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Single Photon Emission Computed Tomography 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

AC	Attenuation correction
AUC	Area under the curve
BIA	Budget impact analysis
CA	Coronary angiography
CAD	Coronary artery disease
CDN	Canadian dollars
CI	Confidence interval(s)
DOR	Diagnostic odds ratio
ECG	Electrocardiogram
GXT	Graded exercise test
ICER	Incremental cost-effectiveness ratio
LR	Likelihood ratio
LVF	Left ventricular function
LYS	Life-years saved
MAS	Medical Advisory Secretariat
MOHLTC	Ministry of Health and Long-Term Care
MPA	Myocardial perfusion analysis
MPI	Myocardial perfusion imaging
MPS	Myocardial perfusion scintigraphy
OCCI	Ontario Case Costing Initiative
OR	Odds ratio
OHIP	Ontario Health Insurance
OHTAC	Ontario Health Technology Advisory Committee
QALY	Quality adjusted life year
RCT	Randomized controlled trial
RR	Relative risk
SD	Standard deviation
PECT	Single photon emission computed tomography
SROC	Summary receiver operating characteristic
WMA	Wall motion analysis
WTP	Willingness to pay

Executive Summary

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

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

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

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

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

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

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

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

Objective

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

SPECT

Cardiac SPECT, or myocardial perfusion scintigraphy (MPS), is a widely used nuclear, non-invasive image acquisition technique for investigating ischemic heart disease. SPECT is currently appropriate for all aspects of detecting and managing ischemic heart disease including diagnosis, risk assessment/stratification, assessment of myocardial viability, and the evaluation of left ventricular function. Myocardial perfusion scintigraphy was originally developed as a two-dimensional planar imaging technique, but SPECT acquisition has since become the clinical standard in current practice. Cardiac SPECT for the diagnosis of CAD uses an intravenously administered radiopharmaceutical tracer

to evaluate regional coronary blood flow usually at rest and after stress. The radioactive tracers thallium (201Tl) or technetium-99m (99mTc), or both, may be used to visualize the SPECT acquisition. Exercise or a pharmacologic agent is used to achieve stress. After the administration of the tracer, its distribution within the myocardium (which is dependent on myocardial blood flow) is imaged using a gamma camera. In SPECT imaging, the gamma camera rotates around the patients for 10 to 20 minutes so that multiple two-dimensional projections are acquired from various angles. The raw data are then processed using computational algorithms to obtain three-dimensional tomographic images.

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

Research Questions

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

Methods

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

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

Inclusion Criteria

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

Exclusion Criteria

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

Summary of Findings

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

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

Background

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

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

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SPECT

Cardiac SPECT, or myocardial perfusion scintigraphy, is a widely used nuclear, non-invasive image acquisition technique for investigating ischemic heart disease. According to the American College of Cardiology Foundation (ACCF) Appropriate Use Criteria Task Force, SPECT is deemed useful for all aspects of detecting and managing ischemic heart disease including diagnosis, risk assessment/stratification, assessment of myocardial viability and evaluation of left ventricular function. (1) Myocardial perfusion scintigraphy was originally developed as a planar imaging technique, but SPECT has since become the clinical standard in current practice. (2)

Cardiac SPECT for the diagnosis of CAD uses an intravenously administered radiopharmaceutical tracer to evaluate regional coronary blood flow, usually at rest and after stress. After the administration of the tracer, its distribution within the myocardium is imaged using a gamma camera. In SPECT imaging, the gamma camera rotates around the patients for 10 to 20 minutes so that multiple two-dimensional projections are acquired from various angles. The raw data are then processed using computational algorithms to obtain three-dimensional tomographic images. (2)

Perfusion Imaging

For the diagnosis of CAD, SPECT images are taken at stress and at rest (or re-injection) and the resulting images compared. Generally, a patient absent significant infarction or coronary stenosis will show homogenous uptake of the tracer throughout the myocardium. A defect in the 'stress images' that is absent or normalized in the 'rest images' usually corresponds to a significant coronary stensosis (3); however, the exact interpretation and criteria used to denote CAD positivity will vary according to the SPECT protocol and tracer used. (4)

The total patient contact time for stress induction, injection and image acquisition is approximately one hour. Stress and rest image acquisitions are normally separated by three to four hours, although rest acquisitions may occur on subsequent days depending on the protocol being used. (3)

Exercise and/or pharmacological agents are used to induce stress for all perfusion studies. When patients can exercise to an appropriate level of cardiovascular stress, stress induction via a conventional treadmill or stationary bicycle is preferred to pharmacologic stress. Pharmacological stress testing is particularly useful in patients who cannot exercise, in which case a pharmacologic agent, such as the positive inotrope, dobutamine; or the vasodilators, adenosine and dipyridamole, are used to induce cardiovascular stress. (2)

Radioactive Tracers

Two radioactive tracers are licensed for use by Health Canada and available commercially for use in myocardial perfusion SPECT in Ontario: thallium (201Tl) and two classes of technetium (99mTc): sestamibi (MIBI) and tetrofosmin. Briefly, thallium is a potassium analogue with a long half life of 73 hours. It emits photons with a low energy of about 80 keV. Technetium analogues, on the other hand, have a half life of only six hours but emit photons with a higher energy, in the range of 140 keV. Because of its higher energy, technetium is less subject to attenuation than thallium, and generally leads to better quality images. (4) Technetium analogues have thus become the isotope of choice for the majority of cardiac SPECT tests. A major disruption in the supply of technetium has, however, threatened supplies in Ontario and worldwide.

On May 14, 2009, the National Research Universal (NRU) reactor at Chalk River was shut down as a result of loss of electrical power in eastern Ontario and western Quebec. The facility produces nearly 50% of the world's molybdenum-99 (Mo-99), a precursor to technetium-99m. During a follow-up inspection, a heavy water leak was detected. The rate of this leak has been slowed and all material has been contained. (5) However, as of December 23, 2009, only 11% of the planned repairs had been completed. A return-to-service date of March 31, 2010 has been targeted by the NRU. (6) The U.S. and Canadian medical communities are most affected by the disruption in molybdenum-99 supply. In lieu of this shortage, the Ontario Ministry of Health and Long-Term Care has issued guidelines for the prioritization of procedures employing technetium. (7)

Attenuation Correction and ECG Gating

A particular problem with SPECT is that of attenuation. Soft-tissue in the breasts, abdomen, and chest wall can degrade SPECT image quality or create artifacts that mimic true perfusion abnormalities thus posing particular problems in obese individuals. The movement of the beating heart may also give way to motion artifacts, impeding image clarity or interpretation. (2) Since the early 1990s, several techniques have been developed to overcome these challenges. These techniques are commonly referred to as attenuation correction (AC) and electrocardiogram (ECG) gating. (8) Both techniques have been shown to improve diagnostic accuracy over traditional SPECT and are even recommended in combination by the American Society of Nuclear Cardiology (ASNC) and the Society of Nuclear Medicine (SNM). (9)

Today, AC has become a catchall phrase to refer to compensation for all phenomena that may affect image acquisition/interpretation. At the very least, this requires measuring errant photon absorption via a transmission scan that employs an external radiation source, such as gadolinium or x-ray (to correct for soft tissue attenuation), as well as correction for Compton scatter and correction for resolution degradation. (10;11)

In ECG-gated SPECT, an ECG guides the SPECT acquisition so the resulting set of images are aggregated and displayed as a continuous cinematic loop resembling a beating heart. By minimizing artifacts caused by cardiac motion, ECG gating generates a clearer image. Gating also provides additional functional information (e.g., wall motion information). (2)

Regulatory Status

SPECT gamma cameras and associated equipment/software are currently licensed by Health Canada as Class II devices.

Evidence-Based Analysis

Objective

The objective of the analysis is to determine the diagnostic accuracy of SPECT in the diagnosis of CAD compared to the reference standard of CA. This analysis is meant to allow for both indirect and direct comparisons with other non-invasive strategies for the diagnosis of CAD, using CA as a reference.

Research Questions

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

Methods

Literature search

A preliminary literature search was performed across OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, EMBASE, the Cochrane Library, and the International Agency for Health Technology Assessment (INAHTA) for all systematic reviews/meta-analysis published between January 1, 2004 and August 22, 2009. If identified, any comprehensive systematic-review/meta-analysis would form the basis for an updated search. The preliminary scan identified a comprehensive systematic review of meta-analyses with search dates no sooner than January 1, 2002 (see Literate Search Results below)).

Due to the vast amount of literature on cardiac SPECT, a decision was made to update the literature base of the MAS review starting from January 1, 2002. A second comprehensive literature search was thus performed on October 30, 2009 across the same databases for studies published between January 1, 2002 and October 30, 2009. Abstracts were reviewed by a single reviewer and, for those studies meeting the eligibility criteria, full-text articles were obtained. Reference lists were also hand-searched for any relevant studies not identified through the electronic search (see Appendix 1 for the full search strategy).

Inclusion Criteria

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

Exclusion Criteria

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

Outcomes of Interest

- TP, FP, FN, TN, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (+LR), negative likelihood ratio (-LR), and diagnostic accuracy
- Adverse events
- Costs

SPECT Techniques

All modern SPECT techniques were investigated:

- Attenuation correction SPECT with or without ECG gating (termed "AC SPECT")
- ECG-gated SPECT without AC (termed "gated SPECT")
- SPECT without AC and without ECG gating (termed "traditional SPECT")

Subgroup Analyses

All subgroup analyses were decided a priori. Multiple univariate analyses were planned for the following subgroups:

Primary analyses:

- by SPECT technique (e.g., traditional vs. AC vs. ECG-gated)
- by isotope (e.g., thallium vs. technetium vs. dual isotop)
- by stress agent [e.g., exercise vs. pharmacologic (any agent) vs. adenosine vs. dobutamine vs. dipyridamole]

Secondary analyses:

- by angiographic definition of CAD (≥50% vs. ≥70% stenosis)
- by method of SPECT interpretation (qualitative vs. quantitative)
- by history of MI (previous MI vs. no previous MI)

Subgroups containing few trials were excluded from subgroup analyses.

Calculations & Statistical Analysis

As indicated in the inclusion/exclusion criteria above, only trials which included enough raw data to derive numbers of TP, FP, FN and TN were included (to allow for meta-analysis of sensitivities and specificities). Wherever possible, accuracy data were calculated to reflect "any CAD" meaning that data reported by disease location (e.g., CAD in the LAD, RCX or circumflex) or by the number of arteries involved (e.g., single vs. multi-vessel CAD) were collapsed if possible to reflect an estimate of "any CAD." All accuracy estimates reported are by patient, not by segment.

Some trials may have reported multiple sets of accuracy data for the same patient group according to stratified variables. In such cases, only one set of values was chosen for inclusion into meta-analysis to avoid artificially over-inflating sample sizes. An attempt was made to choose a set of values most consistent with current Ontario clinical practice/expectations using advice from an expert panel. Such an approach was taken in part because a meta-regression was not possible due to time and resource constraints.

Due to the nature of patient accrual in cardiac SPECT diagnostic trials, large differences in sample sizes were observed between the sample enrolled and the sample that was actually analyzed. As a result, descriptive variables of Mean Age and % Men were presented for only those trials which provided these data according to the population analyzed for diagnostic accuracy (i.e., in those patients who completed CA).

Pooled estimates of sensitivity, specificity and diagnostic odds ratios (DORs) were calculated using a bivariate, binomial generalized linear mixed model. (12) Statistical significance was defined by *P*-values less than 0.05, where false discovery rate adjustments were made for multiple hypothesis testing. (13) 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, 2008) and the curves were adjusted by bivariate model parameters. All other statistics were calculated using STATA version 10.1 (StataCorp; Texas, USA).

Unless otherwise stated, all univariate tests were carried out as indirect comparisons, meaning that pooled estimates were formed by combining single patient arms from all available studies. Comparisons stated as "direct" involved summarizing data only from studies which directly compared the subgroups in question within the same trial, using CA as a reference standard. Indirect comparisons were used in order to facilitate comparisons between technologies, particularly to overcome absences in direct comparative data.

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 (14) 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

Literature Search Results

The preliminary search yielded 624 articles published from January 1, 2004 to August 22, 2009, including a recent, comprehensive systematic review. Published by Heijenbrok-Kal et al. (15), the review compared the diagnostic performance of stress ECHO, SPECT and electron beam computed tomography (EBCT) for CAD using CA as the reference standard. The authors performed a meta-analysis of 351 patient-series including 35,258 patients reported across 11 meta-analyses. Given the vast amount of published literature on cardiac SPECT, it was decided that the studies contained in the Heijenbrok-Kal et al. review would be used as the basis for the MAS evidence-based analysis. Of the 11 meta-analyses it covered, five meta-analyses contained information on 103 studies on SPECT compared to CA for the diagnosis of CAD (see Table 1).

Table 1: Characteristics of meta-analyses included in systematic review by Heijenbrok-Kal, 2007*

Study	Search Dates	Type of Stress	No of Studies (Patients)	CAD	Pooled Sensitivity	Pooled Specificity	Other Technologies Evaluated
O'Keefe et al., 1995 (16)	Database inception until Dec. 1993	Ex SPECT	12 (2549)	73%	90%	72%	Ex echo, Dob echo
		Ad SPECT	8 (925)	80%	89%	83%	
Fleischmann et al., 1998 (17)	Jan 1990 – Oct 1997	Ex SPECT	27 (3237)	78%	87%	64%	Ex echo
Kim et al., 2001 (18)	Jan 1997 – June 1999	Ad SPECT	9 (1207)	80%	90%	75%	Ad echo, Dip echo, Dob echo
		Dip SPECT	21 (1464)	71%	89%	65%	
		Dob SPECT	14 (1066)	66%	82%	75%	
Imran et al., 2003 (19)	Jan 1986 – March 2001	Mix SPECT	13 (2922)	71%	81%	65%	Dip echo
Mowatt et al., 2004 (2)	Jan 1981 – Dec 2001	Mix SPECT	13 (2922)	71%	81%	65%	Ex ECG

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

* Table adapted from Heijenbrok-Kal et al. (15)

To further refine the data obtained from the review by Heijenbrok-Kal et al. (15), additional inclusion/exclusion criteria, as outlined in the Methods section above, were applied. Applying these additional criteria yielded 36 observational studies published between January 1, 1995 and December 31, 2001. (20-55)

As indicated in the Methods section above, an updated search was conducted using the most recent search dates from the review by Heijenbrok-Kal et al. (15) The updated secondary search yielded 3,555 articles published from January 1, 2002 to October 30, 2009. Of these, 50 met the inclusion criteria for this review. (56-105) The total number of studies included for review was therefore 86, comprising a total of 10,870 analyzed patients.

Trial Characteristics

All included trials were published between January 1, 1995 and October 30, 2009 and were either prospective or retrospective observational studies except for one non-randomized, single arm clinical trial (59) and one poorly reported trial that appears to be a randomized controlled trial (RCT) (Table 2). (51)

Across all studies, the majority of patients were male (64.7% overall, n=56 studies) and the mean age was 60.8 (n=56 studies). The mean prevalence of CAD was 65.9% (n=84 studies) with a range of 19.6% to 94.3%. Appendix 2 contains detailed information on study characteristics and results at the individual trial level.

Table 2: Quality of evidence of included studies

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	1
Small RCT unpublished but reported to an international scientific meeting	2(g)	
Non-RCT with contemporaneous controls	3a	85
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	86

RCT refers to randomized controlled trial
Table adapted from Goodman, 1996 (106)

Diagnostic Accuracy of SPECT

Pooled estimates of sensitivity, specificity and DOR varied across trials (Appendix 2) and subgroups (see Table 3). Despite large differences in pooled accuracy estimates, however, no significant differences were observed between subgroups when the subgroups were submitted to significance testing (Table 4). This phenomenon is likely attributable to the high heterogeneity within and between studies, as well as the indirect nature of the comparisons themselves.

