnosing DCM and was compared with clinical diagnosis as a reference standard, it performed poorly at identifying patients who did not have DCM. As LGE-CMR had a higher specificity when compared with clinical diagnosis of DCM, it is likely to be more accurate than EMB when used for this purpose.

ICA was compared with clinical diagnosis to determine the quality of the reference standard (section B3.6.4). The sensitivity was excellent in the 2 included studies, although the specificity varied. The study that provided the best-quality evidence reported a good specificity. Nevertheless, due to the small number of studies and the limited sample sizes, any conclusions should be tentative.

B4 CLINICAL VALIDITY

B4.1 MEASURES OF CLINICAL VALIDITY

The clinical validity of a test depends on the prevalence or pre-test probability (PTP) of the outcome of interest. In this case it is DCM diagnosis or diagnosing the aetiology of DCM.

The key measures used are positive and negative predictive values (PPV and NPV), which are the probabilities of a patient with CM symptoms having DCM, or the probabilities of a patient with idiopathic DCM having a non-ischaemic or inflammatory cause. The PPV and the NPV are dependent on the prevalence of DCM in patients with CM or the prevalence of non-ischaemic or inflammatory aetiology in DCM. The likelihood ratio (LR) is the likelihood that a given test result would be expected in a patient with the outcome (e.g. DCM) compared with the likelihood that the same result would be expected in a patient without the outcome (e.g. CAD, hypertrophic cardiomyopathy (HCM) or other).

Information regarding the Australian prevalence of all outcomes of interest was lacking. In the only study that used LGE-CMR to diagnose DCM, 39.7% of the patients with CM were diagnosed with DCM using the reference standard (Yoshida, Ishibashi-Ueda et al. 2013). It should also be noted that this study was conducted in Japan and its applicability to the Australian population is unknown. The mean prevalence of a non-ischaemic aetiology in patients with idiopathic DCM using ICA as the reference standard was 63.1% (range 31.7–79%; k=6), and 69.4% (range 54.2–72.5%; k=2) when clinical diagnosis was used as the reference standard. These studies mostly included patients without a history or evidence of CAD, and patients in which more information on aetiology was needed after standard tests had been conducted. Thus, these patients fit the patient population outlined in the proposed clinical pathway (see Figure 4). The only Australian study, a small one (n=28) conducted by Hamilton-Craig et al. (2011), reported that 75% of patients with idiopathic DCM had a non-ischaemic aetiology. The 3 studies that used EMB to diagnose inflammation in patients with DCM reported a combined prevalence of inflammatory aetiology of 45.4% (range 35.7–52.2%) among DCM patients. These prevalence rates also have to be interpreted with caution, as it is unknown if they are applicable to the Australian population, and as most of these patients were already suspected of having 'non-ischaemic aetiology' or 'inflammatory aetiology', these rates may be higher than in the general DCM populations presenting for further testing.

B4.1.1 to B4.1.4

The studies that provide data to inform on clinical validity are the same as those that provide diagnostic performance data in section B3. Thus, see sections B3.1 to B3.5 for descriptions of the risk of bias, the characteristics of the evidence base, outcome measures and analysis of these studies.

B4.1.5 Results of the systematic literature review

Is it accurate?

Summary – What is the clinical validity of LGE-CMR in patients with HF symptoms and suspected of DCM?

The studies that provide data to inform on clinical validity are the same as those that provide diagnostic performance data. An LR scattergram was presented and PPVs and NPVs were given to determine clinical validity.

For the purpose of diagnosing DCM, the LRs from the study by Yoshida, Ishibashi-Ueda et al. (2013) indicate that LGE-CMR is conclusive for correctly confirming DCM and likely to correctly exclude DCM. LRs were inconclusive for correctly confirming or excluding inflammatory aetiology in all 3 studies included for this purpose.

However, for determining non-ischaemic aetiology, the combination of LR values showed that LGE-CMR could likely be used to both confirm and exclude non-ischaemic cause (LR+ = 10.8 and LR– = 0.09).

LGE-CMR had the highest PPV when it was used to diagnose non-ischaemic DCM: 95 out of 100 patients (i.e. 95%) would be correctly identified as having non-ischaemic aetiology, compared with only 46–58 out of 100 patients when determining inflammation. Similarly, the NPVs were 86% and 50–86%, respectively, for determining ischaemia and not having inflammation. When LGE-CMR was used to diagnose DCM, 12% of patients diagnosed as having DCM on LGE-CMR and 11% of patients diagnosed as not having DCM would be misclassified.

The LRs were calculated for LGE-CMR, as shown in Table 14 and Figure 15. LR scattergrams plot LR+ against LR–, where the likelihood of correctly identifying DCM (yellow), non-ischaemic aetiology (blue) or inflammatory aetiology (orange) increases along the x-axis and the likelihood of correctly eliminating the presence of DCM, non-ischaemic aetiology or inflammatory aetiology decreases along the y-axis in Figure 15.

Table 14 Likelihood ratios and predictive values for LGE-CMR compared with reference standards

Intervention and purpose of test	Study/studies *Mean prevalence (range)*	Number of studies/ patients	LR+ (95%CI)	LR– (95%CI)	PPV	NPV
LGE-CMR in diagnosing DCM (ref std.: clinical diagnosis)	Yoshida, Ishibashi-Ueda et al. (2013) *39.7%*	K=1 N=136	11.4 (5.2, 24.8)	0.18 (0.10, 0.33)	88%	89%
LGE-CMR in diagnosing non-ischaemic aetiology (ref std.: ICA)	See section B3.6.2 *63.1% (31.7–79%)*	K=6 N=377	12.9 (5.0, 33.5)	0.14 (0.07, 0.27)	95%	81%
LGE-CMR in diagnosing non-ischaemic aetiology (ref std.: ICA or clinical diagnosis)	See section B3.6.2 *65% (31.7–79%)*	K=8 N=521	10.8 (6.1, 19.0)	0.09 (0.04, 0.23)	95%	86%
LGE-CMR in diagnosing inflammatory aetiology (ref. std.: EMB)	Sramko et al. (2013) Voigt et al. (2011) Bohnen et al. (2015) *45.4% (35.7–52.2%)*	N=42 N=23 N=31	1.56 (1.05, 2.31) 1.17 (0.53, 2.55) 1.13 (0.71, 1.78)	0.30 (0.08, 1.17) 0.83 (0.33, 2.08) 0.75 (0.25, 2.28)	46% 58% 55%	86% 50% 56%

CI = confidence interval; CMR = cardiac magnetic resonance (imaging); DCM = dilated cardiomyopathy; EMB = endomyocardial biopsy; ICA = invasive coronary angiography; K = number of studies; LGE = late gadolinium enhancement; LR+ = positive likelihood ratio; LR– = negative likelihood ratio; N = number of patients; NPV = negative predictive value; PPV = positive predictive value

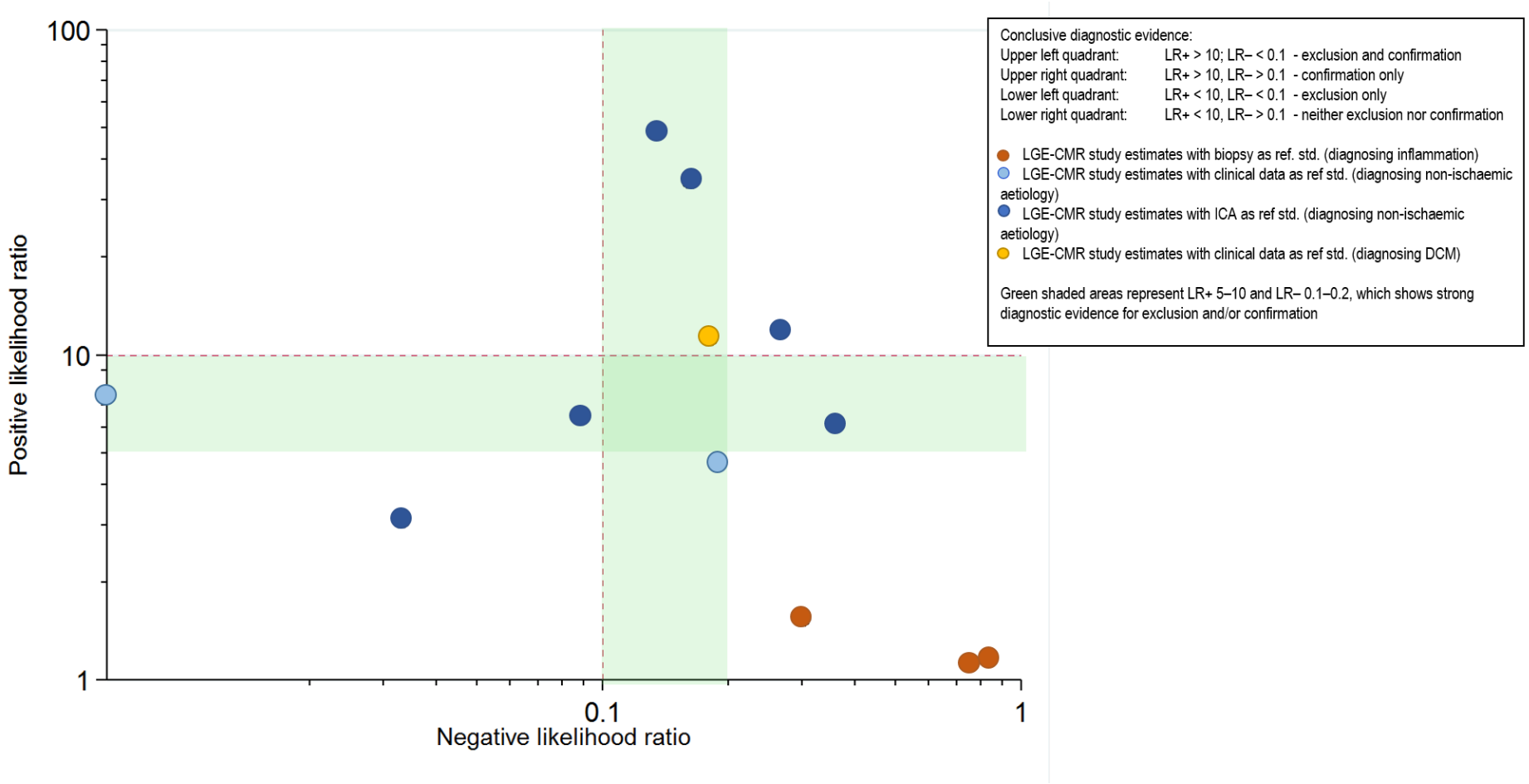


Figure 15 Likelihood ratio scattergram for the diagnosis of DCM / inflammatory aetiology / non-ischaemic aetiology (all included studies on diagnostic performance)

LGE-CMR = late gadolinium enhancement cardiac magnetic resonance (imaging); LR– = negative likelihood ratio; LR+ = positive likelihood ratio

The LRs from the study reporting on the accuracy of diagnosing DCM with LGE-CMR compared with a clinical diagnosis fall within the upper right quadrant of the scattergram (yellow dot in Figure 15). This represents LR+ values conclusive for correctly confirming DCM. Even though the study estimates are not conclusive for excluding DCM (LR– >0.1), it still lies within the 0.1–0.2 range, which means that it is still a strong indicator that a 'negative test result' is likely to correctly exclude DCM.

The LRs from all 3 studies reporting on the accuracy of LGE-CMR compared with EMB in diagnosing inflammatory aetiology are in the lower right quadrant of the scattergram (orange dots in Figure 15). This represents LR values inconclusive for correctly confirming or excluding inflammatory aetiology, and suggests that LGE-CMR does not provide any useful information to either confirm or exclude an inflammatory aetiology.

The 8 studies reporting on the accuracy of LGE-CMR in diagnosing non-ischaemic aetiology compared with either clinical diagnosis (light blue dots) or ICA (dark blue dots) are spread over three quadrants. However, a pooled estimate would fall within the upper left quadrant of the scattergram (LR+ = 10.8 and LR– = 0.09 (Table 12), which would indicate that LGE-CMR can be used to both confirm and exclude non-ischaemic cause in DCM.

The NPVs and PPVs for LGE-CMR were calculated using the prevalences discussed in section B4.1 and the LR values shown in Table 14. LGE-CMR had the highest PPV when it was used to diagnose non-ischaemic DCM. A PPV of 95% means that 95 out of 100 patients with a 'positive' result on LGE-CMR (indicating a non-ischaemic aetiology) would be correctly classified, compared with only 46–58 out of 100 patients being correctly classified when LGE-CMR was used to determine inflammation (with EMB as the reference standard). Similarly, 86 out of 100 patients diagnosed with ischaemic DCM by LGE-CMR would be correctly classified, compared with only 50–86 patients diagnosed as not having a myocardial inflammation. When LGE-CMR was used to diagnose DCM, 12 out of 100 patients diagnosed as having DCM on LGE-CMR, and 11 out of 100 patients diagnosed as not having DCM, would be misclassified.

B4.2 Prognosis or Predisposition

B4.2.1 Results of literature search

The Decision Analytic Protocol prepared for this assessment did not explicitly pose a research question related to the use of CMR for determining the prognosis of patients with DCM. However, scoping searches of the literature showed that CMR is more frequently used for prognostic purposes rather than diagnostic. The prognostic value of CMR was therefore assessed.

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 section A9) (Liberati et al. 2009).

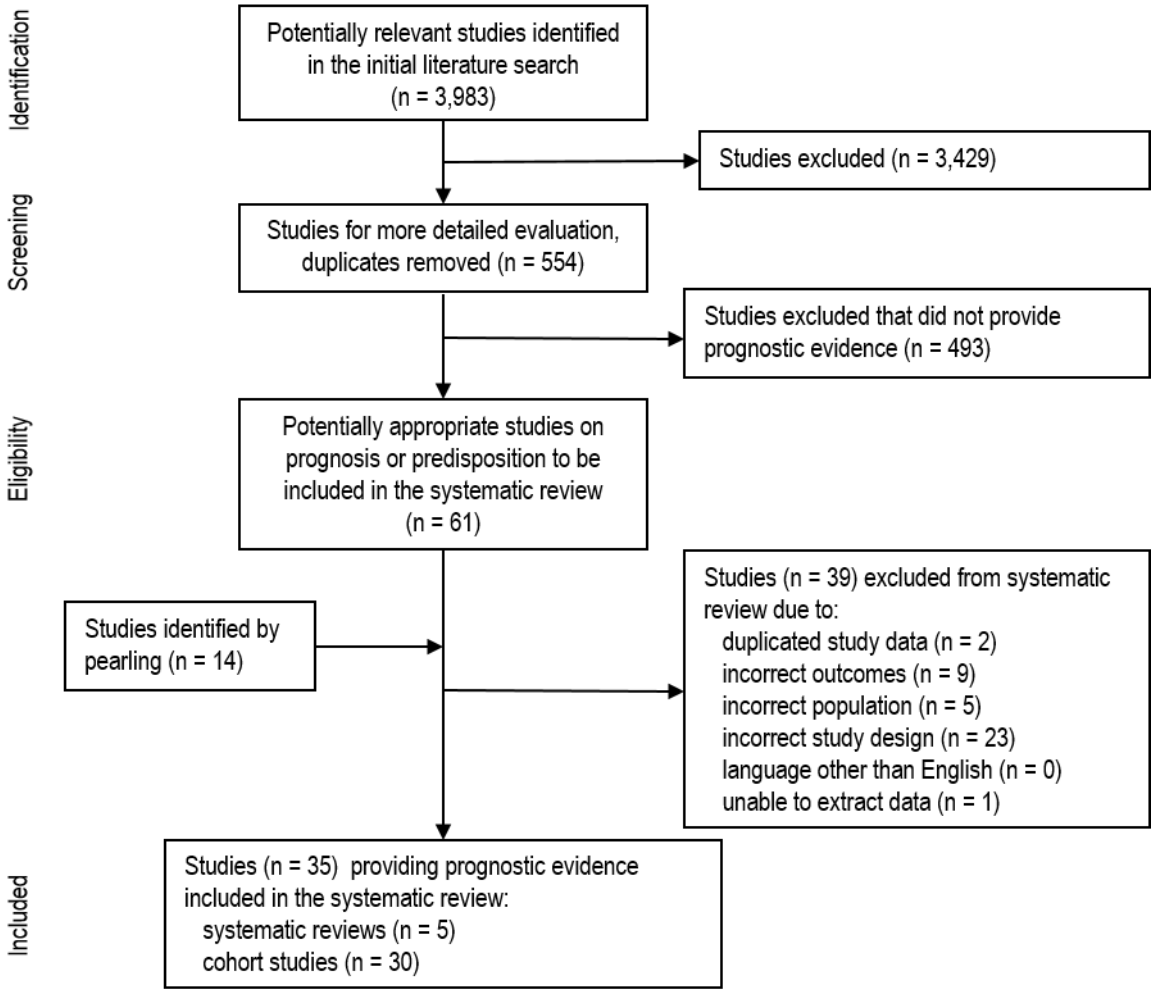


Figure 16 Summary of the process used to identify and select studies for the assessment of the prognostic value of LGE-CMR for patients with DCM

Those studies that technically met the inclusion criteria but were not included in the results section or meta-analyses are listed in Appendix E.

B4.2.2 Characteristics of the evidence base and risk of bias assessment

Four SRs were identified in the systematic literature search that reported on the prognostic value of scar tissue identified by LGE-CMR in patients with DCM, and one SR compared the prognosis of patients diagnosed with NIDCM with those diagnosed with ICM. The quality of these SRs was appraised using the AMSTAR checklist (Shea et al. 2007), and the results along with the study characteristics are listed in Table 77 in Appendix C.

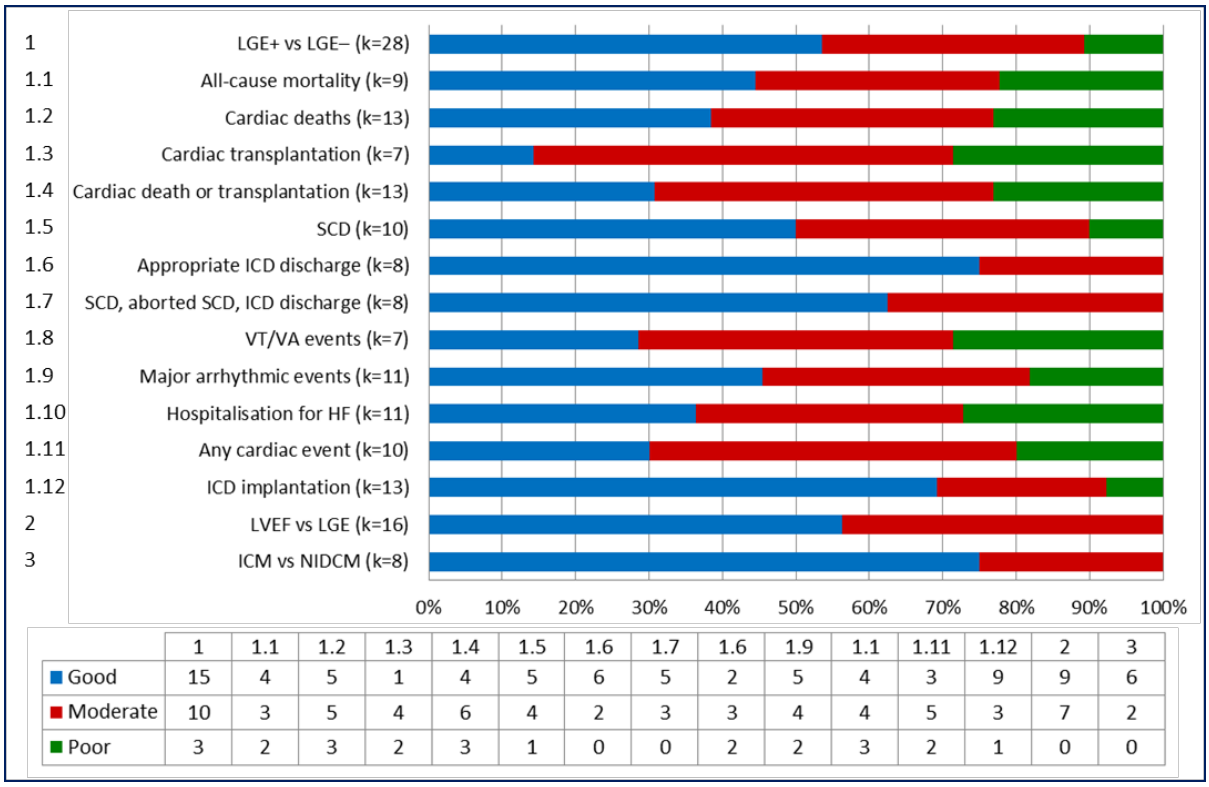
The SR by Scott et al. (2013) was of good quality with a low risk of bias but reported on only one health outcome—the likelihood of having ventricular arrhythmic events in patients diagnosed with DCM due to CAD compared with those diagnosed with NIDCM. The SR by Duan et al. (2015) was also of good quality with a low risk of bias, but included 2 studies that enrolled the same patients (Assomull et al. 2006; Gulati et al. 2013), thus duplicating data in their meta-analyses and introducing uncertainty around the accuracy of the pooled odds ratios (ORs). Two SRs were of moderate quality with a moderate risk of bias, but included at most 7 studies in their meta-analyses (Kuruvilla et al. 2014; Shi et al. 2013). The SR by Kim et al. (2015) was of poor quality with a high risk

of bias, as the authors did not report on the quality of the included studies or the likelihood of publication bias. This SR also included the 2 studies with duplicated data.

These five SRs included between 5 and 15 of a total of 25 cohort studies. Six of these studies did not meet the inclusion criteria and were excluded from further analysis. Assomull et al. (2006) reported on duplicated data; all 101 patients enrolled in that study were included in the study by Gulati et al. (2013). The study by Wu, E et al. (2001) did not report on any adverse health outcomes. The remaining 4 studies enrolled only patients with CAD (Boye et al. 2011; de Haan et al. 2011; Roes et al. 2009; Scott et al. 2011). In addition to these 18 studies, another 12 cohort studies were identified in the literature search that met the inclusion criteria.

Of the included studies, 25 were prospective studies providing level II prognostic evidence (Merlin, Weston & Tooher 2009; NHMRC 2000), and 5 were retrospective cohort studies providing level III-3 evidence. Two of the cohort studies provided comparative prognostic data, comparing the predictive value of LGE-CMR with SPECT. One cohort study investigated the prognostic value of CMR in children with DCM. The quality of these studies was appraised using the SIGN Checklist for Cohort Studies (SIGN 2014), and the results along with the study characteristics are listed in Table 77 to Table 80 in Appendix C. Fourteen of the studies were of high quality with a low risk of bias, 12 were of acceptable quality with a moderate risk of bias, and 4 prospective studies were of unacceptable quality with a high risk of bias.

The risk of bias for the cohort studies reporting on the prognostic value of LGE (LGE+ vs LGE–; overall and for individual health outcomes), the prognostic value of LVEF versus LGE, and the prognosis of ICM versus NIDCM are summarised in Figure 17.



	1	1.1	1.2	1.3	1.4	1.5	1.6	1.7	1.6	1.9	1.1	1.11	1.12	2	3
Good	15	4	5	1	4	5	6	5	2	5	4	3	9	9	6
Moderate	10	3	5	4	6	4	2	3	3	4	4	5	3	7	2
Poor	3	2	3	2	3	1	0	0	2	2	3	2	1	0	0

Figure 17 Summary of the risk of bias for the prognostic cohort studies for each outcome

HF = heart failure; ICD = implantable cardioverter defibrillator; ICM = ischaemic cardiomyopathy; k = number of studies included in each meta-analysis; LGE = late gadolinium enhancement; LVEF = left ventricular ejection fraction; NIDCM = non-ischaemic dilated cardiomyopathy; SCD = sudden cardiac death; VA = ventricular arrhythmia; VT = ventricular tachycardia

B4.2.3 Results of the systematic literature review

Summary – Will the information generated as a result of CMR be of prognostic value in patients with HF symptoms in whom echocardiography is inconclusive or suggests a DCM, compared with SPECT or CTCA?

Overall, a mean of 38% of DCM patients were diagnosed with NIDCM, of whom approximately 38% were LGE+ (13% of the total DCM population). Of the 62% of patients diagnosed with ICM, a mean of 86% were LGE+ (56% of the total DCM population).

A median of 22% of patients who had an ICD implanted for primary prevention had an appropriate ICD discharge (range 11–71%), while appropriate discharges occurred in a median of 61% of patients who had an ICD implanted for secondary prevention. A greater proportion of LGE+ patients who had an ICD / cardiac resynchronisation therapy (CRT) had an appropriate discharge compared with those who were LGE–, regardless of the reason for implantation.

For primary prevention, LGE+ patients were 4.5-times more likely to have an appropriate ICD discharge than LGE– patients. There was a 7.5-fold increase in the number of secondary prevention LGE– patients benefiting by having an appropriate ICD discharge compared with primary prevention LGE– patients (30% vs 4%), and a 3-fold increase in the number of LGE+ patients (85% vs 29%).

Meta-analysis of the data clearly showed that LGE+ NIDCM patients are up to 4-times more likely to experience an adverse cardiac event, and 3-times more likely to die, than those who are LGE–. Conversely, in children with a recent diagnosis of DCM of unknown origin, those who were LGE+ were 2-times more likely to fully recover LV function than those who were LGE–.

This apparent disparity is caused by LGE-CMR detecting the presence of myocardial inflammation in children, whereas what it is detecting in adults is often fibrotic or scarred myocardium. The greatest difference between fibrotic and inflamed myocardium is in its ability to recover. Once the myocardium has become fibrotic it is permanently scarred, leading to worse health outcomes in adults.

It is probable that the presence of LGE is a stronger predictor of cardiac events than %LVEF, even though the results suggested that both %LVEF and the presence of LGE are prognostic factors that can predict which patients are more likely to have an adverse cardiac event. The results also indicated that echocardiography LVEF measurements were less reliable than CMR measurements for predicting the likelihood of a patient having an adverse cardiac event. Nevertheless, current guidelines do not use LGE-CMR in the diagnosis and/or clinical management of congestive heart failure (CHF), but rely heavily on %LVEF for both diagnosis and clinical management of these patients.

Two small cohort studies compared the prognostic value of detecting myocardial scarring by LGE-CMR compared with SPECT in patients diagnosed with DCM, and found opposite results.

One study reported that the odds of having an adverse cardiac event in patients who were LGE+ were 2.7-times greater than for those who were LGE–, whereas the odds for those who had scarring detected by a SPECT perfusion-metabolism mismatch were 4-times greater than for those who did not, indicating that SPECT may be more accurate than LGE-CMR.

The second study found that LGE-CMR could identify non-responders to CRT more reliably than SPECT in patients with NIDCM, and that SPECT imaging in the NIDCM group often showed severe perfusion defects in the LV inferior wall, due to attenuation artefacts, which resulted in the overestimation of scar tissue.

Due to the small study sizes and the limited comparative data available, no conclusions could be made about the prognostic value of detecting myocardial fibrosis by LGE-CMR compared with SPECT or CTCA.

THE PROGNOSTIC VALUE OF DETECTING MYOCARDIAL SCARRING BY LGE-CMR IN PATIENTS WITH NIDCM

As the SRs undertook flawed assessments of the prognostic value of LGE-CMR in NIDCM (see above), and hence provided low-quality evidence (GRADE ⊕⊕⊙⊙; Table 87 in Appendix D), relevant data

were extracted from the individual cohort studies and a meta-analysis of the data was performed using the 'metan' command in Stata 14 (StataCorp 2014).

Twenty-one cohort studies reported hazard ratios (HRs) from univariate Cox regression analysis. These HRs indicated that patients with detectable LGE were more likely to have adverse health outcomes than those with no detectable LGE (Figure 38 in Appendix G).

Twenty-six cohort studies provided data that could be used in meta-analyses to determine the likelihood of experiencing adverse health outcomes in patients who are LGE+ compared with LGE–. The pooled results of the meta-analyses are shown in Figure 18. The pooled RRs clearly show that LGE+ patients are more likely to experience adverse outcomes than those who are LGE–. The forest plots showing the individual RRs for each health outcome are presented in Appendix G. The quality of the evidence for each outcome is reported in Table 88 (Appendix D) and summarised in Figure 18.

When the studies with a high risk of bias and the retrospective studies that provided a lower level of evidence were excluded from the meta-analyses, the pooled RR was either little affected or had a larger point estimate with wider 95%CIs. Figure 18 lists the number of studies providing the best-quality evidence for each outcome and the resultant RR. There was substantial heterogeneity between studies for hospitalisation for HF and any cardiac event, and moderate heterogeneity for all-cause mortality, cardiac deaths, cardiac death or transplantation, and appropriate ICD discharge. The heterogeneity does not resolve by removing the studies that either had a high risk of bias or were of a lower level of evidence than the meta-analysis.

It is possible that there is publication bias associated with all outcomes except sudden cardiac death (SCD) and major arrhythmic events, as there seems to be an absence of studies in the lower left area of the funnel plots (Appendix G). However, the Egger's test did not find any small-study effects ($p>0.05$ for all outcomes), suggesting that there was no bias due to the size of the studies.

Overall, these data suggest that LGE is a strong prognostic marker for the prediction of future adverse health outcomes, with LGE+ patients being up to 4-times more likely to have a cardiac event and 3-times more likely to die from a cardiac event than those who are LGE–.

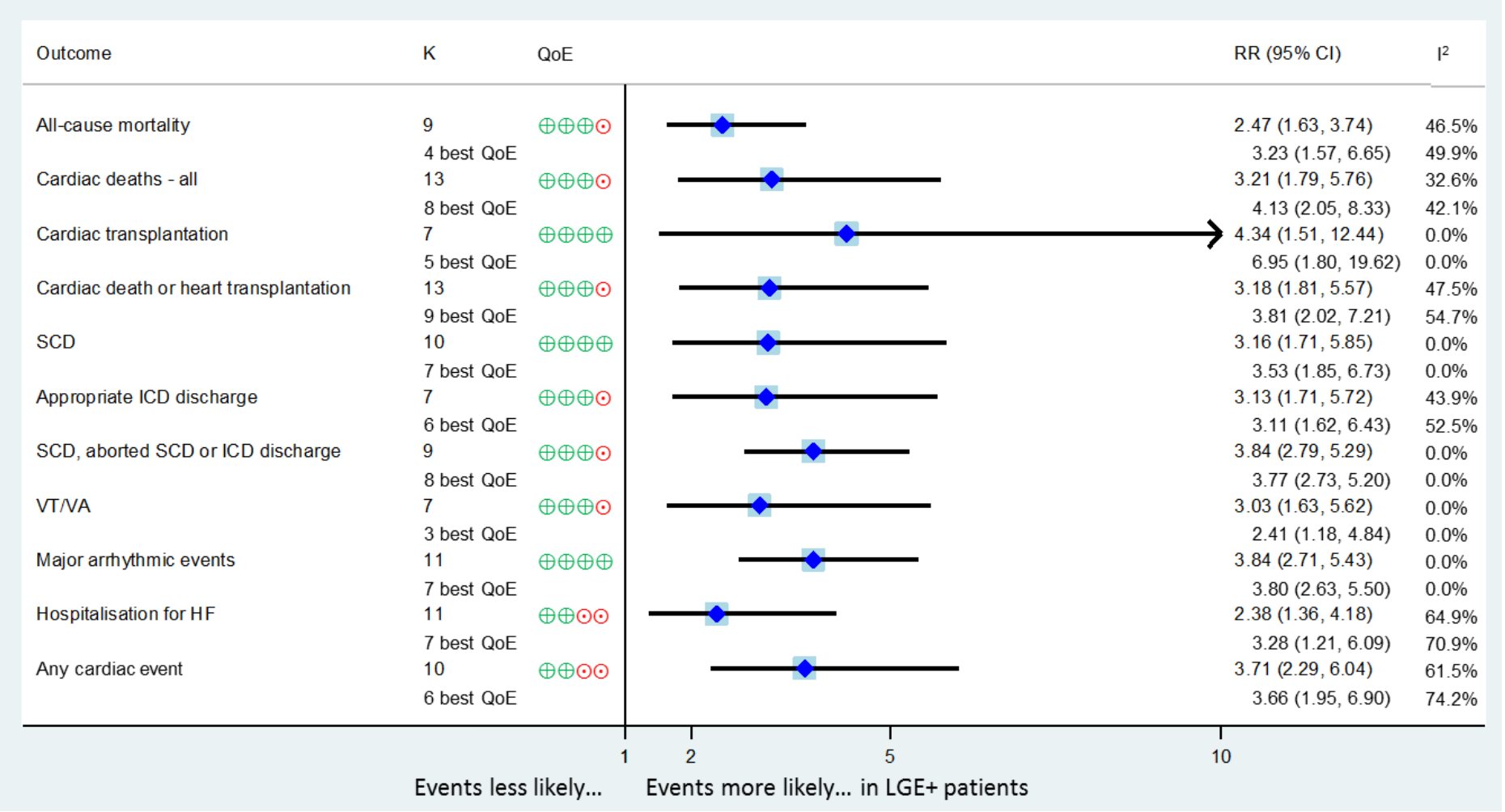


Figure 18 Forest plot showing the pooled RR of having an adverse health outcome in patients who were LGE+ compared with those who were LGE–

CI = confidence interval; HF = heart failure; I^2 = index to measure heterogeneity between studies; ICD = implantable cardioverter defibrillator; K = number of studies included in each meta-analysis; LGE = late gadolinium enhancement; QoE = quality of evidence; RR = relative risk; SCD = sudden cardiac death; VA = ventricular arrhythmia; VT = ventricular tachycardia

THE PROGNOSTIC VALUE OF DETECTING INFLAMMATION IN CHILDREN WITH DCM BY CMR

One prospective cohort study with a moderate risk of bias investigated the role of CMR to assess myocardial inflammation in predicting the health outcomes of children recently diagnosed with DCM (Raimondi et al. 2015). In this study inflammation was assessed using three criteria: (1) evidence of regional or global myocardial oedema seen as an increase in global myocardial signal hyperintensity on T2-weighted images, (2) evidence of myocardial hyperaemia and capillary leak with early gadolinium enhancement (EGE), and (3) evidence of myocardial necrosis and fibrosis (visual assessment) with non-ischaemic regional distribution at LGE. Myocardial inflammation was diagnosed when at least two criteria were present. In this study all children who were diagnosed as CMR+ and included in the analysis were also LGE+, and no child who was CMR– was LGE+. The results of the study are presented in Table 13. All outcomes provided a high quality of evidence (GRADE ⊕⊕⊕⊕; Table 89 in Appendix D).

Table 15 CMR and health outcomes in children recently diagnosed with DCM of unknown origin

Study	Patients	CMR and health outcomes			
Raimondi et al. (2015) France Prospective cohort Moderate risk of bias	N=66 children with recent diagnosis of DCM of unknown origin N=55 children with complete CMR study who are alive with no heart transplant and are available for follow-up		CMR+	CMR–	RR (95%CI)
		Number of children	33	33	
		T2 + EGE + LGE	27	0	
		T2 + LGE	4	0	
		LGE	31	0	
		T2 (no EGE or LGE data)	2	0	
		Clinical outcomes:			
		Death	2	1	2.00 (0.19, 21.00)
		Cardiac transplant	0	1	0.33 (0.01, 7.90)
		Incomplete CMR (no EGE or LGE data)	2	0	
		Lost to follow-up	2	3	
		Number of children in analysis (n=55)	27	28	
		Normalised LV function (by ECG)	22	11	2.07 (1.27, 3.40)
		ITT			2.00 (1.17, 3.43)
		Recurrent LVD after stopping HF drugs	0	0	
		Persisting LVD ITT	5	17	0.31 (0.13, 0.71) 0.29 (0.12, 0.70)
		(Median LVEF = 41%, range 20–54%)			
		Predictors of LV function recovery in a logistic regression model:			
		Presence of myocardial inflammation			OR = 3.76 (p=0.02)
		Elevated troponin levels at baseline			OR = 2.76 (p=0.03)
		Age, gender and baseline CMR LVEF did not predict complete LV recovery			

CI = confidence interval; CMR = cardiac magnetic resonance (imaging); DCM = dilated cardiomyopathy; ECG = electrocardiogram; EGE = early gadolinium enhancement; HF = heart failure; LGE = late gadolinium enhancement; LV = left ventricular; LVD = left ventricular dysfunction; LVEF = left ventricular ejection fraction; OR = odds ratio; RR = relative risk; T2 = global myocardial T2 signal hyper-intensity

These children were all treated optimally, including mechanical circulatory support, intravenous inotropic support, intravenous diuretics, immune globulin therapy, and immunosuppressive and/or steroid treatment as required, and followed for a mean of 24 months (range 6–55 months). During this time 3 children died and 1 child required a heart transplant. There was no difference in the likelihood of death or cardiac transplant in children who were CMR+ for inflammation compared with those who were CMR– (Table 15). Two children did not have complete CMR data (EGE and LGE were not done) and were excluded, along with those who died or required a transplant from the analysis on LV recovery.

During the follow-up period 33/55 children recovered with normal LV function (LVEF >55%) and dimensions on ECG. Additionally, when oral HF treatment was progressively stopped in these children after being stable for at least 6 months, LV dysfunction did not recur. Surprisingly, recovery of LV function was twice as likely in children who were LGE+ compared with those who were LGE– (RR = 2.07, 95%CI 1.27, 3.40). Therefore, the presence of LGE may predict LV functional recovery in children with a recent diagnosis of DCM of unknown origin.

This agrees with the findings reported by Raimondi et al. (2015) that only the presence of myocardial inflammation as detected by CMR and elevated troponin levels, which is also a measure of inflammation as well as heart muscle damage, predicted LV functional recovery in a logistic regression model. They found that the odds of LV recovery were nearly 4-times higher in children with myocardial inflammation by CMR compared with those who had no detectable inflammation.

This result appears to contradict that seen in adults, where the presence of LGE was found to be predictive of adverse health outcomes. However, in adults LGE-CMR was used to detect fibrotic or scarred myocardium as opposed to inflammation. The greatest difference between fibrotic and inflamed myocardium is in its ability to recover. Once the myocardium has become fibrotic it is permanently scarred, leading to worse health outcomes in adults.

In children recently diagnosed with DCM, the damage caused to the myocardium by the inflammation detected by LGE was reversible, with full recovery of LV function possible. Of the 55 children followed in this study, 37 underwent a second CMR scan, either after recovery of LV function or at a median of 23 months after the first scan (Table 16). Of the 21 children who were originally diagnosed as LGE+ after the first scan, only 6 (29%) were still LGE+ following the second scan. Only 3 of these children (14%) still had LV dysfunction, and all these were still LGE+. Of the 16 children who were found to be LGE– at the first scan, none were LGE+ following the second scan, but only 7 (44%) had fully recovered LV function, compared with 18/21 (86%) of those who were LGE+.

Table 16 Outcomes of a second CMR scan conducted at least 6 months after the first CMR scan

Study	Patients	CMR and health outcomes			
Raimondi et al. (2015) France Prospective cohort Moderate risk of bias	N=37 children with DCM who had second CMR during follow-up period	Initial CMR result:	CMR+	CMR–	RR (95%CI)
		Number of children who had 2nd CMR	21	16	
		Median time between CMRs (months)	6.0	23.0	
		LV recovery	18	7	2.88 (1.05, 7.91)
		LV dysfunction	3	9	0.35 (0.13, 0.95)
		LGE+ on 2nd CMR with LV recovery with LV dysfunction	6 3 3	0 0 0	6/21 = 29% CMR+ 18/21 = 86% CMR+ 3/21 = 14% CMR+
		LGE– on 2nd CMR with LV recovery with LV dysfunction	15 15 0	16 7 9	 7/16 = 44% CMR– 9/16 = 56% CMR–

CI = confidence interval; CMR = cardiac magnetic resonance (imaging); DCM = dilated cardiomyopathy; LGE = late gadolinium enhancement; LV = left ventricular; RR = relative risk

THE PROGNOSTIC VALUE OF DETECTING MYOCARDIAL SCARRING BY LGE-CMR COMPARED WITH SPECT IN PATIENTS DIAGNOSED WITH NIDCM

Two cohort studies compared the prognostic value of detecting myocardial scarring by LGE-CMR compared with SPECT in patients diagnosed with DCM (Yokokawa et al. 2009; Yoshida, Takano et al. 2013).

The retrospective cohort study by Yoshida, Takano et al. (2013) had a moderate risk of bias and reported that a similar number of patients had myocardial scarring detected by LGE-CMR (21/50) and by SPECT perfusion-metabolism mismatch (20/50). However, only 8 of these patients were positive by both LGE-CMR and SPECT. Using a univariate Cox regression model, the authors reported that patients who were LGE+ were 2.7-times more likely to have an adverse cardiac event than those who were LGE–, and patients who had scarring detected by a SPECT perfusion-metabolism mismatch were 4-times more likely to have an adverse cardiac event. This indicates that the SPECT results may have been more accurate at predicting adverse cardiac events; however, due to the small sample size of the study, neither observation was statistically significant (p=0.163 and p=0.056, respectively). Although only a small number of patients were positive by both LGE-CMR and SPECT, they were 8-times more likely to have an adverse cardiac event (p=0.007). Therefore, it is possible that clinicians may seek for patients to undergo both SPECT and LGE-CMR as they provide complementary information.

The prospective cohort study by Yokokawa et al. (2009) had a high risk of bias and compared the total and regional scar burden by LGE-CMR and SPECT in patients diagnosed with NIDCM or ICM who either responded or not to CRT. Response to CRT after 6 months was defined as: (1) a ≥5% increase in LVEF or a ≥15% decrease in LV end-diastolic volume, or both; (2) ≥1 point decrease in New York Heart Association (NYHA) functional class; and (3) no hospitalisation for management of decompensated HF during follow-up.

The authors found that 59% (10/17) of DCM patients and 43% (3/7) of ICM patients responded to CRT. The total scar score was significantly higher in the ICM than the NIDCM group by both SPECT and CMR imaging. By LGE-CMR the NIDCM group had significantly higher percentages of regional scar segments and regional scar score in the LV inferior wall of non-responders than responders; whereas by SPECT the regional scar burdens were similarly high in both responders and non-responders. Thus, LGE-CMR could identify non-responders to CRT more reliably than to SPECT in patients with NIDCM.

The authors also noted that SPECT imaging in the NIDCM group often showed severe perfusion defects in the LV inferior wall, due to attenuation artefacts, which resulted in overestimation of scar tissue. However, due to the small study size, these results should be viewed with caution.

THE PROGNOSTIC VALUE OF DETECTING MYOCARDIAL SCARRING BY LGE-CMR IN PATIENTS WITH NIDCM WHO HAVE AN ICD / CARDIAC RESYNCHRONISATION THERAPY WITH ICD (CRT-D) DEVICE IMPLANTATION

Eleven prospective and 1 retrospective cohort studies reported on ICD/CRT device implantation and discharge (Table 78). Four studies enrolled only patients who were to be implanted with an ICD/CRT-D device and 8 studies reported on the proportion of NIDCM patients who had an ICD/CRT device implanted. Three of these studies did not provide any information about the presence or absence of LGE among the patients who received ICDs (Hombach et al. 2009; Muller et al. 2013; Perazzolo Marra et al. 2014).

Overall, a median of 24% (range 14–50%) of patients received the devices at the discretion of the treating physician and according to current guidelines on the implantation of these devices (Figure

19). Five studies provided moderatequality evidence (GRADE ⊕⊕⊕⊙) on the proportion of LGE+ and LGE– patients who received an ICD/CRT device (Table 88 in Appendix D). Among those patients who were LGE+, a median of 25% (range 18–41%) received an ICD/CRT device compared with a median of 10% (range 4–16%) of LGE– patients. The forest plot in Figure 19 shows that NIDCM patients who are LGE+ were 2.5-times more likely to receive an ICD/CRT device implant than those who were LGE–.

Of the 4 studies that enrolled only patients who were to be implanted with an ICD/CRT device, 3 enrolled only patients undergoing the intervention for primary prevention of SCD (Iles et al. 2011; Neilan et al. 2013; Wu, KC et al. 2008). The fifth study, by Piers et al. (2015), enrolled 64 patients for primary prevention of SCD and 23 patients for secondary prevention (those with either sustained monomorphic ventricular tachycardia (VT) or out-of-hospital cardiac arrest with ventricular fibrillation (VF)). The study by Chimura et al. (2015) included 24 patients who received an ICD implant for primary prevention. The median proportion of patients who had an appropriate ICD discharge among primary prevention patients in the 5 studies was 22% (range 11–71%), and among the secondary prevention patients in the study by Piers et al. (2015) 61% had an appropriate ICD discharge (Figure 20). An additional 2 studies reported the proportion of LGE+ and LGE– patients who received an appropriate ICD discharge, but it did not comment on whether it was for primary or secondary prevention (Gulati et al. 2013; Lehrke et al. 2011).

A greater proportion of LGE+ patients who had an ICD had an appropriate ICD/CRT discharge compared with those who were LGE–, regardless of the reason for implantation. The forest plot in Figure 20 shows that, among patients receiving an ICD/CRT device for primary prevention, LGE+ patients were 4.5-times more likely to have an appropriate ICD discharge than LGE– patients. When being treated for secondary prevention, LGE+ patients from the 1 study providing evidence in this population were still almost 3-times more likely to have an appropriate discharge than LGE– patients, even though the total number of both LGE+ and LGE– patients who had an ICD shock increased. There was a 7.5-fold increase in the number of secondary prevention LGE– patients benefiting by having an appropriate ICD discharge compared with primary prevention LGE– patients (30% vs 4%), and a 3-fold increase in the number of LGE+ patients (85% vs 29%).

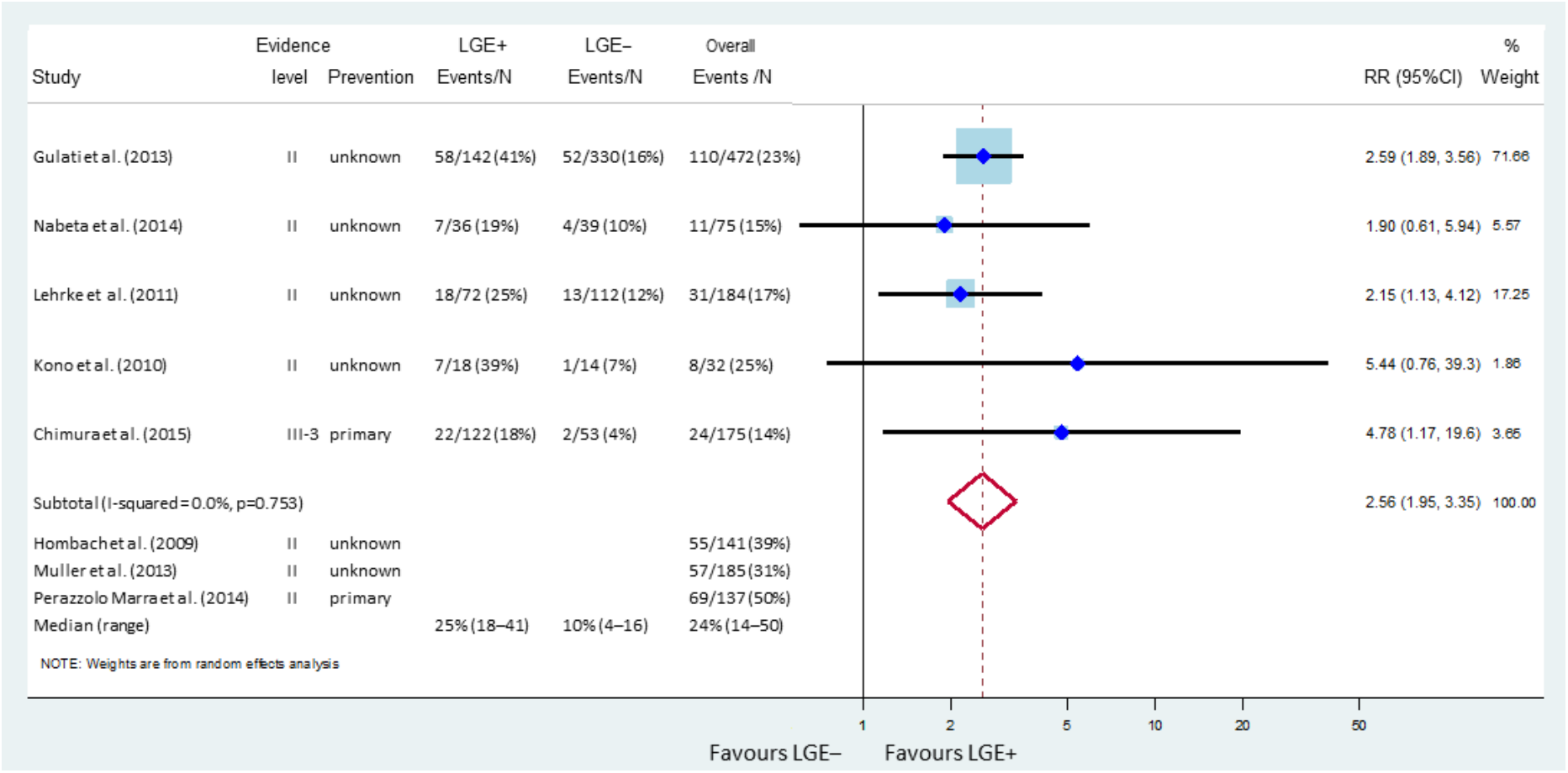


Figure 19 Forest plot showing the RR of having an ICD/CRT implantation in patients who were LGE+ compared with those who were LGE–

CI = confidence interval; CRT = cardiac resynchronisation therapy (device); Evidence level = NHMRC levels of evidence (Merlin, Weston & Tooher 2009; NHMRC 2000); ICD = implantable cardioverter defibrillator; LGE = late gadolinium enhancement; N = number; RR = relative risk

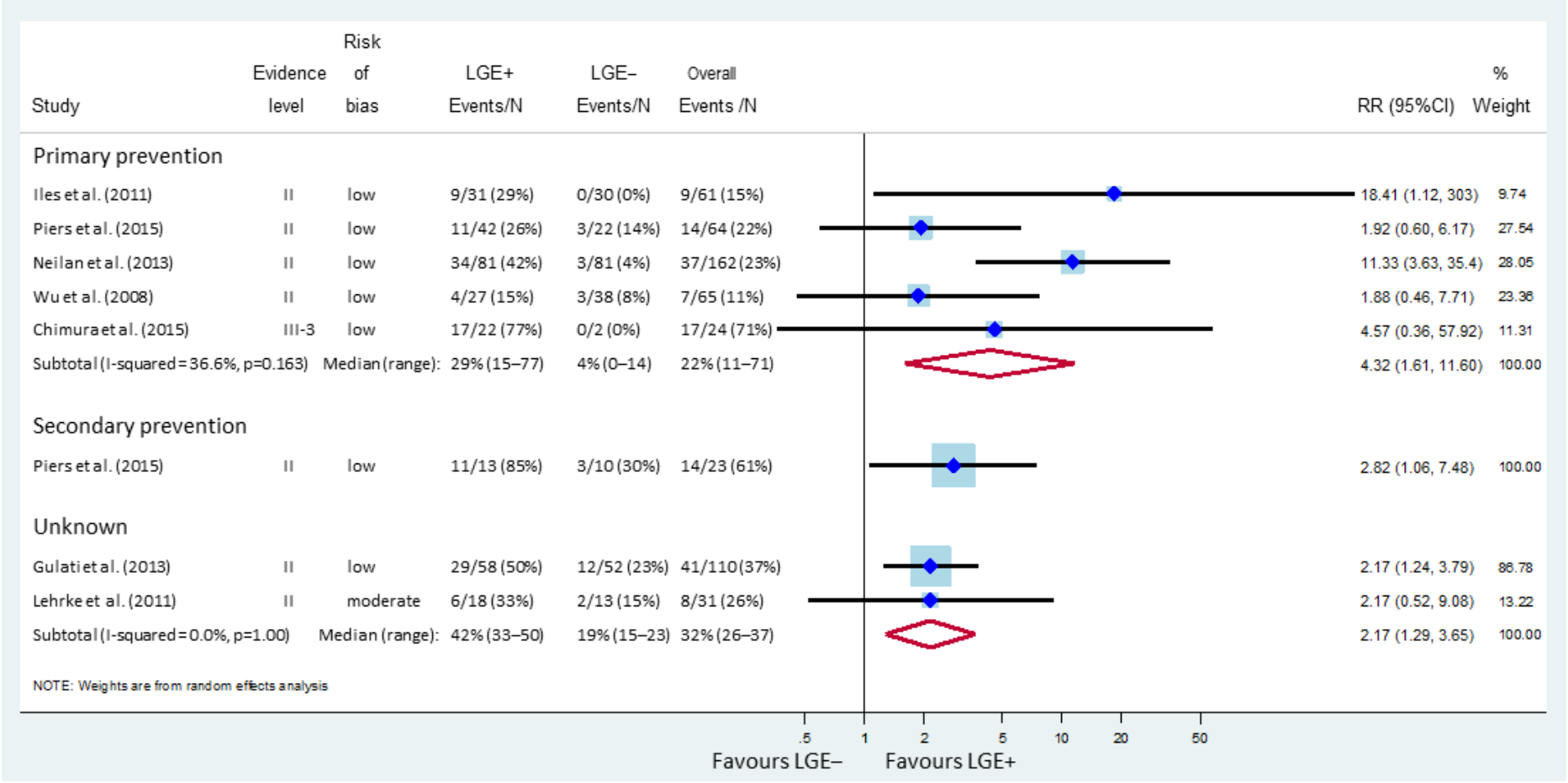


Figure 20 Forest plot showing the RR of having an appropriate ICD/CRT-D discharge in patients who were LGE+ compared with those who were LGE–, and according to reason for ICD/CRT-D implantation

CI = confidence interval; CRT-D = cardiac resynchronisation therapy device with defibrillation capabilities; Evidence level = NHMRC levels of evidence (Merlin, Weston & Tooher 2009; NHMRC 2000); ICD = implantable cardioverter defibrillator; LGE = late gadolinium enhancement; N = number; RR = relative risk

It should be noted that with only 1 small study contributing information on the rate of appropriate discharge among secondary prevention patients, the true differences in health outcomes when treating patients for secondary prevention based on either their LGE status or in comparison with primary prevention patients cannot be determined with any confidence.

THE PROGNOSTIC VALUE OF %LVEF COMPARED WITH THE PRESENCE OR EXTENT OF LGE IN PATIENTS WITH NIDCM

The 2011 *Guidelines for the prevention, detection and management of chronic heart failure in Australia* (National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand (Chronic Heart Failure Guidelines Expert Writing Panel) 2011) does not use LGE-CMR in the diagnosis and/or clinical management of CHF, but it does rely heavily on the %LVEF for both the diagnosis and clinical management of patients. This guideline recommends that ICD implantation should be considered in patients with symptomatic CHF (i.e. NYHA functional class II/III) and LVEF ≤35%. Thus, the prognostic value of LGE was compared with that of low LVEF values in the cohort studies discussed above.

Twelve studies undertook univariate Cox regression analysis and reported the HRs per unit (%) LVEF, and 1 study (Piers et al. 2015) per 10% LVEF decrease. However, only 4 studies found that a lower %LVEF was significantly associated with worse health outcomes (Buss et al. 2015; Gulati et al. 2013; Hombach et al. 2009; Masci et al. 2012). Appendix G shows that, overall, the HRs reported by most studies trended towards worse outcomes in patients with lower %LVEF; that is, there would be 4% fewer adverse cardiac events occurring among patients for each % increase in their LVEF (pooled HR = 0.96, 95%CI 0.94, 0.98).

By comparison, univariate Cox regression analysis in 12 of these 13 studies found that the presence of LGE was significantly associated with worse health outcomes. In the 13th study the presence of LGE was the strongest independent predictor of the primary combined outcome of appropriate ICD therapy, survived cardiac arrest or SCD (Gao et al. 2012). Additionally, 8 studies reported the HR per unit LGE—either per % or per g LGE mass, or per % of LV mass. All except 1 study found a significant association between LGE size and adverse cardiac events. Meta-analysis found that for each unit increase in LGE, there was an 11% increase in the occurrence of adverse cardiac events (Appendix G).

Three studies investigated the HRs for the likelihood of having a cardiac event using LVEF cut-offs of 20%, 30% and 40% (Figure 21). Two studies with mean LVEF values for the enrolled patients of 38% and 43% showed that patients with LVEF ≤30% and ≤40% were 3.4- and 5.4-times, respectively, more likely to have a cardiac event than patients with higher LVEF values (Lehrke et al. 2011; Muller et al. 2013). The HR for the presence of LGE was similar in the study using the 30% cut-off for LVEF (3.5 vs 3.4) but was much reduced and only just reached significance in the study using a 40% cut-off (1.8 vs 5.4; Figure 21).

The 3rd study, by Yoshida, Ishibashi-Ueda et al. (2013), had enrolled patients who were sicker than in the other 2 studies and these patients had a mean LVEF of 22.6 ± 8.8%. Thus, very few patients in this study, if any at all, would have had an LVEF of >35%, let alone approaching normal. Hence, it is not surprising that there was little difference between the number of cardiac events experienced by patients with LVEF values marginally above or below the 20% cut-off. There was a trend towards increased risk of cardiac events in patients who were LGE+ in this study, but the 95%CIs were very wide and did not reach significance.

Together these results suggest that both %LVEF and the presence of LGE are prognostic factors that can predict which patients are more likely to have an adverse cardiac event. However, it is possible that the presence of LGE is a stronger predictor than %LVEF.

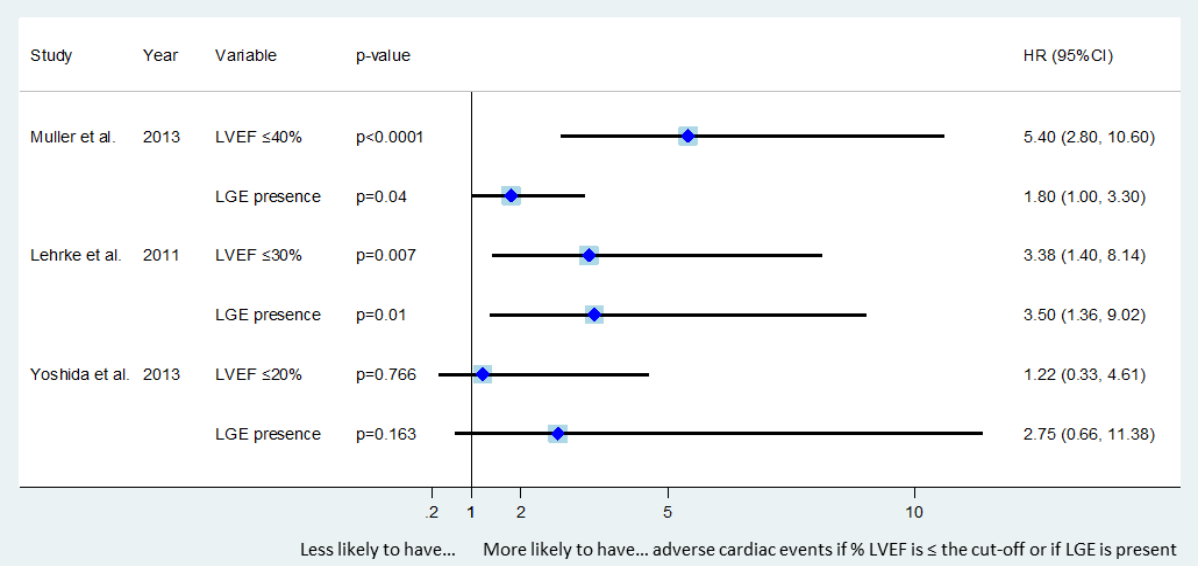


Figure 21 Forest plot showing the HRs of the likelihood of having any cardiac event in patients with either LVEF **≤20**–40% or with LGE present

Note: The HRs were derived from univariate Cox regression analysis.

CI = confidence interval; HR = hazard ratio; LGE = late gadolinium enhancement; LVEF = left ventricular ejection fraction

Appendix G shows that there were differences in the outcomes between the 3 studies that used echocardiography LVEF measurements compared with the 10 using CMR measurements (see section F.2 for a comparison between echocardiography and CMR LVEF measurements). Remarkably, the 3 studies that conducted univariate Cox regression analysis using the echocardiography LVEF measurements had three of the five highest HRs, indicating either no difference in the number of adverse cardiac events with changing LVEF values or trending in the wrong direction. This suggests that CMR measurements may be more reliable than echocardiography measurements for predicting the likelihood of a patient having an adverse cardiac event.

THE PROGNOSIS OF PATIENTS WITH NIDCM COMPARED WITH THOSE WITH ICM

Seven studies enrolled DCM patients with both ischaemic and non-ischaemic disease, as defined by patient history, ICA, CTCA or other non-invasive testing; 1 of these studies did not report the proportion of LGE+ patients who were diagnosed with either NIDCM or ICM.

Overall, a mean of 38% of the DCM patients were diagnosed with NIDCM, of whom approximately 38% were LGE+ (13% of the total DCM population). The proportion of NIDCM patients who were LGE+ in the 20 cohort studies that only reported on NIDCM was similar (mean 43%). Of the 62% of patients diagnosed with ICM, a mean of 86% were LGE+ (56% of the total DCM population). The forest plot in Figure 22 shows that ICM patients are 8-times more likely to be LGE+ than NIDCM patients (GRADE ⊕⊕⊕⊙: moderate quality of evidence). It should be noted that LGE-CMR alone is unable to distinguish between ICM and NIDCM in patients who are LGE–, because the assessment of ICM versus NIDCM is based on the pattern of LGE observed in the CMR images. As the majority of LGE– patients (80%) would have NIDCM, it is possible that some ICM patients who are LGE– could be wrongly classified as NIDCM, based on their LGE-CMR result.

Three studies reported the HR for patients who were dying and/or having an appropriate ICD discharge (Appendix G). All univariate analyses showed that a significantly larger proportion of events occur in ICM patients compared with NIDCM patients. The multivariate analysis performed by Almehmadi et al. (2014), which was adjusted for LVEF, mid-wall hyperenhancement and total

hyperenhancement, did not show a significant difference in event rate but still favoured a greater number of events occurring in ICM patients over NIDCM patients.

Six studies provided data to enable meta-analyses to be undertaken (Figure 23). The quality of the evidence for each outcome is reported in Table 90 (Appendix D) and summarised in Figure 23. All death and cardiac outcomes that could be measured showed that events occurred more commonly in ICM patients compared with NIDCM patients, except for the number of non-life-threatening VT and ventricular arrhythmic events, which occurred equally in both patient subgroups. Hence, it would also be expected that appropriate ICD discharges would occur equally in both ICM and NIDCM patients, as indicated in Figure 23. Thus, ICD/CRT device implantation may be equally effective for both ischaemic and non-ischaemic DCM patients.

One good-quality SR cited in MSAC assessment no. 1237 (Zemrak & Petersen 2011), which assessed whether LGE-CMR predicted mortality and adverse cardiac outcomes in patients with CAD, reported that the presence of LGE was associated with a 4-fold higher probability of dying or having an adverse cardiac event. This is similar to the increased risk observed in LGE+ compared with LGE– NIDCM patients discussed above. Thus, one could hypothesise that ICM patients are more likely to suffer an adverse health outcome than NIDCM patients simply due to the greater proportion of LGE+ patients in the ICM group compared with the NIDCM group (85% vs 38%).

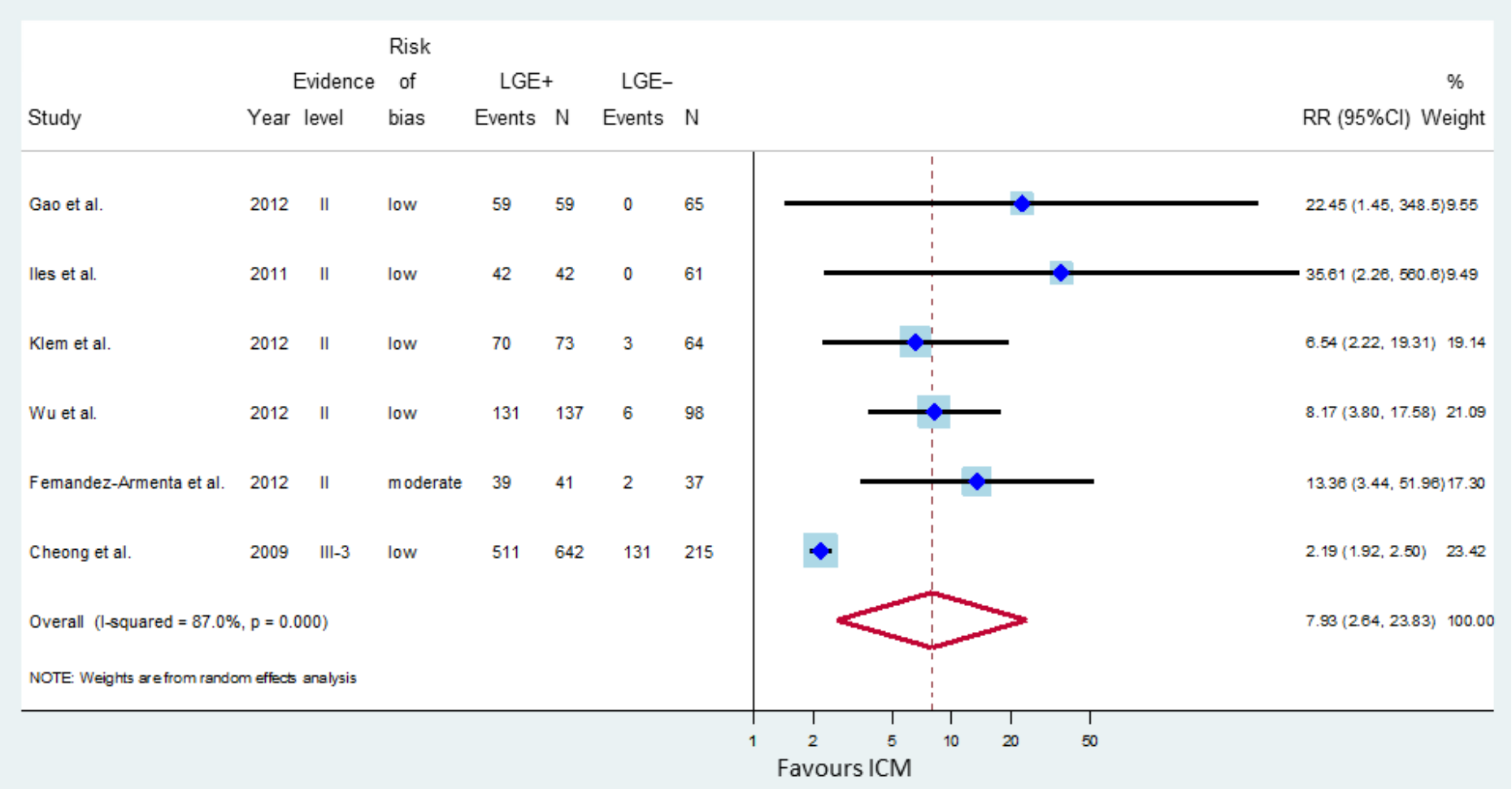


Figure 22 Forest plot showing the likelihood of DCM patients diagnosed with ICM being LGE+ compared with those diagnosed with NIDCM

CI = confidence interval; DCM = dilated cardiomyopathy; Evidence level = NHMRC levels of evidence (Merlin, Weston & Tooher 2009; NHMRC 2000); ICM = ischaemic cardiomyopathy; LGE = late gadolinium enhancement; N = number; NIDCM = non-ischaemic dilated cardiomyopathy; RR = relative risk

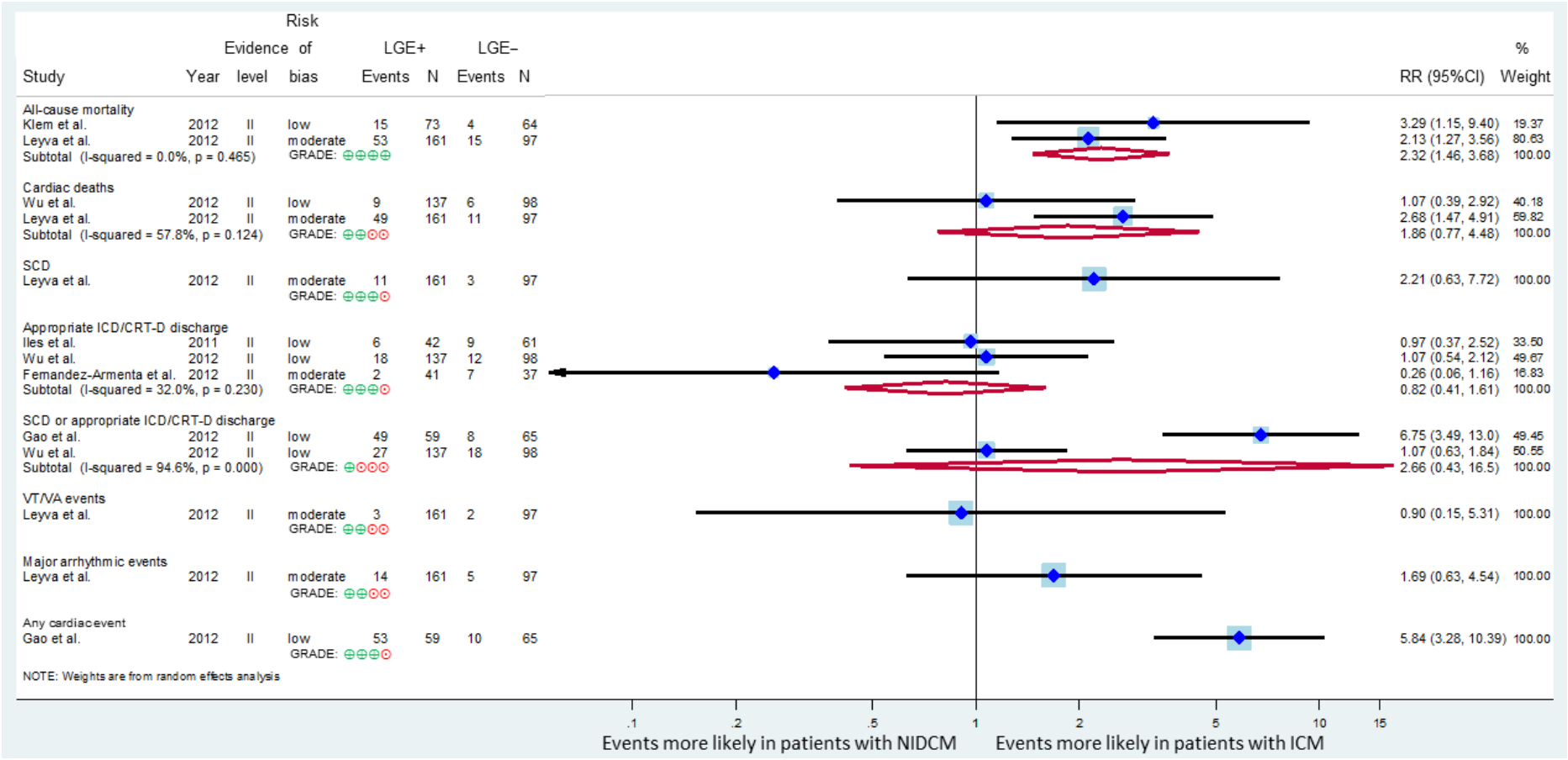


Figure 23 Forest plot showing the RR of having an adverse cardiac event in patients diagnosed with NIDCM compared with those diagnosed with ICM

CI = confidence interval; CRT-D = cardiac resynchronisation therapy device with defibrillation capabilities; Evidence level = NHMRC levels of evidence (Merlin, Weston & Tooher 2009; NHMRC 2000); ICD = implantable cardioverter defibrillator; ICM = ischaemic cardiomyopathy; LGE = late gadolinium enhancement; N = number; NIDCM = non-ischaemic dilated cardiomyopathy; RR = relative risk; SCD = sudden cardiac death; VA = ventricular arrhythmia; VT = ventricular tachycardia

B5 CLINICAL UTILITY

Clinical utility refers to how likely a test is to significantly impact on patient management and health outcomes.

