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Positron Emission Tomography for the Assessment of Myocardial Viability

An Evidence-Based Analysis

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The Medical Advisory Secretariat is part of the Ontario Ministry of Health and Long-Term Care. The mandate of the Medical Advisory Secretariat is to provide evidence-based policy advice on the coordinated uptake of health services and new health technologies in Ontario to the Ministry of Health and Long-Term Care and to the healthcare system. The aim is to ensure that residents of Ontario have access to the best available new health technologies that will improve patient outcomes.

The Medical Advisory Secretariat also provides a secretariat function and evidence-based health technology policy analysis for review by the Ontario Health Technology Advisory Committee (OHTAC).

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Table of Contents

Abbreviations

CABG	Coronary artery bypass graft
CAD	Coronary artery disease
AUC	Area under the curve
CeMRI	Contrast-enhanced magnetic resonance imaging
CI	Confidence interval
CHF	Congestive heart failure
CT	Computed tomography
ECG	Electrocardiogram
FDG	Fluorodeoxyglucose F 18
ICES	Institute for Clinical Evaluative Sciences
LLS	Linear local shortening
LV	Left ventricular
LVEF	Left ventricular ejection fraction
MBq	Megabecquerel
MCE	Myocardial contrast echocardiography
MCi	Mega currie
MeV	Mega electron volt
MRI	Magnetic resonance imaging
NPV	Negative predictive value
NYHA	New York Heart Association
PCI	Percutaneous coronary intervention
PET	Positron emission tomography
QUADAS	Quality Assessment of Diagnostic Accuracy Studies
PPV	Positive predictive value
^{82}Rb	Rubidium 82
ROC	Receiver operating characteristic
RNA	Radionuclide angiography
RWM	Regional wall motion
SPECT	Single photon emission computed tomography
Tc 99m MIBI	Technetium Tc 99m sestamibi
UPA	Unipolar amplitude
UVA	Unipolar voltage amplitude

Executive Summary

Objective

The objective was to update the 2001 systematic review conducted by the Institute For Clinical Evaluative Sciences (ICES) on the use of positron emission tomography (PET) in assessing myocardial viability. The update consisted of a review and analysis of the research evidence published since the 2001 ICES review to determine the effectiveness and cost-effectiveness of PET in detecting left ventricular (LV) viability and predicting patient outcomes after revascularization in comparison with other noninvasive techniques.

Background

Left Ventricular Viability

Heart failure is a complex syndrome that impairs the contractile ability of the heart to maintain adequate blood circulation, resulting in poor functional capacity and increased risk of morbidity and mortality. It is the leading cause of hospitalization in elderly Canadians. In more than two-thirds of cases, heart failure is secondary to coronary heart disease. It has been shown that dysfunctional myocardium resulting from coronary heart disease (CAD) may recover contractile function (i.e. considered viable). Dysfunctional but viable myocardium may have been stunned by a brief episode of ischemia, followed by restoration of perfusion, and may regain function spontaneously. It is believed that repetitive stunning results in hibernating myocardium that will only regain contractile function upon revascularization.

For people with CAD and severe LV dysfunction (left ventricular ejection fraction [LVEF] <35%) refractory to medical therapy, coronary artery bypass and heart transplantation are the only treatment options. The opportunity for a heart transplant is limited by scarcityof donor hearts. Coronary artery bypass in these patients is associated with high perioperative complications; however, there is evidence that revascularization in the presence of dysfunctional but viable myocardium is associated with survival benefits and lower rates of cardiac events. The assessment of left ventricular (LV) viability is, therefore, critical in deciding whether a patient with coronary artery disease and severe LV dysfunction should undergo revascularization, receive a heart transplant, or remain on medical therapy.

Assessment of Left Ventricular Viability

Techniques for assessing myocardial viability depend on the measurement of a specific characteristic of viable myocytes such as cell membrane integrity, preserved metabolism, mitochondria integrity, and preserved contractile reserve. In Ontario, single photon emission computed tomography (SPECT) using radioactive ^{201}thallium is the most commonly used technique followed by dobutamine echocardiography. Newer techniques include SPECT using technetium tracers, cardiac magnetic resonance imaging, and PET, the subject of this review.

Positron Emission Tomography

PET is a nuclear imaging technique based on the metabolism of radioactive analogs of normal substrates such as glucose and water. The radiopharmaceutical used most frequently in myocardial viability assessment is F18 fluorodeoxyglucose (FDG), a glucose analog. The procedure involves the intravenous administration of FDG under controlled glycemic conditions, and imaging with a PET scanner. The images are reconstructed using computer software and analyzed visually or semi-quantitatively, often in conjunction with perfusion images. Dysfunctional but stunned myocardium is characterized by normal perfusion and normal FDG uptake; hibernating myocardium exhibits reduced perfusion and normal/enhanced FDG uptake (perfusion/metabolism mismatch), whereas scar tissue is characterized by reduction in both perfusion and FDG uptake (perfusion/metabolism match).

Review Strategy

The Medical Advisory Secretariat used a search strategy similar to that used in the 2001 ICES review to identify English language reports of health technology assessments and primary studies in selected databases, published from January 1, 2001 to April 20, 2005. Patients of interest were those with CAD and severe ventricular dysfunction being considered for revascularization that had undergone viability assessment using either PET and/or other noninvasive techniques. The outcomes of interest were diagnostic and predictive accuracy with respect to recovery of regional or global LV function, long-term survival and cardiac events, and quality of life. Other outcomes of interest were impact on treatment decision, adverse events, and cost-effectiveness ratios.

Of 456 citations, 8 systematic reviews/meta-analyses and 37 reports on primary studies met the selection criteria. The reports were categorized using the Medical Advisory Secretariat levels of evidence system, and the quality of the reports was assessed using the criteria of the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) developed by the Centre for Dissemination of Research (National Health Service, United Kingdom). Analysis of sensitivity, specificity, predictive values and likelihood ratios were conducted for all data as well as stratified by mean left ventricular ejection fraction (LVEF). There were no randomized controlled trials. The included studies compared PET with one or more other noninvasive viability tests on the same group of patients or examined the long-term outcomes of PET viability assessments. The quality assessment showed that about 50% or more of the studies had selection bias, interpreted tests without blinding, excluded uninterpretable segments in the analysis, or did not have clearly stated selection criteria. Data from the above studies were integrated with data from the 2001 ICES review for analysis and interpretation.

Summary of Findings

- The evidence was derived from populations with moderate to severe ischemic LV dysfunction with an overall quality that ranges from moderate to low.
- PET appears to be a safe technique for assessing myocardial viability.
- CAD patients with moderate to severe ischemic LV dysfunction and residual viable myocardium had significantly lower 2-year mortality rate (3.2%) and higher event-free survival rates (92% at 3 years) when treated with revascularization than those who were not revascularized but were treated medically (16% mortality at 2-years and 48% 3-year event-free survival).
- A large meta-analysis and moderate quality studies of diagnostic accuracy consistently showed that compared to other noninvasive diagnostic tests such as thallium SPECT and echocardiography, FDG PET has:
    - Higher sensitivity (median 90%, range 71%–100%) and better negative likelihood ratio (median 0.16, range 0–0.38; ideal <0.1) for predicting regional myocardial function recovery after revascularization.
    - Specificity (median 73%, range 33%–91%) that is similar to other radionuclide imaging but lower than that of dobutamine echocardiography
    - Less useful positive likelihood ratio (median 3.1, range 1.4 –9.2; ideal>10) for predicting segmental function recovery.
- Taking positive and negative likelihood ratios together suggests that FDG PET and dobutamine echocardiography may produce small but sometimes important changes in the probability of recovering regional wall motion after revascularization.
- Given its higher sensitivity, PET is less likely to produce false positive results in myocardial viability. PET, therefore, has the potential to identify some patients who might benefit from revascularization, but who would not have been identified as suitable candidates for revascularization using thallium SPECT or dobutamine echocardiography.
- PET appears to be superior to other nuclear imaging techniques including SPECT with ^{201}thallium or technetium labelled tracers, although recent studies suggest that FDG SPECT may have comparable diagnostic accuracy as FDG PET for predicting regional and global LV function recovery.
- No firm conclusion can be reached about the incremental value of PET over other noninvasive techniques for predicting global function improvement or long-term outcomes in the most important target population (patients with severe ischemic LV dysfunction) due to lack of direct comparison.

- An Ontario-based economic analysis showed that in people with CAD and severe LV dysfunction and who were found to have no viable myocardium or indeterminate results by thallium SPECT, the use of PET as a follow-up assessment would likely result in lower cost and better 5-year survival compared to the use of thallium SPECT alone. The projected annual budget impact of adding PET under the above scenario was estimated to range from $1.5 million to $2.3 million.

Conclusion

- In patients with severe LV dysfunction, that are deemed to have no viable myocardium or indeterminate results in assessments using other noninvasive tests, PET may have a role in further identifying patients who may benefit from revascularization. No firm conclusion can be drawn on the impact of PET viability assessment on long-term clinical outcomes in the most important target population (i.e. patients with severe LV dysfunction).

Objective

The objective was to update the 2001 systematic review conducted by the Institute For Clinical Evaluative Sciences (ICES) on the use of positron emission tomography (PET) in assessing myocardial viability. The update consisted of a review and analysis of the research evidence published since the 2001 ICES review to determine the effectiveness and cost-effectiveness of PET in detecting left ventricular (LV) viability and predicting patient outcomes after revascularization in comparison with other noninvasive techniques.

Clinical Need

Coronary Artery Disease

Heart failure is a complex syndrome that impairs the ability of the heart to maintain adequate blood circulation, resulting in multiorgan abnormalities and, eventually, death. The prevalence of symptomatic heart failure is estimated at 1.0 to 2.0%. (1) Heart failure is associated with poor functional capacity, decreased quality of life, and increased risk of morbidity and mortality. It is the leading cause of hospitalization in elderly Canadians and accounted for 2% (4,009) of all cardiac deaths in 1992. (2;3),

Between 1996 and 1997, the 1-year mortality rate from heart failure in Ontario was 32.9% for men and 31.1% for women.(2) Jong et al. (4) reported that during the period of April 1994 to March 1997, the average number of Ontarians that were newly hospitalized each year as a result of heart failure was 12,900.

In more than two-thirds of the cases, heart failure is secondary to coronary artery disease (CAD). (5) Despite advances in the management of CAD and heart failure, the prevalence and incidence of left ventricular (LV) dysfunction are increasing dramatically, leading to a heavy burden of illness.

In CAD, stenosis of coronary arteries reduces coronary blood flow and oxygen delivery to the myocardium (ischemia). Severe and prolonged ischemia may result in infarction with irreversible cell injury, cell death, and formation of myocardial scar tissue. Both ischemia and infarction reduce the contractile capacity of the myocardium, resulting in LV dysfunction (an ejection fraction [EF] <40%).(1) Among patients with CAD and severe ventricular dysfunction, mortality rates range from 10% to 60% at 1 year. (6).

Treatment of ischemic heart failure involves optimal medical therapy, including angiotensin-converting enzyme inhibitors, diuretics, spironolactone, β-blockers, and digoxin. Despite advances in medical therapy of heart failure, the prognosis and quality of life for these patients remains poor. Surgery may be necessary to repair damaged heart valves or reduce the ventricular wall tension (partial ventriculectomy). Pacemakers and implantable cardiovertor defibrillator may be effective in patients with severe heart failure, dilated cardiomyopathy, and wide QRS complex. For patients who fail to respond to the above therapies, the remaining treatment options are revascularization using either coronary artery bypass graft (CABG) or percutaneously coronary intervention (PCI) including balloon angioplasty and/or stenting. Heart transplantation is the last treatment option that provides an excellent long-term prognosis, but its use is limited by the supply of donor hearts. The choice of treatment is usually based on an assessment of the patient's clinical and functional status, degree of heart failure, extent of the coronary artery disease, and degree of ischemic injury to the myocardium.

Assessment of Ischemic Heart Failure

Assessment of CAD and heart failure usually include:

- The identification of the affected coronary arteries and the extent of the stenosis (anatomy)
- Assessment of the degree to which blood supply (perfusion) to the myocardium has been affected by the stenosis

- Assessment of viability of the myocardium, that is, the degree to which the function of the myocardium has been affected, and whether the dysfunction is likely to be reversed by revascularization
- Assessment of the risk of cardiac events in the future

Myocardial Viability

Left ventricular dysfunction caused by CAD is sometimes reversible; non-contracting but viable myocardium may have the potential to recover contractile function.

Viable myocardium is defined as myocardial segments characterized by reduced contractile function at rest, but potentially recoverable either spontaneously or with revascularization using either coronary artery bypass graft (CABG) or percutaneous coronary interventions (PCIs).(7) Dysfunctional but viable myocardium is often described as either stunned or hibernating.

Stunned myocardium refers to myocardium in which a short bout of ischemia resulted in a prolonged reduction in myocardial contractile function that eventually recovers.(6) Stunned myocardium is characterized by contractile dysfunction and normal or near normal perfusion.

Hibernating myocardium refers to dysfunctional myocardium with reduced myocardial perfusion but preserved cell viability. Hibernation may be a sum of repetitive and cumulative stunning rather than the result of chronic hypoperfusion. Hibernating myocardium may have normal or near normal perfusion at rest with reduced coronary flow reserve. (8;9),(10)

The differentiation between stunned and hibernating myocardium is complicated because they may coexist. Moreover, necrotic and viable cells may coexist within a given myocardial segment. The likelihood of functional recovery of the segment after revascularization is related to the extent of myocyte injury and the amount of fibrosis in the segment.(11)

Long-term hibernation may lead to irreversible loss of myocardial function. Camici et al. (5) suggest there is a continuum of pathophysiology associated with myocardial hibernation. They have proposed that repetitive stunning results in “functional hibernation” that has no significant changes in contractile protein apparatus, and is associated with rapid functional recovery following revascularization. Without revascularization, “functional hibernation” progresses to “structural hibernation”, with ultrastructural abnormalities within the myocyte and prolonged functional recovery. If blood supply is not restored, myocytes will eventually die through necrosis and or apoptosis (Appendix 1).(5) Thus, stunning, hibernation, and cell death represent a continuum of changes that, if left untreated, lead to cellular dedifferentiation, degeneration, and myocardial fibrosis.(8)

Incidence of Viable Myocardium

It has been reported that 31% to 61% of people with ischemic LV dysfunction have 25% to 30% of viable myocardium. This is believed to be the minimum amount of viable myocardium required for functional recovery after revascularization. (12)

Why Assess Myocardial Viability?

For patients with relatively preserved LV function (ejection fraction >35%) and severe symptoms of angina pectoris that interfere with daily lifestyle, coronary revascularization may be indicated without the need for viability studies. (13)

For the subgroup of CAD patients with severe LV dysfunction (ejection fraction <35%) and symptoms of heart failure refractory to medical therapy, the remaining options are revascularization or heart transplantation. Their opportunity for a heart transplant is limited by the scarcity of donor hearts. Although these patients have high operative risks for procedures including revascularization (14), revascularization has been associated with improved survival in those patients with viable myocardium. (15;16) In such circumstances, a high quality test is critical to assess the presence or

absence of hibernating myocardium, in order to determine whether these patients should undergo revascularization, receive a heart transplant, or remain on medical therapy.

Testing For Myocardial Viability

In the clinical setting, myocardial viability is defined according to the assessment technique. Noninvasive imaging techniques that are being used to indirectly predict the presence of viable myocardium rely on probing different mechanisms associated with cellular viability such as:(17):

- Preserved metabolic activity e.g. myocardial uptake of labeled substrates (e.g., exogenous glucose, acetate) on positron emission tomography (PET) or single photon computerized tomography (SPECT)
- Preserved sarcolemmal membrane integrity as demonstrated in delayed or rest-redistribution SPECT imaging using thallium-201 or contrast enhanced magnetic resonance imaging (CCeMRI)
- Presence of inotropic contractile reserve on stimulation of β-adrenoceptors as assessed by dobutamine echocardiography or stress MRI
- Preserved mitochondrial function measured using radioactive technitium-labelled sestamibi SPECT
- Perfusion status measured by: PET scanning using radioactive water or ammonia, SPECT imaging immediately after ^{201}thallium administration, or contrast enhanced echocardiography.

Disagreement between modalities in terms of the extent of viable tissue demonstrated may relate, in part, to the fact that each modality indirectly examines a different aspect of cellular viability. Moreover, diagnostic accuracy may be calculated based on the number of viable myocardial segments or on the number of patients with viable myocardium.

Work Up to Viability Assessment

Contrast x-ray, nuclear ventriculography, or 2-dimensional echocardiography are usually performed prior to viability assessment to identify dysfunctional segments, and often following revascularization to evaluate changes in global and regional left ventricular function. Quantitative analysis of the left ventriculogram provides information on regional wall motion, end-diastolic/systolic volume, and stroke volumes.

Coronary angiography is often performed to assess coronary artery anatomy and to determine the feasibility of revascularization in the event that the myocardium is determined to be viable. Images obtained can be analyzed to determine parameters of ventricular function, including ventricular ejection fractions, cardiac output, ejection rates, stroke volume, end-diastolic volume, and end-systolic volume, as well as to test the effects of exercise. Similar information may also be obtained by synchronizing the acquisition of PET or SPECT images to the cardiac cycle (gated PET or SPECT imaging).

Noninvasive Tests for Assessing Viability

Dobutamine stress echocardiography and Single photon emission tomography (SPECT) are presently the two most commonly used diagnostic imaging tests to assess myocardial viability.

Dobutamine Stress Echocardiography

Two-dimensional echocardiography uses ultrasound to examine the heart, and has been used to detect contractile reserve in viable myocardium by measuring wall motion and wall thickness of the heart.(7) Contractile reserve describes the ability of a myocardial segment to augment performance in response to a stimulus. (18)

The normal response of the LV to increasing workload is a uniform increase of regional wall motion, regional wall thickening, and a reduction of end-systolic LV cavity size, with minimal changes of diastolic size during exercise on vasodilation. Wall motion and wall thickening at systole may be normal, reduced (hypokinetic), abnormal (dyskinetic), or absent (akinetic) in ischemic dysfunctional LV. Reduced diastolic wall thickness in dysfunctional left ventricular segments is indicative of scar tissue, whereas a hypokinetic or dyskinetic segment with preserved systolic wall thickness is more likely to represent viable myocardium.

Hypoperfused but viable myocardium with impaired systolic function retain a residual contractile reserve, and has the ability to temporarily improve wall motion at systole upon inotropic stimulation, detected by echocardiography. Dobutamine, at low doses (usually 5–10 μg/kg/minute) and high doses (up to 40 ug/kg/minute), has been used as an inotropic stimulant.

Responses of dysfunctional segments to dobutamine stimulation are generally classified as: (19)

- Biphasic (improved wall motion at low doses but worsening at high doses)
- No change (unchanged wall motion response)
- Worsening (deterioration in wall motion without initial improvement) or
- Sustained (improvement in wall motion at low or high doses).

Viable myocardium supplied by a patent infarct-related vessel demonstrates a sustained improvement during infusion of dobutamine. Viable tissue supplied by a stenosed infarct-related artery is characterized by a biphasic response.(7) A biphasic response and any improvement in contractile function with dobutamine (contractile reserve) are generally considered to predict recovery of function.(19)

In the presence of severe CAD, dobutamine, which requires sufficient flow reserve to sustain the beta-adrenergic induced contraction, is less likely to identify viability than is a metabolic indicator.(18) Myocardial regions with subendocardial infarction or diffuse scarring may also have augmented contractile function during dobutamine infusion due to stimulation of subepicardial layers. In these cases, further improvement of function after revascularization is not expected. (18)

Single Photon Emission Computed Tomography (SPECT)

SPECT can be used to assess both perfusion and viability. Myocardial perfusion scintigraphy uses an intravenously administered radiopharmaceutical tracer to evaluate regional coronary blood flow at rest and after stress. After the administration of a tracer, its distribution within the myocardium is imaged using a gamma camera that may be fitted with a high-energy (511 keV) collimator. In SPECT imaging, the raw data are processed to obtain tomographic images. Comparison of the distribution of tracers within the myocardium after stress and at rest can reveal the presence or absence of inducible ischemia and/or infarction.

The most commonly used SPECT tracers are thallium-201 (^{201}Tl) and two classes of technetium tracers, technetium 99m sestamibi and tetrofosmin. These tracers are avidly extracted by cardiac myocytes and hence their initial

myocardial distribution reflects a combination of the distribution of myocytes and regional perfusion. The SPECT tracers are shown in Table 2.

Table 2: Single Photon Emission Computed Tomography Tracers Used for Assessing Perfusion and/or Myocardial Viability *

Radioactive tracers	Mechanism	Imaging procedure	Index of viability
^{201} Thallium	Flow/Membrane integrity	Stress-Redistribution-Reinjection Rest-Redistribution	Defect reversibility/Relative uptake
^{99m}Tc-Sestamibi	Flow/Mitochondrial membrane integrity	Stress-Rest/Rest	Defect reversibility/Relative uptake
^{99m}Tc-Tetrofosmin	Flow/Mitochondrial membrane integrity	Stress-rest/Rest	Defect reversibility/Relative uptake
^{123} I-beta-methyl iodophenyl pentadecanoic acid	Fatty acid uptake	Rest	Reduced uptake compared with flow
^{18}F-FDG	Glucose utilization	Rest	Relative uptake

Table adapted with permission from the Annals of Nuclear Medicine; Matsunari I, Taki J, Nakajima K, Tonami N, Hisada K. Myocardial viability assessment using nuclear imaging. Ann Nucl Med 2003; 17(3):169-179 *FDG indicates F18 fluorodeoxyglucose

Whichever perfusion agent is used, there is a direct correlation between the uptake of radioisotope and tissue viability. More importantly, the extent of the uptake correlates with the likelihood of segmental recovery following revascularization

A problem with SPECT is non-uniform soft-tissue attenuation that degrades the SPECT image quality or creates artefacts that mimic true perfusion abnormalities. The use of attenuation correction can improve the accuracy of viability tests using SPECT techniques.(20) Attenuation correction must be patient specific with an attenuation map created for each image acquisition. (8)

Electrocardiogram (ECG) gating synchronizes the SPECT image with the ECG. Multiple images taken over the cardiac cycle are aggregated and displayed by a computer as a continuous cinematic loop, which resembles a beating heart to provide additional functional information (e.g., wall motion and wall thickness). (21)

Thallium-201 SPECT

^{201} Thallium (^{201}Tl), a potassium analogue, acts as a marker of viability because it needs an intact cell membrane and active transport for uptake. The initial uptake and distribution of ^{201}Tl depends mainly on perfusion, with hypoperfused myocardium having a lower uptake than does myocardium with normal perfusion. Over the next few hours, the tracer exchanges between the intra and extracellular spaces, and hence with the circulation, leading to “redistribution” of the tracer into cells with intact sarcolemmal membrane integrity. The result of this process is that a region of ischemic but viable myocardium, which initially has less than normal uptake, will have similar tracer uptake compared to normal regions over time. In contrast, areas of infarction or fibrosis will have reduced uptake initially that does not change over time (fixed defect). Hence the redistribution image reflects the myocardial viability. Partial redistribution may be seen when there is a mixture of necrosis and reversibly ischemic myocardium.

A rest-redistribution protocol involves obtaining early SPECT images after administration of ^{201} Tl at rest, followed by redistribution imaging in 3 to 4 hours. In practice, redistribution of thallium may not be complete 4 hours after stress injection. Wagdy et al. (22) showed that late redistribution images (acquired 24 hours after administration of ^{201} Tl) detected additional redistribution in 30% of the patients who did not have meaningful redistribution at 4 hours, and in 8% of the segments which were abnormal at 4 hours. Higher sensitivity and specificity may be obtained by delaying

redistribution 24–72 hours, or with re-injection of a small additional amount of ^{201}Tl before acquisition of redistribution imaging. (23), (24)

The rest-reinjection protocol provides information on both stress-induced ischemia and viability, whereas the rest-redistribution protocol provides information only on viability (25).

SPECT with Technitium-99m-Labelled Tracers

Several technetium-labelled tracers have been developed, including ^{99m}Tc sestami, tetrofosmin, and tebroxime. Sestamibi is the most studied and currently most widely used of these agents. Technetium is dispersed into the myocardium in proportion to blood flow mainly through passive diffusion and becomes trapped in the mitochondria by the membrane electrochemical gradient. The uptake of these radioactive substances requires a viable myocardial cell and an intact cell membrane. Both ^{99m}Tc-sestamibi and ^{99m}Tc-tetrofosmin have far less redistribution than thallium. As a result, they must be injected twice, once at rest, and once during stress. Uptake on the resting injection will reflect relative resting blood flow to areas of viable myocardium. Areas of mismatch on stress and rest images represent viable myocardium, but simple reversible ischemia or stunning cannot be distinguished from hibernation.

The addition of nitrates improves tracer uptake and accuracy of the imaging modality. The higher energy of technetium is less subject to attenuation than thallium, and generally leads to better quality images. Tc-agent SPECTs also provide count statistics high enough to allow an ECG-gated acquisition.

123I-BMIPP SPECT

^{123} I-beta-methyl iodophenyl pentadecanoic acid (BMIPP), a fatty acid analog, is not metabolized by beta-oxidation. Because myocardial fatty acid uptake is easily depressed in ischemic myocardium, BMIPP imaging in combination with flow tracer such as ^{201}Tl or 99m Tc sestamibi can also detect potentially reversible myocardium.

Dual Isotope SPECT

ECG-gated SPECT imaging with two isotopes such as thallium (at rest and under stress) and ^{99m}Tc sestamibi are being investigated as a technique for quantifying both the regional myocardial function and stress and rest perfusion in order to assess viability.(26) The dual isotope scanning may be performed simultaneously (dual isotope simultaneous acquisition, DISA) or sequentially.

Viability assessment using magnetic resonance imaging and electromechanical mapping are being explored.

Cardiac Viability Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is being used as a diagnostic tool for myocardial viability based on the assessment of the following morphological and functional parameters:

- Preserved end-diastolic wall thickness
- Dobutamine cine MRI measures preserved contractile reserve during dobutamine stimulation(27)
- Contrast enhanced and delayed enhanced MRI (gadolinium-based) identifies irreversibly damaged myocardial scar tissues. (28;29) Retention of the contrast agent in the myocardium indicates the presence of nonviable myocardium regardless of the age of the infarction.

Electromechanical Mapping

Since myocardial ischemia and infarction result in significantly reduced electrical parameters of the affected myocardium, the local endocardial electrogram has been proposed as an indicator of myocardial viability.(30) Catheter-based mapping systems that provide information about regional electrical, anatomical, and mechanical properties of the left ventricle have been studied as techniques to distinguish between infarcted and ischemic but still viable myocardium. An example is the NOGA (Biosense Webster, Haifa, Israel) system that uses low-intensity

magnetic field energy to determine the location of sensor-tipped catheter electrodes in the LV, and yields information about local electrical activity and regional contractility. Simultaneous registration of the amplitude of endocardial electrical signals, which correlate inversely to the extent of myocardial ischemia, allows construction of real-time 3-dimentional electromechanical maps without x-ray fluoroscopy. The 3-D electromechanical maps provides information on viable myocardium versus scar tissue.(31) It has also been hypothesized that viable myocardium may be characterized by an electromechanical mismatch.(32)

Electroanatomical mapping offers online detection of myocardial viability in the catheterization laboratory. It may enable detection of myocardial viability of dysfunctional myocardium in immediate continuation of coronary angiography.(31)

Outcome Measures of Viability Assessments

The accuracy of noninvasive imaging techniques used to predict viability has been evaluated using one or more of the following outcome measures:

- Recovery of segmental contractile function, mainly wall motion and wall thickening after revascularization, compared to baseline values.
- Recovery of global regional function (improvements in LVEF).
- Impact on long-term clinical outcomes including survival, myocardial infarction (MI), and need for hospitalization or further revascularization.
- Agreement with histological findings
- Impact on functional status and quality of life

New Technology Being Reviewed

Positron Emission Tomography

Positron emission tomography (PET) is a nuclear imaging technology based on the distinct ways in which normal and abnormal tissues use positron-emitting radioactive analogs of common substrates such as sugars, amino acids, and free fatty acids. These substances, known as radiopharmaceuticals, are administered by injection. When a positron emitted from the patient is converted to a photon, two gamma rays are emitted simultaneously at 180 degrees to each other. These gamma rays are detected with a PET scanner, and computer software is used to convert the radiation emission into images. Diagnoses are made by comparing the distribution of the radiation activity to normal patterns, or by measuring the rate of accumulation or disappearance of the radioactivity over time. (33)

Tracers

By using normal substrates of heart muscles (free fatty acids, glucose and lactate) labelled with positron emitting isotopes, PET is able to provide a biological signal on cellular survival and viability. Various PET techniques have been investigated based either on metabolic processes (e.g. preserved myocardial ^{18}F-FDG utilization), flow/membrane integrity (e.g. ^{13}N-Ammonia PET) or ^{15}O water perfusable tissue fraction. Positron-emitting isotopes are commonly produced by a cyclotron (e.g. F-18) with a few produced by a generator (e.g. ^{82} rubidium). Most of the positron-emitting tracers used in diagnostic studies have very short half-lives, ranging from a few minutes to a few hours, thus limiting the distance between the isotope production site and the PET scanning site.

Positron Emission Tomography Scanners

Full ring PET scanners consist of one large crystal detector or have multi-detectors that surround the patient and generally have high detection sensitivity and good spatial resolution.

Hybrid PET-CT scanners have a computed tomography scanner (CT) coupled to the PET scanner. The CT scanner allows attenuation correction and rapid anatomical localization of the abnormality, without the need for performing separate scans.

Some nuclear medicine gamma cameras can be retrofitted for detecting coincidental gamma rays emitted by PET tracers. These cameras have poor spatial resolution, and require longer scanning time.

A detailed description of PET equipment and processes can be found in the original 2001 ICES review (34)

Gated Positron Emission Tomography

Electrocardiogram- (ECG) gated PET synchronizes the acquisition of PET images to the cardiac cycle, and applies computer algorithms for objective quantitation of regional and global LV function parameters such as wall thickening, wall motion, LVEF, end-diastolic volume, end systolic volume, stroke volume, and LV mass. Successful application of this technique allows 3-dimensional co-registration of ventricular function and metabolic information within a single PET examination.

PET Viability Assessment Using Metabolic Markers

Free fatty acids, glucose, and lactate are the major energy sources for the heart. In the normal myocardium, fatty acid is usually the main substrate for oxidative metabolism. Under ischemic conditions, oxidative metabolism in the myocardium is reduced, and glucose becomes the major substrate for the myocardium. The degree of utilization of external glucose such as the radioactive glucose analogue F-18 Fluoro-deoxyglucose (FDG) reflects the metabolic capability and, hence, viability of the myocardium.

PET tracers that can be used in the assessment of myocardial viability are summarized in Table 1.

Table 1: Positron Emission Tomography Tracers Used in Assessing Myocardial Viability

Radioactive tracers	Half-life (Minutes)	Mechanism	Imaging procedure	Index of viability
^{18}F-FDG	110	Glucose utilization (metabolism)	Static/Dynamic	Relative uptake
^{11}C-Acetate	20	Oxidative metabolism	Dynamic	Clearance rate
^{13}N-Ammonia	10	Flow/Metabolic trapping	Dynamic/static	Flow/Retention
^{15}-O-Water	110 seconds	Flow/Diffusion	Dynamic	Flow/Perfusable tissue index
^{82}Rb	76 seconds	Flow/Membrane integrity	Dynamic	Flow/Clearance rate

Table adapted with permission from the Annals of Nuclear Medicine; Matsunari I, Taki J, Nakajima K, Tonami N, Hisada K. Myocardial viability assessment using nuclear imaging. Ann Nucl Med 2003; 17(3):169-179 FDG refers to fluorodeoxyglucose

^{18}F-fluorodeoxyglucose (FDG)

^{18}F-fluorodeoxyglucose (FDG) the most commonly used tracer for viability assessment. Similar to glucose, FDG is taken up by the myocyte, and phosphorylated to FDG-6-phosphate. Unlike glucose-6-phosphate, FDG-6-phosphate is a poor substrate for glycolysis and glycogen synthesis, and therefore, becomes essentially trapped in the myocyte. FDG retained metabolically in the myocardium provides a strong signal for imaging.(11) Uptake of FDG in a myocardial segment reflects the degree of viability of the segment.

A description of the methods used for FDG imaging and analysis is provided in Appendix 2.

Although FDG PET without flow tracers have been used to detect viable myocardium, flow/metabolism combination is believed to provide more comprehensive information on viability, and on the differentiation of hibernation from stunning. (35)

Analysis of FDG PET images in conjunction with perfusion PET or SPECT images usually identifies the following regional perfusion/metabolic patterns:

- Concordant normal blood flow and normal FDG uptake reflects normal and viable myocardium.
- Reduced blood flow associated with preserved or enhanced FDG uptake (perfusion-metabolic mismatch) reflects ischemic but viable myocardium (hibernating).
- Proportionally reduced blood flow and FDG uptake (perfusion-metabolic match) is indicative of infarcted and nonviable myocardium.

C-Acetate

F18 FDG may not be suitable for use in acute myocardial infarction due to accumulation in the necrotic tissue of inflammatory cells that takes up FDG.(20) Instead, the clearance rate of positron emitting ^{11}C-acetate based on preserved oxidative metabolism can be used as a marker of myocardial viability. A potential disadvantage of ^{11}C-acetate as a viability tracer is the necessity for dynamic imaging and an on-site cyclotron for the production of ^{11}C, which has a short physical half-life of 20 minutes. For these reasons, although the results as to the utility of this tracer as a viability marker are promising, ^{11}C-acetate has not gained wide clinical acceptance. (20)

Viability using PET Perfusion Tracers

Myocardial blood flow itself is a marker of viability because viable tissue requires a blood supply. Blood flow is often within the normal or near-normal range in dysfunctional but viable myocardium, suggesting that the majority of reversible dysfunction represents repetitive stunning rather than hibernation. As previously described, PET perfusion results are often used in conjunction with metabolic PET findings to identify viable myocardium that could benefit from revascularization. The following are commonly used PET perfusion tracers.

^{13}N-ammonia

^{13}N-ammonia uptake depends on both perfusion and metabolic retention and its retention rather than absolute myocardial blood flow is a good marker of cellular viability. (20)

^{82}-Rubidium

^{82}-Rb is transported into the cell through an active mechanism similar to that of potassium and thallium, and therefore, its cellular kinetics represent membrane integrity and hence viability. Because of its short half-life (76 seconds), imaging studies can be accomplished within 30 minutes but administration of higher doses is necessary to obtain adequate counts. (36)

$^{15}O_2$-Water

$^{15}O_2$-Water is freely diffusible and metabolically inert. Its accumulation in tissue is almost exclusively a function of blood flow. (36) With $^{15}O_2$-Water imaging, it is also possible to calculate the proportion of the total anatomical tissue that is capable of rapidly exchanging water (water perfusable tissue index) as a marker of tissue viability. (20)

A comparison of the noninvasive techniques for assessing viability including PET prepared by Cowley et al. (37) is provided in Appendix 3.

Literature Review

Objectives

The objectives of this review are to assess the safety, effectiveness, and cost effectiveness of PET for detecting myocardial viability and predicting outcomes after revascularization in patients with CAD and severe LV dysfunction.

The review compares PET with the following viability assessment tests:

- Dobutamine stress echocardiogram
- SPECT (using Thallium 201, 99m-Tc Sestamibi, 99mTc-Tetrofosmin, or F-18 FDG)
- Magnetic resonance imaging (MRI)
- Endocardial electromechanical mapping

Questions

- How does PET compare with other noninvasive imaging techniques in the assessment of myocardial viability in terms of safety?

- What is the diagnostic performance (sensitivity, specificity, diagnostic accuracy, & predictive values) when compared with noninvasive imaging techniques (SPECT, echocardiography, MRI, & electromechanical mapping) used to assess myocardial viability in patients with CAD and severe left ventricular dysfunction?

- Does PET add incremental value over other noninvasive technologies in guiding the selection of appropriate therapy (revascularization, medical therapy, or heart transplantation) for people with severe ischemic LV dysfunction?

- Does PET have incremental value over other noninvasive technologies in predicting outcomes after revascularization (in terms of global LV function, long term survival, cardiac deaths, MI, heart transplantation, additional revascularization)?

- How does PET compare with other noninvasive imaging techniques used to assess myocardial viability in terms of budget impact and cost-effectiveness?

Method

Databases and Search Strategy

The search strategy built on the cardiac strategy reported by ICES in its 2001 *Health Technology Assessment of Positron Emission Tomography* report. (34) The updated Medical Advisory Secretariat (MAS) search was limited to English-language, human articles published in or after January 1, 2001. The search strategy was initially run on September 27, 2004, and was later updated to include studies in the databases as of April 20, 2005. Databases searched included OVID MEDLINE, OVID MEDLINE In-Process and Other Non-indexed Citations, OVID EMBASE, Cochrane CENTRAL, the Cochrane Database of Systematic Reviews, and the INAHTA database. The full search strategy is shown in Appendix 4.

Results of Literature Search

The literature searches yielded 456 citations. Two researchers reviewed the abstracts and full text where necessary,to determine compliance with the following inclusion and exclusion criteria. A study that was published in October 2005

was identified just before the completion of the review was added to the list bringing the total number of studies to 457.

Inclusion Criteria

This review included English-language journal articles that reported primary data on the effectiveness or cost-effectiveness of the use of PET for detecting myocardial viability, obtained in a clinical setting or through analyses of primary data maintained in registers or institutional databases. Studies on the effectiveness of other noninvasive technologies were also considered. Included studies had to meet the following criteria:

- The design and method are clearly described.
- Studies were systematic reviews or randomized controlled trials (RCTs) and observational studies with a minimum sample size of 12 (including abstracts of unpublished studies presented at international conferences)
- Studies were not superseded by a publication with the same purpose, by the same group or a later publication that included the data from the same study (unless the article addressed different outcomes).
- English language articles (published January 1, 2001 to April 20, 2005) that meet the following description.

  Patient
  Patients with chronic coronary artery disease and severe LV dysfunction being considered for revascularization

  Intervention
  PET imaging with F-18 fluoro-deoxyglucose for the purpose of detecting viable myocardium

  Comparisons
  Viability assessments using echocardiography, single photon emission tomography, functional magnetic resonance imaging, or electromechanical mapping

  Outcomes of interest
  - Sensitivity, specificity, likelihood ratios, diagnostic accuracy, positive predictive values, and negative predictive values for the prediction of regional functional recovery (wall motion) after revascularization or global functional improvement (left ventricular ejection fraction) after revascularization
  - Functional status and quality of life after revascularization
  - Prognostic value of PET in predicting long-term clinical outcomes including survival and cardiac events (cardiac deaths, MI, unplanned revascularization) after revascularization
  - Comparison with other noninvasive viability assessment tests with respect to the above outcome measures.
  - Cost-effectiveness ratios of PET in comparison with other noninvasive viability assessment tests.
  - Adverse events related to PET scanning

Exclusion Criteria

- Studies that are duplicate publications (superseded by another publication by the same investigator or group, with the same objective and data)
- Viability studies following acute MI
- Studies on patients with non-ischemic cardiomyopathy
- Animal, phantom, and in-vitro studies
- Reports available only in a foreign language
- Non systematic reviews, editorials, letters
- Case reports
- Studies focusing on the technical aspects of PET

A total of 409 reports were excluded (Table 3).

Table 3: Studies Excluded From the Medical Advisory Secretariat's Literature Review

Reason for Exclusion	Number of Reports Excluded
Off topic (acute MI, non ischemic cardiomyopathy, not technology of interest)	322
<12 subjects	10
Non-primary study, non-systematic review, or case report	53
Editorials/Foreword	1
Technical reports, phantom studies	15
Animal studies	5
Abstracts not of interest	2
Non-English language report	1
Total	409

Quality Assessment and Data Extraction

Forty-eight (48) reports met the selection criteria. These included 8 systematic reviews or meta-analysis, 38 primary studies, and 2 economic modeling reports (Table 4). Of the primary studies, 26 were about PET (1,182 patients) and 12 were about the comparators. One researcher reviewed the full-text reports and extracted data using an electronic data extraction form.

For the 38 primary studies, levels of evidence were assigned according criteria in Table 4. The designation "g" indicates unpublished reports of studies that have been presented to international scientific meetings.

Table 4: Level of Evidence* (Medical Advisory Secretariat Scale)

Type of Study (Design)	Level of Evidence	No. of Eligible Studies
Large RCT, Systematic reviews of RCTs	1	
Large RCT, unpublished but reported to an international scientific meeting	1(g) †	
Small RCT	2	
Small RCT unpublished but reported to an international scientific meeting	2(g)	
Non-RCT with contemporaneous controls	3 a	25
Non-RCT with historical control	3b	
Non-RCT unpublished but reported to an international scientific meeting	3(g)	
Surveillance (database or register)	4a	
Case series, multisite	4b	3
Case series, single-site	4c	10
Case series unpublished but presented to an international scientific meeting	4(g)	
Total		38

*does not include the 3 articles on economic analysis
† "g" designates unpublished reports of studies that have been presented to international scientific meetings

Quality Assessment of Individual Studies

The quality of the individual studies was assessed using criteria of the quality assessment tool for diagnostic accuracy studies (QUADAS) developed by the National Health Service (The United Kingdom). (38)

Data Analysis and Synthesis

Data on sensitivity, specificity, predictive values, and likelihood ratios were analyzed to provide a range and a median. Meta-Disc (39) (a meta-analysis software) was used to test for heterogeneity and, when appropriate, to generate a point estimate with standard error. The meta-analysis software was also used to generate a summary receiver operator characteristic (SROC) curve for diagnostic accuracy if appropriate. A descriptive synthesis was provided when statistical analysis was not appropriate.

Summary of Overall Quality of Evidence

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system (40) was used to summarize the overall quality of evidence supporting the findings relating to each key outcome measure. This system rates the overall quality based on the assessment of four key elements:

- Study design: (type of evidence), broadly categorized as randomized trials and observational studies.
- Study quality - refers to whether there were limitations relating to the methods and execution that may result in biases. The assessment is based on appropriate criteria such as adequacy of allocation concealment, blinding and follow-up.
- Consistency - refers to the similarity of estimates of effect across studies. Important unexplained inconsistency in the results decreases the confidence in the estimate of effects for the outcome.
- Directness - refers to the extent to which the people, interventions, and outcome measures are similar to those of interest.

Quality grades were assigned as follows:

Type of evidence

- Randomized trial = high
- Observational study = low
- Any other evidence = very low

Decrease grade if:

- Serious (-1, reduce GRADE level by 1 so a high grading will become moderate) or very serious (-2, reduce GRADE level by 2 so a high grading will become low) limitation to study quality
- Important inconsistency (-1)
- Some (-1) or major (-2) uncertainty about directness
- Imprecise or sparse data (-1)
- High probability of reporting bias (-1)

Increase grade if:

- Strong evidence of association-significant relative risk of >2 (<0.5) based on consistent evidence from two or more observation studies, with no plausible confounders (+1, increase GRADE level by 1, so a moderate grade will become high. However a high grade will remain high)
- Very strong evidence of association-significant relative risk of > 5 (<0.2) based on direct evidence with no major threats to validity (+2)
- Evidence of a dose response gradient (+1)
- All plausible confounders would have reduced the effect (+1).

GRADE Scoring definitions:

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

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

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

Very low: ⊕◯◯◯ Any estimate of effect is very uncertain.

Presentation of Findings of the Review:

The evidence will be presented in the following order:

- Diagnostic Performance of FDG PET with respect to postrevascularization segmental function improvement
- Diagnostic Performance of FDG PET in comparison to other noninvasive technologies including dobutamine echocardiography, thallium-201 SPECT, SPECT with technetium-labelled tracers, FDG SPECT, MRI, and electromechanical mapping.
- Accuracy and incremental value of FDG PET in predicting postrevascularization global function improvement.
- Accuracy and incremental value of FDG PET in predicting long-term patient outcomes.
- Incremental value of PET in clinical decision making
  Safety
- Economic analysis of FDG PET in myocardial viability assessment (budget impact analysis and cost-effectiveness analysis)

The systematic reviews and selected studies are summarized in Appendices 7–16 and will be discussed in the appropriate section.

Definition of Results of Myocardial Viability Tests

Positive viability test: results of the test indicate the presence of dysfunctional but viable myocardium that should recover contractile function after revascularization

Negative viability test: results of the test indicate that the dysfunctional myocardium is not viable and is not likely to recover contractile function after revascularization.

Former Systematic Reviews

Institute for Clinical Evaluative Scineces (ICES) 2001 Review

The 2001 ICES systematic review (34) included 6 HTAs, 1 RCT, 88 cohort studies, and 24 review articles. Only one published study met Grade A criteria (RCT). The remaining studies were of poorer methodological quality. The review found that:

- The only grade A study by Siebelink et al. (41) compared a PET-guided strategy to a SPECT- guided strategy and failed to show any favourable effect upon patient outcome between the two strategies. However, this study was relatively small and included a number of patients with mild heart failure and, therefore, cannot be used to conclude that PET scanning has no role for the assessment of viability.
- Other studies of poor methodological quality suggested potential benefits, although incremental value of PET over other available noninvasive modalities was not clearly evaluated.

The review concluded that although the available evidence does not support the routine use of PET for the assessment of viability at the time, the state of evidence is evolving, and cardiac PET should be re-evaluated in 2 to 3 years.

Agence d'évaluation des technologies et des modes d'intervention en Santé Review (2001)

The review by the Agence d'évaluation des technologies et des modes d'intervention en Santé (AETMIS) (42) on the use of PET to assess cardiac viability included 4 health technology assessments, 1 RCT and 41 cohort studies. Regarding the use of PET in determining cardiac viability, the AETMIS review concluded that:

- Based on the available evidence, no firm conclusion can be drawn regarding the systematic introduction of PET in day-to-day clinical practice.
- PET is a promising technology for cardiac research that may have important clinical applications in patient management.
- PET might make it possible to optimize the management and prognosis of more severely affected coronary patients.
- Certain publications and AETMIS' own simulation concerning the clinical use of PET to assess myocardial viability suggest a favourable cost-effectiveness ratio.

The AETMIS review stated that in the field of cardiology, the clinical utility of PET is recognized for studying myocardial viability.

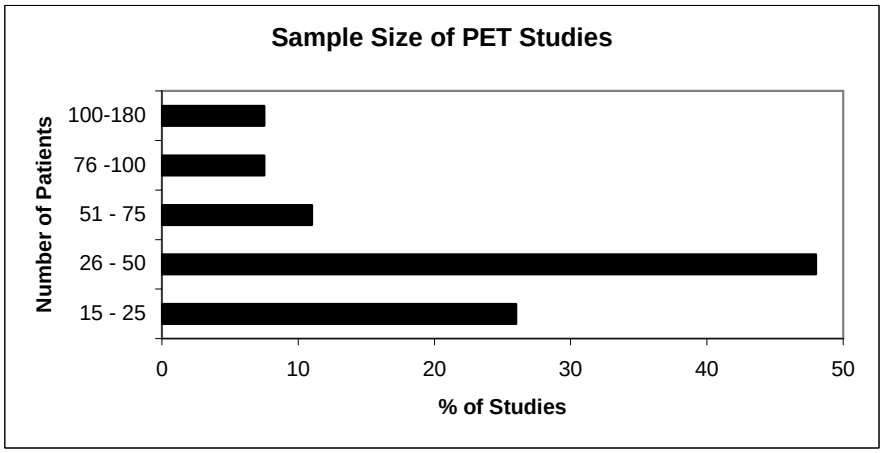
The other systematic reviews and meta-analysis will be discussed under different sections of this report.

Medical Advisory Secretariat Review Update

An Overview of the Quality of Studies

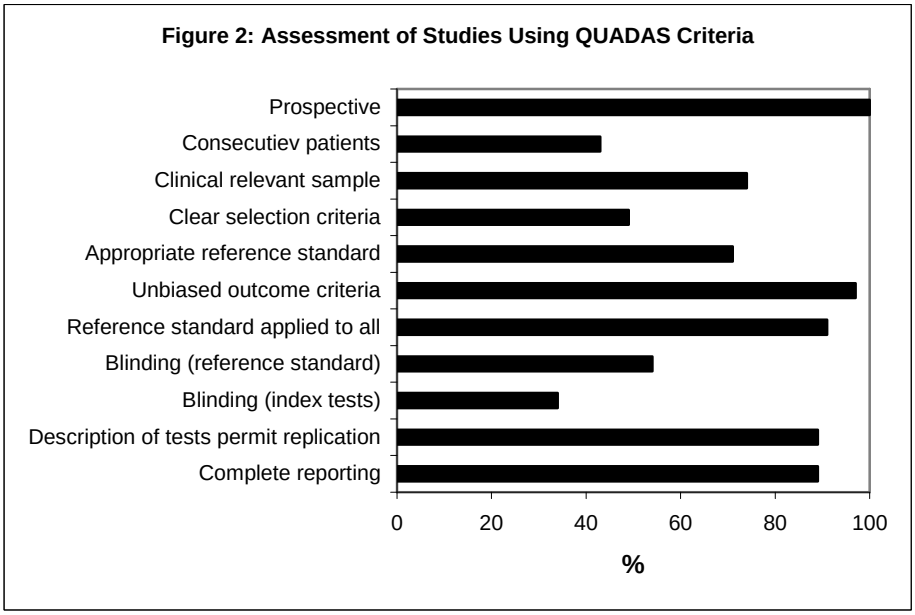
There were no RCTs. The studies on diagnostic or prognostic accuracy generally involved comparison of PET with one or more noninvasive viability assessment tests on the same group of patients. The studies are all prospective and generally small with 74% of the PET studies having 50 patients or less (Figure 1).

Figure 1: Sample Size of Studies in Medical Advisory Secretariat's Review



The quality of the individual studies was evaluated using QUADAS criteria (Appendix 6). Findings of the quality assessment are summarized in Figure 2. Most studies had an objective reference standard, detailed description of the procedures, and well-defined criteria for image interpretation. The reference standard was applied to all patients. However, all studies had pre-selection bias and almost half the studies did not study consecutive patients and/or did not indicate blinding in the interpretation of the images. In most studies, it was difficult to assess whether baseline tests and viability tests were performed with sufficient temporal proximity to ensure that there was no change in the patients' clinical status during the testing period. Analysis of diagnostic accuracy was usually based only on interpretable segments of patients who were successfully revascularized.

Figure 2: Assessment of Studies Using QUADAS Criteria



There was heterogeneity among the studies regarding:

- Severity of LV dysfunction: The studies included patients with a wide range of left ventricular ejection fraction. Some subjects only had moderate rather than severe LV dysfunction.
- Metabolic condition for FDG PET imaging: Different methods were used to control the glycemic condition of the subjects during PET imaging. These included oral glucose load ranging from 25 to 75 grams after fasting or euglycemic hyperinsulinemic clamping.
- Criteria for viability varied from study to study: Although normalized FDG uptake or absolute glucose utilization rate were used in some studies, viability was most often defined by a mismatch between FDG PET and myocardial perfusion. Perfusion was usually determined by SPECT using a variety of tracers including thallium-201, N-13 ammonia, rubidium-82, ^{99}m-Tc sestamibi or ^{99}m-Tc tetrofosmin. The cutoff threshold of uptake in FDG PET and perfusion images, often determined by ROC curve analysis, also varied among the studies. Viability criteria for other noninvasive techniques were also heterogeneous.
- Gold standard used: Most of the studies used improvement in regional wall motion as the gold standard. However, improvements in regional wall motion were defined differently among the studies (e.g. standard deviation vs. wall motion score) and measured with different methods (echocardiography, ventriculography, gated PET etc) among studies and, in some cases, within studies.
- Method of analysis and interpretation of images: Images were analyzed visually in some studies and semi-quantitatively in others. The models used to analyze the images varied from 9 segments to >20 segments. In order to compare polar maps generated from FDG PET with those from perfusion images, manipulation of the images was required, and this might have resulted in misalignment of the images. Diagnostic accuracy was based on all dysfunctional segments in some studies but on successfully revascularized dysfunctional segments in others. Some analyses were based on segments while a small numbers were analyzed based on patients.
- Imaging equipment used: As most of the studies occurred over a long period of time and PET technology is evolving rapidly, the equipment used might not have been the most current and might not reflect the sensitivity and specificity that could be obtained with the new generation PET or PET/CT scanners.
- All studies on segmental recovery reviewed had a follow-up period of at least 3 months after revascularization. Even this period might not have been sufficient for dysfunctional segments to recover contractile function. There is evidence that segmental function recovery could take place as late as 3 years after revascularization.

