HEALTH EVIDENCE REVIEW COMMISSION (HERC)

DRAFT COVERAGE GUIDANCE: CORONARY ARTERY CALCIUM SCORING

Approved by HERC 8/8/2013

HERC COVERAGE GUIDANCE

Coronary artery calcium scoring (CACS) should not be covered.

RATIONALE FOR GUIDANCE DEVELOPMENT

The HERC selects topics for guideline development or technology assessment based on the following principles:

- Represents a significant burden of disease
- Represents important uncertainty with regard to efficacy or harms
- Represents important variation or controversy in clinical care
- Represents high costs, significant economic impact
- Topic is of high public interest

Coverage guidance development follows to translate the evidence review to a policy decision. Coverage guidance may be based on an evidence-based guideline developed by the Evidence-based Guideline Subcommittee or a health technology assessment developed by the Heath Technology Assessment Subcommittee. In addition, coverage guidance may utilize an existing evidence report produced by one of HERC's trusted sources, generally within the last three years.

EVIDENCE SOURCES

Hayes, Inc. (2012). *Coronary artery calcium scoring to assess the risk of coronary artery disease in asymptomatic adults.* Lansdale, PA: Hayes, Inc.

National Institute for Health and Clinical Excellence (NICE). (2010). *Chest pain of recent onset: Assessment and diagnosis of recent onset chest pain or discomfort of suspected cardiac origin.* London: NICE. Retrieved August 31, 2012, from http://www.nice.org.uk/nicemedia/live/12947/47938/47938.pdf

U.S. Preventive Services Task Force. (2009). Using Nontraditional Risk Factors in Coronary Heart Disease Risk Assessment 2009. Retrieved August 31, 2012, from http://www.uspreventiveservicestaskforce.org/uspstf09/riskcoronaryhd/coronaryhdrs.htm

Washington State Health Care Authority Health Technology Assessment Program. (2009). *Coronary artery calcium scoring (CACS) as a diagnostic test for detection of coronary artery disease.* Olympia, WA: Health Technology Assessment Program. Retrieved August 31, 2012, from http://www.hta.hca.wa.gov/calscoring.html

The summary of evidence in this document is derived directly from these evidence sources, and portions are extracted verbatim.

Clinical Background

Coronary artery calcification 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. A close relationship has been confirmed between the extent of coronary artery calcification and the atherosclerotic plaque burden seen in coronary artery disease (CAD), making calcium a potential marker for diseased arteries.

Coronary calcification is pervasive in patients with confirmed CAD and increases with age. Increasing prevalence of coronary artery calcified plaque parallels the increasing prevalence of coronary atherosclerosis over the lifespan. However, the presence of calcified coronary plaque is not strongly correlated with the extent of histopathologic stenosis. 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.

Currently, the most common method for determining coronary artery calcium (CAC) score use computed tomography (CT), either electron beam CT or multidetector CT for the detection and quantification of the amount of coronary artery calcium. However, calcification in vessels may be present in both obstructive and nonobstructive lesions and thus, coronary artery calcium is not specific for obstructive CAD.

The role of coronary artery calcium scoring (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 conventional coronary angiography, 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 conventional coronary angiography and appropriate treatment.

In clinical practice, CACS may be used to determine whether patients presenting with chest pain should have further testing. Coronary artery calcium scoring as a stand-alone diagnostic test, however, is less common. (The more common use appears to be the evaluation of asymptomatic patients.) Coronary artery calcium scoring is increasingly performed in conjunction with CT coronary angiography using multidetector CT.

Electron beam CT and multidetector CT, both used for CACS, 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.

Evidence Review

US Preventive Services Task Force Report on Using Nontraditional Risk Factors in Coronary Heart Disease Risk Assessment

The report pertains only to asymptomatic patients, and makes the following recommendations:

Clinicians should use the Framingham model to assess coronary heart disease (CHD) risk and to guide risk-based therapy until further evidence is obtained. Because adding nontraditional risk factors (including CACS) to CHD assessment requires additional patient and clinical staff time and effort, routinely screening with nontraditional risk factors could result in lost opportunities for provision of other important health services of proven benefit.