B5.1 IMPACT ON CLINICAL MANAGEMENT (THERAPEUTIC EFFICACY)

B5.1.1 Literature sources and search strategy

Articles identified in the broad literature search (described in section B) were assessed for possible inclusion in the impact on clinical management section by application of the appropriate PICO criteria (see Box 8 and 9 in section A9). Additional articles were pearled or found to have possibly relevant data when assessed for inclusion in other sections.

RESULTS OF LITERATURE SEARCH

The PRISMA flowchart in Figure 24 provides a summary of the process of selection and exclusion of studies for evidence of the impact of CMR on the clinical management of patients indicated for DCM.

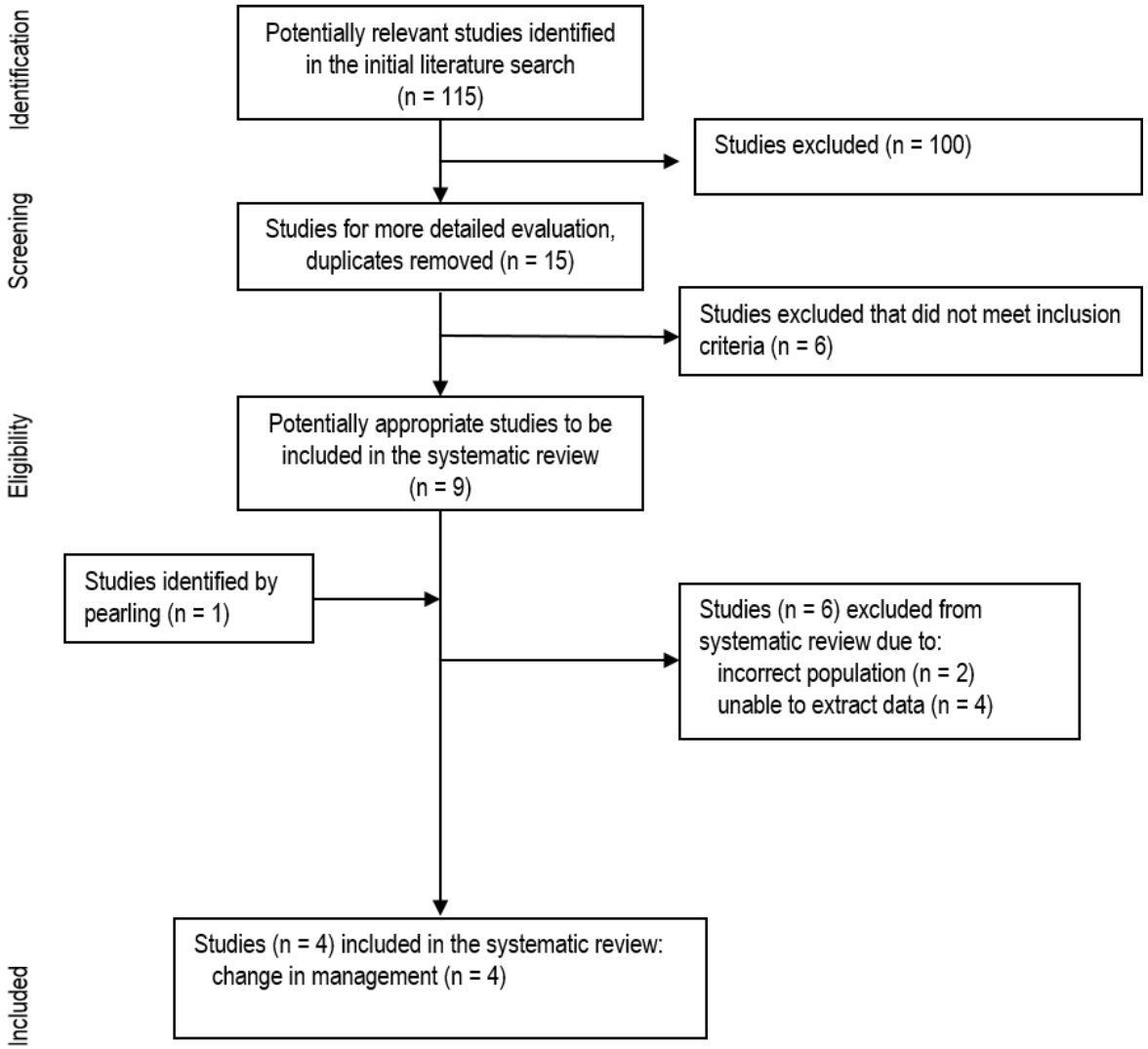


Figure 24 Summary of the process used to identify and select studies for the assessment of the impact of CMR on clinical management of patients suspected of DCM

CMR = cardiac magnetic resonance (imaging); DCM = dilated cardiomyopathy

The characteristics of the included studies are summarised in Table 17, and full study profiles can be found in Table 81, Appendix C. Studies that were considered to be possibly included but were subsequently excluded are listed in Appendix E.

B5.1.2 Risk of bias assessment

The impact on clinical management of a diagnostic test is the second step of linked evidence. It is assessed in order to determine whether management of the DCM population would change should CMR replace a less accurate test in use or be added to current practice.

A summary of included studies for impact on clinical management, including their study design and duration and risk of bias, is provided in Table 17.

One of the 4 studies included for evidence on patient management was a cohort study (rated level III-2 interventional evidence) (Broch et al. 2015), and 3 were case series (rated level IV interventional evidence) with pre- and post-test outcomes assessed prospectively (Abassi et al. 2013; Broch et al. 2015; Bruder et al. 2009; Taylor, AJ et al. 2013). The cohort study was assessed using the SIGN

checklist for cohort studies (Table 81, Appendix C) and was rated as high quality (low risk of bias). The participants of the cohort underwent a range of tests including CMR, and consequently provided within-patient controls that minimised bias. The case series were assessed for quality and bias using the NHLBI Quality Assessment Tool for Case Series Studies, and were all rated as low risk of bias using an adapted scoring system of the tool (Table 81, Appendix C). A GRADE assessment was performed for each outcome (Guyatt et al. 2011).

All studies reported a clear objective, a full description of the study population and intervention, outcome measures and statistical methods. Three of the 4 studies reported that they recruited consecutive patients. One study (Abassi et al. 2013) acknowledged a limitation in patient selection, claiming that clinicians were likely to have selected patients who would benefit from CMR. Two of the studies did not include a follow-up period after CMR had been performed (Abassi et al. 2013; Bruder et al. 2009); however, the remaining 2 studies conducted some level of follow-up to determine the impact of change in management on the patients. Recall bias could not be ruled out in 1 study (Taylor, AJ et al. 2013), which used patient questionnaires to collect data on change in treatment plan 6 months after CMR, although medical records were consulted to provide information where data was missing. Case series studies have no comparator arm and are rated lowest according to the NHMRC recommendations for levels of evidence, and the evidence included here should be considered in this light (NHMRC 2000).

B5.1.3 Characteristics of the evidence base

See Table 81, Appendix C, for details on the individual studies included in the evidence base.

Articles identified in the literature were searched for evidence to inform the linked evidence question of impact on clinical management. Only one article was identified that addressed this question in the specific population of DCM (Broch et al. (2015) included patients with idiopathic DCM); therefore, articles were included that addressed the impact of CMR on the management of broader populations of patients with HF, HF symptoms or unspecified CM.

Three relevant articles were identified in the literature search (Broch et al. 2015; Bruder et al. 2009; Taylor, AJ et al. 2013) and one additional article was identified through pearling (Abassi et al. 2013).

The article by Taylor, AJ et al. (2013) reported on a single-centre trial conducted in patients from the Alfred Hospital Heart Centre, Melbourne, Australia. The study was a prospective observational trial of cardiac patients (n=732) from four pre-specified treatment pathways: CM, viability, tumour/mass and arrythmogenic right ventricular cardiomyopathy (ARVC). The patients underwent assessment and treatment planning using conventional clinical methods, and also underwent CMR to determine its impact on the treatment plan. Through personal communications with the author (A. Taylor), further data were obtained that provided detailed outcomes for the CM group. According to the author, the CM group comprised 90% DCM patients, and thus the data that was provided is considered closely relevant to the population under review.

The pearled study by Abassi et al. (2013) was a single-centre prospective cohort analysis conducted on patients from a single centre in USA (n=150). CMR was performed on HF patients with a treatment plan, following which the clinical impact of CMR was assessed. Patients from the EuroCMR registry[4] who underwent CMR were assessed in the article by Bruder et al. (2013). In this European cohort study, 3,511 patients were recommended for CMR for indications of myocarditis or

[4] The EuroCMR Registry collects and publishes data from patients enrolled throughout Europe. It is an initiative of the European Society of Cardiology Working Group (<visit EuroCMR Registry>)

other CM. The impact of CMR on patient management was reported for this group. Finally, a study conducted in Norway reported diagnostic yield and management outcomes for a group of 102 DCM patients of unknown aetiology who underwent a number of other tests including CMR (Broch et al. 2015).

Study characteristics and key outcomes are provided in Table 17. All outcomes were considered to be critical or important to patients.

Table 17 Key features of the included evidence for impact on clinical management outcomes

Trial/Stud	N	Design/ duration	Risk of bias [a]	Patient population	Key outcome(s)
Bruder et al. (2009)	3,511	Case series with before-and-after data Enrolment period 21 months No follow-up	Low	Patients indicated for myocarditis or CM	New diagnoses Therapeutic consequences Non-invasive imaging ordered after CMR
Abassi et al. (2013)	150	Case series with before-and-after data Enrolment period 6 months No follow-up	Low	Patients with LVEF ≤50% Indications included CM of unknown aetiology (59%); viability (31%); suspected myocarditis (5%); other (5%)	Patients with significant clinical impacts New diagnoses Change in management Predictors of significant clinical impact (single and multivariable analysis)
Taylor, AJ et al. (2013)	488	Case series with before-and-after data Enrolment period 2 years Follow-up at 6 and 12 months	Low	Patients with a treatment plan for CM (90% DCM), ischaemia ruled out	Change in treatment plan: Avoided surgery Avoided implanted device Added implanted device Added surgery
Broch et al. (2015)	88	Cohort study Enrolment period 4 years (October 2008 to November 2012) Follow-up at 1 year after inclusion and long-term (approximately 2–5 years)	Low	Patients admitted to the cardiology department with suspected DCM, but without a known or suspected cause, LVEF ≤40%	New diagnoses Therapeutic consequences

[a] Assessed using the NHLBI Quality Assessment Tool for Case Series Studies

CM = cardiomyopathy; CMR = cardiac magnetic resonance (imaging); DCM = dilated cardiomyopathy; LVEF = left ventricular ejection fraction

B5.1.4 Outcome measures and analysis

See Appendix C for details on the outcomes measured in the studies, along with the statistical methods used to analyse the results. Table 17 lists the key outcomes and their clinical importance in the context of this review.

The evidence for the impact of CMR on clinical management of patients with DCM, CM or HF is reported primarily in outcomes of new or changed diagnoses, change in therapy or management, avoided surgery or invasive procedure, reported as patient numbers and proportions. Case series with pre- and post-test outcomes are considered typical for evidence of clinical management changes (MSAC 2005b). All studies reported a clear description of the statistical methods used, and these are shown in Table 81, Appendix C. Although a change in management is considered more clinically important than a change in diagnosis, the change in diagnosis results are presented first, for chronological reasons.

B5.1.5 Results of the systematic literature review

Does it impact on clinical management?

Summary – Does CMR impact on clinical management?

Three case series and 1 cohort study provided evidence, identified through the literature search and pearling, and extended through personal communications, that was found to be relevant to the impact of CMR on the clinical management of the DCM population.

New and changed diagnoses

The ability of CMR to provide a new diagnosis in patients greatly depends on the prior tests they have undergone. In a sample diagnosed as having idiopathic NIDCM (after standard tests plus ICA), CMR was found to diagnose the aetiology of the DCM in 4/88 cases, 2 of which were subsequently treated with immunosuppressant therapy, which they would not have received without the further testing (GRADE ⊕⊕⊕⊙).

Two case series that reported on broader populations than DCM (i.e. patients indicated for myocarditis or CM; HF patients with LVEF ≤50%) found that CMR provided new diagnoses in 21% and 27% of patients tested, respectively; however, the participants of the study with a higher rate of new CM-related diagnoses had undergone more thorough triaging with prior testing than the other group (GRADE ⊕⊕⊙⊙).

Impact on further diagnostic tests

Low-quality evidence from 1 case series found that when CMR was performed on a cohort of patients with HF symptoms that had undergone prior testing, further non-invasive imaging could be ruled out in 86% of the group. In a group in whom CMR was the first test performed, further imaging could be ruled out in 80.4% of patients (GRADE ⊕⊙⊙⊙).

Devices, procedures or surgery avoided or added

In an Australian population diagnosed through prior testing with NIDCM (N=488 patients), a total of 19 fewer devices were implanted than originally planned, and 1 fewer patient underwent an implantation procedure, as a consequence of undergoing CMR. In addition, there was a reduction of 6 patients undergoing surgery as a consequence of CMR. A total of 61 out of 449 (13.6%) patients had a change in treatment—device implantation or surgery—following CMR at 6 months follow-up. It should be noted that there will be the additional step of CMR stratifying patients with NIDCM and ICM if CMR was to be funded for those with HF symptoms (GRADE ⊕⊕⊙⊙). These data were supported by a further case series that reported an overall reduction in procedures and other services in a small population of HF patients. In broader populations with HF symptoms, a larger proportion of patients were subject to a change in treatment; for example, in 1 case series of patients with HF symptoms (LVEF ≤50%), there was a 27% reduction in catheter-based procedures. In a European registry population of patients undergoing CMR, the test resulted in therapeutic consequences for 44% of participants (GRADE ⊕⊕⊙⊙).

Three case series and 1 cohort study provide before-and-after data on the impact of CMR on patient management, and that evidence is discussed in sections according to the outcomes reported. Further details were sought through personal communication with one author of an Australian case

series, for a subgroup of patients with CMs, of which 90% were estimated to be DCM. This evidence is considered more relevant than that provided by other studies, which were conducted in broader populations of patients with HF or unspecified CM, or the narrower patient group of idiopathic DCM. The evidence from Taylor, AJ et al. (2013) is also highly applicable to the Australian setting, and will be given more attention here.

Impact on the clinical management of patients with an indeterminate result on echocardiography

No studies were identified that explicitly examined the impact of CMR on the management of patients who had an indeterminate result on echocardiography.

Impact on the clinical management of patients with a dilated LV and a low risk of CAD

Two studies were identified as being relevant to the population of those with DCM and a low risk of CAD. In both studies a significant proportion of patients had received an ICA prior to study entry, and were considered to have DCM rather than CAD (Taylor, AJ et al. 2013; Broch et al. 2015).

IMPACT OF DIAGNOSING AETIOLOGY OF NIDCM

In those with a low risk of CAD, the proposed clinical management algorithm suggests that in the absence of CMR, patients would undergo further testing. One study could be considered to provide data on the comparative usefulness of a suite of further tests. Broch et al. (2015), a cohort study identified through the literature search, reported on 102 consecutive patients attending a cardiac clinic and diagnosed with idiopathic DCM. This classification was given after the standard work-up, which included patient history, physical examination, routine blood tests, echocardiography and ICA (which would have excluded ICM). Patients were given an extended work-up that included CMR ± LGE and blood tests for known monogenic causes of NIDCM, right-sided cardiac catheterisation, EMB, exercise test with measurement of peak oxygen consumption, 24-hour ECG and genetic screening. The results of these extended tests are shown in Table 18. In total, of the 102 patients, only 15 (15%) had their diagnosis changed from 'idiopathic DCM' to a specific diagnosis. Blood testing for monogenic causes identified the most possible aetiologies. Of 88 patients who underwent CMR, 2 were diagnosed with non-compaction CM and 2 with CM associated with inflammatory disease by LGE (4.5%).

Table 18 Therapeutic impact of further testing in idiopathic NIDCM

Study Population	Further test	Diagnostic findings	Overlap with CMR results	Therapeutic impact
(Broch et al. 2015) HF patients with LVEF ≤40% with idiopathic NIDCM N=102	CMR N=88 [a]	2 diagnosed with non-compaction CM 2 diagnosed with CM associated with systemic inflammatory disease [b]	N/A	2 cases initiated oral anticoagulation and ICDs were implanted 2 cases initiated appropriate immunosuppressant therapy
	Blood test N=102	16/102 9 parvovirus 4 adenoviral DNA 3 herpes virus 6 DNA	LGE present in 8% of those with viral RNA/DNA LGE present in 40% of those without evidence of viral persistence	Unclear
	Endomyocardial biopsy N=97	2/97 1 diagnosed with cardiac sarcoidosis 1 diagnosed with non-familial transthyretin amyloidosis	1/2 1 patient with cardiac sarcoidosis was suspected on CMR	1 patient with sarcoidosis treated with prednisone
	Exercise testing N=96	3/96 experienced non-sustained VT Diagnostic yield considered 0	None mentioned	2/3 cases of VA prompted ICD implantation Peak oxygen consumption one of several parameters used to stratify for heart transplantation
	24-hour ECG N=89	25/89 experienced non-sustained VT Diagnostic yield considered 0	None mentioned	No direct impact Detection of VT strengthens case for ICD implantation
	Genetic testing N=102	10/102 possible disease-causing mutations 3/10 had family history indicating familial DCM	None mentioned	1/10 findings prompted ICD implantation Allowed for family screening

[a] 88 patients underwent CMR, 81 of whom also underwent LGE.

[b] The 2 patients had LGE of 24.6% and 45.1% of LV volume. One patient was diagnosed with Wegener's granulomatosis and one with sarcoidosis based on extracardiac and cardiac biopsy results.

CM = cardiomyopathy; CMR = cardiac magnetic resonance (imaging); DCN = dilated cardiomyopathy; DNA = deoxyribonucleic acid; ECG = electrocardiography; HF = heart failure; ICD = implantable cardioverter defibrillator; LGE = late gadolinium enhancement; LVEF = left ventricular ejection fraction; N = number of patients; N/A = not applicable; NIDCM = non-ischaemic cardiomyopathy; RNA = ribonucleic acid; VA = ventricular arrhythmia; VT = ventricular tachycardia

DEVICES, PROCEDURES OR SURGERY AVOIDED OR ADDED

The study by Taylor, AJ et al. (2013) reported on patients attending an Australian HF clinic who underwent clinical treatment planning for CM. More than half of the CM patients had already had an ICA, but less than 1% of patients were scheduled for CABG prior to undergoing CMR, so it is likely that the patients being classified as CM in the study were NIDCM rather than ICM. To assess the incremental impact of CMR on treatment of NIDCM, patients underwent scanning prior to undergoing surgery or implantation of the device or devices specified in their treatment plan, after all other tests. Over one-quarter (27%) of patients had already undergone a gated heart pool SPECT, which provided a separate LVEF score.

The study reported the number of patients who avoided device implantations and surgeries as a result of CMR imaging, and also the number who, prior to CMR, did not have a plan for a device or surgery but subsequently underwent either. Decisions regarding cardiac surgery were made in case conferences that included a presentation of CMR findings by a CMR team member. For device implantation, decisions were based on currently accepted guidelines that integrated LVEF measured by CMR. Patient clinical plans were recorded from CMR referrals and confirmed through communications with the clinician or patient. Data for the actual devices implanted and surgeries undergone by the patients was collected through patient questionnaires distributed 6 months following CMR (Taylor, AJ et al. 2013).

Data obtained from the author[5] on the 449 CM patients, of whom it was estimated that 90% were DCM patients, are reported in Table 19 and Table 20. Of 72 patients with a plan prior to CMR to implant a device (ICD, CRT, ICD and CRT, or pacemaker), 21 (29.2%) subsequently avoided having the device implantation. A high proportion (57.6%) of planned CRTs were avoided, while almost one-third (31.8%) of planned ICDs were avoided.

In the group of 375 patients without a treatment plan for device implantation prior to CMR, 20 (5.3%) subsequently did receive a device, and a total of 23 devices were implanted. In the whole group of 488 patients, a total of 19 fewer devices were implanted than originally planned, and 1 fewer patient underwent device implantation overall.

For the whole study population (i.e. including those with ARVC or ischaemia), nearly half of all device changes (either device plans averted or devices implanted in patients without a device plan prior to CMR) were due to what was considered to be more-precise LVEF obtained by CMR, which was either above the recommended threshold of 35% (allowing avoidance of a device) or below the threshold (recommending device implantation).

Other reasons for avoiding device implantation included identification of a previously undiagnosed reversible cause of CM, transmural scar, lack of LV dyssynchrony and exclusion of ARVC. In the broader study, 22 out of 516 patients without a device or surgery plan subsequently underwent implantation of either an ICD or ICD/CRT, of which 16 were implanted on the basis of an LVEF <35% on CMR. Other device recipients were diagnosed by CMR with hypertrophic obstructive CM or ARCV.

[5] Personal communication via email by A. Taylor; received 3 March 2016.

Table 19 Device implantations at 6 months following CMR in HF patients indicated for DCM [a]

	Devices avoided in 72 patients with a device plan N	Devices implanted in 375 patients without a device plan N
ICD	22/69	19
CRT	19/33	2
Pacemaker	1/5	2
Total number of devices implanted	42/107	23
Number of patients affected	21/72 (29.2%)	20/375 (5.3%)

[a] Data obtained through personal communications with A. Taylor.

AICD = automated implantable cardioverter defibrillator; CMR = cardiac magnetic resonance (imaging); DCM = dilated cardiomyopathy; CRT = cardiac resynchronisation therapy; HF = heart failure; ICD = implantable cardioverter defibrillator; N = number

There were also changes in the surgical management of the DCM patients. In the group of 20 patients who had a surgical plan prior to CMR (i.e. coronary artery graft surgery (CAGS), CAGS with ventricular reconstruction, CAGS and valve surgery, valve surgery, possible transplant, transplant, lung transplant or cardiac surgery), 13 (65%) avoided surgery following CMR, while of the 427 patients without a surgical plan prior to CMR, 7 (1.6%) subsequently underwent either valve or cardiac surgery. In total, there was a reduction of 6 patients undergoing surgery.

In summary, a total of 61 out of 449 (13.6%) patients had a change in treatment—device implantation or surgery—following CMR (data from personal communications on the DCM subgroup).

Taylor, AJ et al. (2013) reported on the reasons why surgery plans changed following CMR in the broader CMR-indicated population. The primary reasons for avoiding planned surgery following CMR were findings related to conditions other than DCM, for example lack of myocardial viability in patients planned for CABG or downgrading of the severity of cardiac valve lesions or shunts. The most common reason for newly planned surgery following CMR was identification of the increased severity of a valve lesion.

Table 20 Surgery conducted following CMR in HF patients indicated for DCM [a]

Procedure	Avoided surgeries in 20 patients with a surgery plan N	Added surgery in 427 patients without a surgery plan N
CAGS	2/2	0
CAGS with ventricular reconstruction	2/2	0
Valve surgery	5/7	0
Work up for transplant	3/3	6
Heart transplant	2/5	0
Cardiac surgery	2/3	1
Total number of surgeries	13/20 (65%)	7/427 (1.6%)

[a] Data obtained through personal communications with A. Taylor.

CAGS = coronary artery graft surgery; CMR = cardiac magnetic resonance (imaging); DCM = dilated cardiomyopathy; HF =

heart failure; N = number

In interpreting the change in management data provided by Taylor, AJ et al. (2013), some differences from the way CMR is proposed to be used in this assessment should be kept in mind. The study provided information on a subgroup of patients who had already been diagnosed as having a NIDCM, and had had further investigations, which would have occurred in the absence of CMR (including an ICA in half the cases). Those with ICM had already been ruled out from the CM patient group and are not included. If CMR is to be funded in the proposed population of those with HF symptoms and with a dilated LV (and a low–intermediate risk of CAD), it is proposed to also be used for the earlier step of stratifying patients as having either NIDCM or ICM. Those with ICM will go on for further testing with ICA, and it is not expected that their treatment would change as a result of CMR having identified the ischaemia, compared with other non-invasive imaging having identified the ischaemia[6]. Those with NIDCM would have avoided an ICA through the use of CMR. The impact on treatment would therefore appear smaller through the inclusion of those with ICM. The comparative impact on further imaging, versus the proposed comparators of CTCA and SPECT, is unknown. Overall, the evidence was assessed as low quality using the GRADE system (⊕⊕⊙⊙).

Impact on the clinical management of patients with a dilated LV and an intermediate risk of CAD

No studies were identified that specifically met the criteria of an intermediate pre-test risk of having CAD. However, 2 studies that were included may be applicable to this population. Bruder et al. (2009) reported on a registry that included those indicated for CMR to investigate possible myocarditis or CM; and Abassi et al. (2013) included patients with LVEF ≤50% and indicated for CMR for CM of unknown aetiology (59%), viability (31%), suspected myocarditis (5%) and other diagnoses (5%).

NEW AND CHANGED DIAGNOSES

Two case series reported the number of new diagnoses following CMR (Abassi et al. 2013; Bruder et al. 2009) (Table 21). A diagnosis is considered to be 'new' following CMR if the patient's condition was undiagnosed prior to CMR despite other clinical investigations, and if there was no other diagnosis made. In these studies, diagnosis by CMR was prospective and had the potential to lead to clinical management changes in the group (Abassi et al. 2013; Bruder et al. 2009).

The differences in populations and in prior testing between the 2 studies are reflected in the proportion of patients diagnosed with CM as a result of CMR. Prior tests conducted and new diagnoses are listed in Table 21. In the registry study, the prior testing was less frequent than in the smaller study; that is, 66% compared with 100% of participants in the studies by Bruder et al. and Abassi et al., respectively, underwent echocardiography prior to the intervention. In addition, there was an inclusion criterion of LVEF of ≤50% in the study by Abassi et al., which was not a restriction for the registry population in Bruder et al. (2009). The study by Abassi et al. is likely to have been more rigorously triaged as a result, and thus the population has a higher likelihood of diagnosis of CM by CMR, compared with the registry population (27% vs 21% for all new diagnoses).

Table 21 New diagnoses following CMR for HF or suspected CM

[6] Note that CMR for assessing viability is considered as part of MSAC assessment no. 1237.

Study Population	Prior tests	Patients assessed by CMR (N)	New diagnoses by CMR	N (%)
Abassi et al. (2013) HF patients with LVEF ≤50%, indicated for CMR due to CM of unknown aetiology	Data for whole case series, which included those referred for CMR for viability: 18% prior SPECT 100% prior Echo 59% prior ICA	89	All Non-ischaemic CM Ischaemic CM Muscular dystrophy LV non-compaction CM	24 (27.0) 11 (12.4) 7 (7.9) 4 (4.5) 2 (2.2)
Bruder et al. (2009) Registry patients indicated for myocarditis or CM	Data for whole case series, which included those referred for CMR for suspected CAD and viability: 64.1% transthoracic Echo 25.1% ICA 1.9% transoesophageal Echo 1.8% CTCA 0.3% SPECT 23.1% no imaging	3,511	Unsuspected new diagnosis	737 (21)

ARVC = arrhythmogenic right ventricular cardiomyopathy; CAD = coronary artery disease; CM = cardiomyopathies; CMR = cardiac magnetic resonance (imaging); Echo = echocardiography; ICA = invasive coronary angiography; ICD = implantable cardioverter defibrillator; LV = left ventricular; LVEF = left ventricular ejection fraction; N = number; SPECT = single-photon emission computed tomography

Abassi et al. (2013) reported on the number of changed diagnoses in HF patients (LVEF ≤50%) as a result of conducting CMR. Results are shown for the changes found in patients with a pre-CMR diagnosis of CM of unknown aetiology, and non-ischaemic CM, in Table 22.

Table 22 Changed diagnoses following CMR in patients with HF

Study Population	Pre-CMR diagnosis N		Post-CMR diagnosis N	
Abassi et al. (2013) HF patients with LVEF ≤50%, indicated for CM of unknown aetiology N=150	Non-ischaemic CM	NR	Myocarditis Constriction Hypertrophic CM	4 2 1
	CM of unknown aetiology	89	Non-ischaemic CM Ischaemic CM Muscular-dystrophy CM LV non-compaction	11 7 4 2
	Peripartum CM	1	Myocarditis	1

Source: Abassi et al. (2013)

[a] 88 patients underwent CMR, 81 of whom also underwent LGE.

[b] The two patients had LGE of 24.6% and 45.1% of LV volume. One patient was diagnosed with granulomatosis and one with sarcoidosis based on extracardiac and cardiac biopsy results.

CM = cardiomyopathies; CMR = cardiac magnetic resonance (imaging); HF = heart failure; LGE = late gadolinium

enhancement; LV = left ventricular; LVEF = left ventricular ejection fraction; N = number; NR = not reported

Considered together, the results from these 2 studies reporting on new or changed diagnoses indicate that further clarity may be achieved through the use of CMR; however, the numbers are small and there are no comparative data against the main comparators (CTCA or SPECT), and therefore there is no strong evidence. Overall, the evidence for new and changed diagnoses was assessed as being low quality using the GRADE system (⊕⊕⊙⊙).

IMPACT ON FURTHER DIAGNOSTIC TESTS

Bruder et al. (2009) reported that in the whole cohort analysed (including those suspected of ICM/CAD and those being assessed for viability), CMR provided sufficient information so that no further non-invasive imaging was required in 86% of patients. In 23.1% of patients, CMR was the first imaging procedure performed. Of these patients, CMR was considered to rule out the need for further imaging in 80.4% of cases. The generalisability of these data to the target population (those suspected of NIDCM) is unclear. For the subgroup of patients being referred for CMR due to CM or myocarditis, the results are provided in Table 23. This outcome, taken from 1 case series, was assessed as very low quality (GRADE ⊕⊙⊙⊙).

Table 23 Patients indicated for myocarditis or CM with therapeutic consequences following CMR

Management	N (%)
Invasive angiography or biopsy	221 (6.3)
Non-invasive imaging ordered after CMR:	
Transthoracic Echo	593 (16.9)
Transoesophageal Echo	14 (0.4)
Computed tomography	21 (0.6)

Source: Bruder et al. (2009)

CM = cardiomyopathies; CMR = cardiac magnetic resonance (imaging); Echo = echocardiography; N = number of patients

One article included in the diagnostic accuracy section (Assomull et al. 2011) discussed the use of CMR as a gatekeeper to ICA in patients with HF of unknown aetiology. No change in the rate of ICA actually occurred, only the suggestion that CMR may be used in this way (so it is not technically an included study for this section). In their case series of 120 patients, CMR was 100% sensitive at detecting patients with ischaemia, which meant that every patient who required an ICA would have received one if referral to an ICA was based first on CMR. Conversely, ischaemia was ruled out in 73% of cases, so these patients could have theoretically avoided an ICA. In the proposed clinical management algorithm, CMR would be used as an alternative gatekeeper to CTCA and SPECT, which are currently used in patients with a low to intermediate risk of CAD.

CHANGE IN MANAGEMENT OR THERAPY

Catheter-based procedures avoided and conducted as a result of undergoing CMR were reported in the case series by Abassi et al. (2013), which used an LVEF ≤50% as a criterion for inclusion. Patients were referred for CMR for the following indications: 1) CM of unknown aetiology, 2) viability or 3) suspected myocarditis. Decisions to implant devices or avoid planned procedures were based directly on CMR findings. In this study, catheter-based procedures were the most commonly impacted element of patient management, and 27% of patients underwent changes to these procedures as a result of CMR. These data were reported for all included HF patients (n=150), of

which 59% (n=89) were indicated for CM of unknown aetiology (Table 24). Scar assessment by LGE led to an impact on planned CABG procedures, with some patients avoiding the surgery and others ultimately undergoing CABG as a result of LGE findings. The authors also commented that, in patients without CAD risk factors but with a history or ECG evidence of myocardial infarction (MI), and indicated for CM of unknown aetiology who underwent CMR, the absence of LGE at a young age (<30 years) led to clinicians avoiding angiography. The number of avoided angiographies in this group was not reported. Overall, there was a significant clinical impact in 65% of cases, which included a change in management in 52% of cases, a new diagnosis in 30%, and both occurring in 17% of patients.

Table 24 Catheter-based procedures, vascular surgery, electrophysiology procedures, medications and hospital admissions avoided and conducted following CMR in patients with HF

Procedure or other management	Avoided following CMR N (%)	Added following CMR N (%)
All changes	56 (37)	52 (34)
Angiography	17 (11)	14 (9)
PCI	8 (5)	11 (7)
CABG	7 (5)	7 (5)
ICD	10 (7)	5 (3)
Anticoagulation	9 (6)	9 (6)
Cardiac medication	3 (2)	4 (3)
Hospital admission	2 (1)	2 (1)

Source: Abassi et al. (2013)

CABG = coronary artery bypass grafting; CMR = cardiac magnetic resonance (imaging); HF = heart failure; ICD = implantable cardioverter defibrillator; N = number; PCI = percutaneous coronary intervention

Bruder et al. (2009) reported on the number of patients who underwent therapeutic consequences following CMR in the subgroup that was indicated for myocarditis or CM (Table 23). The total number of patients with therapeutic consequences was 1,545 (44% of 3,511 patients in the subgroup). These data were not stratified into procedures avoided or conducted as a result of undergoing CMR.

Table 25 Patients indicated for myocarditis or CM with therapeutic consequences following CMR (Bruder et al. 2009)

Management	N (%)
Change in medication	797 (22.7)
Intervention or surgery	102 (2.9)
Hospital total:	74 (2.1)
Hospital admission	14 (0.4)
Hospital discharge	60 (1.7)

CM = cardiomyopathy; CMR = cardiac magnetic resonance (imaging); N = number of patients

The evidence for planned devices, procedures and surgeries avoided was taken from 2 case series that investigated broader populations of patients with myocarditis or CMs, or having their viability assessed. Together, the evidence was assessed as low quality using the GRADE system (⊕⊕⊙⊙).

B5.2 THERAPEUTIC EFFECTIVENESS

B5.2.1 Risk of bias assessment

Due to the range of different ways in which CMR may change the management of patients with suspected DCM, data for this section were identified through a rapid review of the literature, searching for high-level evidence on treatment effectiveness, and giving preference to recent and more-comprehensive reviews if several were available on the same topic.

SRs for this section were assessed using the AMSTAR checklist (Shea et al. 2007). Seven well-performed SRs or health technology assessments (HTAs) were included, plus 1 moderate-quality HTA, although the evidence they included was considered to be at a high risk of bias and the subsequent GRADE of evidence was low or very low. Study profiles for the SRs identified may be found in Appendix C (Table 84). Taylor, AJ et al. (2013) provided level III-2 evidence on health outcomes between those who avoided surgery or device implantation as a result of CMR and those who did not. This study was evaluated using the SIGN methodological checklist for cohort studies, and was rated as having a high risk of bias for the outcomes of mortality, NYHA class and incidence of major events.

Broch et al. (2015) provided case report data on the health outcomes after a management change due to CMR, but case reports have an inherently high risk of bias, and no risk of bias checklist was used.

B5.2.2 Characteristics of the evidence base

Two studies included in section B5.1 (impact on clinical management) provided data on the health outcomes of patients who had their management changed as a result of investigations with CMR, compared with device and surgical plans prior to CMR (Taylor, AJ et al. 2013), and with other investigations for idiopathic NIDCM (EMB, genetic testing, 24-hour ECG etc). Taylor, AJ et al. (2013) provide cohort study data comparing the health of those who had their surgical or device plan averted by CMR with those who proceeded with the surgical or device procedure that had been planned prior to CMR. Broch et al. (2015) presented a series of case reports that provided transplant-free survival data in patients who had their management altered as a consequence of receiving a more specific diagnosis by CMR.

A summary of the trial characteristics of studies providing evidence relating to the health impact from the change in management is provided in 26.

Table 26 Key features of the included evidence assessing impact of change in patient management

Trial/Study	N	Design	Risk of bias	Patient population	Key outcome(s)	Result used in economic model
Taylor, AJ et al. (2013)	143	Cohort study	High	Those scheduled for surgery whose management changed from CMR vs those who management did not change	Mortality, NYHA class, adverse events	No
Broch et al. (2015)	4	Case reports	High	Patients whose management was influenced by CMR	Transplant-free survival	No
Theuns et al. (2010)	4,195	SR	Low	Patients with or without ischaemia, treated with ICDs plus OMT vs OMT alone	Survival	No
Windecker et al. (2014)	93,553	SR	Low	Stable CAD treated with revascularisation or not	Survival, myocardial infarctions, subsequent revascularisations	No
Colquitt et al. (2014) and Uhlig et al. (2013)	1,482	HTAs	Low and moderate	Patients with NIDCM or HF with non-ischaemic subgroup	Survival, cardiac deaths, transplantation, SCD, syncope	No
Chen et al. (2013)	719	SR	Low	Patients with viral myocarditis treated with corticosteroids vs no corticosteroids	Survival, transplant free survival	No
Robinson et al. (2015)	145	SR	Low	Adults suspected of having myocarditis, and children with acute encephalitis and myocarditis, treated with intravenous immunoglobulin (IVIG) vs no IVIG	Event-free survival	No
Liu et al. (2013)	687	SR	Low	Patients with viral myocarditis treated with herbal medicines vs no herbal medicine	Cardiac death, quality of life	No
Sadek et al. (2013)	299	SR	Low	Patients with cardiac sarcoidosis, treated with or without corticosteroids	Survival, LV functioning	No

CAD = coronary artery disease; CMR = cardiac magnetic resonance (imaging); ICD = implantable cardioverter defibrillator; HF = heart failure; HTA = health technology assessment; LV = left ventricle; N = number of patients; NIDCM = non-ischaemic dilated cardiomyopathy; NYHA = New York Heart Association; OMT = optimal medical treatment; SCD = sudden cardiac death; SR = systematic review

B5.2.3 Outcome measures and analysis

The outcomes focused on for the impact of change in management section were those that were most likely to be patient relevant; that is, preference was given to the outcomes of mortality and quality of life, with comments also made on LVEF. The results of SRs were provided, with the exception of the analyses of studies comparing ICDs plus optimal medical treatment (OMT) versus

OMT alone (where data from the original studies were derived), due to differences between the HTAs identified and inaccuracies in the data extraction by Theuns et al. (2010).

B5.2.4 Results of the literature review

Does the change in management improve health outcomes?

Summary – Do changes in management resulting from CMR improve health outcomes in patients presenting with HF symptoms and dilated LVs?

In patients presenting with HF symptoms, CMR can be used in several different places in the clinical management algorithms.

For the purposes of distinguishing between ischaemic and non-ischaemic DCM, CMR is proposed as an alternative to SPECT and CTCA, but the comparative accuracy of CMR for this indication, and the potential impact to patient health, are both unknown. Those patients incorrectly classified as ischaemic would be likely to undergo an ICA, which would identify whether they are truly ischaemic or not. Treatment for those falsely identified as having ischaemia would be the same, but with the addition of an invasive diagnostic procedure.

A small number of ischaemic cases who are LGE– will be falsely identified by CMR as NIDCM; however, patients who are LGE– have a better prognosis than those who are LGE+, and the impact of treating these patients as NIDCM is unknown. The effectiveness of ICD treatment was similar in patients with ICM and NIDCM.

Prognostic data suggests that LGE-CMR provides a more accurate measure of LVEF than echocardiography, which is currently key to determining whether a patient with NIDCM is referred for surgery or device implantation. Prognostic data suggests that LGE is a better predictor of outcomes than LVEF, so it is likely that this information will be used to determine whether patients should proceed to surgery or not in the near future. However, no trials were identified to prove that stratifying patients with LGE-CMR results in better health outcomes than the current practice without CMR.

For patients who avoid device implantation or surgery due to the use of CMR, the expected impact would depend on whether the CMR result was correct, or whether they were ruled out from these treatments inappropriately. There is some evidence showing a trend towards delayed ICD treatment for NIDCM not showing the same superiority to OMT that early treatment with an ICD does (GRADE ⨁⊙⊙⊙). It is possible that if some patients are ruled out inappropriately from ICD treatment by CMR, their outcomes may therefore be inferior to the treatment strategy planned prior to CMR. However, the likelihood of this occurring is unknown.

In patients correctly ruled out from more-invasive treatments, it is expected that they will have non-inferior effectiveness outcomes and superior safety outcomes from having avoided the invasive surgical procedure and/or device implantation. One Australian case series compared the mortality rates of those who had invasive treatments avoided due to CMR findings with those who proceeded with invasive treatments and found no significant difference (GRADE ⨁⊙⊙⊙).

Some patients with rare forms of DCM are expected to have their aetiology diagnosed with the use of CMR, which may have been missed in the absence of CMR testing. Although all patients with DCM would receive OMT for HF symptoms, those with myocarditis, sarcoidosis and Wegener's granulomatosis would receive additional immunosuppressants; those with LV non-compaction would receive antithrombotic medication and ICDs; and those with haemochromatosis would also receive regular transfusion-chelation therapy. The evidence supporting these treatments is limited.

Do changes in management resulting from CMR improve health outcomes in family members of someone with DCM?

No evidence regarding the changes expected specifically for family members were identified; therefore, the last step of linked evidence could not be assessed for family members.

In patients presenting with HF, CMR can be used in several different places in the clinical management algorithm (Figure 2 and Figure 4). The impact that CMR is expected to have will differ depending on where in the pathway it is implemented and what prior tests patients have had.

Impact of change in management in patients with indeterminate results on echocardiography

There was no evidence specifically related to the accuracy or impact on patient management of using CMR in patients with an indeterminate result on clinical examination, ECG or echocardiography. It is expected that CMR may replace at least some of the tests currently performed in this population (e.g. gated heart pool SPECT and contrast echocardiography), and in those cases where a dilated LV is detected, it would also replace the alternative tests of CTCA or SPECT. Given the lack of comparative accuracy data, the false positive or negative rates from the different tests are unknown, and the impact of any possible changes in management cannot be determined.

Impact of detecting aetiology of NIDCM in patients with a low risk of CAD

In patients with a low risk of CAD, CMR may be used as either an alternative to or an adjunct to 'further testing' to determine the aetiology of the DCM. In section 5.1 of this assessment, 2 studies reported on changes in management expected due to CMR and other further tests in patients diagnosed with idiopathic NIDCM after the standard tests plus ICA, and showed that CMR may detect some forms of aetiology that were missed through other investigations. The benefit of detecting these aetiologies depends on how much the treatments differ from idiopathic NIDCM, and on the effectiveness of treatment once these patients are diagnosed.

One author proposed that CMR may be used to provide guidance regarding where EMBs should take place to increase tissue yield (Mann et al. 2015). However, no evidence regarding the effectiveness of CMR to triage to biopsy, or the accuracy of using CMR to guide the location of biopsies, was identified. This has not been investigated further.

TREATMENT EFFECTIVENESS FOR MYOCARDITIS

One key benefit of CMR is thought to be the ability to detect DCM cases who have myocarditis, allowing a different treatment strategy to be used, rather than one aimed at idiopathic DCM.

Three Cochrane Reviews were identified that assessed different treatment strategies for viral myocarditis. One reviewed corticosteroids, one intravenous immunoglobulin, and one herbal medicines.

Corticosteroids for viral myocarditis

One high-quality Cochrane SR assessed the effectiveness of corticosteroids for treating viral myocarditis, compared with no intervention, placebo, supportive therapy, antiviral therapy or conventional therapy (Chen et al. 2013). It identified 8 RCTs, with a total of 719 patients. On the key outcomes of all-cause mortality, or death or heart transplant combined, corticosteroids did not show any significant benefit over the alternative treatment strategies (see Figure 25) (GRADE ⊕⊙⊙⊙). However, after 1–3 months of treatment, patients receiving corticosteroids had better LVEF scores on average compared with the control group (k=5, n=442, mean difference = 7.36, 95%CI 4.94, 9.79), but there was substantial heterogeneity (GRADE ⊕⊕⊕⊙). NYHA class and LV end-stage systole diameter were not affected (Chen et al. 2013) (GRADE ⊕⊙⊙⊙).

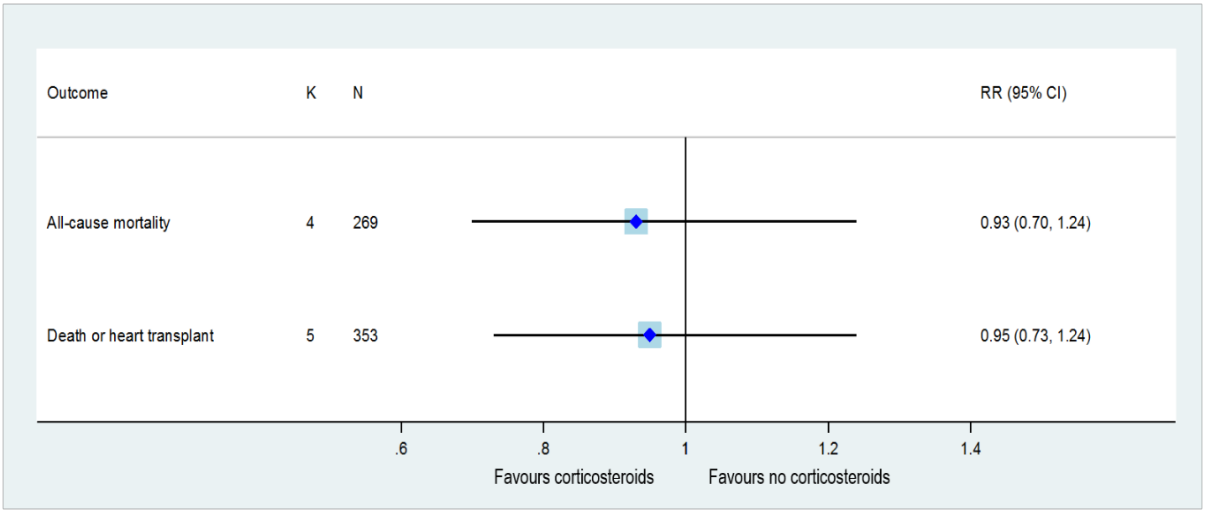


Figure 25 Effectiveness of corticosteroids in treating viral myocarditis at reducing mortality or heart transplants

CI = confidence interval; K = number of studies; N = number of patients; RR = relative risk

Intravenous immunoglobulin for viral myocarditis

A high-quality Cochrane SR assessing intravenous immunoglobulin (IVIG) for viral myocarditis identified only 2 trials that met their inclusion criteria with unclear and high risk of bias (Robinson et al. 2015). One trial included 62 adults suspected of having myocarditis, and the other included 83 children with acute encephalitis and myocarditis. IVIG did not statistically significantly improve the rate of event-free survival in adults (i.e. no death, transplant or LV assist device) compared with placebo (OR 0.52, 95%CI 0.12, 2.30, favouring placebo) (GRADE ⨁⊙⊙⊙). Similarly, there was no statistically significant difference in event-free survival in children with myocarditis and encephalitis when treated in hospital with either IVIG or no therapy, although the results favoured IVIG (OR 7.39, 95%CI 0.91, 59.86) (GRADE ⨁⊙⊙⊙). These studies were considered to provide a very low grade of evidence, due to unclear or high risk of bias, indirectness of the population (in 1 trial only a small proportion of patients had proven myocarditis, while in the other all participants also had encephalitis), plus an imprecise estimate of effect.

Herbal medicines for viral myocarditis

A high-quality Cochrane SR assessed herbal medicines with/without supportive therapy, compared with supportive therapy alone, for treating viral myocarditis. The review identified a total of 20 RCTs, all conducted and published in China (Liu et al. 2013). One RCT reported that, compared with supportive therapy, *Astragalus membranaceus* injections did not reduce the risk of cardiac death (GRADE ⨁⊙⊙⊙). Only 1 study assessed quality of life, as measured on the Short Form-36, and reported that use of Compound Qiangpi pills plus supportive therapy was superior to supportive therapy alone (MD –8.84, 95%CI –10.87, –6.80), and, similarly, that *Shengmai decoction* plus supportive therapy was superior to supportive therapy alone (MD –4.0, 95%CI –6.23, –18.1) (GRADE ⨁⊙⊙⊙). Six trials reported data on adverse events (AEs), and no serious AEs were reported (Liu et al. 2013).

Individual trials reported on the impact of different herbal medicines (with or without supportive therapy) and the number of patients reporting premature beats or arrhythmias (see Figure 28). However, the small size of the trials, limited number of trials of individual herbs, and the risk of bias

within the trials led to the authors to conclude that the results should be interpreted with care (Liu et al. 2013).

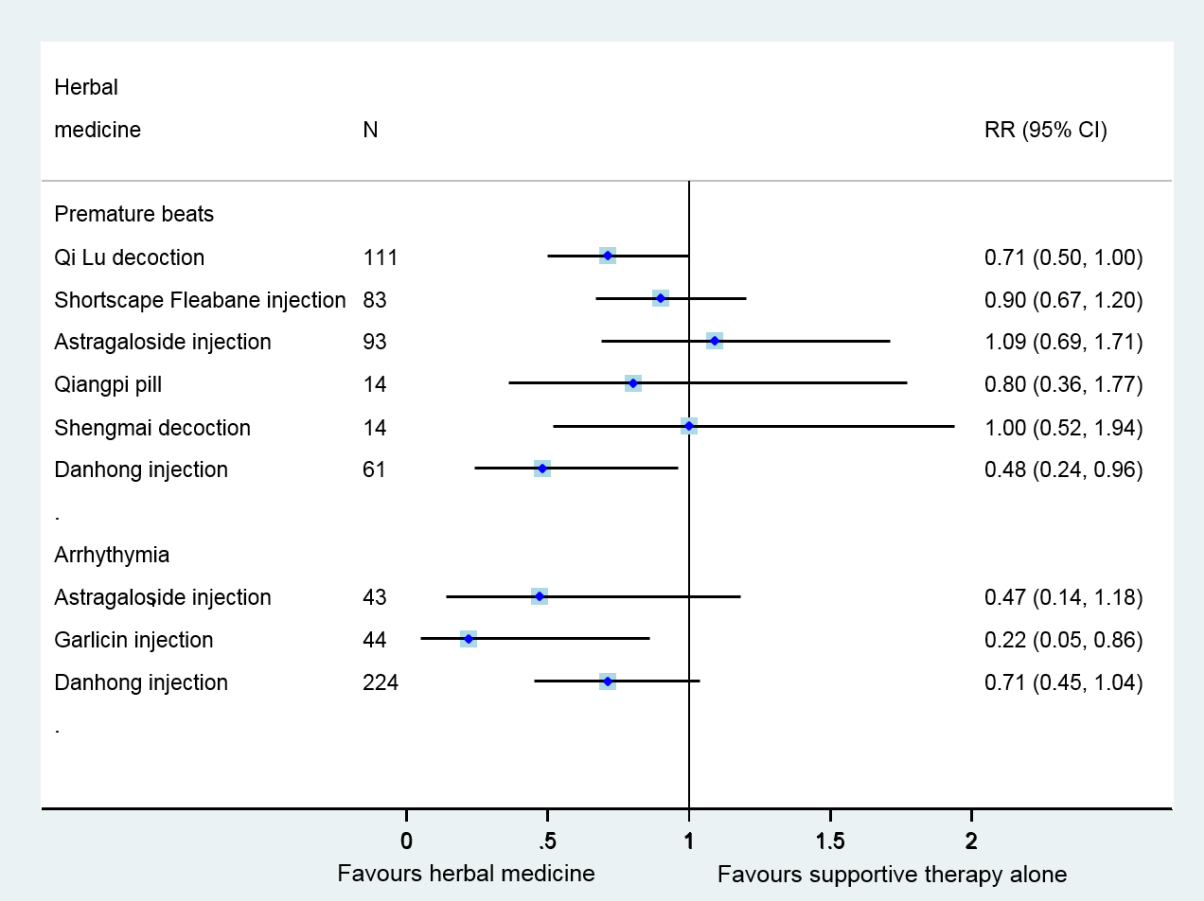


Figure 26 The effectiveness of herbal medicines for reducing number of patients with viral myocarditis who experience premature beats or arrhythmias

CI = confidence interval; N = number of patients; RR = relative risk

TREATMENT EFFECTIVENESS FOR CARDIAC SARCOIDOSIS

In the change in management study by Broch et al. (2015), 1 patient was identified as having systemic inflammatory disease, which was confirmed by EMB as being sarcoidosis. The patient received prednisone (an immunosuppressant) and was alive and transplant-free at 4.7 years follow-up.

One SR was identified that reviewed the published literature on corticosteroid treatment for cardiac sarcoidosis (Sadek et al. 2013). No randomised trials were identified and the 10 cohort studies or case series identified were all of poor to fair quality, presenting results from a total of 257 patients treated with corticosteroids and 42 patients not treated with corticosteroids. The majority of patients in the studies presented with atrioventricular block (AV) block (n=104) followed by HF (n=61) and VT (n=56).

Nine studies reported on mortality. Mortality rates were highly variable between studies and of limited use in informing the role of corticosteroids in reducing mortality (GRADE ⊕⊙⊙⊙). Only 1 study provided individual patient data on LV dysfunction with and without corticosteroids. The 66 patients with mild to moderate LV dysfunction who were treated with corticosteroids predominantly had preservation of normal LV function or an improvement of LV dysfunction. Conversely, 11 out of 13 patients who did not receive corticosteroids had a reduction in LV functioning. Additional before-

and-after case series provided information on a further 25 patients with severe LV dysfunction who had received corticosteroids, but mean LVEF did not change with treatment (Sadek et al. 2013).

The evidence regarding the effectiveness of corticosteroids for cardiac sarcoidosis is very limited. However, there is a trend favouring corticosteroid treatment for improving LV functioning, although the majority of the evidence was in a population presenting with AV block rather than HF symptoms (GRADE ⊕⊙⊙⊙).

TREATMENT EFFECTIVENESS FOR WEGENER'S DISEASE

The article by Broch et al. (2015) stated that CMR detected two patients with systemic inflammatory disease, one of which was diagnosed by an extra-cardiac biopsy as having Wegener's granulomatosis. This was treated by immunosuppressants and the patient was classified as being alive and transplant-free at 5.3 years follow-up.

No SRs were identified that assessed the treatment effectiveness of immunosuppressants for Wegener's disease.

TREATMENT EFFECTIVENESS FOR LV NON-COMPACTION

Left ventricular non-compaction (LVNC) is a myocardial disorder that is characterised by trabeculations and intratrabecular recesses in the ventricular endothelium, and can present with features of DCM. The study by Broch et al. (2015) reported that two cases of LVNC identified by CMR were not detected by any other means. Two conditions prevalent in LVNC are tachyarrhythmia, which can lead to SCD, and clotting of blood in the heart. The two patients identified subsequently received oral anticoagulants and ICDs. One of these patients received a cardiac allograft after 2.2 years and the other was alive and transplant-free at 4.6 years follow-up (Broch et al. 2015). It is unclear whether the diagnosis of LVNC resulted in different treatment than what the patients would have received had they remained with the diagnosis of idiopathic DCM.

No SRs were identified on the treatment effectiveness of treatments for LVNC compared with what patients would receive based on a diagnosis of idiopathic DCM.

TREATMENT EFFECTIVENESS OF HAEMOCHROMATOSIS

Secondary haemochromatosis CM has been described as a DCM (Kremastinos & Farmakis 2011). It has been suggested in the literature that CMR may allow iron overload (haemochromatosis) to be detected (Karamitsos et al. 2009). No studies identified in this assessment provided evidence on the frequency with which CMR may detect haemochromotosis. The treatment for patients with signs of HF and evidence of functional or structural cardiac dysfunction, as well as secondary haemochromatosis, involves both treatment for HF symptoms and the reduction of iron through either phlebotomy (bloodletting), chelation therapy or a combination of the two (Kremastinos & Farmakis 2011).

Although phlebotomy has been considered a cornerstone treatment for haemochromatosis, no randomised trials have been performed to assess the clinical benefit (Assi & Baz 2014). Likewise, dietary restrictions and medications to reduce iron levels appear logical but have not been evaluated with randomised trials (Adams & Barton 2010).

Impact of determining whether the patient has NIDCM or ICM in those with a dilated LV and an intermediate risk of CAD

One of the uses proposed for CMR is to assess whether a patient with DCM has NIDCM or ICM. In section B3.6 the accuracy of using CMR for this purpose is assessed, compared with the reference standards of ICA and clinical diagnosis. Unfortunately, there was insufficient comparative evidence on the accuracy of SPECT and CTCA in the target population to make conclusions on the number of

false positives and negatives that would result from CMR compared with these alternative non-invasive imaging modalities.

IMPACT OF AVOIDING ICAS

One of the potential comparators with CMR is ICA. If a patient is found to have signs of ischaemia on CMR or the other non-invasive techniques of CTCA or SPECT, they would proceed to have an ICA, but if they are classified as non-ischaemic, they would avoid having an ICA. The use of CMR as a gatekeeper to ICA was discussed by Assomull et al. (2011). Due to their invasive nature, ICAs are associated with a risk of complications, which may be avoided in those with NIDCM.

MANAGEMENT OF PATIENTS CLASSIFIED WITH ISCHAEMIA

If a patient is identified as having ischaemia by CMR, CTCA, SPECT or stress echocardiography and is well enough to tolerate an invasive procedure, they would likely proceed to have an ICA, which is the gold standard for confirming whether a patient has ischaemia or not. The results of the ICA would then be used to determine the treatment strategy: whether the patient receives treatment for HF alone, or treatment for HF and CAD (see Figure 2 and Figure 4 for clinical management algorithm). If patients receive a false positive test for ischaemia on CMR, SPECT, CTCA or stress echocardiography, they would therefore undergo an unnecessary invasive imaging test (which has safety implications; see section B7), but would not undergo incorrect treatment.

If patients are classified as LGE–, there is still a small chance that they would have ICM. These patients would inappropriately be classified as NIDCM and miss receiving an ICA and revascularisation. From the prognostic section (B4), it was reported that having ICM was associated with a worse prognosis than NIDCM. However, from a good-quality SR cited in MSAC assessment no. 1237 (Lipinski et al. 2013), it was reported that, in patients with known or suspected CAD, having LGE was a significant predictive factor, with those who were LGE+ having almost 4-times the odds of having a cardiovascular death or non-fatal MI than those who were LGE– (OR = 3.82; 95%CI 2.56, 5.71). The extent to which ischaemic patients who are LGE– would suffer due to being incorrectly diagnosed as NIDCM is therefore unknown.

If a patient is correctly identified as being ischaemic, they would receive treatment for coronary artery disease (CAD). A high-quality SR and network meta-analysis was identified that compared revascularisation techniques and medical treatment in patients with stable CAD (Windecker et al. 2014). Revascularisation included coronary artery bypass grafting (CABG), percutaneous revascularisation (PCI), balloon angioplasty, bare metal stents and drug-eluting stents. One hundred randomised trials in 93,553 patients were included. The results of the network meta-analyses were that CABG reduces risk of death (GRADE ⊕⊕⊙⊙), MI (GRADE ⊕⊕⊙⊙) and subsequent revascularisation (GRADE ⊕⊙⊙⊙), compared with medical treatment. Survival was also improved from drug-eluting stents, but not from other PCI treatment, compared with medical treatment (Windecker et al. 2014). Therefore, a correct diagnosis of ICM is likely to result in treatment that benefits the patient, and patients falsely diagnosed as NIDCM would have a delay in appropriate treatment.

TREATMENT WITH ICDS IN ISCHAEMIC AND NON-ISCHAEMIC DCM

It was hypothesised that if there were clear differences in the way that patients with NIDCM and ICM responded to particular therapies, support would be given to making a distinction between the two sub-types of DCM. One SR was identified that provided subgroup analyses when assessing the impact of ICDs plus OMT, versus OMT alone (Theuns et al. 2010). The meta-analysis provided in Figure 27 includes the same trials as those by Theuns et al. (2010), but extracted the data from the primary trials, due to identification of some errors in the data extraction by Theuns et al. (2010). ICDs were found to be effective at reducing the rate of all-cause mortality in both patients with ICM

and those with NIDCM, although there was a high degree of heterogeneity in the subgroup with ischaemia (see Figure 27) (GRADE ⊕⊕⊙⊙). It is clear from the results below that the information regarding whether patients have ischaemia or not is insufficient to determine whether they should receive an ICD or not, as the results do not appear to differ compared with OMT alone.

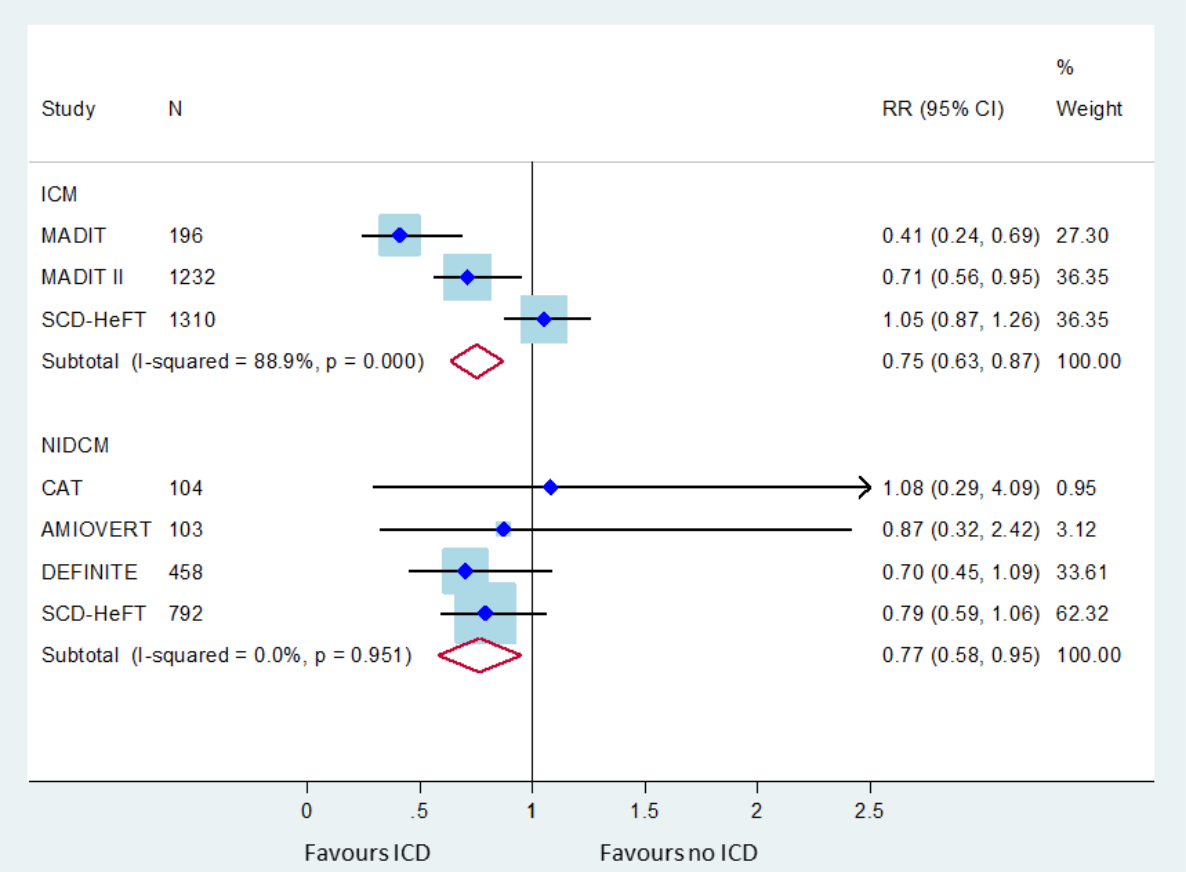


Figure 27 Effectiveness of ICD plus OMT versus OMT alone at reducing all-cause mortality in patients with ICM and NIDCM

AMIOVERT = Amiodarone vs Implantable Defibrillator in Patients with Nonischemic Cardiomyopathy & Asymptomatic Non-sustained Ventricular Tachycardia; CAT = Cardiomyopathy Trial; CI = confidence interval; DEFINITE = The Defibrillators in Nonischemic Cardiomyopathy Treatment Evaluation; ICD = implantable cardioverter defibrillator; ICM = ischaemic cardiomyopathy; N = number of patients enrolled; NIDCM = non-ischaemic dilated cardiomyopathy; MADIT = Multicenter Automatic Defibrillator Implantation Trial; RR = relative risk; SCD-HeFT = Sudden Cardiac Death in Heart Failure Trial

Impact of targeting treatment of NIDCM based on LGE-CMR

The decision regarding whether a patient should receive an ICD currently incorporates the patient's LVEF score. Decisions regarding the use of ICDs may be made on the basis of CMR-determined LVEF, as well as LGE or TWA abnormalities. In the prognostic section (B4.2) it was reported that LVEF determined by LGE-CMR was a better predictor of health outcomes than LVEF determined by echocardiography. Furthermore, LGE status was a better predictor of health outcomes than LVEF, with LGE+ patients being up to 4-times more likely to have a cardiac event and 3-times more likely to die from a cardiac event than those who are LGE–.

