**ABSTRACT**

**Background**

Coronary artery disease (CAD) remains a major public health problem in Australia and globally. A variety of imaging techniques allow for both anatomical and functional assessment of CAD and selection of the optimal investigation pathway is challenging. Cardiovascular magnetic resonance (CMR) is not widely used in Australia, partly due to perceived cost and lack of Federal Government reimbursement compared to the alternative techniques. The aim of this study was to estimate the cost-effectiveness of different diagnostic strategies in identifying significant CAD in patients with chest pain suggestive of angina using the evidence gathered in the CE-MARC trial, analysed from the Australian healthcare perspective.

**Methods**

A decision analytic model coupled with three distinct Markov models allowed eight potential clinical investigation strategies to be considered; combinations of exercise electrocardiogram stress testing (EST), single-photon emission computed tomography (SPECT), stress CMR, and invasive coronary angiography (ICA). Costs were from the Australian healthcare system in Australian dollars, and outcomes were measured in terms of quality-adjusted life-years. Parameter estimates were derived from the CE-MARC and EUROPA trials, and from reviews of the published literature.

**Results**

The most cost-effective diagnostic strategy, based on a cost-effectiveness threshold of $45,000 to $75,000 per QALY gained, was EST, followed by stress CMR if the EST was positive or inconclusive, followed by ICA if the CMR was positive or inconclusive; this held true in the base case and the majority of scenario analyses.

**Conclusions**

This economic evaluation shows that an investigative strategy of stress CMR if EST is inconclusive or positive is the most cost-effective approach for diagnosing significant coronary disease in chest pain patients within the Australian healthcare system.

**Key words:** cardiovascular magnetic resonance; cost-effectiveness; coronary heart disease; stress perfusion

**Introduction**

Coronary artery disease (CAD) remains a major public health problem in Australia and around the globe. A variety of imaging techniques allow for both anatomical and functional assessment of CAD and, as a result, the selection of the optimal investigation pathway is increasingly challenging. In general, there is the need for investigative pathways that are feasible, safe, cost-effective and of high diagnostic accuracy.

Physicians traditionally choose between one or a combination of tests that provide anatomical information regarding the degree of atheroma and stenosis (e.g. computed tomography coronary angiography, CTCA) and/or functional tests to detect ischaemia or reduced myocardial blood flow (e.g. exercise electrocardiogram stress testing (EST), stress echocardiography, stress single-photon emission computed tomography (SPECT), or stress perfusion cardiovascular magnetic resonance (stress CMR)) in order to exclude significant CAD. SPECT is the most common non-invasive ischaemia test worldwide, however it exposes patients to ionising radiation and its diagnostic accuracy is variable. In comparison, CMR with myocardial stress perfusion imaging has no radiation exposure and has high diagnostic performance in the identification of significant coronary ischaemia, with studies showing stress CMR has a sensitivity, specificity, and diagnostic accuracy of 87-89%, 84-93%, and 89-91%, respectively [1, 2]. Compared to the gold standard invasive fractional flow reserve (FFR), stress CMR with adenosine has a high sensitivity of 91% and specificity of 94% for identification of lesion-specific iscaemia[3]. In addition, stress CMR delivers important prognostic information in the intermediate risk chest pain setting [4] , is a stronger predictor of prognosis than SPECT [5], and provides late gadolinium enhancement imaging with additional information on segmental viability.

From a health economics point of view, stress CMR has also been shown to be cost-effective in the diagnosis and management of CAD in a number of countries [6-10] – it has a high diagnostic yield, allowing a reduction in false positive studies (and thus a reduction in costly invasive investigations), and offers better use of resources. Two recent large-scale, multi-centre, randomised comparative effectiveness trials have shown that first line investigation of stable chest pain by stress CMR significantly reduced the rate of ICA where no obstructive disease was found as compared to UK 2010 NICE guidelines [11], and that stress CMR compared to a strategy of ICA +/- FFR resulted in lower overall rates of revascularisation with no difference in major adverse cardiovascular events [12].

Despite these major advantages of stress CMR, it is not publicly funded in Australia, which reduces patient access. Consequently, it is infrequently used in Australia compared to other diagnostic testing strategies. One impediment to public funding of stress CMR in Australia is a lack of local cost-effectiveness data to assist decision makers and physicians in weighing up the benefits of improved diagnostic accuracy, patient safety and experience, and savings on further downstream investigations, versus the isolated monetary cost of the MRI scan.

