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ACCF/AHA EXPERT CONSENSUS DOCUMENT

ACCF/AHA 2007 Clinical Expert Consensus Document on Coronary Artery Calcium Scoring By Computed Tomography in Global Cardiovascular Risk Assessment and in Evaluation of Patients With Chest Pain

A Report of the American College of Cardiology Foundation Clinical Expert Consensus Task Force (ACCF/AHA Writing Committee to Update the 2000 Expert Consensus Document on Electron Beam Computed Tomography)

Developed in Collaboration With the Society of Atherosclerosis Imaging and Prevention and the Society of Cardiovascular Computed Tomography

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TABLE OF CONTENTS

Preamble

This document has been developed as a Clinical Expert Consensus Document (CECD), by the American College of Cardiology Foundation (ACCF) and the American Heart Association (AHA) in collaboration with the Society of Atherosclerosis Imaging and Prevention (SAIP) and Society of Cardiovascular Computed Tomography (SCCT). It is intended to provide a perspective on the current state of the role of coronary artery calcium (CAC) scoring by fast computed tomography in clinical practice. Clinical Expert Consensus Documents are intended to inform practitioners, payers, and other interested parties of the opinion of the ACCF and AHA concerning evolving areas of clinical

practice and/or technologies that are widely available or new to the practice community. Topics chosen for coverage by expert consensus documents are so designed because the evidence base, the experience with technology, and/or the clinical practice are not considered sufficiently well developed to be evaluated by the formal American College of Cardiology/American Heart Association (ACC/AHA) Practice Guidelines process. Often the topic is the subject of considerable ongoing investigation. Thus, the reader should view the CECD as the best attempt of the ACC and AHA to inform and guide clinical practice in areas where rigorous evidence may not yet be available or the evidence to date is not widely accepted. When feasible, CECDs include indications or contraindications. Some topics covered by CECDs will be addressed subsequently by the ACC/AHA Practice Guidelines Committee.

The Task Force on Clinical Expert Consensus Documents makes every effort to avoid any actual or potential conflicts of interest that might arise as a result of an outside relationship or personal interest of a member of the writing panel. Specifically, all members of the writing panel are asked to provide disclosure statements of all such relationships that might be perceived as real or potential conflicts of interest to inform the writing effort. These statements are reviewed by the parent task force, reported orally to all members of the writing panel at the first meeting, and updated as changes occur. The relationships with industry information for writing committee members and peer reviewers are published in the appendices of the document.

Robert A. Harrington, MD, FACC
Chair, ACCF Task Force on Clinical Expert Consensus Documents

Introduction

The Writing Committee consisted of acknowledged experts in the field of coronary artery disease. In addition to members of ACCF and AHA, the Writing Committee included representatives from the SAIP and SCCT. Representation by an outside organization does not necessarily imply endorsement. The document was reviewed by four official representatives from the ACCF, and AHA; organizational review by the SAIP and SCCT, as well as 14 content reviewers. This document was approved for publication by the governing bodies of ACCF and AHA in September 2006. In addition, the governing boards of the SAIP and SCCT reviewed and formally endorsed this document. This document will be considered current until the Task Force on CECDs revises or withdraws it from publication.

Consensus Statement Method

This statement builds on a previous ACC/AHA Expert Consensus Document published in 2000 that focused on electron beam computed tomography (CT) for diagnosis and prognosis of coronary artery disease (1). In preparing the present document, the Writing Committee began with the previous report as a basis for its deliberations and subsequent literature review. In considering the current status of research on CAC measurement and its role in clinical practice, the Expert Panel concluded that the majority of the research on CAC measurement in the past 5 years has focused on 2 areas of clinical interest: 1) Risk assessment in the asymptomatic patient, for the primary purpose of modifying and potentially improving selection of patients for risk reducing therapies, and 2) Use of CAC measurement in symptomatic patients as a means of selecting patients who might require subsequent hospitalization or additional diagnostic or invasive procedures. The Writing Committee also recognized that the AHA was in the process of completing a scientific statement on assessment of coronary artery disease by CT (2), and thus this Writing Committee's attention was focused on evaluating clinical aspects of CAC measurement rather than on technical issues that are covered in the AHA statement (2). Also, the Writing Committee is aware that ACCF has recently published appropriateness criteria using approaches that differ somewhat from those used in developing this Consensus Document. Therefore, readers should be aware that there may be slight differences in language used in this document and the Appropriateness Criteria for Cardiac Computed Tomography and Magnetic Resonance (3) document.

At its first meeting, each member of this ACCF/AHA Writing Committee indicated any relationship with industry. Relevant conflicts of the Writing Committee and peer reviewers are reported in Appendixes 1 and 2, respectively. The next step in the development of this document was to obtain a complete literature review from the Griffith Resource Library at the ACC concerning CAC measurement by fast CT methods from 1998 through early 2005 (National Library of Medicine's Elhill System). Additional relevant prior or subsequently published references have also been identified by personal contacts of the Writing Committee members, and substantial efforts were made to identify all relevant manuscripts that were currently in press. At the first meeting, members of the Writing Committee were given assignments to provide descriptions and analyses of CAC measurement for identifying and modifying coronary event risk in the asymptomatic patient, for modifying the clinical care and outcomes of symptomatic patients suspected of having coronary artery disease (CAD), and for understanding the role of CAC measurement in selected patient subgroups. Each individual contributor to these parts of the document had his or her initial full written presentation critiqued by all other members of this Writing Committee. Outside peer review was also undertaken before the document was finalized.

Considerable discussion among the group focused on the best and most proper way to assess clinical appropriateness of tests such as CAC measurement since there have been no

clinical trials to evaluate the impact of CAC testing on clinical outcomes in either symptomatic or asymptomatic patients. The Writing Committee agreed uniformly that the ideal assessment of cardiac tests would require clinical trials that utilize important patient outcomes such as improving the quality or quantity of a patient's life. However, recognizing that this standard is not available for CAC measurement, the Committee considered other standards of evidence in reaching a consensus opinion. A minority of the Writing Committee felt that CAC testing could not be advised for any clinical indication until clinical trials were available to show benefit on actual patient outcomes. However, the majority of the Writing Committee felt that this standard of evidence is rarely applied in assessment of cardiac testing appropriateness. Therefore, the majority position presented here reflects the concept that prognostic testing such as CAC measurement can be considered reasonable where there is evidence that the test results can have a meaningful impact on medical decision-making.

Introduction to CAC Measurement

Coronary arterial calcification is part of the development of atherosclerosis, occurs almost exclusively in atherosclerotic arteries, and is absent in the normal vessel wall (4–6). Coronary artery calcification occurs in small amounts in the early lesions of atherosclerosis that appear in the second and third decades of life, but it is found more frequently in advanced lesions and in older age. Although there is a positive correlation between the site and the amount of coronary artery calcium and the percent of coronary luminal narrowing at the same anatomic site, the relation is nonlinear and has large confidence limits (7). The relation of arterial calcification, like that of angiographic coronary artery stenosis, to the probability of plaque rupture is unknown (8,9). There is no known relationship between vulnerable plaque and coronary artery calcification (10). Although radiographically detected coronary artery calcium can provide an estimate of total coronary plaque burden, due to arterial remodeling, calcium does not concentrate exclusively at sites with severe coronary artery stenoses (11).

Electron-beam computed tomography (EBCT) and multi-detector computed tomography (MDCT) are the primary fast CT methods for CAC measurement at this time. Both technologies employ thin slice CT imaging, using fast scan speeds to reduce motion artifact. Thirty to 40 adjacent axial scans usually are obtained. A calcium scoring system has been devised based on the X-ray attenuation coefficient, or CT number measured in Hounsfield units, and the area of calcium deposits (12). A fast CT study for coronary artery calcium measurement is completed within 10 to 15 min, requiring only a few seconds of scanning time.

Cardiac computed tomography has been used with increasing frequency in the United States and other countries during the past 15 years, initially with the goal of identifying patients at risk of having obstructive coronary artery disease based on the amount of coronary calcium present. However, in the past 5 to 10 years, fast CT methods have been used primarily for 2 purposes: 1) to assist in coronary heart disease (CHD) risk assessment in asymptomatic patients, and 2) to assess the likelihood of the presence of CHD in patients who present with atypical symptoms which could be consistent with myocardial ischemia.

Many technical aspects are relevant to the choice of EBCT versus MDCT, and these are beyond the scope of this document. A related document, recently prepared by the AHA, addresses these important technical issues (2). In contrast, this document focuses on clinical uses of fast CT for CAC measurement and addresses the appropriateness of CAC measurement in defined clinical circumstances.

Role of Risk Assessment in Cardiovascular Medicine

A major focus of this Consensus Document is the role of CAC measurement in cardiovascular risk assessment. Thus, a brief overview of cardiovascular risk assessment is important to provide a frame of reference for the material that follows.

Risk assessment is often regarded as a key first step in the clinical management of cardiovascular risk factors. Risk assessment algorithms, such as those from the Framingham Heart Study in the United States or from the *Pro*spective *Car*diovascular *M*ünster (PROCAM) study in Germany, or the European risk prediction system called SCORE (Systemic Coronary Risk Evaluation), are among the most common and widely available for estimating multi-factorial absolute risk in clinical practice (13). Each of these risk assessment algorithms, as most often used, projects 10-year, absolute risk, which can be considered short-term or intermediate-term (not lifetime) risk. These risk projections are often regarded by policy makers and clinicians as useful when selecting the most appropriate candidates for drug therapies intended to reduce risk. Cholesterol and blood pressure guidelines in the United States and elsewhere have followed the principle that the intensity of treatment should be aligned with the severity of a patient's risk (14,15). The rationale behind this balance between treatment intensity and patient risk is that proportional risk reduction and cost-effectiveness analyses indicate that there is greater benefit of drug exposure when the patient's risk is high. It has been considered useful to divide patients into several categories depending on their 10-year risk estimates. Three commonly used categories are *high risk*, *intermediate risk*, and *low risk*. Beginning in 2004, the National Cholesterol Education Program (NCEP) further divided the intermediate-risk category into *moderately high risk* and *moderate risk* (16). Table 1 shows the most recent NCEP categories of 10-year absolute risk used to stratify patients for cholesterol-lowering therapy. This classification can be

Table 1. Absolute Risk Categories According to National Cholesterol Education Program Update, 2004

10-Year Absolute Risk Category	Definition of Category
High risk	CHD*, CHD risk equivalents† including 2+ major risk factors‡ plus a 10-year risk for hard CHD greater than 20%§
Moderately high risk	2+ major risk factors‡ plus a 10-year risk for hard CHD 10% to 20%
Moderate risk	2+ major risk factors plus a 10-year risk for hard CHD less than 10%
Lower risk	0 to 1 major risk factor (10-year risk for hard CHD usually less than 10%)§

*CHD includes history of myocardial infarction, unstable angina, stable angina, coronary artery procedures (angioplasty or by-pass surgery), or evidence of clinically significant myocardial ischemia. †CHD risk equivalents include clinical manifestations of non-coronary forms of atherosclerotic disease (peripheral arterial disease, abdominal aortic aneurysm, and carotid artery disease [transient ischemic attacks or stroke of carotid origin or greater than 50% obstruction of a carotid artery]), diabetes, and 2+ risk factors with 10-year risk for hard CHD less than 20%. ‡Major risk factors include cigarette smoking, hypertension (BP greater than or equal to 140/90 mm Hg or on antihypertensive medication), low HDL cholesterol (less than 40 mg/dL), family history of premature CHD (CHD in male first-degree relative less than 55 years; CHD in female first-degree relative less than 65 years), and age (men greater than or equal to 45 years; women greater than or equal to 55 years). §Almost all people with 0 to 1 risk factor have a 10-year risk less than 10%, and 10-year risk assessment in people with 0 to 1 risk factor is thus not necessary. Modified with permission from Grundy SM, Cleeman JI, Merz CN, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. Circulation 2004;110:227–39 (16).

