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Cardiac Magnetic Resonance Imaging for the Diagnosis of Coronary Artery Disease

An Evidence-Based Analysis

Presented to the Ontario Health Technology Advisory Committee in January, 2010

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About the Medical Advisory Secretariat

The Medical Advisory Secretariat is part of the Ontario Ministry of Health and Long-Term Care. The mandate of the Medical Advisory Secretariat is to provide evidence-based policy advice on the coordinated uptake of health services and new health technologies in Ontario to the Ministry of Health and Long-Term Care and to the healthcare system. The aim is to ensure that residents of Ontario have access to the best available new health technologies that will improve patient outcomes.

The Medical Advisory Secretariat also provides a secretariat function and evidence-based health technology policy analysis for review by the Ontario Health Technology Advisory Committee (OHTAC).

The Medical Advisory Secretariat conducts systematic reviews of scientific evidence and consultations with experts in the health care services community to produce the *Ontario Health Technology Assessment Series*.

About the Ontario Health Technology Assessment Series

To conduct its comprehensive analyses, the Medical Advisory Secretariat systematically reviews available scientific literature, collaborates with partners across relevant government branches, and consults with clinical and other external experts and manufacturers, and solicits any necessary advice to gather information. The Medical Advisory Secretariat makes every effort to ensure that all relevant research, nationally and internationally, is included in the systematic literature reviews conducted.

The information gathered is the foundation of the evidence to determine if a technology is effective and safe for use in a particular clinical population or setting. Information is collected to understand how a new technology fits within current practice and treatment alternatives. Details of the technology's diffusion into current practice and input from practising medical experts and industry add important information to the review of the provision and delivery of the health technology in Ontario. Information concerning the health benefits; economic and human resources; and ethical, regulatory, social and legal issues relating to the technology assist policy makers to make timely and relevant decisions to optimize patient outcomes.

If you are aware of any current additional evidence to inform an existing evidence-based analysis, please contact the Medical Advisory Secretariat: MASinfo.moh@ontario.ca. The public consultation process is also available to individuals wishing to comment on an analysis prior to publication. For more information, please visit http://www.health.gov.on.ca/english/providers/program/ohtac/public_engage_overview.html.

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List of Abbreviations

AUC	Area under the curve
BIA	Budge impact analysis
CAD	Coronary artery disease
CI	Confidence interval(s)
CDN	Canadian dollars
DOR	Diagnostic odds ratio
ECHO	Echocardiography
GBP	Great Britain pounds
ICER	Incremental cost-effectiveness ratio
LYS	Life years saved
MAS	Medical Advisory Secretariat
MOHLTC	Ministry of Health and Long-Term Care
MPI	Myocardial perfusion imaging
OCCI	Ontario Cost Casing Initiative
OHIP	Ontario Health Insurance Plan
OR	Odds ratio
QALY	Quality-adjusted life years
RCT	Randomized controlled trial
SPECT	Single-photon emission computed tomography
SROC	Summary receiver operating characteristic
USD	United States dollars
WTP	Willingness-to-pay

Executive Summary

In July 2009, the Medical Advisory Secretariat (MAS) began work on Non-Invasive Cardiac Imaging Technologies for the Diagnosis of Coronary Artery Disease (CAD), an evidence-based review of the literature surrounding different cardiac imaging modalities to ensure that appropriate technologies are accessed by patients suspected of having CAD. This project came about when the Health Services Branch at the Ministry of Health and Long-Term Care asked MAS to provide an evidentiary platform on effectiveness and cost-effectiveness of non-invasive cardiac imaging modalities.

After an initial review of the strategy and consultation with experts, MAS identified five key non-invasive cardiac imaging technologies for the diagnosis of CAD. Evidence-based analyses have been prepared for each of these five imaging modalities: cardiac magnetic resonance imaging, single photon emission computed tomography, 64-slice computed tomographic angiography, stress echocardiography, and stress echocardiography with contrast. For each technology, an economic analysis was also completed (where appropriate). A summary decision analytic model was then developed to encapsulate the data from each of these reports (available on the OHTAC and MAS website).

The Non-Invasive Cardiac Imaging Technologies for the Diagnosis of Coronary Artery Disease series is made up of the following reports, which can be publicly accessed at the MAS website at: www.health.gov.on.ca/mas or at www.health.gov.on.ca/english/providers/program/mas/mas_about.html

1. Single Photon Emission Computed Tomography for the Diagnosis of Coronary Artery Disease: An Evidence-Based Analysis
2. Stress Echocardiography for the Diagnosis of Coronary Artery Disease: An Evidence-Based Analysis
3. Stress Echocardiography with Contrast for the Diagnosis of Coronary Artery Disease: An Evidence-Based Analysis
4. 64-Slice Computed Tomographic Angiography for the Diagnosis of Coronary Artery Disease: An Evidence-Based Analysis
5. Cardiac Magnetic Resonance Imaging for the Diagnosis of Coronary Artery Disease: An Evidence-Based Analysis

Pease note that two related evidence-based analyses of non-invasive cardiac imaging technologies for the assessment of myocardial viability are also available on the MAS website:

1. Positron Emission Tomography for the Assessment of Myocardial Viability: An Evidence-Based Analysis
2. Magnetic Resonance Imaging for the Assessment of Myocardial Viability: an Evidence-Based Analysis

The Toronto Health Economics and Technology Assessment Collaborative has also produced an associated economic report entitled:

The Relative Cost-effectiveness of Five Non-invasive Cardiac Imaging Technologies for Diagnosing Coronary Artery Disease in Ontario [Internet]. Available from: http://theta.utoronto.ca/reports/?id=7

Objective

The objective of this analysis was to determine the diagnostic accuracy of cardiac magnetic resonance imaging (MRI) for the diagnosis of patients with known/suspected coronary artery disease (CAD) compared to coronary angiography.

Cardiac MRI

Stress cardiac MRI is a non-invasive, x-ray free imaging technique that takes approximately 30 to 45 minutes to complete and can be performed using to two different methods, a) perfusion imaging following a first pass of an intravenous bolus of gadolinium contrast, or b) wall motion imaging. Stress is induced pharmacologically with either dobutamine, dipyridamole, or adenosine, as physical exercise is difficult to perform within the magnet bore and often induces motion artifacts. Alternatives to stress cardiac perfusion MRI include stress single-photon emission computed tomography (SPECT) and stress echocardiography (ECHO). The advantage of cardiac MRI is that it does not pose the radiation burden associated with SPECT. During the same sitting, cardiac MRI can also assess left and right ventricular

dimensions, viability, and cardiac mass. It may also mitigate the need for invasive diagnostic coronary angiography in patients with intermediate risk factors for CAD.

Evidence-Based Analysis

Literature Search

A literature search was performed on October 9, 2009 using OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, EMBASE, the Cumulative Index to Nursing & Allied Health Literature (CINAHL), the Cochrane Library, and the International Agency for Health Technology Assessment (INAHTA) for studies published from January 1, 2005 to October 9, 2008. Abstracts were reviewed by a single reviewer and, for those studies meeting the eligibility criteria, full-text articles were obtained. Reference lists were also examined for any relevant studies not identified through the search. Articles with unknown eligibility were reviewed with a second clinical epidemiologist and then a group of epidemiologists until consensus was established. The quality of evidence was assessed as high, moderate, low or very low according to GRADE methodology.

Given the large amount of clinical heterogeneity of the articles meeting the inclusion criteria, as well as suggestions from an Expert Advisory Panel Meeting held on October 5, 2009, the inclusion criteria were revised to examine the effectiveness of cardiac MRI for the detection of CAD.

Inclusion Criteria

- Heath technology assessments, systematic reviews, randomized controlled trials, observational studies
- ≥20 adult patients enrolled.
- Published 2004-2009
- Licensed by Health Canada
- For diagnosis of CAD:
  - Reference standard is coronary angiography
  - Significant CAD defined as ≥ 50% coronary stenosis
  - Patients with suspected or known CAD
  - Reported results by patient, not segment

Exclusion Criteria

- Non-English studies
- Grey literature
- Planar imaging
- MUGA
- Patients with recent MI (i.e., within 1 month)
- Patients with non-ischemic heart disease
- Studies done exclusively in special populations (e.g., women, diabetics)

Outcomes of Interest

- Sensitivity and specificity
- Area under the curve (AUC)
- Diagnostic odds ratio (DOR)

Summary of Findings

1. Stress cardiac MRI using *perfusion analysis* yielded a pooled sensitivity of 0.91 (95% CI: 0.89 to 0.92) and specificity of 0.79 (95% CI: 0.76 to 0.82) for the detection of CAD.
2. Stress cardiac MRI using *wall motion analysis* yielded a pooled sensitivity of 0.81 (95% CI: 0.77 to 0.84) and specificity of 0.85 (95% CI: 0.81 to 0.89) for the detection of CAD.
3. Based on DORs, there was no significant difference between pooled stress cardiac MRI using *perfusion analysis* and pooled stress cardiac MRI using *wall motion analysis* (*P*=0.26) for the detection of CAD.
4. Pooled subgroup analysis of stress cardiac MRI using *perfusion analysis* showed no significant difference in the DORs between *1.5T and 3T* MRI (*P*=0.72) for the detection of CAD.

