Multi-Detector Computed Tomography Angiography for Coronary Artery Disease

An Evidence-Based Analysis

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Ontario

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Executive Summary

Purpose

Computed tomography (CT) scanning continues to be an important modality for the diagnosis of injury and disease, most notably for indications of the head and abdomen. (1) According to a recent report published by the Canadian Institutes of Health Information, (1) there were about 10.3 scanners per million people in Canada as of January 2004. Ontario had the fewest number of CT scanners per million compared to the other provinces (8 CT scanners per million). The wait time for CT in Ontario of 5 weeks approaches the Canadian median of 6 weeks.

This health technology and policy appraisal systematically reviews the published literature on multi-detector CT (MDCT) angiography as a diagnostic tool for the newest indication for CT, coronary artery disease (CAD), and will apply the results of the review to current health care practices in Ontario. This review does not evaluate MDCT to detect coronary calcification without contrast medium for CAD screening purposes.

The Technology

Compared with conventional CT scanning, MDCT can provide smaller pieces of information and can cover a larger area faster. (2) Advancing MDCT technology (8, 16, 32, 64 slice systems) is capable of producing more images in less time. For general CT scanning, this faster capability can reduce the time that patients must stay still during the procedure, thereby reducing potential movement artefact. However, the additional clinical utility of images obtained from faster scanners compared to the images obtained from conventional CT scanners for current CT indications (i.e., non-moving body parts) is not known.

There are suggestions that the new fast scanners can reduce wait times for general CT. MDCT angiography that utilizes a contrast medium, has been proposed as a minimally invasive replacement to coronary angiography to detect coronary artery disease. MDCT may take between 15 to 45 minutes; coronary angiography may take up to 1 hour.

Although 16-slice and 32-slice CT scanners have been available for a few years, 64-slice CT scanners were released only at the end of 2004.

Review Strategy

There are many proven, evidence-based indications for conventional CT. It is not clear how MDCT will add to the clinical utility and management of patients for established CT indications. Therefore, because cardiac imaging, specifically MDCT angiography, is a new indication for CT, this literature review focused on the safety, effectiveness, and cost-effectiveness of MDCT angiography compared with coronary angiography in the diagnosis and management of people with CAD.

This review asked the following questions:

➢ Is the most recent MDCT angiography effective in the imaging of the coronary arteries compared with conventional angiography to correctly diagnose of significant (> 50% lumen reduction) CAD?
➢ What is the utility of MDCT angiography in the management and treatment of patients with CAD?
➢ How does MDCT angiography in the management and treatment of patients with CAD affect long-term outcomes?

The published literature from January 2003 to January 31, 2005 was searched for articles that focused on the detection of coronary artery disease using 16-slice CT or faster, compared with coronary angiography. The search yielded 138 articles; however, 125 were excluded because they did not meet the inclusion criteria (comparison with coronary angiography, diagnostic accuracy measures calculated, and a sample size of 20 or more). As screening for CAD is not advised, studies that utilized MDCT for this purpose or studies that utilized MDCT without contrast media were also excluded. Overall, 13 studies were included in this review.

Summary of Findings

The published literature focused on 16-slice CT angiography for the detection of CAD. Two abstracts that were presented at the 2005 European Congress of Radiology meeting in Vienna compared 64-slice CT angiography with coronary angiography.

The 13 studies focussing on 16-slice CT angiography were stratified into 2 groups: Group 1 included 9 studies that focused on the detection of CAD in symptomatic patients, and Group 2 included 4 studies that examined the use of 16-slice CT angiography to detect disease progression after cardiac interventions. The 2 abstracts on 64-slice CT angiography were presented separately, but were not critically appraised due to the lack of information provided in the abstracts.

16-Slice Computed Tomography Angiography

The STARD initiative to evaluate the reporting quality of studies that focus on diagnostic tests was used. Overall the studies were relatively small (fewer than 100 people), and only about one-half recruited consecutive patients. Most studies reported inclusion criteria, but 5 did not report exclusion criteria. In these 5, the patients were highly selected; therefore, how representative they are of the general population of people with suspicion if CAD or those with disease progression after cardiac intervention is questionable. In most studies, patients were either already taking, or were given, β-blockers to reduce their heart rates to improve image quality sufficiently. Only 6 of the 13 studies reported interobserver reliability quantitatively. The studies typically assessed the quality of the images obtained from 16-slice CT angiography, excluded those of poor quality, and compared the rest with the gold standard, coronary angiography. This practice necessarily inflated the diagnostic accuracy measures. Only 3 studies reported confidence intervals around their measures.

Evaluation of the studies in Group 1 reported variable sensitivity, from just over 60% to 96%, but a more stable specificity, at more than 95%. The false positive rate ranged from 5% to 8%, but the false negative rate was at best under 10% and at worst about 30%. This means that up to one-third of patients who have disease may be missed. These patients may therefore progress to a more severe level of disease and require more invasive procedures. The calculated positive and negative likelihood ratios across the studies suggested that 16-slice CT angiography may be useful to detect disease, but it is not useful to rule out disease. The prevalence of disease, measured by conventional coronary angiography, was from 50% to 80% across the studies in this review. Overall, 16-slice CT angiography may be useful, but there is no conclusive evidence to suggest that it is equivalent to or better than coronary angiography to detect CAD in symptomatic patients.

In the 4 studies in Group 2, sensitivity and specificity were both reported at more than 95% (except for 1 that reported sensitivity of about 80%). The positive and negative likelihood ratios suggested that the test might be useful to detect disease progression in patients who had cardiac interventions. However, 2 of the 4 studies recruited patients who had been asymptomatic since their intervention. As many of the patients studied were not symptomatic, the relevance of performing MDCT angiography in the patient population may be in question.

64-Slice Computed Tomography Angiography

An analysis from the interim results based on 2 abstracts revealed that 64-slice CT angiography was insufficient compared to coronary angiography and may not be better than 16-slice CT angiography to detect CAD.

Conclusions

Cardiac imaging is a relatively new indication for CT. A systematic review of the literature was performed from 2003 to January 2005 to determine the effectiveness of MDCT angiography (16-slice and 64-slice) compared to coronary angiography to detect CAD. At the time of this report, there was no published literature on 64-slice CT for any indications.

Based on this review, the Medical Advisory Secretariat concluded that there is insufficient evidence to suggest that 16-slice or 64-slice CT angiography is equal to or better than coronary angiography to diagnose CAD in people with symptoms or to detect disease progression in patients who had previous cardiac interventions. An analysis of the evidence suggested that in investigating suspicion of CAD, a substantial number of patients would be missed. This means that these people would not be appropriately treated. These patients might progress to more severe disease and possibly more adverse events. Overall, the clinical utility of MDCT in patient management and long-term outcomes is unknown.

Based on the current evidence, it is unlikely that CT angiography will replace coronary angiography completely, but will probably be used adjunctively with other cardiac diagnostic tests until more definitive evidence is published.

If multi-slice CT scanners are used for coronary angiography in Ontario, access to the current compliment of CT scanners will necessarily increase wait times for general CT scanning. It is unlikely that these newer-generation scanners will improve patient throughput, despite the claim that they are faster.

Screening for CAD in asymptomatic patients and who have no history of ischemic heart disease using any modality is not advised, based on the World Health Organization criteria for screening. Therefore, this review did not examine the use of multi-slice CT for this purpose.

Abbreviations

CT	Computed tomography
MDCT	Multi-detector computed tomography
CA	Coronary angiography
CAD	Coronary artery disease
CABG	Coronary artery bypass graft
MRI	Magnetic resonance imaging
Se	Sensitivity
Sp	Specificity
LR	Likelihood ratio
PPV	Positive predictive value
NPV	Negative predictive value
PP	Post-test probability
CCS	Canadian Cardiovascular Society
CCN	Cardiac Care Network
ACC/AHA	American College of Cardiology/American Heart Association

Issue

The Ontario Health Technology Advisory Committee asked the Medical Advisory Secretariat to do a health technology and policy appraisal of the effectiveness and cost-effectiveness of fast scanners for new indications, specifically cardiac imaging.

This health technology and policy appraisal systematically reviews the published literature on multi-detector computed tomography (MDCT) angiography (with contrast) as a diagnostic tool for the newest indication for CT, coronary artery disease (CAD), and applies the results of the review to health care practices in Ontario, Canada.

Background

Clinical Need: Target Population and Condition

CT scanning continues to be an important modality to diagnose injury and disease, most notably for indications of the head and abdomen. (1) Figure 1 shows the distribution of CT scanners per million people and the median wait time for CT scanning in weeks across the Canadian provinces. According to a recent report published by the Canadian Institutes of Health Information (CIHI), (1) there were approximately 10.3 scanners per million people in Canada as of January 2004. Ontario had the fewest number of CT scanners per million people (8 per million) compared to the other provinces. The wait time for CT in Ontario (5 weeks) approaches the Canadian median of 6 weeks.

Figure 1: Number of Computed Tomography Scanners per Million People and Wait Times for Computed Tomography Across Canada, 2004*
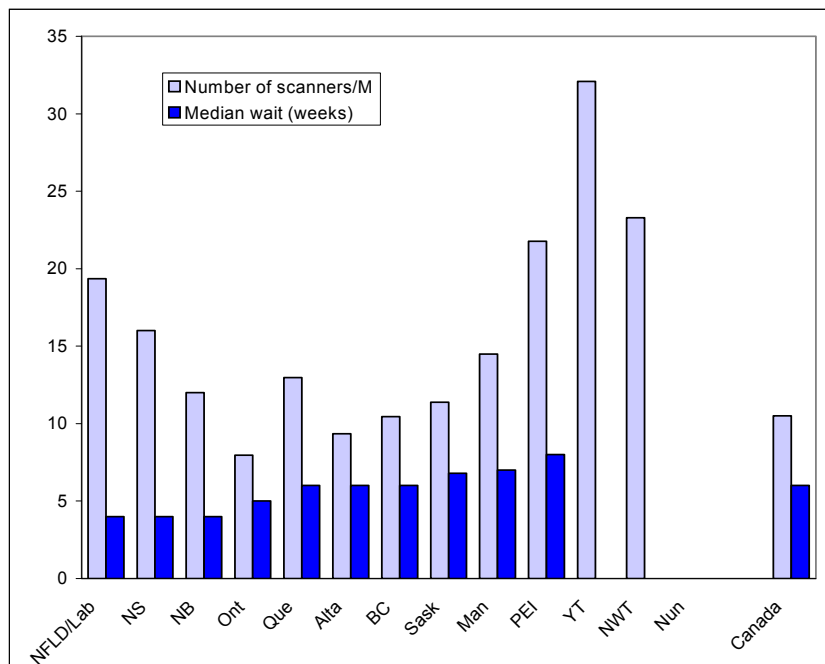
*From: Scanners -CIHI 2004 (1); Statistics Canada 2004 Wait times - CIHI 2003; Statistics Canada 2003; Fraser Institute 2003

Figure 2 shows the distribution of CT scans in Ontario by body site and service type, acquired by routinely collected administrative data. In 2003, 135,043 CT scans were performed for hospital in-patients. Abdominal (35%), head (21%), brain (19%), and lung (11%) CT scans were the most common. Similarly, 143,230 CT scans were performed on an ambulatory or emergency basis during the same time. Head (44%), abdominal (25%), and brain (18%) were the most common indications. These data may underestimate the actual number of scans since the administrative data may not have captured all scans for the years below.

Figure 2: Distribution of Inpatient and Ambulatory/Emergency Computed Tomography Scans by Body Site in Ontario, 2003*

Total inpatients = 135043
Total outpatients = 148230
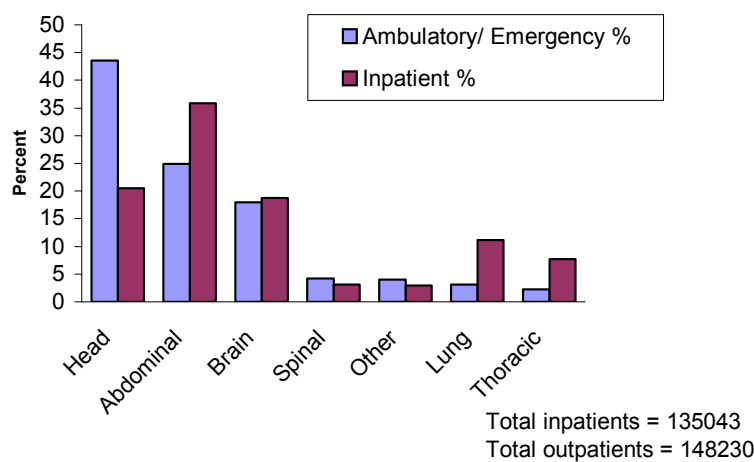
*From: Ontario Ministry of Health and Long-term Care, 2003

On February 3, 2005, the Ontario government announced the infusion of $45.3 million (Cdn) to replace 26 CT scanners and to increase hours of operation at 23 hospitals to improve access to CT imaging. It is estimated that this will result in an additional 81,268 CT exams per year. (3)

The Technology Being Reviewed: Multi-Detector Computed Tomography

General Computed Tomography Scanning in Ontario

Compared to conventional CT scanning, MDCT can provide smaller pieces of information and can cover a larger area faster. (2) Advanced MDCT technology (8, 16, 32, and 64-slice systems) is capable of producing 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 artefact. 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., non-moving body parts) is unknown.

