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Guidelines

Clinical indications for coronary artery calcium scoring in asymptomatic patients: Expert consensus statement from the Society of Cardiovascular Computed Tomography

Harvey Hecht, MD, FSCCT [a, *], Michael J. Blaha, MD, MPH [b], Daniel S. Berman, MD, FSCCT [c], Khurram Nasir, MD, MPH, FSCCT [d], Matthew Budoff, MD, FSCCT [e], Jonathon Leipsic, MD, FSCCT [f], Ron Blankstein, MD, FSCCT [g], Jagat Narula, MD, PhD [a], John Rumberger, MD, FSCCT [h], Leslee J. Shaw, PhD, FSCCT [i]

[a] Division of Cardiology, Icahn School of Medicine at Mount Sinai, Mount Sinai St. Luke's Medical Center, New York, NY, USA
[b] The Johns Hopkins Ciccarone Center for the Prevention of Heart Disease, Baltimore, MD, USA
[c] Department of Medicine, David Geffen School of Medicine, University of California, Los Angeles, CA, USA
[d] Miami Cardiac and Vascular Institute, Baptist Health South Florida, Miami, FL, USA
[e] Division of Cardiology, Los Angeles Biomedical Research Institute at Harbor–UCLA Medical Center, Torrance, CA, USA
[f] Department of Medicine and Radiology, University of British Columbia, Vancouver, Canada
[g] Non-Invasive Cardiovascular Imaging Program, Departments of Medicine (Cardiovascular Division) and Radiology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA
[h] The Princeton Longevity Center, Princeton, NJ, USA
[i] Department of Medicine, Emory University School of Medicine, Atlanta, GA, USA

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ABSTRACT

This expert consensus statement summarizes the available data regarding the prognostic value of CAC in the asymptomatic population and its ability to refine individual risk prediction, addresses the limitations identified in the current traditional risk factor-based treatment strategies recommended by the 2013 ACC/AHA Prevention guidelines including use of the Pooled Cohort Equations (PCE), and the US Preventive Services Task Force (USPSTF) Recommendation Statement for Statin Use for the Primary Prevention of Cardiovascular Disease in Adults. It provides CAC based treatment recommendations both within the context of the shared decision making model espoused by the 2013 ACC/AHA Prevention guidelines and independent of these guidelines.

1. Introduction

In 1999 the first 'guidelines' for the clinical use of coronary artery calcium (CAC) scoring were published.[1] Pathologic data had shown that CAC was pathognomonic of coronary atherosclerosis and that the area of calcification had a direct relationship to coronary atherosclerotic plaque area by direct histomorphologic examination.[2,3] Unlike global risk scores such as the Framingham Risk Score or the Pooled Cohort Equation (PCE), which provide cardiovascular risk estimates based on mean risk factor distributions across a population, the CAC score is a direct marker of atherosclerosis in an individual patient. As such, it provides an assessment of the burden of coronary atherosclerosis, reflecting the integrated lifetime effect of all risk factors in an individual patient.

There is now research spanning several decades on the value of CAC, with the current number of publications from peer-reviewed journals exceeding 1250. Although numerous systematic reviews have been published on CAC,[4–11] the Society of Cardiovascular Computed Tomography (SCCT) has identified the need for a focused expert consensus document that addresses key issues of clinical application, including clinical indications for testing as well as treatment recommendations based on CAC results. The opinions expressed herein are guided by the available evidence and the recommendations of the writing committee members. As such, they are not to be considered as guidelines based strictly on randomized controlled trials.

* Corresponding author.
E-mail address: hhecht@aol.com (H. Hecht).

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This expert consensus statement summarizes the available data regarding the prognostic value of CAC in the asymptomatic population and its ability to refine individual risk prediction,[12–14] addresses the limitations identified in the current traditional risk factor-based treatment strategies recommended by the 2013 ACC/AHA Prevention guidelines[15,16] including use of the Pooled Cohort Equations (PCE),[17–19] and the US Preventive Services Task Force (USPSTF) Recommendation Statement for Statin Use for the Primary Prevention of Cardiovascular Disease in Adults.[20] It provides CAC based treatment recommendations both within the context of the shared decision making model espoused by the 2013 ACC/AHA Prevention guidelines and independent of these guidelines. The Expert Consensus recommendations are summarized in Table 1.

This expert opinion document addresses the following specific goals:

- Perform an updated review of the association of increasing CAC with increasing mortality or major adverse cardiovascular event (MACE) risk, with a focus on more recent data on long term follow-up in the range of 8–15 years.
- Review the evidence on the accuracy of the PCE, including both its discrimination and calibration, which a focus on the potential for risk overestimation.
- Discuss the role of CAC both independent of and within the context of the 2013 ACC/AHA Prevention Guidelines and the USPSTF Recommendation Statement for Statin Use for the Primary Prevention of Cardiovascular Disease in Adults.
- Provide expert consensus on CAC-based treatment recommendations
- Summarize the available evidence for the role of CAC in promoting adherence to risk factor modifying therapies,
- Review data for serial scanning and scanning intervals, as well as the approach to monitoring for symptom development among high risk patients.
- Review the applicability of radiation dose reduction by iterative and model based reconstruction algorithms and the use of 100 kVp voltage setting for CAC imaging.
- Understand the utility of integration of CAC into current screening for lung and breast cancer and into coronary computed tomographic angiography (Coronary CTA).
- Discuss future research directions and cost effectiveness of CAC scanning

2. Prognostic value

Several prospective large scale trials have addressed the prognostic value of CAC with data derived from population and clinical cohorts. These studies are diverse, including the NIH-NHLBI-sponsored Multi-Ethnic Study of Atherosclerosis (MESA)[21] and Framingham Heart Study,[22] other large cohorts such as the Dallas Heart Study[23] and BioImage,[24] as well as international cohorts such as the Heinz Nixdorf Recall study[25]; all of which are largely based on healthy volunteers. In contrast, numerous registries also include clinical cohorts that include referral populations to a clinical center[26–28] and are representative of individuals sent for studies on a clinical basis. Careful differentiation of these two varied types of clinical research is important for interpretation of clinical outcome findings. However both types of studies have yielded consistent results regarding the prognostic valve of CAC scoring.

2.1. Updated evidence on the prognostic value of CAC in asymptomatic individuals

A number of meta-analysis and systematic reviews[4–11] have been published; the current review assimilates these prior reviews, including the ACC's 2007 expert consensus statement on coronary artery calcium scoring[6] and the ACC's 2010 guideline for the assessment of risk in asymptomatic adults,[7] and highlights novel or updated data from 2010 to 2016.