Characteristics of Patients in the Review

Table 5 shows that subjects of the studies were predominantly males, between the age of 56 to 67 years, with multivessel coronary artery disease, previous history of MI and moderate to severe LV dysfunction.

Table 5: Characteristics of Patients in the Studies

Characteristics	% of Studies
Age	Median 61 years, range 56 –67 years
Males	Median 85%. Range 69%–100% (78% of studies had >80% males)
CAD & LV dysfunction	100%
Mean LVEF	≤ 35% in 71% of studies
History of MI	Median 88%, range 50%–100% (reported by 22 studies)
Multivessel disease	median 76%, range 28–93% Mean number of diseased vessel 1.6 – 2.7
≥ NYHA Class III	Range 19% – 63% (reported by 6 studies)
Diabetes	Median 18%, range 8% – 100% (reported by 10 studies)
Previous revascularization	Median 28%, range 10–54% (reported by 6 studies)

CAD refers to coronary artery disease; LV, left ventricular; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association.

Most Common Inclusion and Exclusion Criteria Used in the Studies

Common Inclusion Criteria:

- Chronic coronary artery disease
- Depressed left ventricular ejection fraction (cut-offs varied)
- Regional LV dysfunction
- History of old myocardial infarction
- Being considered for revascularization.

Common Exclusion Criteria:

- Recent MI (cut-offs varied)
- Unstable angina
- LV aneurysm
- Valvular disease requiring surgery
- Unstable coronary syndrome
- Heart disease or LV dysfunction of other etiology.

How Accurate is FDG PET in Predicting Regional (Segmental) Function Improvement After Revascularization?

The diagnostic accuracy of PET in identifying viable myocardium has often been measured using an intermediate assessment criterion, specifically, the recovery of segmental myocardial contractile motion in dysfunctional segments after revascularization. Improvement in segmental contractile function is usually measured by analyzing the wall thickening and wall motion of the dysfunctional segments before and after revascularization using contrast or radionuclide ventriculography, echocardiography, MRI, or ECG gated PET. Diagnostic accuracy was reported either on a segmental basis (as a % of the dysfunctional myocardial segments that recovered function after revascularization) or on a patient basis (as a percentage of the patients with dysfunctional myocardium that achieved improved function in a predefined number of segments after revascularization).

Studies on PET Viability Assessment and Segmental Function Recovery

One meta-analysis (43) and 9 studies provided data on the sensitivity, specificity, accuracy and/or predictive values of PET in predicting segmental function recovery. The sample sizes of the studies ranged from 25 to 41. PET was compared to one or more noninvasive techniques in the same cohort. The mean LVEF ranged from 30% to 49%. Mean follow-up period after revascularization ranged from 3 months to 8 months. PET viability was determined based on FDG uptake in 4 studies, and on perfusion/metabolism mismatch in 5 studies. Six of the studies were analyzed on a segmental basis and three on a patient basis. One study only provided predictive values (44). The meta-analysis and studies are summarized in Table 7 and Appendix 7, and will be described in a later section. The overall quality of the studies is shown in Table 8.

The formulas used for calculating sensitivity, specificity and likelihood ratios are summarized in Table 6.
The sensitivity, specificity, predictive values, and likelihood ratios of FDG PET from the 9 studies were integrated with data from the 2001 ICES review (34) and are summarized in Table 9. Figure 3 provides a graphical presentation of the combined sensitivity and specificity data.

Table 6: 2x2 Table

	After Revascularization	
Results of viability assessment	Improved segmental motion	Segmental motion not improved
Test Positive (viable)	a	b
Test Negative (not viable)	c	d

a, b, c, and d may represent the number of myocardial segments or the number of patients
Sensitivity = True positive rate = a/(a+c)
Specificity = True negative rate = d/(b+d)
False-positive rate = 1 - Specificity
Likelihood ratio for positive test (LR+) = sensitivity/(1-specificity)
Likelihood ratio for a negative test (LR-) = (1-sensitvity)/specificity
Positive predictive value (PPV) = a/(a+b)
Negative predictive value (NPV) = d/(c+d)

Table 7: Summary of Studies on the Diagnostic Accuracy of PET in Predicting Segmental Function Recovery after Revascularization †

Study	Year	No. of Patients	Mean LVEF % (-SD)	Mean Follow-up months	Criteria for PET Viability	Gold Standard for RWM recovery	Mean Sensitivity %	Mean Specificity %	PPV (%)	NPV (%)	Diagnostic Accuracy (%)
Tani (45) (segment)	2001	30	Not reported	5(3)	Normalized FDG uptake >50%	Improvement of wall motion ≥ 1 grade on echocardiogram	90	61	79	78	Not available
Nowak (46) (segment)	2003	42	38 (13)	6.4(0.7)	MIBI ≤70% Normalized FDG uptake >70%	Wall motion improved by 1 score on ventriculogram	80	72	78	74	76
Wiggers (47)	2003	20	29 (6)		FDG uptake ≥69%	Increase in wall motion score ≥ 1 on echo or MRI	78	78	Not reported	Not reported	Not available
Korosoglou (48) (segment)	2004	41	30.9	Range 3–6	Tracer uptake Normal FDG & reduced ↓ MIBI SPECT	Increase in wall motion score ≥ 1 grade on 2-D echocardiogram	90*	44	84	61	77
Koch (47)	2001	25	49 (15)	6	Tracer uptake FDG ≥55% & MIBI <70%	↑wall motion on digitalized angiogram	82	86	NA	NA	NA
Barrington (44) (by region)	2004	25	36 (7.3)	8.1(2.8)	N13H3≤70% & FDG ≥ 68% (hibernation)	Improved wall motion ≥ 1 grade in ≥ 2 adjacent segments	Not available	Not available	75	100	Not available
Lund (49) (by patients)	2002	34	42 (13)	4.8 (2.5)	FDG PET >55%	>+1 SD in RWM in 2 adjacent dysfunctional segments	89	68	50	94	74
Schmidt (27) (by patient)	2004	40	42 (10)	Range 4–6	FDG ≥50% in ≥ 50% infarct related segments	Systolic wall thickening ≥2mm in ≥50% of related segments- MRI	100	73	86	100	90
Wiggers (71) (by patient)	2001	35	35 (7)	88 (45) days	FDG uptake (normalized to segment with max. NH3 uptake) ≥70%	Wall motion improvement ≥ grade in ≥ 2 adjacent segments	100	67	100% (for patients without angina)	NA	80

From the Medical Advisory Secretariat's literature search unless otherwise indicated;

†FDG refers to fluorodeoxyglucose F 18; LVEF, left ventricular ejection fraction; Tc 99m MIBI, technetium Tc 99m sestamibi; NPV, negative predictive value; NR, not reported; PET, positron emission tomography; PPV, positive predictive value; Pts, patients; SPECT, single photon emission computed tomography.

Table 8: Summary of Level of Evidence and Quality Assessment Based on QUADAS * †

	Tani	Nowak	Wiggers 2003	Korosoglou	Koch	Barrington	Lund	Schmidt	Wiggers 2001
MAS Level of evidence	3a	3a	3a	3a	3a	3a	3a	3a	3a
Quality	Moderate	Moderate	Moderate	Low	Low	Moderate	Moderate	Low	Moderate
Limitations			Very small sample			Very small sample			
	Selection bias	Pre-selection bias	Selection bias	Preselection bias	Selection bias	Pre-selection bias	Selection bias		Selection bias
	Index test used as reference				Index test used as reference			Index test used as reference	Index test used as a reference
	Interpretation of index test not blinded		Interpretation of index test not blinded	Inter-pretation of reference standard not blinded		Inter-pretation of index test not blinded		Inter-pretation of standard test not blinded	Inter-pretation of index test not blinded.
							No ITT		

* See Appendix 6 for detailed quality assessment. † Level of evidence according to Medical Advisory Secretariat; QUADAS refers to Quality Assessment of Diagnostic Accuracy Studies; ITT, intention-to-treat.

Tables 7 and 8 showed that all 9 studies were prospective nonrandomizedcomparative studies with moderate to low quality. The most common quality limitations were selection and preselection bias and lack of blinding in the interpretation of the index tests.

Summary Statements on the Predictive Accuracy of PET Regarding Postrevascularization Regional Wall Function

- There is evidence from observational studies that FDG PET can predict regional functional recovery after revascularization with high sensitivity (median 90%) and high negative predictive value but with moderate specificity.
- PET has low negative likelihood ratios indicating that it is an effective tool for ruling out myocardium that is not likely to recover regional contractile function after revascularization.
- PET has low positive predictive values indicating high false-positive rates.
- With a low positive likelihood ratio, PET is only somewhat useful in ruling in people with functional but viable myocardium.
- There was significant heterogeneity in the positive and negative likelihood ratios among studies.

Description and analysis of the evidence that support the above summary statements are presented in the following section.

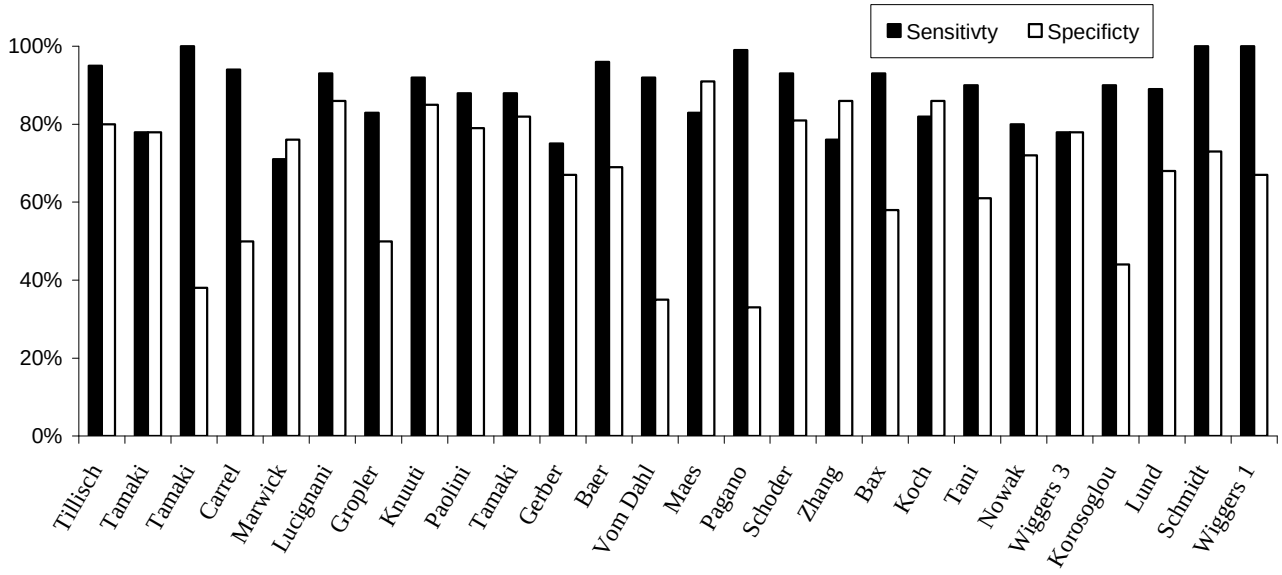
Analysis of Diagnostic Performance of PET based on Segmental Function Recovery After Revascularization (Including Data From 2001 ICES Review)

Table 9: Sensitivity, Specificity, Predictive Values and Likelihood Ratios of PET in Predicting Segmental Function Recovery (Including 2001 ICES Review)

Study	Year	No. of Patients	Mean LVEF % (+/-SD)	Mean Sensitivity %	Mean Specificity %	PPV (%)	NPV (%)	Diagnos-tic Accuracy	LR * Positive test	LR* Negative test
Studies Included in ICES 2001 Review										
Tillisch	1986	17	32(14)	95	80	85	92	88	4.8	0.06
Tamaki	1989	22	NA	78	78	78	78	78	3.5	0.28
Tamaki	1991	11	NA	100	38	-	-		1.6	0.00
Carrel	1992	23	34(14)	94	50	-	-	83	1.9	0.12
Marwick	1992	16	NA	71	76	68	79	74	3.0	0.38
Lucignani	1992	14	38 (5)	93	86	-	-	91	6.6	0.08
Gropler	1993	34	NA	83	50	52	81	63	1.7	0.34
Knuuti	1993	48	53(11)	92	85	-	-		6.1	0.09
Paolini	1994	17	28(4.9)	88	79	-	-	85	4.2	0.15
Tamaki	1995	43	41 (NA)	88	82	76	92	85	4.8	0.15
Gerber	1996	39	33 (10)	75	67	-	-	68	2.3	0.37
Baer	1996	42	40 (13)	96	69	83	92	86	3.1	0.06
Vom Dahl	1996	193	45 (12)	92	35	61	80		1.4	0.23
Maes	1997	23	41 (13)	83	91	-	-	87	9.2	0.19
Pagano	1998	30	24(7)	99	33	66	96	71	1.5	0.03
Schoder	1999	40	30 (6)	93	81	87	90		4.9	0.09
Zhang	1999	60	44 (15)	76	86	88	73	79	5.4	0.27
Additional Studies included in Medical Advisory Secretariat 2005 Update										
Koch (30)	2001	25	49 (15)	82	86	-	-		5.86	0.21
Tani (45)	2001	30	NA	90	61	79	78	79	2.31	0.16
Nowak (46)	2003	42	38 (13)	80	72	78	74	76	2.86	0.28
Wiggers (47)	2003	20	29 (6)	78	78	-	-	77	3.55	0.28
Korosoglou (48)	2004	41	30.9 (NA)	90	44	84	61	77	1.61	0.23
Barrington (44)	2004	25	36 (7.3)	-	-	75	100			
Lund (49)†	2002	34	42 (13)	89	68	50	94	74	2.78	0.16
Schmidt (27)†	2004	40	42 (10)	100	73	86	100	90	3.70	0
Wiggers (50)†	2001	35	35 (7)	100	67	NA	80	80	3.03	0

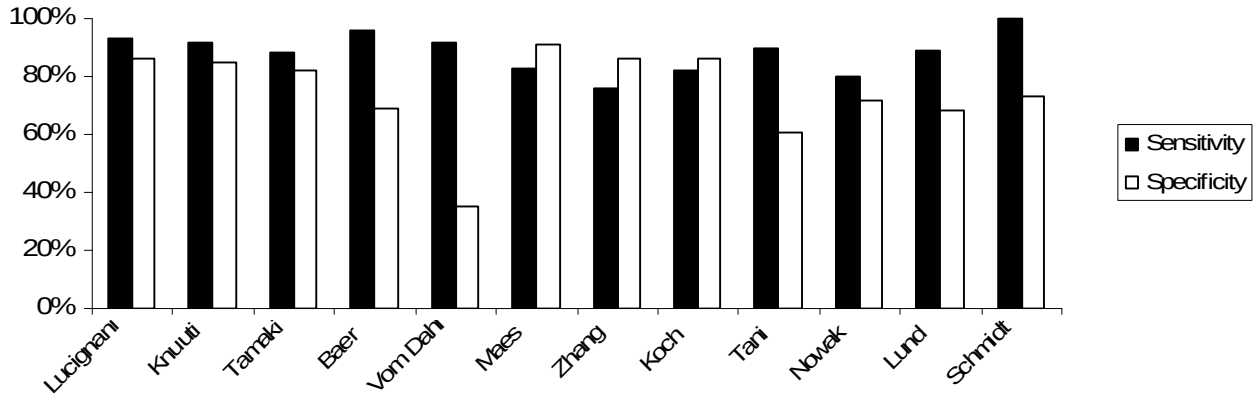
SD refers to standard deviation; PPV, positive predictive value; NPV, negative predictive value; -, not reported; LR, likelihood ratio
* Likelihood ratios added at update † analysis based on number of patients deemed to have viable myocardium rather than based on number of viable segments deemed to be viable.

Figure 3: Sensitivity and Specificity of Positron Emission Tomography in Predicting Segmental Function Recovery (Including Data from 2001 Institute for Clinical Evaluative Sciences Review)

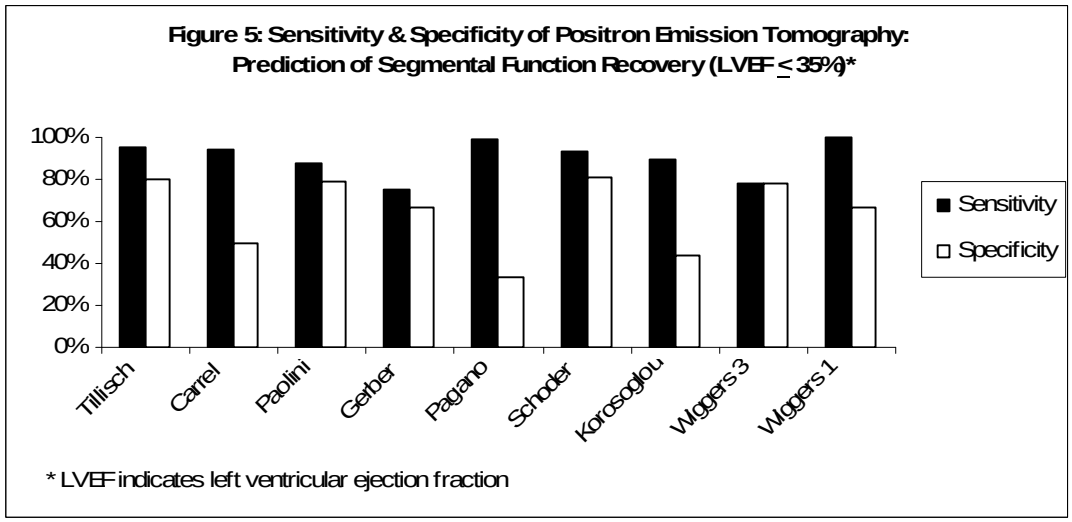


Figures 4 and 5 show the show the sensitivity and specificity of PET in studies in which the mean LVEF of patients was greater tjam 35% compared to studies in which the mean LVEF was less than or equal to 35%.

Figure 4: Sensitivity & Specificity of Positron Emission Tomography: Prediction of Segmental Function Recovery (Mean LVEF > 35%)*



* LVEF indicates left ventricular ejection fraction



There were wide variations in the diagnostic profile of PET reported by the studies, probably due to differences in methodology and definition of viability. Based on the combined data, PET showed a high sensitivity (median 90%, range 71%–100%) and lower specificity (median 73%, range 33%–91%). The NPV was generally higher than PPV, with the exception of the 5 recent studies based on segmental analysis (Table 9). Patient-based analysis yielded higher sensitivity and negative predictive values (median 100% and 94% respectively) than results based on segmental analysis (86% and 74% repectively). Sensitivity of PET in predicting regional function recovery appeared to be similar for studies in which the mean pre-revascularization LVEF of the subjects was equal to or less than 35% compared to studies in which the mean LVEF was greater than 35%. However, specificity appeared to be higher for studies with a mean LVEF greater than 35% (Table 10).

Table 10: Median and Range of Sensitivity and Specificity of Positron Emission Tomography For Predicting Segmental Function Recovery Based on Mean Mean Left Ventricular Ejection Fraction*

Mean LVEF	Sensitivity		Specificity	
	Median %	Range %	Median %	Range %
≤ 35%	90	75–100	67	33–81
>35%	89	76–100	85	35–91

*LVEF refers to left ventricular ejection fraction.

Figure 6: True Positive Rate (TPR) versus False-Positive Rate (FPR)

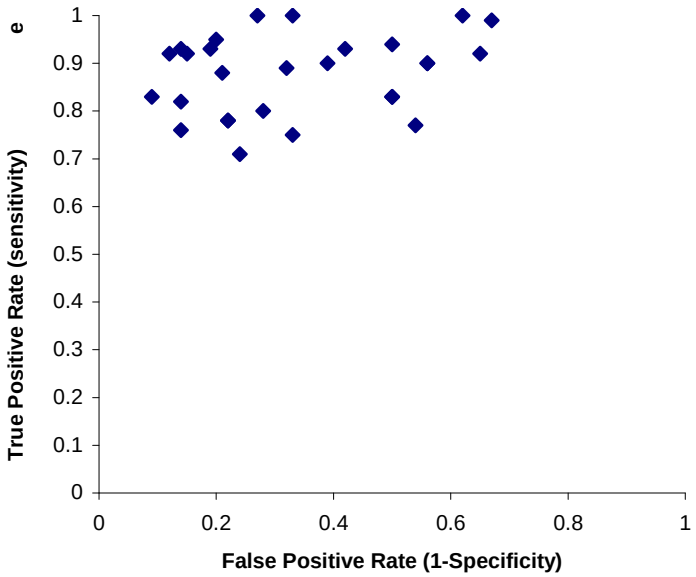


Figure 6 shows the variability of the true positive rates versus the false-positive rates of PET for predicting segmental function recovery. Most of the true positive rates were between 80% to 100%. The plot shows wide variability in the false-positive rates that were up to 70%, and appear to be independent of the true positive rate. There was sufficient information to generate 2x2 tables for 21 studies. Based on this data, Spearman's correlation coefficient (Logit TPR vs. Logit FPR) was 0.296 with a *P*-value of 0.193 (Table 11), confirming that that there was no statistically significant relationship and, therefore, summary receiver operatator characteristics (SROC) curves were not generated.

Table 11: Threshold Analysis (MetaDisc)

Spearman correlation coefficient: 0.296 *P*-value = 0.193
(Logit(TPR) vs. Logit(FPR)

Moses' model (D = a + bS)
Unweighted regression

Var	Coeff.	Std. Error	T	*P*-value
a	2.706	0.273	9.925	0.0000
b(1)	0.252	0.144	1.748	0.0966

No. studies = 21
Filter OFF
Add 1/2 only zero cell studies

Likelihood Ratio Analysis

Likelihood Ratios (LRs) are used to assess how good a diagnostic test is, and to help in the selection of an appropriate diagnostic test or sequence of tests.

Likelihood ratio for positive test (LR+) = sensitivity/(1-specificity)
Likelihood ratio for a negative test (LR-) = (1-sensitvity)/specificity

The LR for a positive test result indicates how much a given positive test result will raise the pre-test probability of (ability to predict) the presence of a target condition (in this case, presence of viable myocardium) and the higher the likelihood ratio for a positive test, the more useful is the test. On the other hand, the likelihood ratio for a negative test result indicates how much a negative test result will lower the pretest probability of having the condition (improving the ability to predict the absence of the condition), hence the lower the LR for a negative test, the more useful the test will be. Likelihood ratios have advantages over sensitivity and specificity measures because they are less likely to change with the prevalence of the disorder, they can be calculated for several levels of symptoms/sign or test, can be used to combine the results of multiple diagnostic tests, and can be used to calculate post-test probability for a target disorder.(51;52)

The following is a guide for interpreting LRs

- Positive LRs >10 or negative LRs <0.1 generate large, and often conclusive changes from pre- to post-test probability (very useful)
- Positive LRs LRs of 5–10 and negative LRs of 0.1 –0.2 generate moderate shifts in pre- to post-test (moderately useful)
- Positive LRs of 2 – 5 and negative LRs of 0.2 –0.5 generate small but sometimes important change in probability (somewhat useful)
- Positive LRs of 1 –2 and negative LRs of 0.5 – 1 alter probability to a small (and rarely important) degree (not useful) (51;52)

Likelihood Ratios of PET in Predicting Segmental Function Recovery

Likelihood ratios for postrevascularization segmental function recovery based on FDG PET viability assessment were calculated using sensitivity and specificity data from the ICES review (34) and the current update (Table 9). The analysis was conducted for all studies and was also stratified by LVEF (>35% or ≤35%) (Figures 7 -9).

Figure 7: Likelihood Ratios of PET in Predicting Segmental Function Recovery (Including ICES Review)

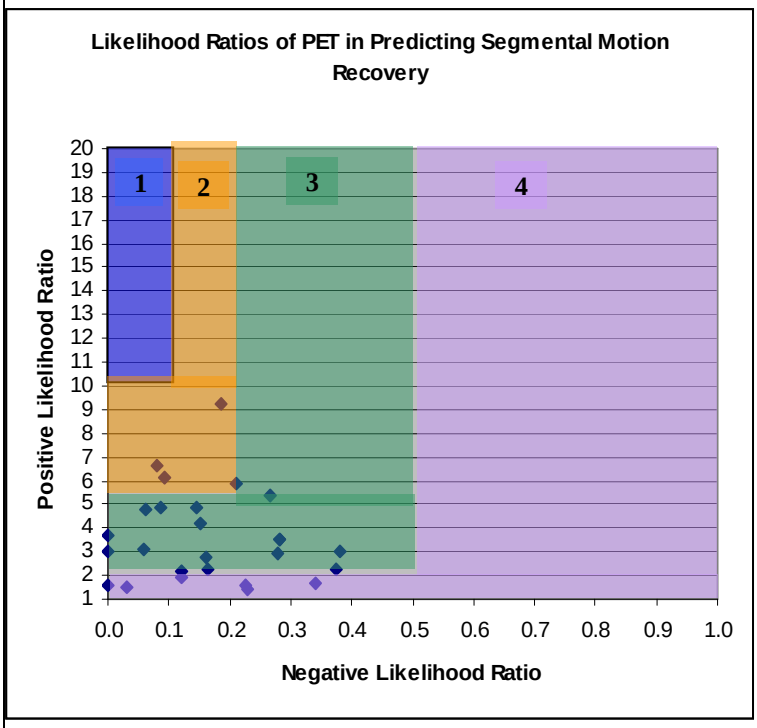


Figure 8: Likelihood Ratios of PET Predicting Segmental Function Recovery (mena LVEF>35%)

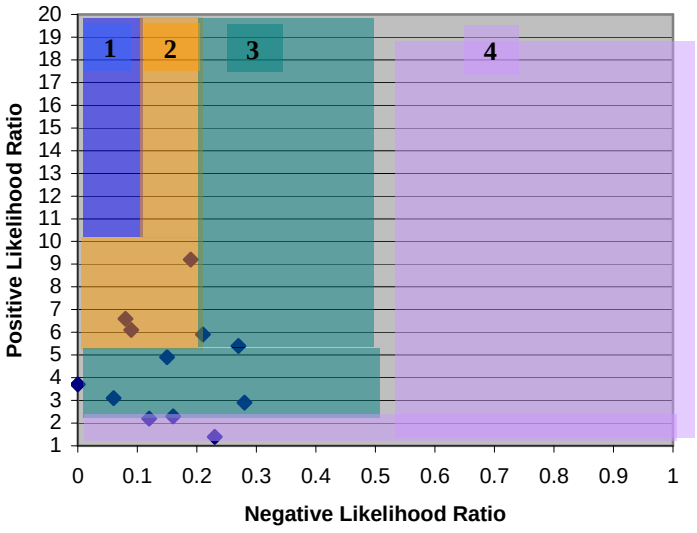
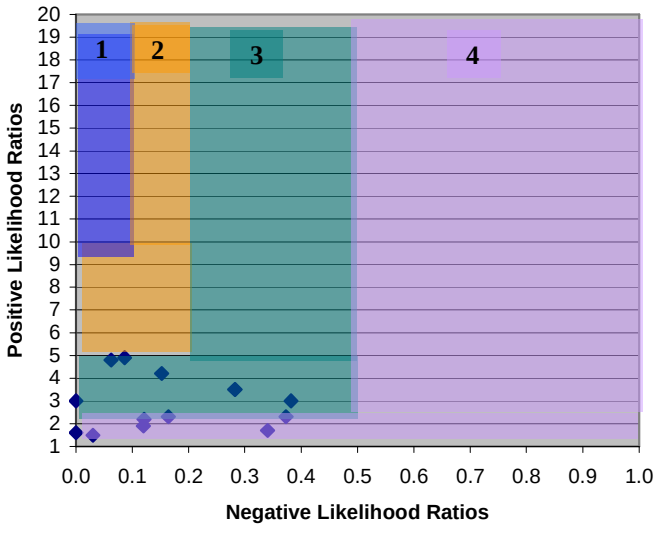


Figure 9: Likelihood Ratios of PET in Predicting Segmental Function Recovery (Mean EF≤35%)



Legend:

1 Very useful

2 Moderately useful

3 Somewhat useful

4 Not useful

Based on studies from the 2001 review and the current update, PET produced better negative likelihood ratios than positive likelihood ratios. Negative likelihood ratios ranged from 0 to 0.38 (median 0.16; ideal <0.1), indicating that FDG PET is effective in detecting dysfunctional myocardium that is not likely to recover contractile function after revascularization. Positive likelihood ratios ranged from 1.4 to 9.2 (median 3.1; ideal >10), and, therefore, PET is only somewhat useful in improving the post-test probability of recovering regional LV function after revascularization (Figure 7). A similar pattern for positive and negative likelihood ratios was observed in stratified analysis based on LVEFs (Figures 8 & 9). Table 12 shows the median values and ranges for positive and negative likelihood ratios stratified according to LVEF values greater than, or less than and equal to 35%.

Table 12: Likelihood Ratios of Positron Emission Tomography For Predicting Segmental Function Recovery Based on Mean Left Ventricular Ejection Fraction

Mean Left Ventricular Ejection Fraction	Positive Likelihood Ratio		Negative Likelihood Ratio	
	Median	Range	Median	Range
≤ 35%	3.03	1.50–4.90	0.12	0.00–0.37
> 35%	4.80	1.40–9.20	0.16	0.00–0.28

The Forest plots showed significant heterogeneity in the LR ratios among studies (Positive likelihood ratio: Cochrane Q = 98.94, $P = 0.000$; negative likelihood ratio: Cochrane's Q =39.77, $P = 0.0053$) and, therefore, it is not appropriate to obtain a point estimate for these measures (Appendices 8 and 9).

How Does PET Compared with Other Noninvasive Myocardial Viability Tests?

Overall Summary

The comparison of PET with other noninvasive technologies with respect to predicting postrevascularization regional functional recovery is summarized in Table 13. This shows a trend of PET dominating in sensitivity and dobutamine echocardiography dominating in specificity. PET and dobutamine echocardiography appear to have similar diagnostic accuracy. However, there are caveats to this interpretation, because of heterogeneity among studies. The comparison of PET with other noninvasive techniques is discussed in greater details in the following sections.

Table 13: PET Compared with Other Noninvasive Viability Assessment Techniques

Study	No. of Patients	Mean LVEF (SD) %	Comparators To PET	Criteria for PET Viability (Tracers for mismatch)	Dominant Technology for Predicting Regional Wall Motion Recovery				
					Sensitivity	Specificity	Accuracy	LR +	LR-
Bax 2001 (Meta-analysis)	598	Median 28 (13)	D. Echo Tl-201 SPECT Tc-tracer SPECT	Mismatch or FDG uptake	PET	D. Echo	PET D Echo	D. Echo	PET
Nowak 2003 (46) (segment)	42	38(13)	O-15 water PET	Mismatch (FDG/MIBI)	PET	PET	PET	NA	NA
Korosoglou 2004 (48) (segment)	41	31	D. Echo (LD) MC Echo MIBI SPECT	Mismatch (FDG/MIBI)	PET	D. Echo	D. Echo MCE	D. Echo	PET D. Echo
Barrington 2004 (44) (by region)	25	36 (7.3)		Mismatch (FDG/NH_3)	(NPV) PET	(PPV) D. Echo	NA	NA	NA
Wiggers 2001 (50) (by patient)	35	35 (7)	D. Echo (LD) Resting ECG Exercise Test	Normalized FDG uptake	PET	D. Echo	PET D. Echo	D. Echo	PET
Tani 2001 (45) (by segment)	30		D. Echo (LD)	Normalized FDG uptake	PET	D. Echo	NA	D. Echo	PET
Lund 2002 (49) (by patients)	34	42 (13)	D Echo (LD) MIBI SPECT PET+ SPECT	FDG uptake	PET D. Echo	SPECT	D. Echo	D. Echo	PET D. Echo
Schmidt 2004 (27) (by patient)	40	42 (10)	D. MRI	FDG uptake	PET	D. MRI	PET D. MRI	D. MRI	D. MRI
Wiggers 2003 (47) (by segment)	20	29 (6)	Electromechanical mapping	FDG uptake	PET	PET	NA	PET	PET

*D Echo refers to dobutamine echocardiography; D MRI, dobutamine magnetic resonance imaging; FDG, fluorodeoxyglucose F 18; LVEF, left ventricular ejection fraction; MCE, myocardial contrast echocardiography; Tc 99m MIBI, technetium Tc 99m sestamibi; NA, not available; NPV, negative predictive value; PET, positron emission tomography; PPV, positive predictive value; RWM, regional wall motion; SPECT, single photon emission computed tomography; Tl 201, thallium 201; Tc tracer, technetium 99m sestamibi.
†Unless otherwise stated.

Summary: Positron Emission Tomography Compared with Other Common Noninvasive Viability Tests

- Observational studies suggest that FDG PET has the highest sensitivity but dobutamine echocardiography has the highest specificity for predicting regional LV function recovery after revascularization.
- FDG PET and dobutamine echocardiography appear to have comparable diagnostic accuracy.
- Likelihood ratio analyses suggest that FDG PET has better negative likelihood than positive likelihood ratio. PET and dobutamine echocardiography are both somewhat useful in predicting postrevascularization regional LV function recovery.
- Thallium SPECT appears to be inferior to PET and dobutamine echocardiography for predicting regional function recovery. It has been shown to underestimate viability in patients with severe LV dysfunction ($\leq$25%).
- FDG PET detected viable myocardium in 43% to 50% of patients found to have non-viable myocardium by thallium-201 SPECT.
- FDG SPECT appears to have good overall concordance with FDG PET in detecting viable myocardium; however, it may overestimate viability in severely dysfunctional regions or in regions with severely reduced FDG uptake on PET.

Overall Quality of Evidence

The quality profile of the evidence of PET in predicting segmental function after revascularization is shown in Table 14. Based on the GRADE system (40), there is low overall quality evidence that PET has higher sensitivity in predicting postrevascularization segmental function compared with dobutamine echocardiography and SPECT.

Table 14: Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) Profile of Evidence on the Accuracy of Positron Emission Tomography to Predict Postrevascularization Segmental Function Recovery Compared to Other Nonnvasive Technologies*

Quality Assessment						Summary of Findings				
No. Of Studies	Design	Quality	Consistency	Directness	Other modifying factors	Number of subjects		Effect	Overall Quality	Outcome
						PET	Comparator	Relative risk (95% CI)		
Higher sensitivity than other noninvasive tests in Predicting Improved Postrevascularization Myocardial Segmental Function										
PET vs. other tests Bax 2001 Pagano 96 Tani 2001 Korosoglou 2004 Lund 2002 Wiggers 2001	Observational comparative	Some limitations*	No important inconsistency	Some uncertainly†	Strong evidence of higher sensitivity	212	212	N/A	⊕⊕□□	Important
Grade Quality	Moderate	Low	Low	Very low	Low				Low	

*Small sample, lack of blinding in some cases
† Some of the study population only had mild LV dysfunction
CI refers to Confidence interval

Description of Evidence

Systematic Review Comparing PET with SPECT and Dobutamine Echocardiography

Bax et al. (43) conducted a systematic review and pooled analyses of 77 studies (1980–January 2000) to determine and compare the sensitivity, specificity, and predictive values to predict improvement of regional LV function after revascularization of the five most frequently used tests for myocardial viability assessment. The 5 tests are dobutamine echocardiography, ^{201}thallium rest-redistribution SPECT, ^{201}thallium rest-reinjection SPECT, SPECT using Tc 99m sestamibi, and FDG PET.

The analyses included studies with sample sizes ranging from 17 to 91. Patients in the studies were predominantly male (59–100%) with a mean age ranging from 48 to 63 years, and mean LVEF ranging from 24% to 48%. No information was provided on the quality of the studies. Weighted means of sensitivities, specificities, positive predictive values, and negative predictive values are summarized in Table 15.

Table 15: Sensitivity and Specificity for the Different Viability Assessment Techniques in Predicting Regional Function Recovery after Revascularization * †

Technique	No. of Patients (No. of studies)	Sensitivity (%) Mean (95% CI)	Specificity (%) Mean (95% CI)	PPV (%) Mean (95% CI)	NPV (%) Mean (95% CI)
Dobutamine echo (LDDE + HDDE)	1,090 (32)	81 (80–82)	80 (79-81)	77 (76–78)	85 (84–86)
Tl-201 rest-redistribution SPECT*	557 (22)	86 (84–88)	59 (56–62)	69 (67–71)	80 (77–83)
Tl-201 reinjection* SPECT	301 (11)	88 (86–90)	50 (47–53)	57 (54–60)	83 (80-86)
Tc-based tracers SPECT	488 (20)	81 (78–84)	66 (63–69)	71 (68-74)	77 (74-80)
F-18 FDG-PET	598 (20)	93 (91–95)	58 (54–62)	71 (68–74)	86 (83–89)
Direct Comparison of Dobutamine Echocardiography and Nuclear Imaging					
Dobutamine Echocardiography	325 (11)	74 (71–77)	78 (75–81)	84 (81–87)	69 (65–73)
Nuclear Imaging	325 (11)	90 (88–92)	57 (53–60)	75 (72–78)	80 (76–84)

*****Table from Bax et al., 2001 (43)
† CI indicates confidence interval; FDG PET, fluorodeoxyglucose F 18 positron emission tomography; SPECT, single photo emission tomography; T1 201, thallium 201; Tc technitium; LDDE, low-dose dobutamine echocardiography; PPV positive predictive value; NPV negative predictive value

Findings:

- FDG PET had the highest sensitivity (93%, $P<0.05$) and highest negative predictive value (86%) compared to the other techniques.
- Dobutamine echocardiography and Tc-SPECT had the lowest sensitivity (81% vs. 93% for PET, $P<0.05$)).
- Dobutamine stress echocardiography had the highest specificity (80% vs. 58% for PET, $P<0.05$) and the highest positive predictive value (77% vs. 71% by PET, $P<0.05$).
- Among the nuclear imaging techniques, FDG-PET appeared to have a better diagnostic profile than thallium and 99m-Tc sestamibi SPECT.
- Pooled results of direct comparisons between nuclear imaging and dobutamine echocardiogram indicate that the nuclear imaging techniques had a higher sensitivity and NPV, whereas dobutamine echocardiography had a higher specificity and PPV.

Limitations

The results of this analysis need to be interpreted with caution since there was much heterogeneity among the studies with respect to:

- The study population (e.g. in the FDG PET studies, mean Patient LVEF ranged from 25% to 53%). Some study subjects only had moderate LV dysfunction.
- Data acquisition varied even for the same technique.
- Time of analysis after revascularization
- Approach to image interpretation.
- There was no discussion on the quality of the studies included in the pooled analysis

Comparison of PET and Dobutamine Echocardiography

The 2001 ICES review (34) stated that comparability of PET with dobutamine echocardiography for viability was still controversial. The review described the prospective study by Pagano et al. (53) that examined segmental LV function recovery after CABG in 30 patients with a mean LVEF of 25%. The results suggested that PET had better sensitivity (99% vs. 60%, $P<0.0001$), but worse specificity (33% vs. 62%, $P<0.0001$) when compared with dobutamine echocardiography. Overall accuracy favored PET over dobutamine echocardiography (71% vs. 61%, $P=0.01$). At 6 months after revascularization, PET showed greater accuracy in the worst functioning akinetic segments as determined by radionuclide angiography. The review stated that the degree to which these differences in accuracy rates for segmental recovery translate into important clinical benefits of PET over other available modalities is unknown. The meta-analysis of Bax et al.(43) showed that PET dominates echocardiography in sensitivity (weighted mean 96% vs. 81% for echocardiography) but echocardiography showed a higher weighted mean specificity than did PET (80% vs. 58%, $P<0.05$).

Head-to-Head Comparisons (Medical Advisory Secretariat Review)

Eight studies (44;45;48-50;53-55) from the ICES review and the current update provided a head-to-head comparison between PET and dobutamine echocardiography in the prediction of segmental function recovery after revascularization. A description of these studies is provided in the following sections. The results of these studies are summarized in Table 16.

Table 16; PET Versus Dobutamine Echocardiography for Predicting Segmental Function Recovery*

Study	n	Mean LVEF (SD)	Sensitivity %		Specificity %		PPV %		NPV %	
			PET	D. Ehco	PET	D. Echo	PET	D Echo	PET	D Echo
Bax 2001 (43)Meta-analysis	111		93	81 ($P<0.05$)	58	80 ($P<0.05$)	71	77 ($P<0.05$)	86	85 (NS)
Baer 1996 (54) (patient based)	42	40(3)	96	92	69	88	83	92	92	88
Gerber 1996 (55)	39	33(10)	75	71	67	87	78	89	63	65
Pagano 1998 (53)	30	24(7)	99	61 $P<0.0001$	33	63 $P<0.0001$	66	68 (NS)	99	54 $P<0.0001$
Tani 2001 (45)	30	NA	90	84	61	80	79	88	78	75
Korosoglou 2004 (48)	41	31	90	83 ($P<0.05$)	44	76 ($P<0.05$)	84	89 (NS)	61	65 (NS)
Lund 2002 (49) (patient-based)	34	42(13)	89	89	68	80	50	62	94	95
Wiggers 2001 (50) (patient-based)	35	35(7)	100	71 ($P<0.05$)	67	81 (NS)				
Barrington 2004 (44)	25	36(7.3)	-	-	-		75	100	100	87

*D Echo refers to dobutamine echocardiography; LVEF, left ventricular ejection fraction; NPV, negative predictive value; NR, not reported; NS, not significant; PET, positron emission tomography; PPV, positive predictive value.

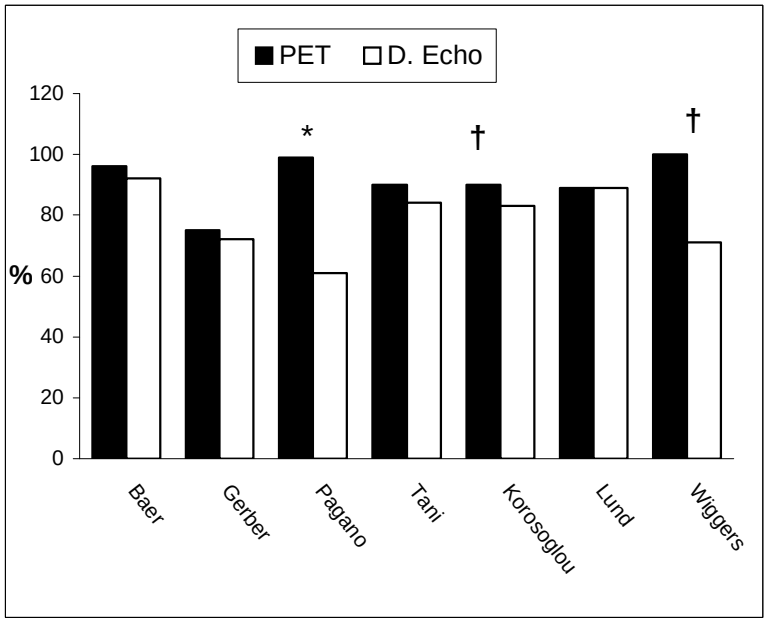
Table 17: Quality of Studies Comparing Positron Emission Tomography with Dobutamine Echocardiography (Based on QUADAS)* †

	Baer	Gerber	Pagano	Tani	Korosoglou	Lund	Wiggers 2001	Barrington
Level of evidence	3a	3a	3a	3a	3a	3a	3a	3a
Quality	Moderate to low	Moderate to low	Moderate	Moderate	Low	Moderate	Moderate	Moderate
Limitations		Small sample	Small sample					Very small sample
	Excluded people with diabetes & 3- vessel disease	Preselectio n bias	Preselection bias	Selection bias	Preselection bias	Selection bias	Selection bias	Preselection bias
				Index test used as reference			Index test used as reference	
		Interpre-tation of reference test not blinded		Index test not blinded	Interpretation of reference standard not blinded	No ITT	Index test not blinded	Index test not blinded
	Only 42/117 had complete revasculari-zation and included in analysis							

*****See Appendix 6 for detailed quality assessment
† Level of evidence according to Medical Advisory Secretariat; ITT refers to intention-to-treat analysis [AU: Verify correct as I have added.]; QUADAS, Quality Assessment of Diagnostic Accuracy Studies.

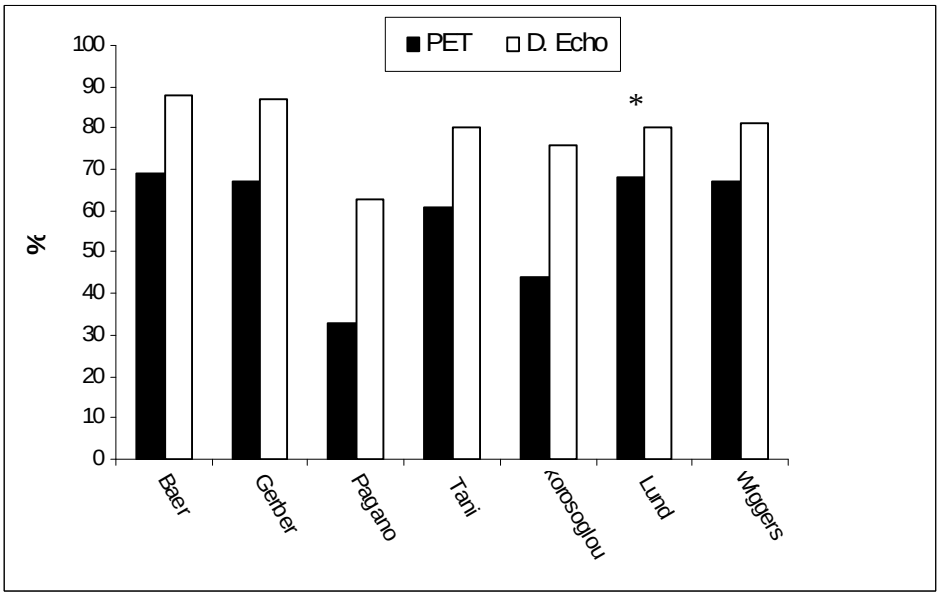
The eight head-to-head comparative studies were prospective nonrandomizedstudies with sample sizes ranging from 30 to 42 and mean LVEFs of 24% to 42%. The quality of these studies ranged from moderate to low (Table 17). All used low-dose dobutamine stimulation. Seven of the studies provided data on sensitivity and specificity. The results are consistent with those of the meta-analysis by Bax et al..(43) PET showed higher mean sensitivity than dobutamine echocardiography in six while echocardiography dominates PET in specificity in six of the seven studies. The median sensitivity of PET in the 7 studies was 90% (range 75%–100%) compared to the median sensitivity of 83% (range 61%–92%) for dobutamine echocardiography. The median specificity of PET was 67% (range 33% –69%) compared to a median specificity of 80% (range 63% –88%) for dobutamine echocardiography. Graphical presentation of the comparison between the two techniques is provided in Figures 10-13.