The Clinical Evaluation of MAgnetic Resonance imaging in Coronary heart disease (CE-MARC) trial was the largest prospective diagnostic accuracy evaluation to date of stress CMR compared with the reference standard of ICA for patients referred to cardiologists for the investigation of symptoms consistent with angina pectoris.[1, 13] All patients underwent EST if physically able, and were scheduled for both SPECT and CMR (in random order) followed by ICA irrespective of clinical intention. Subsequent cost-effectiveness analyses based on this trial demonstrated lower costs with a stress CMR based strategy, both in the UK and other healthcare environments.[6, 9]

The aim of this study was to estimate the cost-effectiveness of different diagnostic testing strategies, including stress CMR, ICA, EST, and SPECT, in identifying significant CAD in patients with chest pain suspicious of angina using the evidence gathered in the CE-MARC study but viewed from the Australian healthcare perspective.

**Methods**

The methods used in this analysis are consistent with those detailed by the National Institute for Health and Care Excellence (NICE) and were based on the UK cost-effectiveness analysis of the CE-MARC trial[6]. The model included a decision analytic model coupled with three distinct Markov models, comparing stress CMR, ICA, EST, and SPECT. Parameter estimates were derived from the CE-MARC[1], and EUROPA[14] trials, and from reviews of the published literature (refer to CE-MARC cost-effectiveness study[6] for full details of all parameters). Costs were from the Australian healthcare system perspective, and outcomes were measured in terms of quality-adjusted life-years (QALYs). The time horizon of the analysis was 50 years, and costs and QALYs were discounted at 5% per annum, consistent with Australian guidelines[15]. Stress echocardiography and CTCA were not assessed in these models as they were not part of the original CE-MARC derivation cohort.

**Base case analysis**

For the base case analysis, the case of a 60 year old male with grade 2 symptoms on the Canadian Cardiovascular Society (CCS) angina scale and pre-test likelihood of significant stenosis requiring revascularization of 39.5% was used; 15.9% of patients were considered to have CAD but not significant coronary artery stenosis (based on CE-MARC data)[1]. The choice of characteristics was based on real patient data from the CE-MARC trial and clinical opinion. Alternative scenarios for age, sex, CCS grade, varying pre-test likelihood of disease, and costs of the diagnostic tests in the Australian healthcare system were also modelled.

**Diagnostic strategies and pathways**

Eight possible diagnostic strategies were derived from the CE-MARC trial for comparison:

1. ICA only
2. EST, followed by ICA if EST positive or inconclusive
3. EST, followed by CMR if EST positive or inconclusive, followed by ICA if the CMR positive or inconclusive
4. EST, followed by SPECT if EST positive or inconclusive, followed by ICA if the SPECT positive or inconclusive
5. CMR, followed by ICA if CMR positive or inconclusive
6. SPECT, followed by ICA if SPECT positive or inconclusive
7. EST, followed by ICA if positive, or followed by CMR if EST inconclusive, followed by ICA if CMR positive or inconclusive
8. EST, followed by ICA positive, or followed by SPECT if EST inconclusive, followed by ICA if SPECT positive or inconclusive.

A major aim of diagnostic testing is to identify high risk patients with significant coronary artery stenosis who may benefit from revascularization (either percutaneous coronary intervention or coronary artery bypass surgery). For the model, it was assumed that all patients who are suspected of having significant coronary stenosis must undergo a coronary angiogram as a definitive test before revascularisation. ICA was regarded as the ‘reference standard’ test (ie, assumed sensitivity and specificity of 100%, no false positives), so it was assumed that no patients would receive an inappropriate revascularization procedure. However, as the non-invasive diagnostic tests (EST, SPECT and stress CMR) are not 100% accurate (ie, sensitivities and specificities below 100%), some patients with clinically significant stenosis requiring revascularisation will not progress across the diagnostic pathways to ICA, as a consequence of a false negative (FN) test. These patients incorrectly identified as not having significant stenosis will not receive an appropriate revascularisation procedure and, as a result, may experience less relief from their angina symptoms until their disease is subsequently correctly managed. It was assumed, however, that these ‘false negative’ cases would have their ischaemia treated by optimal medical therapy. Furthermore, some patients without clinically significant stenosis will progress to ICA, as a consequence of a false positive test, with its associated cost and morbidity/mortality risk. There will also be patients without clinically significant stenosis and hence who do not require revascularisation, but who do suffer from angina, and these patients were assumed to receive risk factor modification and optimal medical management.

