AHA Scientific Statement

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

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Executive Summary

This scientific statement reviews the scientific data for cardiac computed tomography (CT) related to imaging of coronary artery disease (CAD) and atherosclerosis. Cardiac CT is a CT imaging technique that accounts for cardiac motion, typically through the use of ECG gating. The utility

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and limitations of generations of cardiac CT systems are reviewed in this statement with emphasis on CT measurement of CAD and coronary artery calcified plaque (CACP) and noncalcified plaque. Successive generations of CT technology have been applied to cardiac imaging beginning in the early 1980s with conventional CT, electron beam CT (EBCT) in 1987, and multidetector CT (MDCT) in 1999. Compared with other imaging modalities, cardiac CT has undergone an accelerated progression in imaging capabilities over the past decade, and this is expected to continue for the foreseeable future. As a result, the diagnostic capabilities at times have preceded the critical evaluation of clinical application. In this statement, the American Heart Association (AHA) Writing Group evaluates the available data for the application of cardiac CT for CAD.

Cardiac CT uses natural contrast within subjects (utilizing the different brightness of fat, tissue, contrast, and air). Noncontrast CT is a low-radiation exposure technique and, even without premedication or intravenous contrast, can determine the presence or absence of CACP in <10 minutes. The amount of CACP can be measured to provide a reasonable estimate of total coronary atheroma including calcified and noncalcified plaque. The data supporting detection of CACP as a measure of CAD are extensive. Imaging applications that detect CACP include conventional chest radiographs, cinefluoroscopy, conventional and helical CT, EBCT, and MDCT.

The majority of published studies have reported that the total amount of coronary calcium (usually expressed as the "Agatston score") predicts coronary disease events beyond standard risk factors. Although some registries used self-reported risk factor data, data from EBCT reports using measured risk factors demonstrate incremental risk stratification beyond the Framingham Risk Score (FRS). These studies demonstrate that CACP is both independent of and incremental with respect to traditional risk factors in the prediction of cardiac events. Data from Greenland et al[1] demonstrated that intermediate-risk patients with an elevated coronary artery calcium (CAC) score (intermediate FRS and CAC score >300) had an annual hard event rate of 2.8%, or a 10-year rate of 28%, and thus would be considered high risk. The best estimates of the relative risk (RR) from this study indicated that a CAC score >300 had a hazard ratio (HR) of about 4 compared with a score of 0. This would mean that the estimated risk in the intermediate-risk patient with a CAC score of 0 might be reduced by at least 2-fold while the risk of a person with a CAC score of 300+ would be increased by about 2-fold. Thus, the person with a high CAC score and intermediate FRS is now reclassified as high risk. CT information may then be used to guide primary prevention strategies, especially among individuals within the intermediate-risk category, in whom, as suggested by the AHA Prevention Conference V,[2] clinical decision-making is most uncertain. Individuals determined to be at intermediate risk of a cardiovascular disease (CVD) event on the basis of traditional risk factors may benefit from further characterization of their risk through measurement of their atherosclerotic burden with cardiac CT. This AHA Writing Group agrees with the statement from the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III): "In persons with multiple risk factors, high coronary calcium scores (eg, >75th percentile for age and sex) denote advanced coronary atherosclerosis and provide a rationale for intensified LDL-lowering therapy."[3] Guidelines and expert consensus documents[4] have extended the recommendation for use of coronary calcium measurements in clinically selected patients at intermediate risk for CAD (eg, those with a 10% to 20% 10-year FRS) to refining clinical risk predictions and to assessing whether more aggressive target values for lipid-lowering therapies are indicated for select patients.[5] Asymptomatic persons should be assessed for their cardiovascular risk with such tools as the FRS. Individuals found to be at low risk (<10% 10-year risk) or at high risk (>20% 10-year risk) do not benefit from coronary calcium assessment **(Class III, Level of Evidence: B)**. In clinically selected, intermediate-risk patients, it may be reasonable to measure the atherosclerosis burden using EBCT or MDCT to refine clinical risk prediction and to select patients for more aggressive target values for lipid-lowering therapies **(Class IIb, Level of Evidence: B).**

When cardiac CT is used for CACP assessment, the AHA Writing Group strongly recommends a low-dose technique using prospective ECG gating. Although alternative techniques may provide improved resolution or increased precision in measurement, data to support an enhanced predictive ability given the higher radiation exposure are limited. A minimum CT-system configuration of EBCT C150 or more up to date or MDCT 4 channel with 0.5-second gantry rotation or faster is recommended. Although virtually all of the prognostic and epidemiological data derived for CACP have been performed with EBCT, several large prospective trials have documented that cardiac CT (both MDCT and EBCT) measurements can be similarly applied across multiple centers with equally high levels of patient satisfaction and acceptance.

The utility of CACP in symptomatic patients has been widely studied and has been discussed in depth in a previous ACC/AHA statement,[4] as well as in the AHA Cardiac Imaging Committee scientific statement "The Role of Cardiac Imaging in the Clinical Evaluation of Women With Known or Suspected Coronary Artery Disease."[5] The test has been shown to have a predictive accuracy equivalent to alternative methods for diagnosing CAD. These studies may have been subject to referral bias, as a positive test may have been the rationale for subjecting the patient to the invasive angiogram. More comparison work between modalities is clearly needed. A positive cardiac CT examination in which any CACP is identified is nearly 100% specific for atheromatous coronary plaque. CACP can develop early in the course of subclinical atherosclerosis and can be identified histologically after fatty streak formation. CACP is present in the intima of both obstructive and nonobstructive lesions, and thus, the presence of calcified plaque on cardiac CT is not specific to an obstructive lesion. Studies using intracoronary ultrasound have documented a strong association between patterns of CACP and culprit lesions in the setting of acute coronary syndromes.

Cardiac CT studies correlating calcified plaque using EBCT technology and various methods of coronary angiography in more than 7600 symptomatic patients demonstrate negative predictive values of 96% to 100%, providing phy-

sicians with a high level of confidence that an individual without CACP (total calcium score=0) does not have obstructive angiographic CAD. The presence of CACP is extremely sensitive, albeit with reduced specificity, for diagnosing obstructive CAD (95% to 99%) in patients >40 years of age. A recent study of 1195 patients who underwent CACP measurement with EBCT and myocardial perfusion single photon emission CT (SPECT) assessment demonstrated that CACP was often present in the absence of myocardial perfusion scintigraphy (MPS) abnormalities (normal nuclear test) and that <2% of all patients with CACP <100 had positive MPS studies.[6] This is supported by other published reports and is synthesized in a recent appropriateness criteria statement from the American Society of Nuclear Cardiology and the American College of Cardiology.[7,8] CACP measured by cardiac CT has a high sensitivity and negative predictive power for obstructive CAD but markedly limited specificity. Because calcified plaque may be present in nonobstructive lesions, the presence of CACP in asymptomatic persons does not provide a rationale for revascularization but rather for risk factor modification and possible further functional assessment. Clinicians must understand that a positive calcium scan indicates atherosclerosis but most often no significant stenosis. With exceptions, high-risk calcium scores (such as an Agatston score ≥400) are associated with an increased frequency of perfusion ischemia and obstructive CAD. The absence of coronary calcium is most often associated with a normal nuclear test and no obstructive disease on angiography. Coronary calcium assessment may be reasonable for the assessment of symptomatic patients, especially in the setting of equivocal treadmill or functional testing **(Class IIb, Level of Evidence: B).** There are other situations when CAC assessment might be reasonable. CACP measurement may be considered in the symptomatic patient to determine the cause of cardiomyopathy (**Class IIb, Level of Evidence: B**). Also, patients with chest pain with equivocal or normal ECGs and negative cardiac enzyme studies may be considered for CAC assessment **(Class IIb, Level of Evidence: B**).

Coronary calcium assessment for diagnosis of atherosclerosis and obstructive disease and for risk stratification for future cardiac events has undergone significant validation over the past 20 years. CT angiography is a noninvasive technique, performed by either EBCT or MDCT, to evaluate the lumen and wall of the coronary artery. Especially in the context of ruling out stenosis in patients with low to intermediate pretest likelihood of disease, CT coronary angiography may develop into a clinically useful tool. CT coronary angiography is reasonable for the assessment of obstructive disease in symptomatic patients **(Class IIa, Level of Evidence: B).** Several small studies have assessed the value of EBCT and MDCT for detecting restenosis after stent placement. At this time, however, imaging of patients to follow up stent placement cannot be recommended **(Class III, Level of Evidence: C).**

Where MDCT is used for CT angiography, the AHA Writing Group currently recommends a minimum of 16-slice capability, submillimeter collimation, and 0.42-second gantry rotation with retrospective ECG gating. If EBCT is used, 1.5-mm slice thickness should be used. A limitation of EBCT relative to MDCT is its lower power, with EBCT limited to 63 or 100 milliamperes/second (mAs), depending on scanner generation, which becomes important in larger patients because image quality can be affected by noise. Another advantage of MDCT is thinner slice imaging, with section thickness as small as 0.5 mm, whereas EBCT is limited to 1.5 mm. An advantage of EBCT, however, is the lower radiation dose associated with this procedure (1.1 to 1.5 mSv), compared with MDCT angiography (5 to 13 mSv).[9,10] The use of both CT modalities to evaluate noncalcified plaque (NCP) is promising but premature. There are limited data on variability but none on the prognostic implications of CT angiography for NCP assessment or on the utility of these measures to track atherosclerosis or stenosis over time; therefore, their use for these purposes is not recommended **(Class III, Level of Evidence: C)**.

CT technology is evolving rapidly, and these radiation dose estimates are likely to decrease with modification of the hardware and scanning protocols. The clinical relevance of the radiation dose that is administered with cardiac CT is unknown. However, higher radiation doses in general are associated with a small but defined increase in cancer risk later in life. The AHA Writing Group reviewing the available literature endorses the use of a prospective ECG trigger for measurement of CACP with a slice collimation of 2.5 to 3 mm for clinical practice. EBCT systems have an effective dose of 0.7 to 1 mSv (male) and 0.9 to 1.3 mSv (female), and MDCT systems have an effective dose of 1 to 1.5 mSv (male) and 1.1 to 1.9 mSv (female). Higher radiation exposures with retrospective gating for CACP assessment preclude its use for screening. Similarly, for CT angiography, the higher radiation doses (up to 1.5 mSv for EBCT and up to 13 mSv for MDCT) prohibit the use of this test as a screening tool for asymptomatic patients. CT coronary angiography is not recommended in asymptomatic persons for the assessment of occult CAD **(Class III, Level of Evidence: C)**.

The role of cardiac CT in measuring clinically or prognostically meaningful changes in calcified plaque over time and its correlation with other measures of coronary heart disease (CHD) is currently an area of intense investigation. Reductions in the test-to-test variability and improvements in the interreader reliability of the calcium score may allow for serial assessment of coronary calcium scores; however, more studies are required. It is difficult to justify the incremental population exposure to radiation and the cost associated with a repeat CT test to assess "change," until it is better understood what therapies may be of benefit and how clinicians should utilize this data in clinical practice. There is conflicting evidence as to whether vigorous cholesterol-lowering therapy with statins retards the rate of progression of CACP. The AHA Writing Group concluded that this potential use of cardiac CT will require additional validation before any recommendation. Serial imaging for assessment of progression of coronary calcification is not indicated at this time **(Class III, Level of Evidence: C**).

Cardiac CT technology is rapidly evolving. On the basis of the substantial validation data, EBCT remains the reference standard for CACP measurement.[11] MDCT-64 is the current standard for coronary CT angiography and NCP characterization based on publications to date.[12] The trend for improved image

quality with cardiac CT is consistent. It is critical that the cardiac imaging scientific community continue to integrate evolving technological advances with best clinical practices for treatment and prevention of CVD.[7,13]

An area of ongoing clinical research is the application of hybrid positron emission tomography CT (PET-CT) and SPECT-CT scanners that are currently available. This research will allow for the acquisition of metabolic and/or perfusion information as well as anatomic data, including angiographic data and data on coronary calcification. The incremental benefit of hybrid imaging strategies will need to be demonstrated before clinical implementation, as radiation exposure may be significant with dual nuclear/CT imaging. At this time, there are no data supporting the use of hybrid scanning to assess cardiovascular risk or presence of obstructive disease **(Class III, Level of Evidence: C)**.

In summary, cardiac CT has been demonstrated to provide quantitative measures of CACP and NCP. CACP, as determined by cardiac CT, documents the presence of coronary atherosclerosis, identifies individuals at elevated risk for myocardial infarction (MI) and CVD death, and adds significant predictive ability to the Framingham Score (an index of traditional CVD risk factors). Data suggest that cardiac CT may improve risk prediction, especially in individuals determined to be at intermediate risk according to the NCEP ATP III criteria and for whom decisions concerning prevention strategies may be altered based on the test results. The use of cardiac CT angiography for noninvasive assessment of lumen stenosis in symptomatic individuals has the potential to significantly alter the management of CAD and current diagnostic testing patterns. The assessment of progression of CACP and the detection of nonobstructive NCP by cardiac CT angiography warrant further investigation.

Introduction

The AHA has issued 2 prior statements on CAC scanning; one in 1996[14] and a second (in conjunction with the American College of Cardiology [ACC]) in 2000 specifically related to EBCT.[4] The AHA also sponsored the Prevention V Conference, which focused on the identification of the asymptomatic high-risk patient and discussed the potential role of CAC scanning.[2] In light of a rapidly evolving literature since the last ACC/AHA expert consensus statement (2000), the current statement will focus on new data available on using EBCT and MDCT to identify patients with coronary atherosclerosis defined by quantification of coronary artery calcification. EBCT is an especially fast form of x-ray imaging technology that can detect and measure calcium deposits in the coronary arteries.[5] The amount of calcium detected by EBCT is related to the amount of underlying coronary atherosclerosis. During the past decade, there has been a progressive increase in the clinical use of both EBCT and MDCT scanners to identify and quantify the amount of calcified plaque in the coronary arteries. This approach has generated much interest and scrutiny for several reasons. Although coronary calcification can be quantified and calcium scores can be related to the extent and severity of atherosclerotic disease and improving CHD risk prediction, misuse or abuse of these methods as a broad-based "screening" tool has created considerable controversy.