Table 3: Pooled accuracy estimates of included trials stratified by study characteristic

Characteristic	# Trials (Patients)	Pooled Sensitivity (95% CI)	Pooled Specificity (95% CI)	DOR (95% CI)
SPECT Modality (n=86)				
Traditional	63 (7,186)	0.87 (0.85–0.89)	0.70 (0.66–0.75)	15.48 (11.43–19.54)
Gated	19 (2,710)	0.84 (0.79–0.89)	0.78 (0.72–0.85)	18.88 (10.22–27.53)
AC	12 (1,238)	0.87 (0.82–0.92)	0.81 (0.73–0.89)	27.01 (10.73–43.30)
Tracer (n=63)*				
Technetium	39 (3,488)	0.88 (0.85–0.91)	0.70 (0.64–0.76)	16.80 (10.88–22.71)
Thallium	24 (3,338)	0.84 (0.80–0.88)	0.71 (0.64–0.78)	12.88 (7.58–18.18)
Stress agent (n=63)*				
Pharmacologic (any)	33 (3,129)	0.86 (0.82–0.89)	0.76 (0.70–0.82)	18.81 (11.72–25.90)
Dobutamine alone	11 (671)	0.83 (0.76–0.90)	0.81 (0.73–0.90)	20.79 (7.52–34.06)
Adenosine alone	6 (643)	0.88 (0.81–0.95)	0.84 (0.75–0.94)	41.01 (5.54–76.48)
Dipyridamole alone	15 (1,336)	0.88 (0.83–0.92)	0.74 (0.65–0.83)	20.87 (8.93–32.80)
Exercise	20 (2,688)	0.86 (0.82–0.90)	0.68 (0.59–0.76)	13.26 (6.98–19.55)
Method of Interpretation (n=63)*				
Qualitative	50 (4,730)	0.88 (0.86–0.90)	0.70 (0.64–0.75)	16.72 (11.84–21.60)
Quantitative	7 (813)	0.86 (0.79–0.93)	0.73 (0.60–0.85)	15.81 (4.04–27.59)
% Stenosis (n=63)*				
≥50	51 (5,403)	0.87 (0.84–0.89)	0.72 (0.67–0.77)	16.73 (11.92–21.54)
≥70	12 (1,415)	0.88 (0.84–0.93)	0.66 (0.55–0.76)	14.66 (6.28–23.05)
Previous MI (n=63)*				
Yes	37 (4,074)	0.86 (0.83–0.89)	0.69 (0.63–0.75)	13.39 (8.95–17.83)
No	23 (1,928)	0.89 (0.86–0.93)	0.75 (0.69–0.82)	25.37 (14.29–36.45)

Abbreviations: AC, attenuation correction; CI, confidence interval; DOR, diagnostic odds ratio; Ex., exercise; MI, myocardial infarction; Pharma., pharamcologic (any)

*For traditional SPECT studies only (subgroups by tracer, stress agent, method of interpretation, % stenosis and previous MI were not investigated for AC or gated SPECT due to the small number of trials).
Note that a trial may appear more than once as a result of multiple subgroup analysis on the same patient population.

Table 4: Tests of significance between SPECT subgroups

Subgroup	Unadjusted P-Value Sensitivity	Adjusted P-Value Sensitivity	Unadjusted P-Value Specificity	Adjusted P-Value Specificity	Unadjusted P-Value DOR	Adjusted P-Value DOR
SPECT Modality (n=84)						
Gated vs. Traditional	0.3203	0.7687	**0.0378**	0.1512	0.4245	0.5660
AC vs. Traditional	0.9750	0.9750	**0.0194**	0.1164	0.0809	0.3236
AC vs. Gated	0.4732	0.9054	0.6311	0.7535	0.3362	0.5043
AC vs. Non AC (Direct)	0.7089	0.9452	**0.0058**	0.0696	0.0460	0.2760
Tracer (n=63)*						
Technetium vs. Thallium	0.1614	0.7596	0.8263	0.8263	0.3253	0.5043
Stress agent (n=63)*						
Pharmacologic (any) vs. Exercise	0.8200	0.9750	0.1063	0.3156	0.2338	0.4676
Adenosine vs. Dobutamine	0.2532	0.7596	0.6402	0.7535	0.2162	0.4676
Dipyridamole vs. Dobutamine	0.2276	0.7596	0.2471	0.4236	0.9963	0.9963
Adenosine vs. Dipyridamole	0.9040	0.9750	0.1315	0.3156	0.2010	0.4676
Method of Interpretation (n=63)*						
Qualitative vs. Quantitative	0.5804	0.9054	0.6907	0.7535	0.8958	0.9772
% Stenosis (n=63)*						
≥50 vs. ≥70	0.6036	0.9054	0.3168	0.4752	0.6827	0.8192
Previous MI (n=63)*						
No vs. Yes	0.1390	0.7596	0.1589	0.3178	0.0224	0.2688

Abbreviations: AC, attenuation correction; DOR, diagnostic odds ratio; MI, myocardial infarction.
Bolding denotes significance difference at a *P*-value<0.05 in favour of the first listed technology.

Accuracy of SPECT by technique

Of the three SPECT techniques, AC SPECT showed highest pooled sensitivity (87%; range: 73% to 94%) and specificity (81%; range: 57% to 94%). ECG-gated SPECT had a pooled sensitivity of 84% (range: 51% to 97%) and a pooled specificity of 78% (range: 29% to 100%) while traditional SPECT without ECG gating or AC had a pooled sensitivity of 87% (range: 49% to 100%) and the lowest pooled specificity of 70% (range: 29% to 100%).

Figure 1 illustrates SROCs for all included studies stratified by SPECT technique (Forest plots are provided in Appendix 3). As can be seen in the Forest plots in Appendix 3, AC SPET had the narrowest range in both sensitivity and specificity.

Despite the seemingly large differences observed in pooled estimates of specificity between SPECT techniques, there were no statistically significant differences observed in any of the accuracy estimates when comparing SPECT techniques (Table 2), although, for the comparison of AC versus traditional SPECT, the improvement in specificity with AC bordered significance (adjusted *P*-value of 0.1164; unadjusted *P*-value of 0.0194).

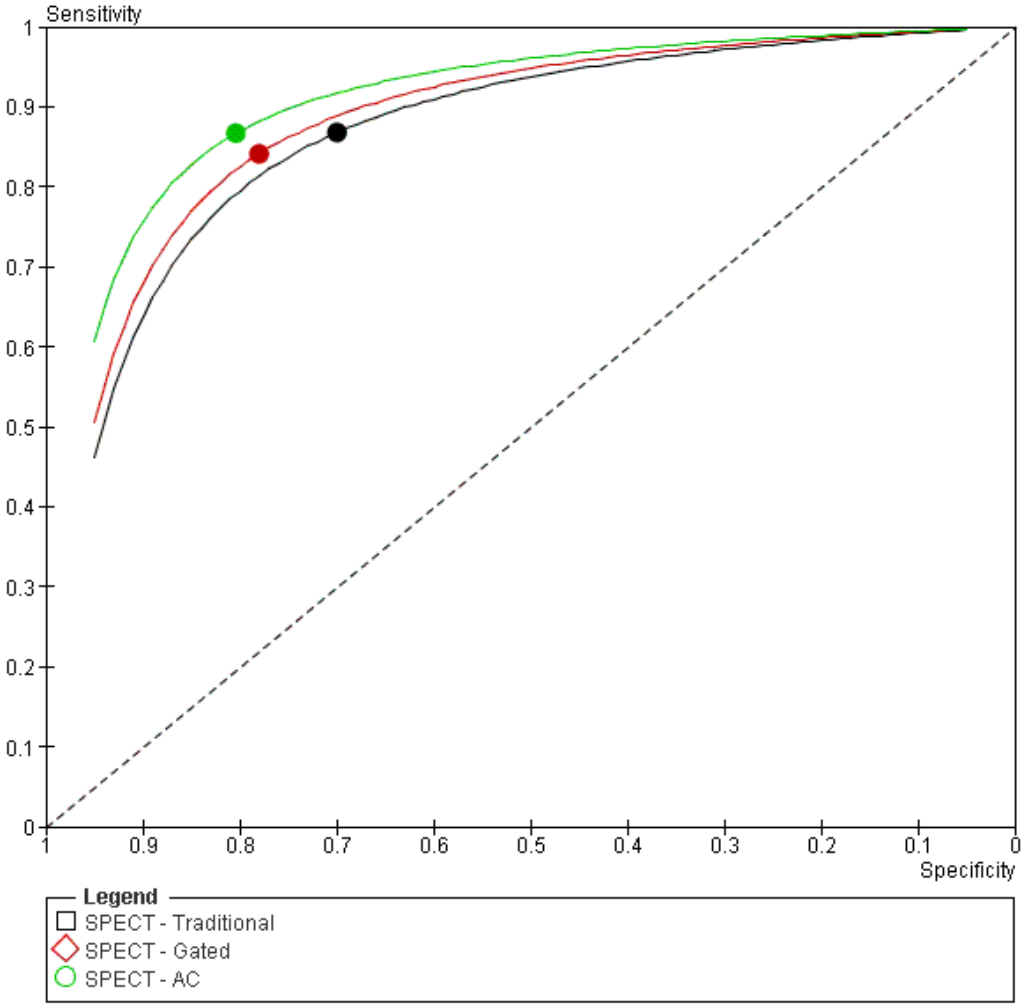


Figure 1: SROC comparing SPECT by technique using the bivariate model paramaters

Studies that compared both SPECT with AC to SPECT without AC (non-AC SPECT) within the same trial (i.e., direct comparison), using CA as a reference standard, mirrored the results of the indirect analyses above. SPECT with AC showed a pooled sensitivity and specificity of 87% and 81%, respectively. Meanwhile, SPECT without AC had a pooled sensitivity of 88% and specificity 61%.

Figure 2 illustrates the direct comparison of AC and non-AC (Forest plots are provided in Appendix 3).

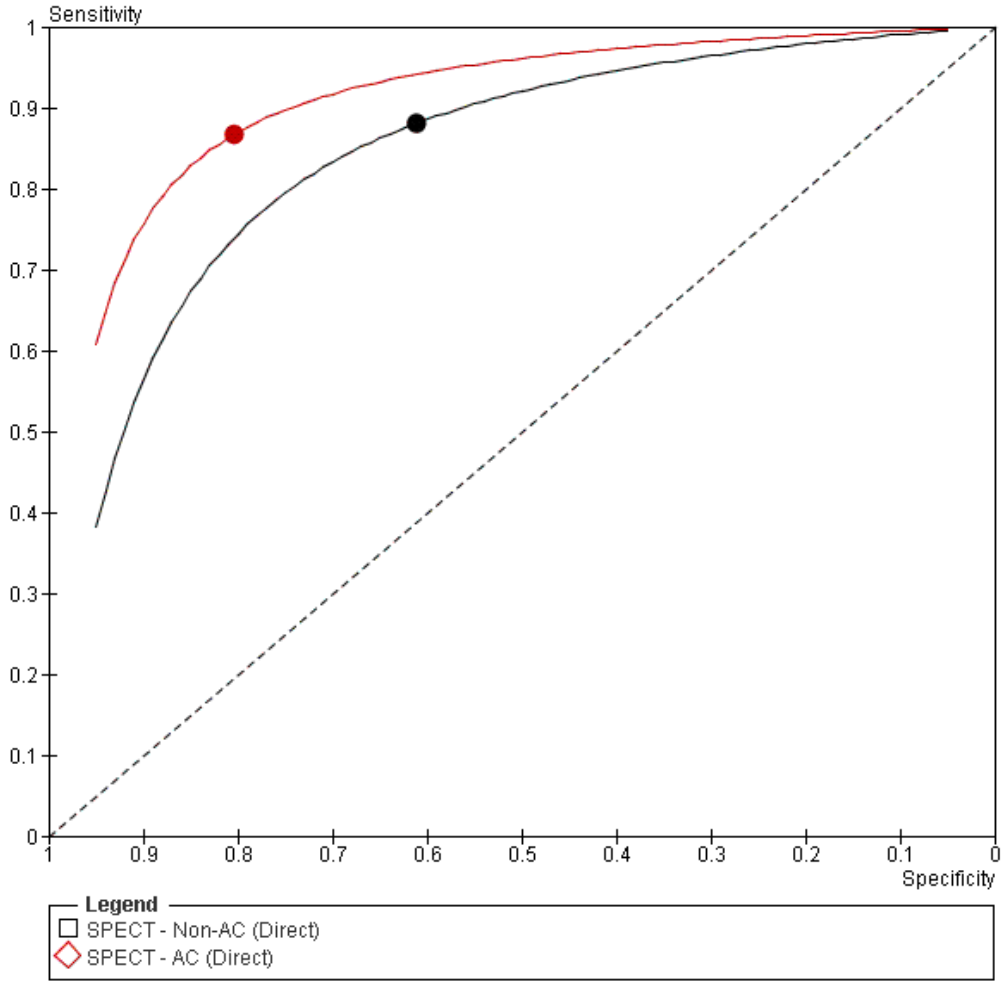


Figure 2: SROC of studies directly comparing AC and Non-AC SPECT

Accuracy of SPECT by stress agent

The use of a pharmacologic stress agent seemed to slightly improve accuracy over the use of exercise stress (Table 3) although the observed differences were not significant (Table 4). The pooled sensitivity of studies using pharmacologic stress alone was 86% (range: 49% to 98%) while the pooled specificity was 76% (range: 28% to 100%). Studies using exercise stress alone yielded a pooled sensitivity of 86% (range: 56% to 100%) and specificity of 68% (range: 36% to 100%).

Figure 3 illustrates the SROC for the comparison by stress agent (the associated Forest plots are provided in Appendix 3).

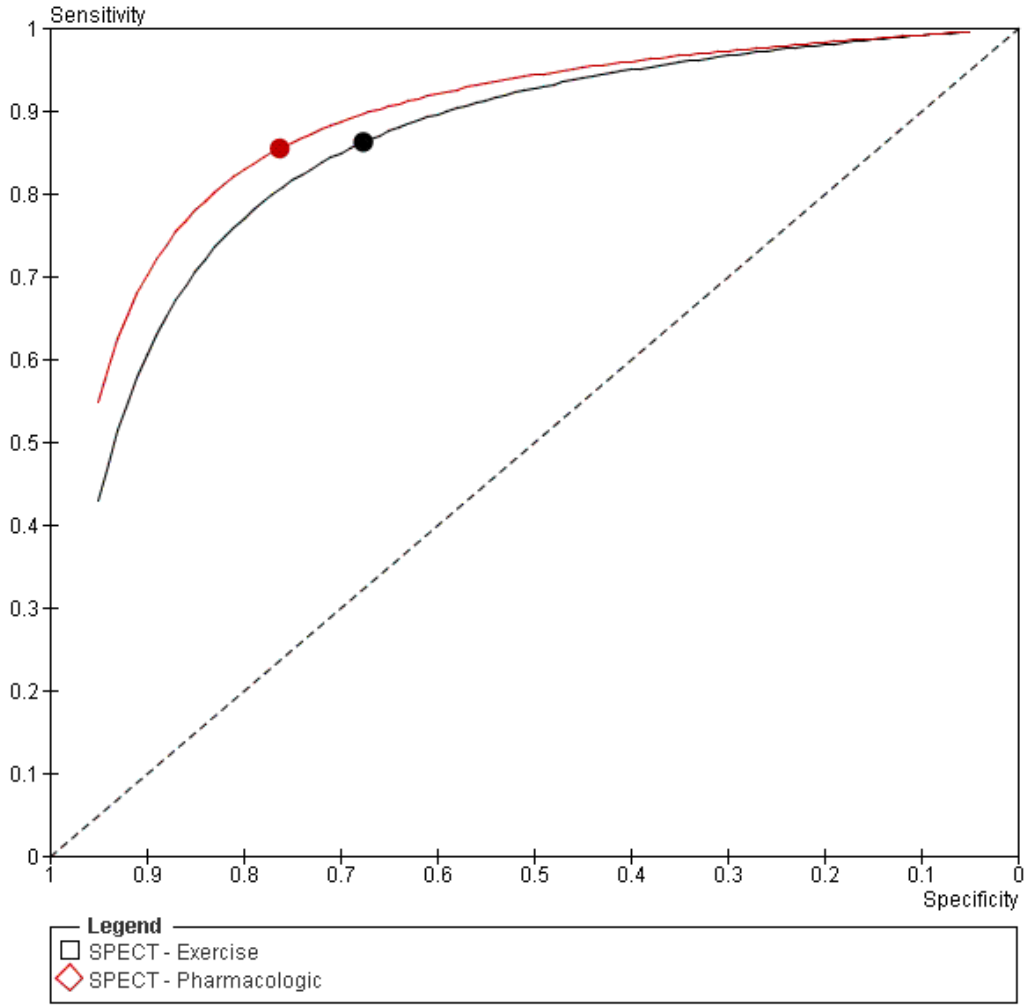


Figure 3: SROC comparing SPECT by stress agent using the bivariate model parameters

Accuracy of SPECT by radioactive tracer

The radioactive tracer used during SPECT analysis also had minimal effect on accuracy estimates (Table 3). Studies using technetium had a pooled sensitivity of 88% (range: 49% to 98%) and specificity 70% (range: 30% to 100%) while studies using thallium had a pooled sensitivity of 84% (range: 56% to 100%) and specificity 71% (range: 44% to 94%). The differences in accuracy estimates between thallium and technetium were not significant (see Table 4).

