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Stress Echocardiography 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
CA	Coronary angiography
CAD	Coronary artery disease
CI	Confidence interval(s)
DOR	Diagnostic odds ratio
ECHO	Echocardiography
LV	Left ventricle
MAS	Medical Advisory Secretariat
MCE	Myocardial contrast echocardiography
MI	Myocardial infarction
OHTAC	Ontario Health Technology Advisory Committee
RCT	Randomized controlled trial
SD	Standard deviation
SROC	Summary receiver operating characteristic
WMA	Wall motion analysis

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 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 worsening of wall motion abnormalities or the development of new wall motion 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 utility[1] 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.

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

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

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 Heijenbrok-Kal et al. (1) 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.

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

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Objective of Analysis

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

Stress Echocardiography

Stress ECHO is a non-invasive technology that images the heart using ultrasound. It's one of the most commonly employed imaging techniques for investigating a variety of cardiac abnormalities and its clinical utility extends beyond simple diagnosis. The technology can be used to assess prognosis and risk stratification in patients with established CAD, to perform preoperative risk assessment, to evaluate patients after revascularization, and to evaluate the severity of heart valve stenosis. (2;3)

Due to its portability and relative affordability, stress ECHO is widely used both in community and hospital settings. Results from an ECHO exam are available in real-time and can thus immediately impact further diagnostic work-up, dictate therapeutic decisions, determine response to therapy and

predict patient outcome. In most clinical settings, the sonographer performs the ECHO exam and the physician interprets the images. The entire outpatient exam takes approximately one hour. (4)

The technology relies on the differential absorption and reflection of sound waves by body tissues of differing properties. A complete stress ECHO exam includes M-mode, 2-dimensional (2-D) images and Doppler imaging with a stress agent. (3) The M-mode measures left ventricle (LV) cavity size and wall thickness, 2-D imaging quantifies cardiac chamber sizes, wall thickness, ventricular function, valvular anatomy and great vessel size, while Doppler imaging measures blood flow velocities, intracardiac pressures and hemodynamics.

In order to diagnose CAD and assess whether myocardial ischemia is present, images obtained at rest are compared to those obtained during or immediately after stress. The normal cardiac response to stress is an increase in heart rate and myocardial contractility. A normal stress ECHO result is thus defined as normal LV wall motion at rest and with stress. The hallmark of stress-induced myocardial ischemia is a worsening of wall motion abnormalities or the development of new wall motion abnormalities (see Table 1). The interpretation of wall motion contractility and function, however, is subjective, which creates the possibility of inter-reader and inter-institutional variability. For regional wall motion analysis (WMA), there are 16 segments that are evaluated on the basis of their contractility (score of 1-5). This information then goes into calculating a wall motion score index (WMSI). The larger the infarct, the higher the WMSI since wall motion abnormalities become more severe. The WMSI also increases if there is viable myocardium that does not receive sufficient blood flow when under stress (2;3)

Standardized protocols exist for performing stress ECHO. The most commonly used stressors are exercise, dobutamine and dipyridamole. Exercise ECHO can be performed either using a treadmill or bicycle protocol, whereby images are obtained during the various levels of exercise or immediately following exercise. Interpretation is based on a comparison of images at rest and at peak exercise. A major challenge of exercise stress ECHO is that images need to be obtained rapidly after exercise. Although exercise is the most widely used stress protocol, patients may be unable to exercise, may exercise submaximally, or their results may be uninterpretable. (3) In these patients, a pharmacological agent is used to induce stress. Dobutamine, a vasoconstrictor, is the most commonly employed pharmacological agent in North America, while dipyridamole, a vasodilator, is more commonly used in Europe. (3) Adenosine is another vasodilator but is used much less frequently. These agents induce ischemia through different hemodynamic mechanisms. Dobutamine primarily increases myocardial oxygen demand and dypyridamole and adenosine mainly decrease subendocardial flow supply.

Table 1: Interpretation of ECHO Images Obtained at Rest and During Stress

Rest	Stress	Diagnosis
Normal	Normal	Normal
Normal	Abnormal	Ischemia
Abnormal	Normal (stunned) or Biphasic (subsequent deterioration at peak – hibernating)	Viability
Abnormal	Abnormal	Necrotic

* Table adapted from Sicari et al. (3)

Stress ECHO reports include a baseline and stress assessment of wall motion and systolic function in addition to the stress protocol that was employed, the exercise time or dose of pharmacological agent used, the maximum heart rate achieved, whether the level of stress was adequate, the blood pressure response, the reason for test termination if the results are incomplete, any cardiac symptoms during the test, and electrocardiographic (ECG) changes or significant arrhythmias. (2)

Clear endocardial definition is vital for optimal image interpretation, yet it is estimated that approximately 30% of patients have sub-optimal stress ECHO exams. (5;6) Opacification of the LV cavity and endocardial border detection can be difficult in obese patients and those with lung disease. To overcome this barrier, contrast agents for LV opacification have been developed to enhance endocardial border detection. (5;6) The Medical Advisory Secretariat has undertaken an evidence-based analysis of myocardial contrast ECHO (MCE) and, based on the evidence found, the addition of contrast imaging in patients with suboptimal ECHO results significantly improved interpretability of the results.

The diagnostic accuracy of stress ECHO exams may also be impacted by gender with men and women exhibiting different CAD patterns and responses to cardiac testing. Women are also more likely to have non-obstructive or single-vessel disease when compared to men, which decreases the diagnostic accuracy. (7-9)

There are no known contraindications for stress ECHO. In terms of safety, it does not involve any ionising radiation, which is an important consideration for repeat testing, and serious side effects are uncommon at less than one in 1000 stress ECHO exams. (10) The most common cardiovascular side effects of those that do occur are angina, hypotension and cardiac arrhythmias. (2)

The combination of its relative ease of use and low risk of adverse events have made stress ECHO a popular method of CAD diagnosis; however, there is also the potential for ECHO to be overused or misused. Some patients may not benefit from a stress ECHO test or would have achieved a similar benefit without the addition of the test. Inappropriate use could be costly and may also prompt potentially harmful subsequent testing or treatment such as unnecessary coronary revascularization. (11)

For the future, it is envisioned by experts in the field that there will be more quantitative methods for assessment, improved image quality and enhanced portability. Several recent advancements in stress ECHO have been developed to overcome some of the challenges with the qualitative interpretation of results and image quality. Real-time 3D ECHO has been introduced to enhance endocardial border definition. Initial studies have been encouraging, but the additional value of this technique over traditional WMA remains unknown. (3) Tissue Doppler imaging is another advancement that enables a quantitative and reproducible assessment of myocardial velocity and deformation. Based on the available evidence and expert feedback, this quantitative approach is not yet ready for widespread use. (3) Lastly, hand-carried cardiac ultrasound devices have been developed to diagnose CAD in emergency rooms and at bedsides, but again, evidence on the diagnostic accuracy and clinical utility of these devices is limited. (12)

Alternative Technologies

Stress ECHO is not the only imaging modality that can be used to diagnose CAD. Alternatives to stress ECHO for the diagnosis of CAD currently licensed for use in Canada include single photon emission computed tomography (SPECT), cardiac magnetic resonance imaging (c-MRI) and computed tomography (CT) angiography. All of these technologies are non-invasive and used to make decisions on which patients should go on to CA, which is the only modality that provides a definitive diagnosis based on anatomical information and the degree of coronary artery stenosis , although its invasive nature increases the risk of adverse events. (13)

Regulatory Status

ECHO units are licensed by Health Canada as class III devices. There are currently 8 ECHO systems licensed for sale in Canada, as summarized in Table 2.

Table 2: Echocardiography systems licensed by Health Canada

Manufacturer	Device
General Electric Medical Systems Israel, Ultrasound	VIVID S6 Ultrasound System VIVID 7 Dimension Ultrasound System VIVID S5 Ultrasound System
Siemens Medical Solutions USA, Inc.	Acuson Sequoia C512 Echocardiography System
Imacor INC.	Imacor Zura Imaging System
St. Jude Medical	View Flex Ultrasound Catheter
Dymax Corporation	Site Rite IV Ultrasound System
Volcano Corporation	S5 Imaging System

Evidence-Based Analysis

Research Questions

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

2. What is the clinical utility[3] of stress ECHO?

Methods

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. Articles with an unknown eligibility were reviewed with a second clinical epidemiologist and then a group of epidemiologists until consensus was established.

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 stratified by segments of the heart)
- English and human studies only

Exclusion Criteria

- 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 or valvular disease)
- Trans-esophageal 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

Statistical Analysis

Pooled estimates of sensitivity, specificity and diagnostic odds ratios (DORs) were calculated using a bivariate, binomial generalized linear mixed model. (14) Statistical significance was defined by P values of less than 0.05, where "false discovery rate" adjustments were made for multiple hypothesis testing. (15) The bivariate regression analyses were performed using SAS version 9.2 (SAS Institute Inc.; Cary, NC, USA). Summary receiver operating characteristic (sROC) curves weighted by inverse variance were produced using Review Manager 5.0.22 (The Nordiac Cochrane Centre, The Cochrane Collaboration,

[3] Clinical utility is defined as a technology that aids in clinical treatment decision-making.

2008). All other statistics were calculated using STATA version 10.1 (StataCorp; Texas, USA). The area under the sROC curve was estimated by numerical integration with a cubic spline (default option).

Quality of Evidence

The quality of the body of evidence was assessed as high, moderate, low, or very low according to the GRADE Working Group criteria (16) as presented below.

- Quality refers to the criteria such as the adequacy of allocation concealment, blinding and follow-up.
- Consistency refers to the similarity of estimates of effect across studies. If there are important and unexplained inconsistencies in the results, our confidence in the estimate of effect for that outcome decreases. Differences in the direction of effect, the magnitude of the difference in effect, and the significance of the differences guide the decision about whether important inconsistency exists.
- Directness refers to the extent to which the interventions and outcome measures are similar to those of interest.

As stated by the GRADE Working Group, the following definitions of quality were used in grading the quality of the evidence:

High	Further research is very unlikely to change confidence in the estimate of effect.
Moderate	Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate.
Low	Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate.
Very Low	Any estimate of effect is very uncertain

Results of Evidence-Based Analysis

The search identified 866 articles published from January 1, 2004 to August 21, 2009. Among these was a high quality systematic review by Heijenbrok-Kal et al. (1), which compared the diagnostic performance of stress ECHO, SPECT and electron beam CT for CAD using CA as the reference standard. The authors performed a meta-analysis on 351 patient-series which were reported in 11 meta-analyses.

Given the vast amount of published literature on stress ECHO, it was decided to use the studies contained in the comprehensive review by Heijenbrok-Kal et al. (1) as a basis for the MAS evidence-based analysis. Out of the 11 meta-analyses contained in this review, there were 7 systematic reviews containing information on 226 studies on Stress ECHO compared to CA for the diagnosis of CAD (see Table 3).

To further refine the analysis, additional inclusion criteria were applied to the 226 studies included in Heijenbrok-Kal et al. (1) systematic review. For feasibility, studies were included if they were published after 1995 and if the sample size was greater than or equal to 20 patients. Applying these additional criteria yielded a total of 105 observational studies containing information on 13, 035 patients, which were used for the MAS evidence-based analysis (see Table 4). In these studies, stress ECHO results were compared to those obtained with CA results in the same patient, thus patients acted as their own controls. Data was abstracted from the original systematic reviews. When information was missing or incomplete, an attempt was made to extract data from the original studies.

