Magnetic Resonance Imaging (MRI) for the Assessment of Myocardial Viability

An Evidence-Based Analysis

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

July 2010

Ontario

Suggested Citation

This report should be cited as follows:

Medical Advisory Secretariat. Magnetic resonance imaging (MRI) for the assessment of myocardial viability: an evidence-based analysis. Ont Health Technol Assess Ser [Internet]. 2010 July [cited YYYY MM DD]; 10(15) 1-45. Available from: http://www.health.gov.on.ca/english/providers/program/mas/tech/reviews/pdf/cardiac_viability _MRI_20100716.pdf

Permission Requests

All inquiries regarding permission to reproduce any content in the *Ontario Health Technology Assessment Series* should be directed to MASinfo.moh@ontario.ca.

How to Obtain Issues in the Ontario Health Technology Assessment Series

All reports in the *Ontario Health Technology Assessment Series* are freely available in PDF format at the following URL: www.health.gov.on.ca/ohtas.

Print copies can be obtained by contacting MASinfo.moh@ontario.ca.

Conflict of Interest Statement

All analyses in the Ontario Health Technology Assessment Series are impartial and subject to a systematic evidence-based assessment process. There are no competing interests or conflicts of interest to declare.

Peer Review

All Medical Advisory Secretariat analyses are subject to external expert peer review. Additionally, the public consultation process is also available to individuals wishing to comment on an analysis prior to finalization. For more information, please visit http://www.health.gov.on.ca/english/providers/program/ohtac/public_engage_overview.html.

Contact Information

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.

Table of Contents

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 ^{18}F-Flurodeoxyglucose

LV Left ventricular

LVEF Left ventricular ejection fraction

MAS Medical Advisory Secretariat

MRI Magnetic resonance imaging

NPV Negative predictive value

OR Odds ratio

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

Executive Summary

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

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 were examined: the diagnostic accuracy in predicting functional recovery and the impact of cardiac MRI viability imaging on prognosis (mortality and other patient outcomes).

Clinical Need: Condition 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.

In 2005, more than 71,000 Canadians died from cardiovascular disease, of which, 54% were due to ischemic heart disease. 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. The prevalence of heart

---

[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.

failure was estimated at one percent of the Canadian population in 1989. Since then, the increase in the older population has undoubtedly resulted in a substantial increase in cases. 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.

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. Concerning medical treatment, despite recent advances, mortality remains high among treated patients, while,heart transplantation is affected by the limited availability of donor hearts and consequently has long waiting lists. The third option, revascularization, is used to restore the flow of blood to the heart via coronary artery bypass grafting (CABG) or, in some cases, through minimally invasive percutaneous coronary interventions (balloon angioplasty and 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). Since only 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 when determining the most appropriate treatment path. Various non-invasive cardiac imaging modalities can be used to assess patients in whom determination of viability is an important clinical issue, specifically:

- dobutamine echocardiography (echo),
- stress echo with contrast,
- 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. During the infusion of low dose dobutamine (5 – 10 µg/kg/min), an improvement of contractility in hypokinetic and akentic segments is indicative of the presence of viable myocardium. 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. 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.

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. These agents allow for the assessment of myocardial blood flow (perfusion) and contractile function (as described above), as well as the simultaneous assessment of perfusion to make it possible to distinguish between stunned and hibernating myocardium.

SPECT

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. The stress-redistribution-reinjection 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 that may represent scar tissue or viable tissue that is severely hypoperfused. The third set of images 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.

The other common Tl-201 viability imaging protocol, rest-redistribution, involves SPECT imaging performed at rest five minutes after Tl-201 is injected and again three to four 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%.

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

Cardiac Positron Emission Tomography

Positron emission tomography (PET) is a nuclear medicine technique 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. The only licensed radionuclide used in PET imaging for viability assessment is F-18 fluorodeoxyglucose (FDG).

During a PET scan, the radionuclides are injected into the body and as they decay, they emit positively charged particles (positrons) that 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 that arrive at the detectors within a predefined temporal window, while single photons arriving without a pair or outside the temporal window do not active the detector. This allows for increased spatial and contrast resolution.

Cardiac Magnetic Resonance Imaging

Cardiac magnetic resonance imaging (cardiac MRI) is a non-invasive, x-ray free technique that 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). DE-MRI, the most commonly used technique in Ontario, uses gadolinium-based contrast agents to define the transmural extent of scar, which can be visualized based on the intensity of the image. Hyper-enhanced regions correspond to irreversibly damaged myocardium. As the extent of hyper-enhancement increases, the amount of scar increases, so there is a lower the likelihood of functional recovery.

Evidence-Based Analysis

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 January 1, 2005 and October 9, 2009
- Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials (RCTs), and observational studies
- Patients with chronic, known coronary artery disease (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 likelihood ratio
- Negative likelihood ratio
- Diagnostic accuracy
- Mortality rate (for prognostic studies)
- Adverse events

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); p=0.0044 respectively]. Marked differences in specificity were observed [73.6 (95% CI: 62.6% - 84.6%) and 47.2 (95% CI: 22.2 – 72.3); p=0.2384 respectively]; however, these findings were not statistically significant.

3. There were no statistically significant differences between the sensitivities or specificities for any other subgroups including mean preoperative LVEF, imaging method for 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.

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 analysis is to assess the effectiveness, safety, and cost-effectiveness of cardiac magnetic resonance imaging (cardiac MRI) for the assessment of myocardial viability.

Objective of Analysis

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).

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)

Left ventricular (LV) systolic dysfunction from coronary artery disease (CAD) [2] is the primary cause of heart failure, accounting for more than 70% of cases. (1-3) The prevalence of heart failure in Canada has been estimated at about 1%. (4) The aging population has resulted in substantial increase in cases with 4.7 million Americans diagnosed with heart failure in the United States and 400,000 new cases per year. (3) 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) In 2005 in Canada, more than 71,000 people died from cardiovascular disease, of which, 54% were due to ischemic heart disease. (5)

Treatment Options

In general, there are three main options for the treatment options of heart failure: medical treatment, heart transplantation, and revascularization. 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. (3;6;7) While heart transplantation improves long-term prognosis, there are inadequate donor hearts and consequently long wait lists for transplantation. (3) The third option, revascularization, is a surgical procedure 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. (1) Both methods, however, are associated with important perioperative risks including mortality, so it is essential to weigh benefits and risks of the procedure to properly select patients for this procedure. (6;7)

Myocardial Viability

Left ventricular dysfunction may be permanent 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. (2) 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. (2;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. (2;7)

Since patients with dysfunctional but viable myocardium benefit from revascularization, the identification and quantification 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 identify viable myocardium:

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

---

[2] 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. (1)

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 µg/kg/min), an improvement of contractility in hypokinetic and akentic segments is indicative of the presence of viable myocardium. (2;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 µg/kg/min) represents viable tissue. (2;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. (2;9;10)

Stress Echo 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. (2;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. (2)

SPECT

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. (2;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. (3)

There are two technetium-99 m tracers: sestamibi (MIBI) and tetrofosmin. The uptake and retention of these tracers is dependent on regional perfusion and the integrity of cellular membranes. (2;9) Viability is assessed using one set of images at rest and defined by segments with tracer activity greater than 50%. (9)

Cardiac PET

Positron emission tomography (PET) is a nuclear medicine technique that is used to image tissues based on the distinct ways in which normal and abnormal tissues metabolize positron-emitting radionuclides. 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 and which releases energy in the form of two 511 keV gamma rays which are emitted in opposite directions (180 degrees) and captured by an external array of detector elements in

the PET gantry. (11;12) Computer software is used to convert the radiation emission into images. (1) The system is set up so that it only detects co-incident gamma rays that arrive 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. (11;12)

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. (13) 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. (13) Hyper-enhanced regions correspond to irreversibly damaged myocardium. (14) As the extent of hyperenhancement increases, the amount of scar increases, so there is a lower the likelihood of functional recovery. (15)

Dobutamine stress magnetic resonance imaging (DSMR)

DSMR is a technique that determines the contractile reserve of dysfunctional myocardium through the application of pharmacological stress with dobutamine. (13) Contractile reserve will be present in viable myocardium.

Delayed Contrast-enhanced Cardiac MRI (DE-MRI)

DE-MRI is a technique which uses gadolinium-based contrast agents to define the transmural extent of scar. The ability of DE-MRI to detect both viable and non-viable segments makes it unique from other cardiac imaging modalities used in the assessment of viability. The transmural extent of scar is visible by regions of increased image intensity, on T1 weighted images acquired after administration of a gadolinium-based contrast agent. (13) Hyper-enhanced regions correspond to irreversibly damaged myocardium (kim et al.) Research has demonstrated that the transmurality of hyperenhancement is vital in determining whether segments will recover function after revascularization. As the extent of hyperenhancement increases, the likelihood of functional recovery decreases. (15)

Regulatory Status

Cardiac MRI systems are licensed by Health Canada as class II and III devices. (16)

Cardiac MRI in Ontario

Although cardiac MRI is widely available in Ontario, its use in viability testing is relatively low due to competition from a large number of non-cardiac indications and the lack of expertise to accurately interpret these studies. Of the centres using cardiac MRI for myocardial viability, DE-MRI is the most routinely used technique in Ontario, thus the following analysis focuses only on studies using it.

Evidence-Based Analysis

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?

Methods

Literature Search

A literature search was performed on October 9, 2009 using OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, EMBASE, the Cochrane Library, and the International Agency for Health Technology Assessment (INAHTA) for studies published from January 1, 2005 to 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 2004. Reference lists were also examined for any additional relevant studies not identified through the search.