In order to take full advantage of the technology, considerable post-processing of images, upgraded software, and increased storage and processing capabilities are required. Table 1 provides example specifications of faster scanners compared to conventional single-slice scanners.

Cited clinical advantages of MDCT scanners over conventional CT scanners for general scanning purposes include these: (2)

➢ Has faster and better spatial resolution; covers more volume; uses contrast media more efficiently
➢ May be useful for pediatrics/geriatrics/bariatrics/cardiology.
➢ May replace other more invasive or cumbersome procedures.
➢ May affect workflow because of faster scanning times (don't 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 to 25 with single scanner.
➢ Images can be sent straight to software, but efficient image management is necessary.

Table 1: Specifications of conventional and MDCT scanners (2)

Scanner	Contiguous slices	Coverage	Time (seconds)
Conventional	10 mm	25 mm	25/rotation
4-slice	5 mm	25 mm	6.25/rotation
64-slice	credit card	40 mm	0.3/rotation

Cited disadvantages include these: (2)

➢ "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. MDCT angiography is being proposed as a minimally invasive replacement for coronary angiography (CA) to diagnose CAD.

According to the Heart and Stroke Foundation of Canada, 54% of all cardiovascular deaths are due to CAD. (4) Patient characteristics (e.g., age, sex, genetics), underlying clinical 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 Ontario in 2000/2001 $457.9 million (Cdn) was spent on invasive ($237.4 million) and non-invasive ($220.5 million) cardiac services. (5) The use of non-invasive cardiac tests in particular is rising rapidly. (5)

Atherosclerosis progression and investigation

CAD is characterized by atherosclerosis, a slow, progressive condition that begins early in life. It occurs when plaque made up of fat such as cholesterol, phospholipids, and calcium accumulates in the arteries, thereby depleting them 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. (4)

There are various stages in the development of atherosclerosis (Appendix 1). Each phase has relatively distinct morphological characteristics that can permanently stabilize or progress. (6) 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 it 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 may experience angina, acute myocardial infarction, 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 " ≥ 70% diameter stenosis of at least one major epicardial artery segment and/or ≥ 50% diameter stenosis of the left main coronary artery." (7)

Existing Diagnostic Tests for Coronary Artery Disease

A range of non-invasive and invasive diagnostic tests is available and used extensively for the investigation of CAD.

Patient history and physical examination: According to the ACC/AHA guidelines, (7) 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 non-cardiac. 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 (CCS) (Appendix 2).

Identification of risk based on the CCS grading, family history, clinical risk factors (e.g., hypertension, diabetes, high cholesterol), and lifestyle factors (e.g., smoking, exercise) can guide the course of diagnostic investigation and treatment. (7)

Electrocardiogram (ECG): This non-invasive 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) non-invasive 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 (SPECT): 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-myocardial infarction, and function of grafted vessels after coronary artery bypass surgery (CABG).

Echocardiography (ECHO): A series of high-frequency sound waves are emitted toward the heart from a hand-held 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 there is leakage). This test takes between 15 and 45 minutes. Transesophageal echocardiography (TEE), whereby a tube emitting sound waves is inserted into the esophagus, can provide even more detailed information that may not be available through conventional ECHO.

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. CA is considered the gold standard tool for the diagnosis of CAD.

Complications resulting from CA may occur in 1 in 1,000 to 1 in 500 cases. (8) 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 IV
- ➢ 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, (9) IVUS may be an adjunctive procedure to CA, because may provide additional information about the composition of plaque in the coronary and peripheral vessels. MSAC also found that IVUS may aid in the accuracy of stent placement and provides statistically significant lower odds of re-stenting at 9 to 12 months compared to non-IVUS-guided stenting (odds ratio [OR], 0.73; 95% confidence interval [CI], 0.54–0.99; P = .04). However, based on the

lack of evidence, MSAC 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).

Other imaging tests that may be used to evaluate the anatomy, function, perfusion, and tissue characterization in patients with ischemic heart disease are electron-beam CT, contrast-enhanced functional magnetic resonance imaging (MRI), 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, coronary angioplasty with the insertion of a stent within the vessel is performed to prevent obstruction. If there are multiple stenoses, a CABG may be required. Further details in the treatment of CAD are beyond the scope of this review.

MDCT for Cardiac Imaging

According to some cardiology and radiology experts (Personal communication 2005), manufacturers' advertising and technology forecasts (10;11) 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 believing that CT-enhanced angiography could replace cardiac catheterization, IVUS, MRI, and ECHO as diagnostic tools for CAD assessment. (10;11)
➢ The indications for MDCT may be expanded to these areas:
   ➢ Diagnosis of non-calcified plaque in coronary arteries,
   ➢ Follow-up after surgical bypass 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.
➢ It may be used for patients who cannot have conventional angiography, because it is less invasive.
➢ Increased use may decrease the necessity for conventional angiography.
➢ Various cardiac tests could become redundant and be eliminated.
➢ Higher patient volumes might be possible to achieve.
➢ It could identify patients who could most benefit from medical therapy early, thereby prolonging the necessity for invasive procedures such as angioplasty and CABG.
➢ It is less expensive, time-consuming, and invasive than CA (takes < 30 minutes with only 1 injection of contrast [X-ray requires intra-arterial catheterization] compared to 1 hour for CA).

Possible limitations of 64-slice CT for coronary vessel imaging are these: (2;10;11)

➢ The effectiveness of 64-slice CT to detect CAD is unknown.
➢ The clinical utility of 64-slice CT in the management of patients with CAD is unknown.
➢ Unnecessary therapeutic angioplasty could increase due to earlier suspicion of disease.
➢ Conventional CA is still necessary to confirm non-invasive imaging (X-ray has higher spatial and temporal resolution); will be additive to CA rather than a replacement.

Screening for Coronary Artery Disease in Asymptomatic Adults

Some clinical cardiac experts (Personal communication 2005) and published peer-reviewed studies (12) 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 has established a set of recommendations on screening as a preventive tool in medicine, (13) and this has been used by many large global health organizations (e.g., World Health Organization). 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 gleaned 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 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 coronary calcification as a screening tool for CAD has been available since the late 1990s with the advent of electron-beam CT (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, (14) screening people at low-risk for heart disease using treadmill exercise testing, resting electrocardiogram (EKG), or EBCT is not recommended. The task force concluded that 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 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.

Given the above conclusions and recommendations by the United States Preventative Task Force and given the fact that fast CT for CAD does not comply with the global screening criteria above, screening for CAD using MDCT will not be evaluated in this report.

Regulatory Status

In Canada, CT scanners are licensed as Class III devices: potentially hazardous and could cause harm if they fail. Currently, 4 companies have licensing clearance for MDCT by Health Canada (Table 2). Only one has licensing clearance for 64-slice CT. All 4 have clearance for 16-slice CT.

Table 2: Computed Tomography Devices Licensed by Health Canada

Siemens AG (Munich, Germany):
Licence 65633, SOMATOM SENSATION 64/SENSATION CARDIAC 64
Licence 60814, SOMATOM SENSATION CARDIAC
Licence 60813, SOMATOM SENSATION 16
Licence 61943, SOMATOM EMOTION 6
Licence 61941, SOMATOM SENSATION 10
Licence 34510, SOMATOM SENSATION 4

General Electric Medical Systems (Milwaukee, WI, USA):
Licence 60610, LIGHTSPEED 16 CT SCANNER SYSTEM
Licence 29420, LIGHTSPEED PLUS CT SCANNER SYSTEM
Licence 32409, LIGHTSPEED ULTRA CT SCANNER SYSTEM
Licence 61757, HISPEED QX/I CT SCANNER SYSTEM
Licence 60610, LIGHTSPEED 16 CT SCANNER SYSTEM
Licence 63325, LIGHTSPEED RT CT SCANNER SYSTEM (8 slice)

Philips Medical Systems (Haifa, IL, USA):
Licence 18575, MX8000 MULTISLICE CT IMAGING SYSTEM
Licence 35033, BRILLIANCE MULTISLICE CT IMAGING SYSTEM

Toshiba Medical Systems Corporation (Tochigi, Japan):
Licence 66981 AQUILION 32 3 AQUILION 32 - CARDIAC FUNCTION ANALYSIS
Licence 64214, AQUILION SUPER 4 EDITION
Licence 65425, AQUILION CFX EDITION

In the United States, CT is regulated under 2 statutes– the Radiation Control for Health and Safety Act and the Medical Device Amendments to the Food, Drug, and Cosmetic Act . (15)

EBCT was accepted by 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. Further, EBCT is indicated for determining specific quantitative information such as volume of calcium or other materials in organs, bone, or tumours; and for angiography. (10)

Insurance Coverage

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 service code for CT of the thorax and for other anatomic sites. This would include MDCT scans. (Personal communication, February 2005).

Safety

General CT scanning poses a risk of radiation exposure. There is generally little difference between single and MDCT capabilities, but MDCT may produce higher radiation doses because of higher X-ray tube currents that are necessary for multiple slices. (16)

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. (16) 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 8to 11 mSv for a typical head, chest and abdominal, or pelvic CT, respectively. (17)

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. (18) According to Mollet (19) the radiation dose using 16-slice CT scans is reportedly 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. (2)

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. (20)

According to a recent report published by the Medicines and Healthcare Products Regulatory Agency (16) in the United Kingdom, consideration of the indications for MDCT is required with careful selection of scanning parameters.

Literature Review on Effectiveness

Objective

There are many evidence-based indications for conventional CT. It is not clear, however, how MDCT will add to the clinical utility and management of patients for established CT indications. Therefore, because cardiac imaging is a new indication for CT, this literature review focused on the safety, effectiveness, and cost-effectiveness of MDCT angiography compared with CA in the diagnosis and management of people with CAD. MDCT for evaluating coronary calcification as a modality for CAD screening was not within the scope of this review.

Questions Asked

➢ Is the latest MDCT angiography technology effective in the imaging of the coronary arteries compared with conventional angiography to diagnose significant (> 50% lumen reduction) CAD?
➢ What is the utility of MDCT angiography in the management and treatment of patients with CAD?
➢ How does MDCT angiography in the management and treatment of patients with CAD affect long-term outcomes?

Methods

Using the standard Medical Advisory Secretariat search strategy, all peer-reviewed published literature and health technology assessments on the most recent MDCT technology and CAD were searched from January 1, 2003 to January 24, 2005.

The abstracts of peer-reviewed publications were identified through OVID MEDLINE, EMBASE, OVID MEDLINE In-Process & Not-Yet Indexed Citations, Cochrane Database of Systematic Reviews, Cochrane CENTRAL, and INAHTA using the following key words:

➢ coronary disease
➢ tomography, X-ray computed; computer assisted tomography
➢ multislice or multidetect$ or multi-slice or multi-detec$ or multi-row or multirow or multispiral or multi-spiral or thin-slice or multi-detector-row
➢ systematic review

The criteria for inclusion were as follows:

➢ 16, 32, 48 or 64-slice CT scanner used
➢ Randomized controlled trial (RCT) or prospective comparison trial with sample size of 20 or more
➢ MDCT angiography compared to CA
➢ Live human study
➢ Indication for CAD
➢ English-language study

The exclusion criteria were as follows:

➢ 4- or 8-slice scanner used
➢ Screening for coronary calcification in asymptomatic people

Outcomes of interest included these:

➢ Sensitivity
➢ Specificity
➢ Positive predictive value (PPV)
➢ Negative predictive value (NPV)
➢ Kappa coefficient

The full text of all included studies was retrieved and critically appraised according to the STARD initiative that evaluates the quality of diagnostic testing studies. (21;22) Diagnostic testing accuracy measures that included all study images (including those that were indiscriminate, where possible), as calculated by the study authors were extracted (sensitivity, specificity, PPV, NPV, and others where included). To understand better the discriminatory power of 16-slice CT angiography compared to CA, composite and summary measures including the false positive rate (FPR), false negative rate (FNR), positive and negative likelihood ratios (LR+ and LR-) were calculated based on the reported diagnostic accuracy. (22-25)

Results of Literature Review

The search identified 138 articles from January 1, 2003 to January 31, 2005. The following 125 articles were excluded from the synthesis:

➢ 9 studies screening asymptomatic people
➢ 9 with an N ≤ 10
➢ 33 that were not 16 slice or higher
➢ 21 studies with no comparison modality

- ➢ 18 compared with modality other than CA
- ➢ 9 non-living human studies
- ➢ 6 with non-cardiac as primary indication
- ➢ 5 non-English-language studies
- ➢ 6 reviews
- ➢ 5 assessments of processing software
- ➢ 2 case reports
- ➢ 2 health technology assessments on screening

Two abstracts presented at the 2005 European Congress of Radiology met the inclusion criteria. They compared 64-slice CT angiography to CA to detect CAD.