Recently, CT scanners with subsecond image acquisition and MDCT (also referred to as multirow or multislice) capability have been studied and proposed as an alternative approach to EBCT for detecting coronary calcification owing to the greater availability of such CT scanners. This scientific statement will compare MDCT and EBCT and serve as a clinical update for the use of CACP in clinical decision-making regarding evaluations for CHD in the asymptomatic individual. Current evidence regarding noninvasive angiography using CT, as well as the future role of these techniques in monitoring atherosclerosis over time and in detecting NCP, will be reviewed.

1. Coronary Artery Calcification and Epidemiology of Coronary Calcium

Arterial calcium development is intimately associated with vascular injury and atherosclerotic plaque. CACP is an active process and can be seen at all stages of atherosclerotic plaque development.[15–17] The long-held notion of so-called "degenerative" calcification of the coronary arteries with aging is incorrect. Since Faber[18] noted in 1912 that Mönckeberg's calcific medial sclerosis did not occur in the coronary arteries, atherosclerosis is the only vascular disease known to be associated with coronary calcification.[4,11,14,19,20] Thus, CACP in the absence of luminal stenosis is not a "false-positive" result but rather evidence of coronary atherosclerosis.[20]

Coronary calcification is nearly ubiquitous in patients with documented CAD[21–23] and is strongly related to age, increasing dramatically after age 50 in men and after age 60 in women (Tables 1 and 2).[24,25] However, coronary plaque and its associated coronary calcification may have only a weak correlation with the extent of histopathologic stenosis.[26,27] The degree of encroachment on the vessel lumen by the atherosclerotic plaque is largely determined by individual variations in coronary artery remodeling. However, the presence of CACP is associated with atherosclerotic plaque size.[26]

Rumberger and colleagues[28,29] examined 13 autopsied hearts and compared measures of CACP using EBCT as compared with direct histological plaque areas and percent luminal stenosis. These studies determined that the total area of CACP quantified by EBCT is linearly and highly correlated ($r=0.90$) with the total area of histological coronary artery plaque. Although the total atherosclerotic plaque burden was tracked by the total calcium burden, not all plaques were found to be calcified, and the total calcium area was approximately 20% of the total atherosclerotic plaque area. Baumgart et al[30] and Schmermund et al[31] compared direct intracoronary ultrasound measures during angiography with EBCT scanning and confirmed a direct association, in vivo, of CACP score with localization and extent of atherosclerotic plaques.

The prevalence of CACP mirrors the prevalence of coronary atherosclerosis in both men and women.[32] The data show the following: (1) the prevalence of CACP increases from only a small percentage in the second decade of life to nearly 100% by the eighth decade in men and women; (2) the prevalence of CACP in women is similar to that in men who

TABLE 1. Descriptive Characteristics of the Total Electron Beam Tomographic CAC Scores in Asymptomatic Men and Women

	Men				Women			
		Total CAC Score				Total CAC Score		
Age, y	n	Mean	SD	Median	n	Mean	SD	Median
<40	3504	12	70	0.5	641	2	14	0
40–44	4238	27	120	1	1024	8	97	0
45–49	4940	57	175	3	1634	18	186	0
50–54	4825	121	305	16	2184	29	135	0.5
55–59	3472	203	411	49	1835	54	189	1
60–64	2288	350	972	113	1334	78	250	3
65–69	1209	464	731	180	731	147	338	24
70–74	540	665	921	309	436	225	515	55
>74	235	836	1053	473	174	258	507	75

Adapted from data presented in Hoff et al.[24]

are a decade younger; (3) the gender difference in prevalence with age is eliminated by approximately age 65 to 70, when the prevalence of coronary calcium in women is similar to that in men of the same age. The prevalence of CACP increases with age, paralleling the increased prevalence of coronary atherosclerosis with advancing age.

1.1. Calcium Detection Methods

This section will discuss methods related to CACP identification.

1.1.1. EBCT Methods

EBCT is a tomographic imaging device developed nearly 20 years ago specifically for cardiac imaging. Although the technique can quantify ventricular anatomy and function[33] as well as myocardial perfusion,[34] it is currently best known for defining and measuring CACP. Over the past decade, there have been more than 1000 articles published regarding EBCT and coronary artery imaging.

EBCT (also referred to as "EBT" and "Ultrafast-CT," General Electric, South San Francisco, Calif) uses unique technology enabling ultrafast scan acquisition times currently of 50 ms, 100 ms, and multiples of 100 ms (up to 1.5 seconds) per slice (Table 3). There have been 3 iterations of EBCT systems since their clinical introduction in the early 1980s. The core imaging methods have remained unchanged, but there have been improvements in image acquisition; in data storage, manipulation, management, and display; and in spatial resolution. The original C-100 scanner was replaced in 1993 by the C-150, which was replaced by the C-300 in 2000. The current EBCT scanner, the "e-speed" (GE/Imatron, South San Francisco, Calif) was introduced in 2003. The e-speed is a multislice scanner and currently can perform a heart or body scan in half the total examination time required by the C-150 and C-300 scanners. In addition to the standard 50-ms and 100-ms scan modes common to all EBCT scanners, the e-speed is capable of high-resolution imaging speeds as fast as 50 ms. This very short acquisition time leads to fewer motion artifacts and improved contrast-to-noise ratios.[35]

EBCT uses a stationary multisource/split-detector combination coupled to a rotating electron beam and produces serial, contiguous, thin-section tomographic scans in syn-

TABLE 2. Electron Beam Tomographic CAC Score Percentiles for Men and Women Within Each Age Stratum

	Age, y								
	<40	40–44	45–49	50–54	55–59	60–64	65–69	70–74	>74
Men (25 251)	3504	4238	4940	4825	3472	2288	1209	540	235
25th Percentile	0	0	0	1	4	13	32	64	166
50th Percentile	1	1	3	15	48	113	180	310	473
75th Percentile	3	9	36	103	215	410	566	892	1071
90th Percentile	14	59	154	332	554	994	1299	1774	1982
Women (9995)	641	1024	1634	2184	1835	1334	731	438	174
25th Percentile	0	0	0	0	0	0	1	3	9
50th Percentile	0	0	0	0	1	3	24	62	75
75th Percentile	1	1	2	5	23	57	145	210	241
90th Percentile	3	4	22	65	121	193	410	631	709

Adapted from data presented in Hoff et al.[24]

TABLE 3. Basic Description of CT System Components

	EBCT	MDCT
Electron source (cathode)	Electron gun	Tungsten filament
Gantry	Fixed: Electron beam rapidly sweeps across tungsten rings	Rotates: Tube and opposing detectors rotate within gantry
Image reconstruction	Partial scan/filtered back-projection Sharp kernel	Partial scan/filtered back-projection Standard kernel
Beam current, mA	Fixed	User selectable
Exposure time for coronary calcium	50 or 100 ms (true prospective)	≥220 ms Dependent on gantry rotation speed and postprocessing
Gating for CT angiography	Prospective trigger	Retrospective gating
Exposure, mAs	Fixed mA × exposure time	User-selectable mA × exposure time
Heart rate limitations*	<110 bpm	<65 bpm
Best z-axis resolution	1.5 mm	0.5 mm

*Heart rate limitations based on the prevalence of studies with significant coronary motion.

chrony with the heart cycle. EBCT is distinguished by its use of a scanning electron beam rather than the traditional x-ray tube and mechanical rotation device used in current "spiral," single, and multiple-detector scanners. The electron beam is steered by an electromagnetic deflection system that sweeps it across the distant anode, a series of 4 fixed tungsten "target" rings. A stationary, single-level or dual-level arc of detectors lies in apposition to the tungsten target rings. In contrast, MDCT physically moves the x-ray tube in a circle about the patient; with EBCT, only the electron beam is moved.

Standardized methods for imaging, identification, and quantification of CAC using EBCT have been established.[4,36] The scanner is operated in the high-resolution, single-slice mode with continuous, nonoverlapping slices of 3-mm thickness and an acquisition time of 100 ms/tomogram.[37] Electrocardiographic triggering is done during end-systole or early diastole at a time determined from the continuous ECG tracing done during scanning.

Historically, the most common trigger time used is 80% of the R-R interval. However, this trigger occurs on or near the P wave during atrial systole, and the least cardiac motion among all heart rates occurs at 40% to 60% of the R-R interval.[38] Therefore, it has been demonstrated that the protocol of triggering at 80% of the R-R interval is not optimal for imaging of the coronary segments near the right or left atrium. Mao et al[39] compared 40% and 80% trigger delay (imaging during early compared with late diastole) and obtained an interscan variability of 11.5% versus 17.4%, respectively. For a more complete discussion on gating, see section 1.5.

1.1.2. MDCT Methods

The current generation of MDCT systems is capable of acquiring 4 to 64 sections of the heart simultaneously with ECG gating in either a prospective or retrospective mode. MDCT differs from single detector–row helical or spiral CT systems principally by the design of the detector arrays and data acquisition systems, which allows the detector arrays to be configured electronically to acquire multiple adjacent sections simultaneously (Table 3). In the current 16-row MDCT systems, 16 sections can be acquired at either 0.5- to 0.75-mm or 1- to-1.5-mm section widths, or 8 sections 2.5-mm thick.

In MDCT systems, like the preceding generation of single detector–row helical scanners, the x-ray photons are generated within a specialized x-ray tube mounted on a rotating gantry. The patient is centered within the bore of the gantry such that the array of detectors is positioned to record incident photons after they have traversed the patient. Within the x-ray tube, a tungsten filament allows the tube current to be increased (mA), which proportionately increases the number of x-ray photons for producing an image. This is a design difference with current generation EBCT systems, which use a fixed tube current.

MDCT systems have 2 principal modes of scanning, which depend on whether the patient on the CT couch is advanced in a step-wise fashion (axial, sequential, or conventional mode) or continuously moved at a fixed speed relative to the gantry rotation (helical or spiral mode). The axial mode is analogous to EBCT in using prospective ECG triggering at predetermined offset from the ECG-detected R wave and is the current mode for measuring coronary calcium at most centers using MDCT.

When prospective gating is performed, the temporal resolution of a helical or MDCT system is proportional to the gantry speed, which determines the time to complete one 360° rotation. To reconstruct each slice, data from a minimum of 180° plus the angle of the fan beam are required, typically approximately 220° of the total 360° rotation. Unless data from several consecutive heartbeats are combined, the temporal resolution is 257 ms for a 50-cm display FOV (field of view) when using a 16-row system with 0.42-second rotation. The newest 64-slice scanners now have rotation gantry speeds up to 330 ms.

1.2. Coronary Artery Calcified Plaque

Calcified plaque or calcified atheroma are the terms used in the AHA consensus paper on the definition of the advanced lesions of atherosclerosis (ie, AHA IVb lesion)—calcified plaque is a subcomponent of atheroma, not a surrogate measure.[40] CACP, as measured on cardiac CT, is defined as a hyperattenuating lesion above a threshold of 130

"Hounsfield Units" (HU) with an area ≥3 adjacent pixels (at least 1 mm^2).

There are currently 2 CT calcium scoring systems widely used: the original Agatston method and the "volume" score method. The Agatston score method involves multiplication of the calcium area by a number related to CT density and, in the presence of partial volume artifacts, can be variable. Also, the Agatston system was designed and is properly used only when the slice thickness of the scan is 3 mm. A calcium score is reported for a given coronary artery and for the entire coronary system; however, most research studies have reported data related to the summed or total "score" for the entire epicardial coronary system.

The Agatston scoring[37] scale is rule based: Calculate an area for all pixels above a threshold of 130 HU, do so every 3 mm (the slice thickness and spacing used by Agatston et al), and multiply it by a density factor. Partial volume effects lead to higher peak values for small lesions (but not for large ones). If the change in peak value happens to be such that it changes the density factor, then it can, theoretically, change the score by a factor of 4. The volume method of Callister et al[41] somewhat resolves the issue of slice thickness and spacing by computing a volume above threshold. The volume score is much less dependent on minor changes in slice thickness.

Current EBCT systems are now able to perform scanning at 1.5 mm, and the latest MDCT systems can provide slice thicknesses that are <1 mm. Use of thinner slices leads to higher radiation doses. In the future, a more universal scoring system may be possible that would be machine independent but, at present, data derived from MDCT should be compared with caution with those derived from EBCT. While the portability of the volume method is affected by the same issues that affect the Agatston method (slice thickness, calcium content), most studies demonstrate improved interscan reproducibility using volumetric scores for both MDCT and EBCT.

The calcium mass score has recently been reported. Basically, the mass score consists of integration of the signal for pixels above a given threshold. For a well-calibrated CT scanner, in the absence of noise, this integration (scaled by pixel volume) will give the total mineral content independent of slice thickness and spatial resolution. Although theoretically better for portability between scanners, this score has not yet undergone sufficient validation (autopsy, histology, outcomes, progression, or angiographic comparison), so its use clinically is premature.[42,43]

The retention of the Agatston score has been predicated on the availability of databases for these scores, which include the availability of outcome data so clinicians understand the significance of a certain score. Volume scores are similar, while mass scores tend to be much lower values for a given patient. Adoption of newer scoring methods will depend on the availability of similar risk stratification and outcome data. Data published by Rumberger et al[44] showed that the Agatston, volume, and mass scores, when applied properly, can provide similar characterization.

1.3. Speed/Temporal Resolution

Cardiac CT is dependent on having a high temporal resolution to minimize coronary motion–related imaging artifacts. Coupling rapid image acquisition with ECG gating makes it possible to acquire images in specific phases of the cardiac cycle. Studies have indicated that temporal resolutions of 19 ms would be needed to suppress all pulmonary and cardiac motion throughout the complete cardiac cycle.[45] Current-generation cardiac CT systems can create individual images at 50 to 100 ms (EBCT) and 83 to 210 ms (MDCT), a level of resolution that cannot totally eliminate coronary artery motion in all individuals.