Since 2010, there have been numerous reports,[27,29–32] and a synthesis of this evidence reveals further validation of the prognostic utility of CAC in asymptomatic individuals. Fig. 1 reveals median rates of major adverse cardiovascular events (% per year) from 7 registries. The cumulative sample size is 84,182 and reflects a diversity of clinical events, including cardiac or all-cause mortality, myocardial infarction, unstable angina hospitalization, late revascularization $\geq$3 months, stroke, and transient ischemic attacks. While these endpoints are varied, a synthesis of findings reveals that there is a direct proportional relationship between CAC and clinical outcomes stratified by the CAC categories 0, 1–99, 100–399, and $\geq$400. Fig. 1 reveals that the annualized MACE rates ranged from 0.1% to 1.6% for those with zero to high risk CAC scores. Relative risk ratios have been reported as high as 20 times greater for high risk CAC as compared with a CAC score of 0.[33] MACE rates increase proportionally with more extensive CAC scores, but also increase further among individuals with intermediate FRS or PCE risk estimates.[29,32,34] Thus, for any given CAC score, higher event rates are observed in diabetes,[35–37] the elderly,[30,38] smokers,[39,40] hypertensives,[41,42] and other high risk patient subsets.[43] Many individuals with a family history of coronary heart disease are known to be at increased risk, and the amount of CAC best identifies the highest risk cases.[44]

Recent reports have extended follow-up and report mortality data beyond 10 years after CAC scanning. Fig. 2 reports the relative risk ratios among published findings on long-term clinical outcomes.[22,27,45–47] This analysis compares event risk among those with 0 CAC versus detectable CAC. A cumulative summary relative

Table 1
SCCT CAC expert consensus recommendations.

1. It is appropriate to perform CAC testing in the context of shared decision making for asymptomatic individuals without clinical ASCVD who are 40–75 years of age in the 5–20% 10-year ASCVD risk group and selectively in the <5% ASCVD group, such as those with a family history of premature coronary artery disease.
2. In patients for whom the development or progression of CAC would support intensification or alteration in preventive management, it may be appropriate to consider repeat CAC scanning at an interval of 5 years for patients with 0 CAC and a 3–5-year interval for patients with >0 CAC.
3. As an alternative to filtered back projection and 120 kVp acquisition, iterative and model based reconstruction and 100 kVp acquisition may be utilized with caution after site-based or literature-based validation for each scanner vendor, with documented <10% difference in mean CAC scores and risk group classification compared to filtered back projection and 120 kVp studies.
4. Consistent with a prior guideline from the SCCT/STR, CAC scoring of noncontrast chest CT scans is appropriate in all lung cancer screening patients and patients greater than 40 years of age without established ASCVD. The presence of CAC should be noted in the report of all NCCT studies.
5. The presence of BAC on mammography should be discussed with the patient and detailed in the final report. Shared decision making regarding dedicated CAC scanning may be considered for patients with BAC.
6. It may be appropriate to include CAC scanning in CCTA protocols in symptomatic patients without established CAD undergoing CTA, and in high risk asymptomatic individuals for whom the CCTA appropriateness criterion is uncertain, as well as in asymptomatic patients referred for preoperative evaluation prior to major surgery.
7. It is appropriate to incorporate CAC scanning in SPECT and PET MPI protocols in patients who are free of known clinical coronary artery disease.

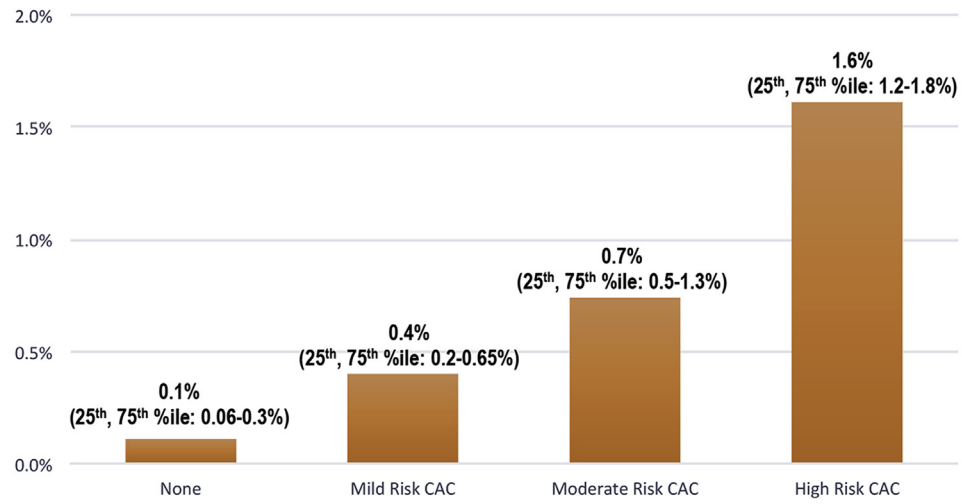

Fig. 1. Median rates of major adverse cardiovascular events (% per year) from 7 registries.
Abbreviations: CAC = coronary artery calcium MACE = major adverse cardiovascular events MI = myocardial infarction TIA = transient ischemic attack UA = unstable angina.

risk ratio for long-term follow-up was 0.29 ($p < 0.0001$); revealing a ~70% reduced risk of MACE for those with absent as compared to detectable CAC. When focusing on cardiovascular disease endpoints, the summary risk ratio for patients with absent CAC was 0.20 ($p < 0.0001$).[22,47] Three reports examined >10 year rates of all-cause mortality and the summary risk ratio was 0.36 ($p < 0.001$).[27,45,46] These analyses noted extremely low event rates of coronary heart disease of ~0.1% per year for the majority of screened patients with CAC = 0. Blaha and colleagues compared multiple "negative risk markers" over long-term follow-up, and reported a similarly low cardiovascular disease event rate noted among individuals with CAC = 0 (4.0% rate of CVD and 2.2% rate of CHD after 10.3 years), much lower than a normal ankle-brachial index or low risk carotid intima-media thickness, flow mediated dilation, or high sensitivity C-reactive protein.[47]