   One study (N=60) was identified that examined stress cardiac MRI using *wall motion analysis* with a *3T* MRI. The sensitivity and specificity of *3T* MRI were 0.64 (95% CI: 0.44 to 0.81) and 1.00 (95% CI: 0.89 to 1.00), respectively, for the detection of CAD.
5. The effectiveness of stress cardiac MRI for the detection of CAD in *unstable patients with acute coronary syndrome* was reported in only one study (N=35). Using *perfusion analysis*, the sensitivity and specificity were 0.72 (95% CI: 0.53 to 0.87) and 1.00 (95% CI: 0.54 to 1.00), respectively, for the detection of CAD.

Ontario Health System Impact Analysis

According to an expert consultant, in Ontario:

1. Stress first pass perfusion is currently performed in small numbers in London (London Health Sciences Centre) and Toronto (University Health Network at the Toronto General Hospital site and Sunnybrook Health Sciences Centre).
2. Stress wall motion is only performed as part of research protocols and not very often.
3. Cardiac MRI machines use 1.5T almost exclusively, with 3T used in research for first pass perfusion.

On November 25 2009, the Cardiac Imaging Expert Advisory Panel met and made the following comments about stress cardiac MRI for perfusion analysis:

1. Accessibility to cardiac MRI is limited and generally used to assess structural abnormalities. Most MRIs in Ontario are already in 24–hour, constant use and it would thus be difficult to add cardiac MRI for CAD diagnosis as an additional indication.
2. The performance of cardiac MRI for the diagnosis of CAD can be technically challenging.

GRADE Quality of Evidence for Cardiac MRI in the Diagnosis of CAD

The quality of the body of evidence was assessed according to the GRADE Working Group criteria for diagnostic tests. For perfusion analysis, the overall quality was determined to be low and for wall motion analysis the overall quality was very low.

Background

In July 2009, the Medical Advisory Secretariat (MAS) began work on Non-Invasive Cardiac Imaging Technologies for the Diagnosis of Coronary Artery Disease (CAD), an evidence-based review of the literature surrounding different cardiac imaging modalities to ensure that appropriate technologies are accessed by patients suspected of having CAD. This project came about when the Health Services Branch at the Ministry of Health and Long-Term Care asked MAS to provide an evidentiary platform on effectiveness and cost-effectiveness of non-invasive cardiac imaging modalities.

After an initial review of the strategy and consultation with experts, MAS identified five key non-invasive cardiac imaging technologies for the diagnosis of CAD. Evidence-based analyses have been prepared for each of these five imaging modalities: cardiac magnetic resonance imaging, single photon emission computed tomography, 64-slice computed tomographic angiography, stress echocardiography, and stress echocardiography with contrast. For each technology, an economic analysis was also completed (where appropriate). A summary decision analytic model was then developed to encapsulate the data from each of these reports (available on the OHTAC and MAS website).

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Objective of Analysis

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Cardiac MRI

Stress cardiac MRI is a non-invasive, x-ray free imaging technique that takes approximately 30 to 45 minutes to complete and can be performed using to two different methods, a) perfusion imaging following a first pass of an intravenous bolus of gadolinium contrast, or b) wall motion imaging. (1;2) Stress is induced pharmacologically with either dobutamine, dipyridamole, or adenosine, as physical exercise is difficult to perform within the magnet bore and often induces motion artifacts. (2)

Myocardial stress perfusion is used to analyze the adequacy of the flow of oxygenated blood to the heart with impaired blood flow indicating the presence of CAD. (1) Stress wall motion imaging is used to test

for the presence of inducible wall motion abnormalities as a result of CAD. The stress images are compared with those obtained under normal (unstressed or resting) conditions.

Alternatives to stress cardiac perfusion MRI include stress single-photon emission computed tomography (SPECT) and stress echocardiography (ECHO). An advantage of cardiac MRI is the lack of a radiation burden that is associated with SPECT. During the same sitting, cardiac MRI can also assess left and right ventricular dimensions, viability and cardiac mass. (1) It may also avoid the need for invasive diagnostic coronary angiography in patients with intermediate risk factors for CAD. (1)

Evidence-Based Analysis

Research Questions

What is the diagnostic accuracy of cardiac MRI in the diagnosis of patients with known or suspected CAD compared to coronary angiography?

Methods

Literature Search

A literature search was performed on October 9, 2009 using OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, EMBASE, the Cumulative Index to Nursing & Allied Health Literature (CINAHL), the Cochrane Library, and the International Agency for Health Technology Assessment (INAHTA) for studies published from January 1, 2005 to October 9, 2008. Abstracts were reviewed by a single reviewer and, for those studies meeting the eligibility criteria, full-text articles were obtained. Reference lists were also examined for any relevant studies not identified through the search. Articles with an unknown eligibility were reviewed with a second clinical epidemiologist and then a group of epidemiologists until consensus was established.

Given the large amount of clinical heterogeneity of the articles meeting the inclusion criteria, as well as suggestions from an Expert Advisory Panel Meeting held on October 5, 2009, the inclusion criteria were revised to examine the effectiveness of cardiac MRI for the detection of CAD.

Inclusion Criteria

- Heath technology assessments, systematic reviews, randomized controlled trials, observational studies
- ≥20 adult patients enrolled.
- Published 2004-2009
- Licensed by Health Canada
- For diagnosis of CAD:
  - Reference standard is coronary angiography
  - Significant CAD defined as ≥ 50% coronary stenosis
  - Patients with suspected or known CAD
  - Reported results by patient, not segment

Exclusion Criteria

- Non-English studies
- Grey literature
- Planar imaging
- MUGA
- Patients with recent MI (i.e., within 1 month)
- Patients with non-ischemic heart disease
- Studies done exclusively in special populations (e.g., women, diabetics)

Outcomes of Interest

- Sensitivity and specificity
- Area under the curve (AUC)
- Diagnostic odds ratio (DOR)

Statistical Analysis

Pooled estimates of sensitivity, specificity and diagnostic odds ratios (DORs) were calculated using a bivariate, binomial generalized linear mixed model. (3) Statistical significance was defined by P values of less than 0.05, where "false discovery rate" adjustments were made for multiple hypothesis testing. (4) The bivariate regression analyses were performed using SAS version 9.2 (SAS Institute Inc.; Cary, NC, USA). Using the bivariate model parameters, summary receiver operating characteristic (sROC) curves were produced using Review Manager 5.0.22 (The Nordiac Cochrane Centre, The Cochrane Collaboration, 2008). The area under the sROC curve (AUC) was estimated by numerical integration with a cubic spline (default option) using STATA version 10.1 (StataCorp; Texas, USA).

Quality of Evidence

The quality of the body of evidence was assessed according to the GRADE Working Group criteria for diagnostic tests. (5)

Literature Search Results

One meta-analysis on the diagnostic performance of stress cardiac MRI for the detection of CAD was identified. (6) Eleven studies published subsequent to that meta-analysis were also identified.

Table 1: Quality of Evidence of Included Studies

Study Design	Level of Evidence	Number of Eligible Studies
Large RCT, systematic review of RCTs	1	1 (systematic review of diagnostic studies)
Large RCT unpublished but reported to an international scientific meeting	1(g)	-
Small RCT	2	-
Small RCT unpublished but reported to an international scientific meeting	2(g)	-
Non-RCT with contemporaneous controls	3a	11
Non-RCT with historical controls	3b	-
Non-RCT presented at international conference	3(g)	-
Surveillance (database or register)	4a	-
Case series (multisite)	4b	-
Case series (single site)	4c	-
Retrospective review, modelling	4d	-
Case series presented at international conference	4(g)	-
	Total	12

RCT refers to randomized controlled trial

Stress Cardiac MRI in Detection of CAD

The most recent meta-analyses of stress cardiac MRI used for the diagnosis of CAD was conducted by Nandalur et al. (the study's literature inclusion cut-off date was January 2007). (6) Diagnosis of CAD (≥50% diameter stenosis) was assessed using stress-induced wall motion abnormalities imaging and perfusion imaging. Catheter x-ray angiography was used as the reference standard.

Thirty-seven studies (N = 2,191 patients) met the inclusion criteria. Perfusion imaging showed a pooled sensitivity of 0.91 (95% CI: 0.88 to 0.94) and a specificity of 0.81 (95% CI: 0.77 to 0.85) on a patient level. Stress induced wall motion abnormalities imaging showed a pooled sensitivity of 0.83 (95% CI: 0.79 to 0.88) and specificity of 0.86 (95% CI: 0.81 to 0.91) on a patient level. For further details of the studies included in the perfusion and wall motion analyses, refer to Appendix 2.