Figure 4 illustrates the SROC for the comparison by radioactive tracer (the associated Forest plots are provided in Appendix 3)

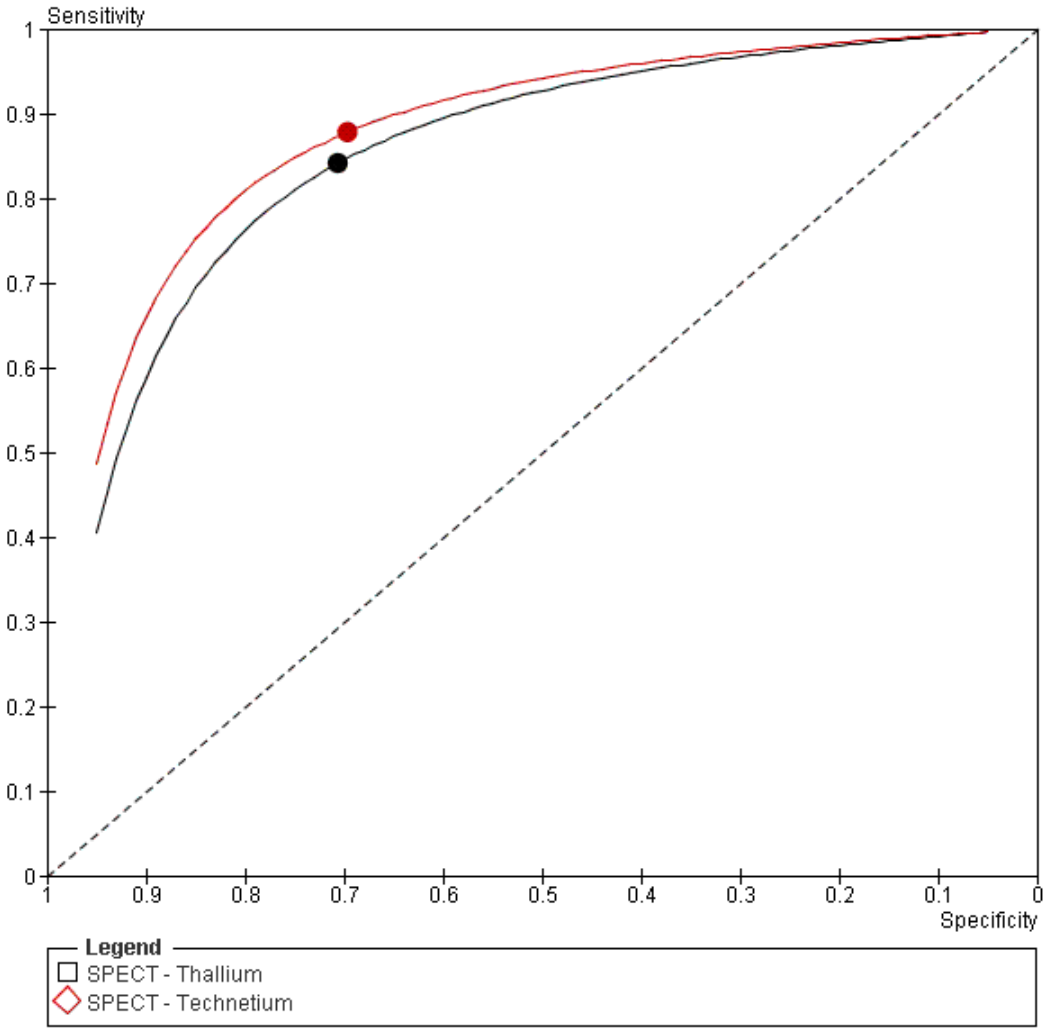


Figure 4: SROC comparing SPECT by radioactive tracer using the bivariate model parameters

Accuracy of traditional SPECT compared to stress echocardiography

Fourteen studies directly compared traditional SPECT without AC or ECG gating to stress echocardiography within the same trial (i.e., direct comparison), using CA as a reference standard. Meta-analysis of direct data mirrored the indirect data (see Table 5). No trials were identified that compared ECG-gated or AC SPECT to stress echocardiography.

Table 5: Diagnostic GRADE evaluation of methodological quality of included trials

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

Abbreviations: CI, confidence interval; ECHO, echocardiography; SPECT, single photon emission computed tomography.

Study Quality

Overall quality of included studies (regardless of subgrouping) was very low according to GRADE criteria (Table 6). Reasons for the downgrading are discussed in the Limitations section below.

Table 6: Diagnostic GRADE evaluation of methodological quality of included trials

Factor	Explanation	GRADE
Risk of Bias		
Study design	Observational / non-randomized clinical trials	High
Limitations	Verificiation/referall bias, lack of proper blinding and generally, poor reporting	Reduced by one level → Moderate
Indirectness		
Outcomes	Accuracy estimates of sensitivity and specificity serve as indirect patient-important outcomes	Reduced by one level → Low
Patient populations, diagnostic test, comparison test, and indirect comparisons	Patient populations under study were mixed with respect to CAD status (trials included both patients with suspected CAD and known CAD) Prevalence of CAD was likely higher in the populations studied than in the population who would seek testing in a real-world setting Technologies/SPECT strategies were indirectly compared using a gold standard and were not generally compared directly in head-to-head trials due to a lack of direct trials	Reduced by one level → Very Low
Important inconsistency in study results	Large heterogeneity in accuracy estimates between studies	Unchanged
Imprecise evidence	Due to large number of trials, precision was acceptable	Unchanged
Publication bias	None detected	Unchanged
Quality of Evidence		**Very Low**

Abbreviations: CAD, coronary artery disease; SPECT, single photon emission computed tomography.

Adverse Events

One of the principal concerns with nuclear/X-ray technologies is the issue of radiation dose. What is termed the 'effective dose' is a useful method of comparing risk among different diagnostic tests as it takes into account the risk of absorbed dose to different organs. Currently, the radiation total effective dose of SPECT or CT varies from three to nine times that of the U.S. background effective dose of 3.0 millisieverts (mSv). (107) The U.S. Food and Drug Administration (FDA) has estimated that a technology that exposes a patient to an effective dose of 10 mSv may be associated with an increase in the possibility of fatal cancer at approximately 1 chance in 2000. This probability is in addition to the natural incidence of fatal cancer of 1 chance in 5 in the U.S. (108)

Although the radiation dose of SPECT and CT may be considered low, it is currently hypothesized that there is a linear, no-threshold dose response relationship between the exposure of ionizing radiation and the development of cancer in human beings. Thus, even relatively low doses of radiation increase the risk of a patient developing malignancy over the patient's lifetime. Accordingly, the lifetime risk of cancer development in a patient becomes an important consideration. (109)

Lifetime radiation risks are of particular concern with respect to children because of a child's increased sensitivity to radiation and because children have more expected years of life after radiation exposure compared to adults. As cardiac diagnostic procedures are more commonly performed in individuals of advanced age, a risk-benefit scenario comes into effect. Accordingly, for a cardiac diagnostic tests performed in older adults, the risk of serious heart disease (or the risk of missing a diagnosis of serious heart disease) is greater than the theoretical risk of radiation-related cancer over a patient's lifetime, since they have fewer years to live than children. Because the potential benefits of correctly diagnosing heart disease far outweigh the risk of radiation-associated cancer in older adults, radiation dosage rarely factors into the decision-making process when devising a clinical diagnostic plan. (107)

It should be noted that stress-only SPECT studies and low dose alternative techniques are currently being investigated in effort to lower the total effective dose, particularly for younger patients.

Aside from radiation-related events, the majority of adverse events associated with SPECT may be attributed to the administration of stress, whether by exercise or a pharmacologic agent. Generally, exercise testing is a low-risk investigation even in patients with known CAD, but serious complications can occur in 2–4 per 1000 tests. (110) Although rare, death may occur at a rate of 1–5 per 10,000 tests. Lastly, while severe side effects with pharmacologic agents are rare, mild side effects are commonly reported in 50% to 80% of patients or more, depending on the specific pharmacologic agent. (111)

Table 7: Total effective dose of various cardiac diagnostic procedures

Test	Effective Dose (mSv)
Average U.S. background rate	3.0/year
Tc-99m tetrofosmin rest-stress (10 mCi + 30 mCi)	10.6/study
Tc-99m sestamibi 1-day rest-stress (10 mCi + 30 mCi)	12.0
Tc-99m sestamibi 2-day stress-rest (30 mCi + 30 mCi)	17.5
TI-201 stress and reinjection (3.0 mCi + 1.0 mCi)	25.1
Dual-isotope (3.0 mCi Tl-201 + 30 mCi Tc-99m)	27.3
Gd-153 transmission for SPECT (AC)	0.05
64-Slice MDCT coronary CTA (female)	13.5–21.4
64-Slice MDCT coronary CTA (male)	9.6–15.2
64-Slice MDCT coronary CTA (female) with ECG pulsing	6.8–14
64-Slice MDCT coronary CTA (male) without ECG pulsing	4.8–10

Data from reference (107)

Limitations

There were several limitations inherent within this analysis. First, the body of literature from1995 to 2002 may not be complete. This evidentiary base was taken from a systematic review of meta-analyses by Heijenbrok-Kal et al. (15) and, while comprehensive, the SPECT portion of this review was based on five meta-analyses, each with differing search strategies and inclusion criteria. There is, therefore, a possibility that some trials may have been missed. The decision to rely on a past systematic review was made to improve feasibility, on account of the breadth of literature published on cardiac SPECT.

A second limitation inherently stems from the trials included in this review. The issue is one of verification bias, also known as referral bias, whereby the results of the diagnostic test being studied may have been used in selecting whether the patient receives confirmatory testing by the gold standard. This form of selection bias will often increase the sensitivity while decreasing the specificity of the diagnostic technology being studied. More recent trials have begun adjusting for verification bias by investigating normalcy rates in place of specificity, although such trials are limited in number and there are too few trials to allow for comparing normalcy rates between cardiac diagnostic technologies. Trials reporting normalcy only were thus excluded from the current analysis and no adjustments were made to control for verification bias as its presence is difficult to deduce without detailed reporting. Verification bias may, therefore, exist as an important confounder.

Third, it should be noted that the gold standard of CA is, in itself, a limited test because its interpretation is often subjective. Differences in how CA was used or interpreted (e.g., qualitatively vs. quantitatively) may have disproportionately influenced the accuracy estimates of the non-invasive tests being studied.

A fourth limitation arises from the indirect nature of subgroup comparisons. By pooling estimates from single arms of trials and comparing arms indirectly, inter-study (i.e., between-study) heterogeneity is substantially increased. This increase in heterogeneity may mask significant differences between trials. Indirect comparisons were used in order to facilitate comparisons between technologies, particularly to overcome absences in direct comparative data. Accordingly, direct comparisons were examined where appropriate and when possible in attempt to confirm the findings of the indirect comparisons.

Lastly, a meta-regression was not possible due to resource constraints. The finding of no significant differences between subgroups may therefore be erroneous if significant differences are being masked by potential confounders. The ability to evaluate important subgroups should be an important consideration for future evidence-based analyses of SPECT considering the complexity of the SPECT technique and its rapid evolution in clinical practice. The need to separately evaluate the transmission source (e.g., external radiation source versus X-ray) used in AC SPECT is one example of a potentially important stratification; however, the current literature base did not permit such stratification due to the small number of studies.

Conclusions

Based on MAS' systematic review and meta-analysis of 86 studies assessing the accuracy of SPECT for the diagnosis of CAD using CA as a reference standard, the following conclusions were made:

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

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 SPECT for the diagnosis of patients with suspected CAD as compared to: stress ECHO, stress contrast ECHO, 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. Also, attenuation-correction SPECT was found to weakly dominate traditional and gated SPECT in the current analyses, providing better effectiveness at the same price, and so was the SPECT technology adopted for the comparisons below.

Economic Analysis Overview

For the two patient populations decision-analytic cost-effectiveness analyses were conducted to evaluate the relative cost-effectiveness of the five non-invasive cardiac imaging technologies. Two decision analytic models were developed for these patient populations with two reported outcomes: the cost per accurate diagnosis of CAD and the cost per true positive diagnosis of CAD. The physician and hospital costs for the non-invasive imaging tests were taken from 2009 Ontario Health Insurance Plan (OHIP) and the Ontario Case Costing Initiative (OCCI) administrative databases. (112;113) A budget impact analysis (BIA) was then performed to assess the effect of replacing a certain proportion of stress echocardiography (ECHO) tests with other cost-effective, non-invasive modalities. The costs presented in this BIA were estimated from Ontario data sources from 2009; the volumes of tests performed were estimated from data from fiscal years 2002 to 2008.

Economic Literature Review

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

Search results

A total of 883 non-duplicate citations were from the two electronic databases. Based on the content of their abstracts, 147 full-text articles were retrieved for further assessment of their inclusion/exclusion. Of these, 122 were rejected leaving 25 articles for inclusion. Following the data extraction process, 13 studies were excluded (2;114-124), with 12 studies being ultimately selected for analysis. (2;114-124), with 12 studies being ultimately selected for analysis.(125-136)

Characteristics of included studies

From the 12 included studies, eight assessed the cost-effectiveness of two of the selected imaging tests (128-131;133;135;136), three evaluated three concomitant technologies (125;132;134), and one study evaluated five technologies. (126) Five studies were cost-effectiveness analyses, where the most common outcome was cost per correct/successful CAD diagnosis. (125;126;133;135;136) The other seven studies were cost-utility analyses using cost per quality adjusted life years (QALYs) as their primary outcome. (127-132;134) 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.(127-129;131;135) The remaining studies used 18 months (134), 3 months (136), and 30 days of analytical time horizon. (130) Four studies did not report the time-horizon used in their analysis.(125;126;132;133)

All studies evaluated at least one form of ECHO against one of the other remaining selected imaging tests.(125-136) The cost-effectiveness of SPECT was studied in nine studies (125;127-129;131;132;134-136), three studies assessed CT angiography in comparison to stress ECHO or MRI (126;130;133), while cardiac MRI was compared to each of the three other selected imaging tests in two studies.(126;134) No full economic analysis between CT angiography and SPECT was found in the published literature.

Literature results for SPECT

SPECT was compared to stress ECHO in nine economic evaluations and was dominated (i.e., had a higher cost and worse outcomes) in three comparisons.(125;128;129) In one study, SPECT was compared to stress ECHO and the authors reported an ICER per correct CAD diagnosis of CDN $5,029 (136). A second economic evaluation reported that SPECT was cost-saving against stress ECHO.(134) In three other comparisons, the base-case ICER per QALY reported for SPECT in comparison to stress ECHO was above the $50,000 threshold.(127;131;135) The last study did not report an ICER, but it was stated that SPECT was cost-effective when the probability of CAD was greater than or equal to 30%.(132)

One study compared the incremental cost-effectiveness of SPECT versus MRI and reported that in the base-case analysis, SPECT was dominant over MRI for producing lower costs and greater number of QALYs.(134)

Table 8: Summary incremental cost-effectiveness ratios across selected studies evaluating SPECT

Study	Comparator	Outcome of interest	Reported as cost-effective?	ICER
Sharples et al., 2007	MRI	Cost per QALY	Yes	Dominant
Bedetti et al., 2008	Stress ECHO	Cost per correct diagnosis	No	Dominated
Garber et al., 1999	Stress ECHO	Cost per QALY	No	USD (1996) $78,444
Hayashino et al., 2004	Stress ECHO	Cost per QALY	No	Dominated
Hernandez et al., 2007	Stress ECHO	Cost per QALY	No	Dominated
Kuntz et al., 1999	Stress ECHO	Cost per QALY	No	USD (1996) $62,800
Lee et al., 2002	Stress ECHO	Cost per QALY	Yes	Not reported*
Sharples et al., 2007	Stress ECHO	Cost per QALY	Yes	Less costly, same QALYs
Shaw et al., 2066	Stress ECHO	Cost per LYS	No	USD (2003) $72,187

Abbreviation: ND = Not defined

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

Conclusion

Overall, CT angiography was found to be cost-effective or cost-saving in all four of the comparisons for 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 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, 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. 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. (137)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. (138)

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

Comparators & Parameter Estimates

The imaging technologies that were compared in the current cost-effectiveness analysis included: CT angiography, stress ECHO (with and without contrast), 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 9 shows a list of the parameters with the 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 in Table 9, 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 9: Parameter estimates for SPECT tests

Pooled Diagnostic Accuracy	Point Estimate	95% Lower	95% Upper
CAD diagnosis: Sensitivity	0.861	0.812	0.910
CAD diagnosis: Specificity	0.821	0.748	0.895
Additional time for test (compared to GXT)	**Average**	**Low**	**High**
Inpatient population: Additional days for test	1.3	1.0	2.0
Uninterpretable test result	**Average**	**Low**	**High**
Outpatient population: % of tests that are uninterpretable	6.9%	0.5%	10.0%
Inpatient population: % of tests that are uninterpretable	7.0%	0.5%	10.0%

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

Figure 5 provides a simplified illustration of the decision-analytic model structure used for the outpatient and inpatient populations. The following two simplifying assumptions were made for the models:

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

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 by THETA. (139;139)

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 which were varied 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 unavailable imaging technologies.

