

Health Technology Assessment

HTA Final Report

**Coronary Artery Calcium Scoring (CACs) as a Diagnostic
Test for Detection of Coronary Artery Disease**

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Health Technology Assessment Program

676 Woodland Square Loop SE

P.O. Box 42712

Olympia, WA 98504-2712

<http://www.hta.hca.wa.gov>

Coronary Artery Calcium Scoring (CACs) as a Diagnostic Test for Detection of Coronary Artery Disease

Provided by:



Spectrum Research, Inc.

Prepared by:

Andrea C. Skelly, PhD, MPH
Erika D. Ecker, BS
Nora B. Henrikson, PhD, MPH
Carin M. Olson, MD, MS
Annie L. Raich, MS, MPH
Ellen M. Van Alstyne, MS
Joseph R. Dettori, PhD, MPH

Biostatistics assistance from
Margaret S. Pepe, PhD, MS
Daryl Morris, MS

This technology assessment report is based on research conducted by a contracted technology assessment center, with updates as contracted by the Washington State Health Care Authority. This report is an independent assessment of the technology question(s) described based on accepted methodological principles. The findings and conclusions contained herein are those of the investigators and authors who are responsible for the content. These findings and conclusions may not necessarily represent the views of the HCA/Agency and thus, no statement in this report shall be construed as an official position or policy of the HCA/Agency.

The information in this assessment is intended to assist health care decision makers, clinicians, patients and policy makers in making sound evidence-based decisions that may improve the quality and cost-effectiveness of health care services. Information in this report is not a substitute for sound clinical judgment. Those making decisions

regarding the provision of health care services should consider this report in a manner similar to any other medical reference, integrating the information with all other pertinent information to make decisions within the context of individual patient circumstances and resource availability.

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EXECUTIVE SUMMARY

Introduction

Coronary artery disease (CAD), also referred to as coronary heart disease (CHD), is the single leading cause of death for both men and women in the United States and is the most common form of cardiovascular disease. Particularly in patients with a low pre-test probability of CAD (e.g. younger persons, women), symptoms of CAD have poor specificity and sensitivity for CAD, so diagnostic testing is used to confirm or refute a clinical suspicion of CAD. Coronary artery calcium scoring (CACS) is one such test that may provide diagnostic information to help either rule out or rule in significant CAD and assist with clinical decision making. CACS provides anatomical information on the amount of calcium in the heart and coronary arteries.

Methods for evaluating comparative effectiveness

Spectrum Research, Inc.'s (SRI) method for technology assessment involves formal, structured systematic search of the peer-reviewed literature across a number of databases (e.g. MEDLINE, EMBASE) in addition to searches of pertinent databases related to clinical guidelines and previously performed assessments. Included studies are appraised using SRI's Level of Evidence (LoE) system which evaluates the methodological quality based on study design and factors that may bias studies. An overall Strength of Evidence (SoE) combines the LoE with consideration of the number of studies and consistency of the findings to describe an overall confidence regarding the stability of estimates as further research is available. Included economic studies were also formally appraised based on criteria for quality of economic studies and pertinent epidemiological precepts.

Throughout the process, SRI sought expert input to ensure that the methodological and clinical components are accurately represented and relevant. In addition, peer-review by clinical experts, researchers and those with expertise in economic and outcomes evaluation were invited to provide an assessment of the systematic review methodology, analyses and report conclusions.

Summary and Implications

1. CACS test characteristics: Validation and accuracy, reliability and reproducibility of CACS compared with CCA.

- The role of coronary artery calcium scoring (CACS) as a diagnostic test is not clear from the literature and there is no consensus on appropriate thresholds for determining a negative versus positive test. It is not likely to be a replacement for conventional coronary angiography (CCA) based on test performance characteristics. Some literature suggests that it might be used for triaging symptomatic patients and that CACS may reduce the use of conventional coronary angiography.
- Based on meta-analysis of LoE I/II studies comparing CACS with the reference standard of conventional coronary angiography, the overall strength of evidence is high.
 - A CACS > 0 is highly sensitive (99%, CI = 98% - 99%) for identifying the presence of obstructive CAD, however specificity was only 35% and 5% of persons (1 – negative predictive value) with a negative test would have

CAD based on pooled estimates from seven studies with a total of N = 7354 patients. Approximately 35% of persons without CAD might avoid unnecessary angiography or additional tests.

- At thresholds of ≥ 100 (5 studies) or ≥ 400 (3 studies) the sensitivity is lower (85% and 78% respectively) but specificity is improved (77% and 83%, respectively). Clear decisions may not be possible based on CACS when using these thresholds to define a positive test.

2. Safety of CACS

The primary safety concerns for CACS relate to radiation exposure and the consequences of incidental findings.

Radiation exposure

- The overall strength of evidence regarding safety is very low primarily due to uncertainties regard the cancer-related risks due to radiation exposure particularly when CACS may lead to additional tests involving radiation. On the other hand, to the extent that CACS has the potential to decrease the use of conventional angiography, overall radiation exposure might be reduced.
- To date, no large-scale epidemiologic studies evaluating cancer risk associated with computed tomography (CT) in general have been published.
- There is uncertainty and controversy with regard to the actual risk of low dose radiation. Quantification of risk specific to CACS for an individual patient is not possible.
- A typical effective dose for CACS is estimated to be 3 mSv (reported range 0.7 - 12 mSv) when retrospective and prospective gating are considered together. Exposure is less when scans are prospectively gated. Some experts consider the potential for harm from radiation exposure to be clinically significant particularly given that patients may be likely to have additional tests using radiation.
- A recent simulation estimating radiation dose and cancer risk suggests that a single scan for CACS may increase lifetime cancer risk. For a single screen at 55 years of age, based on a median effective dose of 2.3 mSv, site-specific estimates for lifetime risk of radiation induced cancer suggest that most cases would be lung cancer (6/100,000 in men, 14/100,000 in women) or breast cancer (4/100,000 in women).
- Decision making between physician and patient should involve a discussion of the potential risks and benefits of CACS (and subsequent testing). Final determination of net benefit for a given clinical scenario reflects the values and judgments of the persons making the decisions.
- The extent to which CACS is an adjunct to coronary CT angiography may increase radiation exposure compared with that for CACS alone.

Consequences of Incidental findings

- The overall strength of evidence is very low.
- Data from two studies suggests that 7%-10% of symptomatic persons will have incidental findings during a CT scan for calcium scoring that require further diagnostic testing and a small percent, 1.2%, will require therapeutic intervention.

- There may be benefits to early detection and treatment of the small percentage of significant pathology found incidentally, however, there is no evidence from these studies that early detection prompted more effective treatment or enhanced patient outcomes.
- The follow-up of less serious findings may create patient anxiety in addition to exposing them to the inconvenience, costs and risks of additional testing.

3. Influence on clinical decision making and patient outcomes

- There is an association between CACS and future events: Patients with higher CACS may experience more cardiac events (e.g. myocardial infarction, revascularization, death) and those with no calcium or low scores may be less likely to have future events. The extent to which CACS truly influences outcomes is unclear, however, since its impact on clinical decision making and treatment is not described.
- Overall, the evidence is low that CACS facilitates clinical decision making. While there are a number of studies describing the potential role of CACS as a triage tool for ruling out CAD and identifying those who should have additional testing, none of the studies included a comparison group. If CACS was a perfectly sensitive test, there were no false negatives and some degree of specificity, the benefit of doing CACS as a first test for triage could be estimated in the absence of an explicit comparison group. Without this or a comparison group, it is difficult to assess the incremental benefit of CACS in clinical decision making.

4. Special populations

- Two moderate quality validation studies in symptomatic diabetic patients suggest that the sensitivity (98-99%) and specificity (25%-39%) of CACS for the detection of any calcium is similar to that for general populations from the meta-analysis of LoE I/II studies but that a higher percent (11%-25%) of persons (1 – negative predictive value) with a negative test would have CAD. The overall strength of evidence is very low.
- Three moderate quality (LoE II/III) studies described performance characteristics for men and women separately. At a CACS >0, the sensitivities for both groups were 96%-100%. Specificities for women ranged for 41%-66% and those for men 24%-57%, some what lower. A higher percent (4% - 11%) of men (1 – negative predictive value) with a negative test would have CAD compared with women (0%-4%). The prevalence of CAD was lower in women (36%-47%) compared with men (53%-70%) Women present with CAD at an older age (~10 years) than men, which may account for the differences.
- Seven LoE I/II studies explored the relationship of age with test performance characteristics. The prevalence of CAD and presence of calcium increases with age. There are, however somewhat mixed results regarding the extent to which age influences test performance characteristics. While some studies suggest that sensitivity and predictive values go up with increasing age, others suggest that the best sensitivity and specificity may be in middle aged patients (40 – 60 years). The overall strength of evidence for studies with regard to age is moderate.

5. Economic implications

- Two full economic studies and one costing evaluate CACS as a stand-alone test compared with conventional angiography.
- The two moderate quality full economic studies suggest that at a disease prevalence of up to 70%, CACS may be more cost effective than conventional angiography, however incremental cost effectiveness is not described.
- Disease prevalence and CACS score cut-off (and corresponding sensitivity and specificity) appear to influence overall cost-effectiveness.
- Models did not include evaluation of incidental findings and the influence of false-negative and false-positive tests is not clear.
- CACS does not appear to function as a stand-alone test in clinical practice. The potential impact of additional testing done in clinical practice needs to be considered and modeled.
- There is insufficient evidence for conclusions on the long-term cost utility of CACS compared with CCA alone or with regard to other non-invasive tests.

Table 1. Overall Strength of Evidence (SoE) Criteria

SoE	Description	Further Research Impact	Domain Criterion Met		
			Quality	Quantity	Consistency
1	High	Very unlikely to change confidence in effect estimate	+	+	+
2	Moderate	Likely to have an important impact on confidence in estimate and <i>may</i> change the estimate	+	-	+
			+	+	-
3	Low	Very likely to have an important impact on confidence in estimate and <i>likely</i> to change the estimate	+	-	-
			-	+	+
4	Very Low	Any effect estimate is uncertain	-	+	-
			-	-	+
			-	-	-

Table 2. Summary of findings and overall strength of evidence

Key Question 1: Evidence regarding test characteristics and reliability		
Outcome	Strength of Evidence	Results
Validity of test	1	<p>The role of CACS as a stand alone diagnostic test is not clear. There is no consensus on threshold. Based on meta analysis of LoE I/II studies</p> <ul style="list-style-type: none"> • A CACS > 0 is highly sensitive (99% , CI = 98% - 99%) for identifying the presence of obstructive CAD, however 5% of persons (1 – negative predictive value) with a negative test would have CAD • At thresholds of ≥ 100 (5 studies) or ≥ 400 (3 studies) the sensitivity is lower (85% and 78% respectively) but specificity is improved (77% and 83%, respectively)
Reliability of test	1	<ul style="list-style-type: none"> • The reliability of CACS (based on Agaston method) appears to be moderate to high based on 3 small LoE II studies and descriptions in it two validation studies
Key Question 2: Evidence regarding safety		
Radiation	4	<ul style="list-style-type: none"> • While simulation and modeling of the effects of radiation exposure provide important insights into the possible changes in risks, the true attributable risk from radiation-based diagnostic tests may be difficult to determine. • Radiation exposure may be reduced to the extent that CACS use avoids doing angiography. On the other hand, exposures may be increased to the extent that positive

		<p>CACS results in additional testing.</p> <ul style="list-style-type: none"> A typical effective dose for CACS is estimated to be 3mSv (reported range 1-12mSv). CACS results may lead to additional testing which involves radiation. In a recently published simulation based on a median effective dose of 2.3 mSv, site-specific estimates for life-time risk of radiation-induced cancer suggest that most cases would be lung cancer (6/100,000 in men, 14/100,000 in women) or breast cancer (4/100,000 in women). Decision making should include discussion of the potential for such risks.
Incidental findings	4	<ul style="list-style-type: none"> 7%-10% of symptomatic persons will have incidental findings during a CT scan for calcium scoring that require further diagnostic testing and a small percent, 1.2%, will require therapeutic intervention based on two studies in symptomatic persons.
Key Question 3: Evidence regarding clinical decision making and patient outcomes		
Triage in emergency department	3	<ul style="list-style-type: none"> Five studies suggest that a CACS = 0 may allow discharge of patients with suspected CAD. These studies, however vary in quality. None employed a comparison group and are considered case series.
Triage in other clinical settings	4	<ul style="list-style-type: none"> One study reported that referral to conventional angiography increased with increasing CACS. No comparison group was employed.
Prediction of future events	3	<ul style="list-style-type: none"> While 3 studies suggest that CACS is a predictor of future cardiac events, none evaluate the role of therapeutic interventions which may influence the occurrence of such events.
Key Question 4: Evidence regarding performance in special populations		
Diabetes	4	<ul style="list-style-type: none"> Sensitivity (98-99%) and specificity (25%-39%) of CACS for the detection of any calcium is similar to that for general populations from the meta-analysis of LoE I/II studies but a higher percent (11%-25%) of persons (1 – negative predictive value) with a negative test would have CAD based on two moderate quality studies.
Gender	3	<ul style="list-style-type: none"> Three studies evaluated CACS characteristics in women vs. men. Sensitivities were similar for both groups at CACS > 0. Specificities for women ranged for 41%-66% and those for men 24%-57%, some what lower. A higher percent (4% - 11%) of men (1 – negative predictive value) with a negative test would have CAD compared with women (0%-4%), however, the prevalence of CAD was lower in women (36%-47%) compared with men (53%-70%) Women present with CAD at an older age (~10 years) than men, which may account for the differences
Age	2	<ul style="list-style-type: none"> Seven LoE I/II validation studies evaluated the influence of age on CACS. In general, the prevalence of coronary artery calcium increases with age. There are conflicting results regarding test performance at various ages.
Key Question 5: Evidence regarding cost-effectiveness		
	4	<ul style="list-style-type: none"> Two moderate quality studies suggest that at a disease prevalence of up to 70%, CACS may be more cost effective than conventional angiography, however incremental cost effectiveness is not described. Cost-effectiveness is influenced by disease prevalence and CACS score cut-off (and corresponding sensitivity and specificity) The influence of additional testing to reflect clinical practice needs to be more fully considered. The influence of false-negative and false positive results is unclear and models did not consider follow-up of incidental findings. There is insufficient evidence for conclusions on the long-term cost utility of CACS compared with CCA alone or with regard to other non-invasive tests.

APPRAISAL

Coronary artery calcium scoring (CACS)

Final Scope

Rationale for the Appraisal

The role of coronary artery calcium scoring (CACS) as a diagnostic test and component of clinical decision making in symptomatic persons in whom coronary artery disease (CAD) is suspected is not well established. Questions remain about the role of CACS as a diagnostic test. Thresholds for the amount and types of plaque that may signify CAD that requires intervention are not well delineated. It is also not clear whether coronary artery calcium (CAC) detection and scoring changes treatment decisions. Evidence regarding which persons might benefit from diagnostic testing and whether early intervention provides better health outcomes or leads to additional unnecessary interventions, especially invasive interventions, is not well described. From a public health perspective, a diagnostic test should only be performed if it leads to the use of interventions that, on average, are likely to improve patient outcomes or if it prevents the use of interventions that are not likely to improve outcomes.

Currently, computed tomography (CT) techniques (electron beam or multi-detector) are the most common methods for determining CACS. In symptomatic persons, CACS has been studied as a noninvasive, indirect method for determining obstructive CAD. The presence of calcium is not specific for obstructive CAD since it may be present in both obstructive and non-obstructive lesions. Conventional coronary angiography (CCA) is considered the definitive method for determining presence of obstructive CAD, despite its limitations and potential for subjectivity. It is an invasive test which has associated risks and higher costs. Proponents of CACS suggest that it may facilitate clinical decision-making by identifying persons with low probability of significant coronary artery stenosis, who may not need further evaluation, and for identifying those who should go on for further evaluation.

Objective

The primary aim of this assessment is to systematically review, critically appraise and summarize research evidence describing characteristics of CACS as a *diagnostic* test for evaluation of CAD in patients in whom CAD is suspected. Available information on the economic impact of this will also be summarized and critically appraised. The use of CACS as a screening test in asymptomatic persons is not addressed in this report.

Key questions

When used to diagnose persons with suspected coronary artery disease (CAD):

1. What are the test characteristics, PPV (positive predictive value), NPV (negative predictive value), sensitivity and specificity, of coronary artery calcium scoring (CACS) compared with the reference standard of coronary angiography for the diagnosis of CAD or other established diagnostic tests for CAD. What is the evidence to describe the reliability (i.e., test-retest, intra-reader, inter-reader performance) of CACS.

2. What is the evidence regarding the safety of CACS?
3. What is the evidence that CACS influences clinical decision making and improves patient clinical outcomes (e.g. mortality)?
4. What is the evidence that CACS may perform differently in special populations (e.g. women, diabetic populations)?
5. What evidence of cost implications and cost-effectiveness for CACS compared with other diagnostic tests?

Outcomes

The primary focus of this report is on diagnostic test performance characteristics that describe the validity and accuracy CACS as a diagnostic tool in symptomatic persons when compared with conventional coronary angiography (CCA; the most appropriate reference standard). Test characteristics that have been included are: sensitivity, specificity, positive predictive value and negative predictive value. Information on the reliability (test- retest, intra- and inter-rater reliability) of CACS and information on cost per correct diagnosis from published economic studies are summarized as well.

Key considerations highlighted by clinical experts:

1. Interventions

Currently, the most common methods for determining CACS use computed tomography (CT), either electron beam CT (EBCT) or multidetector CT (MDCT) for the detection and quantification of the amount of coronary artery calcium. While there is a correlation between the site and amount of coronary artery calcium with vessel narrowing at that site, as with angiographic stenosis, the vulnerability of the plaque and probability of rupture is not known. In addition, calcification in vessels may be present in both obstructive and nonobstructive lesions and thus, CAC is not specific for obstructive CAD.¹

The role of CACS as a diagnostic or clinical decision-making tool in symptomatic persons has not been well defined. It is not likely to be a replacement for CCA, which is the gold standard anatomical test for CAD. Some proponents of CACS suggest that it may be most useful in separating persons who are unlikely to have significant coronary artery obstruction from those who should be referred for additional diagnostic testing. From this perspective, those with little or no calcium are less likely to have CAD requiring further evaluation, hospitalization or intervention. Those with a positive CACS are then often referred for stress tests to evaluate myocardial function, perfusion studies and/or invasive CCA and appropriate treatment. The current ACC/AHA guidelines indicate that non-invasive testing for ischemia be done prior to consideration for revascularization. Since CACS is anatomical test and doesn't detect ischemia, it is likely not a replacement for other non-invasive testing which evaluates cardiac and myocardial function.

In clinical practice, CACS may be used to determine whether patients presenting with chest pain should have further testing. CACS as a stand-alone diagnostic test, however, is less common. (The more common use appears to be the evaluation of asymptomatic

patients.) CACS is increasingly performed in conjunction with CT coronary angiography using MDCT.

EBCT and MDCT, both used for coronary artery calcium scoring, expose the patient to ionizing radiation. Potential adverse health effects associated with radiation exposure may be of concern to patients as well as clinicians. Presumably patients with a positive CACS may also have other diagnostic tests that involve ionizing radiation. Thus, radiation exposure related to CACS should be put in the context of additional testing that may be indicated. If CACS is done in combination with CT angiography and/or with newer MDCT, the exposure is likely to be greater than with CACS alone using EBCT. The potential risks and benefits with regard to such procedures should be discussed with patients. If use of CACS decreases the need for conventional coronary angiography, radiation exposure may be less.

2. **Costs**

The direct procedural costs of CACS are less than that of CCA. Indirect costs related to patient time are also lower.

The precise role of CACS in symptomatic patients is unclear and clinicians may not be comfortable making decisions on the basis of CACS alone. Consequently, additional tests are often done in clinical practice. A positive CACS frequently leads to stress testing or coronary angiography. These factors influence the evaluation of cost-effectiveness as well as radiation exposure and overall risk/benefit.

3. **Patient considerations**

The pre-test likelihood of CAD is largely based on sex, age, type of chest pain as well as other symptoms and factors. This is important when considering use of a diagnostic test and in comparing the results of studies validating tests such as CACS. Predictive values are influenced by the pre-test probability of disease.

Proponents of CACS suggest that a score of 0 (no coronary artery calcified plaque) in symptomatic patients has high negative predictive values, indicating it may be useful in excluding obstructive angiographic CAD.² The predictive values, however, are influenced by a patient's pretest likelihood of disease. In patients with low pre-test probability of CAD, a CACS of zero is associated with low risk of CAD. This may not be the case, however, in patients with higher pre-test likelihoods based on risk factors and clinical symptoms i.e. a negative test may not "rule out" disease to the same extent that it does when the pre-test likelihood is low.^{3,4} In a large study assessing the interrelation of CACS and inducible ischemia in patients with intermediate likelihood of CAD, Schenker, et al reported that 16% of patients with CACS = 0 had myocardial ischemia on provocative testing.⁴

Conventional angiography is an invasive test that requires sedation and carries with it certain risks. CACS is a noninvasive test that can be completed in around 15 minutes and requires no sedation, hospital stay or recovery; it requires only a few seconds of actual scanning time.

A recent simulation study modeling lifetime risk of radiation-induced cancer suggests that even a single scan for CACS determination may increase this risk. Although the typical effective radiation dose is less than that with conventional coronary angiography, the dose is highly variable depending on the equipment and protocol. A 10-fold variation in effective dose has been reported in the literature. There are no standardized protocols for quantification of CACS using MDCT.⁵ Anecdotally, the majority of CACS is currently done with prospective gating which decreases exposure. The ACCF/AHA documents provide guidelines for reducing radiation exposure.

Since scanning includes not only the coronary arteries but surrounding structures as well, potential abnormalities in structures other than the coronary arteries and heart might be observed and further evaluation may be required.

4. **Professional considerations:**

CACS currently is most frequently done with a multidetector or electron beam CT scanner, which are expensive pieces of equipment. Sales of multidetector CT scanners are rising with the increasing popularity of cardiac CTA. The CACS requires minimal physician time as the tests are performed by a technician, read by a computer algorithm, and then confirmed by a physician.

5. **Ethical considerations**

Although CACS is a noninvasive test, it does expose the patient to ionizing radiation, a factor which clinicians need to consider and put in the context of other tests that may be part of the clinical pathway which also may use ionizing radiation. CACS often leads to additional testing. Increased use of MDCT over EBCT and combining of CACS with CT angiography may increase patient exposure to ionizing radiation. The benefits, risks and costs therefore need to be considered and discussed with the patient.

1. **Background**

1.1 **The Condition - Coronary Artery Disease**

Coronary artery disease (CAD), also referred to as coronary heart disease (CHD), is the number one cause of death and disability in the United States for both men and women, affecting more than 16 million Americans, and is the most common form of cardiovascular disease. Each year, CAD kills more Americans than cancer.⁶ In 2005, 652,091 people died of cardiovascular disorders, accounting for 27.1% of all U.S. deaths, with 445,687 (68.3%) of those deaths due to CAD alone.^{6,7} Globally, CAD killed more than 7.6 million people in 2005, which is roughly 43.2% of all cardiovascular-related deaths worldwide.⁸ The increasing prevalence and burden of heart disease is also reflected economically. The total of direct and indirect costs of CAD in 2006 was \$142.5 billion, with \$11.6 billion paid to Medicare beneficiaries (\$11,308 per hospital discharge for coronary atherosclerosis).⁹ Reduction in the prevalence, morbidity and mortality

related to CAD is an important public health goal given the significant disease burden and contribution to total health care costs.

The underlying cause of CAD is atherosclerosis, a systematic disease process in which plaque, comprised of fat, cholesterol, calcium, and other substances found in the blood, builds up within the walls of damaged arteries leading to hardening or narrowing of the vessels. The coronary arteries, which supply blood, oxygen, and vital nutrients to the heart, can become partially or completely blocked due to the build up of plaque. The blocking of the coronary arteries leads to restricted blood flow (ischemia) to the myocardium, weakening it or even causing cell death. Coronary artery plaques are responsible for over 90% of ischemic heart disease (IHD).¹⁰ Common symptoms that occur with CAD are chest pain (angina), arrhythmias, shortness of breath (dyspnea), and in the event of a complete blockage, heart attack. Acute coronary syndromes, such as myocardial infarction (MI) and unstable angina, arise from rupture or erosion of atherosclerotic plaques. Common risk factors for CAD include smoking, high cholesterol, high blood pressure, insulin resistance or diabetes, obesity, metabolic syndrome, sedentary lifestyle, age, and genetics.

CAD develops slowly over time and may be asymptomatic for many years. The onset of symptoms depends on the location and severity of these obstructions; however, the severity of the lesions is poorly correlated with symptoms. Thus, the appropriate diagnostic evaluation of patients who may have CAD is of clinical and practical importance.

Assessment of coronary artery disease

The pre-test likelihood of CAD is largely based on sex, age, type of chest pain as well as other symptoms and factors. The first step in CAD diagnosis is a history and physical which includes consideration of these.

Sensitivity and specificity are the most widely used statistics to describe the accuracy of a diagnostic test. A sensitive test correctly identifies disease in those people who are truly sick, and a test that is specific for a particular disease correctly identifies those people who are well as not having the disease. Ideally, a diagnostic test should achieve both a very high sensitivity and a very high specificity; in reality, however, there is usually a trade off between sensitivity and specificity such that only one can be maximized at a time.

Based on the patient's history and physical, the first diagnostic test to evaluate coronary artery disease (CAD) in patients presenting with signs or symptom may be a simple and noninvasive test called an exercise treadmill test (ETT) which allows for the evaluation of ECG changes in response to exercise. The test is relatively inexpensive, readily available, and the test does not require exposure to radiation. However, wide variability in the diagnostic accuracy of treadmill stress testing as been reported.¹¹ If the results are ambiguous, imaging studies such as a nuclear SPECT (single photon emission computed tomography) perfusion study or a stress echocardiogram may be ordered. Both of these tests have increased accuracy for diagnosis of CAD compared with ETT. They have the

added advantage of allowing localization of ischemia and do not require the patient to exercise, which is beneficial for those patients who are not ambulatory.¹

When further evaluation is warranted, or in the acute setting, coronary angiography, a minimally invasive procedure that uses x-ray imaging to visualize coronary anatomy, may be performed. Coronary angiography is performed by inserting a long, thin, flexible tube called a catheter into the body through the groin, arm, or neck, which is then threaded into the coronary arteries where a dye is injected into the bloodstream. While the dye is flowing through the coronary arteries, an x-ray machine rapidly takes a series of images, offering a detailed look at blood flow through the coronary arteries. This procedure can help recognize and treat various disorders including occlusion due to the build up of plaque, stenosis, thrombosis, and enlargement of the coronary artery luminae.

Recently, assessment of CAC scoring by electron beam computed tomography (EBCT) or multi-detector CT (MDCT) has emerged as a potential noninvasive diagnostic technique for indirect detection of atherosclerotic burden in symptomatic patients.

1.2 The Technology and its Comparator(s)

Coronary artery calcification and detection by ultra-fast computed tomography

Coronary artery calcification (CAC) is part of the development of atherosclerosis. It is an active process that begins as early as the second decade of life and occurs exclusively in atherosclerotic arteries and is absent in the normal vessel wall.^{12, 13} A close relationship has been confirmed both by histopathology and intravascular ultrasound between the extent of CAC and the atherosclerotic plaque burden seen in CAD, making calcium a potential marker for diseased arteries.^{14, 15} Results from the St. Francis Heart Study showed that CAC scores in symptomatic patients, in both univariate and multivariate analyses, were independently predictive of CAD, surpassing the accuracy of historical cardiac risk factors.¹ Such studies, however, do not take into account treatment effects.

Early on, fluoroscopy was the modality of choice for detecting CAC. Around the 1990's, digital subtraction fluoroscopy and conventional computed tomography (CT) started being used and were reported to have greater sensitivity than conventional fluoroscopy in detecting CAC. More recently, ultra-fast computed tomographic scanning, which has the advantages of both rapid image acquisition, allowing the elimination of motion artifacts, and the high contrast and spatial resolution of computed tomography, has raised the question of whether it might be superior to other traditional methods for detecting and measuring CAC and thus a valuable tool in the diagnosis of CAD in symptomatic patients.