Motion artifacts are especially prominent in the mid right coronary artery, where the ballistic movement of the vessel may be as much as 5 to 6 times its diameter during the twisting and torsion of the heart during the cardiac cycle. Blurring of cardiac structures secondary to coronary motion increases in systems with slower acquisition speeds. It should be noted that utilizing more detectors (ie, 4 versus 8 versus 16 versus 64 detector/channel systems) does not improve the temporal resolution of the images (the rotation speed of the scanners does not change) but reduces scan time (ie, breath-hold time) and section misregistration. Generally, the higher x-ray flux (mAs = tube current × scan time) and greater number and efficiency of x-ray detectors available with MDCT devices leads to images with better signal-to-noise ratio and higher spatial resolution when compared with current EBCT scanners.

1.4. Studies Comparing EBCT and MDCT for Calcium Scoring

Several studies comparing these modalities have been published. Becker et al[46] studied 100 patients comparing MDCT with EBCT and reported a variability of 32% between the 2 modalities. Knez et al[47] studied the diagnostic accuracy of MDCT compared with EBCT in 99 symptomatic male patients (60±10 years). The mean variability between the MDCT- and EBCT-derived scores was 17%. The findings of extensive calcification and a good correlation over a large range of values do not fully address the need to measure CACP scores accurately and reproducibly in a given individual. These high correlations may not apply as well to a younger, "asymptomatic" population with generally much lower scores.[48]

Carr et al[49] found agreement could be further improved by calibration of the Agatston score to an external standard. It should be emphasized that the clinical value for CAC determination is to facilitate individual risk assessment, and thus scoring for a given individual should be as accurate as possible. In epidemiologic studies of CACP in broad population groups, measures by MDCT and EBCT may well provide important insight into the atherosclerotic process, a hypothesis currently under investigation in large, population-based studies (Multi-Ethnic Study of Atherosclerosis [MESA][50] and the Heinz Nixdorf RECALL study[51]).

1.5. Reproducibility and Validity of Calcium Scoring

A potential of these technologies is to estimate atherosclerosis burden and to track changes over time in order to assess

efficacy of therapy.[52] This ability to assess progression is dependent on the reproducibility of the technologies. With EBCT, the mean interscan variability, with improved methodology (early diastolic or end-systolic triggering) and hardware improvements available since 1997, has been shown to be approximately 15%, with interreader variability approximately 3% and intrareader variability <1%.[39,53–58] Achenbach demonstrated the median variability to be 5.7% using EBCT.[59]

The interscan variability in several early studies using noncardiac gated MDCT (dual slice) scanners was 32% to 43%.[60,61] The literature clearly supports the use of cardiac gating to improve the measurement of CACP. A study of 75 persons using 4-slice MDCT demonstrated a mean variability of 25% for overlapping images with volume scoring, as compared with 46% for Agatston scoring without overlap.[62] A study of 537 patients undergoing 2 studies on 4-slice MDCT with cardiac gating demonstrated a mean variability of 36% for volume scoring and 43% for Agatston scoring.[63] Other small studies demonstrated variabilities of 20% to 37% for Agatston scoring and 14% to 33% for volume scoring.[64–66]

The National Institutes of Health/National Heart, Lung, and Blood Institute MESA is a population-based study in which 6814 men and women 45 to 84 years of age and free of clinically apparent CVD were recruited from portions of 6 US communities. Cardiac CT (EBCT-C150 and MDCT-4) examinations for measuring CACP were performed during the baseline examination between July 2000 and August 2002 using a standardized protocol.[67] Dual scans were obtained in 3551 MESA participants on an EBCT-C150 and in 3190 participants on an MDCT-4-channel system to evaluate reproducibility of the CT systems for measuring CACP. Both systems were highly concordant on the paired scan series (96% EBCT and 96% MDCT) for the presence or absence of calcified plaque.[68] Chance corrected agreement for both technologies was high with an identical kappa statistic of 0.92. When the mean absolute rescan differences were compared, adjusted for body mass index and extent of CACP, no significant difference was seen between EBCT and MDCT-4 with absolute Agatston unit values (95% confidence intervals [CIs]) by scanner type for GE-Imatron C-150 (EBCT), Siemens Volume Zoom (MDCT-4), and GE LightSpeed Plus (MDCT-4) being 15.8 (15.1,16.6), 17.5 (16.5, 18.5) and 15.7 (14.5,17.1), respectively.

One important limitation of this study was the difference in methodologies used by the scanners. The triggers in this study used 80% gating for EBCT and 50% gating for MDCT.[67] Mao et al[56] demonstrated that the Agatston score variability with EBCT decreases from 24% to 15% with use of an early diastolic trigger rather than the 80% trigger employed in the MESA study ($P<0.05$). The measure of CACP volume in MESA had a mean relative difference of 18% with both technologies, and this 2% improvement as compared with the Agatston score was statistically significant. This improvement in reproducibility with the volume score is consistent with this measure not accounting for information related to plaque density (ie, calcium mass). The results from MESA demonstrate good performance by both cardiac CT technologies with regard to presence, absence, and amount of CACP.

There has been some debate about using retrospective gating instead of prospective gating with MDCT to further improve reproducibility, despite the increased radiation exposure. Ohnesorge et al[69] studied 50 patients using retrospective gating, demonstrating mean variability of 23% (Agatston score) and 21% (volume score) when using nonoverlapping increments of 3 mm. A considerable reduction in rescan variability can be achieved by overlapping the slices obtained (Agatston 12%, volume 8%) with $P<0.01$. Considerably higher mean variability is present for the patient subgroup with low to mild calcification if image data with nonoverlapping increments are used (Agatston 42%, volume 34%). The radiation dose reported for this methodology was >2.6 mSv per patient, representing a 2-fold increase as compared with prospectively gated MDCT studies.

Van Hoe et al[65] evaluated 50 patients and reconstructed the retrospective datasets at 3 different time intervals to try to minimize interscan variability. The mean percentage interscan variability was 30±31% with the use of an image reconstruction window of 40%, 33±37% with use of an image reconstruction window of 50%, and 27±22% with use of the optimal image reconstruction window. The authors stated, "Although we used the same technique as that of Ohnesorge et al,[69] we found mean interscan variability values that were 2 to 3 times higher. No obvious explanation can be given for these striking differences."

Use of retrospective gating in an attempt to improve reproducibility with MDCT is associated with a higher radiation exposure, increased interreader variability, and markedly increased interpretation times. In 1 study of 30 patients, Agatston and volumetric scores were assessed by using 16-detector retrospectively gated MDCT.[70] For each patient, 10 datasets were created that were evenly spaced throughout the cardiac cycle. Nineteen (63%) of 30 patients could be assigned to >1 risk group depending on the reconstruction interval used to measure the calcium score. Agatston and volumetric scores both proved highly dependent on the reconstruction interval used (coefficient of variation ≤63%), even with the most advanced CT scanners. Accurate and reproducible quantification of coronary calcium using retrospective gating seems to require analysis of multiple reconstructions.

The AHA Writing Group proposes that the following minimum requirements be met in scanning for CAC[71]:

1. Use of an electron beam scanner or a 4-level (or greater) MDCT scanner
2. Cardiac gating
3. Prospective triggering for reducing radiation exposure
4. A gantry rotation of at least 500 ms
5. Reconstructed slice thickness of 2.5 to 3 mm to minimize radiation in asymptomatic persons (and to provide consistency with established results)
6. Early to mid-diastolic gating

1.6. Radiation Dose for Cardiac CT

CT uses x-rays, a form of ionizing radiation, to produce the information required for generating CT images. Although all

individuals are exposed to ionizing radiation from natural sources on a daily basis, healthcare professionals involved in medical imaging must understand the potential risks of a test and balance them against the potential benefits. This is particularly important for diagnostic tests that will be given to healthy individuals as part of a disease-screening or risk-stratification program. For healthcare professionals to effectively advise individuals, they must have an understanding of the exposure involved.

The FDA, in describing the radiation risks from CT screening,[72] used the following language:

> In the field of radiation protection, it is commonly assumed that the risk for adverse health effects from cancer is proportional to the amount of radiation dose absorbed and the amount of dose depends on the type of x-ray examination. A CT examination with an effective dose of 10 millisieverts (abbreviated mSv; 1 mSv=1 mGy in the case of x-rays) may be associated with an increase in the possibility of fatal cancer of approximately 1 chance in 2000. This increase in the possibility of a fatal cancer from radiation can be compared with the natural incidence of fatal cancer in the US population, about 1 chance in 5. Nevertheless, this small increase in radiation-associated cancer risk for an individual can become a public health concern if large numbers of the population undergo increased numbers of CT procedures for screening purposes. It must be noted that there is uncertainty regarding the risk estimates for low levels of radiation exposure as commonly experienced in diagnostic radiology procedures. There are some authorities who question whether there is adequate evidence for a risk of cancer induction at low doses. However, this position has not been adopted by most authoritative bodies in the radiation protection and medical arenas.

Effective dose is an estimate of the dose to patients during an ionizing radiation procedure. It measures the total energy entered into the body and then takes into account the sensitivity of the organs irradiated. Although it has many limitations, it is often used to compare the dose from a CT examination or other examination using ionizing radiation to the background radiation a patient experiences in a year. Units are either millirem (mrem) or millisieverts (mSv); 100 mrem is 1 mSv. The estimated dose from chest x-ray is 0.04 to 0.10 mSv, and the average annual background radiation in the United States is 3 to 3.6 mSv.[10]

One drawback of MDCT as compared with EBCT is the higher radiation exposure to the patient (Table 4).[10,11,73–84] The x-ray photon flux expressed by the product of x-ray tube current and exposure time (mAs) is generally higher with MDCT. For example, 200 mA with 0.5-second exposure time yields 100 mAs in MDCT versus 614 mA (fixed tube current) with 0.1-second exposure time yields 61.4 mAs in EBCT.

Hunold et al[10] performed a study of radiation doses during cardiac examinations. Coronary calcium scanning was performed with EBCT and 4-level MDCT using prospective triggering to assess each patient's effective radiation exposure, which was then compared with measurements made during cardiac catheterization. EBCT yielded effective doses of 1.0 and 1.3 mSv for men and women, whereas MDCT using 100 mA, 140 kV, and 500-ms rotation yielded 1.5 mSv for men and 1.8 mSv for women. Invasive coronary angiography yielded effective doses of 2.1 and 2.5 mSv for men and women, respectively.

When similar protocols using single-detector-row CT (SD CT) and MDCT were compared, MDCT resulted in a dose profile approximately 27% higher than that from SD CT in the plane of imaging (8.0 versus 6.3 mGy) and 69% higher adjacent to the plane of imaging (6.8 versus 4.0 mGy).[74] The individual doses to the kidneys, uterus, ovaries, and pelvic bone marrow were 92% to 180% higher with MDCT than with SD CT. The authors concluded, "With image noise constant between SD CT and MDCT, the radiation dose profile both inside and outside the plane of imaging was higher with MDCT than with SD CT. Organ dose also was higher with MDCT than with SD CT."

Because retrospective gating exposes the patient to significantly higher radiation, several techniques have been implemented to reduce those exposures. Mahnken et al[75] studied body-weight dosing (reducing the radiation exposure based on body size) and measured the mean of the effective radiation dose with and without dose modulation. The radiation dose for a calcium scan using MDCT was 4.44 mSv (range, 3.28 to 5.88 mSv) for women and 3.01 mSv (range, 2.52 to 4.18 mSv) for men, whereas with dose modulation, the mean of the calculated radiation dose was 3.34 mSv (range, 2.39 to 3.83 mSv) for women and 2.66 mSv (range, 2.09 to 3.53) for men.

1.6.1. Radiation Exposure During CT Angiography

MDCT angiography requires retrospective gating, associated with significantly greater radiation exposures, to acquire images. Radiation doses of cardiac MDCT scans reported in the literature vary a great deal depending on the scan parameter settings. The tube voltages in the published protocols vary from 120 to 140 kVp, and the tube currents vary from 150 to 600 mA.[76] In contrast, the scan settings of EBCT used for cardiac imaging were fixed, in the older technology, to 130 kVp, 630 mA, and 100-ms exposure time. These EBCT settings have been somewhat altered, however, by the newer e-Speed technology, with both higher kVp and mA potential (140 kVp, 1000 mA). Newer protocols for MDCT angiography allow for increased power utilization, with settings as high as 900 mA possible. These higher settings will further increase the radiation dose, which is an issue to be considered when performing these protocols.

Pitch is calculated as table speed divided by collimator width. A low pitch (low table speed) allows for overlapping data from adjacent detectors. Most commonly, physicians use a low table speed and thin collimation width, leading to a large number of very thin axial slices, which are of great value for imaging the heart with high resolution. The tradeoff for these overlapping images is a markedly higher radiation exposure.[76] These protocols are also responsible for substantial increases in radiation doses, especially for the MDCT

TABLE 4. Radiation Doses With EBCT and MDCT Coronary Angiography

Author, Year[Reference]	EBCT Effective Dose	MDCT Prospective Trigger	MDCT Retrospective Gating	EBCT Angiography	MDCT Angiography	Cardiac Catheterization
Becker, 1999[46]	0.8 mSv		5.3 mSv			3.3 mSv
Ohnesorge, 2002[69]			3.0 mSv (m)			
			4.0 mSv (f)			
Cohnen, 2001[73]			2.8 mSv (m)			
			3.6 mSv (f)			
Jakobs, 2002[84]		2 mSv (m)				
		2.5 (f)				
		1 mSv (m)*				
		1.4 (f)*				
Hunold, 2003[10]	1 mSv (m)	1.5 mSv (m)	3 mSv (m)	1.5 mSv (m)	10.9 mSv (m)	2.1 mSv (m)
	1.3 mSv (f)	1.8 mSv (f)	3.6 mSv (f)	2.0 mSv (f)	13.0 mSv (f)	2.5 mSv (f)
Morin, 2003[9]	0.7 mSv	1.0 mSv	2.6–4.1 mSv	1.1 mSv	9.3–11.3 mSv	
Kopp, 2002[169]			7.6 mSv (m)			
			9.2 mSv (f)			
Achenbach, 2001[166]			6.7 mSv (m)			
			8.1 mSv (f)			
Flohr, 2003[77]		0.5 mSv (m)	1.9–2.2 mSv (m)		5.7–7.1 mSv (m)	
		0.8 mSv (f)	2.8–3.1 mSv (f)		8.5–10.5 mSv (f)	
			1-1.5 mSv (m)*		2.9–5 mSv (m)*	
			1.4–2 (f)*		4.2–7.4 mSv (f)*	
Trabold, 2003[78]			2.9 mSv (m)		8.1 mSv (m)	
			3.6 mSv (f)		10.9 mSv (f)	
			1.6 mSv (m)*		4.3 (m)*	
			2 mSv (f)*		5.6 (f)*	
Carr, 2000[49]	0.6 mSv (m)	0.9–1.5 mSv (m)	4.6 mSv (m)			
	0.7 mSv (f)	1.1–1.9 mSv (f)	5.6 mSv (f)			
Raff, 2005[80]					13 mSv (m)	
					18 mSv (f)	

(m) indicates male; (f), female.
*With dose modulation.

systems, with dose estimates of up to 11 to 13 mSv per study (Table 4).

