*Canadian Agency for Drugs and Technologies in Health*

*Agence canadienne des médicaments et des technologies de la santé*

# Rapid Response Report:

## Peer-Reviewed Summary with Critical Appraisal

**CADTH**

# Positron Emission Tomography for Cardiovascular Disease: A Review of the Clinical Effectiveness

August 2010

*Supporting Informed Decisions*

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**Canadian Agency for Drugs and Technologies in Health**

# Positron Emission Tomography for Cardiovascular Disease: A Review of the Clinical Effectiveness

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August 2010

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Health technology assessment (HTA) agencies face the challenge of providing quality assessments of medical technologies in a timely manner to support decision-making. Ideally, all important deliberations would be supported by comprehensive health technology assessment reports, but the urgency of some decisions often requires a more immediate response.

The Health Technology Inquiry Service (HTIS) provides Canadian health care decision-makers with health technology assessment information, based on the best available evidence, in a quick and efficient manner. Inquiries related to the assessment of health care technologies (drugs, devices, diagnostic tests, and surgical procedures) are accepted by the service. Information provided by the HTIS is tailored to meet the needs of decision-makers, taking into account the urgency, importance, and potential impact of the request.

Consultations with the requestor of this HTIS assessment indicated that a review of the literature would be beneficial. The research question and selection criteria were developed in consultation with the requestor. The literature search was carried out by an information specialist using a standardized search strategy. The review of evidence was conducted by one internal HTIS reviewer. The draft report was internally reviewed and externally peer-reviewed by two or more peer reviewers. All comments were reviewed internally to ensure that they were addressed appropriately.

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This document is prepared by the Health Technology Inquiry Service (HTIS), an information service of the Canadian Agency for Drugs and Technologies in Health. The service is provided to those involved in planning and providing health care in Canada. HTIS responses are based on a comprehensive and systematic search of literature available to CADTH at the time of preparation. The intent is to provide a summary and critical appraisal of the best evidence on the topic that CADTH could identify using all reasonable efforts within the time allowed. This response has been peer-reviewed by clinical experts. The information in this document is intended to help Canadian health care decision-makers make well-informed decisions and thereby improve the quality of health care services. HTIS responses should be considered along with other types of information and health care considerations. It should not be used as a substitute for the application of clinical judgment in respect of the care of a particular patient or other professional judgment in any decision-making process, or as a substitute for professional medical advice. Readers are also cautioned that a lack of good-quality evidence does not necessarily mean a lack of effectiveness, particularly in the case of new and emerging health technologies for which little information can be found, but which may in future prove to be effective. While CADTH has taken care in the preparation of the document to ensure that its contents are accurate, complete, and up to date as of the date of publication, CADTH does not make any guarantee to that effect. CADTH does not guarantee and is not responsible for the quality, currency, propriety, accuracy, or reasonableness of any statements, information, or conclusions contained in the source documentation. CADTH is not responsible for any errors or omissions or injury, loss, or damage arising from or relating to the use (or misuse) of any information, statements, or conclusions contained in or implied by the information in this document or in any of the source documentation.

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# ACRONYMS AND ABBREVIATIONS

| | |
|---|---|
| AGREE | Appraisal of Guidelines Research and Evaluation |
| BOLD-CMR | blood oxygen level-dependent cardiovascular magnetic resonance |
| CAD | coronary artery disease |
| CCT | controlled clinical trial |
| CI | confidence interval |
| CT | computed tomography |
| CVR | coronary vasodilator reserve |
| $^{18}$FDG | 2-deoxy-2-[18F]fluoro-D-glucose |
| HR | hazard ratio |
| HTA | health technology assessment |
| KCE | Belgian Health Care Knowledge Centre |
| LV | left ventricular |
| MAS | Medical Advisory Secretariat (Ministry of Health and Long-Term Care, Ontario) |
| MBF | myocardial blood flow |
| MFR | myocardial flow reserve |
| MRI | magnetic resonance imaging |
| $^{13}NH_3$ | nitrogen-13 ammonia |
| $^{15}O\text{-}H_2O$ | oxygen-15 labelled water |
| PET | positron emission tomography |
| $^{82}$Rb | rubidium-82 chloride |
| RCT | randomized controlled trial |
| SIGN | Scottish Intercollegiate Guidelines Network |
| SPECT | single photon emission computed tomograph |
| Tc | technetium |

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**TITLE:** Positron Emission Tomography for Cardiovascular Disease: A Review of the Clinical Effectiveness

**DATE:** June 2010

# EXECUTIVE SUMMARY

## Context and Policy Issues

Coronary artery disease (CAD) is a leading cause of morbidity and mortality in the Western world. Early detection, followed by treatment, may limit disease progression. Cardiac imaging using positron emission tomography (PET) can be used to evaluate CAD and to help identify patients who can undergo revascularization. Radionuclides are used in PET to assess the viability of the myocardium and left ventricular function. This report reviews the literature on the clinical effectiveness of PET in the diagnosis and management of CAD. The quality of guidelines on the use of PET in the management of CAD is also assessed.

## Research Questions

1. What is the clinical effectiveness of positron emission tomography in the diagnosis and management of coronary artery disease?
2. What are the guidelines on the use of positron emission tomography in the diagnosis and management of coronary artery disease, and what is the quality of the guidelines?

## Methods

A literature search was conducted on key health technology assessment (HTA) resources, including PubMed, MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, Embase, The Cochrane Library (Issue 1, 2010), University of York Centre for Reviews and Dissemination (CRD) databases, ECRI (Health Devices Gold), EuroScan, international health technology agencies, and a focused Internet search. The search was limited to English language articles published between January 1, 2005 and January 20, 2010. Regular alerts are current to March 18, 2010. Filters were applied to limit the retrieval to systematic reviews, health technology assessments, meta-analyses, randomized controlled trials (RCTs), controlled clinical trials, observational studies, and guidelines. Two independent reviewers screened articles using pre-defined criteria.

## Summary of Findings

Two HTAs, one meta-analysis, one RCT, four non-RCTs, and four evidence-based guidelines were included in this review.

In one HTA, the effectiveness of using PET was comparable to that of other imaging techniques in the evaluation of myocardial viability, and the effectiveness of using PET was moderate to good in the evaluation of myocardial perfusion. A second HTA concluded that PET may be useful in identifying patients with severe left ventricular dysfunction who may benefit from revascularization, but it could not determine the impact that the evaluation of myocardial viability using PET would have on long-term clinical outcomes.

The meta-analysis concluded that the use of PET was superior to that of other non-invasive tests in the detection of CAD and that PET should be used more often in diagnosis.

The RCT found that imaging using PET was associated with greater benefit in patients who followed a PET-recommended treatment strategy. Rubidmium-82 ($^{82}$Rb) PET was determined to be a clinically useful tool for assessing the severity of coronary artery stenosis. The measurement of myocardial flow reserve (MFR) using $^{15}O$-$H_2O$-PET may help in the diagnosis of preclinical atherosclerosis in patients with one or more risk factors. The use of technetium (Tc-99m) sestamibi SPECT to assess MFR could be useful in the detection of CAD and the estimation of severity, particularly where PET access is limited. Most of the included studies had limitations in study design and interpretations of findings. Therefore, some caution may be needed when considering the conclusions. The guidelines recommend that PET be used in the diagnosis of CAD for

patients with an intermediate likelihood of risk of developing CAD, or for patients who are obese or who are unable to exercise. The guidelines conflict over the use of PET to identify candidates for revascularization.

## Conclusions and Implications for Decision- or Policy-Making

Overall, the evidence suggests that PET may be a useful tool in the diagnosis of CAD, particularly for patients with an intermediate likelihood of CAD, those who are obese, or those who are unable to exercise. The role of PET in the identification of patients with CAD who may benefit from revascularization is unclear. The lack of evidence from studies with high internal validity and the quality of the evidence that was used by the guideline development groups may be a consideration when deciding to use PET in the diagnosis or management of patients with CAD.