Inclusion Criteria

- English language full-reports
- Published between January 1, 2005 and October 9, 2009
- Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials (RCTs), and observational studies
- Patients with chronic, known coronary artery disease (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 likelihood ratio
- Negative likelihood ratio
- Diagnostic accuracy
- Mortality rate (for prognostic studies)
- Adverse events

Statistical Analysis

Sensitivity, specificity, PPV, and NPV are calculated using a two-by-two table as follows:

Table 1: Two-by-two table for calculations

		Outcome (Functional Recovery)	
		Positive	**Negative**
Diagnostic Test (PET)	**Positive**	TP	FP
	Negative	FN	TN

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

$$\text{Sensitivity} = \frac{\text{TP}}{(\text{TP} + \text{FN})}$$

$$\text{PPV} = \frac{\text{TP}}{(\text{TP} + \text{FP})}$$

$$\text{Specificity} = \frac{\text{TN}}{(\text{TN} + \text{FP})}$$

$$\text{NPV} = \frac{\text{TN}}{(\text{TN} + \text{FN})}$$

$$\text{Positive Likelihood Ratio} = \frac{Sensivity}{(1 - specificity)}$$

$$\text{Diagnostic Accuracy} = \frac{\text{TP} + \text{TN}}{\text{TP} + \text{FN} + \text{FP} + \text{TN}}$$

$$\text{Negative Likelihood Ratio} = \frac{(1 - sensitivity)}{specificity}$$

Pooled estimates of sensitivity and specificity were calculated using Meta-Disc version 1.4 (Madrid, Spain), which calculates weighted averages using the sample size of each study as its weight. 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). All other statistics were calculated using STATA version 10.1 (StataCorp; Texas, USA). The area under the sROC curve was estimated by numerical integration with a cubic spline (default option). Diagnostic odds ratios (DOR) were calculated with a random effects model using the metan command, and a meta-regression was used to compare the diagnostic odds ratios for each subgroup. (17) Statistical significance was defined by *P* values of less than 0.05. Likelihood ratio (LR) plots were produced using the following guidelines:

- Positive LRs greater than ten and negative LRs less than 0.1 generate large and often conclusive changes from pre- to post-test probability (very useful test).

- Positive LRs between five and ten and negative LRs between 0.1 and 0.2 generate moderate shifts from pre- to post-test probability (moderately useful test).

- Positive LRs between two and five and negative LRs between 0.2 and 0.5 generate small but sometimes important changes from pre- to post-test probability (somewhat useful test).

- Positive LRs between one and two and negative likelihood ratios between 0.5 and one alter pre- to post-test probability to a small and rarely important degree (not useful test). (1;18)

Quality of Evidence

The quality of systematic reviews were evaluated using the AMSTAR checklist. The tool consists of 11 questions which are scored as "yes", "no", and "can't answer". (19) The quality of evidence assigned to individual diagnostic studies was then determined using the QUADAS tool. The QUADAS tool is a list of 14 questions that address internal and external validity, bias, and generalizability of diagnostic accuracy studies. Each question is scored as "yes", "no", or "unclear". (ref)

The overall quality of the body of evidence was assessed as high, moderate, low, or very low according to the GRADE Working Group criteria (20), specifically:

- Quality refers to the criteria such as the adequacy of allocation concealment, blinding and follow-up.

- Consistency refers to the similarity of estimates of effect across studies. If there are important and unexplained inconsistencies in the results, our confidence in the estimate of effect for that outcome decreases. Differences in the direction of effect, the magnitude of the difference in effect, and the significance of the differences guide the decision about whether important inconsistency exists.

- Directness refers to the extent to which the interventions and outcome measures are similar to those of interest.

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

High   Further research is very unlikely to change confidence in the estimate of effect.

Moderate   Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate.

Low   Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate.

Very Low   Any estimate of effect is very uncertain

Results of Evidence-Based Analysis

The database search yielded 328 citations published between January 1, 2005 and October 9, 2009. Articles were excluded based on information in the title and abstract. The full texts of potentially relevant articles were obtained for further assessment and subsequently included based on pre-specified inclusion and exclusion criteria. Figure 1 shows the methodology of obtaining the final studies.

Eleven studies (one health technology assessment, two systematic reviews, and eight observational diagnostic accuracy studies) met the inclusion criteria. Given the limited number of studies identified, the review was expanded to include relevant studies from previously published systematic reviews and health technology assessments. The reference lists of the included studies were hand searched to identify any other potentially relevant studies. Any SRs and meta-analyses that were identified in the older literature were reviewed to identify any additional relevant studies; however, these reviews are not summarized separately in this report. Fourteen citations were identified, of which four met the inclusion criteria.

For each included study, levels of evidence were assigned according to a ranking system based on the hierarchy by Goodman. (21) An additional designation "g" was added for preliminary reports of studies that had been presented to international scientific meetings. Table 2 lists the level of evidence and number of studies identified.

Table 2: Quality of evidence of included studies

Study Design	Level of Evidence†	Number of Eligible Studies
Large RCT, systematic review of RCTs	1	3†
Large RCT unpublished but reported to an international scientific meeting	1(g)	0
Small RCT	2	0
Small RCT unpublished but reported to an international scientific meeting	2(g)	0
Non-RCT with contemporaneous controls	3a	8
Non-RCT with historical controls	3b	0
Non-RCT presented at international conference	3(g)	0
Surveillance (database or register)	4a	0
Case series (multisite)	4b	0
Case series (single site)	4c	0
Retrospective review, modelling	4d	0
Case series presented at international conference	4(g)	0
	Total	11

*g refers to grey literature; RCT, randomized controlled trial
†One health technology assessment and 2 systematic reviews of diagnostic accuracy observational studies

Systematic Literature Search (2005 – 2009)

Extended Literature Search

```
Search results
(number of citations)
n = 328
```

```
Potentially relevant studies
identified by searching included
SRs, HTAs and reference lists
(duplicates removed)
n = 14
```

```
Study abstracts reviewed
n = 328
```

```
Citations excluded based on
abstract review
n = 271
```

```
Full text studies reviewed
n = 14
```

```
Full text studies reviewed
n = 57
```

```
Citations excluded based on
full text review
n = 10
```

```
Citations excluded based on
full text review
n = 49
```

```
Additional citations
identified
n = 4
```

Reasons for exclusion

- N < 20 (5);
- inadequate data (2);
- < 3 months follow up (1);
- duplicate studies (2);
- not CAD population (2);
- study design not appropriate (37)

Included Studies

- Health technology assessments (1)
- Systematic review (2)
- 8 observational diagnostic accuracy
  studies (5 from systematic search and 4
  from expanded literature search)
  n (total) = 11

Reasons for exclusion

- N <20 (1);
- inadequate data (1), not CE-MRI (1);
- patient population (3);
- study design (4)

Figure 1: Citation flow chart

Health Technology Assessments

One Health Technology Assessment (HTA) was identified that met the inclusion criteria. This HTA, conducted by the Medical Advisory Secretariat in 2005, evaluated the effectiveness, safety, and cost-effectiveness of PET, dobutamine stress echo, single photon emission computed tomography (SPECT), cardiac MRI, and endocardial electromechanical mapping for the detection of myocardial viability and prediction of long-term outcomes. (1) Based on moderate to low quality of evidence, the findings were as follows:

Diagnostic accuracy

- PET has a higher sensitivity (median, 90%; range, 71% – 100%) and better negative likelihood ratio (median, 0.16; range, 0.0 – 0.38) for predicting regional functional recovery than other diagnostic imaging modalities;

- The specificity of PET (median, 73%; range, 33% – 91%) for predicting regional functional recovery is similar to other radionuclide imaging modalities, but lower than dobutamine echo;

- Given its higher sensitivity, PET is able to identify some patients who might benefit from revascularization that other modalities would not identify;

- Cardiac MRI is a promising technique for viability assessment, but given the small number of poor quality studies on this area, no conclusion can be drawn on the effectiveness of PET versus cardiac MRI; and

- No conclusion can be made comparing the accuracy of PET with other imaging modalities for predicting global functional due to a lack of direct comparisons. (1)

Prognosis

- No firm conclusion can be reached about the incremental value of PET over other non-invasive techniques for predicting long-term outcomes due to lack of direct comparison. (1)

Systematic Reviews

Schinkel et al. (22) conducted a systematic review (SR) comparing the diagnostic accuracy of five cardiac imaging modalities (PET, dobutamine echocardiography, thallium-201 and technetium-99m scintigraphy, and cardiac MRI) for the evaluation of viable myocardium and assessment of patient outcomes. The SR included 151 studies published from 1980 to January 2007 that assessed at least one of the following patient outcomes: regional functional recovery; global LV functional recovery; improvement in heart failure symptoms and exercise capacity; and long-term prognosis. (22)

As the topic of this report is the diagnostic accuracy of myocardial viability and viability prognostication, only the results pertaining to these outcomes are summarized here (Table 3). When regional functional recovery was used as the gold standard, resting cardiac MRI had the highest sensitivity (95%) followed by PET (92%), whereas dobutamine cardiac MRI had the highest specificity (82%) followed by dobutamine echo (78%). When global functional recovery was used as the gold standard, thallium and technetium SPECT had the highest sensitivity (84%) followed by PET (83%). Dobutamine echo had the highest specificity (73%) followed by technetium SPECT (68%). (22)

Table 3: Weighted mean sensitivity, specificity, positive predictive value, and negative predictive value for predicting hibernating myocardium from Schinkel et al.*

Outcome	No. Studies	N	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Positron Emission Tomography						
Regional Function	24	756	92	63	74	87
Global Function	3	253	83	64	68	80
Dobutamine Echocardiography						
Regional Function	41	1,421	80	78	75	83
Global Function	6	287	57	73	63	68
SPECT: Thallium-201						
Regional Function	40	1,119	87	54	67	79
Global Function	5	235	84	53	76	64
SPECT: Technetium-99m						
Regional Function	25	721	83	65	74	76
Global Function	2	98	84	68	74	80
cardiac MRI: Contrast Enhanced MRI						
Regional Function	5	178	84	63	72	78
Global Function						

*cardiac MRI refers to cardiac magnetic resonance imaging; N, sample size; no., number; NPV, negative predictive value; PPV, positive predictive value; revasc., revascularization; SPECT, single photon emission computed tomography

Source: Schinkel AF, Bax JJ, Poldermans D, Elhendy A, Ferrari R, Rahimtoola SH. Hibernating myocardium: diagnosis and patient outcomes. Curr Probl Cardiol 2007; 32(7):375-410.

The second systematic review, conducted by Beanlands et al. (2;23), compared PET, multi-detector computed tomography angiography, and MRI for one or more of the following outcomes: diagnostic accuracy for the detection of CAD, CAD prognostication, diagnostic accuracy of myocardial viability detection, and viability prognostication. This review identified the most recent systematic reviews in the literature for each technology and updated it to include studies published until June 2005.