Table 3: Characteristics of meta-analyses included in Heijenbrok-Kal et al., 2007 systematic review*

Study	Search Dates	Type of Stress ECHO	No of Studies Included	Patient Characteristics	% Diagnosed With CAD on CA	Pooled Sensitivity	Pooled Specificity	Other Technologies Evaluated
O'Keefe et al., 1995 (17)	Up until Dec 1993	Ex ECHO	12 (913 patients)	NR	72	81	89	Ex SPECT, Ad SPECT
		Dob ECHO	14 (1049 patients)		69	81	83	
Fleischmann et al., 1998 (18)	Jan 1990 - Oct 1997	Ex ECHO	24 (2637 patients)	mean age 59 yrs 69% men 20% previous MI	66	85	77	Ex SPECT
Picano et al., 2000 (19)	1985 -1998	Dip ECHO	38 (2856 patients)	26% previous MI	65	73	91	None
		Dob ECHO	59 (5082 patients)	26% previous MI	73	81	83	
de Albuquerque Fonseca et al., 2001 (20)	1997-2000	Dip ECHO	8 (533 patients)	NR	74	72	92	None
		Ex ECHO	8 (533 patients)		74	79	82	
Kim et al, 2001 (21)	Jan 1997- June 1999	Ad ECHO	6 (516 patients)	mean age 65 yrs 71% men 31% previous MI	73	72	91	Ad SPECT, Dip SPECT, Dob SEPCT, EBCT
		Dip ECHO	20 (1835 patients)	mean age 56 yrs 72% men 15% previous MI	67	70	93	
		Dob ECHO	40 (4097 patients)	mean age 59 yrs 66% men 26% previous MI	70	80	84	
Imran et al., 2003 (22)	1986 - March 2001	Dip ECHO	10 (651 patients)	NR	67	70	90	Mix SPECT
Noguchi et al., 2005 (23)	1981 - Dec 2001	Ex ECHO	44 (3714 patients)	mean age 57 yrs 73% men 11% previous MI	70	83	84	None
		Ad ECHO	11 (678 patients)	mean age 64 yrs 76% men 21% previous MI	77	68	81	
		Dob ECHO	80 (7914 patients)	mean age 59 yrs 70% men 13% previous MI	69	80	85	
		Dip ECHO	40 (3466 patients)	mean age 56 yrs 73% men 9% previous MI	70	71	92	

Ad refers to adenosine; CAD, coronary artery disease; Dip, dipyridamole; Dob, dobutamine; ECHO, echocardiography; Ex, Exercise; Mix, combination of stressors; NR, not reported.

* Table adapted from Heijenbrok-Kal et al. (1)

Table 4: Quality of evidence of included studies on stress ECHO

Study Design	Level of Evidence†	Number of Eligible Studies
Large RCT, systematic review of RCTs	1	
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	105 (Patients acted as their own controls)
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	105

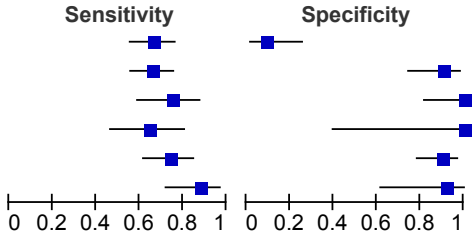
RCT refers to randomized controlled trial;
Table adapted from Goodman, 1996 (24)

The studies were published between 1995 and 2001, the majority of patients were male (67.6%, n=89 studies) and the mean age of patients was 59 years (n=88 studies). Data on women and the elderly was more limited. The prevalence of CAD ranged from 19% to 94%, with a mean value of 70%. In studies that examined pharmacological stress the mean CAD prevalence was slightly higher than in trials involving exercise stress (71.0% versus 66.5%). Appendix 2 further outlines characteristics of the studies included in the analysis.

Of the 105 studies included in the MAS analysis, the majority of studies examined the diagnostic accuracy of stress ECHO with pharmacological agents. A study was counted twice if data was reported on different stress agents. Six studies used adenosine, 26 used dipyridamole and 77 used dobtamine, which is the most commonly used pharmacological stress ECHO agent in Ontario. A further 18 studies employed exercise (dynamic and/or static) as the stressor.

Sensitivity and specificity varied across the different studies and different stress agents. For adenosine, the sensitivity ranged from 0.66 to 0.88 and the specificity ranged from 0.10 to 1.00 (Figure 1). For dipyradamole, the sensitivity ranged from 0.42 to 1.00 and the specificity ranged from 0.14 to 1.00 (Figure 2). For dobutamine, the sensitivity ranged from 0.40 to 1.00 and the specificity ranged from 0.49 to 1.00 (Figure 3). Lastly, for exercise the sensitivity ranged from 0.54 to 0.94 and the specificity ranged from 0.41 to 0.96 (Figure 4).

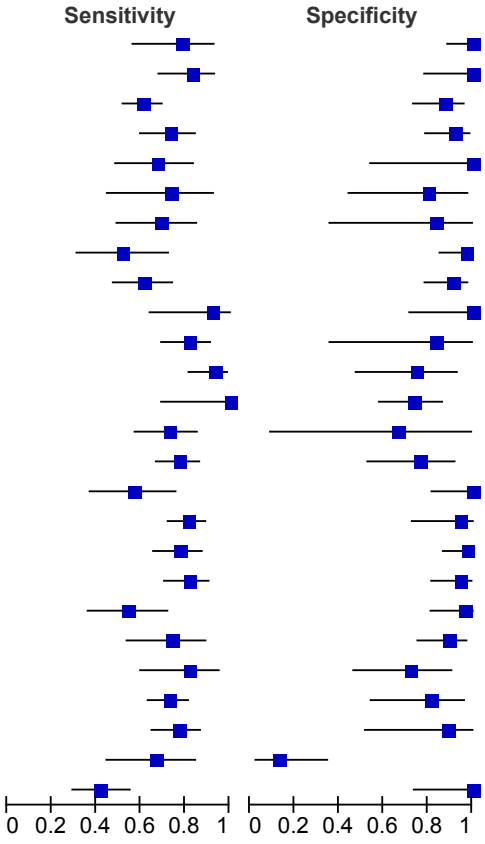
Study	TP	FP	FN	TN	Sensitivity	Specificity
Anthopoulos 1996	59	28	30	3	0.66 [0.55, 0.76]	0.10 [0.02, 0.26]
Anthopoulos 1997	64	3	33	28	0.66 [0.56, 0.75]	0.90 [0.74, 0.98]
Djordjevic-Dikic 1996	30	0	10	18	0.75 [0.59, 0.87]	1.00 [0.81, 1.00]
Fukai 1995	22	0	12	4	0.65 [0.46, 0.80]	1.00 [0.40, 1.00]
Miyazono 1998	46	5	16	45	0.74 [0.62, 0.84]	0.90 [0.78, 0.97]
Tawa 1996	29	1	4	11	0.88 [0.72, 0.97]	0.92 [0.62, 1.00]



*FN refers to false negatives; FP, false positives; TN, true negatives; TP, true positives.

Figure 1: Estimates of sensitivity and specificity derived from studies comparing adenosine stress ECHO to CA for the diagnosis of CAD

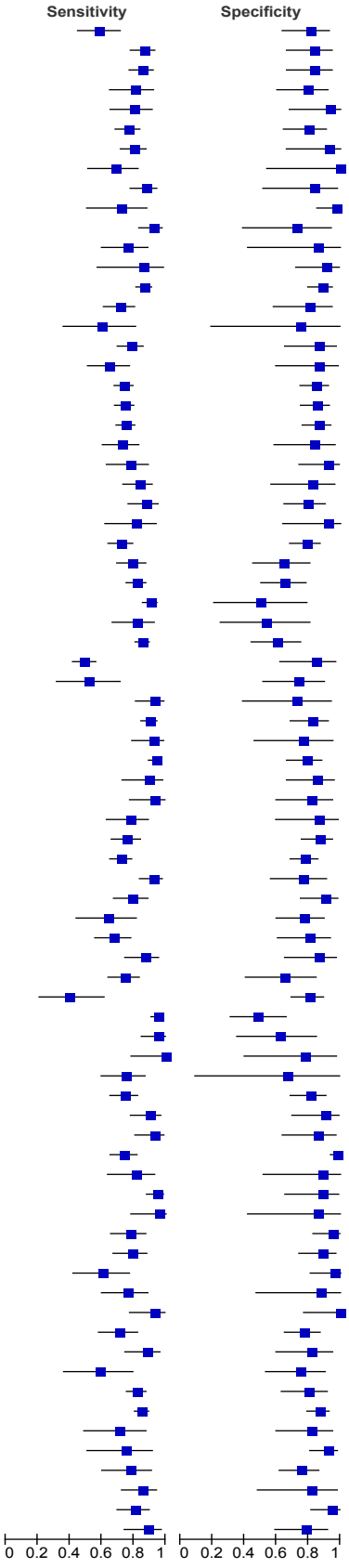
Study	TP	FP	FN	TN	Sensitivity	Specificity
Astarita 2001	18	0	5	30	0.78 [0.56, 0.93]	1.00 [0.88, 1.00]
Batlle 1998	34	0	7	15	0.83 [0.68, 0.93]	1.00 [0.78, 1.00]
Beleslin 1999	78	5	50	35	0.61 [0.52, 0.69]	0.88 [0.73, 0.96]
Bjornstad 1995	41	3	15	35	0.73 [0.60, 0.84]	0.92 [0.79, 0.98]
Bjornstad 1995a	21	0	10	6	0.68 [0.49, 0.83]	1.00 [0.54, 1.00]
Bjornstad 1997	11	2	4	8	0.73 [0.45, 0.92]	0.80 [0.44, 0.97]
Cramer 1996	20	1	9	5	0.69 [0.49, 0.85]	0.83 [0.36, 1.00]
Dagianti 1995	13	1	12	34	0.52 [0.31, 0.72]	0.97 [0.85, 1.00]
Fragasso 1999	35	4	22	40	0.61 [0.48, 0.74]	0.91 [0.78, 0.97]
Gaddi 1999	12	0	1	11	0.92 [0.64, 1.00]	1.00 [0.72, 1.00]
Lanzarini 1995	45	1	10	5	0.82 [0.69, 0.91]	0.83 [0.36, 1.00]
Loimaala 1999	41	4	3	12	0.93 [0.81, 0.99]	0.75 [0.48, 0.93]
Maffei 1998	10	11	0	31	1.00 [0.69, 1.00]	0.74 [0.58, 0.86]
Minardi 1997	32	1	12	2	0.73 [0.57, 0.85]	0.67 [0.09, 0.99]
Parodi 1999	62	5	18	16	0.78 [0.67, 0.86]	0.76 [0.53, 0.92]
Parthenakis 1997	16	0	12	18	0.57 [0.37, 0.76]	1.00 [0.81, 1.00]
Pingitore 1996	75	1	17	17	0.82 [0.72, 0.89]	0.94 [0.73, 1.00]
San 1996	49	1	14	38	0.78 [0.66, 0.87]	0.97 [0.87, 1.00]
San 1998	54	2	12	34	0.82 [0.70, 0.90]	0.94 [0.81, 0.99]
Santoro 1998	18	1	15	26	0.55 [0.36, 0.72]	0.96 [0.81, 1.00]
Scherhag 1997	20	4	7	34	0.74 [0.54, 0.89]	0.89 [0.75, 0.97]
Schillaci 1997	18	5	4	13	0.82 [0.60, 0.95]	0.72 [0.47, 0.90]
Schroder 1996	75	3	28	13	0.73 [0.63, 0.81]	0.81 [0.54, 0.96]
Schroder 1997	50	1	15	8	0.77 [0.65, 0.86]	0.89 [0.52, 1.00]
Sochowski 1995	16	19	8	3	0.67 [0.45, 0.84]	0.14 [0.03, 0.35]
Wagdi 1996	26	0	36	12	0.42 [0.30, 0.55]	1.00 [0.74, 1.00]



*FN refers to false negatives; FP, false positives; TN, true negatives; TP, true positives.

Figure 2: Estimates of sensitivity and specificity derived from studies comparing dipyridamole stress ECHO to CA for the diagnosis of CAD

