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Non-Invasive Cardiac Imaging Technologies for the Assessment of Myocardial Viability

A Summary of Evidence-Based Analyses

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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).

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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.

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List of Abbreviations

AUC	Area under the curve
CAD	Coronary artery disease
CI	Confidence interval(s)
Cardiac MRI	Cardiac magnetic resonance imaging
CT	Computed tomography
ECHO	echocardiography
FDG	F-18-Flurodeoxyglucose
LV	Left ventricular
LVEF	Left ventricular ejection fraction
MI	Myocardial infarction
MRI	Magnetic resonance imaging
NPV	Negative predictive value
PET	Positron emission tomography
PPV	Positive predictive value
RCT	Randomized controlled trial
SPECT	Single-photon emission computed tomography
SR	Systematic review
SD	Standard deviation
sROC	Summary receiver operating characteristic

Background

In July 2009, the Medical Advisory Secretariat (MAS) began work on Non-Invasive Cardiac Imaging Technologies for the Assessment of Myocardial Viability, an evidence-based review of the literature surrounding different cardiac imaging modalities to ensure that appropriate technologies are accessed by patients undergoing viability assessment. 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 that can be used for the assessment of myocardial viability: positron emission tomography, cardiac magnetic resonance imaging, dobutamine echocardiography, and dobutamine echocardiography with contrast, and single photon emission computed tomography.

A 2005 review conducted by MAS determined that positron emission tomography was more sensitivity than dobutamine echocardiography and single photon emission tomography and dominated the other imaging modalities from a cost-effective standpoint. However, there was inadequate evidence to compare positron emission tomography and cardiac magnetic resonance imaging. Thus, this report focuses on this comparison only. For both technologies, an economic analysis was also completed.

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 Assessment of Myocardial Viability 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. 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

Objective of Analysis

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

Clinical Need and Target Population

Left Ventricular Systolic Dysfunction and Heart Failure

Heart failure is a complex syndrome characterized by the heart's inability to maintain adequate blood circulation through the body leading to multiorgan abnormalities and, eventually, death. Patients with heart failure experience poor functional capacity, decreased quality of life, and increased risk of morbidity and mortality. (1)

In 2005, more than 71,000 Canadians died from cardiovascular disease, of which, 54% were due to ischemic heart disease. (2) Left ventricular (LV) systolic dysfunction due to coronary artery disease (CAD) [1] is the primary cause of heart failure accounting for more than 70% of cases. (1;3;4) The prevalence of heart failure was estimated at one percent of the Canadian population in 1989. (5) Since then, the increase in the older population has undoubtedly resulted in a substantial increase in cases.

[1] Coronary artery disease (CAD) occurs when plaque builds up in the coronary arteries leading to stenosis and reducing coronary blood flow and oxygen deliver to the myocardium.

Heart failure is associated with a poor prognosis: one-year mortality rates were 32.9% and 31.1% for men and women, respectively in Ontario between 1996 and 1997. (1)

Treatment Options

In general, there are three options for the treatment of heart failure: medical treatment, heart transplantation, and revascularization for those with CAD as the underlying cause. Despite advances in medical treatment such as the introduction of angiotensin converting enzyme (ACE) inhibitors, angiotensin II inhibitors, β-blockers, spironolactone, and aldosterone antagonists, mortality is still high among patients with heart failure. (4;6;7) While heart transplantation improves long-term prognosis, there are inadequate donor hearts and consequently long waiting lists for transplantation. (4) The third option, revascularization, is a surgical procedure that is used to restore the flow of blood to the heart. This can be achieved by coronary artery bypass grafting (CABG) or minimally invasive percutaneous coronary interventions which include balloon angioplasty and/or stenting. Both methods, however, are associated with important perioperative risks including mortality, so it is essential to properly select patients for this procedure.

Myocardial Viability

Left ventricular dysfunction may be permanent, due to the formation of myocardial scar, or it may be reversible after revascularization. Reversible LV dysfunction occurs when the myocardium is viable but dysfunctional (reduced contractility). There are two types of dysfunctional but viable myocardium: stunned myocardium and hibernating myocardium. Stunned myocardium is characterized by reduced contractile function in the presence of normal (or near normal) resting perfusion. (3) This is caused by short periods of ischemia followed by restoration of perfusion (e.g. after an episode of unstable angina or after ischemia induced by exercise testing). The myocardium may be dysfunctional for several days, but after perfusion returns to normal, function is eventually restored. (7)

Prolonged or repetitive reductions in perfusion may lead to a state of chronically dysfunctional but viable myocardium also known as hibernating myocardium. Hibernating myocardium is characterized by reduced contractile function but maintained cell viability (intact cell membrane and cell metabolism) in areas with reduced perfusion. (3;8) In contrast to stunned myocardium, hibernating myocardium does not recover function spontaneously; it may, however, recover function after restoration of normal blood flow following coronary revascularization. (3;7)

Since patients with dysfunctional but viable myocardium benefit from revascularization, the identification and quantification of the extent of myocardial viability is an important part of the work-up of patients with heart failure to determine the most appropriate treatment path. (9) Various non-invasive cardiac imaging modalities can be used to assess patients in whom determination of viability is an important clinical issue:

- dobutamine echocardiography (echo),
- stress echo with contrast,
- single photon emission computed tomography (SPECT) using either technetium or thallium,
- cardiac magnetic resonance imaging (cardiac MRI), and
- positron emission tomography (PET).