# 1 CONTEXT AND POLICY ISSUES

Coronary artery disease (CAD) is a leading cause of morbidity and mortality in the Western world.[1,2] In Canada, the direct and indirect health care costs of cardiovascular disease represents approximately $22 billion annually.[3] The risk factors that lead to CAD include being older, smoking, hypertension, hyperlipidemia, and a family history of myocardial infarction (MI) before the age of 60 years.[2] Stratification that is based on risk factors only may lead to an under-estimation of the risk in some patient populations including youth and women.[3]

The early detection of CAD followed by the use of treatment strategies may limit disease progression and may reduce the occurrence of the symptoms of ventricular dysfunction.[1,4] Non-invasive cardiac imaging is a tool that is used in the prognosis,[2] diagnosis, and risk stratification of CAD.[4] Cardiac imaging can help in the identification of patients who may be candidates for revascularization.[5] The documented clinical predictors of the survival of patients with CAD include left ventricular (LV) function, severity of coronary atherosclerosis, and severity of ischemia.[2]

Positron emission tomography (PET) is a type of cardiac imaging that can be used to guide treatment and patient management decisions. Radiotracers or radionuclides can be used in PET to assess the viability of the myocardium and LV function,[6] and to provide information about the extent and severity of CAD.[2] The radionuclides, which are administered to a patient, disperse throughout the body and are taken up in specific tissues.[6] A PET scanner is used to image the localization of radionuclides. Several radionuclides are described in Table 1.

This Canadian Agency for Drugs and Technologies (CADTH) report will review the literature regarding the clinical effectiveness of using PET in the diagnosis and management of CAD. In addition, this report is an assessment of the quality of the guidelines on the use of PET in the management of CAD.

# 2 RESEARCH QUESTIONS

1. What is the clinical effectiveness of positron emission tomography in the diagnosis and management of coronary artery disease?
2. What are the guidelines on the use of positron emission tomography in the diagnosis and management of coronary artery disease, and what is the quality of the guidelines?

**Table 1**: Commonly Used Radionuclides in PET Cardiac Imaging[1]

| Radionuclide | Role in Cardiac Imaging |
|---|---|
| oxygen-15 water ($^{15}O$-$H_2O$) | Assessment of myocardial perfusion |
| nitrogen-13 ammonia ($^{13}NH_3$) | Assessment of myocardial perfusion |
| rubidium-82 ($^{82}Rb$) chloride (potassium analogue) | Assessment of myocardial perfusion |
| 2-deoxy-2-[18F]fluoro-D-glucose ($^{18}FDG$) | Assessment of myocardial metabolism |
| carbon-11 ($^{11}C$) | Assessment of myocardial metabolism |

$H_2O$ = water; PET= positron emission tomography.

# 3 METHODS

## 3.1 Literature Search

Peer-reviewed literature searches were conducted to obtain published literature for this review. All search strategies were developed by the Information Specialist, with input from the project team.

The following bibliographic databases were searched through the Ovid interface: MEDLINE, Medline In-Process & Other Non-Indexed Citations, and Embase. Parallel searches were run in PubMed and The Cochrane Library (Issue 1, 2010). The search strategy comprised controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. Methodological filters were applied to limit the retrieval to systematic reviews, health technology assessments (HTAs), meta-analyses, randomized controlled trials (RCTs), controlled clinical trials (CCTs), observational studies, and guidelines. Appendix 1 shows the detailed search strategies.

The search was restricted to English language clinical articles published between January 1, 2005 and January 20, 2010. Regular alerts were established on Embase and MEDLINE, and the information that was retrieved via alerts was current to March 18, 2010.

Grey literature (Appendix 1) was identified by searching the websites of HTA and related agencies, professional associations, and other specialized databases. Google and other Internet search engines were used to search for additional web-based materials and information. These searches were supplemented by hand-searching.

## 3.2 Article Selection

Two reviewers (MM and MC) independently screened the titles and abstracts of the retrieved publications. These reviewers then independently evaluated the full-text publications for final article selection.

Studies were considered for inclusion if they were HTAs, systematic reviews, meta-analyses, RCTs, CCTs, or evidence-based guidelines. Primary studies involving patients with confirmed or suspected CAD or severe LV dysfunction were considered for inclusion if they assessed myocardial perfusion, myocardial oxidation, or myocardial flow reserve for diagnosis, for monitoring prognosis, or for guiding treatment decisions. The interventions were PET or PET/computed tomography (CT) using radionuclides including rubidium-82 chloride ($^{82}$Rb), nitrogen-13 ammonia ($^{13}NH_3$), oxygen-15 water ($^{15}O$-$H_2O$), or 2-deoxy-2-[18F]fluoro-D-glucose ($^{18}$FDG). The comparators included SPECT, quantitative coronary angiography, or magnetic resonance imaging. Secondary studies (HTAs, systematic reviews, and meta-analyses) were excluded if the reported methods did not seem to be systematic (i.e., they did not include a search of more than one database or they did not involve multiple reviewers in literature selection).

Any difference between the two reviewers in the selection of articles for inclusion was resolved by discussion and consensus. Studies that met the inclusion criteria and that were reviewed in a systematic review included in this report were not appraised separately. We did not perform a formal quality assessment of the studies that met the inclusion criteria of this report. The AGREE instrument[7] (Appraisal of Guidelines Research and Evaluation) was used by the two reviewers (MM and MC) to evaluate the quality of the guidelines that were included in this report. Standard domain scores were calculated using the scores that were assigned by the two reviewers.

# 4 SUMMARY OF FINDINGS

Of the 889 citations that were identified in the literature search, 844 were excluded after the screening of titles and abstracts, and 45 were retrieved for full-text screening. Eight publications were identified from grey literature sources or from hand-searching. Twelve publications were included in this report and the

remaining 41 articles were excluded. A flow diagram detailing study selection is provided in Appendix 2.

The 12 publications included two HTAs,[8,9] one meta-analysis,[10] one RCT,[11] four non-RCTs,[12-15] and four evidence-based guidelines.[5,16-18] The characteristics of the included primary studies are summarized in Appendix 3 Table A1. Articles that did not meet the inclusion criteria and that were cited by external reviewers have been included in Appendix 5.

## 4.1 Health Technology Assessments

An HTA was conducted by the Belgian Health Care Knowledge Centre (KCE)[9] to assess the diagnostic accuracy and clinical effectiveness of using PET in all clinical indications (i.e., oncology, neurology, infections, and cardiology). This CADTH report focuses on cardiac indications. A five-year literature search was performed in January 2009. The evidence was presented separately on myocardial viability and myocardial perfusion.

Regarding myocardial viability, authors of the KCE report identified an HTA produced by the Medical Advisory Secretariat (MAS) of the Ministry of Health and Long-Term Care in Ontario[8] and an RCT published in 2007 by Beanlands et al.[11] Both of these publications are summarized in this CADTH report. The authors of the KCE report concluded that the effectiveness of PET was comparable to that of other imaging techniques in the evaluation of myocardial viability.

With respect to myocardial perfusion, the KCE report identified one meta-analysis by Nandalur et al. (2008)[19] that is included in the current CADTH report and one position statement by Beanlands et al. (2007).[5] This position statement was based on a systematic review of 14 studies, 13 of which are included in Nandalur's publication. The position statement was appraised in this CADTH report (Appendix 4 Tables A2 and A3). The authors of the KCE HTA concluded that the effectiveness of using PET in the evaluation of myocardial perfusion is moderate to good.

In an HTA, MAS evaluated the evidence on the use of $^{18}$FDG-PET in the assessment of myocardial viability.[8] This HTA was an update to a 2001 report by the Institute for Clinical Evaluative Sciences. The HTA reviewed the literature that was published between January 2001 and April 2005. Studies were considered for inclusion if they involved patients with CAD and severe LV dysfunction for which revascularization was being considered. The outcomes included diagnostic performance measures, predictive accuracy in the recovery of regional or global LV function, long-term survival, cardiac events, quality of life, change in treatment management, and adverse events. A total of 45 studies, including eight systematic reviews or meta-analyses, were reviewed. The overall quality of the included studies was reported to be low. No RCTs were identified. The data from the updated HTA were combined with the data from the previous report by the Institute for Clinical Evaluative Sciences for analysis, but point estimates were not generated for all diagnostic performance characteristics. The authors of the MAS report stated that there was heterogeneity between the studies. One source of heterogeneity arose in the comparison of PET with the gold standard. In most cases, the gold standard was improvement in regional wall movement, but the manner in which the improvement was assessed (for example, using echocardiography, ventriculography, or magnetic resonance imaging varied between studies.