Figure 10: Comparison of Sensitivity of Positron Emission Tomography and Dobutamine Echocardiography for Prediction of Regional Wall Motion Recovery



* $P < .0001$
† $P < .05$

Figure 11: Comparison of Specificity of Positron Emission Tomography and Dobutamine Echocardiography for Prediction of Regional Wall Motion Recovery



* $P < .05$

Figure 12: Comparison of Positive Predictive Values of Positron Emission Tomography and Dobutamine Echocardiography for Prediction of Regional Wall Motion Recoery

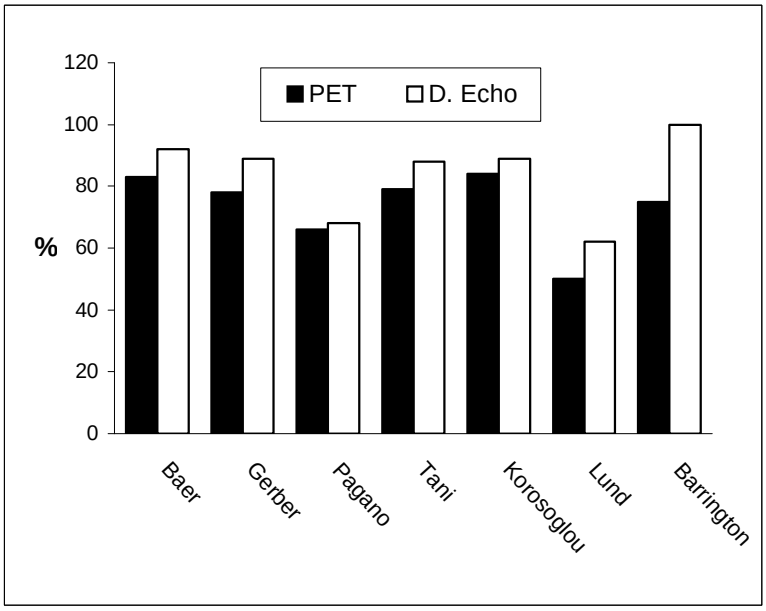
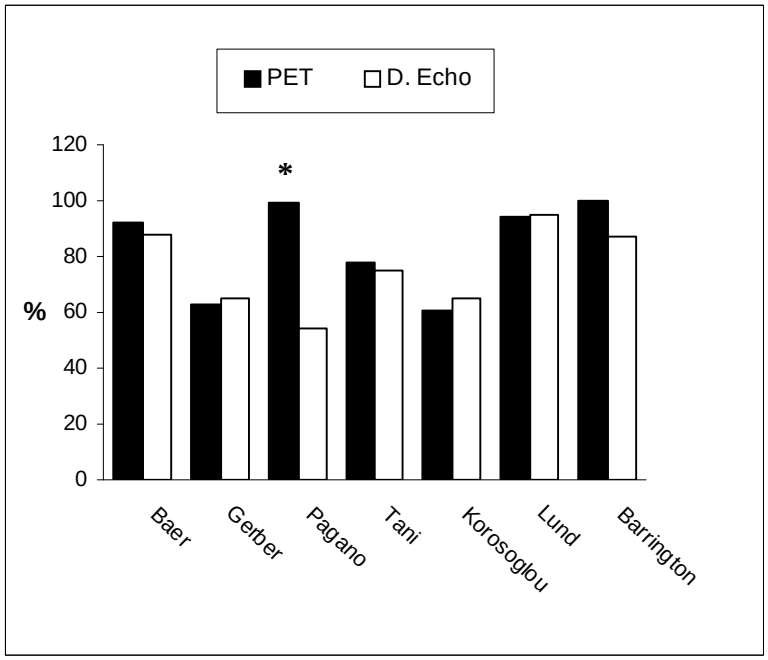


Figure 13: Comparison of Negative Predictive Values of Positron Emission Tomography and Dobutamine Echocardiography for Prediction of Regional Wall Motion Recovery



* $P < .0001$

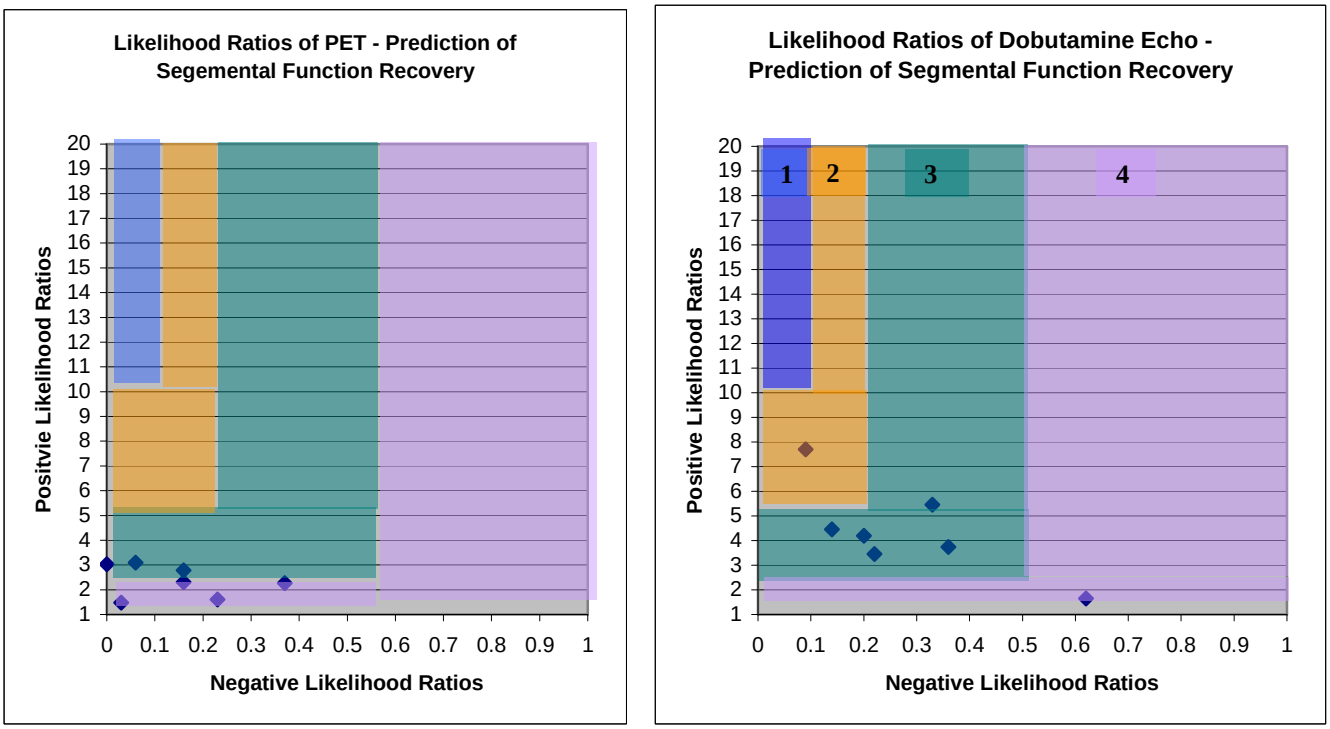
In head-to-head comparisons, PET had slightly better (lower) negative likelihood ratio (median 0.16, range 0 –0.37) compared with dobutamine echocardiography (median 0.22, range 0.09 –0.62) (Table 18; Figure 14). This indicates that PET is a better test than is dobutamine echocardiography for ruling out presence of viable myocardium. On the other hand, PET has lower (less favorable) positive likelihood ratios than dobutamine echocardiography (median 2.31 vs. 4.2 for dobutamine echocardiograpy; range 1.48–3.1 for PET and 1.65–7.7 for echo). This means that echocardiography is better than PET at increasing the posttest probability of recovering segmental function after revascularization than PET. However, the majority of the combined LRs for PET and for dobutamine echocardiography fell within the somewhat useful range, indicating similar utility in predicting segmental recovery after revascularization.

Table 18: Comparison of Likelihood Ratios – FDG Positron Emission Tomography Compared with Dobutamine Echocardiography in Predicting Segmental Function Recovery*

Study	No. of patients	Mean LVEF † % (SD)	FDG PET				Dobutamine Echocardiography			
			Sensitivity	Specificity	Likeli-hood Ratio +	Likeli-hood Ratio -	Sensitivity	Specificity	Likeli-hood Ratio +	Likeli-hood Ratio -
Bax 2001 Meta-analysis (43)	111	Median 28+/-13	0.93	0.58	2.21	0.12	0.81	0.80	4.05	0.24
Baer 1996 (54)	42	40 (13)	0.96	0.69	3.10	0.06	0.92	0.88	7.7	0.09
Gerber 1996 (55)	39	33 (10)	0.75	0.67	2.27	0.37	0.71	0.87	5.46	0.33
Pagano 1998 (53)	30	24 (7)	0.99	0.33	1.48	0.03	0.61	0.63	1.65	0.62
Tani 2001 (45)	30	NA	0.90	0.61	2.31	0.16	0.84	0.80	4.2	0.20
Korosoglou 2004 (48)	41	31	0.90	0.44	1.61	0.23	0.83	0.76	3.46	0.22
Lund 2002 (49) (patient-based)	34	42 (13)	0.89	0.68	2.78	0.16	0.89	0.80	4.45	0.14
Wiggers 2001 (50) (patient-based)	35	35(7)	1.0	0.67	3.03	0.00	0.71	0.81	3.74	0.36

*FDG refers to fluorodeoxyglucose F 18; LVEF, left ventricular ejection fraction; PET, positron emission tomography.
†Unless otherwise indicated.

Figure 14: Comparison of Likelihood Ratios of PET versus Dobutamine Echocardiography for Prediction of Segmental Function Recovery



Legend:

1	Very useful	**2**	Moderately useful	**3**	Somewhat useful	**4**	Not useful

Description of Studies of Direct Comparison Between Positron Emission tomography and Dobutamine Echocardiography (Medical Advisory Secretariat Review)

Lund et al. (49) prospectively compared the accuracy of contractile response by low-dose dobutamine echocardiography (wall thickening), FDG-PET and sustained perfusion by ^{99m}Tc-sestamibi SPECT to predict functional recovery in patients with CAD. The study reported on 34 out of 49 patients who had viability evaluated by all three modalities prior to revascularization by CABG (32%) or PCI (68%). Revascularization was performed blinded to and irrespective of any test results to avoid pre-selection by evidence of viability. Receiver operator characteristic (ROC) curve analysis was used to optimize the performance of each modality. Regional wall motion abnormality (RWMA) was calculated at baseline and follow-up to validate contractile recovery. Reversible LV dysfunction was assumed if RWMA improved >+1 standard deviation after revascularization.

Of the 34 patients, 9 (27%) showed reversible dysfunction. For these patients, RWMA improved from –2.34+/-1.41 to –0.24+/-2.13 (P<0.0001), and ejection fraction improved from 48+/-17% to 59+/-17 % (P<0.01).(49)

ROC curve analysis showed improvement of 2 or more adjacent akinetic segments as the optimal threshold for dobutamine echocardiography. FDG uptake greater than 55% yielded optimal performance for PET, whereas an uptake greater than 60% was the optimal threshold for 99m-Tc sestamibi SPECT. FDG PET and Tc 99-m sestamibi SPECT provided concordant predictability for viability in 79% of patients.(49) The diagnostic performance of the techniques is summarized in Table 19.

Table 19: Sensitivity, Specificity, Diagnostic Accuracy and Predictive Values for Regional Function Recovery (Analysis on Basis of Patient)

	Sensitivity %	Specificity %	Accuracy %	PPV %	NPV %
D Echo ≥ 2 akinetic segments	89	80	82	62	95
PET > 55%	89	68	74	50	94
Tc 99m MIBI SPECT > 60%	56	88	79	63	85
PET > 55% + SPECT > 50%	78	80	79	58	91

Results by Lund et al. (49)
*Tc 99m MIBI SPECT refers to technetium Tc 99m sestamibi single photon emission computed tomography; D echo, dobutamine echocardiography; PET, Positron emission tomography; PPV, positive predictive value; NPV, negative predictive value

Lund et al. also reported that FDG PET and dobutamine echocardiography had similar sensitivities (89%) and negative predictive value (95% vs. 94% respectively) but dobutamine echocardiography had higher specificity, positive predictive value and diagnostic accuracy. 99m-Tc sestamibi SPECT had high specificity (88%) but only intermediate sensitivity (56%). Test performance was optimized by a concordant match of FDG PET at >55% uptake and 99m-Tc sestamibi SPECT at >50% uptake, bringing the diagnostic accuracy and specificity closer to that of dobutamine echocardiography. The sensitivity of the combined nuclear imaging was still lower than that of dobutamine echocardiography.

Multiple logistic regression analysis by Lund et al. showed that improvement of >/=2 adjacent akinetic segments under dobutamine stimulation was the most accurate predictor of functional recovery after revascularization (x^2 =13.94, *P*<0.001). Perfusion imaging with 99m-Tc sestamibi emerged as a useful and independent predictor of reversible dysfunction. The combined use of both nuclear tracers increased the accuracy of PET.(49)

Limitations of the study by Lund et al. (49) are as follows:
- The study was based on small sample size
- Redistribution of the nuclear tracer may represent a potential problem of perfusion imaging with 99mTc sestamibi. However ^{13}N Ammonia PET acquired images early after injection when distribution of this tracer was comparable and proportional to flow measurement.
- No attenuation correction was performed on SPECT images potentially resulting in underestimation of tracer uptake.
- Echocardiogram, one of the tests being evaluated, was also used as the gold standard.

Wiggers et al. (50) compared the diagnostic performance of FDG PET, resting ECG, low-dose dobutamine echocardiography (LDDE) and exercise testing to predict patient-based regional wall motion recovery. Thirty-five patients with a mean LVEF of 35+/-7% underwent the above tests before revascularization. Echocardiography was conducted at baseline and again at follow-up. FDG viability was defined as FDG uptake >/=70% of uptake in a region with highest myocardial blood flow determined on ^{13}N ammonia PET. Absent Q wave on resting ECG and ST segment depression or angina pectoris during exercise testing were also considered indications of viable myocardium. A patient was deemed to have reversible regional function if there were at least 2 adjacent dysfunctional segments that had an improvement in wall motion greater than 1 grade. At follow-up, 14 patients improved wall motion in a mean of 3.3+/-1.2 segments.

FDG PET had the highest sensitivity (100% vs. 93% for exercise testing, 50% for resting ECG and 71% for low dose dobutamine echocardiography) for predicting segmental function recovery. Low-dose dobutamine echocardiography had the highest specificity (81% vs. 67% for FDG PET, 71% for resting ECG, and 33% for exercise testing). Diagnostic accuracy was 80% for PET, 77% for low-dose dobutamine echocardiography , 62% for exercise testing and 58% for resting ECG (*P*<0.05 resting ECG vs. PET). Wiggers et al. concluded that for patients in whom exercise testing showed no viable myocardium, recovery in regional function is unlikely, and further viability testing is not needed; however, these authors recommended that for patients in whom exercise testing showed viable myocardium, further testing using FDG PET or low-dose dobutamine echocardiography is warranted.(50)
Limitations of this study include short follow-up and inclusion of patients with symptoms of heart failure and angina.

Korosoglou et al. (48) compared the diagnostic accuracy of real time myocardial contrast echocardiography (MCE) with low-dose dobutamine echocardiography and combined 99m-Tc sestamibi SPECT and FDG PET for predicting regional function recovery. The tests were performed on 41 patients with CAD and LV dysfunction (LVEF<40%). PET and SPECT images were analyzed quantitatively in 16 segments to identify mismatch between perfusion SPECT and FDG PET. Recovery in regional wall function was defined as $\geq$ 1 grade increase in wall motion on echocardiography 3 to 6 months after revascularization.(48)

Compared to low-dose dobutamine echocardiography, combined use of FDG PET and sestamibi SPECT had significantly higher sensitivity (90% vs. 84%, *P*< .05) but lower specificity (44% vs. 76%, *P*< .05).(48)

Korosoglou et al. (48) concluded that the most specific sign of myocardial viability could be derived from dobutamine stress echocardiography. They proposed that this technique should be used as an initial screening method for detection of myocardial viability, and MCE should be performed in patients who were found to have no viable myocardium by dobutamine stress echocardiography.

Tani et al. (45) prospectively compared LDDE and FDG PET in determining viability and predicting wall motion recovery after revascularization in 30 patients with a history of myocardial infarction and regional wall motion abnormality. For PET, segments with uptake greater than 50% were considered viable. Regional wall motion was determined before revascularization and again at a mean follow-up of 5+/-3 months. Recovery of regional function was defined as an improvement of more than 1 grade in wall motion in rest echocardiography before revascularization and at follow-up. At follow-up, 8 of 41 akinetic segments and 50 of 68 hypokinetic segments showed improvement. There was agreement between findings of FDG PET and low-dose dobutamine echocardiography in 55% of the viable segments and 79% of nonviable segments. PET had higher sensitivity than LDDE in predicting segmental regional wall motion recovery (90% vs. 84%) but lower specificity compared to LDDE (61% vs. 80% for LDDE). Similarly, PET had slightly higher NPV (78% vs. 75%) but lower PPV (79% vs. 88%) compared with low-dose dobutamine echocardiography. It was reported that LDDE can detect functional recovery at a relatively early stage.(45) Limitations include small sample size, short follow-up, and visual assessment of regional wall motion that might have missed minor changes during dobutamine infusion.

Barrington et al. (44) prospectively compared the diagnostic accuracy of four techniques for the detection of hibernating myocardium in 25 males with coronary artery disease (LVEF $\leq$ 40%) that were waiting for CABG. All patients underwent rest-stress ^{99m}Tc-sestamibi and delayed (>18 hour) thallium SPECT, high-dose dobutamine stress echocardiography, and ^{13}NH3/FDG PET. Postoperative improvement in wall motion was measured with echocardiography at a mean follow-up of 8.1 month after revascularization. Images were analyzed using a 13-segment model. Segments with perfusion ammonia uptake greater than 70% or with a perfusion/metabolic mismatch by PET were considered to predict regional function recovery. Recovery of regional LV function was defined as improvement in regional wall motion equal to or greater than 1 grade in at least 2 adjacent segments in a vascular territory at follow-up. ROC curve analyses were used to choose the optimal threshold for potential predictors, and positive and negative predictive values were calculated.

At follow-up, 6 vascular territories in 5 patients (20%) had hibernating myocardium as defined in the study. Tracer uptake of rest MIBI, thallium, ammonia, and FDG was significantly higher in territories with hibernating myocardium than in those with non-viable myocardium. Univariate logistic regression identified normal perfusion, presence of mismatch on PET, the presence of biphasic response, or the development of ischemia with dobutamine as independently predictive of hibernating myocardium.(44) The predictive values are summarized in Table 20.

Table 20 Predictive Values for Hibernating Myocardium (Patient-Based Analysis)* †

Test	Optimal Threshold % of Maximum Uptake	PPV %	NPV %	AUC
FDG PET	68	75	100	0.97
^{13}NAmmonia N 13 PET	66	45	95	0.87
^{13}N ammonia PET/FDG PET mismatch		67	100	
Tc 99m sestamibi SPECT	50	50	96	0.86
High-dose dobutamine echocardiography		100†	87‡	
^{201}Thallium SPECT	Not an independent predictor of hibernation			

*AUC refers to Area under the curve; FDG, fluorodeoxyglucose F 18; PET, positron emission tomography; SPECT, single photon emission computed tomography. †Biphasic response or ischemic response.
‡No change or sustained improvement.

Stepwise multiple logistic regression identified uptake of FDG as the only independent predictor of hibernating myocardium (P =0.035). FDG-PET was the most powerful predictor for hibernating myocardium overall. FDG PET also had the highest NPV (100% vs. 87% for dobutamine echocardiography). All scintigraphic methods also had high NPV (95–96%) while dobutamine echocardiography had the highest PPV (100% vs. 75% for FDG PET).(44) Barrington et al.(44) suggested that echocardiography could be used as a first-line test, with FDG PET as a second-line test when echocardiography is negative for hibernating myocardium. One of the limitations of this study is the low rate of functional recovery (20%) which, according to Barrington et al.(44), probably reflected the type of patients undergoing surgery at the facility.

Comparison between PET and Thallium-201 SPECT

The 2001 meta-analysis by Bax et al. (43) showed that FDG PET had significantly higher sensitivity than both rest-redistribution and rest-reinjection ^{201}thallium SPECT (weighted mean 93% for PET vs. 86% and 88% for thallium-201 rest-reinjection SPECT respectively, P< .05). While FDG also had higher specificity and PPV than thallium rest-reinjection SPECT, it was comparable to thallium rest-redistribution SPECT in both specificity and PPV. (Table 21)

There were no direct comparisons between FDG PET and ^{201}thallium SPECT with respect to accuracy in predicting functional recovery after revascularization. Most studies focused on the concordance between PET and SPECT in defining viable myocardial segments.

In 1998, Srinivasan et al. (56) reported that overall, ^{201}thallium SPECT provided information concordant with FDG PET (92% concordance). However, in a subgroup of patients with LVEF of 25% or lower, at 60% FDG PET threshold value, ^{201}thallium SPECT tended to underestimate myocardial viability. Of the segments with severely irreversible ^{201}thallium uptake defects, FDG PET identified 43% of these segments to be metabolically active and viable.

Akinboboye et al. (57) conducted FDG PET in 33 heart transplant candidates with ischemic cardiomyopathy (LVEF <35%) who were found to have no viable myocardium based on Tl-201 SPECT. FDG PET identified viability in 50% of these patients who underwent successful CABG with similar clinical outcome at 12 months as other patients who received a heart transplant at the same facility.

Gutberlet et al. also assessed the accuracy of thallium-201 SPECT for predicting segmental function recovery after revascularization**.** (58) Their study compared delayed enhanced MRI and dobutamine stress MRI to thallium-201 for the prediction of postrevascularization segmental contractile function recovery in 20 patients with severely impaired LV function (mean LVEF 28.6+/-8.7%). In this study, thallium-201 SPECT yielded a sensitivity of 86%, specificity of 68%, positive predictive value of 94%, and negative predictive value of 44% for predicting postrevascularization segmental function recovery in dysfunctional myocardium. The results pertaining to thallium 201 SPECT are shown in Table 21.

Table 21: Comparison between PET and Thallium in Predicting Segmental Function Recovery*

Study		FDG PET	Thallium SPECT	
Bax et al., 201 Meta-analysis (44)	Sensitivity %	93 (91–95)	RR 86 (84–88)	RI 88 (86–90)
	Specificity %	58 (54–62)	59 (56–62)	50 (47–53)
	PPV %	71 (68–74)	69 (67–71)	57 (54–60)
	NPV %	86 (83-89)	80 (77–83)	83 (80–86)
Gutberlet et al., 2005 (58)			Rest thallium SPECT	
	Sensitivity %		86	
	Specificity %		68	
	PPV %		94	
	NPV %		44	

*FDG refers to fluorodeoxyglucose F 18; PET, positron emission tomography; PPV, positive predictive value; RR, rest/redistribution; RI, rest/reinjection; SPECT, single photon emission computed tomography.

Comparison of Positron Emission Tomography and Single Photon Emission Tomography Using 99m-Tc Sestamibi or Tc-Tetrofosmin for Prediction of Segmental Function Recovery

The meta-analysis by Bax et al. (43) showed that PET has significantly higher sensitivity (93% vs. 81%, $P<0.05$) and NPV (86% vs. 77%, $P<0.05$) compared to 99m-Tc sestamibi SPECT. Specificity and PPV were comparable between the two techniques.

Lund et al. (49) undertook a head-to-head comparison of the accuracy of FDG-PET, ^{99m}Tc-sestamibi SPECT, and dobutamine echocardiography in predicting segmental functional recovery after revascularization among 34 patients with ischemic LV dysfunction. Concordance between FDG PET and 99m-Tc sestamibi SPECT was 70% (kappa =0.59). When both nuclear studies were validated by improved wall motion after revascularization, FDG PET had higher sensitivity (89% versus 56%) but lower specificity (68% versus 88%) compared with 99m-Tc sestamibi SPECT.

Using improvement in wall motion after revascularization as the gold standard, Barrington et al. (44) conducted a direct comparison between FDG PET and 99m-Tc sestamibi SPECT in identifying hibernating myocardium. This study has been described in a previous section. Hibernating myocardium was defined as a mismatch of FDG/N-13 NH3 perfusion PET or a mismatch of 99-mTc sestamibi/ delayed thallium-201 SPECT. Optimal thresholds of tracer uptake were determined by ROC analysis. Using these thresholds, FDG PET had a higher PPV than Tc-99m MIBI SPECT. The tests had similar NPV (Table 22). The area under the ROC curve was higher for FDG PET than for MIBI SPECT (0.97 vs. 0.86). The uptake of FDG in PET was also found to be the most powerful predictor of hibernation. (44)

Table 22: Accuracy of PET vs.Versus 99m-Tc Sestamibi SPECT for Predicting Segmental Function Recovery

Study	Optimal threshold %		Sensitivity %		Specificity %		PPV %		NPV %		Accuracy %	
	FDG PET	MIBI SPECT	FDG PET	MIBI SPECT	FDG PET	MIBI SPECT	FDG PET	MIBI SPECT	FDG PET	MIBI SPECT	FDG PET	MIBI SPECT
Bax et al., 2001 (43) Meta-analysis (all Tc tracers)	NR	NR	93†	81†	58	66	71	71	86	77	NR	NR
Lund et al., 2002 (49) (Segment-based)	>55	>60	89	56	68	88	50	63	94	85	74	79
Barrington et al., 2004 (44) Re hibernation (Patient-based)	68	50	NR	NR	NR	NR	75	50	100	96	NR	NR

*FDG refers to fluorodeoxyglucose F 18; Tc 99m MIBI, technetium Tc 99m sestamibi; NPV, negative predictive value; PET, positron emission tomography; PPV, positive predictive value; NR not reported. †$P < .05$

Studies Using PET as a Reference Standard

Five studies (59-63) compared SPECT using 99m-Tc sestamibi and 99m-Tc tetrofosmin (TF) SPECT with FDG PET (Table 23 & Appendices 11 and 12). These studies showed that 99mTc-sestamibi SPECT had good concordance (86%) with PET in identifying myocardium that would recover regional function after revascularization. Compared to FDG PET, SPECT using tetrofosmin had sensitivity ranging from 61% to 81% even with nitrate or dobutamine administration. The sensitivity improved to 85% with gating. This suggests that PET has superior sensitivity in identifying viable myocardium than SPECT using technetium labelled tracers.

Table 23: Diagnostic Performance of Technetium Single Photon Emission Computed Tomography Using PET as the Reference Standard*

	Imaging Technique for comparison	Sensitivity %	Specificity %	PPV %	NPV %	Accuracy % (kappa)
Kaltoft et al., 2001 (61)	99mTc-sestamibi SPECT	87	82	96	58	Concordance with PET = 86%
Maruyama et al., 2002 (64)	Gated Technitium tetrofosmin SPECT	85	56			
Yoshinaga et al., 2002 (60)	Rest-stress + Low-dose dobutamine stress Gated TF SPECT	76	86	90	69	Concordance with FDG PET = 80% (0.6)
Giorgetti et al., 2004 (62)	Rest Post-nitrate Technitium tetrofosmin SPECT	61	88			72
He et al., 2003 (63)	Post-nitrate TF SPECT	81	86			Concordance with FDG PET 82% (0.53)

FDG refers to fluorodeoxyglucose F 18; PET, positron emission tomography; PPV, positive predictive value; NPV, negative predictive value; NR, not reported.

F-18 FDG Positron Emission Tomography Compared with FDG SPECT

There was no head-to-head comparison between the accuracy of FDG PET and that of FDG SPECT in predicting segmental function recovery after revascularization. Two earlier studies examined the agreement between FDG PET and FDG SPECT in defining viable myocardium.

In 1996, Bax et al. (65) compared FDG PET and FDG SPECT in 20 patients with previous MI and significant CAD on angiography (mean LVEF 39+/-16%) undergoing assessment of myocardial viability. Viability was determined quantitatively in PET as FDG PET/N-13 NH_3 PET mismatch and in SPECT as FDG SPECT/early resting ^{201}Tl SPECT mismatch. FDG/NH_3 PET and FDG/201-thallium SPECT yielded 76% concordance in dyssynergic segments. Concordance was 74% in akinetic or dyskinetic segments and 89% in hypokinetic segments. Of 33 discordant segments, 15 were located in the lateral wall. Concordance between the two techniques based on patients was 85%. In a subgroup of 12 patients with LVEF</=35%, all PET and SPECT data were identical. (65)

In 1998, Srinivasan et al. (56) reported excellent concordance between FDG PET and FDG SPECT (area under the ROC curve was 0.94 –0.96) at thresholds of 40% to 60% uptake. Similar to PET, FDG SPECT provided incremental information regarding viability in segments judged nonviable by thallium-201 SPECT. Despite the good overall concordance between FDG PET and FDG SPECT, Srinivasan et al. found noticeable discordances, especially in regions of severe LV dysfunction and regional asynergy. Discordance between the 2 tests was also noted in regions with severely reduced FDG uptake on PET, 27% of which appeared to have more activity on SPECT. The author suggested that some of these differences might be due to attenuation. Myocardial function after revascularization was not studied.

Three studies compared FDG SPECT with techniques other than FDG PET and provided sensitivity and specificity data on FDG SPECT for predicting segmental function recovery. Slart et al (66) evaluated the accuracy of FDG/99mTc sestamibi SPECT in detecting viable myocardium using FDG PET/sestamibi perfusion SPECT as a reference standard. Two studies by Bax et al. (25;67) compared the prognostic value of FDG SPECT with that of other techniques in predicting regional and global function improvement after revascularization. Studies that provided accuracy and outcome data on FDG SPECT are summarized in Appendix 13 and Table 24.

Table 24: Studies on Diagnostic and Predictive Accuracy of FDG Single Photon Emission Computed Tomography for Identifying Viable Myocardium* (Improvement in Regional Function)

Study	N	Mean LVEF % (SD)	Other Patient Characteristics	Procedure/Comparison	Results
Slart 2005 (66)	58	0.33 (12)		Dual isotope simultaneous acquisition FDG/Tc 99m sestamibi SPECT vs. FDG/ ammonia N 13 PET (gold standard)	Good agreement between FDG/ammonia N 13 PET and visual or quantitative FDG/Tc-99m MIBI SPECT (82%)
Bax 2001 (25)	47	0.30	Ischemic cardiomyopathy	FDG SPECT for predicting improvements in regional and global LV function and in symptoms	Predicting regional function improvement: Sensitivity: 85% Specificity: 80% PPV: 70% NPV: 90% Predicting global function improvement: Sensitivity: 86% Specificity: 92% PPV: 90% NPV: 89% Patients with significant viable myocardium (≥ 6 segments) had the largest improvement in NYHA score (from 3.4+/-0.5 to 1.7+/-0.8, *P* = .001)
Bax 2003 (67))	47	0.30 (8)	Chronic CAD Consecutive patients	Tl-201 SPECT, Low-dose D echo, FDG SPECT and sequential strategies (Tl-201 & low-dose D echo) in predicting improvement in LVEF at 6 months after revascularization	Accuracy of FDG SPECT in predicting improvement in global LV function similar to strategies of sequential testing using Tl-201 SPECT and low-dose D echo: Predictive accuracy of FDG SPECT: Sensitivity 89% Specificity 86% Accuracy 87%

*CAD refers to coronary artery disease; D Echo, dobutamine echocardiography; FDG, fluorodeoxyglucose F 18; LV, left ventricular; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; NPV, negative predictive value; PET, positron emission tomography; PPV, positive predictive value; SPECT, single photon emission computed tomography; Tl-201, thallium-201.

Table 25: Indirect Comparison of FDG PET and FDG SPECT for the Prediction of Improvement in Regional Function Improvement (Segment –Based)*

Procedure	Sensitivity %	Specificity %	PPV %	NPV %
FDG PET (Bax meta-analysis (43)	91–95	54–62	68–74	83–89
FDG SPECT	81–89	75–86	62–78	90–94

*FDG refers to fluorodeoxyglucose F 18; NPV, negative predictive value; PET, positron emission tomography; PPV, positive predictive value; SPECT, single photon emission computed tomography.

The above data suggest that there is good agreement between FDG PET and FDG SPECT in identifying viable myocardium. Recent studies suggest that FDG SPECT has good sensitivity and specificity in predicting both regional and global LV function, and moderate accuracy in predicting improvement in heart failure symptoms. However, experts have indicated that FDG SPECT yields a lower count than PET and could make imaging difficult in obese patients if imaging was preformed without attenuation correction.(6) There is also evidence that FDG SPECT may overestimate viability in patients with severe LV dysfunction or in segments with very low FDG uptake on PET.

FDG PET Compared With Oxygen-15 Water PET

Nowak et al. (46) compared the diagnostic accuracy of volumetric myocardial blood flow measured by oxygen-15 (O-15) water PET with that of FDG PET in predicting functional recovery in dysfunctional myocardial segments. Forty-two consecutive patients with a mean age of 63+/-11 years and mean LVEF of 38+/-13 underwent FDG PET, O-15 water PET and perfusion SPECT using 99m-Tc tetrofosmin. Left ventricular angiography and ventriculography were also preformed to determine wall motion and ejection fraction. Twenty patients underwent revascularization and 15 of these patients were available for follow-up LV angiography and ventriculography at a mean of 64 months after revascularization. Mismatched segments (MIBI uptake</=70% and FDG uptake<70%) with improved function were classified as hibernating myocardium. Forty of 72 dysfunctional segments improved after revascularization. The diagnostic profiles of FDG PET and myocardial blood flow volume based on segmental function improvement were summarized in Table 26. Myocardial blood flow volume did not improve the accuracy of FDG PET in predicting regional function recovery.

Table 26: Comparison of Diagnostic Accuracy & Predictive Values for FDG PET and Myocardial Blood Flow Volume*

	Sensitivity %	Specificity %	PPV %	NPV %	Accuracy %
Normalized FDG Uptake	80	72	78	74	76
Myocardial Blood Flow Volume by O-15 water PET	82	38	62	60	61

*FDG refers to fluorodeoxyglucose F 18; NPV, negative predictive value; O 15-water, oxygen-15-labelled waterPET, positron emission tomography; PPV, positive predictive value.

Comparison Between Positron Emission Tomography and Cardiac Viability Magnetic Resonance Imaging

Reviews on Cardiac Magnetic resonance Imaging

A 2003 Medical Advisory Secretariat review of cardiac MRI (68) included one study that compared MRI to PET in the detection of myocardial scar tissue. (68) This study reported that MRI has comparable sensitivity, specificity, and accuracy to PET for determining myocardial viability. The 2003 MAS review indicated that there was insufficient evidence at that time that MRI was better able to predict which patients may benefit from revascularization.

Current Comparison of PET and Cardiac MRI

Four studies comparing PET with MRI were found. All studies were small prospective nonrandomizedstudies with a sample size of 19 to 41 patients. Three of the studies were correlation studies using PET as a reference standard. Only one study (27) compared the accuracy of FDG PET with that of MRI in predicting postrevascularization regional myocardial function. These studies are summarized in Table 27 and Appendix 14. A description is also provided. The quality of the studies is summarized in Table 28.

Table 27: **Summary of Studies Comparing Positron Emission Tomography Versus Magnetic Resonance Imaging for Prediction of Segmental Function Recovery***

Study	N	Mean LVEF %(SD)	PET Viability Marker	MRI Viability Marker	Gold Standard	Results
Klein et al., 2002 (28)	31	28 (9)	Nonviable: perfusion/FDG matched defect (by segment)	Gadolinium hyperenhancement: - scar tissue (nonviable)	FDG PET	CeMRI (PET as reference) –overall Sensitivity 83% Specificity 88% CCeMRI infarct mass correlates well with PET infarct size.
Kuhl et al., 2003 (29)	23	31 (11)	Nonviable: FDG/perfusion matched defect (by segment)	Gadolinium-hyperenhancement : Scar tissue (nonviable)	FDG PET	CeMRICeMRI (PET as reference) Sensitivity 96% Specificity 84% AUC 0.95 96% concordance between CeMRI & FDG PET for normal segments & nonviable segments but less so for hibernating segments.
Knuesel et al., 2003 (69)	19		Viable FDG uptake>/=50%	Viable rim thickness>4.5mm	FDG PET	Viable tissue by Ce MRI correlated with FDG uptake. 85% of segment with FDG & CeMRI viability improved function significantly.
Schmidt et al., 2004 (27)	40	40 (10)	FDG PET uptake >/=50% in >/=50% of related segments (by patient)	Dobutamine MRI: preserved end-diastolic segment or mean dobutamine induced systolic wall thickening	End systolic wall thickening >/=2 mm in >50% of related segments after revascularizatio n- detected by dobutamine MRI	Predicting regional wall recovery PET D-MRI Sensitivity 100% 96% Specificity 73% 87% PPV 86% 92% NPV 100% 93% Accuracy 90% 93% LR+ 3.7 7.4 LR- 0 0.05

*AUC refers to area under the curve; CeMRI, contrast-enhanced magnetic resonance imaging; D MRI, dobutamine magnetic resonance imaging; FDG, fluorodeoxyglucose F 18; LVEF, left ventricular ejection fraction; LR, likelihood ratio; NPV, negative predictive value; PET, positron emission tomography; PPV, positive predictive value.

Table 28: Quality of Studies Comparing PET with MRI for Prediction of Segmental Function Recovery (based on QUADAS)

	Klein 2002 (28)	Kuhl 2003 (29)	Knuesel 2003 (69)	Schmidt 2004 (27)
MAS Level of evidence	3a	3a	3a	3a
Quality	Moderate	Moderate	Low	Moderate to low
Limitation	Small sample	Very small sample	Unclear spectrum	Small sample
	Pre-selection bias	Preselection bias	No clearly stated inclusion/exclusion criteria	Preselection bias
		No clear inclusion/exclusion criteria	Lack of blinding in interpretation of images	Some subjects only had mild LV dysfunction

See Appendix 6 for detailed quality assessment
*Level of evidence according to Medical Advisory Secretariat; LV refers to left ventricular; QUADAS, Quality Assessment of Diagnostic Accuracy Studies; See Appendix 6 for detailed quality assessment.

Summary Statements on FDG PET Compared with Cardiac Magnetic Resonance Imaging

The following summizes findings of 3 small obserational studies described below:

- There was high concordance between FDG PET and contrast enhanced MRI in segments with normal FDG uptake or matched defect. However, concordance is less explicit in segments with metabolic/perfusion mismatch by PET.
- In people with severe LV function impairment, dobutamine MRI as well as dobutamine echocardiography were predictors of global function recovery after revascularization.
- One study suggested that compared to FDG PET, dobutamine MRI may have comparable or higher capability in predicting regional function improvement.
- MRI appears to be a promising technique for assessing myocardial viability in CAD patients with severe LV dysfunction, but no conclusion can be drawn on the effectiveness of PET versus functional MRI in predicting myocardial viability and outcomes of revascularization due to the small number of studies and methodological flaws in the studies.

Description of Studies

Only one study compared PET with magnetic resonance imaging using actual segmental recovery as the gold standard. Schmidt et al. (27) compared FDG PET and dobutamine stimulation MRI with respect to their accuracy in identifying viable myocardium and predicting regional functional recovery after revascularization. The study included 40 consecutive patients with chronic MI and regional myocardial dysfunction (a- or dyskinesis) and a mean LVEF of 40+/-10%. All patients underwent FDG PET and rest and stress MRI during dobutamine stimulation prior to revascularization to assess viability in the dysfunctional segments. Viability assessed by FDG PET was defined as >/=50% of FDG uptake in >/=50% of the related segments. In dobutamine MRI, an infarct region is deemed viable if more than 50% of the related segments had a mean end-diastolic thickness $\geq$5.5 mm or a mean dobutamine induced systolic wall thickening $\geq$ 2mm. Rest MRI was conducted at baseline and 4 to 6 months after revascularization to assess regional function including end systolic wall thickening. Functional recovery was defined as end systolic wall thickening >/=2mm in more than 50% of related segments

Functional improvement was found in 25 patients (63%). Of these patients 96% showed prerevascularization contractile reserve on dobutamine MRI, and 87% of the regions with persistent akinesia had shown no contractile reserve. Contractile reserve on dobutamine MRI accurately predicted regional function recovery in 93% of the patients. FDG PET showed viability in all patients who had functional recovery after revascularization but 4 deemed viable by PET showed no functional improvement.

Head to head comparison of FDG PET and low-dose dobutamine MRI showed similar accuracy for the identification of viable myocardium and the prediction of functional recovery after successful revascularization (93% accuracy for dobutamine MRI versus 90% for FDG PET). While FDG PET was slightly more sensitive, dobutamine MRI had better specificity. No *P* values were provided (Table 30).

Table 30: FDG PET vs.Versus Dobutamine MRI in the Prediction of Regional Function Recovery

N=40.	Magnetic Resonance Imaging		F-18- FDG PET
	DWT at rest≥5.5 mm	Dobutamine Induced SWT≥2mm	F-18 FDG uptake≥50%
Sensitivity %	100	96	100
Specificity %	53	87	73
Accuracy %	83	93	90
Positive predictive value %	78	92	86
Negative predictive value %	100	93	100

DWT Diastolic wall thickening SWT Systolic wall thickening 18-FDG 18-F fluoro-deoxyglucose

Evaluation of preserved end-diastolic wall thickness results in overestimation of the amount of viable myocardium compared to functional improvement after successful revascularization.

Limitations of the study included:

- Small sample size made subgroup analysis unfeasible.
- No mention of blinding in the interpretation of viability studies and functional improvement.
- Short follow-up (4 to 6 months) period may not be sufficient for full functional recovery to occur.
- Assessing dobutamine-induced contractile reserve was not done in real time and may have compromised the sensitivity to detect subtle contraction reserve or a biphasic response to dobutamine.
- No CeMRI was done.
- The modality being studied (MRI) was also used to evaluate the outcome (functional improvement)
- Mean LVEF of the study subjects was 40+/-10% and hence results cannot be generalized to CAD patients with severe LV dysfunction (LVEF<35%).

Three studies compared contrast enhanced MRI with PET, using PET as a gold standard.

Klein et al. (28) compared MRI hyperenhancement with PET as a gold standard for the detection and quantification of myocardial scar tissue in 31 patients with CAD and reduced LV function (LVEF<35%). All patients underwent gadolinium hyperenhanced MRI, FDG PET and ^{13}N-ammonia perfusion PET imaging.

Nonviable tissue (scar) was defined as regionally increased MRI signal intensity 20 minutes after administration of gadolinium (hyperenhancement). The extent of hyperenhancement was divided into transmural and subendocardial. Segments with reduced blood flow and reduced metabolism (matched defect) were divided into mild (nontransmural) or severe (transmural) defect and were considered scar tissue.

MRI hyperenhancement correlated with metabolic/perfusion mismatch in FDG PET. For 11% of segments defined as normal (viable) by PET, MRI showed hyperenhancement (not viable), whereas 5% with a matched PET defect (not viable) showed no hyperenhancement (viable). PET classified 55% of segments with subendocardial hyperenhancement as normal. Infarct mass quantitated using MRI correlated well with PET infarct size (r=0.81, *P*<0.0001). (28)

The accuracy of MRI hyperenhancement in assessing transmural or both transmural and subendocardial defects as defined by PET in relation to the degree of dysfunction, is shown in Table 29.

Table 29: Sensitivity and Specificity of MRI in Detecting Infarcted Myocardium as Defined by FDG PET

	Transmural		Transmural and Subendocardial	
Segments	**Sensitivity %**	**Specificity %**	**Sensitivity %**	**Specificity %**
All	86	94	83	88
Akinetic	89	84	89	79
Severe hypokinetic	86	90	95	82
Moderate hypokinetic	100	98	100	94

The extent of scar tissue showed a weak inverse correlation (P =0.05) with EF (r=0.42) and with end-diastolic and end-systolic volume (r=0.0.32 and r=0.41, respectively). There was a significant difference between end-diastolic and end systolic wall thickness and wall thickening in viable segments compared with segments with transmural scar defined by PET (P<0.001). However, ROC curve analysis revealed smaller under the curve area for wall thickness and thickening compared with hyperenhancement, (AUC 0.93 for CeMRI, 0.785 for wall thickness, and 0.744 for wall thickening). This suggests that wall thickness and wall thickening may have less diagnostic value than hyperenhancement in distinguishing scar tissue from viable myocardium. (28)

Klein et al. (28) concluded by using PET with ^{13}N ammonia for perfusion and FDG as the metabolic tracer in patients with chronic CAD and severe LV dysfunction, they could found close correlation between the hyperenhancement in MRI and the infarct based on PET with respect to location and size. The results were independent of the severity of contractile dysfunction.

Limitations to this study included:

- Only a few segments revealed a mismatch in PET (hibernating myocardium) 34/1023. Of note, 68% of these segments revealed no hyperenhancement, whereas transmural enhancement occurred in 8%. This suggests that MRI diagnosed hibernating myocardium correctly in many cases.
- It is unknown if patients were enrolled consecutively, hence there may be selection bias.
- Without a measure of recovery of function or other outcome, no conclusion can be drawn regarding which modality was correctly identifying tissue capacity for recovery after revascularization.

Kuhl et al. (29) prospectively compared nuclear imaging (FDG PET and Tc99m--tetrofosmin perfusion SPECT) with gadolinium-based CeMRI in their ability to distinguish viable from nonviable myocardium. Nuclear imaging was used as the reference standard. The study reported on 23 consecutive patients with CAD and LV dysfunction (mean LVEF 31+/-11%) scheduled for viability assessment.

Of the severely dysfunctional segments that showed a matched metabolic/perfusion defect in FDG PET, 98% showed enhancement in CeMRI, indicating scar tissue. In severely dysfunctional segments, the extent of hyperenhancement was 80+/-23% in segments with matched perfusion metabolism defect (PET nonviable) compared to 33+/-25% in segments with perfusion metabolic mismatch (ischemic but viable) (P<0.05). Hyperenhancement in normal segments was 9+/-14%. There was a strong inverse correlation between segmental FDG uptake by PET and segmental extent of enhancement by CeMRI (r=-0.86, P<0.001). The correlation between FDG PET and end-diastolic wall thickness (r=-0.51, P<0.001) or wall thickening (r=-0.41, P<0.001) was lower than that with CeMRI. (29)

ROC curve analysis yielded an optimal segmental hyperenhancement cutoff value of 37% for differentiating PET nonviable from PET viable myocardium, with an area under the curve of 0.95 (95% CI, 0.93 to 0.97). At the hyperenhancement threshold of 37%, the sensitivity and specificity of CeMRI for detecting PET nonviable myocardium as defined by PET were 96% and 84%. There was a 96% concordance between CeMRI and FDG PET for the assessment of viability status of dysfunctional segments with normal metabolism/perfusion or a matched defect. In segments with preserved metabolism but reduced perfusion (mismatch) reflecting hibernating myocardium, the results were less explicit (63% scored viable and 37% scored non-viable by CeMRI).(29)

The limitations of this study are as follows:

- Small sample size with possible preselection bias
- Averaging of FDG PET, MRI and SPECT data
- Possibility that image misalignment may account for some of the discrepancies between PET and CeMRI
- No assessment of recovery of myocardial function after revascularization.

Knuesel et al. (69) conducted CeMRI and FDG PET viability assessment in 19 patients with angiographically confirmed CAD and regional LV dysfunction. The assessments were conducted in a random order within 4 weeks. Patients with insulin-dependent diabetes were excluded from the study. Segmental FDG uptake and segmental amount of unenhanced tissue on CeMRI images were expressed as a fraction of the activity in the segment that showed the highest resting flow on perfusion PET. Systolic wall thickening, viable mass and thickness of viable rim tissue were determined for each myocardial segment. FDG uptake >/=50% as a predictor of functional recovery was used as the reference standard and corresponded to a viable rim thickness of 4.5 mm on CeMRI. Ten patients were followed by MRI 11+/-12 months after revascularization. Segments with preserved FDG metabolism (>/=50% FDG uptake) and a thick viable rim on CeMRI showed functional recovery in 85%, whereas only 13% of thin metabolically nonviable segments improved function (P<0.0005). Metabolically viable segments with a thin viable rim and thick segments improved function in only 36% and 23%of the segments respectively (not significant compared to thin metabolically nonviable segments). These results showed that segments with insufficient viable tissue or considerable scar content may limit their ability to recover function after revascularization, suggesting that combined FDG metabolism and tissue composition by CeMRI can be used to discriminate among various classes of dysfunctional myocardium.

MRI Compared with Other Noninvasive Viability Tests

Dendale et al. (70) reported 81% concordance between echocardiography and MRI in detecting viable and nonviable myocardial segments. Zamorano et al. (71) reported 91% agreement between dobutamine stress echocardiography and MRI in the detection of viable myocardial segments in a group of patients undergoing cardiac transplantation for ischemic cardiomyopathy.

In a study published since the Medical Advisory Secretariat review on MRI, Ansari et al. (72) compared late enhancement cardiovascular MRI and thallium-201 SPECT in 15 patients with ischemic LV dysfunction (mean ejection fraction =35+/-11%). The results of the study suggest that hyperenhancement on MRI significantly correlates with myocardial nonviability determined by thallium-201 SPECT (r = –0.51, P<0.001).

In a 2005 report, Gutberlet et al. (58) reported the results of viability assessment using delayed enhanced MRI and dobutamine stress MRI in 20 patients with severely impaired LV function (mean LVEF 28.6+/-8.7%). The study compared the predictive and prognostic ability of MRI indices using thallium-201 SPECT and recovery of contractile function as reference standards. With thallium-201 SPECT as a reference standard, all MRI indices showed high sensitivity (84% to 94%) but low specificity (39% to 50%). With recovery of contractile function in dysfunctional segments 6 months after CABG as the gold standard, delayed enhanced MRI was superior to rest thallium-201 SPECT in sensitivity, specificity, positive predictive value, and negative predictive value (99% vs. 86%, 94% vs. 68%, 99% vs. 94%, and 94% vs. 44% respectively).

In a study of 41 patients with LVEFs less than 30%, Hausmann et al. (73) compared results of dobutamine echocardiography, dobutamine stress SPECT, dobutamine MRI, contrast enhanced MRI. Parameters for comparison included preoperative biopsy and improvement in LVEF at 23+/- 6 months after revascularization. Hausmann et al reported that preoperative predictors of an LVEF increase equal to or greater than 5% after revascularization were:

- hibernating myocardium located in the anterior wall
- wall thickness increase>15% during preoperative stress echocardiography
- late enhancement in MRI<20% of the left ventricle
- no destruction of myocardial cell architecture and cell hypertrophy>19um on biopsy
- antiapoptotic gene BCL-XL with low expression

Hausmann et al. (73) concluded that in patients with highly impaired LV function, recovery of hibernating myocardium can be predicted preoperatively with MRI or echocardiography with dobutamine stress, and that the results can guide the choice between revascularization and heart transplantation.

Comparison Between Positron Emission Tomography and Endocardial Electromechanical Mapping

Five small observational studies with sample sizes ranging from 21 to 51 that compared PET and electromechanical mapping (EM) were found (Table 31). The mean baseline LVEF ranged from 29% to 52%. The quality of the studies was moderate to low (Table 32). Three studies (31;32;74) used FDG PET as a reference standard, and two studies (30;47) used postrevascularization wall motion as the outcome measure. PET viability was based on perfusion/metabolism mismatch in all studies. Perfusion was measured using thallium-201 in 1 study, ^{99m}Tc sestamibi SPECT in 3 studies, and ^{13}N ammonia PET in one study. In the three studies that used PET as a reference standard, the mean sensitivity of EM mapping was 65%, 69% and 85% while the mean specificity was 69%, 85%, and 90% respectively.(31;32;74) Of the two studies that explored independent outcomes, one study showed that nuclear imaging with PET had better diagnostic performance for predicting regional wall motion 6 months after revascularization compared to electrophysiologic (EP) mapping (sensitivity & specificity: 78% vs. 59% for EP mapping). In the other study, PET was found to have lower sensitivity than EM mapping (82% vs. 91%) but higher specificity (86% vs. 71%). (30;47) Detailed description of the studies is summarized in Appendix 15.

Table 31: Summary of Sensitivity and Specificity of Unipolar Voltage Amplitude from Electromechanical Mapping in Identifying Myocardial Viability as Defined by Positron Emission Tomography*

Reference	No. of patients / Follow-up	Reference standard	PET viability based on	EF baseline EF follow-up (%)	Sensitivity (%)	Specificity (%)	Optimal UV threshold (mV)	Comments
Koch 2001	46 6 mos	Wall motion recovery	FDG PET, ^{99m}Tc MIBI SPECT mismatch	52+/-16 62+/-13	PET 82 UVA 91	PET 86 UVA 71	7.5	Regional wall motion increased in infarct areas when UV>7.5mV; no additional information from LLS
Wiggers 2003 (47)	20 6 mos	Wall motion recovery D Echo	FDG PET ^{99m}Tc MIBI SPECT mismatch	29+/-6 34+/-13	PET 78 UPA 59*	PET 78 UVA 59*	8.4†	Recovery of LV function more predictable by PET or SPECT than by unipolar voltage in dysfunctional myocardium LLS: no difference in reversibly & irreversibly dysfunctional regions
Botker 2001 (31)	31	FDG PET viable	$N^{13}NH_3$ & FDG PET mismatch	30+/-9 ____	UPA 69	UPA 69	6.5	LLS: no difference between normal and dysfunctional myocardium
Keck 2002 (32)	51	FDG PET viable	FDG PET, ^{99m}Tc MIBI SPECT mismatch	51+/-14 ____	UV 65	UV 90	4.5	Stress perfusion: UV in reversible segments not different from normal. LLS cannot predict recovery but differentiates between normal, hypokinetic myocardium and scar tissue
Graf 2004 (74)	21	FDG PET viable	FDG PET, Tl^{201} SPECT mismatch	49+/-17	UV 85	UV 85	5.2	Unipolar voltage (UV) in hypoperfused myocardium is more closely related to F-18 FDG PET than to SPECT myocardial perfusion, especially in perfusion/metabolism mismatch. UV cannot distinguish between normal & hypoperfused segment with mismatch.

*EJ refers to ejection fraction; UPA Unipolar amplitude; LLS linear local shortening; LV left ventricle; Mos months ; 99m-Tc MIBI, sestamibi; catheter: centre-line method from digitalized angiogram; D echo dobutamine echocardiography 3D: 3 dimensional; UV unipolar voltage; Tl-201

thallium-201 ; UPA unipolar amplitude ; †Distinction between reversible and irreversible dysfunction; all other values for sensitivity and specificity distinction are between viable myocardium and scar tissue.

Table 32: Quality of Studies Comparing PET with Electromechanical Mapping

	Kock	Wiggers 2003	Botker	Keck	Graf
MAS Level of evidence†	3a	3a	3a	3a	3a
Quality	Low	Moderate	Moderate to low	Moderate	Moderate to low
Limitation	Selection bias Index test used as reference (detection bias) Only mild LV dysfunction	Preselection bias; 2 different methods used to measure outcomes in different patients (possible detection bias).	Preselection bias No blinding in interpretation of images	Small sample Preselection bias No clear inclusion/ exclusion criteria stated. Only mild LV dysfunction	Very small sample Preselection bias No blinding Only mild LV dysfunction

*See Appendix 6 for detailed assessment of quality. LV refers to left ventricular.
† Level of evidence according to Medical Advisory Secretariat

Summary Statements on Comparison of Positron Emission Tomography and Electromechanical Mapping

Based on small observational studies in patients with mild to moderate LV dysfunction:

- Electromechanical mapping can distinguish between normal and hypoperfused myocardium, but cannot distinguish viable from nonviable segments in hypoperfused myocardium.
- There was conflicting finding on the sensitivity of electromechanical mapping in predicting segmental function recovery after revascularization; however, most of the studies suggest that it is inferior to PET.
- Endocardial electromechanical mapping appears to be an experimental procedure at this time.