Dobutamine Echocardiography

Stress echocardiography can be used to detect viable myocardium. Stress can be induced using exercise or pharmacological agents. Since imaging is difficult during exercise, pharmacologic agents, particularly dobutamine, are most commonly used. (7) During the infusion of low dose dobutamine (5 – 10 ug/kg/min), an improvement of contractility in hypokinetic and akentic segments is indicative of the presence of viable myocardium. (3;7;9) Alternatively, a low-high dose dobutamine protocol can be used in which a biphasic response characterized by improved contractile function during the low-dose infusion followed by a deterioration in contractility due to stress induced ischemia during the high dose dobutamine infusion (dobutamine dose up to 40 ug/kg/min) represents viable tissue. (3;7;9;10) Newer techniques including echocardiography using contrast agents, harmonic imaging, and power doppler imaging may help to improve the diagnostic accuracy of echocardiographic assessment of myocardial viability. (3;9;10)

Stress Echocardiography with Contrast

Intravenous contrast agents, which are high molecular weight inert gas microbubbles that act like red blood cells in the vascular space, can be used during echocardiography to assess myocardial viability. (3;9) The contrast agent allows for the assessment of myocardial blood flow (perfusion) as well as the assessment of contractile function (as described above), and the simultaneous assessment of perfusion makes it possible to distinguish between stunned and hibernating myocardium. (3)

Single Photon Emission Computed Tomography

SPECT can be performed using thallium-201 (Tl-201), a potassium analogue, or technetium-99 m labelled tracers. When Tl-201 is injected intravenously into a patient, it is taken up by the myocardial cells through regional perfusion, and Tl-201 is retained in the cell due to sodium/potassium ATPase pumps in the myocyte membrane. (3;9) The two most common methods of assessing viability using Tl-201 SPECT imaging are stress-redistribution-reinjection and rest-redistribution. The former protocol involves three sets of images. The first two image sets (taken immediately after stress and then three to four hours after stress) identify perfusion defects which may represent scar tissue or viable tissue that is severely hypoperfused. The third set is taken a few minutes after the re-injection of Tl-201 and after the second set of images is completed. These re-injection images identify viable tissue if the defects exhibit significant fill-in (> 10% increase in tracer uptake) on the re-injection images. (9)

The alternative protocol, rest-redistribution, does not involve stress imaging. Instead, imaging is performed at rest 5 minutes after Tl-201 is injected and again 3 to 4 hours later. Viable tissue is identified if the delayed images exhibit significant fill-in of defects identified in the initial scans (> 10% increase in uptake) or if defects are fixed but the tracer activity is greater than 50%. (9) This protocol provides information on viability only, whereas, the stress-redistribution-reinjection protocol also provides information on stress induced ischemia. (4)

There are two technetium-99 m tracers: sestamibi (MIBI) and tetrofosmin. The uptake and retention of these two is dependent on regional perfusion and the integrity of cellular membranes. (3;9) Viability is assessed using one set of images at rest and defined by segments with tracer activity greater than 50%. (9)

Cardiac Magnetic Resonance Imaging

Cardiac magnetic resonance imaging (cardiac MRI) is a non-invasive, x-ray free technique which uses a powerful magnetic field, radio frequency pulses and a computer to produce detailed images of the structure and function of the heart. Two types of cardiac MRI are used to assess myocardial viability: dobutamine stress magnetic resonance imaging (DSMR), and delayed contrast-enhanced cardiac MRI (DE-MRI). DSMR is a technique that determines the contractile reserve of dysfunctional myocardium through the application of pharmacological stress with dobutamine. (11) Contractile reserve will be

present in viable myocardium. DE-MRI uses gadolinium-based contrast agents to define the transmural extent of scar, which can be visualized based on the intensity of the image. (11) Hyper-enhanced regions correspond to irreversibly damaged myocardium. (12) As the extent of hyperenhancement increases, the amount of scar increases, so there is a lower the likelihood of functional recovery. (13)

Positron Emission Tomography

Positron emission tomography (PET) is a nuclear medicine technique that's used to image tissues based on the distinct ways in which normal and abnormal tissues metabolize positron-emitting radionuclides. Radionuclides are radioactive analogs of common physiological substrates such as sugars, amino acids, and free fatty acids that are used by the body. (1;14;15) The only licensed radionuclide used in PET imaging for viability assessment is F-18 fluorodeoxyglucose (FDG).

In PET imaging, the radionuclides are injected into the body and as they decay, they emit positively charged particles, positrons, which travel several millimetres into tissue and collide with orbiting electrons. This collision results in annihilation where the combined mass of the positron and electron is converted into energy in the form of two 511 keV gamma rays, which are then emitted in opposite directions (180 degrees) and captured by an external array of detector elements in the PET gantry. Computer software is then used to convert the radiation emission into images. The system is set up so that it only detects co-incident gamma rays arriving at the detectors within a predefined temporal window; while single photos that arrive without a pair or outside the temporal window do not active the detector. This allows for increased spatial and contrast resolution. (14;15)

Viable myocardium can be identified by several methods. The most common method combines results of FDG PET scans with perfusion scans which may be done using PET perfusion tracers (most commonly, rubidium-82 or ^{13}N-ammonia) or SPECT perfusion imaging tracers (technetium or thallium). Based on the combined perfusion and metabolism information, regions are classified into the following patterns:

- normal tissue: regions with normal perfusion and normal glucose metabolism;
- perfusion/metabolism mismatch: regions with reduced perfusion and maintained glucose metabolism (FDG uptake);
- perfusion/metabolism match: regions with reduced perfusion and reduced glucose metabolism;

The first two patterns represent viable myocardium while the latter represents non-viable, scar tissue. (1;8) Other patterns such as perfusion/metabolism reverse mismatch, which is characterized by normal perfusion and reduced glucose metabolism may also occur. (8) Less commonly, viable myocardium may be determined based on metabolism imaging using FDG PET alone.

