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iREVIEWS

STATE-OF-THE-ART PAPERS

Coronary Artery Calcium Scanning

Past, Present, and Future

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JACC: CARDIOVASCULAR IMAGING CME

CME Editor: Ragavendra R. Baliga, MD

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CME Objective for This Article: At the end of this activity the reader should be able to: 1) utilize coronary artery calcium scanning to improve outcomes for primary prevention patients; 2) appropriately risk stratify asymptomatic patients and tailor treatment accordingly; and 3) improve patient adherence to medication and life style modification.

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Coronary Artery Calcium Scanning

Past, Present, and Future

ABSTRACT

Coronary artery calcium scanning (CAC) has emerged as the most robust predictor of coronary events in the asymptomatic primary prevention population, particularly in the intermediate-risk cohort. Every study has demonstrated its superiority to risk factor–based paradigms, e.g., the Framingham Risk Score, with outcome-based net reclassification indexes ranging from 52.0% to 65.6% in the intermediate-risk, 34.0% to 35.8% in the high-risk, and 11.6% to 15.0% in the low-risk cohorts. CAC improves medication and lifestyle adherence and is cost-effective in specified populations, with the ability to effectively stratify the number needed to treat and scan for different therapeutic strategies and patient cohorts. Data have emerged clearly demonstrating the worse prognosis associated with increasing CAC on serial scans, suggesting a potential role for evaluating residual risk and treatment success or failure. CAC is also strongly associated with the development of stroke and congestive heart failure. (J Am Coll Cardiol Img 2015;8:579–96)

"All truth passes through three stages:
First, it is ridiculed; second, it is violently
opposed; third, it is accepted as self-evident."
– Arthur Schopenhauer (1)

Coronary artery calcium (CAC) scanning for risk assessment in the asymptomatic population has been the subject of more than 2,500 papers in the peer-reviewed literature. Yet its role remains controversial, incorporation into guidelines has been variable, and insurance coverage is virtually nonexistent, with at least 1 major carrier labeling it investigational (2). Despite the overwhelming peer-reviewed data supporting the role of CAC in the primary prevention of coronary heart disease (CHD), its penetration into clinical practice has been inexplicably low. Screening for lung, breast, and colon cancer has been officially endorsed by the U.S. Preventive Services Task Force, the agency on which coverage decisions are largely based. On the other hand, coronary artery disease (CAD), which is responsible for more deaths than all cancers combined, has been considered to lack sufficient evidence to be considered for screening. Instead, reliance is placed on risk assessment by various risk factor–based paradigms. This paper summarizes the data supporting the application of CAC to the care of the individual patient, discusses the ongoing controversy, and outlines directions for future research.

THE CAC SCAN

The CAC scan is a noncontrast, limited chest computed tomography (CT) scan acquired with an ~3 to 5 s breath hold. The presence of CAC is quantified through the entire epicardial coronary system. Coronary calcium is defined as a lesion above a threshold of 130 Hounsfield units, with an area of ≥3 adjacent pixels (at least 1 mm^2). The original calcium score developed by Agatston et al. (3) is determined by the product of the calcified plaque area and maximal calcium lesion density (from 1 to 4 based on Hounsfield units). Standardized categories for the calcium score have been developed with scores of 0 indicating the absence of calcified plaque, 1 to 10 minimal plaque, 11 to 100 mild plaque, 101 to 400 moderate plaque, and >400 severe plaque. The calcium volume score (4) is a more reproducible parameter that is independent of calcium density and may be the parameter of choice for serial studies to track progression or regression of atherosclerosis, but is rarely used. Phantom-based calcium mass scores are applicable to any CT scanner (5), but are never clinically used. Examples of CAC scans displaying varying degrees of plaque are shown in **Figure 1**.

RADIATION. The radiation exposure should not exceed 1.0 mSv (6) and has progressively decreased to ≤1 mSv, comparable to mammography (0.8 mSv). Newer algorithms using iterative reconstruction have decreased the mean dose to 0.37 mSv (7), but are variable from vendor to vendor. Further reductions are to be expected with the implementation of model-based iterative reconstruction, with higher signal-to-noise ratios facilitating lower current, but validation will be required. Several studies have projected a small but finite increase in lifetime attributable cancer risk to CAC scanning, but it is important to note that this is a predicted rather than observed risk (8).

EPIDEMIOLOGY. By comparing a subject's calcium score with that of others of the same age, sex, and ethnicity through the use of large databases of asymptomatic subjects, a calcium percentile is generated (9); higher than the 75th percentile is considered high risk, irrespective of the score, and indicates premature atherosclerosis. Variations according to sex and ethnicity have been described. In the Multi-Ethnic Study of Atherosclerosis (MESA) of 6,110 asymptomatic patients, men had higher calcium levels than women, and the amount and prevalence of calcium continually increased with increasing age (10). In men, Caucasians and Hispanics had the first and second highest scores, respectively; blacks had the lowest scores at the younger ages, and Chinese had the lowest scores at the older ages. In women, Caucasians had the highest scores, Chinese and blacks had intermediate scores, and Hispanics had the lowest score except for Chinese in the oldest age group. However, the MESA demonstrated very strong CAC predictive power for all groups (11).

THE PROGNOSTIC DATA

CORONARY HEART DISEASE. Every prognostic registry, whether prospective or retrospective, population-based or patient-referred, has demonstrated the power of CAC, with relative risks far exceeding all risk factors, whether individually or collectively (**Table 1**) (12). Moreover, CAC has consistently been associated with a greater area under the receiver-operating characteristic curve than combinations of risk factors (e.g., Framingham Risk Score [FRS]), as well as the individual risk factors (**Figure 2**). The notion that risk factors with a relative risk of ~2 (e.g., high-sensitivity C-reactive protein [hs-CRP]) do not add significantly to the area under the curve for conventional risk factors is poorly understood and leads to an overestimation of the importance of the never-ending flow of new risk factors. The poor discriminatory power of risk factors was demonstrated in 542,008 patients presenting with a first myocardial infarction: the percentage with 0, 1, 2, 3, and 4 risk factors was 14.4%, 34.1%, 31.6%, 15.4%, and 4.1%, respectively (13). The categorical nature of risk factors may contribute to their lack of discrimination; simple presence or absence rather than quantitative values may diminish their importance. Moreover, they usually reflect treated residual risk with variable adherence instead of presenting a natural history.

Perhaps the most important study is the MESA, a National Heart, Lung, and Blood Institute-sponsored prospective population cohort registry evaluation of 6,814 individuals followed for 3.8 years (11) in the initial report and as long as 14.5 years in subgroups. Compared with patients with a CAC score of 0, the hazard ratios (HRs) for a coronary event were 7.73 for those with a CAC score of 101 to 300, and 9.67 for a

ABBREVIATIONS AND ACRONYMS

ACC/AHA = American College of Cardiology/American Heart Association

AU = Agatston units

CAC = coronary artery calcium

CHD = coronary heart disease

CI = confidence interval

CT = computed tomography

FH = family history

FRS = Framingham Risk Score

HR = hazard ratio

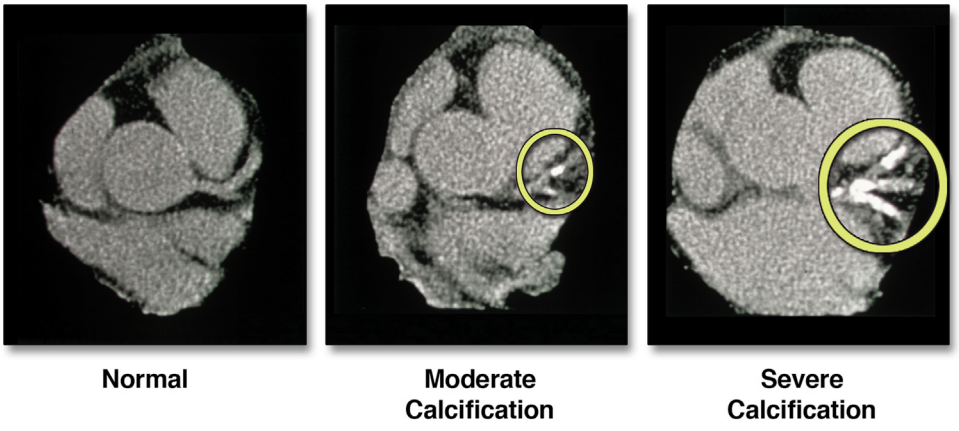
hs-CRP = high-sensitivity C-reactive protein

NNT = number needed to treat

NRI = net reclassification index

RCT = randomized, controlled trial

FIGURE 1 Examples of Coronary Artery Scans



(Left) Normal scan without calcified plaque. **(Middle)** Moderate calcified plaque in the left anterior descending and left circumflex coronary arteries. **(Right)** Severe calcified plaque involving the left main, left anterior descending, and left circumflex coronary arteries. Reprinted with permission from Hecht and Narula (12).