The results of stress cardiac MRI perfusion and wall motion analyses published after the Nandalur et al. systematic review are detailed in Appendix 3.(6) Most of the studies used 1.5 Tesla (T) MRI and included patients with stable CAD.

Stress Perfusion

When the studies included in the Nandalur et al. review (6) were combined with those published afterward, stress perfusion cardiac MRI yielded a pooled sensitivity of 0.91 (95% CI: 0.89 to 0.92) and a specificity of 0.79 (95% CI: 0.76 to 0.82) for the detection of CAD (see Figure 1). The AUC and the DOR for stress perfusion cardiac MRI were 0.930 and 37.91, respectively (Table 2).

In a subgroup analysis of four studies of 3T MRI (7-10) compared to 19 studies of 1.5T MRI, there was no significant difference in the pooled DORs between the two groups (P=0.72). One of the included studies examined the diagnostic accuracy of 3T versus 1.5T MRI. (9) The authors found no significant differences between 3T and 1.5T for the detection of CAD in 61 patients (AUC 0.87 versus 0.78, P=0.23).

The effectiveness of stress cardiac MRI for the detection of CAD in unstable patients with acute coronary syndrome was reported in only one study (N=35). (11) Using perfusion analysis, the sensitivity and specificity were 0.72 (95% CI: 0.53 to 0.87) and 1.00 (95% CI: 0.54 to 1.00), respectively, for the detection of CAD. As only one study was identified that examined unstable patients with acute coronary syndrome, significance testing of the DORs was not conducted between stable and unstable subgroups.

Table 2: AUCs and DORs for stress perfusion cardiac MRI

Group	AUC	DOR	Lower CI	Upper CI
All Perfusion Studies	**0.930**	37.91	24.36	51.45
Subgroups				
1.5T	0.928	37.09	22.44	51.73
3T	0.932	44.41	4.02	84.81
Stable	0.930	39.98	25.23	54.73

AUC refers to area under the curve; CI, confidence interval; DOR, diagnostic odds ratio; NA, not applicable; T, Tesla.

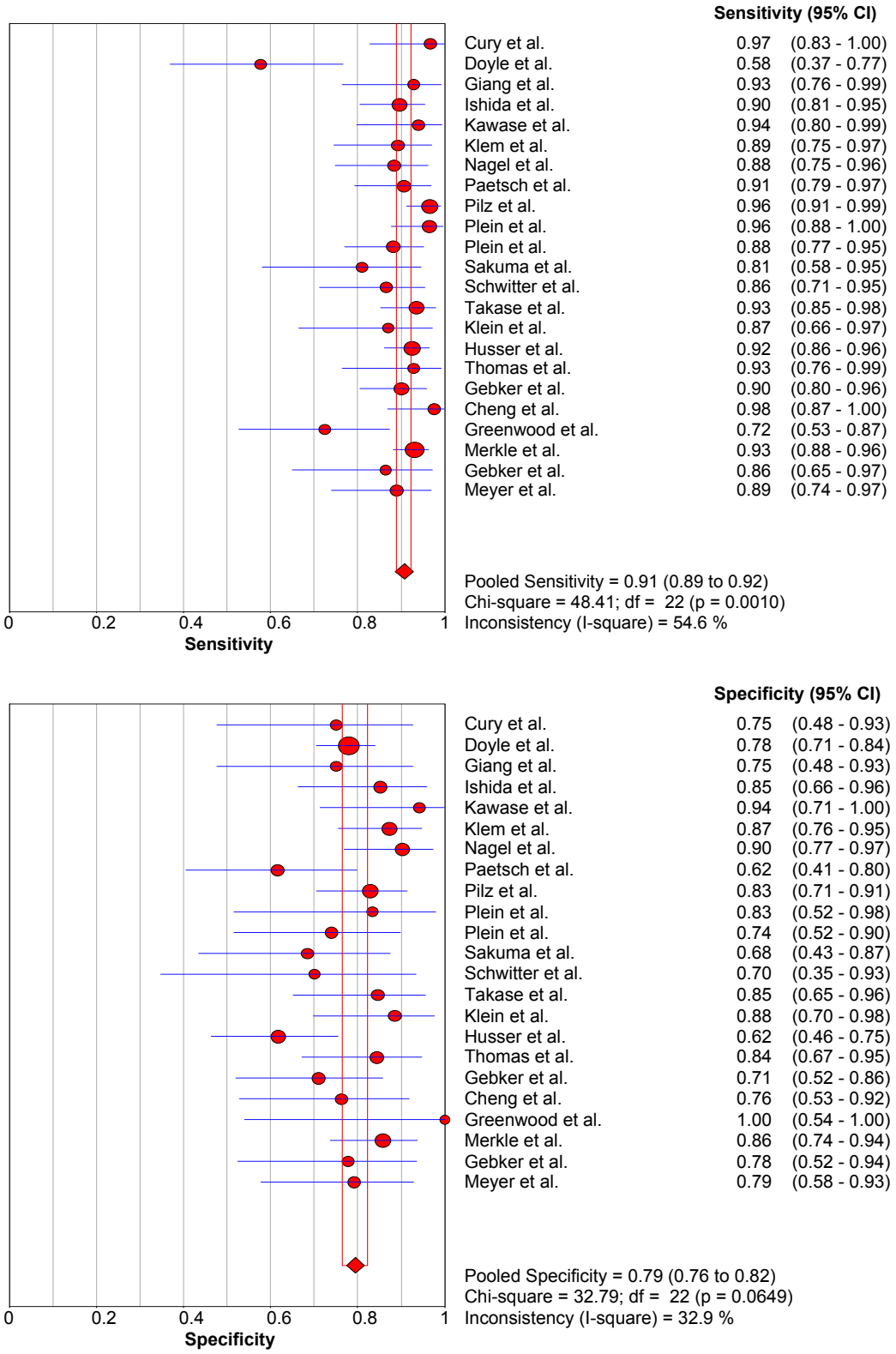


Figure 1: Pooled sensitivity and specificity of stress-induced perfusion cardiac MRI

Stress Wall Motion

As with the analysis of stress perfusion, the results of the studies included in Nandalur et al. (6) were combined with those published subsequent to it. This yielded a pooled sensitivity and specificity for stress wall motion cardiac MRI of 0.81 (95% CI: 0.77 to 0.84) and 0.85 (95% CI: 0.81 to 0.89) (Figure 2, page 15). The overall AUC and DOR for stress wall motion cardiac MRI was 0.926 and 26.27 respectively (Table 3).

No studies were identified that examined unstable patients with acute coronary syndrome.

One study (N=60) was identified that examined stress cardiac MRI using wall motion analysis with a 3T MRI. (7) The sensitivity and specificity of 3T MRI were 0.64 (95% CI: 0.44 to 0.81) and 1.00 (95% CI: 0.89 to 1.00) respectively for the detection of CAD. As only one study was identified that examined wall motion analysis with a 3T MRI, significance testing of the DORs was not conducted between the 1.5T and 3T subgroups.

Table 3: AUC and DOR for stress wall motion cardiac MRI

Group	AUC	DOR	Lower CI	Upper CI
All Wall Motion Studies	0.926	26.27	13.11	39.43
1.5 T	0.921	25.30	11.57	39.04

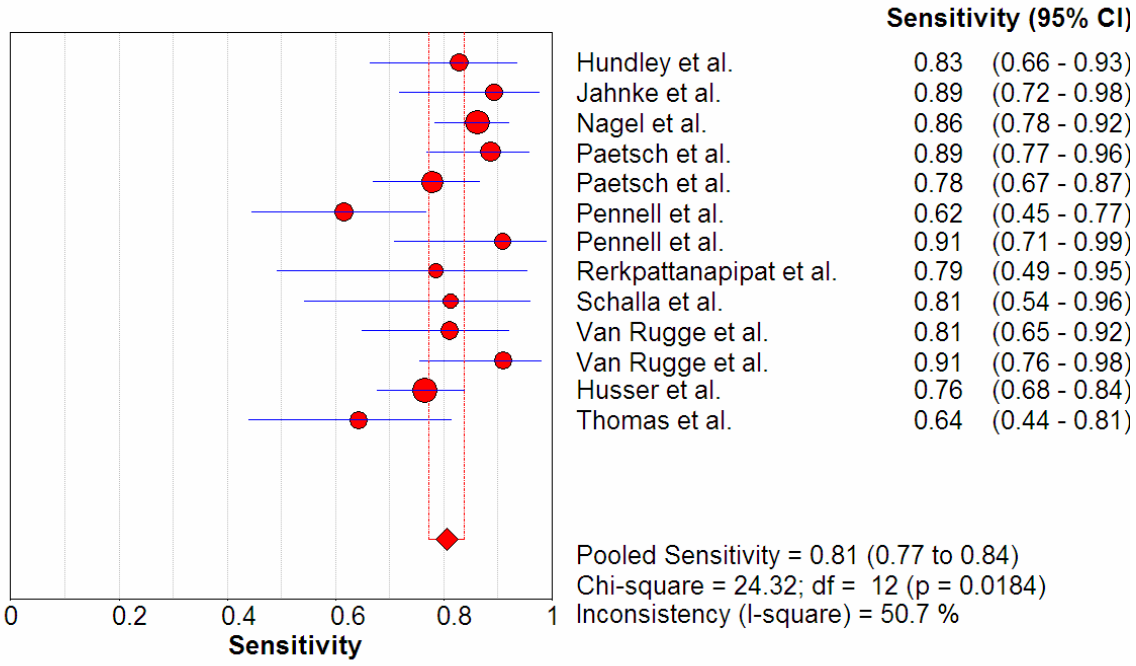
AUC refers to area under the curve; CI, confidence interval; DOR, diagnostic odds ratio; NA, not applicable; T, Tesla.