Coronary calcification is pervasive in patients with confirmed CAD and increases with age most markedly after age 50 in men and after age 60 in women.^{16, 17} Increasing prevalence of coronary artery calcified plaque parallels the increasing prevalence of coronary atherosclerosis over the lifespan.² However, the presence of calcified coronary plaque is not strongly correlated with the extent of histopathologic stenosis.^{18, 19} The

inner lining of both obstructed and non-obstructed vessels contains coronary artery calcified plaque; therefore, the detection of calcified plaque on cardiac CT is not specific to an obstructive lesion.² The absence of calcium in higher risk patients may not “rule out” the possibility of CAD. In a large study assessing the interrelation of CACS and inducible ischemia in patients with intermediate likelihood of CAD, Schenker, et al reported that 16% of patients with CACS = 0 had myocardial ischemia on provocative testing.⁴

The most common ultra-fast CT technologies employed for the detection of CAC are electron beam computed tomography (EBCT) and multi-detector computed tomography (MDCT). EBCT and MDCT for CAC measurement are completed within 10 to 15 minutes, requiring only a few seconds of scanning. Both methods use thin slice CT imaging and due to their extremely rapid scanning speed and use of ECG triggering and gating, have the advantage of reducing motion artifacts. Unlike most other cardiac CT studies for assessing heart morphology, function and coronary anatomy, CAC exams are performed without IV contrast medium and typically by prospective ECG-triggered sequential mode. Coronary artery calcium has a high intrinsic tissue contrast relative to non-calcified soft tissue so radiation dose can be reduced without diminishing the diagnostic value of the study.²⁰ The accuracy of ultra-fast CT is not limited by concurrent medications, the patient’s ability to exercise, or baseline ECG abnormalities. Also, a large portion of the chest is imaged so non-cardiac causes of chest pain or other incidental findings may be identified or ruled out. (See the section on safety for more about incidental findings)

EBCT differs from conventional CTs (which generate x-ray images by mechanically rotating an x-ray tube) by electronically sweeping an electron-beam along a tungsten anode in a stationary tube. This design was developed in the 1980s in order to better image heart structures which are constantly in motion and performs a complete cycle of movement with each heart beat. EBCT testing is relatively inexpensive, costing around \$420, which is comparable to a treadmill exercise test (\$320), and significantly less than exercise echocardiography (\$900) or dobutamine stress echocardiography (\$1000) and coronary angiography (average \$3000).²¹ Still a relatively new technology, EBCT isn’t used routinely to diagnose CAD because its accuracy hasn’t been firmly established. Also, there is insufficient long term evidence to support the cost-effectiveness of CAC by EBCT over other conventional well established methods of testing.¹

MDCT has recently emerged as another cardiac imaging modality that can be used to detect CAC. Although the current temporal resolution of MDCT is not as high as that for EBCT, MDCT has superior spatial resolution and unlike EBCT, can be used for the entire spectrum of routine clinical CT examinations.²⁰ MDCT differs from single detector-row helical or spiral CT scans in that it employs a two-dimensional array of detector elements versus a linear array, allowing multiple slices or sections (4 to 64) of the heart to be acquired simultaneously and with increased imaging speed. MDCT is a promising tool for CAC scoring but further studies are necessary to assess reproducibility and progression. One disadvantage of MDCT as compared with conventional CT is the higher degree of radiation exposure to the patient. In one study, radiation dose was

approximately 27% higher using MDCT versus single detector-row CT; organ dose was also higher with MDCT.²²

Comparators

Exercise electrocardiography (ECG), stress echocardiogram, myocardial perfusion imaging (MPI), and thallium stress test are common, more established, noninvasive technologies used to diagnose and evaluate patients presenting with symptoms suspicious for CAD. Unlike calcium scoring or conventional angiography, which are anatomical tests, these noninvasive test allow assessment of ischemia and myocardial function.

An exercise treadmill test (ETT), also called an exercise stress test or an ECG treadmill test, evaluates the effect of exercise on the heart. ECG monitors the electrical activity of the heart and blood pressure readings are taken at various points throughout the test, measuring the heart's reaction to the body's increased need for oxygen. A stress test may be performed to determine the exercise capacity of the heart, the causes of chest pain, and to identify rhythm disturbances during exercise. The American College of Physicians recommends ETT as the first choice for primary care patients with symptomatic chronic stable angina or with a medium risk of CAD based on a set of common risk factors.²³ However, wide variability in sensitivity and specificity for exercise ETT has been reported across studies.¹¹

Stress echocardiograms use ultrasound imaging to determine how the heart muscles respond to stress. A traditional stress echocardiogram requires patients to exercise on a treadmill or a stationary bike. For individuals who are unable to exercise, dobutamine can be used to increase the heart rate to a certain level, mimicking the effects of exercise. During both tests, blood pressure and heart rhythm (ECG) are monitored and ultrasound images are recorded that show areas of abnormal myocardial function which reflects reduced blood flow (ischemia) because of blocked arteries. A decrease in the left ventricular ejection fraction is an important indicator of possible damage to the heart or other problems with the heart valves or muscle, since the left ventricle performs the greatest amount of work pumping blood. Stress echocardiograms are simple and convenient to perform and do not require exposure to radiation.

Single photon emission computed tomography (SPECT) is a nuclear medicine imaging technique that employs a radioactive tracer which remains in the bloodstream and allows the visualization of blood flow to tissues and organs. When applied to the heart, it is often referred to as myocardial perfusion imaging (MPI) and is one of several types of cardiac stress tests used for the diagnosis of ischemic heart disease. MPI has been found to be comparable with other non-invasive stress tests for ischemic heart disease.¹ A thallium stress test is another nuclear imaging method that creates a picture of the heart by tracking how a radioactive material, thallium, moves through the vessels. These images show how well blood flows into the heart muscle after exercise or a medication-induced increase in heart rate. An abnormal thallium stress test is a possible indicator of a significant blockage of a coronary artery or damage to the heart muscle due to a prior heart attack. In direct-comparison studies of symptomatic persons, CAC detection has

been reported to be comparable to nuclear exercise testing in the detection of obstructive CAD.¹

The current gold standard the anatomic assessment of CAD, and the main comparator for the purposes of this assessment, is coronary angiography, a minimally invasive procedure that uses x-ray imaging to visualize coronary anatomy. The procedure is performed by inserting a long, thin, flexible tube called a catheter into the body through the groin, arm, or neck, which is then threaded into the coronary arteries where a dye is injected into the bloodstream. While the dye is flowing through the coronary arteries, an x-ray machine rapidly takes a series of images, offering a detailed look at blood flow through the coronary arteries. Unlike cardiac CT-quantified calcium scoring, angiography detects obstructive CAD. Major complications are rare with coronary angiography but some potential risks may include bleeding, infection, and pain at the site of insertion, damage to the blood vessels, allergic reaction to the contrast dye, arrhythmias, blood clots, kidney damage, radiation exposure, heart attack, and stroke. Contrast-enhanced computed tomography (CTA) is a non-invasive method of visualizing the coronary arteries and might be useful as a substitute for coronary angiography in various clinical scenarios in which CAD is suspected.

Measures of coronary artery calcium

Agatston score – Named after Arthur Agatston, it is the most widely used method for quantifying CAC. The score is based on the area and the density of the calcified plaques as represented in Hounsfield units (HU), a quantitative measure of radiodensity used to evaluate CT scans. The pixel value of a CT scan is displayed according to the mean attenuation of the tissue that it corresponds to on a scale ranging from -1000 HU (air) to +1000 HU (bone), with water corresponding to 0 HU on the Hounsfield scale. In his landmark study in 1990, Agatston set the threshold for a calcified lesion at a density of 130 HU having an area of ≥ 1 mm in order to eliminate single pixels with a CT density > 130 units due to noise. A lesion score was then determined based on the maximal CT number: 1 = 130 to 199, 2 = 200 to 299, 3 = 300 to 399, and 4 ≥ 400 HU. A score for each region is calculated by multiplying the density score and the area and the total calcium score is then determined by adding up each of those score for all CT slices obtained.²⁴ [A test is considered positive if any calcification is detected within the coronary artery and negative if no calcifications are detectable. Agatston scores of < 10 , 11-99, 100-400, and > 400 have been proposed to categorize individuals into groups having minimal, moderate, increased, or extensive amounts of calcification, respectively. The amount of calcium is related, to some extent, to the overall amount of atherosclerosis.²⁵

Agatston CAC scores of 0, >100 and ≥ 400 are common cut-offs or thresholds seen throughout the literature to exclude or diagnose significant CAD. A score of 0 (no coronary artery calcified plaque) in symptomatic patients has demonstrated high negative predictive values, indicating it may be useful in excluding obstructive angiographic CAD.² A score of > 100 is considered a high calcium score and is consistent with a high risk of a cardiac event within the next 2 to 5 years ($>2\%$ annual risk).¹³ Although there

are exceptions, a CAC score of ≥ 400 has been associated with an increased incidence of perfusion ischemia and obstructive CAD, making it a potential “high-risk” indicator for significant CAD.² It is important to remember that for diagnostic tests with continuous results such as the calcium score, the relative performance of sensitivity and specificity can be varied by changing the cut-off point defining positive or negative results. Which value is most important depends on one’s objective and perspective.

Calcium volume score – A study by Callister in asymptomatic patients concluded that use of the calcium volume score showed better reproducibility than the traditional Agatston score.²⁶ However, partial volume effects may impair the score’s accuracy, leading to overestimation of the calcium content and creating substantial variability between repeat trials.²⁷

Calcium mass – Calcium mass has been shown to be very accurate with little variability but is not well validated and difficult to measure.²⁷ It is rarely used as a practical means of quantifying CAC.²⁸

Safety

Radiation

The primary concern regarding the use of ultra-fast CT for calcium scoring is radiation exposure. To the extent that CACS may avoid the need for angiography, radiation exposure may be reduced. However, if CACS leads to additional testing, it may be increased. Even low levels of radiation are thought to increase the risk of cancer, though the extent by which this occurs is unclear.² In the American population, the collective dose received from medical uses of radiation was estimated to have increased by $> 700\%$ between 1980 and 2006.^{29, 30}

When discussing the potential health risks related to radiation it is necessary to highlight the difference between radiation exposure and radiation dose. Radiation exposure is a measure of the quantity of ionization produced in air by photon irradiation. Radiation dose (“absorbed radiation dose”) refers to the amount of radiation energy deposited in the human body as a result of exposure to ionization and is typically calculated from the exposure and from estimates of energy absorption per kilograms of body weight.³¹

The basic radiation dose parameter in CT is the computed tomography dose index (CTDI) and it is used to express the average dose delivered to the scan volume for a specific test.³² Another important parameter is the effective dose (E), which is meant to reflect the risk of the biological effects of ionizing radiation and is useful in assessing and comparing the potential risk of a specific examination.³¹ E is expressed in SI units of millisieverts (mSv) and corresponds to the amount of whole-body irradiation that would yield a biological risk equivalent to that of an irradiation to only a portion of the body.³³ It is not an exact indicator of the absolute risk of the biological effect on an individual but rather a rough estimate based on evolving knowledge and only applies to types of imaging studies, not to individual patients.³¹ Though E should not be used for

epidemiological purposes, it is useful in comparisons of the biological risk of different medical procedures that use ionizing radiation.³³

The effective dose values for coronary calcium CT have been reported to range from 1.0 to 12 mSv.³³ An AHA document reports that EBCT scanners have an estimated effective dose of 0.7 to 1 mSv in males and 0.9 to 1.3 mSv in females, and MDCT scanners have respective doses of 1 to 1.5 mSv and 1.1 to 1.9 mSv.² The estimated risk of fatal malignancy or death (per 1000 persons) resulting from CT calcium scoring (1 mSv) is 0.05, based on simulation.³³

Factors that may influence the radiation dose include the CT scanner model, number and length of scans, scan mode, ECG triggering or gating, x-ray tube potential, tube current-time product, degree of overlap between adjacent CT slices (pitch), and patient size.³⁴ Recommendations reducing radiation are: to use a prospective ECG trigger as opposed to retrospective gating; to use EBCT scanners versus MDCT scanners; to dose radiation according to body size; to reduce the tube current-time product for small patients; and to not unnecessarily repeat examinations.²

Medical imaging is the largest controllable source of radiation exposure to the American public.³³ There is conflicting evidence regarding the risk of developing cancer at the levels and types of radiation associated with medical imaging and with the exception of mammography, there is currently no federal regulation of patient radiation dose.³¹ Potential benefits and risks, including any related to not performing the test, should be carefully considered before ordering tests that will expose patients to ionizing radiation.

Incidental findings

Cardiac ultra-fast CT scanning for CAC includes images of portions of non-cardiac structures such as the lungs, bones, and upper abdomen. Pathologies unrelated to the heart or coronary arteries, both serious and benign, are sometimes identified incidentally when the entire scan is reviewed. The most common incidental finding is pulmonary nodules. Horton³⁵ analyzed 1326 patients with a mean age of 55 years undergoing EBCT for CAC screening and reported that lung nodules requiring clinical follow-up were seen in 65 (4.9%) patients. The prevalence of incidental findings in any organ system was 8%. In another study of 1000 middle-aged Army personnel, 23 (2.3%) were identified as having pulmonary nodules or other lung-related diseases, 50% of which were considered major, requiring subspecialty referral or potential invasive procedures.³⁶ The identification of potential pathology other than coronary calcium must be considered when evaluating the benefits and costs of cardiac scanning.¹

1.3 Clinical Guidelines

No clear role for EBCT or MDCT calcium scoring in the diagnosis or prognosis of symptomatic patients has been clearly established in the available published literature. Furthermore, studies in symptomatic patients have not shown that clinical outcomes can be favorably altered by the used of CT-determined CAC for CAD.¹ One suggested

application in symptomatic patients may be to triage patients with suspected CAD. Proponents suggest that a CAC score of 0 can be used to rule out the likelihood of significant CAD.^{1,2} Another potential use of CAC is to determine the etiology of cardiomyopathy, specifically to differentiate ischemic from non-ischemic disease.¹

Several clinical guidelines for the diagnosis and treatment of CAD were found on the National Guideline Clearinghouse (NGC) web-site, the primary repository for evidence-based clinical guidelines: <http://www.guideline.gov>.

American College of Cardiology Foundation Clinical Expert Consensus Task Force (ACCF/AHA)¹

The ACCF/AHA 2007 Clinical Expert Consensus Document provided statements regarding the role of CAC by ultra-fast CT in clinical practice. The guidelines are summarized as follows:

- There is a lack of evidence from head-to-head studies comparing CAC measurement to alternative risk assessment techniques for moderate risk patients. At the current time, CAC measurement cannot be determined to be superior, or inferior, to other approaches for CAD risk assessment.
- No clear evidence is available indicating that additional non-invasive testing in patients with high (> 400) calcium scores will result in more appropriate selection of treatment over the currently recommended preventative medical therapies.
- Patients with atypical cardiac symptoms may benefit from CAC testing to help exclude the presence of obstructive CAD. Other competing modalities are available but most have not been compared directly to CAC.
- Available CAC data has come largely from studies in Caucasian, non-Hispanic men, thus discretion should be used in extrapolating current CAC data to women and ethnic minorities
- Current radiology guidelines should be used when determining need for follow-up testing of incidental findings on an ultra-fast CT study, such as was recently published to guide management of small pulmonary nodules. [MacMahon 2005]

American Heart Association²

In 2006, the AHA issued a scientific statement on the use of cardiac computed tomography which reviewed the efficacy of calcium scoring for determining prognosis and diagnosis.

Ratings of recommendations

The AHA often includes an assessment of quality of evidence underlying the recommendation and the benefit versus risk using the following scoring system:

Evidence Level

Level A: Multiple randomized clinical trials or meta-analysis

Level B: Single randomized clinical trial or observational data (case control, longitudinal data)

Level C: Case reports, expert opinion, or current clinical practice

Benefit versus risk

Class I: Benefit >>> risk; procedure or treatment SHOULD be performed (i.e. is recommended, indicated, useful/effective/beneficial)

Class IIa: Benefit >> risk; procedure or treatment IS REASONABLE to perform

Class IIb: Benefit < risk, procedure or treatment MAY BE CONSIDERED

Class III: Risk outweighs the benefit; procedure SHOULD NOT be performed

Conflicting evidence and/or a divergence of opinion regarding its usefulness was found for the following indications:

- Symptomatic patients with chest pain with equivocal or normal electrocardiograms and negative cardiac enzymes (Class IIb, Level of Evidence: B)
- Determining the etiology of cardiomyopathy (Class IIb, Level of Evidence: B)
- Symptomatic patients in the setting of ambiguous stress tests (Class IIb, Level of Evidence: B)
- Asymptomatic patients with intermediate risk of CAD (Class IIb, Level of Evidence: B). May be useful to refine clinical risk prediction and to select patients for more aggressive target values for lipid-lowering therapies.

Indications in which CAC scoring was deemed not useful or possible harmful:

- Low-risk or high-risk asymptomatic patients (Class III, Level of Evidence: B)
- Establishing the presence of obstructive disease for revascularization in asymptomatic persons (Class III, Level of Evidence: C)
- Serial imaging for assessment of progression of coronary calcification (Class III, Level of Evidence: C)
- Hybrid nuclear and CT imaging to assess cardiovascular risk or presence of obstructive disease (Class III, Level of Evidence C)

Furthermore, the report stated that despite growing evidence that calcium scores are an independent predictor of CAD studies have not demonstrated improved clinical outcomes as a results of calcium score screening.

American Heart Association

According to a 2009 scientific advisory from the AHA, the following are the minimum requirements which should be met in scanning for coronary artery calcium (CAC) ^{33,37}:

- Use of an EBCT scanner or a 4-level (or greater) MDCT scanner
- Cardiac gating
- Prospective triggering for reducing radiation exposure
- A gantry rotation of at least 500 ms

- Reconstructed slice thickness of 2.5 to 3 mm to minimize radiation in asymptomatic persons (and to provide consistency with established results)
- Early to mid-diastolic gating
- Equipment or nuclear material in cardiac imaging should be appropriately utilized to maintain patient doses as low as reasonable achievable (ALARA) but consistent with obtaining the desired medical information

American College of Radiology (ACR) Appropriateness Criteria 2008

For assessment of chronic chest pain in patients with low to intermediate probability of CAD:

- CT coronary calcium scoring received a rating of 3 (1 = least appropriate, 9 = most appropriate)
- A score of zero may be useful in excluding cardiac etiology
- Relative radiation level is considered to be medium based on the following:

Relative Radiation Level Designations

Relative Radiation Level	Effective Dose Estimate Range
None	0
Minimal	< 0.1 mSv
Low	0.1-1 mSv
Medium	1-10 mSv
High	10-100 mSv

ACC/AHA expert consensus document on EBCT for the diagnosis and prognosis of CAD^{2, 13}

According to a statement by the ACC/AHA in 2000, the following are interpretations and recommendations for cardiac CT scanning and CAC scoring:

- A negative test (score = 0) makes the presence of atherosclerotic plaque, including unstable or vulnerable plaque, highly unlikely.
- A negative test makes the presence of significant luminal obstructive disease highly unlikely.
- A negative test is consistent with a low risk (0.1% per year) of a cardiovascular event in the next 2 to 5 years.
- A positive test (CAC > 0) confirms the presence of a coronary atherosclerotic plaque.
- The greater the amount of coronary calcium, the greater the atherosclerotic burden in men and women, irrespective of age.
- The total amount of coronary calcium correlates best with the total amount of atherosclerotic plaque, although the true atherosclerotic burden is underestimated.
- A high calcium score (Agatston score >100) is consistent with a high risk of a cardiac event within the next 2 to 5 years (>2% annual risk).
- CAC measurement can improve risk prediction in conventional intermediate-risk patients, and CAC plaque scanning should be considered in individuals at intermediate risk for a coronary event (1.0% per year to 2.0% per year) for clinical decision-making with regard to refinement of risk assessment.
- Decisions for further testing beyond assistance in risk stratification in patients with a positive CAC score cannot be made on the basis of coronary calcium scores

alone, as calcium score, correlates poorly with stenosis severity in a given individual and should be based upon clinical history and other conventional clinical criteria.

1.4 Previous Technology Assessments

Thirteen Health Technology Assessments were found and reviewed, ten of which either performed CAC scoring analyses in asymptomatic patient populations or using computed tomographic angiography (CTA), and were therefore outside the scope of this report and were excluded from assessment.

- Agency for Healthcare Research and Quality (AHRQ), October 3, 2006³⁸
- Ontario Health Technology Advisory Committee (OHTAC), May 2007³⁹
- BlueCross BlueShield Technology Assessment, August 2006⁴⁰
- Berry E et al. (NHS R&D Health Technology Programme), October 1999⁴¹
- Canadian Agency for Drugs and Technologies in Health (CADTH), August 2006⁴²
- National Horizon Scanning Centre, December 2006⁴³
- Belgian Health Care Knowledge Centre (KCE), 2008⁴⁴
- Mowat G, et al. (NHS R&D Health Technology Programme), May 2008
- New Zealand Health Technology Assessment (NZHTA) Evidence Tables, February 3, 2003⁴⁵
- Waugh N et al (NHS R&D Health Technology Programme), October 2006⁴⁶

Three Health Technology Assessments provided limited data or information and are briefly described below:

- The AHRQ did a review of various non-invasive technologies for diagnosing CAD in symptomatic women.⁴⁷ The overall accuracy of CT calcium scoring was found to be low in both men and women, cut-offs of both > 0 and > 100 . A calcium score of 0, however, had a high sensitivity and a low negative likelihood ratio is low, indicating that a calcium score of 0 might be useful to rule out CHD in both women and men.
- The California Technology Assessment Forum (CTAF) investigated the utility of CAC measurement in cardiovascular disease.⁴⁸ The CTAF reviewer recommendation was as follows:
 - As a diagnostic test in patients with symptoms suggestive of CAD does not meet technology assessment criteria 3, 4, or 5 for safety, effectiveness, and improvement in health outcomes.

The report then states that, following clarification of data and testimony from invited experts, the CTAF panel accepted the following recommendation:

As a diagnostic test in patients with symptoms suggestive of CAD (i.e. chest pain) EBCT calcium scoring was determined to be a useful

technology in the prediction of those patients who will have underlying coronary disease.

- The Institute for Clinical Systems Improvement (ICSI) Technology Assessment Committee reported that for the diagnosis of obstructive CAD in symptomatic patients, EBCT or helical CT CAC score is a stronger independent predictor than conventional risk factors.⁴⁹ Direct comparisons of EBCT with other non-invasive tests for diagnosis are lacking, however.

1.5 Medicare and Representative Private Insurer Coverage Policies

The table below provides a summary of payer policies related to coronary artery calcium scoring.

Table 3. Summary of payer policies

Payer (year)	Evidence base available	Policy	Rationale
Centers for Medicare & Medicaid Services (CMS): ^{50, 51} Pub 100-3 National Coverage Determinations: Section 220.1, Version 2 NCA tracking #: CAG-00385N (2008)	NR	<ul style="list-style-type: none"> • No national coverage determination for CTA is appropriate at this time (March 12, 2008); use of CTA to diagnose coronary artery disease will remain at local contractor discretion • No mention of calcium scoring found 	<ul style="list-style-type: none"> • After examining the medical evidence available for CTA in the visualization of coronary arteries, no national coverage determination is appropriate at this time (March 12, 2008) • There is limited evidence regarding the test performance of non-invasive imaging tests for identifying, quantifying, or otherwise characterizing coronary artery stenosis
CMS Regional Coverage LCD ID number L23654 (2008) And Article (A45280) (Washington, Alaska), administered by Noridian Administrative Services (2007)	NR	<ul style="list-style-type: none"> • Demonstration and/or quantification of the presence of coronary calcification in either asymptomatic or symptomatic patients with or without signs of atherosclerotic heart disease has not been shown to improve outcomes and is not covered. Until such time as there may be more evidence of medical necessity, Medicare will not pay for the quantitative evaluation of coronary calcium by MDCT, CTCA, EBCT or other technology. • Cardiac MDCT for coronary calcium scoring is not covered • CPT codes: 0144T 	<ul style="list-style-type: none"> • Lack of evidence of the medical necessity for quantitative evaluation of coronary calcium
Aetna Clinical Policy Bulletin number 0228 (2009) ⁵²	Unable to determine	<ul style="list-style-type: none"> • Calcium scoring is considered medically necessary for diagnostic cardiac CT angiography to assess whether an adequate image of the coronary arteries can be obtained • CPT codes: 0145T, 0146T, 0147T, 0148T, 0149T, 1050T, +0151T • ICD-9 codes: 424.3, 446.1, 	<ul style="list-style-type: none"> • NR

		745.2, 747.40-747.42, 759.82	<ul style="list-style-type: none"> Calcium scoring (e.g., with ultrafast EBCT, spiral (helical) CT, and multislice CT) is considered experimental and investigational for all other indications CPT codes: 0144T HCPCS codes: S8092 	<ul style="list-style-type: none"> Definitive value of calcium scoring for assessing coronary heart disease risk has not been established in the peer-reviewed published medical literature
Cigna HealthCare Coverage Position number 0009 (2008) ⁵³	<p>Symptomatic patients</p> <p>5 studies, N = 4821</p> <p>Asymptomatic patients</p> <p>14 studies, N = 90,253</p>	<ul style="list-style-type: none"> EBCT, spiral CT, or MDCT for the detection and/or quantification of coronary artery calcification is not covered Use of these technologies for screening, diagnosis, or management of coronary artery disease is considered experimental, investigational, or unproven CPT codes: 0144T HCPCS codes: S8092 ICD-9 codes: 414.01 	<ul style="list-style-type: none"> There is insufficient evidence to support the use of MDCT and EBCT scanning for coronary calcium in symptomatic or asymptomatic populations 	
Civilian Health and Medical Program of the Department of Veterans Affairs (CHAMPVA) ⁵⁴ Policy Manual, Benefits, Chapter 2, Section 26.3 (2008)	NR	<ul style="list-style-type: none"> Helical CT for assessment of coronary calcification is not covered CT or EBCT to screen asymptomatic individuals for CAD is not covered 	<ul style="list-style-type: none"> Cardiac CT including image post processing and quantitative evaluation of coronary artery calcium is unproven CTA of coronary arteries (including native and anomalous coronary arteries, coronary bypass grafts) with quantitative evaluation of coronary calcium is unproven 	
Regence of Oregon and Utah; Regence of Idaho and select counties of Washington Medical Policy number 6 (2008) ⁵⁵	<p>2006 AHA scientific statement</p> <p>1999 ACC/AHA Expert Consensus Document</p>	<ul style="list-style-type: none"> Use of CT to detect and quantify coronary artery calcification is considered investigational CPT codes: 0144T, 1047T, 1049T HCPCS codes: S8092 	<ul style="list-style-type: none"> Published studies do not establish a clear role for EBCT in coronary risk stratification in asymptomatic or symptomatic patients No studies have show that clinical outcomes can be favorable altered by the use of CT-based determination of coronary artery calcification in screening for coronary artery disease 	
BlueCross BlueShield (BCBS) of North Carolina Corporate Medical Policy number RAD5050 (2008) ⁵⁶	NR	<ul style="list-style-type: none"> CT to detect coronary artery calcification is not covered Use of CT (e.g., EBCT, spiral or helical CT, multislice or multi-detector CT) to detect coronary artery calcification is considered investigational for all services including: <ul style="list-style-type: none"> screening examination for asymptomatic patients diagnostic study in symptomatic patients assessment of coronary artery 	<ul style="list-style-type: none"> NR for diagnostic purposes No clear role has been established in the literature for EBCT in coronary disease risk stratification in asymptomatic patients No studies have shown that clinical outcomes can be favorably altered by the use of screening EBCT 	

		bypass graft patency <ul style="list-style-type: none"> • measurement of cardiac perfusion • CPT codes: 0144T, 0147T, 0149T • HCPCS codes: S8092 	
United Health Care (July 2009)	NR, appears to use information from ACC/AHA statements and guidelines	<ul style="list-style-type: none"> • Calcium scoring as a triage tool for symptomatic patients to rule out obstructive disease and avoid invasive procedures is covered • Calcium scoring for routine screening is not covered but risk stratification in asymptomatic patients with moderate risk based on the Framingham Score is covered 	<ul style="list-style-type: none"> • States that CACS for triage is proven

ACC: American College of Cardiology; AHA: American Heart Association; CPT: current procedural technology; CT: computed tomography; CTA: computed tomographic angiography; EBCT: electron beam computed tomography; HCPCS: healthcare common procedure coding system; ICD-9: international classification of diseases, 9th addition; MDCT: multidetector computed tomography; NR: not reported

- Medicare (National Coverage Determination)**
The most current information available since March 2008 indicates that The Centers for Medicare and Medicaid Services (CMS) find that no national coverage determination for computed tomographic angiography (CTA) is appropriate at this time. No mention of coronary artery calcium scoring could be found.
- Medicare (Regional Coverage Determination)**
The local regional CMS had determined that there is a lack of evidence of the medical necessity for quantitative evaluation of coronary artery calcium. Coronary artery calcium scoring by multidetector computed tomography (MDCT) is not a covered service. LCD ID number L23654, states: “Demonstration and/or quantification of the presence of coronary calcification in either asymptomatic or symptomatic patients with or without signs of atherosclerotic heart disease has not been shown to improve outcomes and is not covered. Until such time as there may be more evidence of medical necessity, Medicare will not pay for the quantitative evaluation of coronary calcium by MDCT, CTCA, EBCT or other technology.”
- Aetna**
Aetna considers calcium scoring medically necessary for diagnostic cardiac CT to assess whether an adequate image of the coronary arteries can be obtained. Calcium scoring with electron beam CT, spiral or helical CT, and multislice CT is considered experimental and investigational for all other indications. To date, the peer-reviewed published medical literature has produced conclusive evidence of value of calcium scoring for assessing coronary artery disease (CAD) risk.
- Cigna**

Cigna considers electron beam CT, spiral or helical CT, or multidetector CT for screening, diagnosis, or management of coronary artery disease experimental, investigational, or unproven. The detection and/or quantification of coronary artery calcification using these technologies are not a covered service.