TABLE 1 Prognostic Power of Coronary Artery Calcium in Asymptomatic Patients

First Author (Ref. #)	N	Mean Age, yrs	Follow-Up, yrs	CAC Score Cutoff	Comparator Group for RR Calculation	RR Ratio
Arad et al. (22)	1,173	53	3.6	>160	<160	20.2
Park et al. (12)	967	67	6.4	>142.1	<3.7	4.9
Raggi et al. (12)	632	52	2.7	Top quartile	Lowest quartile	13
Wong et al. (62)	926	54	3.3	Top quartile (>270)	First quartile	8.8
Kondos et al. (12)	5,635	51	3.1	CAC >0	No CAC	10.5
Greenland et al. (38)	1,312	66	7.0	>300	No CAC	3.9
Shaw et al. (12)	10,377	53	5	≥400	≤10	8.4
Arad et al. (77)	5,585	59	4.3	≥100	<100	10.7
Taylor et al. (12)	2,000	40–50	3.0	>44	0	11.8
Vliegenthart et al. (23)	1,795	71	3.3	>1,000	<100	8.3
				400–1,000	<100	4.6
Budoff et al. (12)	25,503	56	6.8	>400	0	9.2
Lagoski et al. (18)	3,601	45–84	3.75	>0	0	6.5
Becker et al. (24)	1,726	57.7	3.4	>400	0	6.8 men 7.9 women
Detrano et al. (11)	6,814	62.2	3.8	>300	0	14.1
Erbel et al. (21)	4,487	45–75	5	>75th percentile	<25th percentile	11.1 men 3.2 women
Taylor et al. (12)	1,634	42	5.6	>0	0	9.3

Reprinted with permission from Hecht and Narula (12).
CAC = coronary artery calcium; RR = relative risk.

CAC score >300 ($p < 0.001$). In the 4 racial and ethnic groups, doubling the CAC increased the risk of any coronary event by 18% to 39%. The receiver-operating characteristic curve areas were significantly higher (0.82 vs. 0.77; $p < 0.001$) with the addition of CAC to standard risk factors. There are longer term analyses for several MESA subgroups. In the 2,232 Caucasian subjects with 5-year follow up, the adjusted HR for a CAC score >400 was 5.36 (14). After a median 7.6-year follow-up in the 1,330 intermediate-risk patients, the HR for each SD of ln (CAC + 1) was 2.60 (95% confidence interval [CI]: 1.94 to 3.50). In 3,398 individuals with 7.5-year follow-up in the MESA, CAC density was inversely associated with events, with an HR of 0.73 per SD (15). In the 3,923 patients with a CAC score of 0 to 10, the 10.3-year event rates per 1,000 person-years were 5.5 for a CAC score of 1 to 10 and 2.9 for a CAC score of 0, with a relative risk of 1.86 ($p = 0.004$) for the mild compared with the CAC score of 0 group (16). In patients followed for 14.5 years, smokers were noted to be at higher risk of all-cause mortality than non-smokers at every CAC level (17).

In the 2,684 patients in the female component of the MESA, Lakoski et al. (18) reported an HR of 6.5 for the 32% with a CAC score >0 versus the 68% with a CAC score of 0, even though 90% were low risk by the FRS. In an analysis of all-cause mortality in 44,052 asymptomatic patients followed for 5.6 years, the number of deaths per 1,000 patient-years was 7.48 for a CAC score >10 compared with 1.92 for a CAC score of 1 to 10 and 0.87 for CAC score of 0 (19). In a meta-analysis of 64,873 patients followed for 4.2 years, the coronary event rate was 1% per year for the 42,283 with a CAC score >0 compared with 0.13% per year in the 25,903 patients with a CAC score of 0 (20). In the Heinz Nixdorf Recall Study (21), 4,487 subjects without CHD were followed for 5 years. The prevalence of low (score <100), intermediate (score 100 to 399), and high (score ≥400) CAC scores was 72.9%, 16.8%, and 10.3%, respectively ($p < 0.0001$). The relative risk of a CAC score higher than the 75th versus the 25th percentile or lower was 11.1 ($p < 0.0001$) for men and 3.2 ($p = 0.006$) for women. The relative risk associated with doubling of the CAC score was 1.32 (95% CI: 1.2 to -1.45; $p < 0.001$) in men and 1.25 (95% CI: 1.11 to 1.42; $p < 0.0001$) in women. Adding CAC score to the Adult Treatment Panel III categories improved the receiver-operating characteristic C index from 0.602 to 0.727 in men and from 0.660 to 0.723 in women.

Amalgamation of the data from 5 large prospective, randomized studies, 3 with events defined as CHD death, myocardial infarction, and revascularization (11,22,23) and 2 with CHD death and myocardial infarction (21,24) yields annual event rates that can be translated into 10-year FRS equivalents (**Table 2**). A CAC score >400 is a CHD equivalent, with 10-year event rates exceeding 20% in asymptomatic patients.

ZERO CAC SCORES. Exclusively noncalcified plaques are present in 4% of asymptomatic patients (25). Nonetheless, the event rate in patients with a CAC score of 0 is very low. Raggi et al. (26) demonstrated an annual event rate of 0.11% in asymptomatic subjects with a CAC score of 0 (10-year risk of only 1.1%), and in the St. Francis Heart Study scores of 0 were associated with a 0.12% annual event rate over 4.3 years (22). In the MESA (11), a CAC score of 0 was associated with a 0.11% annual event rate. In a meta-analysis of 64,873 patients followed for 4.2 years (19), the coronary event rate was 0.13% per year in the 25,903 patients with a CAC score of 0 compared with 1% per year for the 42,283 with a CAC score >0. In an analysis of all-cause mortality in 44,052 asymptomatic patients followed for 5.6 years (18), the number of deaths per 1,000 patient-years for the 19,898 patients with a CAC score of 0 was 0.87 compared with 1.92 for those with a CAC score of 1 to 10 and 7.48 for those with a CAC score >10.

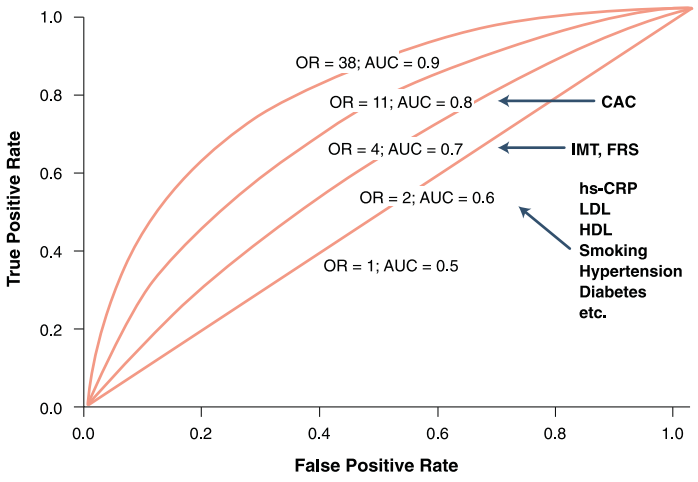
Although noncalcified plaque is by definition not detected by CAC testing, exclusively soft, noncalcified plaque has been seen in only 5% of acute ischemic syndromes in both younger and older populations (27,28) (**Figure 3**). In a more recent meta-analysis (15), only 2 of 183 (1.1%) patients with a CAC score of 0 ultimately received a diagnosis of an acute coronary syndrome after presenting with acute chest pain, a normal troponin level, and equivocal electrocardiography findings. A CAC score >0 had 99% sensitivity, 57% specificity, 24% positive predictive value, and 99% negative predictive value for acute coronary syndrome. Thus, it is uncommon that a patient with an imminent acute ischemic syndrome would have had a CAC score of 0. However, development of chest pain requires further evaluation by CT angiography or functional testing.