When the results for stress cardiac MRI using perfusion analysis were compared to the results for stress cardiac MRI using wall motion analysis, there was a significant difference in pooled sensitivity (*P*=0.001), no significant difference in pooled specificity (*P*=0.07) and no significant difference in the DOR (*P*=0.26).

Summary of Findings

1. Stress cardiac MRI using *perfusion analysis* yielded a pooled sensitivity of 0.91 (95% CI: 0.89 to 0.92) and specificity of 0.79 (95% CI: 0.76 to 0.82) for the detection of CAD.
2. Stress cardiac MRI using *wall motion analysis* yielded a pooled sensitivity of 0.81 (95% CI: 0.77 to 0.84) and specificity of 0.85 (95% CI: 0.81 to 0.89) for the detection of CAD.
3. Based on DORs, there was no significant difference between pooled stress cardiac MRI using *perfusion analysis* and pooled stress cardiac MRI using *wall motion analysis* (*P*=0.26) for the detection of CAD.
4. Pooled subgroup analysis of stress cardiac MRI using *perfusion analysis* showed no significant difference in the DORs between *1.5T and 3T* MRI (*P*=0.72) for the detection of CAD.

   One study (N=60) was identified that examined stress cardiac MRI using *wall motion analysis* with a *3T* MRI. The sensitivity and specificity of *3T* MRI were 0.64 (95% CI: 0.44 to 0.81) and 1.00 (95% CI: 0.89 to 1.00), respectively, for the detection of CAD.
5. The effectiveness of stress cardiac MRI for the detection of CAD in *unstable patients with acute coronary syndrome* was reported in only one study (N=35). Using *perfusion analysis*, the sensitivity and specificity were 0.72 (95% CI: 0.53 to 0.87) and 1.00 (95% CI: 0.54 to 1.00), respectively, for the detection of CAD.



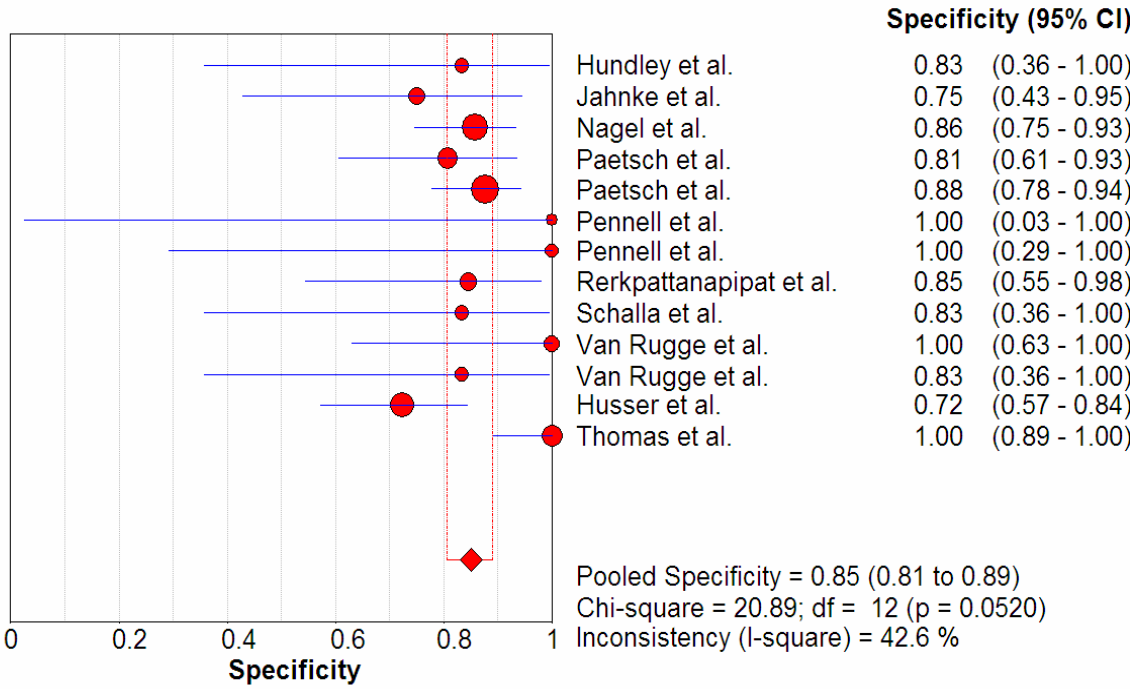


Figure 2: Pooled sensitivity and specificity of stress induced wall motion cardiac MRI

Health System Impact Analysis

Diffusion: Ontario

According to an expert consultant, in Ontario:

1. Stress first pass perfusion is currently done in small numbers in London (London Health Sciences Centre) and Toronto (University Health Network at the Toronto General Hospital site and Sunnybrook Health Sciences Centre).
2. Stress wall motion is only done as part of research protocols and not very often.
3. Cardiac MRI machines use 1.5T almost exclusively, with 3T used in research for first pass perfusion.

On November 25 2009, the Cardiac Imaging Expert Advisory Panel met and made the following comments on stress cardiac MRI for perfusion analysis:

1. Accessibility to cardiac MRI is limited and generally used to assess structural abnormalities. Most MRIs in Ontario are already in 24–hour, constant use and it would thus be difficult to add cardiac MRI for CAD diagnosis as an additional indication.
2. The performance of cardiac MRI for the diagnosis of CAD can be technically challenging.

Diffusion: International

United Kingdom

In 2007, the National Horizon Scanning Centre speculated that myocardial stress perfusion MRI may become the preferred option for CAD detection in intermediate risk patients if MRI imaging capability were to be expanded through training and capital investment. (1)

United States

Cigna covers cardiac MRI as medically necessary for the following (12):

- Stress perfusion study if specific additional information is required following a recent cardiac imaging study (e.g., echo, stress echo, myocardial perfusion imaging, angiography).

Aetna considers cardiac MRI medically necessary for cardiac function, morphology and structure when the following criterion is met (13):

- After it has been determined that echocardiogram is inconclusive.

GRADE Quality of Evidence

The quality of the body of evidence for the use of stress cardiac MRI in the diagnosis of CAD was assessed according to the GRADE Working Group criteria for diagnostic tests (Tables 4). (5) For perfusion analysis, the overall quality was determined to be low and for wall motion analysis the overall quality was very low.

Table 4: Quality assessment of diagnostic accuracy studies

No. of Studies	Design	Limitations	Indirectness	Inconsistency	Imprecise Data	Publication Bias	Quality
Studies of Stress Cardiac MRI Perfusion Analysis for the Detection of CAD							
23	Cross sectional Patients were selected to undergo coronary angiography and thus had a relatively high probability of CAD. Quality reduced by one level → Moderate	No serious limitations	Diagnostic tests considered as surrogate outcomes Surrogate outcome reduced quality by one level → Low	No serious inconsistency	Some imprecision Some imprecision for unstable patients with acute coronary syndrome and 3T subgroups (fewer studies and wide confidence intervals)	Unlikely Possible, but not considered sufficient to downgrade quality of evidence.	Low
Studies of Stress Cardiac MRI Wall Motion Analysis for the Detection of CAD							
15	Cross sectional Patients were selected to undergo coronary angiography and therefore had a relatively high probability of CAD. Quality reduced by one level → Moderate.	No serious limitations	Diagnostic tests considered as surrogate outcomes. † Two studies used 0.5T‡ † According to an expert consultant in Ontario, stress wall motion is only done as part of research protocols and not very often. This, in addition to surrogate outcomes, reduced quality by one level → Very Low. ‡ Most Ontario MRIs operate using 1.5T	No serious inconsistency	Some imprecision§ § Some imprecision for 3T subgroup (1 study with wide confidence interval).	Unlikely‖ ‖ Possible, but not considered sufficient to downgrade quality of evidence.	Very Low

Economic Analysis

DISCLAIMER: The Medical Advisory Secretariat uses a standardized costing method for its economic analyses of interventions. The main cost categories and the associated methods from the province's perspective are as follows:

Hospital: Ontario Case Costing Initiative cost data are used for in-hospital stay, emergency visit and day procedure costs for the designated International Classification of Diseases (ICD) diagnosis codes and Canadian Classification of Health Interventions procedure codes. Adjustments may be required to reflect accuracy in estimated costs of the diagnoses and procedures under consideration. Due to the difficulties of estimating indirect costs in hospitals associated with a particular diagnosis or procedure, the secretariat normally defaults to considering direct treatment costs only.

