

# Multidetector Computed Tomography for Coronary Artery Disease Screening in Asymptomatic Populations

Evidence-Based Analysis

May 2007



Medical Advisory Secretariat  
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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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# Abbreviations

<b>CT</b>	Computed tomography
<b>MDCT</b>	Multidetector computed tomography
<b>ACC/AHA</b>	American College of Cardiology/American Heart Association
<b>BMI</b>	Body mass index
<b>CA</b>	Coronary angiography
<b>CAD</b>	Coronary artery disease
<b>CAC</b>	Coronary artery calcification
<b>CABG</b>	Coronary artery bypass graft
<b>CCS</b>	Canadian Cardiovascular Study
<b>CCN</b>	Cardiac Care Network
<b>CI</b>	Confidence interval
<b>DSCT</b>	Dual-slice computed tomography
<b>EBCT</b>	Electron beam computed tomography
<b>ECG</b>	Electrocardiogram/electrocardiography
<b>ETT</b>	Exercise treadmill test
<b>FDA</b>	Federal Drug Administration (US)
<b>GRADE</b>	Grading of Recommendations, Assessment, Development and Evaluation
<b>IBIS</b>	Integrated Biomarker and Imaging Study
<b>INSIGHT</b>	Intervention as a Goal in Hypertension Treatment
<b>LVH</b>	Left ventricular hypertrophy
<b>MI</b>	Myocardial infarction
<b>MRI</b>	Magnetic resonance imaging
<b>NPV</b>	Negative predictive value
<b>PPV</b>	Positive predictive value
<b>RCT</b>	Randomized clinical trial
<b>SBP</b>	Systolic blood pressure
<b>SHAPE</b>	Screening for Heart Attack Prevention and Education
<b>TCS</b>	Total calcium score
<b>USPSTF</b>	United States Preventive Services Task Force
<b>WHO</b>	World Health Organization

# Executive Summary

## Objective

This evidence-based health technology assessment systematically reviewed the published literature on multidetector computed tomography (MDCT) angiography (with contrast) as a diagnostic tool for coronary artery disease (CAD), and applied the results of the assessment to health care practices in Ontario.

## Clinical Need

Coronary artery disease is the leading cause of death in the western world. Occlusion of coronary arteries reduces coronary blood flow and oxygen delivery to the myocardium (heart muscle). The rupture of an unstable atherosclerotic plaque may result in myocardial infarction. If left untreated, CAD can result in heart failure and, subsequently, death. According to the Heart and Stroke Foundation of Canada, 54% of all cardiovascular deaths are due to CAD. Patient characteristics (e.g., age, sex, and genetics), underlying clinical conditions that predispose to cardiac conditions (e.g., diabetes, hypertension, and elevated cholesterol), lifestyle characteristics, (e.g., obesity, smoking, and physical inactivity), and, more recently, determinants of health (e.g., socioeconomic status) may predict the risk of getting CAD.

In 2004/2005, The Ontario government funded approximately 15,400 percutaneous (through the skin) coronary interventions and 7,840 coronary bypass procedures for the treatment of CAD. These numbers are expected to reach 22,355 for percutaneous coronary interventions and 12,323 for coronary bypass procedures in 2006/2007. It was noted that more than one-half of all first coronary events occur in people without symptoms of CAD. In Ontario in 2000/2001, \$457.9 million (Cdn) was spent on invasive (\$237.4 million) and noninvasive (\$220.5 million) cardiac services. The use of noninvasive cardiac tests, in particular, is rising rapidly.

## The Technology

Computed tomography (CT) is a medical imaging method employing tomography where digital geometry processing is used to generate a 3-dimensional image of the internals of an object from a large series of 2-dimensional X-ray images taken around a single axis of rotation. Multidetector computed tomography is performed for noninvasive imaging of the coronary arteries. Computer software quantifies the amount of calcium within the coronary arteries and calculates a coronary artery calcium score.

Compared with conventional CT scanning, MDCT can provide smaller pieces of information and cover a larger area faster. Advanced MDCT technology (that is, 8-, 16-, 32-, and 64-slice systems) can produce more images in less time. For general CT scanning, this faster capability can reduce the length of time people are required to be still during the procedure and thereby reduce potential movement artifact. However, the additional clinical utility of images obtained from faster scanners compared with the images obtained from conventional CT scanners for current CT indications (i.e., nonmoving body parts) is unknown.

## Review Strategy

The Medical Advisory Secretariat completed a computer-aided search limited to English-language studies



in humans from 1998 to 2007 in multiple medical literature databases, including MEDLINE, EMBASE, The Cochrane Library, and INAHTA/CRD. Case reports, letters, editorials, nonsystematic reviews, and comments were excluded. Additional studies that met the inclusion and exclusion criteria were obtained from reference lists of included studies. Inclusion and exclusion criteria were applied to the results according to the criteria listed below.

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) system was used to evaluate the overall quality of the body of evidence (defined as 1 or more studies) supporting the research questions explored in this systematic review.

### **Summary of Findings and Conclusions**

Screening the asymptomatic population for CAD using MDCT does not meet World Health Organization criteria for screening; hence, it is not justifiable. Coronary artery calcification measured by MDCT is a good predictor of future cardiovascular events. However, MDCT exhibits only moderately high sensitivity and specificity for detection of CAD in an asymptomatic population. If population-based screening were implemented, a high rate of false positives would result in increased downstream costs and interventions. Additionally, some cases of CAD would be missed, as they may not be developed, or not yet have progressed to detectable levels. There is no evidence for the impact of screening on patient management. Cardiovascular risk factors are positively associated with the presence of coronary artery calcification and cardiovascular events; however, risk factor stratification to identify high-risk asymptomatic individuals is unclear given the current evidence-base.

Safety of MDCT screening is also an issue because of the introduction of increased radiation doses for the initial screening scan and possible follow-up interventions.

No large randomized controlled trials of MDCT screening have been published, which indicates an important area of future research.

Lastly, the policy implications for MDCT screening for CAD in the asymptomatic population are significant. There is no evidence on the long-term implications of screening, and the potential impact on the resources of the health care system is considerable.

# Objective

This evidence-based health technology assessment systematically reviewed the published literature on multidetector computed tomography (MDCT) angiography (with contrast) as a diagnostic tool for coronary artery disease (CAD), and applied the results of the assessment to health care practices in Ontario.

## Background

### **Clinical Need: Target Population and Condition**

Coronary artery disease is the leading cause of death in the western world. Occlusion of coronary arteries reduces coronary blood flow and oxygen delivery to the myocardium (the middle and thickest layer of the heart wall). The rupture of an unstable atherosclerotic plaque may result in myocardial infarction (MI). If left untreated, CAD can result in heart failure and, subsequently, death. According to the Heart and Stroke Foundation of Canada, (1) 54% of all cardiovascular deaths are due to CAD. Patient characteristics (e.g., age, sex, genetics), underlying clinical conditions that predispose to cardiac conditions (e.g., diabetes, hypertension, elevated cholesterol), lifestyle characteristics, (e.g., obesity, smoking, physical inactivity) and, more recently, determinants of health (e.g., socioeconomic status) may predict the risk of getting CAD.

In 2004/2005, the Ontario government funded approximately 15,400 percutaneous coronary interventions (PCIs) and 7,840 coronary artery bypass (CABG) procedures for the treatment of CAD. These numbers are expected to reach 22,355 for PCIs and 12,323 for CABG procedures in 2006/2007. It was noted that more than one-half of all first coronary events occur in people without symptoms of CAD. (2) In Ontario in 2000/2001, \$457.9 million (Cdn) was spent on invasive (\$237.4 million) and noninvasive (\$220.5 million) cardiac services. (2) The use of noninvasive cardiac tests, in particular, is rising rapidly. (2)

Recently, the Association for the Eradication of Heart Attack in the United States (3) released its Screening for Heart Attack Prevention and Education (SHAPE) practice guidelines, calling for noninvasive screening to detect subclinical atherosclerosis in asymptomatic men aged 45 to 75 years, and asymptomatic women aged 55 to 75 years who are not considered very low risk. It was estimated that these target populations include approximately 50 million people in the United States. Based on the population of Ontario, this translates to approximately 1.9 million people in this province. Proposed screening methods for detecting asymptomatic coronary artery calcification (CAC) include the use of electron beam computed tomography (EBCT) or MDCT.

### **Screening for Asymptomatic Coronary Artery Disease**

Coronary artery calcification has been observed in all stages of atherosclerotic plaque development. It is, therefore, considered a surrogate marker of CAD. Within coronary vessels, the quantity of coronary calcium correlates moderately closely with the extent of atherosclerotic plaque burden, whereas the presence or absence of calcium is not closely associated with the propensity of an individual atherosclerotic plaque to rupture. It has been suggested that an asymptomatic person's coronary calcium score can be integrated with other risk factors for risk stratification and goal-directed prevention. (4) Different types of CT have been investigated as a tool for detecting and quantifying CAC.

## **Atherosclerosis Progression and Investigation**

Coronary artery disease is characterized by atherosclerosis, a slow, progressive condition that begins early in life. It occurs when plaque comprised of fat, such as cholesterol, phospholipids, and calcium accumulate in the arteries, thereby depleting the arteries of their elasticity. The arteries narrow and subsequently hinder the smooth passage of blood. CAD can lead to angina if blood flow is limited sufficiently or to heart attack if plaque ruptures and suddenly blocks an artery. (1)

There are various stages in the development of atherosclerosis (Appendix 1). Each phase has relatively distinct morphological characteristics that can permanently stabilize or progress. (5) Types 1 and 2 have minimal clinical significance, except to indicate that the disease is progressing. Type 3 may be reversible with lifestyle adjustments, but may also lead to more serious disease. Types 4 and 5 are clinically significant, although arterial narrowing may be minimal and therefore may go undetected without symptoms. People with Type 4 or 5 arterial morphology, those with the accumulation of arterial plaque, may experience angina, acute MI, ischemia, or sudden cardiac death. If detected, these types may require significant clinical intervention. Type 6 has significant lesions with marked calcification in the arteries that may deform arterial shape. People with this type will also require treatment. Untreated, severe CAD may lead to heart attack, stroke, or death.

Clinically significant CAD is defined as “ $\geq 70\%$  diameter stenosis of at least one major epicardial artery segment and/or  $\geq 50\%$  diameter stenosis of the left main coronary artery.” (6)

## **Existing Treatments Other Than Technology Being Reviewed**

### **Existing Diagnostic Tests for Coronary Artery Disease**

A range of noninvasive and invasive diagnostic tests are available and used extensively for the investigation of CAD.

**Patient history and physical examination:** According to the College of Cardiology/American Heart Association guidelines, (6) a detailed clinical history is the most important part of an investigation into chest pain, because this allows the health care provider to assess and predict the likelihood of significant CAD. The factors typically assessed are as follows:

- Quality descriptors of chest pain (for example, squeezing, grip-like, suffocating, heavy)
- Location
- Duration of pain
- Factors that provoke pain
- Factors that relieve pain

Chest pain can be classified as typical, atypical, or noncardiac. It can further be classified as stable or unstable angina, and can be categorized into a class system based on physical function, which was developed by the Canadian Cardiovascular Society (Appendix 2). (7)

Identification of risk based on the Canadian Cardiovascular Society grading, family history, clinical risk factors (e.g., hypertension, diabetes, and high cholesterol), and lifestyle factors (e.g., smoking and exercise) can guide the course of diagnostic investigation and treatment. (6)

**Electrocardiogram (ECG):** This noninvasive test provides information about the electrical activity of the heart over time while the patient is at rest. Specifically, the heart rhythm, size, and position of the myocardial chambers; deformities or damage to the heart; and any electrolyte abnormalities may be detected. This is a short (10 minutes) noninvasive test.

**Exercise stress test:** This test provides information about the electrical activity of the heart during exercise, usually while walking on a treadmill. This test is part of the diagnostic work-up for people who are suspected of having CAD, for people who have already been diagnosed with CAD to investigate disease progression, and for people who have had a heart attack or heart surgery.

**Nuclear imaging such as thallium or single-photo emission computed tomography:** These tests provide information about the flow of blood into the heart. A radioactive tracer is injected into a vein in the arm, and a camera measures the amount of radioactivity that is carried by the blood into the heart. The tracer will not pick up areas with poor blood supply. In this way, the location of damaged areas of the heart can be identified. Indications are the investigation of chest pain, arrhythmia during stress testing, extent, and location of damage post-MI, and function of grafted vessels after CABG.

**Echocardiography:** A series of high-frequency sound waves are emitted toward the heart from a handheld transducer that is held at chest level. The sound waves that bounce back provide information about the muscle of the heart and can detect the integrity of the heart valves (e.g., if they are narrowing or if there is leakage). This test takes between 15 and 45 minutes. Transesophageal ECHO, whereby a tube emitting sound waves is inserted into the esophagus, can provide even more detailed information that may not be available through conventional echocardiography. Stress test echocardiography has similar or better utility compared with nuclear stress imaging.

**Coronary angiography (CA):** If there is suspicion of significant disease, CA is performed to determine if atherosclerosis is present, and the extent and location of stenosis. This is an invasive procedure where a dye is injected into the bloodstream through a catheter that allows the coronary arteries to be examined by X-ray. It takes about 1 hour and is commonly done in catheterization labs. Coronary angiography is considered the gold standard tool for the diagnosis of CAD.

