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Authors

Greenland, Philip
Blaha, Michael J
Budoff, Matthew J
et al.

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THE PRESENT AND FUTURE

JACC STATE-OF-THE-ART REVIEW

Coronary Calcium Score and Cardiovascular Risk



Philip Greenland, MD,^a Michael J. Blaha, MD, MPH,^b Matthew J. Budoff, MD,^c Raimund Erbel, MD,^d Karol E. Watson, MD, PhD^e

ABSTRACT

Coronary artery calcium (CAC) is a highly specific feature of coronary atherosclerosis. On the basis of single-center and multicenter clinical and population-based studies with short-term and long-term outcomes data (up to 15-year follow-up), CAC scoring has emerged as a widely available, consistent, and reproducible means of assessing risk for major cardiovascular outcomes, especially useful in asymptomatic people for planning primary prevention interventions such as statins and aspirin. CAC testing in asymptomatic populations is cost effective across a broad range of baseline risk. This review summarizes evidence concerning CAC, including its pathobiology, modalities for detection, predictive role, use in prediction scoring algorithms, CAC progression, evidence that CAC changes the clinical approach to the patient and patient behavior, novel applications of CAC, future directions in scoring CAC scans, and new CAC guidelines. (J Am Coll Cardiol 2018;72:434–47) © 2018 by the American College of Cardiology Foundation.

Coronary artery calcium (CAC), a highly specific feature of coronary atherosclerosis (1), is one of the most thoroughly studied and widely available tests in cardiovascular medicine. Following important single-center and clinical registry studies, large long-term population-based observational studies were launched in the United States (2,3), Germany (4), and the Netherlands (5) in the late 1990s and early 2000s that have produced consistent, reproducible, and convincing evidence of a strong association between CAC (6) and major cardiovascular outcomes in asymptomatic people. Clinical practice guidelines in the United States (7) and Europe (8) consider CAC scoring to be a potentially

useful way of improving cardiovascular risk assessment in asymptomatic people and serving as a guide for initiating or deferring preventive therapies. Cost-effectiveness analyses (9–14) have concluded that CAC testing is cost effective in asymptomatic populations. Yet such application of CAC scoring in asymptomatic people is still sometimes regarded as experimental or unproven by many health insurance companies in the United States (15).

The purpose of this review is to summarize the evidence concerning CAC, with emphasis on asymptomatic patients, including its pathobiology, modalities for detection, predictive role, use in prediction scoring algorithms, CAC progression, evidence that



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From the ^aDepartments of Preventive Medicine and Medicine, Northwestern University Feinberg School of Medicine, Chicago, Illinois; ^bCiccarone Center for the Prevention of Heart Disease, Johns Hopkins School of Medicine, Baltimore, Maryland; ^cDepartment of Medicine, LA BioMed, Torrance, California; ^dInstitute of Medical Informatics, Biometry and Epidemiology, University Clinic, Essen, Germany; and the ^eDepartment of Medicine, David Geffen School of Medicine at UCLA, Los Angeles, California. The Heinz Nixdorf Recall Study was funded by the Heinz Nixdorf Foundation, the German Aero-Space Center (Deutsches Zentrum für Luft- und Raumfahrt), and the German Research Council Assessment. The MESA study was supported by contracts HHSN268201500003I, N01-HC-95159, N01-HC-95160, N01-HC-95161, N01-HC-95162, N01-HC-95163, N01-HC-95164, N01-HC-95165, N01-HC-95166, N01-HC-95167, N01-HC-95168, and N01-HC-95169 from the National Heart, Lung, and Blood Institute and by grants UL1-TR-000040, UL1-TR-001079, and UL1-TR-001420 from the National Center for Advancing Translational Sciences. Dr. Blaha has received grant funding from the Aetna Foundation and the Amgen Foundation. Dr. Budoff has received funding from the National Institutes of Health and GE. Dr. Blaha is a member of the advisory boards of MedImmune, Akcea, Novartis, Amgen, Sanofi, and Regeneron. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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CAC changes the clinical approach to the patient and patient behavior, novel applications of CAC, and future directions in scoring CAC scans.

PATHOBIOLOGY OF CORONARY ARTERY CALCIFICATION

Vascular calcification was accepted until recently as an inevitable result of aging, and the development of CAC was considered a passive process. The development of CAC is now understood to be an active pathogenic process that is not inevitable, and mechanisms that underlie vascular calcification have been identified. Ectopic bone production, a common feature of atherosclerosis, is the basis for coronary artery calcification (16). Developmental, inflammatory, and metabolic factors all influence the process. Master transcription factors, such as *Msx2*, *Runx2*, *Osterix*, and *Sox9*, have been implicated in vascular calcification, as have potent osteogenic differentiation factors, such as bone morphogenetic proteins 2 and 4. Matrix Gla protein is an inhibitor of bone morphogenetic protein and is highly expressed in calcified human arteries (17). Expression of both pro- and antiosteogenic factors in CAC highlights the extensive regulation of this process.

Inflammation, propagated by apolipoproteins and oxidized phospholipids in the artery wall, is critical to the development of both atherosclerosis and vascular calcification (18,19). Several mediators associated with oxidative stress are implicated in calcification, and oxidative stress may be a key link between inflammation and vascular calcification (20). Lipid oxidation leads to pro-osteogenic mediators, such as minimally modified low-density lipoprotein and oxidized phospholipids (20).

Hyperlipidemia likely has both direct and indirect effects on vascular calcification (21). Glucose can directly promote vascular cell calcification (22), and insulin can inhibit it (23). Adipose-derived factors affect calcification, with leptin promoting (24) and adiponectin inhibiting (25) vascular calcification.