As the topic of this report is the diagnostic accuracy of myocardial viability and viability prognostication, only the results pertaining to these outcomes are summarized here (Table 4). The weighted mean sensitivity for the prediction of regional function recovery was highest for PET (91%) and slightly lower for late-gadolinium enhanced cardiac MRI (81%). Late-gadolinium enhanced cardiac MRI, however, had a higher weighted mean specificity than PET. (2;23)

Table 4: Weighted mean sensitivity and specificity results for diagnostic accuracy of detection of viable myocardium from 2005 Beanlands et al. systematic review

Imaging Technology	No. Studies	N	Weighted Mean Sensitivity (%)	Weighted Mean Specificity (%)
Positron Emission Tomography (weighted by no. segments/patients)	28†	1,047	91/90	61/61
Magnetic Resonance Imaging: Late Gadolinium Enhancement (weighted by no. patients)	13	357	81	83

N refers to sample size; no., number
†Eight individual studies and one meta-analysis with 20 studies

Based on these findings, the following recommendations were made regarding cardiac MRI viability imaging:

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

Class I Indications
1. Asessment of myocardial viability in patients with LV dysfunction or akinetic segments for predicting recovery of ventricular function following revasuclarization
   a. Late Gadolinium Enhancement (Level B evidence);
   b. Dobutamine Stress Wall Motion (Level B evidence)

Class IIa Indication
1. Asessment of myocardial viability to determine prognosis following revascularization in patients with moderate/severe LV dysfunction

   a. Late Gadolinium Enhancement (Level B/C evidence);
   b. Dobutamine Stress Wall Motion (Level B/C evidence)"

Sources: a) Beanlands RS, Chow BJ, Dick A, Friedrich MG, Gulenchyn KY, Kiess M et al. CCS/CAR/CANM/CNCS/CanSCMR joint position statement on advanced noninvasive cardiac imaging using positron emission tomography, magnetic resonance imaging and multidetector computed tomographic angiography in the diagnosis and evaluation of ischemic heart disease--executive summary. Can J Cardiol 2007; 23(2):107-19. b) Beanlands, R. S., Chow, B. J., Dick, A., Friedrich, M. G., Gulenchyn, K. Y., Kiess, M., Leong-Poi, H., Miller, R. M., Nichol, G., Freeman, M., Bogaty, P., Honos, G., Hudon, G., Wisenberg, G., Van Berkom, J., Williams, K., Yoshinaga, K., and Graham, J. CCS / CAR / CANM / CNCS / Can SCMR joint position statment on advanced non-invasive cardiac imaging using positron emission tomography, magnetic resonance imaging and multi-detector computed tomography angiography in the diagnosis and evaluation of ischemic heart disease. Ottawa, ON: Canadian Cardiovascular Society. 2006 [cited: 2009 Aug 26]. 48 p. Available from: http://www.ccs.ca/download/position_statements/cardiac_imaging_Dec11_appen_tables.pdf

Limitations

Both reviews include a systematic review conducted by Bax et al. (24) and use the summary estimates from the Bax et al. in the calculation of new summary sensitivity, specificity, PPV, and NPV estimates. These estimates were thus impacted by the mistakes identified in the Bax review such as the inclusion of a duplicate study and data extraction errors. In addition, the summary estimates for PET in the Beanlands review (25;26) includes data from two studies that were not performed using PET (FDG SPECT studies) and were inappropriate for inclusion in this analysis.

It is also important to note that cardiac MRI results were inconsistent across the two reviews. In Schinkel et al. (22), dobutamine cardiac MRI had a lower mean sensitivity (74%) than contrast-enhanced cardiac MRI (84%); however, in Beanlands et al. (25;26) , dobutamine cardiac MRI had a higher mean sensitivity (91%) than contrast-enhanced cardiac MRI (81%). Furthermore, the weighted mean specificity for both contrast-enhanced and dobutamine cardiac MRI was substantially higher in Beanlands et al. (23;27) than Schinkel et al. (22).

Quality Assessment

Full details on quality assessment of the two included SRs using the AMSTAR checklist are provided in Appendix 2. The Schinkel review (22) met two of the 11 components on the AMSTAR checklist, while the Beanlands review (2;23) met three of the components. The estimates of effect based on these systematic reviews are, therefore, uncertain and may change with higher quality SRs.

Diagnostic Accuracy of MRI to Detect Myocardial Viability

Eight studies that assessed the diagnostic accuracy of cardiac MRI for detecting myocardial viability were identified. All of these studies were prospective trials with further details provided in Table 5. The first four studies in the table were identified through the systematic literature search, and the following four studies were identified using the reference lists of previous systematic reviews and health technology assessments on this topic. A description of the threshold used to define viability and functional recovery (regional and/or global recovery) in each study is shown in Table 6.

Table 5: Characteristics of included viability diagnostic accuracy studies

Author, Year	Viability Assessment Technique	Patient Population	Technique, Mean Timing to Assess Funct. Recovery	No. of Patients	Mean Age ±SD, % Male	Mean LVEF ± SD (%)	History of MI (%)	Diabetes (%)	HT (%)	3 Vessel CAD (%)	Mean # stenosed vessels / Mean # Revasc Vessel	CABG/PCI
Kim et al., 2000	DE-MRI, 1.5T	Pts scheduled to undergo revasc., had abnormalities in regional wall motion	Cine MRI approx. 3 mos after revasc.	50*	63±11 88%	43±13	42	NR	NR	NR	NR	27/14
Schvartzman et al., 2003	DE-MRI, 1.5 T	Pts with CIHD and LV dysfunction (LVEF <50%)	Echo, ≥ 6 mos after revasc.	29	62±11 79%	28±10	NR	NR	NR	NR	NR	29/0
Selvanayagam et al., 2004	DE-MRI , 1.5T	pts referred for isolated coronary grafting	cine & DE MRI, 6 mos post CABG	60†	61±11 87%	62±12	NR	25	72	NR	NR	60/0
Kuhl et al., 2006	Ce-CMR 1.5 T	Pts with chronic ischaemic heart disease, regional wall motion abnormatlities and EF <50% with clinical indication for myocardial viability	Cine-CMR, 6 mos post revasc.	29‡	66±9 72%	32±10	83	34	76	NR	NR PCI, 1.2±0.4; CABG, 3.2±0.7	14/15
Becker et al., 2008	Ce-MRI	Patients with LV dysfunction	Echo, 9±2 mos after revasc.	53§	59±10; 57±7# 62%; 61%	41±8; 39±5	NR	33; 36	62; 59	NR	NR	21/34
Bondarenko., 2008	deCMR 1.5 T	Pts with known CAD & regional wall motion abnormalities scheduled for revasc.	Cine-CMR , 3, 6, 24±12 mos post revasc.	35‖	63±11 83%	39±11	59	17	45	72	NR	25/10
Krittayaphong et al., 2008	Ce-CMR 1.5 T	Pts with CAD and left ventricular EF <45%, stable symptoms scheduled for CABG.	Cine-CMR, 4 mos post CABG	50¶	60.8±9 92%	37.1±12.8	66	NR	60	82	NR	50/0
Hoffman et al., 2009	Ce-CMR, 1.5 T	Pts with ischemic left ventricular dysfunction scheduled to undergo revasc.	echo, 9 ±2 mos post revasc.	59	58±9 62%	40±8	NR	36	60	NR	1.2±0.3 NR	24/35

CABG refers to coronary artery bypass graft; CAD, coronary artery disease; ce-CMR, contrast enhanced cardiac magnetic resonance imaging; D, days; ECHO, echocardiography;; HT, hypertension; LV, left ventricular; LVEF, left ventricular ejection fraction; MI, myocardial infarction; mo, months; MRI, magnetic resonance imaging; MV, multivessel; NR, not reported; PCI, percutaneous coronary intervention; Pts, patients; revasc., revascularization; SD, standard deviation; yr, years

* 41 completed follow up
† only 52 were in the final analysis
‡ show completed follow-up CMR
§ patients originally underwent revascularization; 1 death, 1 evidence of MI
‖ who underwent all 4 CMR examinations
¶ follow-up CMR data was assessed in 44 patients
# patients with functional recovery; patients without functional recovery

Table 6: Summary of the thresholds to define viability and functional improvement by study

Author, Year	Grading of Wall Motion	Grading of Late Gadolinium enhancement (LGE)	Viability threshold	Definition of Functional Improvement
Kim et al., 2000	0=normal 1=mild or moderate hypokinesia 2= severe hypokinesia 3=akinesia 4=dyskinesia	0: no hyperenhancement 1: 1-25% 2: 26-50% 3: 51-75% 4: 76-100%	Regional: ≤25% hyperenhancement	NR
Schvartzman et al. 2003	1=normal contraction 2=mild hypokinesia 3= severe hypokinesia 4=akinesia or dyskinesia	0: 0% 1: 1-24% 2: 25-49% 3: 50-74% 4: 75-99% 5: 100%	Regional: <50% hyperenhancement	Regional: improvement in resting function by ≥1 grade between pre-and post-CABG Echo.
Selvanayagam et al. 2004	0=normal 1=mild or moderate hypokinesia 2= severe hypokinesia 3=akinesia 4-dyskinesia	0: no hyperenhancement 1: 1-25% 2: 26-50% 3: 51-75% 4: >76%	Regional: ≤25% hyperenhancement	Regional: Improvement in contraction by by ≥1 grade
Kuhl et al., 2006	1=normal contractility 2=mild to moderate hypokinesia 3= severe hypokinesia 4=akinesia 5=dyskinesia	NR	Regional: ≤50% hyperenhancement	Regional: Difference in wall motion score between baseline and follow-up examination was ≥1
Becker et al. 2008	1=Normokinetic 2=Hypokinetic 3=Akinetic 4=Dyskinetic	1: 0% 2: 1-25% 3: 26-50% 4: 51-75% 5: 76-100%	Regional: ≤25% hyperenhancement	Global: improvement LVEF >5%
Bondarenko et al., 2008	NR	1: 0% 2: 1-25% 3: 26-50% 4: 51-75% 5: 76-100%	Regional: ≤25% hyperenhancement	Regional: An increase in SWT of ≥1.5mm compared with baseline
Krittayaphong, et al. 2008	1=normal 2=mild or moderate hypokinesia 3=severe hypokinesia 4=akinesia 5=dyskinesia	1: 0% 2: 1-25% 3: 26-50% 4: 51-75% 5: 76-100%	Regional: ≤25% hyperenhancement	Regional: Improvement in regional wall motion score by ≥1 grade Global: improvement LVEF ≥5%
Hoffman et al. 2009	1=Normokinetic 2=Mildly hypokinetic 3= Moderately or severely hypokinetic 4=Akinetic 5=Dyskinetic	1: 0% 2: 1-25% 3: 26-50% 4: 51-75% 5: 76-100%	Regional: ≤25% hyperenhancement, ≤20% hyperenhancement (subgroup)	Regional: Improvement in regional wall motion score by ≥1 grade Global: improvement LVEF >5%