Table 3: Summary of Reports on Multi-Detector Computed Tomography Scanning for Cardiac Investigation

Study, Year	Focus	Study Type	Scanner Type	Study Scope	Conclusions
ECRI 2005; Health technology forecast(11)	MSCT	Forecast and perspectives; no empiric evaluation	8-slice through to 64-slice	No empiric evidence provided	8-slice can provide enough capability for routine CT scanning, although 16-slice scanners have highest market share in the U.S.; only centres with advanced vascular/cardiac programs should consider 64-slice CT
ECRI, 2004; Health technology forecast – Horizon scanning resource (10)	Computed tomography angiography	Review and perspectives; no empirical evaluation	16, 32, 40, and 64 slices	3 case series	-Extensive expected utilization -0 to 1 year for early adoption -Moderate health impact -Substantial financial impact -Substantial process impact (shift from radiology to cardiology possible)
Medical Services Advisory Committee, 2003 (26)	Multi-detector computed tomography	Not full health technology assessment – horizon scanning brief	4- to 16-slice (does not specify in analysis)	19 studies evaluating coronary arteries (diagnostic/ therapeutic)	-MDCT (4 or 16-slice) not comparable to CA; requires full HTA -Safe and non-invasive, but radiation dose high -Throughput may offset high cost of MDCT, but more research required
ECRI, 2002 (2)	Market review	Perspectives and vendor evaluation	Up to 4 slices	Review – no empirical comparisons	"The decision to buy a multi-slice CT scanner depends on the patient population, whether there is a need to increase productivity, the age of existing equipment and the availability of alternative imaging technologies … must be made with clearly defined clinical motives, a realistic financial justification and an understanding that the technology is evolving."

Summary of Existing Health Technology Assessments

Three reports from ECRI (2;2;10) were found and included in this review. One report from Medical Services Advisory Committee (MSAC) in Australia was found that focused on the diagnostic and therapeutic modalities for coronary artery disease, but did not highlight the type of scanners used in the systematic review. (26) A very brief report by the Canadian Coordinating Office for Health Technology Assessment (CCOHTA) from 2003 (27) was found but excluded because it focused on screening for CAD using MDCT.

Table 3 summarizes the findings from the included reviews by ECRI and MSAC. The MSAC report is based on horizon scanning activity and was admittedly not an HTA. Despite this shortcoming, MSAC concluded that the diagnostic accuracy of 4-slice and 16-slice MDCT angiography is not comparable to CA and its use is still in the research stage. They further commented that the segment-based analyses used in the studies included in their report may have increased the likelihood of clinically and statistically significant results by decreasing the variability of the reported measurements. The conclusions made by the ECRI reports were largely based on perspectives, rather than empiric results because of the paucity of literature at the time of these reviews. The most recent ECRI report (11) suggested that although 16-slice CT is rapidly becoming the largest share of the U.S. CT scanning market, 8-slice CT probably provides enough capability necessary for general CT scanning. They further suggested that only centres with advanced cardiac or vascular programs should consider purchasing 64-slice CT scanners.

Summary of Results of Medical Advisory Secretariat Review

Using the search strategy outlined in the methods section above, 13 peer-reviewed articles and 2 abstracts presented at a scientific meeting were included in this systematic review (Table 4). All of the articles focused on 16-slice CT angiography and CAD; the 2 abstracts focused on 64-slice CT angiography.

Details of the methods of these studies are in Appendix 2.

No RCTs were found. The extracted studies all sought to determine the diagnostic accuracy of MDCT angiography compared to CA, the gold standard. Therefore, the studies were all defined as level 3a evidence; that is, recruited participants were those who were scheduled to have CA who received a MDCT scan with contrast either before or after CA as part of the study protocol. The studies analyzed the diagnostic accuracy of MDCT angiography overall and by segment. Results of segment-based analyses are in Appendix 3. All studies received ethics approval and patient consent.

The published studies were stratified into 2 groups based on the study objectives and the population under study. Study group 1 included 9 studies that examined the accuracy of MDCT angiography to diagnose CAD compared to CA in a population of symptomatic patients. True disease was defined in all studies as at least 50% lumen reduction, based on CA. Study group 2 included 4 studies that focused on the ability of 16-slice CT angiography to assess disease prgression either after CABG or after stenting, defined as at least 50% lumen reduction, identified by CA. These 2 groups of studies were analyzed separately. Table 6 shows the quality of the 13 included studies based on the STARD initiative. (21;22) The 2 abstracts on 64-slice CT angiography were analyzed separately.

Table 4: Quality of the Literature on 16-Slice Computed Tomography Angiography for Investigation of Coronary Artery Disease

Study Design	Level of Evidence	No. 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	0
Small RCT unpublished but reported to an international scientific meeting	2(g)	0
Non-RCT with contemporaneous controls	3a	13
Non-RCT with historical controls	3b	0
Non-RCT presented at international conference	3(g)	2
Surveillance (database or register)	4a	0
Case series (multisite)	4b	0
Case series (single site)	4c	
Retrospective review, modeling	4d	
Case series presented at international conference	4(g)	0

*RCT refers to randomized controlled trial.
†g refers to grey literature.

Various measures can be used to determine the diagnostic accuracy of a test. The most common are sensitivity, the rate of the true positives; specificity, the rate of the true negatives; and the associated PPV and NPV compared to a gold standard test. These reported measurements that included all scans and study participants were extracted from the studies.

There are other summary measures that describe the discriminatory power of a diagnostic test that are deemed more comprehensive than the measures described above. (22-25;28;29) These measures typically are desirable to present because they can compare the probability of detecting a disease before the test is administered (pre-test probability) to the probability of disease after the test is administered (post-test probability). (28;29) A nomogram based on Bayes theorem (30) can be used to estimate the post-test probability of detecting the disease based on the pre-test probability and the likelihood ratio (Appendix 4). Table 5 shows the definition and derivation of these measures.

Table 5: Definition and Calculation of Tests for Diagnostic Accuracy Compared to "Gold Standard"

Test	Definition	Calculation
Sensitivity	% of positive tests in people who are true positives	True positives with positive test / Total true positives
Specificity	% of negative tests in people who are true negatives	True negatives with negative test / True negatives
Positive predictive value	% of truly positive people out of positive tests	True positives with positive test / Total positive tests
Negative predictive value	% of truly negative people out of negative tests	True negatives with negative test / Total negative tests
Positive likelihood ratio	Likelihood of a positive test	Sensitivity/1-specificity
Negative likelihood ratio	Likelihood of a negative test	1-sensitivity/specificity
Positive post-test probability	Post-test probability of disease among those with positive result	Pre-test probability of disease and LR+ applied to published nomogram (30)
Negative post-test probability	Post-test probability of disease among those with negative result	Pre-test probability of disease and LR- applied to nomogram (30)

16-Slice CT Angiography in the Diagnosis of Coronary Artery Disease

Study design and quality

Table 6 shows the study attributes of the included studies. Nine relatively small studies focused on patients who were being investigated for CAD and were already scheduled for CA (N = 16 (31); N = 30(32); N=33(33); N = 39(34); N = 51(35); N = 60(36); N = 64(37); N = 72(38); N = 128 (19)).

All studies reported mean ages and the proportions of men and women in their samples. One study reported on disease severity but did not report on comorbid conditions. Patient exclusion criteria were reported, including unstable health, severe cardiac disease, and arrhythmias in all but 3 studies. All studies except 1 required that patients be given β-blockers to stabilize fast heart rates that could impair the integrity of the CT scan.

Table 6: Attributes of Studies Extracted for Systematic Review Based on STARD Initiative (21;22)

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†
*Gilard, 2005(39)	✓	✓	✓				✓	✓	
Hoffmann, 2004(33)	✓	✓	✓	✓		✓	✓	✓	✓
Kuettner, 2005(38)	✓	✓	✓	✓	✓	✓		✓	
Kuettner, 2004(36)	✓	✓	✓	✓		✓		✓	
Martuschelli, 2004(37)	✓		✓	✓		✓	✓	✓	
*Martuschelli, 2004(40)	✓	✓	✓	✓		✓	✓	✓	
Mollet, 2005(35)	✓		✓	✓		✓	✓	✓	✓
Mollet, 2004(19)	✓		✓	✓		✓	✓	✓	✓
*Schuijf, 2004(41)	✓		✓	✓		✓		✓	
*Schlosser, 2004(42)	✓	✓	✓	✓		✓		✓	
Shi, 2004(31)			✓					✓	
Traversi, 2004(34)	✓		✓			✓		✓	
Zhang, 2004(32)	✓		✓			✓			

†CI indicates confidence interval.
*Group 2 studies: Restenosis after coronary artery bypass graft.

Measures of diagnostic accuracy

The sensitivity and specificity of 16-slice CT angiography compared with CA were calculated for significant coronary stenosis (defined as > 50% lumen reduction) for the studies in this systematic review. In the evaluation of diagnostic accuracy, the authors usually first evaluated the visibility of the scans and only included the scans that were readable for comparison with CA. Excluded scans were mainly owing to increased heart rate, movement artifact, or severe calcium calcification.

Table 7 shows the measures of the diagnostic accuracy of 16-slice CT angiography compared with CA to detect CAD reported in the studies and the positive and negative liklihood ratios calculated by MAS. The sensitivity across the studies ranged from 63% to 95%. The positive predictive value (PPV) ranged from 59% to 87%.

The specificity and the negative predictive value (NPV) of a diagnostic test describe how well a test can predict true negatives in people without the disease. The false positive rate (1 minus specificity) determines the probability of being identified with the disease when no disease is present if the test is used, and therefore the probability of receiving unnecessary diagnostic testing and possible intervention. In Table 7 the specificity and NPVs across studies hovered above 90% for all studies apart from 1 outlier (80%) (34).

Table 7: Diagnostic Accuracy of 16-slice Computed Tomography Angiography Compared to Coronary Angiography To Detect Coronary Artery Disease

Author, Year	Patients	N Patients/ Segments	% CAD* (by CA)	Se† (%)	Sp† (%)	PPV† (%)	NPV† (%)	LR+†	LR-†	PP+† (%)	PP-† (%)
		Reported Measures of Diagnostic Accuracy						Medical Advisory Secretariat's Measures of Diagnostic Accuracy			
Hoffmann, 2004(33)	Positive stress test	33/530	67	63	96	64	96	15.8	0.39	96	30
Kuettner, 2004(36)	Scheduled for CA	60/763	60	72	97	72	97	24.0	0.29	97	28
Kuettner, 2005(38)	Suspected CAD	72/117	50	82	98	87	97	41.0	0.18	97	15
Martuscelli, 2004(37)	Suspected CAD	64/729	67	78	98	NS	NS	39.0	0.23	98	32
Mollett, 2004(19)	Non-stented patients	128/1384	83	92	95	79	NS	18.4	0.08	99	23
Mollet, 2005(35)	Stable angina/ atypical chest pain	51/610	63	95	98	87	NS	47.5	0.05	98	8
Shi, 2004(31)	Anomalous coronary arteries	16 patients	53	90	96	NS	97%	22.5	0.10	96	10
Traversi, 2004(34)	Suspected CAD	39/468	NS	80	80	59	92	4.0	0.25	-	-
Zhang, 2004(32)	Suspected CHD	30 patients	70	95	95	NS	NS	19.0	0.05	98	11

*Prevalence of coronary artery disease (CAD) defined as ≥ 50% stenosis according to coronary angiography (CA)
† Se indicates sensitivity; Sp, specificity; PPV, positive predictive value; NPV, negative predictive value; LR+, positive likelihood ratio; LR-, negative likelihood ratio; PP+, post-test probability of positive case; PP-, post-test probability of negative case; NS, not stated

Figure 3 illustrates the heterogeneity of the sensitivity and specificity values for the 9 studies. The sensitivity in 5 (33;34;36-38) of the 9 studies was 85% or below. In 2, (19;31) the sensitivity was between 90% and 95%, and in 1, (35) it was above 95%. The specificity across the studies was relatively stable at more than above 90%, except for 1 value that was an outlier. (34)

Figures 4 and 5 illustrate the relationships between the ability to rule in and rule out disease. Illustratively, a good test should have the plots clustered around the top left corner. Figure 4 shows that 16-slice CT angiography does not consistently detect true positives (from 58% to 95%), but it has a false positive rate of less than 5% (with the exception of one outlier at 20%). (34)