Complications resulting from CA may occur in from 1 in 500 to 1 in 1000 cases. (5) These may include the following:

- Cardiac arrhythmia
- Cardiac tamponade
- Trauma to the artery caused by hematoma
- Low blood pressure
- Reaction to contrast medium
- Hemorrhage
- Stroke
- Heart attack

The risks particularly associated with catheterization include the following:

- Bleeding, infection, and pain at the site of the insertion of the intravenous tube
- Damage to the blood vessels by the soft plastic catheter
- Formation of blood clots on the catheter that could block blood vessels somewhere in the body
- Damage to the kidneys caused by the contrast material

**Intravascular ultrasound (IVUS):** According to a health technology assessment published by the Medical Services Advisory Committee in Australia, (8) IVUS may be an adjunctive procedure to CA, because it may provide additional information about the composition of plaque in the coronary and peripheral vessels. Berry et al. (8) also found that IVUS may aid in the accuracy of stent placement and provides statistically significant lower odds of restenting at 9 to 12 months compared with non-IVUS-guided stenting (odds ratio [OR], 0.73 [95% confidence interval (CI), 0.54–0.99],  $P = .04$ ). However, based on a lack of evidence, Medical Services Advisory Committee recommended against public funding for the use of IVUS in Australia.

In Ontario, IVUS of the coronary arteries is not an insured service (Personal communication, March 2005). In a review by the Medical Advisory Secretariat, IVUS was found to be safe; it had no impact on survival rates or MI. (9) However, IVUS was found to decrease revascularization rates following stenting. (9) Restenosis rates in low-risk patients in Ontario were found to be significantly lower than reported restenosis rates in the studies included in the review. (9) Based on the Medical Advisory Secretariat review, the Ontario Health Technology Assessment Committee recommended against the use of IVUS in routine PCI and that, in the interim, IVUS should be used to guide PCI at the discretion of the physician, for specific high-risk patients in whom angiography guidance is found to be inadequate. (10)

Other imaging tests that may be used to evaluate the anatomy, function, perfusion, and tissue characterization in patients with ischemic heart disease are EBCT, contrast-enhanced functional magnetic resonance imaging, and cardiac positron emission tomography. These imaging modalities are not the standard of practice for the investigation of CAD in Ontario; therefore, they are beyond the scope of this assessment.

### **Treatment for Coronary Artery Disease**

If stenosis of a vessel is found, treatment options are many and need to be individualized. While a detailed description is beyond the scope of this review, in general they involve optimization of lifestyle factors, medication, and percutaneous or surgical procedures to address coronary stenoses.

## **New Technology Being Reviewed**

### **Multidetector Computed Tomography and Computed Tomography Angiography**

Computed tomography is a medical imaging method employing tomography where digital geometry processing is used to generate a 3-dimensional image of the inside of an object from a large series of 2-dimensional X-ray images taken around a single axis of rotation. Multidetector computed tomography is performed for noninvasive imaging of the coronary arteries. Computer software quantifies the amount of calcium within the coronary arteries and calculates a coronary artery calcium score (Table 1).

**Table 1: Coronary Calcium Score**

Agatston/Calcium Score	Presence of Plaque
0	No evidence of plaque
1–10	Minimal evidence of plaque
11–100	Mild evidence of plaque
101–400	Moderate evidence of plaque
Over 400	Extensive evidence of plaque

A 2004 study (11) suggests that MDCT is equivalent to EBCT for the determination and quantification of coronary calcium. While EBCT is used exclusively for the heart, MDCT can be used for other organs.

Compared with conventional CT scanning, MDCT can provide smaller pieces of information and cover a larger area faster. (11;12) Advanced MDCT technology (8-, 16-, 32-, and 64-slice systems) can produce more images in less time. For general CT scanning, this faster capability can reduce how long people are required to be still during the procedure and thereby reduce potential movement artifact. However, the additional clinical utility of images obtained from faster scanners compared with the images obtained from conventional CT scanners for current CT indications (i.e., nonmoving body parts) is unknown.

To take full advantage of the technology, considerable post-processing of images, upgraded software, and increased storage and processing capabilities are required. Table 2 provides example specifications of faster scanners compared with conventional single-slice scanners.

**Table 2: Specifications of Conventional and Multidetector Computed Tomography Scanners**

Scanner	Contiguous Slices, mm	Coverage, mm	Times, Seconds
Conventional	10	25	25/rotation
4-slice	5	25	6.25/rotation
64-slice	Credit card	40	0.3/rotation

Source: ECRI; 2002 (12)

Cited clinical advantages of MDCT over conventional CT for general scanning purposes include these: (12)

- Has faster and better spatial resolution; covers more volume; and uses contrast media more efficiently.
- May be useful for other indications and populations: pediatrics/geriatrics/bariatric/cardiology.
- May replace other more invasive or cumbersome procedures.
- May affect workflow because of faster scanning times (no need to wait for the X-ray tube to cool between patients, and can reconstruct images retrospectively).
- Some users are scanning about 60 patients per day, compared with 25 with single scanner.
- Images can be sent straight to software, but efficient image management is necessary.

Cited disadvantages include these: (12)

- “Not a prerequisite for good patient care.”
- Radiation dose higher than conventional CT or other imaging tools.

## **Computed Tomography for Coronary Artery Disease**

The introduction of faster CT scanners provides some new indications. Most notably, reasonable images of moving body parts, such as the coronary arteries and vessels, can now be obtained, owing to the reduced movement artifact with faster CT. Multidetector computed tomography angiography is being proposed as a minimally invasive replacement for CA to diagnose CAD.

### **Multidetector Computed Tomography for Cardiac Imaging**

According to some cardiology and radiology experts (Personal communication, 2005), manufacturers' advertising, and technology forecasts (13;14) the introduction of 64-slice CT scanning may greatly enhance the capability for examination of the coronary arteries in the following ways:

- The applications for cardiac imaging could greatly increase, with some (13;14) believing that CT-enhanced angiography could replace cardiac catheterization, IVUS, magnetic resonance imaging, and echocardiography as diagnostic tools for CAD assessment.
- The indications for MDCT may be expanded to these areas:
  - Diagnosis of noncalcified plaque in coronary arteries,
  - Follow-up after CABG surgery,
  - Detection and quantification of coronary artery stenosis, and
  - Measurement of ejection fraction and evaluation of myocardial perfusion.
- MDCT may assume the role of "gatekeeper" to cardiac catheterization to rule out atherosclerosis.
- MDCT may be used for patients who cannot have conventional angiography, because it is less invasive.
- Increased use of MDCT may decrease the necessity for CA.
- Various cardiac tests could become redundant and be eliminated.
- Higher patient volumes might be possible to achieve.
- MDCT could identify patients who would most benefit from medical therapy earlier, thereby prolonging the necessity for invasive procedures such as angioplasty and CABG.
- MDCT is less expensive, less time-consuming, and less invasive than CA (takes < 30 minutes with only 1 injection of contrast [X-ray requires intra-arterial catheterization] compared with 1 hour for CA).

Possible limitations of 64-slice CT for coronary vessel imaging are these: (12-14)

- The effectiveness of 64-slice CT to detect CAD is unknown.
- The overall clinical utility of 64-slice CT in the management of patients with CAD is unknown.
- Unnecessary therapeutic angioplasty could increase due to earlier detection of disease.
- Conventional CA is still necessary to confirm noninvasive imaging (X-ray has higher spatial and temporal resolution); MDCT could be additive to CA rather than a replacement.
- Radiation dose is not insignificant, and there would be different amounts of radiation from noncontrast MDCT and contrast CTA MDCT.

In 2005, the Medical Advisory Secretariat completed a health technology policy assessment on the utility of MDCT angiography for CAD. Based on the evidence presented in the report, the Ontario Health Technology Advisory Committee recommended that a field evaluation be conducted to determine the effectiveness and cost-effectiveness of 64-slice MDCT angiography in the investigation of CAD. A field evaluation of 64-slice MDCT angiography is underway. (15)

## Screening for Coronary Artery Disease in Asymptomatic Adults

Some clinical cardiac experts (Personal communication, 2005) and published peer-reviewed studies (16) suggest that as MDCT technology advances, screening asymptomatic people with MDCT might help to identify CAD early so that medical therapy can be started. The aim is to halt or stabilize the progression of CAD, thereby decreasing patient morbidity, reducing the number of invasive procedures needed, and improving overall patient outcomes.

Screening refers to the identification of a risk factor or an early marker of disease in a defined group of people before the condition becomes symptomatic or diagnosed. The goal of screening is to intervene medically to circumvent the progression of the full-blown condition. The Council of Europe (17) has established a set of recommendations on screening as a preventive tool in medicine, and this has been used by many large global health organizations (e.g., World Health Organization [WHO]). The most salient points from the recommendations are these:

- Screening is only one method to control disease and reduce health burdens, and should be placed in the context of the spectrum from health promotion and prevention programs to the organization of health systems.
- Screening raises ethical, legal, social, medical, organizational, and economic issues.
- Effectiveness of a screening tool must be established.
- Screening must be ethical.
- A target population must be defined.
- There must be a treatment, and access to treatment must be available.
- Positive results obtained from screening should always be confirmed by subsequent diagnostic tests before beginning treatment for a condition.
- Information on the positive and negative aspects of screening must be made available to patients.
- Screening programs should be subjected to continuous evaluation, including of participation, technical quality of screening tool, follow-up of those screened, and side effects of false positives and negatives.
- The screening tool must be safe, and the harm of disease must be outweighed by harm proposed by the screening tool.

Various modalities have been proposed for the screening of CAD. The ability to detect CAC as a screening tool for CAD has been available since the late 1990s with the advent of EBCT. In Ontario, EBCT was not adopted as an insured service, because it did not meet the above international standards as a screening tool.

According to a recent report by the United States Preventative Task Force, (18) screening people at low-risk for heart disease using treadmill exercise testing, resting ECG, or EBCT is not recommended. The task force concluded the following:

- Although these modalities could identify some people at higher risk of heart disease, there have been no studies that conclude that this in itself changes patient outcomes
- The additional value of risk identification for CAD is likely to be low
- The additional value of risk identification in older adults may be higher, but it is not clear how this information will affect clinical decision-making
- There is no evidence to suggest that these modalities lead to more effective treatments and risk-reducing interventions than traditional risk factor assessment (Framingham risk predictions)
- Identification of CAD in low-risk people using these 3 modalities could in fact cause more harm than good in that:



- False positives can lead to unnecessary invasive CA to confirm results; but there are some complications associated with CA.
- Unnecessary psychological burden may be placed on disease-free individuals.
- False positives can lead to over-treatment of disease-free people.
- False negatives can prolong treatment for people in whom it is indicated.

## Regulatory Status

Electron beam computed tomography is not now licensed in Canada. One EBCT scanner was licensed by Health Canada as a Class 3 medical device, but the license was discontinued in October 2005. As EBCT is not licensed in Canada, it is beyond the scope of this review.

In Canada, there are several MDCT systems licensed as Class 3 medical devices (Table 3). The Class 3 status indicates that they are considered potentially hazardous and could cause harm if they fail. Currently, 4 companies have licensing clearance for MDCT by Health Canada (Table 3). Only 1 has licensing clearance for 64-slice CT. All 4 have clearance for 16-slice CT.

Screening for CAC using either EBCT or CT is not an insured health service in Ontario. The scanning of the coronary vessels by CT is not an insured service within the Ontario Schedule of Benefits and therefore is not covered by the Ontario Health Insurance Program. However, there is a fee-for-service code for CT of the thorax and for other anatomic sites. This would include MDCT scans (Personal communication, February 2005).

**Table 3: Computed Tomography Devices Licensed in Canada**

Name of device	Licence number
<b>Siemens AG (Munich, Germany)</b>	
SOMATOM SENSATION 64/SENSATION CARDIAC 64	65633
SOMATOM SENSATION CARDIAC	60814
SOMATOM SENSATION 16	60813
SOMATOM EMOTION 6	61943
SOMATOM SENSATION 10	61941
SOMATOM SENSATION 4	34510
<b>General Electric Medical Systems (Milwaukee, Wisconsin, United States)</b>	
LIGHTSPEED 16 CT SCANNER SYSTEM	60610
LIGHTSPEED PLUS CT SCANNER SYSTEM	29420
LIGHTSPEED ULTRA CT SCANNER SYSTEM	32409
HISPEED QX/I CT SCANNER SYSTEM	61757
LIGHTSPEED 16 CT SCANNER SYSTEM	60610
LIGHTSPEED RT CT SCANNER SYSTEM (8 slice)	63325
<b>Philips Medical Systems (Haifa, Illinois, United States)</b>	
MX8000 MULTISLICE CT IMAGING SYSTEM	18575
BRILLIANCE MULTISLICE CT IMAGING SYSTEM	35033
<b>Toshiba Medical Systems Corporation (Tochigi, Japan)</b>	
AQUILION 32 3 AQUILION 32 - CARDIAC FUNCTION ANALYSIS	66981
AQUILION SUPER 4 EDITION	64214
AQUILION CFX EDITION	65425

In the United States, EBCT was accepted by the Food and Drug Administration (FDA) 510(k) for generating 2- and 3-dimensional images of any human anatomic cavity associated with the head, chest, abdomen, pelvis, spine, or organs including blood and lymph vessels. (19) Further, EBCT is indicated for

determining specific quantitative information such as volume of calcium or other materials in organs, including bone, or tumours; and for angiography. (13) In the United States, CT is regulated under 2 statutes, the *Radiation Control for Health and Safety Act, 1985* and the *Medical Device Amendments to the Food, Drug, and Cosmetic Act, 1938*

# Literature Review on Effectiveness

## Objective

To determine the utility and cost-effectiveness of CT screening for CAD in asymptomatic people and evaluate its use relative to WHO criteria for screening programs, along with safety standards and legislation for CT and radiation safety.