*CABG refers to coronary artery bypass graft; ECHO, echocardiography; LVEF, left ventricular ejection fraction; revasc., revascularized; NR, not reported

Regional (Segmental) Functional Improvement

Functional recovery is the surrogate reference standard used to assess viability and can be measured in two ways: regional (segmental) functional recovery and global functional recovery (improvement in LVEF). Regional functional recovery is measured by assessing changes in wall motion (also known as contractile function) before and after revascularization (Figure 2). To assess changes in wall motion, the LV is divided into segments and wall motion is assessed for each segment. If wall motion improves by at least 1 grade after revascularization then the segment is classified as viable.
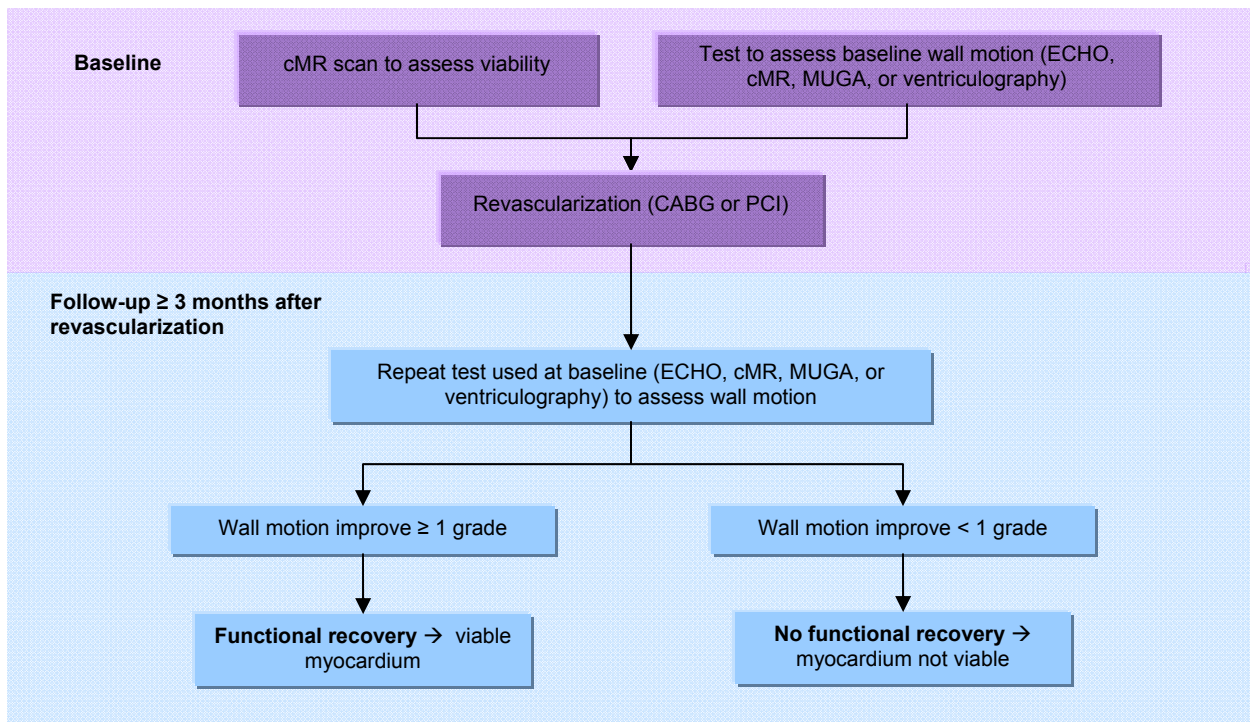
Figure 2: Steps involved in the assessment of regional functional recovery*

*cardiac MRI refers to cardiac magnetic resonance imgaging; ECHO, echocardiography; MUGA, multi-gated acquisition scan (radionuclide ventriculography); PET, positron emission tomography

Of note, the number of segments varied between studies depending on what model was used to divide the LV (common examples include the 17-segment American Heart Association model, an 8 segment model, and a 13-segment model). While regional functional recovery is most commonly reported for each segment, it is sometimes reported on by vascular territory. When vascular territories are used, the segments are grouped into 3 vascular territories per patient. (28) Alternatively, segments are reported on a per patient basis. There are numerous techniques used for grouping segments per patient including reporting results for only one segment per patient or classifying patients as viable or not viable depending on whether there are several adjacent viable segments or if more than 50% of the segments are viable. (29;30)

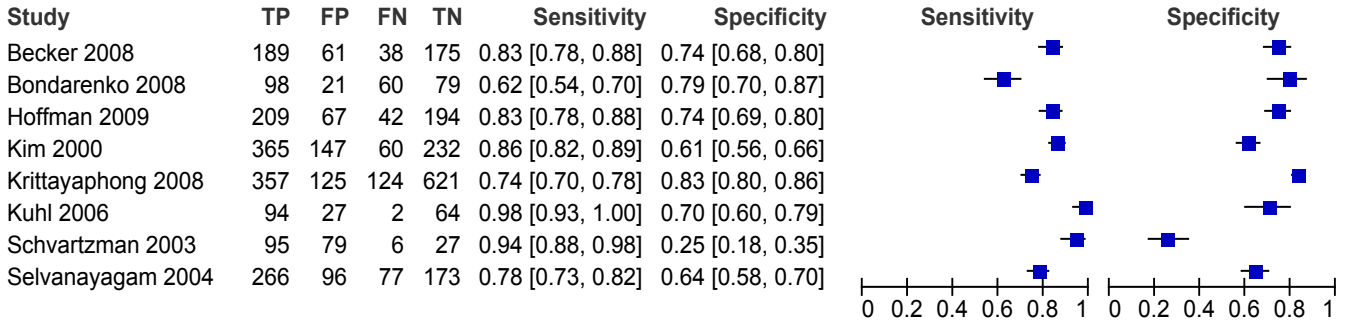Regional functional recovery was assessed in eight studies. The sensitivity, specificity, PPV, NPV, positive LR, negative LR, and diagnostic accuracy of each are reported in Table 7 and Figures 3 and 4 show the sensitivity and specificity forest plots by study. Sensitivity ranged from 62% to 94% and there was substantial heterogeneity in the reported specificity values, which ranged from 25% to 83%.

Table 7: Study results for diagnostic accuracy of cardiac MRI in predicting regional functional recovery after revascularization

Author, Year	Viability Threshold	No. Dysfunctional Segments	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Positive LR	Negative LR	Diagnostic Accuracy (%)
Kim et al., 2000	≤25% hyperenhancement	804	85.9	61.2	71.3	79.5	2.21	0.23	74.3
Schvartzman et al., 2003	<50% hyperenhancement	207	94.1	25.5	54.6	81.8	1.26	0.23	58.9
Selvanayagam et al., 2004	≤25% hyperenhancement	612	77.6	64.3	73.5	69.2	2.17	0.35	71.7
Kuhl et al., 2006	≤50% hyperenhancement	187	97.9	70.3	77.7	97.0	3.30	0.03	84.5
Becker et al., 2008	≤25% hyperenhancement	463	83.3	74.2	75.6	82.2	3.22	0.23	78.6
Bondarenko et al., 2008	≤25% hyperenhancement	258	62.0	79.0	82.4	56.8	2.95	0.48	68.6
Krittayaphong et al., 2008	≤25% hyperenhancement	1227	74.2	83.2	74.1	83.4	4.43	0.31	79.7
Hoffman et al., 2009	≤25% hyperenhancement	512	83.3	74.3	75.7	82.2	3.24	0.23	78.7

LR, refers to likelihood ratio; NPV, negative predictive value; PPV, positive predictive value; revasc., revascularized;

†Sensitivity, specificity, PPV, and NPV values reported in this table vary slightly from those reported in the text of the published report because a different equation was used in the report to calculate these values.

| Study	TP	FP	FN	TN	Sensitivity	Specificity
Becker 2008	189	61	38	175	0.83 [0.78, 0.88]	0.74 [0.68, 0.80]
Bondarenko 2008	98	21	60	79	0.62 [0.54, 0.70]	0.79 [0.70, 0.87]
Hoffman 2009	209	67	42	194	0.83 [0.78, 0.88]	0.74 [0.69, 0.80]
Kim 2000	365	147	60	232	0.86 [0.82, 0.89]	0.61 [0.56, 0.66]
Krittayaphong 2008	357	125	124	621	0.74 [0.70, 0.78]	0.83 [0.80, 0.86]
Kuhl 2006	94	27	2	64	0.98 [0.93, 1.00]	0.70 [0.60, 0.79]
Schvartzman 2003	95	79	6	27	0.94 [0.88, 0.98]	0.25 [0.18, 0.35]
Selvanayagam 2004	266	96	77	173	0.78 [0.73, 0.82]	0.64 [0.58, 0.70]