It is now well established that risk associated with CAC scores 1–10 is higher than among individuals with 0 CAC.[48,49] In a study of 44,052 asymptomatic patients having CAC scores and followed for a mean of 5.6 (45%), 19,898 had CCAC 0 and 5388 (12%) had CAC 1–10. There were 104 deaths in those with no CAC (0.52%) and 58 deaths in those with CAC 1 to 10 (1.06%). The hazard ratio (HR) for all-cause mortality among CAC 1 to 10 versus CAC = 0 after adjustment for traditional risk factors was 1.99 (95% confidence interval [CI]: 1.44 to 2.75) CAC.[48] In MESA, of 6809 individuals in the trial, 3923 had a CAC of 0–10. Of these 508 had a score of 1–10. During follow up of a median of 4.1 years, there were 28 coronary heart disease events. The relative risk ratio was 3 times greater in the group with CAC 1–10 than in the CAC 0 group CAC.[49] In a recent long term follow up of 9715 patients with CAC scanning (average 14.6 years), the risk-adjusted hazard ratio for all-cause mortality in those with CAC 1–10 compared to those with CAC 0 was 1.9 in women and 1.7 in men.[50]

Analyses examining the low long-term risk among individuals with CAC = 0 vs. CAC>0 remain important, as there are competing non-cardiovascular risks that impact life expectancy. As a putative marker of biologic aging,[51] it has been demonstrated that CAC is also able to stratify risk for non-cardiac conditions such as cancer, chronic kidney disease, chronic obstructive lung disease, and hip fracture.[52] Regardless of risk factor burden, a sizeable proportion of patients will have 0 CAC; for example, in the MESA study, 38% of patients with diabetes had a CAC score of 0.[36] Given the long-term utility of a 0 CAC score, it has been suggested that 0 CAC is reflective of a population subset of "healthy agers" with a favorable long term cardiovascular health.[53]

A synthesis of this evidence reveals that patients with 0 CAC have a persistent very low risk of MACE, and few events are observed through a decade of follow-up in this low risk cohort.[54] As the CAC increases, the graded increase in MACE observed with shorter term follow-up that may accelerate beyond 8–10 years of follow-up. The evidence that CAC effectively risk stratifies varied at-risk individuals is substantive and spans diverse populations and patient cohorts.

2.2. Net reclassification index

Several studies have examined how CAC reclassifies individuals into low or high risk strata beyond clinical risk factor or global risk score data[35] using the categorical net reclassification improvement (NRI) calculation.[11,25,27,29,32,55] Importantly, the NRI is a summary statistic representing the number of cardiovascular events and non-events correctly reclassified into higher or lower risk groups when CAC is added to traditional risk factors.[56]

Yeboah and colleagues[29,32] have performed the most comprehensive NRI analyses examining both coronary-specific and cardiovascular disease outcomes. One model, which examined 7-year rates of myocardial infarction, coronary heart disease deaths, resuscitated cardiac arrest, or angina followed by coronary revascularization, reported that CAC had the highest NRI for improving risk over the FRS as compared with brachial flow mediated dilation, ankle brachial index, carotid intima-media thickness, and high sensitivity C-reactive protein.[36] The NRI calculation in the intermediate FRS group was highest for CAC (0.66) and ranged from 0.024 to 0.10 for other biomarkers.

More recently, in 10-year prognostic models across the spectrum of ASCVD risk, Yeboah et al. examined the PCE alone versus a model containing the PCE plus CAC for the prediction total ASCVD events (including stroke), finding a categorical NRI of 0.12 for CAC.[32] This was substantially higher than for any other marker tested. For this analysis, the PCE was re-calibrated to MESA and, thus, reflected the optimized PCE for this dataset. This newer Yeboah et al. analysis

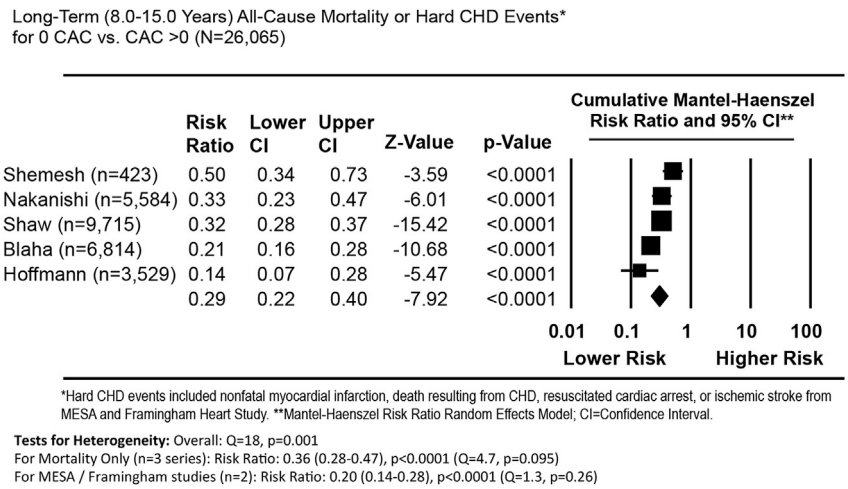

Fig. 2. Long-term (8.0–15.0 years) all-cause mortality or hard coronary heart disease events* for 0 coronary artery calcium vs. coronary artery calcium >0 (N = 26,065).

demonstrates that the CAC score remains the single strongest test for reclassifying events, even when considering both coronary disease and stroke, in the modern era of the PCE.

3. Accuracy of the 2013 prevention guidelines Pooled Cohort Equation (PCE) for risk prediction, the 2016 USPSTF recommendation statement on statins, and incorporation of CAC scoring

The Pooled Cohort Equation (PCE) has recently been developed as a more contemporary global risk score than the Framingham Risk Score and others in common use. The PCE is used in both the 2013 ACC/AHA Cholesterol Guidelines and the 2016 United States Preventive Services Task Force (USPSTF) guidelines. There are robust data, however, on the limitations of global risk scores such as the PCE, which are highly reliant on the age of the patient.[57] An important problem is miscalibration, with consistent reports of overestimation of risk based on observed vs predicted events.[58–62] In a recent report from the MESA, overestimation in risk was observed for all racial and ethnic subgroups.[63] In a large series of 307,591 non-diabetic adults ages 40–75 years of age (Black = 22,283, Asian/Pacific Islander = 52,917, and Hispanic = 18,745), the PCE significantly overestimated the risk of major atherosclerotic cardiovascular disease events.[62] This study raised questions regarding the application of the PCE in women, younger men, and in non-US or diverse racial and ethnic groups, since predictive estimates may be imprecise.[64]