- **Department of Veterans Affairs (VA)**
The medical program for the VA does not cover the use of helical CT scanning for the assessment of coronary calcification. Cardiac CT scanning including image post processing and quantitative evaluation of coronary artery calcium is considered unproven. Likewise, CT or EBCT to screen asymptomatic individuals for CAD and CT angiography with quantitative evaluation of coronary calcium are not covered due to lack of evidence supporting their validity.
- **Regence (Regional Medical Policy)**
Regence's local medical policy for the states of Oregon, Idaho, Utah, and select counties of Washington considers the use of CT to detect and quantify coronary artery calcification investigational. No clear role for EBCT in coronary risk stratification in asymptomatic or symptomatic patients has been established in the available published literature. Furthermore, no studies have show that clinical outcomes can be favorably altered by the use of CT-based determination of coronary artery calcification in screening for coronary artery disease.
- **BlueCross BlueShield of North Carolina (Corporate Policy)**
BlueCross BlueShield does not cover the use of CT to detect coronary artery calcification and is considered investigational for all services.

1.6 Washington State Data

Data from three Washington State Agencies were provided by the Health Technology Assessment Program. HTA coordinates the collection of any relevant agency utilization data. Coronary Artery Calcium Scoring (CACS) is a selected topic. CACS uses a CT to check for the buildup of calcium in plaque on the coronary arteries. This test identifies and quantifies a marker of coronary disease (plaque) and advocates believe it detects earlier stage CAD (before it becomes clinically apparent) that can be intervened on through a combination of non-invasive (lifestyle and medication) or invasive (angiography, stent, CABG) approaches.

Estimates for costs and utilization from the Uniform Medical Plan (UMP) and Washington State's Medicaid Program (DSHS) are presented below in Table A. They provide an estimate of base costs and may not include all costs for Coronary Artery Calcium Scoring (CACS). Information on relevant procedure codes is included after the result tables.

Current State Agency Medical Policy

Medicaid: CCTA is currently a covered service and requires “preauthorization” by Medicaid clinical utilization review consultants.

Uniform Medical Plan: CCTA is currently a covered service only by Exception, subject to preauthorization review. In most cases it was deemed “**investigational**” by UMP medical consultants. According to UMP’s Summary of Benefits, a service or supply is considered experimental or investigational if it is under continued scientific testing and research concerning safety, toxicity, or efficacy and is unsupported by prevailing opinion among medical experts (as expressed in peer-reviewed literature) as safe, effective, and appropriate for use outside the research setting. Providers may request an exception through the UMP medical review staff.

Labor and Industries: This service is not generally within the scope of services covered because heart disease and diagnosis is not typically related to a work place injury. If requested and within scope of services, it would be considered under WAC 296-20-01002 which outlines that in no case shall services which are inappropriate to the accepted decision or which present hazards in excess of the expected medical benefits be considered proper and necessary. Services that are controversial, obsolete, investigational or experimental are presumed to not be proper and necessary. Providers may request an exception through the medical director.

Table A: Claims by Year

UMP & Medicaid

CPT CODE	2005	2006	2007	2008	Total
0144T (CT, heart, w/o contrast, with eval of coronary calcium)	0	12	27	53	92
0147T (CT angiography of coronary arteries with eval of coronary calcium)	0	13	25	19	57
0149T (Cardiac structure and morphology and CT angiography with eval of coronary calcium)	0	0	17	11	28
Total	0	25	69	83	177

Paid Claims by Year

UMP & Medicaid

CPT CODE	2005	2006	2007	2008	Total
0144T (CT, heart, w/o contrast, with eval of coronary calcium)	0	1	3	23	27
0147T (CT angiography of coronary arteries with eval of coronary calcium)	0	8	20	11	39
0149T (Cardiac structure and morphology and CT angiography with eval of coronary calcium)	0	0	13	9	22
Total	0	9	36	43	88

Total Payments* by Procedure by Year

UMP & Medicaid | 2005-2008

CPT Code	2005	2006	2007	2008	Total
0144T	\$0	\$149	\$1,173	\$3,031	\$4,353
0147T	\$0	\$1,645	\$4,043	\$4,593	\$10,281
0149T	\$0	\$ 0	\$7,331	\$4,648	\$11,979
Total	\$0	\$1,794	\$12,547	\$12,272	\$26,613

*Payments include professional and facility fees.

Average Payments* by Procedure by Year

UMP & Medicaid | 2005-2008

CPT Code	2005	2006	2007	2008	Total
0144T	\$0	\$149	\$391	\$132	\$161
0147T	\$0	\$206	\$202	\$418	\$264
0149T	\$0	\$ 0	\$564	\$516	\$577
Total	\$0	\$199	\$349	\$285	\$302

Procedure Codes

CPT Codes

0144T – non contrast cardiac CT with eval of calcium scoring

0147T – cardiac CT angiography with calcium scoring

0149T – cardiac structure and morphology and cardiac CT angiography with calcium scoring

Cardiac Computed Tomography and Coronary Computed Tomographic Angiography (APCs 0282 and 0383)

For CY 2008, CMS will assign the cardiac computed tomography (CCT) and coronary computed tomographic angiography (CCTA) procedures to two new clinical APCs, specifically new clinical APC 0383 (cardiac computed tomographic imaging) and APC 0282 (Miscellaneous Computed Axial Tomography). The median cost of approximately \$314 for APC 0383 was based entirely on claims data for CPT® Category III codes 0145T, 0146T, 0147T, 0148T, 0149T, and 0150T that described CCT and CCTA services, a clinically homogeneous grouping of services. In addition, the individual median costs of these services ranged from a low of approximately \$277 to a high of \$437, reflecting their hospital resource similarity as well. CMS proposed to reassign the other two CCT CPT® codes, specifically CPT® codes 0144T and 0151T, to APC 0282. The inclusion of these two codes in APC 0282 resulted in a CY 2008 APC median cost of about \$105.

2. The Evidence

2.1 Systematic Literature Review

Objectives

The primary aim of this assessment is to systematically review, critically appraise and analyze research evidence describing the performance and safety of CACS as a *diagnostic* test for evaluation of CAD in patients in whom CAD is suspected. Available information on the economic impact of this will also be summarized and critically appraised.

2.2 Methods

Inclusion and exclusion criteria: For Key Questions:

- Retrieval and assessment of studies focused on those of the highest methodological quality.
- The focus of this HTA is on diagnostic application of CACS (as a stand-alone test) in *symptomatic* patients as opposed to screening of asymptomatic patients.

Table 4. Summary of inclusion and exclusion criteria are in the table:

Study Component	Inclusion	Exclusion
Participants	<ul style="list-style-type: none"> • Symptomatic patients with suspected CAD who have not had revascularization (i.e. CABG or stent) • Consecutively enrolled patients • Studies relate to triage of chest pain patients (emergency department) 	<ul style="list-style-type: none"> • Asymptomatic patients and those judged to be at low risk for CAD • Patients who have had previous revascularization (CABG, PTCA or stenting) • Studies of serial assessment of CAC • Evaluation of other cardiac diseases (e.g. valvular disease etiology of cardiomyopathy)
Intervention	<ul style="list-style-type: none"> • Coronary artery calcium scoring (CACS) using computed tomography (EBCT, MDCT, spiral/helical CT, multi-slice CT) 	<ul style="list-style-type: none"> • MRI
Reference Standard:	<ul style="list-style-type: none"> • Coronary artery angiography is reference standard • Studies comparing CACS with other diagnostic tests will only be briefly described for context. 	<ul style="list-style-type: none"> •
Outcomes	<ul style="list-style-type: none"> • Test performance/accuracy parameters (sensitivity, specificity, PPV, PVN, and reliability) • Death, myocardial infarction, patient-reported outcomes • Economic measures (e.g. ICERs, cost per correct diagnosis) 	<ul style="list-style-type: none"> • studies focused on “per-vessel” or “per-segment” analysis without per patient findings
Study Design	<ul style="list-style-type: none"> • Prospective studies directly comparing CACS with the reference standard or other comparators (except reliability studies) will be sought. Retrospective studies will be considered if there are insufficient prospective studies. • CT and coronary angiography carried out within 3 months of each other • For Key Question 5, only formal economic studies will be considered 	<ul style="list-style-type: none"> • Case series • Case reports • Studies that do not directly compare CACS using CT with conventional angiography
Publication	<ul style="list-style-type: none"> • Studies published in English in peer reviewed journals or publically available FDA reports • For Key Question 5 <ul style="list-style-type: none"> ○ Full formal economic analyses (e.g. cost-utility studies) published in English in a peer- 	<ul style="list-style-type: none"> • Abstracts, editorials, letters • Duplicate publications of the same study which do not report on different outcomes • Single reports from multicenter trials

reviewed journal published after those represented in previous HTAs.

- White papers
- Narrative reviews
- Articles identified as preliminary reports when results are published in later versions
- Incomplete economic evaluations such as costing studies

Data sources and search strategy

The clinical studies included in this report were identified using the algorithm shown in Figure 1 below. The search took place in four stages. The first stage of the study selection process consisted of a comprehensive literature search using electronic means and hand searching. We then screened all possible relevant articles using titles and abstracts in stage two. This was done by two individuals independently. Those articles that met a set of *a priori* retrieval criteria based on the criteria above were included. Any disagreement between screeners that were unresolved resulted in the article being included for the next stage. Stage three involved retrieval of the full text articles remaining. The final stage of the study selection algorithm consisted of the selection of those studies using a set of *a priori* inclusion criteria, again, by two independent investigators. Those articles selected form the evidence base for this report.

Figure 1. Algorithm for article selection

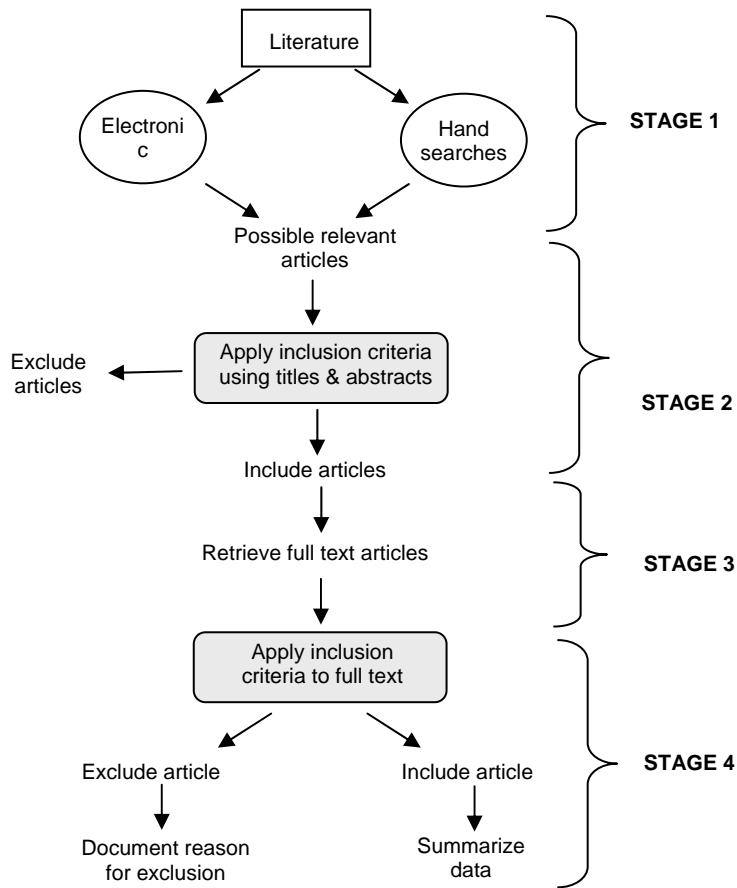
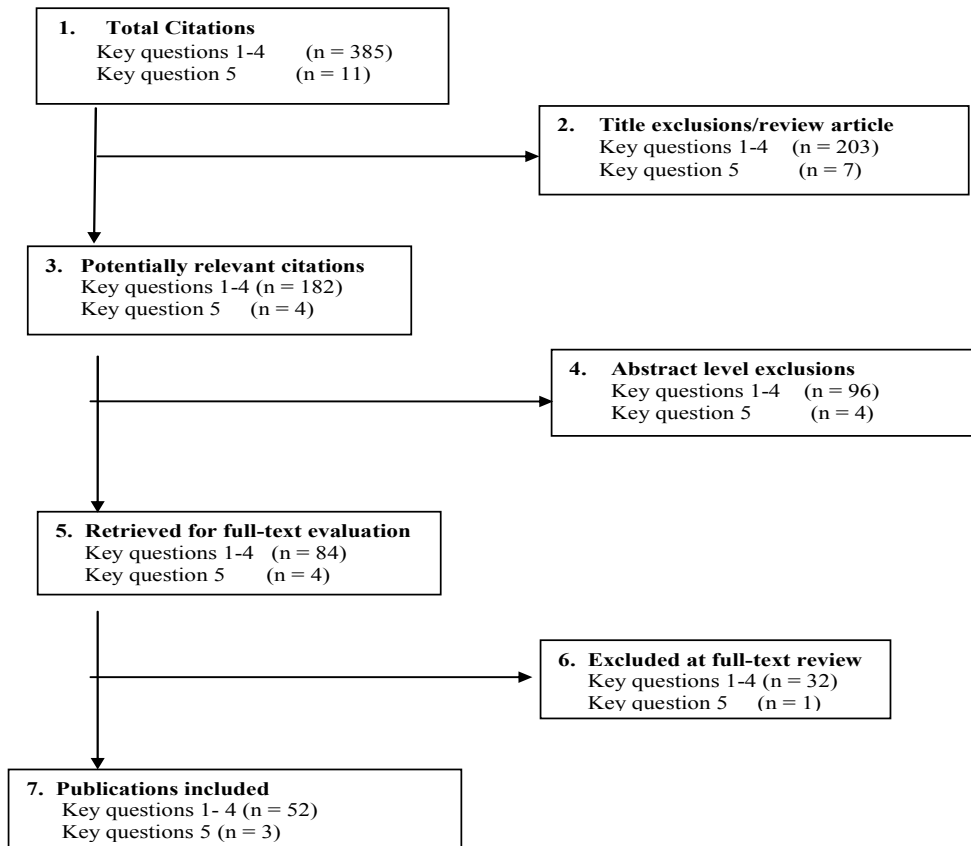


Figure 2. Flow chart showing results of literature search



Categorization of studies and outcomes

Data extraction

For the highest quality (level of evidence I – III, please see below) validation studies, population characteristics, study design, inclusion criteria, diagnostic test characteristics, prevalence of CAD and outcomes were abstracted. Where possible, true positive, true negative, false positive and false negative results were abstracted (or calculated) for meta-analysis based on data provided in the reports.

Study quality assessment: Level of evidence (LoE) evaluation

Details of the Level of Evidence (LoE) methodology are found in Appendix C. Each validation, reliability or economic study chosen for inclusion was given a LoE rating based on the quality criteria described below. Abstraction guidelines were used to determine the LoE for each study included in this assessment. The methodological quality of studies was independently assessed by two reviewers and discrepancies were resolved by discussion.

The method used by Spectrum Research, Inc. (SRI) for assessing the quality of evidence of individual studies as well as the overall quality of evidence incorporates aspects of the

rating scheme developed by the Oxford Centre for Evidence-based Medicine,⁵⁷ precepts outlined by the Grades of Recommendation Assessment, Development and Evaluation (GRADE) Working Group,⁵⁸ and recommendations made by the Agency for Healthcare Research and Quality (AHRQ).⁵⁹ Details are found in Appendix C.

For validation (accuracy) studies, the following criteria were used to assess LoE for individual studies:

Definitions of the different levels of evidence for diagnostic test accuracy/validity studies.

Level	Study type	Criteria
I	Good quality prospective study	<ul style="list-style-type: none"> Broad spectrum of persons with the expected condition Appropriate reference standard used Adequate description of test and reference for replication Blinded comparison of tests with appropriate reference standard Reference standard performed independently of diagnostic test
	Moderate quality prospective study	<ul style="list-style-type: none"> Violation of any one of the criteria for a good quality prospective study (LoE I)
II	Good quality retrospective study	<ul style="list-style-type: none"> Broad spectrum of persons with the expected condition Appropriate reference standard used Adequate description of test and reference for replication Blinded comparison of tests with appropriate reference standard Reference standard performed independently of diagnostic test
	Poor quality prospective study	<ul style="list-style-type: none"> Violation of any two or more of the criteria for a good quality prospective study (LoE I)
III	Moderate quality retrospective study	<ul style="list-style-type: none"> Violation of any one of the criteria for a good quality retrospective study (LoE II)
	Poor quality retrospective study	<ul style="list-style-type: none"> Violation of any two or more of the criteria for a good quality retrospective study (LoE II)
IV	Case-Control Study	

For reliability studies, the following criteria were used to determine the LoE for individual studies:

Definitions of the different levels of evidence for reliability studies

Level	Study type	Criteria
-------	------------	----------

I	Good quality study	<ul style="list-style-type: none"> • Broad spectrum of persons with the expected condition • Adequate description of methods for replication • Blinded performance of tests, measurements or interpretation • Second test/interpretation performed independently of the first
II	Moderate quality	<ul style="list-style-type: none"> • Violation of any one of the criteria for a good quality study
III	Poor quality study	<ul style="list-style-type: none"> • Violation of any two of the criteria
IV	Very poor quality study	<ul style="list-style-type: none"> • Violation of all three of the criteria

There is no universally accepted, standardized approach to critical appraisal of economic evaluation studies. The criteria described in the Quality of Health Economic Studies (QHES) tool⁶⁰ provided a basis for the critical appraisal of included economic studies and was augmented with the application of epidemiologic appraisal precepts (see Appendix C). The QHES employs widely accepted criteria for appraisal, such as choice and quality of cost and outcomes measures, transparency of model and presentation, use of incremental analysis, uncertainty analysis, and discussion of limitations and funding source and was primarily used to facilitate description of primary strengths and limitations of the studies. A weighted global score can be obtained based on these measures with a possible range of scores from 0 (worst) to 100 (best), theoretically providing a common metric to compare study quality. This tool and the weighted score have not yet undergone extensive evaluation for broad use but provide a valuable starting point for critique.

Two individuals critically appraised each study independently using the QHES. Discrepancies were resolved by discussion to arrive at a final appraisal. In addition, elements of critical appraisal consistent with epidemiologic principles and evaluation of bias (e.g., selection bias) were applied. Evaluation of the overall strength of evidence across studies for specific key questions, considers the quality and quantity of available studies as well as the consistency of study estimates.

Overall Strength of Evidence (SoE)

SoE	Description	Further Research Impact	Domain Criterion Met		
			Quality	Quantity	Consistency
1	High	Very unlikely to change confidence in effect estimate	+	+	+
2	Moderate	Likely to have an important impact on confidence in estimate and <i>may</i> change the estimate	+	-	+
			+	+	-
3	Low	Very likely to have an important impact on confidence in estimate and <i>likely</i> to change the estimate	+	-	-
			-	+	+
4	Very Low	Any effect estimate is uncertain	-	+	-
			-	-	+
			-	-	-

Data analysis

Meta-analysis was conducted on the primary validation parameters when data from three or more LoE I-III studies were available. Estimates from LoE I and II studies were pooled separately from estimates for LoE III studies, providing some sensitivity analysis related to study quality. Pooled estimates of sensitivity, specificity, positive predictive value and 1-negative predictive value were calculated.

There is no consensus on thresholds (cut offs) for normal or abnormal CACS scores. One meta analysis and two documents from the American College of Cardiology (ACC) have suggested that a cut off score of 0 might be assumed to be associated with a low risk ($\leq 5\%$) of CAD and potentially used to rule out significant obstructive CAD while a score of ≥ 400 was assumed to be associated with a 90% risk of CAD.^{1, 2, 61} Following consultation with a clinical expert, these two primary cut points were chosen for primary meta-analysis based on the premise that a score of 0 might be used to “rule out” significant CAD and a score of ≥ 400 might signal the need for additional evaluation. Thresholds and methods of determining optimal cut points for scores varied across studies and could not be pooled. Most studies used an angiographic cut off of $\geq 50\%$ decrease in luminal dimension for determination of obstructive CAD.

Meta-analysis using the above thresholds was done if data for true negative, true positive, false negative and false positive could be abstracted or calculated. Meta-analysis was performed using MetaDiSc software version 1.4⁶² and summary ROC curves were calculated using standard methods.⁶³

2.3 Quality of literature available

From a list of 186 potentially relevant study citations from electronic database searches, no randomized controlled trials were found. Multiple reports of the same study and/or of overlapping populations were found. Reports representing the most complete data were retained.

Five meta-analyses were found,^{1, 13, 61, 64, 65} two of which were contained within ACC/AHA guideline documents.^{1, 13} All of these analyses included individual studies that varied widely with respect to quality, based on Spectrum’s LoE determination and only one provided some evaluation of individual study quality.⁶¹ One analysis appears to have combined studies with different population characteristics (i.e. those with suspected CAD, chronic dialysis patients, those with non-ischemic cardiomyopathy) but did describe potential sources of heterogeneity.⁶⁵ The meta-analysis reported by Heijnenbroek-Kal included 21 EBCT studies but it was unclear whether these studies were in symptomatic or asymptomatic populations.⁶⁴ Since the quality of studies varied in these meta-analyses and several appeared to have included populations not relevant to this technology assessment, information from them is provided where appropriate to provide additional context only.

Accuracy (validation) studies

A total of 30 primary studies of accuracy and validity comparing CACS with CCA were identified. Of these, 11 studies⁶⁶⁻⁷⁶ were classified as LoE I or II, 8 as LoE III⁷⁷⁻⁸⁴ and 11

as LoE IV^{14, 85-91} as listed below. Two studies included evaluation of CACS in diabetic populations.^{70, 82} Not all LoE I –III studies had data that could be abstracted for meta-analysis.

Blinded interpretation of the test and reference standard results and independent performance of the test and referent (i.e. the results of one should not influence whether the other is performed) are considered to be of primary importance in decreasing study bias. It was not always clear from reports that these criteria were met. A brief summary of the level of evidence (LoE) determination for these studies is found below.

LoE I	LoE II	LoE III	LoE IV
Leschka 2008	Lau 2005	Hosoi 2002 (DM vs. not)	Konieczynska (2006)
Kajinami 1995	Nixdorf 2008	Shavelle 2000	Haberl 2005
	Becker 2007	Budoff 1996†	Rumberger, Sheedy 1997
	Knez 2004	Tannenbaum 1989	Yao 2004
	Lamont 2002	Herzog 2004	Shivastava 2003
	Haberl 2001	Fallavollita 1994	Broderick 1996
	Leber 2001	Chen 2001	Bielak 2000
	Budoff,2002	Guerici 1998	Yao 2000
	Kwok 2000		Seese 1997
	Khaleeli (2001) †		Baumgart 1997
			Bielak 1994

†Khaleeli focuses on CACS in diabetic patients but compares findings with a non-diabetic cohort previously reported in Budoff 1996.

Table 5. Level of evidence (LoE) summary for LoE I/II validation studies

METHODOLOGICAL PRINCIPLE	Leschka (2008)	Nixdorff (2008)	Becker (2007)	Lau (2005)	Knez (2004)	Budoff (2002)	Lamont (2002)	Haberl (2001)	Leber (2001)	Kwok (2000)	Kajinami (1995)
Study Design											
Prospective cohort design	√	√		√			√				√
Retrospective cohort design			√		√	√		√	√	√	
Case-control design											
Broad spectrum of patients with expected condition	√		√		√			√	√	√	√
Appropriate reference standard	√	√	√	√	√	√	√	√	√	√	√
Adequate description of test and reference for replication	√	√	√	√	√	√	√	√	√		√
Blinded comparison with appropriate reference	√	√	√	√	√	√	√	√	√	√	√
Reference standard performed independently of test	√	√	√	√	√	√	√	√	√	√	√
Evidence Level	I	II	II	II	II	II	II	II	II	II	I

* Blank box indicates criterion not met or could not be determined or information not reported by author

Conventional coronary angiography (CCA) was considered to be the best primary reference test for comparing accuracy of CACS. Since symptomatic patients are most likely to be referred by a cardiologist for angiography as a definitive test based on a clinical suspicion of CAD, there is the potential for referral/verification bias inherent in all studies. Verification bias occurs when results of the index test (CACS here) are used implicitly or explicitly to determine if a subject should have the reference test procedure (coronary arteriography). If so, estimates of sensitivity tend to be biased upward while estimates of specificity tend to be biased downward. However, verification bias does not affect positive and negative predictive values.⁹²

In a large number of studies, it was unclear whether CCA and CACS were performed independently of each other. Few authors specifically stated that the decision to perform one was independent of the decision to perform the other. Where independence could be reasonably inferred, credit was given for this, however, the potential for bias may still be present to the extent that the results of one test may have influenced the decision to perform the other. To the extent to which there is not independence and blinded interpretation, there is the potential for referral/verification bias which may lead to overestimation of test accuracy.

The definition of a “broad spectrum” of patients who are most likely to receive the test now or in the future would be a reflection of the fact that this is primarily a referral population with suspected CAD

While some studies explicitly stated that study design and data collection were prospective, for the largest proportion of studies, it was not clear if the study was prospective or retrospective and no credit for this criterion could be assigned. Most were presumably retrospective analyses even though some data may have been collected prospectively.

Author reporting of blinded interpretation of both tests was not consistent. Several studies indicated that blinded interpretation of one study was done, but did not report that the interpretation of the other study was done in a blinded fashion.

Two of the validation studies^{69, 83} also provided data validating other non-invasive tests versus conventional angiography in the same underlying population. Four studies which directly compared CACS using CT with other non-invasive tests are briefly described for context.^{91, 93-95} Findings from meta-analyses of other noninvasive tests compared with CCA are provided for context.