Figure 3: Sensitivity, Specificity and Prevalence of 16-slice Computed Tomography Angiography Compared to Coronary Angiography To Detect Coronary Artery Disease in Symptomatic Patients
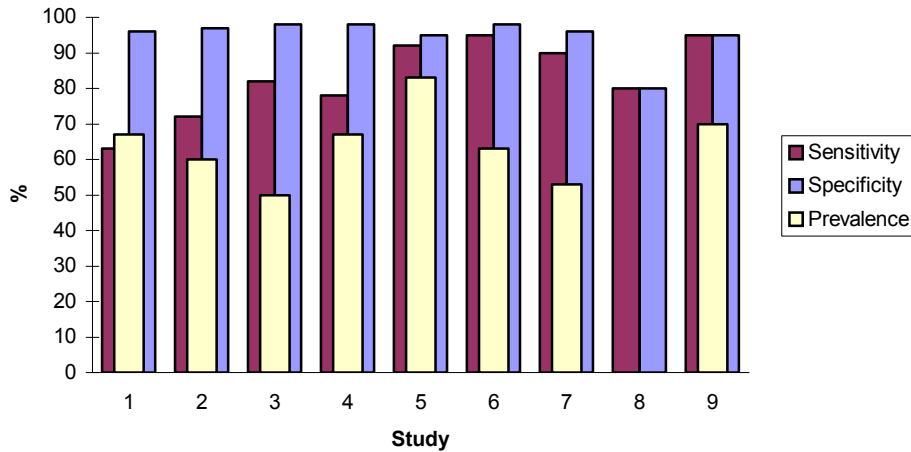
Figure 4: Relationship Between the True Positive Rate (Sensitivity) and the False Positive Rate (1 Minus Specificity) Using 16-Slice Computed Tomography Angiography Compared to Coronary Angiography To Detect Coronary Artery Disease in Symptomatic People
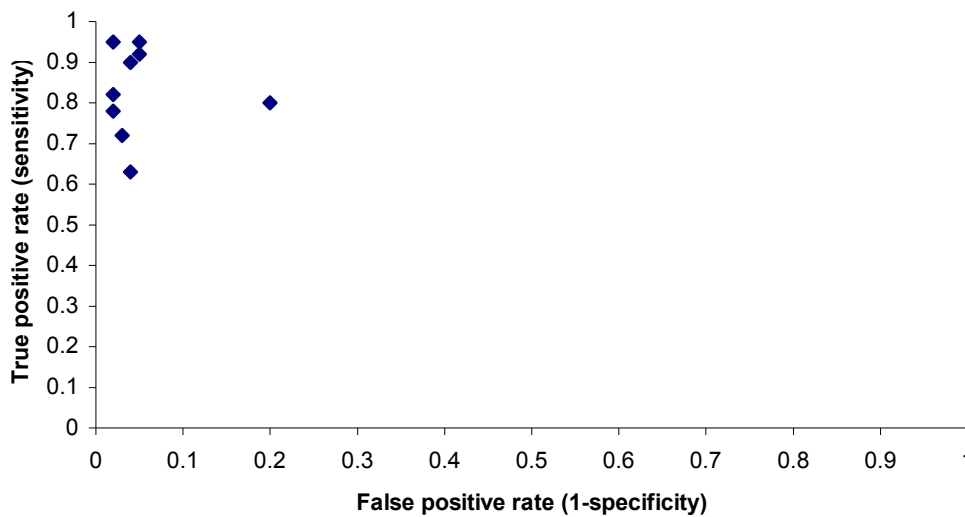
Figure 5 shows that 16-slice CT angiography is a good test to detect no disease in true negatives (95%–99% with 1 outlier), but it has a variable false negative rate of 5% to 10% at best and 20% to 40% at worst. Therefore, from 5% to 10%, upward to 20% to 40% of cases of CAD may be missed using 16-slice CT angiography.

Figure 6 shows the relationship between the positive likelihood (LR+) and negative likelihood (LR-) ratios for 16-slice CT angiography compared to CA in the 9 included studies. The LR+ provides information about how well a test can rule in disease for people who have the condition compared to those who don't have the condition. The LR- provides information about how well the test can rule out disease in people who do not have the condition compared to those who do. Crudely, a test that has a LR+ that is greater than 10 and a LR- that is less than 0.1 is a very useful test. An LR+ of 1 to 2 or less and a LR- of 0.5 to 1 or more indicates a test that may be of little use. (28;29) Again, as Figure 6 suggests, 4 of the 9 studies show that compared to CA, 16-slice CT angiography to detect CAD may useful, but there is heterogeneity across the studies.

The post-test probability of disease utilizes the LR and the pre-test probability, in this case the prevalence of CAD as defined by CA. As Table 6 suggests, the probability of detecting disease after 16-slice CT angiography is quite high among the studies included. The probability of detecting disease despite a negative result is captured through negative post-test probability. As Table 5 suggests, 16-slice CT angiography is not a good test to rule out disease.

Commentary on the Use of 16-Slice MDCT Angiography To Detect Coronary Artery Disease in Symptomatic Patients

Based on the above analysis, the effectiveness of 16-slice CT angiography to detect CAD cannot be established, because of the heterogeneity across studies examined. Compared to conventional CA, 16-slice CT angiography may be a moderately useful test to identify people with disease. This takes into account the composite diagnostic accuracy measures and the relatively high burden of disease in this patient population. A few people may be falsely diagnosed and may undergo unnecessary and potentially invasive procedures to investigate their disease further.

However, 16-slice CT angiography is not a good test to rule out the presence of CAD. This means that some people will be told they are disease-free when CAD is present (false negative). This suggests that from 10% to 30% of people with CAD that are tested with 16-slice CT angiography may not be diagnosed and, therefore, may receive medically necessary treatment.

Figure 5: Relationship Between the True Negative Rate (Sensitivity) and the False Negative Rate (1 Minus Specificity) Using 16-Slice Computed Tomography Angiography To Detect Coronary Artery Disease in Symptomatic People Compared to Coronary Angiography
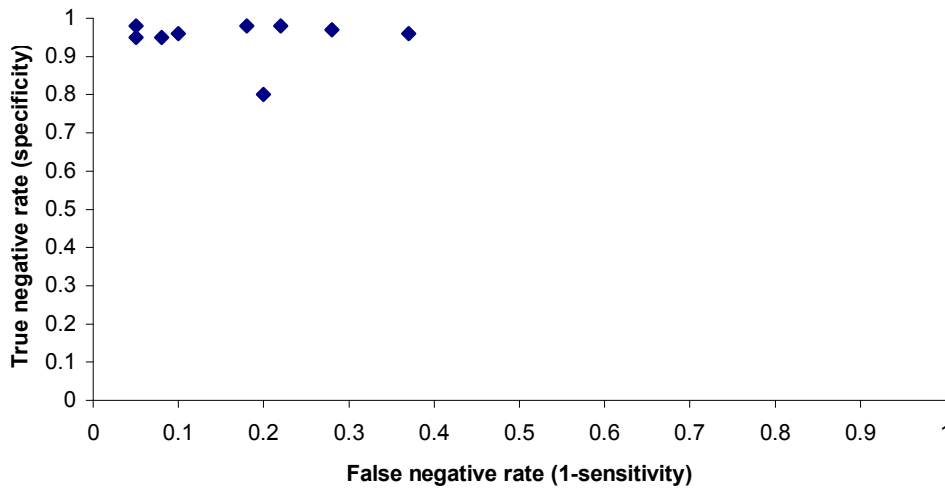
Figure 6: Relationship Between the Positive Likelihood Ratio (LR+) and Negative Likelihood Ratio (LR-) To Detect Coronary Artery Disease in Symptomatic Patients Using 16-Slice Computed Tomography Angiography Compared to Coronary Angiography(28)
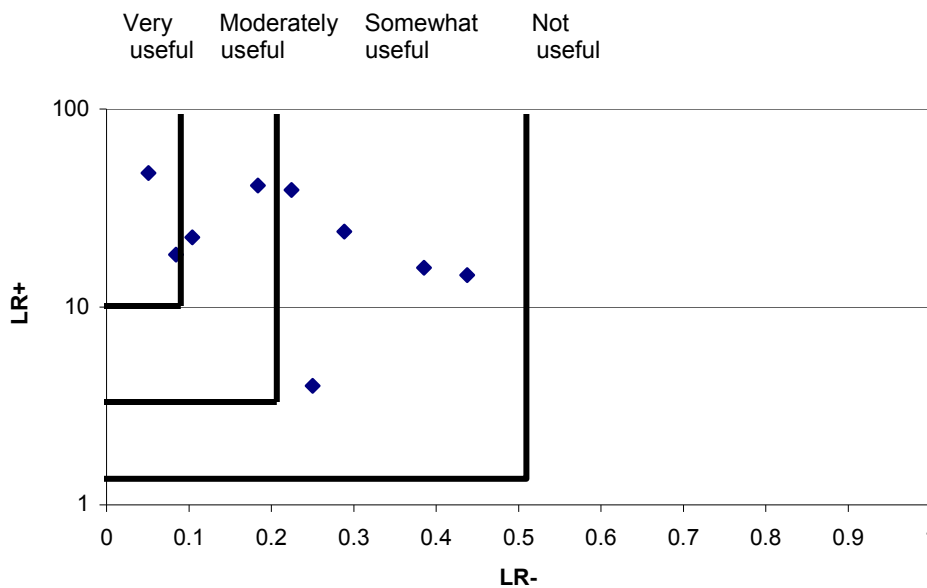
16-Slice CT Angiography for Evaluation of Disease Progression After CABG or Stenting

Study quality

Indicators of study quality as defined by the STARD initiative are shown in Table 6. Four relatively small studies focused on patients who were being investigated for restenosis post-CABG. (N = 22 (41); N = 29 (39); N = 48 (42) N = 96 (40)). All 4 enrolled consecutive patients that were scheduled for CA because of suspected disease progression. The evaluation of restenosis was performed at a mean of 6 months, (39) 14 months, (41) 5 years, (42) and 7 years (40) after their procedure (either CABG or stenting).

One study (41) reported the clinical characteristics of the study sample. Exclusion criteria reported were reported in all but 1 study (39) and included atrial fibrillation, claustrophobia, and renal insufficiency. Two studies (39;40) reported that 100% of patients were either put on β-blockers specifically to bring down the heart rate for the scan or were on β-blockers already. One study (41) reported that 77% of the patients were already on β-blockers.

Measures of diagnostic accuracy

Table 8 shows measures of the diagnostic accuracy of 16-slice CT angiography compared to CA to detect disease progression. Sensitivity ranged from 78% to 100%. Only 2 studies reported PPVs. Specificity ranged from 92% to 100%. The NPV was over 90% in the 3 studies where it was reported.

Table 8: Diagnostic Accuracy of 16-Slice Computed Tomography Angiography Compared to Coronary Angiography in the Evaluation of Disease Progression after Stenting or CABG†

	Reported Measures of Diagnostic Accuracy							Medical Advisory Secretariat's Measures of Diagnostic Accuracy			
Study, Year	Patients†	N Patients/ Segments	Restenosis*, % (by CA)	Se† (%)	Sp† (%)	PPV† (%)	NPV† (%)	LR+†	LR- †	PP+† (%)	PP-† (%)
Gilard, 2005 (39)	29 stented LM artery	29 patients	14	100	92	100	92	12.5	0.001	70	5
Martuscelli, 2004 (40)	CABG	96/251 conduits	Not stated	96	100		99	32.0	0.041		
Schuijf, 2004 (41)	PTCA and Stent	22/65 stents	14	78	100			78.0	0.220	94	10
Schlosser, 2004 (42)	CABG	48/131 grafts	Not stated	96	95	81	99	19.2	0.042		

*Percent restenosis defined as at least 50% lumen reduction according to coronary angiography (CA)
†CABG indicates coronary artery bypass graft; PTCA, percutaneous transluminal coronary angiography Se, sensitivity; Sp, specificity; PPV, positive predictive value; NPV, negative predictive value; LR+, Positive likelihood ratio; LR-, negative likelihood ratio; PP+, post-test probability of disease; PP-, pre-test probability of disease, given a negative test

Figure 7 illustrates the reported sensitivity, specificity, and prevalence estimates for the 4 studies. There was homogeneity of over 90% in sensitivity and specificity, except for 1 sensitivity measure outlier (80%) (41). It is important to point out that the prevalence was defined as 14% in 2 studies that focused on stents where most of the patients were asymptomatic at the time the studies were conducted.

Figures 8 and 9 depict the discriminatory power of 16-slice CT angiography to rule in or out disease. As the data in Figure 8 suggest, 16-slice CT angiography may be a good test to detect restenosis in people who had a previous stent or CABG, but it has an associated false positive rate of about 8%. Further, as

Figure 9 illustrates, 16-slice CT angiography may be a good test to detect people who do not exhibit restenosis with a false negative rate of 5% with the exception of 1 outlier exhibiting a false negative rate of 22%. (41)

Figure 7: Sensitivity and Specificity of 16-Slice Computed Tomography Angiography Compared to Coronary Angiography to Detect Disease Progression after Stenting or CABG*
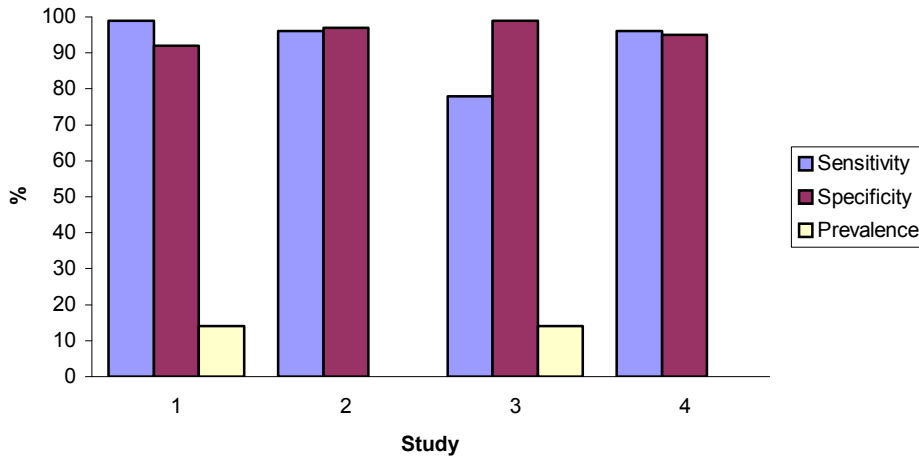
*CABG indicates coronary artery bypass graft.