What is the Incremental Value of PET Viability Assessment in Predicting Improved Global LV Function (Ejection Fraction) After Revascularization?

Improvement of global function after revascularization is probably more important than changes in regional wall function, since improvement in regional wall function does not always result in improved global function. Improved global function is often defined as an absolute increase in LVEF of at least 5% after revascularization. A substantial amount of viable myocardium (25% –30% of LV) is necessary to effect this improvement. (25)

The 2001 ICES review included a prospective study by Soufer et al. (75) that examined the incremental value of FDG PET over ^{99m}Tc sestamibi SPECT. The study reported that in SPECT nonviable segments, PET accurately predicted improvement in ejection fraction after revascularization.

The current review identified one meta-analysis and four prospective observational studies that provided information on the use of PET to predict global functional improvement. These studies are summarized in Appendix 17 and Table 33. They included 34 to 178 patients with mean baseline LVEF ranging from 26% to 41.5%. The quality of the studies ranged from moderate to low (Table 34). Only four of the studies (76), (77), (48), (78) provided accuracy data, and only one study (48) compared FDG PET directly with another noninvasive technique with respect to prediction of improvements in global LV function.

Table 33: Sensitivity and specificity of FDG PET in Predicting Recovery of Global Function (LVEF)

Study	Year	N	Mean LVEF % (SD) pre & post revascularization	Criteria for PET Viability	Gold Standard/ Outcome Measures	Mean Sensitivity %	Mean Specificity %	Accuracy (%)	Comparison
Gerber (77)	2001	178	Improved: Pre 34 (13) Post 46 (13) Not improved Pr e 42 (14) Post 40 (15)	>45% normalized FDG uptake	↑ LVEF >5% by gated angiography, contrast angiography or 2-D Echo	79	55	67	-FDG PET has good sensitivity but only modest specificity for predicting the recovery of global function after revascularization. -Predictive accuracy of FDG PET for improvement in global cardiac function < than previously reported for improvement in segmental cardiac function.
Bax (76)	2002	34	Pre: 32 (9) Post: 34 (10) (NS)	Relative MRG >60% in ≥3 segments	↑ LVEF >5% by radionuclide ventriculography @ rest	100	71	79	Relative MRG * / Absolute MRG / Water perfusable fraction Sen 100% / 90% / 80% Spec 71% / 71% / 67% Accuracy 79% / 76% / 71%
Korosoglou (48)	2004	41	30.9	FDG uptake relative to uptake on MIBI SPECT mismatch	>8% ↑ in EF on 2-D echocardiography @ 3–6 months	83%	64%	-	FDG PET / DE / Real time MCE Sensitivity 83% / 78% / 83% Specificity 64% / 83% / 57% Sensitivities were similar. Dobutamine echocardiography demonstrated the highest specificity in predicting recovery in EF.
Beanlands (79)	2002	82	Pre: 26 (7) Post: mean absolute ↑ 4.3 (1.68)	Scar score calculated from normalized FDG score	↑ LVEF on radionuclide angiogram (RNA)	-	-	-	A multivariate prediction model incorporating PET scar score & clinical variables had a goodness of fit with *P* = .001. Change in LVEF for tertiles of scar scores: Scar Score / Change in LVEF (absolute) Small (0–16%) 9.0+/-1.9% Moderate (16–27.5%) 3.7+/-1.6% Large (27.5–47%) 1.3+/-1.5% *P* =0.003, LVEF for small vs. LVEF large scar score
Zhang (80)	2001	123	Pre 36(5) 3 mos 44 (8) (*P*<0.001) 6 mos 51 (9) (*P* =0.02)			-	-	-	-Only patients with significant hibernating myocardium by PET showed significant improvement in LVEF @ 3 & 6 months after revascularization. LVEF was significantly higher @ 6 months than @ 3 months.

* DE refers to dobutamine echocardiography; EF, ejection fraction; LVEF, left ventricular ejection fraction; MRG, metabolic rate of glucose; NPV, negative predictive value; PET, positron emission tomography; PPV, positive predictive value; Revasc., revascularization; RNA, radionuclide angiography; SD, standard deviation; SPECT, single photon emission computed tomography. †PET tracer uptake score: 1 (normal) to 4 (no uptake)

Table 34: Quality of Studies on the Effectiveness of PET in Predicting Improvement in Global Left Ventricular Function After Revascularization

	Gerber 2001	Bax 2002	Korosoglou 2004	Beanlands 2002	Zhang
MAS Level of evidence	3a	4c	3a	4c	4c
Quality	Moderate to low	Moderate	Low	High to moderate	Moderate
Limitation	Small sample Preselection bias Interpretation of reference test not blinded	Small sample Preselection bias No clear inclusion/exclusion criteria	Pre-selection bias; interpretation of reference standard not blinded	Preselection bias	Preselection bias Some patients only had mild LV dysfunction

See Appendix 6 for detailed quality assessment

Summary of Findings on Prediction of Improvement in Gobal Myocardial Function Ejection Fraction

- Based on small prospective observational studies, there is evidence that FDG PET can predict improvement of global myocardial function after revascularization.
- Significant improvement in postrevascularization LVEF was observed in patients who were found to have hibernating myocardium based on by FDG PET and were revascularized. Improvement was observed as early as 3 months after revascularization and continued to improve at six months.
- Patients without hibernating myocardium or who were treated medically did not show improvement in LVEF.
- FDG PET appears to have higher sensitivity but lower specificity than dobutamine echocardiography in predicting regional function improvement.
- Myocardial scar score based on FDG PET assessment together with perfusion/metabolic mismatch and clinical parameters was shown to predict absolute changes in LVEF after revascularization.
- There is little head-to-head comparison between PET and other noninvasive viability assessment techniques in predicting improvement in global LV function after revascularization.

Overall Quality of Evidence

Table 35 showed that there is low overall quality evidence that PET can predict postrevascularization global function but there is presently insufficient evidence to determine its incremental value over other noninvasive techniques for this outcome.

Table 35: Overall Quality Profile of Evidence on Predicting Postrevascularization Global Myocardial Function by PET

Quality Assessment						Summary of Findings			
No. Of Studies	Design	Quality	Consistency	Directness	Other modifying factors	Number of subjects	Effect Relative (95% CI)	Overall Quality	Outcome
PET predicts Improvement in global Myocardial Function After Revascularization									
Beanlands 2002 (79) Gerber 2001 (77) Zhang 2001 (80) Korosoglou 2002 (48)	Observational comparative	Some limitations*	None	Some uncertainty**	Strong association †	335	41	⊕⊕□□	
Grade Quality	Moderate	Low	Low	Very low	Low			Low	

* Interpretation not always blinded. *Some patients only had mild LV dysfunction † Scar score & LV function CI Confidence Interval

Description of Studies on Prediction of Post Revascularization Improvement in Global Myocardial Function

In their 2001 meta-analysis of studies on predicting regional LV function, Bax et al. (43) pooled available information on LVEF before and after revascularization in 28 studies. Of these, 12 studies used FDG PET to assess viability. Underwood (81) reported these results in a 2004 review (Table 36). The minimum amount of hibernating myocardium deemed necessary to classify a patient as having hibernating myocardium varied from 8% to 53% with a mean of 22%. Most studies considered an improvement of LVEF of at least 5% as significant, but this is mainly because of the interstudy reproducibility of measurement of ejection fraction rather than because this value is known to be clinically significant. (81) The results showed improvement in LVEF in patients assessed as having hibernating myocardium, but no improvement in those without hibernation. The study did not provide a comparison of the accuracies of PET and other noninvasive techniques in predicting improvement in global function

Table 36: Weighted mean LVEF (%) Before and After Revascularization According to the Presence or Absence of Hibernation

Technique	No. of studies	Hibernation				No hibernation		
		LVEF before	%	LVEF after	%	LVEF before %	LVEF after	%
FDG PET	12	37		47		39		40
Thallium SPECT	5	30		38		29		31
Tc-MIBI SPECT	4	47		53		40		39
Dobutamine echocardiography	7	35		42		35		36

Table reproduced with permission from the European Society of Cardiology; 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):815-836.

The study by Korosoglou et al**.** (48) has been described in an earlier section. The study compared FDG PET/MIBI SPECT with low-dose dobutamine echocardiography and real time myocardial contrast enhanced echocardiography (MCE). Improvement in LVEF was defined as a minimum of 8% absolute increase. Sensitivities and accuracy rates for the prediction of increased ejection fraction by the three techniques were similar (78–83%), whereas specificity was higher with low-dose dobutamine stress echocardiography (83% vs. 64% for PET and 57% for MCE).

Gerber et al. (77) reported on a 6-centre European cohort study using a common PET protocol and pooled database to evaluate the predictive accuracy of various FDG PET indices for improvement in global cardiac function (LVEF) 4 – 6 months after revascularization by CABG or PCI. Preoperatively, patients underwent coronary angiography and FDG PET. LVEF and regional wall motion were assessed before and after revascularization. Results were reported for 171 of the 178 patients enrolled after excluding 7 patients because of incomplete revascularization of a dysfunctional region.

ROC curve analysis showed that the presence of more than 3 dysfunctional segments with greater than 45% normalized FDG uptake in PET best predicted postrevascularization global functional recovery. At this optimal threshold, FDG PET had a mean sensitivity of 79%, specificity of 55%, and 67% accuracy for predicting recovery of contractile function after revascularization. The diagnostic accuracy of FDG PET was found to be similar in all patients, ranging from 61% to 71%, irrespective of pre-operative EF. (77)

The limitations of the study by Gerber et al. were as follows:

- Heterogeneity in the equipment used in PET scanning among centres
- Heterogeneity in the technology used in assessing coronary stenosis, preoperative and postoperative global ejection fraction and regional wall motion, even though the same technology was used in the same patient for pre-operative and post operative assessments.
- Angiographic verification of the completeness of revascularization procedures was not regularly performed.

- This is small, nonrandomized study, without clearly stated inclusion or exclusion criteria.
- There is no indication of blinding in the evaluation of outcomes.

Bax et al. (76) conducted a prospective cohort study of 34 patients with chronic ischemic LV dysfunction to compare the accuracy of FDG PET with that of blood flow and water-perfusable tissue fraction (from O^{15}-water PET) in predicting global functional recovery after revascularization, defined as greater than 5% increase in LVEF after revascularization as measured with radionuclide ventriculography. The mean age of the patients was 62+/-10 years, and the mean LVEF was 32+/-9%. . The highest sensitivity was obtained with relative metabolic rate of glucose in FDG PET, whereas the highest specificity was obtained with both relative and absolute metabolic rate of glucose. The relative metabolic rate of glucose provided the highest diagnostic accuracy (Table 37).

Table 37: Diagnostic Performance (and 95% Confidence Intervals) of Various PET Indices for Predicting Recovery of Global Myocardial Function

PET Indices	Sensitivity % (95% CI)	Specificity % (95% CI)	Diagnostic Accuracy % (95% CI)
Relative metabolic rate of glucose	100 (100–100	71 (53–89)	79 (65–93)
Absolute metabolic rate of glucose	90 (71–100)	71(53–89)	76 (62–90)
Perfusable tissue fraction	80 (55–100)	67 (48–86)	71 (53–89)
Myocardial blood flow	80 (55–100)	54 (34–74)	62 (46–78)

95% CI refers to 95% Confidence Interval

Beanlands et al. (79) reported on a multicenter cohort study that explored the relationship between the extent of viable or scarred myocardium and the level of recovery of LV function after revascularization in patients with CAD and severe LV dysfunction (LVEF≤ 35%). The study (PARR 1) included 82 patients with a mean age of 62+/-9 years and a mean EF of 26+/-7%. Fifty-one patients had New York Heart Association (NYHA) class III to IV dyspnea, and 50% had Canadian Cardiovascular Society class III to IV angina. Excluded were patients that had an MI in the preceding 6 weeks, had severe valvular diseases, or had aneurysm requiring resection. Patients underwent baseline PET perfusion imaging (^{13}N ammonia or ^{82}Rubidium) and FDG PET. Radionuclide angiography scanning using 99mTc-labelled tracer was performed to determine LVEF at baseline and after 3 months of follow-up. Scar score and mismatch score (viability) were calculated. Revascularization was performed, 71% within 6 weeks of viability assessment. Complete follow-up data was available for 70 patients.

In univariate analysis, the significant independent predictors of absolute change in LVEF after revascularization were:
- Scar score (P = .001)
- Tracer (P = .043)
- Time to revascularization (within 6 weeks) (P = .008)
- Diabetes (P = .029)

The independent effect of the mismatch score was not significant. There was significant interaction between the perfusion tracer used and mismatch score (P =0.02).(79) Multivariate analyses were performed using stepwise multiple regression method. A multivariate prediction model incorporating clinical variables and PET scar showed a better goodness of fit for predicting absolute change in LVEF. Scar scores were shown to have an inverse relationship with absolute changes in EFs (Table 38).

Table 38: Relationship between Scar Score and Ejection Fraction

Tertiles of Scar Scores, %		Mean change in Absolute EF %
0 –16	(small)	9.0+/-1.9
16–27.5	(moderate)	3.7+/-1.6
27.5–47	(large)	1.3+/-1.5

Beanlands et al. (79) concluded that in patients with severe LV dysfunction, the amount of scar in the myocardium was a significant independent predictor of LV function recovery after revascularization, and that a combination of PET and

clinical parameters predicts the degree of EF recovery. The multivariate predictive model is being applied to a large RCT (PARR 2) to determine the effectiveness of therapy guided by FDG PET.

Findings of the above studies are summarized in Appendix 16 and Table 39.

Table 39: Accuracy & Likelihood Ratios of FDG PET in Identifying Myocardial Viability Based on Improvement in Global LV Function

Study	N	Sensitivity %	Specificity %	Accuracy %	Positive LR	Negative LR
Gerber 2001	178	79	55	67	1.8	0.4
Bax 2002	34	100	71	79	3.4	0.0
Korosoglou 2004	41	83	64	-	2.3	0.3

Based on four studies, the range for positive likelihood for FDG PET (based on improvement in global LV function) was 1.8 to 3.4 and the range of negative likelihood ratios was 0.2 to 0.4 (Figure 15). The one study that provided a direct comparison between FDG PET, low-dose dobutamine echocardiography and myocardial contrast echocardiography showed comparable sensitivity but lower specificity for FDG PET and myocardial contrast echocardiography compared to low-dose dobutamine echocardiography (Figure16).

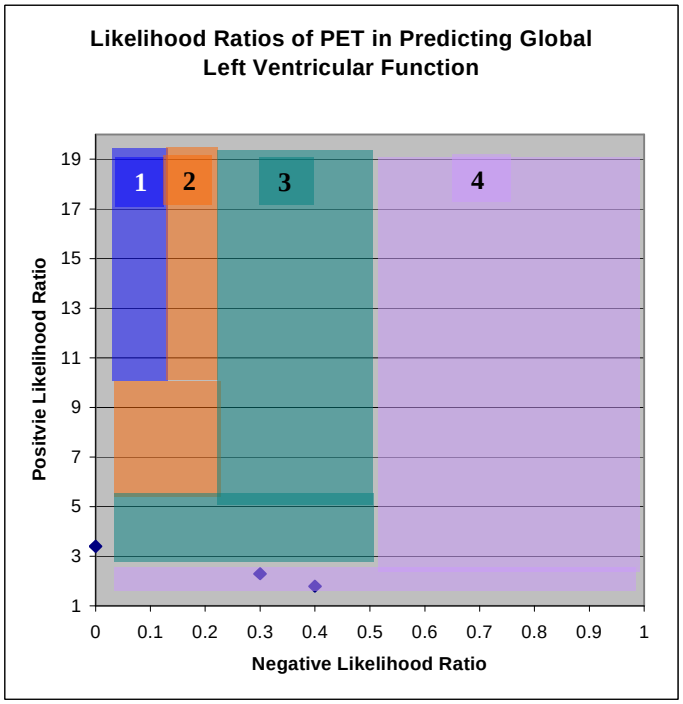
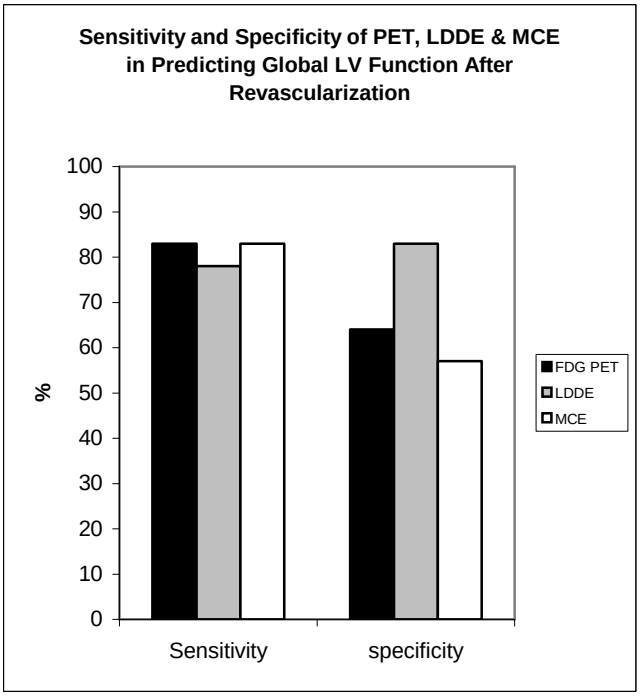


Figure 15: Likelihood Ratios of PET for Predicting Improvement in Global LV Function



PET = Positron Emission Tomography; LDDE = Low-dose dobutamine echocardiography; MCE = Myocardial contrast echocardiography

Figure 16: Comparison of PET, Low-Dose Dobutamine Echocardiography & Myocardial Contrast Echocardiography In Predicting Postrevascularization Global Function

What is the Impact of a PET-Guided Treatment Strategy on Long-Term Patient Outcome?

2001 ICES Review

There has only been one randomized controlled study (41) that explored the incremental benefit of FDG PET on long-term patient outcomes compared to another viability assessment technique. This study had been included in the original review by ICES (34) and is described briefly below. No additional studies were found by the Medical Advisory Secretariat.

In a randomized, controlled study, Siebelink et al. (41) compared prospectively a PET-guided strategy and a SPECT-guided strategy for managing patients being considered for myocardial revascularization. All 103 patients underwent FDG/N-13 ammonia PET and 99m-Tc sestamibi SPECT with pharmacologic stress. Patients were randomized to have either the PET results or the SPECT results provided to their physicians to guide treatment decisions (PET n = 49, SPECT n = 54). For each patient, the revascularization team received a polar map (test results) to guide treatment decision (CABG, angioplasty, or medical therapy) without knowing whether the test results were produced by PET or SPECT. Intended treatments were not different for the two groups. At a mean follow-up of 28+/-1months, there was no statistically significant difference in cardiac event-free survival between the PET group and the SPECT group (cardiac deaths: 4 for the PET group vs. 1 for the SPECT group; total cardiac events: 11 for the PET-guided group and 13 for the SPECT-guided group). Siebelink et al. concluded that either PET or MIBI SPECT could be used equally for making revascularization decisions in patients suspected of having viable myocardium. It should be noted that only one-third of the patients in this study had an LVEF of less than 30% and the study may not have been powered sufficiently to detect a statistically significant difference in cardiac events.

Of the nine observational studies summarized in the ICES review, three reported data on long-term survival and cardiac events based on PET viability assessment and treatment modality. All were rated grade C/D according to the ICES quality scale. These studies suggested that PET viability assessments permit selection of patients who are at low risk of serious complications for revascularization and resulted in lower cardiac events (82); (83)), and improved functional status. (84) However, the review pointed out that there were common methodological limitations to these studies, including potential for preselection bias and lack of blinding to PET results when evaluating patient outcomes

Medical Advisory Secretariat Review

The Medical Advisory Secretariat search yielded 3 meta-analysis, and 3 prospective case series on the impact of PET viability assessment and choice of treatment on long-term patient outcomes (Appendix 19). The quality of these studies is summarized in Table 40, and the characteristics and findings are described below and are summarized in Appendix 19 and Table 41.

Table 40: Quality Assessment of Primary Studies on PET and Prediction of Clinical Outcomes

	Eitzman 1992 (83)	Di Carli 1994 (82)	Lee 1994 (85)	Siebelink 2001 (41)	Zhang 2001 (80)	Santana 2004 (86)	Sawada 2005 (87)	Rohatgi 2001 (88)
MAS Level of evidence	4c	4c	4c	2	4c	4c	4c	4c
Prospective				√	√	√	√	
Randomized				√				
Limitations	Retrospective Preselection bias	Retrospective Preselection bias No assessment of regional or global EF changes	Retrospective Preselection bias Only 19% with CHF	Small sample Possible type 2 error Only 30% of patients had LVEF≤ 30%	Preselection bias Some patients only had mild LV dysfunction	Preselection bias No clear inclusion/ exclusion criteria Only 1/3 of patients revascularized	Narrow spectrum Preselection bias No clear inclusion/exclusion criteria No blinding	Retrospective Preselection bias No exclusion criteria 45 patients lost to follow-up & were not included in analysis
Overall quality	Low	Low	Low	High	Moderate	Moderate	Low	Low

See Appendix 6 for detailed quality assessment

Table 41: Summary of PET Viability Assessment in Predicting Survival/Cardiac Events

Studies included in 2001 ICES Review							Clinical Outcome →			
Study	Type of study	N	Mean Baseline LVEF % (+/-SD)	Follow-up Months (+/-SD)	Criteria for PET Viability	Main Outcome Measures	Viable by FDG PET		Non-Viable by FDG PET	
							Revascularization	Medical Therapy	Revascularization	Medical Therapy
Eitzman 1992	Retrospective	82	34			MI, death, cardiac arrest (%)	11	50 (*P*<0.001)	7.1 (*P*<0.01 vs. PET viable & revasc)	12.5
Lee 1994	Retrospective	137	19% with CHF	17 (9)	Mismatch	Non-fatal ischemic events %	8	48 (*P*<0.001)	5	
Di Carli 1994	Retrospective	93	25	13.6	Mismatch >5% of myocardium	Annual survival rate (%)	88	55 (*P* =0.03)		92 (*P* =0.007) vs. PET viable & revascularized
Siebelink 2001	RCT	103	36 < 30% 67≥ 30%	28	Mismatch	Cardiac event –free survival	No significant difference in cardiac event-free survival between PET guided treatment versus SPECT guided treatment groups but study not sufficient powered to detect a difference.			
Studies included in 2005 Medical Advisory Secretariat Update										
Allman 2002 (89)	Meta-analysis 24 studies	3,088	32 (8)	25 (10)	FDG PET Tl-201 Dobutamine echo	Annual mortality rate %	3. 2 No difference between PET & D-Echo or Tl-^{201} SPECT	16 (*P*<0.0001)	7.7	6.2
DiCarli 2002 (90)	Meta-analysis 5 studies	634	22 (6) to 40(10)	12–31	FDG PET Tl-201 Dobutamine echo	Relative risk of cardiovascular events	Odds ratio in favour of revascularization			
Bourque 2003 (24)	Systematic Review 14 studies	1,173	24–40 (some over 50)	12–46	Varied	Long-term survival	Highest survival rate	Lower survival rate.	Intermediate survival rate regardless of treatment	
Zhang 2001 (80)	Prospective case seriesobs	123	35 (6) 88% multivesseldisease	26 (10) (1–36)	Mismatch	Cardiac event rate (death, MI, or unstable angina, revascul). %	2.4	50 (x^2=23.08, *P*<0.0001)	12%	11.5
Santana 2004 (86)	Prospective case series	90	26 (7)	22 (14)	Mismatch	Cardiac death, MI or worsening heart failure %	11% survival benefit in people with advanced remodelling			
Desideri 2005 (91)	Prospective case series	261	30 Revas 20 Medical	2.1 years (median)	Mismatch	Cardiac death %	15	28 P<0.05	25	
Sawada 2005 (87)	Prospective Case series (People with diabetes)	61	29 (11)	4.3 (2.8) years	FDG/NH3 Mismatch (>2SD difference compared to normal)	Cardiac deaths %	47 Significantly lower	83		

Description of Meta-analysis

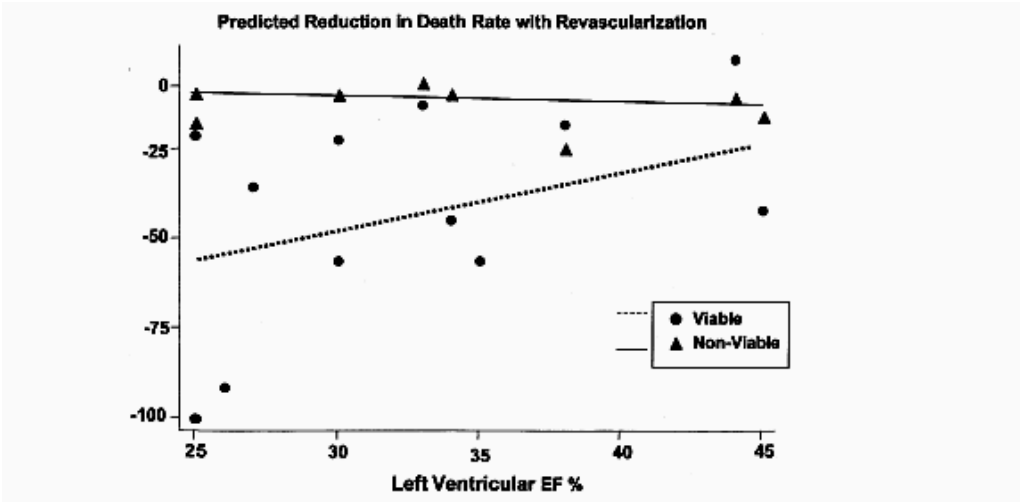
Allman et al. (89) conducted a meta-analysis to examine event-free late survival with revascularization versus medical therapy after myocardial viability testing in patients with severe coronary artery disease and left ventricular dysfunction. The meta-analysis included 24 observational studies (1992–1999) with 3,088 patients. Mean age was 61 years, mean LVEF=32+/-8%, and mean NYHA functional class 2.8. Complete follow-up was achieved for 87.7%, for a mean follow-up period of 25+/-10 months. Of these patients, 35% underwent revascularization, and 65% received medical therapy. Viability testing was performed using one of PET, dobutamine echocardiography or thallium-201 SPECT. A random effect model was used to compare the mortality rates in patients with and without viability treated with revascularization or medial treatment. Weighted average percentage decrease in mortality rates and 95% confidence intervals were calculated. A Chi square test for homogeneity was performed.

Meta-analysis of the 24 studies showed that annual mortality rate was lower in revascularized patients when viability was present compared with those without viability (3.2% per year vs. 7.7%/ per year, x^2 =33, P<0.0001).

Multiple linear regression analysis showed the following:

- Factors most predictive of death included LVEF, presence of viability and use of revascularization (Chi-square=15, P = .004), indicating that, even after adjusting for differences between individual patient populations, revascularization was associated with an enhanced survival rate (β=2.79, z=22.3, P<0.001).
- An inverse relationship between LVEF and reduction in risk of death with revascularization with viability, i.e., as EF decreased, the prognostic benefit with revascularization increased (Figure 17).
- No benefit was associated with revascularization in patients without viability at any level of EF (Figure 17)

Figure 17: Relationship Between Reduction in Death Rates and Left Ventricular Ejection Fraction for Patients With Viable and Patients With Nonviable Myocardium (Allman 2002)



*EF indicates ejection fraction.

Reprinted from the Journal of the American College of Cardiology, vol. 39(7), Allman KC, Shaw LJ, Hachamovitch R, Udelson JE. Myocardial viability testing and impact of revascularization on prognosis in patients with coronary artery disease and left ventricular dysfunction: a meta-analysis, p. 1151-1158, Copyright 2002, with permission from the American College of Cardiology Foundation

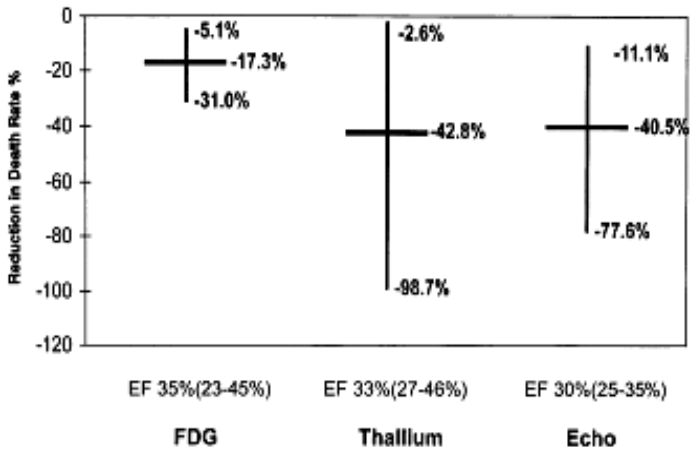
- For patients without viability, annual mortality rates remained high regardless of treatment modality (7.7% for revascularization and 6.2% for medical therapy, x^2 =1.43, P =0.23).
- For medically treated patients, those deemed to have myocardial viability had a 158% higher mortality than those individuals without viability.

- Annual mortality rate was significantly lower in patients with myocardial viability treated with revascularization than treated medically (3.2% vs. 16.0%, x^2 =147, P<0.0001).

PET versus Other technologies in Long-Term Predicting Outcomes

There were no measurable differences between the PET group and the SPECT or dobutamine echocardiography groups in the proportion of patients sent for revascularization. When the survival benefits following revascularization for the three viability assessment groups (FDG PET, ^{120}thallium SPECT, and dobutamine echocardiography) were compared, the confidence limits were wide and overlapping (Figure 18). There were no statistically significant differences between the PET group and other groups in prediction of survival benefit following revascularization.

Figure 18: Decrease in Mortality Rates with Revascularization of Viable Myocardium for Each Testing Technique Shown as Mean Value With 95% Confidence Limits



Reprinted from the Journal of the American College of Cardiology, vol. 39(7), Allman KC, Shaw LJ, Hachamovitch R, Udelson JE. Myocardial viability testing and impact of revascularization on prognosis in patients with coronary artery disease and left ventricular dysfunction: a meta-analysis, p. 1151-1158, Copyright 2002, with permission from the American College of Cardiology Foundation

Allman et al. concluded that the meta-analysis showed a strong association between revascularization and improved survival among patients with CAD and significant LV dysfunction that have evidence of myocardial viability on imaging tests. The likelihood of improved survival was greatest in patients with demonstrated viability and the most severe LV dysfunction. PET did not show any advantage over Thallium-201 SPECT or dobutamine echocardiography in predicting event-free survival after revascularization.

Limitations of This Meta-Analysis:

Without evidence from RCTs, no firm conclusions can be drawn. The studies included in the meta-analysis were observational, nonrandomized, unblinded, and subject to publication and other biases, including patient selection and treatment decision bias. There was heterogeneity in the technical aspects, in the completeness of revascularization, and individual patient's medical therapy regimen. Little detail was provided on the adequacy and aggressiveness of the medical treatment used in the individual studies. There was also heterogeneity in the methodology, protocols and in the criteria for defining clinically significant viability for each imaging technique. The imaging techniques used in the studies may not reflect current practice. Ascertainment of event was not fully complete despite the use of the random effects model. Studies that were not designed to answer the viability/treatment interaction were included in the analyses.

In another systematic review, Bourque et al. (24) conducted a descriptive synthesis of 14 studies (1992-2001) regarding the effect of PET and SPECT viability assessment on treatment strategies and long-term mortality of patients with cardiomyopathy and significant epicardial coronary disease. No meta-analysis was performed. Following viability assessment, patients either underwent revascularization (CABG or PCI) or remained on medical therapy.

All 14 studies are observational with 9 being prospective and 5 retrospective. The median sample size was 85 (range 35 – 135) and the total number of subjects was 1,192. All subjects had ischemic heart disease and left ventricular dysfunction with mean LVEF that ranged from 24% to 40%, and New York Heart Association functional class III-IV ranged from 19% to 100% among studies. However, some studies included patients with LVEF greater than 50%. The median length of follow-up across the studies was 26 months (range 12–46 months). Techniques used to assess myocardial viability in the studies were FDG PET (2), FDG/ammonia PET (1), FDG/^{82}Rubidium PET (1), 99m-Tc MIBI SPECT (2), or ^{201}Thallium SPECT (8).

The authors concluded that despite differences in conclusion among the studies, patients with viability who undergo revascularization have the highest survival rate, whereas patients with viability who are treated medically have a much lower survival rate. Patients without viability have an intermediate survival rate, regardless of treatment. The impact of PET as a viability test compared to SPECT and echocardiogram in predicting survival after revascularization, was not reported.

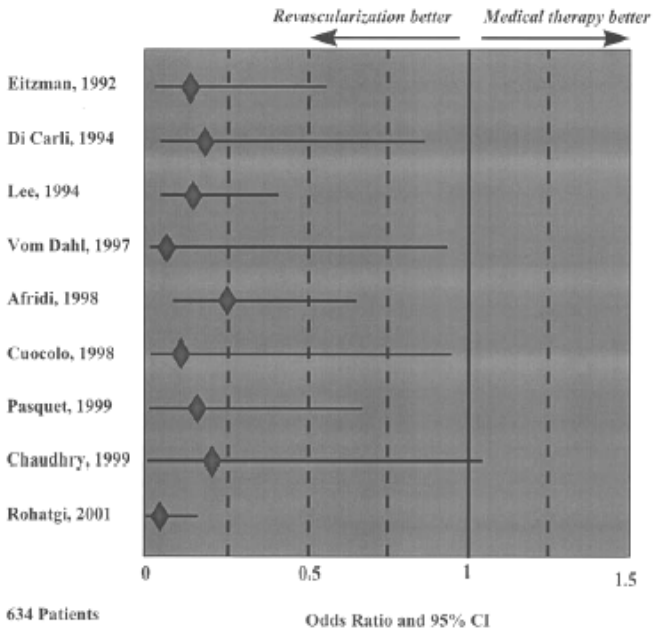
The limitations of this review were as follows:

- Lack of randomized control trials.
- Small sample size: Small sample size and short follow-up periods contribute to a low event rate.
- Inadequate follow-up: It was noted that a 12-month follow-up is not adequate for analysis of long-term mortality. Even 46 months provides an incomplete glimpse of the long-term effects of revascularization and medical therapy in this population.
- Several studies had limited power in detecting differences in mortality rate.
- Extensive differences in study protocol and design
- Heterogeneity in degree of ventricular dysfunction among subjects.

In 2002, Di Carli et al. (90) reported on a meta-analysis of 9 observational studies (published in 1992–2001), to explore the impact of viability assessment and treatment on cardiovascular events after revascularization in patients with moderate to severe LV dysfunction and had hibernating myocardium. Of the 9 studies, 5 had viability assessed using PET (total of 262 patients), while ^{201}thallium SPECT, and dobutamine echocardiography were used to assess viability in the other 4 studies. In all studies, management decisions for patients with and those without evidence of hibernation were made on clinical grounds. No significant differences in relevant clinical and angiographic variables known to affect prognosis were found between those with hibernating myocardium and those without.

The meta-analysis showed that in patients with moderate to severe LV dysfunction and had hibernating myocardiume, the odds ratio of cardiovascular events in patients treated with revascularization compared with those treated with medical therapy was consistently less than 1. This finding suggests that the risk of cardiac events for people with severe ischemic LV dysfunction may be predicted on the basis of myocardial viability and treatment modality (Figure 19). (90)

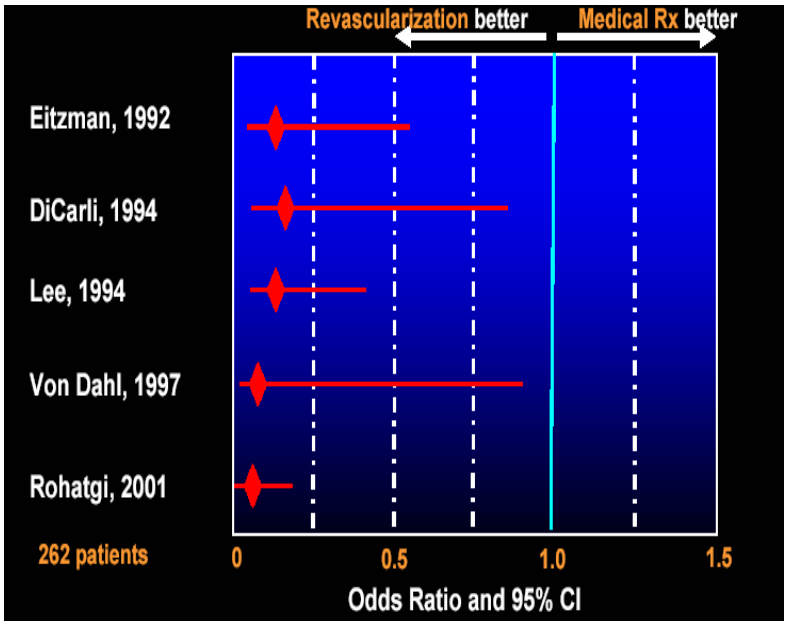
Figure 19: Odds ratio of Cardiovascular Events for patients with moderate to severe left ventricular dysfunction and viable myocardium treated with revascularization compared with medical therapy



Reptinted from the Journal of Nuclear Cardiology, vol. 9(2), ***Di Carli MF. Assessment of myocardial viability after myocardial infarction, p. 229-235, Copyright 2002, with permission from the American Society of Nuclear Cardiology***

Di Carli el al (90) repeated the meta-analysis including only the 5 studies that used PET to assess myocardial viability and found similar results, indicating that viability identified by PET can predict outcomes based on viability status of the myocardium and the choice of treatment (revascularization vs. medical therapy) (Figure 20).

Figure 20: Odds Ratio of Cardiovascular Events For Patients With Left Ventricular Dysfunction and PET Evidence of viability on PET Treated with Revascularization Compared with Medical therapy



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However, the meta-analyses did not provide any information on the accuracy of PET in identifying hibernating myocardium and in predicting postrevascularization patient outcomes compared to the other noninvasive tests. Limiatations included heterogeneity of the studies. Patient selection bias might have accounted for differences in outcomes.

Description of Primary Studies

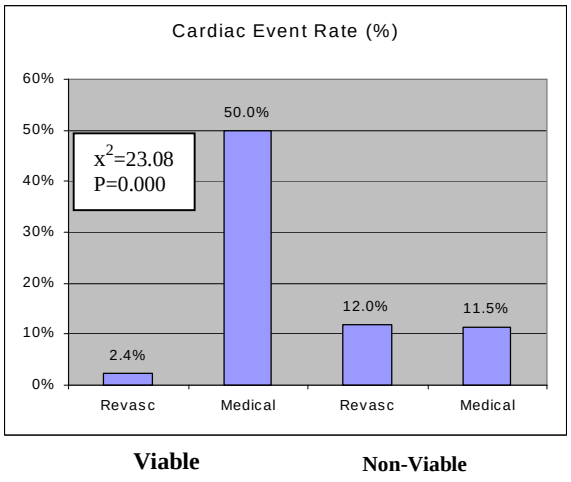
Zhang et al. (80) conducted a prospective cohort study to determine the impact of myocardial viability status defined by hybrid FDG PET/^{99m}Tc-sestamibi SPECT and treatment modality on clinical outcomes of patients with previous MI and LV dysfunction. The study included 123 consecutive subjects with a mean age of 56+/-9 years and a mean LVEF of 35+/-6%, most of whom had multivessel disease. The primary outcomes were cardiac events defined as cardiac death, acute MI, unstable angina, or late revascularization (>3 months). Left ventricular ejection fraction and LV end-diastolic diameter by echocardiography recorded at baseline, 3 months, and 6 months after revascularization, were also examined.

Sixty patients (54.5%) underwent revascularization and 56 (45.5%) received medical treatment as determined by the referring physician without randomization. Patients were divided into 4 groups based on viability status and treatment. There were no statistically significant differences between the 4 groups in terms of age, gender, ejection fraction, NYHA functional class, CCS angina class, and the number of vessels involved. Kaplan-Meier survival analysis and multivariate regression analysis were performed. The mean follow-up period was 26+/-10 months (range 1–36 months, median 28 months).(80)

Findings

- Patients with viable myocardium who underewent revascularization showed an increase in mean LVEF from 36+/-5% to 44+/-8% ($P< .0001$) at 3 months, and to 51+/-9% ($P< .0001$) at 6 months after revascularization.
- For the same group, end diastolic diameer decreased from 62+/-8 mm to 56 +/-5 mm ($P< .001$) at 3 months and to 55+/-5 mm ($P< .001$) at 6 months.
- Patients with no viable myocardium who underwent revascularization showed no statistically significant changes in LVEF or end diastolic diameter after revascularization.
- Among patients with viable myocardium, those who received medical therapy had significantly higher cardiac event rates than patients who underwent revascularization (50% vs 2.4%, $x^2=23.08$; $P< .0001$). (Figure 21)

Figure 21: Rate of Cardiac Events for Patients with Viable And Non-Viable Myocardium

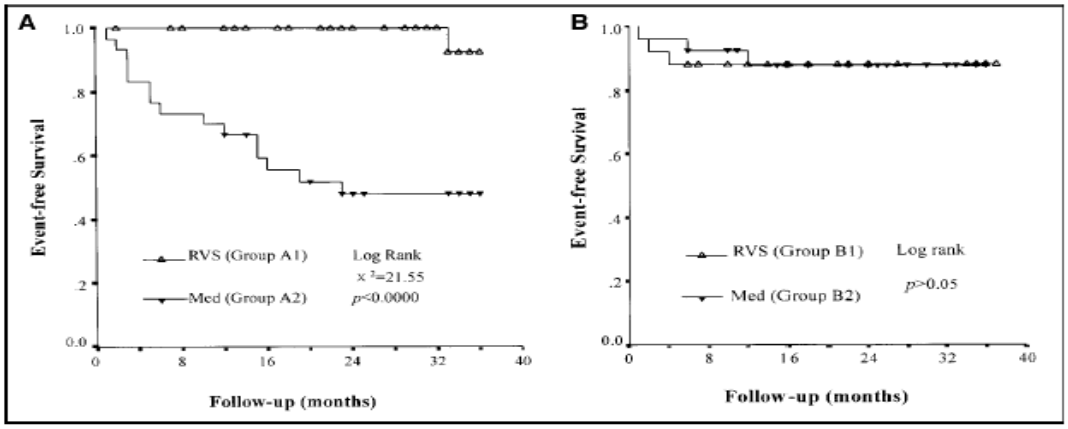


- Medically treated patients with viable myocardium had higher cardiac event rates than patients with no viable myocardium regardless of treatment with revascularization (50% vs 12%, x^2=8.94, *P* = .003) or medical therapy (50% vs 11.5%, x^2=9.45. *P* = .002)

- Among patients treated medically, those with viable myocardium had significantly higher cardiac mortality than those without viable myocardium (26.7% vs 4%; x^2=5.38; *P* = .02)

- The estimated 1-year, 2-year and 3-year cardiac event-free survival rates for patients with viable myocardium based on PET were 100%, 100%, and 92% respectively for those who underwent revascularization and 66%, 48%, and 48% respectively for those who received medical therapy (*P*<0.0001) (Figure 21a).

Figure 21 (a): Event-Free Survival A: With Viable Myocardium B: With Non-Viable Myocardium



RVS refers to revascularized; Med refers to: medical therapy – no revascularization

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- The estimated 1-year, 2-year and 3-year survival rates for patients with viable myocardium were 100%, 100%, and 100% respective for those who underwent revascularization, and 85%, 69%, and 69% for those who received medical therapy (*P* = .001).
- Multivariate analysis using the Cox proportional hazards model showed the following factors independently predicted cardiac events:
  - Viability based on the number of mismatched segments present (RR = 1.4; 95% CI 1.00–1.95, *P*< .05)
  - Canadian Cardiovascular Society angina class (RR = 2.27, 95% CI 0.27–4.03, *P*< .002)
  - NYHA heart failure class (RR 1.90, 95% CI 1.03–3.47, 0.05)
- A high NYHA heart failure class was also an independent predictor for cardiac mortality (*P*< .001).

The authors concluded that assessment of myocardial viability using hybrid FDG PET and ^{99m}Tc-sestamibi SPECT can predict the clinical outcome, and is helpful to decision-making in the treatment strategy for patients with MI and LV dysfunction.

Limitations of this study were as follows:

- Patient selection bias could have accounted for differences in outcomes.
- Nonrandomized and relatively small sample size.

- Patients with a LV aneurysm were included. These patients were shown to have LV remodeling and poor ventricular function. Statistical analysis showed that the prognosis of patients with an aneurysm correlated with the extent of viable myocardium and treatment strategy.

Santana et al. (86) studied 90 consecutive patients with severe ischemic cardiomyopathy (mean LVEF 26+/-7%) to determine the incremental value of ECG-gated FDG PET in viability assessment compared to FDG uptake alone on PET. Patients underwent gated FDG PET and perfusion PET with ^{82}rubidium. Myocardial viability was defined as having perfusion/metabolism mismatch in greater than 15% of the myocardium. The additional parameters obtained from gated PET were end systolic volume, end-diastolic volume, wall motion, and LVEF. Thirty-one of the 90 patients had CABG. The primary end point was composite outcome of cardiac death, MI, or worsening of heart failure at a mean of 22+/-14 months after revascularization.

On Cox regression analysis, event-free survival rate at 2 years was lower for patients with end-diastolic volume greater than or equal to 260 ml (RR = 2.5; *P* = .021) or or end-systolic volume greater than or equal to 200ml (RR = 1.6; *P* = .009). In a risk-adjusted model, end-diastolic volume (x^2=68, *P*<0.0001) & end-systolic volume (x^2 =75, *P* = 0.035) contributed significantly to the estimation of events over the FDG/^{82}Rb mismatch pattern (x^2 =40, *P*<0.001)

In a stratified Cox model, patients with PET mismatch, LVEF less than 25%, and end-diatolic volume greater than 260ml had the lowest event free survival rate (43%) compared with patients with LVEF less than 25% & end-diastolic volume less than or equal to 260ml (84%), and patients with LVEF greater than 25% & end-diastolic volume equal to or less than 260 ml (92%) (*P* = .003).

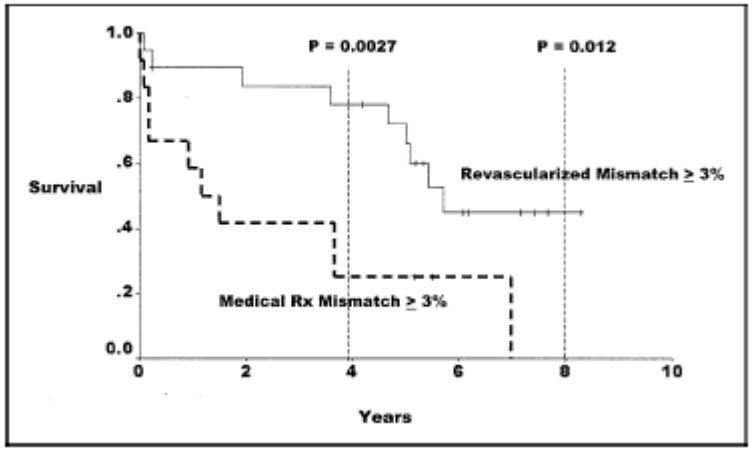
For the 31 patient who underwent revascularization, the procedure was associated with an absolute improvement in event-free survival rate of 22% for patients with LVEF less than or equal to 25% & end-diastolic volume greater than or equal to 260 ml (*P* = .035). Patients with viability and end-diastolic volume greater than or equal to 260 ml had highest event free survival rate with revascularization (86%, absolute improvement of 11%), with no improvement in symptoms of heart failure.

Desideri et al**.** (91) followed 261 patients with CAD (LVEF ranging from 29% to 30%) that had undergone assessment of viability using PET. Of these patients, 94 were revascularized while 167 were not revascularized because of poor target vessels, extensive comorbidity, or patient refusal. The latter group were treated medically using a combination of one or more of the following drugs: diuretics, aspirin, oral anticoagulation, nitrates, beta-blockers, calcium antagonists, digoxin, and amiodarone. At a mean follow-up period of 2.1 years, the rate of cardiac death, the only end point, was significantly higher in patients with viable myocardium that were treated medically compared with patients with viable myocardium that underwent revascularization (28% vs. 15%, *P*< .05). Multivariable analysis identified age (*P* = .005), left branch bundle block (*P* = .001), and the extent of mismatch on PET imaging (*P* = .001) as independent prognostic indicators of cardiac death. The extent of mismatch was strongly related to mortality (Hazard ratio [HR] 1.36, 95% CI: 1.13 – 1.64). An 8% increase in the extent of mismatch determines a 36% increase in risk of cardiac death during follow-up. The analysis also showed that the risk of cardiac death was not significantly increased when the extent of mismatch was less than or equal to 20% (HR 0.97, 95% CI 0.46–2.05), but the risk of death was significantly increased when the extent of mismatch exceeded 20% (HR 3.21, 95% CI 1.38 to 7.49).

Sawada et al. (87) assessed the perfusion-metabolic mismatch in 61 patients with diabetes and ischemic LV dysfunction (mean LVEF = 29+/-11%) using FDG and ^{13}N-ammonia PET. Of the 61 patients, 28 received medical therapy and 33 underwent revascularization mostly by CABG (82%). Patients were followed-up every six months for a mean total of 4.3 (+/-2.8) years. The results showed that:

- Of 61 patents, 60 patients had successful imaging despite presence of diabetes
- Patients with significant mismatch ($\geq$ 3% of LV) had significantly better survival at 4 years and 8 years when treated with revascularization than compared with medical therapy (*P* = .0027 & *P* = .012 respectively) (Figure 21b)

Figure 21(b): Survival of Patients With Significant Mismatch Treated With Revascularization Versus Medical Therapy



Reprinted from the American Journal of Cardiology, vol. 96(1), Sawada S, Hamoui O, Barclay J, Giger S, Fain R, Foltz J, et al. Usefulness of positron emission tomography in predicting long-term outcome in patients with diabetes mellitus and ischemic left ventricular dysfunction, p. 2-8, Copyright 2005, with permission from Excerpta Medica Inc.

- Patients who had LV mismatch ≥3% and the most severe LV dysfunction (EF<30%) derived the greatest benefit from revascularization.
- Four-year survival in patients who had extensive perfusion defect (≥25%) was increased with revascularization (*P* =0.02). This survival benefit was not maintained at 8 years.