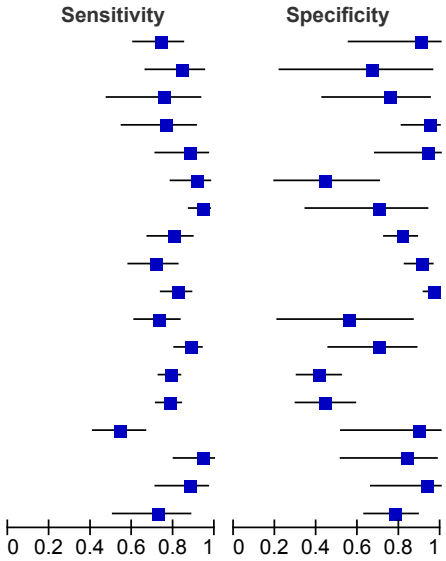
Study	TP	FP	FN	TN	Sensitivity	Specificity
Ahmad 2001	34	6	24	26	0.59 [0.45, 0.71]	0.81 [0.64, 0.93]
Anthopoulos 1996	77	5	12	26	0.87 [0.78, 0.93]	0.84 [0.66, 0.95]
Anthopoulos 1997	83	5	14	26	0.86 [0.77, 0.92]	0.84 [0.66, 0.95]
Ariff 2000	30	6	7	23	0.81 [0.65, 0.92]	0.79 [0.60, 0.92]
Batlle 1998	33	1	8	14	0.80 [0.65, 0.91]	0.93 [0.68, 1.00]
Beleslin 1999	98	8	30	32	0.77 [0.68, 0.84]	0.80 [0.64, 0.91]
Bigi 1995	86	1	21	13	0.80 [0.72, 0.87]	0.93 [0.66, 1.00]
Castini 1995	26	0	12	6	0.68 [0.51, 0.82]	1.00 [0.54, 1.00]
Chan 1995	63	2	9	10	0.88 [0.78, 0.94]	0.83 [0.52, 0.98]
Dagianti 1995	18	1	7	34	0.72 [0.51, 0.88]	0.97 [0.85, 1.00]
Daoud 1995	60	3	5	8	0.92 [0.83, 0.97]	0.73 [0.39, 0.94]
De Bello 1996	29	1	9	6	0.76 [0.60, 0.89]	0.86 [0.42, 1.00]
Derumeaux 1995	12	2	2	21	0.86 [0.57, 0.98]	0.91 [0.72, 0.99]
Dionisopoulos 1997	181	9	28	70	0.87 [0.81, 0.91]	0.89 [0.79, 0.95]
Dolan 2001	65	4	26	17	0.71 [0.61, 0.80]	0.81 [0.58, 0.95]
Elhendy 1996	12	1	8	3	0.60 [0.36, 0.81]	0.75 [0.19, 0.99]
Elhendy 1996a	87	3	24	19	0.78 [0.70, 0.86]	0.86 [0.65, 0.97]
Elhendy 1997	37	2	20	13	0.65 [0.51, 0.77]	0.87 [0.60, 0.98]
Elhendy 1997a	172	11	61	62	0.74 [0.68, 0.79]	0.85 [0.75, 0.92]
Elhendy 1998	164	10	57	59	0.74 [0.68, 0.80]	0.86 [0.75, 0.93]
Elhendy 1998a	171	9	57	58	0.75 [0.69, 0.80]	0.87 [0.76, 0.94]
Elhendy 1998b	48	3	18	15	0.73 [0.60, 0.83]	0.83 [0.59, 0.96]
Elhendy 1998c	35	2	10	23	0.78 [0.63, 0.89]	0.92 [0.74, 0.99]
Elhendy 1999	61	3	12	14	0.84 [0.73, 0.91]	0.82 [0.57, 0.96]
Fragasso 1999	50	9	7	35	0.88 [0.76, 0.95]	0.80 [0.65, 0.90]
Frohwein 1995	22	1	5	12	0.81 [0.62, 0.94]	0.92 [0.64, 1.00]
Geleijnse 1995	103	17	40	63	0.72 [0.64, 0.79]	0.79 [0.68, 0.87]
Hennessy 1997	69	11	18	20	0.79 [0.69, 0.87]	0.65 [0.45, 0.81]
Hennessy 1997a	139	17	31	32	0.82 [0.75, 0.87]	0.65 [0.50, 0.78]
Hennessy 1997b	169	6	18	6	0.90 [0.85, 0.94]	0.50 [0.21, 0.79]
Hennessy 1997c	32	6	7	7	0.82 [0.66, 0.92]	0.54 [0.25, 0.81]
Hennessy 1997d	234	17	40	26	0.85 [0.81, 0.89]	0.60 [0.44, 0.75]
Hennessy 1998	97	3	101	17	0.49 [0.42, 0.56]	0.85 [0.62, 0.97]
Herzog 1999	14	6	13	17	0.52 [0.32, 0.71]	0.74 [0.52, 0.90]
Ho 1995	40	3	3	8	0.93 [0.81, 0.99]	0.73 [0.39, 0.94]
Ho 1997	144	8	16	38	0.90 [0.84, 0.94]	0.83 [0.69, 0.92]
Ho 1997a	35	3	3	10	0.92 [0.79, 0.98]	0.77 [0.46, 0.95]
Ho 1997b	152	13	10	48	0.94 [0.89, 0.97]	0.79 [0.66, 0.88]
Ho 1998	26	4	3	23	0.90 [0.73, 0.98]	0.85 [0.66, 0.96]
Ho 1998a	27	4	2	18	0.93 [0.77, 0.99]	0.82 [0.60, 0.95]
Hoffmann 1996	35	2	10	13	0.78 [0.63, 0.89]	0.87 [0.60, 0.98]
Hoffmann 1996a	72	7	23	48	0.76 [0.66, 0.84]	0.87 [0.76, 0.95]
Hoffmann 1999	132	22	51	78	0.72 [0.65, 0.78]	0.78 [0.69, 0.86]
Huang 1997	62	6	5	20	0.93 [0.83, 0.98]	0.77 [0.56, 0.91]
Iwase 1996	50	3	13	29	0.79 [0.67, 0.89]	0.91 [0.75, 0.98]
Joseph 2000	18	8	10	27	0.64 [0.44, 0.81]	0.77 [0.60, 0.90]
Khattar 1998	50	5	24	21	0.68 [0.56, 0.78]	0.81 [0.61, 0.93]
Kisacik 1996	41	3	6	19	0.87 [0.74, 0.95]	0.86 [0.65, 0.97]
Latcham 1995	64	7	22	13	0.74 [0.64, 0.83]	0.65 [0.41, 0.85]
Lewis 1999	10	13	15	54	0.40 [0.21, 0.61]	0.81 [0.69, 0.89]
Ling 1996	141	18	7	17	0.95 [0.90, 0.98]	0.49 [0.31, 0.66]
Loimaala 1999	42	6	2	10	0.95 [0.85, 0.99]	0.63 [0.35, 0.85]
Mairesse 1995	15	2	0	7	1.00 [0.78, 1.00]	0.78 [0.40, 0.97]
Minardi 1997	33	1	11	2	0.75 [0.60, 0.87]	0.67 [0.09, 0.99]
Nagel 1999	81	10	28	44	0.74 [0.65, 0.82]	0.81 [0.69, 0.91]
Oguzhan 1997	44	2	5	19	0.90 [0.78, 0.97]	0.90 [0.70, 0.99]
Ozdemir 1999	39	3	3	18	0.93 [0.81, 0.99]	0.86 [0.64, 0.97]
Pasierski 2001	86	3	30	129	0.74 [0.65, 0.82]	0.98 [0.94, 1.00]
Peteiro 2001	26	1	6	8	0.81 [0.64, 0.93]	0.89 [0.52, 1.00]
Pingitore 1996	87	2	5	16	0.95 [0.88, 0.98]	0.89 [0.65, 0.99]
Reis 1995	22	1	1	6	0.96 [0.78, 1.00]	0.86 [0.42, 1.00]
San 1996	49	2	14	37	0.78 [0.66, 0.87]	0.95 [0.83, 0.99]
San 1998	52	4	14	32	0.79 [0.67, 0.88]	0.89 [0.74, 0.97]
Santoro 1998	20	1	13	26	0.61 [0.42, 0.77]	0.96 [0.81, 1.00]
Schroder 1996	29	1	9	7	0.76 [0.60, 0.89]	0.88 [0.47, 1.00]
Senior 1996	27	0	2	14	0.93 [0.77, 0.99]	1.00 [0.77, 1.00]
Senior 1998	42	14	17	48	0.71 [0.58, 0.82]	0.77 [0.65, 0.87]
Shaheen 1998	37	4	5	18	0.88 [0.74, 0.96]	0.82 [0.60, 0.95]
Slavich 1996	13	6	9	18	0.59 [0.36, 0.79]	0.75 [0.53, 0.90]
Smart 1997	140	7	31	28	0.82 [0.75, 0.87]	0.80 [0.63, 0.92]
Smart 2000	238	14	42	92	0.85 [0.80, 0.89]	0.87 [0.79, 0.93]
Sochowski 1995	17	4	7	18	0.71 [0.49, 0.87]	0.82 [0.60, 0.95]
Takeuchi 1996	15	4	5	46	0.75 [0.51, 0.91]	0.92 [0.81, 0.98]
Therre 1999	25	13	7	40	0.78 [0.60, 0.91]	0.75 [0.62, 0.86]
Vitarelli 1997	41	2	7	9	0.85 [0.72, 0.94]	0.82 [0.48, 0.98]
Wu 1996	55	2	13	34	0.81 [0.70, 0.89]	0.94 [0.81, 0.99]
Yeo 1996	32	6	4	22	0.89 [0.74, 0.97]	0.79 [0.59, 0.92]



*FN refers to false negatives; FP, false positives; TN, true negatives; TP, true positives.

Figure 3: Estimates of sensitivity and specificity derived from studies comparing dobutamine stress ECHO to CA for the Diagnosis of CAD

Study	TP	FP	FN	TN	Sensitivity	Specificity
Badruddin 1999	42	1	15	9	0.74 [0.60, 0.84]	0.90 [0.55, 1.00]
Bjornstad 1995	26	2	5	4	0.84 [0.66, 0.95]	0.67 [0.22, 0.96]
Chaudhry 2000	12	3	4	9	0.75 [0.48, 0.93]	0.75 [0.43, 0.95]
Dagianti 1995	19	2	6	33	0.76 [0.55, 0.91]	0.94 [0.81, 0.99]
Jun 1996	28	1	4	14	0.88 [0.71, 0.96]	0.93 [0.68, 1.00]
Loimaala 1999	40	9	4	7	0.91 [0.78, 0.97]	0.44 [0.20, 0.70]
Luotolahti 1996	101	3	7	7	0.94 [0.87, 0.97]	0.70 [0.35, 0.93]
Marwick 1995	47	19	12	83	0.80 [0.67, 0.89]	0.81 [0.72, 0.88]
Marwick 1995a	44	8	18	77	0.71 [0.58, 0.82]	0.91 [0.82, 0.96]
Pasierski 2001	95	5	21	127	0.82 [0.74, 0.88]	0.96 [0.91, 0.99]
Peteiro 1999	51	4	19	5	0.73 [0.61, 0.83]	0.56 [0.21, 0.86]
Roger 1995	94	6	13	14	0.88 [0.80, 0.93]	0.70 [0.46, 0.88]
Roger 1997	197	52	55	36	0.78 [0.73, 0.83]	0.41 [0.31, 0.52]
Roger 1997a	151	28	43	22	0.78 [0.71, 0.83]	0.44 [0.30, 0.59]
Schroder 1997	35	1	30	8	0.54 [0.41, 0.66]	0.89 [0.52, 1.00]
Tawa 1996	31	2	2	10	0.94 [0.80, 0.99]	0.83 [0.52, 0.98]
Tian 1996	28	1	4	13	0.88 [0.71, 0.96]	0.93 [0.66, 1.00]
Toumanidis 1996	18	10	7	35	0.72 [0.51, 0.88]	0.78 [0.63, 0.89]



*FN refers to false negatives; FP, false positives; TN, true negatives; TP, true positives.

Figure 4: Estimates of sensitivity and specificity derived from studies comparing exercise stress ECHO to CA diagnosis of CAD

Pooled estimates of sensitivity and specificity were calculated using a bivariate, binomial generalized linear mixed model. (Table 5) When all stress agents were combined, the pooled sensitivity was 0.80 and the pooled specificity was 0.84. There were no significant differences in the estimates of pooled sensitivity and specificity across the different pharmacological stress agents (Table 6). In comparison to pharmacological stress agents, exercise stress had a higher estimate of pooled sensitivity, yet a lower estimated pooled specificity. Nevertheless, the observed differences in sensitivity and specificity between exercise and pharmacological stress were not significant (sensitivity P=0.62, specificity P=0.36). While these differences were not significant, it is important to note that different patient populations would be referred for pharmacological or exercise stress ECHO tests based on ability to exercise.

The diagnostic odds ratio (DOR), which is the odds of a positive test in patients with disease compared with the odds of a positive test results in those without the disease, was also calculated. The DOR for all stress sources combined was found to be 20.64, while for pharmacological stress it was 21.71 and for exercise stress it was 16.11.

Table 5: Estimates of pooled sensitivity, pooled specificity and DORs derived from studies comparing stress ECHO to CA for the Diagnosis of CAD

Type of Stress	No of Studies (no of patients)	Pooled Sensitivity (95%CI)	Pooled Specificity (95%CI)	DOR (95% CI)
All Stress ECHO	127* (13035)	0.80 (0.77 – 0.82)	0.84 (0.82 – 0.87)	20.64 (16.63 – 24.64)
Subgroups				
Pharmacological agents: Combined	109 (11223)	0.79 (0.71 – 0.87)	0.85 (0.83 – 0.88)	21.71 (17.04 – 26.38)
Adenosine	6 (501)	0.79 (0.62 – 0.83)	0.83 (0.70 – 0.96)	12.86 (0.02 – 25.71)
Dobutamine	26 (1931)	0.81 (0.79 – 0.83)	0.84 (0.81 – 0.87)	22.33 (16.45 – 28.21)
Dipyridamole	77 (8791)	0.74 (0.69 – 0.79)	0.90 (0.86 – 0.94)	22.33 (16.45 – 28.21)
Exercise	18 (1812)	0.81 (0.76 – 0.86)	0.79 (0.71 -0.87)	16.11 (7.85 – 24.37)

* A study was counted twice if data was reported on different stress agents. DOR, refers to diagnostic odds ratio

Table 6: Comparisons of pooled sensitivity and pooled specificity

Comparisons	Sensitivity (P-value)	Specificity (P-Value)
ECHO Exercise vs. Pharmacologic	0.62	0.36
ECHO Exercise vs. Adenosine	0.31	0.83
ECHO Exercise vs. Dipyridamole	0.20	0.10
ECHO Exercise vs. Dobutamine	0.99	0.47
ECHO Adenosine vs. Dipyridamole	0.90	0.47
ECHO Adenosine vs. Dobutamine	0.30	0.95
ECHO Dipyridamole vs. Dobutamine	0.09	0.10

Summary Receiver Operator Curves (SROC) were generated (Figure 5) and the AUC was calculated. When all stress agents were combined, the AUC for stress ECHO was 0.895 (Table 7). In ranking the AUC of the different stress agents, dobutamine had the highest AUC, followed closely by dipyridamole, adenosine and exercise (Figure 5).