**Health outcomes**

Health outcomes were reported in terms of QALYs, which combine survival and Health related quality of life (HRQoL) into a single measure. Australian all-cause mortality rates and cardiovascular mortality rates by age and sex were applied to estimate survival[16]. HRQoL was estimated using the EuroQol 5 Dimension (EQ-5D) instrument. Australian population norms for the EQ-5D[17], by age and sex, were combined with other sources and assumptions to estimate QALYs by initial CCS grade and treatment status (whether the patient had received a revascularisation procedure or medical management). Full details of the sources and methods used are previously published[6].

**Resource use and costs**

Costs were reported in 2016-2017 Australian dollars (AUD). Diagnostic testing, revascularisation and ongoing treatment costs were based on Medicare Benefit Schedule (MBS) fees, the National Hospital Cost Data Collection, and published Australian observational studies (Table 1). Costs were inflated to 2016-2017 values using the Australian Institute for Health and Welfare health price index where required[18]. Of note, at the time of publication there was no MBS item for stress CMR imaging, therefore, in the base case a cost of $900 was assumed for stress CMR, as proposed in a recent assessment report for the Medical Services Advisory Committee (MSAC)[19]. However, analyses were conducted to consider the cost differential between SPECT and stress CMR imaging. Costs applied in the model are summarised in Table 1.

**Analysis**

Standard decision rules were used to identify the most cost-effective diagnostic strategy for CAD based on a given set of patient characteristics. This involved ranking strategies in terms of their expected costs and QALYs, removing strategies which result in fewer QALYs and higher costs than one or more other strategies (i.e. dominated) and thus would never be funded, then removing strategies which would also result in fewer QALYs and higher costs if patients received a combination of the other strategies (i.e. extendedly dominated). Incremental cost-effectiveness ratios (ICERs) were calculated for all remaining strategies as follows:

$$ICER= \frac{Cost\_{Diagnostic strategy A}-Cost\_{Diagnostic strategy B}}{QALYs\_{Diagnostic strategy A}-QALYs\_{Diagnostic strategy B}}$$

To assess which option was potentially cost-effective, the range of cost-effectiveness thresholds

for Australia ($45,000–$75,000 per QALY, midpoint $60,000)[20] was used, such that the most effective option with an ICER below the threshold was considered the cost-effective strategy.

To reflect the uncertainty in the evidence used in the model, input parameters were entered as probability distributions. Probabilistic sensitivity analysis was then used to calculate the mean costs and QALYs for each strategy and the probability that a strategy was cost-effective for the cost-effectiveness threshold.

**Results**

Cost effectiveness results for the base case are presented in Table 2, with strategies that result in fewer QALYs and higher costs (dominated and extendedly dominated) excluded. In the base case, 3 of the 8 strategies were not excluded (Strategies 3, 5 and 7).

The least costly strategy that was included was Strategy 3 (EST, followed by CMR if EST positive or inconclusive, followed by ICA if CMR positive or inconclusive). When the next more costly strategy, Strategy 5 (CMR, followed by ICA if CMR positive or inconclusive), was compared with Strategy 3, an ICER of $440,325 per QALY gained was estimated. When the next more costly strategy, Strategy 7 (EST, followed by ICA if positive, or followed by CMR if EST inconclusive, followed by ICA if CMR positive or inconclusive), was compared with Strategy 5, an ICER of $449,208 per QALY gained was estimated. Strategy 3 was therefore the most cost-effective diagnostic strategy based on a cost-effectiveness threshold of $45,000 to $75,000 per QALY gained.

Different scenarios related to sex, age, severity of symptoms (CCS), prior likelihood of disease, and stress CMR costs are displayed in Table 3. Changing the sex of the base case from male to female, reducing or increasing the age to 50 or 70 years old respectively (compared to 60 years old in the male base case), and increasing the severity of symptoms from CCS grade 2 to grade 4 had minimal impact on the results, with Strategy 3 remaining the most cost-effective diagnostic strategy.

Reducing the prior likelihood to 20% (compared with 39.5% in the base-case) led to Strategy 3 dominating all other strategies (ie, lower costs and more QALYs). Increasing the prior likelihood to 60% led to Strategy 7 (EST, followed by ICA if positive, or followed by CMR if EST inconclusive, followed by ICA if CMR positive or inconclusive) being the most cost-effective. Further increasing the prior likelihood to 80% led to Strategy 2 (EST, followed by ICA if EST positive or inconclusive) being the most cost-effective given the upper threshold value of $75,000 per QALY.