Reliability (reproducibility) studies

From a list of 21 studies which explicitly included wording related to reliability in the title and/or abstract, three explicitly stated that symptomatic clinical patients were evaluated were identified.^{86, 96, 97} These studies were moderate in quality (LoE II). In addition two LoE I/II validation study reported on reliability but did not provide adequate detail for determination of its quality as reliability study.

Safety

One study which modeled lifetime risk for radiation-induced cancer in asymptomatic persons was found and included for context.⁵ One systematic review⁹⁸ and two studies with patient populations that included symptomatic persons undergoing EBCT for calcium scoring were identified both of which were contained in the systematic review.^{35, 99} Two studies in asymptomatic persons referred for CACS as a screening test^{36, 100} and one small study in which it was unclear whether patients were symptomatic or asymptomatic¹⁰¹ were also identified. Information from these later three studies is provided for context.

Clinical decision making and patient outcomes

No studies were identified which explicitly compare a decision strategy which included CACS with an alternate decision strategy with out it were found. All were considered case series (LoE IV).

One study which describes the potential influence of CACS on referral for conventional cardiac catheterization was found.¹⁰² Five studies which described use of CACS as a possible triage test in an emergency department setting were identified.^{21, 103-106} These studies did not directly compare decisions based on CACS with a control group and are primarily case series, and thus a lower quality of evidence. It is not clear that actual decisions for discharge or further testing were actually made on the basis of the CACS.

Three studies looking at the ability of CACS to predict cardiac outcomes and mortality are briefly described.¹⁰⁷⁻¹⁰⁹ Although the studies are of good quality and adjust for base line risk factors and other potential confounders, details of patient treatment which may influence such outcomes are not evaluated. The extent to which CACS influenced decision making which might affect these outcomes is not presented. Thus, the extent to which CACS, or any given threshold, may influence treatment and patient outcomes is difficult to assess.

Special populations

Two studies provided data comparing CACS with angiography in diabetic patients were identified and included in the listing of validation studies above.^{70, 82} Both of these studies also included information on non-diabetic patients, but for one study Khaleel⁷⁰, there was overlap with a previously published study⁷⁷ so only the results for diabetic persons are used in this report.

Three (two LoE II, one LoE III) of the validation studies evaluated tests characteristics based on gender.^{68, 110, 111} Seven LoE I/II validation studies provided information on CACS with respect to age.^{66-69, 72, 74, 112}

Formal economic analyses

Two moderate quality full formal economic analyses^{113, 114} were identified. One poorer quality costing study was also found and is included for context.⁹⁵

2.4 Description of study population

Study populations in the validation studies were primarily those with symptoms of CAD. The overall prevalence of CAD determined by angiography ranged from 48.6% to 76.2%.

Table 6. Population characteristics of LoE I/II validation studies

Author (year)	Population	Inclusion criteria	Presenting symptoms
Leschka (2008)	N = 74 age: 62 (\pm 12) years (16-86) % male: 68	<ul style="list-style-type: none"> stable clinical conditions (CCS class I-II and New York Heart Association functional class I-III) 	<ul style="list-style-type: none"> typical angina (n = 40) atypical angina (n = 19) pathological exercise test (n = 12) dyspnea (n = 9)
Kajinami (1995)	N = 251 age: 56 (\pm 14) years % male: 69.3	<ul style="list-style-type: none"> elective coronary angiography between May 1991 and May 1993 chest pain on exertion or at rest or both suggesting angina pectoris ECG findings at rest that indicated possible myocardial ischemia 	NR
Nixdorff (2008)	<i>per-protocol</i> N = 71 age: 62 years % male: 59 <i>ITT</i> N = 79	<ul style="list-style-type: none"> elective coronary angiography due to symptoms suspicious of CAD primary diagnostic procedure, i.e. no previous MI, coronary intervention, or surgery 	NR
Becker (2007)	N = 1347 age: 60 (\pm 21) years % male: 59.6	NR	<ul style="list-style-type: none"> typical angina: 49% (n = 666) atypical angina: 35% (n = 470) exertional dyspnea: 13% (n = 175) heart failure: 3% (n = 40)
Lau (2005)	N = 50 age: 62 (\pm 11) years male: 62 years (37-78); female: 61 years (36-75) % male: 80	<ul style="list-style-type: none"> heart in sinus rhythm elective conventional coronary angiography for suspected CAD 	NR
Knez (2004)	N = 2115 age: 62 (\pm 19) years % male: 66.4	<ul style="list-style-type: none"> symptomatic referral by primary physician due to concern for possible presence of myocardial ischemia 	<ul style="list-style-type: none"> typical or atypical chest pain: 80% (n = 1697) exertional dyspnea: 12% (n = 258) heart failure: 8% (n = 160) abnormal stress test: 52% (n = 1391)
Budoff and Diamond (2002)	N = 1851 age: 58 (\pm 11) years (range, 21-86) % male: 63%	<ul style="list-style-type: none"> primary physician's concern for the presence of myocardial ischemia based on positive noninvasive stress testing, abnormal echocardiogram, or clinical history 	NR
Lamont (2002)	N = 153 age: 58 (\pm 9) years % male: 76	<ul style="list-style-type: none"> symptomatic patients with a positive treadmill stress test according to standard criteria who then underwent coronary angiography all referred by primary physicians to evaluate the possibility of an ischemic cause for the symptoms 	<ul style="list-style-type: none"> typical angina: 37% atypical angina: 39% possible non-cardiac: 24%
Leber (2001)	N = 93 age: 59 (\pm 9) years % male: 85	<ul style="list-style-type: none"> suspected CAD chest pain with an atypical pain character, an atypical pain localization, or an unusual trigger 	NR
Haberl (2001)	N = 1764 age: 20-80 years male: 56 \pm 14 years female: 60 \pm 16 years % male: 69	<ul style="list-style-type: none"> typical or atypical chest pain and/or signs of myocardial ischemia on noninvasive tests (bicycle stress test in most cases) clinical indication for cardiac catheterization 	<ul style="list-style-type: none"> "chest pain" compatible with angina: 65% abnormal stress test: 52% (460/920)
Kwok (2000)	N = 42 age: 55 (\pm 10) years % male: 79	<ul style="list-style-type: none"> recent MI, unstable angina pectoris, or positive stress test 	<ul style="list-style-type: none"> MI: 19% (n = 8) unstable angina: 40% (n = 17) chest pain + abnormal stress test: 40% (n = 17)

NR = not reported; BMI: body mass index; CAD: coronary artery disease; CCS: Canadian Cardiac Society; DM: diabetes mellitus; HTN: hypertension; ITT: intention-to-treat, IV: intravenous; LoE: level of evidence; MI: myocardial infarction.

2.5 Description of study outcomes

The primary outcomes of interest revolve around the performance characteristics of CACS, namely sensitivity, specificity and predictive values.

- Sensitivity is the percent of persons with the disease who test positive
- Specificity is the percent of persons who do not have the disease who test negative
- The positive predictive value (PPV) is the percent of persons with a positive test who have the disease
- The negative predictive value (NPV) is the percent of persons with a negative test who do not have the disease.
- The percent of persons who have a negative test but do have disease is calculated by taking $1 - \text{NPV}$.

For reliability studies, outcomes reported were degree of variation, intra-class correlation or Pearson correlation coefficient, Chronbach's alpha, and/or kappa.

Economic studies reported costs per correct diagnosis.

3. Results

3.1 Key question 1: What are the test characteristics, PPV (positive predictive value), NPV (negative predictive value), sensitivity and specificity, of coronary artery calcium scoring (CACS) compared with the reference standard of coronary angiography for the diagnosis of CAD or other established diagnostic tests for CAD. What is the evidence to describe the reliability (i.e., test-retest, intra-reader, inter-reader performance) of CACS?

Overview of validation findings

A total of 30 primary studies of accuracy and validity comparing CACS with CCA were identified. Of these, 11 studies⁶⁶⁻⁷⁶ were classified as LoE I or II, 8 as LoE III⁷⁷⁻⁸⁴ and 11 as LoE IV^{14, 85-91}. Results from the highest quality studies (LoE I/II) formed the primary focus for analysis. Additional information on all studies may be found in the appendices.

There is not a consensus in the literature with regard to specific thresholds or cut points for what would constitute a positive versus a negative CACS test. The following thresholds were chosen for analysis: $\text{CACS} > 0$, ≥ 100 and ≥ 400 . These were chosen for primary meta-analysis following consultation with a clinical expert and are based on the premise that a score of 0 might be used to "rule out" significant CAD and a score of ≥ 400 might signal the need for additional evaluation as described in the 2006 AHA scientific statement,² the ACCF/AHA consensus document¹ and a recent meta-analysis.⁶¹

Based on information from the highest quality (LoE I/II) studies, comparison of these CACS thresholds with an angiographic threshold of $\geq 50\%$ vessel narrowing for obstructive CAD as the reference standard, these data suggests that:

- A CACS > 0 is highly sensitive (99% , CI = 98% - 99%) for detecting the presence of obstructive CAD, however 5% of persons (1 – negative predictive value) with a negative test would have CAD based on pooled estimates from seven studies with a total of N = 7354 patients. Approximately 35% (specificity) of persons without CAD might avoid unnecessary angiography or additional tests.
- Higher thresholds for CACS of ≥ 100 and ≥ 400 lowered the sensitivity (to 85% and 78% respectively) but improve the specificity (77% and 83%, respectively). Clear decisions may not be possible based on CACS when using these thresholds to define a positive test.

Although it appears that these higher quality studies followed protocols for blinded interpretation of the CACS and angiography and that the two tests were administered independent of the results of one another, these were not uniformly well stated.

The overall prevalence of CAD determined by angiography ranged from 48.6% to 76.2% across the studies used for meta-analysis. The extent to which this prevalence is characteristic of populations who would be referred for CACS as a triage test prior to angiography is not clear. While the sensitivity and specificity are generally not influenced by prevalence, the predictive values are.

Detailed results-validation studies

Patients included in the LoE I/II studies were characterized as symptomatic and/or were referred for CCA for clinical indications. An overview of patient characteristics is provided in the previous section. Not all studies provided data sufficient for meta-analysis at the cut points selected.

Meta-analysis was conducted on the primary validation parameters when data on true positive, true negative, false positive and false negative test results from three or more LoE I-II studies were available or could be calculated from author's report for the above thresholds. Not all studies reported data at these levels. All studies in these analyses used a CCA threshold of $\geq 50\%$ reduction in luminal diameter for present of obstructive CAD. Please see the appendices for summary ROC curves.

CACS > 0

One proposed application of CACS is to use a threshold of 0 to rule out significant CAD.

Data were available from seven LoE I/II studies (a total of 7354 patients) which defined a positive test based on detection of any calcium, i.e. a threshold of > 0 . The table below describes the prevalence of obstructive CAD and CACS test results based on the presence of calcium. The Lamont study included only patients who had positive treadmill stress test, which may account for the higher prevalence of CAD.

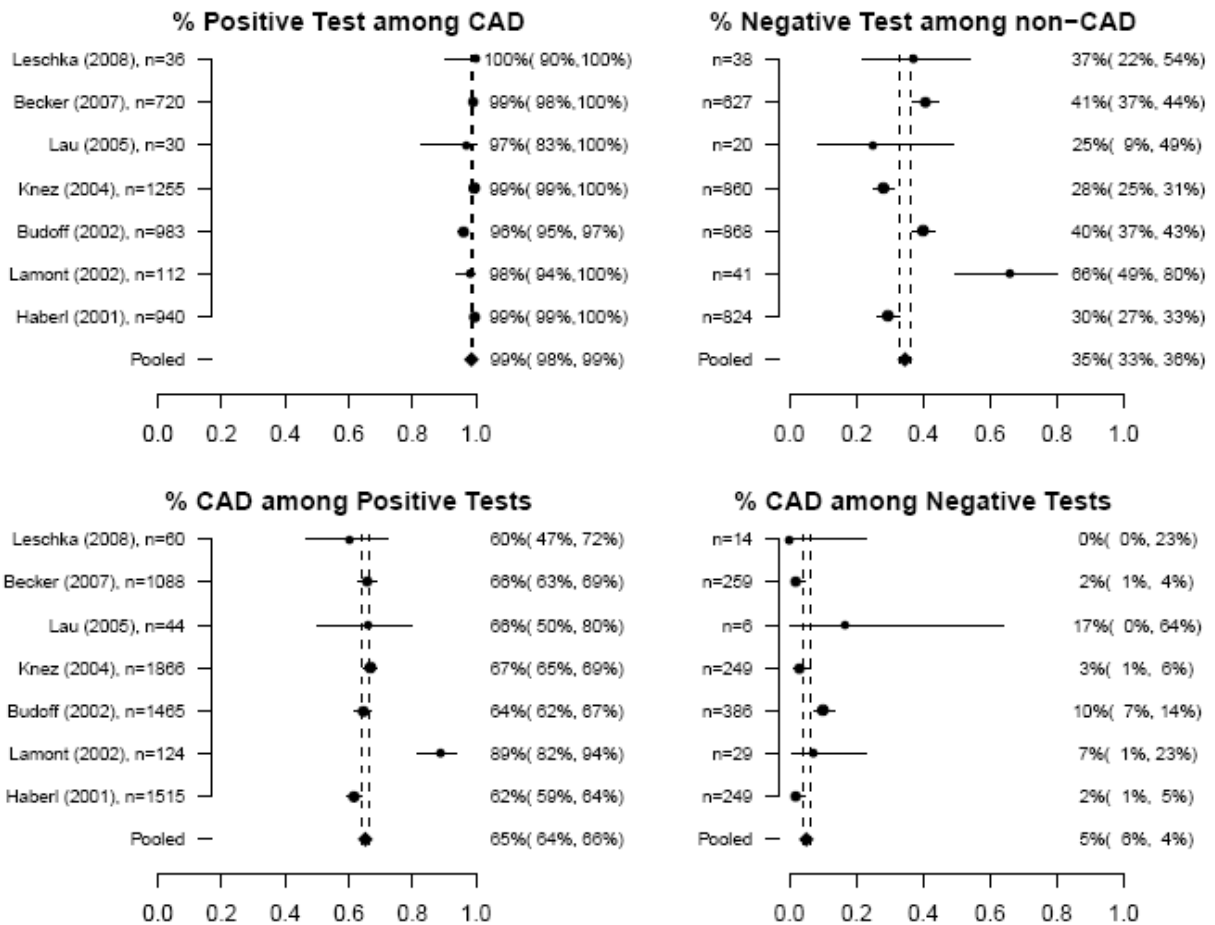
Summary test results for LoE I/II studies reporting data for CACS > 0

Author	Total N	TP, n	TN, n	FP, n	FN, n	CAD, n	CAD, %	LoE
Leschka (2008)	74	36	14	24	0	36	48.6	I
Becker (2007)	1347	715	254	373	5	720	53	II
Lau (2005)	50	29	5	15	1	30	60	II
Knez (2004)	2115	1247	241	619	8	1255	59.3	II
Budoff (2002)	1851	944	347	521	39	983	53	II
Lamont (2002)	153	110	27	14	2	112	73.2	II
Haberl (2001)	1764	935	244	580	5	940	53.3	II

CAD = coronary artery disease; FN = false negative; FP = false positive; TN = true negative; TP = true positive; LoE = Level of evidence

A summary of meta-analysis results for sensitivity, specificity, positive predictive value and 1-negative predictive value for these studies is found in Figure 3. The point estimates and 95% confidence intervals for individual studies and for the pooled estimate are given.

Figure 3. Meta-analysis of test characteristics* for LoE I/II studies reporting data for a CACS threshold of > 0 as a positive test.



*Test characteristics presented:

Upper left panel: sensitivity = % of patients with the disease who test positive

Upper right panel: specificity = % of patients who do not have disease who test negative

Lower left panel: positive predictive value (PPV) = % of patients with a positive test who have the disease

Lower right pane: 1 – negative predictive value (NPV). The negative predictive value is the % of patients with a negative test who do not have the disease so 1- NPV is the percent of patients with a negative test who do have the disease.

The sample size n refers to numbers of subjects in the denominator, that is, subjects with CAD in upper left, without CAD in upper right, with positive tests in lower left, and with negative tests in lower right.

Overall, a CACS score > 0 appears to be sensitive (99%) for detection of CAD, but the specificity is low. An estimated 5% of CAD cases would be missed based on the pooled estimate for 1-negative predictive values shown on the lower right panel of the figure.

The upper left panel shows the sensitivity of $CACS > 0$ as a test for the presence of obstructive CAD. The pooled sensitivity estimate is 99% with the 95% confidence interval of 98% -99%. This indicates that almost all subjects with coronary artery disease score positive on the coronary calcium test at this threshold. There is little variability in the estimates across studies.

If one use of CACS as a diagnostic test is to triage patients as candidates for conventional coronary angiography or further testing, approximately 35% of persons without CAD might avoid unnecessary angiography or additional tests based on a CACS of > 0 (specificity), however, 65% of persons without CAD would be subjected to additional testing unnecessarily (1-specificity). This pooled specificity estimate of 35% (CI = 33%, 36%) is low and variability across studies is noted.

On average, 65% of subjects (95% CI = 64%-66%) with a positive test at this threshold were found to have CAD by conventional angiography (positive predictive value) as see on the lower left panel of the above figure.

However, 5% (95% CI 4%, - 6%) of persons (1 - negative predictive value) with a negative CACS would have CAD, based on pooled estimates from the seven studies, demonstrated in the lower right panel. Missing 5% of patients with CAD may not be acceptable in a clinical setting.

The data were examined for heterogeneity across studies and statistically significant heterogeneity with standard G-squared statistics¹¹⁵ for all four analyses was seen. Nevertheless, the pooled estimates seem to provide good summaries of test performance as most of the estimates from the individual studies are reasonably close to the pooled value. Large sample sizes, as were employed in several of the studies, can make small differences statistically significant. As part of the exploration of heterogeneity, analyses were repeated without the Lamont study. This study population had a higher prevalence of CAD and estimates of specificity and positive predictive value were dissimilar to estimates from the other studies. Repeating the analysis without this study had little effect on the pooled estimates: Sensitivity = 99%, specificity = 34%, positive predictive value = 65%, 1-negative predictive value = 5%.

CACS ≥ 100

Data were available from 5 LoE I/II studies representing a total of 7119 patients which defined a positive test based on a threshold of ≥ 100 . The table below describes the prevalence of obstructive CAD and CACS test results based on this threshold. The prevalence of CAD in the study by Kwok, et al was much higher than the others.

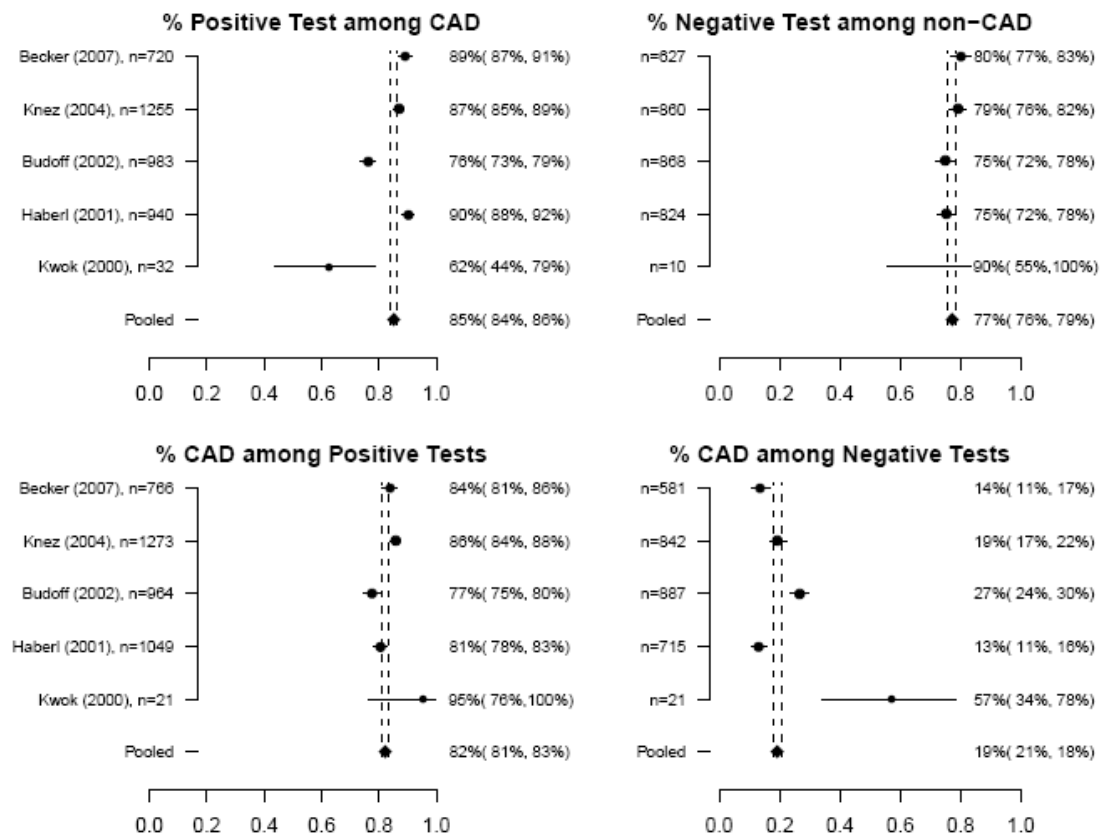
Summary of test results at CACS threshold ≥ 100 .

Author	Total N	TP, n	TN, n	FP, n	FN, n	CAD, n	CAD, %	LoE
Becker (2007)	1347	641	502	125	79	720	53	II
Knez (2004)	2115	1092	679	181	163	1255	59.3	II
Budoff (2002)	1851	747	651	217	236	983	53	II
Haberl (2001)	1764	846	621	203	94	940	53.3	II
Kwok (2000)	42	20	9	1	12	32	76.2	II

CAD = coronary artery disease; FN = false negative; FP = false positive; TN = true negative; TP = true positive; LoE = Level of evidence

A summary of meta-analysis results for the same CACS test parameters using a threshold of 100 is seen in Figure 4.

Figure 4. Meta-analysis of test characteristics* for LoE I/II studies reporting data for a CACS threshold of ≥ 100 as a positive test.



*Test characteristics presented:

Upper left panel: sensitivity = % of patients with the disease who test positive

Upper right panel: specificity = % of patients who do not have disease who test negative

Lower left panel: positive predictive value (PPV) = % of patients with a positive test who have the disease

Lower right panel: 1 - negative predictive value (NPV). The negative predictive value is the % of patients with a negative test who do not have the disease so 1 - NPV is the percent of patients with a negative test who do have the disease.

The sample size n refers to numbers of subjects in the denominator, that is subjects with CAD in upper left, without CAD in upper right, with positive tests in lower left, and with negative tests in lower right.

Using a CACS of ≥ 100 implies that fewer persons with CAD are detected than at the 0 cutoff (sensitivity), (85% rather than 99%), but it also increases substantially the number of persons without CAD who test negative (specificity) (77% versus 35%). In terms of decision making for individuals, a negative test at the CACS 100 cutoff does not imply that the subject is without CAD. Approximately 19% of subjects who test negative with CACS were found to have CAD (1-negative predictive value).

On average, 82% of persons with positive tests at the 100 CACS cutoff had CAD (positive predictive value). When analyses were repeated excluding the Kwok study, which had a population with higher CAD prevalence, pooled estimates were unchanged as the sample size of that study was very small relative to the others.

Again, although statistically heterogeneity was seen in these analyses, the consistency of individual study estimates with the pooled value for most studies suggests that the pooled estimates provide a reasonable summary.

CACS ≥ 400

Data were available from 3 LoE I/II studies which defined a positive test based on a CACS threshold of ≥ 400 representing a total of 195 patients. The table below describes the prevalence of obstructive CAD and CACS test results based on this threshold.

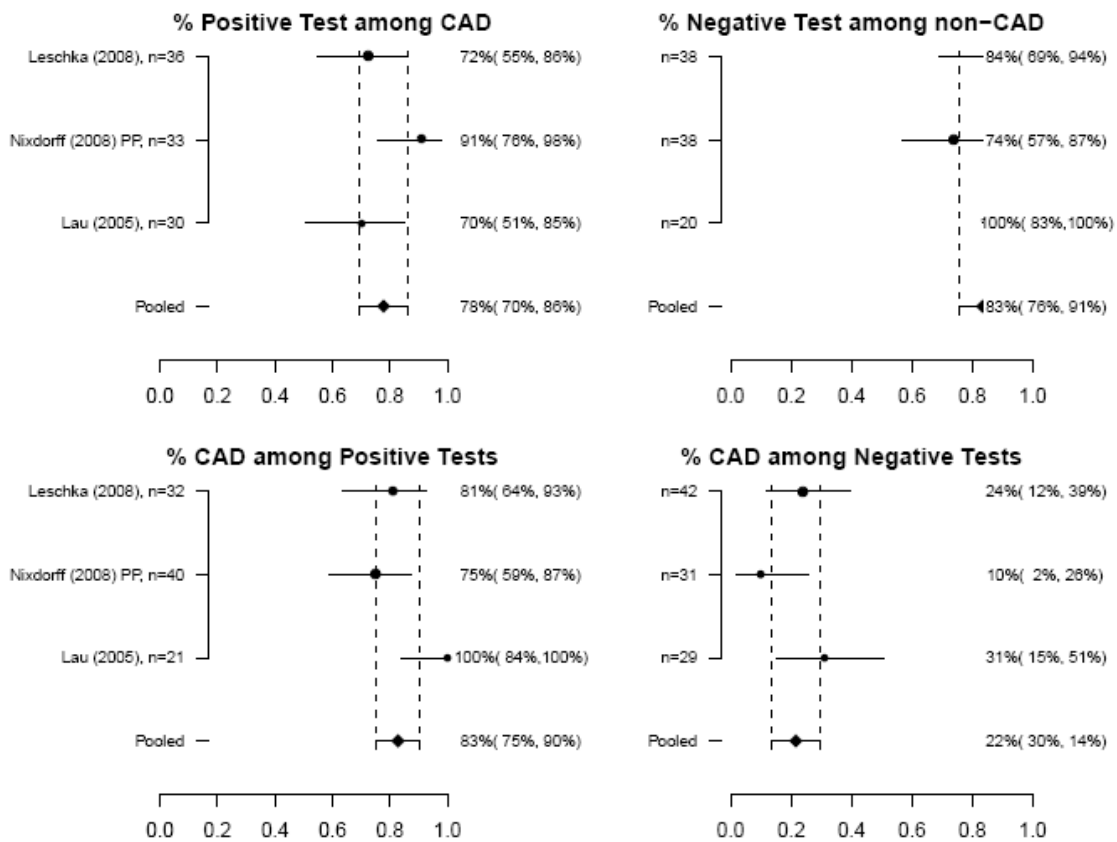
Summary of test results at CACS threshold ≥ 400 .

Author	Total N	TP, n	TN, n	FP, n	FN, n	CAD, n	CAD, %	LoE
Leschka (2008)	74	26	32	6	10	36	48.6	I
Nixdorff (2008) "per-protocol"	71	30	28	10	3	33	46	II
Lau (2005)	50	21	20	0	9	30	60	II

*the "per protocol" analysis reported appears to be based on the number of interpretable studies
CAD = coronary artery disease; FN = false negative; FP = false positive; TN = true negative; TP = true positive; LoE = Level of evidence

A summary of meta-analysis results for the same CACS test parameters using a threshold of 400 is given in the Figure 5. The point estimates and 95% confidence intervals for individual studies and for the pooled estimate are given.

Figure 5. Meta-analysis of test characteristics* for LoE I/II studies reporting data for a CACS threshold of ≥ 400 as a positive test.



*Test characteristics presented:

Upper left panel: sensitivity = % of patients with the disease who test positive

Upper right panel: specificity = % of patients who do not have disease who test negative

Lower left panel: positive predictive value (PPV) = % of patients with a positive test who have the disease

Lower right pane: 1 – negative predictive value (NPV). The negative predictive value is the % of patients with a negative test who do not have the disease so 1- NPV is the percent of patients with a negative test who do have the disease.