Project Scope

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

Technologies Under Review

After an initial review of the literature and consultation with experts, the Secretariat identified five key non-invasive cardiac imaging technologies that are used for the assessment of myocardial viability: positron emission tomography (PET), cardiac Magnetic Resonance (cardiac MRI) Imaging, single photon emission computed tomography (SPECT), dobutamine echocardiography (ECHO), and dobutamine ECHO with contrast. A 2005 review conducted by MAS (1) determined that PET was more sensitive than dobutamine ECHO and SPECT and dominated the other imaging modalities from a cost-effective standpoint. There was, however, inadequate evidence to compare PET and cardiac MRI, which is now the focus of this report.

The diagnostic accuracy of each technology was calculated using regional and global (where possible) functional recovery as the reference standard. Outcomes of interest included sensitivity and specificity. In order to compare across the different imaging modalities, pooled estimates of sensitivity and specificity were calculated as well as summary receiver operator characteristic (sROC) curves and the area under the curve (AUC). The following is a summary of evidence-based analyses of available medical literature regarding the effectiveness of PET and cardiac MRI for the assessment of myocardial viability. Economic analyses were also performed and a decision analytic model was developed.

Research Questions

1. What is the diagnostic accuracy of the imaging modalities for detecting myocardial viability?
2. What is the prognostic value of the viability imaging modalities (mortality and other clinical outcomes)?
3. What is the contribution of the viability imaging modalities to treatment decision making?
4. How does PET compare with cardiac MRI for the assessment of myocardial viability?
5. What is the safety of the viability imaging modalities?

PET for the Assessment of Myocardial Viability

Objective

The objective of this analysis is to assess the effectiveness and safety of PET imaging using FDG for the assessment of myocardial viability. To evaluate the effectiveness of FDG PET viability imaging, the following outcomes were examined: the diagnostic accuracy of FDG PET for predicting functional recovery; the impact of PET viability imaging on prognosis (mortality and other patient outcomes); and the contribution of PET viability imaging to treatment decision making and subsequent patient outcomes.

Evidence-Based Analysis Methods

Research Questions

1. What is the diagnostic accuracy of PET for detecting myocardial viability?
2. What is the prognostic value of PET viability imaging (mortality and other clinical outcomes)?
3. What is the contribution of PET viability imaging to treatment decision making?
4. What is the safety of PET viability imaging?

Literature Search

A literature search was performed on July 17, 2009 using OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, EMBASE, the Cochrane Library, and the International Agency for Health Technology Assessment (INAHTA) for studies published from January 1, 2004 to July 16, 2009. Abstracts were reviewed by a single reviewer and, for those studies meeting the eligibility criteria, full-text articles were obtained. In addition, published systematic reviews and health technology assessments were reviewed for relevant studies published before 2004. Reference lists of included studies were also examined for any additional relevant studies not already identified. The quality of the body of evidence was assessed as high, moderate, low or very low according to GRADE methodology.

Inclusion Criteria

Criteria applying to diagnostic accuracy studies, prognosis studies, and physician decision making studies:

- English language full-reports
- Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials (RCTs), and observational studies
- Patients with chronic, known coronary artery disease (CAD)
- PET imaging using FDG for the purpose of detecting viable myocardium

Criteria applying to diagnostic accuracy studies:

- Assessment of functional recovery $\geq$ 3 months after revascularization
- Raw data available to calculate sensitivity and specificity
- Gold standard: prediction of global or regional functional recovery

Criteria applying to prognosis studies:

- Mortality studies that compare revascularized patients with non-revascularized patients and patients with viable and non-viable myocardium

Exclusion Criteria

Criteria applying to diagnostic accuracy studies, prognosis studies, and physician decision making studies:

- PET perfusion imaging
- < 20 patients
- < 18 years of age
- Patients with non-ischemic heart disease
- Animal or phantom studies
- Studies focusing on the technical aspects of PET
- Studies conducted exclusively in patients with acute myocardial infarction (MI)
- Duplicate publications

Criteria applying to diagnostic accuracy studies

- Gold standard other than functional recovery (e.g., PET or cardiac MRI)
- Assessment of functional recovery occurs before patients are revascularized

Outcomes of Interest

Diagnostic accuracy studies

- Sensitivity and specificity
- Positive and negative predictive values (PPV and NPV)
- Positive and negative likelihood ratios
- Diagnostic accuracy
- Adverse events

Prognosis studies

- Mortality rate
- Functional status
- Exercise capacity
- Quality of Life
- Influence on PET viability imaging on physician decision making

Statistical Methods

Pooled estimates of sensitivity and specificity were calculated using a bivariate, binomial generalized linear mixed model. Statistical significance was defined by P values of less than 0.05, where "false discovery rate" adjustments were made for multiple hypothesis testing. Using the bivariate model parameters, summary receiver operating characteristic (sROC) curves were produced. The area under the sROC curve was estimated by numerical integration with a cubic spline (default option). Finally, pooled estimates of mortality rates were calculated using weighted means.