Resource Use and Costs

Resource use and costs were derived from Ontario data sources: the OHIP and OCCI administrative databases. (112;113) 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 (see Table 10). Note that for contrast ECHO tests, the cost for the contrast medium was added for use in the event of uninterpretable ECHO results. 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, inpatient hospitalization costs 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 SPECT wait time, see Table 9). 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.

Willingness-to-pay

The WTP must be determined by the MOHLTC. As such, all reasonable WTP values are 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 only to guide discussion.

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

- An 'accurate diagnosis' of CAD can be obtained through a coronary angiography for $1,433. 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

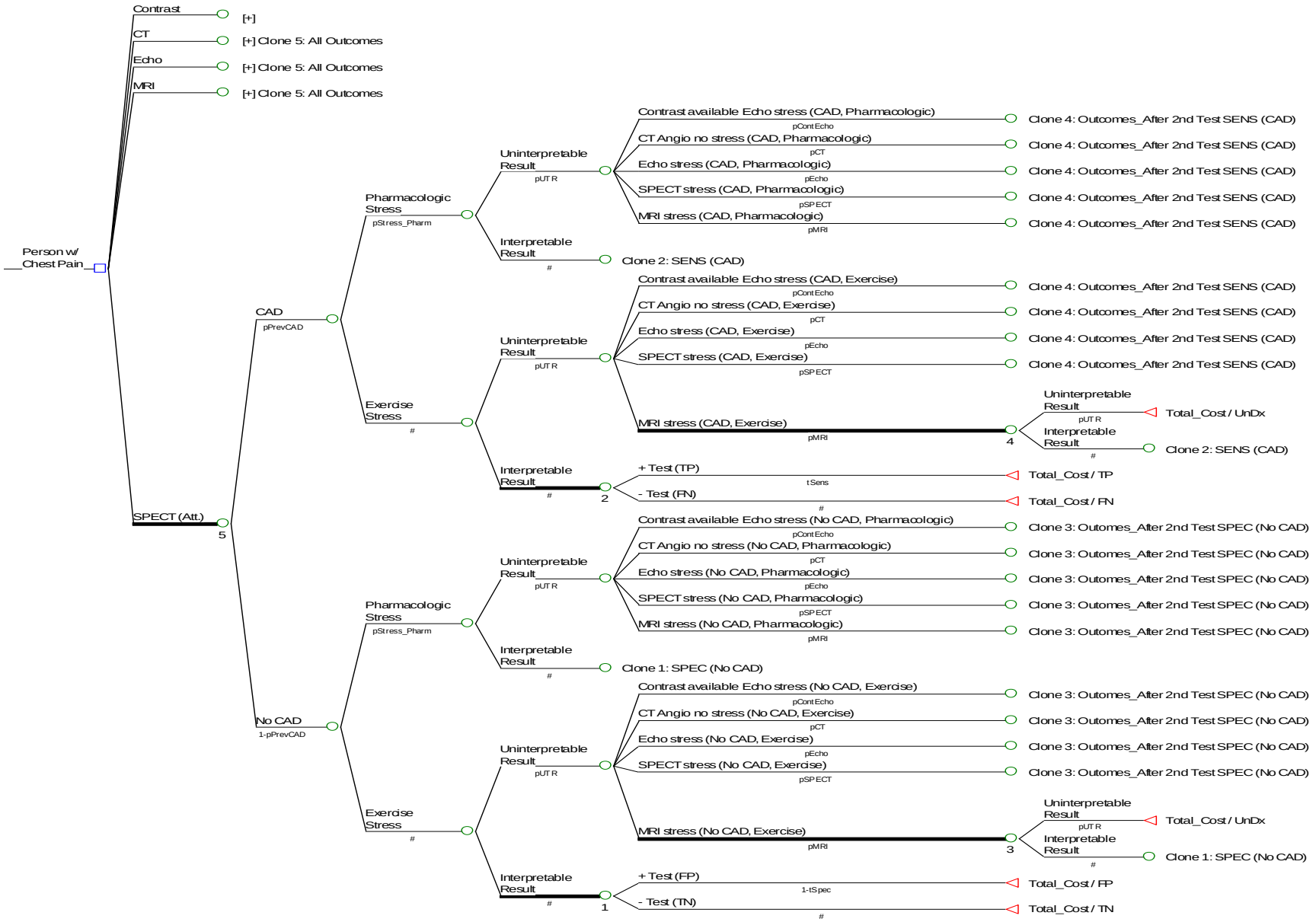


Figure 5: Decision analytic model used to evaluate the cost-effectiveness of cardiac imaging technologies for the diagnosis of CAD

Table 10: 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)	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. (113) 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.

Results and Discussion

As shown in Tables 11 and 12, in stable outpatients SPECT was dominated by CT angiography – it had higher costs and was less effective. In acute inpatients SPECT reported an ICER of $5,113 per accurate diagnosis versus contrast ECHO. At reasonable WTP values (anchored at approximately $804 or $1,433 per accurate diagnosis) SPECT does not, therefore, appear cost-effective.

For stable outpatients, when both CT angiography and contrast ECHO were removed from the analysis, SPECT appeared cost-effective at the higher WTP anchor ($1,433 per accurate diagnosis) only when the prevalence of CAD was greater than 55%. At the lower WTP anchor ($804 per accurate diagnosis), SPECT did not appear to be cost-effective at any CAD prevalence value. Sensitivity analysis also showed that SPECT could be considered a cost-effective strategy for acute inpatients only under a very high prevalence of CAD and for WTP values much higher than these anchors. When contrast ECHO was removed from the analysis, however, SPECT appeared cost-effective for acute inpatients at all reasonable WTP and prevalence values.

To summarize, attenuated SPECT appeared more cost-effective than both traditional and gated SPECT, although SPECT was not considered a cost-effective strategy compared to either contrast ECHO or CT angiography in the stable chest pain patient population. SPECT appeared cost-effective at the higher WTP anchor only in cases where other, more cost-effective technologies were unavailable and where the prevalence of CAD was greater than 55%.

Table 11: Cost-effectiveness analysis base case results for stable outpatients

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

Table 12: Cost-effectiveness analysis base case results for acute inpatients

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

Budget Impact Analysis

The budget impact analysis (BIA) was performed taking the perspective of the MOHLTC and includes both physician and hospital (clinic) costs of non-invasive cardiac imaging tests. Volumes of cardiac tests in Ontario were taken from administrative databases (OHIP, DAD, NACRS) for fiscal years 2004 to 2008 using methodology summarized in The THETA report (139). 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. 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, nuclear cardiac tests (MPI and SPECT) were found to be the second most expensive of the compared cardiac imaging modalities. When the volume of nuclear cardiac tests is shifted to other technologies, all scenarios result in lower projected costs, except for cardiac MRI imaging. If 25% of the nuclear cardiac tests are moved to other imaging technologies, ensuing projected costs would be lower (excluding cardiac MRI): from the largest cost avoidance of about $10.8M per year for stress ECHO testing to the smallest cost avoidance of $5.8M for CT angiography. The largest possible cost avoidance corresponds to replacing 50% of nuclear cardiac tests with stress ECHO imaging ($21.7M per year); the smallest cost avoidance occurs by replacing 5% of nuclear cardiac tests with CT angiography imaging ($1.2M per year), excluding cardiac MRI.

Glossary

Attenuation Correction (AC) SPECT	A SPECT analysis using motion correction, blur correction and/or soft tissue attenuation correction. AC may have been achieved by any one or combination of software, gadolinium line source or CT x-ray radiation methods. Note that trials labelled or analyzed as AC may or may not have also included ECG gating. (Due to the small number of studies, ECG-gated SPECT plus AC was not analyzed as a distinct subgroup.)
Dual Isotope	Any trial which used a different radioactive tracer at stress than at rest within the same SPECT study (i.e., within the same patient).
ECG-Gated SPECT	A SPECT acquisition guided by ECG gating. For the purposes of this review, all trials labelled as ECG-gated SPECT did not report attenuation correction.
Previous myocardial infarction (MI)	Any history of MI or previous MI within the last one month (i.e., "No" signifies that no patient had a previous MI within one month; "Yes" signifies that at least one or more patients had a history of MI or previous MI within the last one month)
Interpretation	Describes the method of SPECT image interpretation used to define CAD positivity. For the purpose of subgroup analysis, all trials reporting visual, visual and semi-quantitative, or semi-quantitative interpretation were labelled as "Qualitative" while trials reporting quantitative or semi-quantitative + quantitative interpretation were labelled as "Quantitative."

Appendices

Appendix 1: Literature Search Strategies

Updated Literature Search: January 2, 2002 to October 30, 2009

Search date: October 30, 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) <1996 to October Week 4 2009>
Search Strategy

1 exp Myocardial Ischemia/ (135175)
2 (coronary adj2 arter* disease*).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] (38944)
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. (125265)
4 (myocardi* adj2 hibernat*).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] (610)
5 (stenocardia* or angina).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] (21606)
6 heart attack*.mp. (1896)
7 exp Heart Failure/ (34267)
8 ((myocardi* or heart or cardiac) adj2 (failure or decompensation or insufficiency)).mp. (60297)
9 exp Ventricular Dysfunction, Left/ (13993)
10 (left adj2 ventric* adj2 (dysfunction* or failure or insufficienc*)).mp. (17297)
11 or/1-10 (226980)
12 exp Tomography, Emission-Computed, Single-Photon/ or exp Myocardial Perfusion Imaging/ (15654)
13 ((single photon adj3 tomograph*) or SPECT or SPET or MPS).ti,ab. (15722)
14 (scinti* adj2 (coronary or heart or myocardi* or cardiac or perfusion or viability or isch?emi* or cad or coronary artery disease or thallium or sestamibi or mibi or technetium)).ti,ab. (3249)
15 or/12-14 (22579)
16 11 and 15 (5932)
17 limit 16 to (english language and humans and yr="2002 -Current") (2933)
18 limit 17 to (case reports or comment or editorial or letter) (479)
19 17 not 18 (2454)

Database: EMBASE <1980 to 2009 Week 43>
Search Strategy

1 exp ischemic heart disease/ (241354)
2 exp coronary artery disease/ (89908)
3 exp stunned heart muscle/ (1537)
4 (coronary adj2 arter* disease*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (72491)
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] (278988)
6 (myocardi* adj2 hibernat*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (1059)
7 (stenocardia* or angina).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (46732)
8 heart attack*.mp. (2053)
9 exp heart failure/ (127353)

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] (109249)
11 exp heart left ventricle failure/ (9478)
12 (left adj2 ventric* adj2 (dysfunction* or failure or insufficienc*)).mp. (16310)
13 or/1-12 (435714)
14 exp single photon emission computer tomography/ (26142)
15 ((single photon adj3 tomograph*) or SPECT or SPET or MPS).ti,ab. (22465)
16 (scinti* adj2 (coronary or heart or myocardi* or cardiac or perfusion or viability or isch?emi* or cad or coronary artery disease or thallium or sestamibi or mibi or technetium)).ti,ab. (6378)
17 or/14-16 (36626)
18 17 and 13 (10134)
19 limit 18 to (human and english language and yr="2002 -Current") (3668)
20 limit 19 to (editorial or letter or note) (366)
21 case report/ (1060365)
22 19 not (20 or 21) (2908)

Appendix 2: Included Studies

Table A1: Characteristics of included studies comparing the accuracy of SPECT to CA for the diagnosis of CAD

Author	Year	N*	Type of SPECT	Tracer	Stress Agent	% Stenosis	% Men†	Mean Age†	Prior MI	Interp.
Aggeli (90)	2007	48	Traditional	Tl	Ad	50	-	-	Yes	V+Q
Amanullah (36)	1997	222	Traditional	Dual	Ad	50	54	71	No	SQ
Astarita (53)	2001	53	Traditional	Tl	Ex	50	55	58	No	V
Banzo (91)	2003	99	Traditional/AC	Tc	Ex+Dip+Ad	70	72	59	Yes	V+SQ
Benoit (59)	1996	72	Traditional	Tc	Ex	50	82	58	Yes	V
Berman (82)	2006	785	Gated	Tc	Ex/Ad	70	-	-	No	V+SQ/Q
Bokhari (95)	2008	218	Gated	Tl+Dual	Ex	50	69	62	No	V+Q
Chammas (105)	2002	58	Traditional	Tc	Ex	60	83	57	No	-
Cramer (54)	1996	35	Traditional	Tc	Dip	50	69	58	No	V
Daou (20)	2002	338	Traditional	Tl	Ex	50	-	-	Yes	V
De (21)	2002	49	Traditional	Tc	-	70	-	-	-	-
DiBello (37)	1996	45	Traditional	Tc	Dob	50	73	43	No	V+SQ
Dondi (70)	2004	130	Traditional/AC	Tc	Ex+Pharma	50	-	-	Yes	V
Elhendy (38)	1998	70	Traditional	Tc	Dob	50	0	58	Yes	V+SQ
Elhendy (83)	2006	88	Traditional	Tc	Ex+Dob	50	0	100	No	V+SQ
Emmett (61)	2002	100	Gated	Tc	Ex	70	77	60	Yes	V+SQ
Ficaro (56)	1996	60	Traditional	Dual	Ex+Pharma	50	63	63	Yes	V/Q
Fragasso (52)	1999	101	Traditional	Tc	Ex	50	54	61	No	V
Gallowitsch (31)	1998	107	Traditional/AC	Tl	Ex/Dip	70	64	64	Yes	V
Gentile (22)	2001	132	Traditional	Tl	Ex+Dip	60	68	71	No	V
Gonzalez (77)	2005	145	Traditional	Tl	Ex+Dip	50	68	60	Yes	V+SQ
Groutars (67)	2003	123	Traditional	Dual	Ex+Ad	50/70	72	59	No	V+SQ
Grossman (71)	2004	74	Gated/Gated+AC	Tc	Ex	50	-	-	-	Q
Hambye (72)	2004	100	Gated/Gated+AC	Tc	Ex+Ad	50	48	64	Yes	SQ+Q
Hannoush (68)	2003	51	Traditional	Tc	Ex+Dip	50	-	-	Yes	V
He (62)	2002	51	Traditional	Tc	Ad	50	-	-	No	V
He (63)	2003	26	Traditional	Tc	Ex	50	81	58	-	V
Heiba (32)	1997	34	Traditional	Tc	Ex	50	-	-	Yes	SQ
Hida (100)	2009	119	Gated	Tc	Ad	75	66	68	No	V
Ho (40)	1997	51	Traditional	Tl	Ex	50	-	-	Yes	V
Ho (39)	1995	54	Traditional	Tl	Dip	50	85	58	Yes	V
Huang (41)	1998	110	Traditional	Tl	Dob	50	74	61	No	V
Huang (42)	1997	93	Traditional	Tl	Dob	50	77	61	Yes	V
Hung (84)	2006	126	Gated	Tl	Dip	70	71	66	Yes	V
Iftikhar (57)	1996	38	Traditional	Tc	Dob	50	-	-	Yes	V
Jeetley (85)	2006	123	Traditional	Tc	Dip	50	71	62	Yes	V+SQ
Johansen (78)	2005	357	Gated	Dual	Ex+Pharma	50	54	57	No	V+SQ
Kajinami (23)	1995	251	Traditional	Tl	Ex	75	69	56	-	V
Katayama (96)	2008	46	Traditional	Tl	Ex+Dip	75	74	71	Yes	SQ
Khattar (24)	1998	100	Traditional	Tc	Dob+Ad	50	70	62	Yes	SQ
Kisacik (58)	1996	69	Traditional	Tc	Ex	50	-	-	Yes	V
Korosoglou (86)	2006	89	Traditional	Tc	Pharma	75	-	-	Yes	V
Lima (64)	2002	255	Gated	Tc	Ex+Pharma	70	65	61	Yes	Q
Lin (87)	2006	40	Traditional	Dual	Dip	50	-	-	Yes	V
Links (60)	2000	69	Gated/Gated+AC	Mixed	Ex+Pharma	50	-	-	Yes	V
Lipiec (97)	2008	103	Traditional	Tc	Dip	50	63	58	Yes	V+Q
Masood (79)	2005	118	Traditional/AC	Tc	Ex+Pharma	50	67	61	No	V/Q1/Q2

