

Non-Invasive Cardiac Imaging Technologies for the Diagnosis of Coronary Artery Disease

A Summary of Evidence-Based Analyses

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Contact Information

The Medical Advisory Secretariat
Ministry of Health and Long-Term Care
20 Dundas Street West, 10th floor
Toronto, Ontario
CANADA
M5G 2C2
Email: MASinfo.moh@ontario.ca
Telephone: 416-314-1092

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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).

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List of Abbreviations

AUC	Area under the curve
AC	Attenuation corrected
CAD	Coronary artery disease
Cardiac MRI	Cardiac magnetic resonance imaging
CT Angio	Computed tomographic angiography
CVD	Cardiovascular disease
CI	Confidence interval(s)
DOR	Diagnostic odds ratio
MAS	Medical Advisory Secretariat
OHTAC	Ontario Health Technology Advisory Committee
RCT	Randomized controlled trial
RR	Relative risk
SD	Standard deviation
SPECT	Single photon emission computed tomography
SROC	Summary receiver operating characteristic
Stress ECHO	Stress echocardiography

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).

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

Please 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 of Analysis

The objective of this report series is to provide an evidentiary platform on effectiveness and cost-effectiveness around non-invasive cardiac imaging technologies for the Ontario Ministry of Health and Long-Term Care.

Clinical Need and Target Population

Cardiovascular disease (CVD) is a highly prevalent chronic condition and is the leading single cause of mortality in Ontario. It is also responsible for an estimated 277,000 person-years of life lost in Ontario, second only to cancer. (1) Coronary artery disease (CAD) is the most common type of CVD in Canada, as it is in other industrialized countries. Further, the economic impact of CVD is considerable with an estimated direct and indirect cost of \$5.5 billion annually. (1)

The diagnosis and management of CAD relies heavily on non-invasive cardiac testing. Over the past decade, the use of non-invasive cardiac testing has risen exponentially in Ontario and elsewhere, a rise that has surpassed both demographic shifts and changes in the prevalence of CAD.(1;2) As seen Figures 1

to 4 below, there has also been rapid growth in the volume of non-invasive cardiac tests in Ontario, with the highest volume of testing occurring among those 50 to 64 years of age. Despite this, there remains considerable uncertainty on the appropriate choice, sequence, and frequency of cardiac imaging tests to perform in different medical situations. There is also growing concern surrounding duplicate testing (Table 1), shifts in settings for imaging services (Table 2), a lack of standardization, the purchase of equipment by non-radiologists, and the risk of radiation exposure for some of the imaging modalities. (3)

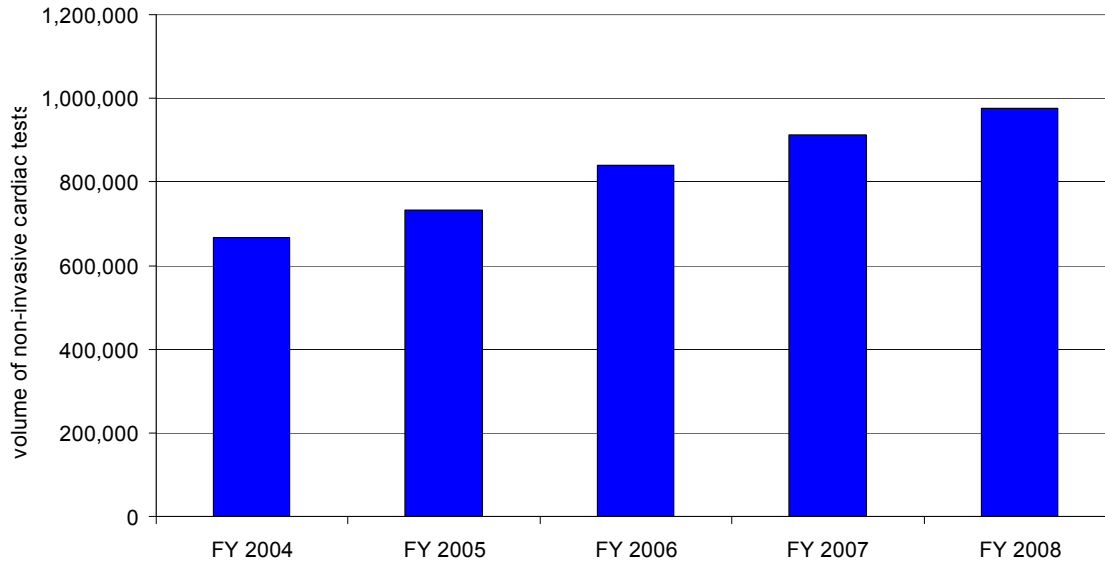


Figure 1: Temporal trends in the use of non-invasive cardiac tests in Ontario, FY 2004 – 2008

Notes:

1. Data for CT Angio and c-MRI were derived from CCI codes in NACRS/DAD; SPECT and ECHO data derived from the Ontario Physician Services database
2. Excludes ECG (resting and stress)
3. Professional fees for in-patient diagnostic services were transferred to physician services payment pool effective Apr 1, 2006 from hospital global budgets.

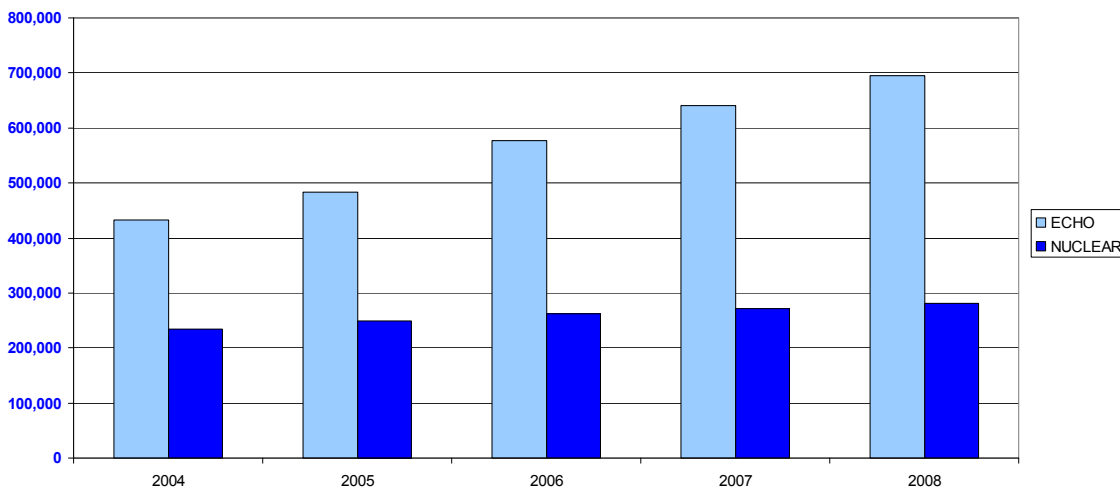


Figure 2: Temporal trends in echocardiography and nuclear cardiac imaging tests in Ontario, FY 2004 – 2008

Notes:

1. Data for SPECT and ECHO data derived from the Ontario Physician Services database
2. Professional fees for in-patient diagnostic services were transferred to the physician services payment pool effective Apr 1, 2006 from hospital global budgets.