Two studies have measured the radiation doses for CT angiography, comparing EBCT and 4-slice MDCT. The first reported EBCT angiography doses of 1.5 to 2.0 mSv, MDCT angiography doses of 8 to 13 mSv, and coronary angiography doses of 2.1 to 2.3 mSv, while the second reported EBCT angiography doses of 1.1 mSv and MDCT doses of 9.3 to 11.3 mSv.[9,10] Newer MDCT studies report that radiation doses are similar with 16-level multidetector scanners and higher with 64 MDCT.[77,78] Studies estimate radiation exposure for 16-row MDCT at 8.8 mSev for a 16×0.75-mm scan protocol with a pitch of 0.28 and power of 370 mA[79] and at 13 and 18 mSv (for men and women, respectively) with 64-row MDCT.[80] It should be noted that nuclear imaging has similar radiation exposure doses for cardiac studies (8 to 12 mSv).[81] Specifically, technetium studies are on the lower end of this spectrum (6 to 8 mSev on average), and thallium studies have been reported as high as 27 mSv.[82]

With the retrospective ECG-gating mode, scan data are acquired and available for the entire phase of the cardiac cycle. In most cases, however, the scan data used for image reconstruction are selected only during the diastolic phase. This implies that a high tube current is required only during the diastolic phase and that a low tube current is acceptable during the remaining cardiac phase. Modulating the tube current online with prospective ECG control (dose modulation) is reported to help reduce radiation exposure substantially without decreasing diagnostic image quality.[83,84]

For MDCT coronary angiography, dose modulation techniques reduce radiation exposures[84] and should be employed whenever possible. The effects of dose reduction are more pronounced for lower heart rates. Also, using the lowest necessary mA during each study will also help limit radiation exposures during these procedures. For MDCT, increased numbers of detectors allow for better collimation and spatial reconstructions. Having more of the heart visualized simultaneously will also allow for reductions in the contrast requirements and breathholding for the patient, further improving the methodology.

In summary, CT technology is evolving rapidly and radiation exposures are likely to be reduced with modification of

the hardware and scanning protocols. The clinical relevance of differences in radiation dose between different technologies is unknown, but most would agree that less radiation is better for patients than more radiation. The AHA Writing Group, reviewing the available literature, endorses the use of a prospective ECG trigger for measurement of CACP with a slice collimation of 1.5 to 3 mm for clinical practice. EBCT systems have an effective dose of 0.7 to 1 mSv (for men) and 0.9 to 1.3 mSv (for women), and MDCT systems have an effective dose of 1 to 1.5 mSv (for men) and 1 to 1.8 mSv (for women).[9,10,76] For CT angiography, the higher radiation doses suggest the need for greater forethought when using these tests, and use of these higher radiation exposure tests in asymptomatic persons for screening purposes is not currently recommended.

2. Clinical Utility of CACP Detection

This is the first time that the AHA evidence-based scoring system (see http://circ.ahajournals.org/manual/manual_IIstep6.shtml) has been incorporated into the AHA's evaluation of cardiac CT. The purpose of the scoring system is to assist the clinician in interpreting these recommendations and formulating treatment decisions. The system is based on both a classification of recommendations and the level of evidence. Each treatment recommendation has been assigned a class and a level of evidence. The use of this system should support but not supplant the clinician's decision making in the management of individual patients' cases.

Classification of Recommendations

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

Level of Evidence

- **Level of Evidence A:** Data derived from multiple randomized clinical trials
- **Level of Evidence B:** Data derived from a single randomized trial or nonrandomized studies
- **Level of Evidence C:** Consensus opinion of experts

2.1. CT Coronary Calcium and Symptomatic Patients

The utility of measuring CAC in symptomatic patients has been widely studied and discussed in depth in a previous ACC/AHA statement,[4] as well as in the recent AHA Cardiac Imaging Committee consensus statement, "The Role of Cardiac Imaging in the Clinical Evaluation of Women With Known or Suspected Coronary Artery Disease."[5] A positive EBCT study (indicating the presence of CACP) is nearly 100% specific for atheromatous coronary plaque[4,5,26–28] but is not highly specific for obstructive disease, as both obstructive and nonobstructive lesions have calcification present in the intima. The presence of CACP by EBCT is extremely sensitive, however, for obstructive (>50% luminal stenosis) CAD (95% to 99%).[4,5,20–22] This has led to much confusion over the interpretation of CACP as a diagnostic test.

TABLE 5. Sensitivity and Specificity of Diagnostic Tests for Evaluation of CAD

	No. of Patients	Sensitivity, %	Specificity, %
Stress treadmill[85]	2456	52	71
Exercise SPECT[85,86]	4480	87	73
Stress echocardiography[85]	2637	85	77
EBCT calcium[22,23,89]	5730	85	75

A large multicenter study on EBCT for diagnosis of obstructive CAD in symptomatic persons (n=1851) found that the sensitivity and specificity of CACP were 96% and 40%, respectively.[22] However, increasing the cutpoint for calcification markedly improves the specificity. In this same study, increasing the CACP cutpoint to >80 decreased the sensitivity to 79%, while increasing the specificity to 72%. In another large study (n=1764) comparing CACP to angiographic disease, use of a CACP score >100 led to a sensitivity of 95% and a specificity of 79% for the detection of significant obstructive disease by angiography.[23] Summing these 2 large studies (n=3615) leads to a sensitivity of 85% with a specificity of 75%. In a meta-analysis of 44 studies, technetium stress was found to have a mean sensitivity of 87% and mean specificity of 64%,[85] similar to the results of CACP. Thus, CACP measurements have a similar accuracy to other commonly accepted modalities for diagnosis of obstructive CAD by angiography (Table 5). For all diagnostic accuracy literature, one must be concerned about posttest referral bias, whereby positive tests are the cause for the referral to the catheterization laboratory. If the test is allowed to be part of the referral pattern, the sensitivity will increase and the specificity will decrease. However, for the 3 studies of EBCT, imaging was performed after the patient was referred for an invasive angiogram. The reason for the low specificity with CAC testing is the presence of CAC in nonobstructive as well as obstructive lesions.

In direct comparison studies, EBCT coronary calcium has been shown to be comparable to nuclear exercise testing in the detection of obstructive CAD.[87,88] The accuracy of EBCT is not limited by concurrent medication, the patient's ability to exercise, baseline ECG abnormalities, or existing wall motion abnormalities. Patients whose studies prove negative would be less likely to undergo invasive angiography. More comparison work between modalities is clearly needed.

Data also support a complementary role for coronary calcium and MPS measurements. A recent study of 1195 patients who underwent CACP measurement and MPS assessment demonstrated that the presence of CACP was the most powerful predictor that a nuclear test would be positive for ischemia and that <2% of all patients with CACP <100

had positive MPS studies.[6] EBCT, owing to its high sensitivity for flow-limiting CAD, may be useful as a filter before angiography or stress nuclear imaging, with more caution in younger patients. Knez et al[89] studied 2115 consecutive symptomatic patients (n=1404 men, mean 62±19 years of age) with no prior diagnosis of CAD, finding CAC in more than 99% of patients with obstructive CAD. No calcium was found in 7 of 872 men (0.7%) and in 1 of 383 women (0.02%) who had significant luminal stenosis on coronary angiography. Seven of these 8 patients with missed obstructive disease and scores of 0 were <45 years of age.

Recent ACC/ASNC appropriateness criteria support that a low calcium score precludes the need for MPS assessment and a high score warrants further assessment.[8] These appropriateness criteria suggest nuclear testing may generally be inappropriate in patients with calcium scores <100, as the probability of obstruction or abnormal scan is very low. However, more recent evidence suggests that MPS may be indicated in patients with diabetes and those with a family history of CAD who have a calcium score <100.[90–92] For the remaining asymptomatic patients, a person with an Agatston score >400 may benefit from functional testing to detect occult ischemia. The use of functional testing is paramount in determining the need for revascularization, as functionally insignificant lesions do not benefit from revascularization.

CACP may also be considered in determining the etiology of cardiomyopathy **(Class IIb, Level of Evidence: B)**. The clinical manifestations of patients with ischemic cardiomyopathy are often indistinguishable from those with primary dilated cardiomyopathy. One large study of 120 patients with heart failure of unknown etiology demonstrated that the presence of CACP was associated with 99% sensitivity for ischemic cardiomyopathy.[93] Another study demonstrated similarly high sensitivity using dual CT to differentiate ischemic from nonischemic cardiomyopathy.[94] Direct comparison studies have demonstrated this methodology to be more accurate than echocardiography and MPS techniques.[95,96] Additional comparative prognostic and diagnostic evidence is required to evaluate the role of CT as compared with conventional stress imaging techniques, as well as an assessment developing marginal cost-effectiveness models.

Another potential application of CACP relates to the triage of patients with chest pain. Three studies have documented that CACP is a rapid and efficient screening tool for patients admitted to the emergency department with chest pain and for whom ECG findings have been nonspecific.[97–99] These studies show sensitivities of 98% to 100% for identifying patients with acute MI and very low subsequent event rates for persons with negative test results. The high sensitivity and negative predictive value may allow early discharge of those patients with nondiagnostic ECG and negative CACP scans (score=0). Long-term follow-up of this cohort demonstrates patients without demonstrated CACP at the time of the emergency visit are at very low risk of subsequent events.[97]

Recommendation: Patients with chest pain with equivocal or normal ECGs and negative cardiac enzyme studies may be considered for CAC assessment **(Class IIb, Level of Evidence: B)**.

For the symptomatic patient, exclusion of coronary calcium may be an effective filter before invasive diagnostic procedures or hospital admission. EBCT studies of more than 7600 symptomatic patients undergoing cardiac catheterization demonstrate negative predictive values of 96% to 100%, allowing physicians a high level of confidence that an individual with no coronary calcium (score=0) does not have obstructive angiographic disease.[21–23,89] Calcium scores <100 are associated with a very low probability (<2%) of abnormal perfusion on nuclear stress tests[6] and <1% probability of significant obstruction (>50% stenosis) on cardiac catheterization.[6,21–23,89] While models suggest this is a cost-effective algorithm, further testing and prospective analysis are required.[100,101]

Recommendation: Coronary calcium assessment may be reasonable for the assessment of symptomatic patients, especially in the setting of equivocal treadmill or functional testing **(Class IIb, Level of Evidence: B).**

2.2. CT Coronary Calcification and Clinical Outcomes in Asymptomatic Individuals

Calcification of the coronary arteries occurs in approximate proportion to the severity and extent of coronary atherosclerosis.[102] In a landmark study of atherosclerosis, persons dying of coronary disease were found to have 2-fold to 5-fold greater amounts of coronary calcification than age-matched controls dying accidentally or of other natural causes.[103] Eight studies have examined the prognostic accuracy of CACP score by EBCT.

The first and longest study of EBCT scanning of the coronary arteries, the South Bay Heart Watch study,[1,104–106] began in 1990 as a prospective study of the prognostic accuracy of cardiac fluoroscopy in 1461 asymptomatic, high-risk individuals. In 1992, 1289 study participants (mean age 66±8 years) underwent EBCT scanning. Although an early analysis revealed no incremental advantage of EBCT scanning over conventional risk factor assessment for hard coronary events,[104] long-term (median=7.0 years) follow-up has demonstrated that the CACP score adds predictive power beyond that of standard coronary risk factors and C-reactive protein.[1,105] In multivariable models, a CACP score >300 was highly statistically significant and independently predictive of fatal or nonfatal MI, compared with a score of 0 (HR=3.9, $P<0.001$). In this study, patients with an FRS of 16% to 20% and a CAC score ≥300 had an annual event rate of 2.8%. This patient group would therefore have the 10-year event rate ≥20% that indicates high risk by current NCEP criteria.

From a retrospective cohort study of 632 asymptomatic persons (mean age 52±9 years, mean follow-up =2.7 years), the annual rate of nonfatal MI or CHD death increased from 0.045% in the lowest quartile of calcium scores to 2.7% among subjects in the highest quartile of calcium scores (a 59-fold increase).[107] Thus, patients with high calcific plaque burden did exceed the high-risk threshold (>2% per year hard cardiac event rate). These investigators demonstrated that EBCT added incremental benefit over and above standard coronary risk factors for risk prediction.[108]

Another study of 1172 asymptomatic persons (mean age 53±11 years, follow-up=3.6 years) demonstrated that a calcium score >160 was highly predictive of nonfatal MI or CHD death with an elevated risk 23.3-fold higher for CACP scores >160 versus CACP <160.[109] This study did not measure risk factors but did multivariable analysis to adjust for self-reported cardiovascular risk factors.

Wong et al[110] reported on 3.3-year follow-up in 926 asymptomatic persons (mean age 54±10 years). The calcium score predicted events independently of age, gender, and other cardiovascular risk factors (risk-adjusted RR=8.8 for scores in the fourth versus first quartile). Kondos et al[111] reported 37-month follow-up in 5635 initially asymptomatic low-risk to intermediate-risk adults (mean age 51±9 years). While follow-up was only obtained in 64% of patients, multivariable modeling demonstrated that patients with scores >170 (top quartile of scores) had an RR for hard cardiac events of 7.24-fold (95% CI, 2.01 to 26.15) as compared with patients without CACP. Finally, in a larger cohort of 10 377 asymptomatic individuals undergoing cardiac risk factor evaluation and CACP measurement with EBCT, a study with a mean follow-up of 5.0 years[112] used a risk-adjusted model to show that CACP was an independent predictor of all-cause mortality ($P<0.001$).