This recommendation is to be used for those who fall into a 10% to 20% (intermediate) 10-year risk category after being screened for CHD risk by using traditional CHD risk factors. Using a risk assessment tool is a key step in managing CHD risk in patients. One validated method of assessing CHD risk is the Framingham model. Persons with low (<10%) Framingham risk scores do not benefit from aggressive risk factor modification, whereas those with high (>20%) Framingham risk scores do benefit. Examples of persons who fall into the intermediate-risk category include a 60-year-old male smoker with untreated hypertension or a 60-year-old female with untreated hypertension and hyperlipidemia. The current recommendation used the Adult Treatment Panel III Framingham risk calculator (available at

http://hp2010.nhlbihin.net/atpiii/calculator.asp?usertype.prof) and does not include diabetic populations.

The USPSTF found no evidence that risk stratification with any nontraditional risk factors including CACS, either independently or in addition to Framingham risk scoring, reduces myocardial infarction or cardiovascular disease mortality compared with risk stratification and treatment on the basis of Framingham scoring alone. Therefore, the USPSTF examined the evidence for the independent and additive predictive value of each nontraditional risk factor in assessing 10-year risk for myocardial infarction and CHD mortality. For those risk factors for which evidence for independent or additive predictive value is available, the USPSTF evaluated the evidence for the effect such factors may have on recategorizing intermediate-risk persons into low- or high-risk groups.

Regarding CACS, the evidence review found poor- to fair-quality evidence indicating that higher CAC scores on electron beam CT predict CHD events independent of Framingham risk factors, on the basis of a systematic review of eight cohort studies. Three good-quality population cohort studies and five fair-quality studies reported that the highest CAC score groups had significantly greater relative risk estimates than the lowest score groups. Although three of the studies met the technical requirements for a good-quality rating, none of them make a convincing case that CAC adds information about intermediate-risk persons. One of the three included only low-risk persons. Another study, from the Rotterdam Coronary Calcification Study, used self-selected participants who were classified into two categories (10-year Framingham risk of >20% or <20%), and results for the intermediate-risk group (10% to 20%) were therefore not reported separately. Several features of the third study, from the South Bay Heart Watch, limit its applicability to an intermediate risk group. The predictive value of a high CAC score was inconsistent; for example, participants with a Framingham risk score of 11% to 15% and participants with a risk score of 16% to 20% had the same baseline risk (7%). The CAC score also seemed to be imprecise; among participants who had a high CAC score, those with a pretest Framingham risk score of 10% to 15% had a higher posttest risk (19%) than those with a pretest score of 16% to 20%. Finally, participants were potentially self-selected. The five studies rated as fair quality were primarily limited by their use of proxy measures to control for Framingham risk factors or their recruitment of self-selected participants.

In summary, although the eight included studies consistently reported statistically significant relative risks for coronary events with increasing CAC scores, no study uniformly met all three of the following conditions: addressed an intermediate-risk cohort, was population-based or free of selection bias, and appropriately measured or controlled for traditional risk factors.

Hayes Report on Use of CACS in Asymptomatic Adults

The available evidence suggests that CACS adds incremental predictive value over traditional risk factor assessments such as the Framingham Risk Score, particularly among asymptomatic adults at intermediate risk of a CAD event. Among three studies, 20% to 55% of those initially classified as intermediate risk were reclassified once CAC scores were considered. However, it is not yet known whether the addition of CACS to standard risk factor assessment will improve patient-important outcomes (i.e., cardiac events). The one randomized trial comparing scanning with conventional risk factor analysis alone reported that CAC scanning was associated with some improvement in clinical risk factors for CAD, but there was no difference in adverse event rate between the scanned and non-scanned groups. Computed tomography-induced radiation exposure is the single biggest safety concern in relation to CACS.