Nonhospital: These include physician services costs obtained from the Ontario Schedule of Benefits, laboratory fees from the Ontario Schedule of Laboratory Fees, drug costs from the Ontario Drug Benefit Formulary, and device costs from the perspective of local health care institutions whenever possible or its manufacturer.

Discounting: For cost-effectiveness analyses, a discount rate of 5% is applied as recommended by economic guidelines.

Downstream costs: All numbers reported are based on assumptions on population trends (i.e. incidence, prevalence and mortality rates), time horizon, resource utilization, patient compliance, healthcare patterns, market trends (i.e. rates of intervention uptake or trends in current programs in place in the Province), and estimates on funding and prices. These may or may not be realized by the system or individual institutions and are often based on evidence from the medical literature, standard listing references and educated hypotheses from expert panels. In cases where a deviation from this standard is used, an explanation is offered as to the reasons, the assumptions, and the revised approach. The economic analysis represents ***an estimate only***, based on the assumptions and costing methods that have been explicitly stated above. These estimates will change if different assumptions and costing methods are applied to the analysis.

Study Question

The objective of this economic analysis is to determine the cost effectiveness of cardiac magnetic resonance imaging (cardiac MRI) for the diagnosis of patients with suspected CAD as compared to: stress ECHO, stress contrast ECHO, SPECT, and CT angiography. The relative cost-effectiveness of these five non-invasive cardiac imaging technologies was assessed in two patient populations: 1) out-patients presenting with stable chest pain; and 2) in-patients presenting with acute, unstable chest pain. Note that the term "contrast ECHO" used in the following sections refers to stress ECHO performed with a contrast medium.

Economic Analysis Overview

A decision-analytic cost-effectiveness analysis was conducted to evaluate the relative cost-effectiveness of five non-invasive cardiac imaging technologies for diagnosing CAD in two patient populations: 1) out-patients presenting with stable chest pain; and 2) in-patients presenting with acute, unstable chest pain. Two decision analytic models were developed for these patient populations with two reported outcomes: the cost per accurate diagnosis of CAD and the cost per true positive diagnosis of CAD.

The physician and hospital costs for the non-invasive imaging tests were taken from 2009 Ontario Health Insurance Plan (OHIP) and the Ontario Case Costing Initiative (OCCI) administrative databases. (14;15) A budget impact analysis (BIA) was performed assessing the effect of replacing a certain proportion of stress ECHO tests with other cost-effective, non-invasive modalities. The costs presented in this BIA were estimated from Ontario data sources from 2009; the volumes of tests performed were estimated from data from fiscal years 2002 to 2008.

Economic Literature Review

The purpose of the systematic review of economic literature was to identify, retrieve, and summarize studies evaluating the cost-effectiveness of selected cardiac imaging tests for the diagnosis of CAD. Medline and the National Health Service Economic Evaluation Database (NHSEED) were searched from their inception up to October 2009. Included studies were those full economic evaluations describing both costs and consequences of a) CT angiography, b) Cardiac MRI, c) SPECT, d) stress ECHO, and e) stress contrast ECHO in the diagnosis of CAD. Article selection was performed by independent pairs of researchers. Target data for extraction included: study first author and year of publication, imaging tests compared, type of economic analysis, reported costs and outcomes, incremental cost-effectiveness ratio (ICER), currency, and patient characteristics (i.e., known or suspected CAD and risk of CAD). The primary outcome of interest for the present systematic review was the ICER of each imaging test in relation to another test of interest.

Literature Search Results

A total of 883 non-duplicate citations were found from the two electronic databases after applying the literature search strategy. Of these, 147 full-text articles were retrieved for further assessment of their inclusion/exclusion, following which, 122 were rejected leaving 25 articles for inclusion in the systematic review. After the data extraction process, 13 studies were excluded (16-27), with 12 studies being ultimately selected for analysis.(28-39) Reasons for the exclusion of articles are described in *The Relative Cost-effectiveness of Five Non-invasive Cardiac Imaging Technologies for Diagnosing Coronary Artery Disease in Ontario* (40).

Characteristics of Included Studies

From the 12 studies included in the present systematic review, eight assessed the cost-effectiveness of two of the selected imaging tests (31-34;36;38;39), three studies evaluated three concomitant technologies (28;35;37), and one study evaluated five technologies.(29)

Five studies were cost-effectiveness analyses, in which the most common outcome was cost per correct/successful CAD diagnosis.(28;29;36;38;39) The remaining seven studies were cost-utility analyses that used cost per quality adjusted life years (QALYs) as their primary outcome.(30-35;37) The time-horizon used across the included studies ranged from 30 days to lifetime and five had 25 years or more of follow-up.(30-32;34;38) The remaining studies used 18 months (37), 3 months (39), and 30 days of analytical time horizon.(33) Four studies did not report the time-horizon used in their analysis. (28;29;35;36)

All included studies evaluated at least one form of ECHO against one of the other remaining selected imaging tests.(28-39) The cost-effectiveness of SPECT was studied in nine studies.(28;30-32;34;35;37-39) Three studies assessed CT angiography in comparison to stress ECHO or MRI.(29;33;36) Cardiac MRI was compared to each of the three other selected imaging tests in two studies.(29;37) No full economic analysis between CT angiography and SPECT was found in the published literature.

Literature results for cardiac MRI

The cost-effectiveness of cardiac MRI was assessed against three selected cardiac imaging tests: stress ECHO, SPECT and CT angiography (see Table 5). Two studies evaluated the cost-effectiveness of MRI versus CT angiography, SPECT, or stress ECHO.(29;37) In one analysis, cardiac MRI was the alternative with lower costs and worst outcome – and thus not cost-effective – with an ICER per QALY of GBP £13,200 against stress ECHO.(37)

Conclusion of systematic review

Overall, CT angiography was found to be cost-effective or cost-saving in all four comparisons of that technology. Stress ECHO was found cost-effective in eight of the 13 comparisons in which it was evaluated, while SPECT was found cost-effective in three of the 9 comparisons. Cardiac MRI was not found to be cost-effective or cost-saving in any of the four comparisons found.

According to the published economic data from the literature, CT angiography is often found to be cost-effective when compared to other technologies. SPECT and stress ECHO were also found to be cost-effective in several of the comparative studies examined, while cardiac MRI was not cost-effective in any study. Limitations to these conclusions apply, such as the analyses found in the literature evaluated other forms of the selected cardiac imaging tests, which may change the proposed relative cost-effectiveness.

Table 5: Summary incremental cost-effectiveness ratios across selected studies evaluating cardiac MRI

Study	Comparator	Outcome of interest	Reported as cost-effective?	ICER
Dewey et al., 2007 (29)	CT Angio	Cost per correct diagnosis	No	Not reported*
	Stress ECHO	Cost per correct diagnosis	No	Not reported†
Sharples et al., 2007 (37)	SPECT	Cost per QALY	No	Dominated
	Stress ECHO	Cost per QALY	No	GBP (2006) £13,200‡

Notes: CT Angio = CT angiography

* Invasive coronary angiography using CT reported lower costs.

† Both not cost effective when compared to CT angiography.

‡ MRI was the alternative reporting lower cost and worst outcome.

Decision analytic Cost Effectiveness Analysis

Design

This study was designed as a cost effectiveness analysis, with primary results reported as incremental cost per true positive diagnosis or incremental cost per accurate diagnosis.

Two populations were defined for evaluating the cost-effectiveness of an accurate diagnosis (i.e., true positive and true negative diagnoses) of CAD:

1) out-patients presenting with stable chest pain; and

2) in-patients presenting with acute, unstable chest pain.

The first population was defined as persons presenting with stable chest pain, with an intermediate risk of CAD following physical examination and a graded exercise test, as defined by the American College of Cardiology / American Heart Association 2002 Guideline Update for the Management of Patients with Chronic Stable Angina.(41) The second population was defined as persons presenting to emergency for acute, unstable chest pain, and who are admitted to hospital, as defined by the American College of Cardiology / American Heart Association 2007 Guidelines for the Management of Patients with Unstable Angina/Non-ST-Elevation Myocardial Infarction.(42)

The analytic perspective was that of the Ontario Ministry of Health and Long-Term Care (MOHLTC).