One meta-analysis and eight primary studies reported the sensitivity, specificity, and predictive values of using $^{18}$FDG-PET for predicting post-revascularization regional functional recovery. In each study, PET was compared with one or more imaging tests, and a pooled analysis was not conducted. Individual findings from the nine publications were reported in the HTA. The authors summarized the findings on how PET compared with other non-invasive imaging tests including dobutamine echocardiography, $^{15}$O-$H_2$O-PET, thallium-201 single photon emission computed

tomography (SPECT), technetium (Tc)-tracer SPECT, and dobutamine magnetic resonance imaging. The dominant technology regarding diagnostic performance characteristics was reported, and the frequency of PET as the dominant technology is described in Table 2. It was not stated if any differences between imaging modalities were statistically significant.

limitations and based on the MAS report, the Ontario Health Technology Advisory Committee recommended[20] that centres with the capacity to offer PET for myocardial viability assessment in patients with severe LV dysfunction continue to do so with the objective of identifying patients who may respond to revascularization or heart transplant.

**Table 2**: Frequency of Dominance of $^{18}$FDG-PET Over Other Non-invasive Tests For Predicting Functional Segmental Recovery[8]

| Diagnostic Performance Characteristic | Frequency of PET as Dominant Technology |
|---|---|
| Sensitivity | 7/8 studies (equivalent to dobutamine echocardiography in 1 study) |
| Specificity | 2/8 studies (dobutamine echocardiography dominant in 5 studies) |
| Positive likelihood ratio | 1/8 studies (dobutamine echocardiography dominant in 5 studies) |
| Negative likelihood ratio | 4/8 studies (equivalent to dobutamine echocardiography in 2 studies) |

$^{18}$FDG-PET = 2-deoxy-2-[18F]fluoro-D-glucose positron emission tomography

The findings suggest that the use of PET has the highest sensitivity for predicting functional recovery after revascularization, and the use of dobutamine echocardiography has the highest specificity. The use of $^{18}$FDG-PET was associated with a better negative likelihood ratio for predicting myocardial function recovery after revascularization compared with other imaging tests. The positive likelihood ratio of using $^{18}$FDG-PET in predicting segmental function recovery was reported to be less useful than dobutamine echocardiography. The authors concluded that PET may be useful in the identification of patients with severe LV dysfunction who may benefit from revascularization in the recovery of LV function, increased survival, lower incidence of cardiac events, and better quality of life. However, the heterogeneity between studies may hinder interpretation. In addition, three of the eight studies included patients with clinical characteristics consistent with severe LV dysfunction (left ejection fraction less than 35%[8]) leading authors to conclude that there was a lack of studies that directly compared the ability of $^{18}$FDG-PET with that of other non-invasive techniques to predict global function improvement or long-term outcomes in patients with severe LV dysfunction. Despite these

## 4.2 Systematic Reviews and Meta-analyses

In 2008, Nandalur et al.[21] conducted a meta-analysis of the evidence on the use of PET in the diagnosis of CAD. The search, which is current to July 2007, included all types of studies that involved at least 10 participants and that defined the cut-off for significant CAD as 50% or more diameter stenosis (not stated if stenosis was in reference to the main branch). Nineteen studies compared PET perfusion imaging using generator-produced $^{82}$Rb-chloride or cyclotron-produced $^{13}$N-ammonia, SPECT using $^{201}$thallium chloride or Tc-99m, coronary imaging with coronary magnetic resonance angiography, or multidetector computed tomographic angiography. A quality assessment of included studies was performed. All the included primary studies were non-randomized controlled studies or observational studies.

The authors evaluated the diagnostic performance of PET in 840 patients for which patient-level information was available using a bivariate mixed effects regression model. The overall prevalence of CAD was 77.4%. The diagnostic performance characteristics are described in Table 3.

| **Table 3:** Diagnostic Performance Measures of PET (Nandalur et al.[22]) | |
|---|---|
| **Diagnostic Performance Measure** | **Summary Estimates (95% CI)** |
| Sensitivity | 0.92 (0.90 to 0.94) |
| Specificity | 0.85 (0.79 to 0.90) |
| Positive likelihood ratio | 6.2 (3.3 to 11.8) |
| Negative likelihood ratio | 0.11 (0.08 to 0.14) |

CI = confidence interval; PET = positron emission tomography

The authors noted several limitations of their analysis. Most of the included studies were of low quality (the mean score based on the Quality Assessment of Studies of Diagnostic Accuracy included in systematic reviews tool was 5.8) as assessed by Nandalur et al. Heterogeneity was identified for several performance characteristics. The study population had a high prevalence of disease. Despite these limitations, the authors concluded that the diagnostic performance of PET in the detection of CAD was superior to that of other non-invasive tests, and they suggested that PET be used more often to diagnose CAD. The summary estimates may wish to be interpreted with caution given the limitations in this study.

## 4.3 Randomized Controlled Trials

In 2007, Beanlands et al.[11] reported results from a multi-centre RCT (PET and Recovery Following Revascularization-2 [PARR-2]) that compared the clinical outcomes of patients with severe LV dysfunction and suspected CAD who received $^{18}$FDG-PET imaging to those of patients who received standard care. The objective of the study was to compare the clinical outcomes of patients who had a treatment strategy that was partly based on the findings from $^{18}$FDG-PET imaging. The primary outcome of interest was occurrence of cardiac death, myocardial infarction, or hospitalization for a cardiac-related cause within a year of randomization. Secondary outcomes included time to the composite event and time to cardiac death. Of the 430 patients who participated in the study, 218 were randomized to receive $^{18}$FDG-PET and 212 were randomized to receive standard care. Patients in the standard care arm did not receive PET, but they were eligible to undergo alternative imaging tests to assess viability. In the $^{18}$FDG-PET treatment arm, 207 of the 218 patients underwent PET imaging as did five patients in the standard care arm. Analyses were done on the intention-to-treat population. A summary of study findings is provided in Table 4.

The authors concluded that the use of PET had an impact on disease management among patients with severe LV dysfunction or suspected CAD as shown in the higher rates of revascularization in the PET arm compared with the standard care arm. In a post-hoc analysis comparing the time to occurrence of the first composite cardiac event in the group that adhered to the recommendations on PET compared with the standard care group, the hazard ratio (HR) favoured the adherent group (HR = 0.62 [95% confidence interval (CI), 0.42 to 0.93; P = 0.019]). There was no statistically significant difference in the number of cardiac deaths between arms (HR 0.72 [95% CI, 0.40 to 1.3; P = 0.25]). In addition, there was no statistically significant difference in cardiac death between arms in patients who had recent coronary angiography. In those patients without recent angiography, there was a statistically significant reduction in cardiac death in the PET arm compared with the standard care arm. The treatment plans of more than 25% of patients did not follow the recommendations that were based on the PET imaging finding. The authors acknowledged that the division of patients into high-, moderate-, and low-myocardial viability may have affected how the patients were subsequently treated, particularly those near the cut-off points (high to moderate and moderate to low). The authors concluded that patients with severe LV dysfunction might not benefit from the use of $^{18}$FDG-PET imaging. The finding that there was no difference between the PET arm

and the standard care arm in cardiac death when angiography was performed suggests that the use of angiography may be adequate for the assessment of myocardial viability, although there may be a reduction in other cardiac events when PET is used.

in Appendix 3 Table A1. The BOLD-CMR and PET images were analyzed by independent assessors who were blinded to the clinical information and imaging (angiograph, BOLD-CMR, or PET) findings. All patients underwent BOLD-CMR and PET. Two patients with CAD did not complete the study protocol.

**Table 4:** Findings from Beanlands et al. (2007)[11]

| Outcome | $^{18}$FDG-PET | Standard Care |
|---|---|---|
| **Myocardial viability** (number of patients) | | |
| High | 58 | NR |
| Moderate | 103 | NR |
| Low | 46 | NR |
| **Revascularization** (number of patients [%]) | | |
| Underwent protocol revascularization | 104 (47.7) | 74 (34.9), P = 0.007 |
| Underwent CABG | 71/104 (68.3) | 55/74 (74.3) |
| Underwent late revascularization | 5 (2.3) | 9 (4.2) |
| **Coronary angiography review** (proportion with available angiography data [%]) | | |
| 2-vessel, 3-vessel, or left main disease with > 50% stenosis | 148/165 (89.7) | 120/135 (88.9) |
| **Adherence** (proportion adhering [%]) | | |
| Adherence to PET recommendations<br>Adherence stratified by myocardial viability | 156/207 (75.4)<br>high 86.2%, moderate 66.0%, low 23.9% | NA |

CABG = coronary artery bypass graft; $^{18}$FDG-PET = 2-deoxy-2-[18F]fluoro-D-glucose position emission tomography; NA = not applicable; NR = not reported; PET= positron emission tomography