In guideline-identified statin candidates, there have been several studies which reported that overestimation may be in part overcome by identification of a high prevalence of CAC = 0,[60,65–67] which may reclassify otherwise higher-risk patients defined by the PCE to a much lower risk stratum (Table 2). In a recent study from MESA, Nasir et al., reported a 10.3 year follow up of 4758 enrollees in whom 247 (5.2%) ASCVD events occurred.[65] Of those for whom the ACC/AHA Cholesterol Management Guidelines recommend statin therapy based on the PCE (PCE ≥7.5%), 41% had CAC = 0. In these individuals, there were 5.2 ASCVD events/1000 patient years, compared to 10.5/1000 person years in those with any CAC. In

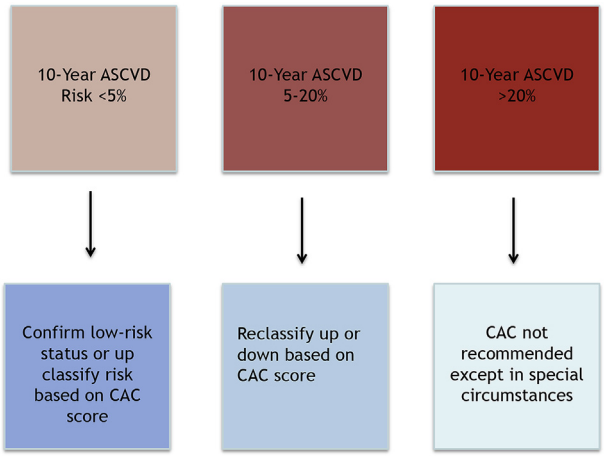

Fig. 3. The role of coronary artery calcium in guiding treatment in the 10-year ASCVD risk categories.
Abbreviations: ASCVD = arteriosclerotic cardiovascular disease. CAC = coronary artery calcium.

Table 2
Distribution of CAC scores and events in Pooled Cohort Equation statin-eligible and statin-ineligible patients.[a]

	n or %	10 year Events	NNT	HR vs. CAC Score = 0
Statin-eligible subjects				
Nasir et al., 2015 (12)	2966			
PCE intensity moderate to high				
CAC 0	41%	5.2/1000 py	64	–
CAC>100	29%	15/1000 py	28	2.9
PCE intensity moderate				
CAC 0	57%	1.5/1000 py	223	–
CAC>100	12%	9.0/1000 py	46	6.3
Pursnani et al., 2015 (40)	941			
CAC score = 0	33%	1.6%		
Statin-ineligible subjects				
Nasir, 2015 (12)	1792			
CAC score = 0	79%	0.9/1000 py		–
CAC score >100	4.3%	9.6/1000 py		6.1
Yeboah, 2016 (8)	3726			
Upward reclassification				
No	93.9%	3%		–
Yes	6.1%	13%		4.0

Abbreviations: CAC = coronary artery calcium; HR = hazard ratio; NCP = noncalcified plaque; NNT = number needed to treat to prevent an event over 10 years; PCE= Pooled Cohort Equations.

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individuals whom the ACC/AHA guidelines "consider" statin therapy (PCE 5.0–7.5%), 57% had CAC = 0, with 1.5 events/1000 patient years, compared to 7.2 in those with any CAC. In a similar report from the Framingham Heart Study of 2435 statin-naïve individuals followed for 9.4-years (n = 74 ASCVD events), Pursnani et al. reported that guideline-eligible statin enrollees with CAC = 0 had a ASCVD event rate of 1.6%.[60] Similar results have now been reported for the Heinz Nixdorf Recall study[66] and the BioImage study.[67] Thus, these studies are consistent in showing a low event rate among statin-eligible patients according to PCE, suggesting possible down-reclassification to a lower risk for which statins would not be recommended, based on the zero CAC.

Up-reclassification into a statin benefit group was evaluated in a separate MESA analysis by, Yeboah et al. who reported that 4185 of 5185 statin naïve individuals had a recalibrated PCE risk <7.5% (thus not recommended for statins).[68] Recalibration was performed to correct the overestimation present with the PCE. In this group, they observed 320 ASCVD events during 10 years of follow-up. Excluding diabetic individuals, guideline recommended CAC thresholds (i.e., CAC ≥300 or ≥75th percentile for age, sex, and ethnicity) reclassified 6.8% of this group to a higher risk statin-eligible risk stratum. The observed 10 year ASCVD event rate for those with a PCE risk <7.5% who were reclassified to a higher risk strata based on CAC was 13.3%. CAC was the most effective tool of those tested for upwardly reclassifying otherwise low risk participants, pointing to a role for CAC in recalibrated risk models.

In summary, analysis of the retrospective data supports significant concerns with regards to the limits of improved discrimination as well as overestimation of risk based on the PCE, with the potential for many truly low risk patients based on CAC findings to be guideline-recommended candidates for lifelong statin therapy and far fewer whose risk is underestimated and for whom statin therapy would not have been recommended. While the USPSTF guidelines limit statins to patients with PCE ≥10% and at least one risk factor, thus potentially avoiding treatment in some patients with CAC = 0, additional research is needing examining the use of CAC within the USPSTF guidelines.

4. The role of CAC in guiding treatment (Fig. 3)

4.1. In the context of shared decision making within the 2013 Cholesterol guideline and the 2016 USPSTF recommendation statement on statins

An essential tenet of patient-centered imaging is that patients have a clear understanding of the benefits and risks of an imaging test, particularly focusing on safety, in the setting of a shared decision making (SDM) discussion. SDM is a broad mandate of the Affordable Care Act[69] that establishes a collaborative process between patients and health care professionals to incorporate the best available scientific evidence and the patient's values and preferences into medical decisions.

The 2013 ACC/AHA Cholesterol Guideline was the first guideline to strongly emphasize the importance of SDM before initiating statin therapy[16,70] to discuss ***patient preferences, adverse effects, and the potential for ASCVD risk reduction benefits.*** The initial step in ascertaining patient preferences is to detail all available options for optimal patient decision making. Consistent with these guidelines, it is appropriate to include the option of CAC testing, with an explanation of its potential role in allowing for no treatment when it is unlikely to result in net benefit. This would apply to having an SDM discussion with all patients without clinical ASCVD or diabetes who are 40–75 years of age and with an estimated 10-year ASCVD risk of 5% or higher based on the PCE (i.e., statins considered or statins recommended groups). For the statin-ineligible group patients (<5% 10-year risk) who profess preference for more certainty, it is also appropriate to discuss the utility of CAC scanning.