Given that it was not possible to statistically compare the AUCs for the different stress agents, a subgroup analysis of the DORs was performed. Comparisons of the different pharmacological stressors and between the pharmacological stressors and exercise revealed that there were no significant differences in the pooled DORs between the different stress agents (Table 8).

Table 7: AUC for stress ECHO

Group	AUC
All Stress ECHO	**0.895**
Subgroups	
Pharmacological agents - combined	0.898
- Adenosine	0.893
- Dobutamine	0.905
- Dipyridamole	0.899
Exercise	0.875

AUC refers to area under the curve

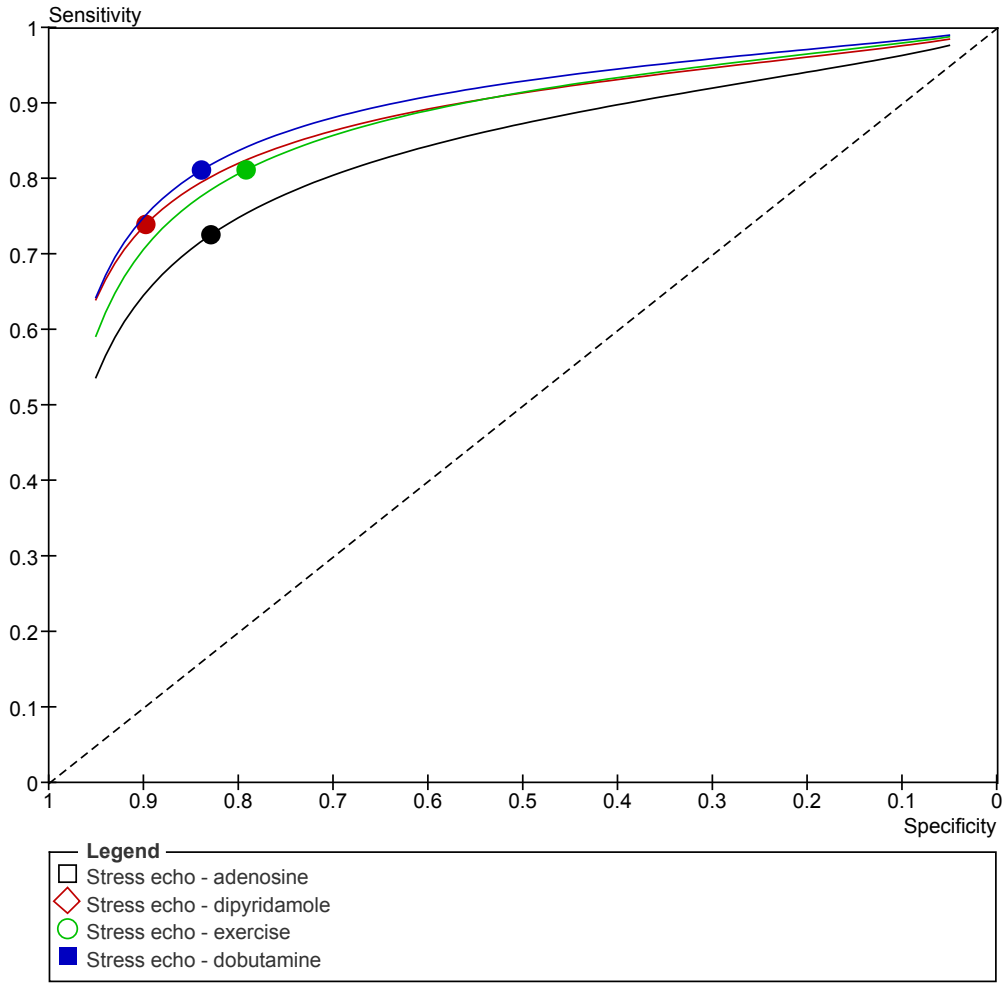


Figure 5: SROC curve for stress ECHO for the Diagnosis of CAD

Table 8: Subgroup analyses of stress agents using DORs for Stress ECHO

Subgroup Comparison – Stress Agents	P-Value
Exercise vs. Adenosine	0.87
Exercise vs. Dipyridamole	0.66
Exercise vs. Dobutamine	0.66
Adenosine vs. Dipyridamole	0.66
Adenosine vs. Dobutamine	0.66
Dipyridamole vs. Dobutamine	0.87
Exercise vs. Adenosine	0.87
Exercise vs. All Pharmacologic	0.66

The definition of what qualified as significant CAD, as measured by the degree of coronary artery stenosis, varied across the studies. The majority of the studies used a threshold of 50% stenosis (n=77), but some studies defined significant disease as 70% stenosis (n=18), and one study used a threshold of 75% stenosis. This information was unknown or not reported for 38 studies. According to Jones et al., it may be possible to include studies with differing thresholds in the same meta-analysis. (25) This is due to the fact that even when the reported thresholds are constant between studies, the true thresholds will differ owing to individual reporting styles and variance in image interpretation. A subgroup analysis was performed to ensure that the diagnostic accuracy did not differ by the definition of CAD. Studies that defined significant CAD as greater than 50% coronary artery stenosis (DOR 21.07, 95%CI: 15.21 – 26.94) did not significantly differ in diagnostic accuracy compared to studies that defined significant CAD as greater than 70% stenosis (DOR 19.50, 95%CI: 8.56 – 30.44; *P*=0.87).

Of the 92 studies that contained information on patient MI history, 66 included patients with a previous MI. The proportion of patients with a previous MI ranged from 8% to 100% (mean= 33.8%). Even though the analysis was intended to focus on patients suspected of CAD and therefore not have a history of previous MI, it was still possible to include these studies in the analysis since the interpreter of the ECHO images was blinded to MI status. In addition, the diagnostic accuracy of studies that included patients with a previous MI (DOR 21.34, 95%CI: 15.05 – 27.63) did not differ from studies that did not include patients with a history of a previous (DOR 20.40, 95%CI: 11.42 – 29.38) (*P*=0.87).

Results of Evidence-Based Analysis: Additional Systemic Reviews

Two additional systematic reviews published after the Heijenbrook-Kal et al. (1) study were identified, however, these reviews focused on different populations to those previously described in the MAS analysis. The studies included in the MAS review did not limit to specific populations. The first of these, by Geleijnse et al. (9) focused on dobutamine stress ECHO for the detection of CAD in women and the second, by Biagini et al. (26), focused on the accuracy of stress ECHO for the diagnosis of CAD and prediction of cardiac events in patients with left bundle branch block (LBBB). Given that these reviews focused on particular populations, they were not directly incorporated into the MAS analysis. Nevertheless, many of the original studies included in these two existing systematic reviews were included in the Heijenbrook-Kal et al. (1) review and were, therefore, in the MAS analysis.
Briefly, Geleijnse et al. (9) included 14 studies (901 patients) that compared the diagnostic accuracy of dobutamine stress ECHO to CA, either solely in women or in both women and men. The pooled sensitivity was 72% and the specificity was 88%. Seven studies compared the diagnostic accuracy of stress ECHO in men and women, achieving a pooled sensitivity of 77% in both women and men and a pooled specificity of 81% in women and 77% in men. The authors concluded that despite some

theoretical limitations, the test has reasonable sensitivity and excellent specificity for the detection of CAD in women. These results are comparable to those found in the MAS analysis (the majority of studies included in the Geleijnse et al. review were also included in the MAS analysis).

A second systematic review by Biagini et al. (26) focused on the diagnostic accuracy of stress ECHO in patients with LBBB. In patients with LBBB, mechanical asynchrony between the left and right ventricle results in abnormal septal motion interfering with the interpretation of wall motion abnormalities. They included information on six studies (226 patients), of which five employed a pharmacological stress agent and one used exercise-induced stress. The pooled estimates of sensitivity and specificity were 74.6% and 88.7%, respectively. Although this meta-analysis obtained different estimates of diagnostic accuracy in LBBB patients, they varied only slightly from those obtained in the MAS analysis.

Limitations of Analysis

One of the limitations of the current analysis is that study selection was based on the Heijenbrok-Kal et al. (1) review for feasibility reasons. As a result, the studies were published between 1995 and 2001 and more recent studies were not included in the analysis. According to experts, improvements in ECHO imaging have occurred since then. In order to verify that there have been no meaningful changes in the diagnostic accuracy of stress ECHO over time, a subgroup analysis was performed to compare the sensitivity and specificity of studies published prior to 2000 (n=117) to those published after 2000 (n=10). Over time, there have been no significant changes in the sensitivity (*P*=0.61) and specificity (*P*=0.20) of stress ECHO (Table 8).

The MAS evidence-based analysis on stress contrast ECHO also examined five studies that directly compared stress ECHO versus MCE that were published between 2004 and 2007 (for additional information please refer to the EBA on stress contrast ECHO). The estimates of pooled sensitivity for stress ECHO are comparable, though the pooled specificity derived from these newer studies is slightly lower compared to those published prior to 2000 (see Table 9). These results conflict with those from the aforementioned subgroup analysis, however, far fewer newer studies were included. It is possible that a more recent year of publication detrimentally impacts estimates of diagnostic accuracy. Potential explanations include publication bias and selection bias in older studies with strict inclusion and exclusion criteria. (1) Overall, there remains uncertainty on the impact of publication date on estimates of diagnostic accuracy but it appears that the differences over time are not significant.

Table 9: Effect of Publication Date on Diagnostic Accuracy

Subgroup Comparison, Year of Publication	Number of studies	Pooled Sensitivity (95%CI)	Pooled Specificity (95%CI)
Studies Published Prior to 2000	117	0.80 (0.78 - 0.82)	0.84 (0.81 - 0.87)
Studies Published After 2000	10	0.76 (0.69 - 0.84)	0.90 (0.84 - 0.96)
Studies Published 2004-2007 (Data derived from studies included in the direct comparison of Stress ECHO versus Contrast Stress ECHO)	5	0.76 (0.70 – 0.81)	0.75 (0.67 – 0.81)

Another limitation of the analysis is that stress ECHO was compared to the reference standard of CA, although these modalities diagnose CAD with different approaches. Diagnosis of CAD with stress ECHO relies on functional information such as wall motion, while diagnosis with CA is based on anatomical information (e.g., the degree of coronary artery stenosis).

GRADE Quality of Evidence

The quality of the body of evidence was assessed according to the GRADE Working Group criteria for diagnostic tests (results in Table 10). Overall, the quality was consistent across the cross-sectional studies that assessed accuracy. In studies with multiple comparisons, the assessors were blinded to data from the other imaging modalities. All studies compared stress ECHO to CA as the reference standard. The majority of studies recruited patients who were referred for CA, which may affect the generalizability of the findings in terms of the pre-test probability of CAD.

As mentioned, there was heterogeneity in the definition of significant CAD, as defined by the percent stenosis. Some studies also included patients with previous MI, however, assessors were blinded to patient history. Lastly, in addition to the subjective interpretation of ECHO images, there was variability in the definition of a positive test result, which may partly explain the different reported sensitivity and specificity across studies. For example, some studies defined a positive test as a new regional wall motion abnormality, while others defined a positive test as the absence of a hyperkinetic contractile response to exercise.

The overall quality of the evidence was graded as low.