## Questions Asked

The following questions were addressed to determine the utility and cost-effectiveness of CT screening for CAD in asymptomatic people:

- Does the use of MDCT meet the WHO criteria (20) for screening people with asymptomatic CAD?
- What are the sensitivity, specificity, and predictive values of MDCT for predicting presence and severity of atherosclerosis?
- What is the reproducibility of MDCT and EBCT screening?
- Do results of CT screening change management of patients?
- What is the impact of MDCT screening of asymptomatic CAD on future cardiovascular clinical events such as incidence of MI and patient survival?
- Is MDCT a safe screening tool for CAD? What is the radiation dose of each diagnostic?
- What is the cost-effectiveness of MDCT screening of asymptomatic CAD to avoid an MI or death?

## Methods

The Medical Advisory Secretariat completed a computer-aided search limited to English-language studies in humans from 1998 to 2007. Case reports, letters, editorials, nonsystematic reviews, and comments were excluded. The search strategy is detailed in Appendix 3. Additional studies that met the inclusion and exclusion criteria were obtained from reference lists of included studies. Inclusion and exclusion criteria were applied to the results according to the criteria listed below.

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) system (21;22) was used to evaluate the overall quality of the body of evidence (defined as 1 or more studies) supporting the research questions explored in this systematic review.

## Literature Search

- MEDLINE
- MEDLINE In-Process and Other Non-Indexed Citations
- EMBASE
- Cochrane Library
- INAHTA/CRD
- Google and reference sections from reviews and extracted articles

## **Population**

- Asymptomatic population

## **Intervention**

- Use of MDCT to screen for CAD

## **Comparators**

- Any non-MDCT diagnostic modality used for CAD screening

## **Outcomes**

- Coronary outcomes in asymptomatic individuals negative for CAC
- Coronary outcomes in asymptomatic individuals with no or few cardiovascular risk factors
- Presence of CAC in asymptomatic individuals with no or few cardiovascular risk factors

## **Inclusion Criteria**

- English-language articles
- Journal articles that reported primary data on the effectiveness or cost-effectiveness of data obtained in a clinical setting
- Journal articles that reported an analysis of primary data maintained in registries or databases
- Study design and methods that were described clearly
- Systematic reviews, randomized controlled trials (RCTs), non-RCTs, or cohort studies that had at least 20 patients, and cost-effectiveness studies
- Relevant populations (i.e., not symptomatic patients)
- Devices licensed by Health Canada

## **Exclusion Criteria**

- Duplicate publications (publications superseded by another publication by the same investigator group with the same objective and data)
- Non-English-language articles
- Nonsystematic reviews, letters, and editorials
- Animal and *in vitro* studies
- Case reports
- Studies that did not examine the outcomes of interest
- Subjects not within the population of interest (i.e., symptomatic patients) or studies that did not describe the population of interest

## **Outcomes of Interest**

- Sensitivity and specificity of MDCT for CAD
- Frequency and distribution of CAC
- CAC predict cardiovascular outcomes
- Risk factor frequency and distribution

- Risk factor association with CAC
- Risk factor association with cardiovascular events
- Safety of MDCT for CAD screening

## Results of Literature Review

There were 6 systematic reviews on the effectiveness of CT screening for asymptomatic populations, 4 observational studies examining MDCT screening for CAD in asymptomatic populations, and 1 RCT and 2 observational studies, on the impact of screening on behaviour modification retrieved from the literature review that met the inclusion and exclusion criteria (Table 4). Descriptions of studies are discussed below according to level of evidence.

One reviewer, who was not blinded to author, institution, or journal of publication, evaluated the eligibility of citations retrieved from literature search. Articles were excluded based on information reported in the title and abstract, and the full document of potentially relevant articles was retrieved for further assessment. A second reviewer extracted data from the included studies and completed the remainder of the literature review. Information on study population, study methods, interventions, and study outcomes were recorded.

**Table 4: Quality of Evidence of Included Studies\***

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

\* RCT refers to randomized controlled trial; g, grey literature.

## Health Technology Assessments and Systematic Reviews

There were 6 systematic reviews and health technology assessments retrieved from the literature search on CT (Table 5). Most of the studies focused on EBCT. Only Waugh et al. (23) included studies on MDCT. However, Waugh et al. concluded that CT screening for CAD in asymptomatic patients was unjustifiable, and they suggested that improving ways to identify asymptomatic persons at high risk of heart disease is needed. (23) Additionally, the other reviews and health technology assessments have not yet endorsed CT screening for asymptomatic populations, but mostly highlighted the associations between screening and CAD outcomes (Table 6).

In a separate, nonsystematic, brief review from the Canadian Coordinating Office for Health Technology Assessment, (24) the prognostic value of MDCT was compared with EBCT. There was some evidence of the comparability of MDCT to EBCT. Prognostic values of MDCT compared with EBCT in asymptomatic individuals had a sensitivity of 74% and a specificity of 70%. However, there was insufficient evidence to recommend CAC screening in asymptomatic people.

**Table 5: Overview of Health Technology Assessments and Systematic Reviews on Multidetector Computed Tomography Screening for Coronary Artery Disease in Asymptomatic Populations\***

Study, Year	Studies Included	Population	Comparator	Outcome Measures	Findings
Waugh et al., 2006 (23)	Observational studies: 6 on EBCT and 1 on CT (1994–Feb. 2006)	Asymptomatic for CAD  Had intervention after screening	Risk factor assessment (risk factor scores)	RR for cardiac death or MI  CAC vs. no CAC (meta-analysis)  Correlation between CAC & risk factor score  Added value of CAC to RF on outcomes  Cost-effectiveness analysis	EBCT and other forms of CT can quantify CAC.  CAC predicts coronary artery events & there is a dose- response relationship; RR, 43; 95% CI, 3.05–6.44  CAC can add to the information from clinical risk scores such as the Framingham score and be used to shift people from intermediate to high or low risk.  No evidence that knowledge of risk scores has affected outcomes.  Statin treatment trials showed reduction in cholesterol but not in CAC.
Pletcher, 2004 (25)	4 observational studies (Jan. 1980–March 19, 2003)  All non-contrast EBCT	Asymptomatic of CAD	None	CAC score-specific OR coronary calcification for CAD events (CAD deaths, nonfatal MI, revascularization) adjusted for age, hypertension, high cholesterol, diabetes, and smoking.	Meta-analysis (random effect)  <u>CAC score</u> <u>Adjusted OR (95% CI)</u> 0                    1 1–100            2.1 (1.6–2.9) 101–400        5.4 (2.2–13) > 400            10 (3.1–34) Heterogeneity – wide 95% CI Coronary calcium score is an independent predictor of coronary events.
Pignone, 2003 (18) for US Preventive Services Task Force	Observational studies mostly on ECG and treadmill testing  Quoted 1 systematic review on EBCT; no review of individual studies  (1996–2002)	Asymptomatic, no previous history of CAD, on whom independent effect of the test on incidence of CAD events were reported	ECG, exercise treadmill testing in predicting risk of future events	Effect of CAC on health outcomes, adoption of risk-reducing behaviours, ability of CAC to independently predict risk of cardiac events (relative risks).	No study on effect of CAC screening on CAD or other health outcomes.  Qualitative synthesis; no meta-analysis.  ECG, ETT, and EBCT each appear to provide some independent prognostic information above and beyond that from traditional risk factor assessment.  The effect of this additional information on clinical decision-making

Study, Year	Studies Included	Population	Comparator	Outcome Measures	Findings
ECRI, 2004 (26)	10 observational studies with > 50 patients each (1996–2004)  All EBCT	7/10 studies on asymptomatic patients	Other risk predictors (cholesterol, hypertension, diabetes, smoking, Framingham model)	RR of coronary events based on CAC score	has not been assessed.  Elevated CAC score predicted future coronary events in low- high-risk individuals, but other tests, such as those to measure BP and cholesterol, had similar predictive values.  Too few studies to permit meta-analysis of the results.  Reported RR for CAD events: asymptomatic patient, low risk (CAC, RR, 21.7; other risk factors, RR, 2.8–5.4)  Asymptomatic patient, high risk (CAC, RR, 2.3–5; other risk factors, RR, 2.3–2.9)
O'Malley, 2000 (27)	4 full reports and 5 published abstracts  5 observational studies included in meta-analysis  All EBCT	Asymptomatic adult patients who had adequate follow-up after EBCT		Combined MI and cardiac death, or MACE	EBCT predicts hard coronary event (i.e., coronary death, MI) and combined outcomes (revascularization).  Meta-analysis: risk ratio of CAC and MACE, 8.66 (95% CI, 2.67–28.13) MI and death, 4.20 (95% CI, 1.57–11.25)  Results need to be interpreted with caution.  Need further study on incremental value over conventional risk prediction.

\*BP refers to blood pressure; CAC, coronary artery calcification; CAD, coronary artery disease; CI, confidence interval; EBCT, electron beam computed tomography; ECG, electrocardiography; ETT, exercise treadmill test; MACE, combined myocardial infarction, death, and revascularization; MI, myocardial infarction; OR, odds ratio; RF, risk factors; RR, relative risk.

**Table 6: Conclusions of Systematic Reviews and Health Technology Assessments on Computed Tomography screening of Coronary Artery Disease in Asymptomatic Populations\***

Review	Recommendations
Waugh, et al., 2006 National Health Service (23)	No RCTs, 6 observational studies of EBCT Evidence of association between CAC and cardiac outcomes EBCT not recommended for screening
Pignone, et al., 2003 U.S. Preventive Services Task Force 2003 (18)	No trials with intervention Evidence of association between CAC and cardiac outcomes EBCT not recommended for screening
O'Malley, et al., 2000 (27)	No trials with intervention Evidence of association between CAC and cardiac outcomes EBCT not recommended for screening
O'Rourke, et al., 2000 (28)	No trials with intervention Evidence of association between CAC and cardiac outcomes
Pletcher & O'Malley, 2004 (25)	CT versus prognosis Meta-analysis supports independent predictive value of CAC scores, but heterogeneity of studies
Institute for Clinical Systems Improvement, 2004 (29)	Narrative reporting of studies CT versus prognosis: supports association between CAC and cardiac events
ECRI, 2004 (26)	CT screening to predict CAD risk No evidence EBCT is a better predictor than other measurements Indirect evidence of the ability of CT to predict future heart disease risk

\*CAC refers to coronary artery calcification; CAD, coronary artery disease; CT, computed tomography; EBCT, electron beam computed tomography; RCT, randomized controlled trial.

### Level 1 Randomized Controlled Trials

There was one 4-arm RCT by O'Malley et al., (30) examining behavioural outcomes of asymptomatic CAD screening. Between January 1999 and March 2001, O'Malley and colleagues randomized a consecutive sample of 450 asymptomatic army personnel, aged 39 to 45 years, scheduled to undergo a standard physical exam. The primary study objective was to determine change in a measure of composite risk (the 10-year Framingham risk factor score) after undergoing screening. People were randomly assigned to 1 of 4 arms of the study: 1) EBCT results provided in a setting of intensive case management; 2) EBCT results provided in a setting with normal case management; 3) EBCT results not provided in a setting of intensive case management; or 4) EBCT results not provided in a setting with normal case management. Allocation sequence was concealed and patients were randomized after determining eligibility for the study. All modifiable risk factors were targeted for intervention (hypertension, obesity, sedentary lifestyle, smoking, high-fat diet, and glucose intolerance) for both care groups. Intensive case management further included an integrated approach of research nurses and dietitians providing frequent contact tailored to participants' stages of behavioural change at 2, 4, 6, 8, 14, and 24 weeks.

Follow-up was at 1 year; after follow-up, patients in the non-result-reporting group were informed of their CAC scores. Data were analyzed by intention-to-treat analysis, and characteristics of patients lost at follow-up were compared with the remaining study population to determine if there were any systematic reasons of drop-out. There was no crossover. Thus, intention-to-treat analysis was accurate.



Study limitations include the inability to show an effect of behaviour, potentially because there was insufficient prevalence of risk factors in the study population. Power calculations for subgroup analysis were not included in initial sample size calculations, and therefore should be interpreted with caution. Additionally, almost 40% of the study population was low risk by conventional standards, and calcification prevalence was only 15%. Lastly, it is possible the consent process may have excluded patients who were more likely to be responsive to behavioural motivation, which may have affected the external generalizability of the results of the study.

### **Level 3A Observational Studies**

There were an additional 2 observational studies examining behavioural outcomes of asymptomatic CAD screening. (31;32)

#### **Study 1**

In a second study by O'Malley et al., (31) a consecutive sample of active smokers who underwent screening by EBCT were surveyed to determine their current motivation to alter their smoking behavior. Coronary artery calcification was present in 42% of the study population. Patients with CAC were more likely to perceive themselves as being at increased cardiovascular risk compared with those without CAC (42% versus 13%,  $P < .01$ ). Most patients (59%) rated themselves as more motivated to quit smoking after undergoing screening. However, there was no relationship between motivational level and smoking behavioural change by the presence of CAC.