The absence of calcified plaque conveys an extraordinarily low 10-year risk (1.1% to 1.7%), irrespective of the number of risk factors (29). In 44,052 asymptomatic patients with a 5.6 ± 2.6-year follow-up, the 5-year survival rate for those with a CAC score of 0 ranged from 99.7% for no risk factors to 99.0% for ≥3 risk factors.

NET RECLASSIFICATION INDEX. The net reclassification index (NRI) has been increasingly used to measure the prediction improvement in the risk reclassification increment of new biomarkers compared with more traditional risk factors on the basis of outcomes. The NRI conferred by CAC in the asymptomatic population by 3 major prospective, population-based studies is shown in **Table 3** (20,30,31). The percentage of patients with an FRS risk estimate correctly reclassified by CAC score on the basis of outcomes ranged from 52.0% to 65.6% in the intermediate-risk group, 34.0% to 35.8% in the high-risk group, and 11.6% to 15.0% in the low-risk group, with NRIs for the entire study population ranging from 19% to 25%.

Comparisons of the NRI for CAC versus the FRS (66%) in the intermediate-risk population with risk markers other than those included in the FRS reveal its overwhelming superiority to ankle-brachial index (3.6%), brachial flow-mediated dilation (2.4%), carotid intima media thickness (10.2%), family history (FH) of premature CHD (16.0%), and hs-CRP (7.9%) (32). In addition, a combination of multiple blood biomarkers, including hs-CRP, interleukin 8,

FIGURE 2 ROC Curve, Its AUC, and Corresponding Odds Ratios



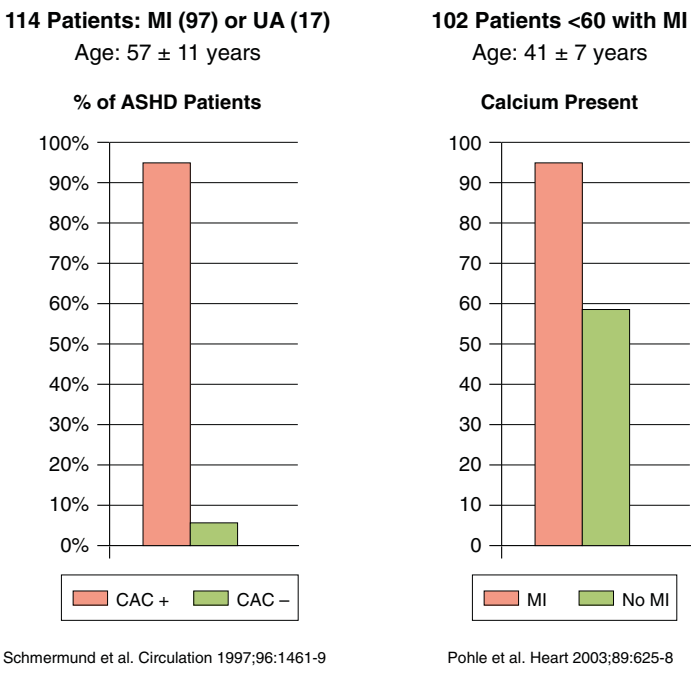
Increased odds ratios associated with novel risk factors are often assumed to have high predictive value for the development of cardiac events. It is only when the odds ratios are in the ≥4 range that the AUC increases to a minimally acceptable level for clinical utility. Coronary artery calcium, with an odds ratio of ~11, is associated with the greatest AUC. AUC = area under the curve; CAC = coronary artery calcium; FRS = Framingham Risk Score; HDL = high-density lipoprotein; hs-CRP = high-sensitivity C-reactive protein; IMT = intima media thickness; LDL = low-density lipoprotein; OR = odds ratio; ROC = receiver-operating characteristic. Reprinted with permission from Hecht and Narula (12).

TABLE 2 Summary of CAC Absolute Event Rates From 14,856 Patients in 5 Prospective Studies (11,19,21,24,25)

CAC Score	FRS Equivalent	10-Year Event Rate, %
0	Very low	1.1–1.7
1–100	Low	2.3–5.9
101–400	Intermediate	12.8–16.4
>400	High	22.5–28.6
>1,000	Very high	37.0

CAC = coronary artery calcium; FRS = Framingham Risk Score.

FIGURE 3 Coronary Artery Calcium in Patients With First Myocardial Infarction or Unstable Angina



(Left) Coronary artery calcium (CAC) was present in 95% of patients 57 ± 11 years of age presenting with first myocardial infarction (MI) or unstable angina (UA) (31). **(Right)** CAC was present in 95% of patients age 41 ± 7 years of age presenting with first MI (32). ASHD = atherosclerotic heart disease; pts = patients. Reprinted with permission from Hecht and Narula (12).

TABLE 3 Reclassification of FRS Risk by CAC Primary Prevention Outcome Studies

Study	% Reclassified	N	Age, yrs	Follow-up, yrs
MESA (31)		5,878	62.2	5.8
FRS 0%–6%	11.6			
FRS 6%–20%	54.4			
FRS >20%	35.8			
NRI	25			
Heinz Nixdorf (21)		4,487	45–75	5.0
FRS <10%	15.0			
FRS 10%–20%	65.6			
FRS >20%	34.2			
NRI	22.4			
Rotterdam (30)		2,028	69.6	9.2
FRS <10%	12			
FRS 10%–20%	52			
FRS >20%	34			
NRI	19			

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NRI = net reclassification index; other abbreviations as in Table 1.

myeloperoxidase, B-type natriuretic peptide, and plasminogen activator type 1, did not add to the C statistic for CAD outcomes of the FRS (0.75 vs. 0.73; p = 0.32), whereas CAC score increased the FRS C statistic to 0.84 (p = 0.003). Moreover, the biomarker combination added nothing to the FRS + CAC score (0.84 vs. 0.84) (33).

CONGESTIVE HEART FAILURE. CAC may be used to differentiate ischemic from nonischemic cardiomyopathies. Budoff et al. (34) demonstrated in 120 patients with heart failure of unknown etiology that the presence of CAC was associated with 99% sensitivity for ischemic cardiomyopathy. Nonetheless, coronary CT angiography has replaced CAC for this indication. In 1,897 asymptomatic patients followed for 6.8 years in the Rotterdam study, the HRs for the development of congestive heart failure increased with increasing CAC score to a peak of 4.1 in the CAC score >400 group, with an NRI of 34% for the prediction of congestive heart failure compared with standard congestive heart failure predictors (35).

STROKE. The strong predictive power of CAC for stroke in asymptomatic patients was demonstrated in 2 major prospective studies. In the Heinz Nixdorf Recall Study of 4,180 asymptomatic patients 45 to 75 years of age followed for 8 years (36), the median CAC score was 105 in those in whom a stroke developed compared with 11 in whom it did not develop (p < 0.001). The HR for log10(CAC + 1) was 1.52, comparable to age per 5 years (1.35), systolic blood pressure per 10 mm (1.25), and smoking (1.75). In 6,779 MESA subjects followed for 9.5 years, the event rate increased and the event-free survival rate decreased (p < 0.0001) with increasing CAC score categories, from 2.0% with a CAC score of 0 to 6.9% with a CAC score >400. The HR for ln(CAC + 1) was 1.13, p < 0.0001) and the addition of CAC score to the FRS demonstrated its incremental value by increasing the C statistic from 0.664 to 0.706 (p < 0.01) (37).