Table 10: GRADE Quality Assessment of Diagnostic Accuracy Studies for Stress ECHO Compared to Coronary Angiography for the Diagnosis of CAD

Factor	Explanation	GRADE
Risk of Bias		
Study design	Observational cross-sectional studies (127 studies)	High
Limitations	No serious limitations	Unchanged
Indirectness		
Outcomes	Diagnostic tests are considered as surrogate outcomes	Reduced by one level → Moderate
Patient populations, diagnostic test, comparison test, and indirect comparisons	Some studies included a mix of patients with known and suspected CAD. In a subgroup analysis, there was no significant difference in diagnostic odds ratio between groups. The threshold in defining significant CAD varied across studies (i.e., >50%stenosis or >70% stenosis), however a subgroup analysis revealed there were no significant difference in diagnostic accuracy between groups. The majority of studies recruited patients who were being referred for coronary angiography which may affect the generalizability of the findings.	Reduced by one level → Low
Important inconsistency in study results	No serious inconsistency	Unchanged
Imprecise evidence	Some imprecision but confidence intervals not overly wide for estimates of sensitivity and specificity	Unchanged
Publication bias	Possible, but not considered sufficient to downgrade quality of evidence	Unchanged
	Quality of Evidence	**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 stress ECHO in the diagnosis of patients with suspected CAD, as compared to contrast ECHO, SPECT, cardiac MRI, and CT angiography. The relative cost-effectiveness of these five non-invasive cardiac imaging technologies was assessed in two patient populations: a) out-patients presenting with stable chest pain; and b) in-patients presenting with acute, unstable chest pain. Note that the term "contrast ECHO" used in the following sections refers to stress echocardiography performed with the availability of contrast medium, if needed, due to poor image quality.

Economic Analysis Overview

For the two patient populations, decision analytic models were developed with two reported outcomes: the cost per accurate diagnosis of CAD (true positives and true negatives) and 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. (27;28) A budget impact analysis (BIA) was then performed to assess the effect of replacing a certain proportion of stress ECHO tests with other cost-effective, non-invasive modalities. The costs presented in the 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 CAD diagnosis. 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 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. Based on the content of their abstracts, 147 full-text articles were retrieved for further assessment. Of these, 122 were rejected leaving 25 articles for inclusion. Following the data extraction process, 13 studies were excluded (29-40), with 12 studies being ultimately selected for analysis.(10;41-51) (52)

Characteristics of Included Studies

From the 12 studies included, eight assessed the cost-effectiveness of two of the selected imaging tests (44-47;49-51), three evaluated three concomitant technologies (10;41;48) and one study evaluated five technologies.(42)

Five studies were cost-effectiveness analyses, where the most common outcome was cost per correct/successful CAD diagnosis. (41;42;49-51) The other seven studies were cost-utility analyses using cost per quality adjusted life years (QALYs) as their primary outcome.(10;43-48) The time-horizon used across the included studies ranged from 30 days to lifetime, with five studies having 25 years or more of follow-up. (43-45;47;50) The remaining studies used 18 months (10), 3 months (51), and 30 days of analytical time horizon.(46) Four studies did not report the time-horizon used in their analysis.(41;42;48;49)

All included studies evaluated at least one form of ECHO against one of the other selected tests.(10;41-51) The cost-effectiveness of SPECT was studied in nine studies (10;41;43-45;47;48;50;51), three studies assessed CT angiography in comparison to stress ECHO or MRI (42;46;49), while cardiac MRI was compared to each of the three other selected imaging tests in two studies.(10;42) No full economic analysis between CT angiography and SPECT was found in the published literature.

Literature Results for Stress ECHO

The cost-effectiveness of stress ECHO was assessed against three selected cardiac imaging tests: SPECT, CT angiography and cardiac MRI (see Table 11). Nine comparisons were made against SPECT and in three of these stress ECHO was considered dominant (i.e., lower cost, better outcomes).(41;44;45) In one comparison, stress ECHO produced the same amount of QALYs as SPECT, but with higher costs, thus it was not considered cost-effective.(10) In three other comparisons, the base-case ICER per QALY reported for stress ECHO versus SPECT was above the $50,000 threshold.(43;47;50) In all three analyses, however, stress ECHO showed lower costs and worse outcomes, thus still accepted as cost-effective. Another analysis of stress ECHO versus SPECT estimated an ICER per correct CAD diagnosis of CDN $5,029, but stress ECHO was found to be the alternative with lower costs and worst outcomes.(51) The final comparison did not report an ICER for the analysis, however, it was stated that stress ECHO was cost-effective only when the probability of CAD was lower or equal to 20%.(48)

When compared against CT angiography, ECHO was not considered cost-effective in all three analyses.(42;46;49) In one of the comparisons, stress ECHO was dominated (i.e., higher cost, worst outcomes).(46) The remaining studies evaluated the cost per correct/successful diagnosis of CAD, but they did not report an ICER value of stress ECHO versus CT angiography. Both studies reported that

under pre-test likelihood or prevalence of CAD greater than 60%, CT angiography was the cost-effective strategy.(42;49)

Two economic evaluations compared stress ECHO to MRI.(10;42) In one analysis, stress ECHO was found to be cost-effective over MRI with a reported base-case ICER per QALY of GBP £13,200.(10) The remaining study did not report an ICER, although it was stated that both stress ECHO and MRI were not considered cost-effective when compared to CT angiography. (42)

Table 11: Summary incremental cost-effectiveness ratios across selected studies evaluating stress ECHO

Study	Comparator	Outcome of interest	Reported as cost-effective?	ICER
Dewey et al., 2007	CT angio	Cost per successful diagnosis	No	Not reported*
Khare et al., 2008	CT angio	Cost per QALY	No	Dominated
Rumberger et al., 1999	CT angio	Cost per correct diagnosis	No	Not reported†
Dewey et al., 2007	MRI	Cost per successful diagnosis	Yes	Not reported‡
Sharples et al., 2007	MRI	Cost per QALY	Yes	GBP (2006) £13,200
Bedetti et al., 2008	SPECT	Cost per correct diagnosis	Yes	Dominant
Garber et al., 1999	SPECT	Cost per QALY	Yes	USD (1996) $78,444**
Hayashino et al., 2004	SPECT	Cost per QALY	Yes	Dominant
Hernandez et al., 2007	SPECT	Cost per QALY	Yes	Dominant
Kuntz et al., 1999	SPECT	Cost per QALY	Yes	USD (1996) $62,800**
Lee et al., 2002	SPECT	Cost per QALY	No	Not reported§
Sharples et al., 2007	SPECT	Cost per QALY	No	More costly, same QALYs
Shaw et al., 2006	SPECT	Cost per LYS	Yes	USD (2003) $72,187**
Tardif et al., 2002	SPECT	Cost per correct diagnosis	ND	CDN (2000) $5,029

Abbreviations: CT angio = CT angiography, ND = Not defined

* At a pre-test likelihood of 60%, CT angiography was cost-effective.

† For prevalence of disease <=70%, CT angiography was considered cost-effective.

‡ Both not cost effective when compared to CT angiography.

§ SPECT was cost-effective when the probability of CAD was >=30%. Stress ECHO was cost-effective when the probability of CAD was <=20%.

** Stress ECHO was the alternative reporting lower cost and worst outcome.

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, and SPECT was found cost-effective in three of the nine 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 might change the proposed relative cost-effectiveness.

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.

Target Population and Perspective

Two populations were defined for evaluating the cost-effectiveness of an accurate diagnosis (i.e. true positive and true negative diagnoses) of CAD: a) out-patients presenting with stable chest pain; and b) 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.(53) 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.(54)

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

Comparators and Parameter Estimates

The imaging technologies that were compared in the current cost-effectiveness analysis included: CT angiography, stress ECHO with and without a contrast medium, cardiac perfusion stress MRI, and 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 12 shows a list of the parameters with corresponding 95% confidence intervals used for both the outpatient and inpatient decision-analytic cost-effectiveness models.

The average wait-time for each cardiac imaging test was 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 shown with a corresponding range of high and low values. The probability of receiving pharmacological stress versus exercise stress is not listed, but reported here for completeness: approximate values of 30% for the stable, outpatient population and 80% for the unstable, inpatient population.

Table 12: Summary parameter estimates for stress ECHO tests

Pooled Diagnostic Accuracy	Point Estimate	95% Lower	95% Upper
CAD diagnosis: Sensitivity	0.795	0.774	0.816
CAD diagnosis: Specificity	0.842	0.819	0.865
Additional time for test (compared to GXT)	**Average**	**Low**	**High**
Inpatient population: Additional days for test	1.5	1.0	2.0
Uninterpretable test result	**Average**	**Low**	**High**
Outpatient population: % of tests that are uninterpretable	15%	10%	30%
Inpatient population: % of tests that are uninterpretable	20%	15%	30%

Note: Sensitivity and specificity estimates are taken from the effectiveness literature review of stress ECHO. 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 and Outcomes

Figure 6 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. This will be one of the four remaining tests that were not used as the first test.
2. Should a second test be required, the type of stress (pharmacological or exercise) that a patient receives will be the same type as used in the first.

The short-term outcome presented in this report focuses on an accurate diagnosis of CAD (i.e. true positive and true negative test results). A second outcome of true positive diagnosis was examined for the two models, with results reported in The Relative Cost-effectiveness of Five Non-invasive Cardiac Imaging Technologies for Diagnosing Coronary Artery Disease in Ontario. (52)

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. The varied parameters included sensitivity and specificity estimates, wait times for imaging tests performed in hospital, as well as the costs of CT angiography, ECHO tests, and cardiac MRI. A third series of sensitivity analyses was conducted that specifically addressed the possibility of unavailable imaging technologies.

Resource Use and Costs

Resource use and costs were derived from Ontario data sources: the OHIP and OCCI administrative databases.(27;28) 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 and listed in Table 13. 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 this 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 stress ECHO wait time, see Table 12). 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 spent in hospital.

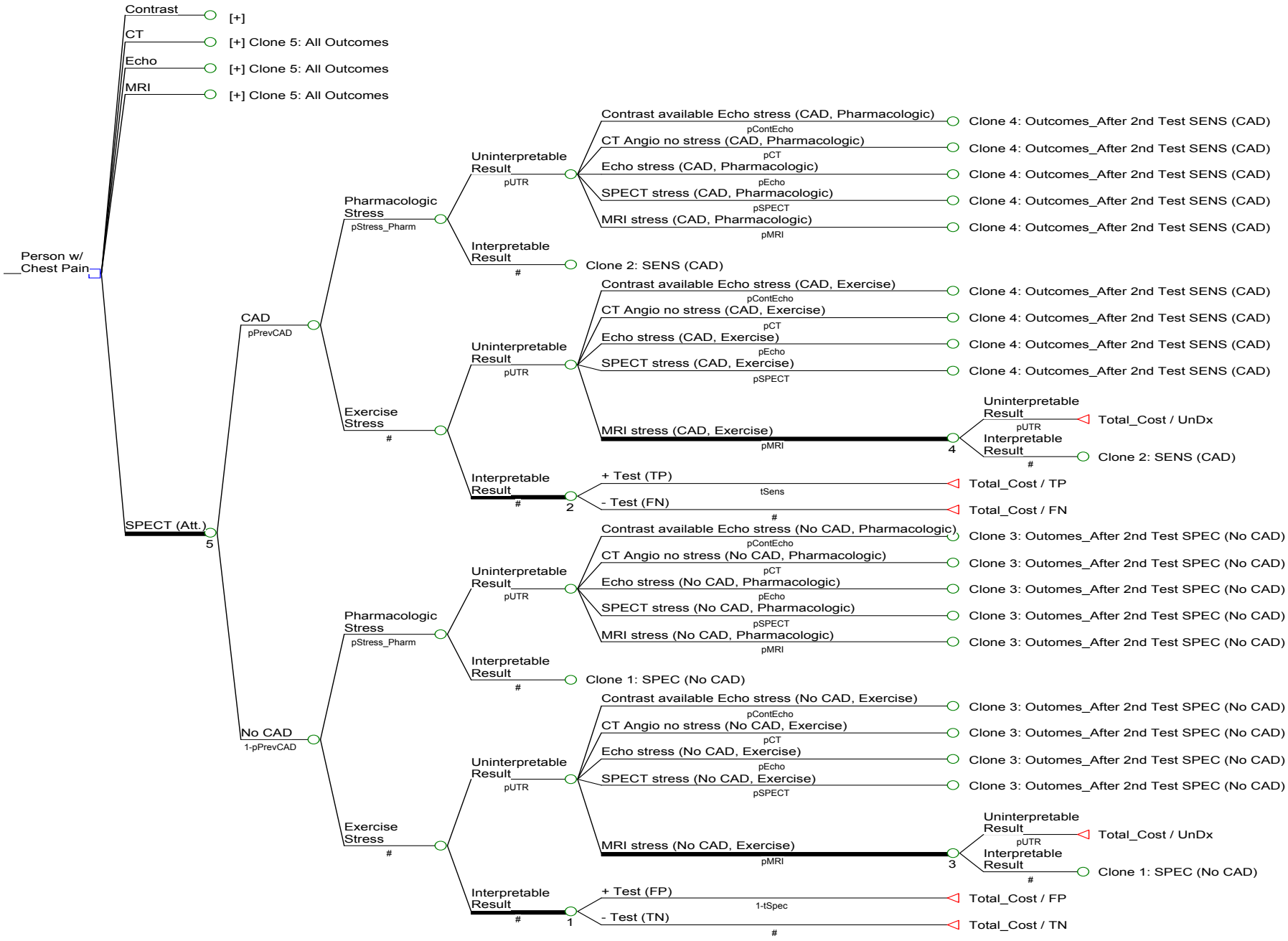


Figure 6: Decision analytic model used to evaluate the cost-effectiveness of cardiac imaging technologies for the diagnosis of CAD