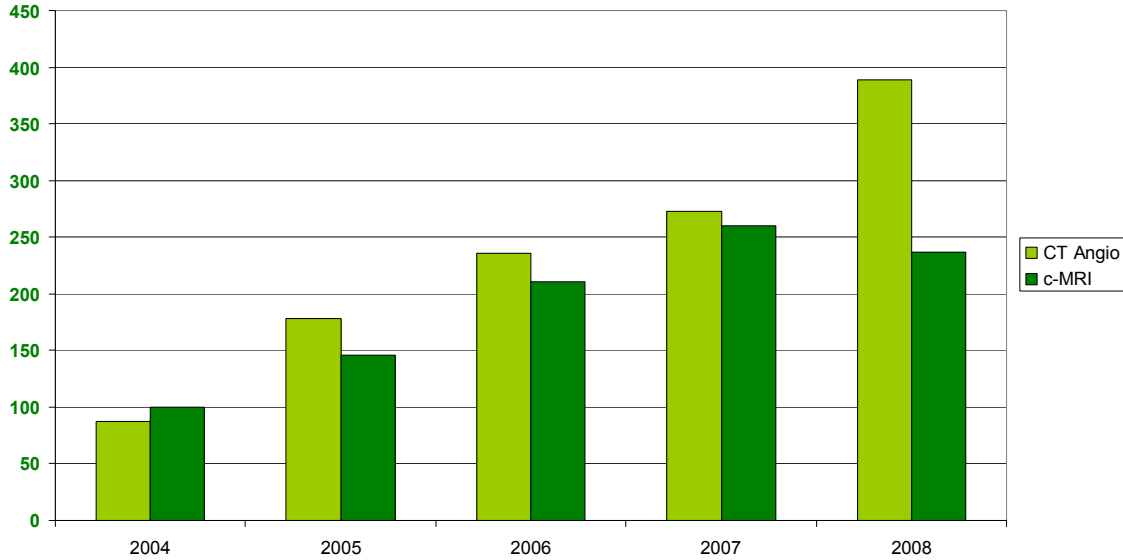


Figure 3: Temporal trends in the use of CT angiography and cardiac MRI tests in Ontario, FY 2004 – 2008

Notes:

1. Data for CT Angio and c-MRI were derived from CCI codes in NACRS/DAD;
2. Professional fees for in-patient diagnostic services were transferred to the physician services payment pool effective Apr 1, 2006 from hospital global budgets.

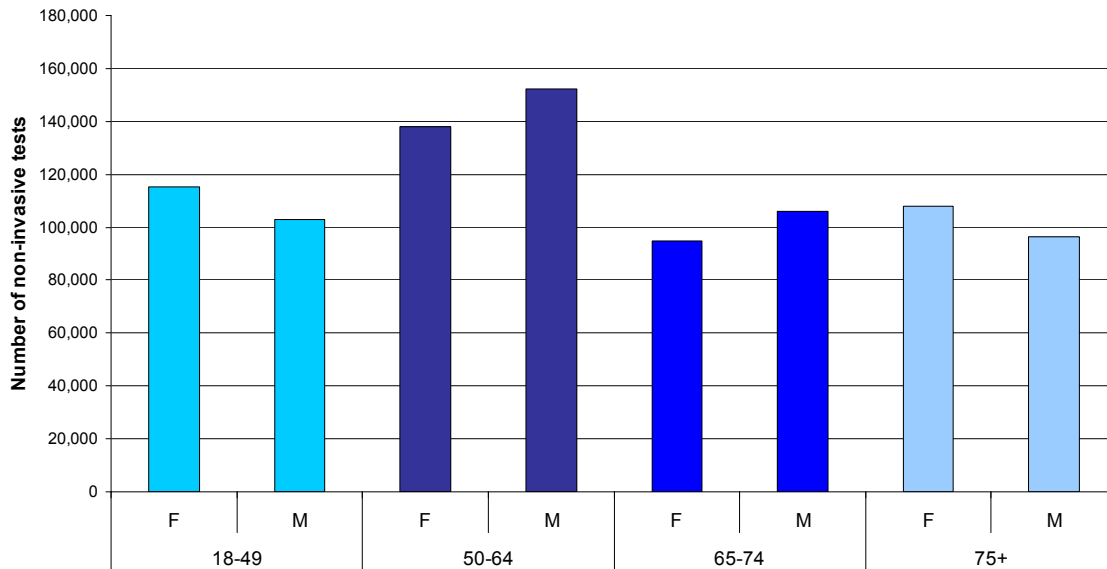


Figure 4: Use of non-invasive cardiac tests in Ontario by age and gender, FY 2007

Notes:

1. Data derived from the Ontario Physician Services database, FY 2007
2. For CT Angio and c-MRI, data were derived from CT thorax and CT MRI
3. Excludes ECG (resting and stress)

Table 1: Patients in Ontario having at least one repeat non-invasive test within 60 days of initial test, FY2008

	No. Patients	Percent with ≥ 1 repeat or sequential test within 60 days	Percent with same test within 60 days	Percent with different test within 60 days
Echocardiography	589,208	19.7%	6.3%	15.4%
Nuclear cardiac imaging	259,340	22.7%	2.8%	21.2%
CT Thorax	192,623	25.9%	9.1%	21.2%
MRI Thorax	15,850	16.5%	2.8%	14.4%

Notes:

1. Data derived from the Physician Services database, FY 2008
2. For CT Angio and c-MRI, data were derived from CT thorax and CT MRI
3. Estimates of repeat tests exclude resting and stress ECG

Table 2: Percent of non-invasive cardiac test ordered by referring physician specialty, FY2008

Referring physician specialty	Nuclear cardiac imaging	Echocardiography	CT Thorax	MRI Thorax
Cardiology	22.2%	16.0%	3.1%	13.4%
Internal Medicine	25.1%	18.3%	41.4%	18.7%
GP/FP	47.9%	62.4%	43.8%	48.7%
Other	4.8%	3.2%	11.7%	19.2%

Notes:

1. Data derived from the Physician Services database, FY 2008
2. For CT Angio and c-MRI, data were derived from CT thorax and CT MRI
3. Records with referring physician specialty unassigned include records with referring physician numbers missing, referring physician being out-of-province or out-of-country physicians, referring physicians being non-medical professionals - chiropractors, dentists, etc..

Project Scope

In July 2009, the Health Services Branch at the Ministry of Health and Long-Term Care asked the Secretariat to provide an evidentiary platform on non-invasive cardiac testing modalities.

Population

The Secretariat focused its review on imaging technologies that are used for the diagnosis of CAD, given that this condition represents the largest burden of illness. Through consultation with Ontario experts, the population with an intermediate risk of CAD was chosen as the population of interest for the evaluation of non-invasive cardiac imaging given that low-risk patients are typically managed without further testing, while high-risk patients are directly referred for an invasive coronary angiography (CA).

In order to further define the population with an intermediate risk of CAD, a conceptual flow diagram illustrating a patient's diagnostic management was developed based on existing literature and expert consultation. As seen in Figure 5, the patient population with suspected CAD was first divided into stable and acute coronary syndrome (ACS) groups. Stable patients are defined as those who are referred for diagnostic testing on an outpatient basis and unstable patients are defined as those who present to the emergency department with symptoms. In the stable suspected CAD group, patients are assigned a risk category based on their pre-test probability of CAD. This is calculated using a number of risk algorithms according to age, gender and symptoms. Typically, a low pre-test probability of CAD is defined as less

than 10% pre-test probability of CAD, intermediate is defined as 10 to 90% probability and high is defined as greater than 90% probability. (4) No subsequent testing is indicated for patients with a low pre-test probability of CAD and they instead are monitored and given medications as appropriate.

Patients with a high probability of CAD and who are unable to exercise are directly referred for invasive CA. Patients with an intermediate or high probability who are able to exercise undergo a stress electrocardiogram (ECG) test and are then re-stratified into risk categories based on the results of the ECG test. Patients with an intermediate risk of CAD, but who are unable to exercise do not undergo a stress ECG. Thus, the primary population of interest is defined as patients with an intermediate risk of CAD based on their pre-test probability of CAD and ECG results, if available. Based on expert consultation, over 80% of non-invasive diagnostic imaging in Ontario is performed in this patient population. There is greater variability in the management of patients in the ACS group. Based on expert opinion, patients with normal chest enzymes are typically admitted for a stress ECG or a non-invasive imaging test. This population was, therefore, chosen as the second of interest for this MAS analysis.

Technologies Under Review

After an initial review of the literature and consultation with experts, the Secretariat identified five key non-invasive cardiac imaging technologies that are used for the diagnosis of patients with suspected CAD. The technologies include Cardiac Magnetic Resonance Imaging (cardiac MRI), Single Photon Emission Computed Tomography (SPECT), 64-Slice Computed Tomographic Angiography (CT Angio), stress Echocardiography (stress ECHO) and stress ECHO with contrast.

Exercise or stress electrocardiography (ECG) was excluded from the analysis since it is a well-established method of assessing cardiac function and well-studied in the peer-reviewed literature. In 1989, a large meta-analysis was published comparing exercise stress ECG to coronary angiography. (5;6) Their literature search included studies published between 1967 and 1987. The meta-analysis identified 147 studies that met the inclusion criteria. These studies included more than 24,000 patients who underwent both exercise stress ECG and coronary angiography. The mean sensitivity was 68% (range 23-100%, SD 16%) and the mean specificity was 77% (range 17-100%, SD 17%). Positron emission tomography (PET) perfusion imaging using ¹³N-ammonia was also excluded from the analysis since it is not yet licensed by Health Canada.