Prognosis by other technologies

There was no direct comparison between PET and other noninvasive technologies for the prediction of long-term outcomes. However, there is evidence that dobutamine echocardiography and thallium-201 SPECT could predict survival and cardiac events after revascularization. (92;93)

A 2003 study by Sawada et al. (94) explored the incremental long-term prognostic value of myocardial viability determined by dobutamine echocardiography in patients with LV dysfunction revascularized with CABG. Follow-up was obtained for 92 patients for a mean of 4.9+/-2.9 years following CABG performed after viability assessment using dobutamine stress echocardiography. Other prognostic factors evaluated were clinical factors, degree of resting LV dysfunction, severity and extent of ischemia, and completeness of revascularization. Results of the analysis showed the following:

- Wall motion scores at low-dose dobutamine echocardiography, reflecting the extent of viable myocardium, was the strongest multivariate predictor of cardiac death at 5 years (hazard ratio 6.7, *P*< .001,).
- Low-dose score (extent of viability) allowed patients to be classified into high, intermediate, and low-risk groups for cardiac death. Frequency of cardiac death at 5 years was lower in the high-viability-low-risk group (24%) and intermediate-risk group (48%) in than the low-viability-high-risk group (82%).
- A biphasic response predicted better survival (hazard ratio 0.5, *P* = .045,), but measures of contractile reserve, which were shown to be predictors of short-term outcome in other studies, were not predictive of long-term outcome.

- Low-dose wall motion score added incremental prognostic value to clinical factors (P = .003) and to combined clinical factors and resting function (P = .024).

Using low dose dobutamine echocardiography, Meluzin et al**.** (92) assessed the myocardial viability of 124 patients with CAD and LVEF less than or equal to 30%. Dysfunctional myocardial segments were defined as viable if they exhibited functional improvement of at least one grade with any dose of dobutamine, or if they exhibited worsening without initial improvement. Patients were considered to have viable myocardium if they had at least two adjacent viable segments. Patients were divided into five groups based on viability status and treatment options (revascularization, medical therapy or heart transplantation). Kaplan Meier survival analysis was conducted after a follow-up period of 27+/-23 months. Patients deemed to have viable myocardium and treated with revascularization had significantly lower cardiac-related death (10% vs. 34%, P< .05) and higher survival at 3 years and 5 years than patients with viable myocardium treated medically (89% vs. 60%, P< .05). The 3-year and 5-year survival of patients with viable myocardium treated with revascularization was also significantly higher than patients without viable myocardium treated with revascularization (67%) or treated medically (60% at 3 years and 50% at five years). The prognostic benefit of revascularization to patients with viability was not manifested until 3 years after the procedure.

Sicari et al. (93) reported on a prospective multicenter observational study consisting of 425 consecutive patients evaluated with low-dose dobutamine echocardiography for myocardial viability. Viability was defined as a change in wall motion score index of at least 0.4 during dobutamine stimulation. The decision for a revascularization procedure was made by the referring physician, taking into consideration clinical presentation, coronary anatomy, LV function, evidence of ischemia, and documentation of viability by independent techniques. Stress echocardiographic data were available to the referring physician. One hundred eighty-eight patients were revascularized with either CABG (118) or PCI (70). Patients were followed for a median of 3.1 years. The only outcome measure was cardiac-related death. For revascularized patients, cardiac related deaths were lower (7.7% vs. 27.2%, P< .003) and survival was higher (90.1% vs. 62%, P< .0078) for patients with viability compared with patients without viability. For patients without viability, mortality was not significantly different by treatment method. Stepwise regression analysis showed that the only independent predictors of cardiac-related deaths were the presence of myocardial viability by dobutamine echocardiography, exerting a protective effect on survival (chi square 8.3, HR 0.2, 95% CI 0.07–0.6, P<0.0039) and ejection fraction.

Summary Statements on Prediction of Long-Term Outcomes by PET

- Based on observational studies, patients with moderate to severe ischemic LV dysfunction and viable myocardium had better survival after revascularization compared to people without viable myocardium. The benefit was found to last up to three years.
- Patients with viable myocardium and the most severe LV dysfunction appear to benefit most from revascularization
- There was no survival benefit associated with revascularization in people found to have no viable myocardium
- People with severe LV dysfunction and viable myocardium that underwent revascularization had better survival compared to those who had viable myocardium but did not undergo revascularization.
- There was some inconsistency in the reported differences in postrevascularization cardiac events between people with viable myocardium and people without viable myocardium.
- Survival benefit and reduction in cardiac events associated with revascularization was also observed in people with severe LV dysfunction and diabetes mellitus who were assessed to have viable myocardium using PET.
- Rest-redistribution reinjection thallium-201 SPECT, low-dose dobutamine echocardiography or FDG SPECT all predict survival after revascularization.
- The only study that directly compared PET with another test with respect to long-term outcomes showed no statistical significant difference in 2-year cardiac events. However, the study might have been underpowered and only one-third of the patients had LVEF greater than 30%.
- There are no studies that directly compared PET with other viability assessment techniques with regard to reduction of mortality or unfavorable cardiac events after revascularization in the most important target population, namely those patients with severe ischemic LV dysfunction. Hence no firm conclusion can be reached regarding the incremental value of PET in predicting long-term outcomes in this target population.

Overall Quality of Evidence

Table 42 shows that based on GRADE, there is low quality overall evidence that viability determined by PET is associated with reduced rates of cardiac events when treated with revascularization.

Table 42: Grade Profile of Evidence - Prediction of Postrevascularization Cardiac Events by PET

Quality Assessment						Summary of Findings					
No. Of Studies	Design	Quality	Consistency	Directness	Other modifying factors	Number of subjects		Effect		Overall Quality	Outcome
						PET	Other	Relative (95% CI)	Absolute		
Cardiac Events (cardiac death, MI, angina and/or heart failure) after Revascularization											
Eitzman 1992 Lee 1994 Zhang 2001 Santana 2004	Observational	Some limitations*	No major inconsistency	Some uncertainty**	Large effect size †	NA	NA			⊕⊕□□	
Grade Quality	Low	Very low	Very low	Very low	Low					Low	

*No clear inclusion/exclusion criteria ** Some patients only had mild LV dysfunction;
† All studies showed PET viability was associated with significant reduction in mortality and cardiac events after revascularization vs. no revascularization

Table 43 showed that based on GRADE, there is low quality evidence that viability determined with PET is associated with reduced rates of cardiac deaths when treated with revascularization.

Table 43: Grade Profile of Evidence - Prediction of Postrevascularization Survival by PET

Quality Assessment						Summary of Findings					
No. Of Studies	Design	Quality	Consistency	Directness	Other modifying factors	Number of subjects		Effect		Overall Quality	Outcome
						PET	Other	Relative (95% CI)	Absolute		
Cardiac death after Revascularization											
Desideri 2005 (91) Sawada 2005 † (87)	Observational	Some limitations*	No major inconsistency	Some uncertainty**	Large effect size	NA	NA			⊕⊕□□	
Grade Quality	Low	Very low	Very low	Very low	Low					Low	

**Only included people with diabetes

Table 44 shows that based on GRADE, there is moderate quality RCT evidence that there is no significant difference in cardiac event-free survival at two years between therapy based on PET viability and therapy based on MIBI SPECT. However, there may be type 2 errors and only one-third of the study patients had severe LV dysfunction.

Table 44: GRADE Profile of Evidence Comparing PET Guided Strategy versus SPECT guided strategy on Cardiac Event Free Survival

Quality Assessment						Summary of Findings					
No. Of Studies	Design	Quality	Consistency	Directness	Other modifying factors	Number of subjects		Effect		Overall Quality	Outcome
						PET-guided	SPECT-guided	Relative (95% CI)	Absolute		
Cardiac event free survival after Revascularization											
Siebelink 2001	RCT		Only one study	Some uncertainty**	-	49	64			⊕⊕ □□	Important
Grade Quality	High	High	High	Moderate						Moderate	

**Only 1/3 of patients had severe LV dysfunction

What is the Impact of PET Viability Assessment on Clinical Decision Making?

Previous reviews had identified a study by Beanlands et al. (95) that showed viability identified by PET had an impact on clinical decision-making regarding treatment for 87 patients with impaired LV function. Viability was assessed using FDG PET/Tc-99m sestamibi SPECT. Physicians completed a questionnaire to indicate their intended management without the viability results, and again after the viability results were available. Information from FDG PET influenced management decisions for 57% of these patients. This percentage increased to 71% for patients with LVEF less than 30%. PET viability imaging resulted in redirection of therapy from transplant to revascularization in 7 out of 11 patients (63%), from medical therapy to revascularization in 8 of 18 patients (44%), and from revascularization to medical therapy in 16 of 38 patients (42%). The kappa score was 0.181, which indicates little agreement between the intended management before and after PET data were available, and that PET had an important influence on clinical decision-making.

Other Relevant Findings

Amount of Viable Myocardium Required for Functional Improvement

Studies included in previous reviews indicate that a minimum amount of viable myocardium is required to effect functional improvement after revascularization, with estimates ranging from 18% to 30%. (96), (97), (98). The greater the amount of viable myocardium detected, the better was the outcome and prognosis of patients after revascularization.(99)

Time course for Functional Recovery

Evidence suggests that hibernating myocardium may take longer to recover function after revascularization than stunned myocardium. A study by Bax et al. (43) demonstrated that a higher percentage of stunned myocardial (61%) segments showed functional recovery at 3 months after revascularization compared to hibernating myocardial segments (31%, $P<.05$). However, more hibernating myocardial segments (61%) recover at 14 months compared to stunned myocardium (9%).

Haas et al. (100) reported similar findings in a prospective cohort study of 29 patients with CAD and an LVEF of 18% to 35%, who underwent assessment of PET viability and regional wall function preoperatively and again at 11 days, 14 weeks, and more than 12 months after CABG. Biopsies of the dysfunctional areas defined by PET were also obtained during surgery. PET showed that in patients with severe ischemic LV dysfunction, stunned myocardium was more prevalent than hibernating myocardium (70% vs. 24%, $P< .01$). Hibernating myocardium was associated with more severe preoperative wall motion abnormalities and incomplete postoperative recovery at 1 year. Complete functional recovery after 1 year was found in 31% of stunned myocardial segments, compared with 18% of hibernating segments ($P< .05$). Hibernating myocardium showed more severe tissue injury as indicated by more severe morphological alterations, including depletion of sarcomeres, accumulation of glycogen, loss of sarcoplasmatic reticulum, and cellular sequestration. Different degrees of myocardial injury coexist in most patients and this determined the time course and the extent of functional improvement after revascularization.

Underlying Difference between Nuclear Imaging Techniques and Dobutamine Echocardiography

There are possible explanations for differences in sensitivity and specificity between nuclear imaging and dobutamine echocardiography in predicting functional recovery after revascularization.

Baumagartner et al. (101) compared three noninvasive tests with the histologic examination of explanted hearts to determine the minimum amount of viable myocytes necessary to yield a positive viability test. The results demonstrated that in asynergic segments, at least 50% of the myocytes had to be viable in order to have a contractile response to dobutamine stress echocardiography, but less than 50% viable myocytes were enough to result in a positive nuclear study. Segments found to be viable by both DSE and either of two other imaging modalities had the highest

percentage of viable myocytes on histopathological examination. Segments that were not viable by dobutamine stress echocardiography or by any of the scintigraphic techniques had the lowest percentage of viable myocytes. Segments found to be viable using scintigraphic methods but not viable using dobutamine echocardiography had a percentage of viable myocytes intermediate to previous two groups.

Nuclear imaging studies are based on preserved metabolism, and may identify areas with viable myocytes but not in quantity sufficient to effect improvement in regional function after revascularization.

Camici and Dutka (5) Postulated that both metabolism and contractile reserve are preserved in the earlier stage of hibernation (functional hibernation) but only metabolism is preserved in the more advanced stage (structural hibernation). According to this concept, segments that have a response to dobutamine stimulation reflect functional hibernation with an intact contractile apparatus, and will manifest early recovery of function after revascularization. On the other hand, PET detects preserved metabolism in both functional and structural hibernation. Myocardium in structural hibernation is likely to require a longer period for recovery than was allowed in most of the studies, resulting in lower specificity for FDG PET than dobutamine stress echocardiography (higher false-positive results).

Other Factors Affecting LV Function Improvement

Beanlands et al. (79) showed that a multivariate model that incorporated the scar score, mismatch score, perfusion tracer used, time to surgery, age, diabetes, previous CABG and tracer/mismatch interaction, explained only 36% of the variation in LVEF after CABG. This suggests the presence of other factors that influenced functional outcome after CABG in the study.

Previous studies have shown that patients with low LV function and severe angina may show survival benefit after revascularization without improvement in LVEF. These patients often show normal rest perfusion and stress-induced ischemia, reflecting myocardium that is neither stunned nor hibernating, but is supplied by severely stenotic coronary arteries. (102)

The amount of inducible ischemia has been shown to be a strong predictor of outcomes in patients with CAD and LV dysfunction and can also differentiate ischemic LV dysfunction from non-ischemic dysfunction.

Progressive LV remodeling as indicated by increased LV volumes and cavity size are predictors of poor outcomes after CABG in patients with CAD and severe LV dysfunction, even if there is evidence of viable myocardium.(86)

In addition, successful revascularization and graft patency are necessary for restoring contractile function to viable myocardium.

Future Research

Future research needs to focus on well designed, randomized, controlled trials that directly compare FDG PET with other noninvasive techniques for the accurate prediction of improvement in postrevascularization survival and cardiac events, rather than in surrogate end points such as improvement in regional and/or global LV function.

Safety

F-18 Fluorodeoxyglucose Positron Emission Tomography

The United States Food and Drug Administration (FDA) approved F-18 FDG in 1994, determining it to be safe for use in PET imaging for the identification of regions of abnormal glucose metabolism associated with epileptic seizures. Since its approval, no adverse events have been reported to the FDA for this application.

In the 2000 *Medical Review of F-18 fluoro-deoxyglucose Positron Emission Topography for Cardiac Indications* (103) of the FDA, Raczkowski cited a review of the prevalence of adverse reactions to positron-emitting radiopharmaceuticals in nuclear medicine from several PET institutions. Silberstein and the Pharmacopeia Committee of the Society of Nuclear Medicine conducted the review using a consensus definition of "adverse reactions" developed by the Committee. No adverse reactions to FDG were identified in either the retrospective examination of records of administered radiopharmaceutical doses, or the prospective examination of administered doses. Raczkowski stated that these data provide additional support for the safety of FDG.

Doses of FDG used for cardiac imaging are generally in the range of 185–375 MBq (5–10 mCi), similar to that used in imaging research for epilepsy. The absorbed radiation from a FDG dose of 370 MBq in a 70 kg adult is estimated to be 6.29 rads for the bladder wall based on a fixed bladder content for three hours. The absorbed dose can be reduced with voiding within 1 to 2 hours after administration (2.20–4.40 rads respectively). (103)

The only safety concern that Raczkowski raised pertains to fasting and glucose loading for patients with glucose intolerance. This is usually addressed using the euglycemic hyperinsulinemic clamp procedure.(103) In summary, Raczkowski stated that specific safety concerns were not identified in the review of the use of FDG in cardiac imaging, or in the types of patients who were included in the studies submitted to the FDA for the review. (103)

Dobutamine Echocardiography

Picano et al. (104) conducted a prospective, multicenter study to examine the safety and tolerability of dobutamine-atropine stress echocardiography. The study examined 2,949 tests performed in 2,799 patients at 24 experienced cardiography laboratories. Of thes 2,799 patients, 782 had a previous MI (> 4weeks) and 736 had typical or atypical chest pain with normal baseline resting function. After resting ECG and echocardiogram, dobutamine was infused intravenously from 5 ug/kg per minutes, increasing stepwise to a maximum of 40 ug/kg/min. Atropine was added when no end point was reached. The end points of the test were positive echocardiogram, maximum atropine dose, 85% of target heart rate, severe chest pain, and/or diagnostic ST-segment changes. Picano et al. (104) reported that in 12% of the overall study population, the test could not be completed mainly because of complex ventricular tachyarrhythmias, nausea, headaches, hypotension and/or bradycardia, and supraventricular tachyarrhythmias. In 1 out of 210 tests, the patient experienced life-threatening complications or side-effects (e.g. MI, ventricular fibrillation, or persistent hypotension) requiring specific treatment and lasting more than 3 hours, or requiring new hospital admission. The study concluded that dobutamine/atropine stress echocardiography is generally well-tolerated, although it may be interrupted by minor, self-limiting side-effects.

Lattanzi et al. (105) conducted a review of 35 original studies with a total of 26,438 dobutamine echocardiography tests to determine the feasibility and safety of this test. Clinical adverse effects (e.g. nausea, headache, tremors, shortness of breath, palpitations, and anxiety) occurred during the test in about 30% of patients and precluded completion of the test in about 5% to 10% of patients. Chest pain was usually linked to dobutamine-induced myocardial ischemia. Adverse effects usually disappeared upon interruption of drug infusion. The incidence of severe adverse reaction occurred in 1 in every 335 tests. In addition, the review also identified 29 isolated published case reports of life-threatening complications during dobutamine echocardiography including deaths. Some adverse reactions were independent of ischemia and were unpredictable. Lattanzi et al. (105) concluded that while the safety of dobutamine stress echocardiography was reported to be outstanding in early reports, further experience presented a

substantially more worrying picture and must be taken into account by physicians and patients when assessing the risk-benefit of the test.

Economic Analysis

Literature Review

Summary of Literature Review on Economic Analysis

Four studies on economic analysis of PET were identified. A brief summary of the findings are provided as follows.

- As a result of the lack of RCT studies, economic analyses on the use of PET were based on data from cohort studies and expert opinion.

- A Quebec analysis using a Monte Carlo-type model concluded that for patients with ischemic LV dysfunction and LVEF less than 30%, treatment guided by thallium SPECT with follow-up FDG PET when results from thallium SPECT were equivocal, was more cost-effective than treatment guided by thallium SPECT and clinical decision. The thallium and FDG PET strategy resulted in an estimated cost saving of $687 to $7,182 (Cdn) and an incremental 5-year survival probability of 0.02 to 0.07.(42)

- An Australian economic analysis using a decision-tree model developed by the Institute of Clinical PET Cardiology Task Force demonstrated that using PET for myocardial viability assessment would produce a cost saving of $300.24 (AUD) per patient. Sensitivity analysis showed that FDG PET would remain cost-effective for values of prevalence of viable myocardium up to 0.76 or values for specificity of PET as low as 0.63.

- Applying results of a study on the influence of PET on medical decision (95) to the same Australian model yielded an estimated cost saving of $2,069.65 (AUD) per patient examined for myocardial viability with PET.

- An analysis from the United Kingdom showed that a PET-guided therapy costs less and produced more benefits than a strategy that provided CABG for all patients without prior FDG PET viability assessment (i.e., a strategy that includes PET dominated the CABG therapy strategy). It was marginally cost-effective in the study population (patients with CAD and LVEF<30%) in relation to medical therapy. With an underlying 50% prevalence rate for hibernating myocardium, the incremental cost per life-year saved of PET-guided therapy was £77,186, which improved to only £52,359 if the prevalence in the population tested was to approach 95%. None of the sensitivity analyses performed produced a cost-effectiveness ratio more attractive than £46,636 per life-year saved.

Descripton of Evidence on Economic Analysis

Dussault et al. 2001

In their 2001 health technology assessment on PET, Dussault et al. (AETMIS, Quebec) (42) used a Monte Carlo-type mathematical model to estimate the anticipated economic impact of evaluating myocardial viability using PET in people with ischemic heart disease and an ejection fraction of less than 30%. A decision-tree was developed in consultation with expert clinicians (Figure 22). The model compared a treatment strategy based on both thallium viability testing and clinical decision for equivocal scans, with a strategy that uses PET as a second line viability test for people with equivocal thallium scans. For each strategy examined, the costs and proportion of individuals surviving at 5 years were estimated. Only the direct costs (costs of the viability tests, costs associated with the use of medical services, and reimbursement of professional fees) were included (Table 45). For measuring efficacy, the patients' mean probability of survival at 5 years after revascularization, medical treatment, and/or transplantation was used.

Figure 22: Decision Tree for Myocardial Viability Assessment

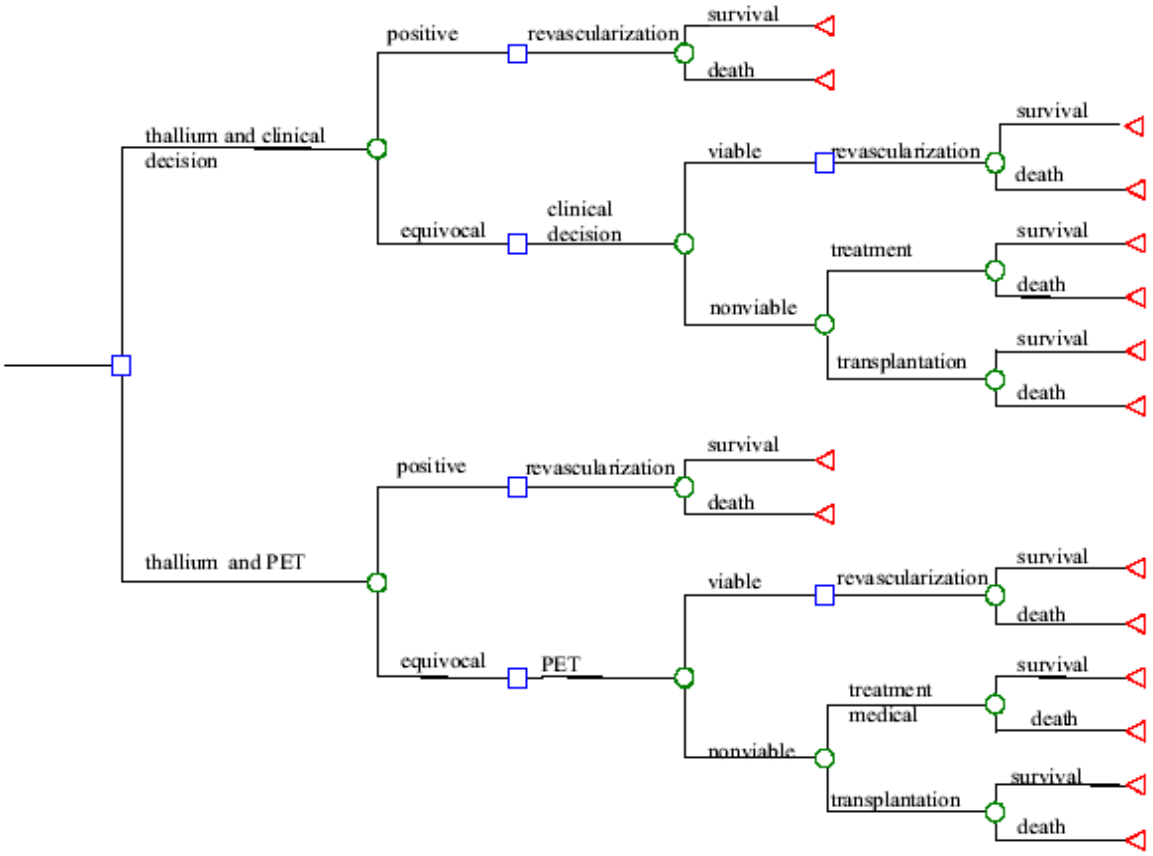


Figure reproduced with permission from AETMIS; Dussault FP; Nguyen VH; Rachet F; Positron emission tomography in Québec. Agence d'évaluation des technologies et des modes d'intervention en santé (AÉTMIS).(AÉTMIS 01-3 RE). 2001. Montréal: AÉTMIS

Table 45: List of the Variables Used in AETMIS Myocardial Viability Model (AETMIS, 2001)

Description	Value	Source
Cost* of a PET scan (hospital)	1,050 - 1,575	Appendix 10
Fee* for PET (physician)	225 - 275	Medical Specialists' Manual (RAMQ)
Fee for a thallium scan (physician)	94.4	Medical Specialists' Manual (RAMQ)
Cost of revascularization	8,262 - 10,099	APR-DRG
Cost of a thallium scan (hospital)	315 - 385	Financial report AS-471
Cost of medical treatment	16,000 - 24,000	Expert opinion
Cost of transplantation	48,000 - 72,000	Expert opinion
5-year postrevascularization survival probability	0.8	Expert opinion
5-year post-medical treatment survival probability	0.5	Expert opinion
5-year posttransplantation survival probability	0.75	Expert opinion
Probability of medical treatment	0.6 - 0.95	Expert opinion
Probability of an unequivocal thallium scan	0.3 - 0.4	Expert opinion
Probability of viable myocardium when the thallium scan is equivocal in the thallium-alone option	0.15 - 0.3	Expert opinion
Probability of viable myocardium when the thallium scan is equivocal in the thallium + PET option	0.5	Beanlands et al. 1997, Dreyfus et al. 1994

* in Canadian dollars

Table reproduced with permission from AETMIS; Dussault FP; Nguyen VH; Rachet F; Positron emission tomography in Québec. Agence d'évaluation des technologies et des modes d'intervention en santé (AÉTMIS).(AÉTMIS 01-3 RE). 2001. Montréal: AÉTMIS

The analyses generated the mean and incremental costs and efficacy intervals by executing the model 1,000 times while modifying the data, and randomly choosing values from a predefined probability distribution. The results and the 95% confidence intervals for costs, 5-year survival probability, the incremental cost, and incremental efficacy are summarized in Table 46.

Table 46: Results of the Economic Analysis for Myocardial Viability (AETMIS, 2001)

Strategy	Cost ($)	Efficacy	Incremental cost ($)	Incremental efficacy
Thallium + clinical decision	10,547 to 29,993	0.63 to 0.71		
Thallium + PET	10,119 to 24,753	0.69 to 0.73	-7,182 to 687	0.02 to 0.07

Table reproduced with permission from AETMIS; Dussault FP; Nguyen VH; Rachet F; Positron emission tomography in Québec. Agence d'évaluation des technologies et des modes d'intervention en santé (AÉTMIS).(AÉTMIS 01-3 RE). 2001. Montréal: AÉTMIS

The AETMIS analyses suggest that, compared a strategy that combined thallium SPECT and clinical decision,, the strategy that used FDG PET in follow-up to thallium SPECT appears to be more cost-effective. It is less expensive (incremental cost of -$7,182 Cdn to $687 Cdn), and has better efficacy (incremental efficacy: 5-year survival probability of 0.02 to 0.07), with a 95% confidence interval. Based on the assumptions made, the model suggests that PET is a very cost-effective intervention in people with LVEF less than 30%.

AETMIS cautioned that the above finding needs to be qualified, since the sources of data used in the analysis were mainly expert opinion because there was a paucity of data in the literature. In addition, for the sake of simplicity, the costs and consequences had not been discounted. Despite the above limitations, sensitivity analysis showed that varying the baseline values did not affect the results of the analyses.

AETMIS concluded that given the state of knowledge at the time of the review, and given the economic perspective specific to the situation in Québec, the use of PET for detecting myocardial viability seems to be an efficient intervention. However, AETMIS also stated that it would be important to document evidence of the incremental efficacy of PET in relation to the diagnostic tools that are currently available.

Miles et al., 2001

Miles et al. (106) reviewed research literature on economic models for PET. The models were applied to various types of cancer, and myocardial viability in Australia. Only the model applied to myocardial viability is reported here. Sensitivity analysis was performed to model the effects that potential differences between populations will have upon the effectiveness of the new imaging modality. Prevalence of disease and specificity of the test were identified as parameters that are most likely to have an impact on cost-effectiveness. Differences in prevalence of a second disease may produce false-positive results for the test in question.

With respect to myocardial viability, Miles et al. used the decision-tree analysis undertaken by the Institute of Clinical PET (ICP) Cardiology Task Force to estimate the cost-effectiveness of using PET for viability assessment in Australia.

Modelling with Australian costs including the cost of PET ($950 each), coronary angiography ($1,546 each), CABG ($12,417 each), and surgical complications (average $4,085 each) resulted in the following, reported in Australian dollars:

- Average cost per patient using a “no PET strategy” of $8,129
- Average cost per patient using a “PET strategy” of $7,828.
- Average saving per patient using a “PET strategy” of $300.24 ($8,129 minus $7,828)

The model assumed prevalence of viable myocardium of 71% and specificity for PET of 74%. Sensitivity analysis indicated that FDG PET would remain cost-effective for values of prevalence of up to 76% or values for specificity of PET as low as 63%.

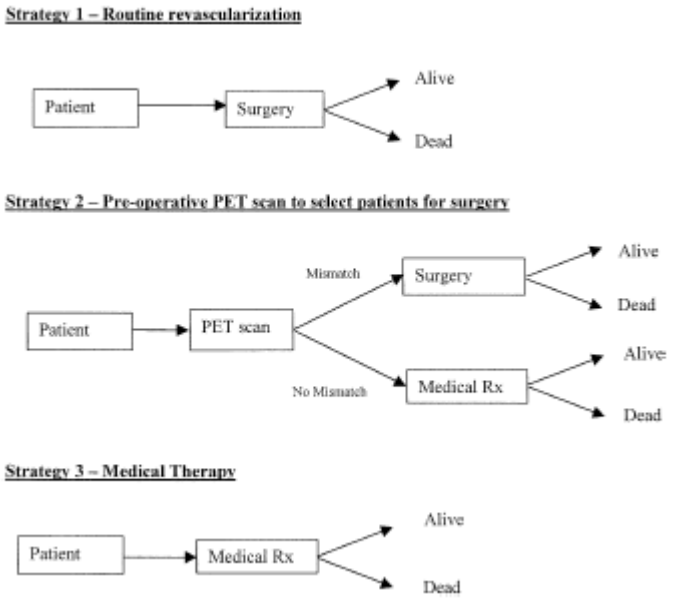
Bealands et al. (95) had reported that FDG PET viability assessment in 87 patients reduced the number of patients inappropriately selected for revascularization. Based on the PET results, 7 of 11 patients (63%) were redirected from heart transplant to revascularization, 16 of 38 (42%) were redirected from revascularization to medical therapy, and 8 of 18 (44%) changed from medical therapy to revascularization. Applying Beanlands' finding to the Australian model, Miles et al. estimated that (all costs reported are Australian dollars):

- The additional cost would be $276,258 including $82,650 for 87 PET scans and $193,608 for 15 additional CABG resulting from PET scans.
- A total cost avoidance of $456,317 ($249,802 for 7 cardiac transplants avoided and $206,515 for 16 CABG avoided).
- A net saving of $180,059 for the 87 patients or a net saving of $2,069.65 per patient.

Jacklin 2002 (107)

Jacklin et al. developed an economic model in the United Kingdom to test the hypothesis that PET would be cost-effective in selecting patients with ischemic heart disease and severe LV dysfunction (EF<30%) for revascularization. The economic model compared 3 management strategies for this patient population (Figure 23):

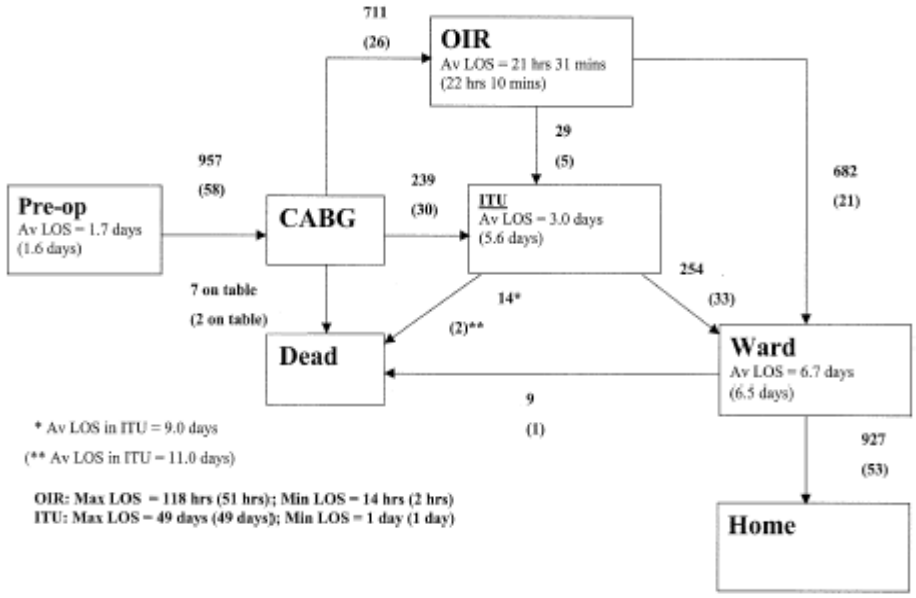
Figure 23: Three Test/Treatment Strategies for Modelling



Reprinted from the Annals of Thoracic Surgery, vol. 73(5), Jacklin PB, Barrington SF, Roxburgh JC, Jackson G, Sariklis D, West PA et al. Cost-effectiveness of preoperative positron emission tomography in ischemic heart disease, p. 1403-1409, Copyright 2002, with permission from Society of Thoracic Surgeons

The cost and outcome (number of life-years generated) of treating 1,000 hypothetical patients were computed using the model for each of the 3 strategies.

Figure 24: Observed Flow of Cardiac Surgical Patients (Values for Patients with Ejection Fraction 30% or less are Shown in Parenthesis)



AV LOS refers toaverage length of stay; CABG, coronary artery bypass grating; ITU' intensive treatment unit; OIR' : overnight intensive recovery; Pre-op, : preoperative

Reprinted from the Annals of Thoracic Surgery, vol. 73(5), Jacklin PB, Barrington SF, Roxburgh JC, Jackson G, Sariklis D, West PA et al. Cost-effectiveness of preoperative positron emission tomography in ischemic heart disease, p. 1403-1409, Copyright 2002, with permission from Society of Thoracic Surgeons

The following costs (Table 47) were based on institution's experience for the specific patient population. Prevalence data for hibernating myocardium and PET characteristics (sensitivity, specificity, and nondiagnostic rate) were obtained from research literature (nonrandomized studies).

Table 47: Variables and Their Default Values

Costs (derived from entire case-mix — Figure 2)	
PET scan	£742
CABG (excluding OIR/ICU/ward costs)	£4,117
OIR/day	£404
ICU/day	£697
Ward/day	£102
Medical therapy/year	£780
Mean length of stay in each clinical area (based on patients with EF < 30%—Fig 2)	
Ward (preoperative)	1.6 days
OIR	1.0 days
ICU	5.6 days
Ward (postoperative)	6.5 days
Hospital survival (based on patients with EF < 30%—Fig 2)	
Overall survival of patients undergoing CABG	91.4%
Survival from operating theater	96.5%
Survival from OIR	100%
Survival from ICU	94.3%
Survival from ward	98.2%
Default values derived from the literature (references given in text)	
% with mismatch defects	50%
PET characteristics	
Sensitivity and specificity	80%
Nondiagnostic rate	5%
One-year survival	
Mismatch defects + CABG	91.4%
Mismatch defects + medical therapy	50%
Match defects + CABG	91.4%
Match defects + medical therapy	92%

CABG = coronary artery bypass grafting; EF = ejection fraction; ICU = intensive care unit; OIR = overnight intensive recovery; PET = position emission tomography.

Reprinted from the Annals of Thoracic Surgery, vol. 73(5), Jacklin PB, Barrington SF, Roxburgh JC, Jackson G, Sariklis D, West PA et al. Cost-effectiveness of preoperative positron emission tomography in ischemic heart disease, p. 1403-1409, Copyright 2002, with permission from Society of Thoracic Surgeons

Jacklin et al. (107) reported the following findings (Table 48):

- Using medical therapy alone was the lowest cost option. (Total cost £666,900 vs. £5,359,146 for PET-guided treatment, and £8,146,717 for CABG alone, for 1,000 hypothetical patients).
- Compared to medical therapy alone, the incremental cost per life-year saved was approximately £77,000 for PET guided therapy, the most cost-effective option.
- Compared to CABG alone, PET-guided therapy cost approximately 3 million less for 1,000 hypothetical patients and saved marginally 60 more life-years.
- Revascularization without PET was the most expensive, and produces less benefit than other strategies (dominated by the cheaper and more effective alternative)
- Sensitivity analysis showed that the prevalence of hibernating myocardium, and the survival rate of patients refused revascularization based on PET results were most likely to influence cost-effectiveness.
- Medical therapy remained the least expensive option in all scenarios. If the prevalence of hibernation drops to 5%, the PET option was more expensive but did not yield any benefit in increased life-years. In this case, PET would be dominated by the medical therapy option. On the contrary, even if the sensitivity of PET drops to 50%, the incremental cost per life-year gained would be £96,519,000, still lower than that of CABG (£181,101 per life-year).

Jacklin et al. concluded that, based on a robust economic model, PET may be cost-effective in the selection of patients with poor LV function referred for CABG. However, there are important areas of uncertainty.

Table 48: Cost and Life Years Obtained From Three Test/Treatment Alternatives for 1,000 Hypothetical Patients

Treatment Strategies	Total Cost	Total Effect (life-years)	Incremental Cost	Incremental Effect (Incremental life-years)	Incremental C/E (Incremental cost per life-year saved)
Medical therapy	£666,900	855.00	----	---	-
Preop PET + CABG	£5,359,146	915.79	£4,692,246	60.79	£77,186
CABG	£8,146,717	913.79	£2,787,572	-2.00	Dominated

CABG refers to coronary artery bypass grafting; C/E, cost-effectiveness; PET, positron emission tomography; Preop, preoperative

Reprinted from the Annals of Thoracic Surgery, vol. 73(5), Jacklin PB, Barrington SF, Roxburgh JC, Jackson G, Sariklis D, West PA et al. Cost-effectiveness of preoperative positron emission tomography in ischemic heart disease, p. 1403-1409, Copyright 2002, with permission from Society of Thoracic Surgeons

Ontario-Based Economic Analysis

Notes & Disclaimer

The Medical Advisory Secretariat uses a standardized costing methodology for all of its economic analyses of technologies. The main cost categories and the associated methods from the province's perspective are as follows**:**

Hospital: Ontario Case Costing Initiative (OCCI) cost data is used for all program costs when there are 10 or more hospital separations, or one-third or more of hospital separations in the ministry's data warehouse are for the designated International Classification of Diseases-10 diagnosis codes and Canadian Classification of Health Interventions procedure codes. Where appropriate, costs are adjusted for hospital-specific or peer-specific effects. In cases where the technology under review falls outside the hospitals that report to the OCCI, PAC-10 weights converted into monetary units are used. Adjustments may need to be made to ensure the relevant case mix group is reflective of the diagnosis and procedures under consideration. Due to the difficulties of estimating indirect costs in hospitals associated with a particular diagnosis or procedure, the Medical Advisory Secretariat normally defaults to considering direct treatment costs only. Historical costs have been adjusted upward by 3% per annum, representing a 5% inflation rate assumption less a 2% implicit expectation of efficiency gains by hospitals.

Non-Hospital: These include physician services costs obtained from the Provider Services Branch of the Ontario Ministry of Health and Long-Term Care, device costs from the perspective of local health care institutions, and drug costs from the Ontario Drug Benefit formulary list price.

Discounting: For all cost-effective analyses, discount rates of 5% and 3% are used as per the Canadian Coordinating Office for Health Technology Assessment and the Washington Panel of Cost-Effectiveness, respectively.

Downstream cost savings: All cost avoidance and cost savings are based on assumptions of utilization, care patterns, funding, and other factors. These may or may not be realized by the system or individual institutions.

In cases where a deviation from this standard is used, an explanation has been given as to the reasons, the assumptions and the revised approach.

The economic analysis represents an estimate only, based on assumptions and costing methods that have been explicitly stated above. These estimates will change if different assumptions and costing methods are applied for the purpose of developing implementation plans for the technology.

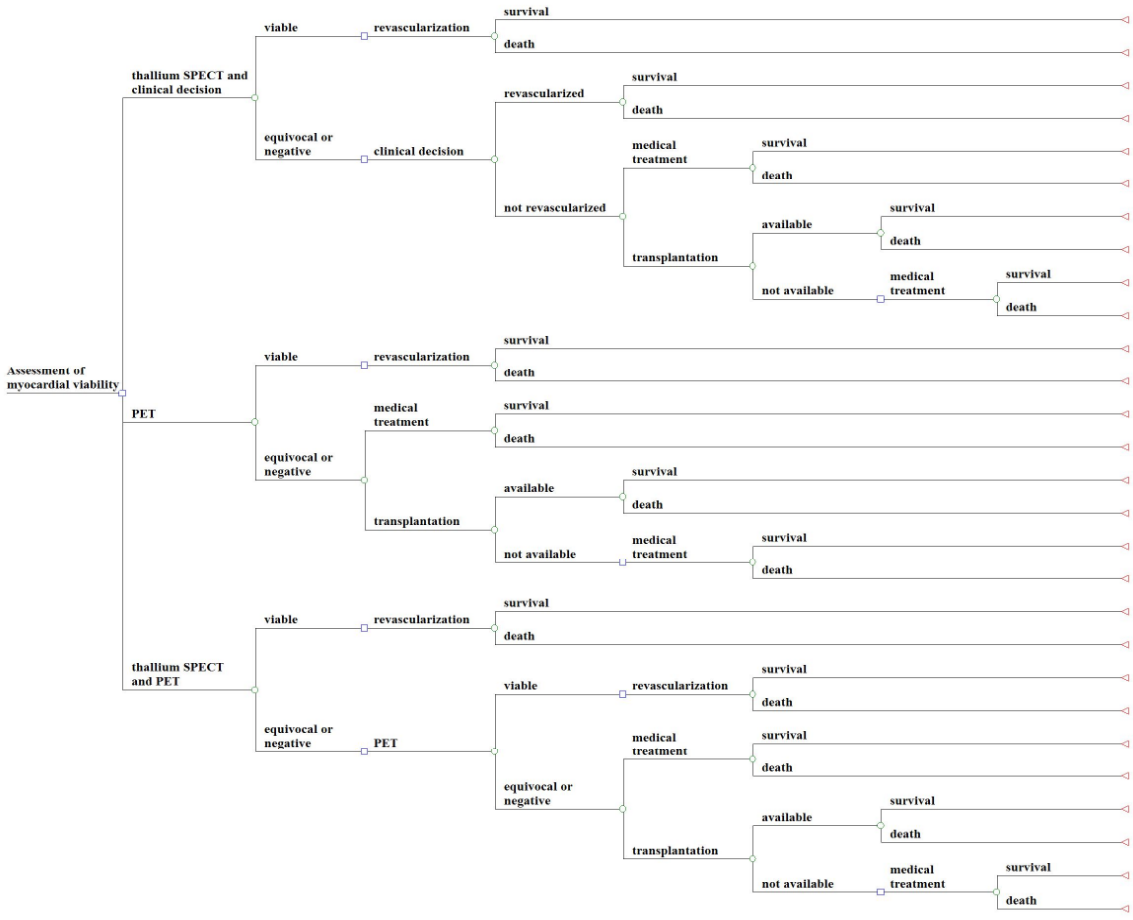
Cost-effectiveness analysis

An economic model was developed to compare the cost-effectiveness of myocardial viability assessment using three different strategies:

- Thallium SPECT and clinical decision: In the current practice, myocardial viability is assessed with ^{201}thallium SPECT. When the results show the presence of viable myocardium, the patient will likely undergo revascularization. When the results are equivocal or negative, a clinical decision will be made as to whether the patient undergoes revascularization, receives a heart transplant or remains on medical therapy.
- PET only strategy: This strategy assumes that patients will undergo revascularization if PET shows the presence of viable myocardium, and either receives a heart transplant or remains on medical therapy if PET shows no viable myocardium.
- ^{201}thallium SPECT + PET: ^{201}thallium SPECT is used as the first line viability assessment test, and PET is used only in patients who have a negative or equivocal result with thallium SPECT. Patients will undergo revascularization if either ^{201}thallium SPECT or PET shows presence of viable myocardium. Patients will receive a heart transplant or remain on medical therapy if PET shows no viable myocardium.

A decision-tree was developed to include the three strategies (Figure 25). For each strategy, the costs and the probability of an individual surviving at five years were estimated. Costs from the health system perspective was considered

Figure 25: Decision-Tree Comparing the Three Strategies for Myocardial Viability Assessment



The hospital costs and reimbursement of professional fees associated with the use of medical services were estimated for each strategy. These are shown in Table 49.

Table 49: List of the Variables Used in the Myocardial Viability Model*

Description	Point Estimate	Range		Distribution	Source
		Low	High		
Cost of CABG, $CDN	13,901	10899	16903	20% variance, normal	MOHLTC
Cost of Medical Management, $ CDN	10,658	1989	38610	20% variance, normal	(108)
Cost of PET scan, $ CDN	946	646	1246	20% variance, normal	An Ontario PET centre
Cost of Thallium SPECT, $ CDN	511			20% variance, normal	An Ontario PET centre
Cost of heart transplant (procedure) $ CDN	52,802			20% variance, normal	MOHLTC
Cost of heart transplant (per year, maintenance), $ CDN	10,000			20% variance, normal	MOHLTC
Probability of equivocal or negative thallium SPECT	0.625	0.500	0.750	Uniform	Expert opinion
Probability of medical treatment for patients with nonviable myocardium	0.775	0.600	0.950	Uniform	Expert opinion
Probability of positive PET (1st. line of treatment)	0.700	0.600	0.800		Expert opinion
Probability of positive PET when thallium is negative or equivocal	0.500	0.400	0.600		(57)
Probability of cases revascularized based on clinical decision when SPECT is equivocal	0.225	0.150	0.300	Uniform	Expert opinion
Probability of 5-year survival after revascularization	0.800	0.750	0.850	Uniform	
Probability of 5-year survival after heart transplant	0.760				CORR database (109)
Probability of available transplantation	0.430				CORR database
Probability of 5-year survival for medical therapy (not viable)	0.450	0.200	0.700	Uniform	

*CABG refers to coronary bypass graft; MOHLTC, MOHLTC, Ministry of Health & Long-Term Care; CORR, Canadian Organ Replacement Register; PET, positron emission tomography; SPECT, single photon emission computed tomography

The mean cost, probability of survival at five years, incremental cost, and incremental effectiveness were calculated for each strategy. The results are presented in Table 50. The PET only strategy and the combined thallium SPECT/PET strategy dominate both the thallium SPECT and the clinical decision strategy because they have lower costs and higher probability of survival at 5 years.

Table 50: Cost-Effectiveness Analysis of Assessment of Myocardial Viability

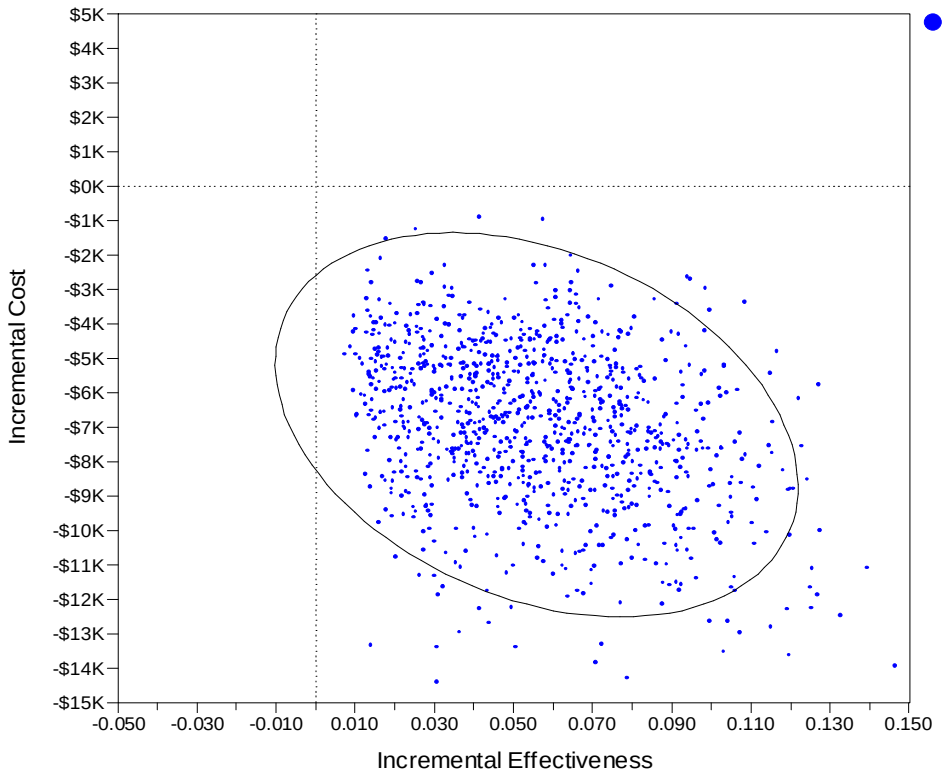
Strategy	Cost ($Cdn)	Incremental Cost ($Cdn)	Effectiveness **	Incremental Effectiveness**	
Thallium SPECT and clinical decision	35,505.44		0.646		
Thallium SPECT + PET	28,633.39	- 6,872.05	0.701	0.055	Dominant strategy*
PET	27,895.76	- 737.63	0.706	0.005	
Thallium SPECT and clinical decision	35,505.44		0.646		Dominated strategy*
PET	27,895.76	- 7,609.68	0.706	0.060	

*Thallium SPECT strategy dominated by both thallium SPECT + PET and PET alone; both are less expensive and more effective
** Probability of 5-year survival

Sensitivity Analysis

Monte-Carlo analyses were used to generate 1,000 simulations, using a value of each variable depicted from the 95% confidence interval within their distribution. The results are shown in Figure 26 where it is clear that all the dots or results show that a combined strategy of thallium-201 SPECT followed by PET exhibits positive incremental effectiveness and negative incremental costs compared with a strategy of thallium -201 SPECT followed by a clinical decision; hence thallium-201 SPECT without a follow-up PET scan is dominated by the strategy that combines the use of SPECT and PET.

Figure 26: Incremental Cost-Effectiveness of a Combined Thallium-201 SPECT and PET Strategy Compared with Thallium-201 and Clinical Decisions Strategy From 1,000 Simulations



Effectiveness = Probability of 5-year survival
*PET indicates positron emission tomography; SPECT, single photon emission computed tomography.

Ontario-Based Budget Impact Analysis

Target population

According to experts, the test most frequently used in Ontario for myocardial viability assessment is delayed (24 hour) thallium-201 SPECT, followed by dobutamine echocardiography. FDG PET is used in a few academic centres with PET capability.

The ICES review (34)stated that patients hospitalized with acute coronary syndrome would not be assessed with PET because the majority will have cardiac stunning rather than hibernation. Experts suggest that because of its high sensitivity and low negative likelihood ratio, FDG PET is best used to identify people with viable myocardium especially when other noninvasive tests showed no viable myocardium.

FDG PET can potentially be used for the following groups:

- Patients with ischemic heart disease, severe LV dysfunction, and predominant heart failure symptoms (rather than angina) and non-viable myocardium suggested on other viability imaging tests. For these patients, FDG PET can aid selection of the most appropriate treatment: revascularization, heart transplant, or medical therapy, as well as aid the selection of the method for revascularization.
- Patients with a moderate to severe fixed stress perfusion defect with some LV dysfunction for whom the information would impact the decision for revascularization.

Cost Comparison of Noninvasive Myocardial Viability Tests

A cardiac PET center in Ontario provided estimated costs of four noninvasive techniques for assessing myocardial viability. These are summarized in Table 51.

Based on expert opinion, the number of patients with ischemic LV dysfunction who require a viability assessment was estimated to be approximately 3,500 per year

Table 51: Comparative Costs of Thallium-201 SPECT, Dobutamine Echocardiography and PET as First Line Viability Assessment

Viability Test	Technical Fee $	Professional Fee $	Cost per study $	Cost of 3,500 studies $	Incremental (Less) cost over SPECT $
SPECT Rest-delayed (perfusion/viability)*	391	120	511	1,788,500	
Dobutamine Stress echocardiography † (stress + rest)	190	169	359	1,256,500	(532,000)
PET (perfusion/viability equivalent)**					
FDG @ $300/scan (high volume)	526	120	646	2,261,000	472,500
FDG @ $600/scan (medium vol)	826	120	946	3,311,000	1,522,500
FDG @ $900/scan (low volume)	1,126	120	1,246	4,361,000	2,572,500
Cardiac MRI (3 sequence, gating, gadolinium) ‡	300	232	532	1,862,000	3,500

All costs in Canadian dollars
* Does not include gating **Aassume equivalent for PET as for SPECT † Represent total costs if include costs incurred to lab
‡ Program receives operating budget for MRI ($900k/3,000 MRI scans). Aggregate technical costs incurred for MIR are not known

Dobutamine echocardiography appears to be the viability test with the lowest cost at about $359 (Cdn) per test. SPECT and CeMRI have similar costs ($511 Cdn and $532 Cdn per test respectively). The unit cost of PET is sensitive to the cost of the FDG. Depending on the cost of FDG, unit cost of a PET viability assessment could range from $646 to $1,246 (Cdn).