PATIENT SUBGROUPS

DIABETES. The 2010 ACC/AHA Risk Assessment Guideline awarded a Class IIa recommendation for all adults older than 40 years of age with diabetes (38). CAC prognostic data have challenged the ingrained concept of diabetes mellitus as a CHD equivalent. Patients with diabetes and a CAC score >0 have higher risks than those without diabetes and similar CAC score, but the absence of CAC conveys a similar low risk in both groups (**Table 4**) (12). Therefore, the more appropriate rationale is for a straightforward

TABLE 4 Relationship of CAC to Events in Asymptomatic Diabetic Patients

First Author (Ref. #)	N	Prevalence	HR	AUC	Event Rates/yr
Wong et al. (12)	1,823	Any CAC No DM, 53% DM, 75.3%			
Becker et al. (12)	DM 716	0 CAC, 15% CAC >400, 42%		CAC, 0.77 FRS, 0.68 UKPDS, 0.71 ($p < 0.01$)	0 CAC, 0.2% >400, 5.6%
Eikeles et al. (12)	DM 589		Compared with CAC 0–10: CAC >1,000, 13.8 CAC 401–1,000, 8.4 CAC 101–400, 7.1 CAC 11–100, 4.0 CAC 0–10, 1	CAC, 0.73 UKPDS, 0.63 ($p < 0.03$)	<10, 0%
Anand et al. (12)	DM 510	CAC <10, 53.7%	Compared with CAC <100: CAC >1,000, 58 CAC 401–1,000, 41 CAC 101–400, 10 CAC 0–100, 1	CAC, 0.92 UKPDS, 0.74 FRS, 0.60 ($p < 0.001$)	
Malik et al. (12)	DM 881 No DM 4,036		Inc CAC 2.9–6.5 Inc CAC 2.6–9.5	CAC+RF: 0.78–0.80 RF: 0.72–0.73 ($p < 0.001$)	1.5% 0.5%

Reprinted with permission from Hecht and Narula (12).
AUC = area under curve; DM = diabetes mellitus; HR = hazard ratio; Inc = increasing; RF = risk factors; UKPDS = United Kingdom Prospective Diabetes Study.

risk classification as with any other risk factor, allowing for the possibility of downgrading risk.

FH OF PREMATURE CHD. The strong association between FH and both clinical and subclinical CHD (39) is well documented (37). Younger patients with an FH have significantly higher CAC scores than similarly aged individuals without an FH, particularly if there is a sibling history of premature CHD (40). In the MESA, the odds ratios for the presence of CAC independent of all risk factors in those with compared with those without an FH were 2.74 with premature CHD in both a parent and a sibling, 2.06 in a sibling alone, and 1.52 in a parent alone (41). Most recently, in the 2,390 asymptomatic patients in the Dallas Heart Study with a mean age of 44 ± 9 years followed for 8 years, the HR for an FH was 2.6 after adjustment for CAC ($p < 0.001$) (42). The event rates for FH + CAC and for CAC alone were 8.8% and 3.3%, respectively ($p < 0.001$). These patients are an overlooked higher risk group who would not qualify for treatment on the basis of the FRS. In recognition of this problem, the 2009 CAC Appropriate Use Criteria (43) considered CAC "appropriate" for asymptomatic patients with an FH and a low global risk estimate.

YOUNG PATIENTS. FH aside, in 2,831 patients 35 to 45 years of age in the CARDIA (Coronary Artery Risk Development in Young Adults) study, the incidence of a CAC score >0 was 9.9% and the incidence of CAC score >100 was 1.8% (44). The percentages increased with increasing FRS, with a CAC score >100 incidence of 17.2% in those with an FRS >10% in whom the number needed to scan to uncover a CAC score >100 was only 6 patients. Although CAC scanning is not guideline recommended in this age group, it can be helpful in statin use decision making in these younger high-FRS individuals.

POST-CAC SCANNING TESTING

The appropriateness of stress testing after CAC scanning in asymptomatic patients is directly related to the CAC score. The incidence of abnormal nuclear stress testing is 1.3%, 11.3%, and 35.2% for CAC scores <100, 100 to 400, and >400, respectively (45) (**Figure 4**). It is only in the >400 group that the pretest likelihood is sufficiently high to warrant further evaluation with myocardial perfusion imaging, for which there is a IIb recommendation (38). Coronary CT angiography is technically feasible in patients with CAC score <1,000; higher CAC scores may preclude accurate evaluation. It is never appropriate to proceed directly to the catheterization laboratory in asymptomatic patients. Evaluation of incidental findings, in particular, lung nodules, should follow standard radiology guidelines (46).

ADHERENCE

CAC has been shown to positively affect initiation of and adherence to medication and lifestyle changes (**Table 5**). In 505 asymptomatic patients, statin

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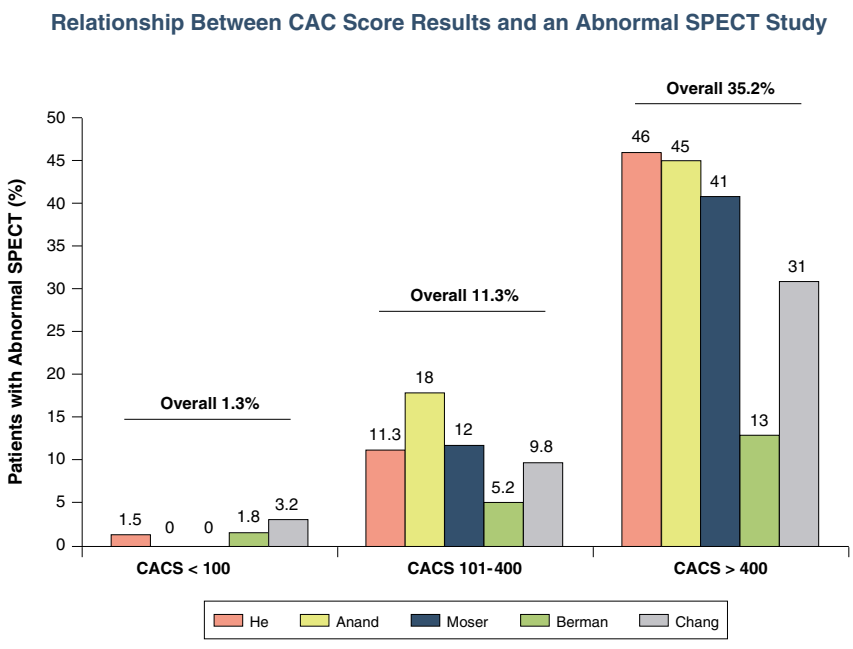
FIGURE 4 Summary of 5 Studies Demonstrating the Relationship Between CAC Categories and Abnormal SPECT Scans



It is only in the CACS >400 group that the pre-test probability is sufficiently high to warrant stress testing. CAC = coronary artery calcium; CACS = coronary artery calcium score; SPECT = single-photon emission computed tomography. Reprinted with permission from Hacker and Becker (45).

adherence 3.6 years after visualizing their CAC scan was 90% in those with a CAC score >400 compared with 75% in those with CAC scores of 100 to 399, 63% in those with CAC scores of 1 to 99, and 44% in those with a CAC score of 0 ($p < 0.0001$) (47). Similarly, in 980 asymptomatic subjects followed for 3 years, aspirin therapy initiation, dietary changes, and exercise increased significantly from those with a CAC score of 0 (29%, 33%, and 44%, respectively) and was highest with CAC scores >400 (61%, 67%, and 56%, respectively) (48). Finally, after a 6-year follow-up of 1,640 asymptomatic subjects, the odds ratios for those with a CAC score >0 compared with a CAC score of 0 for use of statins, aspirin, and a statin + aspirin were 3.53, 3.05, and 6.97, respectively (49). In the EISNER (Early Identification of Subclinical Atherosclerosis by Noninvasive Imaging Research) trial, 2,137 asymptomatic patients were randomized to using CAC to guide treatment or to usual care (50). CAC-directed care produced significant improvement in systolic blood pressure, low-density lipoprotein cholesterol, weight, waist size, and FRS compared with usual care, without an increase in downstream testing. Patients with a CAC score >400 had significantly greater improvement in all parameters than those with a CAC score of 0. In a systematic review of 15 studies, CAC screening enhanced medication adherence in 13 (51).