Table 13: 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.(28) 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. As such, all reasonable WTP values presented in the Results and Discussion section are interpreted at two WTP 'anchors' representing 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 are useful in determining the WTP:

- An "accurate diagnosis" of CAD can be obtained through a coronary angiography for $1,433. It would thus be reasonable to expect the WTP for an accurate diagnosis through a non-invasive test to resemble this amount; however, an accurate diagnosis does not include the value or benefit of providing additional diagnostic or prognostic information from either non-invasive imaging or 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 thus appears to be greater than $804.
- While coronary angiography is invasive, the other tests are non-invasive and would presumably be of greater value (i.e., incur a higher premium). These tests do, however, impose risks not applicable to coronary angiography, such as increased radiation exposure and 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

As shown in Tables 14 and 15, stress ECHO was dominated by both CT angiography and contrast ECHO (that is, it had higher costs and was less effective) in both populations for the outcome of interest (i.e., accurate diagnosis of CAD). Sensitivity analysis results changed very little from those of the base-case analysis, with one exception. When both CT angiography and contrast ECHO were removed from the analysis, stress ECHO appeared to be the most cost-effective strategy for stable outpatients for CAD prevalences ranging between 5% and 30%, and possibly the most cost-effective strategy for a CAD prevalence of up to 95%.

Stress ECHO is generally not cost-effective in comparison to other non-invasive strategies for the diagnosis of CAD in either stable outpatients or acute inpatients. Stress ECHO appears cost-effective only in specific situations where other more cost-effective technologies are unavailable.

Table 14: Cost-effectiveness analysis base case results for stable outpatients

Technology	Cost (C)	Δ Cost	Effect (E)	Δ Effect	C / E	ICER
Stress ECHO (contrast)	$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)
Attenuated SPECT	$634.63		82.80%		$766	(Dominated)
MRI (perfusion)	$835.47		85.15%		$981	(Dominated)

Table 15: Cost-effectiveness analysis base case results for acute inpatients

Technology	Cost (C)	∆ Cost	Effect (E)	∆ Effect	C / E	ICER
Stress ECHO (contrast)	$1,794.58		81.47%		$2,203	0
Attenuated SPECT	$1,982.91	$188.32	85.16%	3.68%	$2,329	$5,113
Stress ECHO	$2,550.87		81.77%		$3,120	(Dominated)
CT angiography	$3,267.39	$1,284.48	91.92%	6.77%	$3,554	$18,981
MRI (perfusion)	$4,918.02		88.05%		$5,585	(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. (52) 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 are reported as general reference tables. To summarize briefly, stress ECHO tests are the least expensive of the compared cardiac imaging modalities. When the volume of stress ECHO tests is shifted to other technologies, all scenarios result in higher projected costs. If 25% of the stress ECHO tests are moved to other imaging technologies, ensuing projected costs would be higher: from a small cost difference of about $166K per year for contrast available stress ECHO testing to a large difference of $10.2M for cardiac MRI testing. The largest possible cost difference corresponds to replacing 50% of stress ECHO tests with cardiac MRI imaging ($20.5M per year); the smallest possible cost difference occurs by replacing 5% of stress ECHO tests with contrast available stress ECHO imaging ($33.2K per year).

Existing Guidelines for ECHO

There are several existing guidelines published by cardiology and echocardiography societies concerning the clinical application of stress ECHO. Some guidelines also focus on appropriateness criteria for stress ECHO. Table 11 below outlines some of the most widely cited guidelines.

Table 11: Guidelines on ECHO

Guideline Developers	Publication Date	Title
ACC/AHA (4)	2003	ACC/AHA/ASE 2003 guideline update for the clinical application of echocardiography: summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/ASE Committee to Update the 1997 Guidelines for the Clinical Application of Echocardiography)
ACC/AHA/ASE (55;56)	2003 update to 1997 guidelines	ACC/AHA/ASE 2003 guideline update for the clinical application of echocardiography: summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/ASE Committee to Update the 1997 Guidelines for the Clinical Application of Echocardiography)
Joint CCS and CSE consensus panel (57)	2004	Guidelines for the Provision of Echocardiography in Canada
ACCF/ASE/ACEP/ASNC/SCAI/SCCT/SCMR (11)	2007	ACCF/ASE/ACEP/ASNC/SCAI/SCCT/SCMR 2007 appropriateness criteria for transthoracic and transesophageal echocardiography: a report of the American College of Cardiology Foundation Quality Strategic Directions Committee Appropriateness Criteria Working Group, American Society of Echocardiography, American College of Emergency Physicians, American Society of Nuclear Cardiology, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, and the Society for Cardiovascular Magnetic Resonance endorsed by the American College of Chest Physicians and the Society of Critical Care Medicine
ASE (2)	2007	American Society of Echocardiography Recommendations for Performance, Interpretation, and Application of ECHO
ACC/ASE/ACEP/AHA/ASNC/SCAI/SCCT/SCMR (58)	2008	ACCF/ASE/ACEP/AHA/ASNC/SCAI/SCCT/SCMR 2008 appropriateness criteria for ECHO: a report of the American College of Cardiology Foundation Appropriateness Criteria Task Force, American Society of Echocardiography, American College of Emergency Physicians, American Heart Association, American Society of Nuclear Cardiology, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, and Society for Cardiovascular Magnetic Resonance: endorsed by the Heart Rhythm Society and the Society of Critical Care Medicine
EAE (3)	2009	Stress Echocardiography Expert Consensus Statement - Executive Summary: European Association of Echocardiography (EAE) (a registered branch of the ESC)

*ACC, American College of Cardiology; ACEP, American College of Emergency Physicians; AHA, American Heart Association; ASE, American Society of Echocardiography; ASNC, American Society of Nuclear Cardiology; CCS, Canadian Cardiovascular Society; CSE, Canadian Society of Echocardiography; EAE, European Association of Echocardiography; SCAI, Society for Cardiovascular Angiography and Interventions; SCCM, Society of Critical Care Medicine SCCT, Society of Cardiovascular Computed Tomography; SCMR, Society for Cardiovascular Magnetic Resonance.

Ontario Health System Impact Analysis

Considerations and/or Implications

The Cardiac Imaging Expert Advisory Panel met on Oct 5th and November 25th, 2009. Experts in ECHO were also consulted and the following comments were made about stress ECHO.

1. There is no limitation as to where or by which physicians ECHO can be provided
2. There is growth in the number of ECHO tests performed outside of major centers.
3. It is estimated that greater than 80% of cardiologists practicing in the community have ECHO and stress capabilities situated on-site within their own clinics. Of these, it is estimated that roughly half of cardiologists practicing in the community perform stress ECHO.
4. Outpatient stress ECHO facilities perform exclusively exercise ECHO.
5. In-hospital stress ECHO labs employ pharmacological stress agents and exercise as stress in roughly equal amounts.
6. Dobutamine is the pharmacological stress agent that is most frequently used in Ontario
7. There are no accessibility issues for ECHO.
8. Since analysis of ECHO images is subjective in nature, the physician's degree of expertise and the technologist's experience largely impacts confidence in test results.
9. ECHO image quality may have improved over time.
10. 3-Dimensional ECHO is still in developmental phases.
11. Newer quantitative methods of interpreting ECHO images are not yet routinely used.
12. The physician billing structure for stress ECHO should be advised to reflect that a minimum ECHO study to perform diagnostic information would include an M-mode, D-dimensional and Doppler component.
13. There are concerns about inappropriate use of stress ECHO. Emerging appropriateness criteria should be examined and adapted for Ontario. This should include training requirements for the performance and interpretation of stress ECHO.

Conclusion

Given the vast amount of published literature on stress ECHO, it was decided to use the studies contained in the comprehensive review by Heijenbrok-Kal et al. (1) as a basis for the MAS analysis. In applying our inclusion and exclusion criteria, 105 observational studies containing information on 13,102 patients were included in our analysis. Six studies examined stress ECHO with adenosine, 26 with dipyridamole and 77 with dobutamine, which is the most commonly used pharmacological stress ECHO agent in Ontario. A further 18 studies employed exercise as the stressor.[4] 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 would be indicated for different patient populations (based on ability to exercise) there were no significant differences in sensitivity and specificity between the two groups.
- Based on the opinions of clinical experts, the diagnostic accuracy of stress ECHO depends on the patient population, the expertise of the interpreter, and the quality of the image.

[4] A study was counted twice if data was reported on different stress agents.

Appendices

Appendix 1: Literature Search Strategies

Search date: August 28, 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 August Week 3 2009>
Search Strategy:

1 exp Myocardial Ischemia/ (301645)
2 (coronary adj2 arter* disease*).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (58420)
3 ((myocardi* or heart or cardiac or coronary) adj2 (viable or viability or perfusion or function or isch?emi* or atheroscleros* or arterioscleros* or infarct* or occlu* or stenos* or thrombosis)).mp. (258913)
4 (myocardi* adj2 hibernat*).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (843)
5 (stenocardia* or angina).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (53364)
6 heart attack*.mp. (2887)
7 exp Heart Failure/ (66084)
8 ((myocardi* or heart or cardiac) adj2 (failure or decompensation or insufficiency)).mp. (107720)
9 exp Ventricular Dysfunction, Left/ (14865)
10 (left adj2 ventric* adj2 (dysfunction* or failure or insufficienc*)).mp. (22713)
11 or/1-10 (462748)
12 exp Echocardiography/ (82415)
13 echocardiogr*.ti,ab. (79353)
14 13 or 12 (106410)
15 11 and 14 (39243)
16 exp Exercise Test/ (41317)
17 (test* adj2 (exercise or bicycle or treadmill or stress or ergometr* or pharmacolog* or dobutamine or dipyridamole or persantine or adenosine or regadenoson or lexiscan)).ti,ab. (31014)
18 16 or 17 (56646)
19 18 and 15 (4497)
20 limit 19 to (english language and humans and yr="2007 -Current") (453)

Database: EMBASE <1980 to 2009 Week 34>
Search Strategy:

1 exp ischemic heart disease/ (238393)
2 exp coronary artery disease/ (88415)
3 exp stunned heart muscle/ (1519)
4 (coronary adj2 arter* disease*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (71532)
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] (275725)
6 (myocardi* adj2 hibernat*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (1057)
7 (stenocardia* or angina).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (46318)
8 heart attack*.mp. (2025)
9 exp heart failure/ (125232)
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] (107656)
11 exp heart left ventricle failure/ (9312)
12 (left adj2 ventric* adj2 (dysfunction* or failure or insufficienc*)).mp. (16093)
13 or/1-12 (430251)
14 exp echocardiography/ (93200)
15 echocardiogra*.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (104880)
16 14 or 15 (104927)
17 exp exercise test/ (16129)
18 exp pharmacologic stress testing/ (258)

19 (test* adj2 (exercise or bicycle or treadmill or stress or ergometr* or pharmacolog* or dobutamine or dipyridamole or persantine or adenosine or regadenoson or lexiscan)).ti,ab. (26337)
20 or/17-19 (33746)
21 16 and 20 (4760)
22 exp exercise electrocardiography/ (2329)
23 21 or 22 (6823)
24 13 and 23 (5316)
25 limit 24 to (human and english language and yr="2007 -Current") (651)

Appendix 2: Studies Examining the Diagnostic Accuracy of Stress ECHO for CAD

Table A1: Characteristics of studies comparing the accuracy of Stress ECHO to coronary angiography for the diagnosis of CAD