Data from the prognostic section (B4) suggested that a perfusion mismatch detected by SPECT, and myocardial scarring detected by LGE-CMR both predicted the likelihood of a cardiac event, and that the information from both combined is superior to one or the other. Perfusion mismatch by SPECT was related to a higher chance of a cardiac event than myocardial scarring on LGE-CMR. Conversely,

in a different study, LGE-CMR was found to identify non-responders to CRT more reliably than SPECT in patients with NIDCM.

The Australian study by Taylor, AJ et al. (2013) showed that when patients had their LVEF re-examined by CMR, fewer patients, on average, were recommended for surgery, due to CMR showing a higher level of LV functioning than echocardiography/SPECT. Taylor, AJ et al. examined patients' health outcomes after 12 months in 143/150 of those who initially had a cardiac device or surgical plan (for CM, ARVC, ischaemia or tumour/mass), comparing those who had their treatment plan altered as a consequence of CMR with those who did not, and reported that the health outcomes were similar, with no significant differences in NYHA class, 12-month survival or incidence of major AEs (i.e. death, hospital admission or deterioration in NYHA class) (Table 27). For the purposes of evaluating the health outcomes after the changes in management, this study was considered to have a high risk of bias, as it is unknown to what degree the patients whose management plans varied differed from those whose management plans remained the same (GRADE ⊕⊙⊙⊙).

Table 27 Health outcomes after changes in management

Outcome	Device or surgical plan averted due to CMR (n=56)	Underwent planned device or surgical procedure (n=87)	Difference
NYHA class	Median = 1 (IQR = 1–2)	Median = 1 (IQR = 1–2)	p=0.88
12-month survival	94%	98%	p=0.57 (I^2)
Incidence of major AEs (i.e. death, hospital admission or deterioration in NYHA class)	35%	33%	p=0.89 (I^2)

Source: Taylor, AJ et al. (2013)

CMR = cardiac magnetic resonance (imaging); NYHA = New York Heart Association; IQR = interquartile range

One prognostic study reported that the regional scar burden as determined by LGE-CMR was also a significant predictor of whether patients would respond to CRT or not, whereas scar burdens were similarly high in both responders and non-responders as assessed by SPECT. Another study found that both myocardial scarring detected on LGE-CMR and SPECT perfusion mismatch were non-significant predictors of the likelihood of having an adverse cardiac event, but that they provided different and possibly complementary information, with the two results combined being a better predictor than one imaging modality by itself.

Although this information suggests that patients are *likely* to fare better when their treatment is determined with the addition of LGE-CMR information, there have not been any trials comparing health outcomes between groups treated according to data with or without CMR results. Had this existed, it would have been presented as direct evidence of effectiveness in section B1.

In the absence of direct evidence, Merlin et al. (2013) suggest that the benefit of a more-accurate diagnosis depends on the patient's prognosis without the treatment, as well as the comparative effectiveness and risk of the treatment in these particular patients. Treatment effectiveness is assessed below. Regardless of CMR findings, all patients are assumed to be treated with OMT for HF symptoms, with the findings of further testing influencing the rate of treatment with ICDs and CRT, or treatment for specific aetiology.

IMPACT OF TREATMENT FOR NIDCM

Two HTAs compared the effectiveness of ICDs with OMT in patients with NIDCM or HF with a non-ischaemic subgroup (Colquitt et al. 2014; Uhlig et al. 2013). The 2 HTAs included 4 RCTs, which were combined using meta-analyses (Bänsch et al. 2002; Bardy et al. 2005; Ellenbogen et al. 2006; Strickberger et al. 2003). Meta-analyses for the individual health outcomes are detailed in Appendix

K. An overall summary of different outcomes is provided in Figure 26. For the outcomes of all-cause mortality and SCD, the meta-analyses favour the use of ICDs (RR 0.78, 95%CI 0.61, 0.98; and RR 0.26, 95%CI 0.09, 0.77) (GRADE ⊕⊕⊕⊙). Other outcomes did not show statistically significant differences (GRADE ⊕⊕⊙⊙). Given the high clinical importance of all-cause mortality and SCD, it could be concluded that having a true positive diagnosis of NIDCM, and receiving treatment with an ICD, is likely to be better than the treatment received from an incorrect diagnosis.

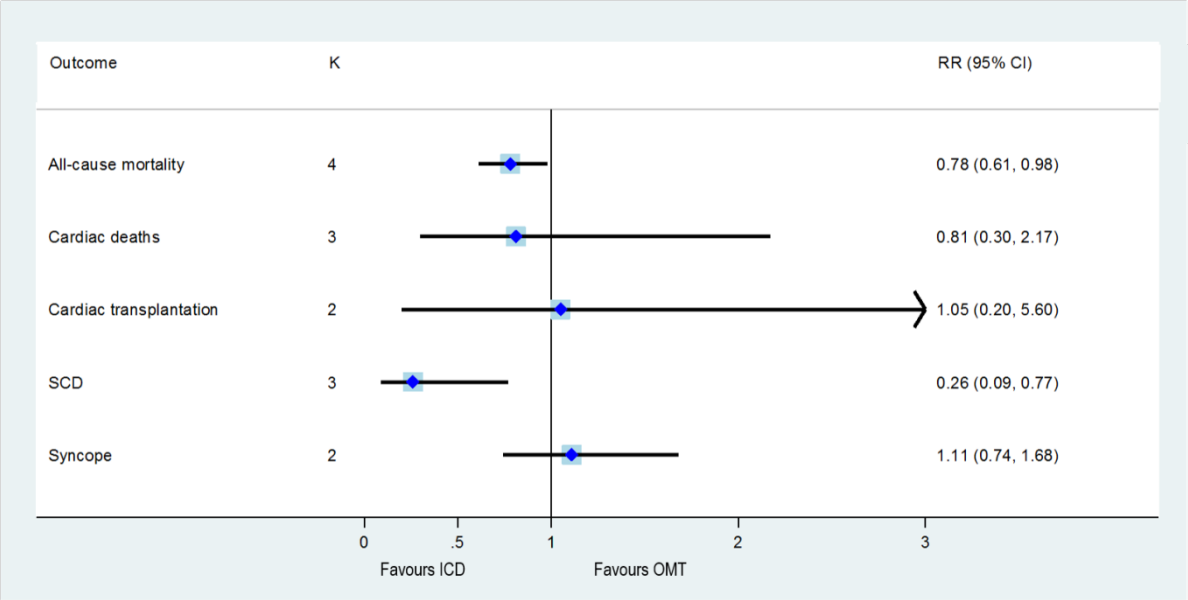


Figure 28 Effectiveness of ICD in addition to OMT versus OMT alone

CI = confidence interval; ICD = implantable cardioverter defibrillator; K = number of studies; OMT = optimal medical treatment; RR = relative risk; SCD = sudden cardiac death

Early versus late treatment for NICDM

One of the trials identified (The Defibrillators in Nonischemic Cardiomyopathy Treatment Evaluation; DEFINITE) performed post-hoc subgroup analyses, assessing the difference in treatment effect of ICDs in patients with recently diagnosed NIDCM or remotely diagnosed with NIDCM, using the cut-points of 3 and 9 months (Kadish et al. 2006). Patients who were randomised to receive an ICD within 3 months of diagnosis fared better than those who were randomised to receive standard medical therapy within 3 months of randomisation (all-cause mortality HR = 0.37, 95%CI 0.14, 0.998; p=0.049), and there was no statistically significant benefit on all-cause mortality in those randomised after 3 months since diagnosis (HR = 0.82, 95%CI 0.47, 1.43, p=0.48). When a cut-off of 9 months was used, there was a trend favouring ICDs in the early treatment subgroup (HR = 0.48, 95%CI 0.23, 1.025, p=0.058), but not in the late subgroup (HR = 0.86, 95%CI 0.46, 1.94, p=0.64). However, despite these differences in the subgroups, there was a non-significant interaction term (p=0.17 for 3-month cut-off, and p=0.25 for 9-month cut-off). The evidence is therefore not sufficiently strong to conclude that there is a difference in ICD benefit based on duration of NIDCM (GRADE ⊕⊙⊙⊙). An overall summary of the findings regarding the health impact of the expected changes to management from CMR, in patients with DCM, is shown in Table 28.

Table 28 Summary of findings assessing whether changes in management based on CMR are beneficial to health outcomes, relative to CTCA or SPECT, or further testing, in patients with DCM or an indeterminate result

Outcomes	Quality of evidence	Findings	Importance
Reclassification of NIDCM patients' prognosis based on CMR, allowing more-targeted treatment	⊕⊙⊙⊙ Very low	There is Australian change in management data that a large proportion of those scheduled for surgery or device implantation have their plan amended due to CMR, and evidence that a small amount of patients without a surgical or device plan have their management amended to undergo invasive treatment. Prognostic data suggests that the treatment amendments are likely to be an improvement, but no studies have proven health benefits.	High
Treatment for rare aetiologies detected by CMR	⊕⊙⊙⊙ Very low	CMR may detect some rare aetiologies of NIDCM that are not diagnosed through the standard tests. There were no SRs reporting mortality benefits due to treatment for these aetiologies. However, for myocarditis, corticosteroids may improve LVEF; and there is very limited evidence suggesting that corticosteroids may maintain or improve LVEF in cardiac sarcoidosis.	Moderate
False positive results for NIDCM	NA	The comparative accuracy against CTCA and SPECT is unknown. Revascularisation for CAD is effective at reducing mortality compared with medical treatment alone, and those who are LGE– may miss appropriate treatment for ICM, although they are a subset of patients who are likely to have better prognosis than those who are LGE+.	High
False negative results for NIDCM	⊙⊙⊙⊙ Clinical advice	Those detected as having ischaemia would receive an ICA, at which point ischaemia would be ruled out. Patients would therefore receive an unnecessary invasive diagnostic test, but treatment would remain the same.	Low

CAD = coronary artery disease; CMR = cardiac magnetic resonance (imaging); CTCA = computed tomography coronary angiography; ICA = invasive coronary angiography; ICM = ischaemic cardiomyopathy; LGE+/– = late gadolinium enhancement; LVEF = left ventricular ejection fraction; NIDCM = non-ischaemic dilated cardiomyopathy; SPECT = single-photon emission computed tomography

Impact of CMR on family members with an indeterminate result or found to have a dilated LV and LV dysfunction through familial screening

It is recommended that all first-degree family members of someone diagnosed with DCM should be screened clinically, including history, physical examination, ECG and echo (Mann et al. 2015). The rationale is that early identification of someone with DCM may allow treatment with ACE inhibitors or β-blockers, to delay or prevent progression of the disease (Mann et al. 2015). CMR is thought to be useful in two scenarios for family members—in cases where the prior tests are indeterminate, and in cases where the family member is found to have LV dysfunction but where further investigations are still warranted, to establish whether the person has familial DCM or CAD. No evidence on the accuracy of CMR in these populations, or showing a change in management in these patients, was identified through the SR. The therapeutic effectiveness was therefore not assessed.

B6 IMPACT OF REPEAT TESTING/MONITORING

Not applicable.

B7 EXTENDED ASSESSMENT OF COMPARATIVE HARMS

B7.1 SAFETY OF LGE-CMR AND COMPARATORS

The safety of CMR, SPECT, GHPS, stress- and contrast echocardiography, ICA and CTCA, specifically in relation to their use in CM, was not identified; thus, an extended assessment of the safety of these techniques has been provided from larger registries, cohort studies etc., and collated in naïve comparisons. These are summarised based on the purpose of the imaging. For further details, see Table 98 to 100 in Appendix J. Further text regarding the safety implications of CMR, echocardiography, SPECT, CTCA, ICA, and their components of radiation risk, stressors and contrast agents, may be found in the concurrent MSAC assessment no. 1237 'Cardiac MRI for myocardial stress perfusion and viability imaging in patients with known or suspected coronary artery disease' (Morona et al. unpublished).

Safety concerns in tests performed after an indeterminate echocardiography result

The tests used after an indeterminate echocardiography are GHPS, contrast echocardiography or CMR, in order to determine if the patient has DCM or some other aetiology for their HF symptoms. All these tests have good safety profiles, with the rate of serious AEs being 3 cases per 10,000 or less (see Figure 29). The long-term mortality attributable to CMR and GHPS were similar, due to the use of contrast for CMR (gadolinium) and radiation for GHPS, with negligible risk of mortality attributable to contrast echocardiography (see Figure 38). Further details may be found in Table 98, Appendix J.

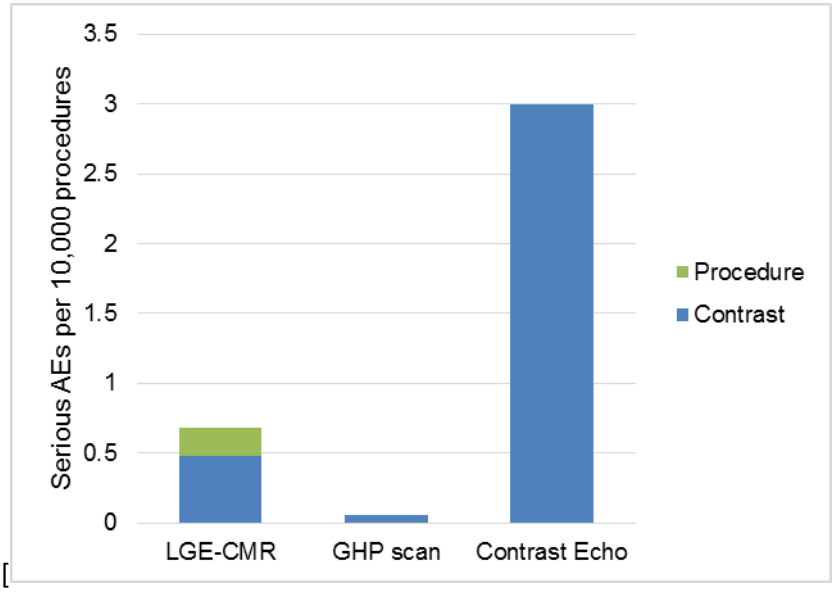


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Figure 29 Estimated risk of serious AEs for different imaging procedures used for investigating whether the patient has DCM (after unclear echocardiography)

AE = adverse event; DCM = dilated cardiomyopathy; Echo = echocardiography; GHP = gated heart pool; LGE-CMR = late gadolinium enhancement cardiac magnetic resonance (imaging)

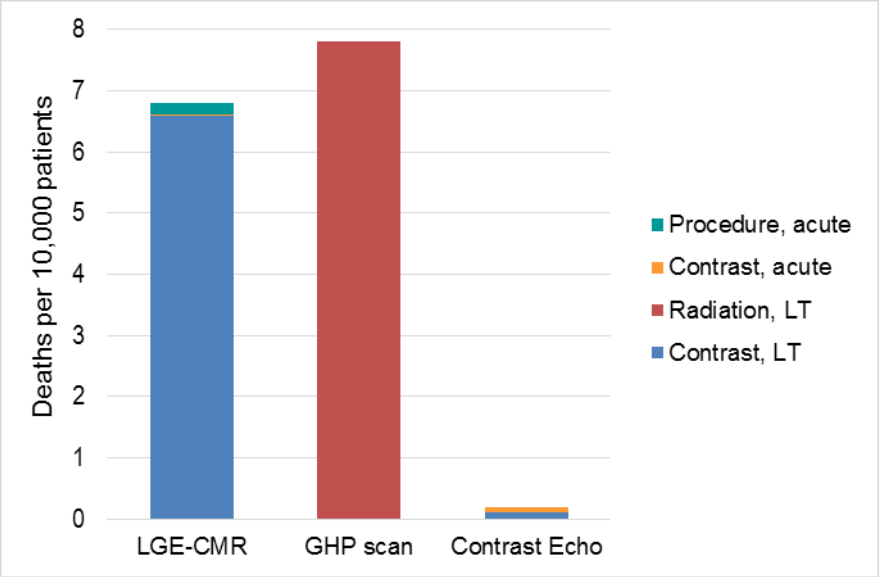


Figure 30 Estimated acute and long-term mortality rates for different imaging procedures used for investigating whether the patient has DCM (after unclear echocardiography)

Echo = echocardiography; GHP = gated heart pool; LGE-CMR = late gadolinium enhancement cardiac magnetic resonance (imaging); LT = long-term

Safety concerns in tests performed to determine the aetiology of NIDCM in patients with a dilated LV and a low risk of CAD

For determining the aetiology of NIDCM, the comparator with CRM is defined as 'further testing', which is predominantly expected to be blood tests. The risks of this are considered negligible. In Australia, EMBs are performed only very rarely, so they are not considered to be a comparator with CMR; however, expert opinion is that CMR would replace (or triage to) a very small number of EMBs. The safety implications of these biopsies are therefore considered, alongside CMR and blood tests in Figure 31 and Figure 32.

Data on EMBs are limited and derived from single centres and registries, and individual complications are based on case reports, so calculable risks or rates are limited. A recent study of 9,508 adult patients using an inpatient database in Japan reported a complication rate of 0.9%, with complications defined as urgent procedures required on the day of biopsy or the day after, including pericardiocentesis and surgical repair, and temporary pacing (Isogai et al. 2015). The in-hospital mortality rate was 1.4% in this study. Other studies have reported lower mortality rates. EMB can be fluoroscopy- or echocardioagram-guided. There are risks associated with fluoroscopy that relate to radiation dose and contrast agent, although details were difficult to find. A study in children and young adults reported that doses for cardiac catheterisation procedures have been falling over the last two decades, and another study of radiation dose during cardiac catheterisation for congenital heart conditions found that dose was not related to fluoroscopy time. (Ghelani et al. 2014; Harbron et al. 2015). The potential complications, and the range of complication rates reported in the literature, are listed in Table 98, Appendix J.

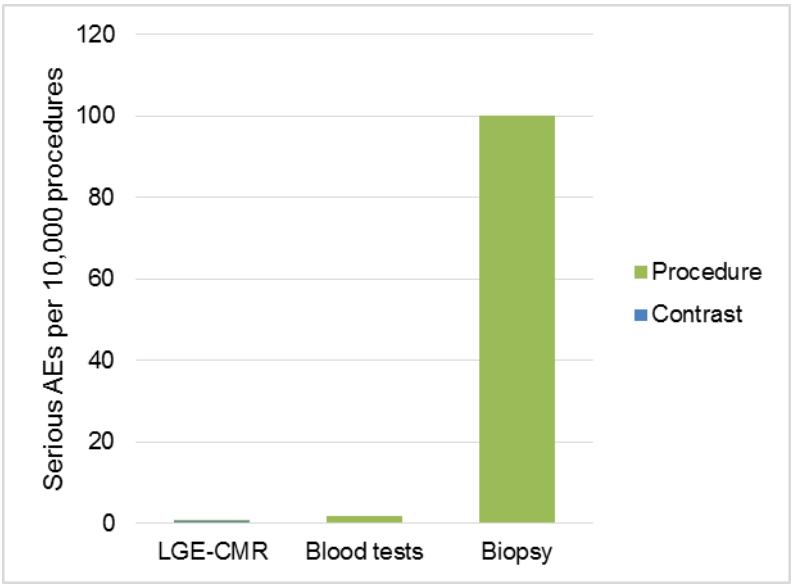


Figure 31 Estimated risk of serious AEs for different imaging procedures used for investigating the aetiology of NIDCM

AE = adverse event; biopsy = endomyocardial biopsy; LGE-CMR = late gadolinium enhancement cardiac magnetic resonance (imaging)

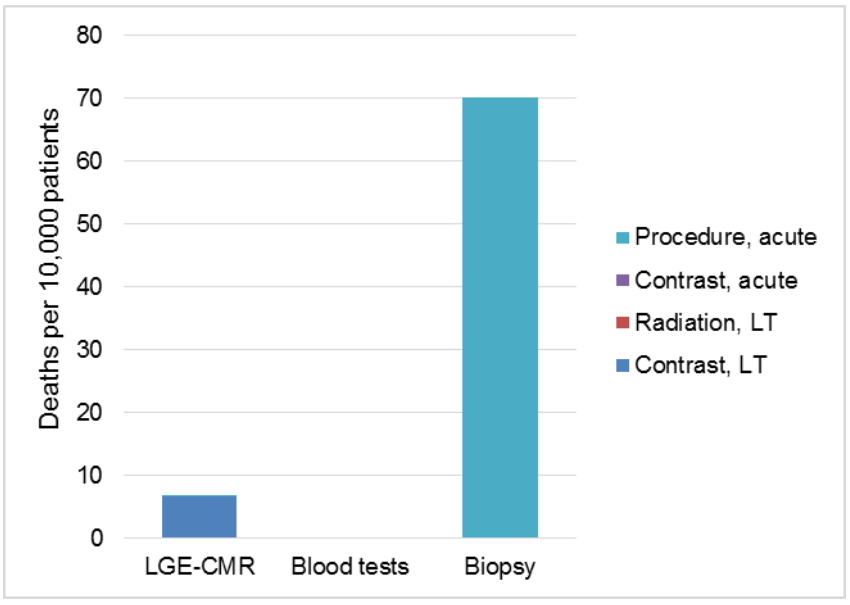


Figure 32 Estimated acute and long-term mortality rates for different imaging procedures used for investigating the aetiology of NIDCM

biopsy = endomyocardial biopsy; LGE-CMR = late gadolinium enhancement cardiac magnetic resonance (imaging); LT = long-term; NIDCM = non-ischaemic dilated cardiomyopathy

Safety concerns in tests performed to determine whether patients with a dilated LV and an intermediate risk of CAD have ischaemia

For the purpose of determining ischaemia, CMR is an alternative to the non-invasive imaging modalities of CTCA, SPECT and stress echocardiography, and an alternative to ICA. ICAs clearly have the highest rate of serious AEs (Figure 33) and mortality (Figure 34), due to the invasive nature of the procedure itself. Using non-invasive imaging to triage to ICA will therefore have superior safety for those who are found to be non-ischaemic, but inferior safety for those who are found to have signs

of ischaemia and have a subsequent ICA. The risks to mortality from the non-invasive techniques are predominantly due to the long-term effects of radiation and contrast. CMR has similar safety to SPECT, marginally superior safety to CTCA, and clearly superior safety to ICA. Further data may be found in Table 99, Appendix J.

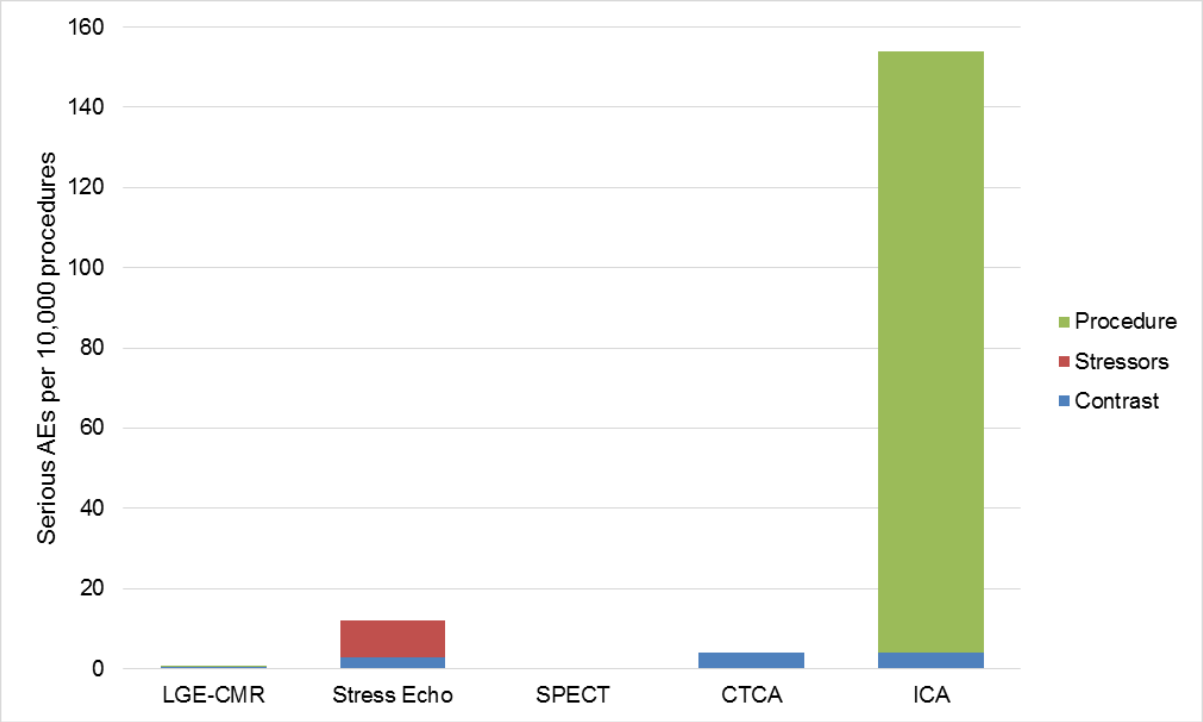


Figure 33 Estimated risk of serious AEs for different imaging procedures used for investigating whether the patient has ischaemia

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

Figure 34 Estimated acute and long-term mortality rates for different imaging procedures used for investigating whether the patient has ischaemia

CTCA = computed tomography coronary angiography; Echo = echocardiography; ICA = invasive coronary angiography; LGE-CMR = late gadolinium enhancement cardiac magnetic resonance (imaging); LT = long-term; SPECT = single-photon emission computed tomography

B7.2 EXTENDED SAFETY ASSESSMENT

From section B5.1, an Australian study reported that use of CMR re-stratified a large proportion of patients who would otherwise have undergone surgery or had an ICD implanted, allowing them to avoid the surgery or implantation. The safety of this change in management is therefore considered here.

There are harms associated with implantable devices; some are related to implantation and include coronary vein dissection, coronary vein perforation, lead dislodgement, infection, adverse psychological symptoms (notably anxiety) and death. In RCTs, AEs included inappropriate discharge; device-related discomfort; permanent explant because of infection, heart transplantation or patient preference; device dysfunction; pocket erosion requiring removal of ICD; dislodgement or migration of leads; dislodgment or fracture of device; bleeding requiring reoperation or transfusion; and unsuccessful first attempt at implantation (National Institute for Health and Care Excellence 2014).

Two papers identified in the results of the systematic search conducted for this review listed inappropriate shock rates from ICDs as a relevant safety consideration when treating patients with CM. These studies both followed up patients with DCM (CAD or NIDCM) over a mean of 49 months, and reported that inappropriate shock rates occurred in 12.0–21.2% of cases (Table 29). Streitner et al. (2013) assessed the relationship between inappropriate shock and mortality, and found a significant association between the two. However, it cannot be assumed that this relationship is causal. Furthermore, Streitner et al. pointed out that recommendations for ICD programming have changed over time. The study used fewer intervals for detection and a lower VF cut-off rate than currently recommended, which may have influenced the incidence of ICD shocks. Grimm commented that patients with inappropriate shock rates appear to have a higher mortality and lower quality of life during follow-up compared with those without inappropriate shock rates (Grimm 2012). However, the evidence cited to substantiate this claim was not specific to DCM patients. The author further reasoned, based on several trials (Grimm, Plachta & Maisch 2006; Sweeney et al. 2005; Wilkoff et al. 2008) conducted in mixed populations indicated for ICD implantation, either for primary or secondary prevention, that the negative impact of inappropriate shock rates on patient survival and quality of life may be mitigated by the following:

- routine use of supraventricular tachycardia discrimination algorithms;
- β-blocker therapy unless contraindicated;
- use of high-rate cut-offs of 200 bpm for VT detection in patients with primary prevention indications;
- long detection intervals of at least 10 seconds (or 30 out of 40 rapid intervals to detect); or
- one or two bursts of anti-tachycardia pacing (ATP) even for rapid VTs up to 250 bpm[7].

Two SRs also provided data on the rate of inappropriate shocks in patients with CAD or NIDCM, and those who had an ICD implanted for primary prevention reasons (Scott et al. 2014 and Persson et al. 2014). The rate of inappropriate shocks varied in the range 3–21%.

Table 29 Rate of inappropriate shocks from ICDs in patients with DCM

[7] Note that advice conflicts with the findings of Streitner and colleagues (2013) that ATP is associated with increased mortality in DCM patients.

Study	Population	Rate of inappropriate ICD therapy	Follow-up	Mortality
Streitner et al. (2013)	N=146 CAD and NIDCM for primary prevention	31/146 patients: 21.2% Inappropriate shock: 12.3% Inappropriate ATP therapy: 15.1%	49.3 months	9/30 with inappropriate ATP died during follow-up 13/116 without inappropriate ATP Impact of shocks vs no shocks on mortality: HR = 3.4, 95%CI 1.3, 9
Grimm (2012)	N=805 consecutive DCM patients	12%	49 months	-
SR by Scott et al. (2014)	K=4 N=4,896 CAD and NIDCM for primary and secondary prevention	253/4,896 patients had inappropriate shock: 5.1%	12–17 months	-
HTA by Persson et al. (2014); Uhlig et al. (2013)	K=15 Patients who had an ICD implanted for primary prevention	3–21%	1–5 years	
SR by Proietti et al. (2015)	K=6 N=192,142 Ischaemic and non-ischaemic CM for primary or secondary prevention	Not stated	3 years	Impact of shocks vs no shocks on mortality: HR = 1.71, 95%CI 1.45, 2.02, p<0.001, I^2=0
SR by Qian et al. (2016)	K=4 Ischaemic and non-ischaemic CM for primary or secondary prevention	Not stated	1.4–4.1 years	Impact of shocks vs no shocks on mortality: HR = 1.54, 95%CI 1.25, 1.89, p<0.001, I^2=1%

ATP = anti-tachycardia pacing; CAD = coronary artery disease; CI = confidence interval; CM = cardiomyopathy; DCM = dilated cardiomyopathy; HR = hazard ratio; HTA = health technology assessment; ICD = implantable cardioverter defibrillator; K = number of studies; N = number of patients; NIDCM = non-ischaemic dilated cardiomyopathy; SR = systematic review

Two further SRs by Qian et al. (2016) and Proietti et al. (2015) provided the most recent and directly comparable pooled data on inappropriate shock rates in composite populations of ischaemic and non-ischaemic CM patients implanted with ICDs for primary or secondary prevention. Comparing patients who had inappropriate shocks with those who did not have any shock, there was a consistent finding across these SRs that inappropriate shock rates were significantly associated with an increase in mortality. Based on the meta-analysis of impact of inappropriate shocks compared

with no shocks (k=4[8]), Qian et al. reported a pooled HR of 1.54 (95%CI 1.25, 1.89); p<0.001, I^2=1%. Similarly, for the same comparison across 6 studies, Proietti et al. reported a pooled HR of 1.71 (95%CI 1.45, 2.02); p<0.001, I^2=0. The analysis provided by Proietti and colleagues included 192,142 patients followed over 3 years[9]. Interestingly, while most of the studies identified and included by the authors of these SRs do overlap, only the data reported by Sood and colleagues (Sood et al. 2014) was common to both the meta-analyses. While this does suggest a potential source of errors or bias in the conduct of these SRs, it does not seem to have affected the findings greatly, and it is reasonable to conclude, based on these data including at least 200,000 patients, that measures to avoid the occurrence of inappropriate shocks are warranted in patients with ICDs implanted for primary or secondary prevention. Furthermore, given the relative scarcity of data on the impact of inappropriate shocks on mortality in patients with DCM, it would be sensible to assume that the more-general data are applicable in this context of the narrower DCM population.

[8] The authors did not report the number of patients includes in the 4 studies, nor did they report on length of follow-up.

[9] While not explicit, it is assumed that this timing refers to either the mean or median follow-up period.

CMR is proposed as an investigative modality that can provide a range of different information that may inform a patients' diagnosis and prognosis, would logically influence the patients' treatment, and hopefully would improve health outcomes.

In the Decision Analytic Protocol, CMR was proposed for use in four populations:

i. patients presenting with HF symptoms in whom echocardiography is inconclusive;
ii. patients presenting with HF symptoms in whom echocardiography suggests a DCM and who have a low–intermediate risk of CAD;
iii. asymptomatic first-degree relatives of someone diagnosed with NIDCM in whom echocardiography is inconclusive; and
iv. asymptomatic first-degree relatives of someone diagnosed with NIDCM in whom echocardiography suggests a DCM that requires further investigations prior to treatment due to an intermediate–high risk of CAD.

Potentially relevant evidence was identified for symptomatic populations (i) and (ii) but not for asymptomatic family members.

The accuracy of LGE-CMR was considered in regards to its ability to detect three separate, but linked, concepts. It is proposed as a means of diagnosing DCM (relevant for patients in whom echocardiography was inconclusive), distinguishing between ischaemic and non-ischaemic DCM (generally after LV dilation and systolic dysfunction has been identified), and detecting the aetiology of NIDCM in those who may otherwise be classified as idiopathic. Furthermore, LGE-CMR can be used to predict a patient's health outcomes and influence their treatment.

B8.1 PATIENTS PRESENTING WITH HF SYMPTOMS IN WHOM ECHOCARDIOGRAPHY IS INCONCLUSIVE

No evidence was identified on the specific population of patients presenting with HF symptoms in whom echocardiography is inconclusive. One study was identified that may potentially be informative. In those who have an inconclusive echocardiography, the initial purpose of CMR is to determine whether patients have DCM or an alternative diagnosis. The evidence on LGE-CMR for the purpose of diagnosing DCM consisted of only 1 retrospective study performed in Japan (n=136; Yoshida, Ishibashi-Ueda et al. 2013). Patients included in this study were those who had HF symptoms, with either LV hypertrophy and/or LV dysfunction. The sensitivity and specificity of LGE-CMR for this purpose, compared with a reference standard of EMB and clinical diagnosis, were good (83% and 93%, respectively), and the LRs indicated that it was conclusive for correctly confirming DCM and was likely to correctly exclude DCM. However, the applicability of these results to those patients in whom an initial echocardiography is inconclusive is unknown.

The current clinical management algorithm for patients with HF symptoms who have an inconclusive echocardiography (Figure 1) suggests that, in the absence of CMR, patients would undergo a contrast echocardiography or a GHPS. The accuracy of CMR compared with these techniques is also unknown. There is a likely benefit of CMR over these techniques; if DCM is identified, CMR can also determine whether there are signs of ischaemia and, in those who are non-ischaemic, determine if there is inflammation or signs of an infiltrative disease. Discussions regarding the accuracy of CMR for determining ischaemia and aetiology within NIDCM are therefore also relevant to this population (see below).

Data from the prognostic studies showed that, in the 3 studies that used echocardiography to determine LVEF, the number of adverse cardiac events did not change with LVEF values or trended

in the opposite direction to what would be expected. Conversely, in the 10 studies that used CMR to determine LVEF, %LVEF was consistently a predictor of the risk of having a cardiac event.

No clinical claims were made about CMR is this specific population. A summary of the small amount of evidence available in patients who had an inconclusive echocardiogram is shown in Table 30.

Table 30 Balance of clinical benefits and harms of CMR, relative to contrast echocardiography or GHPS, in patients with HF symptoms in whom echocardiography is conclusive

Outcomes	Participants (studies)	Quality of evidence	Results	Interpretation	GRADE
Accuracy of CMR for diagnosing DCM	N=136 K=1	Risk of bias: 0 Inconsistency: N/A Indirectness: –1 Imprecision: 0 Publication bias: 0	Sensitivity = 0.83 (0.71, 0.92) Specificity = 0.93 (0.85, 0.97)	CMR is reasonably good at diagnosing DCM, compared with clinical diagnosis and EMB; however, the evidence is not specific to those patients with an inclusive Echo.	Moderate ⊕⊕⊕⊙
Change in management or health outcomes	N/A	N/A	No evidence was available on how CMR would change patient management, or impact on health outcomes, in patients with an inconclusive Echo.	N/A	Not identified ⊙⊙⊙⊙

CMR = cardiac magnetic resonance (imaging); DCM = dilated cardiomyopathy; Echo = echocardiography; EMB = Endomyocardial biopsy; GHPS = gated heart pool scan; HF = heart failure; K = number of studies; N = number of patients

B8.2 Patients Presenting with HF Symptoms in whom echocardiography Suggests a DCM

No direct evidence was available presenting health outcomes following CMR-guided treatment of patients versus health outcomes of patients who were managed without the results of CMR. Two studies provided data on survival following the use of CMR to guide treatment but, given the lack of a comparator, it is difficult to know the impact that CMR had on the patients' health.

Patients with a low risk of CAD

In patients with a low risk of CAD, the purpose of CMR is to determine if there is a treatable aetiology of the NIDCM (diagnosis), and determine the severity of NIDCM (prognosis).

The comparator for the purposes of determining the aetiology is proposed to be 'further testing'. In Australia, further testing currently involves blood tests and would occasionally involve invasive EMB. It is proposed that CMR may be used to triage patients to EMB, but would otherwise be added to the further tests. In the literature, a Norwegian study in patients with idiopathic DCM described further testing as including genetic testing, blood tests, EMB, 24-hour ECG, exercise testing and CMR (Broch et al. 2015).

No information about the safety of any of the non-invasive tests in DCM was identified. The best estimates for safety are based on the use of the test in CAD, and indicate that CMR is safe. EMB has more complications associated with it but the overall complication rate is still relatively low.

Three studies assessed the diagnostic accuracy of LGE-CMR for determining whether there was an inflammatory aetiology in patients with DCM, using EMB as a reference standard. The sensitivity ranged from 0.58 to 0.87, and the specificity ranged from 0.33 to 0.50. However, EMB is not a

perfect reference standard as it is highly dependent on whether the samples are taken from the areas where there is inflammation, and is at risk of missing some cases of inflammation. The low specificity of LGE-CMR compared with EMB is potentially a sign that LGE-CMR detects more cases of inflammation than EMB.

Broch et al. (2015) reported that in a sample of 102 patients diagnosed through standard testing (e.g. patient history, physical examination, routine blood tests, echocardiography, ICA) as having idiopathic DCM, CMR was used in 88 patients, and identified the aetiology of the DCM in 4 patients in total, 3 of whom had not had their aetiology identified through any other means (1 patient with Wegener's granulomatosis and 2 with non-compaction CM), while the remaining 1 with sarcoidosis was also identified through the invasive procedure of EMB. If assessed as an incremental test, in addition to other non-invasive investigations, the number needed to test to diagnose one extra aetiology using CMR was 25. Detecting the aetiology is thought to be beneficial to patients due to the ability to treat the underlying cause (as can be done for myocarditis, sarcoidosis, Wegener's granulomatosis, haemochromatosis etc.) using, for example, immunosuppressant medication, although the quality of the evidence assessing the treatment effectiveness for these rare diseases was low. Another benefit is the ability to rule out the need for family members to be screened.

As well as using CMR to determine if there is an identifiable aetiology for a patient's DCM, it may also be used to assess their prognosis and to determine what treatment strategies are likely to be best (see section on 'Patients who are identified as NIDCM' on page 132).

Patients with an intermediate risk of CAD

In patients with an intermediate risk of CAD, the purpose of CMR is 3-fold—to determine whether there are signs of ischaemia (in which case patients are referred for an ICA); and, in those without ischaemia, determine if any treatable aetiology of DCM can be identified and assess their prognosis.

For determining whether the patient has signs of ischaemia, CMR is proposed as:

- a possible alternative to the non-invasive imaging techniques of CTCA, SPECT and stress echocardiography, all of which may triage patients to ICA if signs of ischaemia are detected; and
- an alternative to patients going directly for an ICA, that is ruling out the need for an ICA if patients have NIDCM, and triaging to ICA if they do show signs of ischaemia.

For the purposes of determining the aetiology of NIDCM, the comparator is:

- 'further testing', as per the population with a low risk of CAD.

Eight studies assessed the accuracy of LGE-CMR for determining whether patients had signs of ischaemia or not, compared with two different reference standards: ICA (k=6) and clinical diagnosis (k=2). The sensitivity of LGE-CMR for classifying NIDCM ranged from 0.68 to 1.00. This means that 0–32% of patients who have NIDCM would be classified as ICM by CMR (false negatives), and would be referred unnecessarily for an ICA.

The specificity of CMR for classifying NIDCM ranged from 0.71 to 1.00, meaning that 71–100% of patients who truly have NIDCM would be able to avoid undergoing an ICA, and would be able to have CMR determine if there is a treatable aetiology for their NIDCM. It also means that 0–29% of patients who have ischaemia would not receive the appropriate ICA if imaged by CMR.

COMPARED WITH CTCA, SPECT AND STRESS ECHOCARDIOGRAPHY

CMR was compared with CTCA against the reference standard of ICA in 1 small study (n=28). The results of the two non-invasive tests were similar but, due to the small number of patients included,

the results had wide, overlapping CIs, and no conclusions on the comparative accuracy of the tests could be made.

Two studies compared the prognostic value of CMR with SPECT but found contradictory results regarding which was superior. No studies compared CTCA with stress echocardiography.

Given the lack of data comparing CMR against the alternative non-invasive tests, comments cannot be made on the clinical impact of receiving CMR rather than CTCA, SPECT or stress echocardiography. The clinical claim made during the development of the Protocol was that CMR had increased diagnostic sensitivity compared with the current non-invasive techniques for investigating and differentiating DCM. However, there were no data to support this claim. Another claim was that CMR has increased safety compared with SPECT and CTCA due to the avoidance of ionising tests (radiation) and subsequent cancer risk. No data were available specifically on the safety of the procedures in the HF or DCM populations. All the non-invasive tests are very safe, although there is a small risk of AEs due to stressors, contrast and radiation. CMR has a similar risk to SPECT and slightly superior safety to CTCA.

In those with an intermediate risk of CAD, the comparators of CTCA, SPECT, stress echocardiography and ICA are not considered to be good at determining the aetiology of NIDCM, so if ischaemia is not detected through these imaging modalities, patients would be referred for further testing. CMR is proposed as an additional test for further testing, and therefore has the benefit of being able to combine its function for assessing the aetiology of DCM at the same time as determining whether the patient has NIDCM or ICM.

COMPARED WITH ICA

For patients with stable CAD, the evidence suggests that revascularisation is effective at improving health outcomes compared with medical treatment alone. It could therefore be implied that those patients who receive a false diagnosis of NIDCM from CMR would be worse off than if they had undergone an ICA, as under the CMR scenario, any treatment for ischaemia would be delayed. ICA is considered the gold standard, so is assumed to correctly identify ischaemia. However, in the included studies, the patients who were falsely classified as having NIDCM by CMR were classified as such due to an absence of LGE. The prognostic data showed that those who were LGE– were less likely to undergo revascularisation and had superior health outcomes, compared with those who were LGE+. The impact of a patient with ischaemia being misclassified as being non-ischaemic due to being LGE– is unknown, but could be hypothesised to be not as bad as if those who were LGE+ were misclassified as non-ischaemic. The impact of delayed, rather than early, treatment for ischaemia is unknown.

Those who are truly classified as NIDCM on CMR would avoid undergoing ICA, which would be beneficial to patient safety because of avoiding an invasive technique. The resulting treatment of patients would likely be the same as if they had received ICA. If patients receive an ICA rather than CMR as the initial test, and are found to not have any signs of ischaemia, they would receive further tests to determine the aetiology of NIDCM. CMR is proposed to be an additional test to assist in determining the aetiology, so under either scenario (ICA or CMR first) patients may end up receiving both tests.

For those patients who are classified as having ischaemia by either CMR or ICA, the treatment and health outcomes are expected to be the same.

Patients who are identified as NIDCM

CMR may be used to re-assess patients' LVEF and determine the prognosis of those who are classified as having NIDCM (either low or intermediate pre-test risk of CAD). This section is relevant to patients who had a low to intermediate pre-test risk of CAD and have had ischaemia ruled out.

One good-quality Australian study assessed whether CMR resulted in a change in management in patients who had been diagnosed as having non-ischaemic CM (predominantly DCM). At least half these patients may have initially been considered to have an intermediate or high risk of CAD but, after undergoing an ICA, those in the CM group had had ischaemia excluded. Treatment decisions had already been made, based on investigations that would occur in the absence of CMR. CMR was then used and the treatments that patients received were documented. Evidence shows that if CMR is listed on the MBS for assessing patients with DCM, it is likely to have a large impact on those who would otherwise undergo a more invasive treatment approach, with a smaller impact on those who are classified by other tests as not requiring surgery or device implantation. In the absence of CMR, clinicians tend to err on the side of caution but, with the additional information gained through CMR, are able to feel more confident in the ability of the patient to have good outcomes through OMT alone[10].

The prognostic data suggest that using CMR to stratify patients to treatments, as occurred in the Australian study by Taylor, AJ et al. (2013), is likely to result in superior or non-inferior effectiveness outcomes compared with not using CMR. Taylor, AJ et al. (2013) reported that health outcomes after 12 months (NYHA classification, mortality and rate of major AEs) were not significantly different between those who had their surgical or device plans avoided due to CMR and those who proceeded with having surgery or device implantation.

Detection of myocardial scarring through LGE-CMR could potentially be used to help assess whether someone should receive an ICD and/or CRT. A median of 25% of those who were LGE+ received an ICD/CRT, while a median of only 10% of those who were LGE– received an ICD/CRT. In patients with an ICD implanted for primary prevention of SCD, those who were LGE+ were 4.5-times more likely to have an appropriate discharge than those who were LGE–. Similarly, in studies that did not restrict included patients to a particular treatment method, those who were LGE+ were 4-times more likely to have an adverse cardiac event, and 3-times more likely to die than those who were LGE–. Conversely, in children, LGE may more often be detecting myocardial inflammation rather than fibrotic or scarred myocardium. Within children with a recent diagnosis of DCM, those who were LGE+ were 2-times more likely to fully recover LV functioning than those who were LGE–.

As well as detecting scarring or inflammation using LGE, CMR may also be used to assess LVEF. LVEF determined by CMR was a better predictor of adverse cardiac events than LVEF determined by echocardiography. Treatment guidelines currently used %LVEF as one criterion for determining whether patients should receive an ICD. However, it appears likely that the presence of LGE is a stronger predictor of adverse cardiac events than LVEF.

In terms of extended safety, there is evidence that inappropriate shocks from implantable cardiac devices increase mortality; this reinforces the importance of appropriate selection of patients to receive these devices for which CMR is useful. Furthermore, many patients implanted with ICDs suffer comorbidities. For the moribund patient, prevention of sudden cardiac death from ICD shock is at odds with palliative care goals at end-of-life; ICD shock at this stage of life is painful and distressing for the patient, which does not facilitate a dignified death. For these patients' families,

[10] Personal communication, A. Taylor, via phone on 3 March 2016.

this is likely to be emotionally distressing. Deactivation of a patient's ICD at end-of-life therefore presents an ethical dilemma, and the ability to more appropriately target ICD treatment would be of benefit to patients and families.

Overall, it is clear that CMR provides information that is useful for determining a patient's prognosis, and could potentially be helpful at deciding which treatments patients should receive. There is no direct evidence proving that CMR does benefit health outcomes, but a linked evidence approach suggests that it is likely to be effective.

Patients who are identified as ICM

CMR may also be used to determine the prognosis of patients with ICM/CAD and to assess viability for revascularisation. However, this is outside the scope of the current review and is considered within the concurrent MSAC assessment no. 1237 'Cardiac MRI for myocardial stress perfusion and viability imaging in patients with known or suspected coronary artery disease' (Morona et al. unpublished).

Overall summary of benefit in patients with LV dysfunction

Based on a linked evidence approach in patients with a low risk of CAD, the addition of CMR to further blood testing is safe and effective for the determination of aetiology of NIDCM, benefiting a small number of patients with rare aetiologies and ruling out the need for familial screening in those cases. It also has the capacity to stratify a significant number of patients to different treatments than they would have received with current tests alone. However, the effectiveness of these changes is unclear (see Table 31).

Table 31 Balance of clinical benefits and harms of CMR + further testing, relative to further testing in patients with a low risk of CAD

Outcomes	Participants (studies)	Quality of evidence	Results	Interpretation	GRADE
LGE-CMR for determining prognosis in those with NIDCM	K=30	Risk of bias: –1 Inconsistency: 0 Indirectness: 0 Imprecision: 0 Publication bias: 0	All-cause mortality RR = 2.47 (95% 1.63, 3.74) Cardiac deaths RR = 3.21 (95%CI 1.79, 5.76) Any cardiac event RR = 3.71 (95%CI 2.29, 6.04)	Those with LGE on CMR have worse cardiac outcomes than those without LGE, and are more likely to have an ICD implanted, and more likely to have an appropriate ICD shock.	Low ⊕⊕⊙⊙ to Moderate ⊕⊕⊕⊙
Effect of CMR on device implantation and surgery for NIDCM	N=488 K=1	Risk of bias: 0 Inconsistency: N/A Indirectness: 0 Imprecision: 0 Publication bias: 0	In those scheduled for devices, 21/72 (29.2%) avoided after CMR In those not scheduled for devices, 20/375 (5.3%) had one implanted after CMR In those scheduled for surgery, 13/20 (65%) avoided it after CMR In those not scheduled for surgery, 7/427 (1.6%) underwent surgery after CMR	CMR is effective at reducing the proportion of patients who receive devices and surgery for treatment of CM, compared with what is done currently in Australia. Only a small proportion of patients who would otherwise not receive devices or surgery have their treatment plan amended by CMR.	Moderate ⊕⊕⊕⊙
Diagnostic yield of CMR	N=102	Risk of bias: –1	CMR identified aetiologies in 4/102	CMR provides unique information, identifying a	Very low

Outcomes	Participants (studies)	Quality of evidence	Results	Interpretation	GRADE
in those classified as having idiopathic DCM	K=1	Inconsistency: N/A Indirectness: –1 Imprecision: –1 Publication bias: 0	patients 3/4 aetiologies not identified by any other further test 1/4 also identified by EMB	small number of cases who would otherwise be classified as having idiopathic NIDCM. None of the other tests could be replaced by CMR, as each reported unique aetiologies.	⊕⊙⊙⊙
Impact of CMR on management of rare aetiologies	N=4 K=1	Risk of bias: –1 Inconsistency: N/A Indirectness: –1 Imprecision: –1 Publication bias: 0	4/4 patients with aetiology identified by CMR likely had their management altered by the findings	For the few patients classified as having a treatable aetiology, or identified as having non-compaction CM, CMR impacts on their management.	Very low ⊕⊙⊙⊙
Effectiveness of corticosteroids for myocarditis	N=719 K=8	Risk of bias: 0 Inconsistency: –1 Indirectness: 0 Imprecision: 0 Publication bias: 0	Mean LVEF difference = 7.36% (95%CI 4.94, 9.79) favouring corticosteroids over no corticosteroids after 1–3 months No significant difference in mortality	Treatment specific for myocarditis may improve cardiovascular functioning, compared with general treatment for HF symptoms.	Moderate ⊕⊕⊕⊙
Effectiveness of corticosteroids for cardiac sarcoidosis	N=299 K=9	Risk of bias: –1 Inconsistency: –1 Indirectness: –1 Imprecision: –1 Publication bias: 0	Mortality was highly variable LVEF may be improved or preserved through corticosteroid use.	The limited evidence available suggests that corticosteroid use is beneficial for preserving or improving cardiovascular functioning in patients with sarcoidosis.	Very low ⊕⊙⊙⊙
Ruling out family members from screening	None	N/A	N/A	If the index case has a non-familial aetiology detected, family members may avoid cascade screening.	Not identified ⊙⊙⊙⊙

CAD = coronary artery disease; CM = cardiomyopathy; CMR = cardiac magnetic resonance (imaging); DCM = dilated cardiomyopathy; EMB = endomyocardial biopsy; HF = heart failure; ICD = implantable cardioverter defibrillator; K = number of studies; LGE = late gadolinium enhancement; LVEF = left ventricular ejection fraction; N = number of patients; NIDCM = non-ischaemic dilated cardiomyopathy; RR = relative risk

Based on a linked evidence approach in patients with an intermediate risk of CAD, CMR has uncertain effectiveness compared with CTCA, SPECT and stress echocardiography for determining ischaemia. It is effective at triaging to an ICA in those with NIDCM. CMR has the capacity to stratify a significant number of patients to different treatments than they would have received with current testing alone. However, the effectiveness of these treatment changes are unclear (see Table 32).

Table 32 Balance of clinical benefits and harms of CMR relative to CTCA, SPECT, stress echocardiography or ICA, in patients with an intermediate risk of CAD

Outcomes	Participants (studies)	Quality of evidence	Results	Interpretation	GRADE
LGE-CMR for determining prognosis in those with NIDCM	K=30 cohort studies	Risk of bias: –1 Inconsistency: 0 Indirectness: 0 Imprecision: 0 Publication bias: 0	All-cause mortality RR = 2.47 (95% 1.63, 3.74) Cardiac deaths RR = 3.21 (95%CI 1.79, 5.76) Any cardiac event RR = 3.71 (95%CI 2.29, 6.04)	Those with LGE on CMR have worse cardiac outcomes than those without LGE, and are more likely to have an ICD implanted, and more likely to have an appropriate ICD shock.	Low ⊕⊕⊙⊙ to Moderate ⊕⊕⊕⊙
Effect of CMR on device implantation and surgery for NIDCM	N=488 K=1 before-and-after case series	Risk of bias: 0 Inconsistency: N/A Indirectness: 0 Imprecision: 0 Publication bias: 0	In those scheduled for devices, 21/72 (29.2%) patients avoided devices due to CMR In those not scheduled for devices, 20/375 (5.3%) had one implanted due to CMR In those scheduled for surgery, 13/20 (65%) avoided it due to CMR In those not scheduled for surgery, 7/427 (1.6%) underwent surgery due to CMR	In those CM patients who are likely to receive a device or surgery based on investigations prior to CMR, CMR is highly effective at reducing the number who receive devices and surgery. Only a small proportion of patients who would otherwise not receive devices or surgery have their treatment plan amended by CMR.	Moderate ⊕⊕⊕⊙
Accuracy of CMR at distinguishing ICM from NIDCM	K=8 diagnostic accuracy studies (K=6 vs ICA, K=2 vs clinical diagnosis)	Risk of bias: 0 Inconsistency: –1 Indirectness: 0 Imprecision: –1 Publication bias: 0	Sensitivity = 0.68–1.00 Specificity = 0.71–1.00	A high proportion of those with NIDCM may avoid ICD if imaged with CMR.	Low ⊕⊕⊙⊙ to High ⊕⊕⊕⊕
Accuracy of CMR vs CTCA, SPECT or stress Echo	K=1 diagnostic accuracy study; 2 prognostic studies	Risk of bias: 0 Inconsistency: –1 Indirectness: 0 Imprecision: –1 Publication bias: 0	Only very limited evidence compared with CTCA Contradictory evidence compared with SPECT No evidence compared with stress Echo	Conclusions on the comparative accuracy or prognostic benefit of CMR vs alternative non-imaging techniques cannot be made.	Very low ⊕⊙⊙⊙
Safety of CMR vs ICD	N/A	N/A	Being an invasive procedure, ICAs have a higher risk of adverse events than non-invasive imaging. CMR rules out the need for those without signs of ischaemia to have an ICA.	CMR is a safer procedure than ICA, and non-ischaemic patients therefore benefit from being imaged with CMR rather than ICA.	Not identified ⊙⊙⊙⊙
Effectiveness of revascular-	N=93,553	Risk of bias: –1	CABG reduces risk of death, myocardial	Correct identification of ICM is likely to be	Low ⊕⊕⊙⊙

Outcomes	Participants (studies)	Quality of evidence	Results	Interpretation	GRADE
isation for ICM	K=100 RCTs	Inconsistency: 0 Indirectness: –1 Imprecision: 0 Publication bias: 0	infarction and subsequent revascularisation, compared with medical treatment alone. No data specific for LGE– patients	beneficial to patient mortality and other outcomes. However, the impact of an incorrect diagnosis of NIDCM in those who are LGE– is unknown.	

CABG = coronary artery bypass graft; CAD = coronary artery disease; CMR = cardiac magnetic resonance (imaging); CTCA = computed tomography coronary angiography; Echo = echocardiography; ICA = invasive coronary angiography; ICD = implantable cardioverter defibrillator; ICM = ischaemic cardiomyopathy; K = number of studies; LGE = late gadolinium enhancement; N = number of patients; NIDCM = non-ischaemic dilated cardiomyopathy; RCT = randomised controlled trial; RR = relative risk; SPECT = single-photon emission computed tomography

SECTION C TRANSLATION ISSUES

C1 OVERVIEW

The clinical data presented in section B, where relevant and appropriate, was incorporated into the related economic analyses, without quantitative translation. The applicability of data is discussed where it is presented under the 'Inputs' section of the relevant analysis. Thus, there are no translation studies to present in section C.

SECTION D ECONOMIC EVALUATION

D1 OVERVIEW

There is inadequate data, particularly with respect to health outcomes, to reliably construct an economic model to generate a full cost–utility or overall cost-effectiveness analysis (CEA) for the proposed MBS listing.

However, the available evidence has allowed some economic analysis of the use of CMR within specific patient populations included in the listing. Based broadly on the populations identified and detailed in section A.4, the following analyses are undertaken:

*Population i: Patients with inconclusive **echocardiogram** results:*

- ***a cost comparison analysis of CMR (vs comparator investigations)**.*

Population ii: Patients diagnosed with DCM on echocardiogram, with a low–intermediate risk of CAD, requiring further diagnostic clarification; this population was further divided into two subgroups:

Subpopulation iiA: patients with low risk of CAD (or where CAD has been investigated and ruled out), and where further identification of non-ischaemic aetiology is necessary:

- ***a (limited) cost-effectiveness analysis of CMR as an additional test***
- ***a cost comparison with other investigations or tests** is presented in Appendix L*

Subpopulation iiB: patients with intermediate risk of CAD, where investigations for CAD are required, including the use of alternative non-invasive techniques to identify CAD and/or invasive ICA as potential comparators:

- ***a (limited) cost-effectiveness analysis vs ICA***
- ***a cost-comparison analysis vs SPECT, CTCA, stress echocardiography***

Populations iii and iv: family members of patients with DCM:

- ***no economic analyses** are presented.*

No relevant evidence that could inform an economic analysis on the use of CMR in these populations was identified during the clinical assessment.

The cost comparison analyses consider CMR and the nominated comparators and, where available, incorporate downstream diagnostic costs and utilise data from the clinical evaluation regarding the accuracy, AE rates and change in management. The consequences of the different testing strategies are discussed.

The outcomes of interest in the economic analyses include incremental costs, costs per testing strategy, incremental cost per appropriate patient management, incremental cost per inappropriate patient management avoided, and incremental cost per unnecessary procedure / invasive test avoided.

A summary of the key characteristics of each economic evaluation are presented in Table 33.

Table 33 Summary of the key characteristics of the economic evaluations

Population	Population i	Population iiA	Population iiB	Population iiB
	Patients with indeterminate Echo	Patients at low risk of CAD or identified with	Patients at intermediate risk of CAD—*for further*	Patients at intermediate risk of CAD—*for non-*

		NIDCM	*investigation with ICA*	*invasive further investigation*
Perspective	Australian healthcare	Australian healthcare	Australian healthcare	Australian healthcare
Comparator(s)	cEcho, GHPS	No CMR testing	ICA	SPECT, CTCA, stress Echo
Type(s) of economic evaluation	Cost-analysis, cost-consequences	Cost-effectiveness analysis	Cost-effectiveness analysis	Cost-analysis
Sources of evidence	Cost derivations using data from MBS and AR-DRG; (Independent Hospital Pricing Authority (IHPA) 2015a)	Taylor, AJ et al. (2013), section B	Assomull et al. (2011), section B	Cost derivations using data from MBS and AR-DRG; (Independent Hospital Pricing Authority (IHPA) 2015a, 2015c), section B
Time horizon	Time to achieve a diagnosis (assumed <1 year —no discounting)	Immediate or 6 months from the baseline	Time to achieve a diagnosis (assumed <1 year—no discounting)	Time to achieve a diagnosis (assumed <1 year—no discounting)
Outcomes	Incremental cost per testing strategy	Cost per additional appropriate patient management, cost per additional inappropriate patient management avoided, cost per additional unnecessary device/surgery avoided	Cost per additional correct diagnosis, cost per additional unnecessary ICA avoided	Incremental costs per testing strategy
Methods used to generate results	Cost analyses	Decision tree analysis	Decision tree analysis	Cost analysis
Software package used	MS Excel 2013	TreeAge Pro 2015	TreeAge Pro 2015	MS Excel 2013

AR-DRG = Australian Refined Diagnosis Related Groups; CAD = coronary artery disease; cEcho = contrast echocardiography; CMR = cardiac magnetic resonance (imaging); CTCA = computed tomography coronary angiography; Echo = echocardiography; GHPS = gated heart pool scan; ICA = invasive coronary angiogram; IHPA = Independent Hospital Pricing Authority; MBS = Medicare Benefits Schedule; NIDCM = non-ischaemic dilated cardiomyopathy; SPECT = single-photon emission computed tomography

The remaining subsections (D.2–D.6) of section D are presented separately for each of the above-detailed analyses, with each analysis presented in full, consecutively.

POPULATION I: PATIENTS WITH INDETERMINATE ECHOCARDIOGRAM

D2.(i) CA Population and setting

This population comprises symptomatic patients who have not obtained conclusive results from an echocardiogram to enable diagnosis. Currently, in this situation, a contrast echocardiography or a GHPS would be undertaken to assess the functioning of the heart and enable diagnosis. Where these tests are indicative of a dilated LV and systolic dysfunction, subsequent tests (CTCA, SPECT, stress echocardiography or ICA) are also likely to be performed to rule out ischaemia (as for Population ii).

In this analysis *CMR is proposed to replace contrast echocardiography or GHPS.* The extent to which it may also replace any subsequent test (e.g. to rule out ischaemia or further investigation) is not estimated in this analysis.

D3.(i) CA Structure and rationale of the economic analysis

In this population, evidence for the effectiveness of CMR compared with an alternative follow-up (GHPS and/or contrast echocardiography) was not identified. A cost analysis (CA) comparing CMR with these comparators is presented. The costs considered in the analysis include those related to testing (including patient co-payments), the cost of referrals for testing (where applicable), and the cost for treating AEs related to the testing methodology. A qualitative summary of clinical differences that should be considered concurrently with the cost analysis is also presented:

- The analyses only consider the costs associated with resolving the initial indeterminate echocardiography result, as there is a high degree of uncertainty in the proportion of initially indeterminate patients who have a dilated LV, and in the risk of CAD in these patients (which determines the type of further testing).
- The analyses assume that CMR yields similar results, diagnostically, to that of GHPS and contrast echocardiography, as the information contained within this report does not provide adequate support for quantifying the consequences of true or false positives or negatives.

D4.(i) CA Inputs to the cost analysis

CMR

A summary of the identified costs associated with CMR is presented in Table 34.

Table 34 Costs associated with proposed CMR testing

Parameter	Estimate	Source
Costs related to testing		
Proportion of patients bulk-billed:	72.8%	MBS data for current CMR services
MBS benefit for bulk-billed patients	$855.20	100% proposed schedule fee
MBS benefit for non-bulk-billed patients	$726.90	85% proposed schedule fee
Average MBS benefit:	$820.26	Weighted
Patient contribution (bulk-billed)	$0.00	
Patient contribution (non-bulk-billed)	$244.36	MBS data for current CMR services
Average patient co-payment	$66.54	Weighted
Gd contrast agent	$38.10	MBS item 63491 (outpatient benefit)
Average patient co-payment	$1.82	Assumption [a]
Subtotal	$926.73	Sum of test costs
Referral costs:		
Specialist referral	$128.74	MBS data for item 110
Average patient co-payment	$50.79	MBS data for item 110
Subtotal	$179.53	Sum of referral costs
Treatment of AEs costs		
Probability of reaction to Gd contrast agent	0.005%	Section B.7

Parameter	Estimate	Source
Cost of treating AEs	$1,084.03	NEP for X61Z [b]
Subtotal	$0.05	Cost of AE per CMR
Total	$1,106.31	

[a] Patient contribution assumed only for patients who were not bulk-billed. No out-of-pocket expenses (i.e. charges above the schedule fee) were assumed. The bulk-bill rate was assumed to be the same as that for currently listed CMR services.

[b] Price weight for AR-DRG X61Z (0.22) (Independent Hospital Pricing Authority (IHPA) 2015a) * the NEP 2016–17 ($4,883) (Independent Hospital Pricing Authority (IHPA) 2016)

AE = adverse events; CMR = cardiac magnetic resonance (imaging); Gd = gadolinium; MBS = Medicare Benefits Schedule; NEP = National Efficient Price

It is assumed that services are provided in the outpatient setting.

Testing costs included in the analyses are those of the CMR and the gadolinium (Gd) contrast agent, assuming that a bulk-billing incentive will apply to the proposed CMR service (as per other CMR services). This infers that for out-of-hospital services that are bulk-billed, the benefits paid by the MBS are 100% of the schedule fee. In order to account for this, an estimated bulk-billing rate is used based on the proportion of current out-of-hospital CMR services that are bulk-billed (72.8% in 2014–15). Therefore, for 72.8% of services the MBS benefit paid is 100% of the schedule fee, and for the remaining billed patients the MBS benefit paid is 85%. Therefore, the average weighted MBS benefit paid is $820.26.

The Protocol for this assessment stated that the total cost for one CMR scan on 1 patient for suspected CMs would be in the range $1,100–$1,200. Given that the proposed item fee is $855.20, for patients that are not bulk-billed, patient co-payments in the order of $200–$300 may be expected. This is consistent with the observed average patient contribution per current CMR service for out-of-hospital billed patients, 2014–15 ($244.36).

The MBS benefit for the Gd contrast agent (MBS item 63491) is assumed to be 85% of the schedule fee (i.e. the outpatient benefit). The patient contribution for the Gd contrast was assumed to be applied only to the proportion that would not be bulk-billed, and assumes that patients would not be charged above the schedule fee (i.e. the patient contribution for billed patients was 15% of the schedule fee). The bulk-bill rate was assumed to be the same as that for currently listed CMR services.

Should CMR be available in this proposed population, all patients will require a specialist referral after the indeterminate echocardiogram prior to receiving CMR. This is costed based on MBS data for item 110 for 2014–15, using the average benefit paid per service and the average patient contribution per service.

Section B7 reports that 4.8 per 100,000 patients experience an adverse reaction to the Gd contrast. The cost of treating the allergic reaction has been estimated by multiplying the price weight for AR-DRG X61Z (Allergic Reactions) by the National Efficient Price (NEP) for 2016–17 (see footnote in Table 34) (Independent Hospital Pricing Authority (IHPA) 2016). Therefore, the cost of treating each AE due to a reaction to the Gd contrast is $1,084.03, which equates to $0.05 per CMR.

The total estimated cost associated with CMR testing is $1,106.31 per patient, as per Table 34.

GHPS

A summary of the costs of a GHPS are presented in Table 35.