TABLE 5 Effect of CAC Scanning on Primary Prevention Patient Adherence

First Author (Ref. #)	N	Follow-Up, yrs	CAC	Statin	Adherence			
					ASA	Diet	Exercise	Statin + ASA
Kalia et al. (47)	505	3.6	>400 100–400 1–99 0	90% 75% 63% 44%				
Orakzai et al. (48)	980	3	>400 0			61% 29%	67% 33%	56% 44%
Taylor et al. (49)	1,640	6	>0 vs. 0	OR 3.5	OR 3.1			OR 7.0

Reprinted with permission from Hecht and Narula (12).
ASA = aspirin; CAC = coronary artery calcium score; OR = odds ratio.

NUMBERS NEEDED TO SCAN AND TREAT

NUMBER NEEDED TO SCAN. In 5,660 asymptomatic MESA subjects (mean age 62.2 ± 10.2 years), 46.4% had a CAC score of 0, 20.6% had a CAC score >100, and 10.1% had a CAC score >300. The number needed to scan to identify a high-risk subject with a CAC score >300 was 7.6, 6.4, 4.2, and 3.3 in the 7.6% to 10%, 10.1% to 15%, 15.1% to 20%, and >20% FRS categories, respectively (52). In the younger CARDIA population of 2,831 patients 35 to 45 years of age, the number needed to scan to uncover patients with a high-risk CAC score >100 (all of whom will be >75th percentile) in those with FRS >10% was only 6 patients (44).

NUMBER NEEDED TO TREAT. Extrapolations of MESA event rates to 4 different anticipated polypill therapies projected the utility of CAC to choose the target population. The projected 5-year numbers needed to treat (NNTs) to prevent an event in the asymptomatic population were 81 to 130, 38 to 54, and 18 to 20 in the 0, 1 to 100, and >100 CAC score groups (53). In the 5,534 statin-naive MESA subjects followed for 7.6 years, the projected NNT with a statin to prevent an event was 30 in those with no lipid abnormalities but a CAC score >100 compared with 154 with 3 lipid abnormalities and a CAC score of 0 (52).

A simulated reanalysis of the JUPITER (Justification for the Use of Statin in Prevention: An Intervention Trial Evaluating Rosuvastatin) trial selected 950 MESA patients who met JUPITER eligibility criteria, with hs-CRP >2 and low-density lipoprotein <130 mg/dl, and matched them with 1,033 MESA subjects with hs-CRP <2 (54). They found no effect of hs-CRP on projected outcomes (HR: 0.9 for hs-CRP >2 compared with <2), with HRs of 1.66 and 9.35 for CAC scores of 1 to 100 and >100, respectively. Moreover, the NNTs to prevent an event with rosuvastatin were 549, 94, and 24 for CAC score of 0, 1 to 100, and >100, respectively. Similarly, using the 2013 Cholesterol Guidelines, a 10.3-year follow-up of the MESA revealed the projected NNTs to prevent an event in the moderate- to high-intensity statin group to be 68 for a CAC score of 0, 42 for a CAC score of 1 to 100, and 24 for a CAC score >100. In the moderate-intensity statin group, the NNTs for the same CAC groups were 246, 47, and 39, respectively (55).

Thus, in both the older and younger populations, CAC efficiently uncovers higher risk patients who most need to be treated and identifies those who will most benefit from therapy irrespective of lipid or CRP abnormalities.

COST-EFFECTIVENESS

With the recent pervasiveness of generic statins and decreased CAC cost to ~$100, only the latest cost-effectiveness analyses are relevant. In 2011, based on the Rotterdam study, CAC was compared with current practice, the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) Guidelines and statins for all asymptomatic intermediate-risk patients over their remaining lifetime (56). In men, the incremental cost-effectiveness ratio of CAC was superior, with $48,800 per quality-adjusted life-years gained. In women, implementing current guidelines was more effective compared with CAC, with a lower cost per additional quality-adjusted life-year of $33,072 versus $35,869.

The most recent analysis integrated statin costs and disutility (preference of patients not to take statins) using MESA risk estimates and CAC distribution in intermediate-risk patients (57). In 55-year-old patients with a 7.5% 10-year FRS, $1 per statin pill price and a disutility equivalent to 2 weeks of perfect health traded away to avoid 10 years on statins, treating only those with a CAC score >0 yielded costs per quality-adjusted life-year of $18,000 and $19,000 for women and men, respectively, compared with $78,000 and $80,000, respectively, for a treat-all plan.

CAC PROGRESSION AND SERIAL SCANNING

THE DATA. All outcome studies have supported the conclusion that calcified plaque progression is significantly and independently associated with a worse prognosis (**Table 6**). In 813 asymptomatic patients, 45 myocardial infarctions occurred in a mean follow-up of 2.1 years. CAC progression was 47% for those with an event compared with 26% for those without an event ($p < 0.01$) (58). In a population of 495 asymptomatic patients on statin therapy, there were 41 myocardial infarctions over a mean period of 3.2 years (59). Patients with and without events had virtually identical achieved low-density lipoprotein cholesterol (118 vs. 120 mg/dl). However, the annual CAC progression was much greater in the event group (42% vs. 17%; $p = 0.0001$), and the relative risk for progressors (defined as >15% annual increase) compared with nonprogressors was 17.2. Moreover, in nonprogressors, the very low risk was the same for every baseline CAC category, whereas in progressors, the risk increased directly with the baseline score (**Figure 5**). The flat survival curves associated with the lack of progression imply successful stabilization of

TABLE 6 Major CAC Progression Studies

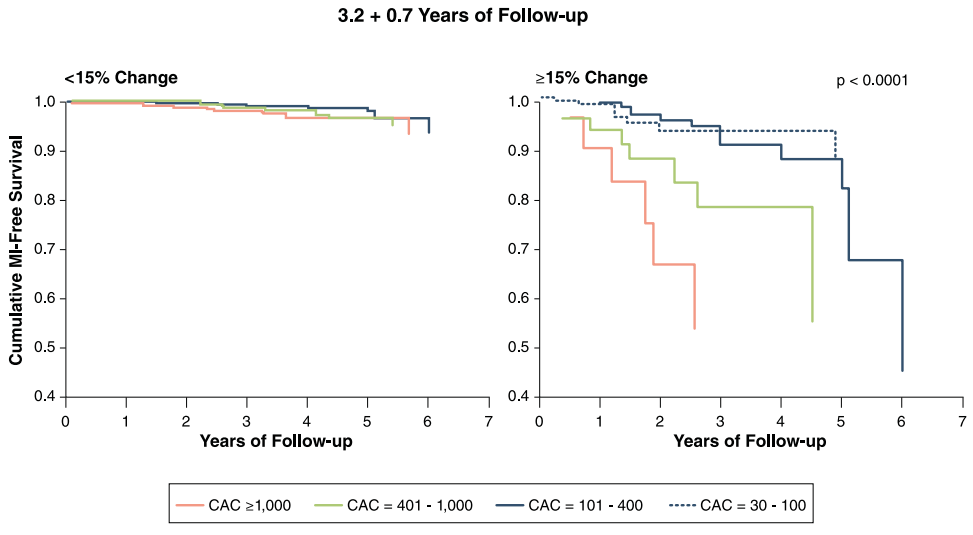
First Author (Ref. #)	N	Follow-Up, yrs	Progression	Progression HR
Raggi et al. (58)	813	2.1	Event: 47% No event: 26% $p < 0.01$	
Raggi et al. (59)	495	3.2	Event: 42% No event: 17% $p < 0.0001$	>15% vs. <15%: 17.2
Budoff et al. (60)	4,609	3.1		>15% vs. <15%: 2.98 $p < 0.0001$
Budoff et al. (61)	6,778	7.6	CAC 0 baseline CAC >0 baseline	>5 AU/yr vs. <5 AU/yr: 1.4 >100 AU/yr: 1.2 >300 AU/yr: 3.8 5%–14%/yr: 1.1 15%–29%/yr: 1.6 >30%/yr: 1.5
Wong et al. (62)	5,662	4.9	Third progression tertile Events/1,000 person-yrs DM + MetS: 30.7 MetS w/o DM: 26.4 Neither: 17.7	Third tertile vs. no progression 8.5 4.1
Kiramijyan et al. (63)	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

AU = Agatston units; MetS = metabolic syndrome; w/o = without; other abbreviations as in Table 4.

the atherosclerotic process. CAC progression >15%/year was associated with a HR of 2.98 ($p < 0.0001$) for all-cause mortality in 4,609 primary prevention patients followed for 3.1 years (60).