An additional component of SDM should detail a discussion regarding any potential adverse effects of statins, as well as the values and preferences that patients place on either taking or avoiding statin therapy. The statin safety concerns identified in the literature include an excess risk of diabetes and myalgia[16,71]; suggested statin induced cognitive impairment has not been adequately documented.[72] For CAC scoring, safety concerns regarding radiation exposure may be voiced, as well as the implications of incidental findings. Guidance is provided on this issue in a recent NHLBI/NCI-sponsored document.[73] Finally, when the physician recommendation or patient decision regarding statin therapy is uncertain, the 2013 Cholesterol guideline supports consideration of CAC in order to further ascertain risk.[16] It is likely that continued appreciation of the use of SDM will expand the use of CAC to improve risk prediction within the context of the 2013 ACC/AHA guideline, the 2016 USPSTF guidelines, and future guidelines.

4.2. Independent of the 2013 Cholesterol guideline shared decision making and 2016 USPSTF recommendation statement on statins

Because of the issues with risk factor-based risk prediction discussed in detail above, physicians may wish to refine treatment decisions based on CAC. The most widespread application is likely to be in the 10-year ASCVD 5–15% risk group in which CAC = 0 and low CAC scores would largely refine risk downward to lowest or low strata, with treatment recommendations based on the score as in Table 4. In the 10-year ASCVD 15–20% risk group, downward risk reclassification may be considered with 0 or low CAC scores. There is little role for risk reclassification in the 10-year ASCVD >20% risk group, other than to provide persuasive confirmation of the high risk status in patients reluctant to take statins or to provide reassurance to those who are statin intolerant if they have 0 or low risk CAC. In the 10-year ASCVD <5% risk group, for those patients who seek greater reassurance, e.g., young patients with a family history of premature CAD which does not factor into the PCE, a 0 or low CAC score would confirm their low risk status and higher scores would identify those targeted for a greater intensity of lifestyle recommendations and treatment (Fig. 3). Young patients with renal disease, or inflammatory diseases, e.g, HIV, rheumatoid arthritis,

Table 3
CAC score determined risk classifications and treatment recommendations in the 5–20% ASCVD risk group.

Score	Risk	Treatment Recommendation
0	very low	statin not recommended[a]
1–99	mildly Increased	moderate intensity statin if < 75th%; moderate to high intensity if > 75th%
100–299	moderately increased	moderate to high intensity statin + ASA 81mg
>300	moderate to severely increased	high intensity statin + ASA 81mg

[a] Excluding familial hypercholesterolemia.

Table 4
CAC progression studies.

Study	N	Follow-up (in years)	Progression	Hazard Ratio for Progressors vs. Non-Progressors
Raggi[98]	813	2.1	Event: 47% No event: 26% p < 0.01	Not reported
Raggi[99]	495	3.2	Event: 42% No event: 17% p<0.0001	>15%vs <15%: 17.2
Budoff[100]	4609	3.1		>15% vs <15%: 3.0 p < 0.0001
Budoff[101]	6778	7.6	CAC 0 baseline CAC>0 baseline	>5AU/y vs < 5AU/y: 1.4 >100 AU/y: 1.2 >300 AU/y: 3.8 5-14%/y: 1.1 14-29%/y: 1.6 >30%/y: 1.5
Wong[102]	5662	4.9	3rd Progression Tertile Events/1000 person years DM + MetS 30.7 MetS w/o DM 26.4 Neither 17.7	3rd tertile vs no progression 8.5 4.1
Kiramijyan[103]	296 DM 300 non-DM	4.7	Event-free survival ΔCAC DM No DM <10% 97.9% 100% 10-20% 95.9% 97.2% 21-30% 92.7% 94% >30% 79.6% 90.6%	DM vs no DM Δ10-20% vs <10%: 1.88 Δ21-30% vs <10%: 2.29 Δ>30% vs <10%: 6.95

AbbreviationsCAC = coronary artery calcium, DM = diabetes mellitus, MetS = metabolic syndrome, y = year.

systemic lupus erythematosis, or other potential risk markers like erectile dysfunction or obstructive sleep apnea in the 10-year ASCVD <5% risk group may also be candidates for CAC evaluation as well.[74–79]

4.2.1. Consensus of expert opinion

It is appropriate to perform CAC testing in the context of shared decision making for asymptomatic individuals without clinical ASCVD who are 40–75 years of age in the 5–20% 10-year ASCVD risk group and selectively in the <5% ASCVD group, such as those with a family history of premature coronary artery disease.

5. Expert opinion treatment recommendations based on CAC scoring results (Table 3)

In these ensuing sections, we propose treatment guidance based on expert opinion. These treatment recommendations are not based on randomized clinical trial evidence but have been extrapolated from retrospective analyses and non-randomized prospective evaluations. These recommendations are in response to frequent requests within the clinical community from generalists and cardiologists to guide treatment based on CAC findings.

The 2013 ACC/AHA Prevention Guidelines[16] helped solidify the importance of absolute risk assessment in determining the net benefit of preventive therapy. In general, patients who are at low risk of a cardiovascular event receive less benefit from therapy, while patients who are at higher risk accrue greater benefits from therapy. Recent studies have emphasized not only the ability of CAC to identify cases of unheralded high cardiovascular risk, but also the ability to identify low risk population strata for whom statin therapy may not be always needed.[80] CAC = 0 appears to be the strongest negative predictor of a cardiovascular event when compared to other measures of subclinical cardiovascular disease, such as ankle-brachial index or carotid intima-media thickness.[47] The so-called "Power of Zero" may allow downward reclassification (i.e., "de-risking") of patients who are considered sufficiently high risk by age alone or by other risk factors that statin therapy would be recommended or considered by Chlolesterol Management Guidelines. There is strong evidence that CAC = 0 can downwardly classify risk when the 10-year ASCVD risk is between 5 and 15% and modest evidence that CAC = 0 can downwardly reclassify risk in patients between 15 and 20% to a level that statin therapy would not be recommended. In general, patients remain high risk regardless of the CAC score when the 10-year ASCVD risk is >20%[65] (Fig. 3).

5.1. Risk classification and lipid lowering therapy (Table 3)

In contemporary practice, CAC scoring is used to guide the initiation and intensity of statin therapy. In patients who have opted for CAC scanning after SDM, or for those who have otherwise already undergone CAC scanning, high intensity statin therapy is recommended in any patients with a CAC ≥300 or above the 75th percentile for age/gender/race, consistent with the 2013 ACC/AHA Prevention Guidelines.[16] Moderate to high intensity statin treatment is recommended for patients with CAC 100–299. In patients with CAC 1–99, moderate intensity statin therapy is recommended for those with CAC percentile <75% and moderate to high intensity for those with CAC percentile ≥75%. Patients with CAC = 0 are considered to be at lowest risk and statins are not uniformly recommended, with the exception of patients with familial hypercholesterolemia or diabetes.