## 4.4 Controlled Clinical Trials

In 2010, Karamitsos et al.[15] investigated the relationship between regional myocardial oxidation and myocardial perfusion in patients with CAD at rest and after pharmacological stress with adenosine infusion. The authors used blood oxygen level-dependent cardiovascular magnetic resonance (BOLD-CMR) and $^{15}$O-$H_2$O-PET. A second objective of the study was to compare BOLD-CMR and $^{15}$O-$H_2$O-PET in the diagnosis of CAD. A total of 34 patients participated in the study, including 10 healthy volunteers and 24 patients with 1- or 2-vessel CAD that was diagnosed using coronary angiography. The methods that were used in the BOLD-CMR and $^{15}$O-$H_2$O-PET imaging appear There was no statistically significant difference in the hemodynamic response after adenosine infusion. The authors reported that BOLD-CMR and PET findings agreed on the presence or absence of CAD in 18 of the 22 (82%) patients in the CAD groups and 100% of patients in the control group. In segmental analyses using PET as the gold standard to identify ischemic segments and applying a cut-off of 50% or more diameter stenosis on angiography, the sensitivity of BOLD-CMR was 60%, and the specificity was 88%. This can be interpreted as 40% of the segments that exhibited reduced blood flow had normal oxygenation. The authors explained the discordance between the abilities of PET and BOLD-CMR to identify ischemic segments as dissociation between regional myocardial infusion and oxygenation in some patients with CAD. The authors suggested that this dissociation may be due to the absence of ischemia in those segments despite the reduced blood flow. No data were available to support this hypothesis. Using a cut-off of 70% diameter

stenosis, the sensitivity of CMR increased to 69%, and the specificity was 92%. The authors concluded that more studies are needed to define the diagnostic performance of BOLD-CMR in the detection of CAD.

In 2008, Anagnostopoulos et al.[13] evaluated the relationship between myocardial blood flow (MBF) and coronary vasodilator reserve (CVR) when assessed using $^{82}$Rb-PET at rest and after diypyridamole vasodilation. The authors also assessed the impact that the degree of vessel stenosis, measured by coronary angiography, had on the relationship between MBF and CVR. A total of 22 patients participated in the study including 15 patients with angiography-confirmed CAD and seven age-matched healthy volunteers with a low likelihood of CAD. In vessels with less than 50% stenosis, the MBF and CVR were similar at rest and after pharmacological stress. In addition, the measurement of CVR allowed the differentiation between vessels with 50% to 69% stenosis and those with 70% to 89% stenosis. The authors reported that hyperemic MBF and CVR are inversely correlated with stenosis and that measurement of these functional outputs using $^{82}$Rb-PET is a clinically useful tool to assess the severity of coronary artery stenosis.

In 2006, Tsukamoto et al.[12] assessed the influence of coronary artery stenosis and risk factors on myocardial flow reserve (MFR) in patients who were suspected to have CAD. A total of 81 participants were enrolled in the study including 74 patients with CAD-like symptoms and seven age-matched healthy volunteers. All patients received coronary angiography and $^{15}O\text{-}H_2O$-PET. The predominant risk factors in the CAD group were diabetes (33.8%), hypertension (47.3%), hyperlipidemia (64.9%), and smoking (31.1%). In patients with CAD, the authors evaluated MFR in areas with significant coronary artery stenosis and in areas without stenosis (remote regions). In areas of stenosis, MFR was inversely correlated with the severity of stenosis. There was no effect from independent risk factors. Conversely, in remote regions, MFR was statistically significantly decreased in patients with diabetes and in those who smoked. The authors concluded that in stenotic regions, MFR was influenced to a greater degree by the severity of stenosis instead of risk factors. In areas without significant stenosis, risk factors had a greater impact on MFR. The authors suggested that the measurement of MFR using $^{15}O\text{-}H_2O$-PET may help in the diagnosis of preclinical atherosclerosis, particularly in patients with one or more risk factors. No further evidence was provided to support this hypothesis, and no further recommendations about the management of patients with preclinical atherosclerosis (routine follow-up imaging or pharmacotherapy) or patients with suspected preclinical atherosclerosis were made.

In 2005, Tsukamoto et al.[14] compared the assessment of MFR using Tc-99m sestamibi SPECT imaging (SPECT-MFR) with the use of $^{15}O\text{-}H_2O$-PET imaging (PET-MFR). A total of 29 subjects participated in the study including 22 patients who were suspected to have CAD and seven healthy volunteers. These volunteers were not age-matched and were statistically significantly younger than those in the CAD group. All patients received Tc-99m sestamibi myocardial perfusion SPECT and $^{15}O\text{-}H_2O$-PET, and Tc-99m sestamibi coronary angiography. MBF was calculated at rest and during pharmacological stress with adenosine triphosphate. Lower MFR values were reported in areas of stenosis compared with areas without stenosis when both imaging modalities were used. The authors reported that SPECT-MFR correlated with PET-MFR, although the estimation based on SPECT-MFR was statistically significantly reduced. Despite the underestimation of MFR after the use of Tc-99m sestamibi, the authors concluded that it might be useful in the detection of CAD and the estimation of disease severity, particularly where access to the use of PET is limited.

## 4.5 Guidelines and Recommendations

Four evidence-based guidelines on the use of PET for the diagnosis or management of patients with CAD or severe LV dysfunction were identified. One guideline is from Canada,[5] one

from Europe,[18] one from Australia,[17] and one from Scotland.[16]

The main objectives of the guidelines were to provide recommendations on the use of non-invasive cardiac imaging in the diagnosis of heart disease, and to provide guidance for the management of patients with heart disease. Two guidelines focussed on the use of radionuclide imaging,[5,18] and two guidelines focussed on the overall management of patients with heart disease.[16,17] Details of recommendations are provided in Appendix 4, Table A2.

The quality of the included guidelines was appraised using the AGREE instrument,[7] which includes 23 questions in six domains (scope and purpose, stakeholder involvement, rigour of development, clarity and presentation, applicability, and editorial independence). Each item was rated on a four-point scale: 4 — Strongly Agree; 3 — Agree; 2 — Disagree; and 1 — Strongly Disagree. Detailed scores for each guideline are provided in Appendix 4, Table A3. The overall assessment of each guideline is rated using the following parameters as suggested in the instrument:

- Strongly recommend: The majority of items and most domain scores are above 60%, indicating high overall quality.
- Recommend with provisos: Most domain scores are between 30% and 60%, indicating that the guideline has a moderate overall quality, possibly due to insufficient information provided in the guideline.
- Would not recommend: The majority of items and most domain scores are less than 30%, indicating low overall quality and serious shortcomings.[7]

One guideline that was produced by the Scottish Intercollegiate Guidelines Network (SIGN)[16] is strongly recommended based on assessment using the AGREE instrument. The SIGN guideline scored highest in all domains. The remaining three guidelines by the European Council of Nuclear Cardiology,[18] the Canadian Cardiovascular Society, and partner organizations,[5] and the National Heart Foundation of Australia[17] are recommended with provisos. Their weaknesses lie in rigour of development, applicability, and editorial independence. None of the guidelines received an AGREE assessment of "would not recommend." The SIGN[16] guidelines and the Canadian Cardiovascular Society[5] guidelines scored highly in rigour of development, but these two guidelines provided recommendations based on the clinical experience of the guideline development group[16] or on evidence derived from one RCT or from non-randomized studies.[5]

The main recommendation on the use of PET in the diagnosis of CAD and the management of patients with CAD was that PET be used in the diagnosis of CAD among patients with intermediate likelihood risk or among patients who are obese or unable to exercise.[5] One guideline recommends that PET be used to define myocardial viability in patients with ischemic heart disease and severe LV dysfunction to identify the extent of recoverable myocardium and the prognosis in patients being considered for revascularization.[5] Another guideline that received the highest AGREE score did not recommend the use of PET to identify patients who would be candidates for revascularization.[16]

## 4.6 Limitations

A limited literature search was conducted for this report. Observational studies without a control group were not included in this report. In addition, articles that were published from January 1, 2005 to March 18, 2010, and of English language, were eligible for inclusion. Potentially relevant evidence that was published before 2005 would have been excluded. Observational studies may constitute a proportion of the evidence base for the diagnostic accuracy of PET in cardiac conditions. Studies that had been reviewed as part of an included systematic review or meta-analysis were not appraised separately for this report.