MODALITIES FOR DETECTION OF CAC

Early studies of CAC used chest radiography, fluoroscopy, or digital subtraction fluoroscopy (26) and began to show the potential value of CAC in predicting the presence of obstructive coronary artery disease (CAD) (27), as well as future coronary events (28-31). Cardiac gating, first introduced with electron-beam computed tomography (EBCT), allowed detection, localization, and quantification with higher sensitivity (6). With the introduction of EBCT, more precise quantification of CAC became

possible, allowing sufficient temporal resolution of the moving heart. However, electron-beam computed tomographic (CT) scanners were inadequate for general CT imaging and have been superseded by multi-detector computed tomographic scanners that are comparable with EBCT for CAC measurement (32). With gantry rotation, MDCT produces hundreds of “snapshot” images from different angles, which are used to reconstruct a complete image. Until recently, only cardiac-gated studies allowed the quantification of CAC. Because of the larger numbers of detectors and faster gantry speeds in current multidetector CT scanners, even nongated studies can provide either semiquantitative (ordinal scores) or quantitative CAC (Agatston scoring), with high correlation with gated CT studies and cardiovascular disease outcomes (33,34). Modern CT scans can be accomplished with 10 to 15 min of total room time at about 1 mSv of radiation, without the need for contrast agents.

EARLY STUDIES OF CAC, CORONARY PLAQUE, AND CLINICAL CAD

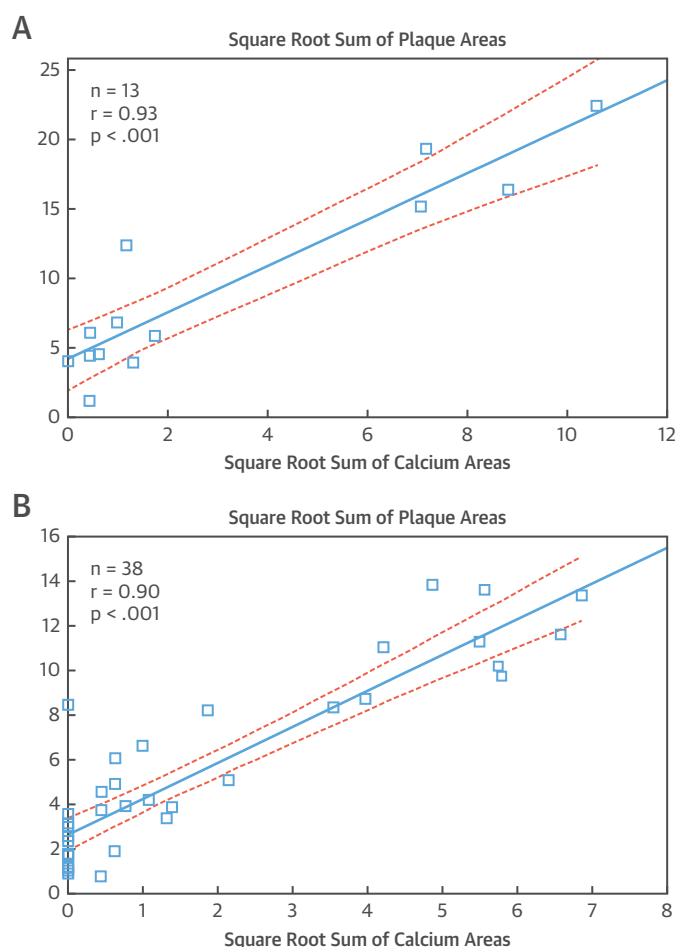
Pathological studies demonstrated a strong correlation between the presence of coronary calcium and CAD. An early focus of CAC testing was to compare results to invasive angiography, to establish the sensitivity and specificity to detect obstructive CAD. Sensitivity for obstructive CAD ranges from 88% to 100% (31,35-37). With high sensitivities for disease, a negative test result has a very low probability of being associated with obstructive CAD, with negative predictive values approaching 100% (38,39).

CAC quantification was found to be an excellent anatomic measure of atherosclerotic plaque burden (36,40). Sangiorgi et al. (40) showed a significant association between coronary calcification area and plaque volume, compared with no association between coronary calcification and lumen area. Rum-berger et al. (36) conducted a histopathologic study of coronary arteries from autopsy hearts that were dissected, straightened, and scanned with EBCT in 3-mm contiguous increments. CAC and coronary artery plaque areas were highly correlated for the hearts as a whole, for individual coronary arteries, and for individual coronary artery segments (Figure 1). Studies of intracoronary ultrasound have also confirmed a direct association of the CAC score with the location and extent of atherosclerotic plaques in vivo (41).

ABBREVIATIONS AND ACRONYMS

ACC	= American College of Cardiology
AHA	= American Heart Association
ASCVD	= atherosclerotic cardiovascular disease
CAC	= coronary artery calcium
CAD	= coronary artery disease
CHD	= coronary heart disease
CT	= computed tomography
EBCT	= electron-beam computed tomography
MDCT	= multidetector computed tomography
SCCT	= Society of Cardiovascular Computed Tomography

FIGURE 1 Associations of Coronary Artery Calcium Area With Plaque Area (Plaque Burden) per Patient



(A) Calcium area with plaque area (per artery). **(B)** Coronary artery calcium (CAC) is highly correlated with plaque burden, both at the level of the individual artery and in the heart as a whole. Reprinted with permission from Rumberger et al. (36).