5.2. Aspirin (Table 3)

Data analysis suggests that the risk of gastrointestinal and other bleeding with aspirin therapy may outweigh its benefits in many patients with CAC <100 in the absence of other risk factors.[81] Therefore aspirin therapy should be considered for most patients with CAC>100, in the absence of bleeding contraindications.

6. Evidence of improved adherence to risk factor modifying treatment and healthy lifestyles following CAC scoring

Data are plentiful on improved physician adherence and patient compliance with preventive therapies among patients undergoing

CAC scoring.[82,83] A recent review of 17 guidelines and 42 observational studies highlighted the inadequacies of lipid-modifying strategies to achieve guideline targets in as many as 68%–90% of patients.[84] Moreover, suboptimal adherence to preventive care is of notable concern with nationwide estimates that only 5% of adults are physically active, only 40% of adults with cardiovascular disease are on statins, and only half of adults have had their cholesterol tested within the previous 5 years.[85,86]

The published evidence supports greater adherence to preventive care following CAC screening.[87,88] A recent systematic review noted that CAC screening enhanced medication adherence in nearly 90% of published reports, including 3 randomized trials and 12 observational studies.[87] These observations suggest that visualization of CAC findings may provide a link to improve patient compliance. There are also several trials that have examined the impact of CAC screening on improving adherence to preventive care with the primary outcome being a change in the FRS.[83,89] The Early Identification of Subclinical Atherosclerosis by Noninvasive Imaging Research (EISNER) trial, the largest randomized trial comparing CAC scanning (n = 1424) to a no scan strategy (n = 713),[83] provided evidence in this regard with the primary endpoint being a change in the FRS at 4-years post-randomization. The primary endpoint revealed that after 4 years of follow-up asymptomatic enrollees group that underwent scanning had minimal nonsignificant change in the FRS (0.002%) compared to a statistically significant but higher increase in the FRS for the group that was not scanned (Δ in FRS = 0.7%. p = 0.003). When compared to those that were not scanned, individuals randomized to a CAC scan had lower systolic blood pressure (p = 0.02), LDL cholesterol (p = 0.04) and reductions in waist circumference (p = 0.01) for those with greater abdominal girth measurements. Moreover, nearly half of the scan group had 0 CAC and the 4-year costs of care were 30% lower when compared to the no scan group (p = 0.001).

There is a link between higher levels of adherence to preventive therapies and therapeutic risk-reduction.[85,86] First, evidence supports that up to 80% of adverse cardiovascular disease outcomes could be prevented by eliminating obesity, poor dietary habits, and physical inactivity.[85] A clinical benefit in risk reduction may be possible if adherence/compliance to risk factor modifying therapies and participation in health lifestyles were improved as a result of CAC scanning. Secondly, current evidence supports that the direct cost of poor adherence ranges from $100–289 billion dollars each year.[85,86] Thus, the impact of CAC-directed improved adherence may not only reduce cardiovascular risk based on improved adherence and compliance but also reduce healthcare costs.

7. Serial scanning, scan intervals, and monitoring for symptom development among high risk patients (Table 4)

7.1. Data

The data on serial CAC scanning is composed of two bodies of evidence.[90] The first is from exploratory controlled clinical trials examining the benefit of statin therapy on reducing CAC progression. These trials were summarized in a 2008 statement from the European Society of Cardiac Radiology and North American Society for Cardiovascular Imaging based on a meta-analysis from 4 trials.[91] The summary effect of statin therapy compared to placebo or varying intensity statin therapy for attenuating CAC progression was not statistically significant (p = 0.40). These early trials revealed that statin therapy did not impact CAC progression, albeit in relatively small randomized trials (mean n~500). A recent post-hoc analysis of 8 prospective randomized serial coronary intravascular ultrasound (IVUS) trials evaluated changes in coronary calcification among 3 groups of patients (those receiving high and low intensity statin therapy and those receiving no statin therapy).[92] The authors concluded that statins promoted coronary calcification, hypothesized as a means of stabilizing atherosclerotic plaque. However, these findings have not been fully corroborated by several studies using virtual histology IVUS which have demonstrated no changes in calcified plaque after statin treatment, while decreases in noncalcified plaque have been observed.[93–96]

Subsequent to the trials of the statin effects on CAC progression, evidence has also accumulated that worsening prognosis occurs for those with increased CAC on repeat scanning. Moreover, the increase in CAC is proportional to the rate of increase in cardiovascular risk (Table 2).[97–103]

7.2. Index CAC = 0

A subset of patients may prefer to defer statin treatment especially if the CAC = 0. Among these patients with a CAC = 0, considerations for repeating CAC scanning depend on an optimal follow-up time period when conversion to detectable CAC (i.e., score >0) is sufficiently high. Min et al. reported on 422 patients, 66.4% of whom were on statin therapy with a baseline CAC score of 0, who underwent annual CAC scanning for 5 consecutive years or until conversion to CAC>0.[104] The overall conversion rate from 0 to >0 CAC was 25.1%, with a mean time to conversion of 4.1 ± 0.9 years. Other data have been consistent with a 3–5 year range.[105]

7.3. Index CAC >0

There are several situations where clinical considerations and patient preferences prompt consideration of repeat scanning. It may be reasonable to consider a repeat CAC scan for patients who have successfully made considerable lifestyle improvements and are compliant with preventive therapies but remain concerned about atherosclerotic disease progression. Serial evaluation may also be reasonable among patients with a CAC score of 100 or higher and may help to guide intensification of preventive care.

With regards to the timing of serial evaluation, a repeat scan can be dictated by patient concern but also a near term interval may be preferable among those with higher CAC scores to evaluate the efficacy of treatment. MESA data suggests that the average time to symptom-driven intervention was ~4 years,[106] and a re-evaluation of progressive disease within the range of 3–5 years may be appropriate. Suspected cardiac symptom onset among patients with high risk CAC scores is a prominent concern and should initiate appropriate clinical evaluation.

7.3.1. Expert consensus

In patients for whom the development or progression of CAC would support intensification or alteration in preventive management, it may be appropriate to consider repeat CAC scanning at an interval of 5 years for patients with 0 CAC and a 3–5-year interval for patients with >0 CAC.