Figure 8: Relationship Between the True Positive Rate (Sensitivity) and the False Positive Rate (1-Specificity) With 16-Slice Computed Tomography Angiography Compared to Coronary Angiography To Detect Disease Progression after Stenting or CABG*
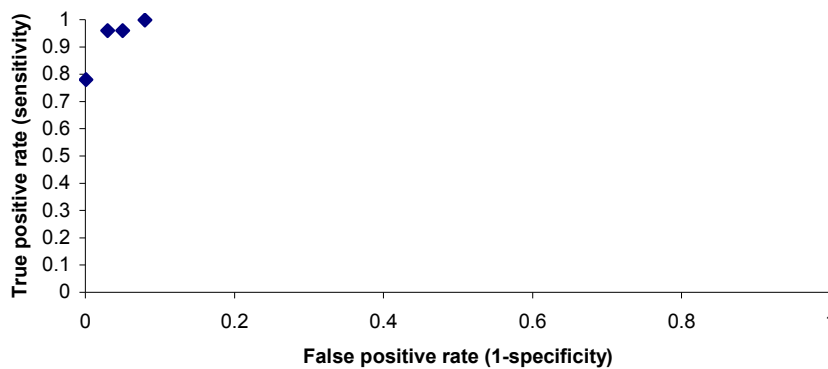
*CABG indicates coronary artery bypass graft.

Figure 9: Relationship Between the True Negative Rate (Specificity) and the False Negative Rate (1-Sensitivity) With 16-Slice Computed Tomography Angiography Compared to Coronary Angiography to Detect Disease Progressions After Stenting or CABG *
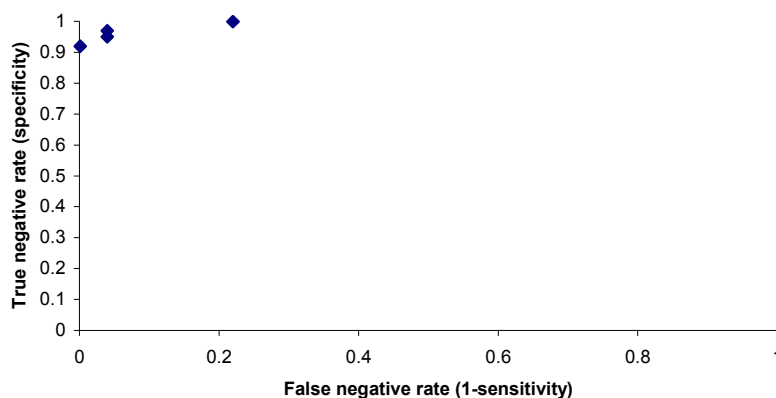
*CABG indicates coronary artery bypass graft.

Figure 10 illustrates the relationship between the LR+ and LR- and accordingly 16-slice CT angiography may be a good test overall. However, based on only 4 studies with such a low prevalence of restenosis owing to the fact that some patients were asymptomatic after they had their cardica procedure (Table 8), effectiveness of 16-slice CT angiography cannot be determined.

Commentary on the Use of 16-slice CT Angiography To Detect Disease Progression After Stenting or CABG

At first glance it appears that, compared to CA, 16-slice CT angiography may be a good test to detect disease progression after previous stenting or CABG. Without accounting for prevalence, there may be a 90% chance of detecting restenosis in people with disease. However, the associated false positive rate is about 5%. This means that about 5% of patients may undergo unnecessary and possibly harmful procedures. The analysis suggests that 16-slice CT angiography may be a good test to rule out disease for those who do not have disease progression after a cardiac intervention, but it has an associated false negative rate of about 5%. Further, many of the patients studied were not symptomatic and this may affect the diagnostic accuracy and relevance of performing MDCT angiography in this patient population.

Limitations specific to the studies that focused on this patient population include these:

➢ Indication of clinical follow-up in these patients is not clearly defined (Personal communications 2005)
➢ The length of patient follow-up with 16-slice CT angiography and CA after the cardiac intervention was variable within and across studies

➢ Disease severity and the reasons for performinig these tests were not defined.

Because of the limitations specific to these studies the diagnostic accuracy and clinical utility of 16-slice CT angiography cannot, at this time, be established.

Figure 10: Relationship Between LR+* and LR-* To Detect Disease Progression after Stenting or CABG* to Detect Disease Progression Using 16-slice Computed Tomography Angiography Compared to Coronary Angiography
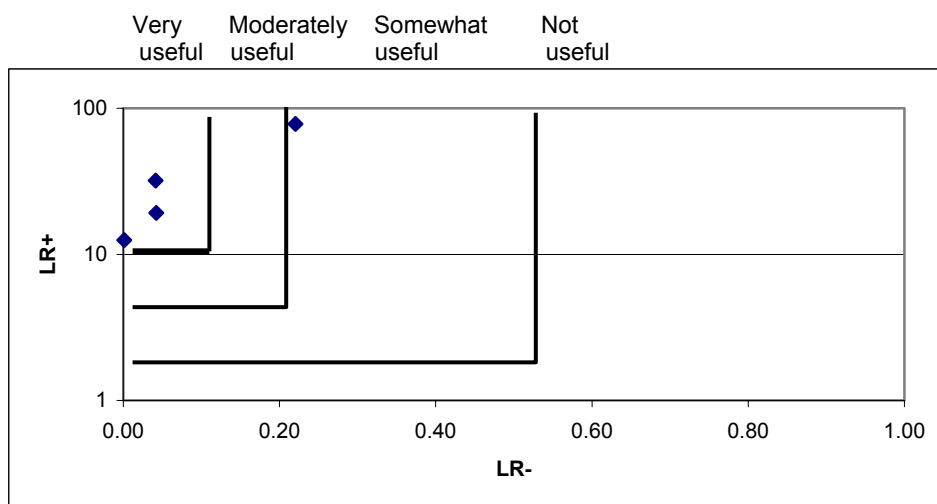
*LR+ indicates positive likelihood ratio; LR-, negative likelihood ratio (28)
CABG refers to coronary artery bypass surgery

Limitations of the Studies in the Systematic Review

For the most part, the studies included the information necessary to be able to draw conclusions. However, there were limitations of the methods that were common across the included studies. These decreased the external validity or generalizability of the results (Table 6).

➢ Some of the studies did not have blind assessors and/or did not report the degree of agreement between the assessors when comparing CA and MDCT angiography results.
➢ The studies included highly selected patients.
➢ Neither duration of illness nor occurrence of comorbid conditions were reported in any of the studies.
➢ B-blockers were required to lower the heart rate so that the MDCT could elicit readable images.
➢ The sample size in these studies was small, and there was no prior determination of numbers needed based on the published prevalence of disease.
➢ The studies included scans of large vessels only (>1.5 mm).
➢ Some studies did not include all of the patients that were scanned and did not account for those that were excluded owing to artifact.
➢ The main results sited were based on vessel segments rather than on patients.
➢ Confidence intervals around diagnostic accuracy measures were done in only a few studies.

> ➤ The studies did not include long-term outcomes; therefore, the test's utility in patient management is unknown.

Scientific Abstracts

Two scientific abstracts that focused on 64-slice CT angiography compared to CA to detect CAD were presented at the 2005 European Congress of Radiology in Vienna. The study samples were relatively small (N = 30 (43); N = 33 (44)). It is important to note that the quality of the designs of the studies could not be evaluated from the information provided in the abstracts.

The diagnostic accuracy reported in the studies and those derived by the Medical Advisory Secretariat are shown in Table 9. In these studies, the sensitivity of 64-slice CT angiography was high (95% or over), while the specificity was lower (89%).

Figure 11 shows that 64-slice CT angiography with an LR+ of just less than 10 and an LR- of less than 0.01, may be moderately useful to detect and rule out CAD. However, one study had a low prevalence of CAD (39%) (44) based on the results of CA; therefore, the positive post-test probability of detecting disease was much lower in 1 of the two studies (81% vs. 95%). The post-test probability of detecting disease despite a negative result (PP-) was ranged from 11% to 15%.

Commentary on the Abstracts on 64-Slice Computed Tomography

Based on the 2 abstracts included in this review, 64-slice MDCT may be useful to detect CAD compared to CA. Given that these data are preliminary, however, its overall effectiveness cannot be determined.

Table 9: Diagnostic Accuracy Measures From 2 Abstracts on 64-Slice Computed Tomography Angiography Compared to Coronary Angiography To Detect Coronary Artery Disease

	Reported Measures of Diagnostic Accuracy							Medical Advisory Secretariat's Measures of Diagnostic Accuracy			
Author, Year	Patients	N Patients	CAD* (by CA), %	Se† (%)	Sp† (%)	PPV† (%)	NPV† (%)	LR+†	LR-†	PP+† (%)	PP-† (%)
Cademartiri, 2005 (43)	Stable angina or acute coronary syndrome	33	71	0.95	0.89	0.95	0.89	8.6	0.056	0.95	0.11
Nikolaou, 2005 (44)	Known or suspected coronary artery disease	30	39	0.96	0.89	0.85	0.97	8.72	0.04	0.81	0.15

*CAD indicates coronary artery disease; CA, coronary angiography.
†Se indicates sensitivity; Sp, specificity; PPV, positive predictive value; NPV, negative predictive value; LR+ positive likelihood ratio; LR-, negative likelihood ratio; PP+, positive post-test probability; PP-, negative post-test probability.

Figure 11: Relationship Between LR+* and LR-* Derived From 4 Studies To Detect Coronary Artery Disease in Symptomatic Patients With 64-Slice Computed Tomography Angiography Compared to Coronary Angiography
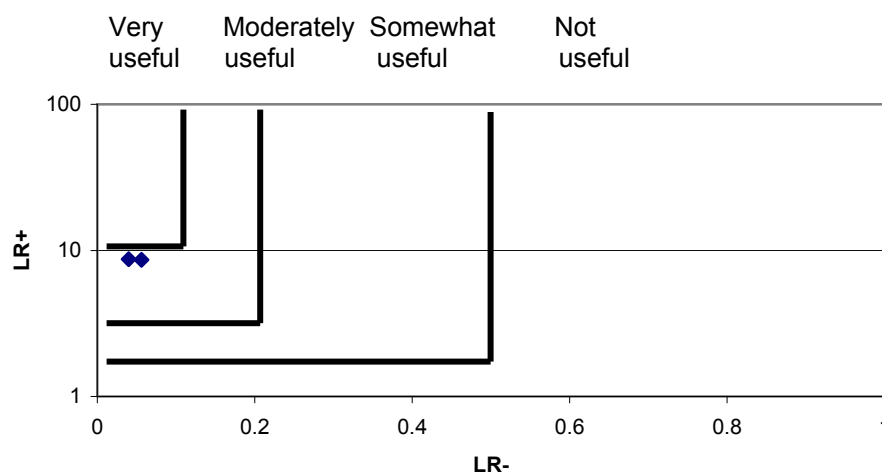
*LR+ indicates positive likelihood ratio; LR-, negative likelihood ratio.

Economic Analysis

There was no literature on the cost-effectiveness of 16-slice or 64-slice CT angiography for CAD.

Ontario-Based Facts

The Ontario government announced early in 2004 that it was earmarking $45.3 million (Cdn) to replace 26 old CT scanners and to increase the hours of operation at 23 hospitals in an effort to improve access to CT imaging. It is estimated that this infusion of money will result in an additional 81,268 CT exams per year. Some of these new scanners will be 64-slice CT scanners, which will be distributed throughout the province. Not all of the new 64-slice scanners will be situated in hospitals that provide specialized cardiac care.

Proponents of MDCT for general scanning suggest that, by virtue of decreasing the scanning time per patient, the waiting times for general CT scanning will be decreased. (2) However, this has not been tested empirically in Ontario hospitals.

Many components affect wait times (Figure 12). Without system supports, it is unclear if wait times for CT would be decreased with the use of faster scanners. Increased staff for moving patients, increased hours of operation and clinically indicated referrals have been identified as the most critical components to reducing wait times for diagnostic imaging (Personal communication January 2005).