As early as 2004, single-center studies suggested a strong risk-predictive value of CAC and incremental value of CAC over traditional risk factors. The South Bay Heart Watch Study demonstrated that CAC further risk-stratified subjects deemed at intermediate risk by the Framingham risk score (42). In 2005, the St. Francis Heart Study showed a much higher risk, comparing CAC >400 versus CAC = 0 and an improvement in the area under the curve from 0.69 to 0.79 with addition of CAC to the Framingham risk score (43). Other studies have shown that the incremental risk predictive value of CAC extended to both younger and older subjects (44), patients with diabetes (45), smokers (46,47), and elderly patients (48,49).

FINDINGS FROM MAJOR POPULATION-BASED COHORT STUDIES

Findings from population-based cohort studies are presented in [Table 1](#).

MESA (Multi-Ethnic Study of Atherosclerosis) is a prospective multicenter cohort sample of 6,814 men and women 45 to 84 years of age, started in 2000 (2). Approximately 38% of the recruited participants were white, 28% African American, 22% Hispanic, and 12% Asian, predominantly of Chinese descent. MESA used electron-beam CT scanners at 3 centers and multi-detector CT systems at 3 centers (50). CAC distributions were similar for EBCT and MDCT (51).

The prevalence of CAC was shown to differ by ethnicity, higher in whites compared with the 3 other ethnic groups (50). Differences across ethnicities were not fully explained by risk factor differences, suggesting that other factors must account for some of the variability in CAC distributions. Most important, CAC convincingly predicted cardiovascular events beyond traditional risk factors, with similar strength in all 4 ethnicities. MESA introduced the presentation of estimated curves for the 50th, 75th, and 90th percentiles of calcium across age, making it possible to determine at a glance what an approximate percentile means for a particular patient (51).

The population-based HNR (Heinz Nixdorf Recall [Risk Factors, Evaluation of Coronary Calcium and Lifestyle]) study had similar goals to the MESA study (4). Random samples of the general population were drawn from residents' registration offices from 3 West German cities and included men and women from 45 to 74 years of age (52). The initial examination between 2000 and 2003 involved 4,487 people who underwent EBCT, and results were blinded until the second examination in 2006 to 2008. The second examination included repeat EBCT (53), and a third visit of the participants was organized after 10 years (2011 to 2014), in addition to yearly written and telephone contact and plans for ongoing future follow-up (54). The mean age in the HNR study was 59 ± 8 years, and 53% of participants were women. Among 1,918 men, CAC prevalence was 82%, and in 2,148 women, CAC prevalence was 55%. CAC ≥ 400 was found in 16.3% of men and 4.4% of women. In subjects with known CAD, 100% of the men (n = 218) and 82% of the women (n = 62) had CAC scores >0, and 77.5% and 41.9%, respectively, were found to have CAC scores ≥ 400 .

On the basis of similar designs and study protocols, the results of the MESA and HNR study cohorts were compared, including 2,220 and 3,126 participants,

TABLE 1 Comparison of 4 Major Prospective Observational Studies of the Coronary Artery Calcium Score: Baseline Characteristics

	MESA	HNR	Rotterdam	Framingham
Year CAC study started	2000-2002	2000-2003	1997-2000	2002-2005
Type of CT scan performed	EBCT at 3 centers, MDCT at 3 centers	EBCT	EBCT	MDCT
Number of participants	6,814	4,487	2,063*	3,238
Age range of participants, yrs (mean)	45-84 (62.2 ± 10.2)	45-74 (59 ± 8)	≥55 (71.1 ± 5.7)	Men >35, women >40 (49 ± 10.9)
Women	53%	53%	57%	54%
Systolic blood pressure, mm Hg	126.6 ± 21.5	133 ± 21	144 ± 21 men, 142 ± 21 women	124.0 ± 16.7
Total cholesterol, mg/dl	194.2 ± 35.7	231.2 ± 38.6	216.6 ± 34.8 men, 232.0 ± 34.8 women	206.0 ± 38.2
Current smoking	12%	23%	18% men, 15% women	26%
Previous CVD included or excluded	Clinical CVD excluded	Clinical CAD excluded†	Not excluded	Excluded from most analyses
Percentage with CAC >0 at baseline examination	Men 52%-70%, women 35%-45%‡	Men 82%, women 55%	91% overall (125)	Men 40.5%, women 20.6%

Follow-up for atherosclerotic cardiovascular disease events was similar in all 4 studies and included hard endpoints such as myocardial infarction and cardiac death but also, in some studies, included soft endpoints such as coronary revascularization for appropriate clinical indications. *Number with CT scans available for analysis at the baseline examination. †Clinical CAD patients were excluded for this table (7% of the overall HNR study). ‡CAC prevalence differed in different ethnic/racial groups in MESA (50).
CAC = coronary artery calcium; CAD = coronary artery disease; CT = computed tomography; CVD = cardiovascular disease; EBCT = electron-beam computed tomography; HNR = Heinz Nixdorf Recall; MDCT = multidetector computed tomography; MESA = Multi-Ethnic Study of Atherosclerosis.

respectively (55). Despite differences in risk factor profiles between the 2 studies, CAC scores were very similar, as well as the age and sex distributions of CAC expressed in percentiles (51). CAC was a similar predictor of events in both studies.

The Rotterdam Study is a prospective cohort study among, initially, 7,983 persons living in the city of Rotterdam in the Netherlands (78% of 10,215 invitees) (56). All participants were at least 55 years of age. Imaging of the heart, vasculature, eyes, skeleton, and brain was completed, and biospecimens were archived. Of 3,370 eligible participants, 2,063 (61%, mean age 71 years) underwent EBCT at first examination (57). Thus, the Rotterdam Study was an older sample than in MESA or in the HNR study. The median CAC was 98 (25th and 75th percentiles: 10 and 430). Despite age and ethnicity differences between cohorts, findings in the Rotterdam Study for CAC and disease risk have been generally similar to those in MESA and in the HNR study (58). A strong and graded association was found between coronary calcification and myocardial infarction, and the association remained present, even in older subjects (57,58).