BP = blood pressure; CHD = coronary heart disease; HDL = high-density lipoprotein.

applied to other CHD risk reduction therapies as well, such as blood pressure lowering.

Matching Intensity of Intervention With Severity of Risk

As previously noted, a principle of cardiovascular disease prevention that is generally accepted is that intensity of intervention for an individual (or population) should be adjusted to the level of baseline risk (17). The goals of this principle are to optimize efficacy, safety, and cost-effectiveness of the intervention. The concept is most often applied to higher-risk individuals who are potential candidates for risk-reducing drugs; but it also is an important consideration for lower risk individuals either in clinical practice or for public health strategies. For higher risk individuals, intensity of intervention is best adjusted to absolute short-term risk; for lower risk individuals, relative risk remains an important consideration because a high relative risk generally translates into a high absolute risk in the long term. This latter concept is most relevant to younger men and middle-aged men and women, whereas in older men and women, the Framingham Risk Score generally applies.

Current Approaches to Global Risk Assessment and to Assessment of Incremental Risk Using New Tests

In current clinical practice, in accordance with a number of guidelines (14,15), it is common that the first step in clinical risk assessment is to identify any high-risk conditions that obviate the need for further risk assessment; these mainly include established atherosclerotic cardiovascular disease (ASCVD) and diabetes (see Table 1, High risk). If none of these high-risk conditions is present, the second step is to identify the presence of major risk factors (also listed in Table 1). If 2 or more major risk factors are present, one should then estimate the 10-year likelihood for development of major coronary events or total cardiovascular events. In the United States, the most-commonly used and most extensively validated quantitative assessment is provided by the multivariable scoring system of the Framingham Heart Study. The Framingham algorithm for "hard CHD" events including myocardial infarction and cardiac death is available through the National Cholesterol Education Program website (http://hin.nhlbi.nih.gov/atpiii/calculator.asp). Framingham scoring includes the following major risk factors: gender, total cholesterol, high-density lipoprotein (HDL) cholesterol, systolic blood pressure (or on treatment for hypertension), cigarette smoking, and age. PROCAM scoring employs a somewhat different set of risk factors: gender, age, low-density lipoprotein (LDL) cholesterol, HDL cholesterol, triglycerides, systolic blood pressure, cigarette smoking, family history, and presence or absence of diabetes (http://www.chd-taskforce.com/). The European SCORE algorithm uses risk factors similar to the Framingham Score.

For each of these risk assessment tools, the most powerful risk factors are age and gender. The other risk factors can be examined for their additive predictive power by determining increments in the area under the curve of the receiver-operating characteristic (ROC). The area under the ROC curve is also known as the C-statistic. An ROC analysis plots sensitivity (fraction of true positives) versus 1-specificity (fraction of false positives) of a risk factor for predicting events. ROC curves are used to evaluate the discrimination of a prediction, and often, the predictive power of a set of risk factors. If a given set of risk factors predicted the development of cardiovascular events perfectly, the curve would reach 100% in the upper left corner (100% sensitivity and 100% specificity), that is, all true positives and no false positives. The area under the curve would be 100% (C-statistic = 1.0). A random and useless predictor would give a straight line at 45 degrees (C-statistic = 0.5) since this would define a test where true positive rate and false positive rate are equal to one another at every possible cutoff value. In the evaluation of additional tests, added to the basic set of Framingham risk factors, the area under the curve would increase when the test provides incremental discrimination. The Framingham algorithm applied to the Framingham population generally gives a C-statistic of approximately 0.8, meaning that the probability is 80% that patients who experience CHD events will have a higher risk score than patients who did not experience an event. An important but unresolved issue is whether discovery and addition of new biochemical risk factors or imaging markers to Framingham or PROCAM algorithms

will increase the C-statistic. In considering the role of CAC measurement for risk assessment, a key issue is whether discriminative ability is improved, often as judged by an increase in the C-statistic compared to that derived from risk factors alone.

Risk Assessment for Coronary Heart Disease in Asymptomatic Populations

Prognosis by Coronary Artery Calcium Measurements

In the prior ACC/AHA expert consensus document published in 2000, only 3 reports on the prognostic capability of CAC scoring were available to develop risk assessment indications in asymptomatic individuals (1). At the time, the ACC/AHA document concluded that the body of evidence using CAC measurement to predict CHD events was insufficient. A critical component to that recommendation was that the independent prognostic value of CAC had not been established. In a separate but similar evaluation using data published through 2002, the U.S. Preventive Services Task Force (USPSTF) concluded that limited clinical outcomes data were available and recommended against routine screening for the detection of silent but severe CAD or for the prediction of CHD events in low risk, asymptomatic adults (see http://www.ahrq.gov/downloads/pub/prevent/pdfser/chdser.pdf).

In the past several years, however, a number of publications have reported on the incremental prognostic value of CAC in large series of patients including asymptomatic self-referred and population cohorts (18–22). A major rationale for the current document is the need for an update including recent publications regarding CAC as it relates to the estimation of CHD death or nonfatal myocardial infarction (MI). Although earlier evidence included the use of "soft" endpoints including coronary revascularization as a primary outcome, more recent data are available on the estimation of CHD death or MI (18–22). Models predicting "hard" cardiac events (i.e., CHD death or MI) are less subjective and less likely to overestimate the predictive accuracy of CAC scoring (23).

Theoretical Relationship Between Coronary Calcification and CHD Events

Atherosclerotic plaque proceeds through progressive stages where instability and rupture can be followed by calcification, perhaps to provide stability to an unstable lesion (8). As the occurrence of calcification reflects an advanced stage of plaque development, some researchers have proposed that the correlation between coronary calcification and acute coronary events may be suboptimal based largely on angiographic series (11). In order to understand this apparent conflict between the stability of a calcified lesion and CHD event rates, one must recognize the association between atherosclerotic plaque extent and more frequent calcified and non-calcified plaque (24). That is, patients who have calcified plaque are also more likely to have non-calcified or "soft" plaque that is prone to rupture and acute coronary thrombosis (24). It is the co-occurrence of calcified and non-calcified plaque that provides the means for estimating acute coronary events. Furthermore, although CAC detection cannot localize a stenotic lesion or one that is prone to rupture, CAC scoring may be able to globally define a patient's CHD event risk by virtue of its strong association with total coronary atherosclerotic disease burden, as shown by correlation with pathologic specimens (1,24).

Approaches to Technology Assessment in CHD Screening

A major criterion utilized in many technology assessments has been that a screening test must have a high level of evidence on the effect of screening on actual health outcomes, such as fewer events, extended life, or better quality of life. This type of analysis requires research detailing an improvement in either quantity or quality-of-life years as a result of the screening procedure. An example of a high level of such evidence was recently published on screening for abdominal aortic aneurysm (AAA) (25). Using this example, a meta-analysis reported reduced mortality in randomized trials of AAA screening. These results allowed for favorable support of AAA screening by the USPSTF resulting in a class B recommendation (i.e., evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes) (26). Lack of similar controlled clinical trial evidence played a central role in the conclusion by the USPSTF not to support CHD screening using CAC measurement (see http://www.ahrq.gov/downloads/pub/prevent/pdfser/chdser.pdf).

Although no studies have shown a net effect on health outcomes of CAC scoring (27), at least one randomized trial is nearing completion (Early Identification of Subclinical Atherosclerosis using NoninvasivE Imaging Research [EISNER]). However, the concept of matching treatment intensity to the degree of cardiovascular risk suggests that efforts to identify the most accurate approach to risk stratification is an initial and critical step that should aid in the best selection of treatment options for patients at risk for cardiovascular disease.

Systematic Reviews and Meta-Analyses

In the sections that follow, we review recent evidence on the prognostic value of CAC and include data from one recent systematic review. A comprehensive data synthesis on this subject was published by Pletcher et al. (23) evaluating the prognostic value of CAC from 4 studies published through 2002 meeting quality-based inclusion criteria. Articles were considered for that meta-analysis if they evaluated the prognostic value of CAC in asymptomatic individuals and also presented data on CHD events. Based on a random-effects model, the summary relative risk ratios were 2.1 (for

Table 2. Quality Assessment Criteria for Evaluation of Reports on the Prognostic Value of CAC

Criteria	Points Assigned by Definition	Kondos	Greenland	Arad	Taylor	Vliegenthart	LaMonte
1. Retrospective vs. prospective study	1 = Retrospective 2 = Prospective	1	2	2	2	2	1
2. Potential for referral bias	0 = Clinically referred patients 1 = Unselected cohort 2 = Population sample	0	1	1	1	2	0
3. Reporting CAC by CHD death or MI	1 = No 2 = Yes	2	2	1	2	2	2
4. Reporting of results by gender or ethnicity	0 = No 1 = Gender only 2 = Ethnicity only 3 = Both	1	0	0	1	0	1
5. Sample size greater than 1000	0 = No 1 = Yes	1	1	1	1	1	1
6. Potential for limited challenge	1 = No reporting of CAC outcomes in low- to high-risk global risk scores 2 = Reporting of CAC outcomes in low- to high-risk global risk scores	1	2	1	2	2	1
7. Risk factor reporting	1 = Historical only 2 = Measured in subset 3 = Measured in all subjects	1	3	2	3	3	1
8. Covariate or risk-adjusted outcomes	Risk Factors	1	2	1	2	2	1
Total score (total possible = 16)		8	13	8	14	14	8

CAC = coronary artery calcification; CHD = coronary heart disease; MI = myocardial infarction.