If new indications for MDCT, such as the investigation of CAD, are introduced into the current complement of reasons to have a CT scan in Ontario, more people will be referred for a CT scan.

Figure 12: Components Needed To Determine Wait Time*

Figure 23. Waiting for Diagnostic Services
An example of patients waiting for diagnostic radiology services.
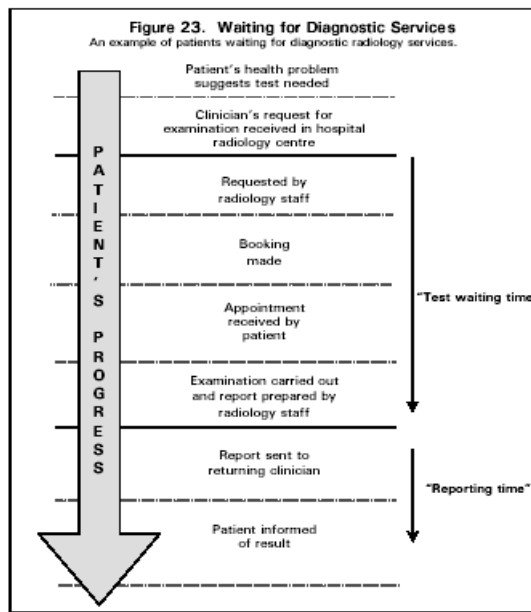
from: The Audit Commission. (2002). *Radiology: Acute Hospital Portfolio. Review of* (London, UK: The Audit Commission, 2002), [online], from <www.audit-ion.gov.uk/Products/AC-Report/AB95E11A-A6C1-4335-9482-9618441DB347/Radiol

*Reprinted with permission from the Canadian Instituite for Health Information (CIHI). Taken from: Medical Imaging in Canada 2004. P. 48 (1)

Because MDCT angiography is not currently the standard method to investigate the presence and extent of CAD, the performance of this test will be additive to the CAs that are being done at present, as there may be doubts about the accuracy of the MDCT results. This could be compounded by the fact that cardiologists have developed a comfort level with CA, which has been regarded as the gold standard for some time. Radiologists currently perform MDCT angiography.

There is already a significant queue for cardiac services in Ontario. Almost 25% of people who urgently require cardiac catheterization are not receiving the procedure within the recommended wait time cut-off. (45) In February 2005, the Ministry of Health and Long-Term Care pledged $8.5 million (Cdn) for 5 new cardiac catheterization machines that are estimated to increase the current capacity by 1,016 procedures. (3)

Despite this addition of new machines, the wait time for CA and other cardiac procedures will increase if both CT angiography and CA are performed on the same patient.

On the other hand, if 64-slice CT angiography is deemed sufficiently effective to replace CA (after clinical research is conducted), the wait time for angiography and other cardiac procedures could decrease, given that a CT angiogram takes 15 to 45 minutes compared to 60 minutes for CA.

Appraisal

Patient Outcomes – Medical, Clinical

➢ Unlike conventional scanners, MDCT scanners can image moving body parts, such as the coronary arteries, the heart, and the peripheral vascular system with high resolution.
➢ There are suggestions that MDCT angiography could replace CA as the gold standard for CAD detection in symptomatic patients because MDCT is minimally invasive and fast.
➢ Compared to CA, 16-slice CT angiography may be only moderately effective to detect CAD and not effective to rule out CAD in symptomatic people, according to an analysis of the published literature.
➢ Because of the high burden of disease in the target population (53%–80%), many people may be incorrectly diagnosed with the disease using CT angiography and subsequently may undergo unnecessary and potentially harmful interventions. There may be even more people with CAD who are erroneously diagnosed as being negative. These patients will not obtain potentially life-saving treatment.
➢ Based on the published literature, the effectiveness of 16-slice CT angiography detect disease progression in patients who previously had a cardiac intervention (stent or CABG) cannot be established because of insufficient evidence.
➢ The patient samples in the published literature are highly selective, which may bias results when applied to the general target populations.
➢ Administration of β-blockers may be necessary to bring down the heart rate of people being investigated for CAD. It is not clear at what point β-blockers need to be prescribed before MDCT angiography is undertaken and if a separate cardiac consult will be needed.
➢ The overall clinical utility of 16-slice CT angiography in the long-term management of CAD is not known.
➢ The results in 2 abstracts presented at a recent clinical meeting are insufficient to assess the diagnostic accuracy and clinical utility of 64-slice CT angiography to detect CAD. Studies are underway in the United States and Europe and should be released toward the end of 2005.
➢ Radiation levels increase with faster scanning capabilities.
➢ MDCT should not be used as population-based screening tool for CAD, based on the World Health Organization's criteria for screening (13) and a United States Task Force Report (February 2004).(14)

Diffusion – International, National, Provincial

➢ 16-slice MDCT scanners are in use worldwide.
➢ Fewer than 20 64-slice CT scanners were operational worldwide at the time of this review; however, hundreds are targeted to go into use by 2005.
➢ In Ontario, 64-slice CT scanners will be operational for some hospitals later in 2005.

Cost

➢ Additional hardware and software costs may be incurred to make use of the full capabilities of MDCT, especially for cardiac post-processing.
➢ There may be additional annual service and maintenance costs associated with the purchase of MDCT scanners.

Stakeholder Analysis

➢ CT technologists may need further training to use MDCT effectively.
➢ Radiologists may need further training to make full use of the software capabilities of MDCT.
➢ Cardiologists may want to be involved in the interpretation of MDCT angiography used to detect CAD.
➢ Patients may be concerned about the additional radiation exposure and the uncertainty of the test results.

System Pressures

➢ Wait times for general CT could rise if the current complement of machines is used for additional indications, such as the investigation of CAD.
➢ Wait times for cardiac services could rise because the inconclusive MDCT results will need to be confirmed by CA.
➢ Some people may be inaccurately diagnosed with the disease. This will result in increased in unnecessary publicly funded downstream interventions and unnecessary comorbidity for these patients.
➢ A larger portion of people with CAD could be missed. The disease in these patients could progress so that more invasive downstream services are needed, with increasingly severe outcomes.
➢ CT scanning of the coronary vessels is not an insured service in Ontario.
➢ Screening for CAD with any modality is not an insured service in Ontario.

Conclusions

A systematic review of the literature was performed from 2003 to January 2005 to determine the effectiveness of MDCT angiography (16-slice and 64-slice) compared to CA to detect CAD. At the time of this report, there was no published literature on 64-slice MDCT for any indications.

Based on this review, the Medical Advisory Secretariat concluded that there is insufficient evidence to determine that 16-slice or 64-slice CT angiography is better than conventional CA to diagnose CAD in people with symptoms or to detect disease progression after previous cardiac interventions. Overall, the clinical utility of MDCT in patient management and long-term outcomes is unknown.

It is unlikely that MDCT angiography will replace CA. Until sufficient evidence is available, it will probably be used adjunctively with other cardiac diagnostic technologies.

With the current compliment of MDCT scanners in Ontario, the use of MDCT angiography may decrease access to CT scanners for general indications, thereby increasing wait times for access to CT scanners.

Screening for CAD in asymptomatic patients using MDCT to examine coronary calcification was not assessed in this review.

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 lead to arterial narrowing or complete obstruction	"Complicated plaques" derived from repeated ruptured plaques that may not cause symptomatic decompensation
Clinical characteristics		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 and asymptomatic adults	Similar in men and women			
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 - 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

From: Stary HC, Chandler AB, Glagov S, et al. A definition of initial, fatty streak and intermediate lesions of athersclerosis. A report from the Committee on Vacular Lesions of the Council on Arteriosclerosis, American Hearth Association. Circulation 1994; 89(5):2462-2478.

Appendix 2: Canadian Cardiovascular Society Classification of Angina Pectoris*

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

From: Gibbons, Abrams J, Chatterjee K, and ACC/AHA Committee members. ACC/AHA 2002 guidline update for the management of patients with chronic stable angina. A report of the Amercian College of Cardilogy/American Heart ASsociation Task Force on Practice Guidelines. 2002. American College of Cardiology Foundation and the American Heart Association Inc.

Appendix 3: Synopsis of Methods and Results of Studies on 16-slice CT Angiography

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Gilard 2005 (39)

Objective: To investigate restenosis after left main coronary artery stenting using 16-slice CT compared to CA
Ethics approval: Not stated; patient consent obtained
Patients included: N = 29 patients who had CA with stenting (76% angioplasty under intravascular ultra sound);
Patients excluded: Not Stated

➢ 70% male; mean age, 63 years (SD, 10)
➢ 10% previous myocardial infarction
➢ 73% left main artery stenosis
➢ 100% β-blocker and 300 mg of clopidogrel, 75 mg or aspirin for 3 days before CA

Controls: CA performed 1 day before MDCT at 6 months (SD, 4 months) after stenting
Recruitment: consecutive recruitment: November 2003 to March 2004; clinical follow-up at 1 and 3 months
MDCT specifications: 16-slice CT x 0.75 mm cross section; gantry rotation time 420 ms, table feed 2.8 mm/rotation; tube current 400 mA; tube voltage 120 kV; contrast agent injected 4 ml/s
Blinded observers: 1 cardiologist read MDCT; 1 cardiologist read CA
Unit of analysis: stents judged as detectable or not detectable; patency determined for detectable stents; restenosis defined as ≥ 50% diameter stenosis
Interobserver and intraobserver agreement κ = 0.95 and κ = 0.96, respectively
All diseased segments: by CA: 100% stents detected; 20% (SD, 26%) stenosis (0%–95%); 14% (4 patients) restenoses detected; by MDCT: 100% stents detected; > 50% restenosis 12% (7 patients); 35%–40% proliferation 3 patients; > 35% proliferation not visible
Left main instrastent restenosis sensitivity: 100%
Left main instrastent restenosis specificity: 92%
Positive predictive value: 100%
Negative predictive value: 92%
Conclusion: 25% fewer stent artifacts with 16-slice compared to 4-slice CT; lumen analysis is not possible in vessels < 3mm; 2 non-visible stents due to calcification; MDCT not practical for patients with arrhythmia or severe calcification.

Hoffmann (33)

Objective: The diagnostic value and limitations of MDCT for detection of CAD in high risk patients
Ethics approval: yes; obtained patient informed consent
Patients included: N = 33 consecutive patients with positive stress test scheduled for inpatient CA for suspected CAD; CCA classification 1 through 3
Patients excluded: unstable clinical condition; arrhythmia; impaired renal function; pregnancy
➢ 82% male; mean age, 57 years (SD, 9)
➢ 52% patients with heart rate > 65 received 5 mg metoprolol intravenously before MDCT
➢ No sinus rhythm
➢ Heart rate 60 bpm (7 bpm) at scan
➢ Scan time 20 seconds (3 seconds)
Controls: CA within 1 day of MDCT
Recruitment: consecutive patients
MDCT specifications: 16 slice CT x 0.75 mm collimation; gantry rotation time 420 ms; table fed 2.8–3.8 mm per rotation; tube energy 120kV; table current 500 mAs; contrast agent administered 4 mL/s.
Blinded observers: 2 assessors; 50% of MDCT scans read twice without observers' knowledge. MDCT read offline; 1 assessor for CA
Unit of analysis: By patient and 530 coronary segments; stenosis defined as narrowing > 50% and > 70% identified in 2 independent planes through visual interpretation; image quality assessed as excellent, limited or not assessable; diagnostic certainty assessed as very uncertain; uncertain; unequivocal; certain; absolutely certain
Interobserver agreement: κ = 0.81 overall; κ = 0.68 for all coronary vessels
All diseased segments: 438/530 (83%) visualized
Prevalence of stenosis: 67%
Sensitivity: 63% (50, 76) for all segments of coronary artery tree; 86% (72, 101) by patient
Specificity: 96% (94, 98); 82% (60, 104) by patient
Positive predictive value: 64%; 90% by patient
Negative predictive value: 96%; 75% by patient
Conclusion: "Test appears to be of limited diagnostic value in high risk CAD patients when all coronary vessels are included." Calcification, motion/noise and contrast-related issues were main causes of false negative findings on MDCT. 16-slice scanners are also not sensitive to varying degrees of stenosis (> 50% vs > 70% stenosis). May be of better use in intermediate-risk patients.

Kuettner 2005 (38)

Objective: To evaluate the diagnostic accuracy of 16-slice MDCT in patients with suspected CAD (>50% lumen reduction)
Ethics approval: yes; patient consent
Patients included: N = 72 patients who were scheduled for CA because of suspected CAD
Patients excluded: known CAD; irregular heart rate; contraindications for iodinated contrast agent; elevated serum creatinine levels
➢ 58% male; mean age, 64 years (SD, 10 years)
➢ 83% patients were on already or received beat-blocker before MDCT
➢ Heart rate 64.1 bpm (SD, 9 bpm) after β-blocker administration
Controls: scheduled for CA
Recruitment: consecutive patients scheduled for CA
MDCT specifications: 16 x 1.5 mm; 3.8 mm/rotation; 133 mA 1t 120 kV;
Blinded observers: 2 readers, blinded to CA results and all clinical information
Unit of analysis: image quality assessed as excellent, good, moderate, heavily calcified, blurred;
Interobserver agreement: Not stated
All diseased segments: 936 segments; 90%; all patients included in analysis
Image feasibility: 72%
Sensitivity: 82%
Specificity: 98%
Positive predictive value: 87
Negative predictive value: 97
Conclusion: Improvement of non-invasive MDCT with 16-slices; complete visualization of coronary tree still not possible; Limitations: radiation exposure, need for iodinated contrast and reduction of heart rate for better visualization; further improvements necessary to challenge CA.