Washington HTA Report (Coronary Artery Calcium Scoring)

The Washington HTA report addresses the use of CACS in symptomatic patients only.

CACS test characteristics
The role of 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 based on test performance characteristics. Some literature suggests that it might be used for triaging symptomatic patients (both stable outpatients, and patients with acute chest pain presenting to the emergency department) and that CACS may reduce the use of conventional coronary angiography.

- A CACS > 0 is highly sensitive (99%, CI = 98% - 99%) for identifying the presence of obstructive CAD, however specificity was only 35%.
- At thresholds of CAC scores ≥ 100 (5 studies) or ≥ 400 (3 studies) the sensitivity is lower (85% and 78% respectively) but specificity is improved (77% and 83%, respectively).

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

- Radiation exposure
  - To date, no large-scale epidemiologic studies evaluating cancer risk associated with 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).
- 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
  - Data from two studies suggests that 7% to 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.

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.
- 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.

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 Level of Evidence (LoE) I/II studies but that a higher percent (11-25%) of persons with a negative test would have CAD.
- 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% to 66% and those for men 24% to 57%, somewhat lower. A higher percent (4-11%) of men 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).

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 CAC 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.

- Coronary artery calcium scoring 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 conventional coronary angiography alone or with regard to other non-invasive tests.

WA HTA Clinical Committee Decision

The WA HTA clinical committee decided against coverage of CACS. Their rationale is outlined below:

- The committee agreed with the evidence report and found that CACS sensitivity and reliability are high for CACS, though specificity is low and like other tests, accuracy is affected by the disease prevalence. While accuracy and reliability are critical, they are only a first step as to whether a test is effective. The committee also agreed that there is no evidence to establish a clinically important threshold: increase in calcium does indicate disease, but the correlation to severity of stenosis is not established – which is key in a disease that is widely prevalent, where serious events occur in some, but are difficult to predict.
- In evaluating effectiveness, the most rigorous question is whether substituting this test, instead of a current diagnostic, results in better treatment and outcomes. In this case, the evidence is insufficient and current clinical practice does not support using this test alone or as a substitute.
- The other diagnostic effectiveness key question discussed by the committee is whether there is evidence that using this test as an added tool to current strategy provides a benefit (clinical or cost). The remaining analysis relate to answering this question.
- One potential use would be in ER where symptomatic patient at low to intermediate risk - could rule out disease. This use would require CACS of 0 value, so the specificity goes down, and at least a 5% group would still receive a negative test, but would have disease. One small retrospective study looked at 4 month follow up on 100 patients in ED where CACS score was taken, along with other tests and concluded that a score of 0 could permit a discharge. CACS studies did not include any RCT or higher quality observational trials to explicitly test what different clinical or treatment choices are made. The clinical expert noted that there is usually a need for a functional test to confirm.
- The committee noted that national guidelines do not endorse the use of CACS, though some have permissive statements for use of the test.

NICE Guideline: Chest Pain of Recent Onset

The NICE guideline does not address the use of CACS in patients presenting with acute chest pain. For patients presenting with stable chest pain in the outpatient setting, they make the following recommendations pertaining to CACS:

> In people without confirmed CAD, in whom stable angina cannot be diagnosed or excluded based on clinical assessment alone, estimate the likelihood of CAD (see Table 1). Take the clinical assessment and the resting 12-lead ECG [electrocardiogram] into account when making the estimate. Arrange further diagnostic testing as follows:
>
> - If the estimated likelihood of CAD is 61–90%, offer invasive coronary angiography as the first-line diagnostic investigation if appropriate.
> - If the estimated likelihood of CAD is 30–60%, offer functional imaging as the first-line diagnostic investigation.
> - If the estimated likelihood of CAD is 10–29%, offer CACS as the first-line diagnostic investigation. If the calcium score is:
> - zero, consider other causes of chest pain
> - 1–400, offer 64-slice (or above) CCTA
> - greater than 400, offer invasive coronary angiography.