Quality of Evidence

The quality of evidence assigned to individual diagnostic studies was determined using the QUADAS tool, a list of 14 questions that address internal and external validity, bias, and generalizibility of diagnostic accuracy studies. Each question is scored as "yes", "no", or "unclear". The quality of the body of evidence was then assessed as high, moderate, low, or very low according to the GRADE Working

Group criteria. 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

Summary of Findings

A total of 40 studies met the inclusion criteria and were included in this review: one health technology assessment, two systematic reviews, 22 observational diagnostic accuracy studies, and 16 prognosis studies. The available PET viability imaging literature addresses two questions: 1) what is the diagnostic accuracy of PET imaging for the assessment; and 2) what is the prognostic value of PET viability imaging. The diagnostic accuracy studies use regional or global functional recovery as the reference standard to determine the sensitivity and specificity of the technology. While regional functional recovery was most commonly used in the studies, global functional recovery is more important clinically. Due to differences in reporting and thresholds, however, it was not possible to pool the global functional recovery.

Functional recovery, however, is a surrogate reference standard for viability and consequently, the diagnostic accuracy results may underestimate the specificity of PET viability imaging. For example, regional functional recovery may take up to a year after revascularization depending on whether it is stunned or hibernating tissue, while many of the studies looked at regional functional recovery 3 to 6 months after revascularization. In addition, viable tissue may not recover function after revascularization due to graft patency or re-stenosis. Both issues may lead to false positives and underestimate specificity.

Given these limitations, the prognostic value of PET viability imaging provides the most direct clinically useful information. This body of literature provides evidence on the comparative effectiveness of revascularization and medical therapy in patients with viable myocardium and patients without viable myocardium. In addition, the literature compares the impact of PET-guided treatment decision making with SPECT-guided or standard care treatment decision making on survival and cardiac events (including cardiac mortality, MI, hospital stays, unintended revascularization, etc).

The main findings from the diagnostic accuracy and prognosis evidence are:

1. Based on the available very low quality evidence, PET is a useful imaging modality for the detection of viable myocardium. The pooled estimates of sensitivity and specificity for the prediction of regional functional recovery as a surrogate for viable myocardium are 91.5% (95% CI: 88.2% – 94.9%) and 67.8% (95% CI: 55.8% – 79.7%), respectively.
2. Based the available very low quality of evidence, an indirect comparison of pooled estimates of sensitivity and specificity showed no statistically significant difference in the diagnostic accuracy of PET viability imaging for regional functional recovery using perfusion/metabolism mismatch with FDG PET with either a PET or SPECT perfusion tracer compared with metabolism imaging with FDG PET alone.
    a. FDG PET + PET perfusion metabolism mismatch: sensitivity, 89.9% (83.5% – 96.4%); specificity, 78.3% (66.3% – 90.2%);
    b. FDG PET + SPECT perfusion metabolism mismatch: sensitivity, 87.2% (78.0% – 96.4%); specificity, 67.1% (48.3% – 85.9%);

c. FDG PET metabolism: sensitivity, 94.5% (91.0% – 98.0%); specificity, 66.8% (53.2% – 80.3%).

Given these findings, further higher quality studies are required to determine the comparative effectiveness and clinical utility of metabolism and perfusion/metabolism mismatch viability imaging with PET.

3. Based on very low quality of evidence, patients with viable myocardium who are revascularized have a lower mortality rate than those who are treated with medical therapy. However, given the quality of evidence this estimate of effect is uncertain so further higher quality studies in this area should be undertaken to determine the presence and magnitude of the effect.
4. While revascularization may reduce mortality in patients with viable myocardium, current moderate quality RCT evidence suggests that PET-guided treatment decisions do not result in statistically significant reductions in mortality compared with treatment decisions based on SPECT or standard care protocols. The PARR II trial by Beanlands et al. found a significant reduction in cardiac events (a composite outcome that includes cardiac deaths, MI, or hospital stay for cardiac cause) between the adherence to PET recommendations subgroup and the standard care group (hazard ratio, .62; 95% confidence intervals, 0.42 – 0.93; P = .019). However, this post-hoc sub-group analysis is hypothesis generating and higher quality studies are required to substantiate these findings.
5. The use of FDG PET plus SPECT to determine perfusion/metabolism mismatch to assess myocardial viability increases the radiation exposure compared with FDG PET imaging alone or FDG PET combined with PET perfusion imaging (total-body effective dose: FDG PET, 7 mSv; FDG PET plus PET perfusion tracer, 7.6 – 7.7 mSV; FDG PET plus SPECT perfusion tracer, 16 – 25 mSv). While the precise risk attributed to this increased exposure is not known, there is increasing concern regarding lifetime multiple exposures to radiation-based imaging modalities. However, the incremental lifetime risk for patients who are older or have a poor prognosis may not be as great as for healthy individuals.

Cardiac MRI for the Assessment of Myocardial Viability

Objective

The objective of this analysis is to assess the effectiveness, and cost-effectiveness of cardiovascular magnetic resonance imaging (cardiac MRI) for the assessment of myocardial viability. To evaluate the effectiveness of cardiac MRI viability imaging, the following outcomes are examined: the diagnostic accuracy of cardiac MRI for predicting functional recovery and the impact of cardiac MRI viability imaging on prognosis (mortality and other patient outcomes).

Research Questions

1. What is the diagnostic accuracy of cardiac MRI for detecting myocardial viability?
2. What is the impact of cardiac MRI viability imaging on prognosis (mortality and other clinical outcomes)?
3. How does cardiac MRI compare with cardiac PET imaging for the assessment of myocardial viability?
4. What is the contribution of cardiac MRI viability imaging to treatment decision making?
5. Is cardiac MRI cost-effective compared with other cardiac imaging modalities for the assessment of myocardial viability?

Literature Search

A literature search was performed on October 9, 2009 using OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, EMBASE, the Cochrane Library, and the International Agency for Health Technology Assessment (INAHTA) for studies published from January 1, 2005 until October 9, 2009. Abstracts were reviewed by a single reviewer and, for those studies meeting the eligibility criteria full-text articles were obtained. In addition, published systematic reviews and health technology assessments were reviewed for relevant studies published before 2005. Reference lists were also examined for any additional relevant studies not identified through the search. The quality of evidence was assessed as high, moderate, low or very low according to GRADE methodology.