Author	Year	N*	Type of SPECT	Tracer	Stress Agent	% Stenosis	% Men†	Mean Age†	Prior MI	Interp.
Matsumoto (88)	2006	56	Gated	Tc	Ex+Pharma	50	-	-	Yes	SQ
McClellan (25)	1996	303	Traditional	Tl	Ex	50	-	-	Yes	V+Q
Michaelides (26)	1999	245	Traditional	Tl	Ex	70	89	52	No	V+Q
Mieres (92)	2007	42	Gated	Tc/Dual	Ex+Ad	50	-	-	No	-
Miller (43)	1997	243	Traditional	Tc	Dip	50	-	-	Yes	V
Mohiuddin (44)	1996	202	Traditional	Tl	Ad	50	59	58	Yes	Q
Nallamothu (27)	1995	321	Traditional	Tl	Ex	50	75	57	-	V+Q
Ogilby (55)	1998	26	Traditional	Tc	Dip	50	73	57	Yes	V
Palmas (33)	1995	70	Traditional	Tc	Ex	50	81	60	Yes	V
Patsilinakos (73)	2004	75	Traditional	Tl	Ad	50	68	69	-	V
Peltier (74)	2004	35	Traditional	Tc	Dip	70	71	62	No	V+Q
Psirropoulos (28)	2002	301	Traditional	Tl	Ex	50	-	-	Yes	-
Rollan (65)	2002	54	Traditional	Tc	Dob	50	-	-	Yes	V
Rubello (34)	1995	120	Traditional	Tc	Ex	50	88	51	Yes	V/Q
Sakuma (80)	2005	40	Traditional	Tl	Ex+Pharma	70	70	65	No	V
San Roman (45)	1998	92	Traditional	Tc	Dob	50	-	-	No	V
Santana-Boado (30)	1998	163	Traditional	Tc	Ex+Dip	50	61	59	No	V
Santoro (46)	1998	60	Traditional	Tc	Dip/Dob	70	-	-	No	V
Schepis (93)	2007	77	Gated+AC	Tc	Ad	50	62	66	No	V+SQ
Schillaci (47)	1997	40	Traditional	Tc	Dip	70	63	55	No	Q
Senior (75)	2004	55	Traditional	Tc	Dob	50	82	-	No	V
Shelley (69)	2003	108	Gated	Tc	Ad	50	-	-	Yes	Q
Shirai (29)	2002	603	Gated	Tl	Ex	70	76	63	Yes	V
Slavich (48)	1996	46	Traditional	Tc	Dob	50	0	59	No	V
Slomka (89)	2006	174	Gated/Gated+AC	Tc	Ex+Pharma	50	67	64	No	Q
Soman (49)	1997	27	Traditional	Tc	Dip/Arb	50	67	58	Yes	SQ
Suzuki (98)	2008	90	Gated	Dual	Ex+Pharma	50	70	63	No	Q
Tadehara (99)	2008	101	Gated	Tc	Ad	50	-	-	Yes	V
Taillefer (35)	1997	85	Traditional	Ti/Tc	Ex/Dip	50/70	0	60	Yes	Q
Takeuchi (50)	1996	61	Traditional	Tl	Ex+Dip	50	-	-	No	V+Q
Thompson (81)	2005	116	Gated/Gated+AC	Tc	Ex/Pharma	70	70	60	No	V
Tsai (66)	2002	86	Traditional	Tl	Ex	50	-	-	Yes	V
Watanabe (51)	1997	140	Traditional	Tl	Dip/Ad	50	64	63	Yes	V
Wolak (103)	2008a	114	Gated/Gated+AC	Tc	Ex+Ad	70	0	65	Yes	Q
Wolak (104)	2008b	188	Traditional	Tc	Ex+Pharma	70	69	64	Yes	Q
Wu (101)	2009	218	Traditional	Tc	Dip	50	62	64	Yes	V
Yao (76)	2004	73	Traditional	Tc	Ex	50	-	-	No	-
Yeih (94)	2007	51	Traditional	Tl	Dob	50	0	63	Yes	V
Yoon (102)	2009	344	Traditional	Tc	Ad+Dip	70	-	-	-	-

Abbreviations: AC, attenuation correction; Ad, adenosine; Arb, arbutamine; Dip, dipyridamole; Dob, dobutamine; Dual, dual isotope; Ex, exercise; Interp., method of SPECT interpretation; Pharma, pharmacologic (agents not specified); Q, quantitative; Q1, quantitative software 1; Q2, quantitative software 2; SQ, semi-quantitative; Tc, technetium; Tl, thallium; V, visual

* Sample analyzed

† Reported only for sample analyzed

‡ Describes trials which included patients any previous MI or previous MI within the last one month (i.e., "No" signifies that no patients had a previous MI within one month; "Yes" signifies that the trial included some, not necessarily all, patients with a history of MI or previous MI within the last one month)

\+ signifies that the an unspecified combination of modalities/tracers/agents were used, in "either/or" fashion

/ signifies that the modalities/tracers/agents were analyzed as distinct subgroups

Abbreviations: AC, attenuation correction; Ad, adenosine; Arb, arbutamine; Dip, dipyridamole; Dob, dobutamine; Dual, dual isotope; Ex, exercise; Interp., method of SPECT interpretation; Pharma, pharmacologic (agents not specified); Q, quantitative; Q1, quantitative software 1; Q2, quantitative software 2; SQ, semi-quantitative; Tc, technetium; Tl, thallium; V, visual

Table A2: Estimates of diagnostic accuracy across included studies

Author	N*	Type of SPECT	Tracer	Stress Agent	% Sten.	MI	Interp.	TP	FP	FN	TN	Sen.	Spe.	PPV	NPV	(+) LR	(-) LR	Acc.
Aggeli, 2007 (90)	48	Traditional	Tl	Ad	50	Yes	V+Q	24	1	6	17	0.80	0.94	0.96	0.74	14.40	0.21	0.85
Amanullah, 1997 (36)	222	Traditional	Dual	Ad	50	No	SQ	159	14	12	37	0.93	0.73	0.92	0.76	3.39	0.10	0.88
Astarita, 2001 (53)	53	Traditional	Tl	Ex	50	No	V	23	16	0	14	1.00	0.47	0.59	1.00	1.88	0.00	0.70
Banzo, 2003 (91)	99	Traditional	Tc	Ex+Dip+Ad	70	Yes	V+SQ	47	26	4	22	0.92	0.46	0.64	0.85	1.70	0.17	0.70
	99	AC						39	14	12	34	0.76	0.71	0.74	0.74	2.62	0.33	0.74
Benoit, 1996 (59)	72	Traditional	Tc	Ex	50	Yes	V	55	1	8	8	0.87	0.89	0.98	0.50	7.86	0.14	0.88
Berman, 2006 (82)	365	Gated	Tc	Ex	70	No	V+SQ	251	40	24	50	0.91	0.56	0.86	0.68	2.05	0.16	0.82
	420			Ad			V+SQ	252	77	28	63	0.90	0.45	0.77	0.69	1.64	0.22	0.75
	785			Ex+Ad			V+SQ	503	117	52	113	0.91	0.49	0.81	0.68	1.78	0.19	0.78
	290			Ex+Ad			Q	186	9	39	56	0.83	0.86	0.95	0.59	5.97	0.20	0.83
Bokhari, 2008 (95)	218	Gated	Tl+Dual	Ex	50	No	V+Q	116	16	27	59	0.81	0.79	0.88	0.69	3.80	0.24	0.80
Chammas, 2002 (105)	58	Traditional	Tc	Ex	60	No	-	30	6	4	18	0.88	0.75	0.83	0.82	3.53	0.16	0.83
Cramer, 1996 (54)	35	Traditional	Tc	Dip	50	No	V	23	1	6	5	0.79	0.83	0.96	0.45	4.76	0.25	0.80
Daou, 2002 (20)	338	Traditional	Tl	Ex	50	Yes	V	167	17	98	56	0.63	0.77	0.91	0.36	2.71	0.48	0.66
De, 2002 (21)	49	Traditional	Tc	-	70	-	-	8	26	4	11	0.67	0.30	0.24	0.73	0.95	1.12	0.39
DiBello, 1996 (37)	45	Traditional	Tc	Dob	50	No	V+SQ	33	1	5	6	0.87	0.86	0.97	0.55	6.08	0.15	0.87
Dondi, 2004 (70)	130	Traditional	Tc	Ex+Pharma	50	Yes	V	104	6	4	16	0.96	0.73	0.95	0.80	3.53	0.05	0.92
	130	AC						100	2	8	20	0.93	0.91	0.98	0.71	10.19	0.08	0.92
Elhendy, 1998 (38)	88	Traditional	Tc	Ex+Dob	50	No	V+SQ	29	7	16	18	0.64	0.72	0.81	0.53	2.30	0.49	0.67
Elhendy, 2006 (83)	70	Traditional	Tc	Dob	50	Yes	V+SQ	44	7	9	28	0.83	0.80	0.86	0.76	4.15	0.21	0.82
Emmett, 2002 (61)	100	Gated	Tc	Ex	70	Yes	V+SQ	62	11	8	19	0.89	0.63	0.85	0.70	2.42	0.18	0.81
Ficaro, 1996 (56)	60	Traditional	Dual	Ex+Pharma	50	Yes	V	38	6	11	5	0.78	0.45	0.86	0.31	1.42	0.49	0.72
	60						Q	41	6	8	5	0.84	0.45	0.87	0.38	1.53	0.36	0.77
Fragasso, 1999 (52)	101	Traditional	Tc	Ex	50	No	V	56	28	1	16	0.98	0.36	0.67	0.94	1.54	0.05	0.71
Gallowitsch, 1998 (31)	68	Traditional	Tl	Ex	70	Yes	V	30	10	6	22	0.83	0.69	0.75	0.79	2.67	0.24	0.76
	68	AC		Ex				35	4	1	28	0.97	0.88	0.90	0.97	7.78	0.03	0.93
	39	Traditional		Dip				12	1	5	21	0.71	0.95	0.92	0.81	15.53	0.31	0.85
	39	AC		Dip				15	1	2	21	0.88	0.95	0.94	0.91	19.41	0.12	0.92
	107	Traditional		Ex/Dip				42	11	11	43	0.79	0.80	0.79	0.80	3.89	0.26	0.79
	107	AC		Ex/Dip				50	5	3	49	0.94	0.91	0.91	0.94	10.19	0.06	0.93
Gentile, 2001 (22)	132	Traditional	Tl	Ex+Dip	60	No	V	101	11	7	13	0.94	0.54	0.90	0.65	2.04	0.12	0.86
Gonzalez, 2005 (77)	145	Traditional	Tl	Ex+Dip	50	Yes	V+SQ	102	12	15	16	0.87	0.57	0.89	0.52	2.03	0.22	0.81
Grossman, 2004 (71)	74	Gated	Tc	Ex	50	-	Q	38	25	1	10	0.97	0.29	0.60	0.91	1.36	0.09	0.65
	74	Gated+AC						35	15	4	20	0.90	0.57	0.70	0.83	2.09	0.18	0.74
	123	Traditional	Dual	Ex+Ad	50	No	V+SQ	102	6	6	9	0.94	0.60	0.94	0.60	2.36	0.09	0.90

Author	N*	Type of SPECT	Tracer	Stress Agent	% Sten.	MI	Interp.	TP	FP	FN	TN	Sen.	Spe.	PPV	NPV	(+) LR	(-) LR	Acc.
Groutars, 2003 (67)																		
	123				70			93	11	3	16	0.97	0.59	0.89	0.84	2.38	0.05	0.89
Hambye, 2004 (72)	100	Gated	Tc	Ex+Ad	50	Yes	SQ+Q	60	3	26	11	0.70	0.79	0.95	0.30	3.26	0.38	0.71
	100	Gated+AC						63	3	23	11	0.73	0.79	0.95	0.32	3.42	0.34	0.74
Hannoush, 2003 (68)	51	Traditional	Tc	Ex+Dip	50	Yes	V	40	4	1	6	0.98	0.60	0.91	0.86	2.44	0.04	0.90
He, 2002 (62)	26	Traditional	Tc	Ex	50	-	V	33	3	1	14	0.97	0.82	0.92	0.93	5.50	0.04	0.92
He, 2003 (63)	51	Traditional	Tc	Ad	50	No	V	18	0	4	4	0.82	1.00	1.00	0.50	81.82	0.18	0.85
Heiba, 1997 (32)	34	Traditional	Tc	Ex	50	Yes	SQ	28	1	2	3	0.93	0.75	0.97	0.60	3.73	0.09	0.91
Hida, 2009 (100)	119	Gated	Tc	Ad	75	No	V	32	7	30	50	0.52	0.88	0.82	0.63	4.20	0.55	0.69
Ho, 1997 (40)	51	Traditional	Tl	Ex	50	Yes	V	29	3	9	10	0.76	0.77	0.91	0.53	3.31	0.31	0.76
Ho, 1995 (39)	54	Traditional	Tl	Dip	50	Yes	V	42	3	1	8	0.98	0.73	0.93	0.89	3.58	0.03	0.93
Huang, 1998 (41)	110	Traditional	Tl	Dob	50	No	V	53	8	12	37	0.82	0.82	0.87	0.76	4.59	0.22	0.82
Huang, 1997 (42)	93	Traditional	Tl	Dob	50	Yes	V	60	5	7	21	0.90	0.81	0.92	0.75	4.66	0.13	0.87
Hung, 2006 (84)	126	Gated	Tl	Dip	70	Yes	V	75	16	6	29	0.93	0.64	0.82	0.83	2.60	0.11	0.83
Iftikhar, 1996 (57)	38	Traditional	Tc	Dob	50	Yes	V	22	1	6	9	0.79	0.90	0.96	0.60	7.86	0.24	0.82
Jeetley, 2006 (85)	123	Traditional	Tc	Dip	50	Yes	V+SQ	79	13	17	14	0.82	0.52	0.86	0.45	1.71	0.34	0.76
Johansen, 2005 (78)	357	Gated	Dual	Ex+Pharma	50	No	V+SQ	94	48	32	183	0.75	0.79	0.66	0.85	3.59	0.32	0.78
Kajinami, 1995 (23)	251	Traditional	Tl	Ex	75	-	V	110	48	23	70	0.83	0.59	0.70	0.75	2.03	0.29	0.72
Katayama, 2008 (96)	46	Traditional	Tl	Ex+Dip	75	Yes	SQ	17	7	5	17	0.77	0.71	0.71	0.77	2.65	0.32	0.74
Khattar, 1998 (24)	100	Traditional	Tc	Dob+Ad	50	Yes	SQ	41	11	19	29	0.68	0.73	0.79	0.60	2.48	0.44	0.70
Kisacik, 1996 (58)	69	Traditional	Tc	Ex	50	Yes	V	45	8	2	14	0.96	0.64	0.85	0.88	2.63	0.07	0.86
Korosoglou, 2006 (86)	89	Traditional	Tc	Pharma	75	Yes	V	48	13	14	14	0.77	0.52	0.79	0.50	1.61	0.44	0.70
Lima, 2002 (64)	255	Gated	Tc	Ex+Pharma	70	Yes	Q	187	12	25	31	0.88	0.72	0.94	0.55	3.16	0.16	0.85
Lin, 2006 (87)	40	Traditional	Dual	Dip	50	Yes	V	19	3	6	12	0.76	0.80	0.86	0.67	3.80	0.30	0.78
Links, 2000 (60)	69	Gated	Mixed	Ex+Pharma	50	Yes	V	43	8	8	10	0.84	0.56	0.84	0.56	1.90	0.28	0.77
	69	Gated+AC						45	1	6	17	0.88	0.94	0.98	0.74	15.88	0.12	0.90
Lipiec, 2008 (97)	103	Traditional	Tc	Dip	50	Yes	V+Q	79	5	10	9	0.89	0.64	0.94	0.47	2.49	0.17	0.85
Masood, 2005 (79)	118	Traditional	Tc	Ex+Pharma	50	No	V	80	14	6	18	0.93	0.56	0.85	0.75	2.13	0.12	0.83
	118	AC					V	81	13	5	19	0.94	0.59	0.86	0.79	2.32	0.10	0.85
	118	Traditional					Q1	60	11	26	21	0.70	0.66	0.85	0.45	2.03	0.46	0.69
	118	AC					Q1	67	4	19	28	0.78	0.88	0.94	0.60	6.23	0.25	0.81
	118	Traditional					Q2	58	7	28	25	0.67	0.78	0.89	0.47	3.08	0.42	0.70
	118	AC					Q2	60	7	26	25	0.70	0.78	0.90	0.49	3.19	0.39	0.72
Matsumoto, 2006 (88)	56	Gated	Tc	Ex+Pharma	50	Yes	SQ	22	1	4	29	0.85	0.97	0.96	0.88	25.38	0.16	0.91
McClellan, 1996 (25)	303	Traditional	Tl	Ex	50	Yes	V+Q	193	12	82	16	0.70	0.57	0.94	0.16	1.64	0.52	0.69
Michaelides, 1999 (26)	245	Traditional	Tl	Ex	70	No	V+Q	196	6	15	28	0.93	0.82	0.97	0.65	5.26	0.09	0.91