Table 1. Percentage of people estimated to have coronary artery disease according to typicality of symptoms, age, sex and risk factors

	Non-anginal chest pain				Atypical angina				Typical angina			
	Men		Women		Men		Women		Men		Women	
Age (years)	**Lo**	**Hi**	**Lo**	**Hi**	**Lo**	**Hi**	**Lo**	**Hi**	**Lo**	**Hi**	**Lo**	**Hi**
35	3	35	1	19	8	59	2	39	30	88	10	78
45	9	47	2	22	21	70	5	43	51	92	20	79
55	23	59	4	25	45	79	10	47	80	95	38	82
65	49	69	9	29	71	86	20	51	93	97	56	84

For men older than 70 with atypical or typical symptoms, assume an estimate > 90%.
For women older than 70, assume an estimate of 61–90% EXCEPT women at high risk AND with typical symptoms where a risk of > 90% should be assumed.

Values are percent of people at each mid-decade age with significant coronary artery disease (CAD)[1].
Hi = High risk = diabetes, smoking and hyperlipidaemia (total cholesterol > 6.47 mmol/litre).
Lo = Low risk = none of these three.
The shaded area represents people with symptoms of non-anginal chest pain, who would not be investigated for stable angina routinely.
Note: These results are likely to overestimate CAD in primary care populations. If there are resting ECG ST-T changes or Q waves, the likelihood of CAD is higher in each cell of the table.

Discussion of the evidence for CACS in the NICE guideline is as follows:

Advantages and Disadvantages

The main advantages of calcium scoring are that calcium scanning takes approximately five minutes to perform and interpret, there is minimal radiation exposure (1.5 to 3 mSv) compared with multislice coronary angiography, no contrast material is required, the quantification of plaque (calcium score) enables non invasive temporal tracking of atherosclerosis burden and, although not of direct relevance to the investigation of CAD, it detects significant extra-cardiac findings in 2% to 3% as a coincidental finding. The disadvantages include the following; does not assess whether significant coronary stenoses are present, does not make a functional assessment of myocardial ischaemia, and left ventricular function is not assessed. Although coronary artery calcium is well correlated with total plaque volume or atherosclerotic burden it is not a direct marker of the vulnerable plaque at risk of rupture. However, the greater the calcium score the greater the potential for increased numbers of potentially lipid-rich plaques.

Evidence of Diagnostic Efficacy

No systematic reviews were identified. Ten studies were reviewed in total. With increasing thresholds of Agatston calcium score ranges, (from > 0 to 100, and > 100 in

[1] Adapted from Pryor DB, Shaw L, McCants CB et al. (1993) Value of the history and physical in identifying patients at increased risk for coronary artery disease. *Annals of Internal Medicine 118*(2),81-90.

3 studies, and from > 0 to 100, >100 to 400, and > 400 in 3 studies) the sensitivity decreased and the specificity increased for the detection of significant CAD. No evidence was found for the diagnostic accuracy of coronary calcium scores to diagnose significant CAD in ethnic minority groups in the UK. From economic modelling undertaken for this guideline, there is evidence that for patients with a low pre-test-probability of CAD (<25%), 64-slice CT coronary angiography preceded by testing using calcium scoring is cost-effective compared to functional testing and invasive coronary angiography.

Economic Evaluations

Of the six economic evaluations included in evidence reviewed for this guideline, only one addressed CACS. Rumberger 1999 compared exercise ECG, stress echocardiography (ECHO), stress thallium and CACS. The incremental analysis showed that electron beam CT using a calcium score threshold of >37, >80 or >168 is cost saving compared with stress ECHO and stress thallium testing. At low to moderate disease prevalence (10% to 20%), electron beam CT using thresholds of >37, >80 or >168 are cost saving compared with exercise ECG. Electron beam CT using a threshold of >0 is cost saving compared with stress thallium testing at 20% CAD prevalence and above.