Inclusion Criteria

- English language full-reports
- Published between Jan. 1, 2005 and Oct. 9, 2009
- Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials (RCTs), and observational studies
- Patients with chronic, known CAD
- Used contrast-enhanced MRI
- Assessment of functional recovery ≥ 3 months after revascularization

Exclusion Criteria

- < 20 patients
- < 18 years of age
- Patients with non-ischemic heart disease
- Studies conducted exclusively in patients with acute myocardial infarction (MI)
- Studies where TP, TN, FP, FN cannot be determined

Outcomes of Interest

- Sensitivity
- Specificity
- Positive predictive value (PPV)

- Negative Predictive value (NPV)
- Positive and negative likelihood ratios
- Diagnostic accuracy
- Mortality rate (for prognostic studies)
- Adverse events

Statistical Methods

Pooled estimates of sensitivity and specificity were calculated using a bivariate, binomial generalized linear mixed model. Statistical significance was defined by P values of less than 0.05, where "false discovery rate" adjustments were made for multiple hypothesis testing. Using the bivariate model parameters, summary receiver operating characteristic (sROC) curves were produced. The area under the sROC curve was estimated by numerical integration with a cubic spline (default option).

Quality of Evidence

The quality of evidence assigned to individual diagnostic studies was determined using the QUADAS tool. The QUADAS tool is a list of 14 questions that address internal and external validity, bias, and generalizibility of diagnostic accuracy studies. Each question is scored as "yes", "no", or "unclear". The quality of the body of evidence was assessed as high, moderate, low, or very low according to the GRADE Working Group criteria. 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

Summary of Findings

1. Based on the available very low quality evidence, MRI is a useful imaging modality for the detection of viable myocardium. The pooled estimates of sensitivity and specificity for the prediction of regional functional recovery as a surrogate for viable myocardium are 84.5% (95% CI: 77.5% – 91.6%) and 71.0% (95% CI: 68.8% – 79.2%), respectively.
2. Subgroup analysis demonstrated a statistically significant difference in the sensitivity of MRI to assess myocardial viability for studies using ≤25% hyperenhancement as a viability threshold versus studies using ≤50% hyperenhancement as their viability threshold [78.7 (95% CI: 69.1% - 88.2%) and 96.2 (95% CI: 91.8 – 100.6), respectively; p=0.0044]. Marked differences in specificity were observed [73.6 (95% CI: 62.6% - 84.6%) and 47.2 (95% CI: 22.2 – 72.3), respectively; p=0.2384]. These findings, however, were not statistically significant.
3. There were no statistically significant differences between the sensitivities or specificities for any other subgroup including mean preoperative LVEF, imaging method of function recovery assessment and length of follow-up.
4. There was no evidence available to determine whether patients with viable myocardium who are revascularized have a lower mortality rate than those who are treated with medical therapy.

Diagnostic Accuracy of PET and cardiac MRI

Indirect Comparison

Since there were few studies that directly compared PET and cardiac MRI, the modalities were compared indirectly based on the results of the individual evidence-based analyses of PET and cardiac MRI described above. This was possible because every study used regional functional recovery as a common reference standard. The pooled estimates of the sensitivity and specificity of PET and cardiac MRI for the detection of regional functional recovery are shown in Table 1. Figure 1 shows the sensitivity and specificity forest plots for each imaging modality. As demonstrated in the table, PET has a higher sensitivity than cardiac MRI, but this difference was not statistically significant (P = .0772). In contrast, cardiac MRI has a higher specificity than PET, but this difference was not statistically significant (P = .6590)

Table 1: Pooled sensitivity and specificity estimates and area under the curve for the diagnostic accuracy of PET and cardiac MRI for the detection of regional functional recovery

Imaging Modality	No. of studies	Pooled Sensitivity (95% CI)	P value	Pooled Specificity (95% CI)	P value
Cardiac MRI	8	84.5% (77.5% - 91.6%)	.0772	71.0% (62.8% - 79.2%)	.6590
PET	20	91.5% (88.2% - 94.9%)		67.8% (55.8% - 79.7%)	

AUC refers to area under the curve; CI, confidence interval; cardiac MRI; cardiac magnetic resonance imaging; No, number; PET, positron emission tomography