8. Radiation dose reduction techniques for CAC scoring

8.1. Iterative and model-based reconstruction algorithms

Using the gold standard of filtered back projection (FBP) reconstruction, the radiation exposure should not exceed 1.0 mSv[107] except for obese patients. Recently developed iterative reconstruction (IR) algorithms are available on all the latest generation scanners and may facilitate the acquisition of <0.5 mSv CAC studies by dramatically increasing the signal to noise ratio at lower mAs. The published results have been variable in their accuracy.[108,109] Adaptive Statistical Iterative Reconstruction significantly

reduced image noise without change in signal. However, the CAC scores decreased from 4.2% to 15.3% with increasing IR levels compared to FBP.[108] Moreover, there were significant changes in risk classification based on CAC strata, reductions in relative risk based on CAC percentiles with increasing IR levels. Based on these findings, the authors recommended that IR should not be used for CAC scoring. In a study of 70 patients, Sinogram-Affirmed Iterative Reconstruction yielded decreases in CAC ranging from 5.8% to 48.4% between FBP and increasing levels of IR from 10% to 50%.[109] Misclassification of risk categories when compared to those based on standard imaging protocols ranged from 4.2% to 28.2% with increasing IR levels; the authors urged that IR should be used with caution. With iDose, the weighted kappa for agreement between risk categories was 0.95, with a 50% reduction in radiation.[110]

Iterative model based reconstruction, with higher signal to noise ratios than IR, potentiate even greater mAs reductions and lower radiation, but have been minimally investigated. In 70 patients, increasing levels of model based reconstruction decreased CAC scores from 12% to 39% compared to filtered back projection and decreased standard risk group classification in 27%.[111] These various approaches to reconstruction should be evaluated for their ability to accurately distinguish patients with a CAC>0 from those with CAC = 0 before widespread acceptance.

8.2. kVp reduction

The second approach to dose reduction, reducing kVp from the standard 120 kVp to 100 kVp, has been evaluated by Nakazato et al., who compared CAC and volume scores from a dual source scanner in 60 patients (28 with 0 CAC) acquired at 120 kVp and 150 mAs, using 130 HU as the calcium cutoff, with scans acquired at 100 kVp and 180 mAs, using a phantom derived 147 HU for definition of calcified plaques.[112] They noted an excellent agreement, with a difference in CAC scores of ~17 ± 20 (K = 0.95). The 100 kVp mean effective radiation dose was lower (1.17mSv vs 1.70mSv, $p < 0.0001$). In a second 120kVp vs 100 kVp study, Marwan et al. evaluated 150 patients with a high pitch dual source scanner and fixed current of 80 mAs, using both 130 HU and 147 HU as the calcium threshold in the 120 kV arm.[113] They reported an excellent agreement (r = 0.99), with systematic overestimation in the 100 kV arm at both CAC thresholds for both Agatston and volume scores but a significant reduction in effective radiation dose from 0.3 to 0.2 mS. The kVp reduction approach always requires recalibration of the standard calcium attenuation threshold of 130 HU to establish the 100 kV threshold for each scanner, posing an obstacle to widespread use.

Slice thickness recommendations are unchanged and remain at 2.5 or 3mm.

8.2.1. Expert consensus

As an alternative to filtered back projection and 120 kVp acquisition, iterative and model based reconstruction and 100 kVp acquisition may be utilized with caution after site-based or literature-based validation for each scanner vendor, with documented <10% difference in mean CAC scores and risk group classification compared to filtered back projection and 120 kVp studies.

9. The role of CAC in screening for lung and breast cancer and for use with CCTA

9.1. Lung cancer

The 2014 U.S. Preventive Services Task Force (USPSTF) endorsement of low-dose lung CT scanning for cancer detection,[114] accompanied by the 2014 Center for Medicare and Medicaid Services decision to provide coverage for lung scans in a defined high-risk population,[115] will add 7 million lung scan-eligible patients to the approximately 7.1 million patients already undergoing non-ECG gated, noncontrast chest CT scans (NCCT) annually in the USA.[116,117] The coronary arteries are in the field of view in all of these scans and can be evaluated for CAC with minimal effort and without additional radiation. The high risk lung cancer population is at high risk for ASCVD due to the numerous shared risk factors, most notably smoking. Accordingly, abnormal CAC will be more frequently observed. The addition of CAC scanning for those undergoing lung cancer screening may provide an opportunity for an assessment of global health, as previously mentioned in the risk assessment section. The inclusion of CAC on NCCT is data currently collected by the American College of Radiology lung cancer registry requiring reporting of moderate and severe CAC.[118] There is moderate-strong concordance between gated and nongated Agatston scores[119–121] and a recent report revealed similar prognostication between gated and nongated CAC scores.[122–125] Thus, it is reasonable not to mandate a specific method of analysis, but to support reporting by any scoring method. It is recommended that the CAC results be discussed with the patient and overseeing physician responsible for their care so as to prompt preventive management discussions. The specific recommendations regarding treatment based CAC categories discussed below are broadly applicable to the CAC score based on NCCT. Some patients with low CAC scores by ECG-gated approaches may be misclassified as CAC 0 on nongated NCCT studies. In patients with poor quality nongated scans, repeat scanning with ECG gating may be reasonable. CAC derived from nongated CT scans is described in detail in a separate SCCT/Society of Thoracic Radiology guideline.[126]

9.1.1. Expert consensus

Consistent with a prior guideline from the SCCT/STR, CAC scoring of noncontrast chest CT scans is appropriate in all lung cancer screening patients and patients greater than 40 years of age without established ASCVD. The presence of CAC should be noted in the report of all NCCT studies.

9.2. Breast cancer

The association of breast arterial calcification (BAC) on screening mammography with ASCVD has been reported. More recently, a strong quantitative association has been reported between BAC and NCCT-identified CAC; the sensitivity and specificity of BAC for CAC was 63% and 76%.[127] In addition, BAC was a stronger predictor of CAC than standard risk factors and was at least as predictive as the PCE. In a series of 292 women, CAC >11 was noted in 68% of women with BAC and 31% of those without BAC. To date, there are no prognostic evaluations and the depth of evidence is limited. However, the presence of BAC may be easily noted during digital mammography with subsequent consideration of follow-up evaluation with formal CAC scanning.

9.2.1. Expert consensus

The presence of BAC on mammography should be discussed with the patient and detailed in the final report. SDM regarding CAC scanning may be considered for patients with BAC.