Comparators & Parameter Estimates

The imaging technologies that were compared in the current cost-effectiveness analysis included: 1) CT angiography, 2) stress ECHO, 3) stress ECHO with the availability of contrast medium if needed, 4) cardiac perfusion stress MRI, and 5) attenuation-corrected SPECT. Test characteristic estimates (i.e. specificity, sensitivity, accuracy) for each cardiac imaging technology were obtained from the systematic review and meta-analysis conducted by MAS and the MOHLTC. Table 6 shows a list of the parameters with corresponding 95% confidence intervals used for both the outpatient and inpatient decision-analytic cost-effectiveness models.

Two additional sets of parameters are shown in Table 6 and described fully in *The Relative Cost-effectiveness of Five Non-invasive Cardiac Imaging Technologies for Diagnosing Coronary Artery Disease in Ontario* (40). The average wait-time for each cardiac imaging test is measured as the additional days needed to wait for a non-invasive test compared to the average wait time for a typical graded exercise stress test (GXT). The proportion of tests deemed uninterpretable by expert opinion is also shown in Table 6, with a corresponding range of high and low values. The probability of receiving pharmacological stress versus exercise stress is not shown in the table, but reported here for completeness: approximate values of 30% for the stable, outpatient population and 80% for the unstable, inpatient population.

Table 6: Summary parameter estimates for cardiac MRI tests: sensitivity, specificity; additional days needed to wait for specific cardiac tests; proportion of non-invasive tests considered uninterpretable

Pooled Diagnostic Accuracy	Point Estimate	95% Lower	95% Upper
CAD diagnosis: Sensitivity	0.907	0.878	0.936
CAD diagnosis: Specificity	0.809	0.750	0.868
Additional time for test (compared to GXT)	**Average**	**Low**	**High**
Inpatient population: Additional days for test	4.5	3.0	7.0
Uninterpretable test result	**Average**	**Low**	**High**
Outpatient population: % of tests that are uninterpretable	5.0%	5.0%	5.0%
Inpatient population: % of tests that are uninterpretable	5.0%	5.0%	5.0%

Note: Sensitivity and specificity estimates are taken from the effectiveness literature review of cardiac MRI.
Other estimates are based on consultations with experts in cardiology.

Time Horizon & Discounting

The time horizon for both decision-analytic models (i.e. for outpatient and inpatient populations) was the time required to determine an accurate, or true positive diagnosis of CAD. As a result, the actual time taken to determine the CAD status of patients may differ across non-invasive test strategies.

Model Structure

Figure 3 provides a simplified illustration of the decision-analytic model structure used for the outpatient and inpatient populations. The following two simplifying assumptions were made for the models:

1. When results of the first cardiac imaging test are un-interpretable, a patient will undergo a second cardiac test; the second test will be one of the four remaining tests that were not used as the first.
2. Should a second test be required, the type of stress (pharmacological or exercise) that a patient receives for the second test will be the same type of stress as the first.

Sensitivity Analyses

Various sensitivity analyses were conducted for the outpatient and inpatient populations. First, the prevalence of CAD was varied from 5% to 95% in 5% increments, while all other model estimates were held constant; willingness-to-pay (WTP) was also varied and a range of results were presented. Second, one-way sensitivity analyses were conducted in which selected estimates were varied over plausible ranges, such as sensitivity and specificity estimates, wait times for imaging tests performed in hospital, and costs of CT angiography, ECHO with contrast available and cardiac MRI. A third series of sensitivity analyses was conducted that specifically addressed the issue of possibly unavailable imaging technologies.

Additional details of the sensitivity analyses performed can be found in *The Relative Cost-effectiveness of Five Non-invasive Cardiac Imaging Technologies for Diagnosing Coronary Artery Disease in Ontario*. (40) The results of the sensitivity analyses are summarized in the Results and Discussion section below.

Resource Use and Costs

Resource use and costs were derived from Ontario data sources: the OHIP and OCCI administrative databases.(14;15) The cost of conducting each cardiac test was calculated as the sum of the test's respective professional fees and technical fees, as described in the Ontario Schedule of Benefits, are listed in Table 7. Note that for ECHO tests with available contrast agent, the cost for the contrast medium was added whenever the contrast was used in the event of uninterpretable ECHO test result. The cost of the contrast medium was estimated as $170 per vial (single use) through consultation with industry experts; only this cost was added to the base test cost of contrast ECHO. In general, where an imaging test result was uninterpretable, an additional cost of follow-up with the patient (physician fee) was incurred, as well as the cost for conducting another cardiac imaging test. For out-patients presenting with stable chest pain, a consultation professional fee of $30.60 (OHIP code A608 for "partial assessment") was used after an uninterpretable test result (one time cost).

In the case of patients presenting with acute, unstable chest pain, costs for inpatient hospitalization were also included in the model. The total cost of hospitalization was calculated based on the average wait time for each cardiac imaging test and a cost per diem for each day spent in hospital (for the cardiac MRI wait time, see Table 6). An additional consultation fee was also used only for the inpatient population: $29.20 (OHIP code C602 for "subsequent visit- first five weeks") was used for each inpatient day (per diem) spent in hospital.

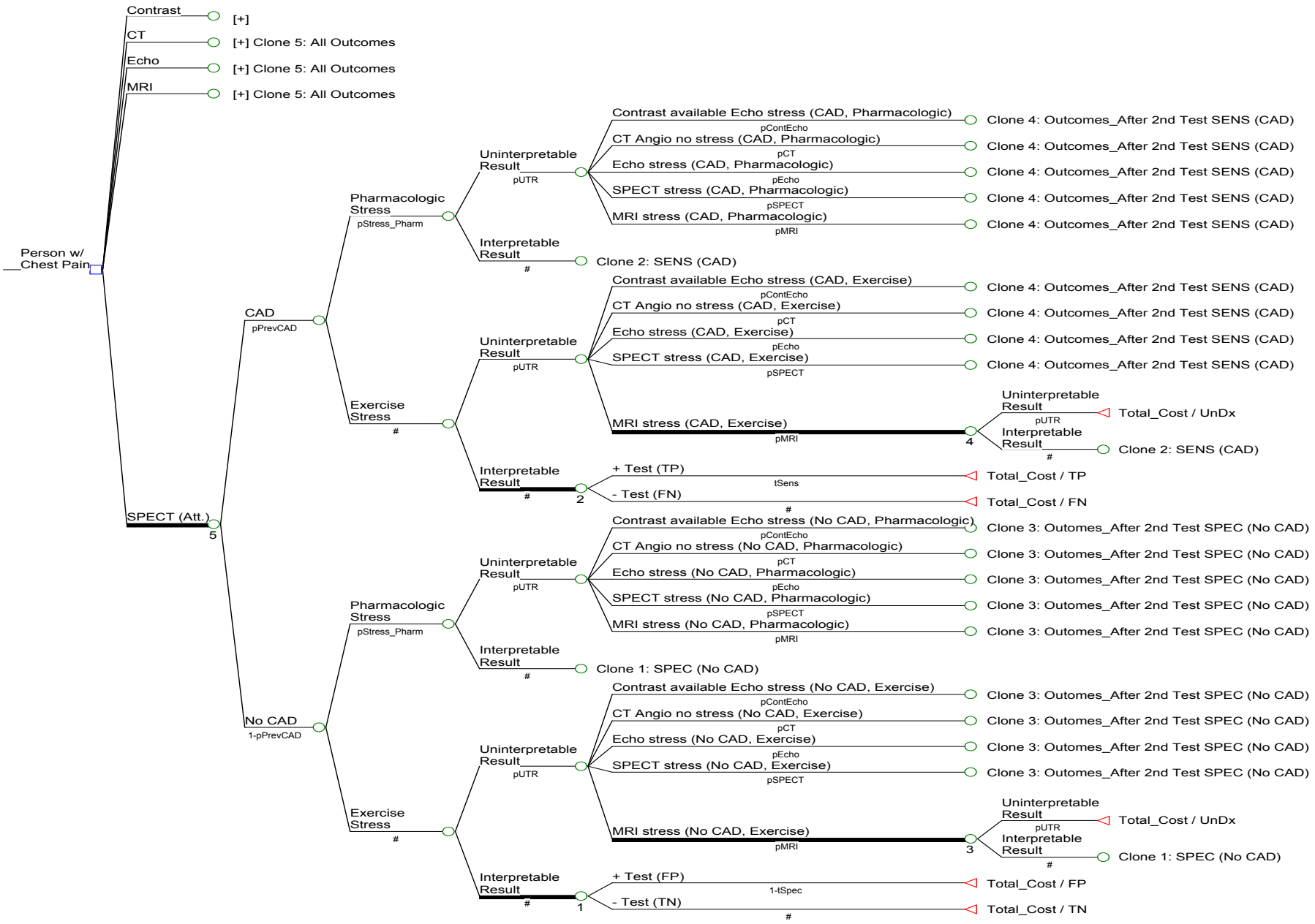


Figure 3: Decision analytic model used to evaluate the cost-effectiveness of cardiac imaging technologies for the diagnosis of CAD