Because of similarities among the 3 cohort studies, meta-analyses including all 3 studies have examined subcohorts of interest. A meta-analysis in low-risk women (59) found that CAC >0 was present in approximately one-third and was associated with an increased risk for atherosclerotic cardiovascular disease (ASCVD) and modest improvement in prognostic accuracy compared with traditional risk factors. A meta-analysis was conducted in elderly subjects

(mean age 70 years) (58) from among 4,778 participants from 3 U.S. cohorts, including MESA, Framingham, and the Cardiovascular Health Study. Over 11 years of follow-up, 405 coronary heart disease (CHD) and 228 stroke events occurred. CAC score (vs. age) had a greater association with incident CHD and modestly improved prediction of incident stroke. Findings were similar in the Rotterdam and HNR cohorts.

The FHS (Framingham Heart Study) added a CAC measurement by MDCT to the examinations of the Framingham Offspring and Third Generation cohorts in 2005. The FHS is limited to white men and women, but distributions of CAC >0 and CAC >100 were very similar to those previously reported from MESA. A novel analysis from the CAC data evaluated whether information on the distribution of CAC and coronary dominance, as detected by MDCT, was incremental to the traditional Agatston score in predicting incident CHD. During a median follow-up of 7 years, the number of coronary arteries with CAC and the presence of CAC in the proximal dominant coronary artery were significantly associated with major CHD events after multivariate adjustment for Framingham risk score and categories of Agatston score. This analysis suggested that additional information from MDCT can augment the traditional Agatston score for risk prediction (60).

The CARDIA (Coronary Artery Risk Development in Young Adults) study measured CAC during follow-up and is the first prospective cohort to include data on CAC among subjects from 32 to 46 years of age.

TABLE 2 Summary of 4 Major Guidelines and Expert Consensus Documents on Use of Coronary Artery Calcium for Risk Assessment in Asymptomatic Patients

Guideline/Statement	Summary of CT Recommendations
2013 ACC/AHA risk assessment guideline	If, after quantitative risk assessment using traditional risk factors, a risk-based treatment decision is uncertain, CAC score may be considered to inform treatment decision making. Class IIb, Level of Evidence: B (7).
2016 European guidelines on CVD prevention	CAC scoring may be considered as a risk modifier in CV risk assessment. Class IIb, Level of Evidence: B (8).
2017 expert consensus from the Society of Cardiovascular Computed Tomography	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% ten-year ASCVD risk group and selectively in the <5% ASCVD risk group, such as those with a family history of premature CAD (91).
2018 U.S. Preventive Services Task Force draft guideline on nontraditional risk factors	In asymptomatic adults, the current evidence is insufficient to assess the balance of benefits and harms of adding CAC score to traditional risk assessment for CVD prevention. Class I (123).

ACC = American College of Cardiology; AHA = American Heart Association; ASCVD = atherosclerotic cardiovascular disease; other abbreviations as in Table 1.

CARDIA showed that CAC >0 is not uncommon in this age group, particularly when a risk factor is present (61,62). Over an approximately 10-year follow-up period, CAC strongly predicted risk beyond traditional risk factors in these young subjects (63).

The Jackson Heart Study measured CAC during follow-up. Among African Americans, CAC predicted risk beyond the traditional risk factors and has been shown to better identify persons most likely to benefit from preventive therapies (64,65).

CAC was measured during follow-up of the Women's Health Initiative, with CAC showing incremental predictive value over risk factors in postmenopausal women (66). CAC is currently being measured in the ARIC (Atherosclerosis Risk in Communities) study, which is expected to provide important insight into its risk predictive capability in adults >75 years of age.

USING CAC IN RISK SCORES FOR CLINICAL DECISION MAKING

For more than 40 years, clinical decisions in preventive cardiology have been based on risk assessment equations (67). Clinical practice guidelines, including those from the United States (7), Europe (8,68), and Canada (69), have universally recommended risk

factor equations that use office-based measurements of blood lipids, blood pressure, age, smoking history, and presence or absence of diabetes as mainstays of clinical risk assessment. Although it is widely recognized that CAC scoring can improve upon these clinical risk assessments, guidelines have not recommended using risk scores that require CAC testing (Table 2). To date, there is only 1 risk score that has incorporated CAC into the model and validated the score in external population samples (70). After 10 years of follow-up, McClelland et al. (70) used MESA data to derive and validate a risk score to estimate 10-year CHD risk using CAC plus traditional risk factors. External validation was conducted in the HNR study and the DHS (Dallas Heart Study). Inclusion of CAC results in the MESA risk score offered significant improvements in risk prediction. External validation in HNR demonstrated very good discrimination and calibration. The MESA risk score is available online (71) and via smartphone application and can be used when communicating risk to patients and when determining risk-based treatment strategies.

CAC scoring was also tested in a cardiovascular event prediction model created by machine learning techniques in the MESA dataset (72). The CAC score was the most important predictor of CHD and all ASCVD combined outcomes, improving on more than 700 other baseline variables.