Kuettner 2004 (36)

Objective: Evaluate the feasibility of detecting coronary artery lesions ≥ 50% using 16-slice CT in 1 centre
Ethics approval: yes; patient consent
Patients included: N = 60 patients scheduled for conventional CA; heterogeneous indications
Patients excluded: irregular heart rate, patients with stents, allergy to contrast media, elevated serum creatinine >1.5mm/dl
➢ 73% male; mean age= 58 ± 12.6 years (20-79 range)
➢ 93% patients received 50 to 100 mg metoprolol tart 45 min before MDCT
➢ Heart rate 63 bpm (SD, 10.3 bpm) after β-blocker administration
➢ Scan time 20 seconds (3 seconds)
Controls: own controls; CA done under normal conditions
Recruitment: Consecutive suitable (based on criteria) patients at one institute approached; 60 consented
MDCT specifications: 16 x 1.5 mm collimation; table feed 3.8mm/rotation; tube current 133 eff. MAs at 120 kV; 20 ml at 4ml/s contrast media administered with 20 ml saline; patients with CABG received 100 ml contrast
Blinded observers: 2 blinded to CA results;
Unit of analysis: Correct diagnosis=rule out significant lesions > 50% or detection of at least 1 > 50% lesion detected with CA; 763 segments
Coronary calcification quantified by Agatston score equivalent for MDCT; visualization scored as excellent (no motion artifact), good (minor motion artifact), moderate (substantial artifact but ability to see significant stenosis), heavily calcified (obscured visualization of lumen), blurred (no luminal assessment visualized).
Interobserver agreement: not stated
All diseased segments: 780
Image feasibility: 79% (could detect the lumen for evaluation)
Sensitivity: 72%
Specificity: 97%
Positive predictive value: 72%
Negative predictive value: 97%
Conclusion: Severe calcification limits interpretability; controlled heart rate is necessary to get better image and to minimize radiation dose; "MDCT not yet considered a replacement for CA but may be a useful tool to rule out significant lesions in patients with low pretest probability".

Martuscelli (37)

Objective: The accuracy of MDCT to detect significant (> 50%) stenosis
Ethics approval: yes, by Department Review Board
Patients included: N = 64 scheduled for CA
Patients excluded: frequent ectopic beats, allergy to iodine contrast agent; renal insufficiency; acute coronary syndromes; heart failure
➢ 92% male; mean age, 58 years (5 years)
➢ 100% patients received 50–100 mg atenolol for 3 days prior to MDCT
➢ Heart rate 59 bpm (SD, 5 bpm) after β-blocker administration
➢ Scan time 22 seconds (SD, 2 seconds; range, 54–74)
Controls: CA done 20 days after MDCT
Recruitment: March and October 2003
MDCT specifications: 16 x 0.625 mm; gantry rotation time 500 ms; tube voltage 120 peak kVp; tube current 10-440 mA in 5-mA parts; table feed 2.9mm/rotation; contrast injection: 120 mL contrast agent 4mL/s; MDCT for heart beat < 60 bpm.
Blinded observers: 2 radiologists, independent of CA
Unit of analysis: Only segments > 1.5mm based on CA were used for analysis; total amount of calcium in coronary tree; segment analysis; images rated as 'evaluable' or 'inevaluable'
Interobserver agreement: κ = 0.76 in detecting significant stenosis
All diseased segments: 729 segments > 1.5 mm included
Image feasibility: 84% (613/729 segments)
Sensitivity: 89%; 78% if all segments analysed
Specificity: 98%
Positive predictive value: 90%
Negative predictive value: 98%
Conclusion: Calcification, motion artifact can impair visualization of vessels in 16-slice CT; MDCT cannot provide information about flow as can CA.

Martuscelli 2004 (40)

Objective: To evaluate the accuracy of 16-slice scanner to detect patency and stenosis (>50% decrease in diameter) of venous and arterial grafts in patients with previous CABG
Ethics approval: yes, institution review board
Patients included: N = 96 consecutive outpatients with previous history of CABG referred for coronary angiography because of suspected disease progression
Patients excluded: multiple ectopic bets; atrial fibrillation; heart rate ≥ 70 bpm despite therapy, renal insufficiency, severe lung disease, severe heart failure (CCS IV); unstable angina
➢ 83% male; mean age, 62 years
➢ 100% patients received 50–100 mg atenolol at least 3 days prior to MDCT
➢ Heart rate 58 bpm (SD, 5 bpm) after β-blocker administration
➢ Scan time 25–32 seconds
➢ Mean time from CABG, 7 years (range 5–10 years)
Controls: "selective angiography of bypass conduits was performed independently 20 days after MDCT"
Recruitment: Consecutive outpatients
MDCT specifications: 16 x 0.625mm; gantry rotation 500 ms; tube voltage 140 kV; tube current 10–440 mA in 5 mA increments; table feed 2.9 mm/rotation; contrast with single injection
Blinded observers: 2 independent cardiologists read MDCT without knowledge of CA
Unit of analysis: scans estimated as visually evaluable or non-evaluable; evaluable assessed as patent or occluded;
Interobserver agreement: κ = 0.95
All diseased segments: 278 conduits (184 venous; 94 arterial)
Image feasibility: 88% by patient; 90% conduits (85 arterial, 166 venous)
Diagnostic Accuracy: 99%
Sensitivity: 97% of conduit stenosis
Specificity: 100%
Positive predictive value: Not stated
Negative predictive value: Not stated
Conclusion: The effective radiation dose is higher than 8 to 9 mSv for the evaluation of the native arteries and much higher than the dose emitted during conventional angiography; information about flow characteristics cannot be obtained. Large amount of iodine contrast needed is also a limitation of MDCT, but 64-slice may require less. Severe respiratory disease was part of exclusion criteria, and patients with unstable angina went straight to CA

Mollet et al 2005 (35)

Objective: To compare the diagnostic value of multi-slice CT angiography to detect significant stenosis (≥ 50% lumen diameter reduction) compared to conventional CA
Ethics approval: yes and written informed consent obtained from patients
Patients included: N = 51 patients schedule for CA to determine CAD in sinus rhythm who never had angioplasty or bypass
Patients excluded: acute coronary syndrome; contraindication to iodinated contrast agent
➢ Atypical chest pain or stable angina
➢ 37 male; mean age 58.9 years (SD, 10 years)
➢ Sinus heart rhythm; mean heart rate, 57.1 bpm
➢ Ability to hold breath for at least 20 seconds
➢ Single oral dose of 100 mg metoprolol for people with heart rate over 70 bpm; 80% β-blocker use
Controls: Own control who had MDCT at least 2 weeks before CA
Recruitment: 7-month period
MDCT specifications: 16-slice detector scanner; 0.75 mm collimation; rotation time 375 ms; table feed 3.0mm/rotation; tube voltage 120kV; effective mA: 500 – 600; CT dose index 51.0 mGy, no tube modulation.
Radiation exposure: 11.8 – 16.3 mSv; iodine content 400 mg/ml
Blinded observers: 1 observer for CA; 2 observers for MDCT
Unit of analysis: Segments ≥ 2 mm on CA compared with MDCT classified as normal, non-significant disease)or significant stenosis (≥ 50% lumen reduction); vessels; patient
Interobserver and intraobserver agreement: κ = 0.73 and κ = 0.80, respectively
All diseased segments: By CA 16% (8/51) normal arteries, 21% non-significant disease, 63% CAD
All segment sensitivity: 95% (86, 99)
All segment specificity: 98% (96,99)
All segment positive predictive value: 87% (76,98)
All segment negative predictive value: 99% (98,99)
Conclusion: "MDCT will not equal either the resolution or real-time imaging capabilities of conventional CA in the foreseeable future…its non-invasive nature renders [it] more patient-friendly with reduced risk of iatrogenic injury…partial voluming and artifacts related to coronary calcification seriously hamper development of reliable software able to detect and quantify the degree of coronary stenosis…vast cases of false positives were calcified.".

Mollet 2004(19)

Objective: To prospectively evaluate the diagnostic performance of CTA to detect significant coronary lesions suitable for revascularization

Ethics approval: yes and informed consent

Patients included: N = 128 patients with stable angina scheduled for CA who could breath-hold for 20s

Patient exclusions: severe coronary syndromes or previous CABG

➢ 88% male; mean age, 58.9 years (SD, 11 years)
➢ 93% β-blockers (60% patients received 100 mg metoprolol 1 hour prior to MDCT if heart rate above 65 bpm; 33% already on β-blockers)
➢ Heart rate 58 bpm (SD, 5 bpm) after β-blocker administration
➢ Scan time 18.2 seconds (SD, 1.4 seconds)
➢ Mean time from CABG 7 years (range 5–10 years)

Controls: mean interval between scan and CA was 19.1 days; only segments ≥ 2 mm were compared to MDCT;

Recruitment: Not stated

MDCT specifications: 16 x 0.75 mm; tube rotation 420 ms; table feed 3 mm/rotation; tube voltage 120kV; tube current 400 mAs; 100 ml contrast injected at flow rate of 4 ms/s;

Blinded observers: 2 independent observers

Unit of analysis: > 50% reduction of lumen considered significant stenosis; arteries with stents were excluded; image quality graded as good, adequate or poor; calcification was graded as non-calcified, moderately calcified, heavily calcified

Interobserver and intraobserver agreement: κ = 0.71 and 0.72, respectively

All diseased segments: 1,384 non-stented segments diameter ≥ 2mm (37 with stents excluded)

Image feasibility: good 75%; adequate 18%; poor 7% (63% motion artifact; 30% severe calcification; 7% low contrast to noise ratio

Diagnostic Accuracy:

Sensitivity: 92% (88, 95) Patient: 100% (96, 100)

Specificity: 95% (93, 96) Patient: 86% (63, 96)

Positive predictive value: 79% (73, 88) Patient: 97% (92, 98)

Negative predictive value: 98% (97, 99) Patient: 100% (81, 100)

Conclusion: 16-slice CT is "a robust tool to detect significantly obstructed coronary artery in the clinically important part of the coronary tree"; 7% that were poor quality were included in the analysis. Only patients with stable angina were included

Schuijf 2004(41)

Objective: To assess the feasibility of using MDCT for evaluation of stent patency
Ethics approval: yes, and patient informed consent
Patients included: N=22 consecutive patients who had undergone percutaneous transluminal coronary angiography (PTCA) with 68 stents, scheduled for CA
Patients excluded: atrial fibrillation; renal insufficiency; allergy to iodine contrast media; claustrophobia; pregnancy
➢   91%% male; mean age, 63 years (SD, 7 years)
➢   77% patients already on β-blockers
Controls: 3 days (SD, 2 days) between MDCT and CA; MDCT: 14 months (SD, 26 months) after stent implant
Recruitment: Not stated
MDCT specifications: 16 x 0.5 mm; rotation time 0.4–-0.5 depending on heart rate; tube current 250 mA at 120 kV; contrast 120–150 ml with flow rate of 4.0 ml/s; slice thickness 0.5mm; ECHO simultaneously recorded
Blinded observers: 1 observer blinded to CA results
Unit of analysis: image quality assessed as poor/not able to be interpreted; adequate; good; detection of stenosis ≥ 50% or ≥ 70% lumen reduction; > 1 interpretable stented segment = interpretable; stents categorized by diameter
Interobserver and intraobserver agreement: Not stated
All stents: 68
Image feasibility: 77% of stents
Reasons for scan insufficiency: motion artifact, metal artifact; small stents; severe calcification
Diagnostic Accuracy: Not stated
Sensitivity: 78% stent patency
Specificity: 73% stent patency
Positive predictive value: Not stated
Negative predictive value: Not stated
Conclusion: assessment of coronary stents is possible using 16-slice MDCT; detection of small in-stent hyperplasia is not yet possible; but only 14% had in-stent restenosis and therefore caution considered for generalizability of results; MDCT may play a role as gate-keeper for invasive procedures because a fair number of patients receive no intervention after CA

Schlosser 2004(42)