CAC score of 1 to 100) and as high as 10 (for CAC greater than 400) as compared to patients with a score of 0 (p less than 0.0001). This meta-analysis (23) offers support for the concept that there is a linear relationship between CAC and CHD events, but the analysis did not address whether CAC measurement is incremental to Framingham Risk Score (FRS) for CHD risk prediction.

Data Quality Issues

A lack of rigor in study methodology was a focus of the 2000 ACC document (1). A detailed review of the quality of the published data on the prognostic value of CAC was also published by Pletcher et al. (23) noting significant heterogeneity in study quality with often a lack of blinded outcome adjudication, greater use of categorical or historical risk factors, and variable tomographic slice thickness (3 vs. 6 mm) contributing to an overestimation of the relative risk of events by CAC measurements. For example, the relative risk ratio was significantly higher for CAC of 101 to 400 (p = 0.01) and greater than 400 (p = 0.004) when self-reported or historical risk factors were employed in a predictive model as compared with measured risk factor data. The clinical implication of this distinction is that physicians interpreting these results may overvalue CAC scores as substantially more predictive than traditional risk factors.

Evaluation of more recent publications indicates that some of the important methodological limitations of earlier reports have been addressed. Notably, more recent publications report the independent prognostic value of CAC in multivariable models including measured risk factor data (18,19,22). Larger sample sizes have also resulted in improved precision in risk prediction models. However, issues of selection or referral bias when using patient cohorts remain pertinent and are likely to have resulted in an overestimation of risk when based on clinical cohorts as compared with population samples (20,22). It is important to recognize that relative risk ratios from patient cohorts have generally been higher than from studies conducted in population samples even when the overall direction of the prognostic findings has been concordant.

Inclusion Criteria and Endpoint Definitions for the Present Analysis

The current document focuses on the ability of CAC scoring to estimate CHD death or MI. This approach allows for a comparison of the expected annual event rates based on the FRS. The FRS estimates that annual rates of CHD death or MI are less than 1.0% for low risk, 1.0% to 2.0% for intermediate risk (Table 1), and greater than 2.0% for high risk. When multiple publications have been reported from the same cohort study (1,4,5,33–36), we employ here only the most recent report in the current analysis (19,20).

The inclusion criteria for this analysis are: 1) data not previously reported in the 2000 document (1); 2) published series on the prognostic value of CAC in asymptomatic cohorts reported since 2002; 3) endpoint data must be reported on the outcome of CHD death or MI over a specified follow-up time period (usually within 3 to 5 years);

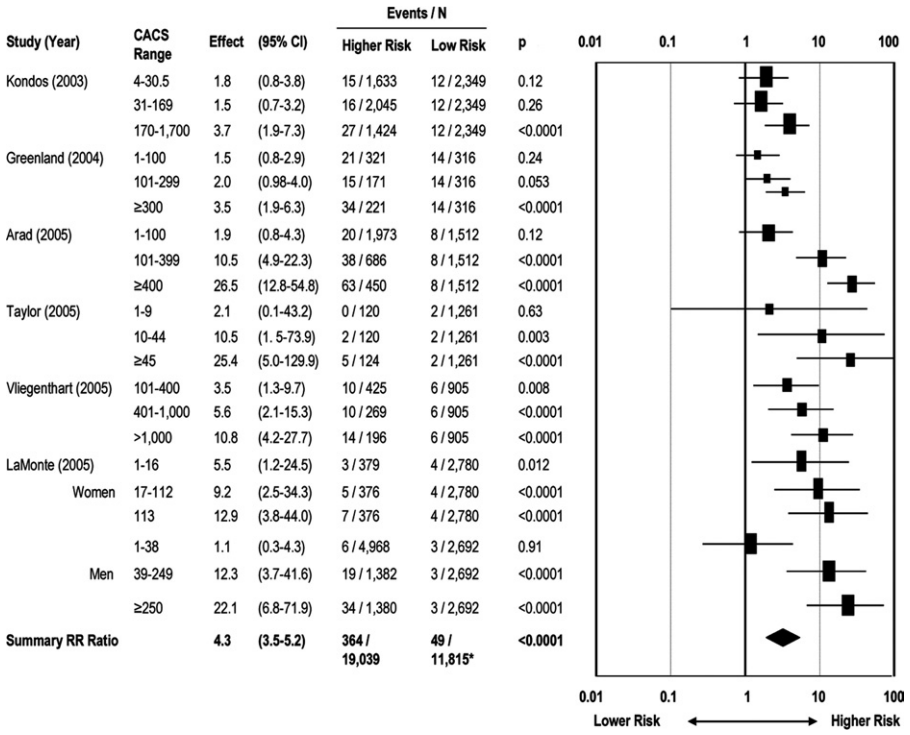

Figure 1. Meta-Analysis on the Prognostic Value of CACS

Relative risk (RR) ratios (95% confidence intervals [CI]) in six published reports (18–22,28). CACS = coronary artery calcification score.

and 4) data extraction must allow for the calculation of univariable relative risk ratios and must also include risk-adjustment for traditional cardiac risk factors (e.g., age, gender, cholesterol, hypertension, etc.) or the FRS.

Two committee members (AJT, LJS) evaluated the quality of each included report with the results of this analysis being included in Table 2. The quality assessment criteria included: 1) documentation of prospective data collection; 2) inclusion of self-referred patient series or from a population sample; 3) reporting of CHD events; 4) reporting of outcome data by gender and ethnicity; 5) sample size greater than 1000 individuals; 6) avoiding potential for limited challenge (i.e., an inclusion of very low to very high-risk patients resulting in a wide spread in the outcome results) by not reporting data within strata of clinical risk; 7) reporting measured versus historical or self-reported risk factor data; and 8) reporting univariable and multivariable prognostic models (i.e., ascertaining the incremental value of CAC scores). A review of the highlighted reports reveals that all studies identified for inclusion were of at least moderate-high quality.

Prognostic Value of CAC Scores From Published Reports From 2003–2005

Several recent cohorts have been published including prospective observational registries in predominantly male, younger and middle-aged (18), unselected (19) and older-aged, higher risk (20) asymptomatic cohorts. A self-referred patient series of 8855 asymptomatic adults was also included in this analysis (21). A recent population sample was also published and included 1795 subjects greater than or equal to 55 years of age who were prospectively enrolled in the Rotterdam coronary calcium study (22). Finally, the prognostic value of CAC scores was recently reported from a large series of 10 746 men and women aged 22 to 96 years who underwent a preventive health examination at the Cooper Clinic in Dallas, Texas (28).

Using a random-effects model, an analytical approach frequently applied to observational data such as that reported in the CAC series, Figure 1 reports on the univariable and summary (weighted average) relative risk ratios from 6 recently published reports in 27 622 patients (n = 395 CHD death or MI). This figure reports the summary relative risk ratio of 4.3 (95% confidence interval [CI] = 3.5 to 5.2) for any measurable calcium as compared with a low-risk CAC (generally using a score of 0) (p less than 0.0001). These data imply that the 3 to 5 year risk of any detectable calcium elevates a patient's CHD risk of events by nearly 4-fold (p less than 0.0001). Importantly, patients without detectable calcium (or a CAC score = 0) have a very low rate of CHD death or MI (0.4%) over 3 to 5 years of observation (n = 49 events/11 815 individuals).

As can be further seen in Figure 1, considerable variability existed in the relative risk ratios across the 6 reports which can, in part, be attributed to variability in the grouping of CAC scores and in the representation of younger individuals and women within each of the risk subsets. In the most

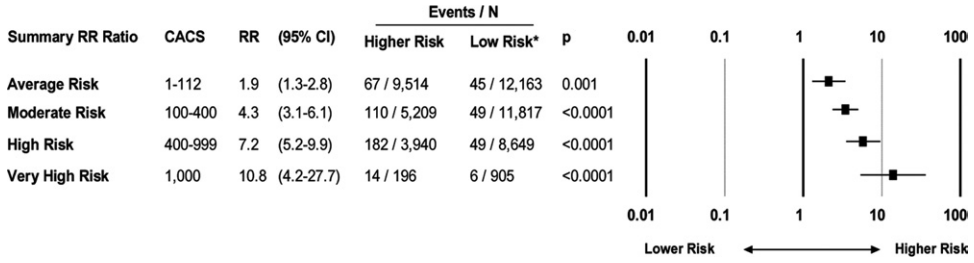

Figure 2. RR Ratios According to Level of Risk for CACS, From Average Risk to Very High Risk

Average risk includes Arad et al. (19), Greenland et al. (20), LaMonte et al. (28), and Taylor et al. (18). Moderate risk includes Arad et al. (19), Greenland et al. (20), LaMonte et al. (28), Taylor et al. (18), and Vliegenthart et al. (22). High risk includes Arad et al. (19), Greenland et al. (20), Kondos et al. (21), LaMonte et al. (28), and Vliegenthart et al. (22). Very high risk includes Vliegenthart et al. (22). *Low-risk N often includes multiple comparisons from a single series (e.g., Taylor CACS of 1 to 9 and 10 to 44 would use the same referent low-risk group comparison). CACS = coronary artery calcification score; CI = confidence interval; RR = relative risk.

recent report from the Cooper Clinic, different CAC ranges in risk groupings were applied for women and men (28). Moreover, both the Walter Reed and Cooper Clinic series evaluated younger asymptomatic cohorts while the Rotterdam study limited enrollment to individuals greater than or equal to 55 years of age (18,22).

The summary relative risk ratios in Figure 2 reveal an incremental relationship where higher CAC scores are associated with higher event rates and higher relative risk ratios. In this figure, a mild risk CAC score (with scores ranging from 1 to 112) was associated with an elevation in CHD death or MI risk with a summary relative risk ratio of 1.9 (95% CI = 1.3 to 2.8, p = 0.001). This mild risk grouping was more often reported in younger populations undergoing preventive health screenings (18,28).

With even higher CAC scores, the 3 to 5 year event rates increased substantially. For scores ranging from 100 to 400, the summary relative risk ratio was 4.3 (95% CI = 3.1 to 6.1) when compared to patients with no detectable coronary calcium (p less than 0.0001). For the high (CAC scores of 400 to 1000) and very high (greater than 1000) risk CAC scores, pooled CHD death or MI rates were 4.6% and 7.1% at 3 to 5 years after CAC testing, resulting in relative risk ratios of 7.2 (95% CI = 5.2 to 9.9, p less than 0.0001) and 10.8 (95% CI = 4.2 to 27.7, p less than 0.0001) when compared to the low-risk group (CAC score = 0) as reference.