Shemesh et al[113] reported on a 3.8-year follow-up of 446 hypertensive patients prospectively followed up after risk factor measurement and CACP. CACP (total coronary calcium score >0) independently predicted cardiovascular events with an odds ratio (OR) of 2.76 (95% CI 1.09 to 6.99, $P=0.032$). Of note, this was the first prognostic study with MDCT (using a dual-slice CT system).

A significant limitation to a number of the early studies, with the exception of the South Bay Heart Watch Study, is that they were retrospective and did not include measured risk factors. However, 6 recently reported prospective studies, all with measured risk factors, now demonstrate the independent and incremental prognostic value of CAC measurement over the FRS.

The St. Francis Heart Study is a prospective observational study of 4613 subjects (59±5 years of age) with 4.3 years of follow-up.[114] A calcium score >100 predicted cardiovascular events, all coronary events, and the sum of nonfatal MI or CHD death events with RR ratios ranging from 9.2 to 11.1. Of note in this prospective series, the calcium score predicted cardiovascular events independently of standard risk factors and high-sensitivity C-reactive protein ($P<0.004$). Additionally, the calcium score also had improved event classification when compared with the FRS (area under the ROC curve 0.79±0.03 versus 0.68±0.03, $P=0.0006$).

Similarly, in a younger cohort of asymptomatic persons, the Prospective Army Coronary Calcium (PACC) Project[115] reported 3-year mean follow-up in 2000 participants (mean age 43 years). Participants were evaluated with measured coronary risk variables and coronary calcium detected by EBCT. Coronary calcium was associated with an 11.8-fold increased risk for incident CHD ($P<0.002$) in a Cox model controlling for the FRS. Among those with CAC, the risk of coronary events increased incrementally across tertiles of coronary calcium severity (HR 4.3 per tertile). A family history of premature CHD was also predictive of incident events. A major limitation of this study is that coronary events occurred in only 9 of the men who participated, with no events reported in women. Thus, the CIs around the RR estimates were rather large. The authors concluded, "In young, asymptomatic men, the presence of CAC provides substantial, cost-effective, independent prognostic value in predicting incident CHD that is incremental to measured coronary risk factors."

The Rotterdam Heart Study[116] investigated a general, asymptomatic population of 1795 elderly subjects. Participants who were followed up prospectively (mean age=71 years) had CAC and measured risk factors. During a mean follow-up of 3.3 years, 88 cardiovascular events, including 50 coronary events, occurred. The multivariable-adjusted RR of coronary events was 3.1 (95% CI, 1.2 to 7.9) for calcium scores of 101 to 400, 4.6 (95% CI, 1.8 to 11.8) for calcium scores of 401 to 1000, and 8.3 (95% CI, 3.3 to 21.1) for calcium scores >1000, respectively, compared with calcium scores of 0 to 100. Risk prediction based on the cardiovascular risk factors improved when coronary calcification was also taken into account.

The Cooper Clinic Study[117] included 10 746 adults who were 22 to 96 years of age and who were free of known CHD. During a mean follow-up of 3.5 years, 81 hard events (CHD death, nonfatal MI) occurred. Age-adjusted rates (per 1000 person-years) of hard events were computed according to 4 CAC categories: no detectable CAC and incremental sex-specific thirds of detectable CAC; these rates were, respectively, 0.4%, 1.5%, 4.8%, and 8.7% (trend $P<0.0001$) for men and 0.7%, 2.3%, 3.1%, and 6.3% (trend $P<0.02$) for women. The association between CAC and CHD events remained significant after adjustment for CHD risk factors. The results revealed a strong, graded association between CAC scores and incident CHD events among asymptomatic individuals free of known CHD at the time of EBCT scanning. The findings were consistent for men and women and held after adjustment for age and conventional CHD risk factors. CAC was associated with CHD events in persons with no baseline CHD risk factors and in younger (<40 years of age) and older (>65 years of age) study participants.

A Munich study determined the extent of CAC by MDCT in 924 patients (443 men, 481 women, 59.4±18.7 years of age).[118] During the 3-year follow-up period, the event rates for coronary revascularization (5.4%/year versus 2.9%/year), MI (3.8%/year versus 1.8%/year), and cardiac death (2.1%/year versus 1.0%/year) in patients with volume scores above the 75th percentile were significantly higher compared with the total study group. Correspondingly, the volume scores in patients with revascularization (397±187), MI (412±176), and cardiac death (422±184) were significantly higher compared with patients without cardiovascular events (218±167). In addition, no cardiovascular events occurred in patients with scores of 0. In this study, 44 of 50 (88%) of MIs occurred in patients with scores in the top 25th percentile, and a receiving operator characteristic (ROC) curve demonstrated that the calcium score outperformed both Prospective Cardiovascular Münster (PROCAM) study and FRS

($P<0.0001$), where 36% and 34% of MIs occurred in the high-risk cohorts, respectively.

From a synthesis of both retrospective and prospective cohort studies, there appears to be a directly proportional relationship between CHD risk and the extent of CAC, as measured by the Agatston score. According to a meta-analysis by Pletcher et al,[119] the risk of major CHD events increased 2.1-fold and 10-fold for scores ranging from 1 to 100 and >400, respectively, as compared with scores of 0. This relationship has been established when predicting all-cause mortality, cardiovascular events, CHD death or nonfatal MI, and overall CHD events. When estimating all-cause mortality, researchers report the independent prognostic value of the coronary calcium score for diabetics and smokers, including specific outcome evaluations in women.[92,120,121]

A study demonstrated the risk stratification in uncomplicated type 2 diabetes in a prospective evaluation of coronary artery calcium and MPS.[91,92] Established risk factors and CAC scores were prospectively measured in 510 asymptomatic individuals with type 2 diabetes (mean age 53±8 years, 61% men) without prior cardiovascular disease. MPS was performed in all subjects with CAC >100 Agatston units (AU) (n=127) and a random sample of the remaining patients with CAC ≤100 AU (n=53). Twenty events occurred (2 coronary deaths, 9 nonfatal MIs, 3 acute coronary syndromes, 3 nonhemorrhagic strokes, and 3 late revascularizations) during a median follow-up of 2.2 years (25th to 75th percentile=1.9 to 2.5 years). Multivariable logistic regression analysis showed that CAC score was the only predictor of myocardial perfusion abnormality ($P<0.001$). In the multivariable model, the CAC score and extent of myocardial ischemia were the only independent predictors of outcome ($P<0.0001$). ROC analysis demonstrated that CAC predicted cardiovascular events with the best area under the curve (0.92), significantly better than the United Kingdom Prospective Diabetes Study Risk Score (0.74) and the FRS (0.60, $P<0.0001$). The RR of a cardiovascular event for a CAC score of 101 to 400 was 10.1 and increased to 58.1 for scores >1000 ($P<0.0001$). The RR for ischemic burden was 5.5 for 1% to 5% burden, increasing to 12.3 for an ischemic burden >5% ($P<0.0001$). No cardiac events or perfusion abnormalities occurred in subjects with CAC ≤10 AU up until 2 years of follow-up. CAC and MPS findings were synergistic for the prediction of short-term cardiovascular events. The authors concluded that subclinical atherosclerosis measured by CAC imaging is superior to the established cardiovascular risk factors for predicting silent myocardial ischemia and short-term outcomes in patients with type 2 diabetes.

2.3. Limitations

The potential risk stratification (whether with CAC or other tests) first requires calculation of the Framingham risk. For example, a 45-year-old man with a total cholesterol of 225 mg/dL, an HDL cholesterol of 45 mg/dL, and systolic blood pressure of 140 mm Hg has a 10-year risk of 4% if he is not a smoker. If the same individual has a systolic blood pressure of 160 mm Hg, his 10-year risk is still only 5%. The article by Greenland et al[1] demonstrated the futility of calcium scanning when the Framingham risk is <10%. In that study, when the FRS was 0% to 9%, there was no increased risk with a CACS ≥301.[1] Similar data are available from the St. Francis Heart Study.[114] Thus, the risk stratification of individuals at low risk for CHD (<10% risk in 10 years) will not change with CACS testing, a conclusion further supported by the US Preventive Services Task Force.[20]

Modifying this case illustrates how noninvasive testing could influence patient treatment in an intermediate-risk patient. Consider the same patient 5 years later, this 50-year-old asymptomatic man who does not smoke, who has a blood pressure level of 140/85 mm Hg (treated), total cholesterol of 225 mg/dL, and HDL cholesterol of 45 mg/dL. This man's risk now falls into the "intermediate" zone with a 10% risk. If further testing were done with EBCT and a coronary calcium score >169 were found, the physician would be able to reassign him to a higher risk category (at least 20% in 10 years) and justifiably proceed more aggressively to reduce his risk factors.[122] Data from Greenland et al[1] demonstrated that intermediate-risk patients with an elevated CAC score (intermediate FRS and CAC >300) had an annual hard event rate of 2.8%, or a 10-year rate of 28%, and thus would be considered high risk. The best estimates of RR from this study demonstrated that a CAC score >300 had an HR of about 4 compared with a score of 0. This would mean that the estimated risk in the intermediate patient with a CAC score of 0 might be reduced by at least 2-fold, while the risk of a person with a CAC score of 300+ would be increased by about 2-fold. Thus, the person with high CAC and intermediate FRS is now reclassified as high risk. If the calcium score were 0 or very low, the patient's posttest risk assessment would be reduced.

Two of the largest studies with measured risk factors demonstrate a posttest probability of events of approximately 0.1% per year for persons without CACP present. Taylor et al[115] prospectively followed 3000 persons (mean age 43 years) for 3 years. CHD events occurred in only 2 of 1263 participants without CAC (event rate 0.16%; $P<0.0001$). Thus, a negative scan was associated with a 0.05% per year risk of events. In another large prospective, cohort study, 4903 asymptomatic persons 50 to 70 years of age were assessed: Only 8 of 1504 persons (0.5%) with scores of 0 had a coronary event over the next 4.3 years, with an annual event rate of only 0.1%. Two small prospective studies demonstrated no events in persons with scores of 0 over 2 to 3 years of follow-up.[91,92] The longest studies performed to date demonstrate that there is still a possible risk of MI or death associated with a negative (0) scan. In this study, 14 events occurred among 316 persons with scores of 0 at baseline over the subsequent median follow-up of 7 years (annual event rate 0.6%, 10-year risk 6.3%).[1]

EBCT is one of many contenders in a crowded field of emerging CAD risk-assessment tools. For example, other noninvasive modalities (eg, carotid intima-media thickness) and blood tests (eg, homocysteine and C-reactive protein) are under investigation with the aim of improving our ability to risk-stratify patients. Clinicians require high standards for assessing the value of new medical therapies and devices; evidence-based methods for evaluating screening strategies

TABLE 6. Characteristics and Risk Ratio for Follow-Up Studies Using EBCT

Author	No.	Mean Age, y	Follow-Up Duration, y	Calcium Score Cutoff	Comparative Group for RR Calculation	Risk Factor Assessment	Relative Risk Ratio
EBCT studies in symptomatic cohorts							
Georgiou[98]	192	53	4.2	Median*	Below median	Measured	13.1
Detrano[123]	491	57	2.5	Top quartile	Bottom quartile	Self-reported	10.8
Keelan[124]	288	56	6.9	Median (>480)	Below median	Measured	3.2
Moehlenkamp[125]	150	63	5	CACP >1000	No CACP	Measured	2.5
EBCT studies in asymptomatic populations							
Arad[109]	1173	53	3.6	CACP >160	CACP <160	Self-reported	20.2
Detrano[104]	1196	66	3.4	CACP >44	CACP <44	Measured	2.3
Park[105] (subset of Detrano[104])	967	67	6.4	CACP >142.1	CACP <3.7	Measured	4.9
Raggi[107]	632	52	2.7	Top quartile†	Lowest quartile	Self-reported	13
Shemesh[113]	446	64	3.8	CACP >0	CACP=0	Measured	2.8
Wong[110]	926	54	3.3	Top quartile	Lowest quartile	Self-reported	8.8
Arad[114]	4613	59	4.3	CACP ≥100	CACP <100	Measured	9.2
Kondos[111]	5635	51	3.1	CACP	No CACP	Self-reported	3.86 (men) 1.53‡ (women)
Greenland[1]	1312	66	7.0	CACP >300	No CACP	Measured	3.9
Shaw[112]	10 377	53	5	CACP 401-1000	CACP ≤10	Self-reported	6.2§
Taylor[115]	2000	43	3	CACP	No CACP	Measured	11.8
LaMonte[117]	10 746	54	3.5	CACP top third	No CACP	Measured	8.7 (men) 6.3 (women)
Vliegenthart[116]	1795	71	3.3	>1000	0-100	Measured	8.1
Becker[118]	924	60	3	Top quartile (75th percentile)	Total study group	Measured	7.3

Duplicate series: Detrano, Park, and Greenland.
CACP indicates coronary artery calcium score; RR, relative risk ratio.
*Using age- and gender-matched cohorts, representing top quartile.
†Using age- and gender-matched cohorts, representing the top quintile.
‡After multivariate analysis, $P<0.05$ for men, P=not significant for women.
§End point was all-cause mortality.

are important, as they ultimately dictate downstream testing, treatments, and costs. Current data support the benefit of CACP as a diagnostic test for particular patient populations in terms of diagnostic efficacy, acceptable safety, and affordability; however, further studies are warranted.

Despite the high quality of risk-stratification evidence, evidence is not available that screening with EBCT improves clinical outcomes by reducing mortality or morbidity from CAD (see section 2.5). In addition, cost-effectiveness models for the use of CACP are currently limited, since no study has demonstrated that EBCT reduces healthcare costs. The evidence does suggest that widespread and routine EBCT screening is unlikely to benefit low-risk or high-risk patients. Few patients with a low pretest probability of CAD will see their risk levels change enough to lead to changes in medical management. Patients with high pretest probabilities or diabetes are essentially at CAD-equivalent risk regardless of calcium score, and treatment of risk factors rather than screening would be more appropriate. There will be an expected decrease in efficacy of this test in older patients (men >70 years of age or women >75 years of age), as atherosclerosis is more widespread in the elderly.