In 6,778 MESA subjects followed for 7.6 years for all CHD events, patients with 0 baseline scores and increases in CAC score >5 Agatston units (AU) per year had a 1.4 HR (61). In those with >0 baseline

FIGURE 5 Progression of CAC and Risk of First MI in 495 Asymptomatic Patients Receiving Cholesterol-Lowering Therapy



(Left) CAC progression of <15% per year is associated with a benign prognosis irrespective of the baseline CAC, implying stabilization of the atherosclerotic process. **(Right)** CAC progression of >15% per year is associated with a poor prognosis directly related to the baseline CAC, implying new plaque formation and inadequacy of treatment. CAC = coronary artery calcium; MI = myocardial infarction. Reprinted with permission from Raggi et al. (59).

scores, HRs of 1.2 and 3.8 were associated with >100 AU per year and >300 AU per year increases, respectively; annual increases of 5% to 14%, 15% to 29%, and ≥30% had HRs of 1.1, 1.6, and 1.5, respectively, compared with <5%. Of particular interest was the greater CAC progression in those taking statins, which has been interpreted as benign conversion of pre-existing noncalcified to calcified plaque by the drug. However, the greater progression in patients with events while on statin therapy negates this theory, supports the predominant formation of new plaque that then becomes calcified, and implies a therapeutic failure of statins to sufficiently halt the atherosclerotic process.

Data in diabetics emphasize their poor prognosis with CAC progression. In 5,662 MESA patients followed for 4.9 years, the HR for the second and third tertiles of progression compared with those without progression were 2.3 and 4.1, respectively, for those with metabolic syndrome without diabetes, and 4.1 and 8.5, respectively, with both metabolic syndrome and diabetes (62). In 296 asymptomatic patients with diabetes and 300 matched nondiabetic control subjects, >30% progression was associated with a 56 ± 11-month event-free survival rate of 79.6% compared with 90.6% for nondiabetic control subjects (63).

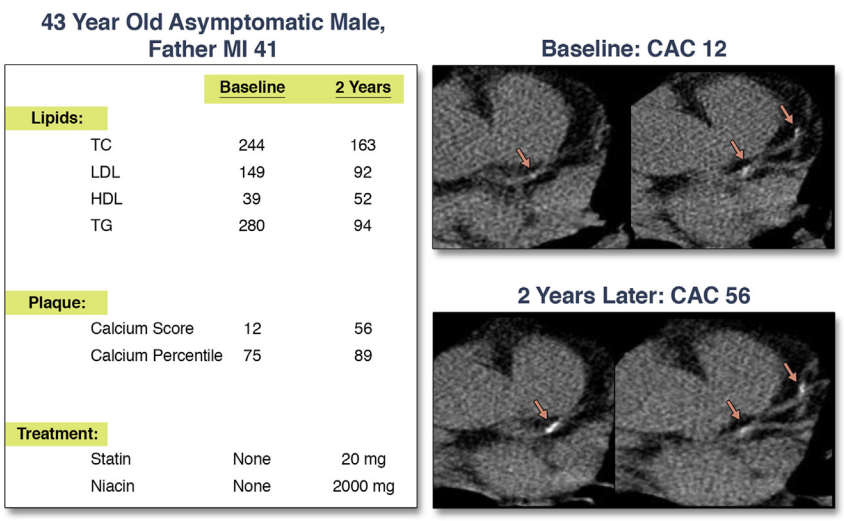
CLINICAL RELEVANCE. After the initial CAC scan, repeat scanning may be used to determine the response to treatment and evaluate residual risk; a significant increase in plaque burden defines treatment failure. Without tracking subclinical atherosclerosis, the only method for assessing residual risk is the unfortunate occurrence of an event or the development of symptoms. The ability to identify treatment nonresponders by excessive increases in CAC offers the opportunity to intervene with more aggressive treatment and possibly affect outcomes.

It must be emphasized that there are neither guideline-supported serial scan recommendations nor outcome studies documenting its efficacy. Nonetheless, when confronted with the clinical problem of assessing treatment response and residual risk in asymptomatic patients, serial scanning deserves consideration.

Inadequate treatment is demonstrated in Figure 6, with excessive progression of CAC despite dramatic improvement in lipid values.

REPEAT SCAN INTERVAL. Asymptomatic patients with a CAC score of 0 need not undergo repeat scanning for at least 4 years. In 422 patients, 66.4% of whom were on statin therapy with a baseline CAC score of 0, annual CAC scanning for 5 consecutive years or until scan conversion yielded 25.1%, CAC developed in a nonlinear fashion during follow-up, at a mean time to conversion of 4.1 ± 0.9 years (64). Conversion from a CAC score of 0 to a CAC score >0 occurred in 2 (0.5%), 5 (1.2%), 24 (5.7%), 26 (6.2%),

FIGURE 6 Progression of CAC Demonstrating Inadequate Treatment



CAC score increased from 12 to 56 over the course of 2 years of intensive lipid-lowering therapy, despite normalization of lipid values. Reprinted with permission from Hecht and Narula (12). TC = total cholesterol; TG = triglycerides; other abbreviations as in Figures 2 and 5.

and 49 (11.6%) in years 1, 2, 3, 4, and 5, respectively. Time to conversion was not related to any risk factor, and the CAC Agatston score on conversion was 19 ± 19.

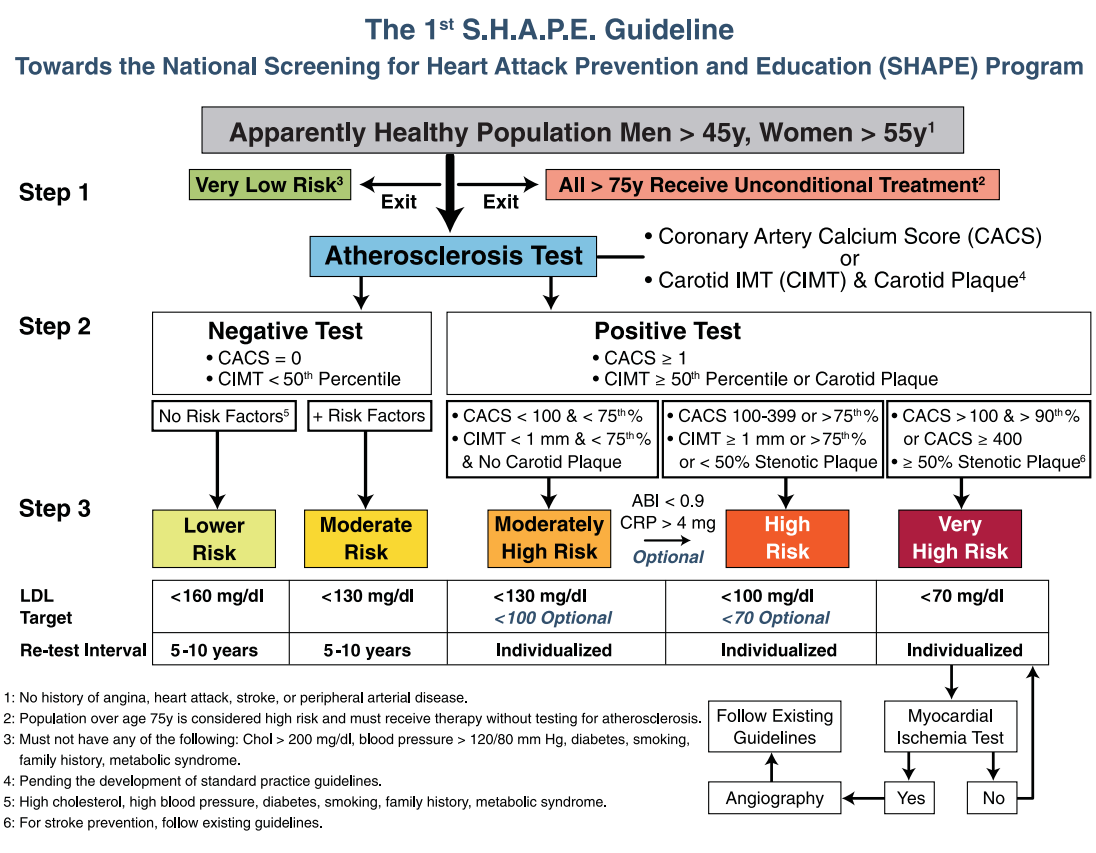
There are no data regarding the optimal time for repeat scanning in patients with a CAC score >0. Rather, logic dictates that the greater the concern, the shorter should be the interval. The low radiation dose makes repeat scanning less problematic.