Independent Prognostic Value of CAC Scores Over Cardiac Risk Factors

A necessary criterion for establishing a high degree of predictive accuracy for CAC measurements is the establishment of the independent contribution of CAC above and beyond risk factor data alone (29). Recent reports have included univariable and multivariable models that have evaluated the independent contribution of CAC in models evaluating risk factors or the FRS (Table 3). From the St. Francis Heart Study, measured risk factor data were available in 1293 of the total enrolled cohort of 4903 asymptomatic individuals. In univariable (p less than 0.0001) and multivariable (p = 0.01) models estimating CHD events at 4.3 years of follow-up, CAC scores were independently predictive of CHD outcome above and beyond both historical and measured risk factors (19). The CAC scores were also predictive of outcome in a multivariable model containing high-sensitivity C-reactive protein (18), similar to a previous report by Park et al. (30). Several reports have also evaluated the independent prognostic contribution of CAC

Table 3. Recent Published Observational Cohort Studies Evaluating the Independent Prognostic Value of Coronary Calcium Measurements in Published Reports From 2003 to 2005

Risk Subset	Year	N	Historical or Measured Risk Factor Data	Univariable RR*	Multivariable RR*	Model Controlling for Additional Variables Besides That Contained in the FRS:
Kondos	2003	8855	Historical	5.8, p = 0.001†	3.9, p = 0.01	
Greenland	2004	1461	Measured	3.9, $p < 0.001$	1.3, $p < 0.001$‡	
Arad	2005	1293	Measured	26.2, $p < 0.0001$	NR, p = 0.01	HsCRP
Taylor	2005	1639	Measured	NR, $p < 0.0001$	11.8, p = 0.002	Family history of CHD
Vliegenthart	2005	1795	Measured	8.2, $p < 0.01$	3.2–10.3, p = 0.03	Family history of MI and BMI
LaMonte	2005	10 746	Historical	1.6 (men) and 1.3 (women), $p < 0.0001$	NR§	

*For RR, a linear trend is presented if not indicated otherwise. Kondos: for any detectable CAC in men only; Greenland: for CAC greater than 300 versus CAC = 0 for univariable RR, evaluated as a continuous measure in the multivariable model; Arad: univariable RR is for score greater than or equal to 400, multivariable RR was NR; Taylor: univariable RR was NR, multivariable risk ratio is in men only and for any CAC score versus CAC = 0; Vliegenthart: multivariable is across a range of CAC from 101 to greater than 1000; LaMonte: risk factors measured in a clinical subset of 3619 subjects; univariable reported separately for men (1.6) and women (1.3), multivariable RR were NR but stated to be similar to age-adjusted models. †For men only. ‡For intermediate to high FRS. §p for risk adjustment was not specified but noted as significant.

BMI = body mass index; CAC = coronary artery calcification; CHD = coronary heart disease; FRS = Framingham Risk Score; HsCRP = high-sensitivity C-reactive protein; MI = myocardial infarction; NR = not reported; RR = relative risk.

Table 4. Predictive Accuracy of CAC for Estimation of CHD Death or Myocardial Infarction Including Unadjusted and Risk-Adjusted Multivariable Models Controlling for the Framingham Risk Score (FRS) and Other Risk Markers

Risk Subset	Year	N	Relative Risk (95% CI) for High Risk CAC	Unadjusted Model Including CAC as a Predictor of CHD Death or MI	Multivariable Model Including CAC + FRS and Other Novel Risk Markers As Predictors of CHD Death or MI	Additional Factors Not Novel Risk Markers Included in the Multivariable Model
Greenland	2004	1461	—	+++	+	—
Arad	2005	1293	—	+++	++	HsCRP
Taylor	2005	1639	4.8 (1.1–20.4)	+++	++	Family history of CHD
Vliegenthart	2005	1795	3.9 (1.4–11.1)	++	+	Family history of MI and body mass index
LaMonte	2005	3619	15.9 (2.2–114.7)	+++	+	

+ Modestly strong predictor. ++ Moderately strong predictor. +++ Strong predictor.
CAC = coronary artery calcification; CHD = coronary heart disease; CI = confidence interval; HsCRP = high-sensitivity C-reactive protein; MI = myocardial infarction.

in multivariable models that controlled for other cardiovascular risk markers, including risk factors not in the FRS, such as a family history of premature CHD (18,22) or body mass index (22) (Table 4).

Predictive Accuracy in Patients With an Intermediate FRS

The concept of Bayesian theory provides a framework to evaluate the expected relationship between the predictive value of CAC score in individuals with low- to high-risk FRS. As defined by Bayesian theory, a test's post-test likelihood of events is partially dependent upon a patient's pretest risk estimate. Thus, for patients with a low risk FRS very few events would be expected during follow-up and the resulting post-test risk estimate for patients with an abnormal CAC score would be expected to remain low. Several reports have noted that the use of CAC score in low-risk populations is not useful in modifying prediction of outcome (20,21). Greenland et al. (20) reported that a high CAC score was predictive of high risk among patients with an intermediate-high FRS greater than 10% (p less than 0.001) but not in patients with a low risk FRS (i.e., score less than 10%). In this report from the South Bay Heart Watch study, only 1 CHD event was noted in 98 patients with a low risk FRS. This report demonstrates the importance of considering the underlying hazard in selecting optimal cohorts for whom CAC testing will be of greater value.

In addition, the recent data provide support for the concept that use of CAC testing is most useful in terms of incremental prognostic value for populations with an intermediate FRS (29). In a secondary analysis of patients with an intermediate FRS from 4 reports (19,20,22,28), annual CHD death or MI rates were 0.4%, 1.3%, and 2.4% for each tertile of CAC score where scores ranged from less than 100, 100 to 399, and greater than or equal to 400, respectively (19,20) (Fig. 3). From this analysis, intermediate-risk FRS patients with a CAC score greater than or equal to 400 (Fig. 3) would be expected to have event rates that place them in the CHD risk equivalent status (event rate greater than or equal to 20% over 10 years (31).

Future Research Needs

The vast majority of prognostic evidence has been reported using an evaluation of risk stratification with absolute measurements of the CAC score. However, some earlier reports applied gender- and age- percentile rankings that may have greater intuitive appeal and understanding for patient education. As such, the percentile rankings have the potential for greater clinical applicability and, therefore, utilization. Only one report has evaluated the comparative predictive ability of absolute CAC scores versus the percentile scores. These investigators noted an improvement in risk detection using percentile ranks (32). An advantage to the use of percentiles is that it has been integrated into the NCEP guidelines where more aggressive care was recommended for patients with a 75th percentile ranking or higher (31). Thus, more information on percentile rankings for prognosis is needed; however, very few research groups have consistently reported CAC data according to percentile ranking. In addition, in our review of the current published evidence, the relative risk ratio for a high risk CAC measurement is higher for clinical registries as compared with population studies (relative risk = 19.3 vs. 5.0); suggesting an overestimation in risk due to selection bias (18–20,22). Data from the ongoing Multi-Ethnic Study of Atherosclerosis (MESA) should allow for more accurate risk estimation of CAC scores as based on a prospectively-derived large population sample (33).

Summary

Since 2000, when the last ACC CECD report on CAC measurement was published, there has been growing evidence on the use of CAC in better-studied cohorts of patients and asymptomatic individuals. CAC scoring has an increasingly high level of quality evidence on its role in risk stratification of asymptomatic patients. Recent evidence is supportive that measurement of CAC is predictive of CHD death or MI at 3 to 5 years. Current evidence also suggests

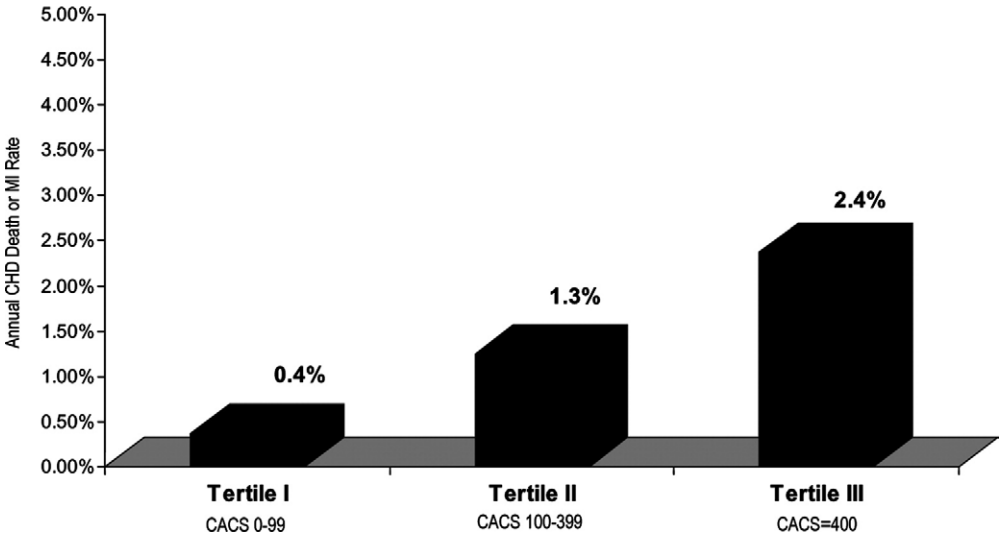

Figure 3. Estimated Annual Risk of CHD Death or MI Rate

Rate shown is by tertile of the Agatston score in patients at intermediate coronary heart disease (CHD) event risk using definitions of an intermediate Framingham Risk Score (FRS) or greater than 1 cardiac risk factor. Intermediate FRS was defined as follows: Greenland et al. (20) 10% to 20%; Vliegenthart et al. (22) 20%; LaMonte et al. (28), greater than 1 cardiac risk factor; and Arad et al. (19) 10% to 20%. CACS = coronary artery calcium score; MI = myocardial infarction.

that the use of CAC is independently predictive of outcome over and above traditional cardiac risk factors. Published reports have largely been derived from patient cohorts where referral bias is operational resulting in an overestimation of CHD death or MI risk estimates. Upcoming data from the MESA study may be helpful to devise population screening strategies for women and in non-whites. The MESA data will also be useful in validating predictive capability by ethnicity and across a broad age range of asymptomatic people. Data employing direct comparisons of CAC measurement versus other imaging modalities or biomarkers are generally not available.