Figure 3: Sensitivity and specificity Forest plots showing the accuracy of cardiac MRI for detecting regional functional recovery
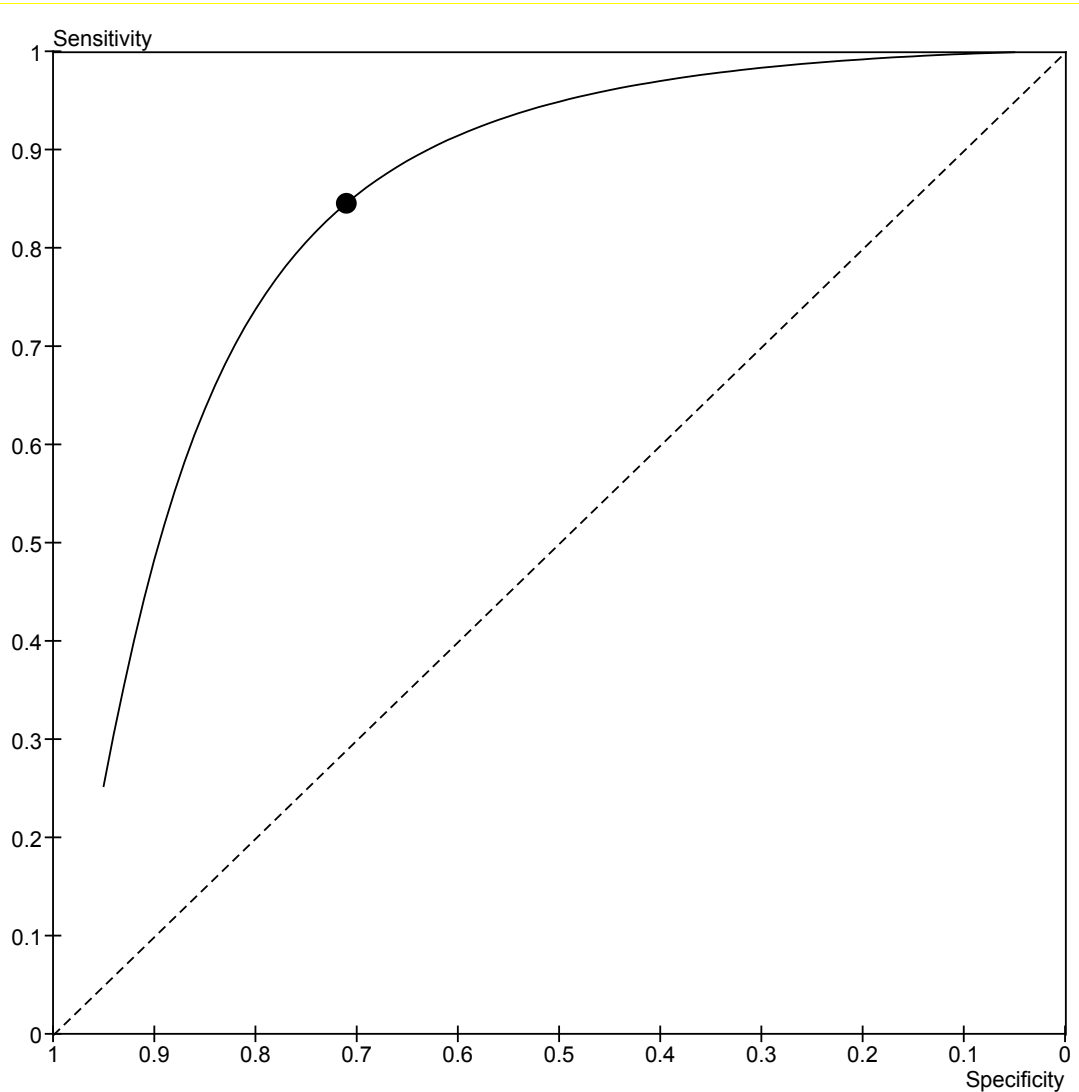
Figure 4: Diagnostic accuracy of cardiac MRI for detecting regional functional recovery, sROC curve

Figure 4 above shows the sROC curve obtained by plotting the sensitivity and specificity. The area under the curve (AUC) is 0.841 which indicates that cardiac MRI is a good test for assessing viability. A likelihood ratio plot (Figure 5) was obtained by plotting the negative likelihood ratio by the positive likelihood ratio. Based on the clustering of points in the somewhat useful area, cardiac MRI is a potentially useful technique for assessing myocardial viability.
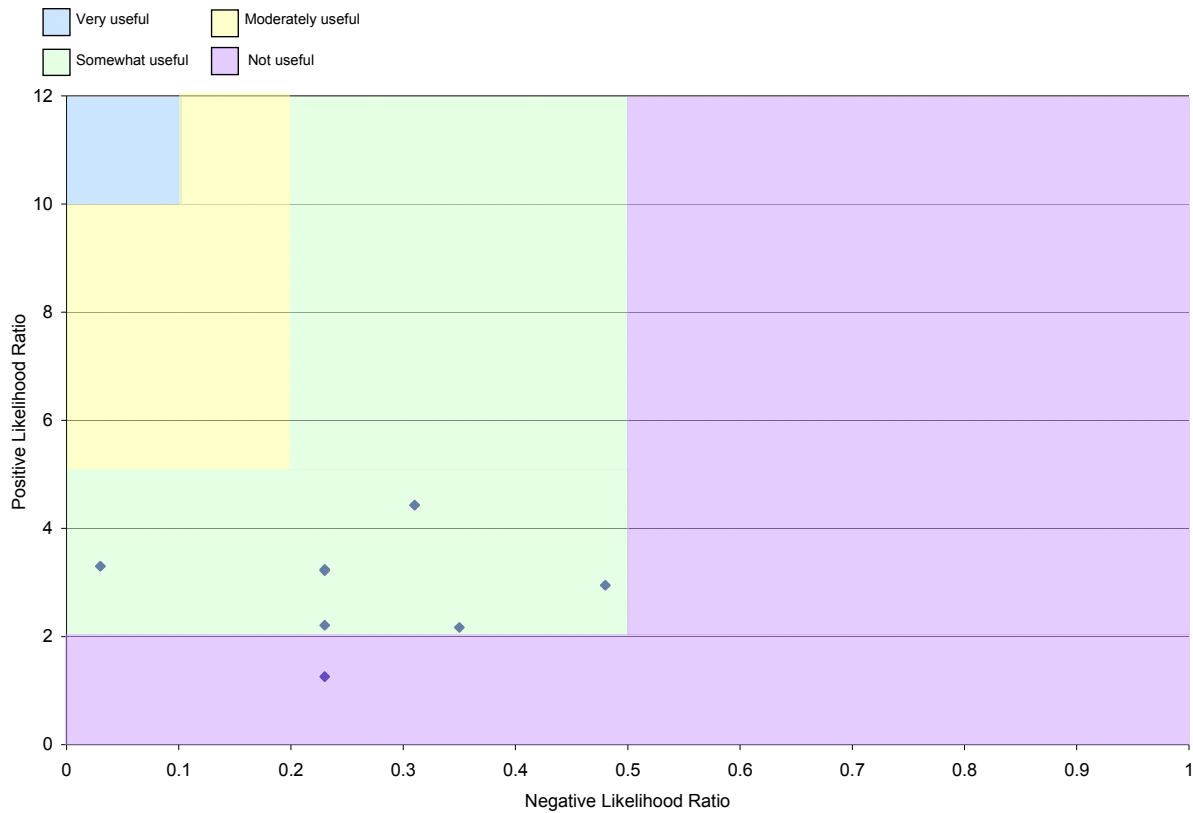
Figure 5: Likelihood ratio plot showing the diagnostic accuracy of cardiac MRI for predicting regional functional recovery

Subgroup Analyses

Wall motion can be measured by ECHO, cardiac MRI, radionuclide ventriculography (MUGA or multi-gated acquisition scan), and coronary angiography/left ventriculography. The accuracy of detecting wall motion abnormalities varies across these technologies because wall motion is assessed semi-quantitatively and is dependent on operator skill and subjective interpretation. Thus, the method of assessing regional functional recovery is a potential confounder that could bias the results of the accuracy studies, so studies were subgrouped based on the method of functional recovery assessment used in each study. (31) ECHO and cardiac MRI were the two imaging modalities used to measure wall motion in the 8 studies included in our analysis.

Thresholds used to determine viability varied across studies. While <25% hyperenhancement is certainly considered viable, hyperenhancement of between 25-50% is often read as likely or possibly viable. Since using a higher threshold will impact significantly on the sensitivity and specificity of MRI for assessment myocardial viability, studies were subgrouped by this factor.

Another common difference between studies potentially affecting the results was the length of follow-up of the studies. Since a longer length of follow-up will better reflect the actual rate of functional recovery studies were subgrouped by this factor to examine any potential bias in the rate of functional recovery. Patients mean pre-revascularization LVEF was also considered an important difference between studies and studies were subgrouped by this factor as well as the other factors mentioned above (Table 8). The stratified sensitivity and specificity forest plots for each subgroup are available in Appendix 3. Similar to the combined data results, for most subgroups the reported sensitivities varied less than the reported specificities (Table 9).

Table 8: Summary of stratification variables for regional functional assessment by study

Study	Method of Regional Functional Recovery Assessment		Length of Follow Up		Viability Threshold		Mean LVEF	
	ECHO	cardiac MRI	<6 months	≥6 months	≤25%	≤50%	<40%	≥40%
Kim 2000		✓	✓		✓			✓
Schvartzman 2003	✓			✓		✓	✓	
Selvanayagam 2004		✓		✓	✓			✓
Kuhl 2006		✓		✓		✓	✓	
Becker 2008	✓			✓	✓			✓
Bondarenko 2008		✓		✓	✓		✓	
Krittayaphong 2008		✓	✓		✓		✓	
Hoffman 2009	✓			✓	✓			✓

cardiac MRI refers to cardiac magnetic resonance imaging; ECHO, echocardiography; LVEF, left ventricular ejection fraction

The results of the subgroup analyses are displayed in Tables 9 and 10. Based on the subgroup analyses, there was a statistically significant difference in the sensitivity of MRI to assess myocardial viability for studies using ≤25% hyperenhancement as a viability threshold versus those using ≤50% hyperenhancement as their viability threshold (p=0.0044) As expected, the sensitivity increased with a greater threshold. 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.

Table 9: Pooled estimates of sensitivity and specificity by subgroup

Subgroup	Sensitivity (%) Pooled estimate (95% CI)	Specificity (%) Pooled estimate (95% CI)	AUC
All Studies	**84.5 (77.5 – 91.6)**	**71.0 (68.8 – 79.2)**	**0.8405**
Mean preoperative LVEF			
LVEF < 40%	86.1 (77.2 – 95.0)	66.8 (51.1 – 82.4)	0.8411
LVEF ≥ 40%	82.7 (72.7 – 92.7)	68.8 (54.0 – 83.6)	0.8164
Method of Functional Recovery Assessment			
ECHO	88.3 (79.6 – 97.0)	59.3 (39.8 – 78.7)	0.8217
cardiac MRI	81.6 (72.0 – 91.2)	72.4 (59.9 – 84.9)	0.8301
Viability Threshold			
≤25% hyperenhancement	78.7 (69.1 – 88.2)	73.6 (62.6 – 84.6)	0.8299
≤50% hyperenhancement	96.2 (91.8 – 100.6)	47.2 (22.2 – 72.3)	0.8725
Length of Follow-Up			
<6 months	80.8 (65.6 – 96.0)	73.7 (55.0 – 92.5)	0.8196
≥6 months	85.5 (78.1 – 92.9)	65.5 (52.6 – 78.5)	0.8407

 AUC refers to area under the curve; cardiac MRI; cardiac magnetic resonance imaging; ECHO, echocardiography; LVEF, left ventricular ejection fraction;

Table 10: Pairwise comparisons of sensitivity and specificity by subgroup

Subgroup	P value Sensitivity	Specificity
Mean preoperative LVEF		
LVEF <40% vs. ≥ 40%	0.6206	0.8528
Method of Functional Recovery Assessment		
ECHO vs. cardiac MRI	0.6186	0.5298
Viability Threshold		
≤25% hyperenhancement vs. ≤50% hyperenhancement	0.0044	0.2384
Length of Follow-Up		
<6 months vs. ≥6 months	0.6206	0.6403

cardiac MRI refers to cardiac magnetic resonance imaging; ECHO, echocardiography; LVEF, left ventricular ejection fraction

Global Functional Improvement

Global LV function is defined as an improvement in global LVEF by five percent or more after revascularization. (1;22) Regional functional improvement does not necessarily result in an improvement in global function because global functional recovery requires a substantial amount of viable myocardium (35% – 50%). (1) Compared with regional wall motion function, global function is more important clinically because it correlates better with symptoms of heart failure, physical capacity, and survival. (31;32)

Six of the eight studies reported on the diagnostic accuracy of MRI for predicting global functional recovery however, the sensitivity, specificity, and positive and negative likelihood ratios were not provided and, therefore, a likelihood ratio plot was not generated. The thresholds for determining global LV function were only reported in three of the six studies (krittaphong, Becker and kim 2000), of which two used an improvement in LVEF by 5% or more after revascularization and one used an improvement in ejection fraction greater than 5% (becker).