COST-EFFECTIVENESS OF CAC IN PREVENTIVE CARDIOLOGY

Cost-effectiveness of CAC testing in the primary prevention context has been evaluated by several independent groups using generally similar assumptions and simulations (9–14). The datasets for 6 separate cost-effectiveness studies have been based on results from the Rotterdam Study, MESA, and the FHS. Critical factors that drive conclusions in all of the cost-effectiveness studies are the cost of statins and the rating of discomfort or side effects from statins, as well as the general desire to avoid lifelong preventive therapy (“disutility”). With relatively small differences in these inputs into the models, conclusions have varied from “treat all” with statins above a fairly low risk threshold (10,12) without performing CAC to “perform CAC in all” in selected risk categories and treat with statins if CAC >0 (11,14). In a recent analysis by Hong et al. (14), outcomes were similar between using CT scans for CAC measurement or the 2013 American College of Cardiology (ACC)/American Heart Association (AHA) guidelines (7,73) to guide long-term statin therapy among subjects at

intermediate cardiovascular risk. However, fewer patients would be treated using a CAC screening strategy. Hong et al. therefore proposed that cost-effectiveness analyses should not be the only criterion for clinical decision making, but a shared decision-making model is most important for clinicians, patients, and policymakers. Their analysis and previous cost-effectiveness analyses are consistent with the concept that CAC testing represents a reasonable option to risk-stratify as well as facilitate shared decision making without any significant downstream adverse outcomes, loss of quality of life, and/or increased costs (14).

CAC PROGRESSION

Because interscan variability of CAC score results is low (~10%), quantitative estimates of CAC progression are possible. MESA reported results of CAC progression in 5,756 participants with an average of 2.4 years between 2 CT scans (74). CAC scores increased by about 20% to 25% per year, and about 20% of subjects with CAC = 0 progressed to CAC >0 within 4 to 5 years. Because CAC progression is most strongly predicted by baseline CAC, the distribution of CAC is always heavily right skewed, underscoring the exponential nature of CAC change over time, which was confirmed by the HNR study (75).

In the HNR study, with CT scans spaced 5 years apart, CAC incidence was identified in a cohort of men and women who had CAC = 0 at the first examination. The probability of incident CAC at 5 years among those with no CAC initially steadily increased with age, from 23% in men 45 to 49 years of age to 67% in the 70 to 74 years of age category. In women, new onset of CAC was seen in 15% (age 45 to 49 years) and 43% (age 70 to 74 years), respectively. Findings were similar after adjusting for traditional risk factors (76).

CAC progression has been associated with higher risk for myocardial infarction and all-cause mortality (77–79). Various studies have used differing algorithms to quantify the degree of CAC progression, which may have influenced the different outcomes among studies (80,81). Lehmann et al. (82), in the HNR study, reported a method to differentiate rapid and slow CAC progression compared with an expected and calculated norm. On the basis of additional HNR data, the prediction of coronary and cardiovascular events was compared for 10 published algorithms (54). Analysis of CAC progression did not add any benefit to risk prediction models that included the most recent CT scan and the most recent

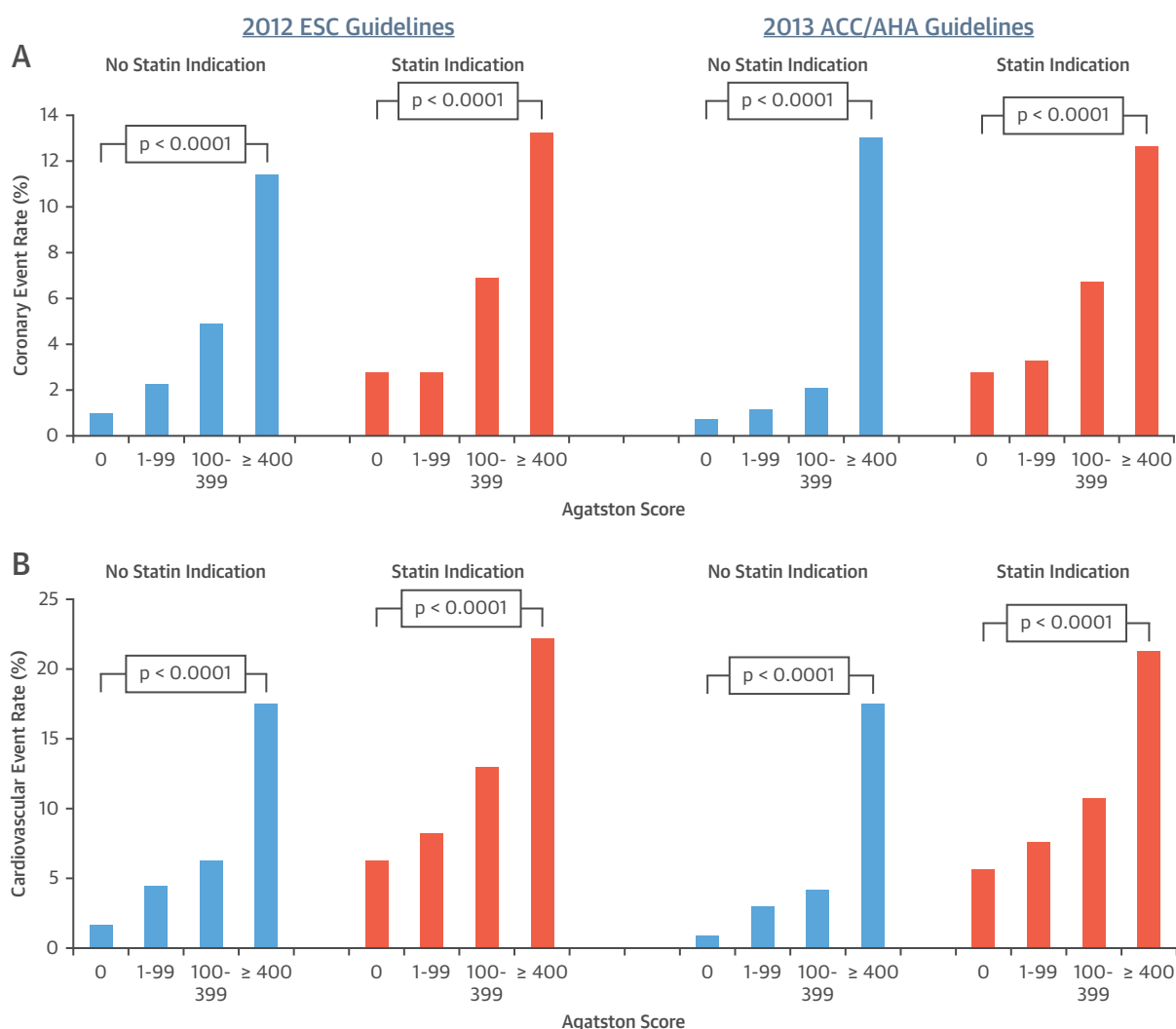
follow-up risk factors. The best coronary disease prognosis was found for participants with “double zero,” meaning CAC = 0 both at baseline and at the CT scan 5 years later. This pair was associated with a 10-year risk of only 1.4%, followed by incident CAC after 5 years with a 10-year risk estimate of 1.8%. Therefore, a repeat scan after 5 years seems to be of additional value, except for those who already have a double-zero CAC scan or have already been classified at high risk because of CAC $\geq$ 400 (54).