10. CAC in CCTA protocols

The inclusion of CAC scanning as part of the CCTA varies from laboratory to laboratory. In symptomatic patients without established CAD undergoing CTA, and in high risk asymptomatic individuals, for whom the CCTA appropriateness criterion is uncertain, as well as in asymptomatic patients referred for

preoperative evaluation prior to major surgery, the inclusion of CAC in CCTA protocols may offer benefits. It provides a metric for risk assessment that is readily quantifiable, and more readily repeated for evaluation of disease progression than CCTA. By providing the total amount and location of calcified plaque, it may significantly factor into a decision whether or not to proceed with CCTA, particularly in centers with readers who are not comfortable with CCTA interpretation in patients with markedly elevated scores. By defining the minimum necessary z axis for inclusion of the coronary arteries in the field of view, it may either reduce the CCTA radiation dose by shortening the z axis, or it may prevent insufficient CCTA data acquisition by lengthening the z axis to visualize the full length of all vessels if portions were not seen on the CAC scan. The benefits of adding CAC scanning in patients referred for CCTA should be balanced against the risks of the increased radiation dose from the CAC scan.

10.1. Expert consensus

It may be appropriate to include CAC scanning in CCTA protocols in symptomatic patients without established CAD undergoing CTA, and in high risk asymptomatic individuals for whom the CCTA appropriateness criterion is uncertain, as well as in asymptomatic patients referred for preoperative evaluation prior to major surgery.

11. CAC in SPECT and PET myocardial perfusion imaging protocols

A limitation of radionuclide MPI—and stress testing in general—is the inability to detect subclinical atherosclerosis, which is common among patients who are referred for cardiac stress testing.[128] CAC scores are now commonly available at the time of SPECT or PET MPI. Most PET-MPI studies and, increasingly, SPECT MPI studies, are performed with hybrid systems with which CAC scanning at the time of MPI is readily available. Further, with these hybrid systems, the extent of CAC can be estimated with reasonable accuracy from the attenuation scans routinely performed for the PET or SPECT study.[129] SPECT-MPI frequently underestimates the extent of obstructive CAD and may misclassify patients with angiographic high risk disease.[130] Knowledge of the presence of extensive coronary calcification could improve these assessments and the selection of patients for MPI by better establishing the pre-scan likelihood of the presence of obstructive CAD.[131] CAC scores add to MPI in prognostic assessment.[132,133] The CAC score can assist in determining if the otherwise equivocal MPI scan is normal or abnormal—and increases interpreter certainty.[134] Addition of CAC scanning to SPECT- or PET-MPI can lead to greater change in post-MPI clinical management than MPI in isolation, by identifying patients with atherosclerosis without obstructive CAD who can benefit from preventive treatment.[135,136]

11.1. Expert consensus

It may be appropriate to consider adding CAC scanning in SPECT and PET MPI protocols for patients without prior history of anatomic evaluation for CAD.

12. Healthcare coverage and cost considerations for CAC scanning

CAC is considered a nontraditional risk marker by the USPSTF, and would require legislative mandates for healthcare coverage on cardiovascular screening or wellness. As such, CAC is predominantly covered by local rather than national coverage policies with some coverage policies in ~35 states, but a majority of patients pay an out-of-pocket expenditure of $75-$150 for CAC imaging. In many cases, CAC is offered with some form of traditional risk factor measurement. However, self-pay for unreimbursed procedures disadvantages many high risk patients with limited financial means. Patients in low socioeconomic strata have high rates of traditional risk factors and are at higher risk of MACE.[137] Thus, the development of coverage policies expanding from traditional risk factors, such as cholesterol or blood pressure measurements, is of primary importance for the cardiovascular community, given the current guideline recommendations and the high rates of costly and lifelong medical therapies. The improved adherence to preventive care is a positive benefit of CAC and should warrant additional discussion within the cardiovascular community.

13. Future research directions

The concept of CAC-guided care leading to improved population health requires implementation of an early intervention model whereby improved patient-centered outcomes are the result of enhanced initiation of effective preventive management strategies with an established therapeutic risk reduction.[138] In our current era, there is an ever increasing demand for high quality evidence in order to demonstrate a clinical benefit to guide medical necessity and healthcare coverage policies and guidance documents, especially from the USPSTF.[139,140] A synthesis of current evidence supports CAC guided improved adherence to risk factor-modifying therapies and compliance with healthy lifestyle behaviors, and should form the basis for additional discussions. The limitations of the PCE to guide selection of candidates for therapeutic intervention are now well documented and should prompt a greater role for adjunct guidance by CAC.

14. Summary

The SCCT community is committed to quality- and patient-centered imaging with prioritization of evidentiary standards of care to guide the use of CT procedures. This document was commissioned by the guidelines committee of the SCCT with the primary aim to target asymptomatic patient populations who may benefit from further individualized risk prediction based on CAC. We identified eligible patient subgroups for CAC scanning including those with preferences for CAC testing, those with questionable clinical risk prediction estimates based on the PCE, and those who prefer to avoid pharmacotherapy in the absence of CAC. We further identify possibilities for adjunct CAC scanning among patients undergoing lung or breast cancer screening.

Our guideline committee identifies the wealth of evidence available for CAC as an important means to refine ASCVD risk and improve risk reclassification over and above global risk scores, such as the PCE. Patient and population series, such as the MESA, have provided substantive evidence on the prognostic value of CAC findings. Clinical trial data are available that establish improved adherence to preventive strategies of care which form a strong basis for inclusion of CAC as an adjunct to current guideline-directed identification of statin-eligible patients.

It is the consensus of this committee that CAC 1) more accurately predicts ASCVD risk than the PCE and other non-traditional tests, empowers the individual patient in his/her medical decision making, and empowers the physician in making treatment recommendations, 2) provides an opportunity to modify treatment recommendations based on CAC as a marker of atherosclerosis in the individual patient, 3) improves adherence to risk-factor modifying therapies and healthy lifestyle behaviors and 4) potentially reduces poor adherence for the large population of asymptomatic patients at-risk for ASCVD.

Disclosure

CAC Guideline Writing Group				
First Name	MI	Last Name	Designation	Relevant Conflicts of Interest
Ron		Blankstein	MD, FSCCT	Grant/Research Support: Gilead Sciences, Researh grant; Consultant: EKOS corporation
Matthew		Budoff	MD, FSCCT	Grant/Research Support: NIH, GE
Harvey		Hecht	MD, FSCCT	Stocks and Stock Options; Arineta
Khuram		Nasir	MD	None to disclose
John		Rumberger	MD, FSCCT	None to disclose
Leslee	J.	Shaw	PhD, FSCCT	None to disclose
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Daniel	S.	Berman	MD, FSCCT	None to disclose
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