Most of the evidence included in this report relates to the use of PET for diagnosis or treatment. There was limited evidence on the use of PET for prognosis. None of the included studies evaluated the use of the hybrid PET-

computed tomography (CT) technology, which is available in some Canadian centres. Most of the articles meeting the inclusion criteria of this review were non-randomized in design. One RCT was identified. The meta-analysis reported heterogeneity in several diagnostic performance characteristics. The guidelines provided recommendations that were based on the clinical experience of the guideline development group or on evidence derived from one RCT or from non-randomized studies.

# 5 CONCLUSIONS AND IMPLICATIONS FOR DECISION- OR POLICY-MAKING

Two HTAs concluded that PET may be useful in the identification of patients with severe LV dysfunction who may benefit from revascularization. Evidence from one meta-analysis showed that the diagnostic performance of PET in the detection of CAD is superior to that of other non-invasive tests including coronary magnetic resonance angiography and multidetector CT angiography. One RCT reported that the use of PET had an impact on the clinical management of patients with severe LV dysfunction or suspected CAD. Patients who underwent PET had higher rates of revascularization compared with patients who received standard care that included evaluation using another non-invasive imaging test. The same study reported that in patients who did not undergo coronary angiography, PET was associated with a statistically significant reduction in cardiac events.

Evidence from non-randomized studies showed that the measurement of MBF using $^{82}$Rb-PET may be useful in the evaluation of CAD severity. In addition, the use of $^{15}O\text{-}H_2O$-PET in the measurement of MFR may help in the diagnosis of preclinical atherosclerosis, particularly in patients with CAD risk factors.

There was discordance between the recommendations in the evidence-based guidelines. The use of PET was recommended in patients who were at intermediate likelihood for CAD, and in those patients who are unable to exercise. One of the four guidelines recommended that PET be used to identify patients with CAD who may be candidates for revascularization, but another guideline recommended against this.

The access to PET scanning for cardiac indications varies in Canada.[23] In 2009, Ontario amended the coverage policy on the use of PET scanning in the assessment of myocardial viability. Ontario continues to collect evidence on PET effectiveness in ongoing evaluation studies and clinical trials.[24] Overall, the evidence, mainly from non-randomized studies, suggests that PET may be a useful tool in the diagnosis of CAD, particularly in patients with an intermediate likelihood of CAD who are obese or who are unable to exercise. There may also be a role for PET in the assessment of severity of disease. The role of PET in the identification of patients with CAD who may benefit from revascularization is unclear. The lack of evidence from studies with high internal validity and the quality of the evidence that was used by the guideline development groups may be a consideration when deciding to use PET in the diagnosis or management of patients with CAD.

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# APPENDIX 1: LITERATURE SEARCH STRATEGY

| OVERVIEW | |
|---|---|
| Interface: | Ovid |
| Databases: | EMBASE <1996 to 2010 Week 3><br>Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1950 - Present<br>**Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid. |
| Date of Search: | January 20, 2010 |
| Alerts: | Weekly search updates began January 20, 2010 until March 18, 2010. |
| Study Types: | Systematic reviews; meta-analyses; health technology assessments; randomized controlled trials; controlled clinical trials; observational studies; guidelines |
| Limits: | Publication years January 1, 2005 – January 20, 2010<br>English language |

| SYNTAX GUIDE | |
|---|---|
| / | At the end of a phrase, searches the phrase as a subject heading |
| exp | Explode a subject heading |
| * | Before a word, indicates that the marked subject heading is a primary topic;<br>or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings |
| * | At the end of a word indicates truncation |
| $ | At the end of a word indicates truncation |
| ADJ# | Adjacency within # number of words (in any order) |
| .ti. | Title |
| .ab. | Abstract |
| .hw. | Heading Word; usually includes subject headings and controlled vocabulary |
| .pt. | Publication type |
| .jw. | Journal word |
| .md. | Methodology |
| .mp. | Mapping alias (searches title, abstract, heading words, table of contents and key phrase identifiers) |

| OVID EMBASE / MEDLINE STRATEGY | |
|---|---|
| **Line #** | **Search Strategy** |
| 1 | exp Positron Emission Tomography/ or (PET Scan or PET Scans or FDG PET or FDGPET or PETCT or PET CT).ti,ab,ot,sh,hw. or (Positron* adj5 Emission* adj5 Tomograph*).ti,ab,ot,sh,hw. or (PET* adj5 (positron* or emission* or tomo graph* or tomograph*)).ti,ab,ot,sh,hw. or Positron*.jn. |
| 2 | exp *Cardiovascular Diseases/ or exp *Cardiology/ |
| 3 | Cardiovascular System/ or Diagnostic Techniques, Cardiovascular/ or Cardiovascular Surgical Procedures/ or Cardiovascular Physiology/ or Cardiology Service, Hospital/ |
| 4 | ((heart or cardiac or chest or cardiovascular or vascular or coronary or artery or arterial or Aortic or myocardial or ventricular) adj2 (Emergenc* or arrest* or disease* or failure* or defect* or malformation* or abnormalit* or infection* or complicat* or blockage* or infarction* or Dysfunct* or Obstruction* or Rupture* or syndrome* or anomal* or Insufficienc*)).ti,ab. |
| 5 | ((Ischemia* or ischaemia* or Thromboembolism or Embolism or Thrombosis* or Aneurysm) adj2 (heart or cardiac or chest or cardiovascular or coronary or myocardial)).ti,ab. |
| 6 | (arteriosclero* or atherosclero* or Arrhythmia* or Cardiomegal* or Cardiomyopath* or Endocarditis or Myocarditis or Pericarditis or Pneumopericard* or (pericardiotomy adj2 syndrome) or Arteriovenous Malformat* or Arteritis* or Capillary Leak Syndrome* or Pulmonary Veno-Occlusive Disease* or Reperfusion Injury or Reperfusion Injuries or Aortitis or Arteritis or Venous Insufficienc*).ti,ab. |
| 7 | 2 or 3 or 4 or 5 or 6 |
| 8 | 1 and 7 |
| 9 | limit 8 to english language |
| 10 | limit 9 to human |
| 11 | limit 10 to yr="2005 -Current" |
| 12 | limit 11 to humans |
| **Systematic Reviews, Meta-analyses, and Health Technology Assessments Filter** | |
| 13 | meta-analysis.pt. |
| 14 | meta-analysis/ or systematic review/ or meta-analysis as topic/ or exp technology assessment, biomedical/ |
| 15 | ((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab. |
| 16 | ((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).ti,ab. |
| 17 | ((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab. |
| 18 | (data synthes* or data extraction* or data abstraction*).ti,ab. |
| 19 | (handsearch* or hand search*).ti,ab. |
| 20 | (mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab. |
| 21 | (met analy* or metanaly* or health technology assessment* or HTA or HTAs).ti,ab. |
| 22 | (meta regression* or metaregression* or mega regression*).ti,ab. |
| 23 | (meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw. |

| OVID EMBASE / MEDLINE STRATEGY | |
|---|---|
| **Line #** | **Search Strategy** |
| 24 | (medline or Cochrane or pubmed or medlars).ti,ab,hw. |
| 25 | (cochrane or health technology assessment or evidence report).jw. |
| 26 | (meta-analysis or systematic review).md. |
| 27 | or/13-26 |
| **Randomized Controlled Trials and Controlled Clinical Trials Filter** | |
| 28 | (Randomized Controlled Trial or Controlled Clinical Trial).pt. |
| 29 | Randomized Controlled Trial/ |
| 30 | Randomized Controlled Trials as Topic/ |
| 31 | Controlled Clinical Trial/ |
| 32 | Controlled Clinical Trials as Topic/ |
| 33 | Randomization/ |
| 34 | Random Allocation/ |
| 35 | Double-Blind Method/ |
| 36 | Double Blind Procedure/ |
| 37 | Double-Blind Studies/ |
| 38 | Single-Blind Method/ |
| 39 | Single Blind Procedure/ |
| 40 | Single-Blind Studies/ |
| 41 | Placebos/ |
| 42 | Placebo/ |
| 43 | Control Groups/ |
| 44 | Control Group/ |
| 45 | (random* or sham or placebo*).ti,ab,hw. |
| 46 | ((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw. |
| 47 | ((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw. |
| 48 | (control* adj3 (study or studies or trial*)).ti,ab,hw. |
| 49 | (Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw. |
| 50 | (allocated adj1 to).ti,ab,hw. |
| 51 | ((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw. |
| 52 | or/28-51 |
| 53 | (Review or editorial or comment or letter or newspaper article).pt. |
| 54 | 52 not 53 |
| **Clinical Practice Guidelines Filter** | |
| 55 | exp practice guideline/ |
| 56 | (cpg or cpgs).ti,ab. |
| 57 | (care adj (path or paths or pathway or pathways or map or maps or plan or plans)).ti,ab. |
| 58 | Recommendation*.ti. |
| 59 | or/55-58 |
| 60 | exp Consensus development conferences/ or "Guidelines"/ or "Health Planning Guidelines"/ or "Practice Guidelines"/ or Health Knowledge, Attitudes, Practice/ or Clinical Protocols/ or critical pathways/ |
| 61 | (guideline or practice guideline or Consensus Development Conference or Consensus |