The sample size n refers to numbers of subjects in the denominator, that is subjects with CAD in upper left, without CAD in upper right, with positive tests in lower left, and with negative tests in lower right.

The sample sizes were comparatively small in the 3 studies that used 400 as a cutoff to define a positive test. Therefore confidence intervals for the pooled estimates of test performance are wide. As expected, the specificity estimate using the 400 CACS cutoff is even higher than at 100 (83% versus 77%), but the uncertainty is considerable and the actual specificity may be as low as 76%. Moreover, even if the estimated values of 83% for specificity and 78% for sensitivity are correct, these may not be high enough to use the test for “ruling in disease”. The extent to which they may assist with referring persons on to the next level of testing is also not clear.

Looking at predictive values, between 10% and 25% of persons who test positive do not have CAD (1-positive predictive value) while 14%-30% of those testing negative have CAD (1-negative predictive value). So again, clear decisions are not possible based on CACS when using the 400 threshold value to define a positive test.

Other thresholds

A number of LoE I/II studies had data for other CACS thresholds as seen in the following table. The pattern of higher sensitivity (> 90%) is seen for thresholds up to 50.

Table 7. Summary of test characteristics at alternate thresholds

Author	Total N	CACS Cut-off	TP, n	TN, n	FP, n	FN, n	CAD, %	Sens	Spec	PPV	NPV
Becker (2007)	1347	>10	698	408	219	22	53.0	97%	65%	76%	95%
Knez (2004)*	2115	> 10	1180	602	258	75	59.3	94%	70%	82%	89%
Budoff (2002)	1851	> 20	885	503	365	98	53.0	90%	58%	71%	84%
Haberl (2001)	1764	≥ 20	914	531	293	26	53.3	97%	64%	76%	95%
Leber (2001)	93	> 46	40	27	22	4	47.3	91%	55%	65%	87%
Lau (2005)	50	≥ 50	27	11	9	3	60.0	90%	55%	75%	79%
Budoff (2002)	1851	> 80	777	625	243	206	53.0	79%	72%	76%	75%
Leber (2001)	93	≥ 130	35	35	14	9	47.3	80%	71%	71%	80%
Kwok (2000)	42	≥ 160	16	9	1	16	76.2	50%	90%	94%	36%
Leber (2001)	93	> 310	25	43	6	19	47.3	57%	88%	81%	69%

*based on volumetric score; CAD = coronary artery disease; FN = false negative; FP = false positive; TN = true negative; TP = true positive; Sens = sensitivity; Spec = specificity; PPV = positive predictive value; NPV = negative predictive value

LoE III validations studies

Seven LoE III studies had sufficient data for meta-analysis comparing a CACS threshold of > 0 with the referent standard of angiography (≥ 50% vessel narrowing).^{77-79, 82-84} Additional information is found in the appendices.

In five of the 6 LoE III studies used in the meta-analysis, blinded interpretation of the CACS and angiograms was reported. In these studies, however, it was not clear that the decision to perform the test and the referent was independent. In one study only 71% of persons who had CACS also had angiography.⁷⁸ These factors increase the potential for bias. One study which used an angiographic threshold of ≥ 75% was not included in the meta-analysis.⁸¹ Additional meta-analysis information for LoE III studies is in Appendix E.

Table 8. The LoE III studies for which data at CACS > 0 were available are listed below.

Author	Total N	TP, n	TN, n	FP, n	FN, n	CAD, n	% CAD
Hosoi (2002)	181	95	26	41	6	114	63
Chen (2001)	116	63	23	29	1	64	55.2
Shavelle (2000)	97	66	14	16	3	69	71
Budoff (1996)	710	404	124	159	23	427	60
Tannenbaum (1989)	54	38	11	0	5	43	80
Herzog (2004)*	38	17	4	16	1	18	47
Fallavollita (1994)	212	100	42	52	18	118	56%

*Used angiographic cut off of ≥ 75% and was not included in meta-analysis

CAD = coronary artery disease; FN = false negative; FP = false positive; TN = true negative; TP = true positive;

Pooled estimates and 95% confidence intervals for test parameters from the LoE III studies are compared with those from LoE I/II studies as follows:

	LoE III studies	LoE I or II studies
Sensitivity	93% (92, 95%)	99 % (98%, 99%)
Specificity	44% (40, 48%)	35% (33%, 36%)
Positive predictive value	71% (69%, 74%)	65% (63%, 66%)
1 – negative predictive value	19% (15%, 23%)	5% (4%, 6%)

The pooled sensitivity estimate for the lower quality studies is somewhat lower compared with the LoE I/II studies and the specificities somewhat higher. The prevalence of angiographically detected CAD in the LoE III studies ranged from 47% to 88% and most had higher prevalence than did the LoE I/II studies. This may partially explain the differences in predictive values.

Only one LoE III study with 181 persons without diabetes provided data using thresholds of 100 and 400 and compared CACS with an angiographic cut off of $\geq 50\%$ luminal narrowing. [Hosoi] The prevalence of CAD was 63%. Test characteristic estimates (95% CI) for CACS of 100 and 400 respectively were:

- Sensitivity: 66% (56%, 74%) and 43% (34%, 53%)
- Specificity: 83% (74%, 92%) and 97% (92%, 100%)
- PPV: 87.2% (80.2%, 94.3%) and 96.2% (90.9%, 100%)
- 1 – negative predictive value: 41.1% (31.2%, 50.9) and 49.6% (41.0%, 58.2)

General findings from LoE IV studies can be found in Appendix F.

Comparison with other diagnostic tests

The validation studies included in this technology assessment used coronary angiography as the reference standard. Since CACS is noninvasive test, it may be helpful to compare its performance characteristics with other non-invasive tests. Since these are not the appropriate reference standard, test characteristics are not reported for comparisons of CACS with them. These other noninvasive tests reflect cardiac physiology and function.⁷⁷ Such noninvasive tests include those that use exercise or drugs (such as dobutamine) to stress the heart to evaluate myocardial function and the extent to which it may have been compromised by obstructed coronary artery blood flow. By contrast, CACS provides anatomic information about calcium amount and distribution, thus, the basis for CACS is different than that for other noninvasive tests. Aspects of cardiac function may be assessed by ETT, echocardiography, or imaging radionuclide tracers. The information in this section is presented to provide context regarding these tests.

Test performance characteristics reported in meta-analyses comparing exercise stress testing (ETT, echocardiography or nuclear perfusion) with angiography are briefly summarized below. For comparison, pooled estimates from the meta-analysis presented for LoE I and II studies in this technology assessment are also listed.

Study	Noninvasive test	Sensitivity	Specificity
Gianrossi ¹¹ (N =24,074 patients; 141 studies)	Exercise ECG	68% (range 23% - 100%)	77% (range 17% - 100%)
Fleischmann ¹¹⁶ (N = 2637; 24 articles*)	Exercise Echo	85% (95% CI 83%, 87%)	77% (95% CI 74%, 80%)
Fleischmann ¹¹⁶ (N = 2637patients; 27 articles*)	Exercise SPECT	87% 95% CI 86, 88)	64% (95% CI 60%, 68%)
Present Spectrum Research HTA (N = 7354 patients; 7 studies)	CT CACS score > 0	99% (95% CI 98%, 99%)	35% (95% CI 33%, 36%)
	(N = 7119 patients; 5 studies)	score ≥ 100	85% (95% CI 84%, 86%)
	(N = 195 patients ; 3 studies)	score ≥ 400	78% (95% CI 86%, 70%)
			83% (95% CI 76%, 91%)

* not unique patient data sets

Two validation studies (one LoE I and the other LoE III) included in this HTA also compared other non-invasive tests to angiography in the same patient population as that used for assessing CACS.^{69, 83} As opposed to studies comparing an individual non-invasive test to angiography, different patient characteristics cannot explain differences between test performance measures. A summary of test performance characteristics for CACS and other noninvasive tests compared with angiography in the same patient population is provided below.

	Sensitivity %	Specificity %	PPV %	NPV %
Kajinami 1995 (LoE I)				
Thallium exercise	83	60	70	76
Stress echo	74	73	77	72
CT calcium score > 19	77	86	86	76
Shavelle 2000 (LoE III)				
Treadmill-ECG	76	60	81	53
Technetium exercise	78	67	83	57
CT calcium score > 0	96	47	80	82
Calcium score > 0 and abnormal treadmill-ECG	72	83	91	57

NPV is negative predictive value; PPV is positive predictive value

Four studies which compared CACS directly with other noninvasive tests were identified and varied in quality.^{91, 93-95} Findings from these other tests at various CACS thresholds are presented below:

Study	Population	Comparison	Ca score cut-off	Findings from comparison test
Janssen 2005	114 outpatients with chest pain and inconclusive clinical findings, rest ECG, and exercise ECG test	Dobutamine magnetic resonance imaging	< 11 and <100 vs ≥ 100	n = 29 patients with CACS <11 • none of the 29 had an abnormal stress MRI n = 46 at CACS < 100 • # with abnormal stress MRI test n = 68 at CACS ≥ 100 • 20 with abnormal stress MRI test
Nishida 2005	83 patients suspected of having ischemic heart disease	Thallium exercise stress test	0 vs. > 0	n = 42 patients with CACS = 0 • 12 had an abnormal thallium scan n = 41 patients with CACS > 0 • 23 had an abnormal thallium scan
Raggi 2000	207 patients with chest discomfort	Exercise treadmill test	0 vs. >0 and <150 vs ≥ 150	n = 82 patients with CACS = 0 • 7 had a positive treadmill test • 23 had an equivocal treadmill test n = 172 patients with CACS <150 • 16 had a positive treadmill test • 52 had an equivocal treadmill test n = 25 patients with CACS ≥ 150 • 4 had a positive treadmill test • 11 had an equivocal treadmill test
Yao 2004	73 clinically stable patients suspected of having coronary artery disease, no history of MI; only 30 had chest pain	Technetium SPECT	0 vs. >0	n = 29 patients with CACS = 0 • 7 had an abnormal SPECT n = 44 patients with CACS > 0 • 24 had an abnormal SPECT

Reproducibility, reliability

Studies in symptomatic patients that evaluated reliability for total calcium scores for patients (versus by vessel or segment) were sought. Since the scoring method described by Agatston in 1990 is the most widely used and reported in the validation literature, only those studies that evaluated the reproducibility of this method were included. Studies comparing slice thickness, contiguous versus overlapping methods, different software or assessment protocols were excluded.

Use of symptomatic subjects was apparent in only three studies of reliability.^{86, 96, 97} In an examination of eleven LoE I and II validation studies, two studies provided limited information on reliability.^{73, 75} The overall quality of reliability studies of CACS in symptomatic patients was moderately high; all were LoE II.

Assessment of level of evidence (LoE) for reliability studies on coronary artery calcium scoring (CACS)

Methodological Principle	Broderick (1996)	Möhlenkamp (2001)	Serafin (2009)
Broad spectrum of patients with expected condition		■	
Adequate description of methods for replication	■	■	■
Blinded comparison of tests/interpretations	■		■
Evidence Level	II	II	II

Evidence from reliability studies in symptomatic subjects suggests that calcium scoring has moderate to good reproducibility in test-retest studies and high interobserver agreement in an inter-rater study.^{86, 96, 97} Two LoE I or II validation studies reported moderate to excellent interobserver agreement between raters but did not provide detail of study design regarding reliability evaluation.^{73, 75}

Methods for determining Agatston score reliability were:

- **Intraclass correlation coefficient:** assesses the consistency of measures made by multiple observers measuring the same quantity. Higher values indicate good consistency of measures, with a maximum value of 1.0.
- **Variability of Agatston score:** indicates the relative difference between scores of two tests in a test-retest study [Bland]. Lower values indicate less variability (more reproducibility) in the scoring of the two tests. The calculation is:

$$\frac{|\text{score from scan 1} - \text{score from scan 2}|}{\text{Average score from both scans}} * 100$$

Table 9. Overview of primary findings for reliability studies on coronary artery calcium scoring (CACS).

Author (year)	Type of study	Calcium score	Measure of reliability	LoE
Broderick (1996) N = 101	Test-retest Inter-rater	NR	Intraclass correlation coefficient = 0.90 (test-retest), 0.99 (inter-rater)	II
Möhlenkamp (2001) N = 50	Test-retest	NR	Variability of Agatston score = 21.8% (mean), 19.2% (median)	II
Serafin (2009) N = 50	Test-retest	Median = 511.3	Variability of Agatston score = 3.9% (median)*	II
Leschka (2008)	Inter-rater	Mean = 720 ± 968 (0 – 4387)	kappa = 0.84	*
Lau (2005)	Inter-rater	NR	Intraclass correlation coefficient = 1.00	*

* Leschka and Lau are LoE I/II validation studies which also reported reliability information. Since they did not describe how reliability was evaluated, it is not possible to provide a LoE determination for this.

In the three studies in which it was clear that symptomatic persons were enrolled, the test-retest reliability was moderate. Various methods were used to evaluate this.

- The reproducibility of the total calcium score as measured by the intraclass correlation coefficient was good (0.90), however this measurement applied only to 17 subjects⁸⁶ based on method and algorithm that mimics the Agatston method for calcium scoring.
- Another study reported that 86% with a CACS = 0 in one scan also had a score of 0 zero in the second. Moderate variability in the calcium score from test to retest (21.8%, 19.2% for the mean and median calcium score, respectively), which decreased with increasing amounts of calcium was reported in another study.⁹⁶ However, the area score exhibited lower variability than the calcium score and also decreased with increasing amounts of calcium. The definition of “moderate variability” was not provided.

Evidence from three studies suggests moderate to high inter-observer agreement between raters of calcium scores.

- Interobserver agreement of two raters as measured by the intraclass correlation coefficient was high (0.99).⁸⁶
- Moderate interobserver agreement (0.84) as measured by the kappa statistic was found in a study that focused on the validation of calcium scoring and computed tomography coronary angiography compared to conventional coronary angiography.⁷⁵
- Excellent interobserver agreement (1.00) as measured by the intraclass correlation coefficient was found in a study that focused on the validation of calcium scoring and CT angiography compared with conventional angiography.⁷³

Factors that might influence reproducibility of calcium scoring include image noise, the number of images acquired, lesion size, overall extent of calcium, motion artifacts and ECG gating, mistrigging, arrhythmia, table movement, patient movement, breathing, and heart rate.

3.2 Key question 2: What is the evidence related to the safety of CACS

The two primary safety issues related to CACS are radiation exposure and the observation and evaluation of incidental findings. Unlike coronary computed tomography angiography, CT calcium scoring does not require a contrast agent, and so avoids the risks of contrast reactions and drug-induced nephropathy.

Radiation exposure

The main safety concern regarding calcium scoring by CT is that it exposes the patient to low to moderate levels of ionizing radiation, which may increase the life-time risk of cancer. To the extent that CACS reduces the need for conventional angiography, exposure might be reduced. To the extent that CACS results in the need for additional testing, it may be increased. To date, no large-scale epidemiologic studies evaluating cancer risk associated with CT in general have been published. A recently published study estimated risks related to CACS based on radiation risk models for cancer incidence.⁵ There is uncertainty and controversy with regard to the actual risk of low dose radiation. Quantification of risk specific to CACS for an individual patient is not possible.

The American College of Radiology's (ACR) 2008 Appropriateness Criteria on the evaluation of chronic chest pain in patients with a low to intermediate probability of CAD lists the relative radiation level of CACS as medium, between 1-10 mSv. In clinical decision making, this level of exposure needs to be put in the context of other tests which also may involve radiation that may be part of the clinical pathway, as the possible cumulative effects of multiple procedures are of concern.

The term radiation exposure may refer to the measurable quantity of ionizing events in air that are produced by x-rays. By contrast, radiation dose describes the quantity of radiation energy deposited in a person as a result of the exposure. Radiation dose may be expressed as the “equivalent effective dose” in units of Sieverts (SV) or milli-Seiverts (mSv). It is typically calculated or modeled based on estimates of energy absorption per body mass unit (e.g. kilograms of body weight) and other factors. While it does not represent the dose received by an individual patient, it does provide a common metric by which different sources of radiation might be compared.³¹

To provide some context, estimates of typical effective dose for environmental and medical sources of radiation are outlined below. Some radiation exposure occurs naturally and during activities of daily living. As seen below, estimated dose for CACS ranges from 0.7 mSv to 12 mSv, based on information from various sources. Estimates include EBCT and MDCT and data may combine prospectively triggered and retrospective gating.

Table 10. Overview of typical effective dose for various radiation sources

Exposure type	Typical effective dose (millisieverts)
Environmental Exposures	
Natural source (average US per year)	3
Round trip cross-country air flight	0.02-0.05
Nuclear power plant worker	3
Exposures from diagnostic radiology	
Dental X-ray	0.005
Chest Xray (PA and lateral)	0.1
Cervical spine X-ray	0.2
Mammogram	0.4
Lumbar spine X-ray	1.5
Head CT	2
CT calcium scoring	3
Range found in validation studies in this report*	(1.2 —10)
Range found in literature 1980-2007 [Mettler]	(1—12)
Range reported in 2006 AHA Statement [Budoff]	(0.7 – 1.9)
Interventional coronary angiography	7
Barium enema with fluoroscopy	8
Virtual colonoscopy	10
Chest CT for pulmonary embolism	15
CT coronary angiography	16

*A list of studies and reported exposures is found in the appendices
Compiled from Mettler 2008; FDA—What are the radiation risks; FDA—Quantities and units; NRC; DOE; Budoff 2006^{2, 30, 117, 118}

The extent to which levels of radiation used for medical procedures increase cancer is unclear. Most data are from the atomic bombing of Japan and nuclear accidents, with risk estimates for low dose exposure extrapolated back from risks for those high dose exposures. Extrapolation of these results to lower doses used in medical imaging is the subject of much controversy. However, data are also available from Japanese who received low doses from the atomic bombs and from people who receive low doses during occupational exposure.^{5, 117, 119}

Two different hypotheses have been advanced for evaluating potential risk for cancer at low radiation doses. The linear quadratic approach states that malignancy risk is so low at low radiation doses that it is nearly impossible to quantify but that there is quadratic increase in risk with increasing dose. The *linear no-threshold hypothesis* implies that extrapolation of malignancy risk at high doses is reasonable to situations with low doses. It states that there is no threshold below which radiation cannot cause malignancy and that the risk increases linearly with increasing dose.³³ This latter approach is more conservative and is the one generally followed. Current guidance from regulatory bodies is that no threshold exists and that exposure should be kept as low as reasonably achievable (ALARA).

In the US, 1 in 5 people will die from cancer. A CT exam delivering a radiation dose of 10 mSv may increase that risk by 1 in 2000, or by 0.05%, based on estimates extrapolated from A-bomb survivors. For comparison, approximately 400 out of 2,000 individuals are expected to develop cancer from all other sources combined.¹¹⁷ While the increased risk for an individual may be considered low, the potential increased risk for the entire population creates many more cases of fatal cancer, especially as the use of CT scans expands. At the rate of CT use from 1991-1996, about 0.4% of all cancers in the US might have been due to radiation exposure during CT scans. By 2006, 1.5 to 2.0% of cancers in the US might have been due to radiation exposure during CT scans.³⁴ Also, as CT scans are being used for younger patients and as life expectancy increases, there are longer life spans during which CT scans might induce cancer.³⁴

The radiation exposure reported during calcium scoring varies more than 10-fold.^{5, 29, 30} Several factors influence the radiation exposure; the model of the CT scanner, the scan mode (e.g., axial or spiral), the voltage and current used, the number of scans, the scan pitch (the overlap between CT slices), the slice thickness, ECG triggering or gating, scanning time, the length of the patient's body that is scanned, and the patient's size. Multi-detector CT gives more radiation exposure than electron beam CT. Higher radiation doses and longer times result in higher exposure. With ECG gating, the CT beam is on taking an image only at a specific point in each cardiac cycle to avoid variation caused by cardiac motion. However, with retrospective gating, the CT beam is on, taking images throughout the cardiac cycle; images at the same points in the cardiac cycles are recreated later. While it allows the person interpreting the scans greater flexibility, retrospective gating gives more radiation exposure than prospective gating. Smaller patients received higher doses because they have less tissue to attenuate radiation. Some factors influence the quality of the images obtained, and the need for

good-quality images must be balanced against the need to minimize radiation exposure.^{2, 5, 34}

To reduce radiation exposure during calcium scoring by CT, the American Heart Association recommends using prospective ECG gating, slice widths of 2.5 to 3 mm, and radiation doses adjusted for body size.² As the technology and techniques improve, radiation exposure could decrease. In reviewing literature published between 1980 and 2007, Mettler et al found a typical radiation exposure of 3 mSv with a range of 1.0 to 12 mSv during calcium scoring.²⁹ However, using equipment, software, and protocols that were up-to-date in 2003, Hunold reported radiation exposures during calcium scoring using electron beam CT of 1.0 mSv for men and 1.3 for women; and using different multi-detector CTs, 1.5 – 5.2 mSV for men and 1.8– 6.2 mSv for women based on measurements from an anthropomorphic phantom.¹²⁰ A recent AHA scientific advisory suggests that with prospective gating, the effective dose is estimated at 1 mSV and gives a range of 0.7 – 1.9 mSV.²

A recent simulation estimating radiation dose and cancer risk suggests that a single scan for CACS may increase lifetime cancer risk.⁵ The authors used a Monte-Carlo simulation based on protocols from three clinical settings and risk models derived from Japanese atomic bomb survivors and medically exposed cohorts. While their model was for screening of asymptomatic persons, it may be reasonable to consider their results for a single CACS determination as applicable to a diagnostic scan in symptomatic patients. A single screening test at age 40 would increase the risk of cancer by 9 per 100,000 for men and 28 per 100,000 for women. For a single screen at 55 years of age, based on a median effective dose of 2.3 mSv, site specific estimates for life-time risk of radiation induced cancer suggest that most cases would be lung cancer (6/100,000 in men, 14/100,000 in women) or breast cancer (4/100,000 in women). Risks are higher for women than for men because of the radiation dose to breast tissue.

The ACR document rates the relative radiation level for CT angiography of the coronary arteries as high. The ACR range for high relative radiation level is 10-100 mSv and CT angiography is at the lower end of that range (2.0 mSV – 16.0 mSv). However, to the extent that CACS would become a routine part of CT angiography, there is the potential for greater radiation exposure in part due to the shift from EBCT to multi-detector CT.

There is potential for increased risk secondary to radiation exposure in general based studies of the atomic bombing of Japan, nuclear accidents and occupational exposures. Quantifying the explicit risk for a specific test like CACS either alone or combination with other tests involving radiation is not possible. While simulation and modeling of the effects of radiation exposure provide important insights into the possible changes in risks, verification with epidemiologic studies presents challenges since many factors which may influence development of malignancy need to be considered such as time for development, presence of additional risk factors and other exposures. The true attributable risk from radiation-based diagnostic tests may be difficult to determine. Some experts consider the potential for harm from radiation exposure to be clinically significant particularly given that patients may be likely to have additional tests using radiation. Decision making between physician and patient should involve a discussion of

the possible risks and potential benefits of CACS (and subsequent testing). Final determination of net benefit for a given clinical scenario reflects the values and judgments of the persons making the decisions.

Incidental findings

Abnormalities may be identified that are unrelated to the reason for getting the imaging study. During the CT scan for calcium scoring, parts of the lung, aorta, chest wall, breasts, spine, skin, and upper abdomen are exposed to radiation and imaged along with the heart.^{35, 99} A small field of view, focusing on the heart, improves resolution for interpreting the cardiac images. But the field of view may be expanded to reveal these other areas for examination.¹⁰¹ The number of incidental findings identified is affected by the scanner used, the slice thickness, and the area imaged. Identification of incidental findings may have benefits as well as drawbacks. Data from two studies of symptomatic persons, suggests that 7%-10% of them will have incidental findings during a CT scan for calcium scoring that require further diagnostic testing and a small percent, 1.2%, will require therapeutic intervention.

One systematic review⁹⁸ and two studies with patient populations that included symptomatic persons undergoing EBCT for calcium scoring were identified both of which were contained in the systematic review.^{35, 99} Two studies in asymptomatic persons referred for CACS as a screening test^{36, 100} and one small study in which it was unclear whether patients were symptomatic or asymptomatic¹⁰¹ were also identified. Information from these later three studies is provided for context.

The quality of reporting in these studies was variable. Slightly different criteria for which incidental findings were considered clinically important were used across studies. Varied methods for identifying such findings were used and included counting of incidental findings from exam reports and re-reading of scans to identify incidental findings. The method used may influence the prevalence of such findings.

Not all incidental findings are clinically important. Clinically important findings affect patient management. Hunold reported the prevalence of incidental finding with therapeutic consequences as well as those with only diagnostic implications. However, in most studies, clinically important incidental findings are defined as those needing further testing or follow-up.⁹⁸ Table 11 provides an overview of study findings. Additional information is found in Appendix G.

Table 11. Summary of studies reporting incidental findings on CT for calcium scoring

Reference	CT characteristics	Population	n	Subjects with clinically important incidental findings n (%)
Hunold 2001	EBCT; 3 mm slices; pulmonary arteries to apex; 32% also had contrast and CT angiography*	9.9% screening exams, others had known or suspected coronary artery disease; age 20-86 y; smoking status not reported	1812	191 (10.5%) had findings with diagnostic implications; 22 (1.2%) had findings with therapeutic consequences
Horton 2002	EBCT; 3 mm slices; pulmonary arteries through apex	Symptomatic and asymptomatic ; age 23-87 y; 25% current or former smokers	1326	103 (7.8) had findings requiring clinical or radiological follow up
Elgin 2002	EBCT; 3 mm slices; axial length not described	Asymptomatic; age 39-46 y; 13% current smokers	1000	54 (5.4%) had findings requiring follow up or additional testing
Schragin 2004	EBCT; 3 mm slices; aortic root through apex	Population screening; age 21-86 y; 41% current or former smokers	1356	57 (4.2%) had findings requiring further evaluation
Law 2008	MDCT; 3 mm slices; carina to apex	Symptomatology not described; mean age 56 y; 17% current or former smokes	140	11 (8%) had findings requiring clinical or radiological follow up

*Authors do not separate out incidental findings for CACS and CT angiography
EBCT is electron beam computed tomography; MDCT is multidetector computed tomography; y is years

Many of the risk factors for coronary artery disease (such as increased age, smoking, and male sex) are also risk factors for other diseases (such as lung cancer) that might be identified on CT scans.⁹⁸ The prevalence and type of incidental findings from CT scans may vary according to the study cohort's risk factors and whether symptomatic or asymptomatic persons were included. These differences may partly explain the variation in prevalence of incidental findings between studies.

In the two studies in symptomatic persons, the majority of extra-cardiac findings requiring further testing were pulmonary nodules that were considered suspicious for tumor.^{35,99} Only Hunold reported the number of findings with therapeutic consequences.⁹⁹ Eleven extra-cardiac findings (0.6% of all findings, 9.4% of the 1175 thoracic or abdominal findings) required therapeutic intervention. The same authors also reported on 136 cardiac related findings (7.5% of all incidental findings, 20% of the 676 cardiac findings) required further evaluation, 11 of which required therapeutic intervention. Calcification of the mitral or aortic valve was the most common finding requiring additional testing and masses in a cardiac chamber were the most common findings requiring therapeutic intervention. Horton did not report on findings requiring therapeutic intervention.

The reporting of an incidental finding often leads to additional diagnostic testing. For example, radiological studies with better spatial resolution such as spiral CT with IV contrast may be done.^{35,99} These may increase overall patient radiation exposure. The additional diagnostic tests raise patient anxiety, have risks, and cost money. The additional testing may identify disease at an early stage and lead to necessary treatment, but may not actually improve survival or other patient outcomes. An apparent improvement in survival may be simply due to lead-time bias. Also, especially among low-risk patients, the incidental finding may not require treatment: the additional testing may be done with no change in the patient's outcome.

3.3 Key Question 3: What is the evidence that CACS influences clinical decision making and improves patient clinical outcomes (e.g. mortality)

Clinical decision making

The role of CACS as a diagnostic test in symptomatic patients is unclear making its influence on clinical decision making difficult to assess. Some authors have suggested that CACS may facilitate triage of patients separating out those in whom the likelihood of significant CAD is low from those who are more likely to have significant CAD and should be evaluated with additional testing.