Table 7: List of cardiac imaging tests and associated OHIP 2009 costs

Technology		List of professional fees				Subtotal	List of technical fees					Subtotal	Total
Cardiac CT	Fee code	X125	X417				Imputed						
	Cost	$89.20	$64.00			**$153.20**	$336.52					**$336.52**	**$489.72**
Cardiac MRI (dobutamine stress with gadolinium contrast)	Fee code	X441	X445	X487	G319		Imputed	G315	G174				
	Multiplier	1.0	3.0	1.0	1.0		1.0	1.0	1.0				
	Cost	$75.55	$37.80	$37.75	$62.65	**$289.35**	$463.06	$33.65	$37.00			**$533.71**	**$823.06**
Cardiac SPECT (exercise stress)	Fee code	J866	J811	J807	G319		J866	J811	J807	G315			
	Cost	$28.70	$55.30	$47.00	$62.65	**$193.65**	$44.60	$97.55	$223.15	$33.65		**$398.95**	**$592.60**
Cardiac SPECT (dobutamine stress)	Fee code	J866	J811	J807	G319		J866	J811	J807	G315	G174		
	Cost	$28.70	$55.30	$47.00	$62.65	**$193.65**	$44.60	$97.55	$223.15	$33.65	$37.00	**$435.95**	**$629.60**
Cardiac SPECT (dipyramidole stress)	Fee code	J866	J811	J807	G112		J866	J811	J807	G111			
	Cost	$28.70	$55.30	$47.00	$75.00	**$206.00**	$44.60	$97.55	$223.15	$41.10		**$406.40**	**$612.40**
ECHO (exercise stress)	Fee code	G571	G578	G575	G319		G570	G577	G574	G315			
	Cost	$74.10	$36.90	$17.45	$62.65	**$191.10**	$76.45	$45.15	$16.45	$33.65		**$171.70**	**$362.80**
ECHO (dobutamine stress)	Fee code	G571	G578	G575	G319		G570	G577	G574	G315	G174		
	Cost	$74.10	$36.90	$17.45	$62.65	**$191.10**	$76.45	$45.15	$16.45	$33.65	$37.00	**$208.70**	**$399.80**
ECHO (dipyramidole stress)	Fee code	G571	G578	G575	G112		G570	G577	G574	G111			
	Cost	$74.10	$36.90	$17.45	$75.00	**$203.45**	$76.45	$45.15	$16.45	$41.10		**$179.15**	**$382.60**

Notes: Fee codes are taken from the 2009 OHIP fee schedule.(15) Imputed technical fees were based on the proportion of average technical fees associated with above ECHO and SPECT fee code combinations. For cardiac SPECT and ECHO stress tests, an average test cost was calculated using dobutamine and dipyramidole fee codes.

Willingness-to-pay

The WTP must be determined by the MOHLTC. For the sensitivity analyses, all reasonable WTP values are presented (see Results and Discussion below) and interpreted at two WTP "anchors". The two anchors represent the estimated cost of the most expensive non-invasive test considered in our model (cardiac MRI perfusion, $804) and the estimated cost of a coronary angiography ($1,433). These anchors are intended to guide discussion only.

Note that the following points might be useful in determining the WTP:

- An "accurate diagnosis" of CAD can be obtained through a coronary angiography for $1,433, thus one might expect the WTP for an accurate diagnosis through a non-invasive test to resemble this amount. It should be remembered, however, that an "accurate diagnosis" does not include the value or benefit of providing additional diagnostic or prognostic information from either non-invasive imaging and coronary angiography.
- The MOHLTC is currently willing to pay up to $804 for a non-invasive test with less-than-perfect diagnostic accuracy – its willingness to pay for an "accurate diagnosis" from such a test may, therefore, be greater.
- These tests are non-invasive, whereas coronary angiography is invasive. This would presumably be "worth" more (i.e., paying a higher premium); Conversely, these tests carry risks not applicable to coronary angiography, such as increased radiation exposure or adverse reaction to contrast agents.
- These tests are not perfectly accurate – an accurate diagnosis from such a test may be valued less than one from a coronary angiography.

Results and Discussion

The base case results are summarized in Tables 8 and 9. The analysis revealed that, for both populations (stable outpatients and acute inpatients), cardiac MRI was dominated by CT angiography. That is, it had higher costs and was less effective.

In sensitivity analyses, MRI was not found to be cost-effective at any reasonable willingness-to-pay for an incremental accurate diagnosis, even after removing CT angiography from the analysis. The present analysis suggests that MRI is not a cost-effective technology for the diagnosis of CAD.

Table 8: Cost-effectiveness analysis base case results for stable outpatients

Technology	Cost (C)	∆ Cost	Effect (E)	∆ Effect	C / E	ICER
Stress contrast ECHO	$433.49		81.83%		$530	N/A
CT angiography	$517.73	$84.24	87.35%	5.52%	$593	$1,527
Stress ECHO	$551.58		81.06%		$680	(Dominated)
SPECT	$634.63		82.80%		$766	(Dominated)
Cardiac MRI	$835.47		85.15%		$981	(Dominated)

Table 9: Cost-effectiveness analysis base case results for acute inpatients

Technology	Cost (C)	∆ Cost	Effect (E)	∆ Effect	C / E	ICER
Stress contrast ECHO	$1,794.58		81.94%		$2,190	N/A
SPECT	$1,982.91	$188.32	83.92%	1.99%	$2,363	$9,489
Stress ECHO	$2,550.87		81.53%		$3,129	(Dominated)
CT angiography	$3,267.39	$1,284.48	87.49%	3.56%	$3,735	$36,055
Cardiac MRI	$4,918.02		85.55%		$5,749	(Dominated)

Budget Impact Analysis

The budget impact analysis (BIA) was performed taking the perspective of the MOHLTC and includes both physician and hospital (clinic) costs of non-invasive cardiac imaging tests. Volumes of cardiac tests in Ontario were taken from administrative databases (OHIP, DAD, NACRS) for fiscal years 2004 to 2008 using methodology summarized in *The Relative Cost-effectiveness of Five Non-invasive Cardiac Imaging Technologies for Diagnosing Coronary Artery Disease in Ontario*. (40) The following technologies were considered in the current BIA for the diagnosis of CAD: ECHO (including both stress and stress with contrast agent available), nuclear cardiac imaging (including MPI and SPECT tests), cardiac MRI, and CT angiography.

In the current BIA, the effect of moving a certain proportion of the volume of specific tests to another, substitute technology was assessed for various scenarios. These scenarios are presented irrespective of whether a technology was found to be cost-effective and reported as general reference tables.

In summary, cardiac MRI tests were found to be the most expensive of the compared cardiac imaging modalities. When the volume of cardiac MRI tests is shifted to other technologies, all scenarios result in lower projected costs, however, the actual number of tests moved is relatively small. If 25% of cardiac MRI tests is moved to other imaging technologies, ensuing projected costs would be lower: from the largest cost avoidance of about $62.1K per year for stress ECHO testing to the smallest cost avoidance of $28.3K for nuclear cardiac imaging. The largest possible cost avoidance corresponds to replacing 50% of cardiac MRI tests with stress ECHO imaging ($124.2M per year); the smallest cost avoidance occurs by replacing 5% of cardiac MRI tests with nuclear cardiac imaging ($5.7K per year).

Existing Guidelines

Canadian Cardiovascular Society/Canadian Association of Radiologists/Canadian Association of Nuclear Medicine/Canadian Nuclear Cardiology Society/Canadian Society of Cardiac Magnetic Resonance Joint Position Statement on Detection of CAD Using Cardiac MRI

The 2007 recommendations were prepared using the standard scoring methods adapted from previous guidelines on imaging from the American College of Cardiology, the American Heart Association and the American Society of Nuclear Cardiology. (2) Recommendations are classified according to the following criteria:

Class I: Conditions for which there is evidence and/or general agreement that a given procedure or treatment is beneficial, useful, and effective.

Class II: Conditions for which there is conflicting evidence and/or divergence of opinion about the usefulness/efficacy of a procedure or treatment.

Class IIa: Weight of evidence/opinion is in favor of usefulness/efficacy.

Class IIb: Usefulness/efficacy is less well established by evidence/opinion.

Class III: Conditions for which there is evidence and/or general agreement that a procedure/treatment is not useful/effective and in some cases may be harmful.

Level of evidence for each class is assigned as one of the following:

Level of Evidence A: Data derived from multiple randomized clinical trials or meta-analyses.

Level of Evidence B: Data derived from a single randomized trial or nonrandomized studies.

Level of Evidence C: Only consensus opinion of experts, case studies, or standard-of-care.

Recommendations

The interpretation of cardiac MRI should be carried out only by physicians and institutions with adequate training and experience.