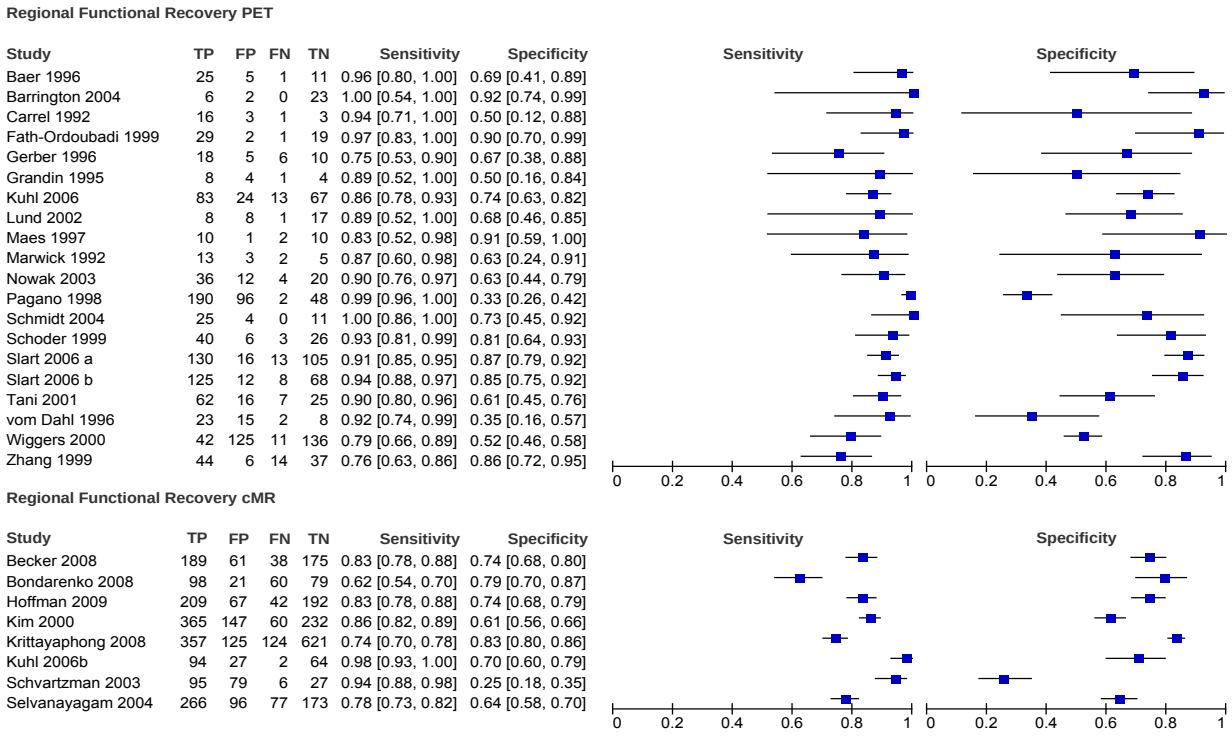

Figure 1: Sensitivity and specificity forest plots of PET and cardiac MRI for the detection of regional functional recovery

Figure 2 shows the summary receiver operating characteristic curves for PET and cardiac MRI. Based on these curves, the area under the curve is 0.893 and 0.841 for PET and cardiac MRI, respectively. Based on these AUCs, PET is a good to excellent test and cardiac MRI is a good test. (16)

The positive and negative likelihood ratios were plotted for each modality (Figure 3). Overall, most points for both modalities cluster in the moderately useful and somewhat useful areas on the plot.

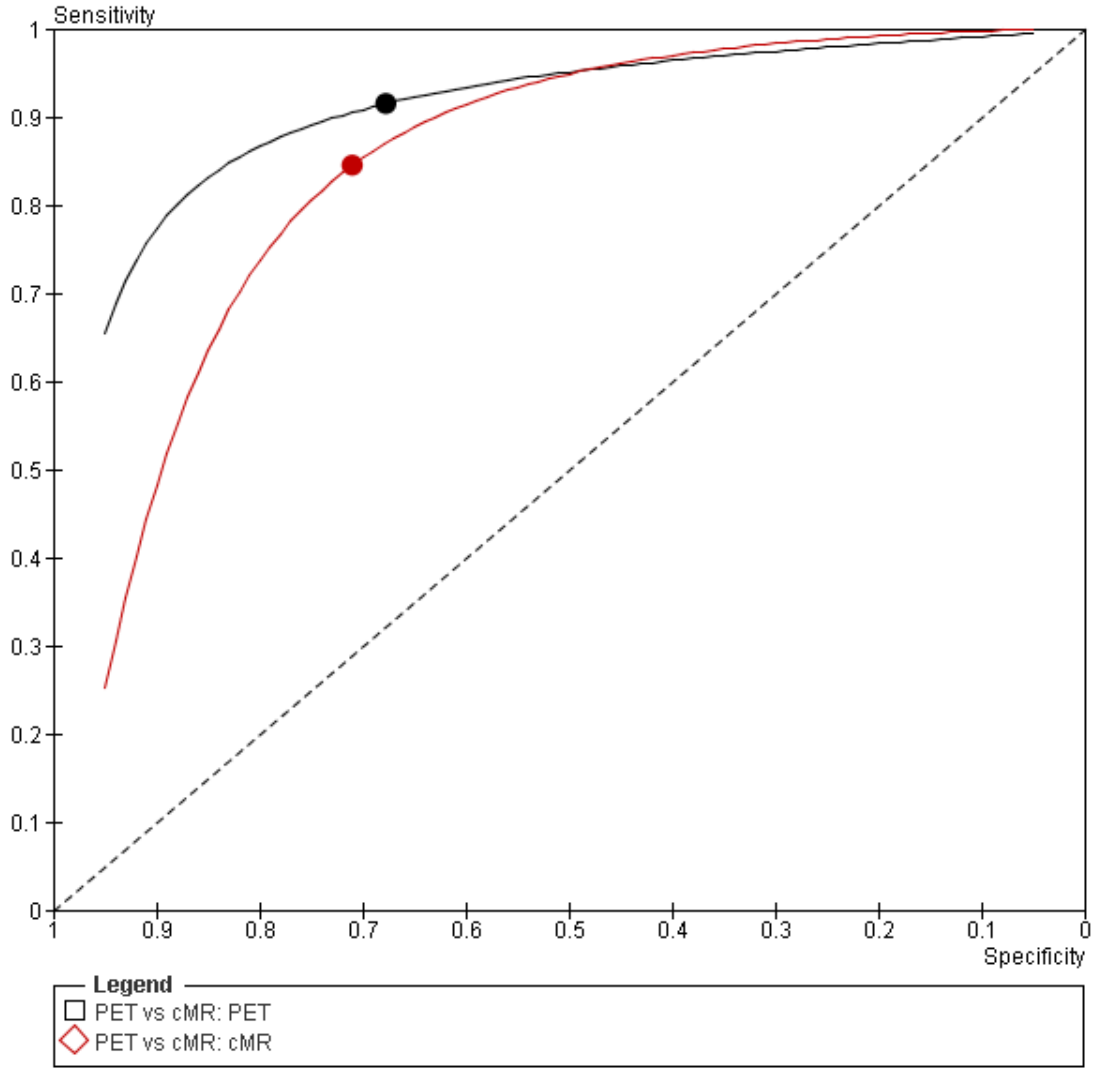

Figure 2: Summary receiver operating characteristic curves showing the diagnostic accuracy of PET and cardiac MRI for the detection of regional functional recovery (indirect comparison)