CAC AND PREVENTIVE THERAPIES

Although there is now ample evidence that CAC improves statistical risk reclassification (83,84), that is, modifying risk estimates in subjects free of events into lower risk categories and those with events into higher risk categories (net reclassification index), there is also evidence that CAC might directly guide risk-based selection of appropriate preventive therapies (85). MESA investigators studied 950 subjects who met inclusion criteria for the JUPITER (Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin) clinical trial (86). Of these “eligible” subjects, 47% had CAC = 0, whereas 25% had CAC >100. Using observed absolute event rates from MESA, coupled with the relative risk reduction observed with rosuvastatin in the JUPITER trial, the 5-year number needed to treat to prevent 1 cardiovascular event varied from 124 for subjects with CAC = 0 to just 19 for those with CAC >100. Similar analyses demonstrating that CAC might identify those expected to derive both the most and the least net benefit from statin therapy have been performed for patients meeting criteria for any one of the statin clinical trials (87), among elderly patients (88), or for all patients with dyslipidemia (89).

Nasir et al. (90) conducted an analysis of the potential impact of CAC on statin allocation in the context of the 2013 ACC/AHA cholesterol treatment guidelines. In MESA participants with a 10-year ASCVD risk of between 5% and 7.5% using the pooled cohort equation (7,90), a finding of CAC = 0 was associated with observed ASCVD event rates less than the guideline-recommended treatment threshold of 7.5% (actual event rate ~1.5%), whereas any CAC >0 was associated with event rates higher than the accepted threshold for statin benefit. Likewise, in participants with 10-year ASCVD risk between 7.5% and 20%, CAC = 0 was associated with event rates below the guideline-based threshold of statin benefit (~4.5%), whereas any CAC >0 was associated with events consistent

FIGURE 2 Cardiovascular Event Rate for Heinz Nixdorf Recall Study Participants



The cardiovascular event rates for participants in the HNR (Heinz Nixdorf Recall) study with and without statin indication according to European Society of Cardiology (ESC) and American College of Cardiology (ACC)/American Heart Association (AHA) guidelines are shown, stratified by coronary artery calcium (CAC). The figure shows a distinct increase in coronary event rates (A) and cardiovascular event rates (B) with increasing CAC score, irrespective of statin indication according to ESC and ACC/AHA guidelines. Reprinted with permission from Mahabadi et al. (92).

with net benefit from statin therapy (~10.5%). In this analysis, CAC had no role in middle-aged adults with a 10-year ASCVD risk >20%. This study directly informed the recommendation by the Society of Cardiovascular Computed Tomography (SCCT) to consider CAC testing, within the context of shared decision making, in intermediate-risk patients between 40 and 75 years of age with a 10-year ASCVD risk between 5% and 20% (91). Mahabadi et al. (92) conducted a similar analysis relating to the

indication for statin therapy using European Society of Cardiology and ACC/AHA guidelines. The CAC score consistently stratified risk for ASCVD events across both statin-recommended and non-statin-recommended groups (Figure 2). Thus, CAC scoring may help match intensified risk factor modification to atherosclerotic plaque burden as well as actual risk, while avoiding statin therapy in patients with low CAC scores and low 10-year event rates (sometimes called derisking) (92,93).