2.4. Recommendations of Professional Societies

In 2000, the ACC/AHA acknowledged the potential of coronary calcium to predict major coronary events.[4] However, due to the mixed data available at the time, routine scanning was not recommended. Subsequently, additional data have been published to strengthen the conclusion that CAC affords incremental risk prognostication (Table 6). The AHA Prevention Conference V concluded that "selected patients" could have CACP testing if initially found to be at intermediate risk (Table 7).[2] That committee agreed with a perspective paper[126] supporting the use of EBCT for risk stratification in intermediate-risk patients, which stated: "Recent work suggests that . . .EBCT. . . can also improve risk prediction in intermediate-risk patients."[109] Thus, with a prior probability of a coronary event in the intermediate range (≥6% in 10 years but ≤20% in 10 years), a calcium score of >100 would yield a posttest probability >2% per year in the

TABLE 7. Interpretation and Recommendations for CT Heart Scanning and CACP Scoring

1.	A negative test (score=0) makes the presence of atherosclerotic plaque, including unstable or vulnerable plaque, highly unlikely.
2.	A negative test (score=0) makes the presence of significant luminal obstructive disease highly unlikely (negative predictive power by EBCT on the order of 95% to 99%).
3.	A negative test is consistent with a low risk (0.1% per year) of a cardiovascular event in the next 2 to 5 years.
4.	A positive test (CAC >0) confirms the presence of a coronary atherosclerotic plaque.
5.	The greater the amount of coronary calcium, the greater the atherosclerotic burden in men and women, irrespective of age.
6.	The total amount of coronary calcium correlates best with the total amount of atherosclerotic plaque, although the true "atherosclerotic burden" is underestimated.
7.	A high calcium score (an Agatston score >100) is consistent with a high risk of a cardiac event within the next 2 to 5 years (>2% annual risk).
8.	Coronary artery calcium measurement can improve risk prediction in conventional intermediate-risk patients, and CACP 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.
9.	Decisions for further testing (such as stress testing or cardiac catheterization) beyond assistance in risk stratification in patients with a positive CACP 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.

Adapted from ACC/AHA expert consensus document on EBCT for the diagnosis and prognosis of CAD.[4]

majority of patients, within the range of a CHD risk equivalent population and within a level requiring secondary prevention strategies.

The NCEP ATP III[3] supports the conclusions of the Prevention Conference V[2] and the ACC/AHA report[4] that high coronary calcium scores confirm an increased risk for future cardiac events, stating:

> Measurement of coronary calcium is an option for advanced risk assessment in appropriately selected persons. In persons with multiple risk factors, high coronary calcium scores (eg, >75th percentile for age and sex) denote advanced coronary atherosclerosis and provide a rationale for intensified LDL-lowering therapy. Moreover, measurement of coronary calcium is promising for older persons in whom the traditional risk factors lose some of their predictive power.

The European Cardiovascular Guidelines state, "The resulting calcium score is an important parameter to detect asymptomatic individuals at high risk for future CVD events, independent of the traditional risk factors."[126]

The Society of Atherosclerosis Imaging published guidelines for calcium scanning, with class I indications including (1) initial diagnostic test in ambulatory adults <65 years of age with atypical chest symptoms, in the absence of established cardiovascular disease; (2) supplementary diagnostic test in adults <65 years of age with indeterminate stress test results; and (3) emergency department evaluation of men <50 years of age and women <60 years of age with chest pain and normal or nondiagnostic ECGs. Class IIa recommendations include use for screening intermediate-risk patients and for assisting physicians in decision-making regarding initiation or change of drug therapy for cholesterol abnormalities in patients without established CVD.[127]

The 2004 AHA statement "Evidence-Based Guidelines for Cardiovascular Disease Prevention in Women"[128] deemed coronary calcification to be evidence of intermediate risk (10% to 20% 10-year risk) with a caveat that some patients with subclinical CVD will have >20% 10-year CHD risk and should be elevated to the high-risk category. The US Preventive Services Task Force recommends against CACP scanning for either the presence of severe coronary artery stenosis or for prediction of CHD events in patients with no CHD symptoms or risk factors, specifically the low-risk patient.[20] This Task Force recommended neither for nor against scanning of intermediate-risk or high-risk patients.

A 2005 AHA scientific statement on cardiac imaging in women addressed the data on CACP[5]: "Given the evolving literature. . . current data indicate that CAD risk stratification is possible. Specifically, low CACP scores are associated with a low adverse event risk, and high CACP scores are associated with a worse event-free survival." This guideline included a recommendation to measure atherosclerosis burden using cardiac CT in clinically selected intermediate–CAD risk patients (eg, those with a 10% to 20% Framingham 10-year risk estimate) to refine clinical risk prediction and to select patients for more aggressive target values for lipid-lowering therapies.[5] Some guidelines (eg, AHA and NCEP ATP III) define intermediate risk as 10% to 20%, while others such as the Bethesda Conference define it as 6% to 20%.[129] A new ACC Clinical Expert Consensus Document for the recommended use of CACP is currently being drafted.

2.5. Utilizing Coronary Calcium Measure to Improve Outcomes

Ideally, there should be evidence that a strategy of refining risk assessments is associated with improved clinical outcomes compared with conventional risk prediction. No study has definitively demonstrated that screening with EBCT improves clinical outcomes by reducing mortality or morbidity from CAD. One study failed to show a significant effect of statins on outcomes when calcium scores were high ($P=0.08$).[130] This study was a double-blind, placebo-controlled, randomized clinical trial of atorvastatin 20 mg daily, vitamin C 1 g daily, and vitamin E (alpha-tocopherol) 1000 U daily versus matching placebos in 1005 asymptomatic, apparently healthy men and women 50 to 70 years of age with coronary calcium scores at or above the 80th percentile for age and gender. All study participants also received

aspirin, 81 mg daily. Mean duration of treatment was 4.3 years.

Treatment reduced low-density lipoprotein cholesterol by 39.1% to 43.4% ($P<0.0001$) and triglycerides by 11.2% to 17.0% ($P\leq0.02$), while reducing clinical end points by 30% (6.9% versus 9.9%, $P=0.08$). Event rates were related to baseline calcium score (prespecified analysis) and have been reduced in a subgroup of participants with baseline calcium score >400 (8.7% versus 15.0%, $P=0.046$ [42% reduction, not a prespecified analysis]). The magnitude of the risk reductions was similar to those in studies published to date of the same cholesterol-lowering agent in primary prevention cohorts.[131]

This study sample, however, was too small to detect a benefit given the surprisingly low overall rate of cardiovascular end points in asymptomatic patients. The authors of the trial acknowledged several limitations. Firstly, the power analysis was based on an event reduction with both statin and antioxidants, and thus, when antioxidants failed to reduce events, the study was significantly underpowered. Furthermore, all patients received aspirin, so this may have also reduced the primary end point in both placebo and treatment groups. However, a large, well-done randomized trial has been performed, yielding similarly negative results.

The 30% reduction in the primary end point of this study is similar to the reduction of atherosclerotic CVD (ASCVD) events seen in other large randomized clinical trials of statins, a class of drugs with unquestionable efficacy in this application.[132] This study had power of just 0.61 to detect a 30% reduction in events. Treatment reduced all CAD events by 28% ($P=0.13$), the sum of nonfatal MI and CHD death by 44% ($P=0.14$), and all ASCVD events occurring >90 days after initiation of therapy by 33% ($P=0.07$).

The definition of high risk on CAC was chosen based on age-based and gender-based cohorts rather than atherosclerosis burden (ie, absolute CAC scores). This was recommended as a risk-stratification technique in the NCEP ATP III report[3] but was later shown to be not as robust a predictor of risk as absolute plaque burden.[131] Thus, the authors established lower calcium score thresholds in younger persons than in older ones. Later evidence revealed that this was incorrect; that is, age was not a significant determinant of events. As a result of this error, the study population contained substantial numbers of low-risk individuals in whom treatment had little effect. Conversely, in 469 subjects with calcium scores >400, treatment reduced the event rate by 42% ($P=0.046$).

Thus, while outcome studies demonstrating that measurement of CAC leads to improved outcomes remains an ideal, the practicality of performing such a study is challenging.

Recommendations: It may be reasonable to measure atherosclerosis burden using EBCT or MDCT in clinically selected intermediate–CAD risk patients (eg, those with a 10% to 20% Framingham 10-year risk estimate) to refine clinical risk prediction and to select patients for more aggressive target values for lipid-lowering therapies **(Class IIb, Level of Evidence: B).**

It is important to recognize that widespread and routine EBCT screening is unlikely to benefit low-risk or high-risk patients. Few patients with low pretest probability of CAD will change risk levels enough as a result of the screening to require changes in medical management. Patients with high pretest probabilities or diabetes are essentially at CAD-equivalent risk regardless of calcium score, and treatment of risk factors would be more appropriate than screening.[133] While several studies demonstrated incremental prognostic ability of CAC in diabetes,[91,92,121] patients with diabetes should be treated for secondary prevention before risk stratification. Furthermore, prior studies have limited generalizability owing to a lack of ethnic diversity in their patient populations.

Recommendation: Low-risk (<10% 10-year risk) and high-risk (>20% 10-year risk) patients do not benefit from CAC measurement **(Class III, Level of Evidence: B).**

2.6. Limitations of the Use of Coronary Calcium for Detecting Obstructive Disease in Asymptomatic Persons

The NCEP ATP III full report states:

> The goal of improved risk assessment is a more selective approach to the use of noninvasive cardiovascular studies and of preventive interventions such as lipid lowering, aspirin, or further blood pressure reduction. It must be understood clearly that an abnormal noninvasive test result in an intermediate-risk, asymptomatic person should be interpreted as a predictor for a future cardiovascular event and not as a mandate for diagnosis of the presence or absence of angiographic CAD.[3]

Because the purpose of CACP screening is to detect subclinical atherosclerosis rather than severe stenoses, the data show that invasive procedures should be reserved for symptomatic patients with inducible ischemia. There is limited information showing benefit of revascularization in terms of prolongation or quality of life in asymptomatic patients.[134–136] To avoid inappropriate or unnecessary follow-up testing or invasive therapeutic procedures in patients who undergo EBCT or MDCT, the clinician should determine a priori that the goal of such noninvasive testing is to refine prognostic assessment and then employ, or not, well-proven preventive interventions based on test outcome.

Recommendation: It is not recommended to use CACP measure in asymptomatic persons to establish the presence of obstructive disease for subsequent revascularization **(Class III, Level of Evidence: C).**

3. Future Directions

3.1. Tracking Progression of Subclinical Atherosclerosis

A proposed use of CACP measurement is to track atherosclerotic changes over time using serial measurements. Before implementation, there are several important questions that need to be answered in regard to rescanning: What incremental change needs to occur between 2 scans for the clinician to be certain, with 95% confidence, that an apparent change is due to a change in the patient? Are there any data showing how often this actually occurs in patients who are reimaged after a year? These questions were answered by 2 studies of

patients with dual scans. The first was a trial of 1376 asymptomatic research participants,[58] not selected because they were at high risk for CAD, who were examined for the quantity of CAC with dual scan runs using EBCT. With these data, 95% limits of agreement were established and used to evaluate differences between scan runs performed approximately 3.5 years apart in 81 participants. Of those 81 participants, 59 (73%) had no apparent change in CAC between the 2 examinations, 21 (26%) had large increases suggesting progression of CAC, and 1 (1%) had a large decrease suggesting regression of CAC. Another study was conducted to develop a model for determining the smallest statistically significant change in the CAC score between serial measurements in a given subject.[137] The study consisted of 2217 pairs of repeated EBCT coronary calcium scans acquired in quick succession. The study evaluated the relationship between the interscan variability and the magnitude of the calcium score, formulating 95% repeatability coefficient equations for the Agatston and volumetric CAC scores. By examining repeatability of quantitative EBCT measurements of CAC as a function of the magnitude of the calcium score, Sevrukov and colleagues[137] developed a model to determine the smallest statistically significant change between serial measurements in a given subject.

Several studies have shown that serial EBCT scanning can be utilized to follow the evolution of CACP and aortic valve calcification.[138–142] Obviously, a noninvasive tool with which sequential testing could be performed safely and reliably would be highly desirable, and in this light, CACP could become a very useful marker of disease progression. There are a number of methodological considerations that are required for the evaluation of sequential imaging. A recent review of the relevant methodologies has recently been published by Taylor et al.[143] Currently, there are only 4 randomized, controlled trials evaluating CACP progression,[130,142,144,145] and these types of studies have not yet been reported with MDCT. The theoretical ability of statin therapy to slow or reverse CACP has demonstrated mixed results in the available literature, raising some doubts about using this tool for tracking progression of atherosclerosis.

There are only 4 published studies of outcomes related to CACP progression. The first study demonstrated, in 817 persons, that EBCT-measured progression was the strongest predictor of cardiac events.[146,147] This observational study suggests that continued accumulation of CACP in asymptomatic individuals is associated with increased risk of MI. A second study measured the change in CACP in 495 asymptomatic persons who underwent sequential EBCT scanning.[146] Statins were initiated in all patients after their initial EBCT scan. MI was reported in 49 patients during a follow-up of 3.2±0.7 years. Interestingly, mean LDL level did not differ between patients experiencing an MI as compared with those who were event free (118±25 mg/dL versus 122±30 mg/dL, MI versus no MI).

On average, MI subjects demonstrated an annual rate of CACP change of 42±23%; event-free subjects showed a 17±25% yearly change ($P=0.0001$). The associated relative risk for acute MI for patients exhibiting >15% CACP progression was elevated 17.2-fold (95% CI 4.1 to 71.2) when compared with those without CACP progression ($P<0.0001$). In a Cox proportional hazard model, the follow-up score ($P=0.034$) as well as a score change >15% per year ($P<0.001$) were independent predictors of time to MI. Thus, from this and other reports, we have learned that the baseline score is a determinant of the rate of change even while it provides information for risk-assessment purposes. Patients with higher baseline scores generally exhibit more progression of CACP scores over time. Thus, the baseline score, rate of change, and also the patient's residual risk on the second scan are important determinants of the risk for future adverse cardiovascular events.