Two studies reported a statistically significant improvement in global functional recovery (Kritta, Kuhl). One study demonstrated a small increase in LVEF that reached significance only at 6 months follow-up (Bondarenko). The other three studies reported an increase in LVEF post revascularization however no p-values were reported (Becker 2008, selvanayagam 2004, Kim). For one of the studies, the authors noted that 44% (18/41) had an increase in LVEF of greater than 5% (Kim) and in another 40% (21/53) of patients had recovery of global LV function (becker 2008).

Limitations

There are a variety of limitations in the included studies.

▪ As comparing MRI results with results from ECHO there is the possibility of segmental misalignment, which could bias the results (33)

▪ One study used a 56 segment model rather than the 16 or 17 segment model to grade affected segments (34)

▪ Two studies had patients that could not complete the follow-up examination and were, therefore, excluded from the final analysis which could have biased the results (35;36)

▪ Recovery of contractile function in a given segment may be incomplete because of the admixture of scarred with viable tissue. Presence of tethering from neighbouring infracted segments as well as paradoxical movements of the heart after surgery may further distress the interpretation of regional cardiac function. Coronary revascularization may also be incomplete in patients with extensive atherosclerosis and diffuse disease (14)

▪ The follow up time used in some studies may be too short thus underestimating recoverable LV function.

▪ Most studies included patients with a higher mean LVEF, lower prevalence of diabetes and hypertension than the Ontario population that would receive viability testing.

▪ Pooled analysis of the diagnostic accuracy of MRI for predicting global functional recovery was not possible due to a lack of reporting of the sensitivity, specificity, and positive and negative likelihood ratios. Furthermore, studies poorly reported results on the diagnostic accuracy of MRI for predicting global functional recovery making results difficult to interpret.

Quality of Evidence: Diagnostic Accuracy of Cardiac MRI

Individual study quality was assessed using the QUADAS checklist (Appendix 2). Similar limitations were observed in the studies that examined regional and global functional recovery. Common study methodological limitations were: not reporting study withdrawals; not reporting uninterpretable or intermediate test results; not clearly describing the selection criteria; not blinding those who interpreted the MRI results; and not blinding those who interpreted the functional recovery results. In addition, the quality of evidence was downgraded due to the limitations in generalizability of the study populations to that of the Ontario population.

The quality of the overall body of evidence was evaluated using GRADE (Tables 11 and 12). The quality of evidence for the diagnostic accuracy of MRI is very low for the prediction of viable myocardium using either regional or global functional recovery as a surrogate for viability. Thus, any estimate of effect is uncertain.

Table 11: GRADE quality of evidence for the diagnostic accuracy of 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 (8 studies)	High
Limitations	Serious limitations*	Reduced by one level → Moderate
Indirectness		
Outcomes	Diagnostic tests are considered as surrogate outcomes	Reduced by one level → Low
Patient populations, diagnostic test, comparison test, and indirect comparisons	Patient populations are generally not representative of the Ontario population that would receive viability testing	Reduced by one level → Very Low
Inconsistency in study results	No serious inconsistencies	Unchanged
Imprecise evidence	No serious imprecision	Unchanged
Publication bias	No publication bias suspected	Unchanged
Quality of Evidence		**Very Low**

*Downgraded due to serious limitations in the quality of evidence of the individual studies including: not reporting study withdrawals; not reporting uninterpretable or intermediate test results; not clearly describing selection criteria; not blinding those who interpreted the MRI results; and not blinding those who interpreted the functional recovery results. For further details, please see the QUADAS scoring available in Appendix 2.

Table 12: GRADE quality of evidence for the diagnostic accuracy of MRI for the detection of myocardial viability based on global functional recovery in patients with known CAD

Factor	Explanation	GRADE
Risk of Bias		
Study design	Observational cohort studies (6 studies)	High
Limitations	Serious limitations*	Reduced by one level → Moderate
Indirectness		
Outcomes	Diagnostic tests are considered as surrogate outcomes	Reduced by one level→Low
Patient populations, diagnostic test, comparison test, and indirect comparisons	Patient populations are generally not representative of the Ontario population that would receive viability testing	Reduced by one level→ Very Low
Inconsistency in study results	No serious inconsistencies	Unchanged
Imprecise evidence	No serious imprecision	Unchanged
Publication bias	No publication bias suspected	Unchanged
Quality of Evidence		**Very Low**

*Downgraded due to serious limitations in the quality of evidence of the individual studies including: not reporting study withdrawals; not reporting uninterpretable or intermediate test results; not clearly describing selection criteria; not blinding those who interpreted the MRI results; and not blinding those who interpreted the functional recovery results. For further details, please see the QUADAS scoring available in Appendix 2.

Cardiac MRI Viability and Prognosis

No studies were found examining the long-term benefit of assessing myocardial viability using cardiac MRI on patient outcomes. In addition, no studies were found examining the contribution of cardiac MRI viability imaging to treatment decision making.

Conclusion

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 those using ≤50% hyperenhancement as their viability threshold [78.7 (95% CI: 69.1% - 88.2%) and 96.2 (95% CI: 91.8 – 100.6); p=0.0044 respectively]. Marked differences in specificity were observed [73.6 (95% CI: 62.6% - 84.6%) and 47.2 (95% CI: 22.2 – 72.3); p=0.2384 respectively]; however, these findings 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.

Appendices

Appendix 1: Literature Search Strategies

The textwords: viab* or hibernat* or functional recovery were applied to the following search:

Cardiac MRI – Final Search WITH Diagnostic Filter

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

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

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

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

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

9   exp heart failure/ (126664)
10   ((myocardi* or heart or cardiac) adj2 (failure or decompensation or insufficiency)).mp. [mp=title, abstract, subject
      headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (108718)
11   exp heart left ventricle failure/ (9421)
12   (left adj2 ventric* adj2 (dysfunction* or failure or insufficienc*)).mp. (16241)
13   or/1-12 (434030)
14   exp nuclear magnetic resonance imaging/ (250643)
15   (magnetic resonance or CMR or MRI or MRA or MR angiography or MR imaging).ti,ab. (185700)
16   15 or 14 (291370)
17   16 and 13 (11807)
18   limit 17 to (human and english language and yr="2005 -Current") (5219)
19   limit 18 to (editorial or letter or note) (597)
20   case report/ (1057346)
21   18 not (19 or 20) (3355)
22   (sensitiv* or diagnos* or accuracy or test*).mp. [mp=title, abstract, subject headings, heading word, drug trade name,
      original title, device manufacturer, drug manufacturer name] (3271056)
23   di.fs. (1443224)
24   21 and (22 or 23) (2541)

Appendix 2: Quality Assessment of Included Systematic Reviews with the AMSTAR Checklist

As detailed in the methods section, the quality of the systematic reviews that were included in this report was assessed with the AMSTAR Checklist. The results of the quality assessment are provided in Table A1. Explanations are provided when 'no', 'can't answer', or 'not applicable' was selected for a checklist component.

Table A1: Quality assessment of included systematic reviews with AMSTAR checklist*

	Author, Year	
AMSTAR Checklist	**Schinkel et al., 2007 (22)**	**Beanlands et al., 2006 (26)**
1. Was an a priori design provided?	No: while the review refers to a previous SR for the inclusion criteria, these criteria only address the diagnostic accuracy analysis and not the prognostication and other symptoms analyses for which no inclusion criteria are specified	Yes
2. Was there duplicate study selection and data extraction?	Can't answer: this information was not provided in the review	Can't answer: this information was not provided in the review
3. Was a comprehensive literature search performed?	Yes	No: key words and MESH terms not stated and a search strategy was not included
4. Was the status of publication (i.e. grey literature) used as an inclusion criteria?	Can't answer: this information was not provided in the review	Can't answer: this information was not provided in the review.
5. Was a list of the studies (included and excluded) provided?	No: excluded studies were not listed	No: excluded studies were not listed
6. Were the characteristics of the included studies provided?	Yes	No: inadequate aggregated information on the characteristics of the participants provided
7. Was the scientific quality of the included studies assessed and documented?	No: there is no mention of a priori methods to assess the quality of the included studies and only a few general statements regarding study quality were provided.	Yes
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?	n/a (see question 7)	Yes
9. Were the methods used to combine the findings of the studies appropriate?	No: tests were not performed to assess the appropriateness of pooling the accuracy or mortality data	No: tests were not performed to assess the appropriateness of pooling the accuracy or mortality data
10. Was the likelihood of publication bias assessed?	No: the likehood of publication bias was not addressed	No: the likehood of publication bias was not addressed
11. Was the conflict of interest stated?	No: the sources of funding for the included studies in the review and potential conflicts of interest for review authors were not reported	No: the sources of funding for the included studies in the review and potential conflicts of interest (beyond specific funding for the literature search and teleconferencing) for review authors were not reported

*Each component of the checklist is scored as yes, no, can't answer, or not applicable

Table A2: Quality of studies investigating the accuracy of MRI for the detection of regional functional recovery (Part I)