Study, Year	N	% male	mean age	Definition of CAD (% CAS)	With CAD on CA (%)	Included patients with previous MI	Percentage with previous MI	Included patients with unstable angina
Adenosine Stress								
Anthopoulos, 1996 (59)	120	60	75	50	0.74	Y	NA	N
Anthopoulos, 1997 (60)	128	61	73	50	0.76	Y	30.0	
Djordjevic-Dikic, 1996 (61)	58	87.9	50	50	0.69	Y	41.4	N
Fukai, 1995 (62)	38	62.8	61	75	0.89	Y	NA	N
Miyazono, 1998 (63)	112	72.3	99	70	0.55	Y	NA	NA
Tawa, 1996 (64)	45	70.1	58	70	0.73	Y	NA	N
Dipyridamole Stress								
Astarita, 2001 (65)	53	54.7	58	50	0.43	N		N
Batlle, 1998 (66)	56				0.73			
Beleslin, 1999 (67)	168				0.76			
Bjornstad, 1995 (68)	94	34.2	59	50	0.60	Y	29.2	N
Bjornstad, 1995 (69)	37	81.1	58	50	0.84	Y	NA	N
Bjornstad, 1997 (70)	25	81	58		0.60	Y	58.0	
Cramer, 1996 (71)	35				0.83			
Dagianti, 1995 (72)	60				0.42			
Fragasso, 1999 (73)	101	54.5	61	50	0.56	N		NA
Gaddi, 1999 (74)	24	100	55	50	0.54	N		N
Lanzarini, 1995 (75)	61	95.1	53	50	0.90	Y	NA	N
Loimaala, 1999 (76)	60	66.7	55	50	0.73	Y	15.0	N
Maffei, 1998 (77)	52				0.19			
Minardi, 1997 (78)	47				0.94			
Parodi, 1999 (79)	101	80.2	55	50	0.79	N		N
Parthenakis, 1997 (80)	46				0.61			
Pingitore, 1996 (81)	110	83.3	60	50	0.84	Y	NA	N
San Roman, 1996 (82)	102	57	62	50	0.62	N		N
San Roman, 1998 (83)	102	49	64	50	0.65	N		N
Santoro, 1998 (84)	60		NA	70	0.55	N		N
Scherhag, 1997 (85)	65				0.42			
Schillaci , 1997(86)	40				0.55			
Schroder, 1996 (87)	119				0.87			

Schroder 1997(88)	74				0.88			
Sochowski, 1995 (89)	46	67.4	58	70	0.52	N		N
Wagdi, 1996(90)	74	86.5	61	50	0.84	Y	NA	N
Dobutamine Stress								
Ahmad, 2001 (91)	90	46.6	NA	50	0.64	Y	NA	N
Anthopoulos, 1996 (59)	120	60	75	50	0.74	Y	NA	N
Anthopoulos, 1997 (60)	128				0.76			
Ariff, 2000 (92)	66	68.2	NA	70	0.56			NA
Batlle, 1998 (66)	56				0.73			
Beleslin, 1999 (67)	168	82	51	50	0.76	Y	50	
Bigi, 1995 (93)	121				0.88			
Castini, 1995 (94)	44	93.2	56	70	0.86	Y	NA	Y
Chan, 1995 (95)	84	79.4	61	70	0.86	Y	NA	N
Dagianti, 1995 (72)	60				0.42			
Daoud, 1995 (96)	76	57.9	60	50	0.86	Y	NA	NA
De Bello, 1996 (97)	45	73.3	53	50	0.84	N		N
Derumeaux, 1995 (98)	37				0.38			
Dionisopoulos, 1997 (99)	288	65	61	50	0.73	N		
Dolan, 2001 (100)	112		61	70	0.81	Y	NA	N
Elhendy, 1996 (101)	24	69.4	59	50	0.83	Y	NA	NA
Elhendy, 1996 (102)	133	76.5	60	50	0.83	Y	NA	N
Elhendy, 1997 (103)	72				0.79			
Elhendy, 1997 (104)	306				0.76			
Elhendy, 1998 (105)	290	69.7	58	50	0.76	Y	NA	N
Elhendy, 1998 (106)	295		NA	50	0.77	Y	NA	N
Elhendy, 1998 (107)	84	63.1	60	50	0.79	Y	NA	N
Elhendy, 1998 (108)	70	0	58	50	0.64	Y	NA	N
Elhendy, 1999 (109)	90	80	57	50	0.81	Y	100	NA
Fragasso, 1999 (73)	101	54.5	61	50	0.56	N		NA
Frohwein, 1995 (110)	40	100	NA	50	0.68	Y	NA	N
Geleijnse, 1995 (111)	223	68.6	58	50	0.64	N		N
Hennessy, 1997 (112)	118				0.74			
Hennessy, 1997(113)	219				0.78			
Hennessy, 1997 (114)	199				0.94			
Hennessy, 1997(115)	52	71.2	56	50	0.75	Y	26.9	N
Hennessy, 1997 (116)	317	72.2	60	50	0.86	Y	NA	N
Hennessy, 1998 (117)	218	72.9	62	50	0.91	Y	NA	N

Herzog, 1999 (118)	50	60	51	50	0.54	Y	8	N
Ho, 1995 (119)	54				0.80			
Ho, 1997 (120)	206	100	58	50	0.78	Y	42.5	
Ho, 1997 (121)	51	76.5	56	50	0.75	Y	NA	N
Ho, 1997 (122)	223	80.7	58	50	0.73	Y	NA	N
Ho, 1998 (123)	56	73.3	60	50	0.52	Y	NA	N
Ho, 1998 (124)	51	0	62	50	0.57	Y	NA	N
Hoffmann, 1996 (125)	60				0.75			
Hoffmann, 1996 (126)	150	79.5	46	50	0.63	Y	9.3	N
Hoffmann, 1999 (127)	283	78.4	56	50	0.65	Y	16.6	N
Huang, 1997 (128)	93				0.72			
Iwase, 1996 (129)	95	69.8	59	70	0.66	Y	NA	N
Joseph, 2000 (130)	63	86.8	65	70	0.44	Y	NA	N
Khattar, 1998 (131)	100	70	62	50	0.74	Y	NA	N
Kisacik, 1996 (132)	69				0.68			
Latcham, 1995 (133)	106	60.7	63	50	0.81	Y	NA	NA
Lewis, 1999 (134)	92	0	57	50	0.27			
Ling, 1996 (135)	183				0.81			
Loimaala, 1999 (76)	60	66.7	55	50	0.73	Y	15	N
Mairesse, 1995 (136)	24	75	61	50	0.63	Y	NA	NA
Minardi, 1997 (78)	47				0.94			
Nagel, 1999 (137)	163	70.7	60	50	0.67	N		N
Oguzhan, 1997 (138)	70	84.3	51	70	0.70	Y	NA	N
Ozdemir, 1999 (139)	63	79.2	52	50	0.67	Y	NA	N
Pasierski, 2001 (140)	248	67	53	50	0.47	N		NA
Peteiro, 2001 (141)	41	78	63	50	0.78	Y	NA	NA
Pingitore, 1996 (81)	110	83.3	60	50	0.84	Y	NA	N
Reis, 1995 (142)	30	62.9	47	50	0.77	Y	NA	NA
San Roman, 1996 (82)	102	57	62	50	0.62	N		N
San Roman, 1998 (83)	102	49	64	50	0.65	N		N
Santoro, 1998 (84)	60		NA	70	0.55	N		N
Schroder, 1996 (87)	46				0.83			
Senior, 1996 (143)	43	74.4	89	50	0.67	Y	NA	N
Senior, 1998 (144)	121	77	62	70	0.49	Y	29	
Shaheen, 1998 (145)	64		NA	70	0.66	NA	NA	NA
Slavich, 1996 (146)	46	0	59	50	0.48	N		
Smart, 1997 (147)	206				0.83			

Smart, 2000 (148)	386	65.5	61	50	0.73	Y	NA	N
Sochowski, 1995 (89)	46	67.4	58	70	0.52	N		N
Takeuchi, 1996 (149)	70	0	65	50	0.29	N		N
Therre, 1999 (150)	85		60	50	0.38	Y	NA	N
Vitarelli, 1997 (151)	59	64.4	52	70	0.81	Y	NA	N
Wu, 1996 (152)	104				0.65			
Yeo, 1996 (153)	64	57.8	57	70	0.56	Y	NA	NA
Exercise Stress								
Badruddin, 1999 (154)	67	91.9	59	50	0.85	Y	NA	N
Bjornstad, 1995 (69)	37	64	57	50	0.84	Y	NA	NA
Chaudhry, 2000 (155)	28	100	66	50	0.57	Y	NA	NA
Dagianti, 1995 (72)	60	79	54		0.42	Y	39	
Jun, 1996	47	83	54		0.68	Y	17	
Loimaala, 1999 (76)	60	66.7	55	50	0.73	Y	15	N
Luotolahti, 1996 (156)	118	85	55		0.92	Y	48	
Marwick, 1995 (157)	161	0	60		0.37	N		
Marwick, 1995(158)	147	59	58		0.42	N		
Pasierski, 2001 (140)	248	67	53	50	0.47	N	NA	NA
Peteiro, 1999 (159)	79	77.5	62	50	0.89	Y	NA	NA
Roger, 1995 (160)	127		NA	50	0.84			NA
Roger, 1997(161)	340	71.8	65	50	0.74	N		NA
Roger, 1997 (162)	244	100	64		0.80	N		
Schroder, 1997 (88)	74				0.88			
Tawa, 1996 (64)	45	70.1	58	70	0.73	Y	NA	N
Tian, 1996 (163)	46	83	54	50	0.70	Y	NA	N
Toumanidis, 1996 (164)	70	71.4	54	50	0.36	N		NA

Note: Data was obtained from existing systemic reviews and an attempt was made to capture missing study information from original publications when possible.
CA, coronary angiography; CAD, coronary artery disease; CAS, coronary artery stenosis; NA, not available

Table A2: Calculated estimates of diagnostic accuracy from studies comparing stress ECHO to coronary angiography for the diagnosis of CAD

Study, Year	TP	FP	FN	TN	Sens (%)	Spec (%)	PPV (%)	NPV (%)	+LR	-LR	Diagnostic Accuracy (%)
Adenosine Stress											
Anthopoulos, 1996 (59)	59	28	30	3	66.3	9.7	67.8	9.1	0.7	3.5	51.7
Anthopoulos, 1997 (60)	64	3	33	28	66.0	90.3	95.5	45.9	6.8	0.4	71.9
Djordjevic-Dikic, 1996 (61)	30	0	10	18	75.0	97.3	98.4	64.3	27.8	0.3	82.1
Fukai, 1995 (62)	22	0	12	4	64.7	88.9	97.8	25.0	5.8	0.4	67.5
Miyazono, 1998 (63)	46	5	16	45	74.2	90.0	90.2	73.8	7.4	0.3	81.3
Tawa, 1996 (64)	29	1	4	11	87.9	91.7	96.7	73.3	10.5	0.1	88.9
Dipyridamole Stress											
Astarita, 2001 (65)	18	0	5	30	78.3	98.4	97.3	85.7	47.7	0.2	89.7
Batlle, 1998 (66)	34	0	7	15	82.9	96.8	98.6	68.2	25.7	0.2	86.7
Beleslin, 1999 (67)	78	5	50	35	60.9	87.5	94.0	41.2	4.9	0.4	67.3
Bjornstad, 1995 (68)	41	3	15	35	73.2	92.1	93.2	70.0	9.3	0.3	80.9
Bjornstad, 1995 (69)	21	0	10	6	67.7	92.3	97.7	37.5	8.8	0.3	72.0
Bjornstad, 1997 (70)	11	2	4	8	73.3	80.0	84.6	66.7	3.7	0.3	76.0
Cramer, 1996 (71)	20	1	9	5	69.0	83.3	95.2	35.7	4.1	0.4	71.4
Dagianti, 1995 (72)	13	1	12	34	52.0	97.1	92.9	73.9	18.2	0.5	78.3
Fragasso, 1999 (73)	35	4	22	40	61.4	90.9	89.7	64.5	6.8	0.4	74.3
Gaddi, 1999 (74)	12	0	1	11	92.3	95.7	96.0	91.7	21.2	0.1	93.9
Lanzarini, 1995 (75)	45	1	10	5	81.8	83.3	97.8	33.3	4.9	0.2	82.0
Loimaala, 1999 (76)	41	4	3	12	93.2	75.0	91.1	80.0	3.7	0.1	88.3
Maffei, 1998 (77)	10	11	0	31	95.2	73.8	47.6	98.4	3.6	0.1	78.1
Minardi, 1997 (78)	32	1	12	2	72.7	66.7	97.0	14.3	2.2	0.4	72.3
Parodi, 1999 (79)	62	5	18	16	77.5	76.2	92.5	47.1	3.3	0.3	77.2
Parthenakis, 1997 (80)	16	0	12	18	57.1	97.3	97.0	60.0	21.1	0.4	73.1
Pingitore, 1996 (81)	75	1	17	17	81.5	94.4	98.7	50.0	14.7	0.2	83.6
San Roman, 1996 (82)	49	1	14	38	77.8	97.4	98.0	73.1	30.3	0.2	85.3
San Roman, 1998 (83)	54	2	12	34	81.8	94.4	96.4	73.9	14.7	0.2	86.3
Santoro, 1998 (84)	18	1	15	26	54.5	96.3	94.7	63.4	14.7	0.5	73.3
Scherhag, 1997 (85)	20	4	7	34	74.1	89.5	83.3	82.9	7.0	0.3	83.1
Schillaci , 1997(86)	18	5	4	13	81.8	72.2	78.3	76.5	2.9	0.3	77.5
Schroder, 1996 (87)	75	3	28	13	72.8	81.3	96.2	31.7	3.9	0.3	73.9
Schroder 1997(88)	50	1	15	8	76.9	88.9	98.0	34.8	6.9	0.3	78.4
Sochowski, 1995 (89)	16	19	8	3	66.7	13.6	45.7	27.3	0.8	2.4	41.3
Wagdi, 1996(90)	26	0	36	12	41.9	96.0	98.1	25.0	10.5	0.6	51.0