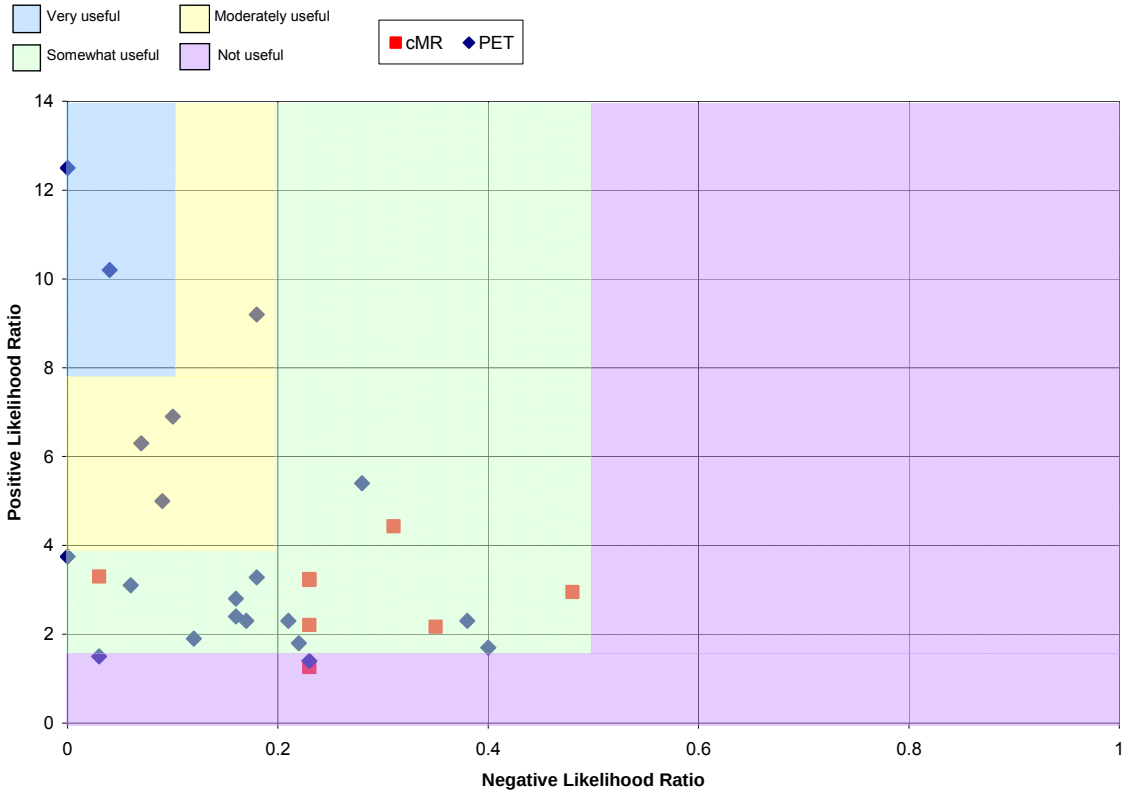

Figure 3: Likelihood ratio plot comparing the diagnostic accuracy of PET and cardiac MRI for the detection of regional functional recovery (indirect comparison)

Direct Comparison

Two of the included studies in the PET analysis provided a direct comparison of the diagnostic accuracy of PET and cardiac MRI directly; however, only one study compared contrast-enhance cardiac MRI (the primary method of cardiac MRI viability assessment in Ontario) with PET. No studies that directly compared PET with cardiac MRI reported global functional recovery.

As shown in Table 2, for the prediction of regional functional recovery after revascularization, PET exhibited a lower sensitivity but a slightly higher specificity (statistical significance not reported). PET and cardiac MRI have similar positive likelihood ratios, so when plotted on a likelihood ratio plot (Figure 4), both modalities fall into the 'somewhat useful' area. These results should be considered with caution as they are based on only one study.

Table 2: Studies Directly Comparing the PET and MRI for the Prediction of Regional Functional Recovery

Author, Year	PET Technique	Cardiac MRI Technique	Cardiac MRI Viability Threshold	Unit of analysis	PET	
					Sensitivity	Specificity
Kuhl et al, 2006 (17)	FDG PET / Tc SPECT	Gadolinium-based contrast agent MR	segmental extent of hyperenhancement ≤50%	Segments	PET: 86.5% cardiac MRI: 97.9%	PET: 73.6% cardiac MRI: 70.3%

*cardiac MRI refers to cardiac magnetic resonance imaging; FDG, F-18-fluorodeoxyglucose; mm, millimetres; ET, positron emission tomography; SPECT, single-photon emission computed tomography; Tc, Technetium