Objective: Diagnostic accuracy of 16-slice MDCT for assessment of CABG grafts compared to CA
Ethics approval: yes and patient informed consent
Patients included: N = 48 with 131 grafts
Patients excluded: arrhythmia or fast heart rate; renal insufficiency; hyperthyroidism; allergy to contrast media
➢ 75% male; mean age, 65 years (SD, 6 years)
➢ Mean heart rate, 64 bpm (SD, 5 bpm)
Controls: CA performed 1 to 8 days after MDCT; 67 months after surgery
Recruitment: 51 consecutive patients; 3 excluded due to arrhythmia
MDCT specifications: 16-slice scanner; gantry rotation 420 ms; collimation 0.75 mm; table feed 1.5 mm/rotation; 0.5 mm reconstruction increment; 120 ml iodine contrast media with infusion of 3.5 ml/s
Blinded observers: Not stated
Unit of analysis: visualization of graft patency graded as no stenosis, < 50% diameter reduction; stenosis > 50% reduction; bypass occlusion; proximal & distal bypass graft anastomoses;
Interobserver and intraobserver agreement: Not stated
Image feasibility: 74% overall (83/112)
Reasons for scan insufficiency: Not stated
Diagnostic Accuracy: Not stated
Sensitivity (all anastomoses): 96%
Specificity: 95%
Positive predictive value: 81%
Negative predictive value: 99%
Conclusion: 16-slice MDCT reliably evaluates differentiation between patent and occluded arterial and venous bypass grafts and can detect bypass stenosis with accuracy. Limitations include administration of β-blockers in a large proportion of patients, necessity for contrast injection, increased radiation exposure – MDCT should be performed when there is a strong indication; but lack of complications and non-invasive nature may compensate for radiation exposure

Shi 2004 (31)

Objective: To evaluate 16-slice CT to identify the origin of anomalous coronary arteries; accuracy of CAD was secondary endpoint
Ethics approval: yes; patient informed consent
Patients included: N = 16 of 242 (6.6%) consecutive patients with anomalous coronary arteries included
Patients excluded:
➢ 69% male; mean age, 57 years
➢ 0% patients already on β-blockers
➢ Mean heart rate, 69 bpm
➢ Scan time Not stated
Controls: CA performed 9–28 days before or after MDCT
Recruitment: July 2002 and February 2004, 242 consecutive patients referred to CA in single centre who also had MDCT, but only 6.6% were evaluated
MDCT specifications: 16 x 0.75 mm collimation; gantry rotation time 420 ms; tube voltage 12kV; 80-100 ml contrast injected with 3.5-4 ml/s flow; breath-hold 23 s; image thickness 8 mm
Blinded observers: 2 blinded
Unit of analysis: presence of anomalous artery; origin, ostial shape and relationship between ostium and adjacent orifice of normal artery; path with respect to the aorta and pulmonary artery; obstruction defined as ≥ 50% lumen reduction of vessels ≥ 1.5 mm in diameter
Interobserver and intraobserver agreement: Not stated
All stents: Not stated
Image feasibility: Not stated
Reasons for scan insufficiency: Not stated
Diagnostic Accuracy: 100% anomalous origins and abnormal courses of the coronary arteries correctly identified by MDCT; CA correctly identified 53% ($P < .16$)
Sensitivity for stenosis: 90%
Specificity: 92%
Positive predictive value: not reported
Negative predictive value: 97%
Conclusion: Accurate diagnostic tool to examine the anatomic course and ostium shape of abnormal coronary arteries; radiation exposure a problem
Limitation: selected out ad hoc, the patients with anomalous arteries and performed MDCT on those; generalizability; no confidence intervals on accuracy measures

Traversi 2004 (34)

Objective: To describe the experience using 16-slice MDCT
Ethics approval:
Patients included: N = 39 with known or suspected CAD (468 segments)
Patients excluded:
➢ Mean age, 57 years
➢ 57% patients already on β-blockers; additional 5% injected with β-blockers prior to MDCT
➢ Mean heart rate < 70 bpm in 73%
➢ Mean breath hold 20 seconds (SD, 5 seconds)
Controls: 39 patients compared to CA
Recruitment: 176 patients with MDCT evaluated; only 39 compared with CA
MDCT specifications: 16-slice; injection of 130 ml if contrast media
Blinded observers: Not stated
Unit of analysis: > 70% arterial stenosis
Interobserver and intraobserver agreement: Not stated
All stents: 468 segments
Image feasibility: 92% for stenosis; 94% in patients who previously had bypass
Reasons for scan insufficiency: motion artifact – increase of heart rate; extensive coronary calcification; extensive masking effect by venous network
Diagnostic Accuracy: 81%
Sensitivity for stenosis: 80%
Specificity: 80%
Positive predictive value: 59%
Negative predictive value: 92%
Conclusion: Role of MDCT has still yet to be defined; has the potential to consolidate a multitude of current investigational tests into 1

Zhang 2004 (32)

Objective: To evaluate the effectiveness of 16-slice MDCT to diagnose CAD
Ethics approval:
Patients included: N = 230 with suspected CHD; 30 "first-class images" compared with CA
Patients excluded:
➢   Mean age, 56.8 years (SD, 8 years)
➢   57% patients already on β-blockers; additional 5% injected with β-blockers prior to MDCT
➢   Mean heart rate < 70 bpm in 73%
➢   Mean breath hold 20 seconds (SD, 5 seconds)
Controls: Not stated
Recruitment: August to December 2003
MDCT specifications: 16 x 1.5mm, rotation 0.42 seconds at 1.mm and slice width 3mm; 120kV, 500 mA, slice collimation 16 mmx0.75; 20 ml contrast media with flow of 3.4 mL/s administered; breath hold 15-20 s
Blinded observers:
Unit of analysis: image quality rated as first-class (no artifacts), second class (1 or 2 interruptions) or third class (significant artifacts); significant stenosis defined as ≥ 75% lumen reduction
Interobserver and intraobserver agreement: Not stated
All stents: Not stated
Image feasibility: Not stated
Reasons for scan insufficiency: Not stated
Diagnostic Accuracy: 96%
Sensitivity: 95%
Specificity: 95%
Positive predictive value: Not stated
**Negative predictive value:** Not stated
Conclusion: CA can be avoided in patients with normal MDCT; CA can be avoided in patients without stenosis but who have plaque by CTA; CA should be performed in patients who are identified with stenosis by MDCT. Therefore, 16-slice MDCT can be used as a screening method to treat CHD patients earlier

Appendix 4: Diagnostic Accuracy of 16-slice CT Angiography by Segment (Where Applicable)

Study, Year	N	Sensitivity, %	Specificity, %	PPV, %	NPV, %
Mollet, 2005 (35)	**610 segments**	**95 (61/64)**	**98 (537/546)**	**87 (61/70)**	**99 (537/540)**
	*LM	100 (5/5)	100 (46/46)	100 (5/5)	100 (46/46)
	*LAD	100 (24/24)	97 (175/181)	80 (24/30)	100 (175/175)
	*CX	88 (15/17)	99 (154/155)	94 (15/16)	99 (154/156)
	*RCA	94 (17/18)	99 (162/164)	90 (17/19)	94 (162/163)
	202 vessels	**96 (51/53)**	**96 (143/149)**	**90 (51/57)**	**99 (143/145)**
	LM	100 (5/5)	100 (46/46)	100 (5/5)	100 (46/46)
	LAD	100 (16/16)	89 (31/35)	80 (16/20)	100 (31/31)
	CX	100 (16/16)	97 (35/36)	93 (13/14)	97 (35/36)
	RCA	94 (17/18)	97 (31/32)	94 (17/18)	97 (31/32)
	51 patients	**100 (31/31)**	**85 (17/20)**	**91 (31/14)**	**100 (17/17)**
Kuettner, 2005 (38)	**117 Lesions**	82	98	87	97
	Excluding segments 9, 10,13	88	98	91	98
	Excluding calcium mass > 300mg, and heart rate > 70 beats/min	86	98	85	98
	Men: 90 lesions	84	98	89	97
	Women: 27 lesions	74	98	76	98
Gilard, 2005 (39)	29 patients Left main intra-stent restenosis	100	92	100	92
Hoffmann, 2004 (33)	All 530 segments:	63 (50–76)	96 (94–98)	64	96
	438 evaluable	70 (57–82)	94 (92–97)	58	97
	Proximal	82 (70–94)	93 (90–97)	68	97
	33 patients:				
	All segments	86 (71–101)	82 (60-104)	90	75
	Proximal segments	86 (67–104)	89 (76-103)	86	89
Kuettner, 2004 (36)	780 segments	72	97	72	97
	60 patients	70	98	70	98
Martuschelli, 2004 (37)	Total patency:	97	100		
	LAD	94	97	91	98
	Proximal LAD	100	96	83	100
	Mid LAD	100	92	87	100
	Distal LAD	67	100	100	98
	Diagonal branch	60	100	100	95
	Circumflex	91	95	71	99
	Proximal/circumflex	100	98	50	100
	Distal circumflex	91	92	77	97
	Obtuse marginal	87	100	100	92
	Ramus intermedius	50	100	100	67
	Right coronary	87	100	100	98
	Proximal right	100	100	100	100
	Mid right artery	91	100	100	98
	Distal right artery	60	100	100	96
	Posterior descending	100	100	100	100
Mollett, 2004 (19)	1384 All segments	92 (88, 95)	95 (92, 96)		
	124 LM	100	100		
	473 LAD	94	93		
	124 Proximal	93	88		
	111 Middle	100	93		
	102 Distal	100	97		
	136 Side branches	70	93		
	395 CX	84	96		
	111 Proximal	89	97		
	102 Middle	76	95		

Study, Year	N	Sensitivity, %	Specificity, %	PPV, %	NPV, %
	182 Side branches	87	97		
	392 RCA	96	94		
	120 Proximal	100	90		
	103 Middle	97	89		
	91 Distal	89	98		
	78 *PDA	67	100		
	686 Non-calcified	87 (76, 97)	98 (96, 98)		
	430 Moderately calcified	90 (80, 97)	95 (92, 97)		
	268 Heavily calcified	98 (92, 94)	85 (78, 90)		
Schuijf, 2004 (41)	**Stents ≥ 50%** 29/36 branches	100	100		
	Persistent 57/70 branches				
	≥ 50%	75	96		
	≥ 70%	50	100		
Schlosser, 2004 (42)	All	96	95	81	99
	*IMA to LAD	75	100	100	97
	SVG to LAD	100	100	100	100
	SVG to LCX	100	100	100	100
	SVG to RCA	100	87	69	100
	112 distal anastomoses (all)	96	68	37	99
Shi, 2004 (31)	N = 16 patients	90	92	Not reported	97
Traversi, 2004 (34)	39 patients 468 segments	80	80	57	92
	In Traversi - **Stenosis:** Nieman 2002 (N = 39; 70% stenosis)	95	86	97	80
	Kaiser 2003 (N = 42)	49	82	53	79
	Ropers 2003 (N = 77)	92	93	82	81
	CABG patency: Smekal 2002 (N = 15)	100	100		
	Ropers 2003 (N = 34)	100	100		

* CX=Circumflex Coronary Artery; LAD=Left Anterior Descending Coronary Artery; LM=Left Main Artery; RCA=Right Coronary Artery; LCX=Left Circumflex Coronary Artery; PDA=Posterior Descending Artery; IMA=Internal mammary Artery; SVG=Saphenous Vein Graft

Appendix 5: Nomogram Based on Bayes Theorem To Relate Pre-Test Probability With Likelihood Ratio (LR) and Post-Test Probability of Detecting Disease (30)
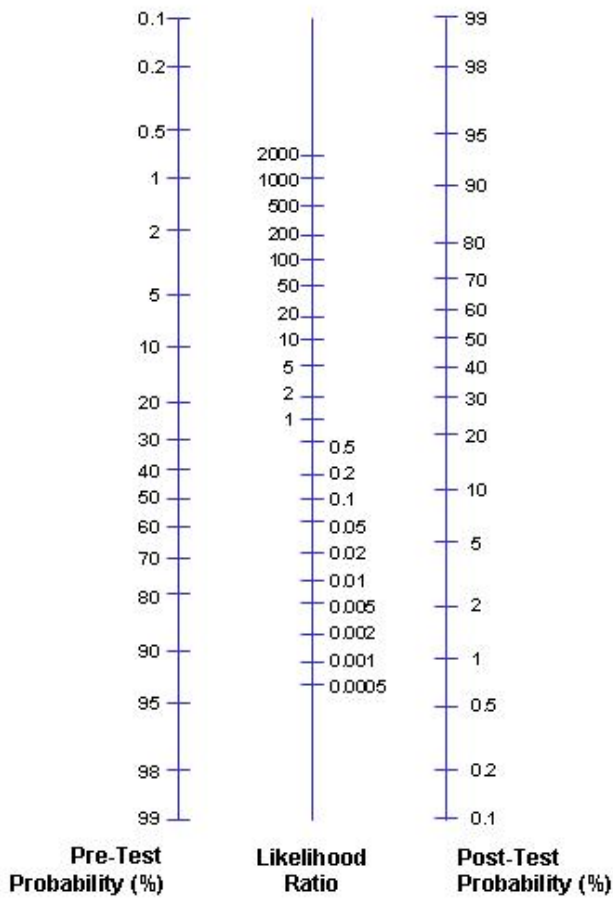
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