Table 35 Costs associated with GHPS in the population with indeterminate echocardiography

Parameter	Estimate	Source
Costs related to testing		
GHPS	$283.16	MBS data for item 61313
Patient co-payment	$22.52	MBS data for item 61313
Subtotal	$305.68	Sum of test costs
Referral costs (including patient co-payment)		
GP referral	$37.36	MBS data for item 23
Patient co-payment	$5.69	MBS data for item 23
Specialist referral	$128.74	MBS data for item 110
Patient co-payment	$53.57	MBS data for item 110
Weighted cost	$112.68	Assuming 50:50 referrals
Treatment of AEs costs	-	
None identified		
Subtotal	$0.00	
TOTAL	$418.36	

AE = adverse events; GHPS = gated heart pool scan; GP = general practitioner; MBS = Medicare Benefits Schedule

The costs related to GHPS include the cost of the scan (based on MBS data for item 61313 for the average benefits paid per service) and the average patient co-payment (based on MBS data for item 61313 for the average patient contribution paid per service) for 2014–15.

All patients require referral to a GHPS after an indeterminate echocardiogram, and so the referral cost has been included, assuming that 50% of patients have GP referral and 50% have specialist referral (as per MSAC Assessment 1129 (Thavaneswaran et al. 2010)). This assumption is tested in sensitivity analyses. The cost of referral and applicable patient co-payment is based on MBS data for 2014–15 reporting the average benefits paid and the average patient contribution for items 23 and 110.

No acute AEs were found to be associated with GHPS (section B.7), and so no costs for the treatment of AEs have been included in the analysis.

The total cost of assessment by GHPS is therefore $418.36 per patient (as per Table 35).

CONTRAST ECHOCARDIOGRAPHY

A summary of the costs of a contrast echocardiogram used in the cost analysis are presented in Table 36.

Table 36 Costs associated with contrast echocardiography in the population with indeterminate echocardiography

Parameter	Estimate	Source
Costs related to testing		

Parameter	Estimate	Source
Contrast agent	$90.00	MSAC Application no. 1129 (Thavaneswaran et al. 2010)
Consumables	$5.00	MSAC Application no. 1129 (Thavaneswaran et al. 2010)
Additional time	$35.98	Assumption [a]
Subtotal	$130.98	Sum of testing costs
Additional costs (including patient co-payment)	-	
Proportion of tests unresolved by contrast	3.6%	Thanigaraj et al. (2001)
Follow-up GHPS	$418.36	See Table 35
Subtotal	$15.10	Further testing costs per cEcho
Treatment of AEs costs	-	
Probability of reaction to contrast agent	0.03%	Section B.7
Cost of treating AE	$1,084.03	NEP for X61Z [b]
Subtotal	$0.33	Cost of AE per cEcho
Total	$146.41	

[a] Assumed applying 15% extra time for a contrast echocardiography (as per MSAC no. 1129) to the average fee charged per 55113 service ($239.86, from MBS data 2014–15)

[b] Price weight for AR-DRG X61Z (0.22) (Independent Hospital Pricing Authority (IHPA) 2015a) * the NEP 2016–17 ($4,883) (Independent Hospital Pricing Authority (IHPA) 2016)

AE = adverse event; cEcho = contrast echocardiography; Echo = echocardiogram; GHPS = gated heart pool scan; MBS = Medicare Benefits Schedule; MSAC = Medical Services Advisory Committee; NEP = National Efficient Price

According to MSAC Application no. 1129 (Thavaneswaran et al. 2010), a contrast echocardiography would be conducted during the same visit as the initial (suboptimal) echocardiography without contrast (MSAC Application no. 1129). Therefore, only the costs associated with administering the contrast agent are included in the analysis, as the costs associated with the initial echocardiogram would be equivalent in each of the comparisons. This is tested in sensitivity analysis, assuming that all contrast echocardiograms occur subsequently (and so too require referral). The included costs are those of the contrast agent, consumables and additional time. Contrast agent and consumables costs have been assumed based on MSAC Application 1129, while additional time is costed based on the assumption that a contrast echocardiograms would take 15% longer to administer (as per MSAC Application 1129), and so an additional 15% of the average fee charged per 55113 service is applied. This is tested in sensitivity analyses, assuming no increase in time and doubling the extra time cost.

Contrast echocardiography may not resolve all suboptimal echocardiograms, and so 3.6% (Thanigaraj et al. 2001) of cases are assumed to require referral for further testing, using GHPS. The cost for referral and testing is that reported in Table 35. The proportion that have persistent suboptimal results after a contrast echocardiography is tested in sensitivity analyses, assuming a higher proportion (15%).

Section B7 reports that 3 per 10,000 patients experience an adverse reaction to the contrast agent. The cost of treating the allergic reaction has been estimated by multiplying the price weight for AR-DRG X61Z (Allergic Reactions) (0.22) (Independent Hospital Pricing Authority (IHPA) 2015a) by the NEP for 2016–17 ($4,883) (Independent Hospital Pricing Authority (IHPA) 2016). Therefore, the cost

of treating each AE due to a reaction to the contrast agent is $1,084.03, which equates to $0.33 per contrast echocardiography.

The total cost of a contrast echocardiography is then calculated to be $146.41, as per Table 36.

D5.(i) CA Results of the cost analysis

The cost analysis for the comparison of CMR with GHPS or contrast echocardiography is presented in Table 37, followed by a discussion of relevant considerations that were not able to be captured in the cost analysis.

Table 37 Incremental cost of CMR compared with GHPS or contrast echocardiography in the population with indeterminate echocardiography

	Cost of CMR	Comparator	Incremental cost
Base-case CMR vs GHPS	$1,106	$418	$688
Base-case CMR vs cEcho	$1,106	$146	$960

cEcho = contrast echocardiography; CMR = cardiac magnetic resonance (imaging); Echo = echocardiogram; GHPS = gated heart pool scan

The additional cost of CMR over GHPS is approximately $688 per person, and over contrast echocardiography it is approximately $960 per person.

A qualitative summary of clinical differences that should be considered concurrently with the cost analysis of CMR vs GHPS or contrast echocardiography includes:

- Patient acceptability—due to the confined space within an MRI scanner and the duration of the time required to be in the scanner (60 minutes), CMR may not be as acceptable to patients as a GHPS or contrast echocardiography.
- Relative accessibility/timeliness—while both CMR and GBPS require a referral subsequent to the suboptimal echocardiogram, CMR is by specialist referral only, whereas referral to GHPS can be made by a GP or specialist. Alternatively, a contrast echocardiography is primarily performed in the same visit as the initial (inconclusive) echocardiography (MSAC Application no. 1129 (Thavaneswaran et al. 2010)); however, it is not listed on the MBS and patients may have to cover any additional expenses associated with the contrast and its administration, which may potentially limit access. Access to CMR may also be limited due to the duration required for CMR and the demand in other medical areas.
- Additional clinical information provided—patients in whom either a GHPS or contrast echocardiography identifies a dilated LV will then require further testing for diagnostic clarification, unlike CMR, which can provide resolution and further diagnostic clarification at the same time. As the proportion of initially indeterminate patients who have a dilated LV is unknown, as is the risk of CAD in these patients (which determines the type of testing for diagnostic clarification), further downstream testing costs have not been included in the analysis, due to a high degree of uncertainty in their quantification. This is a conservative assumption, as any costs included will be incurred in the comparator arm only.
- Incidence of side effects—the incidence of acute AEs related to testing is generally low; however, with use of a GHPS, involving the use of radiotracers, there is a long-term fatal cancer risk of approximately 7.8 per 10,000 patients (section B7); with contrast echocardiography, acute allergic reactions occur in approximately 3 per 10,000 patients; and with CMR, the use of Gd contrast is associated with long-term nephrotic toxicity, with a mortality risk of approx. 6.6 per 10,000 doses (section B7).

D6.(i) CA Sensitivity analyses

Sensitivity analysis were conducted around the incremental cost of CMR compared with GHPS and contrast echocardiography, testing key assumptions (see Appendix K, Table 101 and Table 102, respectively).

CMR is consistently more expensive than either comparator in the population, with indeterminate echocardiogram across all sensitivity analyses tested; however, not all the benefits of CMR have been quantified.

The benefits of CMR that have not been quantified include that CMR can provide resolution to the initial indeterminate echocardiogram and further diagnostic clarification at the same time, whereas for either comparator further testing would be required in those who are found to have a dilated LV. However, CMR may be associated with lower patient acceptability and accessibility issues. Furthermore, the relative accuracy of CMR compared with either GHPS or contrast echocardiography is unknown.

POPULATION IIA: PATIENTS WITH A DILATED LV AND LOW RISK OF CAD (OR KNOWN NIDCM)

In this population the applicant claimed that the key benefit of CMR beyond the diagnostic accuracy for identifying DCM is the ability to define the aetiology and hence alter patient management. Thus, an economic model has been developed to measure the costs and extent to which management is changed. A lack of data on long-term health outcomes precludes further modelling.

D2.(IIA) POPULATION AND SETTING

This subgroup includes patients presenting with HF symptoms, a dilated LV and systolic dysfunction with a low risk of CAD. For the purposes of the economic analysis, patients who have DCM and have already been investigated for ischaemia using other tests, and have been identified as having non-ischaemic disease, are also included in this modelled population. Patients anticipated or shown to have NIDCM will often need further diagnostic clarification to identify the aetiology.

For these patients (i.e. without CAD and with a low risk of CAD), CMR is primarily intended to be used as an adjunct test, but it may replace existing tests in specific circumstances. The alternative investigations for determining the aetiology of DCM may include more-extensive pathology tests, genetic testing, 24-hour ECG, exercise testing with measurement of peak oxygen uptake, and right-sided cardiac catheterisation with EMB (Broch et al. 2015). In Australia the further testing currently involves blood tests and would occasionally involve invasive EMB. It is proposed that CMR may be used to triage or prevent patients requiring EMB.

A simple cost analysis that details the costs of other investigative tests is presented in Appendix L. The remainder of the analysis in population iiA presented in the main body of the report assumes that CMR would be used concurrently with, or in addition to, these other investigative tests (i.e. it has no comparator).

D3.(iiA) CEA Structure and rationale of the economic analysis

STUDIES AND EVIDENCE BASE USED FOR THE ECONOMIC MODEL

Data from the 2 studies (Broch et al. 2015; Taylor, AJ et al. 2013) included in the clinical assessment (see section B.5.1.5) indicate that some patients would be expected to undergo a change in management following CMR.

Taylor, AJ et al. (2013) is a prospective observational study that evaluates the impact of CMR (as an additional test) in altering patient management (i.e. implantable cardiac device and surgical therapy)

in HF patients referred to the Alfred Hospital, Melbourne (subgroup of n=488 CM patients). It is likely to be reasonably applicable to the broader Australian setting and the target population, and therefore forms the basis of the economic analysis[11].

In section B5.1.5, Table 19 and Table 20 present the changes in management identified in Taylor, AJ et al. (2013) with respect to device implantations and surgical procedures performed at 6 months following CMR in HF patients indicated for DCM. In this study, a total of 19 fewer devices were implanted than originally planned, 1 fewer patient underwent an implantation procedure, and there was a reduction of 6 patients requiring surgery as a consequence of undergoing CMR. In addition, 13.6% of the patients had a change in treatment (i.e. device implantation or surgery) following CMR at 6 months follow-up. This data is used in the model to evaluate the economic impact of CMR testing on change in management, and assumes that CMR provides 100% appropriate changes. A sensitivity analysis, assuming 95% appropriate change in management following CMR, will also be presented.

However, it is unknown whether the changes in the treatment plan following CMR are short-term, or what the long-term implications are. No significant difference was found in the health outcomes after 12 months (NYHA classification, mortality, and rate of major AEs) between those who had their surgical or device plans avoided due to CMR findings and those who proceeded with having surgery or device implantation (Table 19 and Table 20). ***The economic model is considerably limited in that (i) it only incorporates the change in management at 6 months follow-up post CMR, (ii) associated patient-relevant health outcomes are not identified, and (iii) the implications of false or delayed treatments are not included.***

PATIENT FLOW IN THE ECONOMIC MODEL

The structure of the economic evaluation is shown in Figure 35.

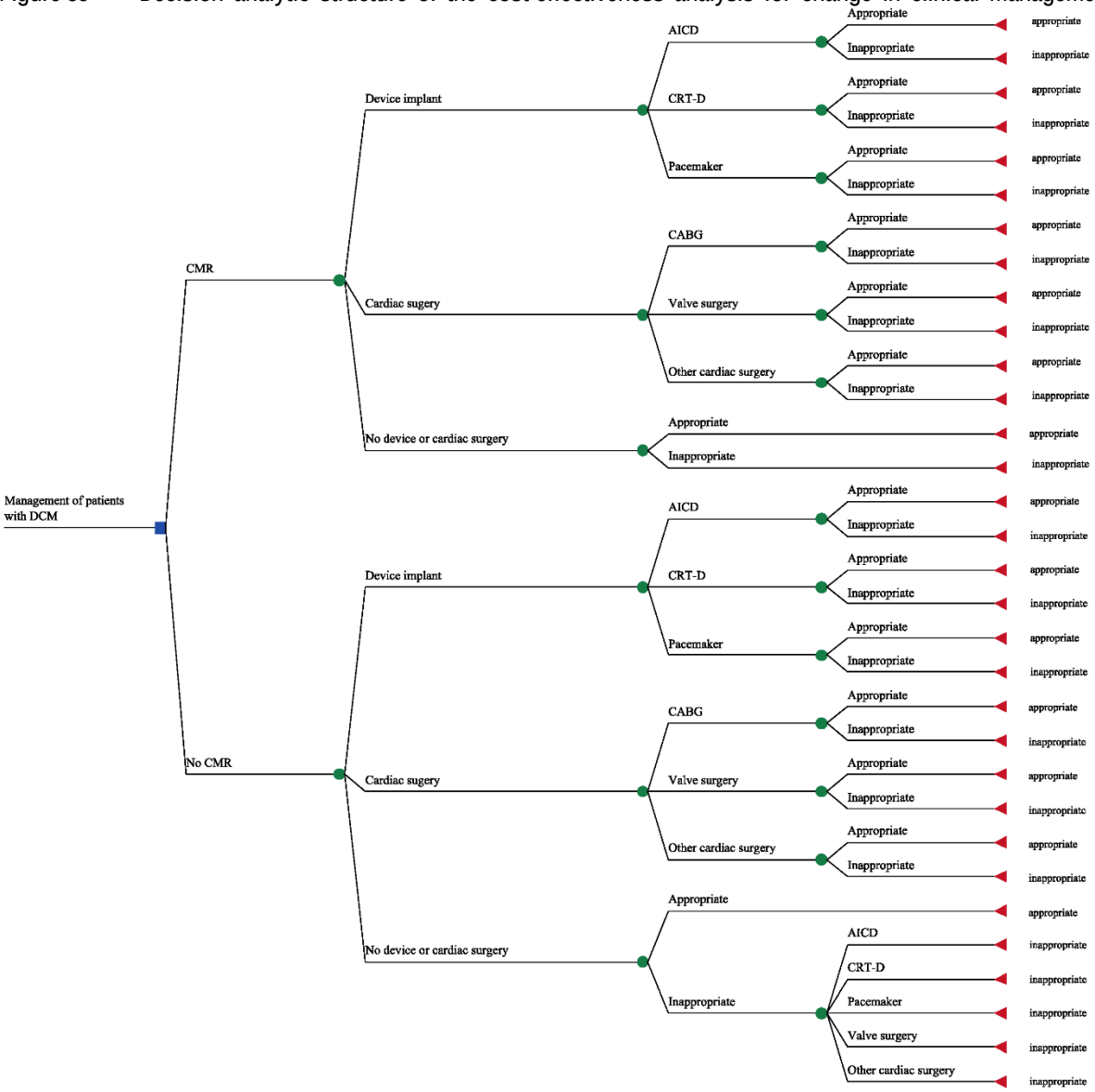
In the intervention arm, all patients undergo CMR testing to guide their management. Implantable devices or surgeries are planned or avoided based on the clinical data obtained through CMR testing. In the control arm, patients undergo procedures as planned, based on the prior examinations (i.e. no CMR testing). The implantable devices planned include automated implantable cardioverter defibrillators (AICDs), cardiac resynchronisation therapy with defibrillator (CRT-Ds) and pacemakers. The surgeries planned include CABG, valvular surgeries, heart transplants and other cardiac surgeries.

Each clinical pathway culminates in a decision that is deemed either appropriate or inappropriate. The base-case analysis assumes CMR to be 100% accurate in informing patients to appropriate clinical management. In patients where CMR rules out more-invasive treatments (assumed inappropriate), it is expected that they will have non-inferior effectiveness outcomes, and superior safety outcomes, from having avoided the invasive surgical procedure and/or device implantation (i.e. a net benefit). This is a known area of uncertainty.

[11] The other study, Broch et al. (2015), is a Norwegian cohort study that reports on specific diagnoses and subsequent managements attributable to various forms of test (see Table 16). While broadly consistent with the findings of Taylor, AJ et al. (2013), the study does not provide comparative information with regard to expected management with or without CMR. Therefore, without externally speculating on comparative treatments, it is not possible to directly incorporate the data into the model.

In reality, if CMR is not always accurate, patients who do not receive device implantation or surgery as a result of CMR findings may have net harm if the CMR was inaccurate and these treatments were actually appropriate. The impact of CMR accuracy in change in management will be assessed in sensitivity analysis.

Figure 35 Decision analytic structure of the cost-effectiveness analysis for change in clinical management



AICD = automated implantable cardioverter defibrillator; Appropriate = appropriate patient management; CABG = coronary artery bypass graft; CMR = cardiac magnetic resonance (imaging); CRT = cardiac resynchronisation therapy; CRT-D = cardiac resynchronisation therapy with defibrillator; DCM = dilated cardiomyopathy; Inappropriate = inappropriate patient management

D4.(iiA) CEA Inputs used in the model

COSTS OF CMR TESTING

The cost of CMR used in the model is $1,106.31, and includes costs associated with testing, associated AEs, Gd contrast agent, specialist referral and the respective patient contributions (as estimated in Table 34). It is assumed that CMR services are provided in the outpatient setting and that a bulk-billing incentive will be applied to the proposed item (consistent with other CMR services).

COSTS OF PROCEDURES (DEVICE IMPLANTATIONS AND CARDIAC SURGERIES)

The costs of all the procedures performed (i.e. implantable devices and cardiac surgeries) included in the base-case model are the weighted average of costs in the public and private health sectors based on the number of separations. The costs of these procedures can vary substantially across the public and private hospitals due to differences in the cost of prosthetic components. CEAs based on the costs estimated to be incurred in the public and private sectors alone are provided in the sensitivity analyses.

The costs of procedures (device implantations and cardiac surgeries) incurred in the public sector are sourced from cost reports published by the Independent Hospital Pricing Authority (IHPA), and are estimated by the NEP for respective AR-DRGs weighted by the respective number of hospital separations with complications and without complications (Independent Hospital Pricing Authority (IHPA) 2015a).

For private hospital costs, reports from National Hospital Cost Data Collection (NHCDC) for Australian Private Hospitals were sought. The NEP for private hospitals was last published for Round 13 (2008–09) (Department of Health 2012). The only relevant data that can be obtained from the latest report were the number of separations for the AR-DRGs used in the modelled costs. An alternative source identified during the search provides the total average medical service charges for various procedures in the private healthcare hospitals[12]. The costs provided were for financial year 2013–14, and were adjusted for inflation (2015 AUD) using the Inflation Calculator provided by the Reserve Bank of Australia (RBA)[13].

COSTS OF IMPLANTABLE DEVICES (ICD AND CRT-D)

ICD and CRT-D are represented by the same AR-DRGs, F01A and B (Implantation and Replacement of AICD, Total System, Major/Minor Complexity); however, the cost of these two procedures differ due to the higher costs of the CRT-D generator, extra LV lead and lead insertion involved in the CRT-D implant. The same alternative source identified during the assessment also provided the pooled average cost of these procedures[12].

In the Taylor, AJ et al. (2013) study, some inferred benefit of CMR testing was associated with the change in the devices implanted, which included changes of planned CRT-Ds to ICDs alone or vice

[12] The source identified was the website of private health insurer HCF. The average charges for claims paid for various medical services are available from their website <http://healthtopics.hcf.com.au/avail_htopics.aspx>; accessed on 24 March 2016.

[13] Price Inflation calculator provided by RBA <http://www.rba.gov.au/calculator/annualDecimal.html>; accessed on 24 March 2016.

versa. The itemised costs of device implantation procedures were therefore essential to the analysis to reflect these implications.

For public hospital costs, the approach used by Taylor, AJ et al. (2013) was used. First, a weighted cost based on NEP for AR-DRGs F01A and B was calculated as $28,414 (see Appendix M). The estimated cost per procedure was than either reduced or increased by an adjustment factor, $3,314[14], for ICD and CRT-D, respectively. The approach to derive the itemised cost of ICD and CRT-D implantation procedures in private hospitals is based on MSAC Application no. 1223[15], with all the costs adjusted for inflation (2015 AUD).

The detailed derivations of costs of ICD, CRT-D, pacemaker, CABG, valvular surgery, other cardiac surgeries and heart transplants for both public and private sectors are provided in Appendix M. A summary of costs of procedures used in the modelled analysis is presented in Table 38.

Table 38 Costs of procedures used in the model

	Costs in public sector	Costs in private sector	Weighted costs (base-case)
Implantable device			
AICD	$25,100	$62,955	$43,387
CRT-D	$31,727	$70,292	$50,357
Pacemaker	$14,257	$15,590	$14,966
Surgery			
CABG	$39,371	$45,656	$41,939
Valve surgery	$49,413	$50,317	$49,854
Heart transplant [a]	$162,479		$162,479
Other	$22,705	$18,570	$21,402

AICD = automated implantable cardioverter defibrillator; CABG = coronary artery bypass graft surgery; CRT-D = cardiac resynchronisation therapy with defibrillator

[a] Transplant not included in base-case model; see below

Heart transplant

Taylor, AJ et al. (2013) reported that, out of five heart transplants planned in CM patients, two were avoided due to CMR testing. The patient population included in this study (patients were referred to a specialised HF hospital) is probably more restricted than the target population. There were approximately 64 heart transplant surgeries (for all indications) performed in 2013–14 in Australia and, thus, five heart transplant surgeries planned in 449 CM patients does not seem representative

[14] Taylor, AJ et al. suggested an adjustment factor of $3,185 to account for the differences in medical services and other additional prosthesis items. A cost adjustment of $3,185 (converted to $3,314 in 2015 AUD) using the following inflation calculator provided by RBA <http://www.rba.gov.au/calculator/annualDecimal.html> is used in the present analysis.

[15] Medical Services Advisory Committee Application no. 1223 'Insertion, replacement or removal of a cardiac resynchronisation therapy device capable of defibrillation (CRT-D) for mild chronic heart failure (NYHA II)', June 2013.

of the proposed population. The cost associated with a heart transplant surgery is substantial and therefore any surgery avoided will favour the intervention arm considerably. As such, the heart transplant surgeries planned and the associated changes were not included in the base-case analyses. A sensitivity analysis including this data on changes in planned heart transplants is presented.

D5.(iiA) CEA Results

MODELLED COSTS

Table 39 Total and incremental costs per patient associated with each arm of the modelled analysis

	No CMR	CMR	Incremental cost
Cost associated with testing	-	$1,106	$1,106
Costs associated with subsequent management	$8,416	$7,713	–$703
Total modelled cost per patient	$8,416	$8,819	$403

CMR = cardiac magnetic resonance (imaging)

The incremental costs per patient associated with each arm of the modelled analysis are presented in Table 39. CMR testing is associated with an overall incremental cost of $403 in the base-case analysis. A cost offset is observed due to the net reduction in the proportion of devices implanted or surgeries performed following CMR. The modelled cost is largely driven by the downstream costs of procedures (devices and surgeries) performed in both model arms. Base-case analysis uses the average costs of procedures performed in the public and private sectors weighted by the number of separations. Sensitivity analysis is presented using the estimated costs in the public and private sectors separately.

MODELLED OUTCOMES

The modelled outcomes of the economic analysis of changes in patients' management following CMR (at 6 months) are summarised in Table 40. Compared with no testing, CMR is associated with a reduction in the number of inappropriate procedures performed (CMR 0% vs no testing 7.1%). Overall, the CMR testing strategy results in 12.8% of inappropriate patient management plans (i.e. procedures missed or inappropriately planned) being avoided compared with the no testing strategy.

Table 40 Change in patients' management following CMR (at 6 months) in HF patients indicated for DCM (n=449) [a]

	No CMR	Post-CMR	Increment
Appropriate patient management			
Devices planned (appropriate):	11.4%	15.8%	4.5%
AICD	7.4%	10.9%	3.6%
CRT-D	3.1%	3.6%	0.4%
Pacemaker	0.9%	1.3%	0.5%
Surgeries planned (appropriate):	0.7%	2.2%	1.6%
CABG	0.0%	0.0%	0.0%
Valve	0.5%	1.8%	1.3%
Other	0.2%	0.5%	0.2%
No devices or surgeries planned (appropriate)	75.2%	82.0%	6.8%

	No CMR	Post-CMR	Increment
Total appropriate patient management plans	87.2%	100.0%	12.8%
Inappropriate patient management			
Devices planned (inappropriate):	4.7%	0.0%	–4.7%
AICD	0.7%	0.0%	–0.7%
CRT-D	3.8%	0.0%	–3.8%
Pacemaker	0.2%	0.0%	–0.2%
Surgeries planned (inappropriate):	2.5%	0.0%	–2.5%
CABG	0.9%	0.0%	–0.9%
Valve	1.1%	0.0%	–1.1%
Other	0.5%	0.0%	–0.5%
No devices or surgeries planned (inappropriate)	5.6%	0.0%	–5.6%
Total inappropriate patient management plans	12.8%	0.0%	–12.8%

[a] Data obtained through personal communications with the author of Taylor, AJ et al. (2013).

AICD = automated implantable cardioverter defibrillator; CABG = coronary artery bypass grafting; CMR = cardiac magnetic resonance (imaging); CRT = cardiac resynchronisation therapy with defibrillator; DCM = dilated cardiomyopathy; N = number of patients

INCREMENTAL COST-EFFECTIVENESS

There are a number of outcomes that may be used to assess cost-effectiveness, although interpretation is limited in that these are not final health outcomes. Table 41 summarises the incremental costs and various incremental outcomes and ICERs for the above comparison.

Table 41 ICER, change in patients' management following CMR (at 6 months) in HF patients indicated for DCM [a]

	No CMR	Post-CMR	Increment
Cost per patient per strategy	$8,416	$8,819	$403
Appropriate patient management			
Total appropriate devices planned	11.4%	15.8%	4.5%
Total appropriate surgeries planned	0.7%	2.2%	1.6%
No devices or surgeries planned (appropriate)	75.2%	82.0%	6.8%
Total appropriate patient management plans	*87.2%*	*100.0%*	*12.8%*
Incremental cost per additional appropriate procedure planned			$6,710
Incremental cost per additional appropriate implantable device planned			$9,062
Incremental cost per additional appropriate cardiac surgery planned			$25,850
Incremental cost per additional appropriate patient management			$3,160
Inappropriate patient management			
Total inappropriate devices planned	4.7%	0.0%	–4.7%
Total inappropriate surgeries planned	2.5%	0.0%	–2.5%

	No CMR	Post-CMR	Increment
No devices or surgeries planned (inappropriate)	5.6%	0.0%	–5.6%
Total inappropriate patient management plans	*12.8%*	*0.0%*	*–12.8%*
Incremental cost per inappropriate procedure avoided			$5,656
Incremental cost per inappropriate implantable device avoided			*$8,617*
Incremental cost per inappropriate cardiac surgery avoided			*$16,460*
Incremental cost per inappropriate patient management avoided			$3,158

[a] Data obtained through personal communications with the author of Taylor, AJ et al. (2013).

CMR = cardiac magnetic resonance (imaging); DCM = dilated cardiomyopathy; ICER = incremental cost-effectiveness ratio

Cost per appropriate management

Given the increase in number of appropriate procedures planned associated with CMR testing and the increase in costs, compared with no testing, CMR results in an incremental cost of $6,710 per additional appropriate procedure planned. When stratified according to the type of procedure, this translates to an incremental cost of $9,062 per additional appropriate implantable device planned and an incremental cost of $25,850 per additional appropriate surgery planned. When overall appropriate change in patient management (i.e. procedures planned and no procedures planned) is considered, CMR is associated with an incremental cost of $3,160 per additional appropriate patient management, compared with no testing.

Cost per inappropriate management avoided

Given the decrease in number of inappropriate procedures planned associated with CMR testing and the increase in costs, compared with no testing, CMR results in an incremental cost of $5,656 per inappropriate procedure avoided. When stratified according to the type of procedure, this translates to an incremental cost of $8,617 per inappropriate implantable device avoided and an incremental cost of $16,460 per inappropriate surgery avoided. When overall inappropriate patient management plans (i.e. procedures planned and no procedures planned) are accounted, CMR is associated with an incremental cost of $3,158 per inappropriate patient management avoided, compared with no testing.

Outcomes obtained per $100,000 of additional expenditure

The ICERs reported above each relate only to a single outcome of interest and cannot be interpreted collectively. To interpret the cost-effectiveness in the context of all identified outcomes, the results can be framed in terms of the collective outcomes that would be expected for a given incremental expenditure.

The CEA model suggests that, for every $100,000 of additional expenditure associated with the proposed listing of CMR, the following 6-month patient outcomes will be achieved: 358 patients will undergo CMR testing, and out of these 15.9 additional appropriate devices and 5.6 appropriate surgeries will be implanted/undertaken, and 16.7 inappropriate device implantations and 8.8 inappropriate surgeries will be avoided.

D6.(iiA) CEA Sensitivity analyses

Sensitivity analyses around the base-case analysis will explore the uncertainty surrounding these conclusions further. The outcome assessed in the sensitivity analysis is cost per appropriate patient management.

CHANGING CMR ACCURACY

CMR accuracy significantly impacts the resulting ICERs, as the decrease in CMR accuracy reduces the incremental effect of CMR testing. CMR testing is potentially cost-effective (i.e. not dominated) only if the CMR accuracy is 88% or higher (and the ICERs improve with increasing CMR accuracy). Some of the ICERs resulting from varying CMR accuracy are presented in Table 42.

Table 42 Sensitivity analysis, ICER of CMR as an additional test, assuming different CMR accuracies

CMR accuracy		ICER
Base-case:	100%	$3,158
Sensitivity analyses:	85%	Dominated
	87%	Dominated
	88%	$52,777
	89%	$22,860
	90%	$14,589
	93%	$6,996
	95%	$5,194

CMR = cardiac magnetic resonance (imaging); Dominated = intervention is more costly and less effective compared with the alternative; ICER = incremental cost-effectiveness ratio

INCLUDING CHANGE IN HEART TRANSPLANT SURGERIES

In the Taylor, AJ et al. (2013) study, two out of five heart transplant surgeries were avoided in HF patients indicated for DCM. However, these changes in planned transplant surgeries were not considered generalisable to the target population subgroup included in the model. Sensitivity analysis incorporating this data was performed. When heart transplant surgeries are included in the model, CMR results as dominant (Table 43); that is, CMR testing is less costly and more effective compared with the no testing strategy.

Table 43 Sensitivity analysis, including changes in heart transplants

Cost-effectiveness	ICER
Incremental cost per appropriate patient management (base-case)	$3,158
Incremental cost per appropriate procedure	Dominant

Dominant = intervention is less costly and more effective than the comparator; ICER = incremental cost-effectiveness ratio

Additional sensitivity analyses using public- and private-sector costs are provided in Appendix O. In conclusion, the incremental cost-effectiveness of CMR compared with no testing is sensitive to the changes in CMR accuracy and procedural costs included in the analysis. When CMR accuracy (base-case assumes 100%) is below 88%, CMR is dominated by the no testing strategy. In contrast, when changes in heart transplant surgeries are incorporated in the model, CMR testing results as dominant, which is less costly and more effective.

POPULATION IIB: PATIENTS WITH INTERMEDIATE RISK OF CAD

D2.(iiB) Population and setting

This subpopulation includes patients presenting with HF symptoms, a dilated LV and systolic dysfunction with an intermediate risk of CAD. In patients assessed with an intermediate risk of CAD, non-invasive imaging or an ICA (invasive) is undertaken to rule out (or identify) ischaemia as the

cause of DCM. In current practice, CTCA, SPECT and stress echocardiography are the possible non-invasive tests used to rule out ischaemia in this population.

In patients with an intermediate risk of CAD, CMR is proposed as a possible alternative to the non-invasive imaging techniques of CTCA, SPECT and stress echocardiography (all of which may triage patients to ICA if ischaemia is likely), and as an alternative to patients going directly for an ICA; that is, ruling out the need for an ICA if patients have NIDCM, and triaging to ICA if they do show signs of ischaemia.

Generally, patients identified with a likely ischaemic cause of DCM would then undergo ICA (if not undertaken initially) and treatment plans based on the subsequent diagnoses.

If ischaemia is not detected, patients would be referred for further testing, which is proposed to include CMR in the current assessment. CMR has the benefit of being able to combine the function for assessing the aetiology of DCM at the same time as determining whether the patient has NIDCM.

Two studies were identified that provided comparative accuracy of ICA and CMR with available diagnostic data as the reference standard. As such, a modelled analysis is presented for this comparison. This is presented as a CEA.

No conclusive evidence relating to the comparative diagnostic accuracy and effectiveness of CMR, and the alternative non-invasive imaging modalities CTCA, SPECT and stress echocardiography, was identified. Therefore, only a simple CA comparing these tests with CMR is able to be presented. The CA comparing CTCA, SPECT and stress echocardiography is presented sequentially after the CEA comparing ICA.

COST-EFFECTIVENESS ANALYSIS (CEA): CMR VS IMMEDIATE ICA

The purpose of CMR testing in this case is to identify, using a non-invasive method, which patients should and should not be referred for further invasive testing.

A literature search identified 1 study that presented the decision tree analysis of LGE-CMR as a gatekeeper to ICA in the UK setting (Assomull et al. 2011). The strategy of using CMR as a gatekeeper to ICA was found to be less expensive than the alternative, which assumed that all patients would undergo ICA. The authors suggested that the economic conclusions of this model would be sensitive to the relative costs of CMR and ICA in each specific healthcare system. Assomull et al. (2011) also discuss the use of CMR as a gatekeeper to ICA in patients with HF of unknown aetiology. No Australian study comparing the economic implications of CMR and ICA in the proposed population was identified. A decision tree analysis based on the model presented in Assomull et al. (2011), but using Australian inputs, is presented in this economic analysis.

D3.(iiB) CEA Structure

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 CMR or ICA. Since conclusions regarding the long-term health outcome effects of treatment strategies chosen post-diagnosis cannot be made with any certainty (see section B.5), the model terminates before this component of the treatment pathway, and neither costs nor health outcomes associated with post-diagnosis treatments are included, which limits interpretation of the analysis.

Patients enter the model with HF symptoms, a dilated LV, systolic dysfunction and an intermediate risk of having CAD. In the intervention arm, patients receive CMR testing for the diagnosis of *non-ischaemic* DCM. A 'positive result for NIDCM' is assumed to direct management to avoid an ICA in each patient with this diagnosis. Patients with a CMR result suggesting ischaemia (in this case 'negative for NIDCM') will receive an ICA as part of CAD management and to confirm that diagnosis.

Figure 36 shows the decision analytic structure of the CEA comparing CMR with ICA.

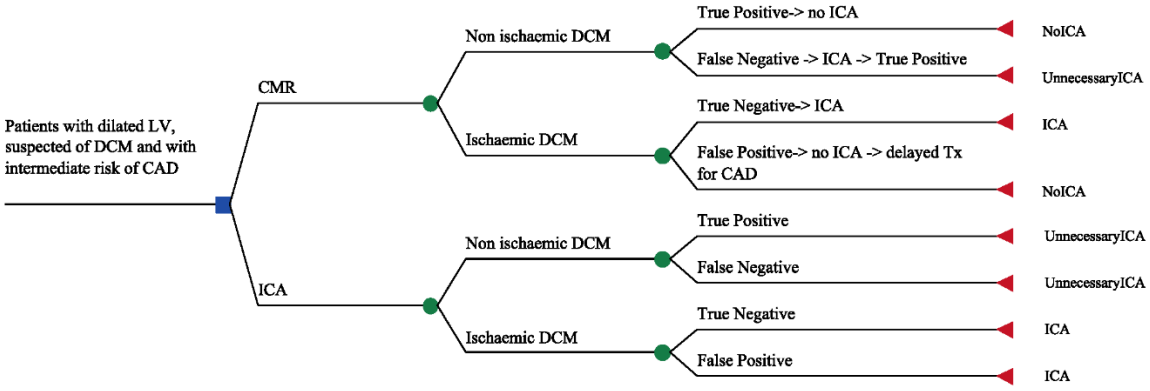


Figure 36 Decision analytic structure of the cost-effectiveness analysis, CMR vs ICA

CAD = coronary artery disease; CMR = cardiac magnetic resonance (imaging); DCM = dilated cardiomyopathy; ICA = invasive coronary angiography; LV = left ventricle; Tx = treatment

Patients with a 'false negative diagnosis for NIDCM' (i.e. incorrectly suggesting a diagnosis of CAD) will have an ICA, and it is assumed that their diagnosis would then be corrected at this time. There is no data available on patients who may have a 'false positive diagnosis of NIDCM' (i.e. when they are, in fact, ischaemic), and the implications of such a result are not included in the model. This is a limitation of the model, but it is anticipated that, as these patients are under close medical attention with further investigation, it is likely that they would receive a corrected diagnosis and appropriate CAD treatment, after a delay.

In the control arm (i.e. without access to CMR), all patients undergo ICA for the diagnosis of NIDCM. Patients with a true positive or false negative result for NIDCM (i.e. a confirmed or missed diagnosis) will effectively have had an unnecessary ICA. The cost of non-invasive testing is assumed to be zero in this arm, and will include costs associated with ICA and related AEs.

In the base-case, it is assumed that all treatment is determined on the basis of the CMR findings. In actual practice, clinicians may refer some patients for an ICA based on their medical history and clinical examinations, irrespective of CMR findings. However, given that CMR was assessed as likely having superior safety, and non-inferior or marginally inferior effectiveness, it is not anticipated that this would occur often. Sensitivity analysis exploring the impact on cost-effectiveness of varying the proportion of patients with CMR findings of NIDCM still being referred to ICA is undertaken.

Other assumptions to note include the following:

- Adverse health outcomes associated with testing related AEs or procedure-related complications are not captured in the cost analysis; however, many of the associated costs, such as adverse reactions caused by contrast agents and microspheres, are incorporated in the economic analyses.
- CMR has the additional benefit, over ICA, of potentially being able to determine the aetiology of DCM at the same time as determining whether the patient has ischaemia or not. This additional benefit is not quantified in this model.

D3.(iiB) CEA Inputs used in the model

DIAGNOSTIC ACCURACY OF CMR AND ICA

Two studies were identified (see section B3.6.4) to provide the diagnostic accuracy of LGE-CMR and ICA using clinical diagnosis as the reference standard in patients with or suspected of NIDCM (Assomull et al. 2011; de Melo et al. 2013).

The study that provided the highest quality evidence with a large patient population (n=120) (Assomull et al. 2011) reported a sensitivity of 1.00 (95%CI 0.96, 1.00) and a specificity of 0.88 (0.82, 0.97) for CMR, and a sensitivity of 0.98 (95%CI 0.92, 1.00) and specificity of 0.87 (95%CI 0.70, 0.96) for ICA, for diagnosing non-ischaemic cause of DCM. The study by de Melo et al. (2013) (n=24) reported a sensitivity of 0.85 (95%CI 0.55, 0.98) and specificity of 0.82 (0.48, 0.98) for CMR, and a sensitivity of 1.00 (95%CI 0.75, 1.00) and specificity of 0.45 (95%CI 0.17, 0.77) for ICA. A summary of the accuracy inputs used in the economic model is provided in Table 44.

Table 44 Diagnostic accuracy inputs used in the economic evaluation

Test	Sensitivity	Specificity	Source	Values tested in sensitivity analyses [95%CI] sensitivity, [95%CI] specificity	Source
CMR	1.00	0.88	Assomull et al. (2011)	[0.55, 0.98], [0.48, 0.98]	de Melo et al. (2013)
ICA	0.98	0.85	Assomull et al. (2011)	[0.75, 1.00], [0.17, 0.77]	de Melo et al. (2013)

CI = confidence interval; CMR = cardiac magnetic resonance (imaging); ICA = invasive coronary angiography

Only tentative conclusions regarding the relative accuracy can be made due to the small number of studies and the limited sample sizes (Figure 14). As such, the accuracy inputs reported in the Assomull et al. (2011) study (larger and higher quality evidence) are used in the base-case economic evaluation, while the 95%CI limits for sensitivity and specificity of CMR and ICA reported by de Melo et al. (2013) are used in the sensitivity analyses.

PREVALENCE OF NIDCM IN THE TESTED POPULATION

The prevalence of NIDCM in the target population is likely to be an important driver of the cost-effectiveness of CMR, but 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.

Eight studies were included in the clinical assessment to provide accuracy estimates of CMR in the proposed population. The mean prevalence of a non-ischaemic aetiology in patients with idiopathic DCM using ICA as the reference standard was 63.1% (range 31.7–79.0%; k=6), and 69.4% (range 54.2–72.5%; k=2) when clinical diagnosis was used as the reference standard. When all studies (both ICA and clinical diagnosis as reference standards) were included, the mean prevalence was 65% (95% CI: 31.7, 79.0%; k=8). The only Australian study, a small one (n=28) conducted by Hamilton-Craig et al. (2012), reported that 75% of patients with idiopathic DCM had a non-ischaemic aetiology.

The applicability of these prevalence rates to the Australian population is unknown, and as most of these patients were already suspected of having 'non-ischaemic aetiology', these rates may be higher than in the general DCM populations presenting for further testing.

A mean prevalence of non-ischaemic aetiology in patients with DCM and an intermediate risk of CAD was assumed to be 65% in the base-case economic analyses (Table 14, section B.4). The 95%CI limits were used in the sensitivity analyses to assess the impact of the prevalence used. The prevalence estimates of NIDCM used in the model and sensitivity analyses are summarised in Table 45.

Table 45 Prevalence of NIDCM in the proposed population

	Source	Prevalence	Sensitivity analyses
CMR in diagnosing non-ischaemic aetiology (ref. std. ICA or clinical diagnosis)	Table 14	65%	95% CI (31.7, 79.0%)

CI = confidence interval; CMR = stress perfusion cardiac magnetic resonance (imaging); ICA = invasive coronary angiography NIDCM = non-ischaemic dilated cardiomyopathy

COSTS ASSOCIATED WITH CMR TESTING

It is assumed that CMR services are provided in the outpatient setting and that a bulk-billing incentive will be applied to the proposed item (consistent with other CMR services). CMR costs are as described previously in Table 34, section D.4.(i), but referral costs are excluded for this set of cost comparisons. A summary of costs associated with CMR testing included in the cost analyses is presented in Table 46

Table 46 Costs associated with CMR testing in the population with intermediate risk of CAD

Parameter	Estimate	Source
Costs related to testing	$926.73	Sum of test costs (excluding referral) (Table 34)
Costs related to treatment of AEs	$0.05	Cost of AE per CMR (Table 34)
Total	$926.78	

AE = adverse events; CAD = coronary artery disease; CMR = cardiac magnetic resonance (imaging)

ICA COSTS (INCLUDING COSTS OF TREATMENT OF AES)

The modelled cost of ICA is based on the NEP for AR-DRGs F42B (Circulatory Disorders, Not Admitted for AMI with Invasive Cardiac Investigations, No Complications, Overnight Stay) and F42C (as above but Same Day) (Independent Hospital Pricing Authority (IHPA) 2015c), weighted by the respective number of hospital separations (Independent Hospital Pricing Authority (IHPA) 2015a). The treatment of AEs related to ICAs is assumed to be the difference between the NEP for AR-DRG F42A (as above but '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 47. Referral costs associated with each test are assumed to be similar and are not included in the analyses.

Table 47 Summary of ICA costs related to testing used in the economic model

-	Cost	Source
ICA	$4,383	NEP (Independent Hospital Pricing Authority (IHPA) 2015c) for AR-DRGs F42B and F42C, weighted by hospital separations (Independent Hospital Pricing Authority (IHPA) 2015a)
AEs related to ICAs	$5,595	NEP (Independent Hospital Pricing Authority (IHPA) 2015a, 2015c) for AR-DRG F42A minus cost of ICA without complications
Proportion of ICA AEs	1.81%	Section B.7.1
Weighted cost of treating AE	$101.27	Cost of treating AE * proportion of AEs experienced
Total ICA cost	$4,484	Sum of ICA cost and cost of AEs

AE = adverse event; AR-DRG = Australian Refined Diagnosis Related Groups; ICA = invasive coronary angiogram; NEP = National Efficient Price

D4.(iiB) CEA Results

The results of the economic evaluation for comparison of CMR (as a gatekeeper for ICA) versus immediate ICA are presented in Table 48.

Table 48 Results of CEA, comparison of CMR (as a gatekeeper for ICA) versus immediate ICA

	CMR	ICA	Increment
Costs			
Test costs (Table 46 and Table 47)	$927	$4,484	–$3,557
Modelled costs of testing strategy	$2,308	$4,484	–$2,176
Testing outcomes			
Total correct diagnoses	95.8%	94.1%	1.7%
Total incorrect diagnoses	4.2%	5.9%	–1.7%
ICAs performed	30.8%	100.0%	–69.2%
ICA in NIDCM+	0.0%	65.0%	–65.0%
ICA in NIDCM–	30.8%	35.0%	–4.2%
Incremental cost per correct initial test result			Dominant
Incremental cost per unnecessary ICA avoided			Dominant

CEA = cost-effectiveness analysis; CMR = cardiac magnetic resonance (imaging); Dominant = intervention is less costly and more effective than comparator; ICA = invasive coronary angiography; NIDCM = non-ischaemic dilated cardiomyopathy

MODELLED COSTS

The CMR testing strategy as a gatekeeper to ICA is determined to be a less-costly option than performing ICA in all patients in the target population. This is driven primarily by the higher costs associated with performing ICA procedures, compared with CMR testing. A cost saving of $2,176 is observed with the CMR testing strategy due to a reduction in the proportion of patients in whom an ICA is performed due to being non-ischaemic.

MODELLED OUTCOMES

There are minor differences in sensitivity and specificity between the ICA and LGE-CMR estimates used in the base-case analysis (based on the Assomull et al. (2011) study). Compared with ICA, LGE-CMR produces a reduction in the false negative rate due to better sensitivity associated with CMR testing (sensitivity of CMR: 100% vs ICA: 98%). This results in a reduction in unnecessary ICAs being performed in the CMR testing arm. In the control arm, all patients undergo ICA testing; therefore, unnecessary ICAs are performed in all patients who are identified to have non-ischaemic aetiology of DCM. In the base-case, the estimated increment in unnecessary ICAs avoided is basically equivalent to the prevalence of NIDCM, as the diagnostic accuracy of both strategies is similar.

COST PER CORRECT INITIAL TEST RESULT

For the outcome of cost per correct initial test result, the differences in the outcomes are small; when compared with ICA, CMR is associated with a decrease in false negative test results; that is, it is more effective. Given that ICA has higher associated costs, it is dominated by CMR in the analysis; that is, CMR is less costly and more effective in terms of diagnosing NIDCM than the comparator ICA.

COST PER UNNECESSARY ICA AVOIDED

Given the decrease in ICAs in NIDCM patients associated with CMR testing, CMR is more effective and less costly than ICA (i.e. CMR is dominant to ICA). Sensitivity analyses around the base-case analysis will explore the uncertainty surrounding the diagnostic accuracy of CMR and ICA, and the prevalence of NIDCM.

D5.(iiB) CEA Sensitivity Analysis

Analysis also indicated that cost-effectiveness was not sensitive to the possibility that CMR would not wholly determine whether or not ICA was undertaken (i.e. an extent of change in management of 100%). Threshold analysis indicated that CMR as a triage test to ICA remained dominant even if clinicians still referred up to 75% of CMR diagnoses of NIDCM for an ICA (i.e. in practice, only avoided 25% of 'avoidable ICAs'), a degree of ongoing referral to ICA that seems above likely plausible limits.

Univariate sensitivity analyses around the variables for diagnostic accuracy of both CMR and ICA, and the prevalence of NIDCM, were conducted using the 95%CIs of point estimates or the range specified previously. As all patients undergo ICA in the comparator arm, the impacts of varying the sensitivity and specificity of ICA are negligible and, thus, not presented.

Variations in the ICER due to changes in the extent to which CMR directs change in management (up to 50%), the sensitivity and specificity of CMR, and the underlying prevalence of NIDCM are shown in a tornado diagram (Figure 37).

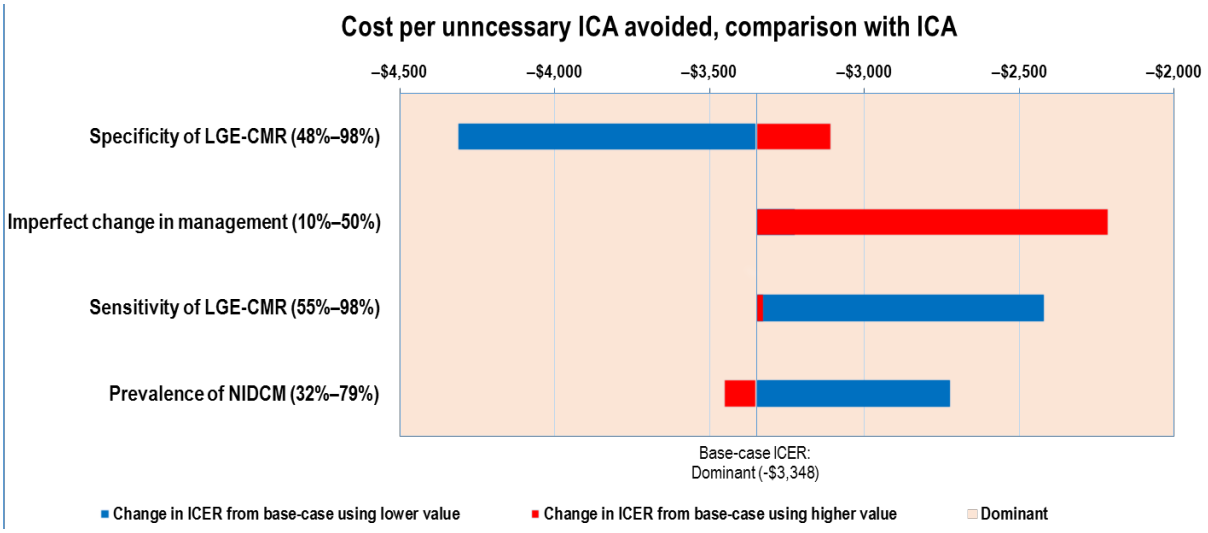


Figure 37 Tornado sensitivity analyses, comparison with ICA

Dominant = intervention is less costly and more effective than comparator; ICA = invasive coronary angiography; ICER = incremental cost-effectiveness ratio; LGE-CMR = cardiac magnetic resonance (imaging) with late gadolinium enhancement; NIDCM = non-ischaemic dilated cardiomyopathy

The use of LGE-CMR in the first instance to identify ischaemic patients for ICA, compared with the strategy of having all patients at intermediate risk of CAD undergo ICA, consistently results in fewer (unnecessary) invasive angiograms (i.e. is more effective) and is less costly. This conclusion held across the base-case and all plausible sensitivity analyses conducted.

COST ANALYSES: CMR COMPARED WITH SPECT, CTCA AND STRESS ECHOCARDIOGRAPHY

D3.(iiB) CA Structure

The clinical management algorithm presented in section A6 suggests that, in some instances, other non-invasive tests (specifically, CTCA, SPECT or stress echocardiography) currently utilised where CMR is proposed are relevant economic comparators. Section B did not identify any comparative evidence relating to change in management or health-outcome effects associated with these tests and CMR. Given the inadequate evidence to estimate cost-effectiveness, simple cost analyses only are presented.

Given the lack of evidence, considerations around diagnostic yield, comparative accuracy, and the implications of false negatives or positives are not incorporated into the analysis. Further, the additional benefit of CMR over other comparators, in simultaneously being able to determine both the aetiology of DCM and whether the patient has ischaemia or not, are not incorporated in the analysis.

D4.(iiB) CA Inputs to the cost analyses

When calculating cost inputs, it is assumed that non-invasive imaging services are provided in the outpatient setting and that a bulk-billing incentive will be applied to the proposed item (consistent with other CMR services).

All tests compared in the analyses require a GP or specialist referral; however, CTCA and CMR can only be referred by a specialist. It is assumed that patients symptomatic with HF would largely be managed by cardiac specialists, and therefore referral costs associated with each test are considered similar and are not included in the analyses.

COSTS ASSOCIATED WITH TREATING AES RELATED TO TESTING

Adverse health outcomes associated with testing-related AEs are not captured in the cost analysis; however, many of the associated costs of test-related AEs are incorporated, including costs associated with:

- allergic reactions to the Gd contrast agent associated with CMR
- AEs related to iodinated contrast agents associated with CTCA
- AEs related to microspheres and pharmacological stressors (e.g. adenosine or dobutamine) associated with stress echocardiography.

The cost of treating AEs related to testing are presented in Table 49 and are based on the NEP for the AR-DRG code (Independent Hospital Pricing Authority (IHPA) 2015a, 2016) most relevant to the event. The International Stress echocardiography 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 F76A (Arrhythmia, Cardiac Arrest and Conduction Disorders) is used in the analysis.

Table 49 Cost of treating AEs

AE	Treatment cost	Source [a]
Gadolinium contrast reaction	$1,084	NEP for AR-DRG X61Z (Allergic Reactions)
Iodinated contrast AE	$8,694	NEP for AR-DRG E64A (Pulmonary Oedema)
Microspheres reaction	$1,084	NEP for AR-DRG X61Z (Allergic Reactions)

AE	Treatment cost	Source [a]
Stressors AEs	$7,239	NEP for AR-DRG F76A (Arrhythmia, Cardiac Arrest and Conduction Disorders)

[a] Price weight for the respective AR-DRGs (Independent Hospital Pricing Authority (IHPA) 2015a) * the NEP 2016–17 ($4,883) (Independent Hospital Pricing Authority (IHPA) 2016).

AE = adverse event; AR-DRG = Australian Refined Diagnosis Related Groups; NEP = National Efficient Price

The AE rates and the weighted cost of treating AEs related to each test used in the economic analyses are presented in Table 50, and are based on those reported in Table 99, Appendix J. For pharmacological stressors, AE rates have been reported by stress type (e.g. adenosine or dobutamine). An average estimate was used in the analyses as the relative use of stress agents in Australia is unknown. Other rare serious AEs related to CMR and other tests reported in section B7.1 (Table 99, Appendix J) are also not included in the economic analyses.

Table 50 Cost of treating AEs associated with the testing strategies

	AE rate	Cost of treating AE	Cost of treating AE per test
CMR (total)		--	$0.05
Gadolinium contrast	0.005%	$1,084	$0.05
CTCA (total)		--	$3.48
Iodinated contrast	0.04%	$8,694	$3.48
Stress Echo (total)		-	$0.98
Stressor	0.009%	$7,239	$0.65
Microspheres	0.03%	$1,084	$0.33
SPECT (total)			$0.01
Radiotracers	0.0006%	$1,084	$0.01

Source: Data from Table 99, Appendix J.

AE = adverse event; CMR = cardiac magnetic resonance (imaging); CTCA = computed tomography coronary angiography; Echo = echocardiography; SPECT = single-photon emission computed tomography

COSTS ASSOCIATED WITH CMR TESTING

The cost of CMR used in the model is $926.78 and includes costs associated with testing, associated AEs, Gd contrast agent and the respective patient contributions as presented in Table 46.

COSTS ASSOCIATED WITH SPECT TESTING

The costs related to SPECT include the cost of the scan (based on MBS data for item 61303 for the average benefits paid per service) and the average patient co-payment (based on MBS data for item 61303 for the average patient contribution paid per service) for 2014–15. Radiotracers used in SPECT are associated with a very low rate of serious AEs and are not included in the cost analyses.

The total cost of testing by SPECT is $538.32 per patient. A summary of the costs used in the cost analysis is presented in Table 51.

Table 51 Costs associated with SPECT in the proposed population with intermediate risk of CAD

Parameter	Estimate	Source
Cost of test	$525.53	MBS benefit for outpatient service for item 61303, 2014–15
Patient co-payment	$12.78	Average patient contribution per SPECT service, 2014–15

Parameter	Estimate	Source
Total	$538.32	

CAD = coronary artery disease; MBS = Medicare Benefits Schedule; SPECT = single-photon emission computed tomography

COSTS ASSOCIATED WITH CTCA TESTING

The costs related to CTCA include the cost of the scan (based on MBS data for item 57360 for the average benefits paid per service) and the average patient co-payment (based on MBS data for item 57360 for the average patient contribution paid per service) for 2014–15, and the costs related to associated AEs. Iodinated contrast agents used in CTCA can cause allergic reactions in 0.04% of cases (Table 99, Appendix J).

The cost of treating the complications related to iodinated contrast has been estimated by multiplying the price weight for AR-DRG E64A (1.78) (Independent Hospital Pricing Authority (IHPA) 2015a) by the NEP for 2016–17 ($4,883) (Independent Hospital Pricing Authority (IHPA) 2016). Therefore, the cost of treating each AE due to a reaction to the iodinated contrast agent is $8,694, which equates to $3.48 per CTCA.

The total cost of testing by CTCA is therefore $695.91 per patient. A summary of the costs used in the cost analysis is presented in Table 52.

Table 52 Costs associated with CTCA in the proposed population with intermediate risk of CAD

Parameter	Estimate	Source
CTCA	$649.81	MBS benefit for outpatient service for item 57360, 2014–15
Patient co-payment	$42.62	Average patient contribution per CTCA service, 2014–15
Costs related to treatment of AEs	$3.48	Cost of AE per CTCA
Total	$695.91	

AE = adverse events; CAD = coronary artery disease; CTCA = computed tomography coronary angiography; MBS = Medicare Benefits Schedule

COSTS ASSOCIATED WITH STRESS ECHOCARDIOGRAPHY

Stress echocardiography is performed in conjunction with exercise ECG (MBS item 11712). The costs related to stress echocardiography include the cost of the scan and exercise ECG (based on MBS data for the average benefits paid per service for items 55117 and 11712) and the average patient co-payment (based on MBS data for the average patient contribution paid per service for items 55117 and 11712) for 2014–15, and costs related to the treatment of AEs.

AEs related to stress echocardiography include complications associated with the use of pharmacological stressors (0.009%)[16] and microspheres (0.03%), as reported in section B.7.1. The costs of treating the complications related to stressors and microspheres have been estimated by multiplying the price weight for AR-DRG F76A (1.49) and AR-DRG X61Z (0.22) (Independent Hospital Pricing Authority (IHPA) 2015a) by the NEP for 2016–17 ($4,883) (Independent Hospital Pricing

[16] For pharmacological stressors, event rates have been reported by stress type (adenosine (0.014%) and dobutamine (0.18%)) in section B.7.1. As the relative use of stress agents in Australia is unknown, an average estimate was used in the analyses.

Authority (IHPA) 2016). The weighted cost of treating AE per stress echocardiography is $0.98 (Table 50).

The total cost of testing by stress echocardiography is then $422.35 per patient. A summary of the costs used in the cost analysis is presented in Table 53.

Table 53 Costs associated with stress echocardiography in the proposed population with intermediate risk of CAD

Parameter	Estimate	Source
Pharmacological stress Echo	$232.21	MBS benefit for outpatient service for item 55117, 2014–15
Patient co-payment	$31.76	Average patient contribution per stress Echo service, 2014–15
Exercise ECG	$130.78	MBS benefit for outpatient service for item 11712, 2014–15
Patient co-payment	$26.63	Average patient contribution per exercise ECG service, 2014–15
Cost of treating AE due to stressors and microspheres	$0.98	Cost of AE per stress Echo (Table 50)
Total	$422.35	

AE = adverse event; CAD = coronary artery disease; Echo = echocardiography; ECG = electrocardiography; MBS = Medicare Benefits Schedule

D5.(iiB) CA Results of the cost analyses: CMR vs SPECT or CTCA or stress echocardiography

The cost analysis for comparisons of CMR with SPECT, CTCA and stress echocardiography is presented in Table 54. CMR testing is associated with an incremental cost of $388.46 compared with SPECT, $230.87 compared with CTCA, and $504.43 compared with stress echocardiography.

Table 54 Incremental cost of CMR vs non-invasive comparators: SPECT, CTCA and stress echocardiography

	Cost of CMR	Cost of comparator	Incremental cost
Base-case CMR vs SPECT	$927	$538	$388
Base-case CMR vs CTCA	$927	$696	$231
Base-case CMR vs stress Echo	$927	$422	$504

CMR = cardiac magnetic resonance (imaging); CTCA = computed tomography coronary angiography; Echo = echocardiography; SPECT = single-photon emission computed tomography

Differences that should be considered concurrently with the cost analysis of CMR versus the alternatives include the following:

- Patient acceptability—due to the confined space within a MRI scanner and the duration of the time required to be in the scanner (60 minutes), CMR may not be as acceptable to patients as SPECT, CTCA or stress echocardiography. In contrast, scanning with SPECT and CTCA involves use of radiation that may be unacceptable to some patients.
- Relative accessibility/timeliness—CMR, SPECT, CTCA and stress echocardiography all require a referral; however, CMR and CTCA are by specialist referral only, whereas referral for SPECT or stress echocardiography can also be made by a GP. Access to CMR may also be limited, due to the duration required for CMR and the demand in other specialties.
- Provision of additional clinical information—CMR can identify causes of DCM other than ischaemia, and thus reduces further downstream testing costs in some cases. It is unknown whether SPECT, CTCA or stress echocardiography can distinguish between the aetiologies of DCM other than ruling out likely ischaemic causes. Insufficient evidence was found during

the clinical assessment to support the comparison of diagnostic accuracy and effectiveness of CMR versus any of these comparators.

And the nature and incidence of side effects varies between testing strategies:

- The Gd agent used in CMR testing may be associated with mortality due to long-term nephrotic toxicity, in addition to acute allergic reactions (approximately 6.6 per 10,000 doses) (see section B.7.1).
- Acute AEs related to the use of radiotracers in SPECT are very rare (0.06 per 10,000 scans) but there is a long-term fatal cancer risk of approximately 7.8 per 10,000 patients (see section B.7.1). LGE-CMR appears to have similar safety, with respect to mortality rate, to SPECT.
- CTCA has, in addition to AEs related to the iodinated contrast agent, a long-term fatal cancer risk of 1.5–7 per 10,000 patients related to the use of radiation doses, and a mortality risk of 8–14 per 10,000 patients (section B.7.1).
- Stress echocardiography patients may suffer an acute event resulting in death (approximately 1.4 per 10,000 patients) due to the use of a stressor, in addition to AEs related to stressors and microspheres (see section B.7.1). The number of serious AEs experienced by patients during stress echocardiography outnumber those resulting from CMR due to the use of a stressor (Table 99, Appendix J).

D6.(iiB) CA Sensitivity analyses

Sensitivity analyses were conducted around some of the assumptions made in the analysis to determine the incremental costs of CMR compared with SPECT, CTCA and stress echocardiography. These included removing the assumption of the bulk-billing incentive for CMR for CM services, and modifications to the CMR patient contribution and the proportion of patients who are bulk-billed. The adjusted assumptions are presented in Table 55 (with adjustments making less than a 10% difference shaded out).

Table 55 Key sensitivity analyses, comparisons of CMR with SPECT, CTCA and stress echocardiography

	Incremental costs vs SPECT	Incremental costs vs CTCA	Incremental costs vs stress Echo
Base-case	$388	$231	$504
Assuming no bulk-billing incentive (base-case: assumes bulk-billing incentive)	$295	$138	$295
CMR patient contribution 15% of Schedule Fee, $128.30 (base-case: $244.36)	$357 [a]	$199	$357
Proportion CMR bulk-billed, 60% (base-case: 72.8%)	$403 [a]	$246 [a]	$403
CMR patient contribution, $300 (base-case: $244.36)	$404 [a]	$246 [a]	$404

[a] Shaded cells represent no significant change, i.e. less than a 10% difference from the base-case incremental cost.

CMR = cardiac magnetic resonance (imaging); CTCA = computed tomography coronary angiography; Echo = echocardiography; SPECT = single-photon emission computed tomography

With respect to the comparison versus CMR, removing the bulk-billing incentive reduces the incremental cost of CMR by approximately 24%.

With respect to the cost comparison of CMR versus CTCA, the incremental difference was most sensitive to removing the assumption of the bulk-billing incentive for CMR for CM services, reducing the incremental cost of CMR by approximately 40%. The analysis was also moderately sensitive to the assumption of the CMR patient contribution being 15% of the Schedule Fee, reducing the incremental cost of CMR by approximately 14%.

The incremental cost of CMR compared with stress echocardiography was found to be sensitive to the assumption of the bulk-billing incentive for CMR and modifications to the CMR patient contribution, reducing the incremental cost of CMR in the range 20–42%.

In summary, CMR is consistently more expensive than other comparators (SPECT, CTCA and stress echocardiography) in the population with intermediate risk of CAD across all analyses tested; however, one benefit of CMR that has not been incorporated into this cost analysis is its ability to assess the aetiology of DCM at the same time as determining whether the patient has NIDCM, whereas with other comparators further testing would be required in those who are identified as non-ischaemic. However, the relative accuracy of CMR compared with SPECT, CTCA and stress echocardiography is unknown, and CMR may also be associated with lower patient acceptability and accessibility issues.

SECTION E FINANCIAL IMPLICATIONS

Estimating the expected extent of usage and the financial implications of the proposed MBS listing for CMR is not straightforward. There is inadequate epidemiological data for a routine step-down approach to identify eligible patients, and a market-based approach is difficult as the suggested comparator items are not restricted to the population in the proposed listing.

To enable estimates to be made for this report, an epidemiological approach has been used, based on available data on newly diagnosed cases of DCM in Australia each year, and back-calculating to estimate the number of CMR tests that would be undertaken to identify these patients among all patients potentially suspected of this condition. Given that the characteristics of patients with suspected DCM are not easily defined, and CMR uptake rates are unknown, there is considerable uncertainty around the estimates presented.

The sources of data used in the financial analysis are presented in Table 56.

Table 56 Parameters and data sources used in the financial analysis

Data	Source
Proportion of indeterminate results with Echo	Base-case: assumed 5%, with consideration of clinical expert opinion suggesting that, with technical advancements in echocardiography imaging, indeterminate results are less than 5% Sensitivity analyses: 10–20%, (Afridi 2015)
Annual incidence of *primary* DCM	Base-case: 7 per 100,000 (Taylor, MR, Carniel & Mestroni 2006) Sensitivity analyses: 10 and 20 per 100,000
Projection of Australian population aged 18 years and older in 2016–21	(See Table 57) ABS data catalogue no. 3222, series B (2013)
Proportion of patients and family members requiring diagnostic clarification using CMR	Assumed, with consideration of feedback provided by clinical experts
CMR uptake rate	Base-case: 100% Scenario analyses: 50% assumed, with consideration of feedback to the Protocol suggesting that CMR for diagnosis of CM 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	For population i (inconclusive Echo): based on study by Taylor, AJ (2013) For population iiB (intermediate risk of CAD): based on Medicare services provided in 2014–15 for MBS items 38218, 59925, 55117, 57360 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 11712, 55113, 55117, 57360, 61303, 61313, 63385, 63388, 63391, 63401 and 63404 in 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, 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, 2014–15

Data	Source
Cost of current tests to the MBS	MBS data for items 11712, 55113, 55117, 57360, 61303 and 61313 for the weighted average MBS benefit paid per service, 2014–15
Patient co-payment for current tests	MBS data for items 11712, 55113, 55117, 57360, 61303 and 61313 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), 2014–15
Cost per service of ICA in public sector	NEP for AR-DRG F42C (Independent Hospital Pricing Authority (IHPA) 2015a)
Cost per service of ICA in private sector	http://healthtopics.hcf.com.au/CoronaryAngiographyAngioplastyandStents.aspx
Respective number of ICA services performed in private and public sectors	Based on respective number of separations for AR-DRG F42A, F42B and F42C in public (Independent Hospital Pricing Authority (IHPA) 2015c) and private hospitals (Independent Hospital Pricing Authority (IHPA) 2015b)

AR-DRG = Australian Refined Diagnosis Related Groups; ABS = Australian Bureau of Statistics; CAD = coronary artery disease; CM = cardiomyopathy; CMR = cardiac magnetic resonance (imaging); DCM = dilated cardiomyopathy; Echo = echocardiography; ICA = invasive coronary angiography; MBS = Medicare Benefits Schedule; MRI = magnetic resonance imaging; NEP = National Efficient Price

To aid the ability to follow calculations, tables used for epidemiological calculations will be allocated row numbers that are consistent and continue consecutively throughout the sections.