Budget Impact Analysis

Scenario 1: PET used as first line viability tests

Should PET be used to replace all thallium SPECT in the assessment of myocardial viability, the incremental cost for 3,500 viability tests could range from $473K to $2.57M depending on the FDG costs (Table 51).

Scenario 2: PET used when ^{201}thallium SPECT or dobutamine echo results are negative or equivocal

In this scenario, some patients will be having both thallium and PET scans.

Assumptions:
Projected number of people that may benefit from a viability assessment 3,500 (expert opinion)

Negative or equivocal thallium or dobutamine. echocardiogram	50%–70% (expert opinion)
Number of patients requiring PET as a second line viability test	1,750–2,450

Table 52: Annual Budget Impact of Using FDG Positron Emission Tomography as Second Line Viability Tests*

Cost of FDG	Unit Cost Per PET Study $(Cdn)	Incremental Cost of 1,750 PET Studies $(Cdn)	Incremental Cost of 2,450 PET Studies $(Cdn)
(perfusion/viability equivalent)			
FDG at $300/scan (high volume)	646	1,130,500	1,582,700
FDG at $600/scan (medium vol)	946	1,655,500	2,317,700
FDG at $900/scan (low volume)	1,246	2,180,500	3,052,700

*FDG refers to fluorodeoxyglucose F-18; PET, positron emission tomography; SPECT, single photon emission computed tomography

Table 53: Comparison of the Incremental Costs of the Two Scenarios (Target Population = 3,500)

Cost of FDG $ (volume)	Unit Cost Per PET Study $	Incremental Cost $			
		Negative/Equivocal Rate of Tl 201 SPECT at 50%		Negative/Equivocal Rate of Tl 201 SPECT at 70%	
		Scenario 1	Scenario 2	Scenario 1	Scenario 2
FDG at 300/scan (high)	646	472,500	1,130,500	472,500	1,582,700
FDG at 600/scan	946	1,522,500	1,655,500	1,522,500	2,317,700
(medium)	1,246	2,572,500	2,180,500	2,572,500	3,052,700
FDG at 900/scan (low)					

*All costs in Canadian dollars; FDG refers to fluorodeoxyglucose F 18; PET, positron emission tomography; SPECT, single photon emission computed tomography; Tl 201, thallium 201.

The budget impact analysis (Tables 52 & 53) shows that the use of FDG PET as a first line myocardial viability test is always less expensive than the use of PET as a second-line viability test, except in the situation when the FDG cost is $900 per scan and the rate of negative/equivocal results on ^{201}thallium SPECT is at 50% (i.e. high FDG costs and low rate of negative/undeterminate findings on ^{201}thallium SPECT). This holds true in sensitivity analyses using a projected target population of 2,000 and 5,000 (Tables 54–56).

Sensitivity Analysis

Table 54: Incremental Cost for 2,000 and 5,000 Positron Emission Tomography Compared With Thallium-201 SPECT (Scenario 1)*

Cost by Viability Test	Cost* per Study	Cost of 2,000 Studies	Incremental Cost of 2,000 PET vs. SPECT	Cost of 5,000 Studies	Incremental of 5,000 PET vs. SPECT
$ (volume)	$	$	$	$	$
SPECT Rest/delayed (perfusion/viability)	511	1,022,000		2,555,000	
PET (perfusion/viability equivalent)					
FDG at 300/scan (high)	646	1,292,000	270,000	3,230,000	675,000
FDG at 600/scan (medium)	946	1,892,000	870,000	4,730,000	2,175,000
FDG at 900/scan (low)	1,246	2,492,000	1,470,000	6,230,000	3,675,000

All costs in Canadian dollars
*FDG indicates fluorodeoxyglucose F 18; PET, positron emission tomography; SPECT, single photon emission computed tomography.

Target Population = 2,000

Number of people who may benefit from assessment of myocardial viability = 2,000
Number of negative or equivocal thallium SPECT (@50% rate = 1,000
Number of negative or equivocal thallium SPECT (@70% rate = 1,400

Table 55: Comparison of the Incremental Costs of the Two Scenarios (Target Population = 2,000)

Cost of FDG	Unit cost per PET study	Negative/Equivocal Rate of thallium SPECT @50%		Negative/Equivocal Rate of thallium SPECT @ 70%	
		Incremental cost of scenario 1	Incremental cost of 1,000 PET scans (scenario 2)	Incremental cost of scenario 1	Incremental cost of 1,400 PET scans (scenario 2)
FDG @ $300/scan (high volume)	646	270,000	646,000	270,000	904,400
FDG @ $600/scan (medium volume)	946	870,000	946,000	870,000	1,324,400
FDG @ $900/scan (low volume)	1,246	1,470,000	1,246,000	1,470,000	1,744,400

All costs in Canadian dollars
*FDG indicates fluorodeoxyglucose F 18; Incr., incremental; PET, positron emission tomography; SPECT, single photon emission computed tomography

Assuming that 2,000 people require myocardial viability assessment, the estimated incremental cost of using PET instead of thallium SPECT as the first line test ranges from $270,000 to $ 1.47 million. The estimated incremental cost of using PET as a follow-up test to ^{201}thallium SPECT ranges from $646,000 to $1.74million (Table 55).

Target Population = 5,000

People requiring assessment of myocardial viability = 5,000
Number of negative or equivocal thallium SPECT (@50% rate = 2,500
Number of negative or equivocal thallium SPECT (@70% rate = 3,500

Table 56: Comparison of the Incremental Costs of the Two Scenarios (Target Population = 2,000)*

Cost of FDG	**Unit Cost Per PET**	**Negative/Equivocal Rate of Thallium-201 SPECT 50%**		**Negative/Equivocal Rate of Thallium-201 SPECT at 70%**	
		Incr. Cost of Scenario 1	**Incr. Cost of Scenario 2**	**Incr. Cost Scenario 1**	**Incr. Cost of 2,500 PET Scans Scenario 2**
$ (volume)	**$**	**$**	**$**	**$**	**$**
FDG at 300/scan (high)	646	675,000	1,615,000	675,000	2,261,000
FDG at 600/scan (medium)	946	2,175,000	2,365,000	2,175,000	3,311,000
FDG at 900/scan (low)	1,246	3,675,000	3,115,000	3,675,000	4,361,000

All costs in Canadian dollars
*FDG indicates fluorodeoxyglucose F 18; Inc., incremental; PET, positron emission tomography; SPECT, single photon emission computed tomography.

Assuming that 5,000 people require myocardial viability assessment, the estimated incremental cost of PET compared to thallium SPECT as the first line test compared ranges from $675,000 to $ 3.68 million. The incremental cost of using PET as a follow-up test to thallium SPECT ranges from $1.62 million to $4.36 million (Table 56).

Summary of Economic Analysis

- In Ontario, a strategy that includes PET in the assessment of myocardial viability in people with CAD and severe left ventricular dysfunction would likely result in lower costs and improved 5-year survival compared to a strategy that uses thallium SPECT alone.

- In Ontarians with CAD and severe left ventricular dysfunction who were found to have no viable myocardium or indeterminate results using thallium SPECT or dobutamine echocardiography, follow-up myocardial viability assessment using PET would likely have an annual budget impact that ranges from $1.5 million to $2.3 million.

Synopsis of Findings

- The evidence was derived from populations with moderate to severe ischemic LV dysfunction with an overall quality that ranges from moderate to low.
- PET appears to be a safe technique for assessing myocardial viability.
- CAD patients with moderate to severe ischemic LV dysfunction and residual viable myocardium had significantly lower 2-year mortality rate (3.2%) and higher event-free survival rates (92% at 3 years) when treated with revascularization than those who were not revascularized but were treated medically (16% mortality at 2-years and 48% 3-year event-free survival).
- A large meta-analysis and moderate quality studies of diagnostic accuracy consistently showed that compared to other noninvasive diagnostic tests such as thallium SPECT and echocardiography, FDG PET has:
  - Higher sensitivity (median 90%, range 71%–100%) and better negative likelihood ratio (median 0.16, range 0–0.38; ideal <0.1) for predicting regional myocardial function recovery after revascularization.
  - Specificity (median 73%, range 33%–91%) that is similar to other radionuclide imaging but lower than that of dobutamine echocardiography
  - FDG PET has less useful positive likelihood ratio (median 3.1, range 1.4 –9.2; ideal>10) for predicting segmental function recovery.
- Taking positive and negative likelihood ratios together suggests that FDG PET and dobutamine echocardiography may produce small but sometimes important changes in the probability of recovering regional wall motion after revascularization.
- PET appears to be superior to other nuclear imaging techniques including SPECT with ^{201}thallium or technetium labelled tracers, although recent studies suggest that FDG SPECT may have comparable diagnostic accuracy as FDG PET for predicting regional and global LV function recovery.
- Given its higher sensitivity, PET is less likely to produce false positive results in myocardial viability. PET, therefore, has potential to identify some patients who might benefit from revascularization, but who would not have been identified as suitable candidates for revascularization using thallium SPECT or dobutamine echocardiography.
- No firm conclusion can be reached about the incremental value of PET over other noninvasive techniques for predicting global function improvement or long-term outcomes in the most important target population (patients with severe ischemic LV dysfunction) due to lack of direct comparison.
- An Ontario-based economic analysis showed that in people with CAD and severe LV dysfunction and who were found to have no viable myocardium or indeterminate results by thallium SPECT, the use of PET as a follow-up assessment would likely result in lower cost and better 5-year survival compared to the use of thallium SPECT alone. The projected annual budget impact of adding PET under the above scenario was estimated to range from $1.5 million to $2.3 million.

Conclusion

- In patients with severe LV dysfunction, that are deemed to have no viable myocardium or indeterminate results in assessments using other noninvasive tests, PET may have a role in further identifying patients who may benefit from revascularization. No firm conclusion can be drawn on the impact of PET viability assessment on long-term clinical outcomes in the most important target population (patients with severe LV dysfunction).

Policy Considerations

Infrastructure for Viability Testing in Ontario

PET

At the time of this report, there are 8 PET scanning facilities in Ontario, 3 of which also have an onsite cyclotron. These sites are as follows:

Toronto -	University Health Network, Princess Margaret Hospital site
	Centre for Addiction and Mental Health (on-site cyclotron)
	Sunnybrook Health Sciences Centre
Hamilton -	Hamilton Health Sciences Centre (on-site cyclotron)
	St. Joseph's Health Care (not yet functional)
Ottawa -	University of Ottawa Heart Institute (on-site cyclotron)
	Ottawa General Hospital
London -	St. Joseph's Health Care London

Myocardial viability assessment using PET is presently conducted mainly at the University of Ottawa Heart Institute within clinical trials. Other Ontario centres that have the capability to conducted cardiac PET studies are the Hamilton Health Sciences Centre, the University Health Network, and St. Joseph's Health Care in London.

SPECT

A March 2004 national inventory of selected imaging equipment prepared by The Canadian Institute of Health Information (110) reported that there are a total of 244 nuclear medicine cameras and 124 SPECT cameras in Ontario.

Clinical Utility

Observational studies have consistently demonstrated better survival and lower cardiac event rates for people with severe ischemic heart failure and viable myocardium when treated with revascularization. Because of this finding, experts advised that it is important to identify all patients with ischemic myocardial dysfunction that have viable myocardium. Experts further advised that because of its high sensitivity, PET has the potential of identifying viable myocardium missed by other noninvasive techniques.

Current Practice in Ontario

According to experts in the field, the choice of technique for assessing myocardial viability varies from centre to centre depending on the available expertise. In Ontario, expertise in performing myocardial viability assessment using PET is presently limited to four centres. The noninvasive viability test most widely available and most commonly used in Ontario is ^{201}-thallium rest-redistribution SPECT. Stress echocardiography (usually dobutamine echocardiography) is more technically challenging and operator-dependent than nuclear studies, and its availability is limited to a few centres that have expertise in this technology.

MOHLTC was informed that in a community setting, viability assessment might not be performed as frequently, and there is greater reliance on coronary angiographic information for decision-making regarding treatment.

Regulatory Status

Since PET radiopharmaceuticals are regulated as an experimental drug under the *Food and Drug Act*, access to PET scanning can only be provided through clinical trials authorized by Health Canada. As an exception, the use of PET radiopharmceuticals may be approved by Health Canada on a case-by-case basis for a small number of individuals under its Special Access Program. PET scanners are medical devices licensed by Health Canada. Installation and operation of a scanner or a cyclotron also requires licenses from the Canadian Nuclear Safety Commission.

Funding of PET in Other Canadian Jurisdictions

Positron Emission Tomography capability in publicly funded facilities is presently available in Quebec, Ontario, Alberta, British Columbia and Manitoba. In Quebec and Manitoba, PET centres receiving operating funding from the government. Alberta, British Columbia, and Ontario are funding clinical trials on the use of PET in staging certain caners. The trials are funded through the provincial cancer agency or boards. Most provinces provide out-of-country or out-of-province PET scans on a case-by-case basis. Quebec is the only Canadian jurisdiction that has a physician's fee code for this procedure.

Quality Assurance Issues

The Ontario PET evaluation initially showed discrepancies between readers of PET scans for oncology and highlighted the need for experience and standardization of protocols in the interpretation and reporting of PET scans.

Sourcing and Cost of Radiopharmaceuticals

Since the half-life of FDG is about two hours, access to a near-by cyclotron is necessary for a centre to conduct viability assessment using PET scanning. The cost per dose of radiopharmaceuticals is highly dependent on the number of doses per run in the cyclotron and on the distance between the scanner and the cyclotron. It is desirable to concentrate PET viability studies to a number of sites in order to achieve a critical volume necessary for keeping the cost/dose of radiopharmaceutical to a minimum. A centre with an on-site cyclotron would have the added advantage of ready access to other short living tracers used in PET perfusion studies (e.g. ^{82}rubidium)

Randomized Controlled Trial in Progress

Beanlands et al. (111) at the University of Ottawa Heart Institute are presently conducting a multicenter randomized controlled trial (PARR-2) to evaluate the clinical outcome and cost-effectiveness of using an FDG-PET guided approach to management of patients with CAD and severe LV dysfunction. The study includes 412 patients age 18 years or older, with documented CAD and LVEF $\leq$ 35%. Patients randomized to the intervention group will undergo perfusion and FDG PET within 2 weeks of randomization. The PET parameters will be included with clinical parameters in a model to yield a point estimate and 95% confidence interval for predicted recovery in EF after revascularization. Recommendation regarding revascularization will be provided to the attending physician based on likelihood of LV functional recovery. Patients randomized to the control group will proceed without PET to the attending physician. An alternative test for viability definition may be considered at the physician's discretion. All patients will be followed for 2 years after treatment. The primary outcome measure is the composite clinical end point of cardiac death, MI, transplantation, or rehospitalization for unstable angina or heart failure. Secondary end points include cost-effectiveness, health quality of life, and ventricular function. Results of this RCT are expected in late 2005.

Glossary

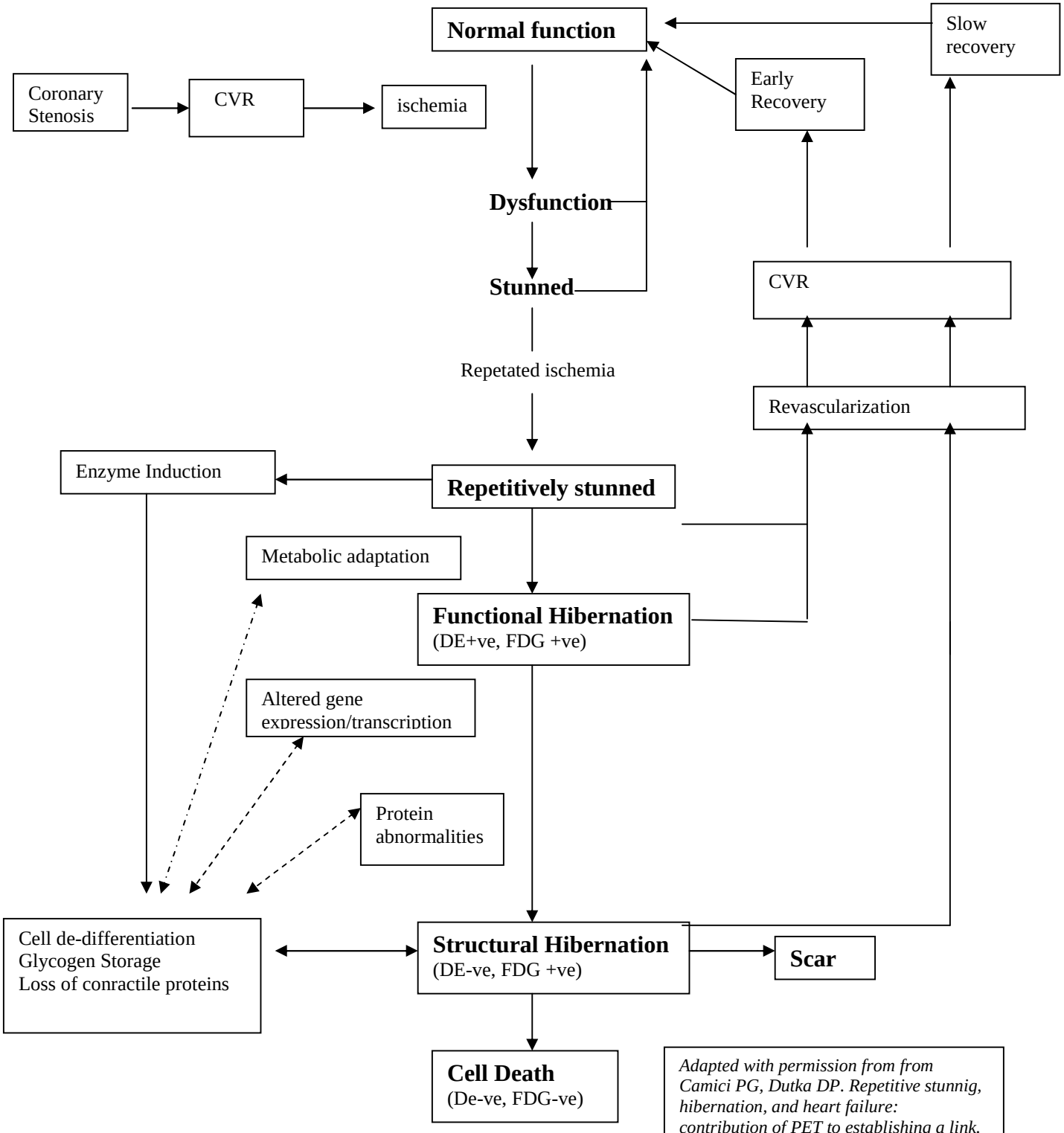
Anoxia	A total lack of oxygen
Akinetic	Pertaining to, characterized by, or causing akinesia (absence, poverty, or lack of control of voluntary muscle movements)
Computed tomography	That in which the emergent x-ray beam is measured by a scintillation counter; the electronic impulses are recorded on a magnetic disk and then are processed by a mini-computer for reconstruction display of the body in cross-section on a cathode ray tube
Coronary angiography	Radiographic visualization of coronary blood vessels following introduction of contrast material; used as a diagnostic aid in such conditions as stroke syndrome and myocardial infarction
Coronary artery bypass graft	A section of vein or other conduit grafted between the aorta and a coronary artery distal to an obstructive lesion in the latter
Diastole	The dilatation, or period of dilatation, of the heart, especially of the ventricles; it coincides with the interval between the second and the first heart sound
Dyskinetic	Pertaining to or characterized by dyskinesia (distortion or impairment of voluntary movement, as in tic, spasm, or myoclonus)
Dyspnea	Breathlessness or shortness of breath; difficult or labored breathing
Dobutamine echocardiography	Ultrasound test that uses dobutamine (a synthetic catecholamine used as an adrenergic with cardiotonic actions) to determine if the heart is getting enough blood with a fast heart beat
Echocardiography	Method of graphically recording the position and motion of the heart walls or the internal structures of the heart and neighboring tissue by the echo obtained from beams of ultrasonic waves directed through the chest wall
Ejection Fraction	Proportion of the volume of blood in the ventricles at the end of the diastole that is ejected during systole; it is the stroke volume divided by the end-diastolic volume, often expressed as a percentage. It is normally 65+/-8%; lower values indicate ventricular dysfunction.
Electrocardiogram	Graphic tracing of the variations in electrical potential caused by the excitation of the heart muscle and detected at the body surface
Electromechanical mapping (definition provided is for cardiac mapping)	Electrophysiological procedure in which electrical potentials recorded by electrodes placed directly on the heart are processed to give a two-dimensional display of the origin and path of an electrical impulse as it depolarizes the heart
^{18}F-fluoro-deoxyglucose	2-deoxy-D-glucose labeled with ^{18}F; used in positron emission tomography in the diagnosis of brain disorders, cardiac disease, and tumors of various organs

Hypokinetic	Pertaining to or characterized by hypokinesia (abnormally decreased mobility; abnormally decreased motor function or activity)
Hypoxia	Reduction of oxygen supply to tissue below physiological levels despite adequate perfusion of the tissue by blood
Infarction	The formation of an infarct
Infarct	Formation of an area of coagulation necrosis in a tissue due to local ischemia resulting from obstruction of circulation to the area, most commonly by a thrombus or embolus
Inotropic	Affecting the force or energy of muscular contractions
Ischemia	Deficiency of blood in a part, usually due to functional constriction or actual obstruction of a blood vessel
Left ventricular ejection fraction	The amount of blood ejected from the left ventricle during each heartbeat expressed as a percentage of the total amount of blood in the left ventricle before its contraction.
Linear local shortening	Regional contractility of the endocardial surface as assessed with electroanatomical mapping. An algorithm is used to calculate the fractional shortening of the regional endocardial surface at end systole.
Magnetic resonance imaging	Method of visualizing soft tissues of the body by applying an external magnetic field that makes it possible to distinguish between hydrogen atoms in different environments
Matched defect	Myocardium with reduction in perfusion and metabolism
Mega becquerel (MBq)	A unit of radioactivity that is a measure of disintegration per second
Mega electron volt (MeV)	A unit of radiation energy equal to 1.602177×10^{-13} joules
Mismatched defect	Myocardium with reduced perfusion but preserved metabolism
Myocardial infarction	Gross necrosis of the myocardium as a result of interruption of the blood supply to the area; almost always caused by atherosclerosis of the coronary arteries, upon which coronary thrombosis is usually superimposed.
Myocardium	The middle and thickest layer of the heart wall, composed of cardiac muscle
Myocardial hibernation	Chronic but potentially reversible cardiac dysfunction caused by chronic myocardial ischemia, persisting at least until blood flow is restored.
Myocardial stunning	Temporarily impaired myocardial contractile function, resulting from a period of ischemia, which persists for some period after reperfusion.
Necrosis	Pathologic death of one or more cells, or of a portion of tissue or organ, resulting from irreversible damage

Percutaneous coronary intervention	A treatment procedure that unblocks narrowed coronary arteries without performing surgery
Positron emission tomography	That accomplished by detection of gamma rays emitted from tissues after administration of a natural biochemical substance (e.g., glucose, fatty acids) into which positron-emitting isotopes have been incorporated
Radionuclide angiography	The measurement of visualization by radiation of any organ after a radionuclide has been injected into its blood supply
Receiver operator characteristic curve analysis	One plotting sensitivity versus [1 - specificity (or false-positive error rate)] to help determine the best cutoff point or points for demarcating dimensional data in diagnostic tests for disease, optimizing the balance between sensitivity and specificity
Sarcolemmal	Pertaining to the membrane that covers smooth, striated and cardiac muscle fibres
Single photon emission tomography	A type of tomography in which gamma photon–emitting radionuclides are administered to patients and then detected by one or more gamma cameras rotated around the patient
Stenosis	Narrowing or constriction of a coronary artery
Systole	The period of heart muscle contraction resulting in a rise of pressure and ejection of blood.
Subendocardial	Beneath the endocardium (the endothelial lining membrane of the cavities of the heart and the connective tissue bed on which it lies)
Transmural	Through the wall of an organ; extending through or affecting the entire thickness of the wall of an organ or cavity
Ventriculography	Radiography of a ventricle of the heart after injection of a contrast medium
X-ray fluoroscopy	Production of an image when x-rays strike a fluorescent screen
Coronary flow reserve	Estimated as the ratio of maximal hyperemic to basal (rest) flow, derived from direct measurement. It depends on perfusion pressure, coronary venous pressure and/or arteriolar tone, and strength of the hyperemic stimulus.
Stenosis flow reserve	Calculated from static quantitative arteriographic dimension - flow at maximum coronary vasodilation relative to flow. It is independent of hemodynamic conditions. It describes the conductance of the stenosis itself as if the arterial segment were excised and studied in vitro under controlled conditions (Demer 1989).

Appendices

Appendix 1: Continuum of Stunned and Hibernating Myocardium



Adapted with permission from from Camici PG, Dutka DP. Repetitive stunnig, hibernation, and heart failure: contribution of PET to establishing a link. AmJ Physiol 2001; 280: H929-H936.

Appendix 2: Protocol for FDG Positron Emission Tomography Imaging and Analysis

The diagnostic quality of the myocardial FDG PET image depends on the concentration of tracer in both myocardium and blood. FDG uptake depends quantitatively on the plasma concentration of glucose and insulin. Attempts have been made to standardize the metabolic environment to optimize FDG uptake in viable tissues during PET viability assessment. Common approaches include:

- Glucose loading with 50–75 grams glucose (to stimulate insulin secretion, regional glucose utilization, and, thus, FDG uptake) and
- Hyperinsulinemic euglycemic-clamp that involves infusing insulin and glucose intravenously at a rate that stabilizes blood sugar at baseline value. Arterial blood samples are drawn at regular intervals to monitor blood sugar levels.(77))

Under the conditions of glucose loading and euglycemic hyperinsulinemia, the substrate use of both the dysfunctional and normal myocardium shifts from fatty acids to glucose. During such maximal insulin stimulation, the magnitude of glucose uptake per unit of tissue correlates well with the amount of viable myocytes per unit of tissue. (77)

Hyperinsulinemic Euglycemic-clamp is particularly important in patients with insulin resistant diabetes mellitus that would result in poor FDG image quality after an oral glucose load.(77)

FDG PET imaging can be either static or dynamic. Static imaging typically involves a 20- to 30-minute image acquisition that begins 40 to 50 minutes after FDG administration. Dynamic imaging for quantitative analysis of the rate of myocardial glucose utilization begins simultaneously with FDG injection, and continues for 60 to 70 minutes, so that time-activity data for blood pool and myocardium can be determined.

Attenuation Correction

Attenuation artifacts result from interaction between the gamma photons emitted by the radioactive tracer within the myocardium and the patient's own tissues. They may be gender-specific, giving rise to predictable patterns of attenuation, or related to patient habits, giving rise to unpredictable soft tissue attenuation in different individuals. Attenuation artifacts may unfavorably affect the diagnostic accuracy of cardiac images. Patients with severe left ventricular dysfunction are likely to have an enlarged left ventricle and are susceptible to diaphramatic attenuation artifacts. This is a potential source of error for all nuclear imaging.

Transmission imaging is usually performed prior to FDG PET scanning to obtain measured attenuation correction.

Analysis and Interpretation

There are different approaches to analyzing perfusion and FDG PET images. (112)

Qualitative analysis: This involves visual analysis of myocardial image slices, and comparing FDG uptake in each dysfunctional segment to uptake in the territory with the best perfusion. The extent and location of regional myocardial reduction in FDG uptake relative to the perfusion status is determined.

Semiquantitative analysis: The LV is divided into a number of segments and the FDG uptake in each segment is graded using a scoring system (e.g. from 0 for highest count to 4 for absent counts). Calculation of summed scores is often performed.

Quantitative analysis*:* In *q*uantitative analysis of PET images, polar maps are derived by combining images from multiple planes so that information about the entire myocardium can be displayed in a single image. FDG and perfusion polar maps (Figure 1) can be normalized to myocardial regions with the highest perfusion. The normalized FDG polar map can be compared with the perfusion polar map to produce a polar map that shows the difference between perfusion and normalized FDG uptake (Figure 2).

Figure 1: Perfusion and Metabolic PET Images Showing a Mismatch Pattern
Mismatch: An N-13 ammonia scan (blood flow) with a region of diminished flow (left) and a corresponding FDG scan showing hypermetabolism in the same region (right). This pattern indicates the ischemic area is still viable.
Image courtesy Dr. Sam Gambhir, Stanford University; Available at
http://www.crump.ucla.edu/software/lpp/clinpetcardio/dietary.html

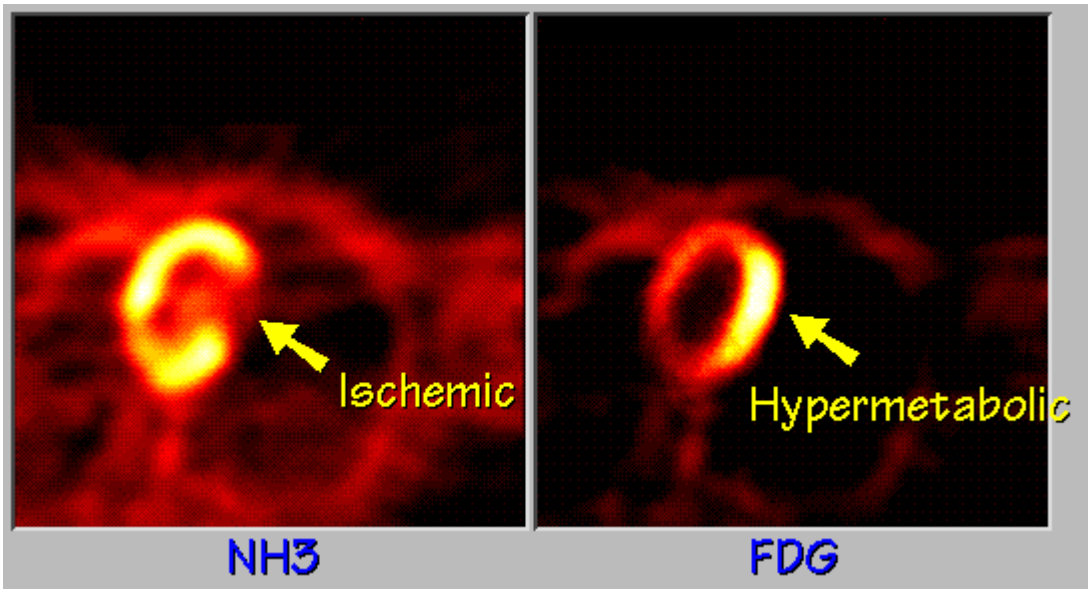
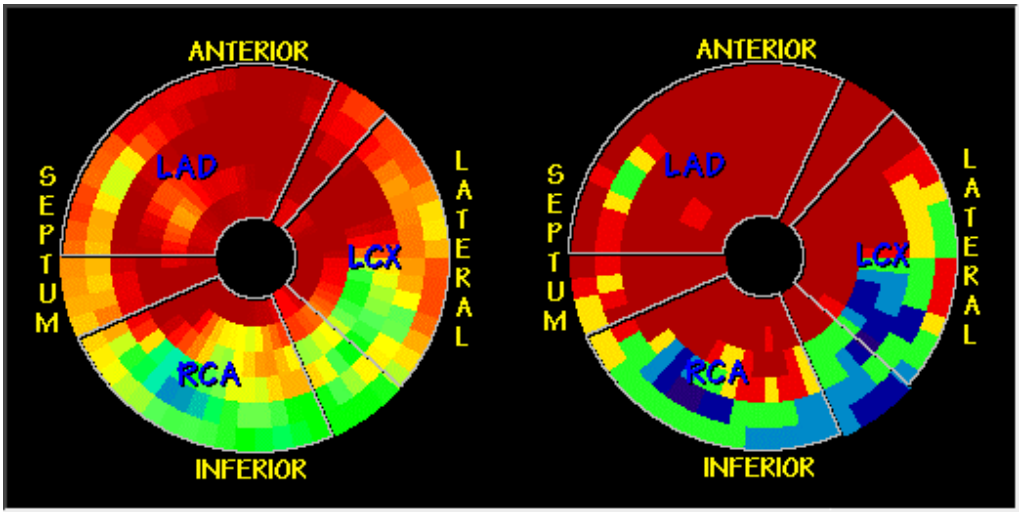


Figure 2: Polar Maps Showing Difference Between Metabolism and Perfusion PET Images
Shown below are the NH3-minus-FDG normalized polar map (left) and polar maps with NH3-minus-FDG normalized to a normal patient data (right). The red colors indicate mismatch between NH3 and FDG. Note that there is a definite mismatch in the anterior and septal regions. The severity of this mismatch compared to normals is made very clear in the polar map on the right (very dark red regions).

Image courtesy Dr. Sam Gambhir, Stanford University; Available at
http://www.crump.ucla.edu/software/lpp/clinpetcardio/dietary.html



Appendix 3: Comparison of Cardiac Functional Diagnostic Imaging

Technology	Basis of data	Main Advantages	Main limitations
FDG PET	*detects changes in energy metabolism	*high resolution and good spatial localization of defects *possibility for attenuation correction *data can be analyzed qualitatively and quantitatively *can be applied to measure various abnormalities (using different tracers)	*minimally invasive *high overall technical cost *limited availability *does not have capabilities of displaying anatomy *need for a cyclotron; FDG is expensive
FDG SPECT	*detects changes in energy metabolism	*lower overall technical cost than for PET *widely available SPECT equipment	*minimally invasive *need for cyclotron for FDG production; FDG is expensive *poorer spatial resolution than PET; lower sensitivity than PET *requires specialized equipment and staff *requires attenuation correction technique
MRS	*detects metabolic changes	*noninvasive *offers possibility of in vivo measurement of myocardial biochemistry can be performed with available MRI equipment *3-D capability with unlimited field of view	*limited spatial resolution *time consuming *patients with ferromagnetic objects in their bodies must be excluded *requires specialized software and expertise *evaluation is limited to the anterior wall of myocardium *abnormalities of PCr and ATP are not specific for ischemia or absence of viability
FMRI	*measures contractile reserve (thickness & WM)	*can be performed on available MRI scanners (permits direct correlation of function with the underlying anatomy) *does not use ionizing radiation *good spatial resolution of LV cavity and wall thickness in diastole and systole	*patients with ferromagnetic objects in their bodies must be excluded *relatively long scanning time *relatively high costs of additional equipment, software
Echo-cardiography	*measures contractile reserve (thickness & WM)	*versatile imaging method for a variety of heart diseases *all cardiac structures visualized and pump function assessed *relative low-cost; no needles or radiation; easy portable *does not depend on ECG-gating (rhythm) *good resolution of LV wall thickness during cardiac cycle	*dependent on operator's skill to acquire images and requires specialized equipment and experienced interpreters (especially stress echo) *stress echo cannot evaluate myocardial perfusion adequately on a routine basis *uncertain definition of LV cavity size
Tc-SPECT	*measures myocardial perfusion and membrane integrity	*lower overall technical cost than for PET *widely available SPECT equipment *Tc-99m sestamibi has better radiation characteristics than TI-201 *time of Tc-99m sestamibi imaging is not critical (minimal redistribution)	*minimally invasive *the utility of Tc-99m sestamibi alone as an indicator of MV is limited (reduced value as MV agent under ischemic and hypoxic conditions) *requires adequate attenuation correction technique
TI-201 SPECT	*measures myocardial perfusion and membrane integrity	*lower overall technical cost than for PET *widely available SPECT equipment *provide assessment of presence and extent of CAD as well as MV	*minimally invasive (requires radioisotope injection) *uptake depends on blood flow, extraction efficiency, retention by viable myocytes *redistribution & uptake depend on time after injection and its blood concentration *suboptimal radiation characteristics

LV refers to left ventricular viability; WM, wall motion; PCr, phosphocreatine; ATP, adonosine triphosphate; MV, myocardial

Used with permission of the Alberta Heritage Foundation for Medical Research's Health Technology Assessment Unit; Cowley D, Corabian P, Hailey D. Functional Diagnostic Imaging in the Assessment of Myocardial Viability. Alberta Heritage Foundation for Medical Research. October 1999, HTA-16.

Appendix 4: Search Strategy

The search strategy built on the cardiac strategy reported by ICES in their 2001 *Health Technology Assessment of Positron Emission Tomography* report. Subject headings, textwords, and synonyms for PET, heart disease, myocardial viability, and commonly used radioisotopes were employed. to ensure comprehensiveness. The search strategy was initially run on September 27, 2004, and was later updated to include studies in the database as of April 20, 2005. Databases searched included OVID Medline, OVID Medline In-Process and Other Non-indexed Citations, OVID Embase, Cochrane CENTRAL, the Cochrane Database of Systematic Reviews, and the INAHTA database. The search was limited to English-language, human articles published in or after January 2001.

Database: Ovid MEDLINE(R) <1999 to April Week 2 2005>
Search Strategy:
---

1 exp Tomography, Emission-Computed/ (16573)
2 positron emission tomography.mp. (7261)
3 pet.mp. (10125)
4 (coincidence adj1 (imaging or detection)).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (170)
5 (gamma camera adj2 (pet or positron emission tomography)).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (46)
6 or/1-5 (20444)
7 exp Fludeoxyglucose F 18/ (3667)
8 exp Rubidium Radioisotopes/ or exp Oxygen Radioisotopes/ or exp Acetates/ or exp AMMONIA/ (5809)
9 rubidium 82.mp. (7)
10 (o water or "0 15 water").mp. [mp=title, original title, abstract, name of substance word, subject heading word] (105)
11 (c acetate or carbon 11 acetate or 11c acetate or c acetate).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (223)
12 (nh3 or nitrogen 13 am?onia or n 13 am?onia or 13n am?onia).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (925)
13 fludeoxyglucose.mp. (15)
14 or/7-13 (10188)
15 6 and 14 (3972)
16 exp Myocardial Ischemia/ (56717)
17 exp Heart Diseases/ (129230)
18 ((heart or coronary or myocardial or cardiac or left ventricular) and (perfusion or viability or metabolism)).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (14697)
19 or/16-18 (136685)
20 15 and 19 (419)
21 limit 20 to (human and english language and yr=2001-2005) (234)
22 limit 21 to systematic reviews (6)
23 21 (234)
24 limit 23 to (case reports or comment or editorial or letter or news or "review" or "review literature" or review, multicase or "review of reported cases") (53)
25 23 not 24 (181)
26 22 or 25 (184)

Database: EMBASE <1996 to 2005 Week 16>
Search Strategy:
---

1 exp Positron Emission Tomography/ (17533)
2 (coincidence adj1 (imaging or detection)).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name] (223)
3 (gamma camera adj2 (pet or positron emission tomography or fdg or fludeoxyglucose)).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name] (60)
4 (pet or positron emission tomography).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name] (21302)

5 or/1-4 (21428)
6 exp Heart Disease/ (222875)
7 exp Heart Muscle Ischemia/ (18826)
8 ((heart or coronary or myocardial or cardiac or left ventricular) and (disease$ or ischemia or perfusion or viability or metabolism)).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name] (108696)
9 or/6-8 (257896)
10 5 and 9 (1744)
11 limit 10 to (human and english language and yr=2001-2005) (761)
12 limit 11 to (editorial or letter or note or "review") (251)
13 11 not 12 (510)
14 Case Report/ (349240)
15 13 not 14 (446)

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <April 19, 2005>
Search Strategy:
---
1 positron emission tomography.mp. (512)
2 pet.mp. (864)
3 (coincidence adj1 (imaging or detection)).mp. [mp=title, original title, abstract, name of substance word] (21)
4 (gamma camera adj2 (pet or positron emission tomography)).mp. [mp=title, original title, abstract, name of substance word] (0)
5 rubidium 82.mp. (2)
6 (o water or "0 15 water").mp. [mp=title, original title, abstract, name of substance word] (25)
7 (c acetate or carbon 11 acetate or 11c acetate or c acetate).mp. [mp=title, original title, abstract, name of substance word] (15)
8 (nh3 or nitrogen 13 am?onia or n 13 am?onia or 13n am?onia).mp. [mp=title, original title, abstract, name of substance word] (241)
9 fludeoxyglucose.mp. (3)
10 ((heart or coronary or myocardial or cardiac or left ventricular) and (perfusion or viability or metabolism)).mp. [mp=title, original title, abstract, name of substance word] (860)
11 (myocardial ischemia or heart disease or coronary artery disease).mp. [mp=title, original title, abstract, name of substance word] (2380)
12 or/1-4 (1008)
13 or/5-9 (286)
14 ((heart or coronary or myocardial or cardiac or left ventricular) and (disease$ or ischemia or perfusion or viability or metabolism)).mp. [mp=title, original title, abstract, name of substance word] (5017)
15 12 and 13 and 14 (9)

Appendix 5: Comparison of 2001 Data and Current Data on Diagnostic Accuracy of FDG PET in Predicting Segmental Function Recovery

FDG PET	2001 Bax Meta-Analysis	2001 ICES Review	2005 Update (Segmental-Based Analysis)	2005 Update (Patient-Based Analysis)	ICES Studies + 2005 Update
Number of studies	20 (598 patients)	17 (672 patients)	6 (183 patients)	3 (109 patients)	26 studies
Sensitivity % Median, Range	93 (weighted mean) 91–95 (95% CI)	87.5 71–100	86 77–90	100 89–100	90 71–100
Specificity % Median, Range	58 (weighted mean) 54–62 (95% CI)	78 33-91	67 44–86	68 67–73	73 33–91
PPV % Median, Range	71 (Weighted mean) 68–74 (95% CI)	76 52–92	78.5 65–84	75 50–86	77 50–88
NPV % Median, Range	86 (Weighted mean) 83–89 (95% CI)	81 73–96	74 61–100	94 80–100	80 61–100
Accuracy % Median, Range	–	–	76 65–77	80.5 74–90	

Appendix 6: Quality Assessment of Studies

	Lund 2002 (49)	Koch 2001 (30)	Korosoglo 2004 (48)	Nowak 2003 (46)	Tani 2001 (45)	Barrington 2004 (44)	Wiggers 2001 (50)	Wiggers 2003 (47)	Schmidt 2004 (27)
Study Design									
MAS Level of evidence	3a	3a	3a	3a	3a	3a	3a	3a	3a
Prospective	√	√	√	√	√	√	√	√	√
Sample size	34	46	41	42	30	25	35	20	40
Consecutive patient assignment			√	√		√			√
QUADAS* Criteria									
Patients drawn from clinically relevant population (spectrum)	Partial	Partial	√	√	Unclear	√	√	√	
With no selection bias			√		Unclear				
Clearly defined selection criteria	√		√			√	√	√	√
Appropriate Reference Standard, not part of index tests	√			√				√	
Objective unbiased outcome criteria	√		√	√	√	√	√	√	√
Reference standard applied to all patients regardless of index test results	√	√	√	√	√	√	√	√	√
Interpretation of reference standard blinded to results of index test	√	√		√	√	√	√	√	
Interpretation of index test blinded to results of reference standard.	√	√	√	√					
Baseline test & viability tests performed close enough to be reasonably sure that target condition did not change between tests	Median 24 days	√	√	?	2-4 weeks	?	?	?	√
Description of tests permit replication	√	√		√	√	√	√	√	√
Complete reporting	√		√	√	√	√	√	√	√
Total % of criteria met	9/13	6/13	9/13	9/13	7/13	9/13	7/13	9/13	8/13
Comments	35% (15 pts) excluded from analysis because of incomplete revascularizaton, missing follow-up, refusal, or reocclusion of target vessel.	-mean LVEF 49% -LV not severely dysfunctional in some pts. -used PET as a reference standard -only 28/46 had patent revac vessel	Some had only moderate LV dysfunction.8/41 pts did not have DSE. 9/41 pts did not undergo revascularization. Complete revasc in 27 CABG & 5 PCI. Visual analysis of MCE feasible in 87% of segments	20 revasc, 15 had RWM assessed @ FU. (141 segments) ventriculography & transthoracic echo used to assess RWM recovery	Lack details on pts -6 pts had LDDES after revascularization; No info on reproducibility; No ROC analysis -Echo (index test used to evaluate outcome	Some had moderate LV dysfunction. Uninterpretable Images: Thallium 1 FDG 2 NH3 1 MIBI 1 pt refused D echo 1 pt did not have test Inter-observer reproducability -Echo as reference standard, one of the index test	-Pts with CABG graft & LVEF<50% - some patients only had mild dysfunction Echo used as reference standard and is one of the index tests	Confirmed CAD & EF<40% 2 reference standards: 3-D echo or MRI	Some only mild LV dysfunction MRI both index test & reference standard.

* QUADAS refers to Quality Assessment of Diagnostic Accuracy Studies

Qualtiy Criteria	Bax 2002 (76)	Gerber 2001 (77)	Beanlands 2002 (79)	Zhang 2001 (80)	Santana 2004 (86)	Sawada 2005 (87)	Sawada 2003 (94)
Study Design							
MAS Level of Evidence	4c	4c	4b	4c	4c	4c	4c
Prospective	√	√	√	√	√	√	√
Sample size	34	178	82	123	90	61	95
Consecutive Patient Assignment				√	√		
QUADAS* Criteria							
Patients drawn from clinically relevant sample (spectrum)	√	√	√	√	√	√	√
No selection bias							
Clearly defined selection criteria			√	√		partial	√
Appropriate Reference Standard, not part of index tests	√	√	√	√	√	√	√
Objective unbiased outcome criteria	√	√	√	√	√	√	√
Reference standard applied to all patients regardless of index test results	√	√	√	√	√	√	√
Interpretation of reference standard blinded to results of index test	√		√		√		NA
Interpretation of index test blinded to results of reference standard.†	√	√	√	√			√
Baseline test & viability tests performed close enough to be reasonably sure that target condition did not change between tests	?	?	√		?	?	NA
Description of tests permit replication	√	√	√	√	√	√	√
Complete reporting	√	√	√	√	√	√	√
Total % of criteria met	9/13	7/13	11/12	11/13	10/13	9/13	9/11
Special Notes	Patients scheduled for CABG	Pts with CAD, had PET & had functional follow-up after CABG or PCI More than 1 reference standard used		Some patients only had mild LV dysfunction	Potential revascularization candidates referred for gated PET viability study Documented CAD & LVEF<40%	Narrow spectrum. Only generalizable to people with ischemic LV dysfunction and diabetes mellitus	-narrow spectrum -preselection bias -some follow-up was retrospective

* QUADAS refers to Quality Assessment of Diagnostic Accuracy Studies

†Quantitative or automatic analysis of images considered blinded interpretation

Quality Criteria	Klein 2002 (28)	Kuhl 2003 (29)	Botker 2001 (31)	Keck 2002 (32)	Wiggers 2003 (47)	Graf 2004 (74)	Knuesel 2003 (69)
MAS Level of Evidence	3a	3a	3a	3a	3a	3a	3a
Prospective	√	√	√	√	√	√	√
Sample size	31	23	31	51	20	21	19
Consecutive Patient Assignment		√		√		√	
QUADAS* Criteria							
Appropriate Spectrum: patients drawn from clinically relevant population	√	√	√		√		Unclear
No selection bias							
Clearly defined selection criteria	√		√		√	√	
Appropriate Reference Standard, not part of index tests	√	√	√	√	√	√	
Objective unbiased outcome criteria	√	√	√	√	√	√	√
Reference standard applied to all patients regardless of index test results	√	√	√	√	√	√	
Interpretation of reference standard blinded to results of index test	√	√		√	√		
Interpretation of index test blinded to results of reference standard.	√			√			
Baseline test & viability tests performed close enough to be reasonably sure that target condition did not change between tests	?	√	?	√	?	√	√
Description of tests permits replication	√	√	√	√	√	√	√
Complete reporting	√	√	√	√	√	?	√
Special Notes	EF<35% Patients scheduled for a PET study	Consecutive patients with LV dysfunction for viability assessment	EF<45% Some only mild LV dysfunction	Proven CAD Mean EF 51+/-14% -Blinding for SPECT & echo	Confirmed CAD & EF<40% 2 reference standards: 3-D echo or MRI	Confirmed CAD, stable angina. Excluded severe LV dysfunction & remodeling Mean EF 49+/-17%	Known CAD on angio. Excluded people with diabetes Mean EF?

* QUADAS refers to Quality Assessment of Diagnostic Accuracy Studies

	Kaltoft 2001 (61)	Slart 2005 (66)	Bax 2001 (25)	Bax 2003 (67)	Gutberlet 2005 (58)	Meluzin 2003 (92)	Sicari 2003 (93)	Hausmann 2004 (73)
MAS Level of Evidence	3a	3a	4c	3a	3a	4c	4b	3a
Prospective	√	√	√	√	√	√	√	√
Sample size	54	58	47	47	20	130	425	41
Consecutive Patient Assignment	√					√	√	
QUADAS Criteria								
Patients drawn from clinically relevant sample (spectrum) EF	√	√	√	√	√	√	√	√
No selection bias						√	√	
Clearly defined selection criteria		√					√	
Appropriate Reference Standard, not part of index tests	√		√	√		√	√	√
Objective unbiased outcome criteria	√	√	√	√	√	√	√	√
Reference standard applied to all patients regardless of index test results	√	√	√	√		√	√	√
Interpretation of reference standard blinded to results of index test		√	√		√	NA	NA	
Interpretation of index test blinded to results of reference standard.					√	√	√	
Baseline test & viability tests performed close enough to be reasonably sure that target condition did not change between tests	√	√	√	?	√			
Description of tests permit replication	√	√	Partial	√	√	√	√	
Complete reporting	?	√	√	√	√	√	√	√
Notes	Severe ischemic cardiomyopathy referred for PET Mean EF 28.2%	Chronic CAD & LV dysfunction Mean EF 33+/-12%	CAD & ischemic cardiomyopathy Scheduled for CABG EF 14–39% Mean EF 30+/-6%	Ischemic cardiomyopathy & depressed LV function scheduled for CABG, mean EF 30+/-8%	Triple vessel CAD with severe LV dysfunction able to have MRI. Needed CABG Mean EF 28.6%	Consecutive potential candidates for revascularizat-ion Confirmed CAD (>50% occlusion) Mean EF 25+/-4%	Consecutive, CAD (>75% occlusion) EF<35% Mean EF 20% – 27%	Pts with EF<30% who underwent CABG Mean EF 26+/-7.7%

* QUADAS refers to Quality Assessment of Diagnostic Accuracy Studies

	Murayam 2002 (64)	Yoshinaga 2002 (60)	He 2003 (63)	Giorgetti 2004 (62)	Picano 1994 (104)			
MAS Level of Evidence	3a	3a	3a	3a	4b			
Prospective	√	√	√	√	√			
Sample size	33	23	36	23	2,799			
Consecutive Patient Assignment		√	√					
QUADAS* Criteria								
Patients drawn from clinically relevant sample (spectrum) EF	Unclear	partial	√	√				
No selection bias	Unclear	√	√					
Clearly defined selection criteria	partial	√	√	√				
Appropriate Reference Standard, not part of index tests		√	√	√				
Objective unbiased outcome criteria	√	√	√	√	√			
Reference standard applied to all patients regardless of index test results	√	√	√	√	NA			
Interpretation of reference standard blinded to results of index test		√		√	NA			
Interpretation of index test blinded to results of reference standard.		√		√	NA			
Baseline test & viability tests performed close enough to be reasonably sure that target condition did not change between tests	unclear	unclear	unclear	unclear				
Description of tests permit replication	√	√	√	√	√			
Complete reporting	√	√	√	√	√			
Notes	Previous MI & proven CAD	Sequential patients with old MI, CAD, & severe segmental dysfunction mean EF 45.5+/-13.4%	Consecutive patients with CAD & regional &/or global LV Mean EF 35+/-6%	Old MI & severe LV dysfunction EF<35%. Mean EF 26+/-8%	Re safety & tolerability of dobutamine stress echocardiography 2,067 test with patient off angina medication			

*QUADAS refers to Quality Assessment of Diagnostic Accuracy Studies.