The diagnostic accuracies of the five technologies were calculated using CA as the reference standard. Outcomes of interest included sensitivity and specificity. In order to compare across the different imaging modalities, pooled estimates of sensitivity and specificity were calculated as well as summary receiver operator characteristic (SROC) curves, the area under the curve (AUC) and diagnostic odds ratios (DOR). The following is a summary of evidence-based analyses of available medical literature around the five key non-invasive cardiac imaging technologies. Economic analyses were also performed and a decision analytic model was developed.

Research Questions

1. What is the diagnostic accuracy of the imaging modality for the diagnosis of patients with suspected CAD compared to CA (reference standard)?
2. Clinical utility is defined as a technology that aids in clinical treatment decision-making. What is the clinical utility of the non-invasive cardiac test?
3. What is the cost-effectiveness of the imaging modality for the diagnosis of patients with suspected CAD?

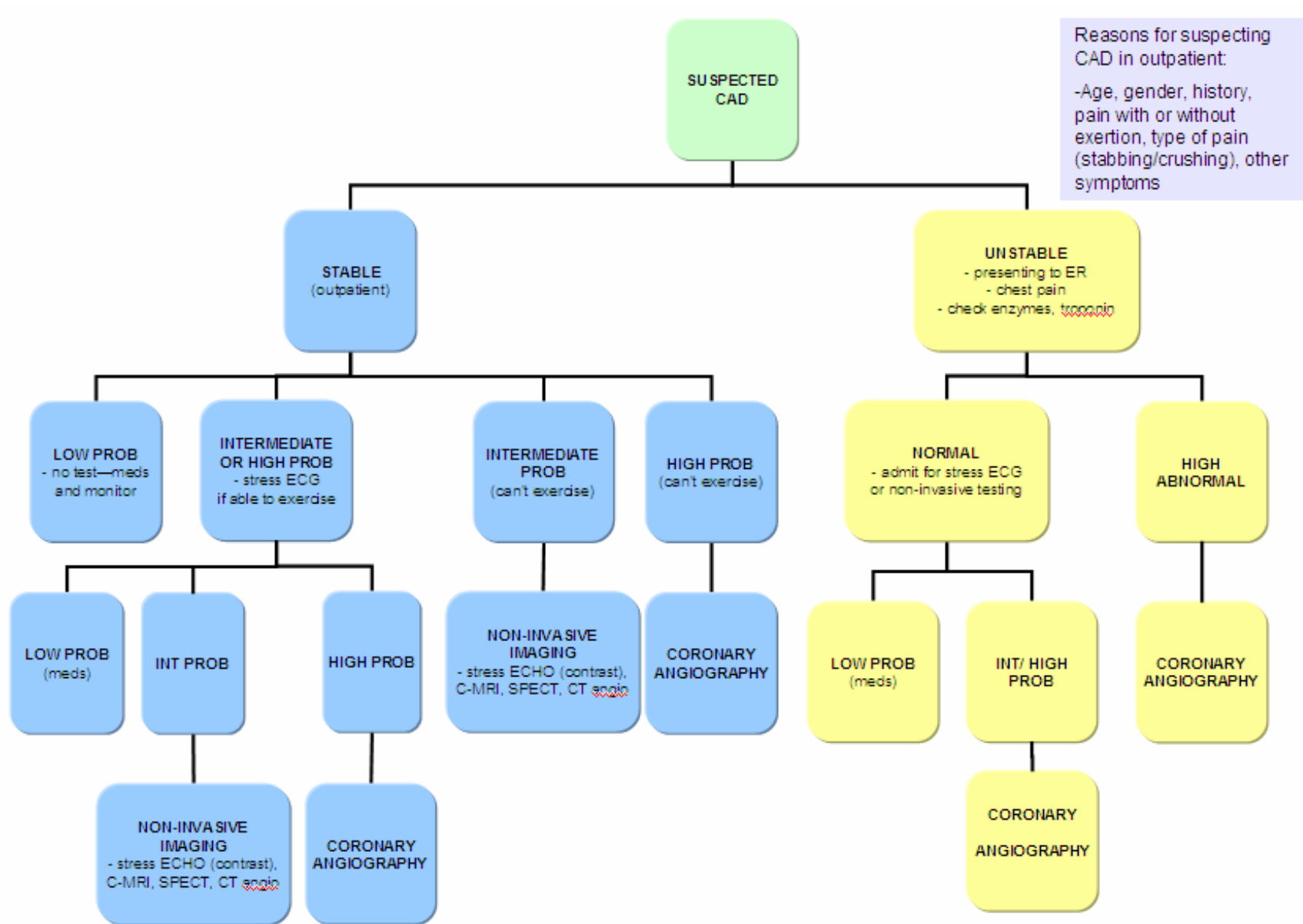


Figure 5: Population diagram illustrating diagnostic management of patients with suspected CAD

Stress Echocardiography for the Diagnosis of Coronary Artery Disease

Objective

The objective of the analysis is to determine the diagnostic accuracy of stress echocardiography (ECHO) in the diagnosis of patients with suspected coronary artery disease (CAD) compared to coronary angiography (CA).

Stress Echocardiography

Stress ECHO is a non-invasive technology that images the heart using ultrasound. It is one of the most commonly employed imaging techniques for investigating a variety of cardiac abnormalities in both community and hospital settings. A complete ECHO exam includes M-mode, 2-dimensional (2-D) images and Doppler imaging.

In order to diagnosis CAD and assess whether myocardial ischemia is present, images obtained at rest are compared to those obtained during or immediately after stress. The most commonly used agents used to induce stress are exercise and pharmacological agents such as dobutamine and dipyridamole. The hallmark of stress-induced myocardial ischemia is a worsening of wall motion abnormalities or the development of new abnormalities. A major challenge for stress ECHO is that the interpretation of wall motion contractility and function is subjective. This leads to inter-observer variability and reduced reproducibility. Further, it is estimated that approximately 30% of patients have sub-optimal stress ECHO exams. To overcome this limitation, contrast agents for LV opacification have been developed.

Although stress ECHO is a relatively easy to use technology that poses only a low risk of adverse events compared to other imaging technologies, it may potentially be overused and/or misused in CAD diagnosis. Several recent advances have been made focusing on quantitative methods for assessment, improved image quality and enhanced portability, however, evidence on the effectiveness and clinical utility of these enhancements is limited.

Evidence-Based Analysis

Research Questions

1. What is the diagnostic accuracy of stress ECHO for the diagnosis of patients with suspected CAD compared to the reference standard of CA?
2. What is the clinical utility¹ of stress ECHO?

Literature Search

A literature search was performed on August 28, 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, 2004 until August 21, 2009. 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.

¹ Clinical utility is defined as a technology that aids in clinical treatment decision-making

Inclusion Criteria

- Systematic reviews, meta-analyses, randomized controlled trials, prospective observational studies, retrospective analyses
- Minimum sample size of 20 enrolled patients
- Comparison to CA (reference standard)
- Definition of CAD specified as either $\geq 50\%$, $\geq 70\%$ or $\geq 75\%$ coronary artery stenosis on CA
- Reporting accuracy data on individual patients (rather than accuracy data stratified by segments of the heart)
- English
- Human

Exclusion Criteria

- Duplicate studies
- Non-systematic reviews, case reports
- Grey literature (e.g., conference abstracts)
- Insufficient data for independent calculation of sensitivity and specificity
- Use of ECHO for purposes other than diagnosis of CAD (e.g., arrhythmia, valvular disease, mitral stenosis, pre-operative risk of MI)
- Transesophageal ECHO since its primary use is for non-CAD indications such as endocarditis, intracardiac thrombi, valvular disorders
- Only resting ECHO performed

Outcomes of Interest

- Accuracy outcomes (sensitivity, specificity, positive predictive value, negative predictive value)
- Costs

Summary of Findings

Given the vast amount of published literature on stress ECHO, it was decided to focus on the studies contained in the comprehensive 2007 review by Heijnenbrok-Kal et al. (7) as a basis for the MAS evidence-based analysis. In applying our inclusion and exclusion criteria, 105 observational studies containing information on 13,035 patients were included. Six studies examined stress ECHO with adenosine, 26 with dipyridamole and 77 with dobutamine, the latter being the most commonly used pharmacological stress ECHO agent in Ontario. A further 18 studies employed exercise as the stressor.² The prevalence of CAD ranged from 19% to 94% with a mean estimated prevalence of 70%. Based on the results of these studies the following conclusions were made:

- Based on the available evidence, stress ECHO is a useful imaging modality for the diagnosis of CAD in patients with suspected disease. The overall pooled sensitivity is 0.80 (95% CI: 0.77 – 0.82) and the pooled specificity is 0.84 (95% CI: 0.82 – 0.87) using CA as the reference standard. The AUC derived from the sROC curve is 0.895 and the DOR is 20.64.
- For pharmacological stress, the pooled sensitivity is 0.79 (95% CI: 0.71 – 0.87) and the pooled specificity is 0.85 (95% CI: 0.83 – 0.88). When exercise is employed as the stress agent, the pooled sensitivity is 0.81 (95% CI: 0.76– 0.86) and the pooled specificity is 0.79 (95% CI: 0.71 – 0.87). Although pharmacological stress and exercise stress would be indicated for different patient populations based on ability to exercise there were no significant differences in sensitivity and specificity.
- Based on clinical experts, diagnostic accuracy on stress ECHO depends on the patient population, the expertise of the interpreter and the quality of the image.

² A study was counted twice if data was reported on different stress agents.

Stress Echocardiography with Contrast for the Diagnosis of Coronary Artery Disease

Objective

The objective of this report is to compare echocardiography (ECHO) performed with microsphere contrast agents (contrast echocardiography) to ECHO performed without contrast and to single photon emission computed tomography (SPECT).

Contrast ECHO

Contrast agents for ECHO have been available since the technology was first introduced in the 1990s. Composed of tiny ‘microbubbles’ of an inert gas encapsulated within a lipid, protein, or polymer coat, these agents act to scatter incident ultrasound waves at the gas/liquid interface to increase the strength of a returning ECHO signal. When injected into a patient’s arm, they are transported throughout even the smallest capillaries to greatly enhance the blood pool signal, which would otherwise appear black on conventional two dimensional ECHO. The enhanced signal then helps cardiologists to determine what parts of the patient’s heart muscle are poorly perfused.

The first commercially available microsphere contrast agent was Albunex, which received approval by the Food and Drug Administration in the United States in 1994. This original microsphere agent was limited by its rapid gas volume loss which caused a decline in the ultrasound signal. It worked well in the right chambers of the heart, but dissolved when passing through the pulmonary capillaries and so was unable to provide contrast in the left side. Second generation agents employed different gases that prolonged the life of the microbubbles within the circulation and increased the reproducibility of results.

Today, the most common use for contrast ECHO is to enhance the definition of the left ventricular (LV) endocardial border for cases of LV opacification. The aim of contrast ECHO is to provide better quantification of LV volume and assessment of LV wall motion than ECHO alone. The newest area of development in the research of contrast ECHO is myocardial perfusion assessment, also known as myocardial contrast ECHO. Theoretically, since myocardial ischemia and infarction affect both perfusion and contractility (wall motion), contrast ECHO could be an ideal non-invasive imaging test as it could assess both perfusion and contractility, simultaneously and in real time.

Notably, critically ill patients on ventilators and those with lung problems are more likely to generate poor or ‘suboptimal’ echocardiograms than other patients, as are obese patients and those who’ve undergone recent chest operations. Contrast agents can potentially be used in 10% to 15% of all studies and in approximately 33% of stress tests due to from such suboptimal echocardiograms. Stress can be induced either pharmaceutically (e.g., through dobutamine, dipyridamol, adenosine) or with exercise. Generally, contrast agents are used more in pharmaceutical stress echocardiograms than in exercise stress echocardiograms.

Evidence-Based Analysis

This MAS analysis sought to address the following research questions:

1. Is contrast ECHO more effective than 99-technetium SPECT in terms its ability to detect CAD?
2. What is the effectiveness of contrast ECHO in assessing patients with suboptimal echocardiograms?
3. Is contrast ECHO safe compared to other cardiac imaging modalities?
4. Is contrast ECHO cost-effective compared to other cardiac imaging modalities?

Literature Search

Literature searches were performed on June 22, 2009 and July 27, 2009 using OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, EMBASE, the Cochrane Library, and the International Agency for Health Technology Assessment (INAHTA) for studies published from January 1, 2004 until June 30, 2009. 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.

Inclusion Criteria

- Systematic reviews, meta-analyses, randomized controlled trials, prospective observational studies, retrospective analyses
- Minimum sample size of 20 enrolled patients (human only)
- The contrast agent used in the study must be licensed by Health Canada
- Comparison to reference standard (coronary angiography for the diagnosis of coronary artery disease)
- Reporting accuracy data on individual patients (rather than accuracy data stratified by segments of the heart)
- English language

Exclusion Criteria

- Non-systematic reviews, case reports
- Grey literature (e.g. conference abstracts)

Outcomes of Interest

- Accuracy outcomes (sensitivity, specificity, positive predictive value, negative predictive value)
- Adverse events
- Costs

Summary of Findings

Twenty-three observational studies were identified that assessed the diagnostic accuracy of contrast ECHO for the diagnosis of CAD. All of these studies used stress ECHO with contrast. In addition, nine retrospective chart reviews were identified, which assessed the safety of contrast ECHO at rest or stress. Based on the results of these studies the following conclusions were made:

- Stress ECHO with contrast has a higher diagnostic accuracy in the diagnosis of CAD than stress ECHO (without contrast).
- Stress ECHO with contrast seems to have a similar diagnostic accuracy to 99 technetium SPECT.
- The addition of contrast to ECHO in patients with suboptimal ECHO results significantly improves interpretability of the results.
- There is not a statistically significantly higher mortality rate in patients who receive contrast compared to those who do not.

Single Photon Emission Tomography for the Diagnosis of Coronary Artery Disease

Objective

The objective of the analysis is to determine the diagnostic accuracy of single photon emission tomography (SPECT) in the diagnosis of coronary artery disease (CAD) compared to the reference standard of coronary angiography (CA). The analysis is primarily meant to allow for indirect comparisons between non-invasive strategies for the diagnosis of CAD, using CA as a reference standard.

SPECT

Cardiac SPECT, or myocardial perfusion scintigraphy (MPS), is a widely used nuclear, non-invasive image acquisition technique for investigating ischemic heart disease. SPECT is currently appropriate for all aspects of detecting and managing ischemic heart disease including diagnosis, risk assessment/stratification, assessment of myocardial viability, and the evaluation of left ventricular function. Myocardial perfusion scintigraphy was originally developed as a two-dimensional planar imaging technique, but SPECT acquisition has since become the clinical standard in current practice. Cardiac SPECT for the diagnosis of CAD uses an intravenously administered radiopharmaceutical tracer to evaluate regional coronary blood flow usually at rest and after stress. The radioactive tracers thallium (201Tl) or technetium-99m (99mTc), or both, may be used to visualize the SPECT acquisition. Exercise or a pharmacologic agent is used to achieve stress. After the administration of the tracer, its distribution within the myocardium (which is dependent on myocardial blood flow) is imaged using a gamma camera. In SPECT imaging, the gamma camera rotates around the patients for 10 to 20 minutes so that multiple two-dimensional projections are acquired from various angles. The raw data are then processed using computational algorithms to obtain three-dimensional tomographic images.

Since its inception, SPECT has evolved and its techniques/applications have become increasingly more complex and numerous. Accordingly, new techniques such as attenuation correction and ECG gating have been developed to correct for attenuation due to motion or soft-tissue artifact and to improve overall image clarity.

Research Questions

1. What is the diagnostic accuracy of SPECT for the diagnosis of CAD compared to the reference standard of CA?
2. Is SPECT cost-effective compared to other non-invasive cardiac imaging modalities for the diagnosis of CAD?
3. What are the major safety concerns with SPECT when used for the diagnosis of CAD?

Methods

A preliminary literature search was performed across OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, EMBASE, the Cochrane Library, and the International Agency for Health Technology Assessment (INAHTA) for all systematic reviews/meta-analysis published between January 1, 2004 and August 22, 2009. A comprehensive systematic review was identified from this search and used as a basis for an updated search.