The CACP score increases by 15% to 20% annually, with greater increases being associated with increased incidence of MI.[52,146] A prospective study using EBCT to measure progression of CACP has just been reported. This prospective observational study evaluated 4613 asymptomatic persons 50 to 70 years of age with EBCT scanning of the coronary arteries at baseline and again at 2 years, with follow-up for 4.3 years.[114] The study demonstrated that the median (interquartile range) calcium score increased by 4 (95% CI 0 to 38) units from baseline to the year 2 scan in subjects who did not sustain a coronary event at any time during the study. In contrast, median (interquartile range) calcium scores increased by 247 (95% CI 40 to 471) units between the baseline and 2-year examinations in 49 subjects who experienced a first coronary disease event after the year 2 scan ($P<0.0001$). Multiple logistic regression demonstrated only age ($P<0.03$), male gender ($P<0.04$), LDL cholesterol ($P<0.01$), HDL cholesterol ($P<0.04$), and 2-year change in calcium score ($P<0.0001$) were significantly associated with subsequent CAD events. Increasing calcium scores were most strongly related to coronary events in this clinical study, similar to the results reported by observational studies.

However, effective treatment based on an increasing score in patients is still unclear. While several small observational studies indicated that vigorous cholesterol lowering retards the rate of progression of CACP,[138–141] a recently published, large randomized clinical trial showed that a combination of atorvastatin 20 mg, vitamin C, and vitamin E had no effect on progression of CACP at 4 years ($P=0.80$).[130] In this study, baseline coronary calcium score was higher in individuals who sustained ASCVD events (581) than in those who did not (361) ($P<0.0001$). The coronary calcium score also increased more from the baseline examination to the 2-year examination in those who subsequently experienced ASCVD events than in those who remained event free (256±430 versus 120±286, $P<0.01$).

In multivariable analysis, including standard CAD risk factors, C-reactive protein, and the baseline coronary calcium score, only the calcium score was significantly associated with disease events ($P<0.0001$). The change in calcium score, which was highly correlated with the baseline calcium score, did not predict events after adjustment for these variables. The failure of change in calcium score to predict ASCVD events seems to be a function of available statistical power, as the analysis was restricted to subjects who experienced a first event after the year 2 follow-up scan (n=34). Whether these results are unique to the drug combination

employed or would be observed with any cholesterol-lowering therapy is unknown. Continued progression of CACP appears to be an independent risk factor for future events, but future studies are needed. Despite this information, it is difficult to justify the incremental population exposure to radiation and the cost associated with a repeat CT test to assess "change" until it is better understood what therapies may be of benefit and how clinicians should utilize this data in clinical practice.

Several large observational studies, such as MESA (utilizing both EBCT and MDCT)[50] and RECALL (using EBCT),[51] are currently under way to also assess the prognostic value of increasing CACP burden in population-based samples. Genetic studies measuring calcified plaque with MDCT, such as the NHLBI's Family Heart Study-SCAN are also ongoing and will utilize the vascular calcium phenotype as a means of identifying genes related to atherosclerosis and CVD.

Recommendation: Serial imaging for assessment of progression of coronary calcification is not indicated at this time **(Class III, Level of Evidence: B).**

3.2. Hybrid Nuclear/CT Imaging

Currently available and an area of ongoing clinical research is the application of hybrid PET-CT and SPECT-CT scanners. This hybrid technology will allow for the acquisition of metabolic and/or perfusion information as well as anatomic data, including angiographic data and data on coronary calcification. Hybrid imaging currently remains a research tool with ongoing problems with image registration. Despite this, several recent reports using serial imaging have noted a high rate of coronary calcium in patients with normal perfusion SPECT. From the Berman series in 1119 patients with normal MPS, 20% had coronary calcium scores (CCS) in the range of 400 to 999 and 11% had CCS $\geq$1000.[6]

From a recent smaller series of 200 patients in whom SPECT was negative for ischemia, 17.5% of patients had CCS $\geq$100.[148] These data highlight the underlying, unaddressed risk faced by patients with normal SPECT results who nevertheless have a significant atherosclerotic disease burden. The future application of hybrid or serial imaging strategies will allow for a more precise delineation of anatomic and physiological components in a single test.

Two additional reports have been published on the use of hybrid scanning to assess cardiovascular risk or the present utility of SPECT imaging post-CT measurement of coronary calcium. The first report, on obstructive disease, was a large prospective series of 510 asymptomatic patients with type 2 diabetes. Patients with a calcium score >100 underwent SPECT imaging. A random sample of patients with a calcium score <100 also underwent SPECT. This report indicated that diabetic patients with a calcium score >100 had an increased frequency of abnormal perfusion defects. The rate of abnormal stress perfusion findings ranged from 23% to 71% for those with calcium scores >100 to >1000. These data are important, as they reveal that for individuals with diabetes a higher rate of abnormal SPECT findings is noted for a lower calcium score threshold of >100, as compared with >400 for an unselected patient series. Similar findings of calcium scores >100, associated with an elevated rate of perfusion abnormalities, were recently reported for patients with a family history of premature CHD.[90]

Recommendation: The incremental benefit of hybrid imaging strategies will need to be demonstrated before clinical implementation, as radiation exposure may be significant with dual nuclear/CT imaging. Therefore, hybrid nuclear/CT imaging is not recommended **(Class III, Level of Evidence: C)**.

3.3. Contrast-Enhanced CT of the Coronary Arteries

When higher resolution image acquisition protocols (thinner slice collimation, higher x-ray tube current) are combined with intravenous injection of contrast agent, EBCT and MDCT permit visualization of the coronary artery lumen, coronary atherosclerotic plaque, and coronary stenoses. The small dimensions of coronary arteries, plaque, and stenoses make imaging by CT quite difficult. Also, the contrast that can be achieved between the vessel lumen, atherosclerotic plaque and vessel wall, and the surrounding structures is lower than that of coronary calcium versus the surrounding tissue. Thus, image acquisition protocols have to be tailored for maximum resolution, and image quality is, on the one hand, more critical but, on the other hand, not as stable as when coronary calcification alone is assessed.

Tremendous progress regarding spatial resolution, temporal resolution, and image noise has been made with the development from 4- to 16- and 64-row MDCT scanners, and their ability to visualize the coronary lumen and coronary atherosclerotic plaque has substantially improved over the past several years. This development is ongoing. At the moment, the use of EBCT, or MDCT equipment with at least 16 slices, submillimeter rotation speed, and rotation times below 500 ms has to be considered a prerequisite for contrast-enhanced coronary imaging since, in the published studies, data for this equipment were substantially more reliable than for previous scanner generations and because 16-detector scanners are now widely available (although no direct comparisons to previous scanner generations have been published).

3.3.1. Electron Beam CT

When EBCT is performed to visualize the coronary lumen, approximately 160 mL of contrast agent is injected intravenously. Atropine is sometimes used to increase the heart rate, since one image is acquired in each cardiac cycle and faster heart rates will thus decrease the overall scan and breathhold time. Sublingual nitrates are usually given to improve image quality. First comparisons between EBCT and invasive coronary angiography starting in the mid-1990s demonstrated the feasibility of stenosis detection.[149–161] Adequate patient selection, careful scan protocols, and careful evaluation of images resulted in a sensitivity to coronary artery stenoses in the proximal and mid segments of the coronary arteries of between 74% and 92%, with specificities of 71% to 95%. However, the limited spatial resolution and long scan time (requiring breathholds of up to 40 seconds) led to image artifacts.

In the early studies using 80% triggering, 11% to 35% of all coronary arteries had to be excluded from evaluation because of severe calcification or motion artifacts.[53] Early EBCT studies suffered from limited spatial resolution of the EBCT scanner (owing to fixed image collimation of 3.0 mm) and use of late diastolic triggering (80% of the R-R interval). More recent studies, with use of end-systolic triggering (where coronary motion is reduced) and 1.5-mm slice thickness, reduce the noninterpretability of coronary segments to 5% to 9% (the remaining noninterpretable segments are almost exclusively the result of dense calcifications) and reveal sensitivities of 90% to 91%, specificities of 93% to 94%, and high negative predictive values (≥96%).[160,161] Limitations that still exist with EBCT include the inability to increase the tube current (which leads to limitations concerning image noise), and the limited availability of the scanner has prevented more widespread evaluation and application of EBCT for detection of coronary stenoses.

3.3.2. Multidetector CT

Initial studies with 4-detector systems demonstrated the ability of mechanical CT scanners to visualize the coronary arteries.[162–173] However, spatial and temporal resolution were still limited and resulting artifacts precluded image evaluation regarding the presence of hemodynamically significant stenoses in a high percentage of cases (up to 32%). It was recognized that severe calcifications were the most frequent reason for impaired evaluability, owing to partial volume effects which are a consequence of limited spatial resolution. With the introduction of 16-detector systems that combined submillimeter collimation with faster gantry rotation times, image quality in coronary CT angiography became more stable. Several studies with inclusion of 22 to 149 individuals showed that with the further development of scanner technology, robustness and accuracy for detecting and ruling out hemodynamically relevant coronary artery stenoses increased substantially.[174–189] Sensitivities ranging from 72% to 98%, as well as specificities from 86% to 98%, have been reported for the detection of coronary artery stenosis (Table 8).

Studies are now being reported that use 64-detector MDCT. The increased collimation width and greater number of slices obtained allow for shorter examination times by reducing both the breathhold and contrast requirements. The acquisition speeds are not much faster than 16-detector scanners, with the fastest gantry rotation currently at 330 ms. Several single-center studies of 64-row MDCT results have been reported (Table 8).

Leschka et al[12] reported CT angiography in 67 patients with suspected CAD and compared the results with invasive coronary angiography. None of the coronary segments needed to be excluded from analysis. CT correctly identified all 20 patients having no significant stenosis on invasive angiography. Overall sensitivity for classifying stenoses was 94%, specificity was 97%, positive predictive value was 87%, and negative predictive value was 99%. Leber et al[190] studied 59 patients with stable angina pectoris. In 55 of 59 patients, 64-slice CT enabled the visualization of the entire coronary tree with diagnostic image quality. Sensitivity for the detection of stenosis <50%, stenosis >50%, and stenosis >75% was 79%, 73%, and 80%, respectively, and specificity was 97%.

Raff et al[80] studied 70 consecutive patients undergoing elective invasive coronary angiography. Patients were excluded for atrial fibrillation. Specificity, sensitivity, and positive and negative predictive values for the presence of significant stenoses were by artery (n=279), 91%, 92%, 80%, and 97%, respectively; by patient (n=70), 95%, 90%, 93%, and 93%, respectively. Subset analysis confirms that patients with calcium scores >400, obesity (body mass index >30 kg/m^2), and heart rates >70 bpm remain a challenge to diagnose. Several additional studies confirmed sensitivities between 95% and 99% and specificities between 93% and 96% for the detection of coronary artery stenoses by 64-slice CT.[191–193]

For all MDCT scanner generations, including 64-row CT, it has been convincingly shown that low heart rates significantly improve image quality and evaluability.[194–197] In addition, the effectiveness of algorithms that modulate the x-ray tube current in synchronization with the patient's ECG to reduce the radiation exposure is higher for lower heart rates.[83,84] Therefore, low heart rates (preferably below 60 bpm) are desirable for MDCT imaging of the coronary arteries, and short-acting β-blockade is often used before scanning. Because of the need for retrospective gating for MDCT angiography, atrial fibrillation and other irregular heart rhythms remain a contraindication.

In a meta-analysis comparing CT angiography to magnetic resonance angiography (MRA),[198] a comparison of sensitivity revealed higher diagnostic accuracy for MDCT (weighted [by the proportional sample size] average: 82%, 95% CI 79% to 90%) when compared with MRA (weighted average: 75%, 95% CI 60% to 84%, $P=0.029$). In this meta-analysis, there was a significant difference that was also observed for the weighted specificity, which was 95% (95% CI 94% to 96%) for MDCT and 87% (95% CI 85% to 88%) for MRA ($P<0.05$). A significantly higher odds ratio (11.5-fold) for the presence of significant stenosis (≥50% diameter stenosis) was observed for MDCT as compared with MRA (6.6-fold) ($P<0.0001$). It is important to note that this report demonstrated improved specificity for MDCT, when compared with MRA, in populations with a lower disease prevalence ($P=0.022$).