One study from a tertiary referral center¹⁰² and five studies describing the use of CACS as a tool for patient evaluation and decision making in the emergency department (ED) were identified.^{21, 103-106} There was wide variation in the definitions of outcomes and use of CACS. None of the studies identified used concurrent or historical controls, making it difficult to effectively evaluate the impact of clinical decisions made based on CACS on patient outcomes compared with other decisions. If CACS was a perfectly sensitive test, there were no false negatives and some degree of specificity, the benefit of doing CACS as a first test for triage could be estimated in the absence of an explicit comparative group. However, without these features or a comparison group, the benefit of CACS as a first test is not clear. The studies are briefly described below. Additional detail is found in Appendix G.

Piers¹⁰² retrospectively evaluated 598 patients with no prior CAD history with a mean estimated 10 years risk of CAD of 6% (8%-10%) who had CACS were divided in four groups based on CACS score. Decisions to do additional tests for evaluation of myocardial ischemia were made by the treating cardiologist and if judged clinically relevant, conventional angiography was performed. Overall 89% (n = 531) underwent tests for ischemia evaluation and 24% had conventional angiography with the majority of these having had tests for ischemia prior to angiography. The authors reported that the probability of referral to CCA increased with increasing CACS (P< 0.001) and that CACS may facilitate decision making.

	Ischemia test done*	CCA done	CAD on CCA†
CACS < 10 (n =304)	263 (86%)	1 (0.3% of 304)	1 (0.03%)
CACS 10-99 (n = 135)	122 (90%)	30 (22%)	13 (9.6%)
CACS 100-399 (n = 89)	85 (96%)	30 (34%)	10 (11%)
CACS ≥ 400 (n = 70)	61 (87%)	60 (86%)	35 (50%)

*Exercise stress test, ST segment analyses on 24 ECG registration or SPECT at clinician discretion;

†not all patients had CCA the number of persons with CAD who did not have CCA is unknown.

From this study it is not clear to what extent CACS as a stand alone test truly affected the decision to refer patients for angiography since 89% of patients had other non-invasive tests prior to catheterization which may have influenced the decision to perform angiography.

Studies from emergency department settings

Five studies were performed in patient populations admitted to emergency departments (ED) with angina-like chest pain and normal or nondiagnostic ECGs and/or normal cardiac enzymes.^{21, 103-106} The spectrum of patients described in these studies was primarily described as low to intermediate risk. Patients were excluded if they had a prior history of coronary artery disease (CAD). Since these studies are not validation studies and are considered only for the purpose of evaluating the influence of CAC scores on clinical decision-making practices, sensitivity and specificity are not reported.

These studies vary in quality and as previously stated, did not employ a comparison group and are considered case series. These studies explore the potential for CACS as a triage tool by looking at the extent to which various outcomes were associated with CACS. Only one study, Geluk, specified an algorithm for decision making based on CACS. The decision to discourage follow-up appears to have been based on combination of exercise testing and CACS, which were performed in random order. In some cases tests were performed after discharge. It is not clear to what extent the actual decision for discharge was based algorithm described.

Authors suggest that the absence of calcium or very low score, usually < 10, may serve as an important diagnostic threshold, allowing physicians to confidently discharge such patients to home without further work-up, serving as a type of triage method for this specific patient population. Based on these studies, clinicians may use high calcium

scores as one factor in deciding which patients need intervention (such as diet, exercise, antiplatelet therapy, or cholesterol-lowering agents) or further cardiac testing. This has not been explicitly evaluated in any of the studies identified.

Geluk¹⁰⁴ prospectively evaluated low-risk patients with symptoms of CAD, normal ECG, and normal troponin to determine the efficacy of CAC scores compared with exercise testing. All patients underwent both calcium scoring by EBCT and exercise testing (or myocardial perfusion scintigraphy for the 7% unable to exercise). The protocol for further treatment depended on the calcium score. Patients with a CAC score of < 10 would be discharged to home and follow-up visits discouraged. Those with scores 10-399 would begin primary prevention measures such as life style modification and pharmacotherapy and additional testing at the judgment of the treating cardiologist. Patients with a CAC score \geq 400 would have coronary angiography. Patients were followed-up after at least 4 months by review of medical records, phone interviews, or phone contact with the patient's general practitioner. The endpoint was a combination of \geq 50% stenosis on angiography, revascularization, myocardial infarction, or cardiac death during follow up. Although only 27% of patients had angiography, all patients were followed up. Among those 159 patients with a calcium score < 10, the stress test was negative in 113, positive in 15, and nondiagnostic in 31. Despite the protocol, 13 had angiography, which did not show any obstructive lesions. None of the 159 patients with a calcium score < 10 had the combined endpoint. Among those 103 patients with a calcium score 10-399, the stress test was negative in 63, positive in 9, and nondiagnostic in 31. Thirty-three of the 103 had angiography, which showed obstructive lesions in 14 (14%), requiring revascularization in 9 (9%). All patients with coronary artery disease in this group received pharmacologic therapy. Among those 103 patients with a calcium score 10-399, 14 (14%) had a combined endpoint. Among those 42 patients with calcium score \geq 400, the stress test was negative in 15, positive in 13, and nondiagnostic in 14. All of the patients with a calcium score \geq 400 had pharmacologic therapy, which resolved symptoms for five. The other 37 had angiography, which showed obstructive lesions in 24 (57%) requiring revascularization in 17 (40%). Among those 42 with calcium score \geq 400, 24 (57%) had a combined endpoint. The authors suggest that the calcium score may be used as a "gatekeeper" for additional invasive and noninvasive testing, providing effective triage in patients with suspected but low risk of CAD. Furthermore, the authors indicate that CACS is diagnostically superior to exercise testing and is a better predictor of future cardiac events.

Georgiou¹⁰⁵ investigated the association between EBCT detected CAC and future cardiac events in a prospective observational study of 192 patients admitted to the ED of a large tertiary care hospital for chest pain with a normal or nondiagnostic ECG. Treating physicians and patients were not told the calcium score. Outcomes were "hard events" (cardiac death or nonfatal MI) or "total events" (cardiac death, nonfatal MI, coronary revascularization, ischemic stroke, or hospitalization for angina) as ascertained by review of hospital records at a mean of 50 months after admission. The presence of calcium (CAC score > 0) was strongly related ($P < .001$) to the occurrence of hard cardiac events

(death, myocardial infarction) and all cardiovascular events (death, myocardial infarction, coronary revascularization, ischemic stroke, subsequent hospitalization for angina). CAC scores ranged from 0 to 4607 and results were categorized by quartiles of calcium scores with 48 patients in each quartile: 0, 1 to 4, 5 to 332, and 333 to 4607. No hard events and two total events occurred in patients in the lowest quartile (CAC score 0). In those patients with a scores from 1 to 4, 5 to 332, and 333 to 4607, one, ten and 19 hard events occurred, and one, 27 and 27 total events occurred, respectively. Thus, all cases of cardiac death and MI occurred in patients with a CAC score of > 0 and the annualized event rate for all cardiovascular events was 0.6% for the 76 subjects with a CAC score of 0 compared to 13.9% for the 38 subjects with a score of > 400 . ($P < .001$) The authors conclude that CACS of 0 may expedite early discharge from the ED in this patient population. They also note that calcium scores “should improve the physician’s ability to stratify individuals at high risk of events, to whom aggressive treatment of risk factors for coronary artery disease can be more appropriately directed, and help direct the admission or discharge of emergency room patients”.

Laudon²¹ reported on a series of 105 patients who received CAC scoring by EBCT within 24 hours of admission to the ED with agina-like chest pain, normal cardiac enzymes, and a normal or nondiagnostic ECG. Since previous studies have shown that the prevalence of CAC increases markedly with age, men had to be under 55 years of age and women under 65 years of age. Other cardiac testing (treadmill exercise test, radionucleotide stress test, angiography, stress echocardiography) was also performed in 100 of the patients (95%) at the discretion of the staff physician without knowledge of the calcium scores. An EBCT examination was considered positive if any coronary calcium was detected (CAC score > 0). All patients were followed up 4 months later using chart review and telephone calls. Among the 54 patients with CACS of 0, other cardiac tests were negative. (One patient’s treadmill exercise test was initially read as positive, but re-read by an independent cardiologist and classified as negative; the authors classified this patient as having a negative cardiac test.) Among the 46 patients with a calcium score > 0 , 14 (30%) had other cardiac tests that were positive. All patients with a calcium score of 0 were free of cardiac events during 4 months of follow-up. The authors suggest that a calcium score of 0 would allow a patient to be discharged “from the ED without further testing, with referral to his or her primary physician for outpatient evaluation.” A calcium score > 0 would require further evaluation in a chest pain unit or in the hospital.

McLaughlin¹⁰⁶ enrolled 134 low-risk patients with the primary goal of evaluating the predictive value of a negative EBCT scan in terms of risk stratification. The population consisted of patients admitted to an emergency room with chest pain, normal or nondiagnostic ECGs, and normal cardiac enzymes. Whether the study was prospective or retrospective is not stated. All patients had calcium scores obtained within 7 days of admission and treating physicians were not told those results. End points were acute MI, percutaneous revascularization, coronary artery bypass, or sudden cardiac death as ascertained by chart review and telephone contact 30 days after the hospitalization. Among the 48 (36%) patients whose calcium score was 0, only one had a cardiac event (a cocaine abuser had an acute MI). Among the 86 patients (64%) whose calcium score was > 0 , there were seven cardiac events. All but one event occurred during the index

hospitalization. The authors conclude that calcium scores should not be used for risk stratification in cocaine abusers; excluding that patient “this test was perfect in predicting which patients may be safely discharge from the emergency room.” Also, “identification of this high-risk subgroup (with calcium score > 0)...may allow for more appropriate evaluation and aggressive treatment in patients admitted from the emergency room to the hospital with chest pain.”

Esteves¹⁰³ evaluated the utility of CAC to predict a normal adenosine stress rubidium-82 (Rb-82) myocardial perfusion positron emission tomography (PET) in 84 patients admitted to a chest pain unit with normal or nondiagnostic ECGs and two negative sets of cardiac enzymes. All patients subsequently had adenosine stress Rb-82 myocardial perfusion PET/CT. No clinical follow-up was performed as the authors used normal PET results as a proxy for good short-term outcomes, citing its wide acceptance as “a tool used to exclude functionally significant coronary stenosis and is associated with a very low risk of short-term cardiac events.” In the 34 patients with a calcium score of 0, the PET scan was normal. In the 50 patients with a calcium score > 0, myocardial perfusion defects were seen in 13 (26%). Also, left ventricular ejection fraction was generated in 72 of the patients and was normal in 30 or 31 (97%) patients with no CAC and in 37 of 41 (90%) patients with CACS > 0. The authors conclude that absence of CAC is predictive of a normal adenosine stress Rb-82 myocardial perfusion PET and that myocardial perfusion imaging probably can be safely avoided in chest pain patients with a CACS = 0, saving the patient from further unnecessary radiation exposure and increased costs.

The extent to which CACS may facilitate decision making in the emergency department is not clear from these studies.

Prediction of future events in non-emergency settings

No randomized trials which demonstrate that treatment of cases detected by the diagnostic test improves patient outcomes were found. In the absence of such studies, even though an association between CACS and future cardiovascular events has been reported, the extent to which various treatment options may have influenced the associations is unclear. It is unknown to what extent use of CACS may truly influence patient outcomes.

Three reports which evaluated the association between CACS and future “hard” events such as death or myocardial infarction were identified. Differences in outcomes measure definition, underlying CAD risk and length of follow-up were found across studies. A brief description of the studies reporting on symptomatic persons is provided below.

Three studies were conducted populations from non-emergency settings.¹⁰⁷⁻¹⁰⁹ In general, all report that CACS above a low threshold appears to be a predictor for hard events and that a CACS = 0 or one that is “low” was associated with few such events. The risk for future events increased with increasing CACS.

Summary of cardiac events occurring at various CACS scores

Author (year)	Total cardiac events	Number of cardiac events		
		CACS = 0 or low range	CACS > 100	CACS > 400 or high range
Keelan (2001) N = 317	n = 22	n = 1*	n = 17	n = 7†
Schmermund (2004) N = 300	n = 40	n = 1*	n = 35	n = 21†
Kennedy (1998) N = 368	n = 13	n = 1	n = 9	n = 7

*At the low range of calcium scores, Keelan reported one hard event in the first quartile of CACS ≤ 12 ; and Schmermund reported one hard event in the first quartile of CACS 0-1.4.

†Keelan reported 7 hard events for CACS ≥ 621 ; and Schmermund reported 21 hard events for CACS > 248.

Using a calcium score cut-off of ≥ 100 compared with calcium scores < 100 , one study found that 71% of hard events (cardiac death and nonfatal MI) occurred in patients in this score range, and reported a unadjusted relative risk of a hard event of 3.20 (95% CI, 1.17-8.71).¹⁰⁷ A second study reported that 88% of hard events (cardiac death, MI, interventional or surgical revascularization) occurred in patients with CS ≥ 100 , and the unadjusted relative risk of a hard event was 12.0, (95% CI of 4.7-30.6).¹⁰⁹ After adjusting for calcium score and age, a relative risk 4.4 (95% CI, 1.5-12.6) was reported. The confidence intervals for these estimates reflect wide variation in the estimates.

The results of these studies should be interpreted cautiously. Definitions of events varied across studies. While all adjusted for potentially confounding risk factors measured at the time of the CACS, none reported on or evaluated the influence of treatment between the time of the CACS determination and final follow-up or event occurrence. The reported mean length of follow-up in these studies varied from 30 months to 83 months with the low range in one study of 12 months. At shorter lengths of follow-up, there may not have been adequate time for observation of events.

3.4 Key Question 4: What is the evidence that CACS may perform differently in special populations (e.g. women, diabetic populations)?

Studies which provided information on CACS in symptomatic diabetic persons and women were found and several validation studies looked at the effect of age on CACS. The high prevalence of CAD among diabetic patients and lower prevalence in women compared with men should be borne in mind when interpreting the predictive values.

The small number and mixed quality of studies of women and diabetic persons do not provide sufficient evidence that CACS may perform differently in these populations.

Persons with diabetes are at higher risk of developing significant CAD compared with non-diabetic persons. Two studies examined a small number of symptomatic diabetic populations as a separate diagnostic group^{70, 82} and evaluated the validity of calcium scoring for the presence of significant coronary artery disease (CAD), defined as $\geq 50\%$ stenosis as determined by angiography. These studies are of moderate quality (LoE II-III). Further details concerning these studies may be found in the appendices.

Table 12. Patient characteristics from studies of diabetic patients

Author (year)	Demographics	Clinical information
Khaleeli (2001)	N = 168 Male: 60% Age: 58 years	<ul style="list-style-type: none"> average of 2.06 nondiabetic cardiac risk factors per patient, including age, tobacco use, hypercholesterolemia, hypertension, family history coronary artery disease: <ul style="list-style-type: none"> 1-vessel: n = 36 2-vessel: n = 41 3-vessel: n = 47
Hosoi (2002)	N = 101 Male: 70% Age: 64 years	<ul style="list-style-type: none"> hypertension: 66% lipidemia: 30% medications to control diabetes: 63%

Setting the cardiac score cut-off at 0 appears to give maximum sensitivity to the presence of CAD, with a high positive predictive value also and a moderately high negative predictive value (75%-89%). Setting the cut-off at 100 maintains a high positive predictive value, with a range of 67%-77% for the sensitivity and similarly 75%-77% for the specificity of the test. A cut-off of 400 leads to high specificity, but low sensitivity, as reported by Hosoi et al.⁸²

Table 13. Summary of CACS test characteristics in diabetic populations

Cut-off >0													
Author	N	TP	TN	FP	FN	Sens	Spec	PPV	NPV	1-NPV	n CAD	% CAD	LoE
Khaleeli (2001)	168	122	17	27	2	98%	39%	82%	89%	11%	124	74%	II
Hosoi (2002)	100	87	3	9	1	99%	25%	91%	75%	25%	88	88%	III
Cut-off >100													
Author	N	TP	TN	FP	FN	Sens	Spec	PPV	NPV	1-NPV	n CAD	% CAD	LoE
Khaleeli (2001)	168	95	34	10	29	77%	77%	90%	54%	46%	124	74%	II
Hosoi (2002)	100	59	9	3	29	67%	75%	95%	24%	76%	88	88%	III
Cut-off >400													
Author	N	TP	TN	FP	FN	Sens	Spec	PPV	NPV	1-NPV	n CAD	% CAD	LoE
Hosoi (2001)	100	43	11	1	45	49%	92%	98%	20%	80%	88	88%	III

CAD: coronary artery disease; FN: false negative.; FP: false positive; LoE: level of evidence; Sens: sensitivity; Spec: specificity; PPV: positive predictive value; NPV: negative predictive value; NR: not reported; TN: true negative; TP: true positive.

The prevalence of CAD is much higher in these studies (74%-88%) in diabetic persons compared with the validation studies in more general populations (49%- 73%) a factor to consider when interpreting the predictive values. Hosoi reported that the sensitivity and specificity were not significantly different between the diabetic and nondiabetic persons in his study.⁸² Kaheeli reports that a cut off of 102 provided optimal sensitivity (77%) and specificity (77%) to detect obstructive CAD in symptomatic diabetic persons. These authors also point out that prevalence of any coronary calcium is higher in symptomatic diabetic patients (89%) than in symptomatic non-diabetic patients (73%).⁷⁰

The pooled estimates from LoE I/II studies in this HTA are listed below for comparison;

	LoE I or II studies
Sensitivity	99 % (98%, 99%)
Specificity	35% (33%, 36%)
PPV	65% (63%, 66%)
1-NPV	5% (4%, 6%)

Three studies reported on the validity of calcium scores in male and female populations^{67, 68, 111} as shown in Table 13. These were LoE II-III, and further details can be found in the appendices.

Table 14. Patient characteristics in male and female study populations

Author (year)	Demographics	Clinical information
Budoff (2002)	N = 387 Age: 58 years Female: 100%	<ul style="list-style-type: none"> • hypertension: 57% • diabetes: 24% • hypercholesterolemia: 48% • current tobacco use: 25% • family history of CAD: 44% • coronary artery disease: 1-vessel: n = 72 2 or more vessels: n = 88
	N = 733 Age: 56 years Male: 100%	<ul style="list-style-type: none"> • hypertension: 49% • diabetes: 17% • hypercholesterolemia: 33% • current tobacco use: 23% • family history of CAD: 44%
Rumberger (1995)	N = 50 Age: 56 years Female: 100%	<ul style="list-style-type: none"> • history of MI: 2%
	N = 89 Age: 47 years Male: 100%	<ul style="list-style-type: none"> • history of MI: 4%
Haberl (2001)	N = 539 Age: 60 years Female: 100%	NR
	N = 1225 Age: 56 years Male: 100%	NR

NR = not reported

A calcium score cut-off of 0 appears to give maximum sensitivity (96%-100%) and negative predictive value for diagnosis of CAD, but specificity and positive predictive value are low, for both male and female patients. A cutoff of > 100 improves the specificity of calcium scoring while sensitivity and negative predictive value are still moderately high.⁶⁸

Examining the value of 1-NPV, a range of 4-11% of men who tested negative but actually had CAD would be missed at the CS = 0 level, whereas only 0-4% of women would be missed. Values at a cut-off of >100, are 11% of men and 18% of women,

The prevalence of CAD was lower in women (36%-47%) compared with men (53%-70%). Women present with CAD at an older age (~10 years) than men, which may account for the differences in the prevalence and predictive values. In two of the studies, men and women were of similar ages^{67, 68} and the third study enrolled a relatively young population of both men and women but women were 10 years older than men on average.¹¹¹ All studies enrolled many fewer women than men.

Table 15. Summary of CACS performance in male and female populations compared with angiography

Cut-off >0													
Author	N	TP	TN	FP	FN	Sens	Spec	PPV	NPV	1- NPV	n CAD	% CAD	LoE
Female populations													
Budoff (2002)	387	154	130	98	5	96%	57%	61%	96%	4%	159	41%	II
Rumberger (1995)	50	18	21	11	0	100%	66%	62%	100%	0%	18	36%	III
Haberl (2001)	539	255	116	168	0	100%	41%	60%	100%	0%	255	47%	II
Male populations													
Budoff (2002)*	733	NR	NR	NR	NR	96%	46%	NR	89%	11%	512	70%	II
Rumberger (1995)	89	46	24	18	1	98%	57%	72%	95%	5%	47	53%	III
Haberl (2001)	1225	680	128	412	5	99%	24%	62%	96%	4%	685	56%	II
Cut-off >100													
Author	N	TP	TN	FP	FN	Sens	Spec	PPV	NPV	NPV	n CAD	% CAD	LoE
Female populations													
Haberl (2001)	539	209	216	68	46	82%	76%	75%	82%	18%	255	47%	II
Male populations													
Haberl (2001)	1225	637	405	135	48	93%	75%	83%	89%	11%	685	56%	II

CAD: coronary artery disease; FN: false negative.; FP: false positive; LoE: level of evidence; Sens: sensitivity; Spec: specificity; PPV: positive predictive value; NPV: negative predictive value; NR: not reported; TN: true negative; TP: true positive.

*Raw data was not extractable from the report; those values reported here are as listed in the report. Other numbers given in this table are as reported in that study or were calculated from the reported numbers.

Seven LoE I/II validation studies looked at the effect of age on calcium scores and diagnostic accuracy.^{66-69, 72, 74, 112} Two studies which detailed results by age are summarized below. Further details on these higher quality studies are available in the appendix and other sections of this report.

Table 16. The effect of age on diagnostic validity of calcium scores.

Author (year)	Age group (years)	N	CACS cut-off	Sens	Spec	PPV	NPV	% CAD
Kajinami (1995)	< 40	16	0.0*	50%	75%	40%	82%	NR
	LoE I							
	40 to ≤ 50	47	2.0*	86%	94%	86%	94%	NR
	50 to ≤ 60	57	2.0*	82%	75%	74%	82%	NR
	60 to ≤ 70	78	4.0*	69%	94%	97%	61%	NR
N = 251	≥ 70	53	4.0 *	78%	76%	88%	62%	NR
Lamont (2002)	< 50	27		93%	83%	88%	91%	56%
	LoE II							
	50-60	59	> 0	98%	50%	86%	88%	76%
N = 153	> 60	67		100%	67%	91%	100%	78%

CAD: coronary artery disease; FN: false negative.; FP: false positive; LoE: level of evidence; Sens: sensitivity; Spec: specificity; PPV: positive predictive value; NPV: negative predictive value; NR: not reported; TN: true negative; TP: true positive.

*Log-transformed total coronary calcification scores. Scoring as follows in Hounsfield units (HU): 1 = 130-199 HU; 2 = 200-299 HU; 3 = 300-399 HU; 4 = 400+ HU.

The prevalence of CAD and presence of calcium increases with age. There are, however somewhat mixed results regarding the extent to which age influences test performance characteristics.

Increase in coronary calcification was found to be significantly associated with increased age, regardless of gender or presence or absence of significant stenosis.^{68, 69} Kajinami et al also reported that the most prominent difference in log-transformed total coronary calcium scores between patients with and without CAD was among men aged 40 to ≥60 years and in women ≥60 years, and that patients with CAD had significantly higher calcium score values than those without CAD.⁶⁹ Sensitivity tended to vary with age with one of the studies⁷² showing an increase with age while the other, Kajinami reporting the highest degree of sensitivity among middle-age patients (40 to ≤60 years) in their study population, while specificity and NPV was found to decrease with age (< 40 years). Data from Knez suggests that the optimal trade-off between sensitivity and specificity occurs in those 50 -70 years based on ROC.¹¹²

Budoff et al found that whereas there was no significant difference in sensitivity for detection of CAD in comparing young and old patients at the cut-off CS > 0, a significant difference was determined in specificity for premenopausal women (age < 60 years, 65%) and postmenopausal women (42%).⁶⁷

In other studies, the absence of any calcium had a high “predictive accuracy” for ruling out obstructive CAD in subjects ≥ 50 years of age in two studies,^{66, 112} and in all age

ranges in one study.⁶⁸ Two studies reported a high rate of false negatives among younger patients.^{74, 112} Knez reported that of eight patients (seven men, one woman) with a calcium score of 0 and found to have to have significant stenosis on coronary angiography, seven were < 45 years old. Similarly, Leber et al reported that three out of four patients with significant stenosis despite low calcium score were also aged < 45 years.⁷⁴

3.5 Key Question 5: What is the evidence of cost implications and cost-effectiveness for CACS compared with other diagnostic tests?

Two full formal economic analyses describing CACS use in symptomatic patients^{113, 121} were identified and were of moderate quality. One poorer quality costing study was also found.⁹⁵ All three articles evaluated the use of CACS as a triage before conventional coronary angiography (CCA). Though all included CCA alone as one comparator modality, each also included different additional noninvasive modalities and cutoff values for calcium score, which makes comparison between studies somewhat challenging.

The two full economic studies form the focus of this report with the costing study only briefly described. The most recent study¹¹³ was conducted in Europe which may limit its generalizability to a US system since referral patterns and reimbursement policies may differ. The two studies are US-based and are at least 10 years old and did not include comprehensive measures, societal perspectives, or time horizons that would allow strong conclusions about the economic value of CACS compared with angiography or other tests.

The two full economic analyses modeled multiple hypothetical cohorts and assumed that all patients with positive or non-diagnostic findings on the initial noninvasive test would receive CCA. Cost-effectiveness is characterized by use of intermediate clinical outcomes rather than survival or quality-adjusted survival. The use of an intermediate outcome (in these studies, cost per correct diagnosis) may be a relevant clinical endpoint but (1) makes it difficult or impossible to compare with economic evaluations conducted in other clinical areas and (2) by definition does not provide information about survival as an outcome. The authors of one study state that quality adjusted life years (QALYs) are not the best measure to use for studying diagnostic interventions, but other studies have successfully used QALYs as the outcome of interest in economic evaluations in related clinical areas,^{122, 123} and at least some experts support the use of QALYs even for diagnostic testing where there is a relative distance between diagnosis and health outcome.¹²⁴

Overall, there is weak evidence (based on the two moderate quality full economic analyses) that at low to moderate pretest disease prevalence of CAD, CACS may have a lower cost per correct diagnosis than angiography alone. However, it is worth noting that CACS may not be the most cost-effective compared with other non-invasive diagnostic pathways. One author concluded that calcium scoring cannot be recommended from an economic perspective.¹¹³ Differences in model assumptions and failure of the studies to

describe an incremental cost-effectiveness ratio for various strategies, make drawing a firm conclusion regarding cost effectiveness of CACS challenging.

- The cost of CCA per test as measured by hospital fees is considerably higher than CACS (nearly 8 times higher, according to Rumberger). However, since CCA is still required as a second test for differential diagnosis of some proportion of people receiving CACS, the value of CACS must be interpreted in the context of total number of conventional angiograms conducted.
- CAD prevalence is an important driver of the cost per correct diagnosis: The costs decreased with increasing pretest likelihood of disease.
 - In one study, modeled CACS costs per correct diagnosis decreased from €2345 to €1897 as pretest CAD likelihood increased from 30% to 40%. Between these likelihoods, CACS was more cost effective than the any of the traditional diagnostic modalities.¹¹³
 - In the other study, at each CACS cutoff chosen, as the prevalence of CAD increased, CACS costs decreased for all modalities. At a threshold of > 0 , modeled CACS costs went from \$24,703 USD when CAD prevalence was 10% to \$6,329 and \$4,957 respectively as prevalence increased to 50% and 70%.¹²¹
- Accuracy of CACS and CACS threshold appear to influence cost effectiveness.
 - Sensitivity analysis done by maximally increasing and decreasing test accuracy (not defined by authors) within the 95% confidence interval suggested that CACS was more cost effective than traditional approaches only at a pretest likelihood of 40% when accuracy was decreased but more cost effective than the alternatives when the accuracy was maximally increased at pretest likelihoods of 20%- 50%.¹¹³
 - At an intermediate disease prevalence of 50%, The direct costs per correct diagnosis in USD were \$6,329, \$5,410, \$5,290 and \$5,186 for CACS thresholds of > 0 , 37, 80 and 168 respectively. The corresponding true positive rates at these cut offs were 96%, 90%, 84% and 72%.¹²¹
- The rates, health consequences and cost impact of false positives and false negatives are not clearly described in these studies for CACS or relative to other testing alternatives.
- The extent to which the models presented reflect clinical practice is unclear. CACS does not appear to function as a stand alone test. Patients with positive CACS will have additional testing to assess function (e.g. stress test) or angiography, which is the definitive anatomical test. Since the role of CACS is not clear, the extent to which clinicians do not trust CACS results may influence the use of tests that are more familiar, such as ETT. The potential impact of these practices on cost and benefit need to be considered.