A second comprehensive literature search was then performed on October 30, 2009 across the same databases for studies published between January 1, 2002 and October 30, 2009. Abstracts were reviewed by a single reviewer and, for those studies meeting the eligibility criteria, full-text articles were obtained. Reference lists were also hand-searched for any additional studies.

Inclusion Criteria

- Systematic reviews, meta-analyses, controlled clinical trials, and observational studies
- Minimum sample size of 20 patients who completed coronary angiography
- Use of CA as a reference standard for the diagnosis of CAD
- Data available to calculate true positives (TP), false positives (FP), false negatives (FN) and true negatives (TN)
- Accuracy data reported by patient not by segment
- English language

Exclusion Criteria

- Non-systematic reviews, case reports
- Grey literature and abstracts
- Trials using planar imaging only
- Trials conducted in patients with non-ischemic heart disease
- Studies done exclusively in special populations (e.g., patients with left branch bundle block, diabetics, minority populations) unless insufficient data available

Summary of Findings

Eighty-four observational studies, one non-randomized, single arm controlled clinical trial, and one poorly reported trial that appeared to be a randomized controlled trial (RCT) met the inclusion criteria for this review. All studies assessed the diagnostic accuracy of myocardial perfusion SPECT for the diagnosis of CAD using CA as a reference standard. Based on the results of these studies the following conclusions were made:

- According to very low quality evidence, the addition of attenuation correction to traditional or ECG-gated SPECT greatly improves the specificity of SPECT for the diagnosis of CAD although this improvement is not statistically significant. A trend towards improvement of specificity was also observed with the addition of ECG gating to traditional SPECT.
- According to very low quality evidence, neither the choice of stress agent (exercise or pharmacologic) nor the choice of radioactive tracer (technetium vs. thallium) significantly affect the diagnostic accuracy of SPECT for the diagnosis of CAD although a trend towards accuracy improvement was observed with the use of pharmacologic stress over exercise stress and technetium over thallium.
- Considerably heterogeneity was observed both within and between trials. This heterogeneity may explain why some of the differences observed between accuracy estimates for various subgroups were not statistically significant.
- More complex analytic techniques such as meta-regression may help to better understand which study characteristics significantly influence the diagnostic accuracy of SPECT.

Cardiac Magnetic Resonance Imaging for the Diagnosis of Coronary Artery Disease

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 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

- Health 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 $\geq 50\%$ 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.

Computed Tomographic Angiography for the Diagnosis of Coronary Artery Disease

Objective

The objective of this report is to determine the accuracy of computed tomographic angiography (CTA) compared to the more invasive option of coronary angiography (CA) in the detection of coronary artery disease (CAD) in stable (non-emergent) symptomatic patients.

CT Angiography

CTA is a cardiac imaging test that assesses the presence or absence, as well as the extent, of coronary artery stenosis for the diagnosis of CAD. As such, it is a test of cardiac structure and anatomy, in contrast to the other cardiac imaging modalities that assess cardiac function. It is, however, unclear as to whether cardiac structural features alone, in the absence cardiac function information, are sufficient to determine the presence or absence of intermediate pre-test risk of CAD.

CTA technology is changing rapidly with increasing scan speeds and anticipated reductions in radiation exposure. Initial scanners based on 4, 8, 16, 32, and 64 slice machines have been available since the end of 2004. Although 320-slice machines are now available, these are not widely diffused and the existing published evidence is specific to 64-slice scanners. In general, CTA allows for 3-dimensional (3D) viewing of the coronary arteries derived from software algorithms of 2-dimensional (2D) images.

The advantage of CTA over CA, the gold standard for the diagnosis of CAD, is that it is relatively less invasive and may serve as a test in determining which patients are best suited for a CA. CA requires insertion of a catheter through an artery in the arm or leg up to the area being studied, yet both tests involve contrast agents and radiation exposure. Therefore, the identification of patients for whom CTA or CA is more appropriate may help to avoid more invasive tests, treatment delays, and unnecessary radiation exposure. The main advantage of CA, however, is that treatment can be administered in the same session as the test procedure and as such, it's recommended for patients with a pre-test probability of CAD of $\geq 80\%$. The progression to the more invasive CA allows for the diagnosis and treatment in one session without the added radiation exposure from a previous CTA.

The visibility of arteries in CTA images is best in populations with a disease prevalence, or pre-test probabilities of CAD, of 40% to 80%, beyond which patients are considered at high pre-test probability. Visibility decreases with increasing prevalence as arteries become increasingly calcified (coronary artery calcification is based on the Agaston score). Such higher risk patients are not candidates for the less invasive diagnostic procedures and should proceed directly to CA, where treatment can be administered in conjunction with the test itself, while bypassing the radiation exposure from CTA.

CTA requires the addition of an ionated contrast, which can be administered only in patients with sufficient renal function (creatinine levels >30 micromoles/litre) to allow for the clearing of the contrast from the body. In some cases, the contrast is administered in patients with creatinine levels less than 30 micromoles/litre.

A second important criterion for the administration of the CTA is patient heart rate, which should be less than 65 beats/min for the single source CTA machines and less than 80 beats/min for the dual source machines. To decrease heart rates to these levels, beta-blockers are often required. Although the accuracy of these two machines does not differ, the dual source machines can be utilized in a higher proportion of patients than the single source machines for patients with heart beats of up to 80 beats/min.

Approximately 10% of patients are considered ineligible for CTA because of this inability to decrease heart rates to the required levels. Additional contra-indications include renal insufficiency as described above and atrial fibrillation, with approximately 10% of intermediate risk patients ineligible for CTA due to these contraindications. The duration of the procedure may be between 1 and 1.5 hours, with about 15 minutes for the CTA and the remaining time for the preparation of the patient.

CTA is licensed by Health Canada as a Class III device. Currently, two companies have licenses for 64-slice CT scanners, Toshiba Medical Systems Corporation (License 67604) and Philips Medical Systems (License 67599 and 73260).

Research Questions

1. How does the accuracy of CTA compare to the more invasive CA in the diagnosis of CAD in symptomatic patients at intermediate risk of the disease?
2. How does the accuracy for CTA compare to other modalities in the detection of CAD?

Research Methods

Literature Search

A literature search was performed on July 20, 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, 2004 until July 20, 2009. 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. The quality of evidence was assessed as high, moderate, low or very low according to GRADE methodology.

Inclusion Criteria

- English language articles and English or French-language HTAs published from January 1, 2004 to July 20, 2009.
- Randomized controlled trials (RCTs), non-randomized clinical trials, systematic reviews and meta-analyses.
- Studies of symptomatic patients at intermediate pre-test probability of CAD.
- Studies of single source CTA compared to CA for the diagnosis of CAD.
- Studies in which sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV) could be established. HTAs, SRs, clinical trials, observational studies.

Outcomes of Interest

- CAD defined as $\geq 50\%$ stenosis.

Exclusion Criteria

- Non-English studies.
- Pediatric populations.
- Studies of patients at low or high pre-test probability of CAD.
- Studies of unstable patients, e.g., emergency room visits, or a prior diagnosis of CAD.
- Studies in patients with non-ischemic heart disease.
- Studies in which outcomes were not specific to those of interest in this report.
- Studies in which CTA was not compared to CA in a stable population.

Comparator

- Coronary angiography.

Measures of Interest

- Sensitivity, specificity;
- Negative predictive value (NPV), positive predictive value (PPV);
- Area under the curve (AUC) and diagnostic odds ratios (DOR).

Results of Literature Search and Evidence-Based Analysis

The literature search yielded two HTAs, the first published by MAS in April 2005, the other from the Belgian Health Care Knowledge Centre published in 2008, as well as three recent non-randomized clinical studies. The three most significant studies concerning the accuracy of CTA versus CA are the CORE-64 study, the ACCURACY trial, and a prospective, multicenter, multivendor study conducted in the Netherlands. Five additional non-randomized studies were extracted from the Belgian Health Technology Assessment (2008).

To provide summary estimates of sensitivity, specificity, area under the SROC curve (AUC) and diagnostic odds ratios (DORs), a meta-analysis of the above-mentioned studies was conducted. Pooled estimates of sensitivity and specificity were 97.7% (95%CI: 95.5% - 99.9%) and 78.8% (95%CI: 70.8% - 86.8%), respectively. These results indicate that the sensitivity of CTA is almost as good as CA, while its specificity is poorer. The diagnostic odds ratio (DOR) was estimated at 157.0 (95%CI: 11.2 - 302.7) and the AUC was found to be 0.94; however, the inability to provide confidence estimates for this estimate decreased its utility as an adequate outcome measure in this review.