Finally, a recent meta-analysis by Stein et al[199] reported the diagnostic accuracy by a patient and segmental analysis. Stein and colleagues also performed a subset analysis for CT results that were read while blinded to the invasive angiographic results. These authors noted that the average sensitivity and specificity values were 95% and 84% for 4-slice CT and increased to 100% for 64-slice CT. Additional analyses by these authors revealed a higher (on average) sensitivity for proximal (90%) stenosis when compared with distal (79%) segments. Diagnostic specificity values were ≥90% for proximal, mid, and distal segments. These authors also noted a high diagnostic accuracy for both 16-slice and 64-slice CT for detecting ≥50% stenosis in the left main coronary artery. Diagnostic sensitivity measurements were similarly high for 16-slice and 64-slice CT for detection of stenosis in the left anterior descending (16-slice=90%, 64-slice=95%), right

TABLE 8. Results of Contrast-Enhanced EBCT and MDCT for the Detection of Coronary Stenoses

Author	Technology	n	Rate of Unevaluable Segments, %	Sensitivity, %	Specificity, %	Negative Predictive Value, %	Remarks
Reports using EBCT							
Nakanishi[150]	EBCT	37	...	74	95	93	Per-artery analysis
Schmermund[151]	EBCT	28	12	83	91	96	Per-segment analysis, mid and proximal segments
Reddy[152]	EBCT	23	...	88	79	94	Per-artery analysis
Rensing[153]	EBCT	37	19	77	94	95	Per-segment analysis, mid and proximal segments
Achenbach[154]	EBCT	125	25	92	94	98	Per-artery analysis, proximal and mid segments
Budoff[155]	EBCT	52	11	78	71	91	Per-artery analysis
Achenbach[156]	EBCT	36	20	92	91	92	Per-segment analysis, proximal and mid segments
Leber[157]	EBCT	87	24	87	93	97	Per-segment analysis, proximal and mid segments
Ropers[158]	EBCT	118	24	90	66	96	
Nikolaou[159]	EBCT	20	11	85	77	95	Per-segment analysis, proximal and mid segments
Lu[160]	EBCT	53	35	69	82	93	Per-artery analysis—80% trigger
Lu[161]	EBCT	80	9	91	94	97	Per-artery analysis—end-systolic trigger
Budoff[161]	EBCT	86	5	90	93	96	Per-artery analysis, 1.5-mm collimation
Reports using 4-slice CT							
Nieman[165]	4-Slice MDCT	31	27	81	97	97	Per-segment analysis, proximal and mid segments
Achenbach[166]	4-Slice MDCT	64	32	91	84	98	Per-artery analysis, all segments >2.0 mm
Knez[167]	4-Slice MDCT	42	6	78	98	97	Per-artery analysis, proximal and mid segments
Vogl[168]	4-Slice MDCT	64	...	75	99	...	Per-segment analysis, 15 segments
Kopp[169]	4-Slice MDCT	102	15	86–93	96–97	98–99	Per-segment analysis, 10 segments
Nieman[170]	4-Slice MDCT	53	30	82	93	97	Per-segment analysis, all segments >2.0 mm
Becker[171]	4-Slice MDCT	28	11	78	71	97	Per-segment analysis, 7 segments
Morgan-Hughes[172]	4-Slice MDCT	30	32	72	86	93	Per-segment analysis, proximal and mid segments
Sato[173]	4-Slice MDCT	54	5	94	97	97	Per-artery analysis, all segments >2.0 mm
Reports using 8-slice CT							
Maruyama[174]	8-Slice MDCT	25	26	73	73	96	Per-segment analysis, all segments
Reports using 16-slice CT							
Nieman[175]	16-Slice CT	59	7	95	86	97	Per-artery analysis, all segments >2.0 mm
Ropers[176]	16-Slice CT	77	12	93	92	97	Per-artery analysis, all segments >1.5 mm
Kuettner[177]	16-Slice CT	58	...	72–98	97–98	97–100	Per-segment analysis, all of 13 segments (in patients with Agatston score <1000)
Mollet[178]	16-Slice CT	128	...	92	95	98	Per-segment analysis, all segments >2.0 mm
Martuscelli[179]	16-Slice CT	64	16	89	98	98	Per-segment analysis, all segments >1.5 mm
Hoffmann[180]	16-Slice CT	33	...	63–89	95–96	96–97	Per-segment analysis, all of 17 segments (proximal and mid segments)
Kuettner[181]	16-Slice CT	72	7	82	98	97	Per-segment analysis, all of 13 segments
Mollet[182]	16-Slice CT	51	...	95	98	99	Per-segment analysis, all segments >1.5 mm
Schuijf[183]	16-Slice CT	45	6	98	97	100	Per-segment analysis, all segments
Morgan-Hughes[184]	16-Slice CT	58	2–37	83–89	97–98	97–99	Per-segment analysis, all of 15 segments (in patients with Agatston score <400)
Hoffmann[185]	16-Slice CT	103	6	95	98	99	Per-segment analysis, all segments >1.5 mm
Achenbach[189]	16-Slice CT	50	4	94	96	99	Per-segment analysis, all segments >1.5 mm
Aviram[188]	16-Slice CT	22	...	86	98	98	Per-segment analysis, all segments >1.5 mm
Kaiser[187]	16-Slice CT	149	23	30	91	83	Per-artery analysis, all segments
Fine[186]	16-Slice CT	50	2	87	97	98	Per-artery analysis, all segments >1.5 mm
Reports using 64-slice CT							
Leschka[12]	64-Slice CT	67	...	94	97	99	Per-segment analysis, all segments >1.5 mm
Raff[80]	64-Slice CT	70	12	86	95	98	Per-segment analysis, all segments
Leber[190]	64-Slice CT	59	...	73–88	97	99	Per-segment analysis, all segments
Mollet[191]	64-Slice CT	52	2	99	95	99	Per-segment analysis, all segments
Ropers[192]	64-Slice CT	82	4	95	93	99	Per-artery analysis, all segments >1.5 mm
Fine[193]	64-Slice CT	66	6	95	96	95	Per-artery analysis, all arteries >1.5 mm
Available meta-analysis							
Schuijf[198]	4-Slice CT	569	22	80	94	...	Per-segment analysis
	8-Slice CT	50	21	80	98	...	
	16-Slice CT	681	4	88	96	...	
	64-Slice CT	396	4	92	95	...	
Stein[199]	4-Slice CT	89	5–18	95	84	...	Per-patient (blinded) analysis
	16-Slice CT	448	0–21	95	84	...	
	64-Slice CT	67	0	100	100	...	

coronary artery (16-slice=91%, 64-slice=93%), and left circumflex coronary arteries (16-slice=82%, 64-slice=94%). Diagnostic specificity values were similar across the arteries but higher for 64-slice (range=92% to 100%) as compared with 16-slice CT (84% to 100%).

3.4. CT Angiography Applications in a Clinical Context

3.4.1. Suspected CAD

The studies that have evaluated the accuracy of EBCT and MDCT "coronary angiography" for the assessment of coronary artery stenoses have been relatively small (up to 149 individuals). They recruited somewhat selected patients (eg, excluding patients with acute coronary syndromes or atrial fibrillation), and all studies have been validated against invasive coronary angiography as a gold standard. No outcomes-based analyses that made further clinical management dependent on the EBCT or MDCT result have been published. However, all studies have convincingly demonstrated a very high negative predictive value of CT coronary angiography (see Table 8). Thus, a "normal" CT coronary angiogram allows the clinician to rule out the presence of hemodynamically relevant coronary artery stenoses with a high degree of reliability. When considering whether to refer a patient for EBCT or MDCT, clinicians must weigh the relative advantages of other testing methods such as exercise testing or stress imaging. The choice of testing will be determined by both local expertise in a given hospital as well as by the patient's specific clinical history. Functional information demonstrating the physiological significance of coronary lesions is still paramount for decision-making related to revascularization.

In a clinical context, the high negative predictive value may be useful for obviating the need for invasive coronary angiography in patients whose symptoms or abnormal stress test results make it necessary to rule out the presence of coronary artery stenoses. Especially if symptoms, age, and gender suggest a low to intermediate probability of hemodynamically relevant stenoses,[200] ruling out hemodynamically relevant stenoses by CT coronary angiography may be clinically useful and may help avoid invasive angiography. CT coronary angiography is reasonable for the assessment of obstructive disease in symptomatic patients **(Class IIa, Level of Evidence: B).**

Use of CT angiography in asymptomatic persons as a screening test for atherosclerosis (noncalcific plaque) is not recommended **(Class III, Level of Evidence: C)**.

3.4.2. Follow-Up of Percutaneous Coronary Intervention

Several smaller studies have assessed the value of EBCT and MDCT to detect restenosis after stent placement. With EBCT, 4-detector MDCT, and 16-detector MDCT, artifacts caused by the stent material prevented, in many cases, adequate visualization of the coronary lumen within the stent. Thus, in-stent restenosis could not be reliably detected in most cases.[201–206] The ability to visualize in-stent restenosis depends on stent design and material, stent size, and scanner technology.[207–209] Thus, further studies may prove that a certain combination of stent type and scanner technology may permit the detection of in-stent restenosis. In a first study performed by 64-slice CT, sensitivity for detection of in-stent restenosis was 83%, but only 8 stenoses were present in the overall study group.[210] Thus, based on current data, imaging of patients to follow up stent placement cannot be recommended **(Class III, Level of Evidence: C).**

3.4.3. Follow-Up After Bypass Surgery

Numerous studies have shown that EBCT and MDCT permit assessment of coronary bypass graft occlusion and patency with high accuracy. In most studies, the accuracy to detect bypass occlusion approached 100%.[211–226] Clinically, however, it might be reasonable in most cases to not only assess the patency of the bypass graft but also the presence of coronary stenoses in the course of the bypass graft or at the anastomotic site, as well as in the native coronary artery system **(Class IIb, Level of Evidence: C).** This is more difficult, owing to the smaller caliber of these vessels, the presence of artifacts caused by metal clips, and the often pronounced coronary calcification. Recent data suggest a high sensitivity for both coronary stenosis as well as assessment of bypass patency versus occlusion. A study of 52 patients using 16-detector MDCT demonstrated 99.4% assessibility of grafts, with a sensitivity and specificity of 100% (54/54) for occlusion and 96% sensitivity and 100% specificity for detecting high-grade stenoses in patent grafts.[227] Although more data are necessary, newer scanners may have the spatial resolution to overcome some of the earlier problems with graft assessment.

3.4.4. Anomalous Coronary Arteries

The presence of anomalous coronary arteries can be a differential diagnosis in patients with suspected coronary disease, chest pain, or syncope. The detailed assessment of anomalous coronary arteries concerning their origin and course can be difficult with invasive coronary angiography. The 3-dimensional nature of CT coronary angiography datasets allows for an exact analysis of anomalous coronary arteries. Both for EBCT and MDCT, numerous case reports suggest and several authors have investigated series of patients and could demonstrate that the analysis of coronary anomalies is straightforward and exact.[228–233] As opposed to magnetic resonance imaging, which also permits the analysis of coronary anomalies in tomographic images, CT requires radiation and a contrast agent. However, the high resolution of the datasets (permitting analysis even of small details) and the speed of image acquisition make it reasonable to use CT as one of the first-choice imaging modalities in the workup of known and suspected coronary anomalies **(Class IIa, Level of Evidence: C).**

3.5. Assessment of NCP

In addition to identifying lesions with significant luminal narrowing, there is also interest in visualizing and characterizing coronary artery plaques beyond the mere assessment of calcium. Some plaques may be at increased risk for erosion or rupture even when such lesions are not associated with a significant degree of luminal stenosis. These so-called unstable plaques are thought to play a role in the development of acute coronary ischemic events. It has been observed that

unstable plaques are generally higher in lipid content, and the use of cross-sectional imaging may be helpful in characterizing plaque composition.

Coronary angiography has traditionally served as the principal imaging modality to evaluate CAD. However, both necropsy and coronary intravascular ultrasound (IVUS) studies have consistently shown that angiographically "normal" coronary artery segments may contain a significant amount of atherosclerotic plaque and that coronary angiography consistently underestimates the amount of coronary atherosclerosis.[234,235] Furthermore, previous angiographic studies have shown that most MIs result from the rupture of a vulnerable plaque in the absence of a significant luminal stenosis. These rupture-prone plaques, which are 7 times more likely to cause disruption than the more severe, extensive plaques, are not visible on 2-dimensional x-ray angiography.[236,237]

Improved spatial and temporal image acquisition with submillimeter slice collimation has facilitated atherosclerotic plaque detection with MDCT. Plaque with density below the vessel contrast is defined as noncalcified plaque. Conversely, structures with densities above the adjacent vessel lumen are considered calcified.[238] Some studies have defined 3 levels of plaque: "soft" plaque, presumably lipid laden with lower densities, intermediate or presumably fibrous plaques, and calcific or high-density plaques.

Recent contrast-enhanced MDCT studies have shown that noninvasive scanning permits accurate detection and differentiation of coronary plaque when compared with IVUS. There have been 6 main studies reported comparing CT technology with IVUS in the detection of lipid-rich and fibrous atheroma, with both MDCT (4 studies) and EBCT (2 studies).[239–243]

Sensitivities for NCP (hypoechoic, lipid-rich) detection by MDCT ranged from 53% to 92%, with the sample size ranging from 14 to 37 patients. In one of the more robust MDCT studies, which evaluated 875 segments, sensitivity for hypoechoic, hyperechoic, and calcific plaques was 78%, 78%, and 95%, respectively. Specificity was a respectable 92%.[239] As expected, the sensitivities for detecting calcific atheroma were relatively higher than for noncalcific plaque in these studies: approximately 88% to 95%. Although the sample sizes are relatively small, they do demonstrate diagnostic accuracy in characterizing noncalcific atheroma, with some difficulty differentiating lipid-laden and fibrous components.

Quantification of coronary atherosclerotic plaque burden by CT technology is currently unsatisfactory.[244] In the study by Achenbach et al,[239] MDCT substantially underestimated plaque volume per segment as compared with IVUS (24 ± 35 mm^3 versus 43 ± 60 mm^3, $P<0.001$).

In another comparison between MDCT and IVUS, plaque areas showed moderate correlation ($r=0.55$) between the 2 methods, with a significant tendency toward overestimation by MDCT (8.3 ± 4.8 mm^3 versus 7.3 ± 3.1 mm^3, $P<0.001$).[245] The limitations of NCP detection may be much more significant than a limited sensitivity or underestimation of plaque burden. The reproducibility of the measure has not been reported. There is no prognostic information to determine whether NCP adds any information on top of risk factors, angiographic disease severity, or calcified plaque, and it is not recommended **(Class III, Level of Evidence: C).** Finally, this procedure requires both contrast administration and radiation exposure, and the risks may outweigh the benefit in individual patients. All of this will need to be studied before NCP detection by CT becomes a clinical tool.

Conclusion

EBCT has undergone a 20-year period of testing for reliability and validity and is now established as a useful technique in identifying individuals with or at risk for CHD. MDCT is a promising tool for coronary calcium scoring while additional studies evaluating progression, reproducibility, and outcomes are currently under way. Radiation doses, reproducibility, and validation studies must be taken into account when choosing a cardiac CT study. Serial coronary calcium scans to noninvasively assess progression rates of coronary calcium and CT angiography to assess NCP are now starting to be reported, but the data are premature at this time. The most promising use of these technologies is calcium scoring for risk assessment of the asymptomatic individual, whereby elevated calcium scores may trigger more vigorous application of both lifestyle and/or pharmacological therapies targeted to lower cardiovascular risk and CT angiography to rule out the presence of coronary stenoses in certain subsets of symptomatic patients.

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Intervention Committee, Council on Cardiovascular Radiology and Intervention, American Heart Association. Role of noninvasive testing in the clinical evaluation of women with suspected coronary artery disease: consensus statement from the Cardiac Imaging Committee, Council on Clinical Cardiology, and the Cardiovascular Imaging and Intervention Committee, Council on Cardiovascular Radiology and Intervention, American Heart Association. *Circulation*. 2005;111:682–696.

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