#### **Study 2**

Wong et al. (32) surveyed 703 people undergoing EBCT screening to determine the extent to which cardiovascular risk-reducing behaviours were initiated as a result of knowledge of newly detected CAC presence after EBCT screening. Surveys were completed after EBCT screening. Cardiovascular risk factor history was obtained from 560 men and 143 women. Follow-up was at 1 to 2 years after initial screening. Patients lost to follow-up were not included in the final sample. There were reported changes in physician-led interventions such as prescribing aspirin and hypercholesterolemia medications. However, more people in the group who had been diagnosed with CAC upon MDCT scan reported losing weight and lowering their intake of fat. There were no differences in smoking cessation levels between the 2 groups.

Study limitations included that it was a self-referred population that responded to media advertisements for screening, which introduces a potential selection bias. In addition, patients who completed follow-up questionnaires were more likely to be older and had higher CAC levels. Finally, the study questionnaire had a limited ability to quantify effects accurately, because the measures included were largely subjective and unquantifiable.

### **Level 4A Observational Studies**

There were 4 identified observational studies examining the clinical effectiveness of MDCT screening for CAD in asymptomatic populations (Tables 7 and 8). Two of the studies were prospective side arms of larger trials of the Intervention as a Goal in Hypertension Treatment (INSIGHT) study (33) and intravascular imaging (34), and one study (35) from Japan was based on CT screening for lung cancer and tuberculosis. All studies were prospective, with patients serving as their own controls. Outcomes of the studies included CAC, cardiovascular event outcomes based on MDCT screening, the clinical utility of MDCT, and identifying risk factors placing asymptomatic patients at high risk for CAD.

**Table 7: Characteristics of Observational Studies on the Clinical Effectiveness of Multidetector Computed Tomography Screening for Coronary Artery Disease in Asymptomatic Populations\***

Study, year	CT Slice, No. CAC Definition	Study Design‡	Objectives	Patients	Conclusions
Shemesh et al., 2004 (33)	2 slice	Prospective, diagnostic study with follow-up	Determine risk factor distribution and frequency	Asymptomatic for CAD	CT good measure for CAC detection
	> 90 Hounsfield units	Side arm of INSIGHT study	Evaluate utility of CT to detect CAC  Determine value of CAC as a predictor of cardiac outcomes	Hypertensive with at least 1 other CAD risk factor  N = 544	Linear relationship between risk factors and CAC, CAC, and CAD outcomes
Moser et al., 2003 (4)	4 slice	Prospective, diagnostic study with follow-up	Determine risk factor stratification for asymptomatic patients undergoing CT screening for CAC	Asymptomatic for CAD; consecutive patients seen at cardiovascular clinic  N = 794	CAC score linear to number of risk factors
	> 130 Hounsfield units				Recommend 3 risk factors as cut-off  Interscan variability of MDCT low  Question screening based on 1–2 risk factors
Van Miegham, 2006 (34)	16 slice	Prospective diagnostic study with follow-up	Evaluate utility of CT to detect CAC	Patients referred for percutaneous coronary intervention  N = 90	Mild angiographic disease associated with large atherosclerotic plaques on MDCT
	> 130 Hounsfield units	Side arm of IBIS study			MDCT moderately high sensitivity and specificity to identify CAC
Itani, 2004 (35)	2 slice	Prospective diagnostic study with follow-up	Evaluate utility of CT screening to detect CAC	Asymptomatic for CAD  N = 6,120	Higher CAC prevalence for cardiac versus non-cardiac deaths
	> 110 Hounsfield units	Patients recruited and scanned from Nagasaki lung cancer and tuberculosis screening program	Estimate risk for CAC as a predictor of future cardiovascular death		Higher risk for cardiac deaths in CAC patients than non-CAC patients

\*CT refers to computed tomography; CAC, coronary artery calcification; CAD, coronary artery disease; IBIS, Integrated Biomarker and Imaging Study; MDCT, multidetector computed tomography; N, number.

‡ In all studies, people acted as their own controls

**Table 8: Attributes of Studies Extracted for Systematic Review for Multidetector Computed Tomography Screening for Coronary Artery Calcification as Predictive of Future Cardiovascular Events\***

Author, Year	Study Question Stated	Consecutive Recruitment	Inclusion Criteria Stated	Exclusion Criteria Stated	Patient Comorbidity/ Disease Severity	Technical Description	Blinded + Kappa	Unreadable Images Reported	CI or SD†
Shemesh et al.; 2004(33)	✓		✓	✓	✓	✓	✓		✓
Moser et al.; 2003 (4)	✓	✓			✓	✓			
Van Miegham et al.; 2006 (34)	✓	✓	✓	✓	✓	✓	✓		✓
Itani et al.; 2004 (35)	✓	✓	✓			✓			✓

\*CI refers to confidence interval; SD, standard deviation.

## Study 1

In the study by Van Miegham et al., (34) one of the objectives was to evaluate the diagnostic utility of MDCT in imaging coronary atherosclerosis. Patients with stable angina, unstable angina, non-ST-segment elevation, or ST-segment MI referred for PCI were eligible for inclusion. Excluded were patients with significant renal dysfunction, prior coronary intervention in the region of interest, life expectancy less than 1 year, or a factor that made follow-up difficult. Ninety consecutive patients were enrolled, and 61 patients underwent 16-slice MDCT. Data from the scan were loaded into a semi-automated vessel-tracking software program. Outcomes were analyzed by 2 independent observers, and disagreements were resolved through consensus. Plaques were categorized as small (< 1mm), medium (1 to 2 mm), or large (> 2 mm). Calcification was classified by the presence of high-density components (> 130 Hounsfield units).

Comparison of MDCT with IVUS found that the sensitivity of MDCT to detect plaque was 60% (30/50) for small plaques, 76% (80/105) for medium plaques, and 79% (26/33) for large plaques. Sensitivity, specificity, and the positive and negative predictive values for detection of any significant plaque was 86%, 69%, 90%, and 61%, respectively.

Study investigators found CT could reliably identify significant epicardial coronary atherosclerosis. Results indicated that nonobstructive coronary plaque could be detected with moderate sensitivity and specificity, but compared with other imaging modalities, high-risk characteristics affecting the accuracy of imaging were common (e.g., hypoechogenic plaque with high strain patterns). Hence, these arguments support recommendations discouraging indiscriminate use of noninvasive coronary imaging to detect subclinical atherosclerosis.

One limitation of the study is that the patient population was heterogeneous. In addition, the study was underpowered to correlate compositional imaging end points with clinical outcomes. Additionally, the suboptimal spatial and temporal resolution of the 16-slice MDCT scanner precluded accurate assessment of small and medium coronary segments (< 2mm). The region of interest selected by MDCT was chosen randomly. Therefore digital coronary segments were inevitably underrepresented. Moreover, the same would be true for IVUS examination of the coronary tree, where for safety reasons only, the larger coronary segments were targeted for investigation.

## Study 2

This study (4) evaluated the clinical utility of 4-slice MDCT in asymptomatic patients in a cardiology

setting. Retrospective analysis was performed on 794 patients (523 men and 271 women) attending a cardiac clinic in the United States. Asymptomatic status was determined by a questionnaire with questions on cardiac risk factors and symptoms prior to CAC screening. Multidetector computed tomography scans were performed at the request of the patient (39%), referral by a family physician (33%), or referral by a cardiologist (28%). After each scan, the patient was consulted by a nurse or physician to discuss the results and implications. Follow-up was performed at 4 months (range, 3–6 months) after screening via a medical record review. Study participants were also assessed on 7 cardiac risk factors based on the results of their questionnaire and medical records. Risk factors included age and sex, body mass index (BMI), systematic hypertension, hypercholesterolemia, active smoking, family history of CAD, and diabetes mellitus. Using a 4-slice MDCT scanner, investigators quantified the total calcium burden in the arteries using Agatston scores based on the sum of the total of all lesion Agatston scores for the individual. Agatston scores are categorized based on stratification for risk of future cardiac events: no CAC (0), minimal CAC (1–10), mild CAC (11–100), moderate CAC (101–400), or severe CAC (> 400).

The average study patient was positive for 3 risk factors. The most prevalent risk factors for men were age/sex (81%), BMI greater than 25 (78%), and hypercholesterolemia (54%). The most prevalent risk factors in women were hypercholesterolemia (66%), family history of CAD (61%), and age/sex (59%). Coronary artery calcification was detected in 53% of patients (422/794). Men had higher mean Agatston scores of 180, with 12% of scores greater than 400, whereas women had a mean Agatston score of 53, with only 4% above 400. Coronary artery calcification was minimal in 12% of the participants (Agatston score 1–10), mild (11–100) in 18%, moderate (101–400) in 14%, and severe in 9%. Scores were shown to be linearly related with the total number of cardiac risk factors in participants.

The 306 patients in the MDCT reproducibility study were similar to the entire study population with respect to CAC prevalence and sex. Interscan variability was shown to be inversely related to Agatston scores. The minimal CAC group had the highest variability (86%) and the severe CAC group had the lowest variability (9.5%). The concordance between Agatston scores of repeated scans was concordant for 280 patients (91.5%) and among the discordant patients disagreement was not larger than a single Agatston score category. Lastly, a Bland-Altman plot of the non-zero Agatston scores indicated good agreement between repeated MDCT scans, especially for scores lower than 1000. Agatston scores over 1000 were more variable (mean difference standard deviation [SD], 69) than for scores lower than 1000 (SD, 39).

Study investigators concluded that CAC screening with MDCT was justified for asymptomatic patients with 3 or more risk factors. However, risk factor assessment was poor at predicting which individuals will have CAC if fewer risk factors are present. Additionally, MDCT interscan variability was shown to be capable of monitoring CAC changes in patients with initial Agatston scores greater than 100. Risk factor assessment is poor if fewer risk factors are present. Moreover, investigators questioned the utility of screening patients with only 1 or 2 cardiovascular risk factors. One-third of patients with 1 to 2 risk factors had observed CAC, yet only 10% had moderate to severe CAC. Investigators also concluded that an Agatston score of 400 would be a cut-off for follow-up to stress myocardial perfusion single photon emission computed tomography testing for diagnosis of CAD. Lastly, MDCT scanning was shown to be capable of monitoring CAC changes in patients with initial Agatston scores greater than 100.

The limitations of the study included retrospective analysis of asymptomatic patients self-referred or physician-referred for CAC screening, which may not be representative of other populations. Moreover, no clinical significance was inferred from the different study groups.

### Study 3

In a study by Shemesh et al., (33), participants of INSIGHT were recruited to determine if CAC, as assessed by dual-slice spiral CT (DSCT), is an independent risk factor for cardiovascular events in hypertensive patients. INSIGHT participants were men and women aged 55 to 80 years old, defined as having hypertension with at least one additional cardiovascular risk factor: hypercholesterolemia, smoking, family history of MI, left ventricular hypertrophy, type I or II diabetes mellitus, previous MI more than 12 months prior to entering the study, presence of stable angina, or asymptomatic CAD confirmed by coronary angiography. Patients in the INSIGHT calcification side-arms study were enrolled from January 1995 to March 1996. A total of 544 patients underwent baseline DSCT, and follow-up was 100% at 3 to 5 years. Of the 544 patients, 98 had documented CAD at baseline and were excluded from the present side-arm study.

Dual-slice spiral CT was performed at a single centre by trained technicians following study protocol, and all results were interpreted by a physician blinded to the clinical data and event incidence. A calcific lesion was defined as an area of the coronary artery that had attenuation above 90 Hounsfield units. Each lesion score was calculated automatically by multiplying the attenuation factor by the lesion area. The total calcium score (TCS) was the sum of all lesion scores. Follow-up data were obtained from all participants at the scheduled follow-ups for INSIGHT. All cardiovascular events were confirmed by an independent critical events committee that was unaware of the DSCT results. Critical events recorded included fatal and nonfatal stroke; or acute coronary events defined as acute MI, sudden cardiac death, or new unstable angina pectoris requiring revascularization. Descriptive statistics were performed to evaluate differences on total calcium scores and incidence of events between categories. Multivariate logistic regression was completed using stepwise and goodness of fit approaches for the prediction of cardiac events. Receiver operator characteristic (ROC) curves were plotted based on the probabilities from the logistic model.

Prevalence of CAC in the study group was 66% (294/446). Patients with CAC were older, more likely to be male, had increased peripheral vascular disease, left ventricular hypertrophy, and higher creatinine and uric acid levels. However, in multivariate analysis, only age and male gender remained independently associated with CAC, and all other predictors were significantly correlated with sex.

At follow-up, 10.5% (47/466) of patients experienced a first cardiovascular event. Cardiac events experienced by participants included acute MI ( $n = 16$ ), sudden cardiac death ( $n = 2$ ), unstable angina resulting in revascularization ( $n = 14$ ), and stroke ( $n = 15$ ). Participants who experienced a cardiovascular event were more likely to be male (70% versus 46%), had a higher prevalence of peripheral vascular disease (14% versus 4%), a longer duration of hypertension (14.2 years versus 11.2 years), higher levels of systolic blood pressure (SBP) (171 mmHg versus 166 mmHg), serum glucose (136 versus 122 mg/dl), creatinine (1.13 versus 1.01 mg/dl), and uric acid (5.97 versus 5.46 mg/dl). In terms of outcomes, 41 of the 47 patients who experienced a cardiovascular event had CAC; of these, 6 cases of CAC were not detected at baseline. Of the 6 patients in which CAC was not detected at baseline, all had SBP levels in the third tertile ( $> 171$  mmHg). The 41 patients who had CAC had equally distributed SBP levels across the tertile at baseline. Patients with CAC had higher levels of total calcium scores than did patients without events (TCS  $297 \pm 509$  versus  $133 \pm 419$ ,  $P = .001$ ).