This meta-analysis was limited by the significant heterogeneity between studies for both the pooled sensitivity and specificity (heterogeneity Chi-square $p=0.000$). To minimize these statistical concerns, the analysis was restricted to studies of intermediate risk patients with no previous history of cardiac events. Nevertheless, the underlying prevalence of CAD ranged from 24.8% to 78% between studies, indicating that there was still some variability in the pre-test probabilities of disease within this stable population. The variation in the prevalence of CAD, accompanied with differences in the proportion of calcification, likely affected the specificity directly and the sensitivity indirectly across studies.

In February 2010, the results of the Ontario Multi-detector Computed Tomography Coronary Angiography Study (OMCAS) became available and were thus included in a second meta-analysis of the above studies. OMCAS was a non-randomized double-blind study carried out across three centers in Ontario. It was conducted following a 2005 MAS review that requested an evaluation of the accuracy of 64-slice CTA for CAD detection. Within 10 days of their scheduled CA, all patients received an additional evaluation with CTA. Included in the meta-analysis with the above-mentioned studies are 117 symptomatic patients with intermediate probability of CAD (10%-90% probability), resulting in a pooled sensitivity of 96.1% (95%CI: 94.0%-98.3%) and pooled specificity of 81.5% (95%CI: 73.0%-89.9%).

Summary of Findings

1. CTA is almost as good as CA in detecting true positives but poorer in the rate of false positives. The main value of CTA may be in ruling out significant CAD.
2. Increased prevalence of CAD decreases study specificity, whereas specificity is increased in the presence of increased arterial calcification even in lower prevalence studies.
3. Positive CT angiograms may require additional tests such as stress tests or the more invasive CA, partly to identify false positives.
4. Radiation exposure is an important safety concern that needs to be considered, particularly the cumulative exposures from repeat CTAs.

Summary of Aggregate Results

The summary results of the five analyses are displayed below in Table 3. Estimates of pooled sensitivity ranked highest to lowest as CT Angio, Cardiac MRI, AC SPECT and traditional SPECT, gated SPECT and stress ECHO with contrast and stress ECHO. Estimates of pooled specificity ranked highest to lowest stress ECHO, AC SPECT, Cardiac MRI, stress ECHO with contrast, CT Angio, gated SPECT and lastly traditional SPECT.

Sensitivity and Specificity were equally weighted for policy decision making purposes and thus AUCs were calculated. CT Angio had the highest AUC followed by Cardiac MRI, AC SPECT, stress ECHO with contrast, stress ECHO, gated SPECT and lastly traditional SPECT. Since it was not possible to calculate standard errors of the AUC and thus not possible to use AUC to examine whether significant differences existed between the different technologies, the DOR was also calculated. The DORs for the different technologies ranked in a similar order to the AUC analysis ranging from a high of 127.57 for CT Angio to a low of 15.37 for traditional SPECT.

The estimates of pooled sensitivity, specificity and DOR were compared across the different cardiac imaging technologies. (Table 4) As noted in the methodology section, probabilities were adjusted for multiple comparisons. For sensitivity, significant differences were noted between CT Angio and all types of SPECT, stress ECHO, stress ECHO with contrast and Cardiac MRI as well as between Cardiac MRI and SPECT (gated and traditional) and stress ECHO and lastly between stress ECHO and SPECT (traditional and AC). For specificity, only the one comparison between traditional SPECT and stress ECHO was significantly different ($P < 0.05$). Significant differences were also observed between the DORs of discrete technologies such as between AC SPECT and CT Angio, gated SPECT and Cardiac MRI, gated SPECT and CT Angio, traditional SPECT and Cardiac MRI, stress ECHO and Cardiac MRI, stress ECHO and CT Angio, stress ECHO with contrast and CT Angio and Cardiac MRI and CT Angio.

Table 3: Summary Estimates of Pooled Sensitivity, Specificity and Diagnostic Odds Ratio for All Non-Invasive Cardiac Imaging Technologies for the Diagnosis of Coronary Artery Disease

Technology	AUC	Sensitivity			Specificity			DOR		
		Estimate	95% Lower CI	95% Upper CI	Estimate	95% Lower CI	95% Upper CI	Estimate	95% Lower CI	95% Upper CI
CT Angio	0.96	0.96	0.94	0.98	0.82	0.73	0.90	108.60	30.22	186.97
Cardiac MRI (perfusion)	0.93	0.91	0.88	0.94	0.81	0.75	0.87	41.13	22.20	60.05
AC SPECT	0.91	0.86	0.81	0.91	0.82	0.75	0.89	28.47	12.09	44.85
Stress ECHO with contrast (wall motion)	0.90	0.84	0.79	0.90	0.80	0.73	0.87	21.64	9.90	33.39
Stress ECHO (exercise + pharma)	0.89	0.79	0.77	0.82	0.84	0.82	0.86	20.64	16.63	24.64
Gated SPECT	0.89	0.84	0.79	0.88	0.78	0.71	0.85	18.75	10.26	27.25
Traditional SPECT	0.88	0.86	0.84	0.88	0.71	0.67	0.76	15.37	11.52	19.21

AC SPECT refers to attenuation corrected single photon emission computed tomography; Cardiac MRI, cardiac magnetic resonance imaging; CT Angio, computed tomographic angiography; gated SPECT, gated single photon emission computed tomography; stress ECHO, stress echocardiography; traditional SPECT, traditional single photon emission computed tomography.

Table 4: Comparisons of Sensitivity, Specificity and Diagnostic Odds Ratio across the Different Non-Invasive Cardiac Imaging Technologies

Comparisons	Sensitivity (P-value)	Specificity (P-value)	DOR (P-value)
AC SPECT vs. stress ECHO (exercise + pharma)	0.03	0.89	0.41
AC SPECT vs. stress ECHO with contrast (wall motion)	0.68	0.89	0.60
AC SPECT vs. Cardiac MRI (perfusion)	0.14	0.89	0.42
AC SPECT vs. CT Angio	0.00	0.89	0.01
SPECT Gated vs. ECHO Stress (exercise + pharma)	0.11	0.44	0.74
SPECT Gated vs. stress ECHO with contrast (wall motion)	0.89	0.89	0.74
SPECT Gated vs. Cardiac MRI (perfusion)	0.03	0.89	0.03
SPECT Gated vs. CT Angio	0.00	0.94	0.00
SPECT Traditional vs. ECHO Stress (exercise + pharma)	0.00	0.00	0.12
SPECT Traditional vs. stress ECHO with contrast (wall motion)	0.62	0.29	0.39
SPECT Traditional vs. Cardiac MRI (perfusion)	0.03	0.09	0.00
SPECT Traditional vs. CT Angio	0.00	0.64	0.00
ECHO Stress (exercise + pharma) vs. MCE (wall motion)	0.11	0.70	0.87
ECHO Stress (exercise + pharma) vs. Cardiac MRI (perfusion)	0.00	0.70	0.02
ECHO Stress (exercise + pharma) vs. CT Angio	0.00	0.70	0.00
Stress ECHO with contrast (wall motion) vs. Cardiac MRI (perfusion)	0.06	0.89	0.13
Stress ECHO with contrast (wall motion) vs. CT Angio	0.00	0.89	0.00
Cardiac MRI (perfusion) vs. CT Angio	0.00	0.89	0.03

AC SPECT refers to attenuation corrected single photon emission computed tomography; Cardiac MRI, cardiac magnetic resonance imaging; CT Angio, computed tomographic angiography; gated SPECT, gated single photon emission computed tomography; stress ECHO, stress echocardiography; traditional SPECT, traditional single photon emission computed tomography.