| OVID EMBASE / MEDLINE STRATEGY | |
|---|---|
| **Line #** | **Search Strategy** |
| | Development Conference, NIH).pt. |
| 62 | (cpg or cpgs or "care map" or "care maps" or "care path" or "care paths" or "care plan" or "care plans" or "care pathway" or "care pathways" or consensus).ti,ab. |
| 63 | ((critical or clinical or practice) adj (path or paths or pathway or pathways or protocol or protocols or guideline or guidelines)).ti,ab. |
| 64 | (Consensus adj development).ti,ab. |
| 65 | (position statement$ or expert consensus or consensus statement$ or practice parameter$ or standards or guideline$ or best practice$ or best-practice$).ti,ab. |
| 66 | or/60-65 |
| 67 | 59 or 66 |
| **Observational Studies Filter** | |
| 68 | epidemiologic methods.sh. |
| 69 | epidemiologic studies.sh. |
| 70 | cohort studies/ |
| 71 | cohort analysis/ |
| 72 | longitudinal studies/ |
| 73 | longitudinal study/ |
| 74 | prospective studies/ |
| 75 | prospective study/ |
| 76 | follow-up studies/ |
| 77 | follow up/ |
| 78 | followup studies/ |
| 79 | retrospective studies/ |
| 80 | retrospective study/ |
| 81 | case-control studies/ |
| 82 | exp case control study/ |
| 83 | cross-sectional study/ |
| 84 | observational study/ |
| 85 | quasi experimental methods/ |
| 86 | quasi experimental study/ |
| 87 | (observational adj3 (study or studies or design or analysis or analyses)).ti,ab,hw. |
| 88 | (cohort adj7 (study or studies or design or analysis or analyses)).ti,ab,hw. |
| 89 | (prospective adj7 (study or studies or design or analysis or analyses or cohort)).ti,ab,hw. |
| 90 | ((follow up or followup) adj7 (study or studies or design or analysis or analyses)).ti,ab,hw. |
| 91 | ((longitudinal or longterm or (long adj term)) adj7 (study or studies or design or analysis or analyses or data or cohort)).ti,ab,hw. |
| 92 | (retrospective adj7 (study or studies or design or analysis or analyses or cohort or data or review)).ti,ab,hw. |
| 93 | ((case adj control) or (case adj comparison) or (case adj controlled)).ti,ab. |
| 94 | (case-referent adj3 (study or studies or design or analysis or analyses)).ti,ab,hw. |
| 95 | (population adj3 (study or studies or analysis or analyses)).ti,ab. |
| 96 | (descriptive adj3 (study or studies or design or analysis or analyses)).ti,ab,hw. |

| OVID EMBASE / MEDLINE STRATEGY | |
|---|---|
| **Line #** | **Search Strategy** |
| 97 | ((multidimensional or (multi adj dimensional)) adj3 (study or studies or design or analysis or analyses)).ti,ab,hw. |
| 98 | (cross adj sectional adj7 (study or studies or design or research or analysis or analyses or survey or findings)).ti,ab,hw. |
| 99 | ((natural adj experiment) or (natural adj experiments)).ti,ab,hw. |
| 100 | (quasi adj (experiment or experiments or experimental)).ti,ab,hw. |
| 101 | ((non experiment or nonexperiment or non experimental or nonexperimental) adj3 (study or studies or design or analysis or analyses)).ti,ab,hw. |
| 102 | (prevalence adj3 (study or studies or analysis or analyses)).ti,ab,hw. |
| 103 | case series.ti,ab,hw. |
| 104 | or/68-103 |
| 105 | (Review or editorial or comment or letter or newspaper article).pt. |
| 106 | 104 not 105 |
| 107 | 12 and (27 or 54 or 67 or 106) |

| OTHER DATABASES | |
|---|---|
| PubMed | Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used. |
| The Cochrane Library, Issue 1, 2010 | Same MeSH, keywords, and date limits used as per MEDLINE search, excluding study types and human restrictions. Syntax adjusted for The Cochrane Library databases. |

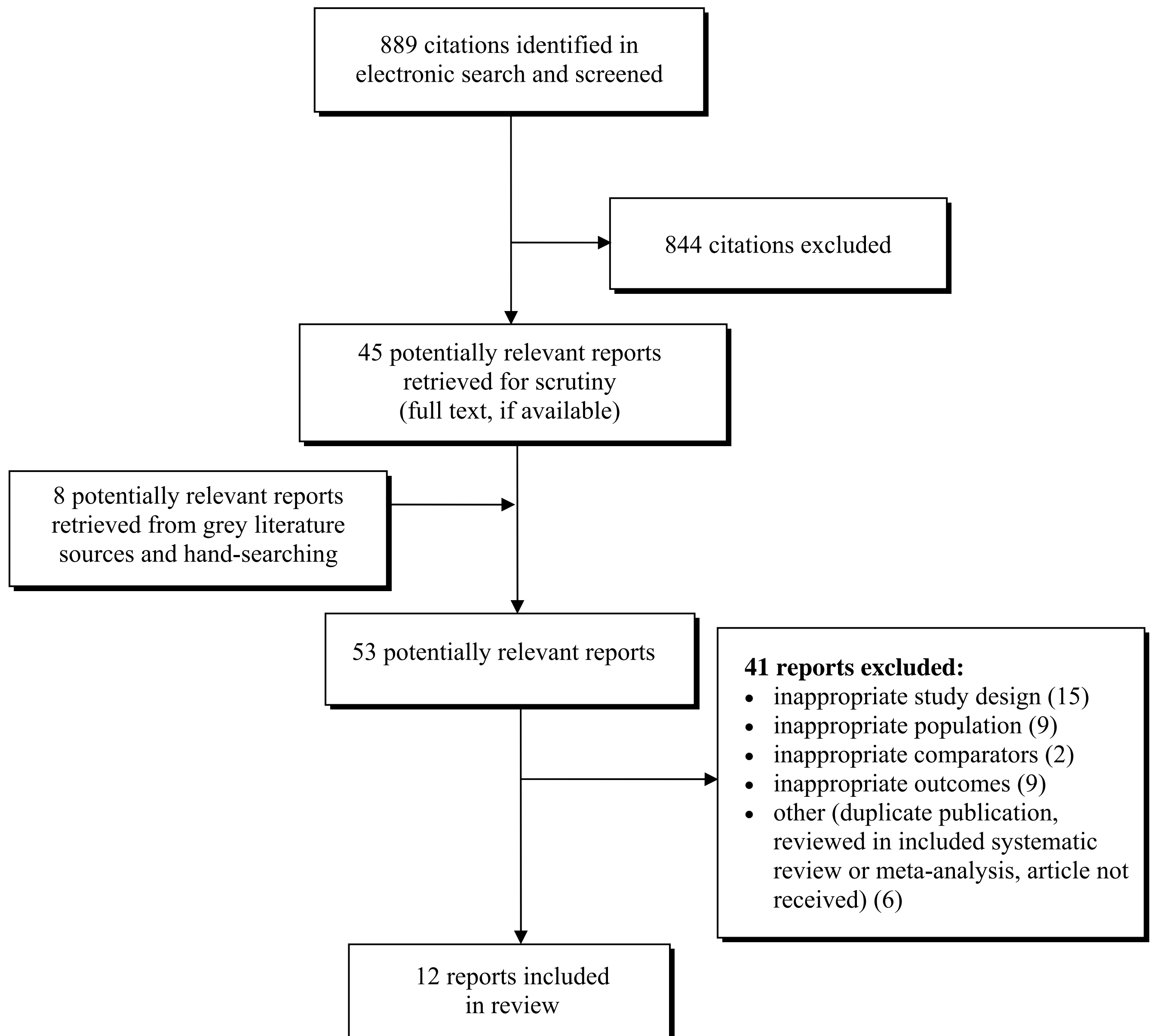
### Grey Literature

| Dates for Search: | January 21, 2010 — January 25, 2010 |
|---|---|
| Keywords: | Positron Emission Tomography OR PET Scan or PET Scans or FDG PET or FDGPET or PETCT or PET CT<br><br>Cardiovascular Disease OR Cardiology or cardiac OR Ischemia or myocardial or arteriosclero* OR atheroscler o* OR Arrhythmia* OR Cardiomegal* or Cardiomyopath* or Endocarditis or Myocarditis or Pericarditis or Pneumopericard* or Arteritis* OR Aortitis OR Arteritis |
| Limits: | Publication years January 1, 2005 — January 25, 2010 |

The following sections of the CADTH grey literature checklist, *Grey matters: a practical search tool for evidence-based medicine* (http://www.cadth.ca/index.php/en/cadth/products/grey-matters) were searched:

- Health Technology Assessment Agencies
- Health Economic
- Databases (free)
- Internet Search
- Open Access Journals.