QUADAS Tool	Author, Year				
	Hoffmann 2008	Schvartzman 2003	Krittayaphong 2008	Becker 2008	Kim 2000
1. Was the spectrum of patients representative of patients who will receive test?*	No	Unclear	No	No	Unclear
2. Were selection criteria clearly described?	No	Yes	Yes	No	Yes
3. Is reference standard likely to correctly classify the target condition?	Yes	Yes	Yes	Yes	Yes
4. Is time period between reference standard and index test short enough to be reasonably sure the target condition did not change between tests?	n/a	n/a	n/a	n/a	n/a
5. Did whole sample or random selection of sample receive verification using reference standard of diagnosis?	Yes	Yes	Yes	Yes	Yes
6. Did patients receive the same reference standard regardless of index test result?	Yes	Yes	Yes	Yes	Yes
7. Was reference standard independent of index test?	Yes	Yes	Yes	Yes	Yes
8. Was execution of index test described in sufficient detail to permit replication of test?	Yes	Yes	Yes	Yes	Yes
9. Was execution of reference standard described in sufficient detail to permit its replication?	Yes	Yes	Yes	Yes	Yes
10. Were index test results interpreted without knowledge of results of reference standard?	Yes	Yes	Yes	Yes	Yes
11. Were reference standard results interpreted without knowledge of results of index standard?	Yes	Unclear	Yes	Yes	Yes
12. Were same clinical data available when test results were interpreted as would be available when test is used in practice?	Unclear	Unclear	Unclear	?	Unclear
13. Were uninterpretable / intermediate test results reported?	Yes	No	No	Yes	Yes
14. Were withdrawals from the study explained?	No	No (no mention of wd)	Yes	Yes	Yes

*Patient characteristics (mean age, percentage male, mean LVEF, percentage with diabetes, percentage with hypertension, and percentage with previous MI) from each study population were compared with the typical patient population undergoing viability testing in Ontario. This typical patient population was defined by the patient population enrolled in the Ontario Cardiac FDG PET Registry (CADRE) study. A study population was considered representative if at least five of the six characteristics were similar (within ± 10) to the reference population. Overall, most study populations had a lower percentage of people with diabetes, and hypertension, and a higher EF than the Ontario reference population.

Table A3: Quality of studies investigating the accuracy of MRI for the detection of regional functional recovery (Part II)

| QUADUS Tool	Kuhl 2006	Bondarenko 2008	Selvanayagam 2004
1. Was the spectrum of patients representative of patients who will receive test?*	Yes?	No	No
2. Were selection criteria clearly described?	Yes	Yes	Yes
3. Is reference standard likely to correctly classify the target condition?	Yes	Yes	Yes
4. Is time period between reference standard and index test short enough to be reasonably sure the target condition did not change between tests?	n/a	n/a	n/a
5. Did whole sample or random selection of sample receive verification using reference standard of diagnosis?	Yes	Yes	Yes
6. Did patients receive the same reference standard regardless of index test result?	Yes	Yes	Yes
7. Was reference standard independent of index test?	Yes	Yes	Yes
8. Was execution of index test described in sufficient detail to permit replication of test?	Yes	Yes	Yes
9. Was execution of reference standard described in sufficient detail to permit its replication?	Yes	Yes	Yes
10. Were index test results interpreted without knowledge of results of reference standard?	Yes	Unclear	Unclear
11. Were reference standard results interpreted without knowledge of results of index standard?	Unclear	Unclear	Yes
12. Were same clinical data available when test results were interpreted as would be available when test is used in practice?	No?	?	?
13. Were uninterpretable / intermediate test results reported?	No	No	No
14. Were withdrawals from the study explained?	Yes? (no mention of wd)	Yes	Yes

*Patient characteristics (mean age, percentage male, mean LVEF, percentage with diabetes, percentage with hypertension, and percentage with previous MI) from each study population were compared with the typical patient population undergoing viability testing in Ontario. This typical patient population was defined by the patient population enrolled in the Ontario Cardiac FDG PET Registry (CADRE) study. A study population was considered representative if at least five of the six characteristics were similar (within ± 10) to the reference population. Overall, most study populations had a lower percentage of people with diabetes, and hypertension, and a higher EF than the Ontario reference population.

# Appendix 3: Subgroup Sensitivity and Specificity Forest Plots

ECHO

Study	TP	FP	FN	TN	Sensitivity	Specificity
Becker 2008	189	61	38	175	0.83 [0.78, 0.88]	0.74 [0.68, 0.80]
Hoffman 2009	209	67	42	194	0.83 [0.78, 0.88]	0.74 [0.69, 0.80]
Schvartzman 2003	95	79	6	27	0.94 [0.88, 0.98]	0.25 [0.18, 0.35]
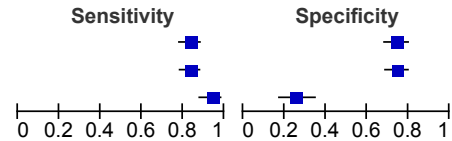
cMR

Study	TP	FP	FN	TN	Sensitivity	Specificity
Bondarenko 2008	98	21	60	79	0.62 [0.54, 0.70]	0.79 [0.70, 0.87]
Kim 2000	365	147	60	232	0.86 [0.82, 0.89]	0.61 [0.56, 0.66]
Krittayaphong 2008	357	125	124	621	0.74 [0.70, 0.78]	0.83 [0.80, 0.86]
Kuhl 2006	94	27	2	64	0.98 [0.93, 1.00]	0.70 [0.60, 0.79]
Selvanayagam 2004	266	96	77	173	0.78 [0.73, 0.82]	0.64 [0.58, 0.70]
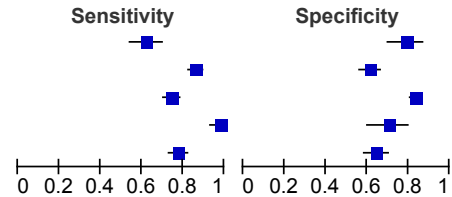
Figure A1: Sensitivity and specificity Forest plots showing the accuracy of cardiac MRI for detecting regional functional recovery stratified by method of functional recovery assessment
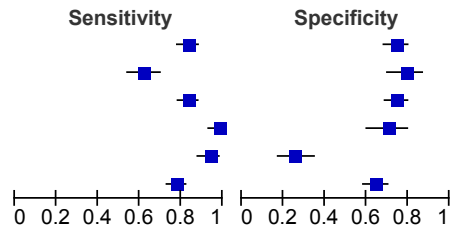
<6 months

Study	TP	FP	FN	TN	Sensitivity	Specificity
Kim 2000	365	147	60	232	0.86 [0.82, 0.89]	0.61 [0.56, 0.66]
Krittayaphong 2008	357	125	124	621	0.74 [0.70, 0.78]	0.83 [0.80, 0.86]
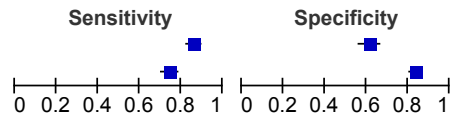
≥6 months

Study	TP	FP	FN	TN	Sensitivity	Specificity
Becker 2008	189	61	38	175	0.83 [0.78, 0.88]	0.74 [0.68, 0.80]
Bondarenko 2008	98	21	60	79	0.62 [0.54, 0.70]	0.79 [0.70, 0.87]
Hoffman 2009	209	67	42	194	0.83 [0.78, 0.88]	0.74 [0.69, 0.80]
Kuhl 2006	94	27	2	64	0.98 [0.93, 1.00]	0.70 [0.60, 0.79]
Schvartzman 2003	95	79	6	27	0.94 [0.88, 0.98]	0.25 [0.18, 0.35]
Selvanayagam 2004	266	96	77	173	0.78 [0.73, 0.82]	0.64 [0.58, 0.70]

Figure A2: Sensitivity and specificity Forest plots showing the accuracy of cardiac MRI for detecting regional functional recovery stratified by length of follow-up

Mean LVEF <40%

Study	TP	FP	FN	TN	Sensitivity	Specificity	Sensitivity	Specificity
Bondarenko 2008	98	21	60	79	0.62 [0.54, 0.70]	0.79 [0.70, 0.87]		
Krittayaphong 2008	357	125	124	621	0.74 [0.70, 0.78]	0.83 [0.80, 0.86]		
Kuhl 2006	94	27	2	64	0.98 [0.93, 1.00]	0.70 [0.60, 0.79]		
Schvartzman 2003	95	79	6	27	0.94 [0.88, 0.98]	0.25 [0.18, 0.35]		

Mean LVEF ≥40%
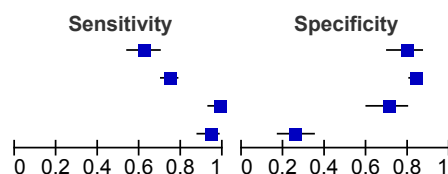
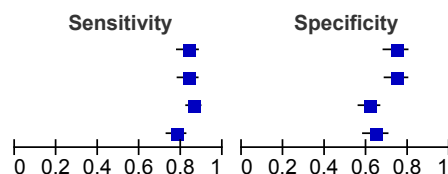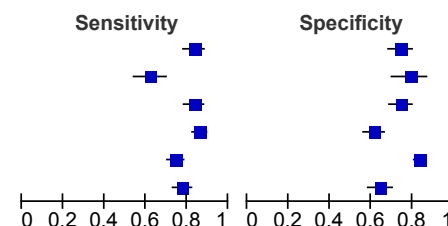| Study	TP	FP	FN	TN	Sensitivity	Specificity	Sensitivity	Specificity
Becker 2008	189	61	38	175	0.83 [0.78, 0.88]	0.74 [0.68, 0.80]		
Hoffman 2009	209	67	42	194	0.83 [0.78, 0.88]	0.74 [0.69, 0.80]		
Kim 2000	365	147	60	232	0.86 [0.82, 0.89]	0.61 [0.56, 0.66]		
Selvanayagam 2004	266	96	77	173	0.78 [0.73, 0.82]	0.64 [0.58, 0.70]		

Figure A3: Sensitivity and specificity Forest plots showing the accuracy of cardiac MRI for detecting regional functional recovery stratified by mean preoperative LV ejection fraction

≤25% hyperenhancement

Study	TP	FP	FN	TN	Sensitivity	Specificity	Sensitivity	Specificity
Becker 2008	189	61	38	175	0.83 [0.78, 0.88]	0.74 [0.68, 0.80]		
Bondarenko 2008	98	21	60	79	0.62 [0.54, 0.70]	0.79 [0.70, 0.87]		
Hoffman 2009	209	67	42	194	0.83 [0.78, 0.88]	0.74 [0.69, 0.80]		
Kim 2000	365	147	60	232	0.86 [0.82, 0.89]	0.61 [0.56, 0.66]		
Krittayaphong 2008	357	125	124	621	0.74 [0.70, 0.78]	0.83 [0.80, 0.86]		
Selvanayagam 2004	266	96	77	173	0.78 [0.73, 0.82]	0.64 [0.58, 0.70]		

≤50% hyperenhancement

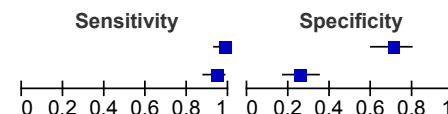| Study	TP	FP	FN	TN	Sensitivity	Specificity	Sensitivity	Specificity
Kuhl 2006	94	27	2	64	0.98 [0.93, 1.00]	0.70 [0.60, 0.79]		
Schvartzman 2003	95	79	6	27	0.94 [0.88, 0.98]	0.25 [0.18, 0.35]		

Figure A4: Sensitivity and specificity Forest plots showing the accuracy of cardiac MRI for detecting regional functional recovery stratified by viability threshold

References

(1) Medical Advisory Secretariat. Positron emission tomography for the assessment of myocardial viability: an evidence-based analysis. Ont Health Technol Assess Ser [Internet]. 2005 Oct [cited 2010 04 22]; 5(16) 1-167. Available from: http://www.health.gov.on.ca/english/providers/program/mas/tech/reviews/pdf/rev_petmyo_100105.pdf.