E1 USE AND COSTS OF CMR FOR DIAGNOSIS OF DCM

CMR is proposed as an additional test in suspected HF patients who have undergone standard clinical evaluations, including clinical examinations, ECG and echocardiography, and require further diagnostic clarification. There is no specific data on the number of patients in Australia investigated for all forms of DCM each year[17]; however, the number of patients in Australia expected to have a positive diagnosis of *primary* DCM can be estimated based on incidence and prevalence estimates.

The following steps have been taken to estimate the broader number of patients with *any suspected DCM* for whom it would be appropriate to use CMR.

1. Estimation of the number of incident cases of *primary* DCM (i.e. idiopathic and familial, but excluding secondary causes such as ischaemia, myocarditis etc.) in Australia for each year of analysis, using population projections and reported incidence rates.
2. Estimation of the total number of suspected HF patients (with a diagnosis of a dilated LV, from any cause, identified by echocardiogram, examination etc.), based on a reported ratio of primary:secondary CMs.
3. An estimate of the number of patients suspected or diagnosed with DCM who will have indeterminate or equivocal echocardiograms (based on the estimated rate of indeterminate echocardiograms); *eligible patient group i, as per section A4*.
4. The number of cases that are suspected or diagnosed with DCM following other clinical evaluation (including echocardiogram), and with a low or intermediate risk of CAD, where

[17] Approximately 700,000 echocardiograms are performed annually in Australia to investigate symptoms or signs of cardiac failure, suspected or known ventricular hypertrophy or dysfunction, or chest pain (MBS statistics, 2014–15, for items 55113 and 55119). According to clinical expert advice, approximately 60% of these will have normal results. Of the abnormal results (40% of the total—approximately 280,000), only a small—but not quantified—portion will relate to suspected DCM.

further diagnostic clarification is required (e.g. to identify specific aetiology/secondary causes); *eligible patient group ii, as per section A4*.

5. An estimate of the expected number of apparent familial cases of DCM eligible for further diagnostic clarification by CMR test; *eligible patient groups iii/iv, as per section A4.*

Uptake of CMR

Feedback to the Protocol suggested that there may be limited access to CMR for diagnosis of CAD due to the generally high demand for MRI in other specialties and indications. Furthermore, patient acceptability may not be high due to CMR requiring spending an extended time in a confined space. Therefore, it was proposed, prior to consideration of the clinical evidence, that the uptake of CMR may be small. However, during preparation of this report, clinical experts advised that, due to the additional clinical value of CMR in providing diagnosis and diagnostic clarification in this population, if available, the uptake rates may be high. The uptake rate of CMR is estimated for each eligible patient group.

1. INCIDENCE OF PRIMARY DCM IN AUSTRALIA

The true prevalence and incidence of DCM in Australia are unknown. Most studies in the literature suggest a prevalence of 1 in 2,500 and an incidence of 7 per 100,000 for primary DCM (Rakar et al. 1997; Taylor, MR, Carniel & Mestroni 2006). However, these figures may underestimate the actual extent of DCM as some patients are asymptomatic until reaching advanced stages of the disease. In the base-case, an incidence of 7/100,000 is used, but the implications of higher incidence rates of 10 and 20 per 100,000 are assessed in sensitivity analyses. Incidence rates are applied to the projected adult population of Australia (Australian Bureau of Statistics 2013) to calculate the number of incident cases in each given year.

Table 57 presents the projected number of incident cases of primary DCM for the financial years 2016–17 to 2020–21.

Table 57 Projected incident cases of primary DCM

Row		2016–17	2017–18	2018–19	2019–20	2020–21
A	Projected number of Australians 18 years and older (Australian Bureau of Statistics 2013)	19,201,809	19,529,153	19,853,831	20,173,593	20,492,073
B	Incident rate per 100,000	7	7	7	7	7
C	Number of incident cases (= A*B)	1,344	1,367	1,390	1,412	1,434

DCM = dilated cardiomyopathy

2. ESTIMATED NUMBER OF SUSPECTED HF PATIENTS WITH DIAGNOSIS OF A DILATED LV

No direct evidence was found to estimate the number of suspected HF patients diagnosed with an impaired LV after echocardiography and other clinical examinations.

Following identification of an impaired LV, various alternative diagnoses are possible, including primary DCM, ICM and CM secondary to valvular diseases or other causes—which may or may not need CMR for differentiation. Use of CMR for differentiation of ICM, however, is a major function of CMR testing, and ICM patients represent the majority of those with secondary CM (Taylor, MR, Carniel & Mestroni 2006). To estimate the total number of patients suspected of HF, either primary or secondary, the number expected to be identified with an ischaemic diagnosis are added to the previously identified incident cases of primary DCM (Table 58). As non-ischaemic secondary causes

represent only a small proportion of secondary HF patients, these have not been separately identified.

The estimated proportion of CM patients with ischaemia varies in the literature, with 1 study providing a range of 50–70% (Taylor, MR, Carniel & Mestroni 2006) and others reporting between 41% and 75% (Cheong et al. 2009; Gao et al. 2012; Iles et al. 2011; Klem et al. 2012; Wu, KC et al. 2008). For this analysis, the base-case estimates the proportion of HF patients with ischaemia as 70%. Table 58 presents the estimated number of suspected HF patients with diagnosis of a dilated LV.

Table 58 Estimated number of suspected HF patients with a dilated LV

Row		2016–17	2017–18	2018–19	2019–20	2020–21
C	Number of incident cases of *primary* DCM	1,344	1,367	1,390	1,412	1,434
D	Number of patients with ICM (C*2.33) [a]	3,136	3,190	3,243	3,295	3,347
E	Number of suspected HF patients with diagnosis of a dilated LV (= C+D)	4,480	4,557	4,633	4,707	4,781

[a] Calculated by multiplying the number of incident cases (A) by 2.33 (proportion of ischaemic/non-ischaemic: 70%/30%)

DCM = dilated cardiomyopathy; HF = heart failure; ICM = ischaemic cardiomyopathy; LV = left ventricular

3. NUMBER OF PATIENTS WITH INDETERMINATE RESULTS WITH ECHOCARDIOGRAPHY (POPULATION I)

The estimated proportion of patients who have indeterminate results obtained from echocardiography is uncertain. The accuracy of transthoracic echocardiograms can be reduced by factors that cause suboptimal acoustic windows, such as chest wall or rib deformities, obesity and obstructive lung disease (O'Donnell et al. 2012). Afridi et al. (2015) suggested that echocardiography may be limited in 10–20% of patients due to the aforementioned reasons. This is in concordance with the 15% estimate advised by the Advisory Panel in MSAC Application no. 1129 (Thavaneswaran et al. 2010). However, clinical experts suggested that, with ongoing technological advancements in imaging, currently very few (less than 5%) of echocardiography results are indeterminate. As such, the base-case assumes that 5% of echocardiography results are indeterminate, but higher estimates of 10% and 20% are tested in sensitivity analyses.

As discussed above, in suspected HF patients, 60% of the echocardiography results are normal. The remaining results are estimated to approximately comprise indeterminate findings (5%) and suspected/diagnosed cases (35%). Therefore, the estimated number of indeterminate echocardiography results can be back-calculated as a ratio of the number of patients with identifiable DCM (equivalent to approximately 5/35 or 14.3% of the suspected/diagnosed cases). Table 59 presents the estimated number of indeterminate results that are eligible for CMR testing.

It is assumed that CMR will be performed in all the cases with indeterminate results. Thus, uptake of CMR will be 100% in this subgroup.

Table 59 Projected number of indeterminate echocardiogram results eligible for CMR testing (population i)

Row		2016–17	2017–18	2018–19	2019–20	2020–21
E	Number of suspected/diagnosed cases of DCM	4,480	4,557	4,633	4,707	4,781
F	Estimated additional patients who may be eligible for CMR following indeterminate Echo results (14.3%*E)	640	651	662	672	683

CMR = cardiac magnetic resonance (imaging); DCM = dilated cardiomyopathy; Echo = echocardiography

4. *NUMBER OF PATIENTS WITH DCM IDENTIFIED ON ECHOCARDIOGRAM REQUIRING FURTHER DIAGNOSTIC CLARIFICATION (PATIENT GROUP II)*

CMR will not be necessary for every case of suspected DCM identified by prior clinical examinations, tests and echocardiograms, as the diagnosis and aetiology may be clear from prior testing. According to clinical expert advice, CMR will be conducted in around 75% of patients with an impaired LV and suspected DCM. Table 60 presents the number of patients eligible for CMR testing for diagnostic clarification of DCM.

Table 60 Estimated uptake of CMR in DCM for diagnostic clarification (population ii)

Row		2016–17	2017–18	2018–19	2019–20	2020–21
E	Number of suspected/diagnosed cases of DCM	4,480	4,557	4,633	4,707	4,781
G	Total number of tests eligible for diagnostic clarification (75%*E)	3,338	3,395	3,451	3,507	3,562

CMR = cardiac magnetic resonance (imaging); DCM = dilated cardiomyopathy

5. *ESTIMATION OF ADDITIONAL FAMILIAL CASES ELIGIBLE FOR CMR TEST (POPULATION III)*

Feedback from clinical experts suggested that, for every index case of DCM, approximately four or five family members undergo DCM screening. The annual incidence rate of DCM in the screened members is around 5%, out of which approximately 40–50% will require diagnostic clarification using CMR, due to indeterminate results on other clinical tests[18]. Table 61 estimates the small additional number of patients identified through screening of family members that would become candidates for CMR. Due to family history, it is assumed that uptake of CMR would be 100% in this group of patients.

Table 61 Projected number of incident familial DCM cases eligible for CMR testing

Row		2016–17	2017–18	2018–19	2019–20	2020–21
C	Number of incident cases of *primary* DCM	1,344	1,367	1,390	1,412	1,434
H	Number of family members screened (without using CMR) = C*4	5,377	5,468	5,559	5,649	5,738
I	Number of incident cases of familial DCM identified by screening (= H*5%)	269	273	278	282	287
J	Number of eligible tests in familial cases (I*40%)	108	109	111	113	115

CMR = cardiac magnetic resonance (imaging); DCM = dilated cardiomyopathy

Total estimated usage of CMR

Based on the sum of the three patient groups identified above, the total estimated number of services eligible and utilised with the introduction of CMR for DCM is presented in Table 62.

[18] Feedback provided by clinical experts during a teleconference with HTA members and Department of Health on 23 February 2016. Clinical experts advised that:

- For every index case of DCM, approximately four or five family members undergo DCM screening.
- The annual incidence rate of DCM in the screened members is around 5%.
- Out of these incidence cases, approximately 40–50% will require diagnostic clarification using CMR, due to indeterminate results on other clinical tests.

Table 62 Estimation of the number of total CMR tests performed in DCM

Row		2016–17	2017–18	2018–19	2019–20	2020–21
F	Number of symptomatic patients with indeterminate echocardiogram results requiring CMR (population i)	640	651	662	672	683
G	Number of CMRs taken up for further diagnostic clarification of DCM (population ii)	3,338	3,395	3,451	3,507	3,562
J	Number of clarifying CMRs in familial cases (population iii)	108	109	111	113	115
K	Total uptake of CMR (F+G+J)	4,086	4,155	4,224	4,292	4,360

CMR = cardiac magnetic resonance (imaging); DCM = dilated cardiomyopathy

These estimates are uncertain. In the Protocol for MSAC Application no. 1393, PASC suggested that the hospital separations provided by the Australian Institute of Health and Welfare (AIHW) principal diagnosis data cubes may provide an estimate for the likely utilisation of CMR for investigating DCM (2,118 diagnoses in 2013–14)[19]. However, in further discussion with clinical experts it was suggested that this number may present an underestimate and that the number of CMR tests in the proposed population would likely be higher, around 4,000 per year. This ballpark estimate is consistent with the calculations presented.

ESTIMATED COST OF CMR TESTING

The proposed MBS item schedule fee for CMR is $855.20. It is intended that the proposed item be co-claimed with MBS item 63491, for which the fee is $44.90 (which covers the cost of administering the Gd contrast agent), which is not included in the proposed CMR item fee.

The majority of comparator tests and current CMR services are assumed to be conducted in an out-of-hospital setting[20], where the benefit paid by the MBS is 85%. The total cost to the MBS per service is $765, derived from the cost of the proposed CMR (85% benefit; $726.90) and the associated use of contrast (MBS item 63491, 85% benefit; $38.10).

The proportion of patients that are bulk-billed (72.8%) and the patient contribution ($244.36) (including the gap and out-of-pocket costs) for LGE-CMR are estimated based on data for current MBS services (items 63385, 63388, 63391, 63401 and 63404) for CMR in 2014–15. Therefore, the estimated patient contribution per LGE-CMR test is $66.54[21], and for the Gd contrast agent is $6.72. The total patient contribution associated with each CMR service is thus $73.26 ($66.54 + $6.72). The total cost of CMR testing is reported in Table 63, disaggregated by payer (the MBS and the patient). The average total cost of CMR testing per year is estimated to be $3.6 million.

[19] Medical Services Advisory Committee, Final Protocol for Application 1393: 'Magnetic resonance imaging of patients with suspected non-ischaemic cardiomyopathies', May 2015.

[20] MBS data was analysed for the proportion of tests conducted in-hospital and out-of-hospital for items 55113, 57360, 61303, 61313, 63385, 63388, 63391, 63401 and 63404 in 2014–15.

[21] $244.36 × (1 − 72.8%)

Table 63 Total cost of CMR testing for DCM

	2016–17	2017–18	2018–19	2019–20	2020–21
Projected number of CMR tests for DCM (row K)	4,086	4,155	4,224	4,292	4,360
Cost of CMR and associated items to the MBS ($765 per service) [a]	$3,125,411	$3,178,692	$3,231,539	$3,283,585	$3,335,423
Cost of CMR and associated items to patients ($73.26 per service) [b]	$299,310	$304,412	$309,473	$314,458	$319,422
Total cost of CMR	$3,424,721	$3,483,104	$3,541,012	$3,598,043	$3,654,845

[a] The cost to the MBS per service is $765, derived from the cost of the proposed CMR (85% benefit; $726.90) and Item 63491 (85% benefit, $38.10).
[b] The cost to a patient per service is $73.26, derived from the estimated patient co-payment for proposed CMR service ($66.54) and patient co-payment for Item 63491 ($6.72).

CMR = cardiac magnetic resonance (imaging); DCM = dilated cardiomyopathy; MBS = Medicare Benefits Schedule

E2 CHANGES IN USE AND COST OF OTHER MEDICAL SERVICES

Estimated market share of current testing

The extent to which utilisation of each of the comparator tests also used in the diagnosis of DCM will change is unknown. The market share estimates of the various currently listed tests is based either on clinical opinion or the respective quantities of MBS services used. Changes in use and cost of comparator services are first calculated separately for each patient group and then combined to estimate the total change in use and cost due to the introduction of CMR.

Population i: Indeterminate echocardiography tests

In the absence of CMR, the majority of patients with an indeterminate echocardiogram would either undergo a GHPS (MBS item 61313) or a contrast echocardiography (the stress or rest echocardiography performed with injection of a contrast agent). As per MSAC Application no. 1129 (Thavaneswaran et al. 2010), contrast echocardiography is assumed to be administered during the same service consultation as the original suboptimal echocardiography (Advisory Panel advice), with no additional MBS item number for the contrast echocardiography procedure or use of the contrast agent; the additional cost of a contrast agent, consumables and additional time are borne by the patients. Following an indeterminate echocardiography, it is assumed that around 80% of patients would have a GHPS and the remaining 20% may have contrast echocardiography. Table 64 summarises the estimated number of comparator tests offset for indeterminate tests.

Table 64 Estimation of the number of comparator tests offset for indeterminate tests

Row		2016–17	2017–18	2018–19	2019–20	2020–21
F	Number of CMR tests for indeterminate Echo	640	651	662	672	683
	Estimated number of subsequent tests potentially offset by proposed CMR					
L	GHPS (= F*80%)	512	521	529	538	546
M	cEcho (= F*20%)	128	130	132	134	137

CMR = cardiac magnetic resonance (imaging); GHPS = gated heart pool scan; cEcho = contrast echocardiography; Echo = echocardiography

Population ii: Diagnostic clarification

To allocate appropriate comparator tests for substitution, the patients expected to utilise CMR for further diagnostic clarification can be classified among three groups based on the pre-test probability (PTP) of CAD and patient characteristics (see Figure 4), with the overall uptake rate of 75% allocated as follows:

- Low PTP (0–15%) of CAD (approximately 15% of patients)—population iiA: All would undergo CMR as these patients will have a higher probability of having NIDCM, and CMR would be expected to provide valuable diagnostic clarification for treatable and non-treatable causes.
- Intermediate PTP (15–85%) of CAD (approximately 70% of patients)—population iiB: Investigation for ischaemia and other causes is required. It is expected that most of these patients (85% of this group, or 60% of the broader 'diagnostic clarification' group) would undergo CMR.
- High PTP (>85%) of CAD (approximately 15% of patients): These patients are assumed to directly undergo coronary angiography, generally foregoing interim CMR or other tests, and are not considered further in this financial analysis.

Patients with a low PTP of CAD (i.e. population iiA) generally undergo a battery of further tests, including serological tests through to, potentially, EMB, to diagnose the suspected cause of DCM (myocarditis, sarcoidosis, alcohol ablation etc.). As a wide array of tests are performed for the diagnostic work-up in this group of patients, and many tests may still be performed post-CMR, it is not possible to accurately quantify the usage and costs of these potential comparator tests, much less the extent to which they may be offset. A conservative approach assuming no offsets is taken for the purposes of this review, which is likely to overestimate the net usage and costs of CMR in this group.

In the patients with an intermediate risk of CAD (i.e. population iiB), SPECT, stress echocardiography, CTCA and ICA are potential comparators used to rule out ischaemia. The respective usage of these tests is based on their statistics, as more-broadly used MBS items, in the financial year 2014–15. The numbers of services for each of the tests reported in 2014–15, and their respective weights, are presented in Table 65.

Table 65 Comparator services, 2014–15

Test	Source	Services	Weight
ICA	MBS item 59925, 2014–15 services	69,508	53.5%
CTCA	MBS item 57360, 2014–15 services	44,974	34.6%
Stress Echo	MBS item 55117, 2014–15 services	8,793	6.8%
SPECT	MBS item 61303, 2014–15 services	6,630	5.1%

CTCA = computed tomography coronary angiography; Echo = echocardiography; ICA = invasive coronary angiogram; MBS = Medicare Benefits Schedule; SPECT = single-photon emission computed tomography

The estimated number of comparator tests performed for diagnostic clarification of DCM is presented in Table 66.

Table 66 Estimation of the number of comparator tests offset for diagnostic clarification

Row		2016–17	2017–18	2018–19	2019–20	2020–21
E	Number of suspected/diagnosed cases of DCM	4,480	4,557	4,633	4,707	4,781

Row		2016–17	2017–18	2018–19	2019–20	2020–21
	Population iiA: low-risk of CAD (15%)					
N	Number of eligible CMR tests (= E*15%) [a]	672	684	695	706	717
O	Number of test offsets	0	0	0	0	0
	Population iiB: intermediate risk of CAD expected to uptake CMR (60%)					
P	Number of eligible CMR tests (E*60%) [b]	2,666	2,711	2,756	2,801	2,845
Q	Offset test: ICA (P*54%)	1,426	1,451	1,475	1,499	1,522
R	Offset test: CTCA (P*35%)	923	939	954	970	985
S	Offset test: stress Echo (P*7%)	180	184	187	190	193
T	Offset test: SPECT (= P*5%)	136	138	141	143	145
G	Total number of eligible CMR tests in population ii	3,338	3,395	3,451	3,507	3,562
	Total number of test offsets (= O+Q+R+S+T = P)	2,666	2,711	2,756	2,801	2,845

[a] Approximately 15% of patients in population ii are likely to have a low risk of CAD and all are expected to undergo CMR for diagnostic clarification.

[b] Approximately 60% of the suspected/diagnosed cases of DCM (population ii) patients (or 85% of the 70% of patients with an intermediate risk of CAD) are expected to undergo CMR. For further clarification see text.

CAD = coronary artery disease; CMR = cardiac magnetic resonance (imaging); CTCA = computed tomography coronary angiography; DCM = dilated cardiomyopathy; Echo = echocardiography; SPECT = single-photon emission computed tomography

Familial DCM

According to the clinical practice algorithm, asymptomatic patients with a family history of DCM and indeterminate echocardiography results undergo GHPS, and patients with a dilated LV and an intermediate risk of CAD undergo either SPECT, stress echocardiography, CTCA or ICA. It is assumed that 5% of these cases will have prior indeterminate echocardiogram and would undergo GHPS in the absence of CMR. The remaining 95% of the cases will have a diagnosis of a dilated LV and will undergo stress echocardiography, SPECT, CTCA or ICA. The relative usage of stress echocardiography, SPECT, CTCA and ICA is assumed to be same as in the patients with diagnostic clarification, as estimated in Table 67.

Table 67 Estimation of the number of comparator tests offset in familial cases

Row		2016–17	2017–18	2018–19	2019–20	2020–21
J	Number of eligible CMR tests	108	109	111	113	115
	Number of test offsets					
U	GHPS (= J*5%)	5	5	6	6	6
V	ICA (= J*51%)	55	56	57	57	58
W	CTCA (= J*33%)	3,523	3,624	3,724	3,724	3,825

Row		2016–17	2017–18	2018–19	2019–20	2020–21
X	Stress Echo (= J*6%)	7	7	7	7	7
Y	SPECT (= J*5%)	5	5	5	5	6
	Total number of test offsets (= U+V+W+X+Y = J)	108	109	111	113	115

CMR = cardiac magnetic resonance (imaging); CTCA = computed tomography coronary angiography; GHPS = gated heart pool scan; Echo = echocardiography; ICA = invasive coronary angiography; SPECT= single-photon emission computed tomography

Table 68 presents a summary of estimates of the comparator tests and CMR tests for all groups of patients in the proposed populations.

Table 68 Estimation of the number of comparator tests aggregated across all the proposed populations

Row		2016–17	2017–18	2018–19	2019–20	2020–21
K	Number of eligible CMR tests	4,086	4,155	4,224	4,292	4,360
	Number of each comparator test offset					
	GHPS (= L+U)	517	526	535	544	552
	Contrast Echo (= M)	128	130	132	134	137
	ICA (= Q+V)	1,481	1,506	1,531	1,556	1,581
	CTCA (= R+W)	958	975	991	1,007	1,023
	Stress Echo (= S+X)	187	191	194	197	200
	SPECT (= T+Y)	141	144	146	148	151
	Total number of test offsets	3,413	3,472	3,529	3,586	3,643

CMR = cardiac magnetic resonance (imaging); CTCA = computed tomography coronary angiography; Echo = echocardiography; GHPS = gated heart pool scan; ICA = invasive coronary angiography; 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 69, based on the average MBS benefit and patient contribution paid per service in 2014–15 for each of the comparator tests (MSAC Application no. 1129 for contrast echocardiography, 57360 for CTCA, 61303 for SPECT, 55117 (in conjunction with 11712 Exercise ECG) for stress echocardiography, and 61313 for GHPS).

ICAs are performed as inpatient services. ICAs performed in public hospitals have no associated MBS services, and the costs of the procedure are incurred by state health budgets; whereas ICAs performed in private hospitals have charges associated with Medicare services and hospital components, and the costs are incurred by Medicare, patients and private health insurers (PHIs). Based on the number of separations for AR-DRG F42 A, B and C in private and public hospitals (Independent Hospital Pricing Authority (IHPA) 2015b, 2015c), approximately 60% of ICAs are performed in private hospitals and 40% in public hospitals. The cost of ICA in a public hospital is based on the NEP for AR-DRG F42C (Circulatory Disorders, Not Admitted for AMI, with Invasive Cardiac Investigative Procedures, No Complications, Same Day Discharge (Independent Hospital Pricing Authority (IHPA) 2015a). This cost is incurred by state health budgets. The cost of ICAs in private hospitals, stratified according to the MBS cost, patient contribution and PHI, was accessed

from a private insurer's webpage[22], and was converted to 2015 AUD using an inflation calculator[23]. According to this data, ICAs performed in private hospitals are associated with costs of $745 to MBS, $207 to patients and $4,426 to the PHI; the total cost of ICA is thus estimated as $5,378 in private hospitals.

Table 69 Estimated disaggregated costs per comparator service

Comparator	MBS cost	Patient cost	PHI cost	State health budget cost
GHPS	$283	$23	-	-
cEcho	$0 [a]	$131	-	-
ICA	$745	$207	$4,426	$2,837
Stress Echo	$365	$60	-	-
CTCA	$650	$43	-	-
SPECT	$526	$13	-	-

[a] There is no MBS item for contrast echocardiography. As per MSAC Application no. 1129 (Thavaneswaran et al. 2010), contrast echocardiography is assumed to be administered during the same procedure as the original suboptimal echocardiography (Advisory Panel advice). There are additional costs for contrast, other consumables and extra time that are not paid by MBS and are added to the patient contribution. Therefore, the average cost per service of contrast echocardiography is assumed to be $0 for the MBS and only the patient contribution is considered for this service.

cEcho = contrast echocardiography; CTCA = computed tomography coronary angiography; GHPS = gated heart pool scan; Echo = echocardiography; ICA = invasive coronary angiography; MBS = Medicare Benefits Schedule; SPECT = single-photon emission computed tomography; PHI = private health insurer

The cost offset with the introduction of CMR for diagnosis or diagnostic clarification of DCM in the proposed populations are presented in Table 70.

Table 70 Total cost offsets by CMR testing for DCM

	2016–17	2017–18	2018–19	2019–20	2020–21
Number of tests offset	-	-	-	-	-
GHPS	517	526	535	544	552
Contrast Echo	128	130	132	134	137
ICA	1,481	1,506	1,531	1,556	1,581
Stress Echo	187	191	194	197	200
CTCA	958	975	991	1,007	1,023
SPECT	141	144	146	148	151
MBS cost offsets	-	-	-	-	-
GHPS	$146,511	$149,009	$151,486	$153,926	$156,356

[22] <http://healthtopics.hcf.com.au/CoronaryAngiographyAngioplastyandStents.aspx>; accessed on 24 March 2016.

[23] Converted to 2015 AUD using inflation calculator provided by RBA; <http://www.rba.gov.au/calculator/annualDecimal.html>; accessed on 24th March 2016.

	2016–17	2017–18	2018–19	2019–20	2020–21
Contrast Echo	$0	$0	$0	$0	$0
ICA	$662,039	$673,325	$684,519	$695,544	$706,524
Stress Echo	$68,346	$69,511	$70,667	$71,805	$72,939
CTCA	$622,714	$633,330	$643,859	$654,229	$664,558
SPECT	$74,242	$75,508	$76,763	$78,000	$79,231
Total offsets to the MBS	$1,573,853	$1,600,683	$1,627,295	$1,653,504	$1,679,608
Patient cost offsets	-	-	-	-	-
GHPS	$11,655	$11,853	$12,050	$12,245	$12,438
Contrast Echo	$16,764	$17,050	$17,334	$17,613	$17,891
ICA	$183,949	$187,085	$190,195	$193,258	$196,309
Stress Echo	$11,233	$11,425	$11,615	$11,802	$11,988
CTCA	$40,843	$41,539	$42,230	$42,910	$43,587
SPECT	$1,805	$1,836	$1,867	$1,897	$1,927
Total offsets to patients	$266,250	$270,788	$275,290	$279,724	$284,140
PHI cost offsets					
ICA	$3,933,522	$4,000,579	$4,067,090	$4,132,594	$4,197,835
State health budgets					
ICA	$1,680,733	$1,709,385	$1,737,804	$1,765,793	$1,793,669
Total costs offset	$7,454,357	$7,581,436	$7,707,480	$7,831,615	$7,955,252

CMR = cardiac magnetic resonance (imaging); CTCA = computed tomography coronary angiography; DCM = dilated cardiomyopathy; Echo = echocardiography; GHPS = gated heart pool scan; MBS = Medicare Benefits Schedule; SPECT = single-photon emission computed tomography

E3 FINANCIAL IMPLICATIONS FOR THE MBS

The financial implications to the MBS resulting from the proposed listing of CMR over the next 5 years are summarised in Table 71.

Table 71 Total costs to the MBS associated with CMR for DCM

-	2016–17	2017–18	2018–19	2019–20	2020–21
CMR					
Number of services	4,086	4,155	4,224	4,292	4,360
Cost to the MBS	$3,125,411	$3,178,692	$3,231,539	$3,283,585	$3,335,423
Tests offset					
Number of services offset	3,413	3,472	3,529	3,586	3,643
Costs offset	$1,573,853	$1,600,683	$1,627,295	$1,653,504	$1,679,608
Net cost to the MBS	$1,551,558	$1,578,008	$1,604,243	$1,630,081	$1,655,815

CMR = cardiac magnetic resonance (imaging); DCM = dilated cardiomyopathy; MBS = Medicare Benefits Schedule

E4 FINANCIAL IMPLICATIONS FOR GOVERNMENT AND OTHER HEALTH BUDGETS

The financial implications of listing CMR for DCM are tentative. CMR may potentially substitute for all non-invasive comparator tests (i.e. CTCA, SPECT and stress echocardiography), but may not avoid the ICAs performed in those patients identified with or highly suspected of CAD. These patients are likely to undergo both ICA and CMR. Thus, CMR will be an additional test in the clinical pathway to provide diagnostic information. As such, the projected financial implications of substituted ICAs are highly uncertain. Assuming that all ICAs are substituted by CMR, the financial implications to other healthcare budgets are presented below.

Patients receiving ICA through the MBS are private patients. Therefore, hospital costs for these patients would be covered privately by PHI companies and not by any state or federal government health budget. The medical services cost of these private patients will have a Medicare cost, patient contribution and a cost covered by a PHI. However, the ICAs performed in public hospitals will have implications to state government healthcare budgets (see Table 69 for more details).

Table 72 presents the estimated financial implications of proposed CMR testing (assuming that all ICAs are offset) on other healthcare budgets. These estimates should be interpreted with caution as not all ICAs would be avoided in clinical practice, in which case the estimates presented will overestimate the financial savings due to CMR listing.

Table 72 Cost implications for other healthcare budgets (maximum, assuming that all ICAs are substituted by CMR)

	2016–17	2017–18	2018–19	2019–20	2020–21
State governments: number of ICA services offset	592	603	613	622	632
Cost offsets to state governments	$1,680,733	$1,709,385	$1,737,804	$1,765,793	$1,793,669
PHIs: number of ICA services offset	889	904	919	934	948
Cost offsets to PHIs	$3,933,522	$4,000,579	$4,067,090	$4,132,594	$4,197,835
Net offsets to other healthcare budgets	$5,614,255	$5,709,964	$5,804,894	$5,898,386	$5,991,504

ICA = invasive coronary angiography; PHI = private health insurer

The implications of listing CMR for DCM to patients are reported in Table 73.

Table 73 Total costs to patients associated with CMR for DCM

	2015–16	2016–17	2017–18	2018–19	2019–20
CMR					
Number of services	4,086	4,155	4,224	4,292	4,360
Cost to patients	$299,310	$304,412	$309,473	$314,458	$319,422
Tests offset					
Number of services offset	3,413	3,472	3,529	3,586	3,643
Costs offset	$266,250	$270,788	$275,290	$279,724	$284,140
Net cost to patients	$33,060	$33,624	$34,183	$34,734	$35,282

CMR = cardiac magnetic resonance (imaging); DCM = dilated cardiomyopathy

E5 IDENTIFICATION, ESTIMATION AND REDUCTION OF UNCERTAINTY

Sensitivity analyses around inputs to the financial model are presented in Table 74.

Table 74 Sensitivity analysis of financial implications of listing CMR for DCM

	2016–17	2017–18	2018–19	2019–20	2020–21
Base-case					
Net cost of CMR to the MBS	$1,551,558	$1,578,008	$1,604,243	$1,630,081	$1,655,815
Net cost of CMR to patients	$33,060	$33,624	$34,183	$34,734	$35,282
Incidence of DCM in Australia: 10 per 100,000 (base-case: 7 per 100,000)					
Net cost of CMR to the MBS	$2,216,512	$2,254,298	$2,291,776	$2,328,687	$2,365,450
Net cost of CMR to patients	$47,229	$48,034	$48,833	$49,619	$50,403
Incidence of DCM in Australia: 20 per 100,000 (base case: 7 per 100,000)					
Net cost of CMR to the MBS	$4,433,023	$4,508,595	$4,583,552	$4,657,374	$4,730,900
Net cost of CMR to patients	$94,458	$96,069	$97,666	$99,239	$100,805
Proportion of indeterminate results with Echo: 10% (base-case: 5%)					
Net cost of CMR to the MBS	$1,552,808	$1,579,280	$1,605,536	$1,631,394	$1,657,149
Net cost of CMR to patients	$33,401	$33,971	$34,535	$35,092	$35,646
Proportion of indeterminate results with Echo: 20% (base-case: 5%)					
Net cost of CMR to the MBS	$1,555,308	$1,581,822	$1,608,121	$1,634,021	$1,659,817
Net cost of CMR to patients	$34,083	$34,664	$35,240	$35,808	$36,373
CMR accessibility and uptake: 50% (base-case: 100%)					
Net cost of CMR to the MBS	$775,779	$789,004	$802,122	$815,040	$827,907
Net cost of CMR to patients	$16,530	$16,812	$17,092	$17,367	$17,641
Number of family members screened per index case of DCM: 5 (base-case: 4)					
Net cost of CMR to the MBS	$1,558,574	$1,585,143	$1,611,497	$1,637,451	$1,663,302
Net cost of CMR to patients	$32,805	$33,365	$33,919	$34,466	$35,010
Proportion of family members requiring CMR test: 40% (base-case: 50%)					
Net cost of CMR to the MBS	$1,558,574	$1,585,143	$1,611,497	$1,637,451	$1,663,302
Net cost of CMR to patients	$32,805	$33,365	$33,919	$34,466	$35,010

CMR = cardiac magnetic resonance (imaging); CTCA = computed tomography coronary angiography; DCM = dilated cardiomyopathy; Echo = echocardiography; MBS = Medicare Benefits Schedule; SPECT = single-photon emission computed tomography; GHPS = gated heart pool scan

SECTION F OTHER RELEVANT CONSIDERATIONS

F1 ETHICAL CONSIDERATIONS

Implantable cardioverter defibrillators (ICDs) are unable to prevent death as a result of progressive HF or comorbid disease (Carlsson et al. 2012). Patients implanted with ICDs often have comorbid conditions and frequently experience a worsening of their condition unrelated to cardiac arrhythmias. At the end-of-life period when preventing SCD is no longer in the best interest of the patient, the issue of ICD deactivation is unavoidable (MacKenzie 2016). In the final days leading to a patient's death, the choice to allow the ICD to remain active or to deactivate the defibrillation function presents an ethical dilemma, not least because defibrillations may occur when they are not in accordance with palliative treatment goals at the end-phase of life. Indeed, automatic defibrillation when death is imminent is painful and distressing to the patient, and likely to be emotionally disturbing to relatives and carers. The ethical dilemma is complicated by differing beliefs about the nature of ICDs: should an ICD be considered as a treatment (similar to other mechanical medical devices such dialysis machines, ventilators etc.) or, given the inherent nature of implanted devices, should the ICD be considered as a transplant, or more frankly as part of the patient's body (Carlsson et al. 2012; England, England & Coggon 2007)?

In the past, commentators on bioethical and medico-legal issues such as England and colleagues (England, England & Coggon 2007) have argued for the middle ground, considering ICDs as 'integral devices'. It is proposed that this avoids the problematic treatment/non-treatment dichotomy. To illustrate simplistically, take as a general example the doctor who decides to discontinue treating a patient with an intravenous drug on the grounds of futility; that is, the drug no longer offers any medical benefit to the patient. This is both a legally and ethically defensible course of medical action, as no patient has the right to demand treatment that is clearly without medical benefit and, indeed, a doctor who provides continued treatment under conditions of futility would be practising outside the scope of care. On the other hand, pragmatic, common-sense considerations aside, it would be both legally and ethically indefensible for a doctor to remove an implanted kidney, hip replacement or arterial stent from a patient under any circumstances.

The problem with the treatment/non-treatment dichotomy as applied to ICD deactivation is essentially two-fold. If an ICD is considered to be a continuing medical intervention/treatment, this permits 'a unilateral decision by a doctor to deactivate the device, even if this is contrary to the patient's wish (on grounds of futility). It also requires deactivation at the patient's insistence (on grounds of autonomy), even if the doctor disagrees with the wisdom of the decision'. Conversely, if an ICD 'is deemed to be equivalent to a part of the patient's body, there will be circumstances in which a doctor will not lawfully be able to deactivate the device, even if it has a negative effect on the patient's quality of life and the patient consents' (England, England & Coggon 2007). Clearly, the dichotomous concepts of an ICD as simply a treatment or, alternatively, assuming a status equivalent to a biological transplant (i.e. part of the patient's body) are of limited utility in the decision on whether and when to deactivate a patient's ICD. By defining an ICD as an integral device, England et al. suggest that the patient maintains a stronger autonomy than they would with external mechanical devices, thus protecting the patient from unilateral, physician-led deactivation on the grounds of benevolent paternalism. At the same time, because an integral device is not actually part of the body, this affords the patient the right to mandate ICD deactivation, even against medical advice, similar to an advance refusal of external defibrillation or resuscitation (England, England & Coggon 2007).

The discussion provided by Carlsson and colleagues highlights that introduction of the 'integral device' terminology has not, unfortunately, led to spontaneously improved clarity in ethical decision-

making around the deactivation of ICDs among patients at the end-of-life phase. In turn, the terms 'replacement therapy' and 'substitution therapy' have been proposed. Replacement therapy refers to an intervention that functions as part of the body and completely replaces physiological function. An intervention classified as 'substitutive' is defined as having not become part of the body and technically excludes implanted devices such as pacemakers or ICDs. However, discussion of whether ICDs should be classified as substitutive or replacement therapy is still ongoing in the literature. Some medical ethicists contend that only the patient's wishes should provide the basis for judging whether it is appropriate to deactivate an ICD, not a constructed distinction between forms of therapy (Kay & Bittner 2009). This is countered by objections to the idealised concept of patient autonomy, which in real life rarely holds true and is supported only from an individualistic viewpoint that does not sufficiently take into account other persons of significance. Further, idealised patient autonomy overlooks the fact that the patient making the decisions is dependent on their body in a specific way (the concept of embodiment), given that a patient may arrive at the view that the device is part of their body, and by extension part of the self, thereby preventing truly rational decision-making (Carlsson et al. 2012).

From this point in the discussion it should be possible to appreciate that the ethical dilemma presented by ICD deactivation at end-of-life is complex. Within the scope of this report, it is neither practical nor necessarily useful to provide an exhaustive exegesis of the volume of literature on the topic. There are many possible individualised answers as to the course of action that could be undertaken in response to the dilemma depending, in particular, on socially and culturally derived values of patients and healthcare professionals (Carlsson et al. 2012). In the context of this report, the answers also depend on norms that have become law in Australia.

Fortunately, clear directives, based largely on prevailing expert opinion of what constitutes legal and ethical practice among terminally ill patients with ICDs, are readily available in the form of international and Australian-produced guidelines (ACI 2014; Epstein et al. 2013; McMurray et al. 2012; Padeletti et al. 2010). Such guidelines emphasise a common and key recurring principle, that a personalised and detailed discussion with the patient and their relatives should always take place when patient health deteriorates and at end-of-life. The discussion and processes surrounding ICD deactivation must be documented. It is also preferable that the patient is informed of the potential for deactivation *prior to implantation* of an ICD, despite the many explanations that healthcare professionals cite for avoiding the discussion at that pre-implantation stage (e.g. unnecessarily distressing the patient, uncertainty of prognosis and lack of experience with discussions about deactivation) (Fitzsimons & Strachan 2012; Hauptman et al. 2008). In instances where the patient is lacking the ability to make an informed choice, it is necessary to engage a legally entitled representative of the patient in deactivation discussions (Carlsson et al. 2012).

Guidelines produced in New South Wales emphasise the benefit of promoting clinician training for communicating treatment limitations, advance care planning and end-of-life care in hospitals and community facilities (ACI 2014). In centres that provide ICD implantation, specific emphasis on communicating the necessary information to enable informed consent or informed choice against deactivating a patient's ICD will facilitate healthcare professionals to care for patients with ICDs at end-of-life in accordance with legal requirements and best-available ethical principles.

Summary/Conclusion

Many patients implanted with ICDs suffer comorbidities. For the moribund patient, prevention of SCD from ICD shock is at odds with palliative care goals at end-of-life. Indeed, ICD shock at this stage of life is painful and distressing for the patient, which does not facilitate a dignified death. For the patient's family, this is likely to be emotionally distressing. Deactivation of a patient's ICD at end-of-life therefore presents an ethical dilemma. The dilemma is complex; a key issue centres on how an

ICD is conceptualised (i.e. just a therapy, part of the body or another distinct definition?), as this has implications for both the patient and healthcare professionals in terms of ethical and legal decision-making. There is no absolute consensus, but sound bioethical and medico-legal considerations are well summarised in formal guidelines on the issue. These guidelines provide clear directives for healthcare professionals involved in the care of patients with ICDs generally, and specifically at the end-of-life. The wide dissemination and use of these guidelines is recommended.

F2 MEASUREMENT OF LVEF BY ECHOCARDIOGRAPHY COMPARED WITH CMR

LVEF is a critical measurement for identification of a dilated LV and impaired ventricular function in both the current and proposed clinical pathways for patients presenting with HF symptoms. Accordingly, an LVEF of ≤35% is a criterion for reimbursement of the Medicare benefit for implantation of a CRT in patients with mild or moderate to severe HF. For Medicare reimbursement of ICD implantation, an LVEF of ≤30% is required for patients 1 month after MI, and an LVEF ≤35% for patients with chronic HF symptoms. Currently, LVEF assessment is performed with echocardiography in the clinical work-up for these patients, although the methodology is not specified in the item descriptors.

Studies identified in this review have brought to light the issue of accuracy of the LVEF measurement assessed by various means. A number of articles refer to CMR as the reference standard in assessment of cardiac structure and function, particularly where the technique is now used in clinical practice (Focardi et al. 2015; Partington, Seabra & Kwong 2010; Xie et al. 2012). Considering that the accurate measurement of LVEF is a determinant of the number of CRT and ICD implantations reimbursed in Australia, it was thought valuable to include here a comparison of LVEF measurements by echocardiography compared with CMR.

Four studies were identified that compared mean LVEF measurements by echocardiography or other non-CMR methods with CMR (Kono et al. 2010; Li et al. 2013; Neilan et al. 2013; Wu, KC et al. 2012). The mean LVEF values are compared in Table 75. In addition, one SR was identified that compared LVEF measured by CMR with CTCA, and LVEF measured by echocardiography; however, there was only an indirect comparison between CMR and echocardiography (Asferg et al. 2012).

Table 75 Mean difference in LVEF measured by echocardiography or non-CMR methods compared with CMR in HF patients

Author Study design Risk of bias	Population	%LVEF by Echo	%LVEF (non-CMR) [a]	%LVEF by CMR	Difference
Kono et al. (2009) Japan Prospective cohort High risk of bias	DCM patients, LVEF <40% N=32	27.9 ± 7.4%		21.3 ± 12.0%	–6.6%
Li et al. (2013) China Retrospective cohort Moderate risk of bias	DCM patients N=145 (LGE+ subgroup)	33.3 ± 8.1%		22.6 ± 8.3%	–10.7%
Neilan et al. (2913) USA Prospective cohort	NIDCM patients for ICD implantation N=162	26 ± 8%		28 ± 9%	+2%

Author Study design Risk of bias	Population	%LVEF by Echo	%LVEF (non-CMR) [a]	%LVEF by CMR	Difference
Low risk of bias					
Mean difference					–5.1%
Wu, KC et al. (2012) USA Prospective cohort Low risk of bias	Chronic ICM and NICM for ICD implantation, LVEF ≤35% N=98 (NICM subgroup)		21 ± 7%	25 ± 10%	+4%
Overall mean difference					–2.8%

[a] Non-CMR LVEF was assessed clinically by echocardiography, SPECT or ventriculography.

CM = cardiac magnetic (imaging);dilated cardiomyopathy; Echo = echocardiography; ICD = implantable cardioverter defibrillator; ICM = ischaemic cardiomyopathy; NICM = non-ischaemic cardiomyopathy; NIDCM = non-ischaemic dilated cardiomyopathy; LGE = late gadolinium enhancement; LVEF = left ventricular ejection fraction

The 2 studies conducted in USA reported higher CMR LVEF values compared with those measured by echocardiography. In contrast, the 2 Asian studies reported lower CMR LVEF values in comparison with echocardiography. This variation may be explained by differences in population or assessment techniques, or may be a random effect. Overall, there was a lower mean LVEF within populations when measured by CMR compared with echocardiography. In the SR by Asferg et al. (2012) there was no difference found in LVEF measured by CMR versus CTCA and that measured by echocardiography versus CTCA, although in HF patients there was a trend towards larger %LVEF measured by CTCA compared with echocardiography.

If CMR rather than echocardiography was used to determine LVEF for CRT or ICD reimbursement eligibility, there is a possibility that this could lead to a larger number of implantations and reimbursements by Medicare. More-accurate information could inform this scenario should reliable diagnostic performance data comparing echocardiography and LVEF become available.

APPENDIX A CLINICAL EXPERTS AND ASSESSMENT GROUP

CLINICAL EXPERTS

Clinical experts who provided clinical input or data.

Name	Expertise
Dr John Younger	Consultant cardiologist at the Royal Brisbane and Women's Hospital and St Andrew's War Memorial Hospital, and senior lecturer at the University of Queensland
Assoc. Prof. John Atherton	Director of Cardiology at the Royal Brisbane and Women's Hospital, and Associate Professor, Department of Medicine, University of Queensland
Assoc. Prof. Andrew Taylor	Cardiologist at the Alfred Hospital working within the Heart Failure and Transplant Unit, where he is Director of Cardiac Magnetic Resonance (CMR) Imaging and Head of Non-Invasive Imaging. He is also a researcher at BakerIDI, with a strong research interest in CMR and heart failure

ASSESSMENT GROUP

AHTA, University of Adelaide, South Australia

Name	Position
Sharon Kessels	Research Officer
Ruchi Mittal	Health Economist
Judy Morona	Senior Research Officer
Skye Newton	Team Leader (Medical HTA)
Ben Ellery	Research Officer
Joanne Milverton	Research Officer
Jacqueline Parsons	Team Leader (Medical HTA)
Arlene Vogan	Health Economist
Camille Schubert	Team Leader (Economics)
Tracy Merlin	Managing Director

NOTED CONFLICTS OF INTEREST

One team member who worked on section B4.2 has two first-degree family members suffering from cardiomyopathy.

One team member involved with most sections of the report has a first-degree family member suffering from Wegener's granulomatosis (however no symptoms of HF or DCM).

There were no further conflicts of interests to declare.

APPENDIX B SEARCH STRATEGIES

BIBLIOGRAPHIC DATABASES FOR GENERAL LITERATURE SEARCH (SECTION B, TABLE 7)

Electronic database	Time period searched
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	1990–12/2015
Embase	1990–12/2015
PubMed	1990–12/2015

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	scholar.google.com
Australian and New Zealand Clinical Trials Registry	www.anzctr.org.au
Pearling	
All included articles had their reference lists searched for additional relevant source material	

SPECIALTY WEBSITES

National Heart Foundation of Australia	www.heartfoundation.org.au
American Heart Foundation	www.heart.org
NHS choices	www.nhs.uk

APPENDIX C STUDIES INCLUDED IN THE SYSTEMATIC REVIEW

Table 76 Profiles of studies on diagnostic performance included in the systematic literature review

Study Country	Study design Quality appraisal	Study population	Inclusion criteria / exclusion criteria	Intervention (CMR ± LGE)	Reference standard / comparator
Assomull et al. (2011) UK	Level: II Quality: low risk of bias Patient selection: ☺ Index test: ? Reference standard: ☺ Flow and timing: ☺ Applicability: ☺ ☺ ☺	120 patients with recently diagnosed HF (<6 months) and reduced LVEF (suspected of DCM) Mean age: 57 ± 11 years 96 men (80%)	Inclusion criteria: Clinically stable in NYHA class I to III HF, ≥35 years of age and scheduled to undergo coronary angiography as part of their clinical workup for HF Exclusion criteria: Any prior history or ECG or biochemical evidence of CAD, chest pain, significant valvular disease, atrial fibrillation, contraindications to CMR	Delayed enhancement: Scanner: 1.5T scanner (Siemens Sonata and Siemens Avanto) Data inquisition: Inversion-recovery gradient-echo sequence Contrast agent: Intravenous Gd-DTPA, 0.1 mmol/kg, 10-minute delay Cine imaging: Scanner: 1.5T scanner (Siemens Sonata and Siemens Avanto) Data inquisition: steady-state, free-precession breath hold cines in long-axis planes and sequential contiguous 7-mm short-axis slices from the atrioventricular ring to the apex. Contrast agent: –	Reference standard: Clinical data A separate consensus group of 3 cardiologists reviewed all the data and ascribed a gold-standard aetiology based on a review of all the available diagnostic data, including tissue characterisation information from LGE-CMR and luminographic data from coronary angiography.
Bohnen et al. (2015)	Level: II	31 patients with HF and reduced LVEF	Inclusion criteria: Presentation with recent-onset HF, LVEF <45% in absence of	Scanner: 1.5T scanner (Achieva, Philips medical systems, Best, The	Reference standard: Endomyocardial biopsy:

Study Country	Study design Quality appraisal	Study population	Inclusion criteria / exclusion criteria	Intervention (CMR ± LGE)	Reference standard / comparator
Germany	Quality: medium risk of bias Patient selection: ? Index test: ☺ Reference standard: ☹ Flow and timing: ☺ Applicability: ☹ ? ☹	Mean age: 51 years (range 34–63) 24/31 men (77%)	significant CAD, clinically indicated EMB and CMR Exclusion criteria: Patients with acute coronary syndrome or arrhythmia	Netherlands) Data inquisition: T1-weighted spin-echo early gadolinium enhancement CMR, and phase-sensitive inversion recovery late gadolinium enhancement CMR Contrast agent: 0.075 mmol/kg gadobenate dimeglumine. T1-mapping was performed using a modified Look-Locker inversion recovery (MOLLI) sequence with a 3(3)5 scheme on 3 representative short-axis positions before and 15 minutes after contrast-media administration.	At least 4 biopsies 1–2 mm in size were obtained from the left (n=12; 39%) or right (n=19; 61%) ventricle. Active myocarditis with ongoing myocardial inflammation was defined by ≥14 infiltrating leukocytes/mm^2, CD3+ and CD68+ macrophages in the presence of myocyte damage and fibrosis. DNA and RNA were extracted and PCR / reverse transcriptase PCR was performed to detect typical viruses in the samples as appropriate.
Casolo et al. (2006) Italy	Level: II Quality: low risk of bias Patient selection: ☺ Index test: ☺ Reference standard: ☺ Flow and timing: ☺ Applicability: ☺ ☺ ☺	60 HF patients with LV dysfunction and dilation enrolled consecutively from a clinic Mean age: 66.4 ± 9.6 years 44/60 men (73%)	Inclusion criteria: HF based on clinical symptoms and documented LV dysfunction (LVEF <40%) and dilation by Echo Exclusion criteria: Contraindications to CMR, severe congestive symptoms, previous revascularisation, significant valve disease, known HCM, infiltrative disorders and history of myocarditis	Scanner: 1.5T scanner (Philips Intera, Best, The Netherlands) Data inquisition: IR-GRE-EPI breath-hold (3D acquisition (slice thickness 5 mm, gap 0.5 mm, and voxel sizes of 1.7x1.4x5.0 mm) Contrast agent: Gd-DTPA, 0.2 mmol/kg, 10–15-minute delay	Reference standard: ICA All the CAD patients had either a stenosis ≥75% of 1 or more major proximal epicardial vessels (39 patients) or a left main vessel disease (2 patients). The severity of CAD in these patients was judged to be in all cases of such an extent to explain the presence of an ischaemic CM by a clinician who blindly reviewed the patients' data.
de Melo et al.	Level: III-1	24 HF patients who	Inclusion criteria:	Scanner: NR	Comparator: ICA

Study Country	Study design Quality appraisal	Study population	Inclusion criteria / exclusion criteria	Intervention (CMR ± LGE)	Reference standard / comparator
(2013) Brazil	Quality: unclear risk of bias Patient selection: ? Index test: ? Reference standard: ? Flow and timing: ? Applicability: ☺ ? ☺	underwent ICA and LGE-CMR to evaluate the aetiology of DCM Mean age: 51.6 ± 12.5 years 19/24 men (79%)	Presence of systolic HF, LVEF <45% documented by Echo in the period up to 1 year after the procedure, onset of HF symptoms >1 month, age ≥18 years Exclusion criteria: Prior history of CAD, positive serology for Chagas disease, valvular heart disease or heart transplantation	Data inquisition: 2 chambers, long axis; 4 chambers, long axis; left ventricular outflow tract, and short-axis images with scanning of the entire left ventricle Contrast agent: Gd-DTPA, 0.2 mmol/kg, 10-minute delay	Ischaemic aetiology was classified as patients with obstructive lesions (≥75%) in left main coronary artery or proximal anterior descending branch, or in 2 or more epicardial vessels Reference standard: Clinical data Global analysis of cases by 2 clinical cardiologists, including all data in clinical history and laboratory tests available in medical records, was defined as the gold standard for the diagnosis of ischaemic CM.
Hamilton-Craig et al. (2011) Australia	Level: II Quality: low risk of bias Patient selection: ☺ Index test:☺ Reference standard: ☺ Flow and timing: ☺ Applicability: ☺ ☺ ☺	28 prospectively enrolled consecutive patients undergoing ICA (suspected of DCM) Mean age: 54 years (range 38–77) 16/28 men (57%)	Inclusion criteria: A new diagnosis of HF (<3 months), LV systolic dysfunction confirmed on Echo, referred for ICA Exclusion criteria: Previous ICA or revascularisation, known history of coronary disease, MI or Q waves satisfying standard ECG criteria for infarction, significant renal impairment, inability to lie flat or hold breath, inability to provide	Scanner: 1.5T scanner (GE Medical systems, Milwaukee, WI, USA), with an 8-element cardiac phased array coil Data inquisition: inversion-recovery fast gradient-echo sequence Contrast agent: 0.2 mmol/kg Gd-DTPA, 10- and 20-minute delay	Comparator: CTCA Dual-source 64-slice CT angiography (Somaton Definition, Siemens Medical, Erlangen, Germany) with 330 ms rotation time. Presence, distribution and severity of coronary plaque were assessed using a modivide AHA 17-segment model. Luminal stenosis of ≥50% in 2 proximal vessels was considered significant. Reference standard: ICA Significant coronary stenosis sufficient to cause LV dysfunction

Study Country	Study design Quality appraisal	Study population	Inclusion criteria / exclusion criteria	Intervention (CMR ± LGE)	Reference standard / comparator
			informed consent		was defined as stenosis >50% in proximal/mid segments of 2 major coronary arteries or significant left main / proximal LAD stenosis.
McCrohon et al. (2003) UK	Level: III-3 Quality: Unclear risk of bias Patient selection: ? Index test: ? Reference standard: ☺ Flow and timing: ? Applicability: ? ☺ ☺	90 patients with chronic stable HF with a dilated heart and LV systolic dysfunction (63 DCM and 27 CAD), 15 control subjects (normal ventricular function and ECG and no cardiac risk factors). Mean age (years) and gender (M:F, %): DCM: 54 ± 14, 65:35 CAD: 67 ± 10, 93:7 Control: 57 ± 10, 47:53	Inclusion criteria: Patients: clinical diagnosis of HF made on the basis of compatible clinical presentation and history combined with systolic LV dysfunction and dilation by Echo or radionuclide imaging. They underwent ICA. Controls: normal systolic function and a low (<10%) 10-year risk for coronary events Exclusion criteria: Presence of contraindications for CMR, suspected infiltrative heart disease (no evidence of hilar lymphadenopathy or suggestive skin, eye, joint, neurological or gastrointestinal disorder in the included patients in 1.5–11 years of follow-up), HCM, previous revascularisation, significant valve disease or a history of myocarditis	Scanner:1.5T scanner (Siemens Sonata, Erlangen, Germany) Data inquisition: inversion-recovery segmented gradient-echo sequence Contrast agent: 0.1 mmol/kg Gd-DTPA, 10–15-minute delay	Reference standard: ICA The patients had either unobstructed coronary arteries and no identifiable secondary cause (DCM), or angiographically documented CAD (>50% stenosis in ≥1 coronary arteries) and a history of myocardial infarction.
Mor-Avi et al. (2008) USA	Level: III-1	16 patients with CM (LVEF <40% on Echo), referred for clinically	Exclusion criteria: Previous cardiac surgery, atrial fibrillation or other cardiac	Scanner: 1.5T scanner (Sigma Excite, General Electric, Milwaukee, Wisconsin) with an 8-element phased-array cardiac	Reference standard: ICA Each arterial segment was graded for stenosis using a 0–3 scale: 0 =

Study Country	Study design Quality appraisal	Study population	Inclusion criteria / exclusion criteria	Intervention (CMR ± LGE)	Reference standard / comparator
	Quality: low risk of bias Patient selection: ? Index test: ☺ Reference standard: ☺ Flow and timing: ☺ Applicability:☹ ☺ ☺	indicated ICA Mean age: 62 ± 11 years 11 men (68.8%)	arrhythmias, pacemaker or defibrillator implantation, claustrophobia and other known contraindications for CMR imaging, and dyspnoea precluding a 10–20-second breath hold or any history of chronic obstructive coronary disease.	coil. Data inquisition: Turbo-FLASH segmented technique with inversion recovery Contrast agent: Gd-based, 10-minute delay	normal; 1 = <50% stenosis; 2 = 50–70% stenosis; 3 = >70% stenosis.
Sramko et al. (2013) Czech Republic	Level: II Quality: low risk of bias Patient selection: ☺ Index test: ☺ Reference standard: ☹ Flow and timing: ☺ Applicability: ☺ ☺ ☹	42 patients with DCM and a history of HF <6 months. Mean age and gender: Idiopathic DCM: 45 ± 12 years, 19/27 men (70%) Inflammatory DCM: 42 ± 8 years, 11/15 men (73%)	Inclusion criteria: Presence of left ventricular dilation and LVEF <45% in the absence of CAD (ruled out by cardiac catheterisation, severe systemic arterial hypertension, and primary valve disease) Exclusion criteria: A history of drug abuse, excessive alcohol consumption and/or presenting with sustained supraventricular tachyarrhythmias	Scanner: 1.5T scanner (Avanto, Siemens medical solutions, Erlangen, Germany) Data inquisition: phase-sensitive inversion-recovery sequence Contrast agent: 0.2 mmol/kg Gadobutrol, 10–15-minute delay	Reference standard: EMB: Biopsy was done by way of the internal jugular vein using a flexible bioptome under fluoroscopic guidance. Immunohistochemistry for the characterisation of inflammatory cell infiltrates was performed on paraffin sections treated with monoclonal antibodies. Quantitative PCR was performed for the detection of common cardiotropic viruses in the specimens.
Valle-Munoz et al. (2009) Spain	Level: II Quality: low risk of bias Patient selection: ☺ Index test: ☺ Reference standard: ☺	100 consecutive patients admitted with acute HF and LV systolic dysfunction (dilated). Mean age: 60.4 ± 14.1 years 68/100 men (68%)	Inclusion criteria Clinical presentation and ECG evidence of LV systolic dysfunction (LVEF <40%), increased LV end-diastolic diameter (>95th percentile according to size) Exclusion criteria:	Scanner: 1.5T scanner (Siemens Sonata Magnetom, Erlangen, Germany) Data inquisition: 3D inversion-recovery gradient-echo pulse sequences Contrast agent: 0.15 mmol/kg Gd-DTPA, 10-minute delay	Reference standard: ICA A coronary angiogram was performed on all patients in order to determine the presence of significant CAD (stenosis ≥70% in at least 1 major coronary artery), with the patients being classified under two groups according to the angiogram results:

Study Country	Study design Quality appraisal	Study population	Inclusion criteria / exclusion criteria	Intervention (CMR ± LGE)	Reference standard / comparator
	Flow and timing: ? Applicability: ☺ ☺ ☺		Previous history of CAD, Q waves on the ECG consistent with criteria established for infarction, available diagnostic data at the time of diagnosis to suggest CAD, contraindications for CMR, available diagnostic data suggesting HCM, infiltrative heart disease, or myocarditis		1) patient with LV dysfunction with significant CAD (CAD+) 2) patient with LV dysfunction without significant CAD (NICM)
Voigt et al. (2011) Germany	Level: II Quality: low risk of bias Patient selection: ☺ Index test: ☺ Reference standard: ☹ Flow and timing: ☺ Applicability: ☺ ☺ ☹	23 patients with DCM who underwent EMB Mean age and gender: Inflammatory lesions absent: 48.0 ± 4.2 years, 10/11 men (91%) Inflammatory lesions present: 47.2 ± 5.2 years, 10/12 men (83%)	Inclusion criteria: Unexplained chronic HF (class II–III); disease duration of >3 months; Echo LV end-diastolic diameter >55 mm; LVEF ≤45%, exclusion of relevant CAD by ICA; exclusion of other primary disease (e.g. hypertension, valvular heart disease, congenital heart disease and chronic alcohol excess) that may lead to chronic HF; no clinical suspicion of acute myocarditis or MI, no recent symptoms of viral illness, no history of pericarditis-type chest pain, no ECG changes suggestive of pericarditis or acute myocardial injury; no clinical suspicion of cardiac amyloidosis, sarcoidosis or hemochromatosis	Scanner: 1.5T scanner (Siemens Magnetom Sonata or Magnetom Avanto, Erlangen, Germany) Data inquisition: inversion-recovery gradient-echo sequence Contrast agent: 0.1 mmol/kg Gd-DTPA, 4-minute delay; additional imaging 10–15 minutes after an additional dose of 0.1 mmol/kg Gd-DTPA	Reference standard: EMB: A minimum of 4 biopsy specimens were harvested under sterile conditions from the interventricular septum and/or left ventricular free wall. Biopsy specimens were investigated within 24 hours, and acute myocarditis was excluded based on the Dallas criteria. Definition of myocardial inflammation: 1) ≥14 CD3-positive T-lymphocytes and/ or CD68-positive macrophages/mm^2 detected by immunochemistry in a diffuse or focal pattern 2) enhanced expression of HLA class II molecules
Won et al. (2015)	Level: II	83 patients undergoing CMR within 2 months of a new diagnosis of HF	Exclusion criteria: Known history of severe CAD, previous myocardial infarction or	Scanner: 1.5T or 3.0T MRI system (Avanto, Timtrio, or Verio; Siemens, Erlangen,	Reference standard: ICA Significant CAD was defined as a ≥70% diameter stenosis in a

Study Country	Study design Quality appraisal	Study population	Inclusion criteria / exclusion criteria	Intervention (CMR ± LGE)	Reference standard / comparator
USA	Quality: low risk of bias Patient selection: ? Index test: ☺ Reference standard:☺ Flow and timing: ? Applicability: ☹ ☺ ☺	with LVEF ≤40% and a coronary angiogram within 6 months of the CMR scan Mean age: 58.8 ± 12.1 years 59 men (70.8%)	previous coronary revascularisation; known history of structural heart disease such as HCM or congenital heart disease; evidence of severe left-sided valvular disease; or diagnosis of ST-segment elevation myocardial infarction on admission	Germany) Data inquisition: CMR was performed using a standard clinical protocol for evaluation of patients with CM, including use of LGE sequences, cine images and, when applicable, resting first-pass perfusion. Contrast agent: Gd	coronary ≥2 mm in calibre by visual assessment of the coronary angiogram, or pressure gradient <0.80 if fractional flow reserve measurement was performed.
Yoshida, Ishibashi-Ueda, et al. (2013) Japan	Level: III-1 Quality: low risk of bias Patient selection: ☺ Index test:☺ Reference standard: ☺ Flow and timing: ? Applicability:☹ ☺ ☺	136 patients who were admitted for the management of HF, who received biopsy and CMR Mean age: 52 ± 17 83/136 men (61%)	Inclusion criteria: Patients admitted to the institution for management of HF, with LV hypertrophy and/or LV dysfunction, who had EMB and LGE-CMR Exclusion criteria: Substantial valvular or IHD; congenital heart disease; constrictive pericarditis; idiopathic restrictive CM; ambiguous final diagnosis; DCM with LVEF >55%, poor-quality CMR; inadequate myocardial biopsy	Scanner: 1.5T scanner (Sonata, Siemens Medical Solutions, Erlangen, Germany) Data inquisition: a steady-state free precession sequence applied for cine CMR Contrast agent: 0.15 mmol/kg Gd-DTPA, at 2-, 5-, 10-, and 20-minute delays Diagnosis: The characteristics of DCM for CMR included dilation and impaired contraction of 1 or both ventricles and an LVEF <55%. Moreover, the wall thickness was normal or decreased.	Comparator: endomyocardial biopsy 3–5 specimens were obtained from each patient. Specimens were immediately fixed in 15% formalin for 24 hours, embedded in paraffin and cut into 4-mm thick sections. The sections were stained with haematoxylin and eosin and Masson's trichrome. Some of the specimens were frozen for PCR analysis for the detection of enterovirus when myocarditis was suspected. A histological diagnosis of DCM was performed by examining the following criteria: interstitial fibrosis, replacement fibrosis, inflammatory cell infiltrates, cellular hypertrophy and myocardial cell degeneration. Reference standard: Clinical data:

Study Country	Study design Quality appraisal	Study population	Inclusion criteria / exclusion criteria	Intervention (CMR ± LGE)	Reference standard / comparator
					Clinical data were defined as any method that could be used to diagnose HF other than Echo, CMR or EMB, such as the collection of a patient's medical history, laboratory tests, scintigraphy and coronary angiography. The final diagnosis was made prior to patient discharge by an expert team of cardiologists using all the available data, including the results of biopsy, CMR and other diagnostic modalities.