Dobutamine Stress											
Ahmad, 2001 (91)	34	6	24	26	58.6	81.3	85.0	52.0	3.1	0.5	66.7
Anthopoulos, 1996 (59)	77	5	12	26	86.5	83.9	93.9	68.4	5.4	0.2	85.8
Anthopoulos, 1997 (60)	83	5	14	26	85.6	83.9	94.3	65.0	5.3	0.2	85.2
Ariff, 2000 (92)	30	6	7	23	81.1	79.3	83.3	76.7	3.9	0.2	80.3
Batlle, 1998 (66)	33	1	8	14	80.5	93.3	97.1	63.6	12.1	0.2	83.9
Beleslin, 1999 (67)	98	8	30	32	76.6	80.0	92.5	51.6	3.8	0.3	77.4
Bigi, 1995 (93)	86	1	21	13	80.4	92.9	98.9	38.2	11.3	0.2	81.8
Castini, 1995 (94)	26	0	12	6	68.4	92.3	98.1	33.3	8.9	0.3	71.9
Chan, 1995 (95)	63	2	9	10	87.5	83.3	96.9	52.6	5.3	0.2	86.9
Dagianti, 1995 (72)	18	1	7	34	72.0	97.1	94.7	82.9	25.2	0.3	86.7
Daoud, 1995 (96)	60	3	5	8	92.3	72.7	95.2	61.5	3.4	0.1	89.5
De Bello, 1996 (97)	29	1	9	6	76.3	85.7	96.7	40.0	5.3	0.3	77.8
Derumeaux, 1995 (98)	12	2	2	21	85.7	91.3	85.7	91.3	9.9	0.2	89.2
Dionisopoulos, 1997 (99)	181	9	28	70	86.6	88.6	95.3	71.4	7.6	0.2	87.2
Dolan, 2001 (100)	65	4	26	17	71.4	81.0	94.2	39.5	3.8	0.4	73.2
Elhendy, 1996 (101)	12	1	8	3	60.0	75.0	92.3	27.3	2.4	0.5	62.5
Elhendy, 1996 (102)	87	3	24	19	78.4	86.4	96.7	44.2	5.7	0.3	79.7
Elhendy, 1997 (103)	37	2	20	13	64.9	86.7	94.9	39.4	4.9	0.4	69.4
Elhendy, 1997 (104)	172	11	61	62	73.8	84.9	94.0	50.4	4.9	0.3	76.5
Elhendy, 1998 (105)	164	10	57	59	74.2	85.5	94.3	50.9	5.1	0.3	76.9
Elhendy, 1998 (106)	171	9	57	58	75.0	86.6	95.0	50.4	5.6	0.3	77.6
Elhendy, 1998 (107)	48	3	18	15	72.7	83.3	94.1	45.5	4.4	0.3	75.0
Elhendy, 1998 (108)	35	2	10	23	77.8	92.0	94.6	69.7	9.7	0.2	82.9
Elhendy, 1999 (109)	61	3	12	14	83.6	82.4	95.3	53.8	4.7	0.2	83.3
Fragasso, 1999 (73)	50	9	7	35	87.7	79.5	84.7	83.3	4.3	0.2	84.2
Frohwein, 1995 (110)	22	1	5	12	81.5	92.3	95.7	70.6	10.6	0.2	85.0
Geleijnse, 1995 (111)	103	17	40	63	72.0	78.8	85.8	61.2	3.4	0.4	74.4
Hennessy, 1997 (114)	69	11	18	20	79.3	64.5	86.3	52.6	2.2	0.3	75.4
Hennessy, 1997(113)	139	17	31	32	81.8	65.3	89.1	50.8	2.4	0.3	78.1
Hennessy, 1997 (112)	169	6	18	6	90.4	50.0	96.6	25.0	1.8	0.2	87.9
Hennessy, 1997(115)	32	6	7	7	82.1	53.8	84.2	50.0	1.8	0.3	75.0
Hennessy, 1997 (116)	234	17	40	26	85.4	60.5	93.2	39.4	2.2	0.2	82.0
Hennessy, 1998 (117)	97	3	101	17	49.0	85.0	97.0	14.4	3.3	0.6	52.3
Herzog, 1999 (118)	14	6	13	17	51.9	73.9	70.0	56.7	2.0	0.7	62.0
Ho, 1995 (119)	40	3	3	8	93.0	72.7	93.0	72.7	3.4	0.1	88.9
Ho, 1997 (120)	144	8	16	38	90.0	82.6	94.7	70.4	5.2	0.1	88.3

Ho, 1997 (121)	35	3	3	10	92.1	76.9	92.1	76.9	4.0	0.1	88.2
Ho, 1997 (122)	152	13	10	48	93.8	78.7	92.1	82.8	4.4	0.1	89.7
Ho, 1998 (123)	26	4	3	23	89.7	85.2	86.7	88.5	6.1	0.1	87.5
Ho, 1998 (124)	27	4	2	18	93.1	81.8	87.1	90.0	5.1	0.1	88.2
Hoffmann, 1996 (125)	35	2	10	13	77.8	86.7	94.6	56.5	5.8	0.3	80.0
Hoffmann, 1996 (126)	72	7	23	48	75.8	87.3	91.1	67.6	6.0	0.3	80.0
Hoffmann, 1999 (127)	132	22	51	78	72.1	78.0	85.7	60.5	3.3	0.4	74.2
Huang, 1997 (128)	62	6	5	20	92.5	76.9	91.2	80.0	4.0	0.1	88.2
Iwase, 1996 (129)	50	3	13	29	79.4	90.6	94.3	69.0	8.5	0.2	83.2
Joseph, 2000 (130)	18	8	10	27	64.3	77.1	69.2	73.0	2.8	0.5	71.4
Khattar, 1998 (131)	50	5	24	21	67.6	80.8	90.9	46.7	3.5	0.4	71.0
Kisacik, 1996 (132)	41	3	6	19	87.2	86.4	93.2	76.0	6.4	0.1	87.0
Latcham, 1995 (133)	64	7	22	13	74.4	65.0	90.1	37.1	2.1	0.4	72.6
Lewis, 1999 (134)	10	13	15	54	40.0	80.6	43.5	78.3	2.1	0.7	69.6
Ling, 1996 (135)	141	18	7	17	95.3	48.6	88.7	70.8	1.9	0.1	86.3
Loimaala, 1999 (76)	42	6	2	10	95.5	62.5	87.5	83.3	2.5	0.1	86.7
Mairesse, 1995 (136)	15	2	0	7	96.8	77.8	88.2	93.3	4.4	0.0	89.8
Minardi, 1997 (78)	33	1	11	2	75.0	66.7	97.1	15.4	2.3	0.4	74.5
Nagel, 1999 (137)	81	10	28	44	74.3	81.5	89.0	61.1	4.0	0.3	76.7
Oguzhan, 1997 (138)	44	2	5	19	89.8	90.5	95.7	79.2	9.4	0.1	90.0
Ozdemir, 1999 (139)	39	3	3	18	92.9	85.7	92.9	85.7	6.5	0.1	90.5
Pasierski, 2001 (140)	86	3	30	129	74.1	97.7	96.6	81.1	32.6	0.3	86.7
Peteiro, 2001 (141)	26	1	6	8	81.3	88.9	96.3	57.1	7.3	0.2	82.9
Pingitore, 1996 (81)	87	2	5	16	94.6	88.9	97.8	76.2	8.5	0.1	93.6
Reis, 1995 (142)	22	1	1	6	95.7	85.7	95.7	85.7	6.7	0.1	93.3
San Roman, 1996 (82)	49	2	14	37	77.8	94.9	96.1	72.5	15.2	0.2	84.3
San Roman, 1998 (83)	52	4	14	32	78.8	88.9	92.9	69.6	7.1	0.2	82.4
Santoro, 1998 (84)	20	1	13	26	60.6	96.3	95.2	66.7	16.4	0.4	76.7
Schroder, 1996 (87)	29	1	9	7	76.3	87.5	96.7	43.8	6.1	0.3	78.3
Senior, 1996 (143)	27	0	2	14	93.1	96.6	98.2	87.5	27.0	0.1	94.3
Senior, 1998 (144)	42	14	17	48	71.2	77.4	75.0	73.8	3.2	0.4	74.4
Shaheen, 1998 (145)	37	4	5	18	88.1	81.8	90.2	78.3	4.8	0.1	85.9
Slavich, 1996 (146)	13	6	9	18	59.1	75.0	68.4	66.7	2.4	0.5	67.4
Smart, 1997 (147)	140	7	31	28	81.9	80.0	95.2	47.5	4.1	0.2	81.6
Smart, 2000 (148)	238	14	42	92	85.0	86.8	94.4	68.7	6.4	0.2	85.5
Sochowski, 1995 (89)	17	4	7	18	70.8	81.8	81.0	72.0	3.9	0.4	76.1
Takeuchi, 1996 (149)	15	4	5	46	75.0	92.0	78.9	90.2	9.4	0.3	87.1

Therre, 1999 (150)	25	13	7	40	78.1	75.5	65.8	85.1	3.2	0.3	76.5
Vitarelli, 1997 (151)	41	2	7	9	85.4	81.8	95.3	56.3	4.7	0.2	84.7
Wu, 1996 (152)	55	2	13	34	80.9	94.4	96.5	72.3	14.6	0.2	85.6
Yeo, 1996 (153)	32	6	4	22	88.9	78.6	84.2	84.6	4.1	0.1	84.4
Exercise Stress											
Badruddin, 1999 (154)	42	1	15	9	73.7	90.0	97.7	37.5	7.4	0.3	76.1
Bjornstad, 1995 (69)	26	2	5	4	83.9	66.7	92.9	44.4	2.5	0.2	81.1
Chaudhry, 2000 (155)	12	3	4	9	75.0	75.0	80.0	69.2	3.0	0.3	75.0
Dagianti, 1995 (72)	19	2	6	33	76.0	94.3	90.5	84.6	13.3	0.3	86.7
Jun, 1996	28	1	4	14	87.5	93.3	96.6	77.8	13.1	0.1	89.4
Loimaala, 1999 (76)	40	9	4	7	90.9	43.8	81.6	63.6	1.6	0.2	78.3
Luotolahti, 1996 (156)	101	3	7	7	93.5	70.0	97.1	50.0	3.1	0.1	91.5
Marwick, 1995 (157)	47	19	12	83	79.7	81.4	71.2	87.4	4.3	0.2	80.7
Marwick, 1995(158)	44	8	18	77	71.0	90.6	84.6	81.1	7.5	0.3	82.3
Pasierski, 2001 (140)	95	5	21	127	81.9	96.2	95.0	85.8	21.6	0.2	89.5
Peteiro, 1999 (159)	51	4	19	5	72.9	55.6	92.7	20.8	1.6	0.5	70.9
Roger, 1995 (160)	94	6	13	14	87.9	70.0	94.0	51.9	2.9	0.2	85.0
Roger, 1997(161)	197	52	55	36	78.2	40.9	79.1	39.6	1.3	0.5	68.5
Roger, 1997 (162)	151	28	43	22	77.8	44.0	84.4	33.8	1.4	0.5	70.9
Schroder, 1997 (88)	35	1	30	8	53.8	88.9	97.2	21.1	4.8	0.5	58.1
Tawa, 1996 (64)	31	2	2	10	93.9	83.3	93.9	83.3	5.6	0.1	91.1
Tian, 1996 (163)	28	1	4	13	87.5	92.9	96.6	76.5	12.3	0.1	89.1
Toumanidis, 1996 (164)	18	10	7	35	72.0	77.8	64.3	83.3	3.2	0.4	75.7

FN, false negative; FP, false positive; LR, likelihood ratio; Sens, sensitivity; Spec, specificity; NPV, negative predictive value; PPV, positive predictive value; TN, true negative; TP, true positive

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