Appendix 7: Summary of Studies – Prediction of Recovery of Regional Wall Motion

Studies/ year	Objective	Method	Selection / Spectrum/Patient characteristics	Reference Standard	Blinding/ PET analysis & Definition of viability	Results	Limitations
Bax 2001 (43)	To determine accuracy of PET & other tests in predicting improvement in regional LV function after revascularization	Meta-analysis 77 studies N=3,034 patients (1) calculate weighted mean sensitivity, specificity, PPV, & NPV of FDG PET, dobutamine echo, & SPECT; (2) direct comparison of D. Echo & nuclear imaging	Inclusion: Prospective studies in patients with chronic CAD, revascularized after viability assessment. Allow assessment of sensitivity, specificity, PPV & NPV Patient characteristics Mean age 48–63 Mean LVEF 24–48%	Improvement of regional LV function (regional wall motion) after revascularization Follow-up 7 days – 14 months	Weighted sensitivities , specificities, PPV & NPV were calculated (test viable segment./segments with recovery after revascularization	-FDG PET –highest sensitivity (93%, *P*<0.05) & highest negative predictive value (86%) -Dobutamine echo had highest specificity (80% vs. 58% for PET) & highest positive predictive value (77% vs. 71% for PET)	Some study subjects were had only mild LV dysfunction Heterogeneity in data acquisition, time of analysis after revascularization, approach to image interpretation & choice of viability marker.
Barrington 2004 (44)	To compare accuracy of PET, Dobutamine echocardiography SPECT (rest & stress thallium; 99m-Tc sestamibi) in predicting hibernating myocardium	Prospective cohort, N=25 males PET imaging with Siemens ECAT 951R scanner & 250 MBq FDG after 25-50 glucose & 1 dose insulin injection following overnight fast. Perfusion PET prior to FDG PET with 550 MBq N-13 NH3 SPECT: 99m-Tec MIBI resting and stress using dipyridamole or adenosine. -Delayed 18-h Thallium at rest All imaging within 2–4 weeks	Consecutive, CABG candidates Inclusion LVEF</=40% candidate for revascularization. Exclusion unstable angina, MI<4 months, valvular HD, LV aneurysm, contraindication to stress tests Patient Characteristics Mean age 57.8 years Mean LVEF 36.2 (+/-7.3)% Mean no. diseased vessels = 3.5	Improved wall motion ≥1 grade in at least 2 adjacent segments by resting echocardiogram @ mean follow-up of 8.1+/-2.8 months (range 6 – 12 months) Attrition accounted for	Blinding in interpreting echo. PET & SPECT images analyzed in 13 Segments. FDG uptake relative to that in the hottest 10% of pixels. -ROC analysis for optimal threshold Viability defined as: normal perfusion or perfusion/FDG uptake mismatch	FDG PET PPV 75%, NPV100%; Echo NPV 87%, PPV 100%. FDG PET only predictor on multivariate analysis Coefficient of repeatability: MIBI 5.5%; Tl-201 7.5%,; NH3 7.3%; FDG 4.9%. Kappa score for interobserver reproducibility for D echocardiography 0.59	-small sample -not clear how CABG decisions were made -No attenuation correction for SPECT -echocardiogram, one of the index tests was used as the gold standard.

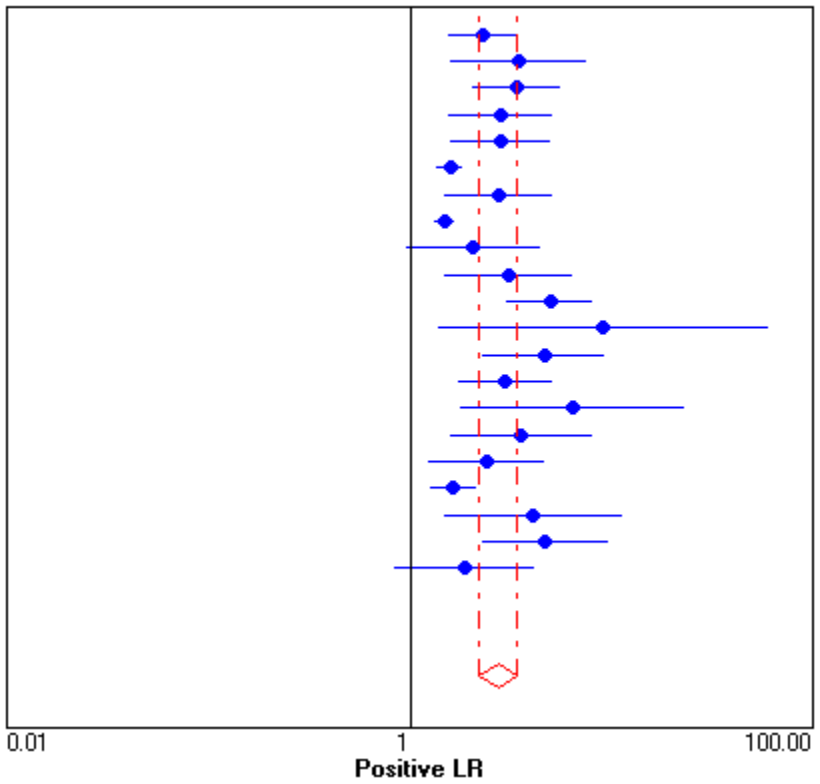
Studies/ year	Objective	Method	Selection / Spectrum/Patient characteristics	Reference Standard	Blinding/ PET analysis & Definition of viability	Results	Limitations
Lund 2002 (49)	To compare of accuracy of LDD echo, FDG PET and 99-mTc MIBI SPECT in predicting functional recovery after coronary revascularization	Prospective cohort N=49 (reported on 34) Coronary angiogram @ baseline. Perfusion SPECT with 370 MBq 99m-Tc sestamibi -Dynamic PET image with Siemens ECAT EXACT & 370 MBq FDG 1 hour after 10% glucose infusion +short acting insulin 1 hour PET scanner with attenuation correction -ECG gated echo @ rests & with 5, 10, 20 ug/kg/min of dobutamine 36 CABG 68 PCI	Patients referred for PET study Inclusion: chronic MI, severe regional LV dysfunction & proximal occlusion of infarct-related coronary artery. Exclusion: severe post MI angina, unstable coronary syndrome, valvular disease, IDDM etc. Patient Characteristics Mean age =60 (+/-9) years Mean LVEF = 42 (+/-13)% 47% multivessel disease 92% previous MI	Improved regional wall motion >+1SD in 2 adjacent dysfunctional segments on coronary angiogram & ventriculogram @ 4-6 months after revascularization.	-blinding in interpretation of echo & angiogram - PET & SPECT analyzed quantitatively w a semiautomatic analysis program & 9-segment model. Mean uptake calculated. -ROC analysis for optimal threshold Viability defined as: PET: FDG uptake>55% D Echo: increased wall thickening during D. echocardiography	-LDD echo was the most accurate predictor of functional recovery (optima cutoff: improvement of >/=2 adjacent akinetic segments w D) -Optimal threshold for FDG PET >55% uptake -a concordant match of FDG uptake & preserved perfusion increased accuracy of nuclear modalities	-Patient enrollment not consecutive -Mean EF 42%, some patients had mild LV dysfunction -No attenuation correction for SPECT
Korosogrlou 2004 (48)	To compare accuracy of real time myocardial contrast echocardiography (MCE), low-dose dobutamine echo (DSE) & 99m-Tc Sestamibi SPECT/FDG PET in predicting functional recovery	Prospective N=41 Wall motion by 2-D echo before & after revascularization. All imaging within 2 weeks of revascularization. Before revascularization: PET- scanned with Siemens ECAT EXACT scanner during euglycemic hyperinsulinemic clamp. SPECT with 3-head gamma camera with low energy, high-resolution collimators & 700 MBq sestamibi.	Consecutive patients with confirmed CAD (≥70% occlusion) & LV dysfunction Inclusion Confirmed impaired LV function LVEF </=40% Exclusion Significant valvular disease, unstable angina, decompensated heart failure MI<4weeks. Patient characteristics Mean age = 65 years Mean LVEF = 31% Multivessel disease = 93% (38/41)	Improved wall motion >/= 1 grade on 2-D echo @ 3-6 months after revascularization	Blinding in PET/SPECT Quantitative analysis of 16 segments Viability definition: Metabolic: Maintained FDG uptake & decreased uptake of Tc-sestamibi on SPECT MCE: visual & quantitative analyses DSE: wall motion normal @ rest, or increase>/=1 grade after dobutamine or systolic function ↓ by >/= 1grade	MACE (normal A values) Sensitivity 89% Specificity 64% Accuracy 81% DSE Sensitivity 83% Specificity 76% Accuracy 81% FDG PET/SPECT Sensitivity 90% Specificity 44% Accuracy 77% MCE & DSE Sensitivity 96% Specificity 63% Accuracy 83%	-For MCE, cut-off threshold for viability selected within same group of patients -Echocardiography, one of the index test was used as the gold standard.

Studies/ year	Objective	Method	Selection / Spectrum/Patient characteristics	Reference Standard	Blinding/ PET analysis & Definition of viability	Results	Limitations
Nowak 2003 (46)	Prediction of functional recovery using blood flow volume by O-15 H2O PET	Prospective cohort. N=42 Angiogram & ventriculography Static PET with Siemans ECAT EXACT 922/47 scanner & 223+/-58MBq FDG after 50g oral glucose load & for diabetes IV insulin before glucose. Dynamic PET scans @ rest with 700–1,000 MBq O-15 water. Attenuation correction in PET images. Perfusion SPECT with dual head gamma camera & 425+/-59 MBq Tc-99m tetrofosmin	Consecutive patients scheduled for FDG PET viability study Inclusion/exclusion criteria not stated Patient characteristics 35/42 males Mean age 63+/-11 years Mean LVEF 38+/-13 % 79% had previous MI mean of 2.2 diseased vessel	Hibernation defined as wall motion improvement of at least 1 score on ventriculogram (6.4+/-0.7 months) or transthoracic echocardiography (17.1+/-4.5 months) after revascularization Mean follow-up (	Blinded interpretation of all tests. Calculation of myocardial blood flow volume & quantitative analysis of relative FDG uptake / normalized to segment with 100% perfusion by 18 segments Definition of viability Mismatch: 99mTc TF uptake</=70% & FDG uptake >70%	15/20 patients successfully revascularized had follow-up. ROC analysis confirmed 70% FDG uptake optimal for predicting functional recovery Sensitivity 80% Specificity 72% PPV 78%, NPV 74% Accuracy 76% MBF vol not significantly reduced in hibernating myocardium & did not improve accuracy of FDG PET by itself	-No inclusion and exclusion criteria or exclusion criteria. -Two different gold standards used to assess improvement in RWM after revascularization -Follow-up period differ for the two groups using different gold standards.

Tani 2001 (45)	Compare LDDSE & FDG PET in determining myocardial viability & predicting functional recovery as (wall motion)	Prospective cohort LDDSE vs. FDG N=30 All patients had LDDE & FDG PET Echo with IV dobutamine infusion starting at 5ug/kg/min increasing to 10ug/kg/min. Monitored with ECG & BP. Static PET imaging with a Shimadzu-SET 1400 W-10 PET scanner (HEADTOME IV Shimadzu Corp, Kyoto, Japan) & 148–407 MBq 24 PTCA, 6 CABG Wall motion by rest echocardiogram before & after revascularization.	Patients post-infarct angina and regional wall motion abnormalities on rest echocardiography Inclusion/exclusion criteria not stated. <u>Patient characteristics</u> Mean age = 62+/-11 years	Improved wall motion>1 grade between rest echocardiogram before & @ 6months after revascularization	Interpretation of echo (reference standard) blinded to PET results. <u>PET</u> normalized FDG uptake (to maximal count) in each of 13 LV segments graded using a color map & 4 point scale from normal (1), to severely reduced (4) Viability definition PET: Segment with FDG uptake >50% (grade 1 & 2) LDDE: wall motion increased >1grade in dyssynergic segments under dobutamine stimulation.	- of 390 segments analyzed, 41(37%) akinetic and 1 % dyskinetic. 53% improved 7months after revascularization Agreement in finding 55% for viable & 24% for nonviable (79% total) 16% of segments viable by PET but nonviable on LDDSE <u>Predicting regional wall motion recovery:</u> PET LDDSE Sensitivity 90% 84% Specificity 61% 80% PPV 79% 88% NPV 78% 75% LDDSE can detect functional recovery at a relatively early stage.	-Small sample -Patient enrollment was not consecutive Inclusion/exclusion criteria not stated -LDDE performed after CABG in 6 patients -RWM visually assessed -echocardiography, one of the index tests was used as the gold standard

Studies/ Year	Objective	Method	Selection / Spectrum/Patient characteristics	Reference Standard	Blinding/ PET analysis & Definition of viability	Results	Limitations
Wiggers 2001 (50)	Compare diagnostic performance of FDG PET, resting ECG, LDDE & exercise testing to predict reversible myocardial dysfunction	Prospective cohort N=35 Before revascularization, all patients underwent -exercise testing with a bicycle ergometer (ECG & BP recorded), -N-13 NH3 & FDG PET using Siemens EXACT HR 961. -Echo with IV dobutamine infusion @ 5 increasing to 20 ug/kg/min -RWM assessed before & after revascularization using echocardiography. -33 patients CABG, 2 PCI.	Candidates for CABG Inclusion LVEF<50% Exclusion MI<3 months, unstable angina, LV aneurysm, inability to perform exercise test, L bundle block, previous CABG, congenital heart disease, cardiomyopathy Patient characteristics Mean age = 62+/-8 years Mean LVEF = 35+/-7% Males = 33/35 NYHA class >3 in 29% 91% had MI	Increase in wall motion score >1 on rest echocardiogram in > 2 adjacent segments	Interpretation of echo blinded to angiogram & clinical data PET & LDDE images analyzed in 16 segments. Relative FDG uptake as a % of segment with highest MBF Viability definition Resting Exercise EG: no Q wave or ST depression +/- angina (exercise ECG) PET: relative FDG uptake≥70% LDDE: ↑wall motion≥ 1 score or biphasic or sustained improvement under dobutamine stimulation	14 patients: improved regional wall motion; improved wall motion score index 1.7+/->0.2 to 1.6+/-0.2 (*P*<0.01) Global LVEF (34+/-6 to 36+/-7, *P* =0.24 Patients with no improved RWM, LVEF ↓ from 36+/-7 to 32+/-8% (*P*<0.01) & WM index ↓ from 1.8+/-0.2 to 1.9+/-0.2 (*P*<0.01) Sensitivity: FDG PET 100%, exercise ECG 93% vs. resting ECG 50% (P<0.02), LDDE 71% (*P*<0.01 vs. PET). Specificity: PET 67% vs. exercise testing 33% (*P*<0.02), LDDE 81%, resting ECG 71% Accuracy PET 80%; LDDE 77% Exercise testing 62% Resting ECG 58% (*P*<0.05vs. PET)	-Patient enrolment was not consecutive -echocardiography, one of the index test was used as the gold standard -May have included patients with only mild LV dysfunction. -

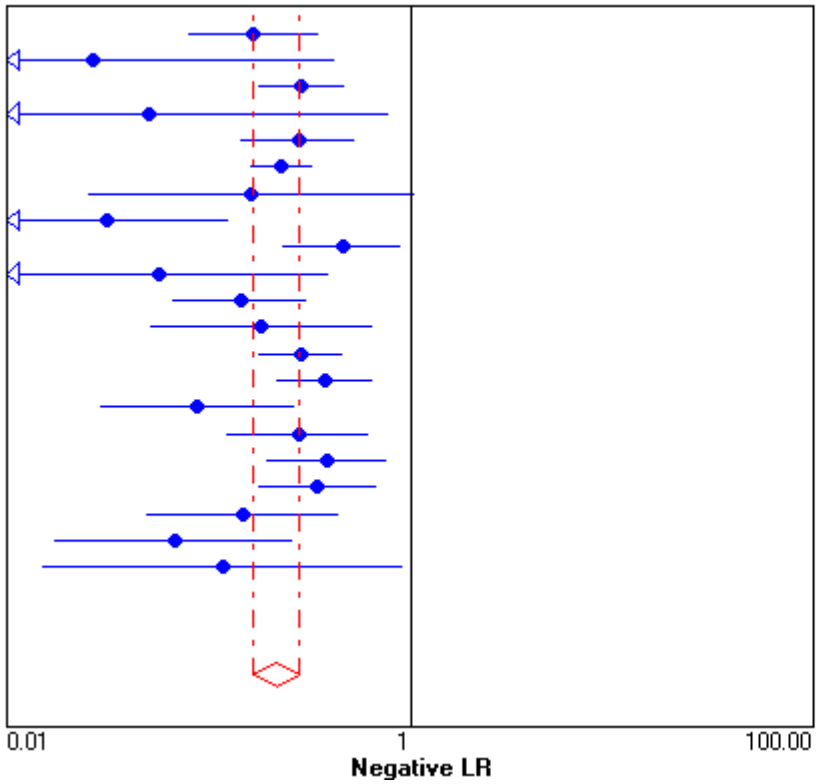
Appendix 8: Test for Heterogeneity of Positive Likelihood Ratios



	Positive LR (95% CI)
Tani 2001	2.30 (1.56 - 3.40)
Schmidt 2004	3.49 (1.59 - 7.65)
Wiggers 2003	3.40 (2.07 - 5.59)
Wiggers	2.84 (1.57 - 5.11)
Nowak 2003	2.84 (1.60 - 5.06)
Korosoglou 2004	1.60 (1.38 - 1.85)
Lund 2002	2.78 (1.50 - 5.14)
Pagano 1998	1.48 (1.32 - 1.67)
Gerber 1996	2.08 (0.97 - 4.44)
Baer 1996	3.08 (1.48 - 6.39)
Tamaki 1995	4.98 (3.06 - 8.09)
Maes 1997	9.17 (1.39 - 60.42)
Zhang 1999	4.66 (2.33 - 9.32)
Marwick 1992	2.98 (1.74 - 5.09)
Lucignani 1992	6.48 (1.79 - 23.43)
Tamaki 1989	3.60 (1.61 - 8.05)
Tamaki 1991	2.40 (1.24 - 4.65)
Groppler 1993	1.65 (1.26 - 2.16)
Paolini 1994	4.13 (1.50 - 11.36)
Tillisch 1986	4.73 (2.30 - 9.72)
Carrel	1.88 (0.84 - 4.23)

Random Effects Model
Pooled Positive LR = 2.75 (2.21 to 3.42)
Cochran-Q = 98.94; df = 20 (p = 0.0000)

Appendix 9: Test for Heterogeneity of Negative Likelihood Ratios



	Negative LR (95% CI)	
Tani 2001	0.17	(0.08 - 0.35)
Schmidt 2004	0.03	(0.00 - 0.42)
Wiggers 2003	0.29	(0.18 - 0.48)
Wiggers	0.05	(0.00 - 0.78)
Nowak 2003	0.28	(0.14 - 0.54)
Korosoglou 2004	0.23	(0.16 - 0.33)
Lund 2002	0.16	(0.03 - 1.06)
Pagano 1998	0.03	(0.01 - 0.13)
Gerber 1996	0.46	(0.23 - 0.91)
Baer 1996	0.06	(0.01 - 0.39)
Tamaki 1995	0.14	(0.07 - 0.31)
Maes 1997	0.18	(0.05 - 0.66)
Zhang 1999	0.29	(0.18 - 0.46)
Marwick 1992	0.38	(0.22 - 0.65)
Lucignani 1992	0.09	(0.03 - 0.27)
Tamaki 1989	0.28	(0.12 - 0.62)
Tamaki 1991	0.39	(0.19 - 0.77)
Groppler 1993	0.35	(0.18 - 0.68)
Paolini 1994	0.15	(0.05 - 0.44)
Tillisch 1986	0.07	(0.02 - 0.26)
Carrel	0.12	(0.01 - 0.93)

Random Effects Model
Pooled Negative LR = 0.22 (0.17 to 0.28)
Cochran-Q = 39.77; df = 20 (p = 0.0053)

Appendix 10: PET vs.Versus 99m-Tc Sestamibi Using 99mTc-Sestamibi in Predicting Segmental Functional Recovery –

Studies/ Year	Objective	Method	Selection / Spectrum/Patient characteristics	Reference Standard	Blinding/ PET analysis & Definition of viability	Results	Limitations
Kaltoft 2001 (61)	To determine diagnostic accuracy of semi quantitative rest 99m-Tc MIBI SPECT in detecting viable myocardium using FDG/NH3 PET as a reference standard	Prospective cohort study N= 54 (reported on 50) In random order within a median of 14 days: Perfusion & metabolic PET Dynamic perfusion imaging with Siemens/CTI 961 ECAT PET scanner &740 MBq N-13 ammonia. Static imaging with 370 MBq FDG after 50g oral glucose load. <u>99m-Tc Sestamibi SPECT</u> Using a single headed rotating gamma camera & high resolution collimator & 700 MBq+/-10% MIBI	Consecutive patients with severe ischemic cardiomyopathy referred for PET viability study Inclusion/exclusion criteria not stated Patient characteristics Mean age = 57+/-7 years Mean LVEF = 28.2% Mean number of diseased vessel = 2.5	PET mismatch	9 segment analysis for both PET & SPECT. - visual analysis using a 5 point scale (0=normal, 4=absent activity) -score based on activity in >50% of the segment area -SPECT activity in volume-weighted polar maps Viability definition: PET: Normal perfusion or mismatch (perfusion score >2 & FDG score <2) SPECT – defect size<50% of segment area or mean activity > 50% in >50% of segment area	313/440 dysfunctional segments viable, and 65 non viable by both technique. Segmental concordance of 86% -62 segments discordant. In comparison with PET 99m-Tc MIBI SPECT has: sensitivity 87% specificity 82% PPV 96% NPV 58%	No blinding stated for interpretation of PET or SPECT images -No specific inclusion or exclusion criteria (e.g. EF) provided -No mention of blinding in interpretation of PET or SPECT images. Might have image misalignment -No attenuation correction for SPECT -No follow-up of outcomes after revascularization

Appendix 11: PET Versus 99m Tc-Tetrofosmin SPECT

Studies/ Year	Objective	Method	Selection / Spectrum/Patient characteristics	Reference Standard	Blinding/ PET analysis & Definition of viability	Results	Limitations
Maruyama 2002 (59)	To assess the value of gated SPECT 99m Tc Tetrofosmin (TF) wall thickening in addition to TF exercise/rest myocardial SPECT in comparison with FDG PET in viability assessment	Prospective cohort N=33 (27 males) PET: Image acquired with SET-2400W (Headtome V) (Shimadzu Medical Co., Kyoto, Japan) & 370 MBq FDG after 75 g glucose load following overnight fast. SPECT exercise & rest gated SPECT with triple headed rotating gamma camera & 370 MBq 99m Tc Tetrofosmin	<u>Exclusion</u> Left bundle branch block Unstable angina MI </=4weeks before study <u>Patient Characteristics</u> Male = 27/33 Mean age = 62+/-8 years Mean number of diseased vessel = 1.8	FDG uptake on PET>50% of maximum count	Quantitative analysis of PET & SPECT using 24-segment polar maps SPECT Segmental Viability definition SPECT: Viable if TF activity >70% of maximum uptake or if TF activity ↑ by 10% from exercise to rest or % wall thickening >lower limit of the normal value	689/792 segments studied were PET viable. -Exercise/rest TF SPECT perfusion predicting PET viability Sensitivity 79% Specificity 70% -Exercise/rest TF SPECT with wall thickening from gating Sensitivity 85% Specificity 56% TF SPECT underestimates viability. Adding wall thickening improves sensitivity but decreases the specificity.	-Patient enrolment was not consecutive -Not clear how patients were referred No inclusion criteria provided -No blinding mentioned in the interpretation of PET & SPECT images -No attenuation correction for SPECT

Yoshinaga 2002 (60)	To determine whether low-dose dobutamine stress gated SPECT can provide additional info on myocardial viability over & above stress-rest tetrofosmin SPECT	Prospective cohort N= 23 (21 met criteria) FDG PET Siemens/CTI ECAT EXACT HR+ scanner with 555 MBq FDG after 50g oral glucose load. Hyperinsulinemic euglycemic clamp for glucose intolerant patients SPECT Stress perfusion SPECT using exercise or adenosine triphosphate &300 MBq Stress 9mTc tetrofosmin. Rest SPECT with 600 MBq TF. Dobutamine stress ECG gated SPECT Stress 99mTc tetrofosmin (300 MBq) with infusion of dobutamine @ 5 –7.5 ug/kg/min Rest 2-D Echo for wall motion before & after revascularization	Consecutive patients with previous MI assessed for viability Inclusion -Q-wave MI -Asynergy on resting echocardiography -normal sinus rhythm Exclusion LV aneurysm -unstable angina -MI<4 weeks Patient characteristics Males = 18/23 Mean age = 67+/-7.6 years Mean LVEF = 45.5 +/-13.4 % Mean number of diseased vessel = 1.8	Improvement in LV wall motion score ≥ 1 point on M-mode & 2-D echocardiography after revascularization	Blinding in interpreting wall motion on gated SPECT & echo. & echo images Quantitative assessment of PET, SPECT & echo images in 16 segments. -Gated SPECT-wall motion assessed visually & quantified on 4 point scale. TF uptake analyzed qualitatively using a 4 point scale Viability definition PET: mean segmental FDG uptake ≥ 50% of maximum uptake. Gated SPECT: Viable defined as hypokinetic areas with ≥1 point improvement in score	For detection of viable segments: Rest/stress SPECT alone Sensitivity 41% * Specificity 90% PPV 86% NPV 49% ** Concordance with FDG PET = 60% (kappa value =0.26) Combined stress/rest perfusion SPECT + LDSG SPECT Sensitivity 76%* Specificity 86% PPV 90% NPV 69%** Concordance with FDG PET 80% (kappa value =0.6) Better than rest/stress SPECT alone (*P,0.001, **P<0.05)	did not state how patients were referred -2 pts excluded ** 1 with severe diabetes & inadequate FDG uptake ** 1 unable to complete DSE because of paroxysmal atrial fibrillation -Echocardiography, one of the index tests used as the gold standard. -Mean EF of patients 45.5%, some patients had preserved global LV function despite abnormal RWM.

Giorgetti 2004 (62)	To determine accuracy of rest/post nitrate Tc-99m tetrofosmin SPECT in identifying viable tissue as compared with hybrid SPECT/PET approach	Prospective cohort N=23 (19 male) All patients underwent baseline ECG & echocardiogram and PET Imaging with Siemens/CTI ECAT HR+ scanner & 370 MBq FDG following a 50g oral glucose load after fasting -Oral glucose load 50g after fasting SPECT Rest 99m-Tc tetrofosmin gated SPECT (296-370 MBq) & repeat during nitrate infusion (740-888 MBq) Scanning with double headed gamma camera	Inclusion Previous MI LVEF<35% Exclusion Acute coronary artery syndrome, LV dysfunction from other etiology Patient characteristics Males = 19/23 Mean age = 62+/-10 years Mean LVEF =26+/-8% by G SPECT Mean number of diseased vessels = 2.2	Viability as defined by PET	-Software used for automatic quantitative analysis of RWM & wall thickening from 3-D gated SPECT. -20 segment polar map Viability Definition PET: normal perfusion & normal FDG or Mismatch (low<80% of maximum and %FDG activity/ % perfusion >1.2) SPECT: ↓ perfusion if <80% of max. uptake	64% of 460 segments dysfunctional by quantitative gated SPECT Resting 99m-Tc Tetrofosmin SPECT Sensitivity 48% Specificity 93% Global accuracy 67% Post nitrate SPECT Sensitivity 61% Specificity 88% Global accuracy 72% Rest/post nitrate mismatch Sensitivity 92% Specificity 95% Global accuracy 93%	-Small sample -No consecutive patient enrolment -No mention of blinding in interpreting images -PET instead of postrevascularization functional recovery or patient outcome used as gold standard. -No attenuation or scatter correction for SPECT scans
He 2003 (63)	To assess the relationship between tetrofosmin uptake after nitrate administration & metabolic activity as assessed by PET in patients with ischemic LV dysfunction	Prospective cohort N=36 All patients underwent: Echocardiography to evaluate LV function @ rest (wall motion scored 1 for normal to 3 for dyskinesia) Baseline & nitrate (isosorbide dinitrate) SPECT on separate days with 740 MBq 99m-Tc tetrofosmin performed with a rotating gamma Camera PET Imaging using a whole body scanner with EXACT 47 (Siemens Medical Systems, Enlargen, Germany) with 555MBq FDG 3 after a 50g glucose load	Consecutive Inclusion Documented CAD History of MI Regional or global dysfunction @ echocardiography Exclusion Unstable angina MI<8weeks Patient characteristics Mean age = 56 +/-11 years Mean LVEF = 35+/-6% Triple vessel disease =0 Double vessel disease = 28%	Viability as defined by PET	All images analyzed in 13 segments -Segmental tetrofosmin & FDG uptake expressed as a % of the activity in the region with the maximum TF activity. Viability definition tetrofosmin uptake ≥55% Segments with TF uptake <55% at base line and increase > 10% in peak activity after nitrate administration considered reversible defect. -On PET, viability defined as FDG uptake >50%	-13% of 468 segments were hypokinetic & 28% akinetic or dyskinetic. -Overall concordance between baseline SPECT & PET = 72% of 131 akinetic or dyskinetic segments (k of 0.35) -concordance between nitrate SPECT & PET =82% (k=0.53) - tetrofosmin SPECT for detecting PET defined viability Sensitivity 69% Specificity 86% After nitrate administration Sensitivity 81% (P<0.05 vs. baseline) Specificity 86% (NS) -On stepwise logistic regression analysis, tetrofosmin uptake ≥55% on SPECT after nitrate admin was a significant predictor of preserved metabolic activity on PET (x^2=0.38.10, P<0.001)	-small sample No patient with triple vessel disease -No blinding mentioned in interpretation of PET and SPECT images. -3 of 39 patients excluded from analysis because of inadequate FDG uptake PET instead of postrevascularization outcome used as the gold standard No attenuation correction for SPECT

Appendix 12: FDG SPECT in Detecting Viable Myocardium and Predicting Functional Improvement after Revascularization

Studies/ year	Objective	Method	Selection / Spectrum/Patient characteristics	Reference Standard	Blinding/ PET analysis & Definition of viability	Results	Limitations
Slart 2005 (66)	To compare dual isotope simultaneous acquisition (DISA) with 99m-Tc sestamibi/FDG SPECT and FDG PET in detecting viability in patients with CAD & LV dysfunction	Prospective cohort N= 58 All patients underwent DISA and PET on the same day: Dynamic N-13 ammonia PET (400 MBq), & 99m-Tc sestamibi SPECT (600 MBq) were performed during dipyridamole stress. FDG PET and FDG SPECT performed after injection of 400 MBq FDG. Insulin given as necessary. Dynamic PET acquisition on Siemens/CTI ECAT-951/31 system SPECT performed with Siemens MultiSPECT dual-headed camera with extra-high energy collimators. MRI performed to assess regional wall motion within 1 week	Inclusion: Chronic CAD & LV dysfunction Exclusion Unstable angina and/or heart failure requiring hospitalization Baseline Characteristics Males = 79% Mean age = 65+/-9 year Mean LVEF = 33+/-12% MI>3 months = 29% Contractile function assessed with MRI	Viability defined by FDG/N-15 NH3 PET	Blinding to PET results for MRI interpretations Quantitative analysis All nuclear imaging tests were analyzed quantitatively & displayed in a 17-segment polar map. Average counts per segment measured & normalized to the segment with the highest average counts. Viability definition Segment viable: perfusion>/=75% or perfusion<75% but FDG exceeded perfusion by at least 10% (mismatch) Visual analysis For DISA SPECT, segmental MIBI & FDG uptake also scored visually using a 4-grade scoring system form 1(normal uptake, 75–100%) to 4 (absent uptake, <25%) Viable when perfusion score=1 or FDG score>perfusion score. Nontransmural if perfusion defect (score 2 or 3) showed a matched pattern.	Quantitative analysis: -Good correlation between normalized N-13NH3 & 99m-Tc sestamibi (r=0.82, P<0.001) and between FDG PET & FDG SPECT (r=0.83; P<0.001). Agreement between DISA and FDG/NH3 PET for assessment of viability for all segments = 82% (k-statistic 0.59, 95% CI 0.53–0.64; SE 0.027) – no significant difference Discordant results in 49% of segments in basal anterior wall and 5% in mid-inferior wall. Agreement for dysfunctional segments only is 82%, k statistic of 0.63 (95% CI 0.56–0.70), no significant difference. Using visual analysis, agreement between DISA & PET was 83%, K statistic of 0.58 (95% CI 0.52–0.63) with no significant difference. There was no significant difference between quantitative and visual DISA SPECT analysis.	-no consecutive patients enrollment -2% of segments excluded from analysis because of uninterpretable PET results. -No follow-up on outcomes after revascularization -No attenuation correction for SPECT images

Studies/ year	Objective	Method	Selection / Spectrum/Patient characteristics	Reference Standard	Blinding/ PET analysis & Definition of viability	Results	Limitations
Bax 2001 (25)	To determine whether preoperative viability testing using FDG SPECT predicts postoperative improvement in LVEF & heart failure symptoms.	Prospective study N=47 FDG SPECT Imaging on same day as perfusion SPECT during hyperinsulinemic euglycemic clamping Perfusion SPECT Resting Thallium-201 (Or 99m-Tc tetrofosmin SPECT Resting echocardiography to evaluate RWM at base line and 3–6 months after CABG (mean 4.3+/-1.8 months) Radionuclide ventriculography To evaluate LVEF @ baseline & follow-up Assess change in NYHA functional class Mean interval between SPECT & CABG = 2.2+/-1.3 months	Patients with CAD & ischemic cardiomyopathy scheduled for CABG (CABG decision not based on viability results) Patient Characteristics Males = 85% Age (range) = 43–76 years Mean LVEF = 30%+/-6% Previous MI = 98% Average number of diseased vessel = 2.7+/-0.5	Increase in LVEF≥5% on radionuclide ventriculography after CABG	Blinding to SPECT results in interpretation of echo results. Perfusion & FDG SPECT images analyzed quantitatively with 13-segment polar maps. ROC analysis for optimal threshold. Segmental tracer uptake compared with normal databases. Perfusion defect: activity < normal minus 2 SDs Transmural match (tracer activity<60%) Criteria for viable segment Normal perfusion or Perfusion-FDG mismatch	Prevalence of viable segments =124/346 = 36% SPECT viable & improved RWM = 105/149 SPECT nonviable & improved RWM = 19/64 Sensitivity = 85% Specificity = 80% PPV = 70% NPV = 90% For predicting LVEF improvement: Sensitivity = 86% Specificity = 92% PPV = 90% NPV = 89% Multivariate analysis: no. of viable segment the only predictor of improvement in LVEF after CABG (optimal: ≥ 4 segments – also predicts improvement in NYHA score (PPV 76%, NPV 71%)	-Patient enrolment not consecutive -No confirmation of successful CABG 3–6 month follow-up might not have been adequate for improvement in function or heart failure symptoms. -Did not address long-term survival or cardiac events Only resting perfusion performed. Exercise induced ischemia not evaluated.

Studies/ year	Objective	Method	Selection / Spectrum/Patient characteristics	Reference Standard	Blinding/ PET analysis & Definition of viability	Results	Limitations
Bax 2003 (67)	To compare sequential strategy of dobutamine echocardiography & Tl-201 SPECT with FDG SPECT in predicting LV function improvement after CABG	Prospective cohort N=47 Before CABG patients underwent: echocardiography @ rest, Tl-201 rest SPECT on Siemens single-headed Rota camera Tl rest perfusion using 111 MBq Tl-201 DSE – low dose using 5 & 10 ug/kg/min FDG SPECT Performed with a triple head gamma camera with high energy collimator and 185 MBq FDG after admin of a nicotinic acid derivative. LVEF assessed with radionuclide ventriculography before & 6 months after CABG	Consecutive patients with ischemic cardiomyopathy scheduled for CABG based on clinical findings. Baseline Patient Characteristics Males = 91% Mean age = 58+/-7 years Mean LVEF = 30+/-8% Q-wave MI (> 3 months) = 62%	Improvement in LVEF > 5% on radionuclide ventriculography 6 months after CABG	Blinding – DSE interpretation Images analyzed in 16 segments Tl-201 SPECT: patient considered viable if >8 dysfunctional segments had >/=50% Tl-201 activity. Patients with<5 viable dysfunctional but viable segments considered non-viable. With 5–8 viable segments considered uncertain, referred for DSE (strategy 1). DSE: Patients considered viable if >4 dysfunctional segments had improvement during dobutamine stimulation. Patients with 2–4 viable segments were considered uncertain & were referred for Tl-201 (strategy 2) SPECT FDG SPECT: segment viable when FDG activity >/=50%, patients viable when there were >4 dysfunctional but viable segments.	LVEF improved from 30+/-8% to 34+/-9% (P =0.02) 40% had improved LVEF>5%-Patients with improved LVEF showed more viable segments on FDG SPECT (7.9+/-2.8 vs. 4.1+/-1.8, P<0.05) % % % Sen Spec accuracy DSE 63 * 89 79 Tl-201 95 57 ** 87 Strat 1 89 89 89 Strat 2 89 86 87 * [<0.05 vs. Tl-201, FDG SPECT & strategies 1 and 2 ** P<0.02 vs. DSE, FDG SPECT and Strategies 1 & 2 Sequential testing by Tl-201 SPECT and DSE has a comparable accuracy to FDG SPECT to predict improvement in LVEF after CABG.	-Patient enrolment was not consecutive -Only low-dose dobutamine echo and rest SPEC were performed which would not provide information on stress induced ischemia -No redistribution study on Tl-201 imaging -Possible misalignment of nuclear images & DSE images. -3–6 month follow-up might not have been sufficient.

Appendix 13: Summary of Studies PET Versus MRI

Studies/ year	Objective	Method	Selection / Spectrum/Patient characteristics	Reference Standard	Blinding/ PET analysis & Definition of viability	Results	Limitations
Klein 2002 (28)	To compare MRI hyperenhancement with PET for detection & quantification of myocardial scar tissue	Prospective cohort N=31 (26 males) <u>CeMRI</u> Consecutive cine short axis views acquired using 1.5 T scanner (ACS Phillips). Process repeated after bolus injection of 0.2mmol/kg gadolinium DTPA in end diastole. PET Imaging with Siemens/CTI ECAT EXACT or HR+ Perfusion PET using 740 MBq N-13 NH3 FDG PET with 370 MBq FDG. Patients Received glucose & insulin before & during imaging. -rest perfusion imaging with N-13 NH3 -FDG PET	Patients scheduled for a diagnostic PET study <u>Inclusion</u> CAD EF<35% assessed by echocardiography or contrast ventriculography <u>Exclusion</u> MI<6 weeks, unstable angina, contraindication for MRI, NYHA IV <u>Patient characteristics</u> Males = 26/31 Mean age = 59 +/-10 years LVEF = 28+/-9 % Had history of MI = 84% 87% had >1 diseased coronary vessel Mean end-diastolic volume 258+/-78 ml, end systolic vol 190+/-74 ml	Viability defined by PET Viable = normal blood flow with normal or ↑FDG uptake (normal) **or** ↓ blood flow with preserved or ↑ FDG uptake (mismatch)	Blinded interpretation of PET & MRI images using a 33 segment model. CeMRICeMRI - Area of hyperenhancement delineated manually & divided into transmural & subendocardial. LV mass, EF & regional wall thickness end-diastolic & end systolic calculated using software MRI Viability definition Nonviable (scar) = ↑ signal intensity 20 minutes after Gd-DTPA administration.	MRI compared to PET detecting pts with scar tissue Sensitivity 96% Specificity 100% detecting transmural defects Sensitivity 86% Specificity 94% detecting any defect Sensitivity 83% Specificity 88% MRI detected scar tissue in 11% of PET normal segments -5% PET non-viable showed no scar in MRI -Visual scar score: PET 44.3+/-9.1; MRI 47.6+/-11.1 (r=0.91 *P*<0.0001) MRI Relative infarct mass 19+/-16% correlates well with PET infarct size of 20+/-18% (r=0.81 slope 0.7, *P*<0.0001) Extent of scar tissue showed a weak inverse correlation with EF (r=.0.42 *P* =0.05) & end-diastolic & end systolic volume significant difference in wall thickening & wall thickness in PET viable segments compared to non-viable segments by PET	-Small sample Patient enrolment was not consecutive -No follow-up re wall motion improvement or patient outcomes after revascularization -Patients had a low incidence of hibernation. CeMRI needs to be studied in a population with high incidence of hibernation.

DPTA diethyenetriamine pentacetic acid

Studies/ year	Objective	Method	Selection / Spectrum/Patient characteristics	Reference Standard	Blinding/ PET analysis & Definition of viability	Results	Limitations
Kuhl 2003 (29)	To compare CeMRI with FDG PET for the detection of myocardial viability in patients with chronic ischemic heart disease & LV dysfunction	Prospective cohort N=26 (reported on 23) SPECT 99mTc tetrofosmin SPECT for assessment of rest blood flow PET 2-D dynamic imaging with Siemens/CTI ECAT EXACT HR+ scammer & 370 MBq FDG during hyperinsulinemic-euglycemic clamping. -images reconstructed with Hanning filter CeMRI ECG-gated cine MRI imaging using 1.5 tesla whole body scanner (Siemens, Erlangan, Germany). Process repeated after injection of Gadolinium based contrast @ a rate of 3 ml/second.	Consecutive patients with LV dysfunction scheduled for myocardial viability assessment Inclusion/exclusion criteria not stated Patient characteristics Mean age = 65 (range 41–81) Mean LVEF = 31+/-11% Had previous MI = 78% Multiple vessel disease = 17/31 patients	Viability defined by PET Viable defined as FDG≥50% & tetrofosmin≥50% **or** FDG≥50% & tetrofosmin≤50% Nonviable defined as matched reduction in FDG & tetrofosmin uptake	PET interpreted blinded to MRI results All images analyzed in a 17 segment model. MRI – scar tissue analyzed quantitatively MRI- wall motion assessed by visual interpretation using a scale of 1 (normal) to 5 (dyskinetic) -ROC analysis for accuracy of CeMRI & PET SPECT: normal perfusion tetrosfosmin uptake>/=50% Nonviable definition by MRI Hyperenhancement>/=3SD of signal of non-enhanced myocardium	99/391 segments - normal WM or mild dysfunction, 75% showed no hyperenhancement -30% (49/165)of segments nonviable, 98% showed enhancement in CeMRI -strong inverse correlation between FDG uptake & segmental extent of enhancement (SHE) (r=-0.86, *P*<0.001) -CeMRI predicting viability by FDG PET Area under ROC curve 0.95, 95% CI 0.93–0.97) -@ an optimal threshold of SHE </=37%, CeMRI had a sensitivity 96% & specificity 84% -96% concordance between FDG PET & CeMRICeMRI in segments with normal metabolism & perfusion or matched defect, complete agreement PET & MRI in 11/23 patients. Low correlation between FDG uptake & end-diastolic wall thickness or thickening	-Small sample -3 patients excluded due to scanning within 2 weeks of acute MI) -Possibility of image misalignment among when comparing techniques -CeMRI sequence susceptible to artifacts associated with patient movement or imperfect breath-holding. -PET instead of functional recovery or patient outcome after revascularization was used as a gold standard.

Studies/ year	Objective	Method	Selection / Spectrum/Patient characteristics	Reference Standard	Blinding/ PET analysis & Definition of viability	Results	Limitations
Knuesel 2003 (69)	Compare PET and contrast enhanced MRI in characterizing myocardium and subsequent functional outcome after revascularization in patients with chronic LV dysfunction	Prospective study N=19 MRI Using 1.5T system of GE Medical Systems 20 min after administration of 0.25 mmol/kg of contrast medium Gd-DTPA-BMA. PET Using whole body scanner (Advance, GE Medical Systems). Perfusion PET with 400–600 MBq N-13 ammonia. FDG PET using 250 MBq FDG. after 50g oral glucose load & blood sugar maintained <6mmol/L with insulin if necessary Revascularization: CABG in 8 patients PCI in 2 patients MR to determine segmental contractile function 9–12 months after revascularization	Patients with known CAD & hypokinetic or akinetic regions on echocardiography or LV angiography No inclusion or exclusion criteria provided Patient characteristics Males = 18/19 Mean age = 58+/-8 years Mean LVEF Revascularized group 41+/-10.9% No revascularized group 30+/-12.8% 3-vessel or left main disease = 63%	Segmental contractile recovery defined as systolic wall thickening >15% on MR 9–12 months after revascularization. (based on visual analysis)	Blinding not stated. Analysis of 7-8 slices each divided into 8 segments. MRI: automatic generation of total mass of viable & non viable tissues & mean thickness of viable rim. PET Viable segment defined >50% of FDG uptake relative to reference segment Mismatch = Relative FDG uptake per gm of tissue/blood flow ≥ 1.4	Before revascularization, among 1176 dysfunctional segments: MR & PET concordant = 87% PET & MR both viable: 77% (85% recovered function) PET & MR both nonviable 10% (87%did not recover function) After revascularization: 71% of all dysfunctional segments improved function. Of segments with improved function: 93% viable by PET & MR Of segments that did not improve function: 38% viable by PET & MR, 28% nonviable by both PET & MR. PET viable & MR nonviable segments: 64% did not recover function (28% scar content) PET nonviable & MR viable segments: 77% did not recover function. (41% scar content) P<0.01 & P<0.0001 compared to viable segments. Intra-observer variability for quantification of viable myocardium =-0.8+/-8.1% Interobserver variability = 2.0+/-6.8% Mean difference between manual & automatic analysis = 2.6+/-5.1%.	-Patient enrolment not consecutive -No mention of blinding in interpreting gold standard or index tests -MR, one of the index tests, was also used as the gold standard for assessing functional outcome -Success of revascularization was not confirmed.

Studies/ year	Objective	Method	Selection / Spectrum/Patient characteristics	Reference Standard	Blinding/ PET analysis & Definition of viability	Results	Limitations
Schmidt 2004 (27)	Determine value of dobutamine induced systolic wall thickening & preserved end-diastolic wall thickness (EDWT) by MRI compared to FDG PET glucose metabolism in Predicting functional improvement in chronically a- or dyskinetic infarct region after successful	Prospective cohort N=40 MRI Baseline rest MRI & MRI study after IV dobutamine @ 10 ug/kg/min with continuous ECG & BP monitoring Rest MRI 4–6 months after revascularization PET Imaging with (CTI ECAT EXACT 921 after 370 MBq injection of FDG 1 hour following oral 50g glucose load. 21/40 had CABG 19/40 PCI	Consecutive patients referred for assessment of myocardial viability, Inclusion documented history of previous MI and regional a- or dyskinesia by L Ventriculography & infarct related coronary artery>/=80% stenosis. Exclusion unstable angina, NYHA class IV, atrial fibrillation, history of sustained tachycardia or diabetes. Patient characteristics Males =37/40 Mean age = 57+/-9 years Mean LVEF = 42+/-10% Previous MI = 100% Mean number of diseased vessel = 2.1	Functional improvement in infarct region: systolic wall thickening ≥2mm in ≥50% of related segments measured by rest MRI 4–6 months after successful revascularization documented by angiography	Tomograms converted to a polar map MRI reviewed in cinematic mode. Segmental systolic wall thickening calculated (end systolic wall thickness – end-diastolic thickness) contraction reserve during dobutamine stimulation calculated. PET FDG uptake normalized to a myocardial reference segment with maximum uptake & perfusion by a coronary artery with</=70% diameter stenosis and have normal wall motion by ventriculogram. Viability definition *FDG PET* - Entire infarct region viable if FDG uptake >/=50% in >/= 50% of infarct related segments. *Dobutamine MRI*: Segment is viable if end-diastolic wall thickness >/=5.5cm or mean dobutamine induced systolic wall thickening >/=2mm. Entire region viable if >/=50% of the related segments fulfill 1 of the above viability criteria	80% pts had EDWT>/=5.5cm -Dobutamine contraction reserve in 65% pts -6pts had disagreement of the above -FDG viability in 73% of pts -97% of FDG viable pts had preserved EDWT & 86% had dobutamine induced SW thickening -Recovery of LV regional function in 63% of patients, all had preserved EDWT prior. 96% had dobutamine-induced contraction reserve in infarct region -FDG PET viability observed in all 25 pts with regional functional recovery -4 pts with FDG PET viability showed no functional improvement -FDG PET predictive PPV 86% NPV 100% Accuracy 90% dobutamine preserved contraction reserve MRI PPV 92% NPV 93% Accuracy 93% Preserved EDWT MRI PPV 786% NPV 100% Accuracy 83%	Small sample -No blinding in interpreting MRI or PET images -Dobutamine MRI imaging not real time, may have impact on sensitivity -MRI (one of the index tests) used to evaluate RWM improvement -Patients with diabetes excluded from the study Possible image misalignment resulting in discordance between MRI & PET

Appendix 14: Comparison of MRI and Thallium SPECT

Studies/ year	Objective	Method	Selection / Spectrum/Patient characteristics	Reference Standard	Blinding/ PET analysis & Definition of viability	Results	Limitations
Gutberlet 2005 (58)	To compare dobutamine stress MRI & delayed enhanced MRI with Tl-201 SPECT with respect to prediction of functional recovery 6 months after CABG.	Prospective N= 20 <u>Rest stress MRI</u> Stress with IV dobutamine (5–10 mg/kg body weight) Regional systolic wall thickness monitored with an ECG gated breath-hold balanced FFE cine-sequence. <u>Delayed enhancement MRI</u> echo sequence 10-20 minutes after IV administration of a double dose (0.2mmol/kg) of gadolinium-DPTA. <u>Gated Tl-201 SPECT</u> Rest imaging using a Siemens MultiSPECT 3-head gamma camera & a mean dose of 80 MBq of Tl-201. CABG within 1 seek of imaging MR & SPECT imaging repeated 6 months after CABG	<u>Inclusion</u> Triple vessel CAD LVEF<45% Need CABG <u>Exclusion</u> Contraindication to MRI <u>Patient characteristics</u> Males = 95% Mean age = 63.7+/-7.3 years Mean LVEF = 28.6% Previous MI = 50% (mean of 16 months before imaging)	(1) Viability defined by Tl-SPECT (2) RWM recovery after CABG	Blinded interpretation of all images using a 12-segment model. Rest & dobutamine stress MRI – qualitative analysis for wall motion Delayed enhancement MRI images analyzed quantitatively MRI viable: Akinetic or dyskinetic segment showed hypokinesia with a systolic wall thickening of $\geq$ 2 mm during low-dose dobutamine stress Area with signal >2 SD above mean = scar tissue. Non viable if extent of hyperenhancement>50%. Tl-201 images analyzed quantitatively by computer. Uptake normalized to area with maximum uptake. Tl-201 criteria Tl-201 defect at rest in >50% of area = nonviable	Based on gated Tl-201 SPECT MRI – delayed enhancement %Sen Spec PPV NPV DE MRI 93 39 83 65 MRI WT 94 36 82 65 MRI WMS 84 50 85 49 Based on regional wall motion recovery % Sen Spec PPV NPV DE MRI 99 94 99 94 MRI WT 96 35 90 57 MRI WMS 88 90 98 56 ^{201}Tl SPECT 86 68 94 44 DE-MRI had higher sensitivity, specificity, PPV and NPV than other techniques. Delayed enhancement on MRI did not differ significantly postoperatively. 66% were subendocardial Total area of scar tissue: mean = 21.7% Slight inverse correlation between total extent of delayed enhancement and postoperative EF (r-value = 0.46) And between thallium uptake and extent of DE (r-value = 0.64)	-Small sample size -Patient enrolment not consecutive -MRI, one of the index tests used as one of the reference standards.