If EST was deemed inappropriate, ie. the patient cannot exercise on a treadmill, then this led to Strategy 5 (CMR, followed by ICA if CMR positive or inconclusive) dominating all other strategies.

Because there was no set price for stress CMR at the time of this study, the cost increment of stress CMR compared with SPECT was varied to assess the impact on cost-effectiveness in the base case. If CMR costs were the same as SPECT or if the cost was $100 more than SPECT, the results were similar. If the CMR cost was increased to $250 and $500 more than SPECT then Strategy 3 became more costly and less effective than the other strategies, and thus no longer appeared among the non-dominated strategies. In these scenarios Strategy 5 (CMR, followed by ICA if CMR positive or inconclusive) became the most cost-effective strategy at the lower threshold value of $45,000 per QALY.

**Discussion**

The results of this economic evaluation based on strategies and modelling from the CE-MARC trial, show that Strategy 3 (EST, followed by CMR if EST is positive or inconclusive, followed by ICA if the CMR is positive or inconclusive) is the most cost-effective diagnostic strategy in diagnosing significant coronary disease in patients with stable chest pain at the Australian cost-effectiveness thresholds. These findings are consistent with the extensive published trial literature on stress CMR showing high diagnostic accuracy [1], high prognostic discrimination [5, 21], clinical utility in acting as an effective gate-keeper for diagnostic ICA [11], and as an effective first line strategy for guiding revascularisation decisions in patients with stable angina[12]. These data support the wider use of stress CMR in Australian clinical practice.

At present, however, there remain issues surrounding the perceived cost and accessibility of stress CMR in Australia. It is important to consider this because imaging tests for cardiovascular diseases contribute a large proportion of healthcare costs. Although an argument is often made that “simple” tests, such as EST, may cost less on face value, careful evaluation is needed about the cumulative cost of downstream investigations that may occur because of false-positive results.

Stress CMR is a mature imaging modality for the investigation of coronary artery disease, which is acknowledged in international clinical guidelines. The United Kingdom (UK) leads development in this field and Australia is in the early stages of adoption. CMR trends in Australia are difficult to measure and currently there is limited reimbursement available for CMR scans. In 2008 there were 20,597 CMR scans performed in the UK and 38,485 in 2010, an increase of over 85% in only two years [22]. This increase in demand is being driven predominantly by the most common indications for CMR including the assessment of ischaemia and viability, and cardiomyopathy and heart failure[22]. In contrast, within Australia, there is currently no reimbursement for CMR to investigate and manage most of these pathologies. Also, of note, Australia has different CMR related infrastructure compared to the UK - although it has more MRI units per million population than the UK [23], there is a disproportionately lower utilisation rate of MRI [24]. Not all magnets in Australia are suitably equipped to perform CMR (eg. they need specific cardiac coils and cardiac software), and both adequate staffing (trained physicians) and appropriate reimbursement remain challenges to the expansion of this technology in Australia.

The secondary analyses evaluating different scenarios also showed that stress CMR remains cost-effective at higher incremental costs than SPECT. However, in the scenario analyses, when the incremental cost of CMR was $250-$500 more than SPECT, strategy 5 became dominant (CMR, followed by ICA if CMR positive or inconclusive). Changing the prior likelihood of disease in the scenarios analyses supported the use of stress CMR in the low-to-intermediate risk populations. Increasing the prior likelihood of disease to high risk (>80%) pushed stress CMR out and led to Strategy 2 (EST followed by ICA if positive) being the most cost-effective. This information may be helpful in terms of setting future restrictions on access to stress CMR in Australia.

**Limitations**

The approach of using costs based on the MBS excludes any potential out-of-pocket patient co-payments above the MBS fee that may occur at certain institutions and service providers in Australia, particularly in private healthcare.

This study doesn’t include strategies and costs for stress echocardiography and CT coronary angiography, which are both frequently utilised in Australia. However, these investigations were not part of the CE-MARC trial upon which this cost effectiveness analysis was based and their inclusion would have necessitated the adoption of multiple assumptions, rather than relying on robust randomized clinical trial outcomes data.

**Conclusions**

This economic evaluation shows that an investigative strategy using stress CMR if EST is inconclusive or positive followed by ICA if the stress CMR is positive or inconclusive is the most cost-effective approach for diagnosing significant coronary disease in chest pain patients within the Australian healthcare system. These findings support more widespread adoption of stress CMR for CAD assessment in Australian clinical practice, and are consistent with the high diagnostic accuracy of stress CMR and cost effectiveness of this modality demonstrated in other healthcare systems.

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