- There is insufficient evidence for conclusions on the long-term cost utility of CACS compared with CCA alone or with regard to other non-invasive tests.

Economic study detail

The table below provides a summary of the perspectives and data sources used in the economic studies.

Table 17 Overview of economic studies for CACS

	Design	Perspective and Costing	Data sources and Population	Primary Strengths	Primary Limitations
Dewey 2006	Cost-effectiveness; Cost per correctly identified obstructive CAD patient in Euros German health care system 10 year time horizon	Societal perspective Direct and indirect costs Provider perspective for MSCT break even costs	Data from meta-analyses Established German reimbursement rates Hypothetical cohort of suspected CAD patients aged from 30-69 years	Sensitivity analysis done on test parameters, CCA costs and complications Costs of missed diagnosis included 5% annual discounting for complications	EBCT performance data from meta-analysis which included other diagnostic modalities and populations Details of search and primary sources not provided EBT specific sensitivity data were not detailed Price per year is not detailed
Rumberger 1999	Cost-effectiveness US system Cost per correctly diagnosed obstructive CAD	Perspective not stated, appears to be provider perspective Total direct costs Local non-Medicare fee schedule	Data from 213 patients from a previous study used for model input parameters Hypothetical cohorts of 100 pts for each of 8 possible pathways were modeled	Test and its complications included Sensitivity analysis for different prevalence and thresholds	Details of cost, prevalence for complications not provided No sensitivity analysis on cost or other model assumptions
Raggi 2000	Cost-only US system Cost per patient tested in USD	Mean reimbursement from 3 Tennessee payers Direct costs only Apparently payer perspective	N = 207 Age 50 years (\pm 9) range 35-67 mean pretest probability 29% (median 22%) Persons with low to intermediate pretest probability of CAD who received EBCT and ETT in random order	Sensitivity analysis for test parameters and pretest likelihood < 15%, \geq 15% to < 85% Considered cost of additional testing	Limited sensitivity analysis Model doesn't include complications Date of costs not given

USD = United States Dollars, MSCT = multi-slice computed tomography; EBCT = electron beam computed tomography; ETT = exercise treadmill testing

The quality of these studies was variable. QHES scores were 76 and 70 (out of 100) for the full analyses and 46 for the costing study. The two full analyses evaluated the effect of varying CAD prevalence and CACS threshold on cost per correct diagnosis. One study, [DEWEY] briefly described sensitivity analyses around model assumptions and cost inputs but these were not fully described for CACS. The other did not report any additional sensitivity analysis. The sensitivity analyses should ideally permit a transparent assessment of relative contributions of inputs that drive the model results, for

example, use of tornado plots. Thus, a clear understanding of the drivers of cost-effectiveness is difficult.

The cost per correct diagnosis is provided in these studies, however, incremental cost-effectiveness ratios for one strategy versus another were not described in either of the full economic studies. Though the analyses included CCA alone as one comparator modality, each also included different additional noninvasive modalities and cutoff values for calcium score, which makes comparison between studies somewhat challenging.

The sensitivities and specificities for CACS used in the two full economic studies compared with those in the present HTA are provided below.

	Sensitivity (95% CI)	Specificity (95% CI)
Present HTA LoE I/II studies		
CACS >0	99% (98%, 99%)	35% (33%, 36%)
CACS ≥100	85% (84%, 86%)	77% (76%, 79%)
CACS ≥ 400	78% (70%, 86%)	83% (76%, 91%)
Dewey		
(Cut-off not specified)	92.3% (90.7%, 94.0%)	51.2% (47.5%-54.9%)
Rumberger		
CACS >0	95% (CI not reported)	46%(CI not reported)
CACS = 37	90%	77%
CACS = 80	84%	84%
CACS = 168	71%	90%

CI = confidence interval

Results of formal economic studies

Each of the formal economic analyses employed different modeling assumptions and diagnostic pathways of interest. A summary of the primary results of each are presented in Table 18.

Table 18. Overview of results from full economic studies

	Diagnostic pathway of interest	Comparator(s)	Relevant results	Results of sensitivity analysis	Author conclusions
Dewey 2007	CACS followed by CCA for positive or nondiagnostic results (cutoff calcium scores not presented—but used sensitivity = 92.3 and specificity = 51.2)	CCA alone; MSCT, stress MRI; exercise ECG, or stress echocardiography CACS followed by CCA for positive or non-diagnostic results	<p>At prevalence 10%-50%, MSCT most cost effective pathway (CER= €4435 @10%, €1469 @ 50%)</p> <p>At prevalence 60%, MSCT and CCA alone were equally cost-effective (CER=€1345)</p> <p>At prevalence >70%, CCA alone was most cost-effective pathway (€1153 @70%, €807 @100%)</p> <p>At prevalence 30%-40%, CACS was more cost-effective than all other pathways except MSCT (CER €2345 @30%, €1897 @40)</p> <p>At prevalence >50%, CCA more cost effective than CACS.</p> <p>Prevalence at which CCA alone becomes more cost-effective than CACS > 60%</p> <p>(note MSCT found to be more cost-effective than CACS)</p>	<p>Altering sensitivity/specificity, complication rates, did not alter order of main findings</p> <p>Altering reimbursement rate for CCA altered prevalence at which CCA became most cost-effective (50%-80%)</p> <p>MSCT was only most cost-effective option at reimbursement rate ≤€260; at higher cost was overtaken by other noninvasive modalities</p> <p>Break-even analysis: 64 months @ 10 coronary exams per day; 23 months in higher volume facility</p>	<p>Up to 50% pretest likelihood of CAD, CACS is more cost-effective from societal perspective than CCA alone; above 50% prevalence CCA is most cost-effective option. (Note MSCT found to be more cost-effective than CACS at prevalence <60%)</p> <p>Calcium scoring cannot be recommended from an economic perspective</p>
Rumberger 1999	CACS with EBCT followed by confirmation with CCA for positive or nondiagnostic results (cutoffs CACS > 0; CACS = 37, CACS = 80, CACS =168)	CCA alone; treadmill exercise testing alone (TMET), with 2D echocardiography (ECHO), or with thallium scintigraphy (THALLIUM) (all exercise pathways followed by confirmation with CCA for positive or nondiagnostic results)	<p>For disease prevalence at or below 70%, the least costly and most cost-effective pathway considered was a CACS cutoff of 168 (sens = 71%, spec = 90%).</p> <p>At 100% prevalence, angiography alone had the lowest cost per correct diagnosis.</p> <p>Angiography alone cost per correct diagnosis: \$35,400 @ 10% prevalence, \$3540@ 100% prevalence</p> <p>CACS at a score 168 cost per correct diagnosis: \$15,016 at 10% prevalence, \$4071 at 100% prevalence.</p> <p>Prevalence at which CCA alone becomes more cost-effective than CACS = >70%</p>	Results presented for varying levels of disease prevalence and CS cutoff scores; costs not varied	In population with prevalence ≤70%, CACS with EBCT minimized direct costs and maximized cost-effectiveness; at 70%-100% prevalence CCA is superior option

MSCT = multi-slice computed tomography; EBCT = electron beam computed tomography; CER = cost-effectiveness ratio; CACS = coronary artery calcium score

The most recent and detailed evaluation by Dewey takes a modified societal perspective, using a time horizon of 10 years. A decision-analytic model was used and included evaluation of six different strategies for patients presenting with stable chest pain: CACS (based on EBCT), CCTA, stress echo, stress ECG, dobutamine stress MRI and immediate CCA. The main inputs to the model were test sensitivity and specificity, prevalence of disease in the population, rate of nondiagnostic exams, and rate of complications; the outcome of interest was correct diagnosis of CAD. Costs included were reimbursement rates for examinations, subsequent tests, treatment of complications, and treatment of subsequent myocardial infarction (hospitalization and rehabilitation). Measures of productivity loss cost were also included for subsequent myocardial infarction. Sources for clinical data came largely from meta-analyses, and cost data from German reimbursement schedules and author decision. Detailed methods of data abstraction were not provided. Sensitivity analysis included varying levels of test accuracy, complication rate of angiography, and costs. They also conducted a break-even analysis from a provider perspective. Results for each strategy as a stand alone procedure were provided but incremental differences among strategies were not presented.

The authors combined benefits and costs with a cost-effectiveness analysis, using cost per correct diagnosis as the unit of analysis, which they present for all the modalities at several levels of prevalence in the population. In general, cost-effectiveness increased as the prevalence of disease increased. At disease prevalence above 60%, angiography alone was the most cost-effective option of the modalities examined; at 30% to 40% prevalence CACS was most cost effective except for MSCT; and at 10%-20% prevalence and 40%-60% prevalence MSCT was most cost-effective. The relative cost-effectiveness was not changed with sensitivity analysis, except for the varying of reimbursement cost of MSCT. The authors conclude that MSCT, not CACS, is the most cost-effective noninvasive modality at prevalence below 60%. However, comparing only CACS with angiography alone, CACS remained more cost-effective at prevalence up to 50%.

Limitations of the Dewey study deserve mention. First, the use of an intermediate outcome (correct diagnosis) may be a relevant clinical endpoint but makes it difficult or impossible to compare with economic evaluations conducted in other clinical areas. Additionally, they use a mathematical model instead of patient-level data. Finally, the generalizability of a German study to a US system is unknown, both in clinical relevance and costs. Specifically, their finding that reimbursement rates were the only variable that changed the order of cost-effectiveness of various non-invasive modalities may be significant for international comparisons.

Rumberger (1999)¹²¹ undertook an economic evaluation of CACS with EBCT for the diagnosis of CAD, compared with angiography alone, treadmill exercise, stress echocardiography, stress thallium (followed by CCA if indicated). Using data from a published study of a Mayo Clinic cohort of men and women under evaluation for CAD for the clinical inputs, the model included sensitivity, specificity, nondiagnostic rate, rate

of complications, and non-Medicare fees for testing and for a hypothetical cohort of patients. Several cutpoints of calcium score were explored in the model: >0, 37, 80, and 168, as were several prevalence rates (10%, 20%, 50%, 70%, and 100%). Only direct costs of testing and its complications were considered.

The authors report that for disease prevalence at or below 70%, the least costly and most cost-effective pathway considered was a CACS with a calcium score cutoff of 168. Compared to angiography alone, whose cost per correct diagnosis ranged from \$35,400 at 10% prevalence to \$3540 at 100% prevalence, CACS at a cutoff score of 168 was \$15,016 at 10% prevalence and \$4071 at 100% prevalence. At 100% prevalence, angiography alone had the lowest cost per correct diagnosis.

This study is a very short-term economic evaluation of the direct costs and outcomes of CACS as a triage diagnostic strategy for CAD. It provides some useful information on the relative cost and cost per correct diagnosis of various noninvasive modalities, but the lack of a defined perspective (it appears to be a hospital perspective since only hospital fees are included), survival or quality-adjusted survival or long-term time horizon makes the usefulness of the study as an economic evaluation limited.

Raggi (2000)⁹⁵ conducted a costing study to determine the relative costs of exercise treadmill testing (ETT) with CACS as the initial test for investigation of chest pain, with the hypothesis that CACS using EBCT is effective and/or lower cost than ETT in people with low to intermediate CAD likelihood—as such, they examined two primary diagnostic algorithms: CACS or ETT followed by myocardial perfusion imaging (MPI) and CCA. The authors constructed a Bayesian model and conducted a clinical study. For the clinical study, people underwent ETT and CACS in random order. Clinical outcomes collected were treadmill score, calcium score and positive, negative, or equivocal test result. Cost of testing was based on Tennessee reimbursement rates and published literature and is presented in a cost-per-patient format.

For the Bayesian model, the authors considered the CACS and ETT diagnostic pathways, the performance of MPI and angiography as the initial test, using inputs from published literature. For sensitivity, the model varied levels of calcium score and test sensitivity/specificity, and published 95% confidence intervals for their cost estimates.

The results of the modeling study suggested that both diagnostic pathways (ETT and CACS) were lower cost than angiography alone at all levels of prevalence, with CACS as the lowest cost and with cost savings greatest at lower disease prevalence. Compared with a cost of \$4800 per patient tested for angiography, the primary CACS pathway ranges from \$330 at 0% prevalence, to about \$1500 per patient tested at 50% prevalence, to about \$2200 per patient tested for 100% prevalence (numbers extrapolated from graph). In the clinical study, the CACS pathway was found to be cost-saving, with the primary pathway costing \$599 per patient tested and the ETT pathway was \$1701. (The clinical study did not compare CACS to CCA alone.)

This study is a cost-only study and cannot be considered a full economic evaluation. The data presented may give some estimate of budget impact, and the strength of having clinical data to support a mathematical model is probably of some value. However, the authors do not set out to determine the value of CACS as a diagnostic intervention using a synthesis of costs and benefits. Nor does the study take a long-term perspective, so the value of CACS beyond the initial testing cost is not considered. Overall, this study offers very limited information on the cost of CACS compared to angiography and none on its cost-effectiveness.

Further economic modeling

The following are areas for which there is insufficient evidence for a comprehensive assessment of economic value. These should be considered for future economic evaluations.

- Better delineation and modeling of the costs and consequences of false positive and false negative results in the short- and long- term (e.g. presentation of patients with false negative results at a future time).
- The costs and consequences of additional or unnecessary testing should be considered. The cost of follow-up and care related to incidental findings should also be considered in modeling.
- The long-term costs and outcomes of CACS compared to CCA alone on survival.
- The long-term risks to CACS, including risks radiation exposure with CACS.
- The long-term impact of CACS compared to CCA alone from a patient perspective (eg. anxiety/reassurance, test invasiveness, out of pocket costs, cost of time spent in testing), shown to be relevant in other imaging settings.^{124, 125}
- Sensitivity analysis to determine the relative impact of test characteristics, pretest disease prevalence, cost, and other relevant variables on overall cost utility of CACS.

Summary and Implications

1. CACS test characteristics: Validation and accuracy, reliability and reproducibility of CACS compared with CCA.

- The role of coronary artery calcium scoring (CACS) as a diagnostic test is not clear from the literature and there is no consensus on appropriate thresholds for determining a negative versus positive test. It is not likely to be a replacement for conventional coronary angiography (CCA) based on test performance characteristics. Some literature suggests that it might be used for triaging symptomatic patients and that CACS may reduce the use of conventional coronary angiography.

- Based on meta-analysis of LoE I/II studies comparing CACS with the reference standard of conventional coronary angiography, the overall strength of evidence is high.
 - A CACS > 0 is highly sensitive (99%, CI = 98% - 99%) for identifying the presence of obstructive CAD, however specificity was only 35% and 5% of persons (1 – negative predictive value) with a negative test would have CAD based on pooled estimates from seven studies with a total of N = 7354 patients. Approximately 35% of persons without CAD might avoid unnecessary angiography or additional tests.
 - At thresholds of ≥ 100 (5 studies) or ≥ 400 (3 studies) the sensitivity is lower (85% and 78% respectively) but specificity is improved (77% and 83%, respectively). Clear decisions may not be possible based on CACS when using these thresholds to define a positive test.

2. Safety of CACS

The primary safety concerns for CACS relate to radiation exposure and the consequences of incidental findings.

Radiation exposure

- The overall strength of evidence regarding safety is very low primarily due to uncertainties regard the cancer-related risks due to radiation exposure particularly when CACS may lead to additional tests involving radiation. On the other hand, to the extent that CACS has the potential decrease the use of conventional angiography in some patients, overall radiation exposure would be reduced.
- To date, no large-scale epidemiologic studies evaluating cancer risk associated with computed tomography (CT) in general have been published.
- There is uncertainty and controversy with regard to the actual risk of low dose radiation. Quantification of risk specific to CACS for an individual patient is not possible.
- A typical effective dose for CACS is estimated to be 3 mSv (reported range 0.7 - 12 mSv) when retrospective and prospective gating are considered together. Exposure is less when scans are prospectively gated. Some experts consider the potential for harm from radiation exposure to be clinically significant particularly given that patients may be likely to have additional tests using radiation.
- A recent simulation estimating radiation dose and cancer risk suggests that a single scan for CACS may increase lifetime cancer risk. For a single screen at 55 years of age, based on a median effective dose of 2.3 mSv, site-specific estimates for lifetime risk of radiation induced cancer suggest that most cases would be lung cancer (6/100,000 in men, 14/100,000 in women) or breast cancer (4/100,000 in women).
- Decision making between physician and patient should involve a discussion of the potential risks and benefits of CACS (and subsequent testing). Final determination of net benefit for a given clinical scenario reflects the values and judgments of the persons making the decisions.
- The extent to which CACS is an adjunct to coronary CT angiography may increase radiation exposure compared with that for CACS alone.

Consequences of Incidental findings

- The overall strength of evidence is very low.
- Data from two studies suggests that 7%-10% of symptomatic persons will have incidental findings during a CT scan for calcium scoring that require further diagnostic testing and a small percent, 1.2%, will require therapeutic intervention.
- There may be benefits to early detection and treatment of the small percentage of significant pathology found incidentally, however, there is no evidence from these studies that early detection prompted more effective treatment or enhanced patient outcomes.
- The follow-up of less serious findings may create patient anxiety in addition to exposing them to the inconvenience, costs and risks of additional testing.

3. Influence on clinical decision making and patient outcomes

- There is an association between CACS and future events: Patients with higher CACS may experience more cardiac events (e.g. myocardial infarction, revascularization, death) and those with no calcium or low scores may be less likely to have future events. The extent to which CACS truly influences outcomes is unclear, however, since its impact on clinical decision making and treatment is not described.
- Overall, the evidence is low that CACS facilitates clinical decision making. While there are a number of studies describing the potential role of CACS as a triage tool for ruling out CAD and identifying those who should have additional testing, none of the studies included a comparison group. If CACS was a perfectly sensitive test, there were no false negatives and some degree of specificity, the benefit of doing CACS as a first test for triage could be estimated in the absence of an explicit comparison group. Without this or a comparison group, it is difficult to assess the incremental benefit of CACS in clinical decision making.

4. Special populations

- Two moderate quality validation studies in symptomatic diabetic patients suggest that the sensitivity (98-99%) and specificity (25%-39%) of CACS for the detection of any calcium is similar to that for general populations from the meta-analysis of LoE I/II studies but that a higher percent (11%-25%) of persons (1 – negative predictive value) with a negative test would have CAD. The overall strength of evidence is very low.
- Three moderate quality (LoE II/III) studies described performance characteristics for men and women separately. At a CACS >0, the sensitivities for both groups were 96%-100%. Specificities for women ranged for 41%-66% and those for men 24%-57%, some what lower. A higher percent (4% - 11%) of men (1 – negative predictive value) with a negative test would have CAD compared with women (0%-4%). The prevalence of CAD was lower in women (36%-47%) compared with men (53%-70%) Women present with CAD at an older age (~10 years) than men, which may account for the differences.

- Seven LoE I/II studies explored the relationship of age with test performance characteristics. The prevalence of CAD and presence of calcium increases with age. There are, however somewhat mixed results regarding the extent to which age influences test performance characteristics. While some studies suggest that sensitivity and predictive values go up with increasing age, others suggest that the best sensitivity and specificity may be in middle aged patients (40 – 60 years). The overall strength of evidence for studies with regard to age is moderate.

5. Economic implications

- Two full economic studies and one costing evaluate CACS as a stand-alone test compared with conventional angiography.
- The two moderate quality full economic studies suggest that at a disease prevalence of up to 70%, CACS may be more cost effective than conventional angiography, however incremental cost effectiveness is not described.
- Disease prevalence and CACS score cut-off (and corresponding sensitivity and specificity) appear to influence overall cost-effectiveness.
- Models did not include evaluation of incidental findings and the influence of false-negative and false-positive tests is not clear.
- CACS does not appear to function as a stand-alone test in clinical practice. The potential impact of additional testing done in clinical practice needs to be considered and modeled.
- There is insufficient evidence for conclusions on the long-term cost utility of CACS compared with CCA alone or with regard to other non-invasive tests.

Table 2. Overall Strength of Evidence (SoE) Criteria

SoE	Description	Further Research Impact	Domain Criterion Met		
			Quality	Quantity	Consistency
1	High	Very unlikely to change confidence in effect estimate	+	+	+
2	Moderate	Likely to have an important impact on confidence in estimate and <i>may</i> change the estimate	+	-	+
			+	+	-
3	Low	Very likely to have an important impact on confidence in estimate and <i>likely</i> to change the estimate	+	-	-
			-	+	+
4	Very Low	Any effect estimate is uncertain	-	+	-
			-	-	+
			-	-	-

Table 2. Summary of findings and overall strength of evidence

Key Question 1: Evidence regarding test characteristics and reliability		
Outcome	Strength of Evidence	Results
Validity of test	1	<p>The role of CACS as a stand alone diagnostic test is not clear. There is no consensus on threshold. Based on meta analysis of LoE I/II studies</p> <ul style="list-style-type: none"> A CACS > 0 is highly sensitive (99% , CI = 98% - 99%) for identifying the presence of obstructive CAD, however 5% of persons (1 – negative predictive value) with a negative test would have CAD At thresholds of ≥ 100 (5 studies) or ≥ 400 (3 studies) the sensitivity is lower (85% and 78% respectively) but specificity is improved (77% and 83%, respectively)
Reliability of test	1	<ul style="list-style-type: none"> The reliability of CACS (based on Agaston method) appears to be moderate to high based on 3 small LoE II studies and descriptions in it two validation studies
Key Question 2: Evidence regarding safety		
Radiation	4	<ul style="list-style-type: none"> While simulation and modeling of the effects of radiation exposure provide important insights into the possible changes in risks, the true attributable risk from radiation-based diagnostic tests may be difficult to determine. Radiation exposure may be reduced to the extent that CACS use avoids doing angiography. On the other hand, exposures may be increased to the extent that positive CACS results in additional testing. A typical effective dose for CACS is estimated to be 3mSV (reported range 1-12mSv). CACS results may lead to additional testing which involves radiation. In a recently published simulation based on a median effective dose of 2.3 mSv, site-specific estimates for life-time risk of radiation-induced cancer suggest that most cases would be lung cancer (6/100,000 in men, 14/100,000 in women) or breast cancer (4/100,000 in women). Decision making should include discussion of the potential for such risks.
Incidental findings	4	<ul style="list-style-type: none"> 7%-10% of symptomatic persons will have incidental findings during a CT scan for calcium scoring that require further diagnostic testing and a small percent, 1.2%, will require therapeutic intervention based on two studies in symptomatic persons.
Key Question 3: Evidence regarding clinical decision making and patient outcomes		
Triage in emergency department	3	<ul style="list-style-type: none"> Five studies suggest that a CACS = 0 may allow discharge of patients with suspected CAD. These studies, however vary in quality. None employed a comparison group and are considered case series.
Triage in other clinical settings	4	<ul style="list-style-type: none"> One study reported that referral to conventional angiography increased with increasing CACS. No comparison group was employed.
Prediction of future events	3	<ul style="list-style-type: none"> While 3 studies suggest that CACS is a predictor of future cardiac events, none evaluate the role of therapeutic interventions which may influence the occurrence of such events.
Key Question 4: Evidence regarding performance in special populations		
Diabetes	4	<ul style="list-style-type: none"> Sensitivity (98-99%) and specificity (25%-39%) of CACS for the detection of any calcium is similar to that for general populations from the meta-analysis of LoE I/II studies but a higher percent (11%-25%) of persons (1 – negative predictive value) with a negative test would have CAD based on two moderate quality studies.
Gender	3	<ul style="list-style-type: none"> Three studies evaluated CACS characteristics in women vs. men. Sensitivities were similar for both groups at CACS > 0. Specificities for women ranged for 41%-66% and those for men 24%-57%, some what lower. A higher percent (4% - 11%) of men (1 – negative predictive value) with a negative test would have CAD compared with women (0%-4%), however, the prevalence of CAD was lower in women (36%-47%) compared with men (53%-70%) Women present with CAD at an older age (~10 years) than men, which may account for the differences

Age	2	<ul style="list-style-type: none"> • Seven LoE I/II validation studies evaluated the influence of age on CACS. In general, the prevalence of coronary artery calcium increases with age. • There are conflicting results regarding test performance at various ages.
Key Question 5: Evidence regarding cost-effectiveness		
	4	<ul style="list-style-type: none"> • Two moderate quality studies suggest that at a disease prevalence of up to 70%, CACS may be more cost effective than conventional angiography, however incremental cost effectiveness is not described. • Cost-effectiveness is influenced by disease prevalence and CACS score cut-off (and corresponding sensitivity and specificity) • The influence of additional testing to reflect clinical practice needs to be more fully considered. • The influence of false-negative and false positive results is unclear and models did not consider follow-up of incidental findings. • There is insufficient evidence for conclusions on the long-term cost utility of CACS compared with CCA alone or with regard to other non-invasive tests.