The consensus of the Committee was that the body of evidence is supportive of recommendations from the USPSTF that unselected screening is of limited clinical value in patients who are at low risk for CHD events, typically estimated using a low FRS less than 1.0% per year (see http://www.ahrq.gov/downloads/pub/prevent/pdfser/chdser.pdf).

A subset analysis of the predictive accuracy of CAC in patients with an intermediate FRS reveals that for a score greater than or equal to 400, the patient's 10-year CHD risk would achieve risk equivalent status similar to that noted with diabetes or peripheral arterial disease (31). Thus, clinical decision-making could potentially be altered by CAC measurement in patients initially judged to be at intermediate risk (10% to 20% in 10 years).

The accumulating evidence suggests that asymptomatic individuals with an intermediate FRS may be reasonable candidates for CHD testing using CAC as a potential means of modifying risk prediction and altering therapy. On the other hand, there is little to be gained by testing with CAC in patients with a low FRS. Furthermore, patients with a high FRS should be treated aggressively consistent with secondary prevention goals based upon the current NCEP III guidelines and thus should not require additional testing, including CAC scoring, to establish this risk evaluation (31). Additionally, the current CAC literature does not provide support for the concept that high-risk asymptomatic individuals can be safely excluded from medical therapy for CHD even if CAC score is 0.

Role of CAC Scoring in Assessment of Symptomatic Patients

Diagnosis of Coronary Stenosis in Patients With Possible CHD by CAC

The utility of coronary artery calcium measurement in symptomatic patients has been widely studied and discussed in depth in the previous ACC/AHA statement (1). It was also extensively reviewed in the recent American Heart Association Cardiac Imaging Committee Consensus Statement—The Role of Cardiac Imaging in the Clinical Evaluation of Women With Known or Suspected Coronary Artery Disease (34). One conclusion of these reports was that a positive CT study (defined as presence of any CAC) is nearly 100% specific for atheromatous coronary plaque (34,35). Since both obstructive and non-obstructive lesions can have calcification present in the intima, CAC is not specific for obstructive coronary disease.

In the symptomatic patient, CAC has been evaluated as a noninvasive diagnostic technique for detecting obstructive CAD. To define its test characteristics and to compare it with other noninvasive tests, a meta-analysis was performed and published in the previous ACC/AHA consensus statement (1). In the previous meta-analysis, a total of 3683

patients were considered among 16 studies evaluating the diagnostic accuracy of CAC measurement (1). Inclusion criteria were: diagnostic catheterization for patients without prior history of coronary disease or prior cardiac transplantation. Patients were symptomatic and referred to the cardiac catheterization laboratory for diagnosis of obstructive CAD. On average, significant coronary disease (greater than 50% or greater than 70% stenosis by coronary angiography) was reported in 57.2% of the patients. Presence of CAC was reported on average in 65.8% of patients (defined as a score greater than 0 in all but one report). The weighted-average or summary odds were elevated 20-fold with a positive CAC (score greater than 0) (95% CI 4.6 to 87.8). Additional summary odds ratios were also calculated with various anatomic and calcium score cut points. For detection of minimal, greater than 50%, and greater than 70% stenosis at cardiac catheterization, the summary odds increased from 6.8-fold (95% CI 3.0 to 15.6) to 16.4-fold (95% CI 5.1 to 53.1) to 50-fold (95% CI 24.1 to 103.0); that is, the odds of significant coronary disease increased when greater angiographic lesion thresholds were used for significant disease (although the confidence bounds widened). Higher coronary calcium scores increased the likelihood of detecting significant coronary disease (greater than 50% or greater than 70% luminal stenosis). A threshold of detectable calcium or a score greater than 5 was associated with an odds of significant disease of 25.6-fold (95% CI 9.6 to 68.4).

Schmermund et al. (36) examined 291 patients with suspected CHD who underwent risk factor determination as defined by the NCEP, CAC measurement, and clinically indicated coronary angiography. A simple noninvasive index (NI) was constructed as the following: log(e)(LAD score) + log(e)(LCx score) + 2[if diabetic] + 3[if male]. Receiver-operating characteristic curve analysis for this NI yielded an area under the curve of 0.88 ± 0.03 (p less than 0.0001) for separating patients with, versus without, angiographic 3-vessel and/or left main CAD. Various NI cutpoints demonstrated sensitivities from 87% to 97% and specificities from 46% to 74%. Guerci et al. (37) studied 290 men and women undergoing coronary arteriography for clinical indications. A coronary calcium score greater than 80 (Agatston method) was associated with an increased likelihood of any coronary disease regardless of the number of risk factors, and a coronary calcium score greater than or equal to 170 was associated with an increased likelihood of obstructive coronary disease regardless of the number of risk factors (p less than 0.001). Kennedy et al. (35) studied 368 symptomatic patients undergoing cardiac catheterization. By multivariate analysis, only male sex and coronary calcification were significantly related to extent of angiographic disease. Receiver-operating characteristic curve analysis showed that the amount of coronary calcium was a significantly better discriminator of disease than were the standard risk factors. In all three studies, CAC scoring improved diagnostic discrimination over conventional risk factors in the identification of persons with angiographic coronary disease.

More recently, large multi-center studies have been reported using fast CT for diagnosis of obstructive CAD in symptomatic persons (n = 1851), who underwent coronary angiography for clinical indications. Study prediction models were designed to be continuous, adjusted for age and sex, corrected for verification bias, and independently validated in terms of their incremental diagnostic accuracy. The overall sensitivity was 95%, and specificity was 66% for coronary calcium score to predict obstructive disease on invasive angiography. The logistic regression model exhibited excellent discrimination (receiver operating characteristic curve area of 0.84 ± 0.02) and calibration (chi-square goodness of fit of 8.95, p = 0.44) (38). Increasing the cut-point for calcification markedly improved the specificity, but decreased the sensitivity. In the same study, increasing the CAC cutpoint to greater than 80 decreased the sensitivity to 79% while increasing the specificity to 72%. In another large study (n = 1764) comparing CAC to angiographic coronary obstructive disease, use of a CAC score greater than 100 resulted in a sensitivity of 95% and a specificity of 79% for the detection of significant obstructive disease by angiography (39). Summing these 2 large studies (n = 3615) leads to an estimated sensitivity of 85%, with a specificity of 75%. There is some concern, due to study design, that these studies (similar to validation of many non-invasive cardiovascular tests) are subject to verification bias, which could raise the sensitivity and lower the specificity. A large study, evaluating consecutive symptomatic persons undergoing cardiac catheterization, addresses this concern. 2115 consecutive symptomatic patients (n = 1404 men; mean age = 62, SD ± 19 years old) with no prior diagnosis of CAD were included in this study. These patients were being referred to the cardiac catheterization laboratory for diagnosis of possible obstructive coronary artery disease, without knowledge of the CAC scan results. The scan result did not influence the decision to perform angiography. Overall sensitivity was 99%, and specificity was 28% for the presence of any coronary calcium being predictive of obstructive angiographic disease. With volume calcium score greater than 100, the sensitivity to predict significant stenoses on angiography decreased to 87% and the specificity increased to 79% (40).

Comparison With Other Tests for CHD Diagnosis. It is appropriate to compare CAC scoring by fast CT with the older more mature diagnostic modalities. The equipment and personnel for performing stress electrocardiography, myocardial perfusion imaging, and echocardiography are readily available. The electrocardiographic (ECG) exercise test, like the echocardiogram, can be performed in the doctor's office and does not require exposure to radiation.

Exercise ECG Test. Gianrossi et al. (41) investigated the reported diagnostic accuracy of the exercise ECG for CAD obstructive disease in a meta-analysis. One hundred forty-

seven consecutively published reports involving 24 074 patients who underwent both coronary angiography and exercise testing were summarized. Wide variability in sensitivity and specificity was found (mean sensitivity was 68%, with a range of 23% to 100% and a standard deviation of 16%; mean specificity was 77%, with a range of 17% to 100% and a standard deviation of 17%).

Myocardial Perfusion Imaging and Stress Echocardiography. Fleischmann et al. (42) reviewed the contemporary literature to compare the diagnostic performance of exercise echocardiography and exercise nuclear perfusion scanning in the diagnosis of CAD. Forty-four articles (not unique patient data sets) met inclusion criteria: 24 reported exercise echocardiography results in 2637 patients with a weighted mean age of 59 years, of whom 69% were men, 66% had angiographic coronary disease, and 20% had prior myocardial infarction; and 27 reported exercise SPECT in 3237 patients, of whom 70% were men, 78% had angiographic coronary disease, and 33% had prior myocardial infarction. In pooled data weighted by the sample size of each study, exercise echocardiography had a sensitivity of 85% (95% CI 83% to 87%) with a specificity of 77% (95% CI 74% to 80%). Exercise perfusion yielded a similar sensitivity of 87% (95% CI 86% to 88%) but a lower specificity of 64% (95% CI 60% to 68%) (42).

There are more recent direct comparison studies available in patients who underwent both CAC measurements, as well as either exercise electrocardiography and/or nuclear imaging, with results compared to cardiac catheterization. Shavelle et al. (43) reported 97 patients who underwent technetium stress testing (technetium-stress), treadmill-ECG, and fast CT coronary scanning within 3 months of invasive coronary angiography for the evaluation of chest pain. The relative risk of obstructive angiographic CAD for an abnormal test was higher for fast CT CAC scores (4.53) than either treadmill-ECG (1.72) or technetium-stress (1.96). The accuracy of fast CT was significantly higher (80%) than either treadmill testing (71%) or technetium-stress (74%) in the diagnosis of obstructive CAD. The combination of a positive CAC (calcium score greater than 0) and abnormal treadmill-ECG raised the specificity to 83% for obstructive disease).

Kajinami et al. (44) evaluated 251 symptomatic patients who underwent coronary angiography, fast CT, ECG, and thallium exercise testing. The ECG and thallium exercise tests had overall sensitivity of 74% and 83%, respectively, and specificity of 73% and 60%, respectively. The sensitivity and specificity of CAC scoring were 77% and 86%, respectively. In a related study (45), 150 patients underwent thallium stress testing, fast CT, and coronary angiography. The relative risk of an abnormal thallium stress test was 3.5, compared to 14.9 for an elevated CAC score as detected by fast CT. Yao et al. (46) compared technetium-99m single-photon emission tomography and fast CT in 51 patients with suspected CAD. Although differences were found between the 2 testing methods in patients with single-vessel CAD, the sensitivity, specificity, and accuracy were comparable in patients with multivessel CAD.