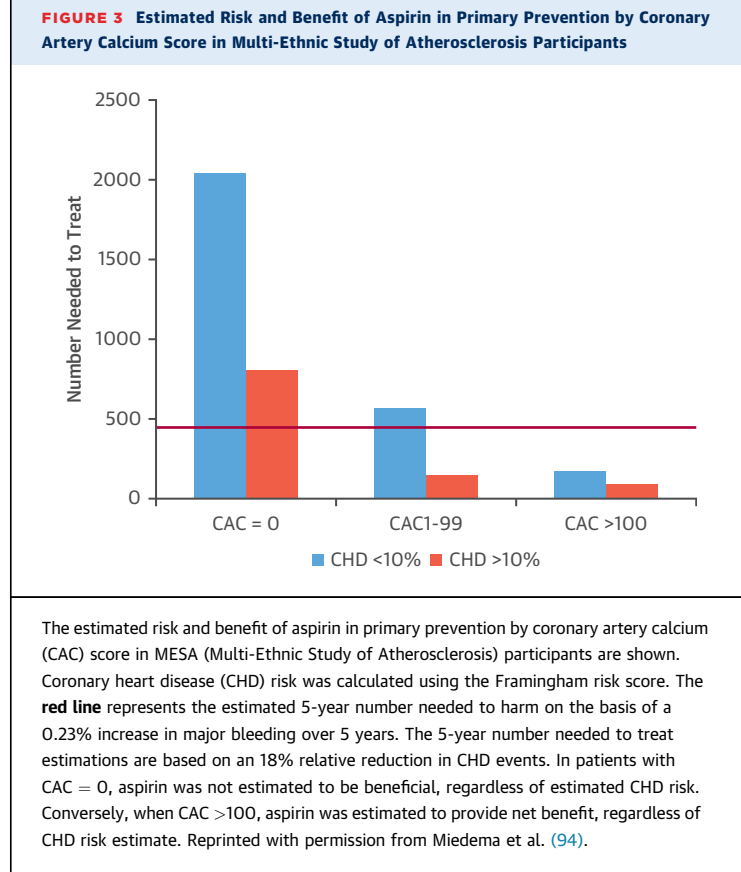
CAC may also have value in the decision to recommend prophylactic daily aspirin. Miedema et al. (94) studied the potential net benefit of aspirin in 4,229 subjects free of diabetes in MESA. This analysis found that there would be a predicted net harm with aspirin therapy when CAC = 0 (number of bleeds exceeding number of ASCVD events prevented), and net benefit of aspirin therapy, regardless of risk factors, in those with CAC >100 (Figure 3). These data also helped inform recent SCCT guidelines recommending consideration of aspirin therapy for all patients with CAC >100 (91).

With more formal incorporation of absolute risk assessment in future cholesterol and blood pressure guidelines, CAC may take on a greater role in the selection of cholesterol and blood pressure therapeutic targets. For example, subjects with CAC >100 have event rates closer to stable secondary prevention (89) and could benefit from low-density lipoprotein cholesterol goals of <70 mg/dl (95). McEvoy et al. (96) demonstrated that the 10-year number needed to treat of pursuing aggressive blood pressure targets varies considerably by baseline CAC status (99 for CAC = 0 vs. 24 for CAC >100).

CAC AND CLINICIAN AND PATIENT BEHAVIOR

Risk reclassification by any test, including CAC, will result in clinical benefit only if there is an impact on patient or physician behavior. The EISNER (Early Identification of Subclinical Atherosclerosis by Noninvasive Imaging Research) study randomized 2,137 volunteers to CAC scanning versus no CAC scanning and followed subjects for the 4-year change in risk factors and 10-year estimated risk score (97). In the primary analysis, those randomized to CAC scanning experienced a net favorable change in blood pressure, low-density lipoprotein cholesterol, and waist circumference, along with a lower Framingham risk score at the 4-year follow-up. Medical costs in the CAC scanning group were similar to those in the no-scanning group, with decreased costs in those with CAC = 0 balanced by increased spending in those with CAC ≥400 (i.e., closer association between risk and medical expenditure in the CAC scanning arm of the trial) (98).

Observational studies suggested an impact of high CAC score on initiation and continuation of preventive medications (99), and more definitive evidence has been provided by a recent meta-analysis. In a pooled analysis of 6 studies including 11,256 participants, with a mean follow-up time ranging from 1.6 to



6 years, Gupta et al. (100) demonstrated significantly higher odds of aspirin initiation, lipid-lowering medication initiation and continuation, antihypertensive medication initiation, increased exercise, and dietary change in subjects with CAC >0 compared with those with CAC = 0. Findings persisted after adjustment for demographic factors as well as cardiovascular risk factors.

CAC USING NONGATED CHEST CT IMAGING

Several studies have confirmed a role for identifying CAC on nongated chest CT imaging (34,101). Although a formal quantitative CAC score cannot be obtained from a nongated study, experienced readers can provide a qualitative CAC assessment (none, mild, moderate, or severe) that correlates closely with traditional CAC score groups (0, 1 to 100, 101 to 400, and >400) (102,103). The role of CAC in nongated chest CT imaging takes on importance with the increasing acceptance of lung cancer screening in those between 55 and 80 years of age who have a 30-pack-year smoking history and who have smoked within the past 15 years. Leigh et al. (104) demonstrated that CAC predicted ASCVD risk in all smokers

and in those eligible for lung cancer screening, although the improvement over the risk factor score alone was modest. Recent guidelines from the SCCT/Society of Thoracic Radiology provide a Class I indication for evaluation and reporting of at least qualitative CAC scoring on all noncontrast chest CT examinations (91).

CAC IN SINGLE-PHOTON EMISSION CT AND POSITION EMISSION TOMOGRAPHIC PERFUSION IMAGING

A limitation of routine stress testing is the reliance on functional data (i.e., evidence of ischemia), with an inability to quantify the anatomic atherosclerosis burden. However, CAC scoring can be added to single-photon emission computed tomography and positron emission tomography myocardial perfusion imaging using hybrid scanners (105). CAC scores obtained from the attenuation scans obtained at the time of perfusion imaging are highly predictive of risk, including in patients for whom there is no evidence of myocardial ischemia (106,107). CAC testing at the time of stress testing can improve assessment of pre-test risk (38), increase interpreter certainty (108), and lead to more risk-based preventive medical decision making compared with stress testing alone (109).