Studies/ year	Objective	Method	Selection / Spectrum/Patient characteristics	Reference Standard	Blinding/ PET analysis & Definition of viability	Results	Limitations
Ansari 2004 (72)	Compare late enhancement MRI with thallium-201 rest resdistribution SPECT for the detection of viable myocardium	Prospective comparative study N=15 All patients underwent: -Contrast MRI after 0.1 mmol/kg Gd-DPTA injection Precontrast & post-contrast cine images were obtained - SPECT imaging @ rest & @ 4 hours after 3.5mCi thallium-201 injection using a triple headed gamma camera with low energy high resolution collimation.	Inclusion >21 years LV dysfunction EF<50% Documented MI Having rest-redistribution SPECT Exclusion Contraindication for MRI Pregnant Problems with iron metabolism/storage Unstable medical condition Patient characteristics Mean age 60 (9) yrs Males 100% Mean LVEF 35% (11) Prior revascularization 27%	Myocardial nonviability by thallium 201 SPECT	Interpretation of thallium blinded to MRI results MRI & SPECT images analyzed in 6 segments. SPECT: Definition of nonviable <50% of thallium uptake	Total # of segments =558 Of the nonviable segments by SPECT, 89% showed late enhancement on MRI. Of 469 segments viable by SPECT, 33% showed some nonviability on late enhancement MRI. 84% of segments that were nonviable on MRI were also nonviable by thallium SPECT There was a statistically significant correlation between thallium uptake & late % enhancement on MRI for all segments combined (r= -0.51, *P*<0.001) The strongest relationship occurred in the anterior (r= -0.69, P<0.0001) & anterior septal segments (r = -0.611, *P* = 0.0002), but weakest in the inferior and inferior-septal segments. .	-Small sample -some patients only had mild LV dysfunction Preselection bias -Using thallium-201 SPECT with low specificity as a gold standard -Did not validate whether the findings on MRI predicted LV function or clinical improvement after revascularization.

Appendix 15: PET Versus Endocardial Electromechanical Mapping

Studies/ year	Objective	Method	Selection / Spectrum/Patient characteristics	Reference Standard	Blinding/ PET analysis & Definition of viability	Results	Limitations
Koch 2001 (30)	To compare assessment of myocardial viability using endocardial mapping with results of FDG PET and with data on functional recovery on angiography (in 25 patients) after successful revascularization	Prospective cohort N=46 Biplane angiography immediately before mapping Electroanatomical mapping using NOGA (Biosense-Webster, Diamond Bar, CA) intraventricular mapping & navigation system. Unipolar signals @0.5 Hz to 400 Hz were recorded. SPECT on same day as PET after angiogram before mapping; injection of 10 mCi 99m-Tc sestamibi & imaged with a double headed gamma camera. PET image acquisition 30-45 min after 6-8 mCi FDG injection using an ECAT EXACT (CTI Siemens, Knoxville, Tennessee) PET scanner following 50g dextrose loading Revascularization immediately after mapping.	Inclusion Patients with History of MI>2 weeks, regional wall motion abnormality at rest, & clinical indication for a PCI Exclusion Not stated Patient characteristics Males = 32/46 Mean age = 59 +/-10 years Mean LVEF = 49 +/-15% Previous MI = 40/46 Mean number of diseased coronary vessel = 1.6	Viability defined by PET/SPECT Improvement in RWM by digital angiogram after revascularization	Mapping Color-coded maps of unipolar electrogram amplitudes reconstructed & analyzed in 12 regions; the mean values for the peak-to-peak amplitude of the unipolar electrogram were calculated for each region. Sestamibi and FDG uptake expressed as a percentage of the region with the maximal sestamibi uptake. - nuclear polar maps divided into 12 regions matching 12 regions of the electroanatomical regional polar maps. PET Viability definition: Normal perfusion = sestamibi uptake>70% Viable = sestamibi uptake<70% & FDG uptake≥50% Scar = sestamibi uptake & FDG uptake both <50%	-Unipolar electrogram amplitude: Compared to nuclear imaging: Normal perfusion 11.8+/-3.6 mV Perfusion/FDG mismatch 9.4+/-3.6 mV Scar by PET/SPECT 6.5+/-2.6 mV (*P*<0.001) for all. -At the optimal amplitude threshold of 7.5 mV, detecting viability defined by PET/SPECT Sensitivity 77% Specificity 75% AUC 0.92 (95% CI: 0.80 to 0.98) -For patients with regional unipolar electrogram amplitude >7.5mV, LVEF ↑from 52+/-16% to 62+/-13% (P =0.01) No change for <7.5mV -significant correlation between linear local shortening & RWM (r=0.61, *P*<0.001) Regional electrical function correlated closely with recovery of RWM Predicting improvement in RWM: Mapping sensitivity 91%, specificity 71% PET/SPECT Sensitivity 82%, specificity 86%	-Patient enrolment was not consecutive No blinding in the interpretation of PET, SPECT or mapping Images -Patients had mild LV dysfunction -Possible image misalignment among the techniques may affect the degree of concordance -Basal part of LV gave low endocardial amplitude because of fibrous nature. -3-4 week time lapse between PET & SPECT -electromechanical mapping results dependent on point density & training of the interventional cardiologist.

Appendix 15: PET Versus Endocardial Electromechanical Mapping (continued)

Studies/ year	Objective	Method	Selection / Spectrum/Patient characteristics	Reference Standard	Blinding/ PET analysis & Definition of viability	Results	Limitations
Keck 2002 (32)	To validate NOGA electromechanical viability parameters with combined FDG PET metabolic & SPECT perfusion imaging, & echocardiography	Prospective consecutive cohort N=51 Patient had nuclear imaging & echocardiography within 8 days before mapping. Electroanatomical mapping using NOGA 3-D navigation technology (Biosense-Webster) Perfusion SPECT stress perfusion SPECT using 500–600 MBq 99m-Tc tetrofosmin during exercise or dipyridamole. Rest SPECT on next day. FDG PET 31 patients with fixed SPECT defect underwent FDG PET (250 MBq) during insulin & glucose infusion (dose?)	Consecutive patients with proven CAD Exclusion criteria Not stated Patient characteristics Mean age = 61+/-9.7 Mean LVEF = 51+/-14% Previous MI = 82%	Viability defined by FDG PET/TF SPECT	Blinding: interpretation of Echo & SPECT results Analysis: All images analyzed in a 9 segment model Echo: RWM analyzed semiquantitative using a scoring system 1=normal 2=hypokinetic 3=akinetic 4=dyskinetic SPECT Semiquantitative 1=normal 2=perfusion deficit 3=perfusion defect a = reversible, b =partially reversible c = fixed PET: FDG uptake normalized to segment with highest perfusion uptake. Polar map scored visually 1=normal uptake 2=limited uptake 3-no uptake (nonviable)	Linear local shortening (LLS) of segments LLS higher for normal (9.2+/-5.1) or hypokinetic (6.6+/-5.0%) than dyskinetic (3.7+/-4.4%) segments) (P =0.0001) -LLS threshold of 9% defined normal contracting segment (sensitivity 90%) & LLS of 4% identified akinetic or dyskinetic with (specificity 85%) -Normally perfused segments had significantly higher unipolar voltage (11.2+/-5.0 mV) and LLS (8.2+/-5.0%), compared with fixed perfusion defects (UV of 6.3+/-3.0mV & LLS of 3.5+/-4.0%) (P =0.001) -Segments with fixed perfusion defect but were PET viable had a significantly higher unipolar voltage than scar tissue (7.25+/-2.7 mV vs. 5.0+/-3.1 mV, P =0.029) -A threshold of UV of 6 MV, LLS of 4% or FI fractionation index >1.5, each identified a fixed perfusion defect with a specificity of 90% A threshold of UV of 10 mV, LLS of 9% or FI<1.1 defined a normally perfused segment with a sensitivity of 90% A threshold of UV of 4.5 mV & FI of 1.5 identified truly non-viable myocardium	-mean LVEF 51%, some patients only had mild LV dysfunction -No follow-up on results after revascularization -Not all patients had PET 10/459 segment had no NOGA points 13/459 echo cannot be interpreted 436 segments analyzed Possible misalignment of segment in images Difficult to determine the borders of large defects on mapping Use of a fixed threshold might underestimate viability Accuracy of mapping in predicting functional recovery not examined.

Appendix 15: PET Versus Endocardial Electromechanical Mapping (continued)

Studies/ year	Objective	Method	Selection / Spectrum/Patient characteristics	Reference Standard	Blinding/ PET analysis & Definition of viability	Results	Limitations
Wiggers 2003 (47)	1) To compare the ability of electromechanical mapping and PET & SPECT to discriminate between myocardium with and without postrevascularization recovery of function in patients with severe heart failure (2) to identify the optimal threshold value of electromechanical mapping measurements for the prediction of postrevascularization myocardial function	Prospective cohort N=20 Patients underwent Electromechanical mapping using NOGA(Biosense-Webster, Haifa, Israel) at a median of 24 days before revisualization FDG PET(11 pts) or T99m-Tc sestamibi SPECT (9 pts) for viability assessment at a median of 54 days before revascularization Paired 3-D echocardiography (11) or MRI (9) to assess regional & global LV function echocardiography or MRI (9 pts) before & 6 months after revascularization FDG PET imaged with Siemens/CTI ECAT EXACT HR + whole body scanner after injection of 370 MBq FDG under a hyperinsulinemic, euglycemic clamp (5mmol/l) SPECT: imaged using a dual-headed rotating gamma camera & a high resolution collimator following injection of 700 MBq 99m-Tc sestamibi. 55% of patients had CABG 45% PCI Mean follow-up 184+/-69 days	Inclusion -significant CAD confirmed by coronary angiography -LVEF<40% Exclusion Peripheral vascular disease Aortic stenosis Unstable ischemic syndrome LV thrombus on echocardiography or MRI Patient characteristics Mean age = 60+/-16 years Mean LVEF = 29+/-6% Previous MI = 85% Mean number of diseased vessels = 2.4 (64% with triple vessel disease)	Improvement in regional LV function ↑ by >1 wall motion score after revascularization on MRI or 3-D echocardiogram 6 months after revascularization	Blinding: interpretation of wall motion blinded to viability data. Images analyzed in a 9 segment model FDG PET & SPECT normalized to region with maximal tracer uptake. -Postrevascularization wall motion graded as: (1) control regions with normal WM before revascularization (2) viable regions with RWM score increased ≥ 1 (3) irreversible dysfunctional region with no recovery @ follow-up	LVEF increased to 34+/-13% (<0.05 vs. baseline) -58/115 dysfunctional regions reversible (RDM), 57 irreversible (IDM) -RDM had statistically significantly higher UV A, normalized UVA and higher tracer uptake than IDM -NOGA local shortening (LLS) did not distinguish between RDM & IDM -BY ROC curve analysis, myocardial tracer uptake had better diagnostic performance than UVA (AUC 0.76+/-0.05 vs. 0.64+/-0.05, *P*<0.05) and better than normalized UVA (AUC 0.82+/-0.04 vs. 0.70+/-0.05, *P*<0.05) -For prediction of reversible dysfunctional myocardium: UVA Threshold (optimal) Sensitivity= specificity 8.4mV 59% 83% normalized, Tracer uptake 65% 69% 78% -Optimal cutoff value for distinguishing RDM and IDM FDG uptake of 68% -diagnostic performance of endocardial electromechanical mapping < PET & SPECT	-Small sample -Patient enrolment not consecutive Possible preselection criteria No attenuation correction for SPECT MRI, the test being studied, was also used as one of the gold standards. Two different techniques used to assess improvement in regional wall motion after revascularization

Appendix 15: PET Versus Endocardial Electromechanical Mapping (continued)

Studies/ year	Objective	Method	Selection / Spectrum/Patient characteristics	Reference Standard	Blinding/ PET analysis & Definition of viability	Results	Limitations
Botker 2001 (31)	To evaluate electromechanical mapping in detecting myocardial viability in patients with ischemic cardiomyopathy	Prospective observation N=31 Patients underwent: 3-D echocardiography to identify dysfunctional regions; PET - perfusion scan using 740 MBq N-13 NH3 and metabolic PET under hyperinsulinemic euglycemic clamp following an injection of 370 MBq FDG using ECAT EXACT HR whole body scanner (CTI/Siemens) Electromechanical mapping Under fluoroscopy guidance to measure the electrical activity and (unipolar voltage amplitude) & regional contractility on the endocardium	Inclusion Significant coronary artery obstruction LVEF<45% Exclusion Peripheral vascular disease Aortic stenosis Unstable ischemic syndrom Atrial fibrillation LV thrombus Patient characteristics Mean age 62 (8) yrs Males 27/31 Mean LVEF 30 (9)% 3 vessel disease 70% Previous MI 73%	FDG/NH3 PET PET nonviable: Dysfunctional and matched reduction of perfusion and metanolism (NH3<0.8 & FDG <0.7)	Images were analyzed in a 9-segment model. .	7 segments uninterpretable. 272 segments were compared. Normal & viable segments had higher voltage amplitude than dysfunctional and nonviable segments Optimal discriminatory threshold of normalized unipolar voltage amplitude = 68% of values in normal segments. @ this threshold sensitivity & specificity = 78% vs. 69% in nominal voltage values (@ optimal threshold of 6.5 mV. Between patient variability was mainly responsible for the large variability. Correlation between number of nonviable segments and average voltage amplitude (r=0.55, *P*<0.01) Viable PET had higher local shortening values than nonviable (5.6+/-3.9 3.2+/-3.8%) but considerable overlap	-preselection bias -Some patients only had mild LV dysfunction. -No validation of viability status by means of LV function or clinical outcome after revascularization.

Appendix 15: PET Versus Endocardial Electromechanical Mapping (continued)

Studies/ year	Objective	Method	Selection / Spectrum/Patient characteristics	Reference Standard	Blinding/ PET analysis & Definition of viability	Results	Limitations
Graf 2004 (74)	To investigate the relation between electrical properties of myocardial tissue as measured by electromechanical properties and images of myocardial perfusion (Tl201-SPECT) and glucose metabolism(FDG PET) for viability assessment.	Prospective consecutive cohort N=21 Patients under went: Diagnostic angiogram & contrast ventriculogram, Tl-201 rest perfusion SPECT & F-18 FDG PET before NOGA mapping FDG PET PET scan with high resolution, full ring PET camera (Advance, GE) after injection of 400–500 MBq FDG following a 75g oral glucose after ≥ 6 hr fasting -insulin injection to achieve & maintain blood glucose level at 140 mg/dL Tl-201 rest perfusion SPECT using a dual-detector gamma camera with a noncircular clockwise orbit after injection of 100 MBq Tl-201. Attenuation & scatter correction. NOGA mapping performed under fluoroscopic guidance to measure unipolar voltage amplitude (UVA) & local linear shortening (LLS).	Consecutive patients Inclusion -Angiographically proven sever CAD -Stable angina pectoris Exclusion -Unstable angina -MI≤3 weeks -LVEF<30% -Wall thickness <10mm in any part of LV -severe valvular disease -severe peripheral atherosclerotic disease Patient characteristics Males = 16/21 Mean age = 61+/-11 years Mean LVEF = 49+/-17% Previous MI = 62% Multivessel disease = 13/21	Viability defined by FDG PET/Thallium SPECT	All images analyzed in a 12 segment model. ROC curve analysis to identify optimal threshold -FDG & Tl uptake normalized to regions with maximal Tl201 uptake. Hypoperfused Tl-201 uptake<70% Viability definition Viable: Normal Tl-201 uptake>70% or -Perfusion /metabolism mismatch (Tl201 uptake<70%, FDG uptake >70%) -Perfusion /metabolism match (^{201}Tl uptake<70% FDG uptake>50% &< 70%) -nonviable (Tl-201<70%, FDG ≤50%)	UVA cannot distinguish between normal segments & hypoperfused segments with PET/perfusion mismatched (10.8+/-4.6mV vs. 9.3+/-3.4 mV) -UVA in normal segments >UVA in hypoperfused with P/M matched segments (10.8+/-4.6mV vs. 6.9+/-3.1mV, P =0.001) and > nonviable segments (10.8+/-4.6mV vs. 4.1+/-1.1mV, P =0.0001) -In hypoperfused segments, UV more closely related to metabolic activity than perfusion (UV vs. perfusion r=0.38, SEE 3.2, *P*<0.001) (FDG vs. UV r=0.6, SEE=2.8, *P*<0.0001) -Glucose metabolism related to UVA in hypoperfused segments with P/M mismatch (r=0.45, r2=0.21, SEE-3.1, *P*<0.05) -@ optimal UVA of 5.2mV, UVA sensitivity & specificity for detecting PET viable segment was 85%. -UAC was 0.9+/-0.04	-Results cannot be generalized to patients with EF<30% -No blinding in interpretation of tests. -Thallium performed at reset but no delayed thallium study was performed. -Use of polar maps might have resulted in misalignment among techniques leading to disagreement. -Basal portion of the septal & posterolateral segments difficult to evaluate in mapping. -No follow-up on functional recovery or patient outcomes after revascularization

Appendix 16: Summary of Studies – Improvement in Global Cardiac Function (Ejection Fraction)

Studies/ Year	Objective	Method	Selection / Spectrum/Patient characteristics	Reference Standard	Blinding/ PET analysis & Definition of viability	Results	Limitations
Bax 2002 (76)	To determine accuracy of PET indexes in predicting improvement in LVEF	Prospective cohort N=34 Before revascularization: -25 frame dynamic PET with O-15 water (inhaling O-15 CO_2) & Siemens ECAT scanner. -36 frame dynamic PET with 185 MBq FDG under euglycemic hyperinsulinemic clamp -RWM (qualitative 0–3) & LVEF by radionuclide ventriculography using 740MBq Tc- sodium pertechnetate -All had CABG independent of PET	Patients scheduled for CABG No inclusion or exclusion criteria provided. <u>Patient</u> characteristics Mean age 61+/-9 years Mean LVEF = 32+/-9% All had MI Mean number of diseased vessel = 2.2 No unstable angina or MI between PET & CABG	Improved global LV function defined as increased LVEF by >5% on radionuclide ventriculography 4 – 6 months after revascularization	Blinding to PET results in interpretation of RWM & LVEF 9 segment analysis MBF & MRG calculated -Relative glucose utilization =segmental metabolic rate of glucose (MRG) normalized to the median MRG of the remote normal segments -ROC analysis for optimal threshold Viability definition	-56% of 127 dysfunctional segments improved function. -<u>Optimal cut-off:</u> -3/9 LV segments (33% LV) with PTF >0.6gm/ml >6/9 segments with MBF>0.70 ml/min >3 segments with >0.25 umol/g/min MRG PTF: Sensitivity 80%, specificity 67% MBF: Sensitivity 80%, specificity 54% Absolute MRG: Sensitivity 90%, specificity 71% Relative MRG: Sensitivity 100%, specificity 71%	-Patient enrolment was not consecutive -No inclusion/exclusion criteria provided -Possible misalignment of PET & ventriculography images -Successful revascularization was not confirmed for all patients
Gerber 2001 (77)	To determine the accuracy of quantitative FDG PET in assessment of myocardial viability	Prospective European multicenter cohort study. N=178 Before revascularization: -multiframe dynamic emission PET scan with IV infusion of 10-15 mCi FDG under hyperinsulinemic euglycemic clamp -Global & RWM assessed with multiple gated angiography, contrast angiography, or 2-D echo Cardiography -72 CABG, 22 PCI. -Follow-up: 4-6 months	Patients with CAD who had FDG PET with functional follow-up. No specific selection inclusion/exclusion criteria <u>Patient characteristics</u> Males 92% Mean age 58+/-10 years (range 34–77) Mean LVEF 38 +/-14% Previous MI 81% Multivessel disease in 72% Significant difference among centres	Increase in LVEF >5% assessed by multiple gated angiography, contrast angiography, or 2-D echo-cardiography 2–6 months after revascularization	Blinding not mentioned. -PET images analyzed by 8 regions of interests - Absolute FDG & relative FDG uptake (compared to maximum value of remote normally contracting segment in each patient; 8-segment analysis; ROC analysis for optimal threshold	-Mean 4.1+/-1.9 dysfunctional segments - Glucose utilization in nonviable segments<viable segments (P < .001) -FDG PET sensitivity 79%, specificity 55% & accuracy 67% @ optimal threshold of >3 dysfunctional segments with a>45% normalized glucose uptake.	-Patient enrolment was not consecutive -No blinding in test interpretation -PET analysis performed locally by each co-investigator. -Diverse equipment used in PET study -Different gold standards used at different centres. -Significant differences in patients characteristics among centres

Appendix 16: Summary of Studies – Improvement in Global Cardiac Function (Ejection Fraction) (continued)

Studies/ Year	Objective	Method	Selection / Spectrum/Patient characteristics	Reference Standard	Blinding/ PET analysis & Definition of viability	Results	Limitations
Beanlands 2002 (79)	(1)To determine whether the extent of viable or scarred myocardium is important in the level of recovery of LV function in patients with severe CAD & severe LV dysfunction and (2) to develop a model for predicting the degree of recovery after revascularization	Prospective multicenter cohort study; N=82 Baseline resting perfusion PET with N-13 ammonia (300-370 MBq) or rubidium-82 (370-740 MBq) **or** perfusion SPECT using 99m-Tc sestamibi (740 MBq) FDG PET static imaging with Siemens ECAT ART whole body scanner & 75-370 MBq FDG in postprandial state after a 50-g oral glucose load. Insulin for people with impaired glucose tolerance Radionuclide angiography -ECG gated equilibrium blood pool imaging protocol, using Tc-99 labelled red blood cells for measuring ejection fraction. All patients revascularized, 71% within 6 weeks of FDG PET scan	Patients being scheduled for revascularization Inclusion CAD & severe LV dysfunction with LVEF</=35% Scheduled for revascularization Exclusion MI</=6weeks Severe valve disease requiring valve replacement Needing aneurysm resection Inability to obtain informed consent Patient characteristics Males = 89% Mean age 62+/-9 years Mean LVEF = 26+/-7% L main or 3-vessel disease = 70%	LVEF by Radionuclide angiography 3 months after revascularization	Blinding interpretation of all tests. Image analysis in 460 sectors. Sum of % of all sectors =raw perfusion score & raw FDG score. Sectors >/=80% of maximum perfusion = normal FDG uptake normalized to perfusion in the maximum zone sectors. Calculate sum of normalized FDG score Perfusion/metabolism mismatched score & scar score calculated as a % of the total LV myocardium	Change in EF=4.3+/-1.68% -Scar score (*P* =0.001) tracer (*P* =0.043), time to operation (within 6 weeks)(*P* =0.008) and diabetes (*P* =0.029) independently & significantly associated with absolute change in LVEF after adjustment for other factors. A multivariable model with absolute change in ejection fraction achieved a better goodness of fit 9P=0.001). Change in EF *Scar score 0%–16% (mean change in EF 9+/-1.9%) Scar score 16–27.5% (mean change in EF 3.7+/-1.6%) *Scar score 27.5–47% (mean change in EF 1.3+/-1.5%) **P* =0.002 -A 10-point incremental increase in the extent of scar would↓ the change in EF by 3.38% to 0.94+/-2.16%+/-0.94%. -A 10-point increase in mismatch using PET perfusion would ↑ the change in EF by 1.99% to 6.31+/-2.3%	-Patient enrolment was not consecutive -Generalizability limited to mostly males aged 53–73 years old with multivessel disease & vessels suitable for CABG. -Different techniques (PET and SPECT) used for perfusion study

Studies/ year	Objective	Method	Selection / Spectrum/Patient characteristics	Reference Standard	Blinding/ PET analysis & Definition of viability	Results	Limitations
Hausmann 2004 (73)	To analyze factors influencing functional improvement after CABG of hibernating myocardium in selected patients with end stage CAD.	Prospective observational N=41 All patients received low-dose dobutamine echocardiography, Dobutamine SPECT Dobutamine MRI Contrast enhanced MRI with gadolinium DTPA and when necessary PET Hibernating myocardium (area of interest) identified preoperatively. Wall motion analysis of LV performed in a segment model. All patients underwent CABG. Biopsies from the areas of interest were obtained intra-operatively. Dobutamine echocardiography, MRI and SPECT repeated 6 months after CABG. Mean length of follow-uP = 23+/-6 months.	Patients with LVEF<30% who underwent CABG. Patient characteristics Males = 39/41 Mean age = 63.6+/-9.9 years Mean LVEF = 26.0+/-7.7% History of MI with hospitalization = 78%	LVEF increase≥ 5% @ follow-up after revascularization	Blinding not mentioned Method of analysis not described Criteria for hibernating myocardium on echocardiography End-diastolic wall thickness =7–10 mm, Systolic wall thickness increase <20%, or hypo-akinesis.	All patients received complete revascularization 37/41 patients had 6 month follow-up after CABG Group I (n=23) increased LVEF≥ 5% Group II (n=14%) increase in LVEF<5% During dobutamine echo wall thickness increased a mean of 19.7+/-4.8% in Group I vs. a mean increase of 6.1+/-3.4% in group II (P<0.05) SPECT could not distinguish patients of groups I from II but hyperenhancement MRI could. Biopsy showed more severe myocardial cell hypertrophy and less severe destruction of cell architecture in biopsies of group I compared to group II> Gene expression of the pro-apoptotic genes BAK and BAX lowered compared to expression in normal myocardium & significantly more severe	Patient enrolment not consecutive Method of analyzing viability test results not described. Viability tests were not described

Appendix 17: Studies Assessing Clinical Improvement Following Revascularisation From 2001 ICES Review *(all but one* are C/D Grade)*

Study	Year	Main Outcome Measure(s)	Results	Methodological Criteria					
				Pts	Selection	Spectrum	Blinded	Revasc	Other
*Siebelink(41)	2001	13N/FDG-PET vs.. 99Tc-sestamibi SPECT	No difference between PET and SPECT in cardiac event-free survival (death, MI, revascularization) at 28+/-1 mos	103	RCT	LVEF ≤30% in only 35% of sample; NYHA-2.5	Yes	50% revascu-larized in each grp	Only Grade A study found.
Marwick (113)	1999	Functional capacity, QOL; Mortality; F/U 17 mos Compared PET to dobutamine echo.	All received PET, 47/63 also received dobutamine echo. Degree of improvement of exercise capacity correlated with the extent of viability by PET (r=0.54, *P*<0.001). In contrast, extent of viability by dobutamine echo did not correlate with improved exercise capacity. Multivariate analysis: Extent of viability by PET predicted improved exercise capacity and change in functional class, but not improved QOL. No deaths in cohort.	63	?Consecutive ?CABGs Pre-selection bias	Mean EF = 28%	No	63/63 CABG	Prospective; Many patients did not receive dobutamine echo; Incremental benefits unknown.
Pagano (53)	1998	Functional capacity, QOL; Mortality	Viability correlated with change in EF; No correlation between viability and functional capacity and QOL.	35	Pre-selection bias	Mean EF =23%	Yes	31/35 CABG	Prospective; Incremental benefits unknown.
Beanlands(114)	1998	Mortality 17+/- 7 mos	FDG-PET guided revascularization and triage: Early Revasc < 35d mean = 12 d (O% preop; 11% post-op mortality; LVEF from 24% to 29%) vs.. Late Revasc ≥35d mean = 145 d (24% preop; 7.8% post-op mortality, LVEF change not significant)	46	Pre-selection bias	All EF < 35% Mean EF = 26% majority had angina	No	35/46	Prospective; why 35 days chosen as cutoff between early and late revasc was unclear; Incremental effects of PET over usual waiting-lists unknown; Incremental benefits unknown.
Haas(115)	1997	Death; Mean F/U ~ 12 mos.	Viability studies permit selection of patients who are at low risk of serious periop complications. Compared 2 grps: *Grp A* with angina Sx and angio (no PET) vs.. *Grp B* with PET viability to supplement clinical and angio info (scar ≥40% meant no CABG); Listed baseline characteristics well matched; Grp A higher perioperative event rate (30d mortality = 11.4% vs. 0%, *P* =0.04) ; 30d to 1-	76	Consecutive 3-vessel disease and poor LV function referred for CABG	Mean EF =29%. No signif. difference between Grp A&B All EF <35%	No	100% CABG	Retrospective; Non-randomized; Incremental benefits unknown.

Study	Year	Main Outcome Measure(s)	Results	Methodological Criteria					
				Pts	Selection	Spectrum	Blinded	Revasc	Other
			yr mortality equivalent (2.9%)						
Soufer(75)	1995	Global LV function – incremental over MIBI-SPECT	71% Concordance Discordance: + PET/ - SPECT 36% to 48%, (*P*<0.001) - PET/+ SPECT 39% to 40%, (*P* = ns)	37	Pre-selection bias	Mean EF = 44%	LVEF blinded	13 CABG	Prospective
Di Carli (84)	1995	Functional status	Extent of PET mismatch correlated linearly with % improvement in functional status (r=0.87, *P*<0.001); Multivariate analysis: Extent of PET mismatch and age predicted improvement in functional status	41	Consecutive referrals for PET and CABG; Preselection bias	Mean EF = 28%	Yes	36/41 CABG	Prospective; No assessment of regional or global EF change; Incremental benefits unknown.
Di Carli (82)	1994	Mortality; mean follow-up 13.6 months	Overall mortality = 15%; Multivariate analysis: predictors of survival were less extensive mismatch (*P* =0.02) Less revascularization (*P* =0.04); Among Medical Rx only (n=50), ROC = 5% cut-off for extent of mismatch: If mismatch>5% of myocardium, annual survival=55%; if mismatch ≤5%, annual survival was 92%. Among revascularized, extent of mismatch also predictive of survival. Medical vs.. Revascularization: Survival = if no mismatch	93	Consecutive referrals for PET at UCLA Pre-selection bias	Mean EF =25% 68% NYHA III-IV	No	43/93	Retrospective; Incremental benefits unknown.
Lee (85)	1994	Non-fatal ischemic events; Death 17+/- 9 mos.	Medical Rx FDG+ = 48% vs.. Revasc Rx FDG+ = 8% (*P*< 0.001) vs.. Revasc Rx FDG- = 5%; Cox: FDG+ No Revasc predicted non-fatal; age + LV dysfunction predicted death	137	Preselection bias	Majority with angina; only 19% with CHF Sx;	No	50%; decision clinical	Retrospective; Incremental benefits unknown.
Eitzman(83)	1992	MI, death, cardiac arrest	Medical Rx FDG+ = 50% vs.. Revasc Rx FDG+ = 11% vs.. No Revasc FDG- = 12.5% vs.. Revasc Rx FDG- = 7.1%, (*P* < 0.01)	82	Preselection bias	Mean EF =34%	Yes	40/82	Retrospective; Incremental benefits unknown.

Legend: angio refers to coronary angiography; CABG=heart bypass surgery; CAD=coronary artery disease; d=days; EF=ejection fraction; F/U=follow up; Incremental benefits unknown= Incremental benefits of PET over other imaging modalities were unknown; LV=left ventricle; mos=months; NYHA=New York Heart Association Class; QOL=quality of life; Rx=treatment; Revasc=Revascularized; ROC=receiver operating characteristics; Rx=Treatment; Sx=symptom(s); *only 'A' Grade study

Appendix 18: Prognostic Value of PET on Long-Term Outcomes (Survival and Cardiac Events) After Revascularization

Meta-analysis	Objective	Studies Included	Method of Analysis	Outcome Measures	Results	Limitations
Allman 2002 (89)	Meta-analysis to examine event free late survival with revascularization versus medical therapy after myocardial viability testing	24 viability studies (observational) n=3,088 patients with severe CAD & LV dysfunction Mean age 61 years Mean LVEF 32+/-8% Mean NYHA functional class 2.8 Mean follow0up 25+/-10 months Number of viability studies included (1966-Aug. 1999): FDG PET 11 Tl-201 SPECT 6 Echocardiography 7	Meta-analysis of mortality rates by viability status & treatment modality using a randoms effect model. Weighted average % decrease in mortality rate & 95% CI were calculated. Meta-regression to assess risk-adjusted relationship between severity of LV dysfunction, presence of viability, revascularization & survival benefits.	Annual reduction in mortality rate	Annual Mortality rate: viable: revascularized 3.2% vs. medical 16% (79.6% reduction, x^2=147, <0.0001) Non-viable: revascularized 7.7% vs. medical 6.2% (not significant) Inverse relationship between LVEF and reduction in mortality with revascularization in patients with viable myocardium, not in nonviable. - Reduction in annual mortality rate PET viable after revascularization = 42.8% (95% CI 2.6% - 98.7%), no significant difference from ^{201}Tl or echocardiography	-Observational studies Heterogeneity in patients, protocol, imaging technique, equipment, & criteria for viability. Some studies were not designed to answer the viability/treatment interaction No information on medical therapy used. .
Bourque 2003	Systematic review To examine the effect of nuclear viability imaging on treatment strategies & long-term mortality of patients with cardiomyopathy & significant epicardial CAD.	14 studies (1992 – 2001) on long-term mortality after viability study & revascularization 9 studies prospective, 5 retrospective n = 1,192 patients Mean LVEF = 24%–40% NYHA functional class III– Reduction in annual mortality rate = 42.8% (95% CI 2.6% - 98.7%) = 19%–100% Viability by FDG PET alone or with perfusion (4), Tl-201 S/R or RR (8), Tc-labeled tracer (2) Treatment: revascularization (CABG or PCI), or medical therapy Median follow-up = 26 months (12–46 months)	-Quality assessment using criteria for prognostic studies -Descriptive synthesis Cox proportional – hazards analysis	Mortality rate at follow-up	In general, Cox proportional-hazards analysis revealed viability to be a significant predictor of survival in 10 of 12 studies. The other common significant model survival covariates were revascularization (5/12 studies), age (4/12), LVEF (3/12),	-Some studies included patients with LVEF >50% Heterogeneity: degree of LV dysfunction, viability assessment techniques & criteria for viability. -No separate analysis for studies that used PET for viability assessment -Only 3/14 studies adjusted survival curves for significant covariate -Low event rate (4–37) -Some studies had inadequate follow-up (e.g. 12 months) Inclusion of studies not designed to answer viability/treatment interaction

MBF myocardial blood flow; MRG metabolic rate of glucose; PTF water perfusable tissue fraction; FDG F-18 fluoro-deoxyglucose; CABG coronary artery bypass graft

Appendix 18: Prognostic Value of PET on Long-Term Outcomes after Revascularization (continued)

Meta-analysis	Objective	Studies Included	Method of Analysis	Outcome Measures	Results	Limitations
Di Carli 2002 (90)	Meta-analysis to evaluate the risk of cardiac events in patients with hibernating myocardium treated medically compared with those undergoing revascularization	9 studies (1992-2001), Total n=634 N of individual studies = 42–203 Patients with CAD and moderate to severe LV dysfunction. Most with a history of MI and multivessel CAD Mean LVEF = 22–40% Viability assessment by PET (4), dobutamine echo (3), or SPECT (2) Patients had revascularization or medical therapy based on clinical grounds Survival & cardiovascular events (MI, unstable angina, ventricular arrhythmia & hospital re-admission) were evaluated during a mean follow-up of 12–33 months	Meta-analysis of odds ratio and 95% CI of cardiovascular events for patients treated with revascularization compared with medical therapy.	Cardiac events @ follow-up	The odds ratio for cardiac events occurring in people with hibernation after revascularization were $\leq$ 0.25 compared with those treated with medical therapy. Successful revascularization of patients with viable myocardium is often followed by a significant alleviation of anginal pain and in some patients, heart failure symptoms. DiCarlie repeated the meta-analysis with only the studies with PET viability assessment and found odds ratio for postrevascularization cardiac events for people with hibernating myocardium were consistently less than 0.25 compared to patients with hibernation and treated with medical therapy alone.	-Lack of details on the studies included -Heterogeneity among studies Studies may not be designed to measure long-term cardiac events.

Appendix 18: Prognostic Value of PET on Long-Term Outcomes (Survival and Cardiac Events) after Revascularization (continued)

Studies	Objective	Method	Selection/Spectrum/ Patient Characteristics	Reference Standard/Outcome measures	Image analysis / Definition of Viability	Results	Limitations
Zhang 2001 (80)	To determine whether myocardial viability by FDG PET & ^{99m}-Tc MIBI predict clinical outcomes of patients with previous MI & LV dysfunction & whether revascularization improve LV function in patients with viability	Prospective cohort N=123 consecutive FDG PET Scanning with Chinese PET-B03 using 296–370MBq FDG by IV with blood glucose maintained @ 120-160mg/dL using oral glucose & insulin injection as necessary (after 13 hour fast) SPECT Perfusion imaging with Siemens multi-SPECT 3 scanner & 740–925 MBq ^{99m}-Tc-MIBI by IV. 2-D Echo for LVEF and LV end-diastolic diameter (EDD) @ baseline & 3 & 6 month follow-up Treatment decision by referring MD (no randomization) 54% had revascularization (9 PTCA & 58 CABG) 45% had medical therapy Mean follow-up of 26+/-10 months	Consecutive patients Inclusion Previous MI, rest LVEF </=45%. Exclusion MI <8 weeks, unstable angina, cardiomyopathy, valvular disease, previous CABG or PTCA Patient characteristics Males = 114/123 Mean age =56 +/-9 years Mean LVEF = 35+/-6% Previous MI 100% Multivessel disease 88.6%	Cardiac events (cardiac death, acute MI, unstable angina, late revascularization (>3months))	Coronary angiograms interpreted blinded to clinical data. Visual analysis of PET & SPECT images by 9 segments, blinded to clinical data using a 4-point scoring system. Viability definition >2 segments with perfusion-metabolism mismatch indicates myocardial viability	Viable/ revascularized (A1) =42; Viable/medical therapy (A2) = 30 Nonviable/revascularized (B1) =25 Nonviable/medical therapy (B2)=26 A1: LVEF 36+/-5% to 44+/-8% (P<0.0001) 3 months, EDD decreased in A1 -No significant change in LVEF & EDD in B1 Viable (A) Rate of cardiac events Viable: revascularized 2.4% vs. medical treatment 50% (x^2=23.08; P<0.0001) Non viable: revascularized 12% vs. medical treated 11% (No statistical difference) Cardiac mortality rate Viable: revascularized 0% vs. medical therapy 26.7% (x^2 >8.94, P =0.003) Number of mismatch segments, CCS angina class & NYHA class were independent predictors for cardiac events	-Included patients with LV aneurysm -Patients included were had only mild to moderate LV dysfunction -No randomization -No information on medical therapy - Not sure on what basis were treatment decisions made.

LDD echo refers to low-dose dobutamine echocardiography; SPECT Single photon emission computerized tomography

Studies	Objective	Method	Selection/Spectrum/ Patient Characteristics	Reference Standard/Outcome measures	Image analysis / Definition of Viability	Results	Limitations
Santana 2004 (86)	To determine the incremental value of ECG Gated PET in viability assessment compared to FDG uptake alone.	Prospective study, n = 90 All patients had gated FDG PET and perfusion PET with Rb-82. Parameters measured: metabolism & perfusion, wall motion, end-diastolic & end systolic volume, LVEF 31/90 patients had CABG -Gated PET imaging with Siemens ECAT EXACT 921 scanner with 370 MBq FDG after a 50g oral glucose load. PET perfusion scan with 1,300–1,850 MBq Rb-82. Excluded 47 from original 137 27 Imaging issues 20 LVEF>40%	Consecutive patients with severe ischemic cardiomyopathy who underwent ECG gated FDG PET and rest perfusion PET. <u>Inclusion</u> LVEF<40% No other inclusion or exclusion <u>Patient Characteristics</u> Mean age = 62+/-10 years Mean LVEF 26+/-7% Previous MI = 100%	Composite outcome of cardiac death, MI or worsening of heart failure to NYHA class IV @ a mean follow-up of 22+/-14 months Based on medical records and interviews (Blinding)	All images analyzed as normal, match, or mismatch Criteria for mismatch: >3/20 segments had moderately reduced uptake of Rb-82 and FDG uptake >Rb-82 within the same area.	-PET mismatch in 42% of patients -In a risk stratified Cox model, LVEF & remodeling end-diastolic volume (EDV) had incremental prognostic value over perfusion-metabolism mismatch on PET. -2-year event-free survival rate was considerably higher for patients with relatively preserved LVEF & heart sized than those with severely reduced LVEF (LVEF<25%) and advanced cardiac remodeling (EDV$\geq$260ml) -There is interaction between mismatch, LVEF and EDV. Patients with mismatch, LVEF<25% & EDV$\geq$260ml had the lowest event-free survival rate. -Coronary revascularization in patients with residual viability but advanced cardiac remodeling may result in improvement in survival rates (survival benefits of 11%) but this was not associated with consistent improvement in heart failure symptoms (70% with unchanged or worsening symptoms).	-Sample size not sufficient to detect differences in categorical assessment of mismatch subsets -Only 31 patients were revascularized. -Revascularization nonrandomized -Estimation of LV mass did not account for thinned-out scar tissue. No clear exclusion criteria.

Studies	Objective	Method	Selection/Spectrum/ Patient Characteristics	Reference Standard/ Outcome measures	Image analysis / Definition of Viability	Results	Limitations
Sawada, 2005 (87)	To investigate the value of perfusion-metabolism imaging for prediction of long-term prognosis in patients with diabetes and LV dysfunction	Prospective Observational N= 61 PET imaging with Siemens 951/31 R 31 slice tomography fasting with no diabetes medication. Perfusion PET With 20 mCi NH3 FDG PET With 10 mCi FDG with blood glucose maintained 120mg/dL with administration of glucose or insulin as necessary. Followed-up every 6 months. End point –cardiac deaths determined through interview and chart review at a mean follow-up of 4.3 years.	Eligibility Patients with diabetes & ischemic LV dysfunction and underwent PET Exclusion criteria not stated. <u>Patient characteristics</u> Males = 51/61 Mean age = 58+/-9 years Mean LVEF = 29+/-11% Required insulin = 46% Three vessel disease = 78% No significant difference in age, severity of CHF, EF, & extent of CAD between patients that had revascularization & those that had medical therapy.	Primary outcome is cardiac death defined as death due to heart failure, MI, or sudden death within 1 hour of symptoms without an obvious noncardiac cause.	No blinding stated. Circumferential profiles of NH3 & FDG intake analyzed in 16 regions of interest & compared to uptake of normals in database. Decreased tracer uptake defined as at least 2 SDs below normal. <u>Perfusion-metabolism mismatch</u> defined as FDG-NH3 difference>2 SD above the mean FDG-NH3 difference of the normal database.	72% of patients had perfusion-metabolism mismatch 33/61 had revascularization (82% CABG) 28/61 medical therapy. For revascularized patients, no significant clinical or imaging predictors of cardiac death. <u>Patients on Medical Therapy</u> Advanced CHF (class III/IV, *P* =0.026) & a large extent of LV mismatch (<u>≥</u>3%) predicted cardiac death (*P* =0.021). Mismatch was sole independent predictor in multivariate analysis. LV mismatch>3% found in 89% of cases of cardiac death compared with 18% of survivors. Long-term survival was significantly better among patients who received medical therapy and had no significant mismatch compared with those who had mismatch <u>≥</u> 3% (*P* =0.007) <u>For patients with LV mismatch>3%</u> Survival was better in the revascularized group than the medical group both at 4 years (*P* =0.0027) & at 8 years (0.012) The improvement in 8-year survival was observed in patients with EF<30% but not in patients with EF>30%. Patients with perfusion defect<u>≥</u> 25% had improved 4-year survival with revascularization (*P* =0.02).	Enrolment – not consecutive -No exclusion criteria stated. -Interpretation of images not blinded to clinical data. -Of the original 63 patients assessed with PET, 2 had uninterpretable PET images

Appendix 19: Summary of Studies on Prognostic Value of Dobutamine Echocardiography and Thallium-201 Imaging on Long-Term Outcomes

Studies/ year	Objective	Method	Selection / Spectrum/Patient characteristics	Reference Standard	Blinding/ PET analysis & Definition of viability	Results	Limitations
Meluzin 2003 (92)	To compare long-term results in patients with chronic CAD & viability defined by low-dose dobutamine echocardiography & treated with revascularization, transplant or medical therapy	N=130 Coronary angiography 1 week before LDDE Echocardiography at rest & under dobutamine stimulation @ 5 & 10 tg/kg/min. Images analyzed off-line. Standard echocardiography performed 3–6 months (mean 4+/-1 month) after revascularization. 66 pts had revascularization (54 CABG, 8 PCI)), 13 had heart transplantation and 51 received medical therapy. Clinical decision on treatment was based on clinical criteria (angina) & results of coronary angiography. For patients with symptoms of heart failure but no angina, result of dobutamine echo was taken into account (18% of patients)	Consecutive patients. Inclusion Criteria LVEF $\leq$30% Diameter stenosis$\geq$ 50% in >1 major coronary artery No MI or unstable angina within 6 weeks Able to evaluate RWM of all 16 myocardial segments with echo No cardiac disease except CAD No need for aneurymectomy Patient characteristics Mean age Mean age = 57+/-9 years Mean LVEF 25+/-4% History of MI = 94%	Cardiac & all cause mortality, non-fatal cardiac events (MI, unstable angina, hospitalization for HF)	Blinded interpretation of dobutamine echocardiograms Regional wall thickening assessed visually using a 16 segment model & a 4-point scale (1-normal, 4=dyskinetic) Patient defined as having viable myocardium if $\geq$ 2 adjacent segments that show functional improvement $\geq$ 1 grade. Interobserver concordance 93% for scoring segments 92% for contractile reserve Intra-observer concordance Wall motion score 96% Contractile reserve 95%	71 patients had dysfunctional but viable myocardium. 39 pts revascularized 29 on medical therapy 3 received transplant 45 pts deemed nonviable (23 revascularized & 22 on medical therapy) Kaplan Meier survival analysis: patients had comparable survival @ 1 year, the 3 year (89% vs. 60%, P<0.05)& 5 year-survival (89% vs. 50%) was significantly better for patients with viable myocardium treated with revascularization than medical therapy No significant difference in survival free of cardiac events.	-Decision on the treatment of some patients based on dobutamine echocardiography results -High-dose dobutamine stimulation was not used and did not have information on stress-induced ischemia. -Successful revascularization was not confirmed

Studies/ year	Objective	Method	Selection / Spectrum/Patient characteristics	Reference Standard	Blinding/ PET analysis & Definition of viability	Results	Limitations
Sicari 2003 (93)	Assess the prognostic value of myocardial viability recognized as a contractile response to low-dose dobutamine stimulation.	Prospective multicenter observational study N= 425 2-D echo at rest and in combination with 5 then 10 ug/kg/min of dobutamine. Revascularization by CABG or PCI Follow-up data @ a median of 3.1 years Decision of treatment made by referring MD based on clinical information. Results of stress echo available to MD. 188 revascularized (118 CABG, 70 PCI) 237 medically treated.	Consecutive patients who met the following criteria CAD >75% stenosis in >1 major coronary artery Chronic ischemic disease MI>3months LVEF<35%on 2-D echo 13/16 segments can be visualized on LDDE	Primary end points: cardiac death	Peripheral reading of echocardiograms from quality controlled centres. Wall motion score index on a scale of 1 (normal) to 4 (dyskinetic) Viability defined as a rest-stress variation in wall motion score index $\geq$0.4	In the revascularized group, patients with viability had less cardiac death than those without viability (7.7% vs. 27.2%, P<0.003) At 3-years, Kaplan Meier survival for revascularized patients was 90.1% for those with viability vs. 62% for those without viability (P< .0078) Viable: cardiac death 7.7% for revascularized vs. 36% for medical therapy P<0.002) Independent predictors of survival were presence of viability (x^2 =8.3, hazard ratio 0.2, 95% confidence interval 0.07–0.6, P<0.0039) & EF	-Nonrandomized

Studies	Objective	Method	Selection/Spectrum/ Patient Characteristics	Outcome measures	Image analysis / Definition of Viability	Results	Limitations
Sawada 2003 (94)	To assess the incremental prognostic value of myocardial viability in CABG patients with LV dysfunction using dobutamine echocardiography	Prospective observational N=95 All patients had: Dobutamine echocardiography @ 5, 10 & 50 ug/kg/min CABG Follow-up obtained for all patients: 72 prospective follow-up 23 retrospective follow-up Univariate and multivariate analysis performed. Mean follow-up 4.9 (2.9) yrs Analysis based on 93 patients (2 died perioperatively)	Included -Patients with> 4 dysfunctional segments -Had dobutamine echocardiography -Had CABG within 5 months of the test Excluded MI</= 1 week Incomplete D echo imaging Ischemic events before CABG Patient Characteristics Mean age 60 (9) yrs Mean EF 33% (10) Males 77% Akinetic myocardium 24% >Class III CHF 33%	Cardiac death defined as death due to CHF, MI, ventricular arrhythmia, or sudden death within 1 hour of onset without an obvious non-cardiac cause.	Blinded ejection measurement & interpretation of D. Echo images Definition of Viable Segment-improvement in wall motion score from rest to low dose of >/=0.2 Patient-contractile reserve in at least 25% of V myocardium Interobserver agreement (blinded & clinical observers) = 95% (correlation coefficient 0.94 for resting score and 0.87 for low dose score.)	43% of patients had worsening CHG & 32% worsening angina Cardiac death = 38% (36/95) Non cardiac death = 10/95 -low dose wall motion (LDWM) score reflecting extent of viable myocardium was the best predictor of 5-year outcomes (multivariate analysis. (*P*<0.001) Hazard ratio of 6.7 (2.8–15.8) Cardiac deaths LDWM score<2 24% LDWM score 2.0–2.49 48% LDWM score >2.5 82% (Annual cardiac mortality 21%) At 5 years, better survival for group with best LD wall motion score (<2) (*P* =0.019) -Biphasic response was also an independent predictor of survival (*P* =0.045), hazard ratio 0.5 (0.2–0.99) - other predictors of short term outcomes (measure of contractile reserve) did not predict long-tem outcome - LDWM score added incremental value to clinical variables (*P* =0.003) And to clinical variables + resting WM score (*P* =0.024) -ROC curve analysis showed optimal threshold value of low dose WM score for predicting cardiac death = 1.95. -The presence & extent of stress-induced ischemia did not add prognostic value. -CABG in patients with very limited viability was associated with very poor prognosis.	Highly select patient population (preselection bias) -Only applicable to patients with severe LV dysfunction & CABG -Fewer patients might have been on ACE inhibitors according to current standards ACE was associated with higher cardiac deaths -Successful revascularization was not confirmed with angiography.

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