Risk factors significantly associated with the prediction of coronary events were presence of calcium, TCS  $> 0$  (OR, 2.78; 95% CI, 1.08–7.15), duration of hypertension ( $> 5$  years) (OR, 1.20; 95% CI, 1.01–1.45), SBP (15 mmHg) (OR, 1.64; 95% CI, 1.19–2.27), and serum creatinine (0.25 mg/dl) (OR, 1.48; 95% CI 1.11, 1.97). Additionally, presence of CAC was independently predictive of cardiac events (OR, 2.76; 95% CI 1.09–6.99). Lastly, sensitivity and specificity of the predicted probability of a

cardiovascular event was plotted on a ROC curve based on the estimates of the logistic regression model. It was found that sensitivity and specificity were improved when the presence of CAC was included in the model.

Coronary calcium scores, as measured by DSCT, were found to be of value in predicting cardiovascular events in a high-risk group of asymptomatic hypertensive patients with at least one additional cardiovascular risk factor. Limitations to the study included an insufficient sample size to stratify results by sex, the relatively small sample size, a study population not generalizable to the general population, failure to include all the estimates for predictors of events in the multivariate predictive model (gender and sex odds ratios), and a relatively short follow-up time (3–4 years).

#### **Study 4**

In another study, (35) a prospective follow-up was completed on a Japanese population undergoing chest CT for lung cancer and tuberculosis in the Nagano area of Japan. A total of 6,120 participants (3,377 men and 2,743 women) were invited to CT chest screening using a mobile spiral CT unit between 1996 and 1997. Participants were asymptomatic of cardiovascular conditions, and had no prior MI, coronary angioplasty, or CABG. The mobile CT unit consisted of a bus with a built-in CT scanner. Computed tomography data was analyzed using software to calculate the locations of and calcification density of coronary arteries. Follow-up was completed between May and October 2000, examining death certificates from the Nagano region. Accidental deaths and suicides were not included, and follow-up rates were not reported.

The prevalence of CAC was 19.7%: 24.6% in men and 13.7% in women. Fourteen patients subsequently died of cardiac disease, and CAC was detected in 10 of these cases. Another 64 patients died from noncardiac deaths and CAC was detected in 31 patients of these cases. Prevalence of CAC appeared higher in the cardiac death group than in the noncardiac death group, but this failed to achieve statistical significance. (71.4% versus 48.4%,  $P = .084$ ). The mean interval from CT examination to death was 13.9 months in the cardiac death group and 21.0 months in the noncardiac death group. The relative risk of CAC for cardiac death was 2.66 (95% CI, 0.76–9.37).

In the study population with CAC, there was a significantly higher MI rate than in those without CAC for both men and women (men: 5.5% versus 0%; women: 3.7% versus 0%;  $P > .05$ ). Mortality in men did not differ between the CAC affected and nonaffected groups (13% versus 12%,  $P > .05$ ). In women, however, mortality in the CAC group was significantly higher than in those without CAC (26% versus 8.9%,  $P < .05$ ). The study's authors concluded that CAC, as detected by a mobile helical CT unit, was predictive of future cardiac events. However, there was a 48.8% CAC prevalence rate in the noncardiac death group, potentially resulting in clinically relevant outcomes, particularly depending on degree of calcification, and posing an increased risk to the noncardiac-event group. Limitations to the study included nonblinding of outcome evaluators, short follow-up period, nonreporting of completeness of follow-up, no evaluation of severity of cardiac outcomes other than survival, and, lastly, no evaluation of risk factors or other potential confounding variables in participants.

# Summary of Medical Advisory Secretariat Review

## World Health Organization Criteria for Screening and Multidetector Computed Tomography Screening for Coronary Artery Disease in Asymptomatic Populations

Criteria for the establishment of screening programs based on the WHO guidelines (20) are outlined in Table 9. Multidetector computed tomography screening of asymptomatic individuals does not currently meet all the WHO criteria; therefore, it is not justifiable. Additional issues not addressed by the WHO criteria include defining a target population, particularly with regards to risk stratification as a precursor to screening; CAC cut-off levels for referral to further testing and treatment; absence of RCTs on screening program effectiveness; and adequate resources to support access to screening and the subsequent increases in follow-up testing and treatment. Additional ethical questions raised include the risks and benefits of screening, and safety issues regarding screening programs.

**Table 9: Multidetector Computed Tomography Screening for Coronary Artery Disease in Asymptomatic Populations, General Risk and High Risk, and WHO Criteria for Screening\***

WHO Criteria for Screening	Criteria Satisfied	Rationale
Important health problem	Fully	Yes, more than one-half of all first coronary events occur in asymptomatic people.
Accepted treatment	Partially	Effective treatment for early CAD, particularly statins. However, treatment data not based on CAC levels.
Latent or early stage is recognizable	Partially	CAC is a precursor to CAD. CAC is a detectable early stage of disease in asymptomatic people who are at high risk. However, some people at high-risk will also be CAC negative.
Suitable test is available	Partially	CT has been validated to detect high levels of CAC to predict future coronary events. However, CAC measurement is imprecise. Additionally, CT radiation doses may cause concern regarding the suitability of the test.
Test is acceptable	Unknown	Acceptability of the test is unknown. Screening and prevention may be attractive, but radiation dose may be unacceptable and deter acceptability of the CT screening.
Natural history of disease understood	Partially	CAC in asymptomatic individuals is high risk but may not necessarily progress to cardiovascular events, Conversely, CAD, or cardiovascular events may occur without the presence of CAC in some individuals.
Agreed policy on whom to treat as patients	No	No evidence based guidelines or policies exist regarding what levels of CAC to be treated. Presence of CAC encompasses a wide spectrum of risk
Cost of case finding is effective	No	Lack of evidence on cost-effectiveness. No studies for MDCT screening for CAD in asymptomatic populations.
Case finding is a continuous process	Partially	Case finding may be continuous, particularly with the development of risk stratification as a precursor to screening. Algorithms for risk stratification have not been conclusively developed at this time.

\* CAC refers to coronary artery calcification; CAD, coronary artery disease; CT, computed tomography, MDCT, multidetector computed tomography; WHO, World Health Organization.

Source: Wilson and Jeung, 1968 (20)

## Sensitivity and Specificity of Multidetector Computed Tomography for Coronary Artery Calcification

Only the study by Van Mieghem et al. (34) included clinical utility information of MDCT for measurement of coronary plaque and CAC. Multidetector computed tomography was compared with IVUS. The presence of calcification was calculated for the entire region of interest and in 5 mm subsegments at baseline in 61 patients (for a total of 67 vessels). Coronary plaque was defined as greater than 50% external elastic membrane area obstruction or the presence of calcification on 2 consecutive slices. The sensitivity, specificity, and positive and negative predictive values for the entire region of interest was 86%, 69%, 90%, and 61% respectively (Table 10).

Comparison of MDCT and IVUS found the sensitivity of MDCT to detect plaque was 60% (30/50) for small plaques, 76% (80/105) for medium plaques, and 79% (26/33) for large plaques. The sensitivity, specificity, positive and negative predictive values in 5-mm subsets was 74%, 73%, 72%, and 74% respectively. The sensitivity of MDCT to detect plaque was 60% (30/50) for small (< 1mm), 76% (80/105) for medium (1–2 mm), and 79% (26/33) for large (> 2mm) plaques. The corresponding likelihood ratios for the entire region of interest would be a positive likelihood ratio of 2.77 and negative likelihood ratio of 0.20. The corresponding ratios for 5mm subsegments would be a positive likelihood ratio of 2.74 and a negative likelihood ratio of 0.36.

**Table 10: Accuracy of Multidetector Computed Tomography for the Detection of Significant Coronary Plaque: Comparison With Intravascular Ultrasound for the Entire Region of Interest and for its 5 mm Subsegments\***

	Entire Region of Interest		5 mm Subsegments	
	N	% (95% CI)	N	% (95% CI)
Sensitivity	44/51	86 (74–93)	136/185	74 (67–79)
Specificity	11/16	69 (44–86)	140/192	73 (66–79)
Positive predictive value	44/49	90 (78–96)	136/188	72 (66–78)
Negative predictive value	11/18	61 (39–80)	140/189	74 (67–80)

\* Significant plaque on IVUS was defined as mean plaque area obstruction ( $[\text{Vessel area} - \text{Lumen area} / \text{Vessel area}] \times 100$ )  $\geq 50\%$ , or the presence of calcium on 2 consecutive slices on IVUS.

†CI refers to confidence interval; N, number; IVUS, intravascular ultrasound.

*This table was published in Journal of the American College of Cardiology; Van Mieghem CA, McFadden EP, de Feyter PJ, Bruining N, Schaar JA, Mollet NR et al. Noninvasive detection of subclinical coronary atherosclerosis coupled with assessment of changes in plaque characteristics using novel invasive imaging modalities: the Integrated Biomarker and Imaging Study (IBIS). 2006; 47(6): 1134-42, Copyright Elsevier (2006).*

## Reproducibility of Multidetector Computed Tomography for Coronary Artery Calcification Screening

Only one study (4) examined the reliability of MDCT for CAC screening. In a subset consisting of 306 patients, participants underwent MDCT scanning 2 times with a 5-minute delay and repositioning between scans. Interscan variability was expressed as the absolute difference in calcium scores divided by the mean score. The 306 patients included in the MDCT reproducibility study were similar to the entire study population with respect to CAC prevalence (53%) and sex (men 67% and women 33%). Interscan variability was shown to be inversely related to Agatston scores. The minimal CAC group had the highest variability (86%), and the severe CAC group had the lowest variability (9.5%; Table 11). The concordance between Agatston scores for repeated scans were concordant for 280 patients (91.5%; Table 12). Among the discordant patients, even at lower Agatston scores, disagreement was not larger than a



single Agatston score category. Lastly, a Bland-Altman plot of the nonzero Agatston scores indicated good agreement between repeated MDCT scans, especially for scores under 1,000. Agatston scores over 1,000 were more variable (mean difference SD, 69) than for scores lower than 1,000 (SD, 39; Figure 1).

**Table 11: Comparison of Interscan Variability of Agatston Score Obtained by Use of Prospective Electrocardiography-Triggered Multidetector Computed Tomography**

Degree of calcification	Mean Agatston score	Patients (No.)	Agatston score variability (%) [mean $\pm$ SD (median)]
None	0	130	0.0 $\pm$ 0.0 (0.0)
Minimal	1-10	32	86.0 $\pm$ 58.9 (74.3)
Mild	11-100	60	25.6 $\pm$ 28.8 (13.8)
Moderate	101-400	61	14.7 $\pm$ 12.1 (10.9)
Severe	>400	23	9.5 $\pm$ 10.6 (5.0)

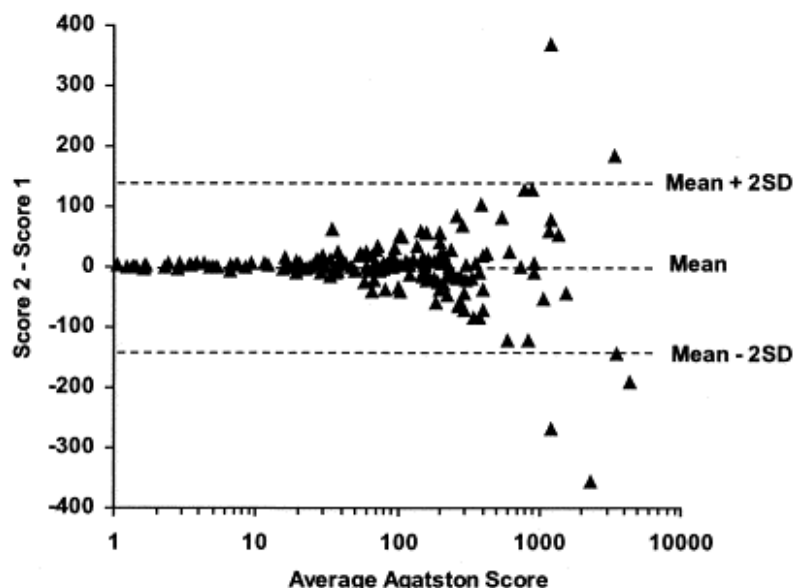
*This table was published in the Journal of Nuclear Cardiology, Vol. 10(5), Moser KW, O'Keefe JH, Jr., Bateman TM, McGhie IA. Coronary calcium screening in asymptomatic patients as a guide to risk factor modification and stress myocardial perfusion imaging, pp. 590-8, Copyright American Society of Nuclear Cardiology (2003).*

**Table 12: Concordance Between Agatston Scores for the 306 Patients in the Multislice Computed Tomography Reproducibility Substudy**

Scan 1 (Agatston score)	Scan 2 (Agatston score)				
	0	1-10	11-100	101-400	>400
0	130	4	0	0	0
1-10	4	24	5	0	0
11-100	0	2	53	4	0
101-400	0	0	2	52	2
>400	0	0	0	3	21

*This table was published in the Journal of Nuclear Cardiology, Vol. 10(5), Moser KW, O'Keefe JH, Jr., Bateman TM, McGhie IA. Coronary calcium screening in asymptomatic patients as a guide to risk factor modification and stress myocardial perfusion imaging, pp. 590-8, Copyright American Society of Nuclear Cardiology (2003).*

**Figure 1: Bland-Altman Analysis of Non-Zero Agatston Scores in the Multidetector Computed Tomography Reproducibility Study**



*This figure was published in the Journal of Nuclear Cardiology, Vol. 10(5), Moser KW, O'Keefe JH, Jr., Bateman TM, McGhie IA. Coronary calcium screening in asymptomatic patients as a guide to risk factor modification and stress myocardial perfusion imaging, pp. 590-8, Copyright American Society of Nuclear Cardiology (2003).*

### Computed Tomography Screening Results Changing Treatment

No studies have addressed whether the addition of CT to measure CAC would change management of individuals compared with standard risk assessment. However, 3 studies (30-32) examined the impact of EBCT screening on patient motivation to change or modify risk factor-related behavior, including smoking, diet, and physical activity levels. Knowledge of CAC status, number of risk factors, physician led-interventions, and intensive case management were associated with reduction or stabilization of risk factors, with the exception of smoking-related behaviour (Table 13).