Schmermund et al. (47) also compared fast CT CAC measurement to nuclear stress test results in a cohort of 308 symptomatic patients. The association of CAC score with angiographically detected obstructive coronary disease remained highly significant after excluding the influence of all interrelated risk factors and SPECT variables (p less than 0.0001).

Data also support a complementary role for coronary calcium and myocardial perfusion scanning (MPS) measurements. He et al. (48) noted a threshold phenomenon with almost no observable myocardial hypoperfusion among patients with a CAC score less than 100 and with a marked increase in the frequency of an abnormal MPS in patients with high CAC values (greater than 100) (48). A recent study of 1195 patients who underwent CAC measurement and MPS assessment demonstrated that CAC was the most powerful predictor of an ischemic nuclear test, and that less than 2% of all patients with CAC less than 100 had positive MPS studies (49). CAC score, due to its high sensitivity for flow-limiting CAD, may be useful as a filter prior to invasive coronary angiography or stress nuclear imaging.

Other Uses of CAC Measurement in Symptomatic Persons. Another potential use of CAC is to determine the etiology of cardiomyopathy. The clinical manifestations of patients with ischemic cardiomyopathy are often indistinguishable from those patients with primary dilated cardiomyopathy. One large study in 120 patients with heart failure of unknown etiology demonstrated the presence of CAC was associated with 99% sensitivity for ischemic cardiomyopathy (50). Another study also demonstrated similarly high sensitivity using fast CT to differentiate ischemic from non-ischemic cardiomyopathy (51). This methodology has been demonstrated to be more accurate than echocardiography and MPS techniques in direct-comparison studies in this population (52,53). 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 CAC scoring relates to the triage of chest pain patients. Three studies have documented that CAC is a rapid and efficient screening tool for patients admitted to the emergency department with chest pain and nonspecific electrocardiograms (54–56). These relatively small-scale studies (with sample sizes ranging from 105 to 192) showed sensitivities of 98% to 100% for identifying patients with acute MI and very low subsequent event rates for persons with negative tests. The high sensitivity and high negative predictive value may allow early discharge of those patients with non-diagnostic ECG and negative CAC scans (scores = 0). Long term follow-up of one patient cohort demonstrated a very low risk of events

in patients without demonstrated CAC at the time of emergency room visit (54). However, unlike the case with evaluations of asymptomatic patients (20), prognostic studies of CAC in symptomatic patients have generally been limited by biased samples (e.g., patients referred for invasive coronary angiography) and small numbers of hard outcome events. Future studies should include larger numbers of patients and should allow for adequate length of follow-up and assessment of larger numbers of hard endpoint events, especially all-cause mortality and myocardial infarction (57).

Summary. For the symptomatic patient, exclusion of measurable coronary calcium may be an effective filter before undertaking invasive diagnostic procedures or hospital admission. Scores less than 100 are typically associated with a low probability (less than 2%) of abnormal perfusion on nuclear stress tests (48,49), and less than 3% probability of significant obstruction (greater than 50% stenosis) on cardiac catheterization (38,39). The presence of CAC by fast CT is extremely sensitive for obstructive (greater than 50% luminal stenosis) CAD (95% to 99%), but has limited specificity. CAC studies of over 7600 symptomatic patients demonstrate negative predictive values of 96% to 100%, allowing for a high level of confidence that an individual with no coronary calcium (score = 0) has no obstructive angiographic disease (38–40).

In direct-comparison studies, CAC detection in the symptomatic person has been shown to be comparable to nuclear exercise testing in the detection of obstructive CAD. Given the prognostic information that is implicit in exercise capacity, even when it is combined with imaging, fast CT starts with a disadvantage compared with existing modalities in symptomatic patients who can exercise. Anatomic testing, such as cardiac CT (whether with contrast in the form of CT angiography or without contrast, such as CAC assessment), should be relegated to second line testing or considered when functional testing is either not possible or indeterminate. The accuracy of CAC is not limited by concurrent medication, the patient's ability to exercise, baseline wall motion, or electrocardiogram abnormalities.

Use of Coronary CT for Assessment of Progression or Regression of Coronary Atherosclerosis

Serial noninvasive monitoring of calcified atherosclerosis using CAC measurement has been proposed as a means of monitoring medical treatment for CAD as well as assessing change in CVD prognosis (58). The validity of serial coronary calcium measurements as a method to monitor progression of atherosclerosis requires: 1) that progression of coronary calcium has biologic relevance to atherosclerosis activity; 2) that progression of coronary calcium can be detected relative to inter-test variability; 3) that changes in coronary calcium severity have prognostic relevance; and 4) that modification of cardiovascular risk factors modulates the progression of coronary calcium. Each of these points is subsequently discussed.

Biologic Relevance of Coronary Atherosclerosis Progression

The extent of coronary calcium found on fast CT is broadly related to plaque burden, but there is a high degree of site-to-site variability in the presence and extent of calcium within any single atherosclerotic plaque. Pathology studies have shown that the extent of coronary calcium within plaques tends to be related to the presence of healed plaque ruptures (59). Moreover, vulnerable plaques tend to be those with less extensive calcium deposits frequently seen in a spotty distribution (59), a finding supported by intravascular ultrasound studies of patients with acute coronary syndromes (60). The biology of progression of calcium within atherosclerosis is complex, genetically-directed, and partially modified by drugs that have the potential to alter the fundamental biology of the calcification process. Statins, for example, can both inhibit and promote tissue calcification upon interaction with different types of vascular cells (61).

The associations between CAC progression and clinical cardiovascular risk factors are not well understood. Present data indicate that CAC progression is most strongly related to the baseline CAC score with only a limited relationship to standard cardiovascular risk factors (62,63).

Accuracy of Serial Coronary Calcium Assessments

Progression of coronary calcium is typically evaluated as a percentage of the baseline calcium score value. Early studies of the inter-test variability of CAC measurements indicated inter-scan variability as high as 25% to 50% of the calcium score value (62,64,65). More recently, imaging protocol refinements specific to electron beam CT scanning, including a reduction of the electrocardiographic gating interval to approximately 40% to 60% of the relative risk interval, and utilizing 3-mm slice thickness, have reduced the inter-test variability to 15% or less (66). The standard deviation of the interscan variability reported in the recent literature is approximately 10% (64). In contrast, annual CAC progression rates typically exceed 20% (62,64,65), thus permitting accurate determination of the presence or absence of true progression in individual patients across relatively short (1 to 2 year) time horizons. The ability to track CAC progression is most accurate in patients with intermediate and higher CAC scores because the absolute error in CAC measurement would approximate the actual CAC score in patients with low scores (CAC score 1 to 30), and even small changes in the absolute calcium score would be a relatively large fractional change.

Prognostic Relevance of CAC Score Changes

There have been 3 reports from the work of Raggi and colleagues on the relationship between changes in CAC score and outcomes (67–69). In these studies including a

general population (67) analyzed by diabetic status (68) and treatment with statins (69), subjects who suffered an MI demonstrated an approximately 2-fold greater annual CAC increase than event-free survivors. In the presence of definite CAC score progression (greater than 15%/year), there was a significant increase in relative risk of myocardial infarction compared to subjects with stable scores. Notably, the finding of CAC progression increased the associated cardiovascular risk across all levels of CAC severity (69). Furthermore, the detection of stable CAC was associated with a low risk of cardiovascular events, even among those with extensive CAC. A major limitation of using calcium score progression as a marker of risk is that the positive predictive value appears to be low with substantial overlap among those with and without future events. Nonetheless, serial monitoring of atherosclerosis to refine risk prediction remains a potentially attractive hypothesis in need of ongoing investigation. Confirmatory reports from screening populations are needed to assess the strength and generalizability of these findings.

Modification of CAC Progression

Progression of CAC is frequently observed across modest (3 to 7 year) time horizons to a degree primarily related to the extent of baseline coronary calcification (70,71). Several pharmacological interventions, including statins and calcium channel blockers, have been associated with delayed progression of CAC. The earliest work primarily involved statins in observational study designs, including 2 published observational studies on the effect of reducing LDL cholesterol with statins in which CAC progression was found to be lower during statin treatment (72,73). These data, however, have been contradicted by 2 large statin clinical trials that failed to confirm this finding, including a placebo-controlled study using calcium scores (74) and a study of post-menopausal women treated to moderate versus intensive LDL cholesterol reductions using calcium volume scores (75). The CAC findings of the latter 2 studies are in contrast to the definitive reduction in cardiovascular risk associated with statin therapy and suggest that either longer periods of monitoring of CAC would be necessary to detect an effect of statins, that statins fundamentally alter the relationship between calcified plaque extent and cardiovascular outcomes, or that statins are affecting the noncalcified plaque and therefore no change is detectable by CAC measurement. Management of other cardiovascular risk factors, for example, hypertension or diabetes, has not been examined relative to the progression of coronary calcium.

Summary and Implications

Although progression of CAC can be detected using fast CT methods, its determinants are largely unknown and the relationship to clinical outcomes is still unclear. Because progression of CAC is not clearly modifiable through standard risk reducing therapies, and CAC measurement involves both costs and radiation exposure, clinical monitoring of CAC progression through serial fast CT scanning is not recommended at this time.

Cost-Effectiveness of Coronary Calcium Scoring for Risk Assessment of Cardiac Death or MI

Establishing the cost-effectiveness of testing, especially screening tests, is quite challenging. To establish effectiveness, CAC measurement would have to be shown to enhance life, prolong life, or both (76). This task can be relatively straightforward with therapies for which there are randomized controlled clinical trials establishing efficacy in terms of quality of life, events, or mortality. These types of studies do not exist for CAC measurement, as noted earlier in this report, and in general do not exist for any cardiovascular test. Standards for cost-effectiveness analysis call for evaluating effects on survival, quality of life and cost using a lifetime time horizon (76). Even for therapies which have major clinical impact, such as lowering of LDL cholesterol, and where the clinical trial data are consistent and convincing, this is challenging to accomplish. For a single test, which might be expected to have a smaller impact than a major therapeutic strategy, establishing cost-effectiveness can be a difficult, if not unrealistic goal.

In the absence of clinical trial data, cost-effectiveness is generally approached with simulations in which decisions, test results, and outcomes are estimated, with as much information coming from the medical literature as possible. For tests, such as CAC measurement, simulations can be especially difficult because the test results can lead to many different possible decisions and thus many different potential outcomes. Furthermore, for evaluating any test or therapy, it is essential to understand the nature of the intervention and the comparators. In the case of CAC measurement, there are several possible ways to view how the test would affect care and outcome, and the comparators may not be clear.