CAD = coronary artery disease; CM = cardiomyopathy; CMR = cardiac magnetic resonance (imaging); CTCA = computed tomography coronary angiography; DCM = dilated cardiomyopathy; ECG = electrocardiogram; Echo = echocardiography; EMB = endomyocardial biopsy; HCM = hypertrophic cardiomyopathy; HF = heart failure; LGE-CMR = late gadolinium enhancement cardiac magnetic resonance (imaging); LV = left ventricular / left ventricle; LVEF = left ventricular ejection fraction; ICA = invasive coronary angiography; IQR = interquartile range; MI = myocardial infarction; NICM = non-ischaemic cardiomyopathy; NIDCM = non-ischaemic dilated cardiomyopathy; NYHA = New York Heart Association; PCR = polymerase chain reaction

Table 77 Study profiles of included prognostic SRs

Study Country	Level of evidence Quality appraisal [a]	Aim of the SR Study population	Inclusion criteria / exclusion criteria	Outcomes assessed
Duan et al. (2015) China	NHMRC Level I AMSTAR: 64% (7/11) Good quality	To evaluate the association between LGE-CMR and major AEs in DCM patients Adult patients with DCM who had undergone LGE-CMR and were followed up	Search period: Up to 2 March 2014 Databases searched: PubMed, Ovid and EMBASE Inclusion criteria: Studies that included patients with DCM who had undergone LGE-CMR and were followed up were included if they reported on the outcomes assessed in this review. Exclusion criteria:	Major cardiovascular events: all-cause mortality cardiac death / transplantation hospitalisation for deteriorated HF Major arrhythmia events: a composite of SCD, sustained VT or VF appropriate ICD discharge/pacing SCD

Study Country	Level of evidence Quality appraisal [a]	Aim of the SR Study population	Inclusion criteria / exclusion criteria	Outcomes assessed
			Studies not in English, abstracts or session presentations Number of included studies: 13	
Kim et al. (2015) USA	NHMRC Level I AMSTAR: 18% (2/11) Poor quality	To discuss the evidence of CMR-derived myocardial scar for the prediction of adverse cardiovascular outcomes in NICM Adult patients with NICM (mostly DCM)	Search period: Not reported Databases searched: Not reported Inclusion criteria: Studies evaluating the relationship of myocardial scar and outcomes in NICM Exclusion criteria: None reported Number of included studies: 15	Major cardiovascular events: all-cause mortality arrhythmia events
Kuruvilla et al. (2014) USA	NHMRC Level I AMSTAR: 55% (6/11) Moderate quality	To evaluate the prognostic role of LGE-CMR imaging in patients with NICM Adult patients with NICM (mostly DCM)	Search period: Search was conducted in August 2013. Databases searched: PubMed, Cochrane CENTRAL and EMBASE Inclusion criteria: Studies evaluating myocardial fibrosis in patients with NICM using LGE-CMR and inclusion of hard end points Exclusion criteria: Studies that evaluated ICM, acute myocarditis, and HCM and infiltrative CM (including cardiac amyloidosis), and abstracts Number of included studies: 9	Major cardiovascular events: all-cause mortality hospitalisation for HF composite endpoint of SCD, aborted SCD or appropriate ICD therapy
Scott et al.	NHMRC Level I	To better gauge the predictive accuracy of	Search period:	Arrhythmic endpoints:

Study Country	Level of evidence Quality appraisal [a]	Aim of the SR Study population	Inclusion criteria / exclusion criteria	Outcomes assessed
(2013) UK	AMSTAR: 64% (7/11) Good quality	LGE-CMR for SCD risk stratification Adult patients with CAD or NICM who had undergone LGE-CMR and were followed up	From 1966 to August 2012 Databases searched: PubMed, EMBASE and the Cochrane library Inclusion criteria: Studies that examined the relationship between the extent of LV scar (including core scar, the peri-infarct or 'grey' zone, and measures of scar transmurality), quantified by LGE-CMR and one or more arrhythmic endpoints, and that involved patients with CAD or NICM Exclusion criteria: Studies not in English, abstracts or session presentations Studies that used a composite endpoint including arrhythmias, but where the majority of endpoints that occurred were non-arrhythmic and data for individual endpoints were not presented Studies where the only endpoints presented were all-cause mortality, cardiac mortality or mortality due to pump failure Studies where the results were reported so that a 2x2 table of results could not be constructed, and those involving overlapping or duplicate cohorts of patients Number of included studies: 11	SCD resuscitated cardiac arrest occurrence of VAs appropriate ICD therapy
Shi et al. (2013) China	NHMRC Level I AMSTAR: 55% (6/11) Moderate quality	To evaluate the prognostic value of LGE-CMR in DCM patients Adult patients with DCM	Search period: January 2000 to May 2011 Databases searched: PubMed, MEDLINE, the Cochrane library and EMBASE Inclusion criteria: Studies complying with the following criteria were enrolled: 1) CMR was performed in DCM patients	Major cardiovascular events: all-cause mortality cardiac death SCD aborted SCD hospitalisation for HF

Study Country	Level of evidence Quality appraisal [a]	Aim of the SR Study population	Inclusion criteria / exclusion criteria	Outcomes assessed
			2) the selected clinical outcomes were recorded in DCM patients 3) the correlation between LGE and clinical outcomes of DCM patients explored 4) sufficient information to allow estimation of pooled ORs and 95%CIs. Exclusion criteria: Studies with fewer than 20 patients, patients undergoing CRT, where the same study population was assessed in more than 1 report (the study with the most details and or the study published the most recently was chosen), where the selected clinical outcomes could not be extracted Number of included studies: 5	

[a] Quality appraisal was undertaken using the AMSTAR checklist (Shea et al. 2007).

AE = adverse event; CAD = coronary artery disease; CI = confidence interval; CM = cardiomyopathy; CMR = cardiac magnetic resonance (imaging); CRT = cardiac resynchronisation therapy; DCM = dilated cardiomyopathy; HCM = hypertrophic cardiomyopathy; HF = heart failure; ICD = implantable cardioverter defibrillator; ICM = ischaemic cardiomyopathy; LGE = late gadolinium enhancement; LV = left ventricular; NHMRC = National Health and Medical Research Council; NICM = non-ischaemic cardiomyopathy; OR = odds ratio; SCD = sudden cardiac death; SR = systematic review; VA = ventricular arrhythmia; VF = ventricular fibrillation; VT = ventricular tachycardia

Table 78 Study profiles of included non-comparative prognostic cohort studies in adults

Study Country	Level of evidence Quality appraisal	Study population	Inclusion criteria / exclusion criteria	LGE-CMR	Intervention and outcomes
Almehmadi et al. (2014)	Prospective cohort	N=318 consecutive patients with ICM and NICM, and an LVEF <55%: n=248 (78%) LGE+	Inclusion criteria: consecutive patients with systolic dysfunction referred for LGE-CMR between April 2008 and April 2012 were	Scanner: 3-T scanner with a 32-channel cardiac coil Cardiac function sequence: sequential short-axis views at 10-	ICD implantation: Not described Outcomes: HR for likelihood of having:

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Canada	NHMRC level II SIGN: acceptable quality with a moderate risk of bias	n=70 (22%) LGE– Patient characteristics: age = 62.0 ± 12.9 years; male = 73%; QRS interval = 131.9 ± 31.5 milliseconds; LBBB = 40%; LVEF (CMR) = 32.6 ± 11.9%; history of VA = 11%, ICM = 47%; NYHA class III–IV = 46%; medications: ACE inhibitor = 59%, ARB = 22%, β-blockers = 77% n=169 (53%) had NICM n=50 (30%) LGE+ n=119 (70%) LGE– Median follow-up: 467 (IQR 16–1,422) days	studied. Systolic dysfunction was defined as an LVEF ≤55% because this value corresponds to the lower limit of the 95%CI in healthy subject. Exclusion criteria: patients clinically suspected to have HCM, restrictive CM (sarcoidosis or amyloidosis), or arrhythmogenic right ventricular CM. Patients were also excluded if standard contraindications to LGE-CMR existed, inclusive of a GFR of ≤30 mL/min/1.73 m^2	mm intervals using a standard SSFP-based cine pulse sequence LGE sequence: phase-sensitive inversion recovery gradient-echo pulse sequence Contrast agent: 0.15–0.2 mmol/kg; Gadovist Time delay: 10–15 minutes LV function: Cine images were examined to determine LV and right ventricular end-systolic volumes and end-diastolic volumes, in addition to LV mass by semi-automated endocardial and epicardial contour tracing. LGE diagnosis: The scoring of all LGE fibrosis patterns was as follows: 1) subendocardial 2) mid-wall striae 3) mid-wall patchy 4) subepicardial 5) right ventricular insertion point 6) diffuse.	SCA or appropriate ICD discharge hospitalisation for severe HF non–SCD in LGE+ patients compared with those that are LGE–
Buss et al. (2015)	Prospective cohort	N=210 consecutive patients with DCM	Inclusion criteria: consecutive patients with	Scanner: 1.5-T scanner with a cardiac phased array receiver coil	ICD implantation: Not described

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Germany	NHMRC level II SIGN: acceptable quality with a moderate risk of bias	Includes 101 patients from Lehrke et al. (2011) with extended follow-up: n=79 (38%) LGE+ n=131 (62% LGE– Patient characteristics: age = 52 ± 15 years; male = 76%; LVEF (CMR) = 36.1 ± 13.8%; family history of CM = 13%; mean NYHA class = 2.1 ± 0.7; medications: ARB/ACE inhibitor = 93%, β-blockers = 88% Median follow-up: 5.3 years	DCM who were prospectively included in the study, and myocardial deformation was analysed retrospectively after referral to the Cardiomyopathy Center at the University Hospital Heidelberg between May 2005 and November 2009. Exclusion criteria: contraindications to CMR: cardiac pacemaker or ICD, other incompatible metallic implants, severe claustrophobia, obesity preventing patient entrance into the scanner bore, pregnancy and lactation. Chronic renal failure of GFR <30 mL/min/1.73 m^2 was added after July 2007.	Cardiac function sequence: Cine images were obtained using a breath-hold segmented-k-space balanced fast-field echo sequence (SSFP) employing retrospective ECG gating in long-axis planes as well as in contiguous short-axis slices. LGE sequence: Not reported Contrast agent: Not reported Time delay: Not reported LV function: LV volumes, LVEF and LV myocardial mass were derived from short-axis slices. LGE diagnosis: The presence and extent of LGE was evaluated by 2 independent, blinded, experienced observers.	Outcomes: HR for likelihood of having: cardiac death an aborted SCD hospitalisation for severe HF in LGE+ patients compared with those that are LGE–
Cheong et al. (2009) USA	Retrospective cohort NHMRC level III-3 SIGN: high quality with a low	N=857 patients who had complete LGE-MRI evaluation with LV functional analysis N=643 patients with CAD: n=511 (79%) LGE+ n=132 (21%) LGE– Patient characteristics: age = 61.7 ± 11.7 years;	Inclusion criteria: patients referred for DE-MRI between 2001 and 2004 who had complete LGE-MRI evaluation with LV functional analysis Exclusion criteria: patients diagnosed with HCM, myocarditis, sarcoidosis or other infiltrative CM	Scanner: 1.5-T scanner with a 5-element cardiac coil used with vector-cardiac gating Cardiac function sequence: Standard bright-blood cine images, including vertical long-axis view, as well as a set of short-axis series covering the entire LV using a steady-state free-precession sequence	ICD implantation: Presence or absence not mentioned Outcomes: HR for likelihood of having: mortality or cardiac transplantation NIDCM vs ICM in LGE+ patients compared with those

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	risk of bias	male = 71%;
		median LVEF (CMR) = 39% (IQR 26, 52);
		CHF = 56%
		N=215 patients without CAD:
		n=38 (18%) LGE+
		n=177 (82%) LGE–
		Patient characteristics:
		age = 51.3 ± 16.0 years;
		male = 57%;
		median LVEF (CMR) = 52% (IQR 33, 60);
		CHF = 33%
		Median follow-up: 4.4 years
				LGE sequence: inversion-recovery prepared, T1-weighted, gradient-echo sequence
				Contrast agent: gadolinium chelate, 0.2 mmol/kg
				Time delay: 15 minutes
				LV function: Endocardial and epicardial contours were prescribed manually on the series of short-axis cine slices of the LV at end diastole and end systole to obtain end-diastolic volume, end-systolic volume, LVEF and LV mass.
				LGE diagnosis: The scoring system used on the LGE data:
				1 = no LGE
				2 =1–25% LGE (thin subendocardial scar)
				3 = 26–50% LGE (dense subendocardial scar)
				4 = 51–75% LGE (near-transmural scar)
				5 = 76–100% LGE (transmural scar)
					that are LGE–

Chimura et al. (2015)	Retrospective cohort	N=175 NICM patients with HF who had an LVEF <35%	Inclusion criteria: NICM patients who had an LVEF	Scanner: 1.5-T scanner with a standardised protocol	ICD implantation: ICD implantations were undertaken using standard

Study Country	Level of evidence Quality appraisal	Study population	Inclusion criteria / exclusion criteria	LGE-CMR	Intervention and outcomes
Japan	NHMRC level III-3 SIGN: high quality with a low risk of bias	without sustained VT: n=122 (70%) LGE+ n=53 (30%) LGE– n=7 patients received an ICD n=17 patients received a CRT-D Patient characteristics: age = 60 ± 15 years; male = 63%; QRS interval = 121 ± 31 milliseconds; LBBB = 33%; LVEF (Echo) = 29 ± 5.4%; presence of AF = 17%; documentation of VT = 5%; NYHA class: II = 31%, III = 69%; medications: ACE inhibitor/ARB = 95%, β-blockers = 94% Mean follow-up: 5.1 ± 3.3 years	<35% and NYHA class II or III without sustained VT, who were referred with HF at their initial visit between January 2005 and June 2014 Exclusion criteria: contraindications to CMR existed, including significant renal dysfunction (GFR of ≤30 mL/min/1.73 m^2) and implanted devices such as pacemakers and/or defibrillators	Cardiac function sequence: Cine images were acquired with a steady-state, free-precession sequence in long-axis planes and contiguous short-axis slices. LGE sequence: inversion-recovery gradient-echo sequence Contrast agent: 0.1 mmol/kg Gd-DTPA Time delay: 10 minutes LV function: Details not reported LGE diagnosis: The presence or absence of LGE was visually determined by 2 independent blinded readers and divided into 6 groups according to the LGE pattern: 1) septal subendocardial 2) lateral subendocardial 3) septal mid-wall, 4) lateral mid-wall 5) septal subepicardial 6) lateral subepicardial 7) papillary muscle pattern.	techniques at a median of 16 days following the CMR. The ICD devices were programmed to detect VF and VT. Outcomes: HR for likelihood of having: ICD implantation appropriate ICD therapy life-threatening arrhythmic events in LGE+ patients compared with those that are LGE–
Cho et al.	Prospective	N=79 patients with ECG-	Inclusion criteria: patients with ECG-proven LV systolic	Scanner: Gyroscan Intera system	ICD implantation: Presence or

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(2010) Korea	cohort NHMRC level II SIGN: unacceptable quality with a high risk of bias	proven LVEF <35%: n=42 (49%) LGE+ n=37 (51%) LGE– N=69 patients with idiopathic DCM: n=38 (55%) LGE+ n=26 (45%) LGE– Patient characteristics: age = 56.6 ± 13.2 years; male = 53%; QRS interval = 104.3 ± 22.7 milliseconds; LVEF (Echo) = 26.5 ± 7.9%; presence of AF = 18%; NYHA class III–IV = 23%; medications: ACE inhibitor = 88%, ARB = 15%, β-blockers = 76% Mean follow-up: 33.4 ± 1.7 months	dysfunction (LVEF <35%). All subjects were admitted to hospital and underwent ICA at initial diagnosis to exclude CAD. Exclusion criteria: previous history of CAD, chronic renal insufficiency with serum creatinine >2 mg/dL, pregnancy, life expectancy of less than 6 months because of other medical conditions, significant primary valvular heart disease and previous history of acute myocarditis	Cardiac function sequence: Cine images were performed with a steady-state free precession sequence. LGE sequence: inversion recovery T1-weighted segmented gradient-echo sequence Contrast agent: 0.2 mmol/kg of Gd-DTPA Time delay: 10–15 minutes LV function: Details not reported LGE diagnosis: presence of LGE was determined by 2 experienced radiologists and divided into groups according to the pattern of: 1) LGE: FPE = focal patchy enhancement and was defined as LGE involving <50% of the 12 segments 2) DME = diffuse myocardial enhancement was defined as involving >50% of all segments.	absence not mentioned Outcomes: HR for likelihood of having: cardiac death hospitalisation for HF cardiac transplantation in LGE+ patients compared with those that are LGE–
Fernandez-Armenta et al. (2012)	Prospective cohort NHMRC level II	N=78 consecutive HF patients with DCM and severe LV dysfunction (LVEF <35%): n=54 (69%) LGE+ n=24 (31%) LGE–	Inclusion criteria: Consecutive HF patients with DCM and severe LV dysfunction (LVEF <35%) who were referred for primary prevention CRT-D	Scanner: 1.5-T scanner Cardiac function sequence: Cine images were acquired during repeated breath-holds and synchronised with the ECG. A	ICD implantation: Clinical and Echo evaluation was performed before device implantation and every 6 months thereafter. Outcomes:

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Spain	SIGN: acceptable quality with a moderate risk of bias	n=15 LGE+ patients had NICM n=39 had ICM Patient characteristics: age = 64 ± 11 years; male = 83%; QRS interval = 159 ± 33 milliseconds; LBBB = 63%; LVEF (CMR) = 22 ± 7%; presence of AF = 22%; ICM = 53%; NYHA class: II = 27%, III = 68%, class IV = 5%; medications: ARB/ACE inhibitor = 89%, βblockers = 82% Median follow-up: 25 (IQR 15–34) months	implantation. The aetiology was considered to be ischaemic if there was >70% DS of a coronary artery on angiography, a history of proven MI or evidence of ischaemia on image stress testing. A CMR was performed before device implantation to assess LV function, and identify and characterise scar tissue. Exclusion criteria: contraindications to CMR examination	standard steady-state free precession cine sequence was applied on 10 mm-thick, sequential short-axis slices. LGE sequence: segmented gradient-echo sequence with inversion–recovery Contrast agent: 0.2 mmol/kg of Gd-DTPA Time delay: 10 minutes LV function: An experienced observer manually traced the borders of the epicardium and endocardium on short-axis slices to calculate LV myocardial volume. LGE diagnosis: presence of LGE was determined by an experienced blinded observer. Scar tissue was defined as hyperenhanced areas with signal intensity at least two SDs above that of normal myocardium.	HR for likelihood of having: appropriate CRT-D discharge cardiac death in LGE+ patients compared with those that are LGE–
Gao et al. (2012) Canada	Prospective cohort NHMRC level II	N=124 consecutive patients who had LVEF ≤35% and were diagnosed with DCM Patient characteristics: age = 61 ± 11 years;	Inclusion criteria: Consecutive patients referred to the electrophysiology service for consideration of ICD who had an LVEF ≤35% and were on maximal tolerated HF therapy for	Scanner: 3-T scanner equipped with a 32-channel cardiac coil Cardiac function sequence: Assessed in sequential short-axis views at 10-mm intervals using a standard steady-state free-precession (SSFP)-based 'cine'	ICD implantation: implantations were performed in a standard fashion at a median of 27 days (IQR 8–45) following CMR. ICD devices were programmed to detect VF and VT. Outcomes:

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	SIGN: high quality with a low risk of bias	male = 81%; QRS interval = 136 ± 30 milliseconds; LBBB = 44%; LVEF (CMR) = 26 ± 7%; ICM = 48%; primary prevention ICD = 56%; secondary prevention ICD = 8%; CRT-D implantation = 36%; NYHA class = 2.5 ± 0.9; medications: ACE inhibitor = 71%, ARB = 25%, β-blockers = 80% N=59 patients with ICM: all LGE+ N=65 patients with NIDCM: n=46 (71%) LGE+ n=19 (29%) LGE– Mean follow-up: 632 ± 262 days	≥3 months. Prior to enrolment all patients underwent ICA or CTCA to determine CM aetiology. Exclusion criteria: standard contraindications to LGE-CMR, inclusive of a GFR of ≤30 mL/min/1.73 m^2	pulse sequence LGE sequence: standard, segmented inversion recovery gradient-echo pulse sequence Contrast agent: 0.15–0.2 mmol/kg Gadovist Time delay: 10–15 minutes LV function: Cine images were examined to determine the LV end-systolic volume, LV end-diastolic volume and LV mass by semi-automated endocardial and epicardial contour tracing. LGE diagnosis: The presence or absence of any LGE was visually determined by an experienced blinded CMR interpreter, and the most dominant pattern scored: 1) subendocardial based 2) mid-wall 3) subepicardial.	HR for likelihood of having: SCD or survived SCA appropriate ICD discharge non-SCD cardiac death in LGE+ patients compared with those that are LGE– HR for likelihood of having: SCD or survived SCA appropriate ICD discharge cardiac death (not SCD) in NIDCM patients compared with ICM patients
Gulati et al. (2013)	Prospective cohort	N=472 consecutive patients with DCM confirmed by CMR	Inclusion criteria: patients with DCM of at least 6 months' duration and	Scanner: 1.5-T scanner and a standardised protocol	ICD implantation: Not described Outcomes:

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UK	NHMRC level II SIGN: high quality with a low risk of bias	Includes Assomull et al. (2006) cohort of 101 patients with extended follow-up: n=142 (30%) LGE+ n=330 (70%) LGE– Patient characteristics: age = 51.5 ± 14.7 years; male = 69%; history of VF or sustained VT = 5%; history of AF = 17%; family history of DCM = 8%; LBBB = 27%; LVEF (CMR) = 26 ± 7%; implantation of: ICD = 7%, CRT-P = 13%; CRT-D = 13%; NYHA class I = 41%, II = 37%, III = 20%, IV = 2%; medications: ACE inhibitor = 91%, β-blockers = 68% Median follow-up: 5.3 years (range 31 days to 11.0 years; 2,557 patient-years)	confirmed by CMR prior to inclusion. Confirmation on the basis of (1) increased LV end-diastolic volume indexed to body surface area and reduced LVEF; and (2) absence of subendocardial LGE indicative of previous MI Exclusion criteria: Not reported	Cardiac function sequence: Cine images were acquired with a steady-state, free-precession sequence in long-axis planes and contiguous short-axis slices. LGE sequence: inversion-recovery gradient-echo sequence Contrast agent: 0.1 mmol/kg gadopentetate dimeglumine or gadobutrol Time delay: 10 minutes LV function: LV volumes, LVEF, and mass were measured using dedicated software. The values for LV volume and mass were indexed by body surface area. LGE diagnosis: The presence and location of mid-wall fibrosis were assessed by 2 independent expert readers who were blinded to all available diagnostic data. Mid-wall fibrosis was only considered present if the area of enhancement was confined to intramural and/or subepicardial layers and the extent of mid-wall fibrosis was quantified.	HR for likelihood of having: all-cause mortality cardiac death cardiac transplantation SCD aborted SCD or appropriate ICD discharge HF death hospitalisation for CHF in LGE+ patients compared with those that are LGE–

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Hombach et al. (2009) Germany	Prospective cohort NHMRC level II SIGN: high quality with a low risk of bias	N=141 consecutive patients with idiopathic DCM: n=36 (26%) LGE+ n=105 (73%) LGE– Patient characteristics: age = 56.1 ± 13.3 years; male = 77%; LVEF (CMR) = 32 ± 14%; QRS interval >110 milliseconds = 67%; AF = 40%; NYHA class I = 12%, II = 11%, III = 46%, IV = 31%; medications: ACE inhibitor = 87%, β-blockers = 90% Median follow-up: 1,339 days (IQR 822–1,676; 483 patient-years)	Inclusion criteria: patients with idiopathic DCM were enrolled during a period of 4 years. Diagnosis was established by clinical examination, Echo and normal coronary angiograms. Exclusion criteria: patients with a history of previous coronary intervention or MI, patients with inflammatory CM due to chronic inflammation in myocardial biopsy	Scanner: 1.5-T whole-body scanner Cardiac function sequence: Resting LV and RV function were determined with 3D cine imaging applying a multiple breath-hold segmented k-space balanced FFE sequence (steady-state free-precession) in short- and long-axis views. LGE sequence: 3D spoiled turbo gradient-echo sequence with a selective 180° inversion recovery pre-pulse Contrast agent: 0.2 mmol/kg Gd-DTPA Time delay: 10–15 minutes LV function: LV and RV volumes and functional parameters were analysed off-line on a workstation using short-axis volumetry. LGE diagnosis: LGE was quantitatively assessed.	ICD implantation: Not described Outcomes: HR for likelihood of having: all-cause mortality cardiac death SCD cardiac death, SCD or appropriate ICD discharge cardiac death, SCD or hospitalisation for HF in LGE+ patients compared with those that are LGE–
Iles et al. (2011) Australia	Prospective cohort NHMRC level II	N=103 patients with advanced HF planned for ICD implantation Patient characteristics:	Inclusion criteria: Subjects presenting at the Alfred Hospital, Melbourne, between July 2003 and October 2009 with advanced HF, and planned for	Scanner: 1.5-T scanner Cardiac function sequence: The LV function was assessed by a steady-state free-precession pulse sequence.	ICD implantation: All devices were implanted using standard surgical techniques: choice of device was at the discretion of the implanting physician and the device was activated at

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	SIGN: high quality with a low risk of bias	age = 54 ± 13 years; male = 77%; LVEF (CMR) = 26 ± 9%; NYHA class = 2 (IQR 2–3); medications: ACE inhibitor/ARB = 95%, β-blockers = 92% N=42 patients with ICM –: all LGE+ N=61 patients with NICM: n=31 (51%) LGE+ n=30 (49%) LGE– Median follow-up: 573 (IQR 379–863) days	implantation of ICD according to international guidelines for primary prevention of SCD Exclusion criteria: Patients who suffered from claustrophobia or uncontrolled arrhythmias, or had a history of a metallic prosthetic implant contraindicating CMR, previous VA causing haemodynamic compromise or requiring treatment, recent MI (<3 months) or myocarditis Only subjects with successful device implantation and a minimum of 6 months of follow-up and/or an event were included in the data analysis.	LGE sequence: inversion-recovery gradient-echo sequence Contrast agent: 0.2 mmol/kg Gd-DTPA Time delay: 10 minutes LV function: The LV function was evaluated globally utilising the biplane area-length method using 2- and 4-chamber long-axis views. LGE diagnosis: LGE was assessed by 2 independent blinded expert readers and was defined as being present only if it was identified in both long-axis and short-axis views.	completion of implantation. Initial programming of the ICD was for shock only. During follow-up, anti-tachycardia pacing was only programmed after an episode of VT. Outcomes: HR for likelihood of having: appropriate ICD discharge in LGE+ patients compared with those that are LGE–, and in NIDCM patients compared with ICM patients
Klem et al. (2012) USA	Prospective cohort NHMRC level II SIGN: high quality with low	N=137 patients undergoing evaluation for possible ICD placement N=73 patients with CAD: n=70 (96%) LGE+ n=3 (4%) LGE– Patient characteristics:	Inclusion criteria: patients referred to the electrophysiology service and scheduled for an EPS and/or ICD placement between 1 July 2002 and 1 July 2004. The reasons for referral to the electrophysiology service	Scanner: 1.5-T scanner with phased-array receiver coils Cardiac function sequence: Cine images were acquired in multiple short-axis and 3 long-axis views with a steady-state free precession sequence. LGE sequence: segmented	ICD implantation: implantation procedure not reported. The decision for ICD implantation was guided by standard consensus criteria but was at the discretion of the treating physician after discussion with the patient. Outcomes: HR for likelihood of having:

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	risk of bias	age = 65.3 ± 10.9 years; male = 74%; NYHA class: I = 29%, II = 29%, III = 36%, IV = 7%; LVEF (CMR) = 30.5 ± 14.0%; QRS interval = 115.2 ± 30.3 milliseconds; LBBB = 15%; RBBB = 14%; medications: ACE inhibitor = 66%, ARB = 12%, β-blockers = 78% N=64 patients without CAD: n=37 (58%) LGE+ n=27 (42%) LGE– Patient characteristics: age = 52.3 ± 16.2 years; male = 50%; NYHA class: I = 47%, II = 20%, III = 27%, IV = 3%; LVEF (CMR) = 40.9 ± 20.6%; QRS interval = 108.3 ± 33.2 milliseconds; LBBB = 16%;	were low LVEF meeting criteria for an ICD; mild LV dysfunction with palpitations, frequent premature ventricular contractions, and/or non-sustained VT; evaluation of wide-complex tachycardia; syncope; and presumed cardiac arrest. Exclusion criteria: patients with contraindications for CMR (prior pacemaker or defibrillator) or under 18 years of age	inversion-recovery gradient-echo sequence Contrast agent: 0.15 mmol/kg gadoversetamide Time delay: 10 minutes LV function: LV volumes, mass, and LVEF were quantitatively measured from the stack of short-axis cine images using standard techniques. LGE diagnosis: LGE assessment was masked to all patient information by a single reader. Regional enhancement was scored according to the spatial extent of LGE+ tissue within each segment 0 = no LGE, 1 = 1–25%, 2 = 26–50%, 3 = 51–75%, 4 = 76–100% LGE	all-cause mortality appropriate ICD discharge SCD cardiac death VF/VT events hospitalisation for CHF ICD implantation in LGE+ patients compared with those that are LGE–, and in NIDCM patients compared with ICM patients

Study Country	Level of evidence Quality appraisal	Study population	Inclusion criteria / exclusion criteria	LGE-CMR	Intervention and outcomes
		RBBB = 13%; medications: ACE inhibitor = 48%, ARB = 9%, β-blockers = 55% Mean follow-up: 24 (IQR 19.9–29.0) months			
Kono et al. (2010) Japan	Prospective cohort NHMRC level II SIGN: unacceptable quality with a high risk of bias	N=32 patients who were diagnosed with DCM and with an LVEF of <40%: n=18 (56%) LGE+ n=14 (44%) LGE– Patient characteristics: age = 61.1 ± 11.5 years; male = 59%; LVEF (Echo) = 27.9 ± 7.4%; LVEF (CMR) = 21.3 ± 12.0%; medications: ACE inhibitor = 91%, β-blockers = 94% Mean follow-up: 30.8 ± 12.9 months	Inclusion criteria: Patients who were referred to the Hyogo Brain and Heart Center between August 2003 and January 2005, had an ECG-assessed LVEF of <40% and were diagnosed with DCM but had not been previously treated Exclusion criteria: the presence of any contraindications for CMR and contrast medium, ICM or HCM, infiltrative heart disease, significant valvular disease or persistent arrhythmias	Scanner: 1.5-T scanner with a cardiac five-channel coil Cardiac function sequence: Cine images covering both ventricles were obtained using a breath-hold steady-state free-precession sequence. LGE Sequence: inversion-recovery gradient-echo sequence Contrast agent: 0.1 mmol/kg Gd-DTPA Time delay: 15 minutes LV function: LV volume and function were measured on short-axis slices with standard techniques. LGE Diagnosis: LGE was assessed by 2 independent blinded expert readers and was defined as being present only if it was identified in both long-axis	ICD implantation: ICD implantation was considered with the occurrence of NSVT on Holter ECG, either on admission or during the follow-up period, or with the presence of critical arrhythmia. The physicians made the decision for ICD implantation while blinded to the CMR data. Outcomes: HR for likelihood of having: all-cause mortality cardiac death VF/VT events hospitalisation for CHF ICD implantation in LGE+ patients compared with those that are LGE–

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				and short-axis views.	
Lehrke et al. (2011) Germany	Prospective cohort NHMRC level II SIGN: acceptable quality with a moderate risk of bias	N=184 consecutive patients with DCM NOTE: patients included in Buss et al. (2015): n=72 (39%) LGE+ n=112 (61%) LGE– Patient characteristics: age = 51.6 ± 1.1 years; male = 75%; LVEF (CMR) = 31% (IQR 21–42); history of AF = 13%; family history of DCM = 15%; NYHA class: I = 22%, II = 48%, class III = 29%; medications: ACE inhibitor = 81%, ARB = 19%, β-blockers = 86% Mean follow-up: 658 ± 30 days	Inclusion criteria: consecutive patients with DCM who were referred to the Cardiomyopathy Center between May 2005 and April 2008 with depressed systolic function (LVEF <50%) in the absence of significant CAD (≥50% DS on ICA and/or a history of coronary revascularisation or MI). All patients had chronic HF of at least 12 months' duration and were examined in a clinically stable condition (NYHA functional class ≤III). Patients initially diagnosed as having DCM displaying a pattern of LGE suggestive of MI were excluded from the final analysis. Exclusion criteria: valvular disease, hypertensive heart disease and congenital abnormalities, contraindications to CMR: cardiac pacemaker or ICD, other incompatible metallic implants, severe claustrophobia, obesity	Scanner: 1.5-T scanner with a five-element cardiac phased-array receiver coil Cardiac function sequence: Cine images were obtained using a breath-hold segmented-k-space balanced fast-field echo sequence (SSFP) employing retrospective ECG gating in long-axis planes as well as in contiguous short-axis slices. LGE sequence: 3D inversion-recovery gradient-echo pulse sequence Contrast agent: 0.1 mmol/kg Gd-DTPA Time delay: 10 minutes LV function: Ventricular volumes, ejection fraction and LV myocardial mass were derived from short-axis slices after manual tracing of epicardial and endocardial borders. LGE diagnosis: LGE was assessed by 2 independent blinded experienced observers. The pattern of LGE was characterised as mid-wall,	ICD implantation: Not described Outcomes: HR for likelihood of having: ICD implantation appropriate ICD discharge SCD hospitalisation for HF cardiac transplantation in LGE+ patients compared with those that are LGE–

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			preventing patient entrance into the scanner bore, pregnancy, and lactation. Chronic renal failure of GFR <30 mL/min/1.73 m^2 was added after July 2007.	epicardial, patchy/foci or diffuse.	
Leyva et al. (2012) UK	Prospective cohort NHMRC level II SIGN: acceptable quality with a moderate risk of bias	N=258 patients with DCM or ICM N=161 patients with ICM Patient characteristics: age = 69.3 ± 9.4 years; male = 88%; QRS interval = 136.9 ± 32.6 milliseconds; LVEF (CMR) = 23.9 ± 10.9%; permanent AF = 17%; CRT-D implantation = 20%; NYHA class: III = 76%, IV = 24%; medications: ACE inhibitor/ARB = 92%, β-blockers = 63% N=97 patients with DCM: n=20 (21%) LGE+ n=77 (79%) LGE– Patient characteristics:	Inclusion criteria: Patients with DCM or ICM who were recruited from a single centre and who successfully underwent CRT device implantation and CMR imaging between September 2000 to July 2009 Exclusion criteria: Patients with hypertrophic or restrictive CM, primary valvular disease or myocarditis, as well as patients with presumed NICM with fibrosis in distributions other than mid-wall (subepicardial, epicardial or patchy)	Scanner: 1.5-T scanner with a phased-array cardiac coil Cardiac function sequence: Short-axis LV stack was acquired using a steady state in free-precession sequence. LGE sequence: segmented inversion-recovery technique Contrast agent: 0.1 mmol/kg Gd-DTPA Time delay: 10 minutes LV function: LV end-diastolic and LV end-systolic volumes were quantified using semiautomatic manual planimetry of all short-axis cine images with MASS analysis software. LGE Diagnosis: Scars were classified into subendocardial, mid-wall, epicardial, transmural or patchy. Scars in a subendocardial or transmural distribution following coronary artery territories were	ICD implantation: CRT device implantation was undertaken using standard techniques under local anaesthesia. With the exception of 2 DCM patients who received CRT-D for secondary prevention, all others received CRT-P. Outcomes: HR for likelihood of having: all-cause mortality cardiac death cardiac transplantation SCD hospitalisation for MACE hospitalisation for HF hospitalisation for AF in LGE+ patients compared with those that are LGE–, and in NIDCM patients compared with ICM patients

Study Country	Level of evidence Quality appraisal	Study population	Inclusion criteria / exclusion criteria	LGE-CMR	Intervention and outcomes
		age = 66.7 ± 13.0 years; male = 62%; QRS interval = 144.2 ± 29.1 milliseconds; LVEF (CMR) = 23.9 ± 9.7%; permanent AF = 20%; CRT-D implantation = 2%; NYHA class: III = 73%, IV = 27%; medications: ACE inhibitor/ARB = 93%, β-blockers = 52% Median follow-up: 2.8 years (maximum 8.7 years)		regarded as ischaemic in aetiology, whereas mid-wall scars and absence of scar were regarded as indicative of a non-ischaemic aetiology.	
Li et al. (2013) China	Retrospective cohort NHMRC level III-3 SIGN: acceptable quality with a moderate risk of bias	N=293 patients with DCM: n=145 (49%) LGE+ n=148 (51%) LGE– Patient characteristics: age = 49.2 ± 14.9 years; male = 87%; QRS interval = 113.9 ± 28.1 milliseconds; LVEF (Echo) = 33.3 ± 8.1; LVEF (CMR) = 22.6 ± 8.3%; history of AF = 24%;	Inclusion criteria: patients with DCM who were admitted in Fuwai Hospital from June 2005 to September 2011 Exclusion criteria: Not reported	Scanner: 1.5-T scanner with a phased-array cardiac coil Cardiac function sequence: Not reported. LGE sequence: phase-sensitive inversion recovery spoiled gradient-echo sequence Contrast agent: 0.2 mmol/kg Gd-DTPA Time delay: 15–20 minutes LV function: Not reported	ICD implantation: Not described Outcomes: HR for likelihood of having: all-cause mortality in LGE+ patients compared with those that are LGE–

Study Country	Level of evidence Quality appraisal	Study population	Inclusion criteria / exclusion criteria	LGE-CMR	Intervention and outcomes
		history of sustained VT = 18%; CRT-D implantation = 2%; NYHA class III–IV = 68%; medications: ACE inhibitor/ARB = 91%, β-blockers = 95% Mean follow up: 3.2 years		LGE diagnosis: Not reported	
Looi et al. (2010) New Zealand	Prospective cohort NHMRC level II SIGN: unacceptable quality with a high risk of bias	N=103 patients with DCM who had a clinical presentation of HF and an ECG demonstrating LVEF <50%: n=31 (30%) LGE+ n=72 (70%) LGE– Patient characteristics: age = 58 ± 13 years; male = 76%; LVEF (CMR) = 32 ± 12%; NYHA class: I = 75%, II = 18%, III = 4% Mean follow-up: 660 ± 346 days	Inclusion criteria: Patients with DCM, prospectively identified between 1 December 2003 and 31 August 2006, were included in the analysis if they had a clinical presentation of HF and an ECG demonstrating impaired LV systolic function (LVEF <50%), and had successfully completed an LGE-CMR. Exclusion criteria: patients with ICA-documented significant CAD (>50% DS in any coronary artery), significant valvular disease, CM of known cause including HCM, alcohol- or chemotherapy-induced or infiltrative CM	Scanner: 1.5-T scanner with a synergy cardiac coil Cardiac function sequence: Electrocardiographically gated steady-state free-precession cine images were acquired in the 2 and 4 chamber, LV outflow tract and short-axis views. LGE sequence: 3D inversion-recovery segmented gradient-echo sequence Contrast agent: 0.15 mmol/kg Gd-based contrast agent (Omniscan) Time delay: 10 minutes LV function: LV end-diastolic and end-systolic volumes, and LVEF were calculated from the short-axis cine images. LGE diagnosis: Areas of LGE	ICD implantation: Not described Outcomes: HR for likelihood of having: all-cause mortality cardiac death HF VA cardiac transplantation MACE in LGE+ patients compared with those that are LGE–

Study Country	Level of evidence Quality appraisal	Study population	Inclusion criteria / exclusion criteria	LGE-CMR	Intervention and outcomes
				were defined as subendocardial, mid-myocardial or transmural on visual analysis by a consensus of 2 independent cardiologists	
Machii et al. (2014) Japan	Retrospective cohort NHMRC level III-3 SIGN: acceptable quality with a moderate risk of bias	N=83 patients with ES-HCM or DCM N=72 patients with DCM: n=48 (67%) LGE+ n=24 (33%) LGE– Patient characteristics: age = 64 ± 14 years; male = 72%; LVEF (CMR) = 34.4 ± 8.3%; BBB = 15%; family history = 11%; syncope = 7%; presence of VT/VF = 29%; presence of AF = 29%; CRT-D/ICD implantation = 10%; NYHA class = 2.5 ± 0.9; medications: ACE inhibitor/ARB = 78%, β-blockers = 76% Mean follow-up: 39.6 ±	Inclusion criteria: patients admitted for treatment of HF and/or for a differential diagnosis of CM who underwent CMR from April 2003 to August 2009, and were diagnosed with ES-HCM and DCM Exclusion criteria: patients diagnosed with cardiac sarcoidosis or with significant CAD (≥50% DS) by ICA	Scanner: 1.5-T scanner Cardiac function sequence: Breath-hold cine magnetic resonance images were obtained in contiguous short-axis planes with the patient in a resting state. LGE sequence: inversion recovery prepared fast gradient-echo sequence Contrast agent: 0.2 mmol/kg Gd-DTPA-BMA Time delay: 15 minutes LV function: LV end-diastolic and end-systolic volumes, LVEF and LV mass were acquired from the 2-D FIESTA cine images in short-axis view. The values for LV volume and mass were indexed by dividing them with body surface area. LGE diagnosis: 2experienced cardiovascular radiologists interpreted the CMR images without knowledge of clinical findings. Regional analyses of	ICD implantation: Not described Outcomes: HR for likelihood of having: cardiac death SCD hospitalisation for HF in LGE+ patients compared with those that are LGE–

Study Country	Level of evidence Quality appraisal	Study population	Inclusion criteria / exclusion criteria	LGE-CMR	Intervention and outcomes
		19.0 months		LGE-CMR images were performed using the 17-segments model, and each LV segment was scored using a 5-point scoring system (0 = no LGE, 1 = 1–25% of transmural extent of LGE, 2 = 26–50%, 3 = 51–75%, 4 = 76–100%).	
Masci et al. (2012) Italy	Prospective cohort NHMRC level II SIGN: acceptable quality with a moderate risk of bias	N=125 NICM patients with or without a history of mild HF: n=50 (40%) LGE+ n=75 (60%) LGE– Patient characteristics: age = 59 ± 14 years; male = 66%; median duration of NICM: LGE– = 12 (IQR 4–60), LGE+ = 30 (IQR 9–96); LBBB = 34%; LVEF (CMR) = 26 ± 7%; NYHA class: I = 41%, II = 37%; medications: ACE inhibitor = 61%, ARB = 31%, β-blockers = 87%. Median follow-up: 14.2 (IQR 6.5–28.8) months	Inclusion criteria, NICM patients without (stage B of HF) or with a history of mild HF symptoms (stage C of HF, NYHA classes I–II), with evidence of LV systolic dysfunction at transthoracic ECG (LVEF <50%) and absence of CAD were prospectively enrolled between May 2004 and December 2008. Exclusion criteria: patients presenting with active myocarditis, congenital heart disease, HCM, infiltrative disease, or moderate-to-severe valvular heart disease	Scanner: 1.5-T scanner with a phased-array surface receiver coil Cardiac function sequence: Biventricular function was assessed by breath-hold steady-state free-precession cine imaging in cardiac short-axis, vertical and horizontal long-axis. LGE sequence: segmented inversion-recovery T1-weighted gradient-echo pulse sequence Contrast agent: 0.2 mmol/kg Gd-DTPA Time delay: 8–20 minutes LV function: LV and right ventricular volumes and ejection-fractions were determined using cine short-axis images, as well as LV mass. Volumes and LV mass were normalised to body surface area. LGE diagnosis: All CMR studies	ICD implantation: Not described Outcomes: HR for likelihood of having: cardiac death hospitalisation for HF in LGE+ patients compared with those that are LGE–

Study Country	Level of evidence Quality appraisal	Study population	Inclusion criteria / exclusion criteria	LGE-CMR	Intervention and outcomes
				were analysed by the consensus of 2 experienced operators, who were unaware of clinical and follow-up data. The presence of DE was visually determined on post-contrast images.	
Muller et al. (2013) Germany	Prospective cohort NHMRC level II SIGN: acceptable quality with a moderate risk of bias	N=185 patients who presented for evaluation of newly diagnosed NICM: n=94 (51%) LGE+ n=91 (49%) LGE– DCM = 55% Myocarditis = 35% HCM or hypertensive CM = 8% Storage disease = 2% Patient characteristics: age = 51.2 ± 15.9 years; male = 71%; QRS interval = 103 ± 23 milliseconds; LVEF (CMR) = 43.3 ± 16.0%; NYHA class ≥II = 62%; medications: ACE inhibitor = 81%, ARB = 14%, β-blockers = 89% Median follow-up: 21 months	Inclusion criteria: patients who presented for evaluation of newly diagnosed NICM and recent findings suggestive of cardiac structural damage (impaired global or regional LV function, LV enlargement, increase of cardiac enzymes, pericardial effusion or ECG abnormalities) Exclusion criteria: patients with history of MI or ischaemic scar on CMR as a sign of unrecognised myocardial damage due to CAD	Scanner: 1.5-T scanner Cardiac function sequence: breath-hold steady-state free-precession (SSFP) pulse sequence LGE sequence: 2D inversion-recovery segmented k-space gradient-echo sequence Contrast agent: 0.15 mmol/kg gadobutrol (Gadovist) Time delay: 10–15 minutes LV function: End-diastolic volumes (EDV) and end-systolic volumes (ESV) were used to determine LVEF (EDV – ESV/EDV x 100). LGE diagnosis: LGE image analysis was conducted by 2 experienced independent investigators who visually judged the occurrence (presence vs absence), localisation and pattern of LGE. Areas of LGE were	ICD implantation: Not described Outcomes: HR for likelihood of having: ICD implantation all-cause mortality cardiac death heart transplantation aborted SCD appropriate ICD discharge sustained VT hospitalisation for HF in LGE+ patients compared with those that are LGE–

Study Country	Level of evidence Quality appraisal	Study population	Inclusion criteria / exclusion criteria	LGE-CMR	Intervention and outcomes
		(at least 6 months)		allocated to the American Heart Association 17-segment model.	
Nabeta et al. (2014) Japan	Prospective cohort NHMRC level II SIGN: high quality with a low risk of bias	N=75 patients with newly diagnosed idiopathic DCM and an LVEF <45%: n=36 (48%) LGE+ n=39 (52%) LGE– Patient characteristics: age = 56 ± 13 years; male = 65%; QRS interval = 115 ± 26 milliseconds; LBBB = 13%; LVEF (Echo) = 30.2 ± 7.3%; NYHA class: I = 17%, II = 68%, III = 15%; medications: ACE inhibitor/ARB = 99%, β-blockers = 95% Follow-up: 1 year (at least 6 months)	Inclusion criteria: patients with newly diagnosed IDCM and an LVEF of <45% on baseline ECG who were referred to the hospital between January 2007 and June 2012 Exclusion criteria: presence of significant CAD, myocarditis, severe valvular heart disease and/or chronic renal failure (GFR <30 mL/min). Patients whose CMR images were of poor quality were also excluded. Patients who underwent mitral valvoplasty and/or left ventriculectomy during the follow-up period and those who were unable to be followed for >6 months were also excluded.	Scanner: 1.5-T scanner with a eight-channel phased-array coil Cardiac function sequence: Not done LGE sequence: segmented inversion recovery fast gradient-echo sequences Contrast agent: 0.2 mmol/kg Gd Time delay: 15–20 minutes LV function: Not done LGE diagnosis: The presence of LGE was determined by 2 experienced and independent observers blinded to patient outcome.	ICD implantation: Not described Outcomes: HR for likelihood of having ICD/CRT-D implantation major VA hospitalisation for HF in LGE+ patients compared with those that are LGE–
Neilan et al. (2013) USA	Prospective cohort NHMRC level II	N=162 consecutive patients with NIDCM who underwent an LGE-CMR study followed by an ICD insertion: n=81 (50%) LGE+	Inclusion criteria: consecutive patients with NIDCM who underwent an LGE-CMR study followed by an ICD insertion between	Scanner: 1.5-T or 3-T scanner Cardiac function sequence: Cine steady-state free-precession imaging LGE sequence: T_2-weighted	ICD implantation: Not described Outcomes: HR for likelihood of having: cardiac death appropriate ICD therapy

Study Country	Level of evidence Quality appraisal	Study population	Inclusion criteria / exclusion criteria	LGE-CMR	Intervention and outcomes
	SIGN: high quality with a low risk of bias	n=81 (50%) LGE– Patient characteristics: age = 55 ± 14 years; male = 65%; HF duration = 13 (IQR 9–16); family history of DCM = 8%; CRT implantation = 24%; QRS interval = 117 ± 30 milliseconds; LVEF (Echo) = 26 ± 8%; LVEF (CMR) = 28 ± 9); NYHA class: II = 56%, class III = 44%; medications: ACE inhibitor/ARB = 95%, β-blockers = 98% Mean follow-up: 29 ± 18 months	2003 and 2011 Exclusion criteria: Significant CAD by both clinical history and cardiac investigation, infiltrative CM based either on history or CMR findings and a prior indication for placement of an ICD (e.g. syncope, cardiac arrest, or sustained VAs)	inversion recovery prepared fast-spin echo sequence Contrast agent: 0.15 mmol/kg Gd-DTPA Time delay: 10–15 minutes LV function: Not done LGE diagnosis: LGE was interpreted as present or absent by the consensus of 2 CMR-trained physicians. The distribution of LGE was characterised as either mid-wall, epicardial, focal/involving the right ventricular insertion points, or diffuse.	SCD hospitalisation for HF in LGE+ patients compared with those that are LGE–
Perazzolo Marra et al. (2014) Italy	Prospective cohort NHMRC level II SIGN: high quality with a low	N=137 consecutive patients with unexplained LV dilatation and dysfunction diagnosed with NICM: n=76 (55%) LGE+ n=61 (45%) LGE– Patient characteristics: age = 47 (IQR 37–60) years;	Inclusion criteria: consecutive patients referred to the Heart Failure and Heart Transplantation Unit for unexplained LV dilatation and dysfunction who had an LVEF <50%, the absence of flow-limiting CAD (≥50% DS) by ICA, and the absence of either valvular or	Scanner: 1.5-T scanner with a phased-array cardiac coil Cardiac function sequence: Not done LGE sequence: 2D segmented fast low-angle shot inversion recovery sequence Contrast agent: 0.2 mmol/kg	ICD implantation: Not described Outcomes: HR for likelihood of having: SCA or appropriate ICD discharge hospitalisation for severe HF non–SCD in LGE+ patients compared with those

Study Country	Level of evidence Quality appraisal	Study population	Inclusion criteria / exclusion criteria	LGE-CMR	Intervention and outcomes
	risk of bias	male = 79%; LBBB = 33%; LVEF (Echo) = 33% (IQR 28–40); NYHA class: I = 24%, II = 35%, III = 38%, IV = 3%; medications: ACE inhibitor/ARB = 88%, β-blockers = 78% Median follow-up: 3 years (range 31 days to 9.6 years)	hypertensive heart disease and congenital heart abnormalities Exclusion criteria: recent onset of HF, diagnosis of HCM, restrictive CM, arrhythmogenic right ventricular CM, suspected infiltrative heart disease, or other specific CMs, haemodynamically unstable conditions, contraindication to CMR (claustrophobia, pacemaker, ICD, metallic clips, atrial fibrillation, severe obesity preventing the patient from entering the scanner bore, and pregnancy), and chronic renal failure with a GRF of <30 mL/min	gadobenate dimeglumine Time delay: 10 minutes LV function: Not done LGE diagnosis: The presence, location and extent of LGE were independently assessed by 2 experienced observers who were blinded to patient available diagnostic data and outcomes. The pattern of LGE distribution was characterised as either epicardial, mid-wall or patchy/junctional.	that are LGE–
Piers et al. (2015) The Netherlands	Prospective cohort NHMRC level II SIGN: high quality with a low risk of bias	N=87 patients with NIDCM and LVEF ≤35% undergoing ICD/CRT-D implantation: n=55 (63%) LGE+ n=32 (37%) LGE– N=64 primary prevention N=10 sustained monomorphic VT N=13 out-of-hospital cardiac	Inclusion criteria: all patients with NIDCM who underwent LGE-CMR before ICD implantation at Leiden University Medical Centre or Maastricht University Medical Centre between 2004 and 2012 Exclusion criteria: patients who had devices implanted at the Maastricht University	Scanner: 1.5-T scanner Cardiac function sequence: A standardised protocol was followed, including cine imaging in long-axis and short-axis views. LGE sequence: inversion-recovery 3-dimensional turbo-field echo sequence with parallel imaging. Contrast agent: 0.15 mmol/kg Gd	ICD implantation: ICDs were typically programmed to include 3 zones: monitor zone (ATP), fast VT zone (ATP and shock) and VF zone (ATP during charging, and shock). Outcomes: HR for likelihood of having: VAs in LGE+ patients compared with those

Study Country	Level of evidence Quality appraisal	Study population	Inclusion criteria / exclusion criteria	LGE-CMR	Intervention and outcomes
		arrest with VF N=46 had CRT-D Patient characteristics: age = 56 ± 13 years; male = 62%; history of AF = 16%; QRS interval = 132 ± 32 milliseconds; LVEF (CMR) = 29 ± 12%; NYHA class: I = 32%, II = 37%, III–IV = 31% Median follow-up: 45 months (IQR 23–67)	Medical Centre but were followed at another centre; patients with CAD, sarcoidosis, amyloidosis or subendocardial LGE in a coronary artery perfusion territory	(Magnevist) Time delay: 15 minutes LV function: The LV and RV end-diastolic and end-systolic endocardial contours were traced on cine images to calculate LV mass, end-diastolic and end-systolic volumes, and LVEF. LV volumes and mass were normalised to body surface area. LGE diagnosis: Myocardial scar was assessed while the observer was blinded to available diagnostic data and outcome, and was considered to be present only if LGE was visible in 2 orthogonal views. LGE was defined by signal intensity ≥35% of maximal myocardial signal intensity.	that are LGE–
Shimizu et al. (2010) Japan	Prospective cohort NHMRC level II SIGN: high quality with a low risk of bias	N=60 consecutively enrolled DCM patients who underwent cardiac assessment: n=11 (18%) ≥10% LGE n=49 (82%) <10% LGE Patient characteristics: age = 59 ± 12 years; male = 77%; disease duration = 2.3 ±	Inclusion criteria: consecutively enrolled DCM patients who underwent cardiac assessment in the cardiology department between February 2005 and March 2006 Exclusion criteria: any of the standard contraindications for CMR, such as the presence of a	Scanner: 1.5-T scanner with a cardiac-dedicated phased-array coil Cardiac function sequence: CMR studies were ECG-triggered by standard software and images were acquired during diastole to minimise artefacts due to cardiac motion. LGE sequence: gradient-echo (segmented True FISP with	ICD implantation: Not described Outcomes: HR for likelihood of having a: cardiac death hospitalisation for HF in LGE+ patients compared with those that are LGE–

Study Country	Level of evidence Quality appraisal	Study population	Inclusion criteria / exclusion criteria	LGE-CMR	Intervention and outcomes
		4.2 years; LVEF (Echo) = 30 ± 9%; LVEF (CMR) = 23 ± 10; medications: ACE inhibitor/ARB = 43%, β-blockers = 27% Mean follow up: 406 ± 241 days for LGE+ and 425 ± 174 days for LGE– patients	pacemaker, implantable defibrillator and intracerebral aneurysm clips	inversion recovery pulse) sequence Contrast agent: 0.2 mmol/kg Gd-DTPA Time delay: 10 minutes LV function: Not reported LGE diagnosis: All areas of LGE were independently traced by 2 cardiologists who were blinded to the clinical history of the patients. Patients were classified as having advanced LGE when %LGE was ≥10%, and non-advanced LGE when %LGE was <10%.	
Wang et al. (2015) China	Prospective cohort NHMRC level II SIGN: acceptable quality with a moderate risk of bias	N=63 consecutive patients diagnosed with DCM: n=31 (49%) LGE+ n=32 (51%) LGE– Patient characteristics: age = 53.9 ± 11.5 years; male = 70%; history of VF or sustained VT = 5%; history of AF = 25%; LBBB = 17%; LVEF (CMR) = 24.4 ± 8.5%;	Inclusion criteria: consecutive patients diagnosed with DCM from October 2009 to April 2013 Exclusion criteria: patients with severe valvular disease, active myocarditis, hypertensive heart disease, tachycardia-induced CM, arrhythmogenic RV CM, infiltrative CM, HCM, diabetes mellitus, alcohol abuse, persistent AF, metal fragments in the body, implanted ferromagnetic devices or otherwise	Scanner: 1.5-T scanner Cardiac function sequence: Breath-hold retrospective ECG-gated cine true-FISP (fast imaging with steady-state precession) sequence to acquire contiguous short-axis images. LGE sequence: Not reported Contrast agent: Not reported Time delay: Not reported LV function: The LVEF and RVEF were calculated using Simpson's rule.	ICD implantation: Not described Outcomes: HR for likelihood of having a: cardiac death (HF) cardiac transplantation in LGE+ patients compared with those that are LGE–

Study Country	Level of evidence Quality appraisal	Study population	Inclusion criteria / exclusion criteria	LGE-CMR	Intervention and outcomes
		NYHA class: I = 19%, III = 48%, IV = 33%; medications: ACE inhibitor/ARB = 48%, β-blockers = 57% Median follow up: 804 (IQR 381–1,035) days	unsuitable to undergo CMR, chronic lung disease, previous pulmonary embolism or idiopathic pulmonary hypertension	LGE diagnosis: The presence of LGE in mid-wall myocardium of LV and septum was visually assessed.	
Wu, KC et al. (2008) USA	Prospective cohort NHMRC level II SIGN: high quality with a low risk of bias	N=65 consecutive non-selected patients with NICM and LVEF ≤35% undergoing ICD implantation for primary prevention of SCD: n=27 (42%) LGE+ n=38 (58%) LGE– Patient characteristics: age = 55 ± 12 years; male = 65%; duration of CM = 4.0 ± 4.1 years; LVEF (CMR) = 24 ± 9.5%; NYHA class: I = 15%, II = 48%, III = 40%; medications: ACE inhibitor/ARB = 87%, β-blockers = 95% Median follow-up: 17 months	Inclusion criteria: consecutive non-selected patients with NICM and LVEF ≤35% undergoing ICD implantation for primary prevention of SCD between April 2004 and April 2007 Exclusion criteria: patients with prior arrhythmic indications for ICD placement (such as a history of syncope, cardiac arrest or VAs); NYHA class IV; and acute myocarditis, congenital heart disease, HCM or infiltrative heart disease. Renal insufficiency with GFR <30 mL/min was added as an exclusion in July 2006.	Scanner: 1.5-T scanner Cardiac function sequence: Cine images were acquired with a steady-state free-precession pulse sequence in long-axis planes and contiguous 8-mm short-axis slices. LGE sequence: inversion-recovery fast gradient-echo pulse sequences Contrast agent: 0.2 mmol/kg gadodiamide (Omniscan) Time delay: 15–30 minutes LV function: LVEF, volumes and mass were quantified from the cine images by standard methods. LV volumes and mass were normalised to body surface area. LGE diagnosis: Two observers blinded to the clinical outcome independently determined the dichotomous presence or absence	ICD implantation: Not described Outcomes: HR for likelihood of having a: cardiac death SCD appropriate ICD discharge hospitalisation for CHF in LGE+ patients compared with those that are LGE–

Study Country	Level of evidence Quality appraisal	Study population	Inclusion criteria / exclusion criteria	LGE-CMR	Intervention and outcomes
				of LGE.	
Wu, KC et al. (2012) USA	Prospective cohort NHMRC level II SIGN: high quality with a low risk of bias	N=235 patients with chronic ICM and NIDCM with an LVEF of ≤35% undergoing clinically indicated primary prevention ICD implantation: n=171 (73%) LGE+ n=64 (27%) LGE– N=137 patients with ICM: n=131 (95%) LGE+ n=6 (5%) LGE– Patient characteristics: age = 61 ± 11 years; male = 85%; median time since diagnosis = 4.4 (IQR 0.9–10.7); QRS interval = 117 ± 27 milliseconds; LVEF (non-CMR) = 25 ± 7%; LVEF (CMR) = 28 ± 8%; history of AF = 20%; LBBB = 16%; biventricular ICD = 24%; NYHA class: I = 31%, II = 37%, III = 31%; medications: ACE	**Inclusion criteria:** patients were from the CMR imaging arm of the PROSE-ICD (Prospective Observational Study of Implantable Cardioverter Defibrillators), which enrolled patients receiving ICD therapy for primary prevention of SCD between November 2003 and December 2010 **Exclusion criteria:** other indications for ICD placement (e.g. sustained VA, cardiac arrest, syncope); contraindications to CMR (e.g. existing cardiac device); NYHA functional class IV; acute myocarditis or acute sarcoidosis or infiltrative disorders such as amyloidosis, or hemochromatosis, congenital heart disease, or HCM; or renal insufficiency	**Scanner:** 1.5-T whole-body scanner **Cardiac function sequence:** Short and long-axis cine images were acquired with a steady-state free precession sequence. **LGE sequence:** inversion-recovery fast gradient-echo sequence **Contrast agent:** 0.15-0.2 mmol/kg of gadodiamide (Omniscan) or gadopentetate dimeglumine (Magnevist) **Time delay:** 15 minutes **LV function:** LVEF, volumes, and mass were quantified by standard methods. **LGE diagnosis:** Two observers blinded to clinical outcome determined the dichotomous presence or absence of LGE	**ICD implantation:** Not described **Outcomes:** HR for likelihood of having a: SCD or appropriate ICD discharge; Appropriate ICD discharge; Inappropriate ICD discharge Hospitalisation for HF; in LGE+ patients compared with those that are LGE–

Study Country	Level of evidence Quality appraisal	Study population	Inclusion criteria / exclusion criteria	LGE-CMR	Intervention and outcomes
		inhibitor/ARB = 88%, β-blockers = 94% N=98 patients with NIDCM: n=40 (41%) LGE+ n=58 (59%) LGE– Patient characteristics: age = 52 ± 12 years; male = 63%; median time since diagnosis = 1.05 (IQR 0.3–5.4); QRS interval = 123 ± 33 milliseconds; LVEF (non-CMR) = 21 ± 7%; LVEF (CMR) = 25 ± 10%; history of AF = 14%; LBBB = 33%; biventricular ICD = 40%; NYHA class: I = 14%, II = 46%, III = 40%; medications: ACE inhibitor/ARB = 89%, β-blockers = 93% Median follow-up: 3.6 years			

[a] Quality appraisal was undertaken using the SIGN checklist for cohort studies (SIGN 2014).

ACE = angiotensin converting enzyme; AF = atrial fibrillation; ARB = angiotensin II receptor blocker; ATP = anti-tachycardia pacing; CAD = coronary artery disease; CI =

confidence interval; CHF = congestive heart failure; CM = cardiomyopathy; CMR = cardiac magnetic resonance (imaging); CRT-D = cardiac resynchronisation therapy device with defibrillation capabilities; CRT-P = cardiac resynchronisation therapy with pacing; DCM = dilated cardiomyopathy; DE = delayed enhancement; DS = diameter stenosis; DTPA = diethylenetriamine pentaacetic acid; ECG = electrocardiogram; Echo = echocardiography; EPS = electrophysiology study; ES-HCM = end-stage hypertrophic cardiomyopathy; Gd = gadolinium; GFR = glomerular filtration rate; HCM = hypertrophic cardiomyopathy; HF = heart failure; HR = hazard ratio; ICA = invasive coronary angiography; ICD = implantable cardioverter defibrillator; ICM = ischaemic cardiomyopathy; IQR = interquartile range; LBBB = left bundle branch block; LGE = late gadolinium enhancement; LV = left ventricular; LVEF = left ventricular ejection fraction; MACE = major adverse cardiac events; MI = myocardial infarction; NHMRC = National Health and Medical Research Council; NICM = non-ischaemic cardiomyopathy; NIDCM = non-ischaemic dilated cardiomyopathy; NSVT = non-sustained ventricular tachycardia; NYHA = New York Heart Association; RBBB = right bundle branch block; RV = right ventricular; SCA = sudden cardiac arrest; SCD = sudden cardiac death; SD = standard deviation; SIGN = Scottish Intercollegiate Guidelines Network quality assessment tool; VA = ventricular arrhythmia; VF = ventricular fibrillation; VT = ventricular tachycardia

Table 79 Study profiles of included comparative prognostic studies

Study Country	Level of evidence Quality appraisal	Study population	Inclusion criteria / exclusion criteria and outcome	LGE-CMR	Comparator
Yokokawa et al. (2009) Japan	Retrospective cohort NHMRC level III-3 SIGN: unacceptable quality with a high risk of bias	N=24 consecutive patients (6 women) admitted for implantation of CRT systems N=17 patients with DCM Patient characteristics: age = 68 ± 9 years; male = 71%; LVEF (SPECT) = 28 ± 14%; NYHA class: II = 12%, III = 65%, IV = 23%; medications: ACE inhibitor/ARB = 47%, β-blockers = 76% N=7 patients with ICM Patient characteristics: age = 63 ± 5 years; male = 86%; LVEF (SPECT) = 25 ±	Inclusion criteria: consecutive patients admitted for implantation of CRT systems between July 2006 and November 2007 Exclusion criteria: not reported Outcome: Response to CRT after 6 months follow-up, defined as: 1) having a ≥5% increase in LVEF and/or a ≥15% decrease in LVEDV 2) having a ≥1 point decrease in NYHA functional class; and 3) having had no hospitalisations for management of decompensated HF during	Scanner: 1.5-T or 3-T scanner equipped with a Nova gradient, and a 5-element cardiac synergy coil Cardiac function sequence: not done LGE sequence: inversion recovery gradient ECG sequence Contrast agent: 0.15 mmol/kg Gd-DTPA Time delay: 10–15 minutes LV function: not done LGE diagnosis: Contrast-enhancement images were analysed by a computer-assisted, semi-automatic technique to measure the LGE areas, and transmural scar scores were assigned according to the 17-segment	MIBI SPECT: MIBI (720 MBq) was injected intravenously, and images were acquired in an upright position 30 minutes later. Scar diagnosis: The SPECT images were divided into 17 segments. The regional tracer uptake was scored semi-quantitatively, and each segment was assigned a score from 0 to 4 (0 = normal uptake, 1 = mildly reduced uptake, 2 = moderately reduced uptake, 3 = severely reduced uptake, and 4 = defect. The scar identified by SPECT was defined as a segment with reduced tracer uptake on the images acquired at rest.

Study Country	Level of evidence Quality appraisal	Study population	Inclusion criteria / exclusion criteria and outcome	LGE-CMR	Comparator
		7%; NYHA class: II = 4%, III = 57%, IV = 29%; medications: ACE inhibitor/ARB = 43%, β-blockers = 86%	follow-up	model.	
Yoshida, Ishibashi-Ueda, et al. (2013) Japan	Prospective cohort NHMRC level II SIGN: acceptable quality with a moderate risk of bias	N=50 consecutive patients with DCM admitted for treatment of decompensated HF were assessed by MIBI-BMIPP dual SPECT and CMR Patient characteristics: age = 57.0 ± 12.3 years; male = 72%; duration of HF = 12.1 ± 23.2 months; LVEF (Echo) = 22.6 ± 8.8%; NYHA class: II = 66%, III = 28%, IV = 6%; medications: ACE inhibitor/ARB = 96%, β-blockers = 90% LGE+ = 42% (21/50) SPECT mismatch = 40% (20/50) LGE+ and SPECT mismatch = 16% (8/50) Median follow-up:	Inclusion criteria: consecutive patients with DCM admitted for treatment of decompensated HF Exclusion criteria: patients with possible myocarditis and typical clinical features such as signs of progressive viral infection or myocardial oedema Outcome: HR for likelihood of having a cardiac event if fibrosis is diagnosed by LGE-CMR compared with SPECT To determine agreement regarding the regional distribution of a mismatch between SPECT and LGE segments of CMR, the summed segments with mismatches and LGE in each myocardial area were analysed.	Scanner: 1.5-T or 3-T scanner Cardiac function sequence: A steady-state free-precession sequence was applied for cine CMR. LGE sequence: steady-state free precession sequence Contrast agent: 0.15 mmol/kg Gd hydrate (Omniscan) Time delay: 10 minutes LV function: LV end-diastolic volume, LVEF and LV mass were acquired from 2D cine images in the short-axis view. LGE diagnosis: 2 other experienced independent observers who were blinded to patient outcomes evaluated the CMR images. The extent of LGE in each segment was visually classified as scores from 0 to 6 as follows: 0 = none; 1, 2, 3 and 4 = endocardial distribution with transmural extent <25%, 25–49%, 50–74% and ≥75%,	MIBI-BMIPP dual SPECT: Patients at rest were simultaneously injected with MIBI (555 MBq) and BMIPP (148 MBq) intravenously and then assessed by dual-radionuclide SPECT imaging 40–60 minutes later. Mismatch diagnosis: 2 experienced independent observers who were blinded to patient outcomes evaluated the myocardial SPECT images. The 17 LV segments were semi-quantified according to a 5-level fixed defect scale of 0–4 representing, respectively, normal, mildly, moderately and severely reduced uptake. The TDS was defined as the sum of the defect scores for each ventricular segment. A perfusion-metabolism mismatch was defined as segments in which BMIPP and MIBI scores differed.