**Table 13: Studies Examining Risk Factor Behaviour Modification After Electron Beam Computed Tomography Screening for Coronary Artery Disease\***

Study, Year	Design	Intervention(s)	Results
Wong, et al., 1996 (32)	Survey	EBCT + physician-led interventions of prescription of aspirin and hypercholesterolemia medications	CAC group more prescriptions than non-CAC group (RR, 3.45, $P < .01$ ).  CAC group reported more weight loss (RR, 1.67; $P < .001$ ), decrease in fatty intake (RR, 1.58; $P < .01$ ), and increase in anxiety (RR, 2.73; $P < .001$ ).
O'Malley, et al., 2002 (31)	Survey	EBCT	No significant differences in smoking cessation. CAC group (42%) more likely to consider selves at increased cardiovascular risk.  No differences between CAC and non-CAC groups in motivations to quit or modify smoking behaviour.

Study, Year	Design	Intervention(s)	Results
O'Malley, et al., 2003 (30)	RCT (4 arm)	EBCT results + intensive case management of risk factors	Intensive case management improved 10-year Framingham risk factor score -0.06% versus 0.74% ( $P < .01$ ).
		EBCT results + normal care	CAC results did not affect ability to achieve reduction or stabilization of risk factors.
		No EBCT results + intensive case management	Adjusting for knowledge of CAC score and psychological factors, only number of risk factors present and intensive case management had effect on improving or stabilizing risk.
		No EBCT results + standard care	

\*CAC refers to coronary artery calcium; EBCT, electron beam computed tomography; RCT, randomized controlled trial; RR, relative risk.

### Coronary Artery Calcium as a Predictor of Future Coronary Events

Analysis of the value of CAC for predicting future coronary events included types, frequency and severity of cardiac events; survival; and subgroup analysis. (33;35) All of the studies found a positive significant association of CAC as predictive of CAD events (Table 14).

**Table 14: Studies Using Coronary Artery Calcification, as Measured by Computed Tomography as a Predictor for Future Cardiovascular Events\***

Study, Year	Predictor	Outcomes	Results
Shemesh et al., 2004 (33)	CAC	First cardiovascular event	OR, 2.76 (95% CI, 1.90–6.99) MVOR, 2.78 (95% CI, 1.08–7.15)
Itani et al., 2004 (35)	CAC	Cardiac deaths	RR, 2.66 (95% CI, 0.76–9.37)

\*CAC refers to coronary artery calcification; CI, confidence interval; MVOR, multivariate odds ratio; OR, odds ratio; RR, relative risk.

Forty-seven (10.5%) patients from the INSIGHT study experienced cardiac events after MDCT screening. Individuals with presence of CAC comprised 87% of the cardiac events group in the INSIGHT study (41/47). (33) Cardiovascular events included acute MI ( $n = 16$ ), sudden cardiac death ( $n = 2$ ), unstable angina resulting in revascularization ( $n = 14$ ), and stroke ( $n=15$ ). Patients with cardiovascular events had higher total calcification scores ( $297 \pm 509$ ) than did patients without events ( $133 \pm 419$ ) ( $P = .001$ ). Coronary artery calcification was a significant independent predictor for cardiovascular events (OR, 2.76; 95% CI, 1.09–6.99). In multivariate analysis, when all other risk factors were included in the model, CAC had similar predictive values for coronary events (multivariate odds ratio (MVOR), 2.78; 95% CI, 1.08–7.15). Lastly, the sensitivity and specificity of the predicted probability for a cardiovascular event based on the logistic regression model indicated that the presence of CAC in the model yielded a nonsignificant improved prediction of events: the area under the ROC curves was 0.75 when including CAC as a variable in the model, versus 0.71 when not including the CAC variable in the model.

Prevalence of CAC in the Nagano screening study population was 19.7% (1206/6120): 24.6% among men, and 13.7% among women. (35) There were 14 cardiac deaths in the Nagano screening study at 4-year follow-up, including acute MI ( $n = 9$ ), cardiac failure ( $n = 4$ ), and angina pectoris ( $n = 1$ ). Coronary artery calcification was detected in 10 (71.4%) of 14 patients who died of cardiac disease. The 31

(48.4%) of 64 patients who died of other disease also had CAC. The prevalence of CAC was higher in the patients who died of cardiac causes than in group of patients who died of other, that is, noncardiac, causes (71.4% versus 48.4%,  $P = .084$ ). The relative risk of CAC for cardiac death was nonsignificant: RR, 2.66; 95% CI, 0.76–9.37].

Overall, CAC may be a predictor of future cardiovascular events; however, confidence intervals were wide in both studies and nonsignificant in the Nagano screening study. However, it is important to note that the results reported in Table 14 were for presence or absence of CAC, irrespective of total Agatston score. Given the wide range of Agatston scores (1– 400+) and implications for degree of calcification in the coronary arteries, a more appropriate analysis might have considered the predicative value Agatston score classification (minimal, mild, moderate, severe) for future cardiovascular events.

### Analysis of Risk Estimates

Two studies (4;33) examined the relationship between risk factors and that of MDCT screening for CAC (Table 15). Established cardiovascular risk factors in patients were evaluated with respect to association with frequency and distribution of CAC and cardiovascular event outcomes.

**Table 15: Results of Cardiovascular Risk Factor Analysis on Stratifying Risk for Multidetector Computed Tomography Screening for Asymptomatic Coronary Artery Disease\***

Study, Year	Risk Factors Evaluated	Risk Factors Associated with CAC outcomes**	Risk Factors Associated with CAD/event outcomes	Recommendations
Shemesh, et al., 2004 (33)	Age, sex, BMI, systolic and diastolic blood pressure, heart rate, total cholesterol, triglycerides, fasting glucose, serum creatinine, uric acid, duration of hypertension, diabetes mellitus, smoking, family history of CAD, peripheral vascular disease, LVH, proteinuria, presence of calcification, TCS, and randomization to nifedipine.	Age, male sex, creatinine, uric acid, peripheral vascular disease, and LVH.	Male sex, systolic blood pressure, fasting glucose, creatinine, uric acid, duration of hypertension > 5 years, peripheral vascular disease, CAC prevalence, TCS score units.  In multivariate logistic regression: > 5 years of hypertension, systolic blood pressure, creatinine, and presence of CAC.	Results suggest that CAC as measured by MDCT predicts cardiovascular events in symptomatic hypertensive patients who have at least 1 other cardiovascular risk factor and should be considered in the risk stratification of hypertensive patients.
Moser et al., 2003 (4)	Age, sex, BMI, systematic hypertension, hypercholesterolemia, active smoking, family history of CAD, diabetes mellitus.	Linear relationship between number of risk factors and CAC.  All patients with 0 risk factors were CAC negative.  Only 10% of patients with 1–2 risk factors had moderate to severe	N/A to risk factor analysis.	CAC screening with MDCT is justified for patients with 3 or more risk factors.  Risk factor assessment is poor at predicting CAC if fewer risk factors are present. Not specific which individual risk factors increase risk of CAC.

Study, Year	Risk Factors Evaluated	Risk Factors Associated with CAC outcomes**	Risk Factors Associated with CAD/event outcomes	Recommendations
		CAC scores.		
		Patients with 3 or more risk factors were most likely to have moderate to severe calcification.		

\*BMI refers to body mass index; CAC, coronary artery calcification; CAD, coronary artery disease; LVH, left ventricular hypertrophy; MDCT, multidetector computed tomography; TCS, total calcium score.

In the INSIGHT study (33) of patients with hypertension, information on established risk factors was obtained prior to screening. Established risk factors were age, sex, BMI, systolic and diastolic blood pressure rate, heart rate, total cholesterol level, level of triglycerides, fasting glucose level, serum creatinine level, uric acid level, duration of hypertension in years, diabetes mellitus, smoking, family history of CAD, peripheral vascular disease, LVH, presence of proteinuria, presence of calcification, TCS greater than 0, and randomization to nifedipine. Baseline characteristics of patients, including risk factors, were compared between the CAC group and non-CAC group, as well as the cardiovascular event group and cardiovascular nonevent group. Age, male sex, peripheral vascular disease, LVH, proteinuria, and levels of creatinine and uric acid were significantly more prevalent in the CAC group than in the group without calcification ( $P < .05$ ). However, in multivariate logistic regression analysis for prediction of CAC presence, only age and male sex were independent predictors; all other predictors were significantly associated with sex.

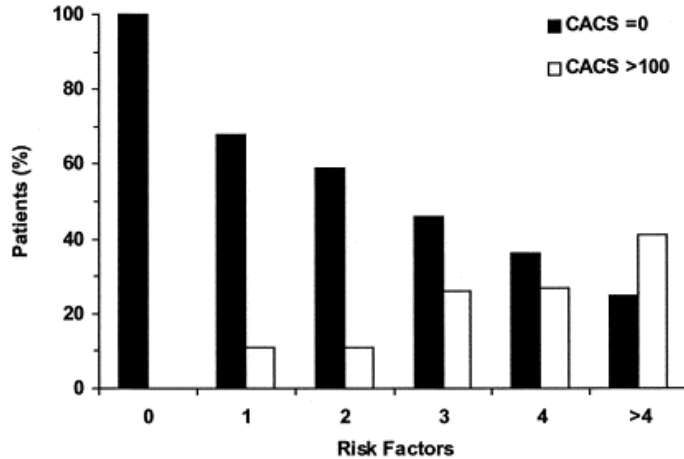
Individuals who developed a cardiovascular event were more likely to be male compared with those who did not have a cardiovascular event (70% versus 46%), had a higher prevalence of peripheral vascular disease (13% versus 4%), longer duration of hypertension (14.2 years versus 11.2 years), higher levels of SBP (171 mmHg versus 166 mmHg), serum glucose (136 mg/dl versus 122 mg/dl), creatinine (1.13 mg/dl versus 1.01 mg/dl), and uric acid (5.97 versus 5.46 mg/dl) ( $P < .05$ ). Patients who experienced cardiovascular events had higher levels of calcification than did those who did not, with a mean TCS of  $297 \pm 509$  in comparison to  $133 \pm 419$  ( $P = .001$ ). In multivariate analysis, CAC was an independent predictor for cardiovascular events (OR, 2.75; 95% CI, 1.09–6.99). Levels of creatinine ( $P = .007$ ), SBP ( $P = .003$ ), and duration of hypertension greater than 5 years ( $P = .049$ ), were also significantly associated with prediction of cardiovascular event outcomes.

Patient history surveys, which included questions on risk factors, were given to patients before CAC screening in the study by Moser et al. (4) Risk factors evaluated were age, sex, BMI, systematic hypertension, hypercholesterolemia, active smoking, family history of CAD, and diabetes mellitus. The average patient in the study, irrespective of sex, was positive for 3 of 7 possible risk factors. The most prevalent risk factors for men were age/sex (81%), BMI greater than 25 (78%), and hypercholesterolemia (54%). In women, the most common risk factors were hypercholesterolemia (66%), family history of CAD (61%), and age/sex.

The frequency of CAC was 53% (422/794). All patients with negative MDCT ( $n = 12$ ) had no risk factors. There was an inverse relationship between the number of cardiovascular risk factors and a normal MDCT screen. As can be seen in Figure 2, 70% of patients with 1 risk factor had a normal MDCT scan. A normal scan was observed in 60% of patients with 2 risk factors, 46% of patients with 3 risk factors, 38% of patients with 4 risk factors; and only 25% of patients with more than 4 risk factors (Figure 2).

Conversely, as the number of risk factors increased, so did the percentage of patients with moderate to severe CAC (Agatston score > 100) (Figure 3). Only 10% of patients with 1 to 2 risk factors had moderate to severe CAC (Agatston score > 100), compared with 40% of patients with greater than 4 risk factors.