FUTURE DIRECTIONS: IMPROVING THE CAC SCORE

When a formal approach to CAC scoring was introduced in 1990 (6), little was known about the relationship among calcification, total atherosclerotic plaque, and ASCVD risk. However, since then, the understanding of why CAC scoring predicts risk has matured, with increasing attention paid to potential ways to improve the Agatston score. The Agatston score is limited in its assumption that scores should be upweighted with higher calcium density, its failure to capture information about the regional distribution of calcified plaque, and its fixed scanning parameters (120 kV, 3-mm slice thickness) (110). Following evidence demonstrating that low attenuation of a plaque is a high-risk feature, studies have suggested that the Agatston score predicts risk better if it is inversely weighted for calcium density (111). In addition, studies have shown that the regional distribution of CAC (in particular the total number of coronary arteries with CAC) adds prognostic information to the Agatston score, with higher risk in those with more diffuse plaque distributions (112,113).

CAC scoring can be accomplished with little ionizing radiation with simple modifications to the scanning protocol. For example, radiation could be reduced to well below 1 mSv of radiation with use of a lower energy photon, although CAC scores must then be recalibrated (114). In addition, emerging micro-calcification may be detected using thinner slices, allowing detection of higher risk cases among those with CAC = 0 (115).

The need for a new CAC score is a matter of current debate (116). A new CAC score may potentially incorporate extracoronary calcification, as evidence mounts that aortic valve calcification, aortic calcification, and mitral annular calcification add risk predictive value, particularly from stroke and other cardiovascular outcomes (117).

FUTURE DIRECTIONS: CAC AND NONCARDIOVASCULAR DISEASE RISK

CAC provides a summary measure of atherosclerotic disease, reflecting the cumulative lifetime effect of both measurable (i.e., risk factors) and unmeasurable (i.e., all genetic and environmental factors) risk determinants directly on vulnerable tissue (118). Given its role as a “risk integrator,” there is increasing interest in the role of CAC in predicting non-cardiovascular disease outcomes. CAC has been shown to predict incident cancer, chronic kidney disease, chronic obstructive pulmonary disease, and hip fracture independent of age, sex, and risk factors (119). CAC has also been shown to be an independent predictor of dementia (120). Ongoing work seeks to clarify the role of CAC in predicting risk for ASCVD versus cancer across the life span (121). CAC also appears valuable in identifying long-term “healthy agers”: those surviving into old age with CAC = 0 (122).

CAC AND GUIDELINES

In 2010, the ACC/AHA guidelines on risk prediction in asymptomatic patients assigned CAC a Class IIA recommendation for intermediate-risk patients and a Class IIB recommendation in low- to intermediate-risk patients and advised against CAC testing in very low-risk patients, as defined by the Framingham risk score. In 2013, the ACC/AHA guidelines on risk assessment gave CAC a Class IIb recommendation for patients in whom risk or the decision to treat with statins is unclear. Recent 2017 guidelines from the SCCT recommended consideration of CAC testing (equivalent of a Class II recommendation), in the context of shared decision making, for subjects with a

CENTRAL ILLUSTRATION Proposed Decision-Making Approach to Selective Use of Coronary Artery Calcium Measurement for Risk Prediction

Using 10-year ASCVD risk estimate plus coronary artery calcium (CAC) score to guide statin therapy

Patient's 10-year atherosclerotic cardiovascular disease (ASCVD) risk estimate:	<5%	5–7.5%	>7.5–20%	>20%
Consulting ASCVD risk estimate alone	Statin not recommended	Consider for statin	Recommend statin	Recommend statin
Consulting ASCVD risk estimate + CAC				
If CAC score =0	Statin not recommended	Statin not recommended	Statin not recommended	Recommend statin
If CAC score >0	Statin not recommended	Consider for statin	Recommend statin	Recommend statin
Does CAC score modify treatment plan?	✗ CAC not effective for this population	✓ CAC can reclassify risk up or down	✓ CAC can reclassify risk up or down	✗ CAC not effective for this population

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The figure shows a modified approach to the guideline-based decision making by incorporating a consideration of coronary artery calcium (CAC) testing to reclassify a patient's risk up or down where it would make a clinically important change in the clinical decision. Adapted with permission from Nasir et al. (90).

10-year ASCVD risk of 5% to 20% or in those with <5% 10-year risk but with another strong indication, such as a family history of premature CAD (91). Other guidelines (8,123) have provided recommendations similar to the 2013 ACC/AHA risk assessment guideline; see Table 2 for a summary of recommendations.

CONCLUSIONS

Coronary artery calcification has emerged as the most predictive single cardiovascular risk marker in asymptomatic persons, capable of adding predictive information beyond the traditional cardiovascular risk factors. CAC scoring appears to be useful for making decisions about preventive statin and/or aspirin use. In most studies, CAC testing has been shown to be cost effective compared with alternative approaches when factoring in patient preferences about taking preventive medications. In the **Central Illustration**, we suggest

a clinical approach, modified from the ACC/AHA lipid treatment guideline (73) and from Nasir et al. (90,124), incorporating a broader use of CAC testing in selected individuals.

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ADDRESS FOR CORRESPONDENCE: Dr. Philip Greenland, Department of Preventive Medicine, Northwestern University Feinberg School of Medicine, 680 North Lake Shore Drive, Suite 1400, Chicago, Illinois 60611. E-mail: p-greenland@northwestern.edu. Twitter: [@NUFeinbergMed](https://twitter.com/NUFeinbergMed), [@MichaelJBlaha](https://twitter.com/MichaelJBlaha), [@kewatson](https://twitter.com/kewatson).

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