CAC AND CLINICAL PRACTICE GUIDELINES

OLDER GUIDELINES. The Screening for Heart Attack Prevention and Education (SHAPE) recommendation was the first CAC-based paradigm and was met with great controversy (65) (**Figure 7**). CAC assessment was incorporated into the 2010 ACC/AHA Risk Assessment Guideline with a Class IIa status (recommendation in favor of treatment or procedure being useful/effective). Measurement of CAC was considered reasonable for risk assessment in asymptomatic adults at intermediate risk, and all diabetic patients 40 years of age or older (38). The 2009 CAC Appropriate Use Criteria deemed CAC appropriate for intermediate-risk patients as well as for low-risk individuals with a family history of premature disease (43). In 2012, the European Society of Cardiology awarded a similar Class IIa recommendation and suggested CAC for cardiovascular risk assessment in asymptomatic adults at moderate risk (66).

2013 GUIDELINES. The 2013 ACC/AHA Cholesterol Guideline (67) and the 2013 ACC/AHA Risk Guideline (68) created an entirely risk factor-based pooled cohort equation untested by randomized clinical trials, using the same risk factors as the 2010 version but with different weightings, now modified by race. Despite the plethora of positive CAC data published

FIGURE 7 The Screening for Heart Attack Prevention and Education (SHAPE) Guidelines



The SHAPE Guideline of 2006 was the first to recommend treatment in primary prevention based primarily on subclinical atherosclerosis as defined by coronary artery calcium and carotid intima medial thickening, rather than on risk factors. ABI = ankle-brachial index; CRP = C-reactive protein; LDL = low-density lipoprotein. Reprinted with permission from Naghavi et al. (65).

since 2010, they downgraded CAC to a Class IIb recommendation for whom only those few patients not in their 4 primary risk categories will be eligible. In addition to unwarranted radiation and cost assumptions, the primary stated reason was the change in endpoints to include stroke, for which there was perceived to be inadequate CAC outcome data. The 2013 guidelines (68) noted that the Class IIb recommendation is consistent with the recommendations in the 2010 ACCF/AHA guideline for patients with a 10-year CHD risk of <10%. However, it is entirely inconsistent with the Class IIa 2010 guideline recommendation for the 10% to 20% group (38), which is now excluded from CAC evaluation because they will all receive statins according to the new recommendations. It is precisely this very large group for which the NRI of the FRS by CAC in 3 major population-based prospective outcome studies has ranged from 52% to 66% (**Table 3**). Moreover, several analyses, on the basis of outcomes in more recent trials than were used to create the pooled cohort equation, have demonstrated that the 2013 guidelines grossly overestimate the number of patients who should be treated by statins (69,70). Application of the 2013 guidelines to 4,967 MESA patients followed for 10.3 years confirms overtreatment fears (55). The guideline would have classified 2,249 (49%) as moderate-high intensity statin candidates, but 41% had a CAC score of 0 with only 5.2 hard events per 1,000 person-years, compared with only 21% with a CAC score >100 and 15.2 events per 1,000 patient-years. Of the 610 candidates for moderate-intensity statin treatment, 57% had a CAC score of 0 with 1.5 events per 1,000 patient-years. Thus, almost 50% of the patients designated for statin treatment had low event rates for which there are no data supporting statin treatment. Undertreatment was noted as well; 5% of those who would not be considered for statin therapy had a CAC score >100 and 8.7 events per 1,000 patient-years.

Of critical importance is the emphasis on the use of CAC to determine appropriate treatment and aid decision making in the individual patient rather than for population screening for which the requisite outcome data are still lacking. The NRI data clearly demonstrate the ability of the CAC score to personalize treatment rather than extrapolating from easily calculated global risk factor-based equations derived from large population studies to the individual. Consequently, the 2010 guideline, rather than the 2013 guidelines, should be used for patients at intermediate risk (10% to 20% FRS) to determine the need for statin treatment (71). With an NRI of ~33%, use for high-risk patients may be reasonable as well (**Table 3**). The MESA NRI of 54.4% for the 6% to 20% FRS group included low- to intermediate-risk patients (6% to 10%), but specific numbers for this group were not presented. However, as previously noted, the number needed to scan to uncover a high-risk patient with a CAC score >300 in the 7.5% to 10.0% FRS group in the MESA was only 7 (52), which may make it reasonable to use for these patients as well, although further confirmation is needed.

As discussed in the following, the absence of randomized, controlled trials (RCTs) for CAC remains a critical issue. However, because neither CAC nor the risk factor-based pooled cohort equation have been validated by RCTs it would seem logical to favor the one with the greater prognostic power.

CAC LIMITATIONS

OUTCOME STUDIES. There are no outcome randomized trials demonstrating clinical benefit. The absence of such trials for the risk factor-based paradigms as well does not mitigate their need for CAC. Unfortunately, the very low event rates in the asymptomatic population greatly inflate the cost and duration of a CAC RCT sufficiently powered to provide robust answers. In addition, the ethical complexity of design needed to reconcile randomization of patients in all risk groups to treatment versus no treatment at all levels of CAC may be daunting. Nonetheless, the importance of such a trial cannot be overemphasized, and the National Institutes of Health must undertake this effort, without which approval by the U.S. Preventive Services Task Force will not occur. Screening for breast, colon, and lung cancer and abdominal aortic aneurysm was implemented only after their RCTs demonstrated improved outcomes (72–75) and Congress, through the Center for Medicare and Medicaid Services, legislated their availability. Ironically, more expensive care of sick patients manifesting the end stages of their disease states does not require legislative approval and is guided for coverage with evidence development decisions. It has a far easier path to Center for Medicare and Medicaid Services approval and private sector insurance coverage than screening tests, which could have prevented their deadly and costly sequelae. Although the CAC cost has declined to the $100 range, it is still prohibitive for low-income populations who will, therefore, not benefit unless insurance coverage is mandated.

Several studies have used changes in the FRS to evaluate the influence of CAC on risk factor modification, with varying results (50,76). The effect of statin treatment on outcomes in a high-risk CAC

group was evaluated in the St. Francis Heart Study randomized clinical trial of atorvastatin and vitamins C and E versus placebo (77). In 1,005 asymptomatic subjects with CAC >80th percentile, there was exploratory evidence of a reduction in events after 4.3 years of follow-up in the subgroup of participants with a baseline CAC score >400 (15.0% vs. 8.7%; p = 0.046). However, importantly, this was not a prespecified analysis.

INCIDENTALOMAS. The discovery of incidentalomas and their subsequent evaluation have generated negative responses. The frequency of clinically significant findings is 1.2%, with indeterminate findings in 7.0%. The associated costs do not have a negative impact on the cost-effectiveness of CAC (78). Standard guidelines on how to handle these findings may reassure patients and physicians (46).