Author	N*	Type of SPECT	Tracer	Stress Agent	% Sten.	MI	Interp.	TP	FP	FN	TN	Sen.	Spe.	PPV	NPV	(+) LR	(-) LR	Acc.
Mieres, 2007 (92)	42	Gated	Tc/Dual	Ex+Ad	50	No	-	14	3	2	23	0.88	0.88	0.82	0.92	7.58	0.14	0.88
Miller, 1997 (43)	243	Traditional	Tc	Dip	50	Yes	V	185	29	18	11	0.91	0.28	0.86	0.38	1.26	0.32	0.81
Mohiuddin, 1996 (44)	202	Traditional	Tl	Ad	50	Yes	Q	144	6	16	36	0.90	0.86	0.96	0.69	6.30	0.12	0.89
Nallamothu, 1995 (27)	321	Traditional	Tl	Ex	50	-	V+Q	216	17	51	37	0.81	0.69	0.93	0.42	2.57	0.28	0.79
Ogilby, 1998 (55)	26	Traditional	Tc	Dip	50	Yes	V	18	0	2	6	0.90	1.00	1.00	0.75	90.00	0.10	0.92
Palmas, 1995 (33)	70	Traditional	Tc	Ex	50	Yes	V	60	1	6	3	0.91	0.75	0.98	0.33	3.64	0.12	0.90
Patsilinakos, 2004 (73)	75	Traditional	Tl	Ad	50	-	V	31	11	4	29	0.89	0.73	0.74	0.88	3.22	0.16	0.80
Peltier, 2004 (74)	35	Traditional	Tc	Dip	70	No	V+Q	18	2	4	11	0.82	0.85	0.90	0.73	5.32	0.21	0.83
Psirropoulos, 2002 (28)	301	Traditional	Tl	Ex	50	Yes	-	33	136	26	106	0.56	0.44	0.20	0.80	1.00	1.01	0.46
Rollan, 2002 (65)	54	Traditional	Tc	Dob	50	Yes	V	23	12	3	16	0.88	0.57	0.66	0.84	2.06	0.20	0.72
Rubello, 1995 (34)	120	Traditional	Tc	Ex	50	Yes	V	98	5	9	8	0.92	0.62	0.95	0.47	2.38	0.14	0.88
	120						Q	100	5	7	8	0.93	0.62	0.95	0.53	2.43	0.11	0.90
Sakuma, 2005 (80)	40	Traditional	Tl	Ex+Pharma	70	No	V	17	7	4	12	0.81	0.63	0.71	0.75	2.20	0.30	0.73
San Roman, 1998 (45)	92	Traditional	Tc	Dob	50	No	V	54	9	8	21	0.87	0.70	0.86	0.72	2.90	0.18	0.82
Santana-Boado, 1998 (30)	163	Traditional	Tc	Ex+Dip	50	No	V	88	7	8	60	0.92	0.90	0.93	0.88	8.77	0.09	0.91
Santoro, 1998 (46)	60	Traditional	Tc	Dip	70	No	V	32	3	1	24	0.97	0.89	0.91	0.96	8.73	0.03	0.93
	60			Dob				30	5	3	22	0.91	0.81	0.86	0.88	4.91	0.11	0.87
Schepis, 2007 (93)	77	Gated+AC	Tc	Ad	50	No	V+SQ	32	3	10	32	0.76	0.91	0.91	0.76	8.89	0.26	0.83
Schillaci, 1997 (47)	40	Traditional	Tc	Dip	70	No	Q	21	5	1	13	0.95	0.72	0.81	0.93	3.44	0.06	0.85
Senior, 2004 (75)	55	Traditional	Tc	Dob	50	No	V	21	1	22	11	0.49	0.92	0.95	0.33	5.86	0.56	0.58
Shelley, 2003 (69)	108	Gated	Tc	Ad	50	Yes	Q	64	8	0	36	1.00	0.82	0.89	1.00	5.50	0.00	0.93
Shirai, 2002 (29)	603	Gated	Tl	Ex	70	Yes	V	106	13	131	353	0.45	0.96	0.89	0.73	12.59	0.57	0.76
Slavich, 1996 (48)	46	Traditional	Tc	Dob	50	No	V	18	4	4	20	0.82	0.83	0.82	0.83	4.91	0.22	0.83
Slomka, 2006 (89)	174	Gated	Tc	Ex+Pharma	50	No	Q	115	7	22	30	0.84	0.81	0.94	0.58	4.44	0.20	0.83
	174	Gated+AC						117	10	20	27	0.85	0.73	0.92	0.57	3.16	0.20	0.83
Soman, 1997 (49)	27	Traditional	Tc	Dip	50	Yes	SQ	19	2	2	4	0.90	0.67	0.90	0.67	2.71	0.14	0.85
	27			Arb				21	2	0	4	1.00	0.67	0.91	1.00	3.00	0.00	0.93
Suzuki, 2008 (98)	90	Gated	Dual	Ex+Pharma	50	No	Q	58	5	5	22	0.92	0.81	0.92	0.81	4.97	0.10	0.89
Tadehara, 2008 (99)	101	Gated	Tc	Ad	50	Yes	V	50	14	4	33	0.93	0.70	0.78	0.89	3.11	0.11	0.82
Taillefer, 1997 (35)	48	Traditional	Tl	Ex	50	Yes	Q	24	8	8	8	0.75	0.50	0.75	0.50	1.50	0.50	0.67
	48		TC	Ex	50			23	3	9	13	0.72	0.81	0.88	0.59	3.83	0.35	0.75
	37		Tl	Dip	50			24	0	8	5	0.75	1.00	1.00	0.38	75.00	0.25	0.78
	37		TC	Dip	50			23	0	9	5	0.72	1.00	1.00	0.36	71.87	0.28	0.76
	48		Tl	Ex	70			22	10	6	10	0.79	0.50	0.69	0.63	1.57	0.43	0.67

Author	N*	Type of SPECT	Tracer	Stress Agent	% Sten.	MI	Interp.	TP	FP	FN	TN	Sen.	Spe.	PPV	NPV	(+) LR	(-) LR	Acc.
	48		TC	Ex	70			21	3	7	17	0.75	0.85	0.88	0.71	5.00	0.29	0.79
	37		Tl	Dip	70			21	4	2	10	0.91	0.71	0.84	0.83	3.20	0.12	0.84
	37		TC	Dip	70			20	3	3	11	0.87	0.79	0.87	0.79	4.06	0.17	0.84
	85		Tl	Ex/Dip	50			48	8	16	13	0.75	0.62	0.86	0.45	1.97	0.40	0.72
	85		TC	Ex/Dip	50			46	3	18	18	0.72	0.86	0.94	0.50	5.03	0.33	0.75
	85		Tl	Ex/Dip	70			43	14	8	20	0.84	0.59	0.75	0.71	2.05	0.27	0.74
	85		TC	Ex/Dip	70			41	6	10	28	0.80	0.82	0.87	0.74	4.56	0.24	0.81
Takeuchi, 1996 (50)	61	Traditional	Tl	Ex/Dip	50	No	V+Q	14	13	4	30	0.78	0.70	0.52	0.88	2.57	0.32	0.72
Thompson, 2005 (81)	116	Gated	Tc	Ex+Pharma	70	No	V	78	14	10	14	0.89	0.50	0.85	0.58	1.77	0.23	0.79
	116	Gated+AC						76	6	12	22	0.86	0.79	0.93	0.65	4.03	0.17	0.84
Tsai, 2002 (66)	86	Traditional	Tl	Ex	50	Yes	V	60	11	3	12	0.95	0.52	0.85	0.80	1.99	0.09	0.84
Watanabe, 1997 (51)	70	Traditional	Tl	Dip	50	Yes	V	34	8	7	21	0.83	0.72	0.81	0.75	3.01	0.24	0.79
	70			Ad				40	3	6	21	0.87	0.88	0.93	0.78	6.96	0.15	0.87
	140			Dip/Ad				74	11	13	42	0.85	0.79	0.87	0.76	4.10	0.19	0.83
Wolak, 2008a (103)	114	Gated	Tc	Ex+Ad	70	Yes	Q	55	12	14	33	0.80	0.73	0.82	0.70	2.99	0.28	0.77
	114	Gated+AC						56	12	13	33	0.81	0.73	0.82	0.72	3.04	0.26	0.78
Wolak, 2008b (104)	188	Traditional	Tc	Ex+Pharma	70	Yes	Q	124	13	19	32	0.87	0.71	0.91	0.63	3.00	0.19	0.83
Wu, 2009 (101)	218	Traditional	Tc	Dip	50	Yes	V	123	33	7	55	0.95	0.63	0.79	0.89	2.52	0.09	0.82
Yao, 2004 (76)	73	Traditional	Tc	Ex	50	No	-	28	3	7	35	0.80	0.92	0.90	0.83	10.13	0.22	0.86
Yeih, 2007 (94)	51	Traditional	Tl	Dob	50	Yes	V	20	3	8	20	0.71	0.87	0.87	0.71	5.48	0.33	0.78
Yoon, 2009 (102)	344	Traditional	Tc	Ad+Dip	70	-	-	191	83	28	42	0.87	0.34	0.70	0.60	1.31	0.38	0.68

* Sample analyzed
Blank rows below author indicate the presence of subgroups
Abbreviations: AC, attenuation correction; Ad, adenosine; Arb, arbutamine; Dip, dipyridamole; Dob, dobutamine; Dual, dual isotope; Ex, exercise; Interpret., method of SPECT interpretation; LR, likelihood ratio; MI, myocardial infarction; NPV, negative predictive value; Pharma, pharmacologic (agents not specified); PPV, positive predictive value; Q, quantitative; Q1, quantitative software 1; Q2, quantitative software 2; Sen., sensitivity; Spe., specificity; Sten., stenosis; SQ, semi-quantitative; Tc, technetium; Tl, thallium; V, visual

Appendix 3: Forest Plots of Sensitivity and Specificity for Included Studies

SPECT - AC

Study	TP	FP	FN	TN	Sensitivity	Specificity
Banzo 2007	39	14	12	34	0.76 [0.63, 0.87]	0.71 [0.56, 0.83]
Dondi 2004	100	2	8	20	0.93 [0.86, 0.97]	0.91 [0.71, 0.99]
Ficaro 1996	43	2	6	9	0.88 [0.75, 0.95]	0.82 [0.48, 0.98]
Gallowitsch 1998	50	5	3	49	0.94 [0.84, 0.99]	0.91 [0.80, 0.97]
Grossman 2004	35	15	4	20	0.90 [0.76, 0.97]	0.57 [0.39, 0.74]
Hambye 2004	63	3	23	11	0.73 [0.63, 0.82]	0.79 [0.49, 0.95]
Links 2000	45	1	6	17	0.88 [0.76, 0.96]	0.94 [0.73, 1.00]
Masood 2005	81	13	5	19	0.94 [0.87, 0.98]	0.59 [0.41, 0.76]
Schepis 2007	32	3	10	32	0.76 [0.61, 0.88]	0.91 [0.77, 0.98]
Slomka 2006	115	7	22	30	0.84 [0.77, 0.90]	0.81 [0.65, 0.92]
Thompson 2005	76	6	12	22	0.86 [0.77, 0.93]	0.79 [0.59, 0.92]
Wolak 2008a	56	12	13	33	0.81 [0.70, 0.90]	0.73 [0.58, 0.85]

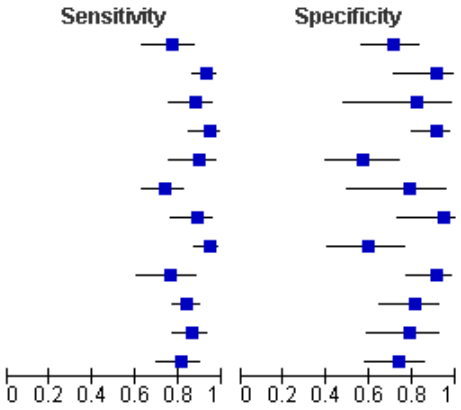


Figure A1: Forest plot of sensitivity and specificity for included AC SPECT studies

SPECT - Gated

Study	TP	FP	FN	TN	Sensitivity	Specificity
Berman 2006	186	9	39	56	0.83 [0.77, 0.87]	0.86 [0.75, 0.93]
Bokhari 2008	116	16	27	59	0.81 [0.74, 0.87]	0.79 [0.68, 0.87]
Emmett 2002	62	11	8	19	0.89 [0.79, 0.95]	0.63 [0.44, 0.80]
Grossman 2004	38	25	1	10	0.97 [0.87, 1.00]	0.29 [0.15, 0.46]
Hambye 2004	60	3	26	11	0.70 [0.59, 0.79]	0.79 [0.49, 0.95]
Hida 2009	32	7	30	50	0.52 [0.39, 0.65]	0.88 [0.76, 0.95]
Hung 2006	75	16	6	29	0.93 [0.85, 0.97]	0.64 [0.49, 0.78]
Johansen 2005	94	48	32	183	0.75 [0.66, 0.82]	0.79 [0.73, 0.84]
Lima 2002	187	12	25	31	0.88 [0.83, 0.92]	0.72 [0.56, 0.85]
Links 2000	43	8	8	10	0.84 [0.71, 0.93]	0.56 [0.31, 0.78]
Matsumoto 2006	22	1	4	29	0.85 [0.65, 0.96]	0.97 [0.83, 1.00]
Mieres 2007	14	3	2	23	0.88 [0.62, 0.98]	0.88 [0.70, 0.98]
Shelley 2003	64	0	8	36	0.89 [0.79, 0.95]	1.00 [0.90, 1.00]
Shirai 2002	37	7	36	121	0.51 [0.39, 0.63]	0.95 [0.89, 0.98]
Slomka 2006	117	10	20	27	0.85 [0.78, 0.91]	0.73 [0.56, 0.86]
Suzuki 2008	58	5	5	22	0.92 [0.82, 0.97]	0.81 [0.62, 0.94]
Tadehara 2008	50	14	4	33	0.93 [0.82, 0.98]	0.70 [0.55, 0.83]
Thompson 2005	78	14	10	14	0.89 [0.80, 0.94]	0.50 [0.31, 0.69]
Wolak 2008a	55	12	14	33	0.80 [0.68, 0.88]	0.73 [0.58, 0.85]

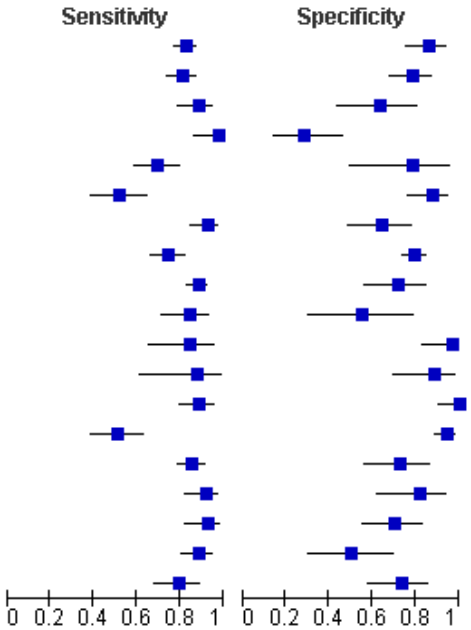


Figure A2: Forest plot of sensitivity and specificity for included ECG-gated SPECT studies