Safety

Radiation

Of primary concern with nuclear/X-ray technologies such as SPECT or CT Angio is that of radiation dose to the patient. Currently, the radiation dosage in terms of effective dose of SPECT or CT varies from anywhere to three to nine times higher than that of the average U.S. background effective dose of 3.0 millisieverts (mSv) (Table 1). (The effective dose is a useful method of comparing risk among different diagnostic tests as it takes into account the different risks of absorbed dose to various organs.) (8)

The U.S. Food and Drug Administration has estimated that a technology that exposes a patient to an effective dose of 10 millisieverts (mSv) may be associated with an increase in the possibility of fatal cancer at approximately 1 chance in 2000. This probability is in addition to the natural incidence of fatal cancer of 1 chance in 5 in the U.S. (9)

Although the additional risk appears low, it is currently hypothesized that there is a linear, no-threshold dose response relationship between the exposure of ionizing radiation and the development of cancer in human beings. Thus, even relatively low doses of radiation increase the risk of a patient developing malignancy over the patient's lifetime. Accordingly, the lifetime risk of a patient becomes an important consideration. (10)

Lifetime radiation risks are of particular concern with respect to children because of a child’s increased sensitivity to radiation and because children have more expected years of life after radiation exposure compared to adults. Because cardiac diagnostic procedures are more commonly performed in individuals of advanced age, a risk-benefit scenario comes into effect. Accordingly, for a cardiac diagnostic test being performed in an older adult, the risk of serious heart disease (or the risk of missing a diagnosis of serious heart disease) is greater than the theoretic risk of radiation-related cancer over the patient’s lifetime since the patient has fewer years to live than a child. Because the potential benefits of correctly diagnosing heart disease far outweigh the risk of radiation-associated cancer in older adults, radiation dosage rarely becomes a factor when deciding which test to use for diagnosing CAD. (11)

Table 5: Total effective dose of various cardiac diagnostic procedures

Test	Effective Dose (mSv)
Average U.S. background rate	3.0/year
Tc-99m tetrofosmin rest-stress (10 mCi + 30 mCi)	10.6
Tc-99m sestamibi 1-day rest-stress (10 mCi + 30 mCi)	12.0
Tc-99m sestamibi 2-day stress-rest (30 mCi + 30 mCi)	17.5
Tl-201 stress and reinjection (3.0 mCi + 1.0 mCi)	25.1
Dual-isotope (3.0 mCi Tl-201 + 30 mCi Tc-99m)	27.3
Gd-153 transmission for SPECT (AC)	0.05
64-Slice MDCT coronary CTA (female)	13.5–21.4
64-Slice MDCT coronary CTA (female)	9.6–15.2

Data from reference (12)

- There have also been safety concerns with regards to the use of contrast agents in ECHO. Several studies have been published assessing the safety of contrast agents and results indicate that there is not a significantly higher mortality rate in patients who receive contrast compared to those who do not. (13)
- There are also minor risks involved with the use of stress agents in cardiac testing. In the case of stress ECHO, results from multicenter trials have indicated that exercise is a safer than pharmacological stress and that among pharmacological stress, dipyridamole is safer than dobutamine. Nevertheless, complications arising from the use of stress agents are quite rare. (14)

Limitations of the Analysis and GRADE Quality of the Evidence

A methodological limitation of the current analysis is that the diagnostic accuracies of the five non-invasive imaging technologies were indirectly compared. To our knowledge, there is no published study that directly compares the diagnostic accuracy of all five non-invasive imaging tests in the population of interest. In order to indirectly compare technologies, the diagnostic accuracy of each technology was calculated using CA as the reference standard and there was consistency in inclusion and exclusion criteria across the discrete analyses.

In order to ensure the indirect comparison approach was valid, an additional analysis was undertaken whereby studies that directly compared stress ECHO and SPECT were evaluated. Studies were included in this exploratory analysis if they were included in the original analyses of either stress ECHO or SPECT

(indirect approach), yielding a total of 14 studies (908 patients) that were published between 1995 and 2006. (Table 7) The estimates of sensitivity and specificity derived from studies that directly compared stress ECHO and SPECT were similar to those obtained with the original indirect approach. (Table 6)

Table 6: Diagnostic Accuracy of Studies Directly and Indirectly Comparing Stress Echocardiography to SPECT

	Stress ECHO		SPECT	
	Indirect	Direct	Indirect	Direct
Pooled Sensitivity (95% C.I.)	0.80 (0.77 – 0.82)	0.78 (0.72 – 0.84)	0.86 (0.84–0.89)	0.89 (0.85 – 0.93)
Pooled Specificity (95% C.I.)	0.84 (0.82 – 0.87)	0.88 (0.83 – 0.94)	0.71 (0.67– 0.76)	0.70 (0.59 – 0.80)

SPECT, single photon emission computed tomography; stress ECHO, stress echocardiography

Studies that directly compared stress ECHO with contrast to stress ECHO without contrast and stress ECHO with contrast to SPECT were also examined as part of the analysis on stress ECHO with contrast. Again, results with the indirect approach yielded similar results to those obtained from studies that directly compared technologies. For additional information, please refer to the analysis on stress ECHO with contrast.

Another limitation of the current analyses is that the definition of significant CAD as defined by the degree of coronary artery stenosis varied across the studies. The majority of the studies used a threshold of 50% stenosis, however some studies did define significant disease as 70% stenosis. Subgroup analyses were performed to ensure diagnostic accuracy did not differ by definition of CAD. In addition, some studies included patients with a previous MI. Even though the analyses were intended to focus on patients suspected of CAD and therefore not include patients with a history of previous MI, it was still possible to include these studies in the analyses since the interpreters of the diagnostic test images were blinded to MI status. Subgroup analyses were also performed in this instance to ensure diagnostic accuracy did not differ by studies that included patients with previous MI compared to those studies that did not include these patients. Lastly, there was significant heterogeneity in patient populations.

The overall quality of the evidence for each technology was assessed using the diagnostic GRADE methodology. (15) Table 8 below briefly summarizes the results of the quality assessments across the different technologies. For more detailed results, please consult the individual evidence-based analyses. The quality of the evidence was downgraded for all technologies since diagnostic tests are considered as surrogate outcomes. The quality was also downgraded due to heterogeneity in study populations, variation in the definition of significant CAD and the fact that most studies recruited patients who were referred for CA and thus not necessarily reflective of the intermediate risk group and may impact the generalizability of findings. The overall quality of the evidence was graded as low to very low for all technologies.

Table 7: Characteristics of Studies that Directly Compared SPECT and Stress ECHO

Author, Year	N	Definition of CAD (% Stenosis)	SPECT				Stress ECHO		
			Tracer	Method of Stress	Sensitivity	Specificity	Method of Stress	Sensitivity	Specificity
Astarita, 2001 (16)	53	≥50	TI	Ex	1.00	0.47	Dip	0.78	1.00
Cramer, 1996 (17)	35	≥50	TC	Dip	0.79	0.83	Dip	0.69	0.83
DeBello, 1996 (18)	45	≥50	TC	Dob	0.87	0.86	Dob	0.76	0.86
Elhendy, 1998 (19)	70	≥50	TC	Dob	0.64	0.72	Dob	0.78	0.92
Fragasso, 1999 (20)	101	≥50	TC	Ex	0.98	0.36	Dob	0.88	0.80
Ho, 1995 (21)	54	≥50	TI	Dip	0.98	0.73	Dob	0.93	0.73
Khattar, 1998 (22)	100	≥50	TC	Dob/Adenosine	0.68	0.73	Dob	0.68	0.81
Kisacik, 1996 (23)	69	≥50	TC	Ex	0.96	0.64	Dob	0.87	0.86
Korosoglou, 2006 (24)	89	≥75	TC	Pharmacologic	0.77	0.52	Pharmacologic	0.82	0.78
Rollan, 2002 (25)	54	≥50	TC	Dob	0.88	0.57	Dob	0.84	0.89
San Roman, 1998 (26)	92	≥50	TC	Dob	0.87	0.70	Dob	0.79	0.89
							Dip	0.82	0.94
Santoro, 1998 (27)	60	≥70	TC	Dip	0.97	0.89	Dip	0.55	0.96
				Dob	0.91	0.81	Dob	0.61	0.96
Schillaci, 1997 (28)	40	≥70	TC	Dip	0.95	0.72	Dip	0.82	0.72
Slavich, 1996 (29)	46	≥50	TC	Dob	0.82	0.83	Dob	0.59	0.75

CAD refers to coronary artery disease; dip, dipyridamole; dob, dobutamine; ex, exercise; SPECT, single photon emission computed tomography; stress ECHO, stress echocardiography; TI, thallium; TC, technetium.