(2) Schinkel AF, Bax JJ, Poldermans D. Clinical assessment of myocardial hibernation. Heart 2005; 91(1):111-7.

(3) Bax JJ, van der Wall EE, Harbinson M. Radionuclide techniques for the assessment of myocardial viability and hibernation. Heart 2004; 90 Suppl 5:v26-v33.

(4) Chow CM, Donovan L, Manuel D, Johansen H, Tu JV. Regional variation in self-reported heart disease prevalence in Canada. Can J Cardiol 2005; 21(14):1265-71.

(5) Heart and Stroke Foundation of Ontario. Statistics [Internet]. [updated 2009; cited 2009 Dec 14]. Available from: http://www.heartandstroke.on.ca/site/c.pvI3IeNWJwE/b.3581729/k.359A/Statistics.htm#heartdisease

(6) Senior R. Diagnostic and imaging considerations: role of viability. Heart Fail Rev 2006; 11(2):125-34.

(7) Underwood SR, Bax JJ, vom DJ, Henein MY, Knuuti J, van Rossum AC et al. Imaging techniques for the assessment of myocardial hibernation. Report of a Study Group of the European Society of Cardiology. Eur Heart J 2004; 25(10):815-36.

(8) Lalonde L, Ziadi MC, Beanlands R. Cardiac positron emission tomography: current clinical practice. Cardiol Clin 2009; 27(2):237-55.

(9) Rizzello V, Poldermans D, Bax JJ. Assessment of myocardial viability in chronic ischemic heart disease: current status. Q J Nucl Med Mol Imaging 2005; 49(1):81-96.

(10) Ghesani M, Depuey EG, Rozanski A. Role of F-18 FDG positron emission tomography (PET) in the assessment of myocardial viability. Echocardiography 2005; 22(2):165-77.

(11) Di Carli MF, Hachamovitch R. New technology for noninvasive evaluation of coronary artery disease. Circulation 2007; 115(11):1464-80.

(12) Chacko GN. PET imaging in cardiology. Hell J Nucl Med 2005; 8(3):140-4.

(13) Tomlinson DR, Becher H, Selvanayagam JB. Assessment of myocardial viability: comparison of echocardiography versus cardiac magnetic resonance imaging in the current era. Heart Lung Circ 2008; 17(3):173-85.

(14) Kim RJ, Wu E, Rafael A, Chen E-L, Parker MA, Simonetti OP et al. The use of contrast-enhanced magnetic resonance imaging to identify reversible myocardial dysfunction. N Engl J Med 2000; 343:1445-53.

(15) Strzelczyk J, Attili A. Cardiac magnetic resonance evaluation of myocardial viability and

ischemia. Semin Roentgenol 2008; 43(3):193-203.

(16)   Health Canada. Medical devices active licence listing [Internet]. [updated 2009 Feb 19; cited 2009 Oct 8]. Available from: http://webprod.hc-sc.gc.ca/mdll-limh/dispatch-repartition.do?type=active&lang=eng

(17)   Pai M, McCulloch M, Colford J. STATA meta-analysis commands version 6 [Internet]. California, U.S.A.: Systematic Reviews Group, UC Berkeley; [updated 2004; cited 2009 Nov 23]. Available from: http://www.medepi.net/meta/software/STATA_Metaanalysis_commands_V6_March2004.pdf

(18)   Jaeschke R, Guyatt GH, Sackett DL, the Evidence-Based Medicine Working Group. How to use an article about a diagnostic test [Internet]. [updated 2007 Aug 15; cited 2009 Nov 23]. Available from: http://www.cche.net/usersguides/diagnosis.asp

(19)   Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. BMC Med Res Methodol 2007; 7:10.

(20)   Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S et al. Grading quality of evidence and strength of recommendations. BMJ 2004; 328(7454):1490.

(21)   Goodman, C. Literature searching and evidence interpretation for assessing health care practices. Stockholm, Sweden: Swedish Council on Technology Assessment in Health Care. 1996 81 p. SBU Report No. 119E.

(22)   Schinkel AF, Bax JJ, Poldermans D, Elhendy A, Ferrari R, Rahimtoola SH. Hibernating myocardium: diagnosis and patient outcomes. Curr Probl Cardiol 2007; 32(7):375-410.

(23)   Shah DJ, Kim HW, Kim RJ. Evaluation of ischemic heart disease. Heart Failure Clinics 2009; 5(3):315-32.

(24)   Bax JJ, Poldermans D, Elhendy A, Boersma E, Rahimtoola SH. Sensitivity, specificity, and predictive accuracies of various noninvasive techniques for detecting hibernating myocardium. Curr Probl Cardiol 2001; 26(2):147-86.

(25)   Beanlands RS, Chow BJ, Dick A, Friedrich MG, Gulenchyn KY, Kiess M et al. CCS/CAR/CANM/CNCS/CanSCMR joint position statement on advanced noninvasive cardiac imaging using positron emission tomography, magnetic resonance imaging and multidetector computed tomographic angiography in the diagnosis and evaluation of ischemic heart disease--executive summary. Can J Cardiol 2007; 23(2):107-19.

(26)   Beanlands, R. S., Chow, B. J., Dick, A., Friedrich, M. G., Gulenchyn, K. Y., Kiess, M., Leong-Poi, H., Miller, R. M., Nichol, G., Freeman, M., Bogaty, P., Honos, G., Hudon, G., Wisenberg, G., Van Berkom, J., Williams, K., Yoshinaga, K., and Graham, J. CCS / CAR / CANM / CNCS / Can SCMR joint position statement on advanced non-invasive cardiac imaging using positron emission tomography, magnetic resonance imaging and multi-detector computed tomography angiography in the diagnosis and evaluation of ischemic heart disease [Internet]. Ottawa, ON: Canadian Cardiovascular Society. 2006 [cited: 2009 Aug 26]. 48 p. Available from: http://www.ccs.ca/download/position_statements/cardiac_imaging_Dec11_appen_tables.pdf

(27)   Schinkel AF, Bax JJ, Poldermans D. Clinical assessment of myocardial hibernation. Heart 2005; 91(1):111-7.

(28)   Barrington SF, Chambers J, Hallett WA, O'Doherty MJ, Roxburgh JC, Nunan TO. Comparison of sestamibi, thallium, echocardiography and PET for the detection of hibernating myocardium. Eur J Nucl Med Mol Imaging 2004; 31(3):355-61.

(29)   Maes AF, Borgers M, Flameng W, Nuyts JL, van de WF, Ausma JJ et al. Assessment of myocardial viability in chronic coronary artery disease using technetium-99m sestamibi SPECT. Correlation with histologic and positron emission tomographic studies and functional follow-up. J Am Coll Cardiol 1997; 29(1):62-8.

(30)   Wiggers H, Nielsen TT, Bottcher M, Egeblad H, Botker HE. Positron emission tomography and low-dose dobutamine echocardiography in the prediction of postrevascularization improvement in left ventricular function and exercise parameters. Am Heart J 2000; 140(6):928-36.

(31)   Gerber BL, Ordoubadi FF, Wijns W, Vanoverschelde JL, Knuuti MJ, Janier M et al. Positron emission tomography using(18)F-fluoro-deoxyglucose and euglycaemic hyperinsulinaemic glucose clamp: optimal criteria for the prediction of recovery of post-ischaemic left ventricular dysfunction. Results from the European Community Concerted Action Multicenter study on use of(18)F-fluoro-deoxyglucose Positron Emission Tomography for the Detection of Myocardial Viability. Eur Heart J 2001; 22(18):1691-701.

(32)   Slart RH, Bax JJ, van Veldhuisen DJ, van der Wall EE, Irwan R, Sluiter WJ et al. Prediction of functional recovery after revascularization in patients with chronic ischaemic left ventricular dysfunction: head-to-head comparison between 99mTc-sestamibi/18F-FDG DISA SPECT and 13N-ammonia/ 18F-FDG PET. Eur J Nucl Med Mol Imaging 2006; 33(6):716-23.

(33)   Schvartzman PR, Srichai MB, Grimm R, Obuchowski NA, Hammer DF, McCarthy P et al. Nonstress delayed-enhancement magnetic resonance imaging of the myocardium predicts improvement of function after revascularization for chronic ischemic heart disease with left ventricular dysfunction. Am Heart J 2003; 146:535-41.

(34)   Selvanayagam JB, Jerosch-Herold M, Porto I, Sheridan D, Cheng AS, Petersen SE et al. Resting myocardial blood flow is impaired in hibernating myocardium: a magnetic resonance study of quantitative perfusion assessment.[see comment]. Circulation 2005; 112(21):3289-96.

(35)   Becker M, Lenzen A, Ocklenburg C, Stempel K, Kuhl H, Neizel M et al. Myocardial deformation imaging based on ultrasonic pixel tracking to identify reversible myocardial dysfunction. J Am Coll Cardiol 2008; 51(15):1473-81.

(36)   Kuhl HP, Lipke CS, Krombach GA, Katoh M, Battenberg TF, Nowak B et al. Assessment of reversible myocardial dysfunction in chronic ischaemic heart disease: comparison of contrast-enhanced cardiovascular magnetic resonance and a combined positron emission tomography-single photon emission computed tomography imaging protocol. Eur Heart J 2006; 27(7):846-53.