Class I Indications

1. Assessment of anomalous coronary arteries (Level C evidence)
2. Detection of coronary stenosis greater than 50%
   - Stress function (wall motion) with dobutamine (Level B evidence)

Class IIa Indication

1. Detection of coronary stenosis greater than 50%
   - Stress first pass perfusion (Level B evidence)

Class III (no benefit or harmful)

1. Contraindication to MRI
2. Contraindication to gadolinium contrast
3. Inability to perform sufficient breath-hold

Appendices

Appendix 1: Literature Search Strategies

Search date: October 9, 2009
Databases searched: OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, OVID EMBASE, Wiley Cochrane, Centre for Reviews and Dissemination/International Agency for Health Technology Assessment

Database: Ovid MEDLINE(R) <1950 to October Week 1 2009>
Search Strategy:

1 exp Myocardial Ischemia/ (303880)
2 (coronary adj2 arter* disease*).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] (59129)
3 ((myocardi* or heart or cardiac or coronary) adj2 (viable or viability or perfusion or function or isch?emi* or calci* or atheroscleros* or arterioscleros* or infarct* or occlu* or stenos* or thrombosis)).mp. (264079)
4 (myocardi* adj2 hibernat*).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] (841)
5 (stenocardia* or angina).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] (53614)
6 heart attack*.mp. (2920)
7 exp Heart Failure/ (66770)
8 ((myocardi* or heart or cardiac) adj2 (failure or decompensation or insufficiency)).mp. (108898)
9 exp Ventricular Dysfunction, Left/ (15128)
10 (left adj2 ventric* adj2 (dysfunction* or failure or insufficienc*)).mp. (23015)
11 or/1-10 (468470)
12 exp Magnetic Resonance Imaging/ (217527)
13 (magnetic resonance or CMR or MRI or MRA or MR angiography or MR imaging).ti,ab. (202157)
14 13 or 12 (284269)
15 limit 14 to (english language and humans and yr="2005 -Current") (81790)
16 11 and 15 (3119)
17 limit 16 to (case reports or comment or editorial or letter) (843)
18 16 not 17 (2276)
19 (sensitiv* or diagnos* or accuracy or test*).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] (3903994)
20 di.fs. (1614280)
21 19 or 20 (4579293)
22 21 and 18 (1685)

Database: EMBASE <1980 to 2009 Week 40>
Search Strategy:

1 exp ischemic heart disease/ (240457)
2 exp coronary artery disease/ (89477)
3 exp stunned heart muscle/ (1533)
4 (coronary adj2 arter* disease*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (72192)
5 ((myocardi* or heart or cardiac or coronary) adj2 (viable or viability or perfusion or function or ischemi* or atheroscleros* or arterioscleros* or infarct* or occlu* or stenos* or thrombosis)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (277966)
6 (myocardi* adj2 hibernat*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (1056)
7 (stenocardia* or angina).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (46605)
8 heart attack*.mp. (2041)
9 exp heart failure/ (126664)
10 ((myocardi* or heart or cardiac) adj2 (failure or decompensation or insufficiency)).mp. [mp=title, abstract,

subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (108718)
11 exp heart left ventricle failure/ (9421)
12 (left adj2 ventric* adj2 (dysfunction* or failure or insufficienc*)).mp. (16241)
13 or/1-12 (434030)
14 exp nuclear magnetic resonance imaging/ (250643)
15 (magnetic resonance or CMR or MRI or MRA or MR angiography or MR imaging).ti,ab. (185700)
16 15 or 14 (291370)
17 16 and 13 (11807)
18 limit 17 to (human and english language and yr="2005 -Current") (5219)
19 limit 18 to (editorial or letter or note) (597)
20 case report/ (1057346)
21 18 not (19 or 20) (3355)
22 (sensitiv* or diagnos* or accuracy or test*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (3271056)
23 di.fs. (1443224)
24 21 and (22 or 23) (2541)

Appendix 2: Studies Incorporated into the Nandalur et al. Systematic Review (6)

Table A1: Stress cardiac MRI in the detection of CAD: perfusion analysis by patient

Author	N	TP (n)	FN (n)	FP (n)	TN (n)	Sensitivity	Specificity	Stenosis Definition (%)	Tesla (T)
Cury et al.	46	29	1	4	12	0.97	0.75	≥70	1.5
Doyle et al	184	15	11	35	123	0.57	0.78	≥70	1.5
Giang et al.	44	26	2	4	12	0.93	0.75	≥50	1.5
Ishida et al.	104	69	8	4	23	0.90	0.85	≥70	1.5
Kawase et al.	50	31	2	1	16	0.94	0.94	>70	1.5
Klem et al.	92	33	4	7	48	0.89	0.87	≥70	1.5
Nagel et al.	84	38	5	4	37	0.88	0.90	≥75	1.5
Paetsch et al.	79	48	5	10	16	0.91	0.62	>50	1.5
Pilz et al.	171	109	4	10	48	0.96	0.83	>70	1.5
Plein et al.	68	54	2	2	10	0.96	0.83	≥70	1.5
Plein et al.	82	52	7	6	17	0.88	0.74	>70	1.5
Sakuma et al.	40	17	4	6	13	0.81	0.68	>70	1.5
Schwitter et al.	47	32	5	3	7	0.86	0.70	≥50	1.5
Takase et al.	102	71	5	4	22	0.93	0.85	>50	1.5

TP refers to true positive; FN refers to false negative; FP refers to false positive; TN refers to true negative

Table A2: Stress cardiac MRI in the detection of CAD: wall motion analysis by patient

Author	N	TP (n)	FN (n)	FP (n)	TN (n)	Sensitivity	Specificity	Stenosis Definition (%)	Tesla (T)
Baer et al.	23	18	5	0	0	0.78	NA*	>70	1.5
Baer et al.	32	27	5	0	0	0.84	NA*	≥50	1.5
Hundley et al.	41	29	6	1	5	0.83	0.83	>50	1.5
Jahnke et al.	40	25	3	3	9	0.89	0.75	≥50	1.5
Nagel et al.	172	94	15	9	54	0.86	0.86	≥50	1.5
Paetsch et al.	79	47	6	5	21	0.89	0.81	>50	1.5
Paetsch et al.	150	60	17	9	64	0.78	0.88	≥50	1.5
Pennell et al.	40	24	15	0	1	0.62	1.00	Not stated	0.5
Pennell et al.	25	20	2	0	3	0.91	1.00	≥50	0.5
Rerkpattanapipat et al.	27	11	3	2	11	0.79	0.85	>70	1.5
Schalla et al.	22	13	3	1	5	0.81	0.83	>75	1.5
Van Rugge et al.	45	30	7	0	8	0.81	1.00	>50	1.5
Van Rugge et al.	39	30	3	1	5	0.91	0.83	≥50	1.5

TP refers to true positive; FN, false negative; FP, false positive; NA, not applicable; TN, true negative

* Specificity cannot be calculated since TN/(TN+FP)=0/0

Appendix 3: Studies Published After the Nandalur et al. Systematic Review (6)

Table A3: Stress cardiac MRI for the detection of CAD in studies published after most recent systematic review: perfusion analysis by patient

Author	N	TP (n)	FN (n)	FP (n)	TN (n)	Sensitivity (%)	Specificity (%)	Stenosis Definition (%)	Tesla (T)
Klein et al. 2008 (43)	49	20	3	3	23	87	88	>50	1.5
Husser et al. 2009 (44)	166	110	9	18	29	92	62	>70	1.5
Thomas et al. 2008 (7)	60	26	2	5	27	93	84	>50	3.0
Gebker et al.2008 (10)	101	63	7	9	22	90	71	≥50	3.0
Cheng et al. 2007 (9)	61	39	1	5	16	98	76	≥50	3.0
Greenwood et al. 2007*(11)	35	21	8	0	6	86	100	≥70	1.5
Merkle et al. 2007 (45)	228	160	12	8	48	93	86	>50	1.5
Gebker et al. 2007 (46)	40	19	3	4	14	86	78	≥50	1.5
Meyer et al. 2008 (8)	60	32	4	5	19	89	79	≥70	3.0

TP refers to true positive; FN refers to false negative; FP refers to false positive; TN refers to true negative

* Unstable angina (MRI early after acute ST elevation MI)

Table A4: Stress cardiac MRI for the detection of CAD in studies published after most recent systematic review: wall motion analysis by patient

Author	N	TP (n)	FN (n)	FP (n)	TN (n)	Sensitivity (%)	Specificity (%)	Stenosis Definition (%)	Tesla (T)
Husser et al. 2009 (44)	166	91	28	13	34	77	72	>70	1.5
Thomas et al. 2008* (7)	60	18	10	0	32	64	100	>50	3.0

TP refers to true positive; FN refers to false negative; FP refers to false positive; TN refers to true negative

* Tagged MRI

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