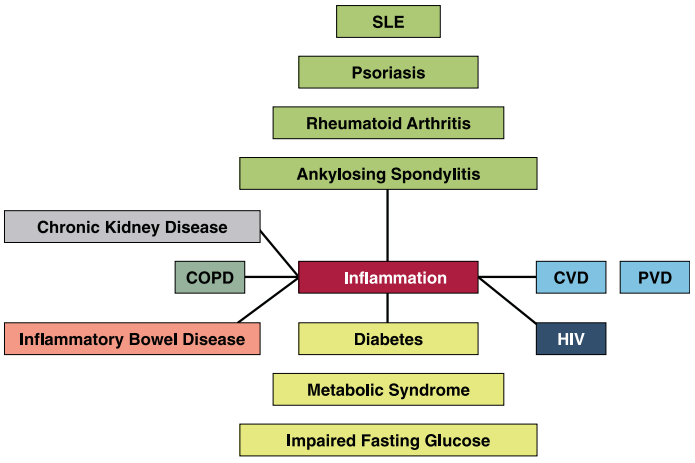
ANXIETY. Patient concern related to CAC findings has also been cited as a harm. Anxiety is not an intended consequence, but a certain amount is appropriate and inevitable when informed of increased cardiac risk and may motivate increased adherence. However, for those with high anxiety related to FH or a high calculated risk score, concern can often be calmed if reclassified to significantly less risk by CAC.

FUTURE DIRECTIONS

INFLAMMATORY DISEASES. Inflammation as the common pathway of atherosclerosis is one of the tenets of cardiovascular disease. Nonetheless, the focus of early identification of risk by CAC scanning has been on intermediate-risk patients irrespective of associated disease states. It is now clearly understood that cardiovascular risk is high and is often the leading cause of death in a broad spectrum of diseases with the common link of inflammation (**Figure 8**); they have been evaluated to varying degrees by CAC. There is now sufficient evidence to warrant formal evaluation of CAC scanning for patients with the inflammatory diseases shown in **Figure 8** who may not otherwise be in the intermediate-risk category, particularly younger patients with renal (79), rheumatological (80), and autoimmune disorders (81), as well as those with human immunodeficiency virus (82).

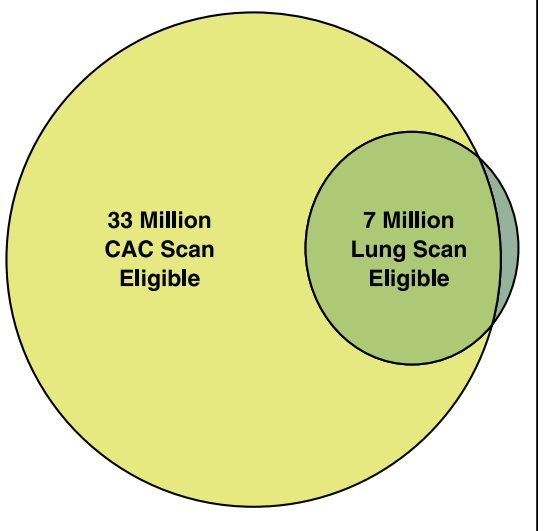
COMBINED HEART AND LUNG SCAN. The 2014 U.S. Preventive Services Task Force endorsed low-dose lung CT scanning for cancer detection (83), followed

FIGURE 8 Inflammatory Diseases Associated With a Higher Risk of Coronary Artery Disease



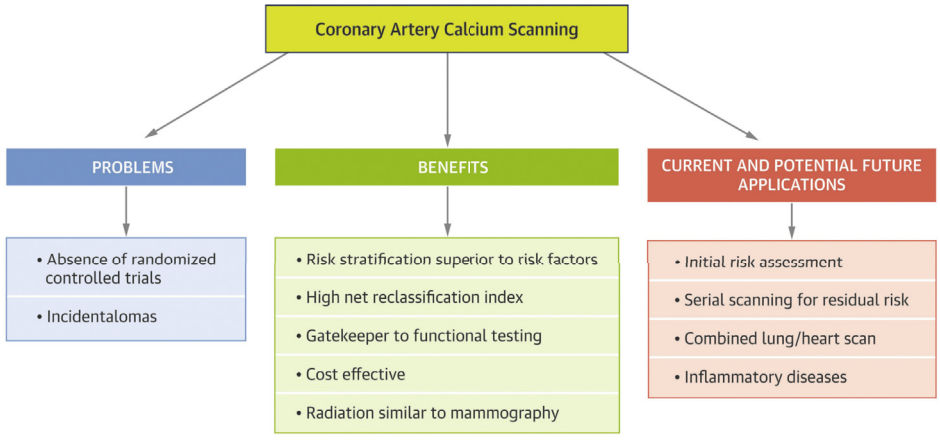
High cardiovascular risk is associated with a broad spectrum of diseases characterized by inflammation, and coronary disease is often their leading cause of death. Many patients would not be stratified appropriately by standard risk-factor-based paradigms and are candidates for coronary artery calcium scanning. COPD = chronic obstructive pulmonary disease; CVD = cardiovascular disease; HIV = human immunodeficiency virus; PVD = peripheral vascular disease; SLE = systemic lupus erythematosus. Reprinted with permission from Hecht and Narula (12).

FIGURE 9 U.S. Estimates and Overlap of CAC- and Lung Scan–Eligible Patients



The number of eligible patients in the United States is estimated at 33 million for coronary artery calcium (CAC) scanning and 7 million for lung scanning. Excluding lung scan–eligible patients who have established coronary disease (5.3%, unpublished data from the International Early Lung and Cardiac Action Program database) yields an overlap of 6.6 million lung scan–eligible patients who would be expected to benefit from CAC scanning. Reprinted with permission from Hecht et al. (86).

CENTRAL ILLUSTRATION **Problems, Benefits, and Current and Future Applications of Coronary Artery Calcium Scanning**



Hecht, H.S. J Am Coll Cardiol Img. 2015; 8(5):579–96.

Coronary artery calcium scanning has numerous benefits and current and future potential applications that support its widespread use. There are few problems, most notably the absence of randomized clinical trials.

by the 2014 Center for Medicare and Medicaid Services decision to provide coverage for lung scans in a defined high-risk population (84). There will be an estimated 6.6 million lung scan–eligible patients, almost all of whom will be at intermediate or high risk of CAD, who will have scans analyzable for CAC (85) (**Figure 9**). Lung CT scanning is routinely performed without electrocardiography gating, whereas CAC scanning uses gating to minimize motion artifact. Although CAC is apparent on nongated chest CT screening and several analytic approaches have been used to obtain Agatston scores, they are less than ideal. Fortunately, electrocardiography gating can be implemented without an increase in radiation, and CAC scoring on all chest CT scans has been recommended (86).

ENVIRONMENTAL. Second-hand tobacco smoke (87) and traffic associated particulate matter exposure (88) have been associated with increased CAD risk and increased CAC. The ability to identify patients adversely affected by other environmental and work-related pollutants will be an area of interest.

DOSE REDUCTION. As discussed previously, radiation has already been significantly reduced by the combination of reducing current (milliamperes) and increasing the signal-to-noise ratio using new reconstruction algorithms. It is likely that reducing the voltage to 100 kVp will be implemented after suitable validation, with an expected further 40% decrease in radiation exposure.

CONCLUSIONS

Despite the remarkable mass of robust data supporting the prime role of CAC in risk assessment of the intermediate-risk population as well as several large subgroups, with the concept of atherosclerosis itself being a more potent predictor of CAD than risk factors for atherosclerosis having been validated in every study, CAC has not been incorporated into the mainstream of clinical cardiology and has been downgraded in the 2013 guidelines. The paucity of insurance coverage, lack of physician education, greatly exaggerated radiation fears, concerns about downstream testing, and the resistance to paradigm changes, as well as criticism of the lack of randomized, controlled outcome studies, contribute to the lack of acceptance. As the data continue to accumulate with follow-up periods up to 15 years, accompanied by increasing public and physician awareness, the importance of CAC will be more universally accepted (**Central Illustration**).

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