Table 8: GRADE Quality of the Evidence – Summary Table

Factor	Explanation	GRADE
Risk of Bias		
Study design	Observational cross-sectional studies	High
Limitations	No serious limitations for most technologies; For some technologies, limitations were noted pertaining to verification/referral bias, lack of proper blinding, etc...	Unchanged or reduced by one level for some technologies
Indirectness		
Outcomes	Diagnostic tests are considered as surrogate outcomes	Reduced by one level
Patient populations, diagnostic test, comparison test, and indirect comparisons	Heterogeneity in study populations Variation in definition of significant CAD Study recruitment in patients referred for coronary angiography → may affect generalizability	Reduced by one level
Important inconsistency in study results	No serious inconsistency for most technologies; For some technologies, large heterogeneity in accuracy estimates between studies was noted	Unchanged or reduced for some technologies
Imprecise evidence	Some imprecision but not sufficient to downgrade	Unchanged
Publication bias	Possible, but not considered sufficient to downgrade	Unchanged
Quality of Evidence		Low to 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.

Objectives

To determine the relative cost-effectiveness of five cardiac imaging technologies for the diagnosis of patients with suspected CAD in two patient populations: out-patients presenting with stable chest pain with an intermediate risk of CAD following physical examination and a graded exercise test (stable outpatients); and patients presenting to emergency and subsequently admitted to hospital with an acute chest pain syndrome, low-intermediate risk of CAD, with a normal ECG and negative cardiac biomarker (acute inpatients). The five cardiac imaging technologies are: stress ECHO, stress contrast ECHO, SPECT, cardiac MRI, and CT angiography.

Methods

The economic analysis consisted of three components: a systematic review of full economic evaluations of the relevant imaging technologies; a de novo cost-effectiveness analysis using a short term decision-analytic model; and a budget impact analysis from the perspective of the Ontario Ministry of Health and Long Term Care (MOHLTC). The systematic review of existing full economic evaluations was based upon a systematic search of Medline and the National Health Service Economic Evaluation Database (NHSEED) from their inception up to October 2009. Only full economic evaluations describing both the costs and consequences of adopting one or more of the cardiac imaging technologies for the diagnosis of CAD were included in the systematic review. The primary outcome of interest was the incremental cost-effectiveness ratio (ICER) of each imaging technology in relation to another imaging technology of interest.

The de novo cost-effectiveness analysis was conducted using a short term decision analytic model to determine the cost-effectiveness of the imaging tests in CAD diagnosis for each of the two patient populations in Ontario. The primary outcome measure was accurate diagnosis of CAD resulting from non-invasive imaging. Resource use and costs were derived from Ontario data sources. A series of sensitivity analysis were conducted to determine the robustness of the results to alternative assumptions

and to explore feasibility issues associated with the technologies in Ontario. It was also assumed that the contrast agent is administered at the same time of the initial echocardiogram once it is deemed suboptimal, and not at a subsequent visit.

The budget impact analysis assessed the impact on the budget of the MOHLTC of replacing various proportions of each technology with an alternative technology (for example replacing 10% of SPECT tests with stress contrast ECHO, or 25% of stress ECHO tests with CT angiography).

Results

In the previous studies identified in the systematic review, CT angiography was 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 found to be cost-effective in any study.

In the base case cost-effectiveness analysis, for stable outpatients, CT angiography was found to be less costly and more effective than stress ECHO, SPECT and cardiac MRI, but not stress contrast ECHO. The ICER of CT angiography versus stress contrast ECHO was \$1,527 per accurate diagnosis. Stress contrast ECHO thus appears to be the most cost-effective, non-invasive diagnostic test for stable outpatients at either WTP anchor. It also appears to be the most cost-effective non-invasive diagnostic test for acute inpatients at either WTP anchor.

In sensitivity analyses, where the prevalence of CAD in the population under consideration was allowed to vary, CT angiography appeared cost-effective for stable outpatients at a higher prevalence of CAD or when stress contrast ECHO was unavailable. It also appeared cost-effective for acute inpatients at higher prevalence values when hospital wait times were equalized across technologies. If CT angiography was unavailable then stress contrast ECHO appeared cost-effective across all prevalence values for both populations. If neither CT angiography nor stress contrast ECHO were available then stress ECHO appeared cost-effective for stable outpatients, while SPECT appeared cost-effective for acute inpatients.

The budget impact analysis found that replacing 25% of stress ECHOs currently performed without the use of contrast with the strategy of stress ECHO testing with the use of contrast if necessary would cost the MOHLTC an estimated \$830,000 over the next 5 years. Replacing the same number of tests with CT angiography would cost an estimated \$13.1m over 5 years. Replacing 25% of SPECTs with stress contrast ECHO would save the MOHLTC an estimated \$42.2m over 5 years, while replacing the same number of tests with CT angiography would save an estimated \$28.8m over the same time frame. Replacing existing cardiac MRI tests with stress contrast ECHO or CT angiography would not have a large budget impact since cardiac MRI is not widely adopted as a diagnostic test for CAD.

Conclusion

New options for non-invasive cardiac diagnostic imaging appear to have broadly similar sensitivity and specificity values in comparison to widely used current technologies. CT angiography and stress contrast ECHO are consistently more economically attractive than competing technologies, offering the potential for significant cost savings if they are used as replacement technologies for current, widely used tests. It is also assumed that the contrast agent is administered at the same time of the initial echocardiogram once it is deemed suboptimal, and not at a subsequent visit. Clinical policy regarding their implementation and expanded use should consider issues of radiation-related risk, long-term clinical and economic consequences of diagnostic imaging strategies (not considered here), the extent to which these tests may be used as complementary rather than replacement tests, and quality standards in the performance and interpretation of imaging technologies.

Ontario Health System Impact Analysis

To assist in the interpretation and contextualization of the evidence for Ontario, a Cardiac Imaging Expert Advisory Panel of was assembled and met on five occasions over a period of 6 months. The following comments were made about non-invasive cardiac imaging technologies for the diagnosis of CAD.

- The use of technologies could be considered for different settings (e.g., emergency vs. outpatient).
- The importance of sensitivity and specificity may vary by clinical setting.
- It is important to note that use of some technologies extends beyond the diagnosis of CAD to include other purposes such as risk stratification and prognosis.
- It is not possible to derive conclusions regarding the sequence of different diagnostic tests.
- For generalizability of results, study populations do not necessarily reflect the patients who would undergo these tests in Ontario and the definition of intermediate risk patients may vary.
- There are several stress agents used for ECHO, of which dobutamine is the most commonly used in Ontario.
- MRI is rarely performed in Ontario for the diagnosis of CAD
- There have been no significant changes in 64-slice CT Angio technology over the last 5 years.
- In terms of SPECT, ECG-gating is near standard in the province while attenuation correction is common, but not as widespread.
- CT Angio is widely accessible, however, proper infrastructure, training and standards may limit the feasibility of this technology. There are limitations in terms of feasibility for all technologies.
- Concerns were raised regarding the lack of adequate training and the need for standardization in usage of ECHO in Ontario.
- Quality control is an important consideration for all technologies.

Overall Conclusions

1. Based on low to very low quality evidence, the following conclusions were drawn:
 - a. In terms of sensitivity, there are statistically significant differences favoring CT angiography over other technologies and differences favoring cardiac MRI over other technologies. There is less variation in estimates of specificity across the technologies.
 - b. The high sensitivity for CT angiography derived from this systematic review could not be confirmed by a field evaluation study recently reported as an interim report by PATH.
 - c. Although tests of significance were not performed on AUCs, it appears that there is little difference in the combined sensitivity and specificity as measured with AUCs across the technologies.
2. In terms of feasibility, there is variation in availability of technologies across the province. There is limited access to CT Angiography and availability of expertise in interpreting results, as well as limited access to cardiac MRI. Quality assurance issues also apply to other cardiac imaging modalities.
3. In terms of safety, there are growing concerns regarding cumulative radiation exposure with certain technologies such as CT angiography and SPECT. Safety concerns have also been raised for contrast ECHO and this is currently being examined by Health Canada.
4. In terms of value for money, for stable patients, stress ECHO with contrast if necessary and/or CT angiography appear to be cost-effective for the diagnosis of CAD.
5. In terms of value for money, for low/intermediate risk patients presenting with chest pain syndrome (negative cardiac enzymes), results indicate that only stress ECHO with contrast if necessary was cost-effective irrespective of WTP and prevalence of CAD.
6. CT angiography, unlike other imaging technologies, relies on anatomical images and does not provide functional information. There is, therefore, uncertainty regarding its clinical utility compared with functional cardiac imaging.

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