SPECT - Traditional

Study	TP	FP	FN	TN	Sensitivity	Specificity
Aggeli 2007	24	1	6	17	0.80 [0.61, 0.92]	0.94 [0.73, 1.00]
Amanullah 1997	159	14	12	37	0.93 [0.88, 0.96]	0.73 [0.58, 0.84]
Astarita 2001	23	16	0	14	1.00 [0.85, 1.00]	0.47 [0.28, 0.66]
Banzo 2007	47	26	4	22	0.92 [0.81, 0.98]	0.46 [0.31, 0.61]
Benoit 1996	55	1	8	8	0.87 [0.77, 0.94]	0.89 [0.52, 1.00]
Chammas 2002	30	6	4	18	0.88 [0.73, 0.97]	0.75 [0.53, 0.90]
Cramer 1996	23	1	6	5	0.79 [0.60, 0.92]	0.83 [0.36, 1.00]
Daou 2002	167	17	98	56	0.63 [0.57, 0.69]	0.77 [0.65, 0.86]
De 2002	8	26	4	11	0.67 [0.35, 0.90]	0.30 [0.16, 0.47]
DiBello 1996	33	1	5	6	0.87 [0.72, 0.96]	0.86 [0.42, 1.00]
Dondi 2004	104	6	4	16	0.96 [0.91, 0.99]	0.73 [0.50, 0.89]
Elhendy 1998	29	7	16	18	0.64 [0.49, 0.78]	0.72 [0.51, 0.88]
Elhendy 2006	44	7	9	28	0.83 [0.70, 0.92]	0.80 [0.63, 0.92]
Ficaro 1996	41	6	8	5	0.84 [0.70, 0.93]	0.45 [0.17, 0.77]
Fragasso 1999	56	28	1	16	0.98 [0.91, 1.00]	0.36 [0.22, 0.52]
Gallowitsch 1998	42	11	11	43	0.79 [0.66, 0.89]	0.80 [0.66, 0.89]
Gentile 2001	101	11	7	13	0.94 [0.87, 0.97]	0.54 [0.33, 0.74]
Gonzalez 2005	102	12	15	16	0.87 [0.80, 0.93]	0.57 [0.37, 0.76]
Groutars 2003	102	6	6	9	0.94 [0.88, 0.98]	0.60 [0.32, 0.84]
Hannoush 2003	40	4	1	6	0.98 [0.87, 1.00]	0.60 [0.26, 0.88]
He 2002	33	3	1	14	0.97 [0.85, 1.00]	0.82 [0.57, 0.96]
He 2003	18	0	4	4	0.82 [0.60, 0.95]	1.00 [0.40, 1.00]
Heiba 1997	28	1	2	3	0.93 [0.78, 0.99]	0.75 [0.19, 0.99]
Ho 1995	29	3	9	10	0.76 [0.60, 0.89]	0.77 [0.46, 0.95]
Ho 1997	42	3	1	8	0.98 [0.88, 1.00]	0.73 [0.39, 0.94]
Huang 1997	53	8	12	37	0.82 [0.70, 0.90]	0.82 [0.68, 0.92]
Huang 1998	60	5	7	21	0.90 [0.80, 0.96]	0.81 [0.61, 0.93]
Iftikhar 1996	22	1	6	9	0.79 [0.59, 0.92]	0.90 [0.55, 1.00]
Jeetley 2006	79	13	17	14	0.82 [0.73, 0.89]	0.52 [0.32, 0.71]
Kajinami 1995	110	48	23	70	0.83 [0.75, 0.89]	0.59 [0.50, 0.68]
Katayama 2008	17	7	5	17	0.77 [0.55, 0.92]	0.71 [0.49, 0.87]
Khattar 1998	41	11	19	29	0.68 [0.55, 0.80]	0.72 [0.56, 0.85]
Kisacik 1996	45	8	2	14	0.96 [0.85, 0.99]	0.64 [0.41, 0.83]
Korosoglou 2006	48	13	14	14	0.77 [0.65, 0.87]	0.52 [0.32, 0.71]
Lin 2006	19	3	6	12	0.76 [0.55, 0.91]	0.80 [0.52, 0.96]
Lipiec 2008	79	5	10	9	0.89 [0.80, 0.94]	0.64 [0.35, 0.87]
Masood 2005	80	14	6	18	0.93 [0.85, 0.97]	0.56 [0.38, 0.74]
McClellan 1996	193	12	82	16	0.70 [0.64, 0.76]	0.57 [0.37, 0.76]
Michaelides 1999	196	6	15	28	0.93 [0.89, 0.96]	0.82 [0.65, 0.93]
Miller 1997	185	29	18	11	0.91 [0.86, 0.95]	0.28 [0.15, 0.44]
Mohiuddin 1996	144	6	16	36	0.90 [0.84, 0.94]	0.86 [0.71, 0.95]
Nallamothu 1995	216	17	51	37	0.81 [0.76, 0.85]	0.69 [0.54, 0.80]
Ogilby 1998	18	0	2	6	0.90 [0.68, 0.99]	1.00 [0.54, 1.00]
Palmas 1995	60	1	6	3	0.91 [0.81, 0.97]	0.75 [0.19, 0.99]
Patsilinakos 2004	31	11	4	29	0.89 [0.73, 0.97]	0.72 [0.56, 0.85]
Peltier 2004	18	2	4	11	0.82 [0.60, 0.95]	0.85 [0.55, 0.98]
Psirropoulos 2002	33	136	26	106	0.56 [0.42, 0.69]	0.44 [0.37, 0.50]
Rollan 2002	23	12	3	16	0.88 [0.70, 0.98]	0.57 [0.37, 0.76]
Rubello 1995	100	5	7	8	0.93 [0.87, 0.97]	0.62 [0.32, 0.86]
Sakuma 2005	17	7	4	12	0.81 [0.58, 0.95]	0.63 [0.38, 0.84]
San Roman 1998	54	9	8	21	0.87 [0.76, 0.94]	0.70 [0.51, 0.85]
Santana-Boado 1998	88	7	8	60	0.92 [0.84, 0.96]	0.90 [0.80, 0.96]
Santoro 1998	30	5	3	22	0.91 [0.76, 0.98]	0.81 [0.62, 0.94]
Schillaci 1997	21	5	1	13	0.95 [0.77, 1.00]	0.72 [0.47, 0.90]
Senior 2004	21	1	22	11	0.49 [0.33, 0.65]	0.92 [0.62, 1.00]
Slavich 1996	18	4	4	20	0.82 [0.60, 0.95]	0.83 [0.63, 0.95]
Soman 1997	19	2	2	4	0.90 [0.70, 0.99]	0.67 [0.22, 0.96]
Taillefer 1997	48	8	16	13	0.75 [0.63, 0.85]	0.62 [0.38, 0.82]
Takeuchi 1996	14	13	4	30	0.78 [0.52, 0.94]	0.70 [0.54, 0.83]
Tsai 2002	60	11	3	12	0.95 [0.87, 0.99]	0.52 [0.31, 0.73]
Watanabe 1997	74	11	13	42	0.85 [0.76, 0.92]	0.79 [0.66, 0.89]
Wolak 2008b	124	13	19	32	0.87 [0.80, 0.92]	0.71 [0.56, 0.84]
Wu 2009	123	33	7	55	0.95 [0.89, 0.98]	0.63 [0.52, 0.73]
Yao 2004	28	3	7	35	0.80 [0.63, 0.92]	0.92 [0.79, 0.98]
Yeih 2007	20	3	8	20	0.71 [0.51, 0.87]	0.87 [0.66, 0.97]
Yoon 2009	191	83	28	42	0.87 [0.82, 0.91]	0.34 [0.25, 0.43]

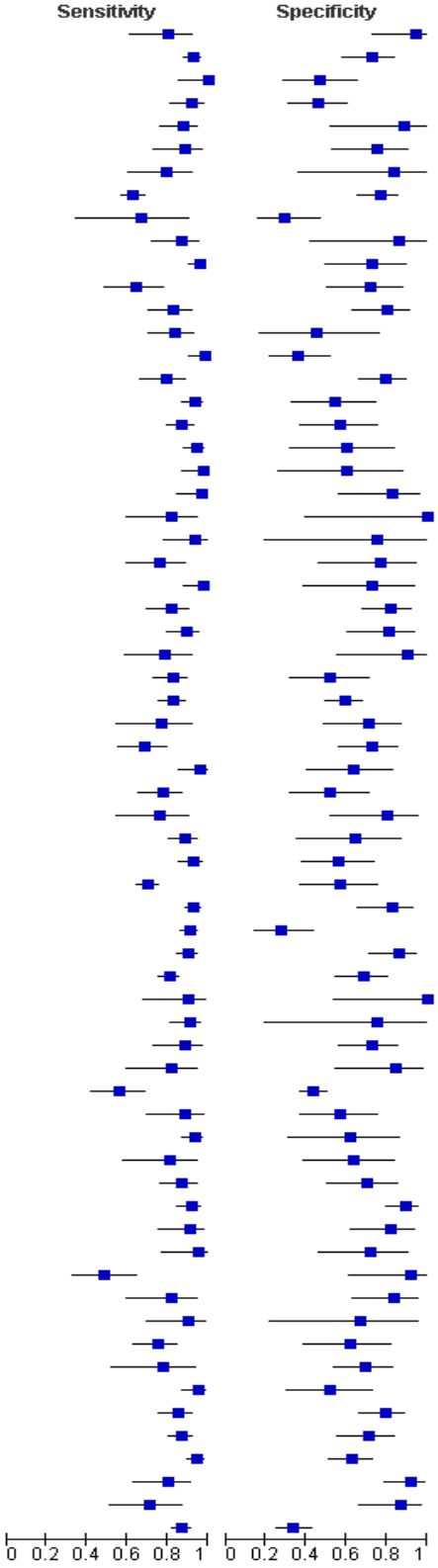
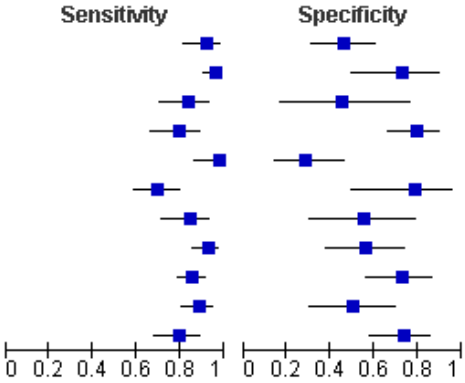


Figure A3: Forest plot of sensitivity and specificity for included traditional SPECT studies

SPECT - Non-AC (Direct)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Banzo 2007	47	26	4	22	0.92 [0.81, 0.98]	0.46 [0.31, 0.61]
Dondi 2004	102	6	4	16	0.96 [0.91, 0.99]	0.73 [0.50, 0.89]
Ficaro 1996	41	6	8	5	0.84 [0.70, 0.93]	0.45 [0.17, 0.77]
Gallowitsch 1998	42	11	11	43	0.79 [0.66, 0.89]	0.80 [0.66, 0.89]
Grossman 2004	38	25	1	10	0.97 [0.87, 1.00]	0.29 [0.15, 0.46]
Hambye 2004	60	3	26	11	0.70 [0.59, 0.79]	0.79 [0.49, 0.95]
Links 2000	43	8	8	10	0.84 [0.71, 0.93]	0.56 [0.31, 0.78]
Masood 2005	80	14	6	18	0.93 [0.85, 0.97]	0.56 [0.38, 0.74]
Slomka 2006	117	10	20	27	0.85 [0.78, 0.91]	0.73 [0.56, 0.86]
Thompson 2005	78	14	10	14	0.89 [0.80, 0.94]	0.50 [0.31, 0.69]
Wolak 2008a	55	12	14	33	0.80 [0.68, 0.88]	0.73 [0.58, 0.85]



SPECT - AC (Direct)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Banzo 2007	39	14	12	34	0.76 [0.63, 0.87]	0.71 [0.56, 0.83]
Dondi 2004	100	2	8	20	0.93 [0.86, 0.97]	0.91 [0.71, 0.99]
Ficaro 1996	43	2	6	9	0.88 [0.75, 0.95]	0.82 [0.48, 0.98]
Gallowitsch 1998	50	5	3	49	0.94 [0.84, 0.99]	0.91 [0.80, 0.97]
Grossman 2004	35	15	4	20	0.90 [0.76, 0.97]	0.57 [0.39, 0.74]
Hambye 2004	63	3	23	11	0.73 [0.63, 0.82]	0.79 [0.49, 0.95]
Links 2000	45	1	6	17	0.88 [0.76, 0.96]	0.94 [0.73, 1.00]
Masood 2005	81	13	5	19	0.94 [0.87, 0.98]	0.59 [0.41, 0.76]
Slomka 2006	115	7	22	30	0.84 [0.77, 0.90]	0.81 [0.65, 0.92]
Thompson 2005	76	6	12	22	0.86 [0.77, 0.93]	0.79 [0.59, 0.92]
Wolak 2008a	56	12	13	33	0.81 [0.70, 0.90]	0.73 [0.58, 0.85]

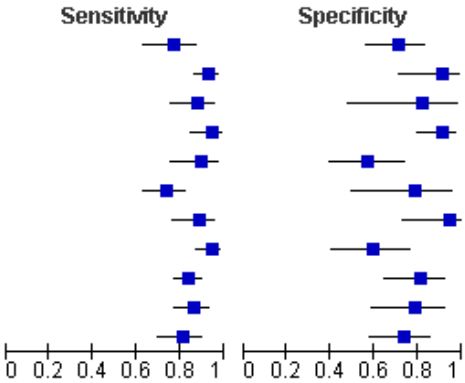
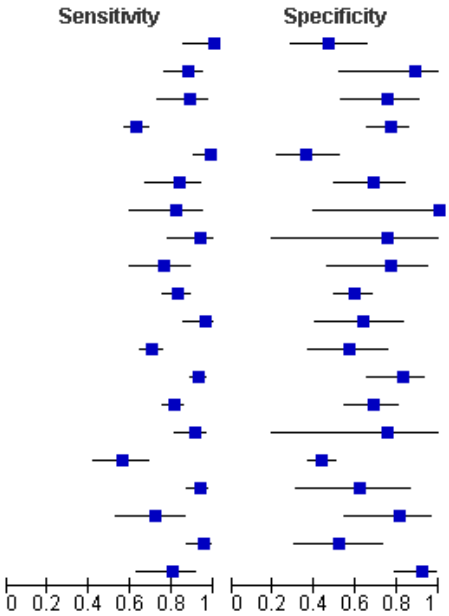


Figure A4: Forest plot of sensitivity and specificity of AC vs .non-AC SPECT trials

SPECT - Exercise

Study	TP	FP	FN	TN	Sensitivity	Specificity
Astarita 2001	23	16	0	14	1.00 [0.85, 1.00]	0.47 [0.28, 0.66]
Benoit 1996	55	1	8	8	0.87 [0.77, 0.94]	0.89 [0.52, 1.00]
Chammas 2002	30	6	4	18	0.88 [0.73, 0.97]	0.75 [0.53, 0.90]
Daou 2002	167	17	98	56	0.63 [0.57, 0.69]	0.77 [0.65, 0.86]
Emmett 2002	56	28	1	16	0.98 [0.91, 1.00]	0.36 [0.22, 0.52]
Fragasso 1999	30	10	6	22	0.83 [0.67, 0.94]	0.69 [0.50, 0.84]
Gallowitsch 1998	18	0	4	4	0.82 [0.60, 0.95]	1.00 [0.40, 1.00]
He 2003	28	1	2	3	0.93 [0.78, 0.99]	0.75 [0.19, 0.99]
Heiba 1997	29	3	9	10	0.76 [0.60, 0.89]	0.77 [0.46, 0.95]
Ho 1997	110	48	23	70	0.83 [0.75, 0.89]	0.59 [0.50, 0.68]
Kajinami 1995	45	8	2	14	0.96 [0.85, 0.99]	0.64 [0.41, 0.83]
McClellan 1996	193	12	82	16	0.70 [0.64, 0.76]	0.57 [0.37, 0.76]
Michaelides 1999	196	6	15	28	0.93 [0.89, 0.96]	0.82 [0.65, 0.93]
Nallamothu 1995	216	17	51	37	0.81 [0.76, 0.85]	0.69 [0.54, 0.80]
Palmas 1995	60	1	6	3	0.91 [0.81, 0.97]	0.75 [0.19, 0.99]
Psirropoulos 2002	33	136	26	106	0.56 [0.42, 0.69]	0.44 [0.37, 0.50]
Rubello 1995	100	5	7	8	0.93 [0.87, 0.97]	0.62 [0.32, 0.86]
Taillefer 1997	23	3	9	13	0.72 [0.53, 0.86]	0.81 [0.54, 0.96]
Tsai 2002	60	11	3	12	0.95 [0.87, 0.99]	0.52 [0.31, 0.73]
Yao 2004	28	3	7	35	0.80 [0.63, 0.92]	0.92 [0.79, 0.98]