The NICE guideline authors performed their own economic analysis of a diagnostic strategy that incorporated the use of calcium scoring using 64-slice CT coronary angiography as a precursor to full 64-slice CT coronary angiography. This was done as a way of minimizing the risk of radiation from 64- slice CT coronary angiography, a risk which was not explicitly incorporated into the other models. Results of the base case analysis indicate that for lower risk groups (5% and 20%), the use of calcium scoring as a first line testing strategy is likely to be cost-effective and should be followed by either 64-slice CT coronary angiography alone or with additional invasive coronary angiography as a confirmatory 3rd test. In higher risk populations, (CAD prevalence greater than 40%), a strategy of sending all patients directly to invasive coronary angiography is likely to be cost-effective. The model indicates that MPS with SPECT is excluded through dominance or extended dominance at every level of CAD prevalence. It also indicates that exercise ECG is only cost-effective as a first line investigation strategy at 5% CAD prevalence, but that even in this instance replacing exercise ECG with calcium scoring is likely to improve effectiveness at a reasonable level of additional cost.

Overall Summary

There is no evidence that risk stratification in asymptomatic patients using CACS reduces myocardial infarction or cardiovascular disease mortality compared with risk stratification and treatment on the basis of Framingham scoring alone. Coronary artery

calcium scoring may have a diagnostic role in the “rule out” of obstructive CAD in emergency department patients with acute chest pain and normal ECGs and initial cardiac enzymes, and in outpatients with stable chest pain with a low probability of obstructive CAD. However, there is little data available to support long-term outcomes using calcium scoring as a strategy, and it does not appear to function as a stand-alone test in clinical practice. The potential impact of radiation exposure, both from the CACS and from additional testing done to confirm the diagnosis or to evaluate incidental findings, needs to be considered, and current studies do not adequately address these concerns. One economic evaluation suggests that the most cost-effective course of action for stable outpatients with a low probability of CAD (10-29%) is CACS, followed by CCTA if the CACS score is 1-400, or invasive angiography if the score is greater than 400, however, this was from the perspective of the UK National Health Service, and applicability to the US setting is limited given differences in costs and the non-existence of accepted follow up algorithms.

COMMITTEE DELIBERATIONS-EbGS

Discussion centered around potential use in asymptomatic, intermediate-risk patients, however, it was felt that the evidence and pathways for use were insufficient to support a coverage recommendation at this time.

COMMITTEE DELIBERATIONS-VbBS

The VbBS decided to make no change in the lack of coverage.

HERC DELIBERATIONS

At its August 8, 2013 meeting, the HERC approved the coverage guidance and accepted the VbBS recommendation to make no associated changes to the prioritized list.

PROCEDURE

Electron beam coronary computed tomography
Multidetector coronary computed tomography
Coronary Artery Calcium Scoring

DIAGNOSES

Coronary artery disease
Chest pain

APPLICABLE CODES

CODES	DESCRIPTION
ICD-9 Diagnosis Codes	
410	Acute myocardial infarction
411	Other acute and subacute forms of ischemic heart disease
413	Angina pectoris
414	Other forms of chronic ischemic heart disease
786.5	Chest pain
ICD-9 Volume 3 (Procedure Codes)	
87.41	Computed axial tomography of the heart
CPT Codes	
75571	Computed tomography of heart, without contrast, with qualitative evaluation of coronary calcium
HCPCS Codes	
None	

Note: Inclusion on this list does not guarantee coverage

Coverage guidance is prepared by the Health Evidence Review Commission (HERC), HERC staff, and subcommittee members. The evidence summary is prepared by the Center for Evidence-based Policy at Oregon Health & Science University (the Center). This document is intended to guide public and private purchasers in Oregon in making informed decisions about health care services.

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