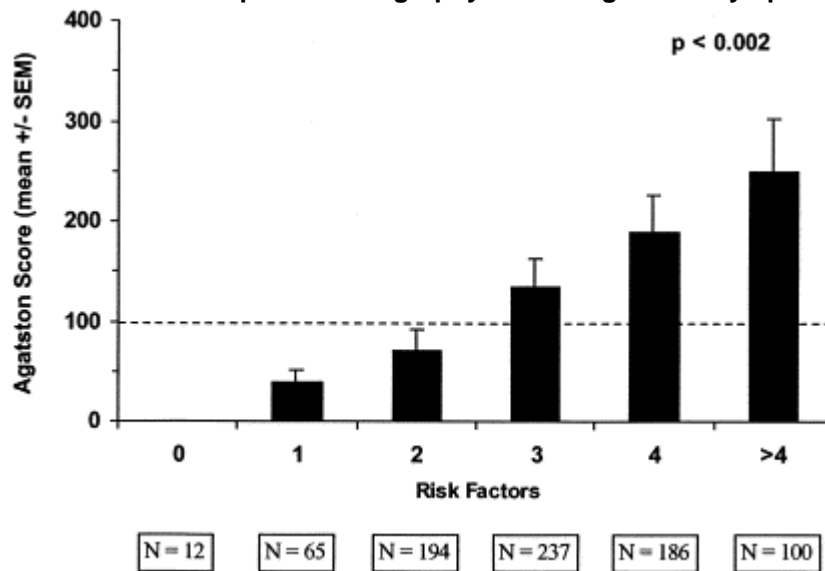
**Figure 2: Effect of Cardiac Risk Factors on Percentage of Patients With No Coronary Artery Calcification Versus Moderate to Severe Coronary Artery Calcification**



*This figure was published in the Journal of Nuclear Cardiology, Vol. 10(5), Moser KW, O'Keefe JH, Jr., Bateman TM, McGhie IA. Coronary calcium screening in asymptomatic patients as a guide to risk factor modification and stress myocardial perfusion imaging, pp. 590-8, Copyright American Society of Nuclear Cardiology (2003).*

Coronary artery calcification scores were shown to be linearly related with the total number of cardiac risk factors in participants. The average study patient had 3 risk factors. Each group with greater than 3 risk factors had an Agatston score over 100. Men had higher mean Agatston scores, at 180, with 12% of scores over 400, whereas women had a mean Agatston score of 53, and only 4% were above 400. Coronary artery calcification was minimal (Agatston score 1–10) in 12% of participants, mild (11–100) in 18%, moderate (101–400) in 14%, and severe (over 400) in 9%. On average, moderate to severe CAC was associated with 3 or more risk factors. In more than one-quarter of these risk factor groups, patient Agatston scores were greater than 100, hence justifying screening in this population. However, for patients with 1 or 2 risk factors, whether screening was justified is unclear. About 10% of this population had moderate to severe CAC, suggesting that CAC screening may be useful for patients without a high-risk profile.

**Figure 3: Number of Cardiovascular Risk Factors and Mean Agatston Score Determined by Multidetector Computed Tomography Screening in an Asymptomatic Population**



*This figure was published in the Journal of Nuclear Cardiology, Vol. 10(5), Moser KW, O'Keefe JH, Jr., Bateman TM, McGhie IA. Coronary calcium screening in asymptomatic patients as a guide to risk factor modification and stress myocardial perfusion imaging, pp. 590-8, Copyright American Society of Nuclear Cardiology (2003).*

### Safety of Screening

General CT scanning poses a risk of radiation exposure. There is generally little difference between single detector and multidetector CT capabilities, but MDCT may produce higher radiation doses because of the higher X-ray tube currents that are necessary for multiple slices. (36)

Over the past few years, CT manufacturers have added the capability to vary the X-ray tube current, which can optimize the use of the X-ray and minimize the radiation dose. (36) However, the attenuation of the capability decreases with increased slice thickness. The radiation exposure from a conventional CT scanner may emit effective doses of 2 to 4 mSv, 5 to 7 mSv, and 8 to 11 mSv for a typical head, chest and abdominal, or pelvic CT, respectively. (37) Studies included in this analysis had radiation doses of 0.7 mSv (4-slice MDCT) (4) to 3.6 mSv (2-slice). (35)

The effective radiation dosage for 4-slice MDCT angiography has been reported as being 6.7 to 10.9 mSv for male patients, and from 8.1 to 13.0 mSv for female patients, compared with 2.1 mSv for male patients and 2.5 mSv for female patients with CA. (38) According to Mollet, (39) the radiation dose using 16-slice CT scans is between 6.7 and 13.0 mSv. In contrast, MDCTs may deliver less radiation to the patient because more slices can be imaged in one pass. (12)

According to a report (40) to the Ontario Health Technology Advisory Committee from the University Health Network Usability Factors Lab, the average Canadian receives a natural background radiation of between 2 and 4 mSv in their day-to-day lives per year, without coming into contact with any diagnostic imaging facility or systems. Dose limits for Canadian workers are set by Health Canada, but patient radiation exposure is not regulated, nor have specific radiation level exposure limits been recommended for patients undergoing diagnostic X-ray procedures. (40) The cumulative risk of cancer to age 75 years

attributable to diagnostic X-rays is about 1.1% in Canada; corresponding to 784 cases of cancer per year. (40) These figures may underestimate the cancers attributed to X-rays due to the increasing radiation dose from diagnostic X-rays increasing over the past few years. The cancer risk from 100 mSv was estimated to be 1 out of 100 people by one agency (41) and 6 out of 1,000 people by another. (40) The lifetime risk for cancer per CT scan for an individual is estimated to be 1 in 1,000. (40) The effective dose of a typical CT examination of the chest was equivalent to 3 times the amount of natural background radiation received by the average Canadian per year. (40) However, it was noted that a typical CT examination could have up to 400 times more radiation than a plain film chest x-ray. (40)

Many scanners now can provide the expected radiation dose based on patient and imaging study characteristics, and radiation dose can be reduced by a factor of 2 if the X-ray tube current is manually lowered during cardiac cycles that are not of interest. (42) It is believed that there is a linear dose-effect relationship of radiation with CT scanner screening. (40)

According to a recent report published by the Medicines and Healthcare Products Regulatory Agency in the United Kingdom, (36) consideration of the indications for MDCT is required with careful selection of scanning parameters.

### **Overall Conclusions of Medical Advisory Secretariat Review**

Screening the asymptomatic population for CAD using MDCT does not meet all of the WHO criteria for screening, hence it is not justifiable.

Multidetector computed tomography exhibits moderately high sensitivity and specificity for the detection of CAD in an asymptomatic population. If population-based screening were to occur, a high rate of false positives would result in increased downstream costs and interventions, without evidence of effectiveness. Additionally, some cases of CAD would be missed: those cases that have not yet developed, or that have not progressed to detectable levels.

Coronary artery calcification measured by MDCT is a good predictor of future cardiovascular events. Cardiovascular risk factors are positively associated with the presence of CAC and cardiovascular events; however, risk factor stratification to identify high-risk asymptomatic individuals is unclear given the current evidence base.

Safety of MDCT screening is also an issue, because of the introduction of increased radiation doses for the initial screening scan and possible follow-up interventions.

No large RCTs of screening trials have been published, which is an important area of future research.

Additionally, future research should also place an increased emphasis on how to identify high-risk asymptomatic people for CAD.

### **Economic Literature Review and Ontario-Based Cost Analysis**

No studies examining the cost-effectiveness of MDCT screening for CAD in asymptomatic populations were found. No Ontario-based costs-analysis was performed for MDCT screening for CAD in the asymptomatic population as there was insufficient evidence to determine clinical effectiveness and justify screening.



## **Existing Guidelines for Use of Technology**

There are no guidelines available for MDCT screening for CAD from the Canadian Task Force on Preventive Health Care or from the United Kingdom National Screening Committee. The United States Preventive Services Task Force (43) has established guidelines for screening asymptomatic populations for CAD, and is reviewing additional risk factors for intermediate CAD risk. The American College of Cardiology recently released a clinical expert consensus guidelines document on the use of CAC scoring by CT in global cardiovascular risk assessment and in evaluation of patients with chest pain. (44)

### **United States Preventive Services Task Force (2004)**

#### **Summary of Recommendations**

The United States Preventive Services Task Force recommends against routine screening with resting ECG, the exercise treadmill test, or EBCT scanning for coronary calcium, for either the presence of severe coronary artery stenosis or the prediction of CAD events in adults at low risk for CAD events.

### **American College of Cardiology (2007)**

#### **Summary of Recommendations**

The consensus of the American College of Cardiology Committee was that the body of evidence supports recommendations from the USPSTF that unselected screening is of limited clinical value in patients who are at low risk for CHD events.

There is little to be gained by testing with CAC in patients with a low Framingham risk score. Patients with a high Framingham risk score should be treated aggressively, consistent with secondary prevention goals based upon current guidelines and thus should not require additional testing, including CAC scoring, to establish this risk evaluation. The current CAC literature does not provide support for the concept that high-risk asymptomatic individuals can be safely excluded from medical therapy for CHD even if CAC score is 0.

The committee judged that it may be reasonable to consider use of CAC measurement in asymptomatic patients with intermediate CHD risk (between 10% and 20% 10-year risk of estimated coronary events), based on available evidence that shows incremental risk prediction information in this (intermediate risk) patient group. This conclusion is based on the possibility that such patients might be reclassified to a higher risk status based on high CAC score, and subsequent patient management may be modified.

The committee does not recommend use of CAC measurement in patients with low CHD risk (below 10% 10-year risk of estimated CHD events) This patient group is similar to the “population screening” scenario, and the committee does not recommend screening of the general population using CAC measurement.

The committee does not advise CAC measurement in asymptomatic patients with high CHD risk (greater than 20% estimated 10-year risk of estimated CHD events, or established coronary disease, or other high-risk diagnoses), as they are already judged to be candidates for intensive risk reducing therapies based on current guidelines.

No evidence is available that allows the committee to make a consensus judgment on reducing the treatment intensity in patients with calcium score 0 in patients who are considered intermediate risk before coronary calcium score. Accordingly, the committee felt that current standard recommendations for treatment of intermediate-risk patients should apply in this setting.

In general, CAC measurement has not been compared to alternative approaches to risk assessment in head-to-head studies with other potentially competing tests in intermediate-risk patients for modifying cardiovascular disease risk estimate. Therefore, this question cannot be adequately answered from available data.

## Policy Development

### Policy Considerations

#### Patient Outcomes – Medical, Clinical

Multidetector computed tomography has been found to detect CAC with moderately high sensitivity and specificity. Coronary artery calcification has also been established as a significant predictor of future cardiovascular events. Individuals with the presence of cardiovascular risk factors are at a higher risk for CAC and cardiovascular events. However, risk stratification for MDCT screening asymptomatic populations of CAC has not been established.

Due to the moderate sensitivity and specificity of MDCT, there may be a number of patients receiving false-positive results, resulting in increased health care costs. Moreover, screening may also detect abnormal findings in the lung.

Radiation levels increase with faster scanning capabilities, potentially putting patients at increased risk if screened repeatedly, and increasing total rates of population radiation exposure due to increased MDCT scanning. Based on the published literature, effectiveness of MDCT screening for CAC in a general asymptomatic population or a high-risk asymptomatic population has not been established. Moreover, WHO criteria for screening programs have not been met.

Lastly, EBCT is not currently licensed, but if it is licensed in the future, it may have an impact on risk estimates for a population-based CAC screening program. Electron beam computed tomography is considered the gold standard for the evaluation of CAC, and may improve rates of detection.

#### Regulatory Framework

No Ontario or federal regulations or guidelines exist specifically for CT scanner testing. Computed tomography is excluded from the Ontario *Healing Arts Radiation Protection Act R.R.O. 1990, Regulation 543; X-Ray Safety Code*, but a federal safety code for the installation, use, and control of radiological X-ray equipment, including CT scanners, is scheduled for publication in 2007/2008. (40) In addition, unlike other diagnostic X-ray machines, CT scanners are not specifically inspected by the Ontario X-ray Inspection Services. The lack of comprehensive Ontario CT regulations, guidelines, or standards has led to significant variability in the frequency and methods of CT scanner testing, as found in the Ontario CT survey. (40) The Ontario Health Technology Advisory Committee (45) had previously recommended that the *Healing Arts Radiation Protection Act* and its regulations be amended to include guidelines on the

installation process, use, and testing of CT scanners, and to permit provincial inspection and oversight.

With respect to screening programs, it would be unethical to establish a screening program given that program effectiveness has not been clearly established, and access to screening and further treatment upon a positive screen may be delayed with respect to access to care.

### **Demographics**

Age and sex have been established to be the most significant risk factors for CAC presence and disease progression. Other risk factors have also been found to be significantly associated with CAC and CAD outcomes, but to a lesser extent. Risk stratification for CAC screening has been proposed as a basis for a screening program; however, risk estimates are unclear and a risk factor-based screening program has not been established as effective.

### **Diffusion – International, National, Provincial**

Multidetector computed tomography is in use worldwide. There has been an increase in the number of CT systems in Ontario, as well as an increase in referral to CT imaging. Diffusion of MDCT screening for CAD would be limited by access to and waitlists for CT screening. Given the current waitlists for CT, additional resources would need to be invested if a screening program were introduced.

### **Cost**

To date, there have been no studies examining MDCT screening for CAD. Although studies for EBCT screening have been published, there have only been a few. Until more reliable clinical effectiveness estimates are established, it will be difficult to determine the costing and cost-effectiveness of MDCT screening for asymptomatic CAD. If effectiveness of MDCT screening for asymptomatic CAD were established, then cost savings would be assumed due to decreasing cardiovascular events and increases in life expectancy for some patients. If a screening program were implemented, then there would be increased costs due to additional CT scans, physician fees, maintenance fees, technician salaries, follow-up of positive scans, treatment of patients with CAC/CAD, and investigation of false-positive scans.