SPECT - Pharmacologic

Study	TP	FP	FN	TN	Sensitivity	Specificity
Aggeli 2007	24	1	6	17	0.80 [0.61, 0.92]	0.94 [0.73, 1.00]
Amanullah 1997	159	14	12	37	0.93 [0.88, 0.96]	0.73 [0.58, 0.84]
Cramer 1996	23	1	6	5	0.79 [0.60, 0.92]	0.83 [0.36, 1.00]
DiBello 1996	33	1	5	6	0.87 [0.72, 0.96]	0.86 [0.42, 1.00]
Elhendy 1998	29	7	16	18	0.64 [0.49, 0.78]	0.72 [0.51, 0.88]
Gallowitsch 1998	12	1	5	21	0.71 [0.44, 0.90]	0.95 [0.77, 1.00]
He 2002	33	3	1	14	0.97 [0.85, 1.00]	0.82 [0.57, 0.96]
Ho 1995	42	3	1	8	0.98 [0.88, 1.00]	0.73 [0.39, 0.94]
Huang 1997	53	8	12	37	0.82 [0.70, 0.90]	0.82 [0.68, 0.92]
Huang 1998	60	5	7	21	0.90 [0.80, 0.96]	0.81 [0.61, 0.93]
Jeetley 2006	22	1	6	9	0.79 [0.59, 0.92]	0.90 [0.55, 1.00]
Khattar 1998	79	13	17	14	0.82 [0.73, 0.89]	0.52 [0.32, 0.71]
Korosoglou 2006	41	11	19	29	0.68 [0.55, 0.80]	0.72 [0.56, 0.85]
Lin 2006	48	13	14	14	0.77 [0.65, 0.87]	0.52 [0.32, 0.71]
Links 2000	19	3	6	12	0.76 [0.55, 0.91]	0.80 [0.52, 0.96]
Lipiec 2008	79	5	10	9	0.89 [0.80, 0.94]	0.64 [0.35, 0.87]
Miller 1997	185	29	18	11	0.91 [0.86, 0.95]	0.28 [0.15, 0.44]
Mohiuddin 1996	144	6	16	36	0.90 [0.84, 0.94]	0.86 [0.71, 0.95]
Ogilby 1998	18	0	2	6	0.90 [0.68, 0.99]	1.00 [0.54, 1.00]
Patsilinakos 2004	31	11	4	29	0.89 [0.73, 0.97]	0.72 [0.56, 0.85]
Peltier 2004	18	2	4	11	0.82 [0.60, 0.95]	0.85 [0.55, 0.98]
Rollan 2002	23	12	3	16	0.88 [0.70, 0.98]	0.57 [0.37, 0.76]
San Roman 1998	54	9	8	21	0.87 [0.76, 0.94]	0.70 [0.51, 0.85]
Santoro 1998	62	8	4	46	0.94 [0.85, 0.98]	0.85 [0.73, 0.93]
Schillaci 1997	21	5	1	13	0.95 [0.77, 1.00]	0.72 [0.47, 0.90]
Senior 2004	21	1	22	11	0.49 [0.33, 0.65]	0.92 [0.62, 1.00]
Slavich 1996	18	4	4	20	0.82 [0.60, 0.95]	0.83 [0.63, 0.95]
Soman 1997	40	4	2	8	0.95 [0.84, 0.99]	0.67 [0.35, 0.90]
Taillefer 1997	47	0	17	10	0.73 [0.61, 0.84]	1.00 [0.69, 1.00]
Watanabe 1997	74	11	13	42	0.85 [0.76, 0.92]	0.79 [0.66, 0.89]
Wu 2009	123	33	7	55	0.95 [0.89, 0.98]	0.63 [0.52, 0.73]
Yeih 2007	20	3	8	20	0.71 [0.51, 0.87]	0.87 [0.66, 0.97]
Yoon 2009	191	83	28	42	0.87 [0.82, 0.91]	0.34 [0.25, 0.43]

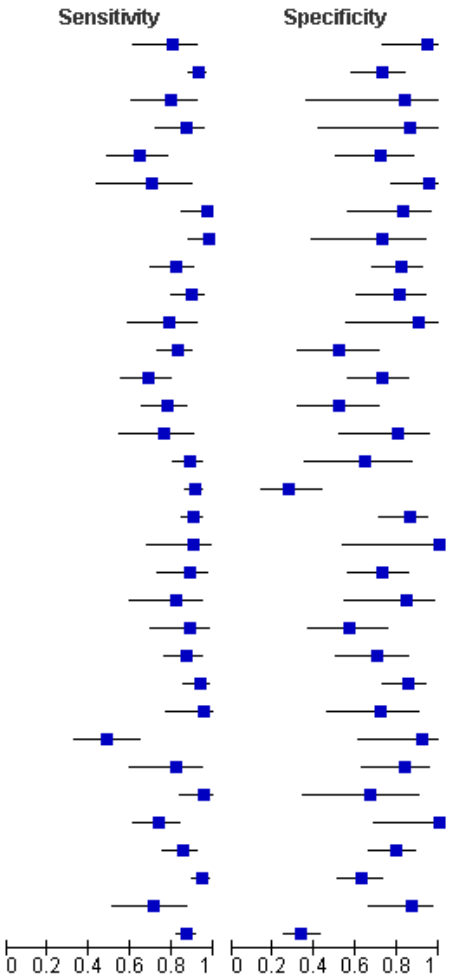
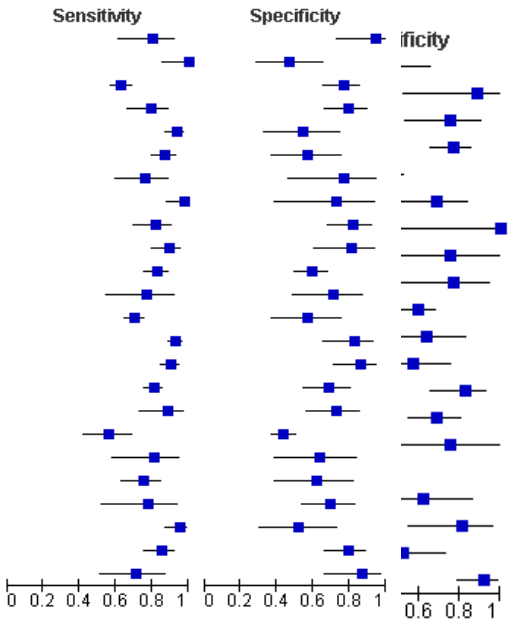


Figure A5: Forest plot of sensitivity and specificity of SPECT by stress agent

SPECT - Thallium

Study	TP	FP	FN	TN	Sensitivity	Specificity
Aggeli 2007	24	1	6	17	0.80 [0.61, 0.92]	0.94 [0.73, 1.00]
Astarita 2001	23	16	0	14	1.00 [0.85, 1.00]	0.47 [0.28, 0.66]
Daou 2002	167	17	98	56	0.63 [0.57, 0.69]	0.77 [0.65, 0.86]
Gallowitsch 1998	42	11	11	43	0.79 [0.66, 0.89]	0.80 [0.66, 0.89]
Gentile 2001	101	11	7	13	0.94 [0.87, 0.97]	0.54 [0.33, 0.74]
Gonzalez 2005	102	12	15	16	0.87 [0.80, 0.93]	0.57 [0.37, 0.76]
Ho 1995	29	3	9	10	0.76 [0.60, 0.89]	0.77 [0.46, 0.95]
Ho 1997	42	3	1	8	0.98 [0.88, 1.00]	0.73 [0.39, 0.94]
Huang 1997	53	8	12	37	0.82 [0.70, 0.90]	0.82 [0.68, 0.92]
Huang 1998	60	5	7	21	0.90 [0.80, 0.96]	0.81 [0.61, 0.93]
Kajinami 1995	110	48	23	70	0.83 [0.75, 0.89]	0.59 [0.50, 0.68]
Katayama 2008	17	7	5	17	0.77 [0.55, 0.92]	0.71 [0.49, 0.87]
McClellan 1996	193	12	82	16	0.70 [0.64, 0.76]	0.57 [0.37, 0.76]
Michaelides 1999	196	6	15	28	0.93 [0.89, 0.96]	0.82 [0.65, 0.93]
Mohiuddin 1996	144	6	16	36	0.90 [0.84, 0.94]	0.86 [0.71, 0.95]
Nallamothu 1995	216	17	51	37	0.81 [0.76, 0.85]	0.69 [0.54, 0.80]
Patsilinakos 2004	31	11	4	29	0.89 [0.73, 0.97]	0.72 [0.56, 0.85]
Psirropoulos 2002	33	136	26	106	0.56 [0.42, 0.69]	0.44 [0.37, 0.50]
Sakuma 2005	17	7	4	12	0.81 [0.58, 0.95]	0.63 [0.38, 0.84]
Taillefer 1997	48	8	16	13	0.75 [0.63, 0.85]	0.62 [0.38, 0.82]
Takeuchi 1996	14	13	4	30	0.78 [0.52, 0.94]	0.70 [0.54, 0.83]
Tsai 2002	60	11	3	12	0.95 [0.87, 0.99]	0.52 [0.31, 0.73]
Watanabe 1997	74	11	13	42	0.85 [0.76, 0.92]	0.79 [0.66, 0.89]
Yeih 2007	20	3	8	20	0.71 [0.51, 0.87]	0.87 [0.66, 0.97]



SPECT - Technetium

Study	TP	FP	FN	TN	Sensitivity	Specificity
Banzo 2007	47	26	4	22	0.92 [0.81, 0.98]	0.46 [0.31, 0.61]
Benoit 1996	55	1	8	8	0.87 [0.77, 0.94]	0.89 [0.52, 1.00]
Chammas 2002	30	6	4	18	0.88 [0.73, 0.97]	0.75 [0.53, 0.90]
Cramer 1996	23	1	6	5	0.79 [0.60, 0.92]	0.83 [0.36, 1.00]
De 2002	8	26	4	11	0.67 [0.35, 0.90]	0.30 [0.16, 0.47]
DiBello 1996	33	1	5	6	0.87 [0.72, 0.96]	0.86 [0.42, 1.00]
Dondi 2004	104	6	4	16	0.96 [0.91, 0.99]	0.73 [0.50, 0.89]
Elhendy 1998	29	7	16	18	0.64 [0.49, 0.78]	0.72 [0.51, 0.88]
Elhendy 2006	44	7	9	28	0.83 [0.70, 0.92]	0.80 [0.63, 0.92]
Fragasso 1999	56	28	1	16	0.98 [0.91, 1.00]	0.36 [0.22, 0.52]
Hannoush 2003	40	4	1	6	0.98 [0.87, 1.00]	0.60 [0.26, 0.88]
He 2002	33	3	1	14	0.97 [0.85, 1.00]	0.82 [0.57, 0.96]
He 2003	18	0	4	4	0.82 [0.60, 0.95]	1.00 [0.40, 1.00]
Heiba 1997	28	1	2	3	0.93 [0.78, 0.99]	0.75 [0.19, 0.99]
Iftikhar 1996	22	1	6	9	0.79 [0.59, 0.92]	0.90 [0.55, 1.00]
Jeetley 2006	79	13	17	14	0.82 [0.73, 0.89]	0.52 [0.32, 0.71]
Khattar 1998	41	11	19	29	0.68 [0.55, 0.80]	0.72 [0.56, 0.85]
Kisacik 1996	45	8	2	14	0.96 [0.85, 0.99]	0.64 [0.41, 0.83]
Korosoglou 2006	48	13	14	14	0.77 [0.65, 0.87]	0.52 [0.32, 0.71]
Lipiec 2008	79	5	10	9	0.89 [0.80, 0.94]	0.64 [0.35, 0.87]
Masood 2005	80	14	6	18	0.93 [0.85, 0.97]	0.56 [0.38, 0.74]
Miller 1997	185	29	18	11	0.91 [0.86, 0.95]	0.28 [0.15, 0.44]
Ogilby 1998	18	0	2	6	0.90 [0.68, 0.99]	1.00 [0.54, 1.00]
Palmas 1995	60	1	6	3	0.91 [0.81, 0.97]	0.75 [0.19, 0.99]
Peltier 2004	18	2	4	11	0.82 [0.60, 0.95]	0.85 [0.55, 0.98]
Rollan 2002	23	12	3	16	0.88 [0.70, 0.98]	0.57 [0.37, 0.76]
Rubello 1995	100	5	7	8	0.93 [0.87, 0.97]	0.62 [0.32, 0.86]
San Roman 1998	54	9	8	21	0.87 [0.76, 0.94]	0.70 [0.51, 0.85]
Santana-Boado 1998	88	7	8	60	0.92 [0.84, 0.96]	0.90 [0.80, 0.96]
Santoro 1998	30	5	3	22	0.91 [0.76, 0.98]	0.81 [0.62, 0.94]
Schillaci 1997	21	5	1	13	0.95 [0.77, 1.00]	0.72 [0.47, 0.90]
Senior 2004	21	1	22	11	0.49 [0.33, 0.65]	0.92 [0.62, 1.00]
Slavich 1996	18	4	4	20	0.82 [0.60, 0.95]	0.83 [0.63, 0.95]
Soman 1997	19	2	2	4	0.90 [0.70, 0.99]	0.67 [0.22, 0.96]
Taillefer 1997	46	3	18	18	0.72 [0.59, 0.82]	0.86 [0.64, 0.97]
Wolak 2008b	124	13	19	32	0.87 [0.80, 0.92]	0.71 [0.56, 0.84]
Wu 2009	123	33	7	55	0.95 [0.89, 0.98]	0.63 [0.52, 0.73]
Yao 2004	28	3	7	35	0.80 [0.63, 0.92]	0.92 [0.79, 0.98]
Yoon 2009	191	83	28	42	0.87 [0.82, 0.91]	0.34 [0.25, 0.43]

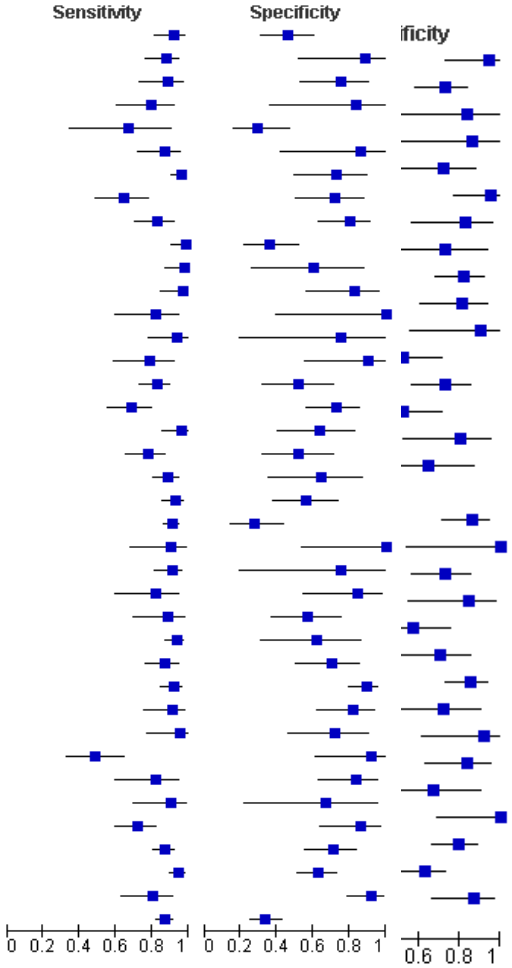


Figure A6: Forest plot of sensitivity and specificity of SPECT radioactive tracer

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