Despite these challenges, there have been several attempts to assess the cost-effectiveness of CAC scoring. O'Malley et al. (77) constructed a decision analytic model of the addition of CAC score to the FRS. The base case assumed that any CAC greater than 0 would increase the relative risk 4-fold. Multiple additional assumptions were made, some of which the Writing Committee members considered difficult to justify. The base case offered an incremental cost-effectiveness ratio (ICER) of $86 752 for a 42-year-old subject. The ICER was sensitive to the gain in life expectancy for early intervention, the utility of being at risk, and the added prognostic value of CAC. This study offers good insight into some of the problems in assessing the cost-effectiveness of CAC, but it is the judgment of the Writing Committee that it is not sufficiently grounded in data to be useful for medical decision making. The authors

updated this analysis using the hazard ratio from the Prospective Army Coronary Calcium project, finding an ICER of $31 500 (18). This conclusion was sensitive to variation in the extent to which CAC actually predicts events (sensitivity analysis) and to assumed degree of the efficacy of primary prevention strategies (in sensitivity analysis). Furthermore, there were only 9 coronary events used to establish the hazard ratios. The analysis is also limited by the assumptions in the model. Shaw et al. (78) developed a similar decision-analytic model, finding that in individuals with estimated risk of coronary events below 0.6% per year, the ICER approached $500 000, but was $42 339 if the estimated event rate was 1% per year, and $30 742 if the event rate was 2% per year. This model was also highly dependent on the underlying assumptions, as is always the case for any cost-effectiveness model.

Summary and Conclusion

While several serious efforts to understand the cost-effectiveness of CAC measurement have been made, the Committee felt that models were not, and could not be, sufficiently well grounded in data to offer results that could be used for medical decision making or establishing policy at this time.

Special Considerations

CAC Scores and Gender

Gender differences in utility and accuracy of imaging tests are typically related to differences in the epidemiology of coronary heart disease, with women having later onset of clinical CHD than men. Gender differences in incidence and prevalence of CAD are most marked in middle-aged populations, the typical target age group for CHD screening. In addition, emerging data suggest that there may be actual gender differences in the anatomy of atherosclerosis. Thus, it is important to consider gender-specific data when evaluating the potential uses of any new cardiac test.

Epidemiology

Women develop coronary atherosclerosis 10 years later than men, on average, and the occurrence of coronary calcification tracks with this later onset of CAD. These differences start to diminish at about age 60 (79). These gender differences in occurrence of coronary calcium support the association of CAC with coronary atherosclerosis and underline the importance of age- and gender-specific reference points for CAC scoring (80).

Risk Assessment

In general, studies of the use of coronary calcium as a component of the CHD risk assessment include fewer women than men. Studies also vary according to the analysis of women as a separate subgroup. Because many of the existing studies have included women and men of similar age (typically between ages 50 and 60), the reported 10-year event rates for women have been predictably lower than in men. Thus, many studies have been underpowered and included women at too low risk to show benefit of CAC screening exclusively in women.

Two studies included a large enough sample of women (81) or adequate numbers of elderly patients to reach conclusions about CAC testing in women. In a prospective, observational study by Raggi et al. (81), the relationship between CAC and all-cause mortality was analyzed by gender in 10 377 asymptomatic individuals, of whom 40% were women. The mean follow-up period was 5 ± 3.5 years. For women, the ROC C-statistic for the prediction of all-cause mortality by the NCEP ATP-3 Framingham risk calculator was 0.672 for women and increased significantly to 0.75 with data from CAC scores added to the prediction models (p less than 0.0001). This analysis is limited by the use of self-reported risk factors but showed similar relationships in the predictive ability of CAC in men and women. Mortality was determined using the Social Security National Death Index, thus these data are not specific to CHD events. In a study of older individuals (mean age = 71 years), the relationships between CAC score and incident myocardial infarction were similar in men and women (22) and remained significant in risk factor- and gender-adjusted models (22).

Summary

There are limited data broadly specific to women on the relationship between CHD outcomes and CAC. Existing data confirm an association between CAC scores and all-cause mortality and CHD events in elderly women. Future studies must include enough women within an appropriately high clinical risk stratum (at least intermediate Framingham risk) to be able to draw significant, clinically relevant conclusions specific to women.

Ethnicity

The majority of studies which have demonstrated the association between the degree of coronary calcium, the burden of atherosclerosis, and the risk for cardiovascular events associated with coronary calcium have included primarily Caucasian subjects. Significant racial/ethnic differences exist in the prevalence of cardiovascular risk factors and mortality. Blacks generally have a higher prevalence of hypertension, diabetes and obesity, and a higher age-adjusted mortality from coronary heart disease and cardiovascular disease than whites (82,83). Some of these differences are attributed to socioeconomic status, access to care, and lifestyle factors.

Potential differences in coronary calcium prevalence and severity between racial/ethnic groups have begun to

be evaluated. A few studies have been published which have compared the prevalence and/or severity of CAC in black and white subjects. Some have found that blacks have less coronary calcium than whites, and others have shown no significant differences. The largest study was reported from MESA, which included 6814 men and women between the ages of 45 and 84 years without evidence of clinical cardiovascular disease (84). The prevalence of coronary calcium was highest in the white men (70.4%) and lowest in the black men (52.1%). The prevalence in Hispanic and Chinese men was intermediate between the two (56.5% and 59.2%, respectively). Similar results were seen in women, with white women having the highest prevalence (44.6%), black and Hispanic women the lowest (36.5% and 34.9%, respectively), and Chinese women intermediate (41.9%). After adjusting for cardiovascular disease risk factors the prevalence of coronary calcium was 22% lower in blacks compared with whites, 15% lower in Hispanics, and 8% lower in Chinese. Similar results were seen in analyses of the severity of coronary calcium in these racial/ethnic groups (33). The MESA study recently published detailed tables and figures describing the racial/ethnic distribution of coronary calcium in a relatively unbiased population sample (85). The exact estimated percentile for a particular age in years is available at the MESA public Web site (http://www.mesa-nhlbi.org/CACReference.aspx). At this Web site, one can enter an age (in years), gender, race/ethnicity (for the 4 race/ethnicity groups included in MESA), and optionally an observed calcium score and obtain the estimated percentiles for that subset, and the estimated percentile for the particular calcium score entered.

The Prospective Army Coronary Calcium (PACC) Project also found a higher prevalence of coronary calcium in white (19.2%) than black (10.3%) active-duty military personnel with a mean age of 42 years; the difference persisted after adjusting for cardiovascular disease risk factors (86). Budoff et al. (87) described similar findings in white men referred for CAC testing compared with black men; however, in this study, black women had a higher prevalence of coronary calcium than white women. In addition, Asian men and women had a lower prevalence of coronary calcium, and the prevalence in Hispanics was similar to the whites. The Cardiovascular Health Study (CHS) included older adults (67 to 99 years) and found higher CAC scores in whites compared with blacks, especially in men (88). Interestingly, a subgroup analysis of subjects with a history of prior MI also showed lower coronary calcium scores in the black subgroup. Budoff et al. (89) described ethnic differences in coronary calcium and angiographic stenosis in patients referred for clinically indicated coronary angiography who also underwent a research fast CT for CAC score. Again, it was observed that blacks had a lower prevalence of coronary calcium (62%) compared with whites (84%). This correlated with a lower prevalence of significant angiographic coronary artery obstruction (49% in blacks and 71% in whites). Hispanics also had a lower prevalence of coronary calcium (71%) and stenosis (58%) than whites, but there were no differences in Asians, who were underrepresented in this study. Sekikawa et al. (90) compared the prevalence of coronary calcium in 100 Americans (99% white) and 100 Japanese and found a significantly lower prevalence of coronary calcium in the Japanese men (13%) than the American men (47%).

In contrast, the Dallas Heart Study is a population-based probability sample that includes 1289 men and women between the ages of 18 and 65 years, of whom 50% are black. In this study the prevalence of coronary calcium (Agatston score greater than 10) was similar between black (37%) and white (41%) men, and between black (29%) and white (23%) women (91). In addition, the Coronary Artery Risk Development in Young Adults (CARDIA) study also found no difference in the prevalence of coronary calcium in young black and white adults between the ages of 28 and 40 years (92), and no difference was found in coronary calcium scores between black and white postmenopausal women in the Women's Health Initiative Observational Study (93).

Overall, the majority of studies demonstrate a lower prevalence and extent of coronary calcification in blacks compared to whites despite generally a higher prevalence of cardiovascular risk factors in blacks. None of the studies has shown a higher prevalence of coronary calcium in black men despite the greater age-adjusted prevalence of CHD mortality although some do show no difference between the 2 groups. Only a few studies have described coronary calcium in Hispanic or Asian American populations. Studies evaluating racial/ethnic disparities in CAC measurement are somewhat limited at this time due to lack of follow-up for cardiovascular events. Outcome studies are needed to determine whether the same coronary calcium score might have a different prognosis depending on race/ethnicity. As race/ethnicity is not always a discrete characteristic, if this is the case, interpretation of these scores would be difficult. It is unclear whether racial/ethnic differences translate to differences in the pathophysiology of atherosclerosis, that is, differing degrees of calcification for the same degree of atherosclerosis, or whether some ethnic groups have a lower burden of atherosclerotic plaque than whites. At this time, there is limited information on how to use coronary calcium data derived from primarily white populations to predict CHD in non-white populations. In terms of racial differences in risk assessment, it should be noted that despite ethnic differences in the use of the FRS for this purpose, there is population-based evidence that pre-test assessments of risk can be reliably made in black men and women based on the FRS (94). Thus, the FRS remains the standard approach to risk assessment even in ethnic minorities.

Chronic Kidney Disease (CKD) and End-Stage Renal Disease (ESRD)

Patients with CKD and ESRD often die from cardiovascular diseases. The AHA has recommended that these patients be placed in the "highest risk" category and therefore receive aggressive preventive therapies (95). There is a remarkably high prevalence of coronary calcium in patients with ESRD who are undergoing dialysis, especially in young adults compared with controls (96,97). The presence and degree of coronary calcium in these patients may be associated with the number of years on dialysis, the intake of supplemental calcium, and the mean calcium-phosphorus ion product (98–100). The use of non-calcium phosphate binders is associated with less progression of coronary calcium than is calcium carbonate (101). These findings suggest that altered calcium metabolism is related to the pathogenesis of arterial calcification in these patients.