Study Country	Level of evidence Quality appraisal	Study population	Inclusion criteria / exclusion criteria and outcome	LGE-CMR	Comparator
		33 months		respectively; 5 = patchy distribution and 6 = mid-wall linear distribution (both reflected a non-ischaemic morphology	

[a] Quality appraisal was undertaken using the SIGN checklist for cohort studies (SIGN 2014).

ACE = angiotensin converting enzyme; ARB = angiotensin II receptor blocker; BMIPP = 123I–15-(p-iodophenyl)-3(R,S)-methylpentadecanoic acid; CMR = cardiac magnetic resonance (imaging); CRT = cardiac resynchronisation therapy; DCM = dilated cardiomyopathy; DTPA = diethylenetriamine pentaacetic acid; ECG = electrocardiogram; Echo = echocardiography; Gd = gadolinium; HF = heart failure; ICM = ischaemic cardiomyopathy; LGE = late gadolinium enhancement; LV = left ventricular; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; MIBI = ^{99}mTc-2-methoxy isobutyl isonitrile; NHMRC = National Health and Medical Research Council; NYHA = New York Heart Association; SIGN = Scottish Intercollegiate Guidelines Network quality assessment tool; SPECT = single-photon-emission computerised tomography

Table 80 Study profiles of included prognostic cohort studies in children

Study Country	Level of evidence Quality appraisal	Study population	Inclusion criteria / exclusion criteria	LGE-CMR	Intervention and outcomes
Raimondi et al. (2015) France	Prospective cohort NHMRC level II SIGN: acceptable quality with a moderate risk of bias	N=55 children who had developed for 3 months or less symptoms consistent with HF related to DCM of unknown origin: n=33 (50%) CMR+ n=33 (50%) CMR– Patient characteristics: age = 2.2 years (range 1 day to 16 years);	Inclusion criteria: Over a period of 4 years, all children <18 years of age who had developed for 3 months or less symptoms consistent with HF related to DCM of unknown origin Exclusion criteria: ischaemic DCM, arrhythmogenic RV dysplasia, any previous cardiac surgical procedures, association with a congenital heart defect, treatment with chemotherapeutic agents or pharmacological cardiotoxicity, endocrine	Scanner: 1.5-T scanner with a 32-channel, phased-array cardiac coil Cine-CMR: CMR parameters of the LV were obtained by acquiring short-axis view, 4-chamber view, and 2-chamber view as steady-state free precession (FIESTA) images. Contrast agent: 0.2 mmol/kg Gd chelate (Dotarem) Early GE sequence: enhanced cine-SSFP and black-blood-prepared double inversion recovery fast spin-echo images with T1 weighting	Initial management: Mechanical circulatory support by ECMO (median duration 13 days, range 2–17 days) was required in 4 patients of the CMR+ group. Patients with severe HF received either intravenous inotropic support when necessary or intravenous diuretics. Immune globulin therapy, steroids or immunosuppressive treatment was given on a case-by-case decision basis. After the acute phase of the disease, patients received ACE inhibitors in combination with β-blockers. Oral diuretic therapy with furosemide or spironolactone was pursued after discharge only in children with evidence of congestive HF. Anticoagulation with warfarin was given to

Study Country	Level of evidence Quality appraisal	Study population	Inclusion criteria / exclusion criteria	LGE-CMR	Intervention and outcomes
		male = 50%; overt HF = 52%; fever = 23%; chest pain = 26%; ECG anomalies = 56%; elevated troponin level = 53%; LVEF (CMR) = 30% (10–49); pericardial effusion = 12% Mean follow-up: 24 months (range 6–55)	disorders known to cause myocardial damage, chronic cardiac arrhythmias, immunologic diseases (maternal lupus or Sjogren syndrome), and any vasculitis, inborn errors of metabolism associated with LV dysfunction, known neuromuscular disorders, and children with known familial history of DCM or in whom existence of a DCM in another family member could be identified	Time delay: 10 minutes LGE sequence: inversion recovery gradient-echo pulse sequence LV function: LV volume and LVEF were measured from short-axis images. DCM diagnosis: Criteria used to diagnose myocardial inflammation were: 1) evidence of regional or global myocardial oedema 2) evidence of myocardial hyperaemia and capillary leak with EGE 3) evidence of myocardial necrosis and fibrosis (visual assessment) with non-ischaemic regional distribution at LGE. Myocardial inflammation was diagnosed when at least two criteria were present.	children with LVEF ≤30% at hospital discharge. Outcomes: OR for predicting LV functional recovery for: presence of myocardial inflammation, and elevated troponin levels at baseline

[a] Quality appraisal was undertaken using the SIGN checklist for cohort studies (SIGN 2014).

ACE = angiotensin converting enzyme; CMR = cardiac magnetic resonance (imaging); DCM = dilated cardiomyopathy; ECG = electrocardiogram; ECMO = extracorporeal membrane oxygenation; EGE = early gadolinium enhancement; Gd = gadolinium; HF = heart failure; LGE = late gadolinium enhancement; LV = left ventricular; LVEF = left ventricular ejection fraction; NHMRC = National Health and Medical Research Council; OR = odds ratio; SIGN = Scottish Intercollegiate Guidelines Network quality assessment tool

Table 81 Study profiles for studies reporting change in management

Study	Level Quality appraisal	Study population	Inclusion criteria / Exclusion criteria / Objective	Study	Outcomes assessed for change in management
Bruder et al. (2013) Europe (57 centres in 15 countries) Prospective multicentre (non-comparative) cohort study	Level IV: Quality: good Risk of bias: low	3,511 patients undergoing CMR for myocarditis/CM (31.9% of total who underwent CMR) Patient characteristics: age (years) <44 58.2%, 45–59 32.5%, 60–74 21.2%, >75 14.5%	Inclusion criteria: Consecutive patients undergoing CMR according to the ACCF/ACR/SCCT/SCMR/ASNC/NASCI/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 in Europe	CMR imaging 88% of patients received a Gd-based contrast agent (1.28 mmol/kg bodyweight)	Myocarditis/CM indication: Total (out of 11,040): Completely new diagnoses Therapeutic consequences: - changes in medication - invasive procedure - hospital discharge - hospital admission Impact on management (new diagnosis and/or therapeutic procedure) Non-invasive imaging ordered after CMR: - transthoracic Echo - transoesophageal Echo - computed tomography Imaging failure rate Note that results are not separated for myocarditis and other CMs.
Taylor, AJ et al. (2013) Australia Prospective observational study, single centre	Level IV Quality: Good Risk of bias: low	Total number of scans = 732 Number of CM scans = 488 (67%) For CM: Patient characteristics:	Inclusion criteria: All patients referred to the Alfred Hospital, Melbourne, Australia for clinical CMR between 1 July 2007 and 30 June 2009, referred and funded [a] under 4 pre-specified clinical pathways: CM, viability, tumour/mass and ARVC	CMR imaging: Scanner 1.5-T, cardiac coil, electrocardiographic gating Data collection instrument: Questionnaire sent	Number of cardiac surgical interventions averted by CMR (defined as the number of planned interventions who at 6 months post CMR did not undergo, and had no plan to undergo, the intervention that was planned prior to CMR scanning) Change to device plan

Study	Level Quality appraisal	Study population	Inclusion criteria / Exclusion criteria / Objective	Study	Outcomes assessed for change in management
		age 49.4 ± 16.3 years male = 322 (66%) median NYHA Class (IQR) = 2 (1–2)	Exclusion criteria: Patients who were scanned for research purposes or non-funded indications	6 months post CMR procedure	Change to surgical plan Note: No specific results for CM; however, the CM population is 67% (449/666) of the total, so could the results be applied to the CM population?
Abassi et al. (2013) USA Prospective observational study, single centre	Level IV Quality: Good Risk of bias: low	N=150 patients with HF referred for CMR over a 6-month period Patient characteristics: age (mean) 54 years male 57% LVEF mean 38% (± 11%)	Inclusion criteria: LVEF ≤50% by prior imaging studies NYHA class: I = 26%; II = 49%; III = 49%; IV = 1% Exclusion criteria: NR	CMR imaging: (using SCMR standardised protocols) Late-Gd enhancement Image analysis was performed by blinded physician.	Significant clinical impact (defined as an entirely 'new diagnosis' and/or a 'change in management' Change in patient management New diagnoses
Broch et al. (2015) Norway Case series	Level-III-3 Quality: Moderate: Risk of bias: low	N=102 consecutive patients with a diagnosis of idiopathic DCM Patient characteristics: age (mean ± SD) 51 ± 14 years male 73 (74%) NYHA class (n): I = 15; II = 61; III =	Inclusion criteria: Suspected DCM, LV end diastolic internal diameter ≥6.5 cm and ejection fraction ≤40% Exclusion criteria: Ischaemic, hypertensive and valvular heart disease, patients with a known or suspected cause of CM including myocarditis, patients with an implanted cardiac device or severe concomitant disease Objective	CMR LGE (unless contraindicated) Right-sided heart catheterisation EMB Genetic testing Genomic analysis for viral detection Conventional and	Diagnostic yield Therapeutic consequences

Study	Level Quality appraisal	Study population	Inclusion criteria / Exclusion criteria / Objective	Study	Outcomes assessed for change in management
		20; IV = 6 N=88 patients underwent CMR N=81 patients underwent CMR + LGE	To assess the value of diagnostic testing beyond physical examination, blood tests, Echo and ICA for idiopathic CM	electron microscopy Exercise and peak oxygen testing Ambulatory 24-hour ECG	

[a] CMR scanning was funded under a New Technology Grant from the Victorian Policy Advisory Committee on Clinical Practice and Technology under four pre-specified clinical pathways: CM, viability, tumour/mass and ARVC.

ARVC = arrythmogenic right ventricular cardiomyopathy; CM = cardiomyopathy; CMR = cardiac magnetic resonance (imaging); DCM = dilated cardiomyopathy; ECG = electrocardiogram; Echo = echocardiography; EMB = endomyocardial biopsy; Gd = gadolinium; HF = heart failure; ICA = invasive coronary angiography; LGE = late gadolinium enhancement; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; IQR inter quartile range; N = number; NR = not reported

Table 82 Study profiles of included HTAs comparing ICD with OMT in DCM (therapeutic effectiveness)

Study Country	Level of evidence Quality appraisal	Aim of the SR Study population	Inclusion criteria / exclusion criteria	Outcomes assessed
Colquitt et al. (2014) UK	NHMRC Level I AMSTAR: 73% (8/11) Good quality	To assess the clinical effectiveness and cost-effectiveness of: ICDs in addition to OPT for people who are at increased risk of SCD as a result of VAs despite receiving OPT CRT-P or CRT-D in addition to OPT for people with HF as a result of LVSD and cardiac dyssynchrony despite receiving OPT CRT-D in addition to OPT for people with both conditions	Search period: From inception to November 2012 Databases searched: MEDLINE, EMBASE and The Cochrane Library. Bibliographies of included articles and manufacturers' submissions to NICE were searched, and experts in the field were asked to identify additional published and unpublished references. Inclusion criteria: English-language RCTs that included patients at increased risk of SCD as a result of VAs or with HF as a result of LVSD and cardiac dyssynchrony or both, comparing ICD/CRT with OPT and reporting on health outcomes Exclusion criteria: Studies not in English, abstracts or session presentations Number of included studies: 26 RCTs reported in 78 publications 3 RCTs included patients with NIDCM	All-cause mortality Adverse effects of treatment HRQoL Symptoms and complications related to tachyarrhythmias and/or HF HF hospitalisations Change in NYHA class Change in LVEF

Study Country	Level of evidence Quality appraisal	Aim of the SR Study population	Inclusion criteria / exclusion criteria	Outcomes assessed
			1 RCT included patients with HF (non-ischaemic subgroup)	
Uhlig et al. (2013) USA	NHMRC Level I AMSTAR: 55% (6/11) Moderate quality	To evaluate the effectiveness of treatment with an ICD versus control treatment without an ICD for primary prevention of SCD Adult patients potentially eligible to receive an ICD for primary prevention of SCD	Search period: The first search was performed on November 2011, with a final update on December 2012. Databases searched: MEDLINE and the Cochrane Central Register of Controlled Trials Inclusion criteria: RCTs or nRCSs (with concurrent controls) were eligible if they provided relevant data directly comparing an ICD to no ICD, including antiarrhythmic drug treatment, or to different ICD interventions in patients potentially eligible to receive an ICD for primary prevention of SCD and if they included at least 10 participants per study group. Exclusion criteria: Not reported Number of included studies: 13 RCTs and 4 nRCSs 3 RCTs included patients with NIDCM 1 RCT and 1 nRCS included patients with HF (non-ischaemic subgroup) 1 nRCSs included patients with LVD (non-ischaemic subgroup)	All-cause mortality Arrhythmic deaths

CRT = cardiac resynchronisation therapy; CRT-P = cardiac resynchronisation therapy using biventricular pacing; CRT-D = cardiac resynchronisation therapy using biventricular pacing and defibrillation; DCM = dilated cardiomyopathy; HF = heart failure; HRQoL = health-related quality of life; HTA = health technology assessment; ICD = implantable cardioverter defibrillator; LVEF = left ventricular ejection fraction; LVSD = left ventricular systolic dysfunction; NHMRC = National Health and Medical Research Council; NIDCM = non-ischaemic dilated cardiomyopathy; NICE = National Institute for Health and Care Excellence; nRCS = non-randomised comparative studies; NYHA = New York Heart Association; OMT = optimal medical treatment; OPT = optimal pharmacological therapy; RCT = randomised controlled trial; SCD = sudden cardiac death; VA = ventricular arrhythmia

Table 83 Study profiles of included RCTs and nRCSs comparing ICD with optimal pharmaceutical treatment in DCM (therapeutic effectiveness)

Study, country Level of evidence Quality appraisal	Population	Inclusion criteria / exclusion criteria	Intervention	Control	Outcomes assessed

AMIOVIRT trial
 	
Strickberger et al. (2003)
 	
USA
 	
NHMRC Level II
 	
SIGN RCT: High quality with a low risk of bias
	N=103 patients with NIDCM, LVEF ≤0.35, and asymptomatic NSVT were randomised to receive either amiodarone or an ICD in addition to OPT.
	Intervention group:
	age = 58 ± 11 years;
	gender = 67% male;
	mean duration of NIDCM = 2.9 ± 4.0 years;
	LBBB = 42%;
	RBBB = 16%;
	mean LVEF = 22 ± 10%;
	NYHA class: I = 18%, II = 64%, III = 16%; CAD >70% = 5%
	Control group:
	age = 60 ± 12 years;
	gender = 74% male;
	mean duration of NIDCM = 3.5 ± 3.9 years;
	LBBB = 53%;
	RBBB = 8%;
		Inclusion criteria: NYHA class I to III, age ≥18 years, the absence of CAD
		Exclusion criteria: syncope, pregnancy, a contraindication to amiodarone or defibrillator therapy, or concomitant therapy with a Class I antiarrhythmic drug
		Mean follow-up: 2.0 ± 1.3 years
			N=51
			ICDs were inserted using conventional non-thoracotomy techniques. Defibrillator follow-up was performed every 4 months. This included evaluation of stored electrograms and sensing and pacing functions.
				N=50
				Amiodarone therapy was initiated at a dose of 800 mg/day. The amiodarone dosage was decreased to 400 mg/day after 7 days and to 300 mg/day after 1 year. Among the patients treated with amiodarone, thyroid function studies, aspartate and alanine transaminase plasma levels, and a chest X-ray were obtained at baseline and every 4 months during follow-up. Serum concentrations of amiodarone and desethylamiodarone were obtained at 4 months and 1 year after initiation of amiodarone therapy.
					All-cause mortality
					Cardiac death
					SCD
					Cardiac transplant
					HRQoL

Study, country Level of evidence Quality appraisal	Population	Inclusion criteria / exclusion criteria	Intervention	Control	Outcomes assessed
	mean LVEF = 23 ± 8%; NYHA class: I = 13%, II = 63%, III = 24%; CAD >70% = 11%				

CAT trial
 	
Bänsch et al. (2002)
 	
Germany
 	
NHMRC Level II
 	
SIGN RCT: Adequate quality with a moderate risk of bias
	N=104 patients with symptomatic DCM and LVEF ≤30%
	Intervention group:
	age = 52 ± 10 years;
	gender = 86% male;
	median duration of symptoms = 3.0 years;
	sinus rhythm = 80%;
	LBBB = 85%;
	RBBB = 8%;
	mean LVEF = 24 ± 6%;
	NYHA class: II = 67%, III = 33%;
	inducible VT = 6%;
	inducible VF = 16%
	Control group:
	age = 52 ± 12 years;
	gender = 74% male;
	median duration of symptoms =
		Inclusion criteria: symptomatic DCM for ≤9 months, LVEF ≤30%, NYHA class II or III, age 18–70 years, the absence of CAD
		Exclusion criteria: patients with CAD, a history of prior MI, myocarditis, excessive alcohol consumption, a history of symptomatic bradycardia, VT and VF, listed for heart transplantation at the time of presentation, significant valvular disease, and hypertrophic or restricted CM
		Median follow-up: 5.5 ± 2.2 years
			N=50
			Patients assigned to ICD therapy underwent implantation of a transvenous defibrillator system, under general anaesthesia. A defibrillation threshold of <20 J was mandatory. All devices were capable of storing episode data and electrograms. A VT zone with a detection rate of 200 bpm was programmed in all patients. All shocks were programmed to a maximum output of 30 J. The pacemaker rate was programmed to 40 bpm.
				N=54
				Treatment not described
					Primary endpoint:
					All-cause mortality at 1 year
					Secondary endpoint:
					All-cause mortality at 2 and 6 years
					Cardiac transplant at 1 year
					Survival of cardiac arrest
					Cardiac death at 1 year
					Sustained VT
					Sustained VA requiring treatment
					SCD at 1 year

Study, country Level of evidence Quality appraisal	Population	Inclusion criteria / exclusion criteria	Intervention	Control	Outcomes assessed
	2.5 years; sinus rhythm = 87%; LBBB = 82%; RBBB = 0%; mean LVEF = 25 ± 8%; NYHA class: II = 64%, III = 36%; inducible VT = 0%; inducible VF = 4%				

DEFINITE trial
 	
Kadish et al. (2004)
Ellenbogen et al. (2006)
Passman et al. (2007)
 	
USA
 	
NHMRC Level II
 	
SIGN RCT:
	N=458 patients with non-ischaemic DCM, LVEF <36%, and PVC or non-sustained VT
	Intervention group:
	age = 58.4 ± 13.8 years;
	gender = 72% male;
	mean duration of CHF = 2.39 years;
	history of AF = 23%;
	mean (range) LVEF = 21% (7–35);
	LBBB = 20%;
	RBBB = 4%;
	PVC only = 9%; non-sustained
		Inclusion criteria: aged between 21 and 80 years, LVEF <36%, the presence of ambient arrhythmias, a history of symptomatic HF and the presence of non-ischaemic DCM
		The absence of clinically significant CAD as the cause of the CM was confirmed by coronary angiography or a negative stress imaging study
		Exclusion criteria: patients with NYHA class IV congestive HF, not candidates for the implantation of a cardioverter–defibrillator, had undergone electrophysiological testing within the prior 3 months, had
			N=229
			Standard oral medical therapy plus an ICD
			Patients who were randomly assigned to the ICD group received a single-chamber device approved by the FDA. The ICDs were programmed to back up VVI pacing at a rate of 40 bpm and to detect VF at a rate of 180 bpm.
			All patients were evaluated at 3-month intervals.
				N=229
				Standard oral medical therapy for HF
				All patients received ACE inhibitors and β-blockers, digoxin and diuretics therapy as required.
				The use of amiodarone was discouraged unless patients had symptomatic AF or arrhythmias requiring treatment.
				According to pre-specified criteria, patients in the SMT group received an ICD if they had a cardiac arrest or an episode of unexplained syncope that was consistent with the occurrence of an arrhythmic
					Primary endpoint:
					All-cause mortality
					Secondary endpoint:
					SCD from arrhythmia
					Other outcomes:
					Cardiac death
					HF death
					Arrhythmia events
					HRQoL

Study, country Level of evidence Quality appraisal	Population	Inclusion criteria / exclusion criteria	Intervention	Control	Outcomes assessed

Adequate quality with a moderate risk of bias	VT only = 22%;
	PVC and non-sustained VT = 69%;
	NYHA class: I = 25%, II = 54%, III = 21%
	Control group:
	age = 58.1 ± 12.9 years;
	gender = 70% male;
	mean duration of CHF = 3.27 years;
	history of AF = 26%;
	mean (range) LVEF = 22% (10–35);
	LBBB = 20%;
	RBBB = 3%:
	PVC only = 10%; non-sustained VT only = 23%;
	PVC and non-sustained VT = 68%;
	NYHA class: I = 18%, II = 61%, III = 21%
		permanent pacemakers, cardiac transplantation appeared to be imminent, and familial CM was associated with SCD, acute myocarditis or congenital heart disease
		Median follow-up: 29.0 ± 14.4 months
				event.	

SCD-HeFT trial Bardy et al.	N=2,521 patients with mild to moderate chronic, stable CHF from ischaemic or non-ischaemic	Inclusion criteria: from 16 September 1997 to 18 July 2001 patients aged at least 18 years with NYHA class II or III chronic,	N=829 N=431 ischaemic CHF N=398 non-ischaemic	Control group 1 (amiodarone + OPT) N=845	The primary end point of the trial was death from

Study, country Level of evidence Quality appraisal	Population	Inclusion criteria / exclusion criteria	Intervention	Control	Outcomes assessed

(2005)
Packer et al. (2009)
 	
USA, Canada and New Zealand
 	
SIGN RCT: Adequate quality with a moderate risk of bias
	causes, and LVEF <36%
	Patients were randomised to receive either OPT plus amiodarone, a placebo or an ICD.
	Intervention group:
	median age = 60.1 (IQR 51.9–69.2) years;
	gender = 77% male;
	history of AF or flutter = 17%; non-sustained VF = 25%; syncope = 6%;
	median (range) LVEF = 24% (IQR 19–30);
	medications: ACE inhibitor = 83%, ARB = 14%, β-blocker = 69%
	Control group 1:
	median age = 60.4 (IQR 51.7–68.3) years;
	gender = 76% male;
	history of AF or flutter = 16%; non-sustained VF = 23%; syncope = 6%;
	median (range) LVEF = 25% (IQR 20–30);
		stable CHF due to ischaemic or non-ischaemic causes and a LVEF of no more than 35%
		Exclusion criteria: not reported
		Median follow-up: 45.5 months (range 24–72.6)
			CHF
			ICD therapy was intentionally selected to consist of shock-only, single-lead therapy. The goal was to treat only rapid, sustained VT or VF. The ICD was uniformly programmed to have a detection rate of 187 bpm or more. Because of the potential for antibradycardia pacing to worsen CHF, it was initiated only if the intrinsic rate decreased to less than 34 bpm, the lowest trigger limit possible. OPT was also provided.
				N=426 ischaemic CHF
				N=419 non-ischaemic CHF
				Control group 2 (placebo + OPT)
				N=847
				N=453 ischaemic CHF
				N=394 non-ischaemic CHF
				Placebo and amiodarone were administered in a double-blind fashion with the use of identical appearing 200-mg tablets
				The dose was based partly on weight. After a loading dose of 800 mg daily was given for 1 week and 400 mg daily for 3 weeks, patients weighing more than 90.9 kg received 400 mg daily, patients weighing 68.2 –90.9 kg received 300 mg daily, and patients weighing less than 68.2 kg received 200 mg daily. Physicians could lower the loading or maintenance dose if a patient had bradycardia.
					any cause.
					All deaths were classified as sudden or non-sudden, as cardiac or non-cardiac; and when the event was cardiac, as resulting from VT, bradyarrhythmia, HF or other cardiac causes

Study, country Level of evidence Quality appraisal	Population	Inclusion criteria / exclusion criteria	Intervention	Control	Outcomes assessed
	medications: ACE inhibitor = 87%, ARB = 14%, β-blocker = 69% Control group 2: median age = 59.7 (IQR 51.2–67.8) years; gender = 77% male; history of AF or flutter = 14%; non-sustained VF = 21%; syncope = 7%; median (range) LVEF = 25% (IQR 20–30); medications: ACE inhibitor = 85%, ARB = 16%, β-blocker = 69%				

Quality appraisal using the SIGN checklist for RCTs

ACE = angiotensin converting enzyme; AF = atrial fibrillation; ARB = angiotensin II receptor blocker; bpm = beats per minute; CAD = coronary artery disease; CHF = congestive heart failure; CM = cardiomyopathy; DCM = dilated cardiomyopathy; FDA = Food and Drug Administration; HRQoL = health-related quality of life; ICD = implantable cardioverter defibrillator; LBBB = left bundle branch block; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NHMRC = National Health and Medical Research Council; NIDCM = non-ischaemic dilated cardiomyopathy; nRCS = non-randomised comparative studies; NYHA = New York Heart Association; OPT = optimal pharmacological therapy; PVC = premature ventricular complexes; RBBB = right bundle branch block; RCT = randomised controlled trial; SCD = sudden cardiac death; SIGN = Scottish Intercollegiate Guidelines Network quality assessment tool; VA = ventricular arrhythmia; VF = ventricular fibrillation; VT = ventricular tachycardia

Table 84 Study profiles of included SRs comparing treatments in patients with myocarditis (therapeutic effectiveness)

Study Country	Level of evidence Quality appraisal	Aim of the SR Study population	Inclusion criteria / exclusion criteria	Outcomes assessed
Chen et al. (2013) China	NHMRC Level I AMSTAR: 100% (11/11) Good quality	To assess the clinical effectiveness of corticosteroids vs other treatments in patients with acute or chronic viral myocarditis (using different diagnostic criteria)	Search period: From inception to July 2012 Databases searched: The Cochrane Library, MEDLINE, OVID, EMBASE, BIOSIS Previews, Web of Science, LILACS, Chinese Biomed Database, CNKI and WANFANG Databases Inclusion criteria: RCTs of corticosteroids for viral myocarditis compared with no intervention, placebo, supportive therapy, antiviral agents therapy or conventional therapy, including trials of corticosteroids plus other treatment versus other treatment alone, irrespective of blinding, publication status or language Number of included studies: 8 RCTs	All-cause mortality Transplant-free survival Severe adverse effects of treatment Cardiac function (NYHA class, LVEF, LVEDD, LVSD) Cardiac enzyme Number and type of adverse events Length of hospital stay, quality of life and cost-effectiveness
Liu et al. (2013) China	NHMRC Level I AMSTAR: 82% (9/11) Good quality	To assess the clinical effectiveness of herbal medicines for acute and chronic viral myocarditis	Search period: Inception to January 2013 for English databases Inception to 2011 for Chinese databases Databases searched: CENTRAL on the Cochrane Library, MEDLINE, EMBASE, LILACS, The Chinese biomedical database, China National Knowledge Infrastructure, Chinese VIP information, Chinese Academic Conference Papers Database and Chinese Dissertation Database, AMED, the Cochrane Complementary Medicine Field Trials Register, and hand searching of Chinese journals and conference proceedings. Inclusion criteria: RCTs of herbal medicines (minimum of 7 days of treatment), compared with placebo, no intervention, or conventional intervention. Trials of herbal medicine plus a conventional drug versus the drug alone were also included. No language	Mortality Incidence of complications Cardiac function Biochemical response

Study Country	Level of evidence Quality appraisal	Aim of the SR Study population	Inclusion criteria / exclusion criteria	Outcomes assessed
			restriction. Number of included studies: 20 RCTs	
Robinson et al. (2015) United States of America	NHMRC Level I AMSTAR: 91% (10/11) Good quality	To assess the clinical effectiveness of intravenous immunoglobulin for presumed viral myocarditis in children and adults	Search Period: Inception to January 2014 Databases searched: CENTRAL, DARE, MEDLINE, EMBASE, CINAHL, EMSCO, Web of Science, LILACS, trial registries and conference proceedings. No language restrictions. Inclusion criteria: RCTs, where participants had a clinical diagnosis of acute myocarditis with LVEF≤45%, LVEDD >2 SDs below the mean, with cardiac symptoms <6 months; participants had no evidence of non-infectious or bacterial cardiac disease; and participants randomised to receive at least 1 g/kg of IVIG versus no IVIG or placebo. Excluded studies where onset of myocarditis was reported to occur <6 months post-partum. Number of included studies: 2 RCTs	Mortality Transplant-free survival Improvement in LVEF, LVEDD and LVSD Hospitalisation status Improvement in functional symptoms (NYHA class or other objective test)

AMSTAR = Assessing the Methodological Quality of Systematic Reviews; CENTRAL = Cochrane Central Register of Controlled Trials; CINAHL = Cumulative Index to Nursing and Allied Health Literature; DARE = Database of Abstracts of Reviews of Effects; IVIG = intravenous immunoglobulin; LILACS = Latin American and Caribbean Health Science Information Database; LVEF = left ventricular ejection fraction; LVEDD = left ventricular end-diastolic dimension; LVSD = left ventricular systolic dysfunction; NHMRC = National Health and Medical Research Council; NYHA = New York Heart Association; RCT = randomised controlled trial; SDs = standard deviations; SR = systematic review

Table 85 Study profiles of studies included for assessment of the impact of change in management (therapeutic effectiveness)

Study	Level and Quality appraisal	Study population	Inclusion criteria / Exclusion criteria / Objectives	Intervention	Comparator	Outcomes assessed for change in management
Taylor, AJ et al. (2013) Australia Prospective observational	Level III-2 Quality: Poor SIGN for cohort studies:2/12	Total number of scans = 732 Number of CM scans = 488 (67%) Patient	Inclusion criteria: All patients referred to the Alfred Hospital, Melbourne, Australia for clinical CMR between 1 July 2007 and 30 June 2009, referred and funded [a] under four pre-	Surgical or device plan that was amended or avoided through the use of CMR	Surgical or device plan that remained the same after CMR	Mortality NYHA class Rate of adverse events

Study	Level and Quality appraisal	Study population	Inclusion criteria / Exclusion criteria / Objectives	Intervention	Comparator	Outcomes assessed for change in management
study, single centre	High risk of bias	characteristics: For CM: age 49.4 ± 16.3 years male 322 (66%) median NYHA Class (IQR) 2 (1–2)	specified clinical pathways: CM, viability, tumour/mass and ARVC, who had a surgical or device plan prior to undergoing CMR Exclusion criteria: Patients who were scanned for research purposes or non-funded indications			
Broch et al. (2015) Norway Case reports	Quality: N/A Risk of bias: N/A	N=102 consecutive patients with a diagnosis of idiopathic DCM Patient characteristics: age (mean ± SD) 51 ± 14 years male 73 (74%) NYHA class (n) I 15; II 61; III 20; IV 6 N=88 patients underwent CMR N=81 patients underwent CMR + LGE	Inclusion criteria: Suspected DCM, LV end diastolic internal diameter ≥6.5 cm and ejection fraction ≤40% Exclusion criteria: Ischaemic, hypertensive and valvular heart disease, patients with a known or suspected cause of CM including myocarditis, patients with an implanted cardiac device or severe concomitant disease	Treatments received after having aetiology diagnosed by CMR	NA	Transplant-free survival after treatment for aetiologies detected by CMR

ARVC = arrhythmogenic right ventricular cardiomyopathy; CM = cardiomyopathy; CMR = cardiac magnetic resonance (imaging); DCM = dilated cardiomyopathy; IQR = interquartile range; LGE = late gadolinium enhancement; LV = left ventricular; NYHA = New York Heart Association; SD = standard deviation; SIGN = Scottish Intercollegiate Guidelines Network (quality assessment tool)

APPENDIX D 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 86 Evidence profile table for the accuracy of LGE-CMR compared with the reference standards for patients with HF symptoms (suspected of DCM) or DCM patients

Outcome	No. of participants, No. of studies Study design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Effect per 1,000 patients/year Study prevalence	QoE Importance
	LGE-CMR to diagnose DCM (ref. std. = available diagnostic data)						39.7%	
True positives False negatives	N=54 patients K=1 study Cross-sectional (cohort-type accuracy study)	Not serious (QUADAS-2 low risk of bias)	Not serious	Not serious	Not serious	None	330 (282–365) 67 (32–115)	High ⊕⊕⊕⊕
True negatives False positives	N=82 patients K=1 study Cross-sectional (cohort-type accuracy study)	Not serious (QUADAS-2 low risk of bias)	Not serious	Not serious	Not serious	None	561 (513–585) 42 (18–90)	High ⊕⊕⊕⊕
	LGE-CMR to diagnose non-ischaemic						63.1%	

Outcome	No. of participants, No. of studies Study design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Effect per 1,000 patients/year Study prevalence	QoE Importance
	DCM (ref. std. = ICA)							
True positives False negatives	N=238 patients K=6 studies cohort- & case-control-type studies	Not serious (QUADAS-2 low risk of bias)	Serious [a]	Not serious	Serious [b]	None	429–631 0–202	Low ⊕⊕⊙⊙
True negatives False positives	N=139 patients K=6 studies cohort- & case-control-type studies	Not serious (QUADAS-2 low risk of bias)	Serious [a]	Not serious	Serious [b]	None	262–369 0–107	Low ⊕⊕⊙⊙
	LGE-CMR to diagnose non-ischaemic DCM (ref. std. = available diagnostic data)						69.4%	
True positives False negatives	N=100 patients K=2 studies Cross-sectional (cohort-type accuracy study)	Not serious (QUADAS-2 low risk of bias)	Not serious	Not serious	Not serious	None	590–694 0–104	High ⊕⊕⊕⊕
True negatives False positives	N=44 patients K=2 studies Cross-sectional (cohort-type accuracy study)	Not serious (QUADAS-2 low risk of bias)	Not serious	Not serious	Not serious	None	251–269 37–55	High ⊕⊕⊕⊕
	LGE-CMR to diagnose inflammatory cause						45.4%	

Outcome	No. of participants, No. of studies Study design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Effect per 1,000 patients/year Study prevalence	QoE Importance
	(ref. std. = EMB)							
True positives False negatives	N=44 patients K=3 studies Cross-sectional (cohort-type accuracy study)	Not serious (QUADAS-2 low risk of bias)	Serious [a]	Not serious	Serious [b]	None	263–395 59–191	Low ⊕⊕⊙⊙
True negatives False positives	N=53 patients K=3 studies Cross-sectional (cohort-type accuracy study)	Not serious (QUADAS-2 low risk of bias)	Serious [a]	Not serious	Serious [b]	None	180–273 273–366	Low ⊕⊕⊙⊙

[a] An imperfect reference standard was used.
[b] The confidence intervals of the sensitivity and/or specificity were (too) large.
DCM = dilated cardiomyopathy; EMB = endomyocardial biopsy; HF = heart failure; ICA = invasive coronary angiography; LGE-CMR = late gadolinium enhancement cardiac magnetic resonance (imaging); QoE = quality of evidence

Table 87 Evidence profile for the SRs investigating the prognostic value of using LGE-CMR to predict health outcomes in patients with DCM

Outcome	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Summary of findings HR_p, OR_p (95%CI)	Quality of evidence	Importance
All-cause mortality	K=4 SRs (level I)	Not serious (1 low, 2 moderate, 1 high risk)	Not serious	Not serious	Serious (duplication of data)	Confounding would suggest spurious effect, while no effect was observed	OR_p = 3.43 (2.26, 5.22), k=5 HR_p = 2.48 [1.78, 3.44] k=3 OR_p = 3.27 (1.94, 5.51), k=3 OR_p = 1.71 (0.80, 3.68), k=4	Low ⊕⊕⊙⊙	Critical (9/9)
SCD	K=2 SRs (level I)	Not serious (1 low, 1	Not serious	Not serious	Very serious (duplicated data, wide	None	OR_p = 3.33 (1.80, 6.17), k=9 OR_p = 2.05 (0.56, 7.50), k=4	Low ⊕⊕⊙⊙	Critical (9/9)

Outcome	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Summary of findings HR_p, OR_p (95%CI)	Quality of evidence	Importance
		moderate risk)			95%CIs)				
Hospitalisation for HF	K=3 SRs (level I)	Not serious (1 low, 2 moderate risk)	Not serious	Not serious	Serious (duplicated data)	Confounding would suggest spurious effect, while no effect was observed	OR_p = 2.87 (1.53, 5.39), k=10 OR_p = 2.91 (1.16, 7.27), k=5 OR_p = 3.91 (1.99, 7.69), k=5	Low ⊕⊕⊙⊙	Important (4/9)
Major arrhythmic events	K=3 SRs (level I)	Not serious (1 low, 1 moderate, 1 high risk)	Not serious	Not serious	Serious (duplicated data)	Confounding would suggest spurious effect, while no effect was observed	OR_p = 4.19 (2.92, 6.02), k=12 HR_p = 4.98 [3.21, 7.73], k=8 ORp = 5.32 (3.45, 8.20), k=7	Low ⊕⊕⊙⊙	Critical (7/9)

CI = confidence interval; CMR = cardiac magnetic resonance (imaging); DCM = dilated cardiomyopathy; HF = heart failure; HR_p = pooled hazard ratio; LGE = late gadolinium enhancement; OR_p = pooled odds ratio; SCD = sudden cardiac death; SR = systematic review

Table 88 Evidence profile for the prognostic value of using LGE-CMR to predict health outcomes in patients with DCM

Outcome	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Summary of findings RR (95%CI)	Quality of evidence	Importance
All-cause mortality	K=6 prospective cohort (level II) K=3 retrospective cohort (level III-3)	Not serious (2/9 high risk)	Not serious (moderate heterogeneity; I^2 = 46.5%)	Not serious	Not serious	Publication bias strongly suspected (no studies in lower left of funnel plot)	110/647 (17%) of LGE+ had event 91/989 (9.2%) of LGE– had event RR = 2.47 (1.63, 3.74), k=9 RR = 3.23 (1.57, 6.65), k=4 best	Moderate ⊕⊕⊕⊙	Critical (9/9)
Cardiac deaths	K=11 prospective cohort (level II) K=2 retrospective cohort (level III-3)	Not serious (3/13 high risk)	Not serious (moderate heterogeneity; I^2 = 32.6%)	Not serious	Not serious	Publication bias not suspected (no studies in lower left of funnel plot)	81/758 (11%) of LGE+ had event 43/1,053 (4.0%) of LGE– had event RR = 3.21 (1.79, 5.76), k=13 RR = 4.13 (2.05, 8.33), k=8 best	Moderate ⊕⊕⊕⊙	Critical (9/9)

Outcome	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Summary of findings RR (95%CI)	Quality of evidence	Importance
Cardiac transplantation	K=7 prospective cohort (level II)	Not serious (2/7 high risk)	Not serious (no heterogeneity; I^2 = 0%)	Not serious	Not serious	Publication bias undetected	13/451 (2.9%) of LGE+ had event 4/794 (0.5%) of LGE– had event RR = 4.34 (1.51, 12.44), k=7 RR = 5.95 (1.80, 19.62), k=5 best	High ⊕⊕⊕⊕	Critical (7/9)
Cardiac death or transplantation	K=12 prospective cohort (level II) K=1 retrospective cohort (level III-3)	Not serious (3/13 high risk)	Not serious (moderate heterogeneity; I^2 = 47.5%)	Not serious	Not serious	Publication bias strongly suspected (no studies in lower left of funnel plot)	115/732 (16%) of LGE+ had event 55/1,044 (5.3%) of LGE– had event RR = 3.18 (1.81, 5.57), k=13 RR = 3.81 (2.02, 7.21), k=9 best	Moderate ⊕⊕⊕⊙	Critical (7/9)
SCD	K=8 prospective cohort (level II) K=2 retrospective cohort (level III-3)	Not serious (1/10 high risk)	Not serious (no heterogeneity; I^2 = 0%)	Not serious	Not serious	Publication bias undetected	27/586 (4.6%) of LGE+ had event 14/833 (1.7%) of LGE– had event RR = 3.16 (1.71, 5.85), k=10 RR = 3.53 (1.85, 6.73), k=7 best	High ⊕⊕⊕⊕	Critical (9/9)
Appropriate ICD discharge	K=6 prospective cohort (level II) K=3 retrospective cohort (level III-3)	Not serious (7/9 high risk)	Not serious (moderate heterogeneity; I^2 = 43.9%)	Not serious	Not serious	Publication bias strongly suspected (no studies in lower left of funnel plot)	121/292 (41%) of LGE+ had event 26/248 (10%) of LGE– had event RR = 3.13 (1.63, 3.74), k=7 RR = 3.11 (1.62, 6.43), k=6 best	Moderate ⊕⊕⊕⊙	Important (6/9)
SCD, aborted SCD or ICD discharge	K=8 prospective cohort (level II) K=1 retrospective cohort (level III-3)	Not serious (0/9 high risk)	Not serious (no heterogeneity; I^2 = 0%)	Not serious	Not serious	Publication bias strongly suspected (no studies in lower left of funnel plot)	193/998 (19%) of LGE+ had event 45/838 (5.4%) of LGE– had event RR = 3.84 (2.79, 5.29), k=9 RR = 3.77 (2.73, 5.20), k=8 best	Moderate ⊕⊕⊕⊙	Important (6/9)

Outcome	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Summary of findings RR (95%CI)	Quality of evidence	Importance
VT/VA events	K=5 prospective cohort (level II) K=2 retrospective cohort (level III-3)	Not serious (2/7 high risk)	Not serious (no heterogeneity; I^2 = 0%)	Not serious	Not serious	Publication bias strongly suspected (no studies in lower left of funnel plot)	52/409 (13%) of LGE+ had event 12/392 (3.1%) of LGE– had event RR = 3.03 (1.63, 5.62), k=7 RR = 2.41 (1.18, 4.84), k=3 best	Moderate ⊕⊕⊕⊙	Important (5/9)
Major arrhythmic events	K=9 prospective cohort (level II) K=2 retrospective cohort (level III-3)	Not serious (2/11 high risk)	Not serious (no heterogeneity; I^2 = 0%)	Not serious	Not serious	Publication bias undetected	114/652 (17%) of LGE+ had event 40/875 (1.6%) of LGE– had event RR = 3.84 (2.71, 5.43), k=11 RR = 3.80 (2.63, 5.50), k=7 best	High ⊕⊕⊕⊕	Critical (7/9)
Hospitalisation for HF	K=10 prospective cohort (level II) K=1 retrospective cohort (level III-3)	Not serious (3/11 high risk)	Serious (substantial heterogeneity; I^2 = 64.9%)	Not serious	Not serious	Publication bias strongly suspected (no studies in lower left of funnel plot)	114/611 (19%) of LGE+ had event 75/903 (8.3%) of LGE– had event RR = 2.38 (1.36, 4.18), k=11 RR = 2.48 (1.21, 6.09), k=7 best	Low ⊕⊕⊙⊙	Important (4/9)
Any cardiac event	K=8 prospective cohort (level II) K=2 retrospective cohort (level III-3)	Not serious (2/10 high risk)	Serious (substantial heterogeneity; I^2 = 61.5%)	Not serious	Not serious	Publication bias strongly suspected (no studies in lower left of funnel plot)	164/549 (30%) of LGE+ had event 68/637 (11%) of LGE– had event RR = 3.71 (2.29, 6.04), k=10 RR = 3.66 (1.95, 6.90), k=6 best	Low ⊕⊕⊙⊙	Critical (8/9)
ICD implantation	K=4 prospective cohort (level II) K=1 retrospective cohort (level III-3)	Not serious (1/5 high risk)	Not serious (no heterogeneity; I^2 = 0%)	Not serious	Not serious	Publication bias strongly suspected (no studies in lower left of funnel plot)	112/390 (29%) of LGE+ had event 72/548 (13%) of LGE– had event RR = 2.56 (1.95, 3.35), k=5 RR = 2.48 (1.86, 3.25), k=3 best	Moderate ⊕⊕⊕⊙	Important (6/9)

best = RR of the studies providing the best-quality evidence, i.e. if high risk and level III-3 studies are removed from analysis; CI = confidence interval; CMR = cardiac magnetic resonance (imaging); DCM = dilated cardiomyopathy; HF = heart failure; ICD = implantable cardioverter defibrillator; LGE = late gadolinium enhancement; RR = relative risk; SCD = sudden cardiac death; VA = ventricular arrhythmia; VT = ventricular tachycardia

Table 89 Evidence profile for the prognostic value of using LGE-CMR to predict health outcomes in children newly diagnosed with DCM

Outcome	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Summary of findings RR (95%CI)	Quality of evidence	Importance
Death	K=1 prospective cohort (level II)	Not serious (moderate risk)	Not serious	Not serious	Not serious	None	2/33 (6.1%) of LGE+ had event 1/33 (3.0%) of LGE– had event RR = 2.00 (0.19, 21.00)	High ⊕⊕⊕⊕	Critical (9/9)
Cardiac transplantation	K=1 prospective cohort (level II)	Not serious (moderate risk)	Not serious	Not serious	Not serious	None	0/33 (0%) of LGE+ had event 1/33 (3.0%) of LGE– had event RR = 0.33 (0.01, 7.90)	High ⊕⊕⊕⊕	Critical (7/9)
Normalised LV function	K=1 prospective cohort (level II)	Not serious (moderate risk)	Not serious	Not serious	Not serious	None	22/27 (81%) of LGE+ had event 11/28 (39%) of LGE– had event RR = 2.07 (1.27, 3.40) (ITT) RR = 2.00 (1.17, 3.43)	High ⊕⊕⊕⊕	Not important (3/9)

CI = confidence interval; CMR = cardiac magnetic resonance (imaging); DCM = dilated cardiomyopathy; ITT = intention to treat; LGE = late gadolinium enhancement; RR = relative risk

Table 90 Evidence profile for the prognosis of ICM patients compared with NIDCM patients

Outcome	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Summary of findings RR (95%CI)	Quality of evidence	Importance
LGE+	K=5 prospective cohort (level II) K=1 retrospective cohort (level III-3)	Not serious (0/6 high risk)	Not serious (no heterogeneity; I^2 = 0%)	Not serious	Not serious	Publication bias strongly suspected (no studies in lower left of funnel plot)	852/994 (86%) of ICM had event 207/540 (38%) of NIDCM had event RR = 2.56 (1.95, 3.35), k=5 RR = 2.48 (1.86, 3.25), k=3 best	Moderate ⊕⊕⊕⊙	Critical (8/9)

Outcome	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Summary of findings RR (95%CI)	Quality of evidence	Importance
All-cause mortality	K=2 prospective cohort (level II)	Not serious (0/2 high risk)	Not serious (no heterogeneity; I^2 = 0%)	Not serious	Not serious	Publication bias undetected	110/234 (47%) of ICM had event 19/161 (12%) of NIDCM had event RR = 2.32 (1.46, 3.68), k=2	High ⊕⊕⊕⊕	Critical (9/9)
Cardiac deaths	K=2 prospective cohort (level II)	Not serious (0/2 high risk)	Serious (substantial heterogeneity; I^2 = 57.8%)	Not serious	Serious (wide 95%CIs)	Publication bias undetected	58/289 (20%) of ICM had event 17/195 (8.7%) of NIDCM had event RR = 1.86 (0.77, 4.48), k=2	Low ⊕⊕⊙⊙	Critical (9/9)
SCD	K=1 prospective cohort (level II)	Not serious (moderate risk)	Not serious	Not serious	Serious (wide 95%CIs)	Publication bias undetected	11/161 (6.8%) of ICM had event 3/97 (3.1%) of NIDCM had event RR = 2.21 (0.63, 7.72), k=1	Moderate ⊕⊕⊕⊙	Critical (9/9)
Appropriate ICD discharge	K=3 prospective cohort (level II)	Not serious (0/3 high risk)	Not serious (moderate heterogeneity; I^2 = 32.0%)	Not serious	Serious (wide 95%CIs)	Publication bias undetected	26/220 (12%) of ICM had event 28/196 (14%) of NIDCM had event RR = 0.82 (0.41, 1.61), k=2	Moderate ⊕⊕⊕⊙	Important (6/9)
SCD or ICD discharge	K=2 prospective cohort (level II)	Not serious (0/2 high risk)	Very serious (considerable heterogeneity; I^2 = 94.6%)	Not serious	Very serious (very wide 95%CIs)	Publication bias undetected	76/196 (39%) of ICM had event 26/163 (16%) of NIDCM had event RR = 2.66 (0.43, 16.5), k=2	Very low ⊕⊙⊙⊙	Important (6/9)
VT/VA events	K=1 prospective cohort (level II)	Not serious (moderate risk)	Not serious	Not serious	Very serious (very wide 95%CIs)	Publication bias undetected	3/161 (1.9%) of ICM had event 2/97 (2.1%) of NIDCM had event RR = 0.90 (0.15, 5.31), k=1	Low ⊕⊕⊙⊙	Important (5/9)
Major arrhythmic events	K=1 prospective cohort (level II)	Not serious (moderate	Not serious	Not serious	Very serious (very wide	Publication bias undetected	14/161 (8.7%) of ICM had event 5/97 (5.2%) of NIDCM had event	Low ⊕⊕⊙⊙	Critical (7/9)

Outcome	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Summary of findings RR (95%CI)	Quality of evidence	Importance
		risk)			95%CIs)		RR = 1.69 (0.63, 4.54), k=1		
Any cardiac event	K=1 prospective cohort (level II)	Not serious (low risk)	Not serious	Not serious	Serious (wide 95%CIs)	Publication bias undetected	53/59 (90%) of ICM had event 10/65 (15%) of NIDCM had event RR = 5.84 (3.28, 10.39), k=1	Moderate ⊕⊕⊕⊙	Critical (8/9)

best = RR of the studies providing the best-quality evidence, i.e. if high risk and level III-3 studies are removed from analysis; CI = confidence interval; ICD = implantable cardioverter defibrillator; ICM = ischaemic cardiomyopathy; LGE = late gadolinium enhancement; NIDCM = non-ischaemic dilated cardiomyopathy; RR = relative risk; SCD = sudden cardiac death; VA = ventricular arrhythmia; VT = ventricular tachycardia

Table 91 Evidence profile table for the impact of change in management due to CMR for patients indicated for DCM

Outcome	No. of participants No. of studies Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations (e.g. publication bias)	Result N (%)	QoE Importance
New diagnoses	3,600 patients 2 studies Case series	Not serious (NHLBI: Low risk of bias)	Serious [a]	Serious [b]	Not serious	None	761 (21%)	Low ⊕⊕⊙⊙ Critical (8/10)
Changed diagnoses	150 patients 1 study Case series	Serious [c] (NHLBI: Low risk of bias)	Not serious	Serious [b]	Not serious	None	32 (21.3%)	Very low ⊕⊙⊙⊙ Important (4/10)
Diagnostic yield	88 patients 1 study Cohort study	Not serious (SIGN: low risk of bias)	Not serious	Not serious	Not serious	None	4 (4.5%)	Moderate ⊕⊕⊕⊙ Important (4/10)
Impact on further diagnostic	3,511 patients 1 study	Not serious (NHLBI: Low risk of bias)	Not serious	Serious [d]	Not serious [b]	None	491 (14%)	Very low ⊕⊙⊙⊙ Important

tests	Case series							(4/10)
Device implantations avoided and added	447 patients 1 study Case series	Not serious (NHLBI: Low risk of bias)	Not serious	Not serious	Not serious	None	41 (9.2%)	Low ⨁⨁⊙⊙ Critical (7/10)
Surgery avoided and added	447 patients 1 study Case series	Not serious (NHLBI: Low risk of bias)	Not serious	Not serious	Not serious	None	20 (4.5%)	Low ⨁⨁⊙⊙ Critical (7/10)
Procedures avoided and added	150 patients 1 study Case series	Serious [c] (NHLBI: Low risk of bias)	Not serious	Serious [b]	Not serious	None	108 (72%)	Very low ⨁⊙⊙⊙ Important (5/10)
Therapeutic consequences	3,511 patients 1 study Case series	Not serious (NHLBI: Low risk of bias)	Not serious	Serious [d]	Not serious [b]	None	1547 (44%)	Low ⨁⨁⊙⊙ Critical (7/10)

[a] Study populations are somewhat different to each other.
[b] Study populations vary from that under investigation in this review.
[c] Possible selection bias.
[d] Patients did not undergo the same level of pre-testing.
CMR = cardiac magnetic resonance (imaging); DCM = dilated cardiomyopathy; QoE = quality of evidence; N = number; NHLBI = National Heart, Lung and Blood Institute quality assessment tool; SIGN = Scottish Intercollegiate Guidelines Network quality assessment tool

APPENDIX E EXCLUDED STUDIES

DIAGNOSTIC PERFORMANCE

Could not locate full text article

Li, X, Lu, M, Yu, Y, Liu, B, Zhao, S, Cheng, H, Yin, G, Zhang, Y, Dai, L, Lan, T, Yang, X, Wan, J & Cui, C 2015, 'Comparative study of peripartum cardiomyopathy and idiopathic dilated cardiomyopathy MRI', *Chinese Journal of Radiology (China)*, vol. 49, no. 6, pp. 430–434.

Different language

Tong, K, Zhang, J, Wang, J, Zhou, X, Lei, X, Xu, Y & Zhi, G 2012, 'Quantification of left and right ventricular systolic function in patients with dilated cardiomyopathy using real-time three-dimensional echocardiography', *Journal of Central South University (Medical Sciences)*, vol. 37, no. 6, pp. 561–566.

Marra, MP, De Lazzari, M, Corbetti, F, Angelini, A, Cacciavillani, L, Tarantini, G, Tona, F, Thiene, G, Iliceto, S & Basso, C 2011, 'Contrast-enhanced cardiac magnetic resonance versus endomyocardial biopsy for myocardial fibrosis detection in non-ischemic dilated cardiomyopathy', *Giornale Italiano di Cardiologia*, vol. 12, no. 12, p. e42.

Conference abstracts

Amzulescu, MS, Pouleur, AC, Rousseau, MF, Ahn, SA, De Meester De Ravenstein, C, Vancraeynest, D, Pasquet, A, Vanoverschelde, JL & Gerber, BL 2014, 'Degree of left ventricular myocardial trabeculation and non-compaction phenotype do not influence the prognosis of non-ischemic dilated cardiomyopathy', *European Heart Journal*, vol. 35, pp. 797–798.

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Article does not contain relevant data

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Wrong population

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APPENDIX F RELEVANT MBS ITEMS FOR THE COMPARATORS

Table 92 Gated heart pool scan (GHPS)

MBS item number	Description	Fee
61313	GATED CARDIAC HEART POOL STUDY, (equilibrium), with planar imaging and single photon emission tomography OR planar imaging or single photon emission tomography (R) Bulk bill incentive Fee: $303.35 Benefit: 75% = $227.55 85% = $257.85	$303.35

Table 93 Stress echocardiography (Echo)

Category 5 – Diagnostic Imaging Services
MBS Item 55116 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 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

Category 5 – Diagnostic Imaging Services
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

Table 94 Invasive coronary angiography (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)		
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)		

Table 95 Computed tomography coronary angiography (CTCA)

Category 5 – Diagnostic Imaging Services
MBS Item 57360 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) (K) Bulk bill incentive (Anaes.) Fee: $700.00 Benefit: 75% = $525.00; 85% = $623.80
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

Table 96 Exercise or pharmacologic (adenosine or dobutamine) single-photon emission computed tomography (SPECT)

Category 5 – Diagnostic Imaging Services
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
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
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

Category 5 – Diagnostic Imaging Services
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
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
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
MBS Item 61653 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) (NK) Bulk bill incentive Fee: $354.85 Benefit: 75% = $266.15; 85% = $301.65
MBS Item 61654 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) Bulk bill incentive Fee: $417.45 Benefit: 75% = $313.10; 85% = $354.85

Table 97 Reference standard: endomyocardial biopsy (EMB)

MBS item number	Description	Fee
38275	MYOCARDIAL BIOPSY, by cardiac catheterisation Multiple Services Rule (Anaes.) Fee: $298.20 Benefit: 75% = $223.65 85% = $253.50	$298.20

APPENDIX G FURTHER ANALYSIS FOR SECTION B4.2

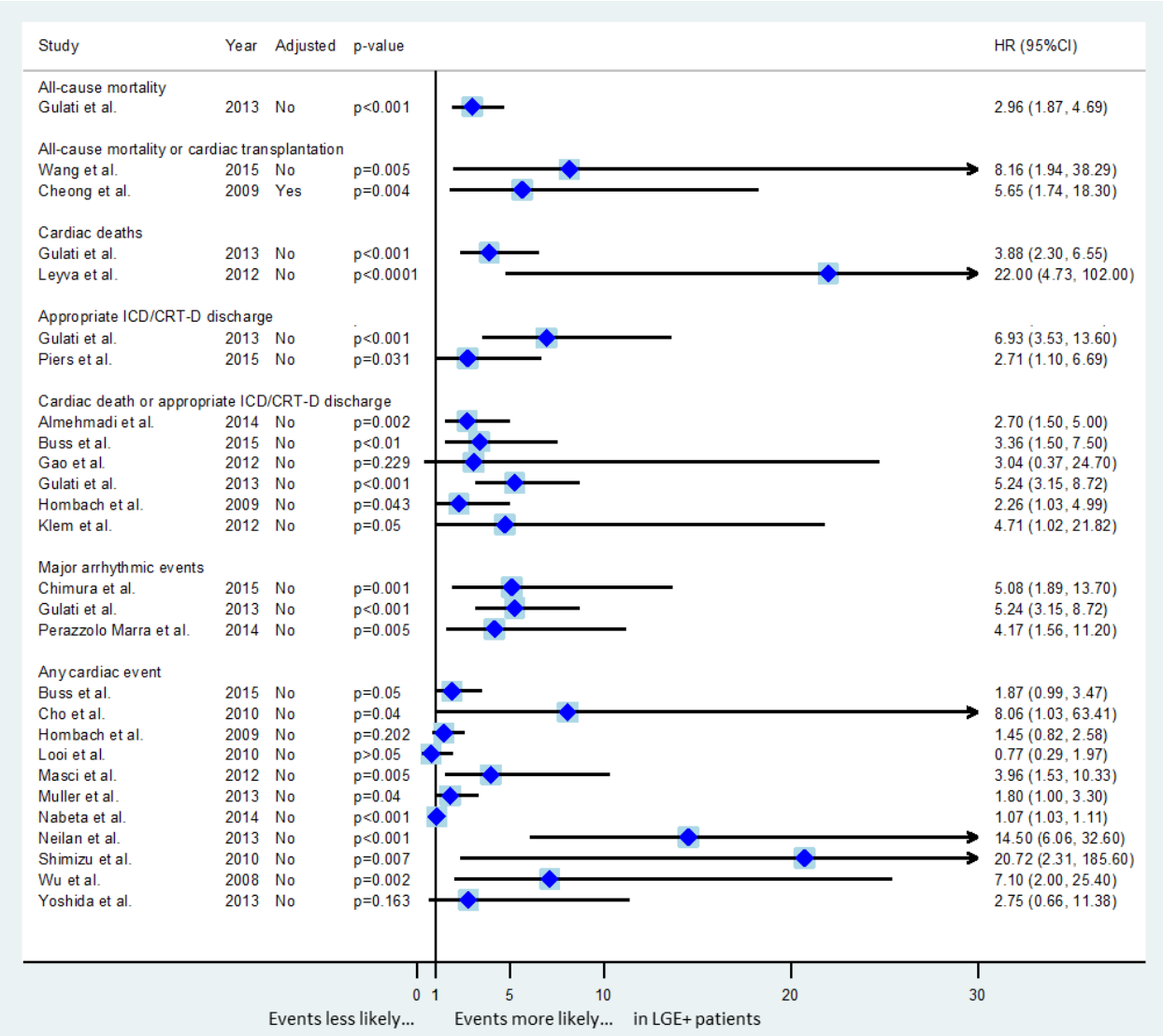


Figure 38 Forest plot showing the HRs for the presence of LGE for different health outcomes

The HRs were derived from univariate Cox regression analysis conducted in individual cohort studies.