# APPENDIX 2: SELECTION OF PUBLICATIONS



# APPENDIX 3: SUMMARY OF INCLUDED STUDIES

| **Table A1:** Characteristics of RCTs and CCTs | | | | |
|---|---|---|---|---|
| **Study and Year** | **Inclusion Criteria, Exclusion Criteria** | **Interventions** | **Objectives and Outcomes** | **Patient Characteristics** |
| **RCT** | | | | |
| Beanlands, 2007[11] | **Included:**<br>• 18 years of age or older<br>• suspected to have CAD<br>• ejection fraction < 35%<br>• patients being considered for revascularization or workup, transplantation workup, heart failure workup, or whose physician requested PET to assist in decision-making<br><br>**Excluded:**<br>• patients for whom decision about disease management had been made, who were unsuitable for revascularization, or who required emergency surgery<br>• patients with comorbidities that may have compromised survival over study duration<br>• patients < 4 weeks post-myocardial infarction | **$^{18}$FDG-PET:** Methodology published by Beanlands et al. in 2002<br><br>**Standard care:** Any non-invasive imaging technique other than $^{18}$FDG-PET | 1) Compare clinical outcomes (cardiac events [cardiac death, myocardial infarction] or cardiac hospital stay) between treatment groups<br>2) Compare clinical outcomes in patients who received $^{18}$FDG-PET with or without coronary angiography | **$^{18}$FDG-PET group:** Men 184/218 (84.4%); mean age 63.0 ± 10.0 years<br><br>**Standard care group:** Men 179/212 (84.4%); mean age 62.0 ± 10.3 years |
| **CCTs** | | | | |
| Tsukamoto, 2005[14] | **Included:**<br>• patients suspected of having CAD<br>• normal healthy volunteers | **Tc-99-SPECT:** 2-day rest/stress protocol using ATP (0.16 mg/kg/min)<br><br>**$^{15}$O-$H_2$O:**<br>• total inhaled dose 2,000 MBq $^{15}$O-CO and | Compare measurements of regional MBF and MFR using Tc-99m-sestamibi with those made using $^{15}$O-$H_2$O-PET | **CAD group:** Men 17/22 (77.3%); mean age 64.0 ± 10.0 years; previous history of: MI: (n = 8) Revascularization: (n = 4) |

| Table A1: Characteristics of RCTs and CCTs | | | | |
|---|---|---|---|---|
| **Study and Year** | **Inclusion Criteria, Exclusion Criteria** | **Interventions** | **Objectives and Outcomes** | **Patient Characteristics** |
| | | 1,000 MBq $^{15}O\text{-}H_2O$<br>• attenuation correction performed<br>• analysis by 3 physicians | | Angioplasty: (n = 2)<br>CABG: (n = 2)<br><br>**Healthy volunteers:**<br>Men 7/7 (100%); mean age 33.4 ± 4.5 years |
| Tsukamoto, 2006[12] | **Included:**<br>• CAD group suspected to have CAD<br>• control group with no known CAD and normal electrocardiogram<br><br>**Excluded:**<br>• CAD group of patients with history of MI or CABG | **$^{15}O\text{-}H_2O$:**<br>• total inhaled dose 2,000 MBq of $^{15}O\text{-}CO$ and 1,000 MBq of $^{15}O\text{-}H_2O$<br>• attenuation correction performed<br>• analysis by 2 physicians | Assess influence of coronary artery stenosis and risk factors on MFR in patients with CAD | **CAD group:**<br>Men 53/74 (71.6%); mean age 63.0 ± 9.8 years<br><br>**Healthy volunteers:**<br>NR |
| Anagnostopoulos, 2008[13] | **Included:**<br>• CAD group with angiography-confirmed CAD<br>• control group with absence of symptoms and risk factors<br><br>**Excluded:**<br>• patients with history of CABG or valvular heart disease | **$^{82}$Rb-PET/CT:**<br>• 1,480 to 2,220 MBq of 82Rb<br>• 6 frames over 6 minutes<br>• dipyridamole 0.142 mg/kg/min<br>• attenuation correction performed | 1) Quantify MBF at rest and during vasodilation using $^{82}$Rb-PET-CT in patients with atherosclerosis<br>2) Examine relationship between blood flow changes in severity of CAD | **CAD group:**<br>Men 7/15 (46.7%); mean age 60.0 ± 11.0 years<br><br>**Healthy volunteers:**<br>NR |

| Table A1: Characteristics of RCTs and CCTs | | | | |
|---|---|---|---|---|
| **Study and Year** | **Inclusion Criteria, Exclusion Criteria** | **Interventions** | **Objectives and Outcomes** | **Patient Characteristics** |
| Karamitsos, 2010[15] | **Included:**<br>• CAD group with 1- or 2-vessel disease recently documented using coronary angiography<br>• control group with no known CAD, negative family history, no risk factors<br><br>**Excluded:**<br>CAD group of patients with 3-vessel disease, MI in previous 3 months, contraindications to MRI, contraindications to adenosine | **BOLD-CMR**:<br>• 3T system<br>• images obtained during 1 breath hold over 6 heart beats<br>• 4 to 6 images acquired at rest and during infusion of 140 µg/kg/min<br><br>**PET:**<br>• 20-minute scan used for attenuation correction<br>• $^{15}O\text{-}H_2O$ bolus dose of 2.18 MBq/kg at infusion of 10/mL/min for 20 seconds<br>• same dose of adenosine as BOLD-CMR group | 1) Characterize relationship between regional perfusion and oxygenation in healthy volunteers and in patients with CAD<br>2) Compare BOLD-CMR and PET to diagnose CAD | **CAD group:**<br>Men 16/22 (72.7%);<br>mean age 62 ± 8 years<br><br>**Healthy volunteers:**<br>Men 6/10 (60%);<br>mean age 58 ± 6 years |

ATP = adenosine triphosphate; BOLD-CMR = blood oxygen level-dependent cardiovascular magnetic resonance; CABG = coronary artery bypass graft ; CAD = coronary artery disease; CCT = controlled clinical trial; CHD = congestive heart disease; CHF = congestive heart failure; CNCS = Canadian Nuclear Cardiology Society; CT = computed tomography; $^{18}$FDG-PET = 2-deoxy-2-[18F]fluoro-D-glucose position emission tomography; kg = kilogram; LV = left ventricular; MBF = myocardial blood flow; MBq = megabecquerel ; MFR = myocardial flow reserve; mg = milligram; MI = myocardial infarction; min = minute; µg – microgram; mL = millilitre; MRI = magnetic resonance imaging; NR = not reported; $^{15}$O-CO = oxygen-15-labelled carbon monoxide; $^{15}O\text{-}H_2O$ = oxygen-15-labelled water; PET= positron emission tomography; $^{82}$Rb = rubidium-82 chloride; RCT = randomized controlled trial; SPECT = single photon emission computed tomography; T = tesla; Tc-99m-sestamibi = technetium sestamibi.