References

1. Greenland P, Bonow RO, Brundage BH, et al. ACCF/AHA 2007 clinical expert consensus document on coronary artery calcium scoring by computed tomography in global cardiovascular risk assessment and in evaluation of patients with chest pain: a report of the American College of Cardiology Foundation Clinical Expert Consensus Task Force (ACCF/AHA Writing Committee to Update the 2000 Expert Consensus Document on Electron Beam Computed Tomography) developed in collaboration with the Society of Atherosclerosis Imaging and Prevention and the Society of Cardiovascular Computed Tomography. *J Am Coll Cardiol*. Jan 23 2007;49(3):378-402.
2. Budoff MJ, Achenbach S, Blumenthal RS, et al. Assessment of coronary artery disease by cardiac computed tomography: a scientific statement from the American Heart Association Committee on Cardiovascular Imaging and Intervention, Council on Cardiovascular Radiology and Intervention, and Committee on Cardiac Imaging, Council on Clinical Cardiology. *Circulation*. Oct 17 2006;114(16):1761-1791.
3. Greenland P, Bonow RO. How low-risk is a coronary calcium score of zero? The importance of conditional probability. *Circulation*. Apr 1 2008;117(13):1627-1629.
4. Schenker MP, Dorbala S, Hong EC, et al. Interrelation of coronary calcification, myocardial ischemia, and outcomes in patients with intermediate likelihood of coronary artery disease: a combined positron emission tomography/computed tomography study. *Circulation*. Apr 1 2008;117(13):1693-1700.
5. Kim KP, Einstein AJ, Berrington de Gonzalez A. Coronary artery calcification screening: estimated radiation dose and cancer risk. *Arch Intern Med*. Jul 13 2009;169(13):1188-1194.
6. Lloyd-Jones D, Adams R, Carnethon M, et al. Heart disease and stroke statistics--2009 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation*. Jan 27 2009;119(3):e21-181.
7. Kung HC, Hoyert DL, Xu J, Murphy SL. Deaths: final data for 2005. *Natl Vital Stat Rep*. Apr 24 2008;56(10):1-120.
8. Mathers C, Boerma T, Ma Fat D. *The global burden of disease: 2004 update*. Geneva 27, Switzerland: World Health Organization (WHO); 2008. ISBN 978 92 4 156371 0.
9. Thom T, Haase N, Rosamond W, et al. Heart disease and stroke statistics--2006 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation*. Feb 14 2006;113(6):e85-151.
10. Schoen F. Chapter 13, The Heart. In: Cotran RS KV, Collins T, ed. *Robbins Pathophysiologic Basis of Disease*. sixth ed. Philadelphia, London, Toronto, Montreal, Sydney, Tokyo: W. B. Saunders Company; 1999:543-599.
11. Gianrossi R, Detrano R, Mulvihill D, et al. Exercise-induced ST depression in the diagnosis of coronary artery disease. A meta-analysis. *Circulation*. Jul 1989;80(1):87-98.
12. Wexler L, Brundage B, Crouse J, et al. Coronary artery calcification: pathophysiology, epidemiology, imaging methods, and clinical implications. A

- statement for health professionals from the American Heart Association. Writing Group. *Circulation*. Sep 1 1996;94(5):1175-1192.
13. O'Rourke RA, Brundage BH, Froelicher VF, et al. American College of Cardiology/American Heart Association Expert Consensus Document on electron-beam computed tomography for the diagnosis and prognosis of coronary artery disease. *J Am Coll Cardiol*. Jul 2000;36(1):326-340.
 14. Baumgart D, Schmermund A, Goerge G, et al. Comparison of electron beam computed tomography with intracoronary ultrasound and coronary angiography for detection of coronary atherosclerosis. *J Am Coll Cardiol*. Jul 1997;30(1):57-64.
 15. Mintz GS, Pichard AD, Popma JJ, et al. Determinants and correlates of target lesion calcium in coronary artery disease: a clinical, angiographic and intravascular ultrasound study. *J Am Coll Cardiol*. Feb 1997;29(2):268-274.
 16. Hoff JA, Chomka EV, Krainik AJ, Daviglius M, Rich S, Kondos GT. Age and gender distributions of coronary artery calcium detected by electron beam tomography in 35,246 adults. *Am J Cardiol*. Jun 15 2001;87(12):1335-1339.
 17. Uretsky BF, Rifkin RD, Sharma SC, Reddy PS. Value of fluoroscopy in the detection of coronary stenosis: influence of age, sex, and number of vessels calcified on diagnostic efficacy. *Am Heart J*. Feb 1988;115(2):323-333.
 18. Sangiorgi G, Rumberger JA, Severson A, et al. Arterial calcification and not lumen stenosis is highly correlated with atherosclerotic plaque burden in humans: a histologic study of 723 coronary artery segments using nondecalcifying methodology. *J Am Coll Cardiol*. Jan 1998;31(1):126-133.
 19. Simons DB, Schwartz RS, Edwards WD, Sheedy PF, Breen JF, Rumberger JA. Noninvasive definition of anatomic coronary artery disease by ultrafast computed tomographic scanning: a quantitative pathologic comparison study. *J Am Coll Cardiol*. Nov 1 1992;20(5):1118-1126.
 20. Lee JK, Sagel SS, Stanley RJ, Heiken JP. *Computed Body Tomography with MRI Correlation*. Vol 1. 4 ed: Lippincott, Williams and Wilkins; 2003.
 21. Laudon DA, Vukov LF, Breen JF, Rumberger JA, Wollan PC, Sheedy PF, 2nd. Use of electron-beam computed tomography in the evaluation of chest pain patients in the emergency department. *Ann Emerg Med*. Jan 1999;33(1):15-21.
 22. Thomson FJ, Paulson EK, Yoshizumi TT, Frush DP, Nelson RC. Single versus multi-detector row CT: comparison of radiation doses and dose profiles. *Acad Radiol*. Apr 2003;10(4):379-385.
 23. Snow V, Barry P, Fihn SD, et al. Evaluation of primary care patients with chronic stable angina: guidelines from the American College of Physicians. *Ann Intern Med*. Jul 6 2004;141(1):57-64.
 24. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M, Jr., Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. *J Am Coll Cardiol*. Mar 15 1990;15(4):827-832.
 25. Hoffmann U, Brady TJ, Muller J. Cardiology patient page. Use of new imaging techniques to screen for coronary artery disease. *Circulation*. Aug 26 2003;108(8):e50-53.

26. Callister TQ, Cooil B, Raya SP, Lippolis NJ, Russo DJ, Raggi P. Coronary artery disease: improved reproducibility of calcium scoring with an electron-beam CT volumetric method. *Radiology*. Sep 1998;208(3):807-814.
27. McCollough CH, Ulzheimer S, Halliburton SS, Shanneik K, White RD, Kalender WA. Coronary artery calcium: a multi-institutional, multimanufacturer international standard for quantification at cardiac CT. *Radiology*. May 2007;243(2):527-538.
28. Pelberg R, Mazur W. *Cardiac CT Angiography Manual*. illustrated ed: Springer 2007.
29. Mettler FA, Jr., Thomadsen BR, Bhargavan M, et al. Medical radiation exposure in the U.S. in 2006: preliminary results. *Health Phys*. Nov 2008;95(5):502-507.
30. Mettler FA, W. H, Yoshizumi TT, Mahesh M. Effective doses in radiology and diagnostic nuclear medicine: A catalog. *Radiology*. 2008;248(1):254-263.
31. Morin RL, Gerber TC, McCollough CH. Radiation dose in computed tomography of the heart. *Circulation*. Feb 18 2003;107(6):917-922.
32. Shope TB, Gagne RM, Johnson GC. A method for describing the doses delivered by transmission x-ray computed tomography. *Med Phys*. Jul-Aug 1981;8(4):488-495.
33. Gerber TC, Carr JJ, Arai AE, et al. Ionizing radiation in cardiac imaging: a science advisory from the American Heart Association Committee on Cardiac Imaging of the Council on Clinical Cardiology and Committee on Cardiovascular Imaging and Intervention of the Council on Cardiovascular Radiology and Intervention. *Circulation*. Feb 24 2009;119(7):1056-1065.
34. Brenner DJ, Hall EJ. Computed tomography--an increasing source of radiation exposure. *N Engl J Med*. Nov 29 2007;357(22):2277-2284.
35. Horton KM, Post WS, Blumenthal RS, Fishman EK. Prevalence of significant noncardiac findings on electron-beam computed tomography coronary artery calcium screening examinations. *Circulation*. Jul 30 2002;106(5):532-534.
36. Elgin EE, O'Malley PG, Feuerstein I, Taylor AJ. Frequency and severity of "incidentalomas" encountered during electron beam computed tomography for coronary calcium in middle-aged army personnel. *Am J Cardiol*. Sep 1 2002;90(5):543-545.
37. Achenbach S, Daniel WG, Moshage W. Recommendations for standardization of EBT and MSCT scanning. *Herz*. Jun 2001;26(4):273-277.
38. Matchar DB, Mark DB, Patel M, et al. Non-Invasive Imaging for Coronary Artery Disease. Vol Agency for Healthcare Research and Quality (AHRQ), Rockville MD. October 3, 2006. Duke Evidence-based Practice Center (EPC), Contract No. 290-02-0025.
39. Ontario Health Technology Advisory Committee (OHTAC). OHTAC Recommendation: Multidetector Computed Tomography for Coronary Artery Disease Screening in Asymptomatic Populations. May 2007.
40. BlueCross BlueShield. *Contrast-Enhanced Cardiac Computed Tomographic Angiography in the Diagnosis of Coronary Artery Stenosis or for Evaluation of Acute Chest Pain*: Technology Assessment Program; August 2006.
41. Berry E, Kelly S, Hutton J, Harris KM, Roderick P, Boyce JC. *A systematic literature review of spiral and electron beam computed tomography: with*

- particular reference to clinical applications in hepatic lesions, pulmonary embolus and coronary artery disease. *Health Technol Assess: NHS R&D HTA Programme*.
42. Murtagh J, Warburton RN, Foerster V, et al. *CT and MRI for selected clinical disorders: a systematic review of economic evaluations*. Canadian Agency for Drugs and Technologies in Health (CADTH). August 2006.
 43. The National Horizon Scanning (NHS) Centre Technology Briefing. *Computed tomography (CT) screening in risk assessment for coronary artery disease. December 2006*. University of Birmingham, Edgbaston, Birmingham, B15 2TT, England: Department of Public Health and Epidemiology.
 44. Van Brabandt H, Camberlin C, I C. *64-Slice computed tomography imaging of coronary arteries in patients suspected for coronary artery disease. Health Technology Assessment (HTA): Brussels: Belgian Healthcare Knowledge Center (KCE); 2008. Kce Reports 82 C (D/2008/10.273/42)*.
 45. Hall K. . *What is the prognostic value of calcium scoring in screening asymptomatic populations for cardiovascular disease? NZHTA Report 2003: New Zealand Health Technology Assessment (NZHTA), ISBN 1-877235-46-6*.
 46. Waugh N, Black C, Walker S, McIntyre L, Cummins E, G H. *The effectiveness and cost-effectiveness of computed tomography screening for coronary artery disease: systematic review. Health Tech Assess: NHS R&D HTA Programme*.
 47. Grady D, Chaput L, Kristof M. Results of Systematic Review of Research on Diagnosis and Treatment of Coronary Heart Disease in Women. Evidence Report/Technology Assessment No. 80. Vol AHRQ Publication No. 03-0035. Rockville, MD: Agency for Healthcare Research and Quality. May 2003. (Prepared by the University of California, San Francisco-Stanford Evidence-based Practice Center under Contract No 290-97-0013.); 2003.
 48. Tice T. Utility of Coronary Artery Calcium Measurement in Cardiovascular Disease. San Francisco: California Technology Assessment Forum (CTAF). February 16, 2005.
 49. Institute for Clinical Systems Improvement. Electron-Beam and Helical Computed Tomography for Coronary Artery Disease: Technology Assessment Committee. #34 Update. May 2004; 2004.
 50. Centers for Medicare and Medicaid (CMS). Pub 100-03 Medicare National Coverage Determinations: Cardiac Computed Tomographic Angiography (CTA). 6/27/2008. Available at:
<http://www.cms.hhs.gov/transmittals/downloads/R85NCD.pdf>.
 51. Centers for Medicare and Medicaid Services (CMS) Regional Coverage Article. Article for Coding Guidelines-Coronary Calcium Scoring-Multidetector Computed Tomography for the Heart and Great Vessels (A45280). *Noridian Administrative Services, LLC*. Available at:
http://www.cms.hhs.gov/mcd/viewarticle_pdf.asp?article_id=45280&article_version=4&contractor_id=115.
 52. Aetna. Clinical Policy Bulletin: Cardiac CT, Coronary CT Angiography and Calcium Scoring. 5/06/09. Available at:
http://www.aetna.com/cpb/medical/data/200_299/0228.html.

53. CIGNA HealthCare. Electron Beam Computed Tomography (EBCT) and Multidetector Computed Tomography for Coronary Artery Calcification. 12/15/2008. Available at:
<http://webdav.specri.com/web/documents/medicalwriters/TECHNOLOGY%20ASSESSMENT/Spectrum%20HTAs/Coronary%20Artery%20Calcium%20Scoring/Payers/Cigna%20EBCT%20and%20MDCT%20for%20coronary%20artery%20calcification%20coverage%20policy.pdf>.
54. Department of Veteran Affairs Health Administration Center (CHAMPVA). CT (Computed Tomography). 2/29/08. Available at:
<http://www.va.gov/hac/forbeneficiaries/champva/policymanual/champva/chapter2/1c2s26-3.htm>.
55. Regence. Computed Tomography to Detect Coronary Artery Calcification. 10/14/08. Available at: <http://blue.regence.com/trgmedpol/radiology/rad06.html>.
56. BlueCross BlueShield of North Carolina. Computed Tomography to Detect Coronary Artery Calcification. 3/2008. Available at:
<http://webdav.specri.com/web/documents/medicalwriters/TECHNOLOGY%20ASSESSMENT/Spectrum%20HTAs/Coronary%20Artery%20Calcium%20Scoring/Payers/BCBSNC%20policy.pdf>.
57. Phillips B, Ball C, Sackett D. Levels of evidence and grades of recommendation. Available at: http://www.cebm.net/levels_of_evidence.asp.
58. Atkins D, Best D, Briss PA, et al. Grading quality of evidence and strength of recommendations. *Bmj*. Jun 19 2004;328(7454):1490.
59. West S, King V, Carey TS, et.al. Systems to Rate the Strength of Scientific Evidence. Evidence Report/Technology Assessment No. 47 (Prepared by the Research Triangle Institute-University of North Carolina Evidence-based Practice Center, Contract No. 290-97-0011): Agency for Healthcare Research and Quality, Rockville, MD; 2002.
60. Ofman JJ, Sullivan SD, Neumann PJ, et al. Examining the value and quality of health economic analyses: implications of utilizing the QHES. *J Manag Care Pharm*. Jan-Feb 2003;9(1):53-61.
61. Dendukuri N, Chiu K, Brophy JM. Validity of electron beam computed tomography for coronary artery disease: asystematic review and meta-analysis. *BMC Med*. 2007;5:35.
62. Zamora J, Abaira V, Muriel A, Khan K, Coomarasamy A. Meta-Disc: a software for meta-analysis of test accuracy data. *BMC Medical Research Methodology*. 2006;6(31).
63. Moses LE, Shapiro D, Littenberg B. Combining independent studies of a diagnostic test into a summary ROC curve: data-analytic approaches and some additional considerations. *Stat Med*. Jul 30 1993;12(14):1293-1316.
64. Heijenbrok-Kal MH, Fleischmann KE, Hunink MG. Stress echocardiography, stress single-photon-emission computed tomography and electron beam computed tomography for the assessment of coronary artery disease: a meta-analysis of diagnostic performance. *Am Heart J*. Sep 2007;154(3):415-423.
65. Nallamothu BK, Saint S, Bielak LF, et al. Electron-beam computed tomography in the diagnosis of coronary artery disease: a meta-analysis. *Arch Intern Med*. Mar 26 2001;161(6):833-838.

66. Becker A, Leber A, White CW, Becker C, Reiser MF, Knez A. Multislice computed tomography for determination of coronary artery disease in a symptomatic patient population. *Int J Cardiovasc Imaging*. Jun 2007;23(3):361-367.
67. Budoff MJ, Diamond GA, Raggi P, et al. Continuous probabilistic prediction of angiographically significant coronary artery disease using electron beam tomography. *Circulation*. Apr 16 2002;105(15):1791-1796.
68. Haberl R, Becker A, Leber A, et al. Correlation of coronary calcification and angiographically documented stenoses in patients with suspected coronary artery disease: results of 1,764 patients. *J Am Coll Cardiol*. Feb 2001;37(2):451-457.
69. Kajinami K, Seki H, Takekoshi N, Mabuchi H. Noninvasive prediction of coronary atherosclerosis by quantification of coronary artery calcification using electron beam computed tomography: comparison with electrocardiographic and thallium exercise stress test results. *J Am Coll Cardiol*. Nov 1 1995;26(5):1209-1221.
70. Khaleeli E, Peters SR, Bobrowsky K, Oudiz RJ, Ko JY, Budoff MJ. Diabetes and the associated incidence of subclinical atherosclerosis and coronary artery disease: Implications for management. *Am Heart J*. Apr 2001;141(4):637-644.
71. Kwok B, Lim YT. Electron-beam computed tomography for symptomatic coronary disease. *Asian Cardiovascular and Thoracic Annals* 2000;8(1):46-49.
72. Lamont DH, Budoff MJ, Shavelle DM, Shavelle R, Brundage BH, Hagar JM. Coronary calcium scanning adds incremental value to patients with positive stress tests. *Am Heart J*. May 2002;143(5):861-867.
73. Lau GT, Ridley LJ, Schieb MC, et al. Coronary artery stenoses: detection with calcium scoring, CT angiography, and both methods combined. *Radiology*. May 2005;235(2):415-422.
74. Leber AW, Knez A, Mukherjee R, et al. Usefulness of calcium scoring using electron beam computed tomography and noninvasive coronary angiography in patients with suspected coronary artery disease. *Am J Cardiol*. Aug 1 2001;88(3):219-223.
75. Leschka S, Scheffel H, Desbiolles L, et al. Combining dual-source computed tomography coronary angiography and calcium scoring: added value for the assessment of coronary artery disease. *Heart*. Sep 2008;94(9):1154-1161.
76. Nixdorff U, Kufner C, Achenbach S, et al. Head-to-head comparison of dobutamine stress echocardiography and cardiac computed tomography for the detection of significant coronary artery disease. *Cardiology*. 2008;110(2):81-86.
77. Budoff MJ, Georgiou D, Brody A, et al. Ultrafast computed tomography as a diagnostic modality in the detection of coronary artery disease: a multicenter study. *Circulation*. Mar 1 1996;93(5):898-904.
78. Chen LC, Ding PY, Chen JW, et al. Coronary artery calcium determined by electron beam computed tomography for predicting angiographic coronary artery disease in moderate- to high-risk Chinese patients. *Cardiology*. 2001;95(4):183-189.
79. Fallavollita JA, Brody AS, Bunnell IL, Kumar K, Canty JM, Jr. Fast computed tomography detection of coronary calcification in the diagnosis of coronary artery

- disease. Comparison with angiography in patients < 50 years old. *Circulation*. Jan 1994;89(1):285-290.
80. Guerci AD, Spadaro LA, Goodman KJ, et al. Comparison of electron beam computed tomography scanning and conventional risk factor assessment for the prediction of angiographic coronary artery disease. *J Am Coll Cardiol*. Sep 1998;32(3):673-679.
 81. Herzog C, Britten M, Balzer JO, et al. Multidetector-row cardiac CT: diagnostic value of calcium scoring and CT coronary angiography in patients with symptomatic, but atypical, chest pain. *Eur Radiol*. Feb 2004;14(2):169-177.
 82. Hosoi M, Sato T, Yamagami K, et al. Impact of diabetes on coronary stenosis and coronary artery calcification detected by electron-beam computed tomography in symptomatic patients. *Diabetes Care*. Apr 2002;25(4):696-701.
 83. Shavelle DM, Budoff MJ, LaMont DH, Shavelle RM, Kennedy JM, Brundage BH. Exercise testing and electron beam computed tomography in the evaluation of coronary artery disease. *J Am Coll Cardiol*. Jul 2000;36(1):32-38.
 84. Tanenbaum SR, Kondos GT, Veselik KE, Prendergast MR, Brundage BH, Chomka EV. Detection of calcific deposits in coronary arteries by ultrafast computed tomography and correlation with angiography. *Am J Cardiol*. Apr 1 1989;63(12):870-872.
 85. Bielak LF, Rumberger JA, Sheedy PF, 2nd, Schwartz RS, Peyser PA. Probabilistic model for prediction of angiographically defined obstructive coronary artery disease using electron beam computed tomography calcium score strata. *Circulation*. Jul 25 2000;102(4):380-385.
 86. Broderick LS, Shemesh J, Wilensky RL, et al. Measurement of coronary artery calcium with dual-slice helical CT compared with coronary angiography: evaluation of CT scoring methods, interobserver variations, and reproducibility. *AJR Am J Roentgenol*. Aug 1996;167(2):439-444.
 87. Haberl R, Tittus J, Bohme E, et al. Multislice spiral computed tomographic angiography of coronary arteries in patients with suspected coronary artery disease: an effective filter before catheter angiography? *Am Heart J*. Jun 2005;149(6):1112-1119.
 88. Konieczynska M, Tracz W, Pasowicz M, Przewlocki T. Use of coronary calcium score in the assessment of atherosclerotic lesions in coronary arteries. *Kardiol Pol*. Oct 2006;64(10):1073-1079; discussion 1080-1071.
 89. Rumberger JA, Sheedy PF, Breen JF, Schwartz RS. Electron beam computed tomographic coronary calcium score cutpoints and severity of associated angiographic lumen stenosis. *J Am Coll Cardiol*. Jun 1997;29(7):1542-1548.
 90. Yao Z, Liu XJ, Shi RF, et al. A comparison of 99Tcm-MIBI myocardial SPET and electron beam computed tomography in the assessment of coronary artery disease in two different age groups. *Nucl Med Commun*. Jan 2000;21(1):43-48.
 91. Yao ZM, Li W, Qu WY, Zhou C, He Q, Ji FS. Comparison of (99m)Tc-methoxyisobutylisonitrile myocardial single-photon emission computed tomography and electron beam computed tomography for detecting coronary artery disease in patients with no myocardial infarction. *Chin Med J (Engl)*. May 2004;117(5):700-705.

92. Pepe M. *The Statistical Evaluation of Medical Tests for Classification and Prediction*. New York: Oxford University Press; 2003.
93. Janssen CH, Kuijpers D, Vliegenthart R, et al. Coronary artery calcification score by multislice computed tomography predicts the outcome of dobutamine cardiovascular magnetic resonance imaging. *Eur Radiol*. Jun 2005;15(6):1128-1134.
94. Nishida C, Okajima K, Kudo T, Yamamoto T, Hattori R, Nishimura Y. The relationship between coronary artery calcification detected by non-gated multi-detector CT in patients with suspected ischemic heart disease and myocardial ischemia detected by thallium exercise stress testing. *Ann Nucl Med*. Dec 2005;19(8):647-653.
95. Raggi P, Callister TQ, Cooil B, Russo DJ, Lippolis NJ, Patterson RE. Evaluation of chest pain in patients with low to intermediate pretest probability of coronary artery disease by electron beam computed tomography. *Am J Cardiol*. Feb 1 2000;85(3):283-288.
96. Mohlenkamp S, Behrenbeck TR, Pump H, et al. Reproducibility of two coronary calcium quantification algorithms in patients with different degrees of calcification. *Int J Cardiovasc Imaging*. Apr 2001;17(2):133-142; discussion 143.
97. Serafin Z, Laskowska K, Marzec M, Sinjab TA, Lasek W, Wlodarczyk Z. Coronary artery calcium distribution and interscan measurement variability in end-stage renal and coronary heart disease patients. *Acta Radiol*. Apr 2009;50(3):288-295.
98. Jacobs PC, Mali WP, Grobbee DE, van der Graaf Y. Prevalence of incidental findings in computed tomographic screening of the chest: a systematic review. *J Comput Assist Tomogr*. Mar-Apr 2008;32(2):214-221.
99. Hunold P, Schmermund A, Seibel RM, Grönemeyer DH, Erbel R. Prevalence and clinical significance of accidental findings in electron-beam tomographic scans for coronary artery calcification. *Eur Heart J*. 2001;22(18):1748-1758.
100. Schragin JG, Weissfeld JL, Edmundowicz D, Strollo DC, Fuhrman CR. Non-cardiac findings on coronary electron beam computed tomography scanning. *J Thorac Imaging*. Apr 2004;19(2):82-86.
101. Law YM, Huang J, Chen K, Cheah FK, Chua T. Prevalence of significant extracoronary findings on multislice CT coronary angiography examinations and coronary artery calcium scoring examinations. *J Med Imaging Radiat Oncol*. Feb 2008;52(1):49-56.
102. Piers LH, Salachova F, Slart RH, et al. The role of coronary artery calcification score in clinical practice. *BMC Cardiovasc Disord*. 2008;8:38.
103. Esteves FP, Sanyal R, Santana CA, Shaw L, Raggi P. Potential impact of noncontrast computed tomography as gatekeeper for myocardial perfusion positron emission tomography in patients admitted to the chest pain unit. *Am J Cardiol*. Jan 15 2008;101(2):149-152.
104. Geluk CA, Dikkers R, Perik PJ, et al. Measurement of coronary calcium scores by electron beam computed tomography or exercise testing as initial diagnostic tool in low-risk patients with suspected coronary artery disease. *Eur Radiol*. Feb 2008;18(2):244-252.

105. Georgiou D, Budoff MJ, Kaufer E, Kennedy JM, Lu B, Brundage BH. Screening patients with chest pain in the emergency department using electron beam tomography: a follow-up study. *J Am Coll Cardiol*. Jul 2001;38(1):105-110.
106. McLaughlin VV, Balogh T, Rich S. Utility of electron beam computed tomography to stratify patients presenting to the emergency room with chest pain. *Am J Cardiol*. Aug 1 1999;84(3):327-328, A328.
107. Keelan PC, Bielak LF, Ashai K, et al. Long-term prognostic value of coronary calcification detected by electron-beam computed tomography in patients undergoing coronary angiography. *Circulation*. Jul 24 2001;104(4):412-417.
108. Kennedy J, Shavelle R, Wang S, Budoff M, Detrano RC. Coronary calcium and standard risk factors in symptomatic patients referred for coronary angiography. *Am Heart J*. Apr 1998;135(4):696-702.
109. Schmermund A, Stang A, Mohlenkamp S, et al. Prognostic value of electron-beam computed tomography-derived coronary calcium scores compared with clinical parameters in patients evaluated for coronary artery disease. Prognostic value of EBCT in symptomatic patients. *Z Kardiol*. Sep 2004;93(9):696-705.
110. Budoff MJ, Shokooch S, Shavelle RM, Kim HT, French WJ. Electron beam tomography and angiography: sex differences. *Am Heart J*. May 2002;143(5):877-882.
111. Rumberger JA, Sheedy PF, 3rd, Breen JF, Schwartz RS. Coronary calcium, as determined by electron beam computed tomography, and coronary disease on arteriogram. Effect of patient's sex on diagnosis. *Circulation*. Mar 1 1995;91(5):1363-1367.
112. Knez A, Becker A, Leber A, et al. Relation of coronary calcium scores by electron beam tomography to obstructive disease in 2,115 symptomatic patients. *Am J Cardiol*. May 1 2004;93(9):1150-1152.
113. Dewey M, Hamm B. Cost effectiveness of coronary angiography and calcium scoring using CT and stress MRI for diagnosis of coronary artery disease. *Eur Radiol*. May 2007;17(5):1301-1309.
114. Rumberger JA. Cost effectiveness of coronary calcification scanning using electron beam tomography in intermediate and high risk asymptomatic individuals. *J Cardiovasc Risk*. Apr 2000;7(2):113-119.
115. Agresti A. *Categorical Data Analysis (section 3.3.2)*. New York: Wiley; 1990.
116. Fleischmann KE, Hunink MG, Kuntz KM, Douglas PS. Exercise echocardiography or exercise SPECT imaging? A meta-analysis of diagnostic test performance. *Jama*. Sep 9 1998;280(10):913-920.
117. US Food and Drug Administration. Radiation-emitting products. What are the radiation risks from CT? Available at: <http://www.fda.gov/Radiation-EmittingProducts/RadiationEmittingProductsandProcedures/MedicalImaging/MedicalX-Rays/ucm115329.htm>. Accessed July 15, 2009.
118. US Food and Drug Administration. Radiation-emitting products. Radiation quantities and units. Available at: <http://www.fda.gov/Radiation-EmittingProducts/RadiationEmittingProductsandProcedures/MedicalImaging/MedicalX-Rays/ucm115335.htm>. Accessed July 15, 2009.
119. Brenner DJ. Radiation risks potentially associated with low-dose CT screening of adult smokers for lung cancer. *Radiology*. May 2004;231(2):440-445.

120. Hunold P, Vogt FM, Schmermund A, et al. Radiation exposure during cardiac CT: effective doses at multi-detector row CT and electron-beam CT. *Radiology*. Jan 2003;226(1):145-152.
121. Rumberger JA, Behrenbeck T, Breen JF, Sheedy PF, 2nd. Coronary calcification by electron beam computed tomography and obstructive coronary artery disease: a model for costs and effectiveness of diagnosis as compared with conventional cardiac testing methods. *J Am Coll Cardiol*. Feb 1999;33(2):453-462.
122. Garber AM, Solomon NA. Cost-effectiveness of alternative test strategies for the diagnosis of coronary artery disease. *Ann Intern Med*. May 4 1999;130(9):719-728.
123. Sharples L, Hughes V, Crean A, et al. Cost-effectiveness of functional cardiac testing in the diagnosis and management of coronary artery disease: a randomised controlled trial. The CECaT trial. *Health Technol Assess*. Dec 2007;11(49):iii-iv, ix-115.
124. Hollingworth W. Radiology cost and outcomes studies: standard practice and emerging methods. *AJR Am J Roentgenol*. Oct 2005;185(4):833-839.
125. Mushlin AI, Kern LM, Paris M, Lambert DR, Williams G. The value of diagnostic information to patients with chest pain suggestive of coronary artery disease. *Med Decis Making*. Mar-Apr 2005;25(2):149-157.