Some studies suggest that patients with CKD and ESRD develop calcification in the tunica media layer of the arterial wall, unlike the typical intimal calcification that is known to be associated with plaque burden (102). The role of medial calcification as a marker of cardiovascular risk is not well defined. Some studies reveal an association between coronary calcium and prevalent cardiovascular disease in patients undergoing dialysis (98), and coronary calcium score is associated with risk for total mortality (103). An association between the degree of coronary calcium and luminal stenosis on angiography has been reported (104), however, other studies did not show this association (105).

In summary, the role of CAC scoring in determining risk in patients with CKD and/or ESRD is unclear due to a limited number of clinical studies in these populations. Further prospective studies are needed to determine the utility of CAC testing in patients with CKD and ESRD for predicting risk for CVD events.

Diabetes

Numerous cross-sectional studies have documented that patients with diabetes have a higher prevalence and extent of coronary calcium than non-diabetic patients (106–111). However, there is less information available about the utility of coronary calcium as a predictor of risk in diabetic patients. The South Bay Heart Watch Study found that baseline coronary calcium predicted risk in the non-diabetic subgroup, but not in the diabetic subgroup (n = 269) (110). However, Raggi et al. (106) found that coronary calcium predicted all-cause mortality in diabetics referred for fast coronary CT scanning. Raggi et al. (106) also found that patients with diabetes have a greater increase in risk for mortality associated with a given degree of calcium than the non-diabetic patients. A recent study (112) suggested that CAC scoring may be superior to established cardiovascular risk factors for predicting silent myocardial ischemia and short-term cardiovascular outcomes among stable, uncomplicated type 2 diabetic patients. However, while prospectively conducted, the study included a very small number of hard coronary events and must be confirmed by a larger study.

Patients with diabetes are considered to be in the highest risk category according to the Adult Treatment Panel III guidelines (14). Consistent with the observation that diabetics have a high burden of atherosclerosis, asymptomatic diabetic patients without known CAD have a similar prevalence of CAC as non-diabetic patients with obstructive CAD (107). Diabetic patients without any evidence of coronary calcification have a survival rate similar to non-diabetic patients with a zero calcium score during 5 years of follow-up (106). These results suggest that coronary calcium might be useful to further stratify short-term risk in diabetic patients. However, until studies from non-referral populations with longer follow-up, including fatal and non-fatal cardiovascular events are completed, CAC scores should not be used to modify treatment goals in diabetic patients.

Incidental Findings in Patients Undergoing CAC Testing

Coronary calcium measurement by fast CT scanning of the heart includes imaging of a portion of the lungs, mediastinum, bones and upper abdomen, in addition to the aorta. The identification of potential pathology other than coronary calcium must be considered when evaluating the benefits and costs of cardiac CT scanning. The most common incidental finding is pulmonary nodules. The prevalence of incidental findings depends on the age of the population, the prevalence of smoking, and the definition of an abnormality. Lung nodules that required clinical follow-up were identified in 4.9% of 1326 patients (non-calcified lung nodules less than 1 cm, 4.0%, and lung nodules greater than 1 cm, 0.9%) in a study by Horton et al. (113) in patients with a mean age of 55 years, of whom 7% were active smokers and 18% former smokers. In 1000 active duty Army personnel with a mean age of 42 years of whom 13% were active smokers, the prevalence of pulmonary incidental findings including nodules and other pulmonary pathology was 2.3%. Of these, approximately 50% were considered major, requiring subspecialty referral or potential invasive procedures (114). In both studies, the prevalence of incidental findings in any organ system was 8%; however, in the Army personnel study, 40% were considered minor; whereas, in the Horton study, minor findings were not included.

Occasionally a serious finding with potentially important medical information is detected outside the coronary arteries when coronary calcium screening examinations are performed; therefore, it is important that the entire examination be reviewed. However, with this review, benign lesions will be detected as well, which can lead to additional, and possibly unnecessary, testing and anxiety. It is recommended that current radiology guidelines be used to make recommendations for follow-up testing of noncardiac pathology, such as was recently published to guide follow-up for small pulmonary nodules (115).

Summary and Final Conclusions

This document has updated information on CAC measurement with particular emphasis on data that have appeared since 2000 when the previous ACC/AHA Expert Consensus Document was published. In considering the data presented here, the Expert Consensus Committee felt that specific clinical examples should be highlighted and clinical recommendations linked to these examples for use by clinicians.

The following clinical scenarios were noted to be relevant to CAC measurement, and the Committee's consensus on these questions is noted.

1. What is the role of coronary calcium measurement by coronary CT scanning in asymptomatic patients with intermediate CHD risk (between 10% and 20% 10-year risk of estimated coronary events)?
   The Committee judged that it may be reasonable to consider use of CAC measurement in such patients based on available evidence that demonstrates incremental risk prediction information in this selected (intermediate risk) patient group. This conclusion is based on the possibility that such patients might be reclassified to a higher risk status based on high CAC score, and subsequent patient management may be modified.
2. What is the role of coronary calcium measurement by CT scan in patients with low CHD risk (below 10% 10-year risk of estimated CHD events)?
   The Committee does not recommend use of CAC measurement in this selected patient group. This patient group is similar to the "population screening" scenario, and the Committee does not recommend screening of the general population using CAC measurement.
3. What is the role of coronary calcium measurement by fast CT scan in asymptomatic patients with high CHD risk (greater than 20% estimated 10-year risk of estimated CHD events, or established coronary disease, or other high-risk diagnoses)?
   The Committee does not advise CAC measurement in this selected patient stratum as they are already judged to be candidates for intensive risk reducing therapies based on current NCEP guidelines.
4. Is the evidence strong enough to reduce the treatment intensity in patients with calcium score = 0 in patients who are considered intermediate risk before coronary calcium score?
   No evidence is available that allows the Committee to make a consensus judgment on this question. Accordingly, the Committee felt that current standard recommendations for treatment of intermediate risk patients should apply in this setting.
5. Is there evidence that coronary calcium measurement is better than other potentially competing tests in intermediate risk patients for modifying cardiovascular disease risk estimate?
   In general, CAC measurement has not been compared to alternative approaches to risk assessment in head-to-head studies. This question cannot be adequately answered from available data.
6. Should there be additional cardiac testing when a patient is found to have high coronary calcium score (e.g., CAC greater than 400)?
   Current clinical practice guidelines indicate that patients classified as high risk based on high risk factor burden or existence of known high-risk disease states (e.g., diabetes) are regarded as candidates for intensive preventive therapies (medical treatments). There is no clear evidence that additional non-invasive testing in this patient population will result in more appropriate selection of treatments.
7. Is there a role of CAC testing in patients with atypical cardiac symptoms?
   Evidence indicates that patients considered to be at low risk of coronary disease by virtue of atypical cardiac symptoms may benefit from CAC testing to help in ruling out the presence of obstructive coronary disease. Other competing approaches are available, and most of these competing modalities have not been compared head-to-head with CAC.
8. Can coronary calcium data collected to date be generalized to specific patient populations (women, African American men)?
   CAC data are strongest for Caucasian, non-Hispanic men. The Committee recommends caution in extrapolating CAC data derived from studies in white men to women and to ethnic minorities.
9. What is the appropriate follow-up when an incidental finding in the lungs or other non-cardiac tissues is found on a fast coronary CT study?
   Current radiology guidelines should be considered when determining need for follow-up of incidental findings on a fast CT study, such as that which was recently published to guide follow-up of small pulmonary nodules (115).

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APPENDIX 1. WRITING COMMITTEE RELATIONSHIPS WITH INDUSTRY—ACCF/AHA 2007 CLINICAL EXPERT CONSENSUS DOCUMENT ON CORONARY ARTERY CALCIUM SCORING BY COMPUTED TOMOGRAPHY IN GLOBAL CARDIOVASCULAR RISK ASSESSMENT AND IN EVALUATION OF PATIENTS WITH CHEST PAIN

Name	Consultant	Research Grant	Scientific Advisory Board	Speakers' Bureau	Steering Committee	Stock Holder	Other
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Dr. Matthew J. Budoff	None	None	None	• General Electric	None	None	
Dr. Mark J. Eisenberg	None	None	None	None	None	None	
Dr. Scott M. Grundy	None	None	None	None	None	None	
Dr. Michael S. Lauer	None	None	None	None	None	None	
Dr. Wendy S. Post	None	• Novartis • Pfizer • Merck	None	None	None	None	• Honoraria: Merck, Pfizer, Wyeth
Dr. Paolo Raggi	None	None	None	None	None	None	
Dr. Rita F. Redberg	None	None	None	None	None	None	
Dr. George P. Rodgers	• Biophysical	None	• Scientific Advisory Council	None	None	• Biophysical	
Dr. Leslee J. Shaw	None	• General Electric/ Amersham	None	None	None	None	
Dr. Allen J. Taylor	None	None	None	None	None	None	
Dr. William S. Weintraub	None	None	None	None	None	None	

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APPENDIX 2. PEER REVIEWER RELATIONSHIPS WITH INDUSTRY—ACCF/AHA 2007 CLINICAL EXPERT CONSENSUS DOCUMENT ON CORONARY ARTERY CALCIUM SCORING BY COMPUTED TOMOGRAPHY IN GLOBAL CARDIOVASCULAR RISK ASSESSMENT AND IN EVALUATION OF PATIENTS WITH CHEST PAIN

Name	Representation	Consultant	Research Grant	Scientific Advisory Board	Speakers' Bureau	Steering Committee	Stock Holder	Other
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Dr. Kim A. Eagle	• Official Reviewer—ACCF Board of Trustees	• Robert Wood Johnson Foundation • Sanofi-Aventis • NHBLI	• Pfizer • NIH • Bristol-Myers Squibb • Biosite • Cardiac Sciences • Blue Cross Blue Shield of Michigan	None	None	None	None	None
Dr. Kendrick Shunk	• Official Reviewer—AHA	None	None	None	None	None	None	None
Dr. Richard F. Wright	• Official Reviewer—ACCF Board of Governors	None	None	None	None	None	None	None
Dr. Daniel S. Berman	• Content Reviewer—Individual Reviewer	• Tyco-Mallinckroot	• Bristol-Myers Squibb • Astellas • General Electric	• Spectrum Dynamics	None	None	• Spectrum Dynamics	• Software royalties
Dr. John J. Carr	• Content Reviewer—Individual Reviewer	None	None	None	None	None	None	None
Dr. Daniel Edmundowicz	• Content Reviewer—Individual Reviewer	None	None	None	None	None	None	None
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Dr. Victor A. Ferrari	• Content Reviewer—Individual Reviewer	None	• GlaxoSmithKline • Novartis	None	None	None	None	None
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Dr. Maleah Grover McKay	• Content Reviewer—ACCF Imaging Committee	None	None	None	None	None	None	None
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