CI = confidence interval; CRT-D = cardiac resynchronisation therapy with defibrillator; HR = hazard ratio; ICD = implantable cardioverter defibrillator; LGE = late gadolinium enhancement

APPENDIX H FURTHER ANALYSES FOR SECTION B5.2

COMPARISON BETWEEN REVASCULARISATION AND OMT IN PATIENTS WITH ICM

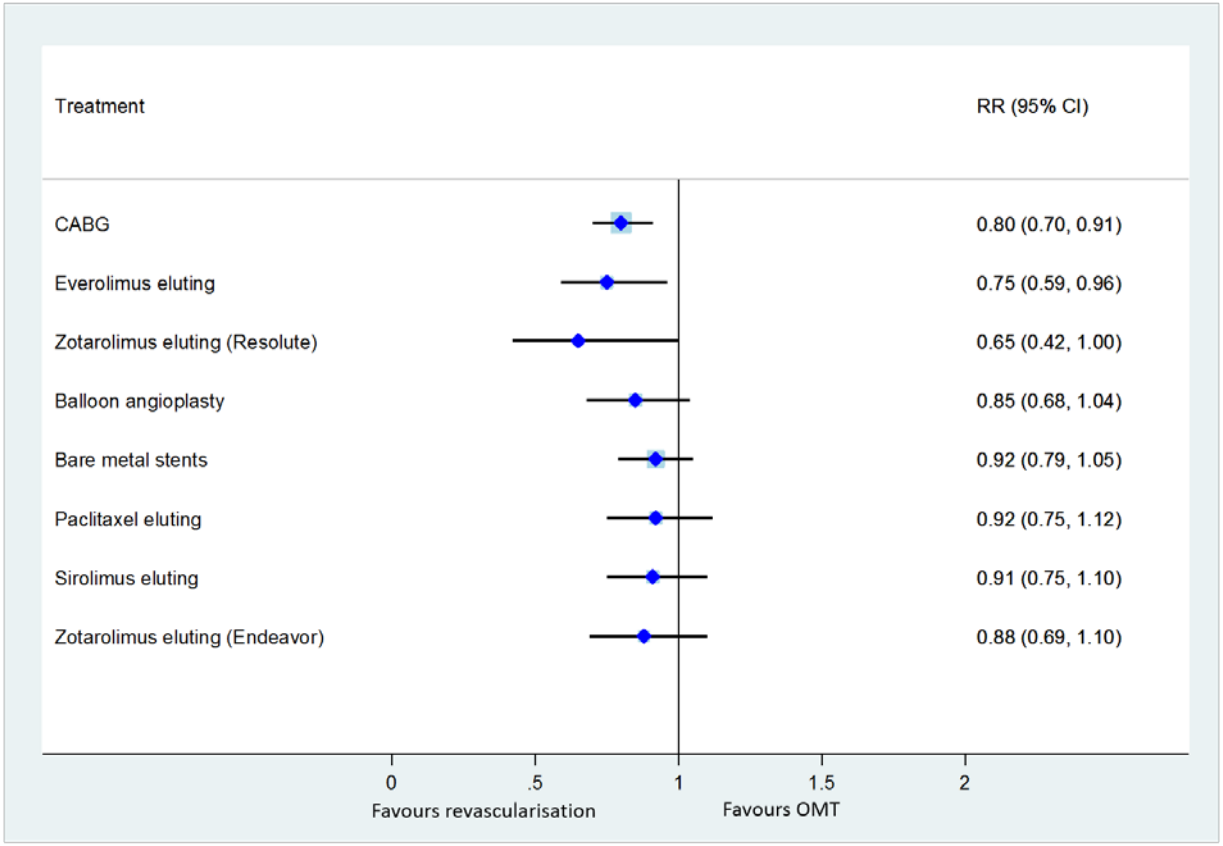


Figure 39 All-cause mortality after revascularisation versus OMT

CABG = coronary artery bypass graft; CI = confidence interval; ICM = ischaemic cardiomyopathy; OMT = optimal medical treatment; RR = relative risk

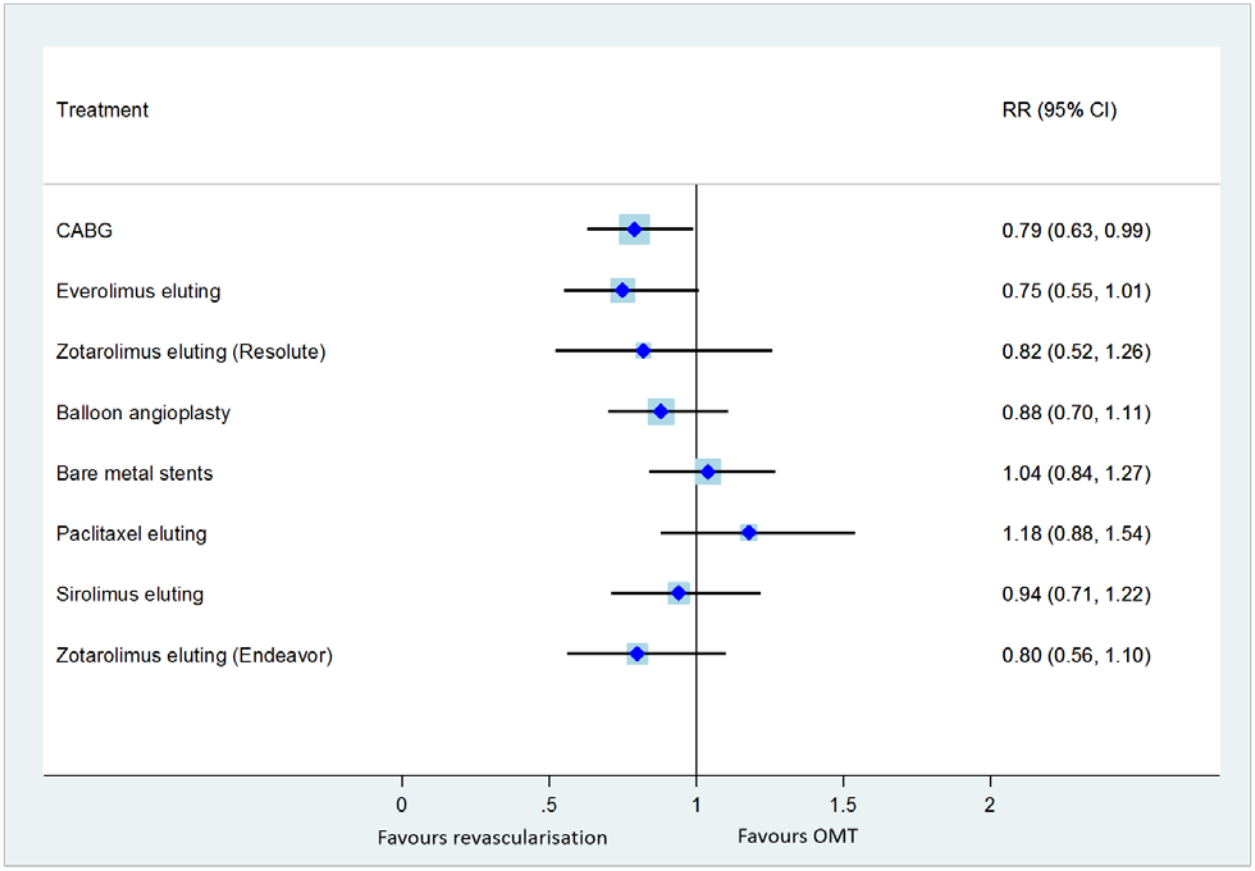


Figure 40 Myocardial infarctions after revascularisation versus OMT

CABG = coronary artery bypass graft; CI = confidence interval; OMT = optimal medical treatment; RR = relative risk

COMPARISON BETWEEN ICDS PLUS OMT VS OMT ALONE IN PATIENTS WITH NIDCM

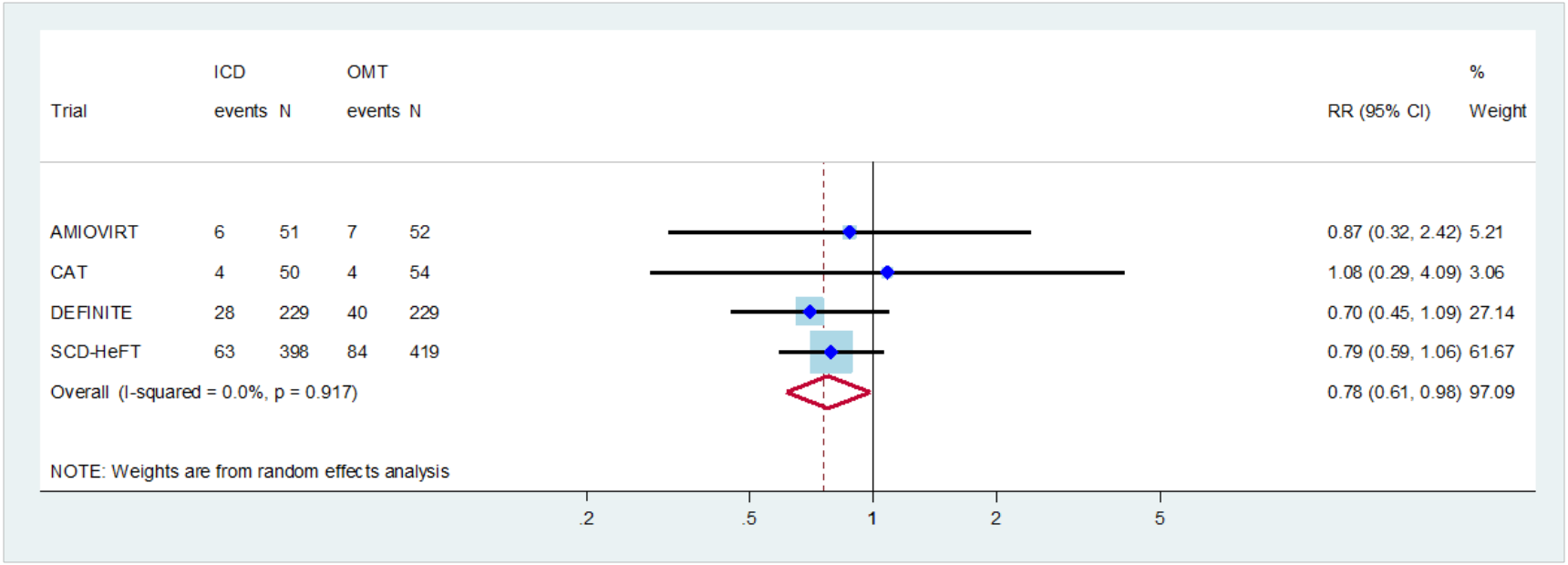


Figure 41 All-cause mortality from ICD plus OMT vs OMT alone

AMIOVIRT = Amiodarone versus Implantable Defibrillator (study); CAT = Cardiomyopathy Trial; CI = confidence interval; DEFINITE = Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation (trial); ICD = implantable cardioverter defibrillator; N = number of patients; NIDCM = non-ischaemic dilated cardiomyopathy; OMT = optimal medical treatment; RR = relative risk; SCD-HeFT = Sudden Cardiac Death in Heart Failure Trial

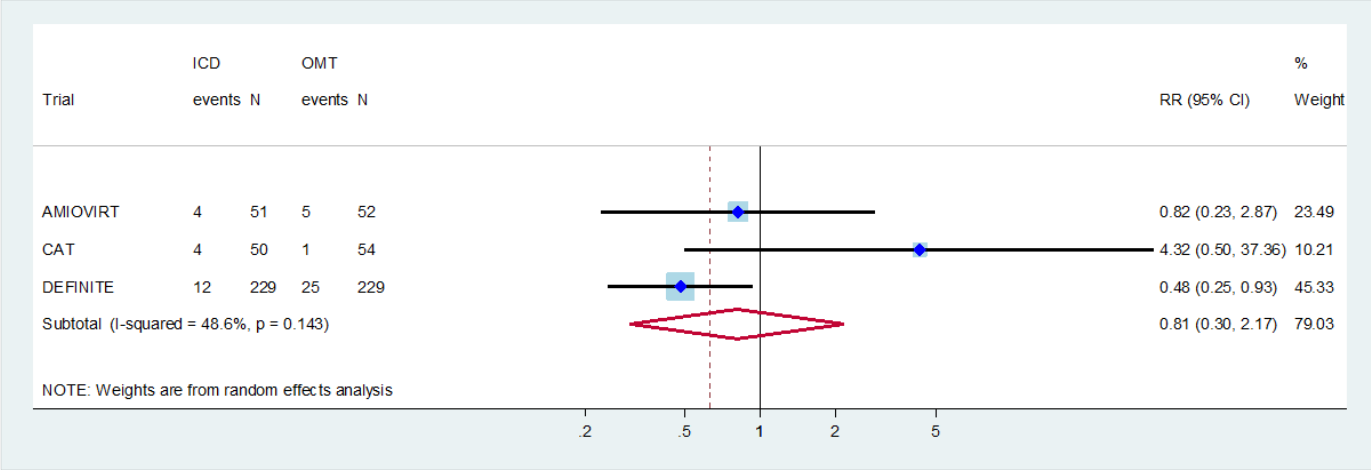


Figure 42 Cardiac deaths after ICD plus OMT vs OMT alone

AMIOVIRT = Amiodarone versus Implantable Defibrillator (study); CAT = Cardiomyopathy Trial; CI = confidence interval; DEFINITE = Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation (trial); ICD = implantable cardioverter defibrillator; N = number of patients; OMT = optimal medical treatment; RR = relative risk

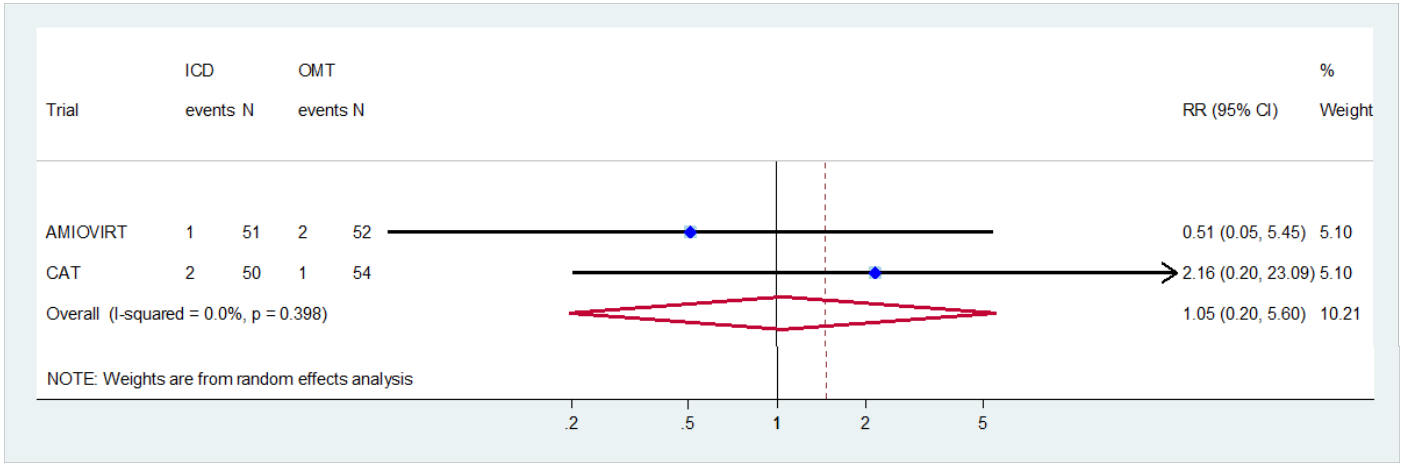


Figure 43 Cardiac transplantation after ICD plus OMT vs OMT alone

AMIOVIRT = Amiodarone versus Implantable Defibrillator (study); CAT = Cardiomyopathy Trial; CI = confidence interval; ICD = implantable cardioverter defibrillator; N = number of patients; OMT = optimal medical treatment; RR = relative risk

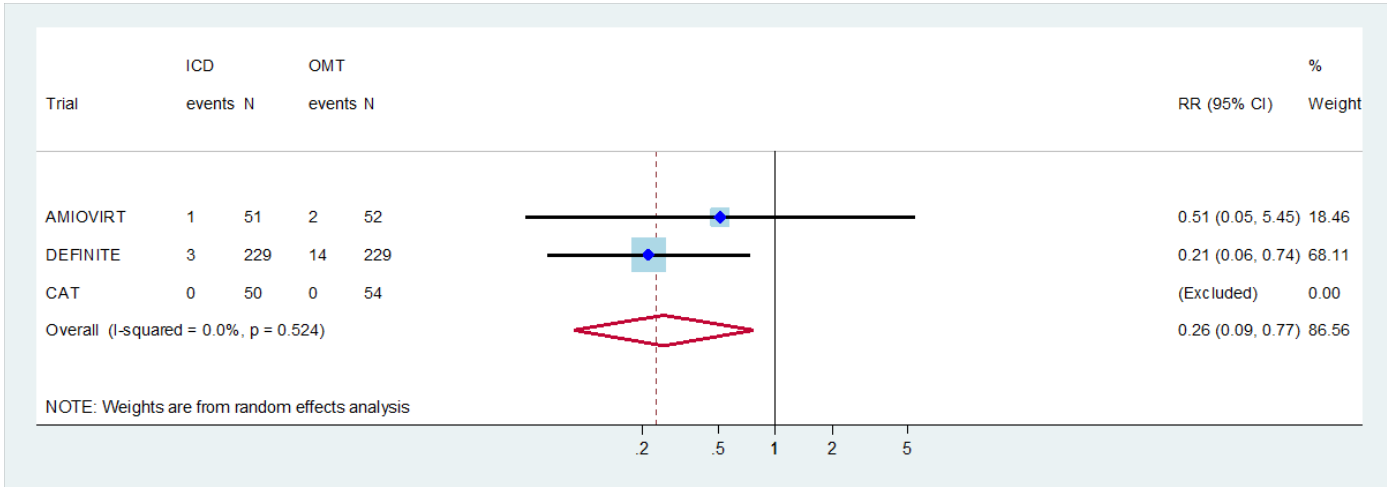


Figure 44 Sudden cardiac deaths after ICD plus OMT vs OMT alone

AMIOVIRT = Amiodarone versus Implantable Defibrillator (study); CAT = Cardiomyopathy Trial; CI = confidence interval; DEFINITE = Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation (trial); ICD = implantable cardioverter defibrillator; N = number of patients; OMT = optimal medical treatment; RR = relative risk

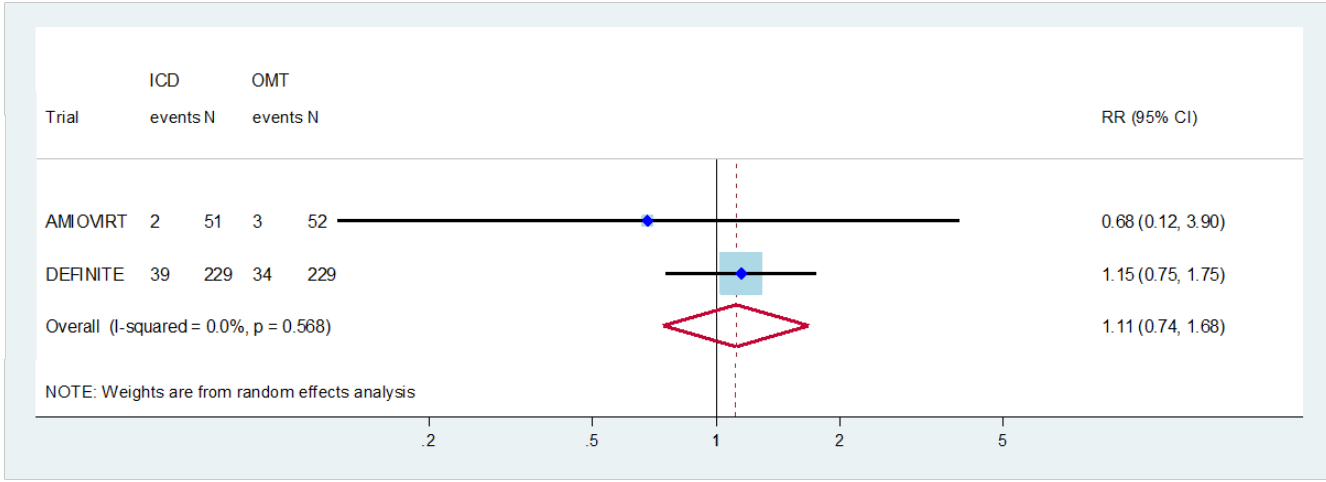


Figure 45 Syncope after ICD plus OMT vs OMT alone

AMIOVIRT = Amiodarone versus Implantable Defibrillator (study); CI = confidence interval; DEFINITE = Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation (trial);CI = confidence interval; ICD = implantable cardioverter defibrillator; N = number of patients; OMT = optimal medical treatment; RR = relative risk

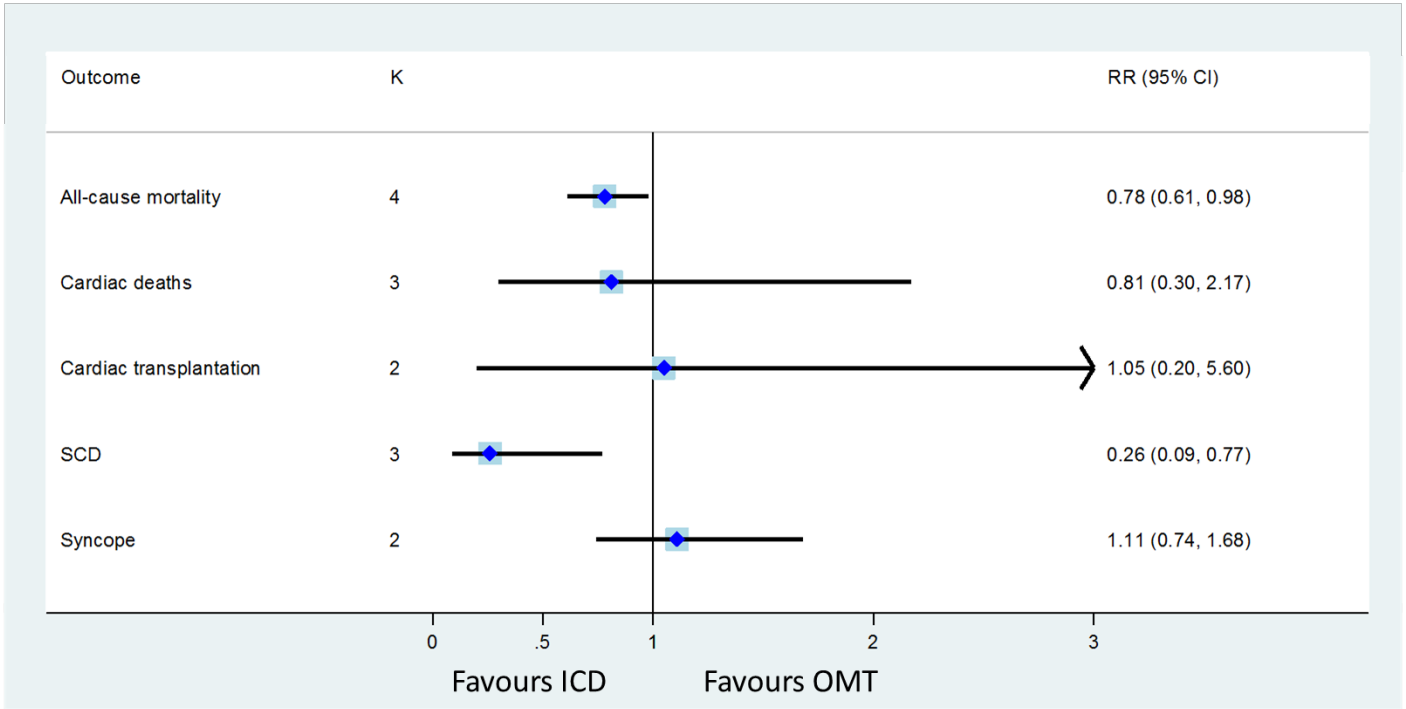


Figure 46 Summary of pooled RRs for different health outcomes

CI = confidence interval; ICD = implantable cardioverter defibrillator; K = number of events; OMT = optimal medical treatment; RR = relative risk; SCD = sudden cardiac death

APPENDIX I PICO CRITERIA AND CLINICAL MANAGEMENT ALGORITHMS FOR POPULATIONS III AND IV

Box 7 Criteria for identifying and selecting studies to determine the safety of CMR in asymptomatic individuals with a family history of DCM

Selection criteria	Description	
Population	Asymptomatic individuals with a family history of NIDCM in a first-degree relative in whom Echo is inconclusive	Asymptomatic individuals with a family history of NIDCM in a first-degree relative in whom Echo suggests a DCM that requires further investigation due to an intermediate or high risk of CAD
Intervention	CMR	CMR
Comparators	- Stress Echo - GHPS - SPECT - CTCA - ICA	- CTCA - SPECT
Outcomes	Safety: - Gadolinium contrast adverse reaction - Claustrophobia - Physical harms from follow-up testing - Other AEs arising from CMR or comparative tests	Safety: - Gadolinium contrast adverse reaction - Claustrophobia - Physical harms from follow-up testing - Other AEs arising from CMR or comparative tests
Systematic review question	What is the safety of CMR compared with stress Echo, GHPS, SPECT, CTCA or ICA in patients with a family history of DCM in whom Echo is inconclusive?	What is the safety of CMR compared with CTCA and SPECT in patients with a family history of DCM in whom Echo suggests a DCM that requires further investigation due to an intermediate or high risk of CAD?

AE = adverse event; CAD = coronary artery disease; CMR = cardiac magnetic resonance (imaging); CTCA = computed tomography coronary angiography; DCM = dilated cardiomyopathy; Echo = echocardiography; GHPS = gated heart pool scan; ICA = invasive coronary angiography; MRI = magnetic resonance imaging; NIDCM = non-ischaemic dilated cardiomyopathy; SPECT = single-photon emission computed tomography

NB: clinical advice has been sought to determine whether ICA is a correct comparator, but feedback has not been received.

Box 8 Criteria for identifying and selecting studies to determine the direct effectiveness of CMR in asymptomatic individuals with a family history of DCM

Selection criteria	Description	
Population	Asymptomatic individuals with a family history of NIDCM in a first-degree relative in whom Echo is inconclusive	Asymptomatic individuals with a family history of NIDCM in a first-degree relative in whom Echo suggests a DCM that requires further investigation due to an intermediate or high risk of CAD
Intervention	CMR	CMR
Comparators	- Stress Echo	- CTCA

	- GHPS - SPECT - CTCA - ICA	- SPECT
Outcomes	Health outcomes: - Cardiac disease-specific mortality - Survival - Cardiac hospitalisation - Adverse cardiac event over defined period - Quality of life scores Cost-effectiveness: - Cost - Cost per QALY or DALY - ICER	Health outcomes: - Cardiac disease-specific mortality - Survival - Cardiac hospitalisation - Adverse cardiac event over defined period - Quality of life scores Cost-effectiveness: - Cost - Cost per QALY or DALY - ICER
Systematic review question	What is the effectiveness and cost-effectiveness of CMR compared with stress Echo, GHPS, SPECT, CTCA or ICA in patients with a family history of DCM in whom echocardiography is inconclusive?	What is the effectiveness and cost-effectiveness of CMR compared with CTCA and SPECT in patients with a family history of DCM in whom Echo suggests a DCM that requires further investigation due to an intermediate or high risk of CAD?

CAD = coronary artery disease; CMR = cardiac magnetic resonance (imaging); CTCA = computed tomography coronary angiography; DALY = disability adjusted life year; DCM = dilated cardiomyopathy; Echo = echocardiography; GHPS = gated heart pool scan; ICA = invasive coronary angiography; ICER = incremental cost-effectiveness ratio; NIDCM = non-ischaemic dilated cardiomyopathy; QALY = quality adjusted life year; SPECT = single-photon emission computed tomography

NB: clinical advice has been sought to determine whether ICA is a correct comparator, but feedback has not been received.

Box 9 Criteria for identifying and selecting studies to determine the prognostic value of CMR in asymptomatic individuals with a family history of DCM

Selection criteria	Description	
Population	Asymptomatic individuals with a family history of NIDCM in a first-degree relative in whom Echo is inconclusive	Asymptomatic individuals with a family history of NIDCM in a first-degree relative in whom Echo suggests a DCM that requires further investigation due to an intermediate or high risk of CAD
Prior tests	Clinical examination, ECG, Echo	Clinical examination, ECG, Echo
Index test	CMR assessment of myocardial structure and function, including tissue characterisation, in addition to prior tests	CMR assessment of myocardial structure and function, including tissue characterisation, in addition to prior tests
Comparators	Prior tests only	Prior tests only
Outcomes	HR, RR, mortality rates	HR, RR, mortality rates
Systematic review question	What is the prognostic value of CMR compared with stress Echo, GHPS, SPECT, CTCA or ICA in patients with a family history of DCM in whom Echo is inconclusive?	What is the prognostic value of CMR compared with CTCA and SPECT in patients with a family history of DCM in whom Echo suggests a DCM that requires further investigation due to an intermediate or high risk of CAD?

CAD = coronary artery disease; CMR = cardiac magnetic resonance (imaging); CTCA = computed tomography coronary angiography; DCM = dilated cardiomyopathy; ECG = electrocardiogram; Echo = echocardiography; GHPS = gated heart

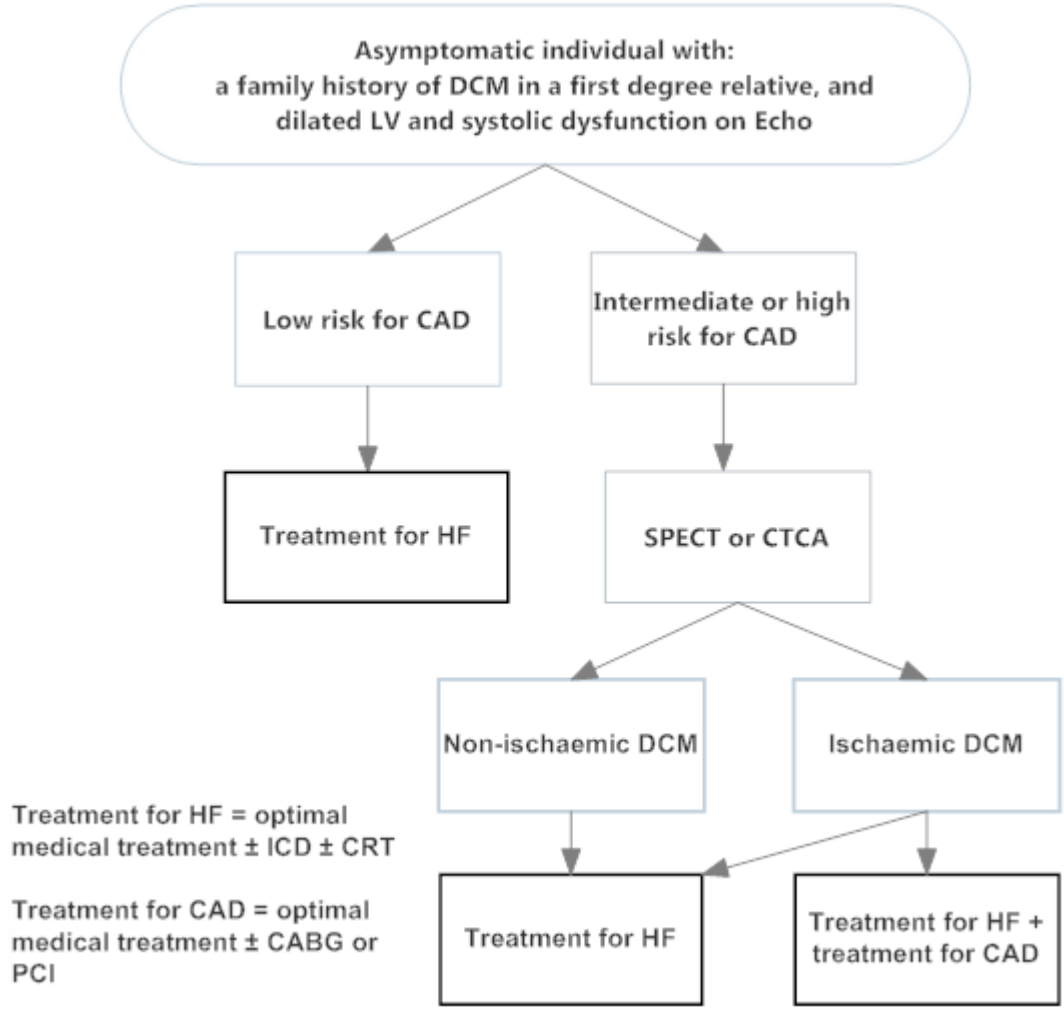
pool scan; HR = hazard ratio; ICA = invasive coronary angiography; MRI = magnetic resonance imaging; NIDCM = non-ischaemic dilated cardiomyopathy; RR = relative risk; SPECT = single-photon emission computed tomography

Box 10 Criteria for identifying and selecting studies to determine the therapeutic efficacy (change in management) of CMR in asymptomatic individuals with a family history of DCM

Selection criteria	Description
Population	Asymptomatic individuals with a family history of NIDCM in a first-degree relative in whom: Echo is inconclusive, or Echo suggests a DCM that requires further investigation due to an intermediate or high risk of CAD
Prior tests	Clinical examination, ECG, Echo
Index test	MRI assessment of myocardial structure and function, including tissue characterisation
Comparators	Watchful waiting in the context of OMT
Outcomes	Change in clinical diagnosis, change in treatment pathway (e.g. initiated, ceased, modified, avoided), patient compliance, time to initial diagnosis, time from diagnosis to treatment, rates of re-intervention
Systematic review question	Is there a change in management from CMR in patients with a family history of DCM in whom Echo is inconclusive, compared with watchful waiting in the context of OMT?

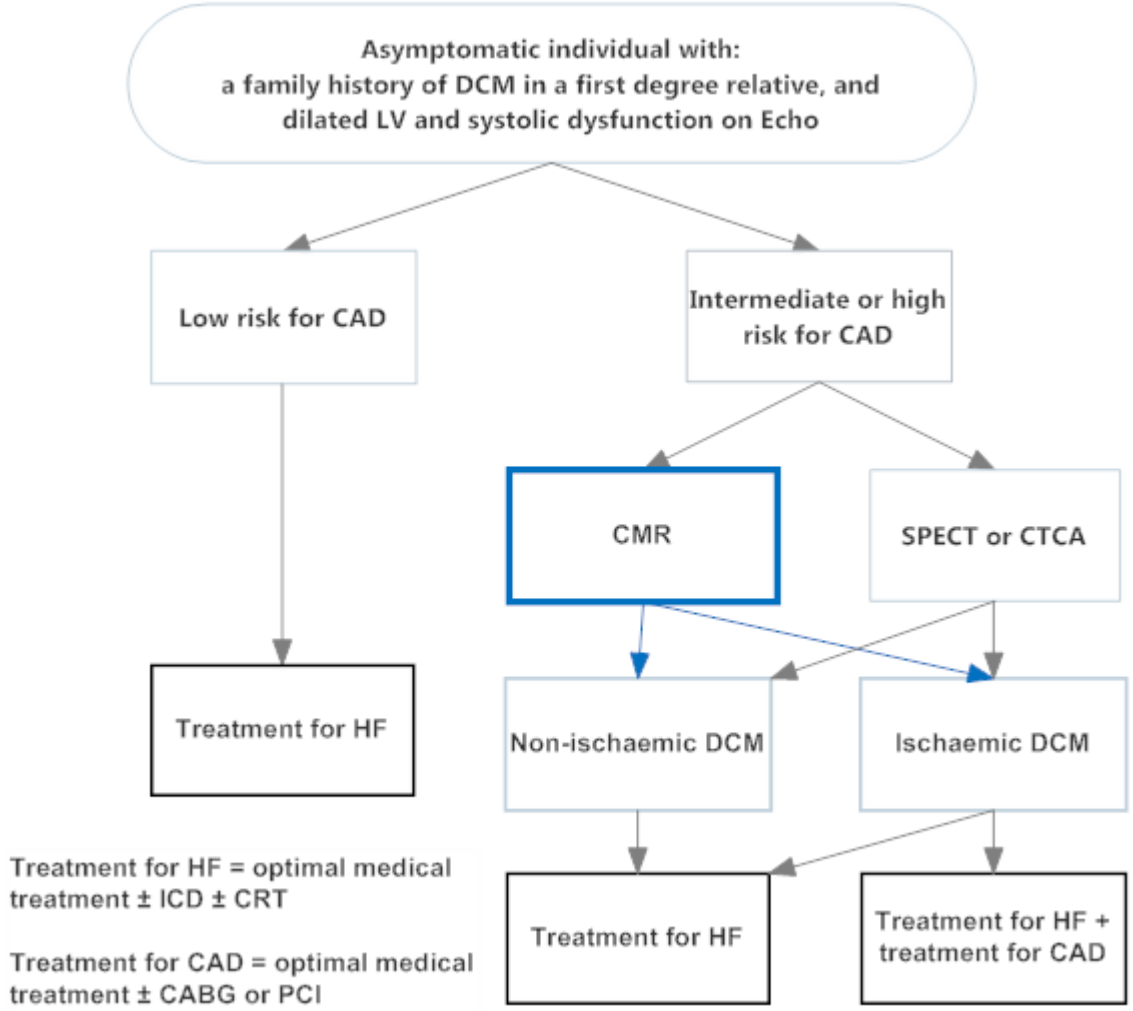
CAD = coronary artery disease; CMR = cardiac magnetic resonance (imaging); CTCA = computed tomography coronary angiography; DCM = dilated cardiomyopathy; ECG = electrocardiogram; Echo = echocardiography; ICA = invasive coronary angiography; MRI = magnetic resonance imaging; NIDCM = non-ischaemic dilated cardiomyopathy; OMT = optimal medical therapy

Figure 47 Current clinical management algorithm for asymptomatic family members with dilated LV and systolic dysfunction on Echo



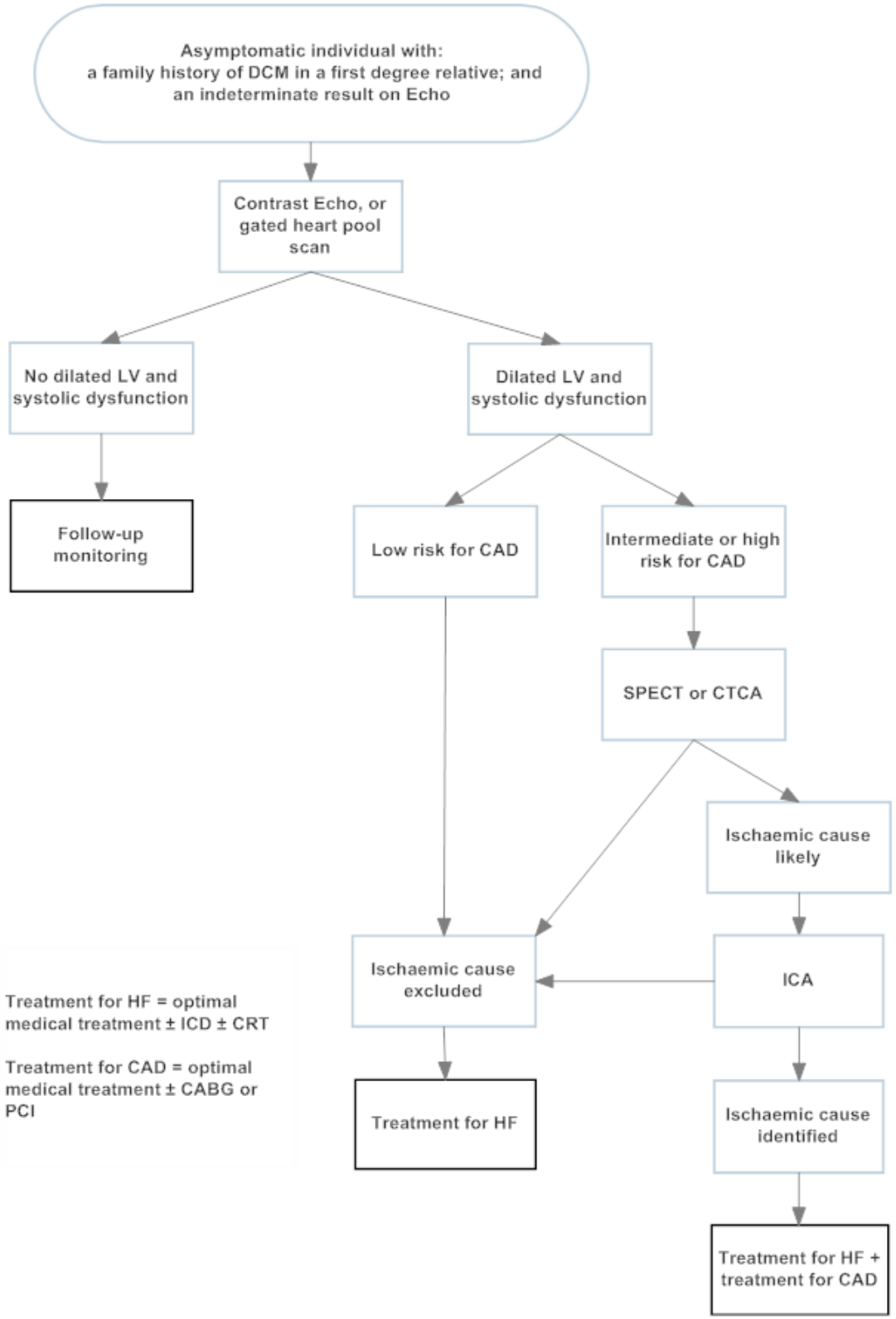
CABG = coronary artery bypass graft; CAD = coronary artery disease; CTCA = computed tomography coronary angiography; DCM = dilated cardiomyopathy; Echo = echocardiography; HF = heart failure; LV = left ventricle; PCI = percutaneous coronary intervention

Figure 48 Proposed clinical management algorithm for asymptomatic family members with dilated LV and systolic dysfunction



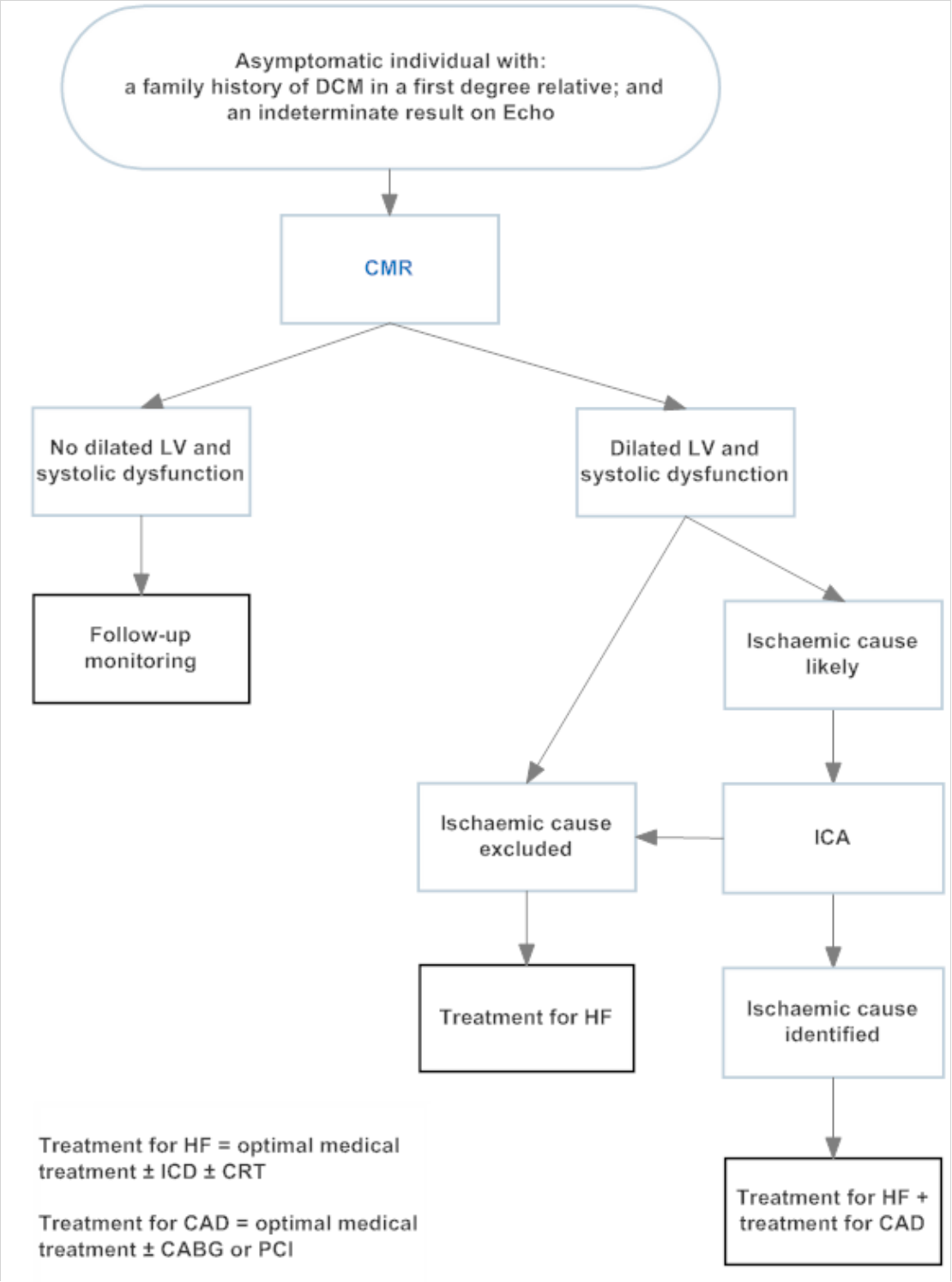
CABG = coronary artery bypass graft; CAD = coronary artery disease; CMR = cardiac magnetic resonance (imaging); CRT = cardiac resynchronisation therapy; CTCA = computed tomography coronary angiography; DCM = dilated cardiomyopathy; Echo = echocardiography; HF = heart failure; ICD = implantable cardioverter defibrillator; LV = left ventricle; PCI = percutaneous coronary intervention; SPECT = single-photon emission computed tomography

Figure 49 Current clinical management algorithm in asymptomatic family members, who have an indeterminate result on Echo



CABG = coronary artery bypass graft; CAD = coronary artery disease; CRT = cardiac resynchronisation therapy; CTCA = computed tomography coronary angiography; DCM = dilated cardiomyopathy; Echo = echocardiography; HF = heart failure; ICA = invasive coronary angiography; ICD = implantable cardioverter defibrillator; LV = left ventricle; PCI = percutaneous coronary intervention; SPECT = single-photon emission computed tomography

Figure 50 Proposed clinical management algorithm for asymptomatic family members with an indeterminate result on Echo



CABG = coronary artery bypass graft; CAD = coronary artery disease; CMR = cardiac magnetic resonance (imaging); CRT = cardiac resynchronisation therapy; DCM = dilated cardiomyopathy; Echo = echocardiography; HF = heart failure; ICA = invasive coronary angiography; ICD = implantable cardioverter defibrillator; LV = left ventricle; PCI = percutaneous coronary intervention

APPENDIX J FURTHER ANALYSES FOR SECTION B7.1

Table 4 to Table 6 provide further details on the extended safety of investigations used for patients with HF symptoms. The data in these tables are replicated in Figure 29 to Figure 32 in section B7.1.

Table 98 Summary of potential safety concerns for tests investigating whether the patient has DCM (after unclear Echo)

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
GHPS 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	-
cEcho Serious AEs: 3/10,000 scans Mortality: 0.1/10,000 patients	0	0	Microspheres of contrast Serious AEs: 3/10,000 scans Long-term death rate: 0.1/10,000 patients	Heat from ultrasound

Sources: Cooper (2015); Cooper et al. (2007); Einstein et al. (2012); From et al. (2011); Ghelani et al. (2014); Knuuti et al. (2014); Varga et al. (2006)

AE = adverse event; DCM = dilated cardiomyopathy; Echo = echocardiography; GHPS = gated heart pool scan; LGE-CMR = late gadolinium enhancement cardiac magnetic resonance (imaging)

Table 99 Summary of potential safety concerns for tests investigating whether the patient has ischaemia

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
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	-
Stress Echo Serious AEs: 5–21/10,000 scans Mortality: 1–2/10,000 patients	0	Exercise Serious AEs: 1.5/10,000 tests Death: 0.1/10,000 patients Dipyridamole	Microspheres of contrast (not common) Serious AEs: 3/10,000 scans Long-term death rate:	Heat from ultrasound

Test / overall mortality rate	Radiation dose	Stressors	Contrast agents and tracers	Other
		Serious AEs: 7.7/10,000 tests Death: 0.4/10,000 patients Adenosine Serious AEs: 1.4/10,000 tests Death: 0.1/10,000 patients Dobutamine Serious AEs: 18/10,000 tests Death: 1.4/10,000 patients	0.1/10,000 patients	
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: Cooper (2015); Cooper et al. (2007); Einstein et al. (2012); FDA website: 'What are the radiation risks from CT?'[24]; From et al. (2011); Ghelani et al. (2014); Knuuti et al. (2014); Varga et al. (2006)

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

Table 100 Summary of potential safety concerns for tests investigating the aetiology of NIDCM

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
Blood tests Serious AEs: 2/10,000 Mortality: 0/10,000	0	0	0	Haematoma: 20/10,000 Severe hypotonic circulatory reactions: 2/10,000 Thrombophlebitis:

[24] Available from <FDA website>; accessed on 20 October 2015

Test / overall mortality rate	Radiation dose	Stressors	Contrast agents and tracers	Other
				0.2/10,000
EMB Overall complications: 1% Mortality: 3–140/10,000 patients	Fluoroscopy: risk estimated from data from cardiac catheterisation procedures: Time 12–55 minutes Dose 0.007– 0.23 mSv per cm^2 Additional fatal cancers: 0–0.12/10,000 patients		-	Perforation with pericardial tamponade Arrhythmias Heart block Pneumothorax Puncture of arteries Pulmonary embolisation Nerve paresis Venous haematoma Damage to tricuspid valve Creation of arterial venous fistula Access site bleeding Deep venous thrombosis

Sources: Burkhardt et al. (2015); Cooper (2015); Cooper et al. (2007); Einstein et al. (2012); From et al. (2011); Ghelani et al. (2014); Knuuti et al. (2014); Newman (1997); Varga et al. (2006)

AE = adverse event; EMB = endomyocardial biopsy; LGE-CMR = late gadolinium enhancement cardiac magnetic resonance (imaging); NIDCM = non-ischaemic dilated cardiomyopathy

APPENDIX K SENSITIVITY ANALYSES FOR COST ANALYSIS: POPULATION I

SENSITIVITY ANALYSES FOR COST ANALYSES OF CMR VS GHPS OR CECHO

Table 101 Sensitivity analyses for cost comparison of CMR to GHPS

	Cost of CMR	Cost of GHPS	Incremental cost
Base-case	$1,106.31	$418.36	$687.95
Assuming no bulk-billing incentive (base-case: assumes bulk-billing incentive)	$1,012.95	$418.36	$594.59
Assuming only specialist referral to GBPS (base-case: 50% specialist; 50% GP)	$1,106.31	$487.99	$618.32
Assuming only GP referral to GBPS (base-case: 50% specialist; 50% GP)	$1,106.31	$348.72	$757.58
CMR patient contribution, $128.30 (base-case: $244.36)	$1,074.71	$418.36	$656.35
CMR patient contribution, $300.00 (base-case: $244.36)	$1,121.46	$418.36	$703.10
Proportion of CMR bulk-billed, 60% (base-case: 72.8%)	$1,121.13	$418.36	$702.77
Proportion of CMR bulk-billed, 80% (base-case: 72.8%)	$1,097.92	$418.36	$679.56

CMR = cardiac magnetic resonance (imaging); GHPS = gated heart pool scan; GP = general practitioner

Table 102 Sensitivity analyses for cost comparison of CMR to cEcho

	Cost of CMR	Cost of cEcho	Incremental cost
Base-case	$1,106.31	$146.41	$959.90
Assuming separate service for cEcho (base-case: no separate service for cEcho)	$1,106.31	$498.95	$607.36
Assuming no CMR bulk-billing incentive (base-case: assumes bulk-billing incentive)	$1,012.95	$146.41	$866.54
Proportion of cEchos remaining unresolved, 15% (base-case: 3.6%)	$1,106.31	$194.06	$912.25
No extra time required for cEcho (base-case: 15% extra time)	$1,106.31	$110.43	$995.88
Double the extra time required for cEcho (base-case: 15% extra time)	$1,106.31	$182.39	$923.92
Cost of contrast, $60 (base-case: $90)	$1,106.31	$116.41	$989.90
CMR patient contribution, $128.30 (base-case: $244.36)	$1,074.71	$146.41	$928.30
CMR patient contribution, $300 (base-case: $244.36)	$1,121.46	$146.41	$975.05
Proportion of CMR bulk-billed, 60% (base-case: 72.8%)	$1,121.13	$146.41	$974.72
Cost of contrast, $100 (base-case: $90)	$1,106.31	$156.41	$949.90
Proportion of CMR bulk-billed, 80% (base-case: 72.8%)	$1,097.92	$146.41	$951.51

cEcho = contrast echocardiogram; CMR = cardiac magnetic resonance (imaging); GP = general practitioner

APPENDIX L COST ANALYSIS: POPULATION IIA: OTHER TESTS FOR SECONDARY CAUSES OF NIDCM

Costs associated with some of the other tests performed for diagnosing secondary causes of NIDCM are presented. The costs considered in the analysis include those related to testing, the cost of specialist referrals for testing (where applicable), and the cost for treating AEs related to the testing methodology.

EMB

The costs related to EMB include those associated with referrals, surgical procedures, AEs and pathology testing of the collected specimens. The costs related to surgery include right heart catheterisation (MBS item 38200, schedule fee $445.40), myocardial biopsy (MBS item 38275, schedule fee $298.20) and anaesthesia (MBS item 21941, schedule fee $138.60). The Multiple Operations Rule applies to items in the surgical group, and the schedule fee for benefits purposes is calculated in accordance with the formula provided in the footnote[25]. Costs related to pathology testing include viral genome detection (MBS item 69496, schedule fee $43.05) and the ultrastructural examination of the biopsy specimens using electron microscopy (MBS item 72851, schedule fee $184.35). Weighted referral costs as described in Table 34 are used.

Due to its invasive nature, EMB may cause cardiac complications, such as perforation with pericardial tamponade, pneumothorax, heart block, puncture of arteries and pulmonary embolisation. Safety and complication issues related to EMB are discussed in section B.7.1. The overall complication rate associated with EMB is reported as 1% (Table 98, Appendix J). The costs associated with treating these AEs are calculated as the difference in the price weights for AR-DRGs F16A and F16B (Interventional Coronary Procedures, Not Admitted for AMI, Without Stent Implant, With Complications and Without Complications) multiplied by the NEP 2016–17 (see footnote in Table 103) (Independent Hospital Pricing Authority (IHPA) 2016).

A summary of costs associated with right-sided cardiac catheterisation with EMB are presented in Table 103. Patient co-payments are included in the costs and are assumed to be 15% of the schedule fee.

Table 103 Costs associated with EMB (including patient co-payments)

Parameter	Estimate	Source
Costs related to surgery [a]	$733.10	Sum of items below (3 lines)
Right heart catheterisation	$445.40	MBS schedule fee for item 38200*100%
Myocardial biopsy	$149.10	MBS schedule fee for item 38275*50%
Anaesthesia	$138.60	MBS schedule fee for item 21941
Costs associated with pathology testing	$227.40	Sum of pathology costs below (2 lines)
Microbial nucleic acid detection	$43.05	MBS schedule fee for item 69496
Electron microscopy	$184.35	MBS schedule fee for item 72851
Referral costs (weighted)	$112.68	See above

[25] Multiple Operations Rule—fees are aggregated in accordance with the formula: 100% for the item with the greatest schedule fee + 50% for the item with the next greatest schedule fee + 25% for each other item.

Treatment of AE costs	$33.05	Cost of AE per EMB (2 lines following)
Probability of complications related to EMB	1%	See Table 98, Appendix J
Cost of treating AEs	$3,305.30	Difference of NEP for AR-DRG F16A and F16B [b]
TOTAL	$1,106.23	

[a] Multiple Operation Rule applies to MBS items (38200 and 38275) included in this group, and the schedule fee for benefits purposes is the aggregate of the fees calculated in accordance with the formula: 100% for the item with the greatest schedule fee + 50% for the item with the next greatest schedule fee + 25% for each other item.

[b] Difference in the price weights for AR-DRGs F16A and F16B (Interventional Coronary Procedures, Not Admitted for AMI, Without Stent Implant, With Complications and Without Complications) (Independent Hospital Pricing Authority (IHPA) 2015a) * the NEP 2016–17 ($4,883) (Independent Hospital Pricing Authority (IHPA) 2016).

AEs = adverse events; AR-DRG = Australian Refined Diagnosis Related Groups; EMB = endomyocardial biopsy; MBS = Medicare Benefits Schedule; NEP = National Efficient Price

SUMMARY OF TEST COSTS

A summary of costs associated with proposed CMR and some of the other tests performed in this subgroup of patients is provided in Table 104 for comparative or contextual purposes. The referral cost is not included in the costings of these tests (except for genetic testing) as multiple tests can be referred in a single visit.

Table 104 Summary of costs associated with some of the tests performed in patients suspected of NIDCM

Test	Estimate	Source
CMR	$1,106.31	Table 34
EMB	$1,005.82	Table 103, Appendix L
24-hour ECG	$167.45	MBS schedule fee for item 11709
Exercise testing with measurement of peak oxygen uptake [a]	$290.80	MBS schedule fee for item 11712 + MBS schedule fee for item 11500
Genetic testing [b]	$314.00	Ingles et al. (2012), range $200–600
Quantitation in serum, plasma or urine	$17.70	MBS schedule fee for item 66512 [c]

[a] Exercise testing with measurement of peak oxygen uptake involves two items: exercise ECG (MBS item 11712, schedule fee: $152.15) and respiratory function tests (MBS for item 11500, schedule fee: $138.65).

[b] Source: Ingles et al. (2012); includes an initial and follow-up consultation with a clinical geneticist and the cost of the laboratory test

[c] Five or more tests performed described in MBS item 66500

CMR = cardiac magnetic resonance (imaging); ECG = electrocardiography; EMB = endomyocardial biopsy; MBS = Medicare Benefits Schedule; NIDCM = non-ischaemic dilated cardiomyopathy

APPENDIX M ADDITIONAL INFORMATION FOR CEA: POPULATION IIA

COST DERIVATIONS FOR IMPLANTABLE DEVICES

Table 105 Cost per ICD/CRT-D implantation procedure in the public sector

	AR-DRG	Seps	Weight	Cost [a]
Implantation or replacement of AICD, total system with catastrophic complications	F01A	668	23.6%	$46,730
Implantation or replacement of AICD, total system without catastrophic complications	F01B	2,158	76.4%	$22,191
Weighted cost (adjusted for inflation) [b]				$28,414 [b]

[a] Price weight for the respective AR-DRGs (Independent Hospital Pricing Authority (IHPA) 2015a) * the NEP 2016–17 ($4,883) (Independent Hospital Pricing Authority (IHPA) 2016)

[b] $27,991 converted to $28,414 in 2015 AUD using inflation calculator provided by Reserve Bank of Australia; < www.rba.gov.au/calculator/annualDecimal.html>; accessed 24 March 2016.

AICD = automated implantable cardioverter defibrillator; AR-DRG = Australian Refined Diagnosis Related Groups; CRT-D = cardiac resynchronisation therapy with cardiac-defibrillator; ICD = implantable cardioverter defibrillator; NEP = National Efficient Price; Seps = number of hospital separations

Table 106 Cost of hospitalisation for ICD/CRT-D implantation in the private sector

Row	Description	Estimated value	Source
	Cost per hospitalisation for implantation, with complications		
A	Total average cost per hospitalisation for implantation	$69,902	AR-DRG F01A
B	Prostheses component cost	$57,512	AR-DRG F01A
C	Total cost per hospitalisation for implantation, with complications (excluding prostheses component)	$14,288	C = (A – B) converted to 2015 AUD [a]
	Cost per hospitalisation for implantation, with no complications		
D	Total average cost per hospitalisation for implantation	$56,626	AR-DRG F01B
E	Prostheses component cost	$52,311	AR-DRG F01B
F	Total cost per hospitalisation for implantation, with no complications (excluding prostheses component)	$4,976	F = (D – E) converted to 2015 AUD [a]
	Weighted average cost per hospitalisation for ICD implantation		
G	Probability of implant-related complications	7%	MSAC Application no. 1223
H	Probability of no implant-related complications	93%	MSAC Application no. 1223
I	Weighted average cost per hospitalisation for ICD implantation	$5,628	Row I = (C*G) + (F*H)
	Weighted average cost per hospitalisation for CRT-D implantation		
J	Probability of implant-related complications	13%	MSAC report no. 1223
K	Probability of no implant-related complications	87%	MSAC report no. 1223
L	Weighted average cost per hospitalisation for CRT-D implantation	$6,187	Row I = (C*J) + (F*K)

Source: Private Sector National Cost Weights Cost Collection Report for AR-DRG v 5.1, Round 13 (2008–09), adopted from MSAC Application no. 1223

[a] Costs are converted to 2015 AUD using inflation calculator provided by Reserve Bank of Australia; < www.rba.gov.au/calculator/annualDecimal.html>; accessed 24 March 2016.

AR-DRG = Australian Refined Diagnosis Related Groups; CRT-D = cardiac resynchronisation therapy device capable of defibrillation; ICD = implantable cardioverter defibrillator

Table 107 Total cost per ICD device implantation procedure in a private hospital

Resource type	Unit cost	% of fee claimable [a]	Cost per procedure	Bearer of cost	Source
Medical services					
Insertion of defibrillator lead	$1,052.65	100%	$1,052.65	MBS/PHI	MBS 38384
Insertion of pacemaker lead	$638.65	50%	$319.35	MBS/PHI	MBS 38350
Insertion of generator	$255.45	25%	$63.90	MBS/PHI	MBS 38365
Anaesthesia	$138.60	100%	$138.60	MBS/PHI	MBS 21941
Prostheses components					
Defibrillation lead	$9,000.00	NA	$9,000.00	PHI	PL product group 8.07
Pacemaker lead	$1,294.00	NA	$1,294.00	PHI	PL product group

Resource type	Unit cost	% of fee claimable [a]	Cost per procedure	Bearer of cost	Source
					8.08.08–8.09
ICD generator	$45,458.00	NA	$45,458.00	PHI	PL product group 8.03
Hospital services					
Hospitalisation for ICD implantation	$5,628.00	NA	$5,628.00	Private hospitals	Table 12
Total cost per ICD implant			$62,955.00		

Source: Medicare Benefits Schedule (March 2016), MSAC Application no. 1223, Private Sector National Cost Weights Cost Collection Report for AR-DRG v 5.1, Round 13 (2008–09)

[a] The percentage of fee claimable is determined in accordance with the MBS Multiple Services Rule.

ICD = implantable cardioverter defibrillator; MBS = Medicare Benefits Schedule; NA = not applicable; PHI = private health insurer

Table 108 Total cost per CRT-D device implantation procedure in a private hospital

Resource type	Unit cost	% of fee claimable [a]	Cost per procedure	Bearer of cost	Source
Medical services					
Insertion of LV lead	$1,224.60	100%	$1,224.60	MBS/PHI	MBS 38368
Insertion of defibrillator lead	$1,052.65	50%	$526.35	MBS/PHI	MBS 38384
Insertion of pacemaker lead	$638.65	25%	$159.70	MBS/PHI	MBS 38350
Insertion of generator	$255.45	25%	$63.90	MBS/PHI	MBS 38365
Anaesthesia	$138.60	100%	$138.60	MBS/PHI	MBS 21941
Prostheses components					
LV lead	$6,240.00	NA	$6,240.00	PHI	PL product group 8.08.11
Defibrillation lead	$9,000.00	NA	$9,000.00	PHI	PL product group 8.07
Pacemaker lead	$1,294.00	NA	$1,294.00	PHI	PL product group 8.08.08–8.09
CRT-D generator	$51,786.00	NA	$45,458.00	PHI	PL product group 8.03
Hospital services					
Hospitalisation of CRT-D implantation	$6,187.00	NA	$6,187.00	Private hospitals	Table 106
Total cost per CRT-D implant			$70,292.00		

Source: Medicare Benefits Schedule (March 2016), MSAC Application no. 1223, Private Sector National Cost Weights Cost Collection Report for AR-DRG v 5.1, Round 13 (2008–09)

[a] The percentage of fee claimable is determined in accordance with the MBS Multiple Services Rule

CRT- D = cardiac resynchronisation therapy device capable of defibrillation; LV = left ventricular; MBS = Medicare Benefits Schedule; NA = not applicable; PHI = private health insurer

COST PER PACEMAKER IMPLANTATION PROCEDURE

Table 109 Cost per pacemaker implantation procedure in public sector

	AR-DRG	Seps	Weight	Cost [a]
Implantation or replacement of pacemaker, total system with catastrophic complications	F12A	1,346	20.4%	$22,728
Implantation or replacement of pacemaker, total system without catastrophic complications	F12B	5,248	79.6%	$11,818
Weighted cost (adjusted for inflation) [b]				$14,257

[a] Price weight for the respective AR-DRGs (Independent Hospital Pricing Authority (IHPA) 2015a) * the NEP 2016–17 ($4,883) (Independent Hospital Pricing Authority (IHPA) 2016)

[b] $14,045 converted to $14,257 in 2015 AUD using inflation calculator provided by Reserve Bank of Australia; < www.rba.gov.au/calculator/annualDecimal.html>; accessed 24 March 2016

AR-DRG = Australian Refined Diagnosis Related Groups; NEP = National Efficient Price; Seps = number of hospital separations

Table 110 Cost per pacemaker implantation procedure in private sector

	Medicare	PHI	Cost
Total average hospital component		$13,895	$13,994
Total average medical services	$722	$598	$1,364
Sum	$722	$14,493	$15,358
Total cost, adjusted for inflation (2015 AUD) [a]			$15,590 [a]

Source: <http://healthtopics.hcf.com.au/CardiacPacemakersDefibrillators.aspx?gender=male&topic=chest>; accessed 24 March 2016

[a] Converted to 2015 AUD using inflation calculator provided by Reserve Bank of Australia; < www.rba.gov.au/calculator/annualDecimal.html>; accessed 24 March 2016

PHI = private health insurer

COST PER CABG SURGERY

Table 111 Cost per CABG implantation procedure in public sector

	AR-DRG	Seps	Weight	Cost [a]
Coronary bypass without invasive cardiac investigation with catastrophic complications	F06A	2,240	39.1%	$39,199
Coronary bypass without invasive cardiac investigation without catastrophic complications	F06B	1,883	32.8%	$29,405
Coronary bypass with invasive cardiac investigation with catastrophic complications	F05A	1,105	19.3%	$53,462
Coronary bypass with invasive cardiac investigation with catastrophic complications	F05B	508	8.9%	$39,809
Weighted cost (adjusted for inflation) [b]				$39,371

[a] Price weight for the respective AR-DRGs (Independent Hospital Pricing Authority (IHPA) 2015a) * the NEP 2016–17 ($4,883) (Independent Hospital Pricing Authority (IHPA) 2016)

[b] Converted to 2015 AUD using inflation calculator provided by Reserve Bank of Australia; < www.rba.gov.au/calculator/annualDecimal.html>; accessed 24 March 2016

AR-DRG = Australian Refined Diagnosis Related Groups; CABG = coronary artery bypass grafting; NEP = National Efficient Price; Seps = number of hospital separations

Table 112 Cost per CABG surgery in private sector

	Medicare	PHI	Cost
Total average hospital component		$28,735	$28,915
Total average medical services	$7,750	$6,873	$16,063
Sum	$7,750	$35,608	$44,978
Total cost, adjusted for inflation (2015 AUD) [a]			$45,656

Source: <http://healthtopics.hcf.com.au/CoronaryArteryBypassGraft.aspx?gender=male&topic=chest>; accessed 24 March 2016

[a] $44,978 converted to $45,656 (2015 AUD) using inflation calculator provided by Reserve Bank of Australia; < www.rba.gov.au/calculator/annualDecimal.html>; accessed 24 March 2016

CABG = coronary artery bypass grafting; PHI = private health insurer

COST PER VALVULAR SURGERY

Table 113 Cost per valvular surgery in public sector

	AR-DRG	Seps	Weight	Cost [a]
Cardiac valve procedures with CPB Pump W Invasive Cardiac Investigation complications	F03A	458	11.6%	$66,055
Coronary bypass without invasive cardiac investigation without catastrophic complications	F03B	111	2.8%	$38,223
Coronary bypass with invasive cardiac investigation with catastrophic complications	F04A	2,554	64.6%	$50,470
Coronary bypass with invasive cardiac investigation with catastrophic complications	F04B	831	21.0%	$34,996
Weighted cost (adjusted for inflation) [b]				$49,413

[a] Price weight for the respective AR-DRGs (Independent Hospital Pricing Authority (IHPA) 2015a) * the NEP 2016–17 ($4,883) (Independent Hospital Pricing Authority (IHPA) 2016)

[b]$48,679 converted to 2015 AUD using inflation calculator provided by Reserve Bank of Australia; < www.rba.gov.au/calculator/annualDecimal.html>; accessed 24 March 2016

AR-DRG = Australian Refined Diagnosis Related Groups; CPB = cardiopulmonary bypass; NEP = National Efficient Price; Seps = number of hospital separations

Table 114 Cost per valvular surgery in private sector

	Medicare	PHI	Cost
Total average hospital component		$33,093	$33,261
Total average medical services	$7,839	$7,011	$16,308
Sum	$7,839	$40,104	$49,569
Total cost, adjusted for inflation (2015 AUD) [a]			$50,317

Source: <http://healthtopics.hcf.com.au/HeartValveReplacement.aspx?gender=male&topic=chest>; accessed 24 March 2016

[a] $49,569 converted to $50,317 (2015 AUD) using inflation calculator provided by Reserve Bank of Australia; < www.rba.gov.au/calculator/annualDecimal.html>; accessed 24 March 2016

PHI = private health insurer

COST PER OTHER CARDIAC SURGERY

Table 115 Cost per other cardiac surgeries in public sector

	AR-DRG	Seps	Weight	Cost [a]
Other cardiothoracic procedures without CPB pump with catastrophic complications	F09A	436	39.4%	$36,711
Other cardiothoracic procedures without CPB pump without catastrophic complications	F09B	500	45.1%	$13,358
Other cardiothoracic procedures without CPB pump, died or transferred to acute facility <5 days	F09C	172	15.5%	$12,200
Weighted cost (adjusted for inflation) [b]				$22,705

[a] Price weight for the respective AR-DRGs (Independent Hospital Pricing Authority (IHPA) 2015a) * the NEP 2016–17 ($4,883) (Independent Hospital Pricing Authority (IHPA) 2016)
[b] $22,368 converted to 2015 AUD using inflation calculator provided by Reserve Bank of Australia; < www.rba.gov.au/calculator/annualDecimal.html>; accessed 24 March 2016

AR-DRG = Australian Refined Diagnosis Related Groups; CPB = cardiopulmonary bypass; NEP = National Efficient Price; Seps = number of hospital separations

Table 116 Cost per valvular surgery in private sector

	AR-DRG	Seps	Weight	Cost [a]
Other cardiothoracic procedures without CPB pump with catastrophic complications	F09A	129	29.9%	$25,941
Other cardiothoracic procedures without CPB pump without catastrophic complications	F09B	303	70.1%	$11,916
Weighted cost (adjusted for inflation) [b]				$18,570

[a] Source: Private Sector National Cost Weights Cost Collection Report for AR-DRG v 5.1, Round 13 (2008–09).
[b] $16,104 (2009 AUD) converted to $18,570 (2015 AUD) using inflation calculator provided by Reserve Bank of Australia; < www.rba.gov.au/calculator/annualDecimal.html>; accessed 24 March 2016

AR-DRG = Australian Refined Diagnosis Related Groups; CPB = cardiopulmonary bypass; Seps = number of hospital separations

COST PER HEART TRANSPLANT SURGERY

Table 117 Cost per heart transplant surgery in public sector (and assumed for private sector).

	AR-DRG	Seps	Weight	Cost [a]
Heart transplant	A05Z	64		$160,065
Cost (adjusted for inflation) [b]				$162,479

[a] Price weight for the respective AR-DRGs (Independent Hospital Pricing Authority (IHPA) 2015a) * the NEP, 2016–17 ($4,883) (Independent Hospital Pricing Authority (IHPA) 2016)
[b] Converted to 2015 AUD using inflation calculator provided by Reserve Bank of Australia; < www.rba.gov.au/calculator/annualDecimal.html>; accessed 24 March 2016

AR-DRG = Australian Refined Diagnosis Related Groups; CPB = cardiopulmonary bypass; NEP = National Efficient Price; Seps = number of hospital separations

In Australia, heart transplant surgeries are predominantly performed in public hospitals. The number of separations in the private hospital cost report 2013–14 for A05Z (Heart Transplant) was less than 5, and hence was redacted. Therefore, the private sector costs and weighted costs are assumed to be similar to the costs in the public sector.

APPENDIX N SENSITIVITY ANALYSES FOR COST-EFFECTIVENESS ANALYSES: POPULATION IIA

USING PUBLIC SECTOR COSTS

When public sector costs are used in place of weighted costs, all ICERs increase marginally due to the increase in incremental cost of CMR testing ($514 compared with $403 per patient in the base-case), resulting in an increase in incremental cost per inappropriate patient management avoided ($4,022 compared with $3,158 in the base-case) (Table 118).

Table 118 Sensitivity analysis, ICERs using public sector costs

Cost-effectiveness	ICER
Incremental cost per inappropriate patient management avoided (base-case)	$3,158
Incremental cost per inappropriate procedure avoided	$7,203
Incremental cost per inappropriate implantable device avoided	$10,974
Incremental cost per inappropriate cardiac surgery avoided	$20,963
Incremental cost per inappropriate patient management avoided	$4,022

Base-case = weighted cost public and private sector; CMR = cardiac magnetic resonance (imaging); ICER = incremental cost-effectiveness ratio

USING PRIVATE SECTOR COSTS

When private sector costs are used in place of weighted costs, all ICERs decrease due to the decrease in incremental cost of CMR testing ($279 compared with $403 per patient in the base-case), resulting in a decrease in incremental cost per inappropriate patient management avoided ($2,188 compared with $3,158 in the base-case) (Table 119).

Table 119 Sensitivity analysis, ICERs using private sector costs

Cost-effectiveness	ICER
Incremental cost per inappropriate patient management avoided (base-case)	$3,158
Incremental cost per inappropriate procedure avoided	$3,919
Incremental cost per inappropriate implantable device avoided	$5,971
Incremental cost per inappropriate cardiac surgery avoided	$11,407
Incremental cost per inappropriate patient management avoided	$2,188

CMR = cardiac magnetic resonance (imaging); ICER = incremental cost-effectiveness ratio

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