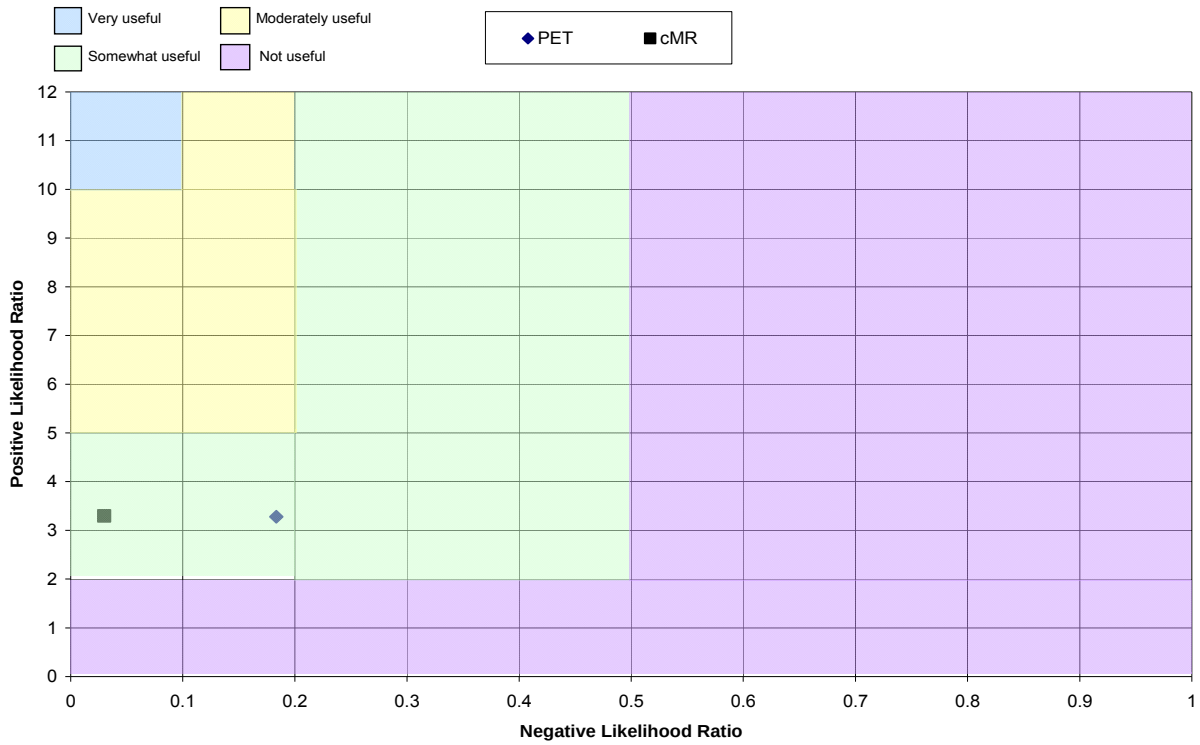

Figure 4: Likelihood ratio plot comparing the diagnostic accuracy of PET and cardiac MRI for the detection of regional functional recovery after revascularization (direct comparison)

Quality of Evidence

The quality of evidence for studies *directly* comparing the diagnostic accuracy of PET and cardiac MRI for the detection of regional functional recovery was assessed using the GRADE methodology. (18) Overall, the quality of evidence is low (Table 3).

Table 3: GRADE Quality of Evidence for studies comparing PET and cardiac MRI for the detection of viable myocardium based on regional functional recovery in patients with known CAD

Factor	Explanation	GRADE
Risk of Bias		
Study design	Observational cohort studies	High
Limitations	No serious limitations	Unchanged
Indirectness		
Outcomes	Diagnostic tests are considered as surrogate outcomes	Reduced by one level→ Moderate
Patient populations, diagnostic test, comparison test, and indirect comparisons	No serious issues	Unchanged
Inconsistency in study results	No serious inconsistencies	Unchanged
Imprecise evidence	Serious imprecision (sparse data)*	Reduced by one level → Low
Publication bias	No publication bias suspected	Unchanged
Quality of Evidence		**Low**

*Downgraded due to serious limitations: only one study identified compared PET and cardiac MRI directly (sparse data).

Limitations

There are three major limitations that impact the direct and indirect comparisons of PET and cardiac MRI. First, the results of the direct and indirect comparisons were inconsistent. Since, both comparisons are based on low quality of evidence, these findings are uncertain. Second, the diagnostic accuracy data for PET and cardiac MRI could only be pooled and compared for regional functional recovery, but global functional recovery may be more important clinically. Finally, no cardiac MRI studies were identified that examined prognosis and therefore a comparison of the clinical utility of these imaging modalities could not be performed.

Conclusions

Diagnostic Accuracy

1. Based on very low quality of evidence, PET and cardiac MRI are good tests for the prediction of regional functional recovery as a surrogate for viability.
2. Based on very low quality evidence, the diagnostic accuracy of PET using sensitivity is higher than that of cardiac MRI (91.5% vs. 84.5% respectively), but this difference is not statistically significant (P = .0772).

Clinical Utility

PET

1. Very low quality evidence suggests that revascularization may be more beneficial than medical treatment for those patients who have viable myocardium. Given the quality of evidence, this estimate of effect is very uncertain.
2. There are no studies regarding the comparative effectiveness of heart transplantation versus revascularization predicated on the basis of viability assessment.
3. Moderate quality evidence suggests that there are no significant differences in clinical outcomes and survival for patients whose treatment plan was based on viability assessment with PET, SPECT, or standard care.
4. The 2005 economic analysis conducted by MAS showed that PET viability imaging was more cost-effective than SPECT (dominated). (1)

Cardiac MRI

1. At the time of this review, there is no available evidence on the clinical utility of cardiac MRI viability imaging.

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