# APPENDIX 4: SUMMARY AND ASSESSMENT OF INCLUDED GUIDELINES

| **Table A2:** Included Guidelines | | | |
|---|---|---|---|
| **Organization, Year** | **Objective** | **Recommendations On Use of PET (level of evidence or grade recommendation according to guideline authors)** | **AGREE Assessment** |
| European Council of Nuclear Cardiology, 2008[18] | Provide recommendations on use of radionuclide imaging techniques including gated PET for evaluation of cardiac function | **Gated PET perfusion and metabolic imaging:**<br>LVEF can be calculated using gated $^{18}$FDG-PET imaging and commercially available software algorithms, and may be preferable over myocardial perfusion imaging using SPECT; recommendation not made. | Recommend with provisos |
| CCS/CAR/CANM/CNCS/ CanSCMR, 2007[5] | Systematically review evidence on PET, MRI, and multidetector CT in diagnosis and evaluation of ischemic heart disease | **Myocardial perfusion imaging:**<br>**Class I* indications —**<br>• Pharmacological myocardial perfusion imaging using PET for the diagnosis of CAD in patients with intermediate likelihood and/or risk stratification of:<br>o having nondiagnostic, noninvasive imaging tests, or when such a test does not agree with clinical diagnosis (p109)[5] (Level B)[†]<br>o being prone to artifact that could lead to an equivocal result on another test, such as obese patients (p109)[5] (Level B)[†]<br>o being unable to exercise, or having left bundle branch block or ventricular pacing (p109)[5] (Level B).[†]<br>**Class IIa* indications —**<br>• Pharmacological myocardial perfusion imaging using PET for the diagnosis of CAD in patients with intermediate likelihood and/or risk stratification of being able to exercise (p109)[5] (Level B)[†]<br>• For diagnosis and risk stratification of patients being considered for high-risk non-cardiac surgery who have intermediate clinical risk predictors or mild clinical risk predictors with poor functional capacity (p109)[5] (Level B/C).[†] | Recommend with provisos |

| Table A2: Included Guidelines | | | |
|---|---|---|---|
| **Organization, Year** | **Objective** | **Recommendations On Use of PET (level of evidence or grade recommendation according to guideline authors)** | **AGREE Assessment** |
| | | **Class IIb* indications —**<br>• Exercise PET using myocardial perfusion imaging for the diagnosis of CAD or risk stratification (p110)[5] (Level B)[†]<br>• Quantification of MBF to determine the hemodynamic significance of a given stenosis or to diagnose balanced multivessel disease (p110)[5] (Level B/C)[†]<br>• Quantification of MBF to define impaired microvascular function (p110)[5] (Level B/C).[†]<br>**Class III* (no benefit or harmful) —**<br>• Contraindications to all pharmacological agents (dipyridamole, adenosine, dobutamine)<br>• Unstable pattern of ischemic chest pain<br>• Contraindications to radiation exposure (p110).[5]<br><br>**Myocardial $^{18}$FDG-PET viability imaging:**<br>**Class I* indications —**<br>• Define myocardial viability in patients with:<br>o Ischemic heart disease and severe LV dysfunction to identify extent of recoverable myocardium and prognosis in patients being considered for revascularization or cardiac transplantation (p111)[5] (Level B)[†]<br>o Moderate to large fixed perfusion defects, or with equivocal results on another viability test (p111)[5] (Level B).[†]<br>**Class IIa* indications —**<br>• Moderate systolic LV dysfunction and ischemic heart disease to identify the extent of recoverable viable myocardium and prognosis in patients being considered for revascularization or cardiac transplantation (p111)[5] (Level B).[†] | |

| **Table A2:** Included Guidelines | | | |
|---|---|---|---|
| **Organization, Year** | **Objective** | **Recommendations On Use of PET (level of evidence or grade recommendation according to guideline authors)** | **AGREE Assessment** |
| | | **Class III* (no benefit or harmful) —**<br>• Contraindications to insulin;<br>• Severe untreated hypokalemia;<br>• Contraindications to radiation exposure. (p111)[5] | |
| Scottish Intercollegiate Guidelines Network, 2007[16] | Evaluate diagnostic tests that are effective at determining diagnosis and underlying cause of disease | Routine use of myocardial viability testing with dobutamine stress echocardiography, PET, SPECT, or MRI to identify patients most likely to benefit from revascularization is not recommended (p9)[16] (recommended best practice based on clinical experience of guidelines development group) | Strongly recommend |
| National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand, 2006[17] | Obtain better health outcomes by improving management of CHF and reducing unwarranted variation from best practice treatment of CHF in Australia | Nuclear cardiology, stress echocardiography, and PET can be used to assess reversibility of ischemia and viability of myocardium in patients with CHF who have myocardial dysfunction and CHD (p16)[17](Grade of recommendation, D)‡ | Recommend with provisos |

AGREE = Appraisal of Guidelines Research and Evaluation; CAD = coronary artery disease; CANM = Canadian Association of Nuclear Medicine; CanSCMR = Canadian Society of Cardiovascular Magnetic Resonance; CAR = Canadian Association of Radiologists; CCS = Canadian Cardiovascular Society; CHD = coronary heart disease; CHF = congestive heart failure; CNCS = Canadian Nuclear Cardiology Society; CT = computed tomography; $^{18}$FDG-PET = 2-deoxy-2-[18F]fluoro-D-glucose position emission tomography; LV = left ventricular; LVEF = left ventricular ejection fraction; MBF = myocardial blood flow; MRI = magnetic resonance imaging; PET= positron emission tomography; SPECT = single photon emission computed tomography.

*American College of Cardiology and American Heart Association classifications I, II, and III:
Class I: Conditions for which there is evidence and/or general agreement that a given procedure or treatment is useful and effective.
Class II: Conditions for which there is conflicting evidence and/or divergence of opinion about the usefulness/efficacy of a procedure or treatment.
Class IIa: Weight of evidence/opinion is in favour of usefulness/efficacy.
Class IIb: Usefulness/efficacy is less well-established by evidence/opinion.
Class III: Conditions for which there is evidence and/or general agreement that the procedure/treatment is not useful/effective and, in some cases, may be harmful.

† Levels of evidence for individual class assignments:
Level A: Data derived from randomized clinical trials.
Level B: Data derived from a single randomized trial, or from non-randomized studies.
Level C: Consensus opinion of experts.

‡Grade of Recommendation: D = no evidence available — panel consensus judgment.

| Table A3: AGREE Domain Scores and Overall Assessment | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Organization, Year** | **Scope and Purpose (%)** | **Stakeholder Involvement (%)** | **Rigour of Development (%)** | **Clarity and Presentation (%)** | **Applicability (%)** | **Editorial Independence (%)** | **Overall Assessment (%)** |
| European Council of Nuclear Cardiology, 2008[18] | 72 | 46 | 33 | 58 | 22 | 33 | Recommend with provisos |
| CCS/CAR/CANM/CNCS/ CanSCMR, 2007[5] | 67 | 46 | 71 | 58 | 33 | 33 | Recommend with provisos |
| Scottish Intercollegiate Guidelines Network, 2007[16] | 89 | 60 | 90 | 75 | 72 | 75 | Strongly recommend |
| National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand, 2006[17] | 83 | 50 | 36 | 67 | 39 | 61 | Recommend with provisos |

AGREE = Appraisal of Guidelines Research and Evaluation; CANM = Canadian Association of Nuclear Medicine; CanSCMR = Canadian Society of Cardiovascular Magnetic Resonance; CAR = Canadian Association of Radiologists; CCS = Canadian Cardiovascular Society; CNCS = Canadian Nuclear Cardiology Society.

# APPENDIX 5: ADDITIONAL ARTICLES CITED BY EXTERNAL REVIEWERS (not meeting inclusion criteria)

1. Dorbala S, Hachamovitch R, Curillova Z, Thomas D, Vangala D, Kwong RY, et al. Incremental prognostic value of gated Rb-82 positron emission tomography myocardial perfusion imaging over clinical variables and rest LVEF. *JACC Cardiovasc Imaging*. 2009 Jul;2(7):846-54. PubMed: PM19608135

2. D'Egidio G, Nichol G, Williams KA, Guo A, Garrard L, deKemp R, et al. Increasing benefit from revascularization is associated with increasing amounts of myocardial hibernation: a substudy of the PARR-2 trial. *JACC Cardiovasc Imaging*. 2009 Sep;2(9):1060-8. PubMed: PM19761983

3. Herzog BA, Husmann L, Valenta I, Gaemperli O, Siegrist PT, Tay FM, et al. Long-Term Prognostic Value of 13N-Ammonia Myocardial Perfusion Positron Emission Tomography. Added Value of Coronary Flow Reserve. *J Am Coll Cardiol*. 2009;54(2):150-6. PubMed: PM19573732

4. Desideri A, Cortigiani L, Christen AI, Coscarelli S, Gregori D, Zanco P, et al. The extent of perfusion-F18-fluorodeoxyglucose positron emission tomography mismatch determines mortality in medically treated patients with chronic ischemic left ventricular dysfunction. *J Am Coll Cardiol*. 2005;46(7):1264-9. PubMed: PM16198841