### **Stakeholder Analysis**

Health professionals may need further training to ensure they know how to use the MDCT technology expertly. Computed tomography technologists may need further training to use MDCT effectively and safely. Radiologists may need additional training to use vessel tracking software in conjunction with MDCT. Cardiologists may want to be involved with the interpretations of MDCT results, as well as be involved with the treatment of patients found positive for CAC and CAD.

### **System Pressures**

Wait times for MDCT may increase if MSCT is used for population-based screening of asymptomatic patients for CAD, particularly if the current CT scanning capacity remains static. Additionally, cardiac service wait times may also rise as inconclusive MDCT results may need to be confirmed by angiography. There are 118 CT scanners in Ontario as of January 1, 2006. (46) Presently, 90% completion wait times in Ontario for CT average 62 days, with 72% of scans completed within the access target of 28 days (Table 16). (47) Although there has been a net decrease of 19 days for wait list

completion, a recommendation for population-based screening would overwhelm CT system capacity.

**Table 16: 90% Completion Rates for Computed Tomography Wait List Time in Ontario**

Service	Baseline, Days (Aug/Sept 2005)	Current, Days (Dec 06/Jan 07)	Access Target, Days	Completed in Target, %	Current vs. Baseline Net Change, Days	Change, %
Computed tomography	81	62	28	72	-19	-23.5

Source: Ministry of Health and Long-Term Care Ontario. (47)

For patients inaccurately diagnosed with CAD, unnecessary interventions and potential comorbidity will increase. Screening may also detect findings in the lung, which will also require further medical investigation. Patients with missed CAD may have unmonitored disease progression, resulting in more invasive outcomes and increasingly severe outcomes. Lastly, neither CT scanning of coronary vessels, nor screening for CAD with any modality, are insured services in Ontario.

## Recommendations

Using the Grading of Recommendation Assessment, Development and Evaluation (GRADE) system, (21) potential Ontario Health Technology Advisory Committee recommendations will be explored. The GRADE methods will be applied to the body of evidence for the clinical utility of MDCT screening for asymptomatic CAD (Table 17, Table 18). Given that the quality of the body of evidence in this review is low, estimates of effect are uncertain, and the strength of recommendations is limited to level C (1 or 2).

**Table 17: GRADE Assessment Profile of Clinical Utility of Coronary Artery Disease as a Predictor of Future Cardiovascular Events‡**

Quality Assessment						Summary of Findings				
Studies	Design	Quality	Consistency	Directness	Other Modifying Factors	Number of Subjects		Effect	Quality of Evidence	Outcome
						Group A	Group B	OR /RR		
Shemesh (33) Itani (35)	Observational 4A	LOW	Yes	No (high-risk and Japan) (-1)	Risk estimate >2 (+1)	N/A*	N/A*	N/A†	Low	Critical

\* Unable to report Group A and Group B due to study reporting.

† Heterogeneous studies; meta-analysis inappropriate.

‡ GRADE refers to Grading of Recommendation Assessment, Development and Evaluation; N/A, not applicable; OR, odds ratio; RCT, randomized controlled trial; RR, relative risk.

**Table 18: GRADE Assessment Profile of Multidetector Computed Tomography Screening Effect on Behavior Change‡**

Quality Assessment						Summary of Findings				
Studies	Design	Quality	Consistency	Directness	Other Modifying Factors	Number of Subjects		Effect	Quality of Evidence	Outcome
						Group A	Group B	OR /RR		
Wong (32) O'Malley (31) O'Malley (30)	1 large RCT 2 observational 3A	No serious limitations	Some consistency	No (2/3 studies on army personnel) (-1)	None	N/A*	N/A*	N/A†	Low	Critical

\* Unable to report Group A and Group B due to study design and reporting.

† Heterogeneous studies, meta-analysis inappropriate.

‡ GRADE refers to Grading of Recommendation Assessment, Development and Evaluation; N/A, not applicable; OR, odds ratio; RCT, randomized controlled trial; RR, relative risk.

# Appendices

## Appendix 1: Stages of Atherosclerosis

Characteristics	Type 1	Type 2	Type 3	Type 4 and 5	Type 6
Morphology	Development of macrophages made up of lipids (foam cells) within arterial wall intima.	Accumulation of foam cells (fatty streak) within arterial wall.	Pre-atheroma lesions develop external to arterial walls.	Accumulation of plaque (atheroma) that may rupture.  Rupture causes subsequent hematoma that leads to arterial narrowing or complete obstruction.	"Complicated plaques" derived from repeated ruptured plaques that may not cause symptomatic decompensation.
Clinical characteristics	Microscopically, not visible to the untrained eye.	Microscopically visible.	Small calcium deposits on exam may be visualized.	Lipid core (phospholipids and cholesterol) covered with thin cap (fibroatheroma).	Lesions that form from fibromuscular tissue that forms from repeated rupture and repair.  Extent of calcification corresponds to lesion size.  More stable than types IV or V, because the additional calcium provides resistance to stress.
Determinants	Evident in some children, asymptomatic adults.	Similar in men and women.	N/A	N/A	N/A
Clinical significance	None.	None: disease progression beginning.	May be reversible.	May exhibit minimal arterial narrowing and therefore may go undetected by angiography.  Degree of narrowing produced by plaque may be related to severity of outcomes.	Lesions may grow significantly and may deform the arterial shape.  Lesions are detectable using angiography.  Prevalent in patients with chronic angina.  More readily identifiable using noninvasive techniques such as fluoroscopy and CT.
Outcomes of interest	None.	None.	May lead to more serious progression.	Angina.  Acute myocardial infarction.  Ischemia/silent infarction.  Sudden cardiac death.	Plaques containing extensive calcium associated with fewer acute cardiac syndromes.

## Appendix 2: Canadian Cardiovascular Society Classification of Angina Pectoris

Class 0	Class I	Class II	Class III	Class IV
Asymptomatic	<p>Ordinary physical activity, such as walking and climbing stairs, does not cause angina.</p> <p>Angina occurs with strenuous, rapid or prolonged exertion.</p>	<p>Slight limitation of ordinary activity.</p> <p>Angina occurs on walking or climbing stairs rapidly, walking uphill, walking or climbing stairs after meals, in cold or wind, or under emotional stress, or only during the few hours after awakening.</p> <p>Angina occurs on walking more than 2 blocks on the level and climbing more than 1 flight of ordinary stairs at a normal pace and in normal conditions.</p>	<p>Marked limitation of ordinary physician activity.</p> <p>Angina occurs on walking 1 to 2 blocks on the level and climbing 1 flight of stairs in normal conditions and at a normal pace.</p>	<p>Inability to carry on any physical activity without discomfort; anginal symptoms may be present at rest.</p>

Source: As in ACC/AHA 2002(6) , Campeau 1976 (7) and in the Ontario Cardiac Care Network (48)

### Appendix 3: Literature Review Search Strategy

Database: Ovid MEDLINE(R) <1996 to August Week 5 2006>

Search Strategy:

- 
- 1 coronary artery disease.mp. or exp Coronary Arteriosclerosis/ (25960)
  - 2 exp Calcinosis/ (7996)
  - 3 exp Heart Diseases/ (220511)
  - 4 2 and 3 (1986)
  - 5 1 or 4 (27193)
  - 6 exp Mass Screening/ (43282)
  - 7 screen\$.mp. (159062)
  - 8 (asymptomatic or subclinical or silent or healthy or unknown).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (288024)
  - 9 6 or 7 or 8 (434874)
  - 10 5 and 9 (4117)
  - 11 exp Tomography, X-Ray Computed/ (89696)
  - 12 computed tomograph\$.mp. (43765)
  - 13 (ct scan\$ or EBCT or MDCT).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (18930)
  - 14 or/11-13 (113996)
  - 15 10 and 14 (501)
  - 16 limit 15 to (humans and english language and yr="1998 - 2006") (435)
  - 17 (random\$ or meta-analysis or metaanalysis or systematic\$ review\$.mp. [mp=title, original title, abstract, name of substance word, subject heading word] (297061)
  - 18 16 and 17 (29)
  - 19 16 (435)
  - 20 limit 19 to (case reports or comment or editorial or letter or "review") (115)
  - 21 19 not 20 (320)
  - 22 18 or 21 (325)

Database: EMBASE <1980 to 2006 Week 36>

Search Strategy:

- 
- 1 \*coronary artery disease/ or exp coronary artery atherosclerosis/ (29025)
  - 2 exp Artery Calcification/ (2406)
  - 3 \*mass screening/ (2553)
  - 4 screen\$.mp. (275443)
  - 5 (asymptomatic or subclinical or silent or healthy or unknown).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (446069)
  - 6 1 or 2 (30798)
  - 7 or/3-5 (701032)
  - 8 6 and 7 (3954)
  - 9 exp Computer Assisted Tomography/ (224173)
  - 10 (computed tomograp\$ or EBCT or MDCT).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (74909)
  - 11 8 and (9 or 10) (578)
  - 12 limit 11 to (human and english language and yr="1998 - 2007") (444)
  - 13 (random\$ or meta-analysis or metaanalysis or systematic\$ review\$.mp. [mp=title, abstract, subject



headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]  
(374358)

14 12 and 13 (36)

15 12 (444)

16 limit 15 to (editorial or letter or note or "review") (125)

17 15 not 16 (319)

18 14 or 17 (325)

# Glossary

## **Agatston score**

Score of coronary calcification.

## **Angina**

Pain or discomfort in the chest or adjacent areas caused by insufficient blood flow to the heart muscle.

## **Angina pectoris**

A disease marked by brief paroxysmal attacks of chest pain caused by deficient oxygenation of the heart muscles.

## **Atherosclerotic material**

Deposits of fatty substances, cholesterol, cellular waste products, etc., that can build up in the inner lining of an artery. This buildup is often referred to as "plaque."

## **Clinically significant**

Results are clinically significant when they make enough difference to you and your patient to justify changing your way of doing things.

## **Computed tomography**

Computed tomography (CT) is an imaging method that uses x-rays to create cross-sectional pictures of the body.

## **Coronary angiography**

Coronary angiography is a procedure that uses a special dye (contrast material) and x-rays to see how blood flows through the heart.

## **Coronary artery calcification (CAC)**

Plaque buildup in the coronary arteries.

## **Coronary artery disease (CAD)**

The formation of yellowish plaques containing cholesterol, lipid material and lipophages within the coronary arteries which may cause angina pectoris, myocardial infarction, and sudden death.

## **Coronary stenosis**

Abnormal narrowing of blood vessels supplying blood to the heart muscle.

## **Diabetes mellitus (DM)**

An endocrine disorder characterized by metabolic abnormalities and by long-term complications involving many parts of the body including the eyes, kidneys, nerves, and blood vessels.

Type 1 DM: or juvenile-onset DM, is often used as a synonym for insulin dependent diabetes.

Type 1 DM may result from an immune-mediated destruction of insulin producing cells of the pancreas resulting in a decrease in production, requiring exogenous insulin therapy.

Type 2 DM: or maturity-onset DM, is marked by resistance to insulin, or insufficient insulin secretion. Approximately 30% of the patients with type 2 DM eventually require insulin.

**Diagnostic accuracy of a test**

The sum of true positives and true negatives divided by the total number of the patients tested.

**Electroencephalogram (EEG)**

A recording of the electric currents developed in the brain. The recorded information is used to diagnose a variety of neurological conditions.

**False negatives**

Those who were tested negative but in fact have the disease.

**False positives**

Those who were tested positive but do not have the disease.

**Hypertension**

High blood pressure (blood pressure is the force of blood against the walls of arteries).

**Incidence**

The number of new cases of a disease in a specified population over a defined period of time.

**Intention-to-treat analysis**

Patients assigned to a particular treatment group by the study protocol should be retained in that group for the purpose of analysis of the study results no matter what happens. Patients redefined or dropped from a study early on as a result of protocol violations unlikely to create bias may validly be considered exceptions to this rule.

**Ischemic heart disease**

An insufficient supply of blood to the heart, usually due to a blocked artery.

**Myocardial infarction**

A heart attack occurs when an area of heart muscle dies or is permanently damaged because of an inadequate supply of blood to that area.

**Odds ratio**

The ratio of the odds of disease for the experimental group relative to the odds of disease in the control group.

**Prevalence**

The number of all new and old cases of a disease in a defined population at a particular point in time.

**Primary outcome**

The prespecified outcome of greatest importance. Primary outcomes should be explicitly indicated as such in the report of a randomized controlled trial.

**Randomized controlled trial (RCT)**

An experiment in which investigators randomly assign eligible subjects (or other units of study) into groups to receive or not receive one or more interventions that are being compared. The results are analyzed by comparing outcomes in the groups.

**Receiver operating characteristic (ROC) curve**

A graphical representation of the performance and utility of a test. It displays the relationship between

true positive and false positive rates.

**Restenosis**

A recurrence of narrowing equal to or greater than 50% of the diameter of the blood vessel.

**Sensitivity**

Determined by the division of the number of true positives by the total number of patients who have the disease.

**Specificity**

The number of true negatives divided by the number of patients who do not have the disease.

**Statistically significant**

A result that is at least 95% likely to be accurate; a result that would be produced by chance no more than 5% of the time.

**Stent**

A metal or plastic tube that is inserted into a coronary artery to prevent constriction and closure of a blood vessel.

**Ultrasound**

An imaging technique.

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