Coronary Artery Calcification

Kazuhiro Osawa, Rine Nakanishi, Matthew Budoff
Los Angeles, CA, USA

ABSTRACT

Coronary artery calcification (CAC) is an established marker of subclinical atherosclerosis and an independent predictor of future coronary heart disease in the asymptomatic primary prevention population, particularly in the intermediate risk cohort. CAC also helps in reclassifying those patients and their risk of cardiovascular events into higher or lower risk categories. MESA (Multi-Ethnic Study of Atherosclerosis) is a National Heart, Lung, and Blood Institute—sponsored population-based medical research study involving 6,814 men and women from 6 U.S. communities without a medical history of clinical cardiovascular disease. The evidence from this population cohort revealed that CAC scoring was independently predictive and highly effective at risk stratification of major adverse cardiac events. This review provides available data based on MESA. We focus on the utility of CAC for cardiovascular disease risk stratification of individuals, and we describe its diagnostic value in identifying patients at risk.

Coronary artery calcification (CAC) scanning provides a distinct means of measuring atherosclerosis and is an established predictor for adverse cardiovascular events [1,2]. CAC can form in the advanced phase of atherosclerosis and reflects a linear estimate of the overall plaque burden of coronary artery atherosclerosis. The presence of a greater CAC score is associated with a higher risk of adverse cardiovascular events and all-cause mortality [3—5]; thus, guidelines suggest patients with an excessively high CAC score should be treated as high-risk patients. MESA (Multi-Ethnic Study of Atherosclerosis) is a National Heart, Lung, and Blood Institute—sponsored population-based medical research study involving 6,814 men and women without medical history of clinical cardiovascular disease (CVD) from 6 U.S. communities including Baltimore, Maryland; Chicago, Illinois; Forsyth, North Carolina; Los Angeles, California; New York, New York; and St. Paul, Minnesota. The purpose of MESA is to investigate the correlations between risk factors including CAC and progression of subclinical CVD using cardiac computed tomography. One cardinal question was whether the CAC score could improve risk prediction beyond the traditional risk factors in an asymptomatic population of the same age, sex, and ethnicity. It is important for clinicians to understand the diagnostic value of the CAC score and its implications for long-term prognosis in asymptomatic individuals. In this review, we describe the available data supporting the application of CAC.

WHICH SUBPOPULATIONS HAVE MORE CAC?

Bild et al. [6] clearly defined the distribution of CAC score among a wide range of patients by age, sex, or race/ethnicity and defined their normal values of CAC. They revealed that the relative risks for having CAC compared with Caucasians was 0.78 in African Americans (95% confidence interval [CI]: 0.74 to 0.82), 0.85 in Hispanics (95% CI: 0.80 to 0.91), and 0.92 in Chinese (95% CI: 0.85 to 0.995) [6]. McClelland et al. [7] then reported that men had a much greater CAC scores than did women of the same age and, moreover, increasing age showed positive correlation with CAC. Among the different race/ethnic subgroups studied in MESA (Chinese, Hispanics, Caucasians, and African Americans), the CAC score was highest in Caucasian and Hispanic men, with African Americans having significantly lower prevalence and severity of CAC. Similarly, Caucasian and Hispanic women had the highest CAC score [7]. Incidence and progression of CAC strongly correlated with traditional atherosclerotic factors such as age, sex, race, body mass index, history of hypertension, diabetes, and family history of heart attack [8—13]. DeFilippis et al. [14] reported both a higher Framingham risk score (FRS) calculated with age, sex, blood pressure, total cholesterol, high-density cholesterol, and smoking history, and a higher Reynolds risk score, which could be calculated as FRS plus high-sensitivity C-reactive protein (hs-CRP) levels and parental history, could predict the incidence and progression of CAC. Furthermore, Ahmed et al. [15] reported an interesting relationship between lifestyle and CAC score from the MESA population. Diet, body mass index, smoking status, and physical activity levels determine the lifestyle score, which is positively correlated with CAC and mortality [15].

THE UTILITY OF CAC FOR PREDICTING CHD/CVD EVENTS

All adults without known CVD should undergo an office-based assessment to identify those at higher risk for coronary events using quantitative risk predictive estimate systems, such as the FRS or the new American College of Cardiology/American Heart Association (ACC/AHA) Pooled Risk Calculator. FRS is a traditional risk

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From the Los Angeles Biomedical Research Institute at Harbor, University of California-Los Angeles, Los Angeles, CA, USA. Correspondence: M. Budoff (mbudoff@labiomed.org).

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stratification of CVD and could predict the 10-year cardiovascular risk of an individual and categorize risk for developing CVD into low (10-year risk of <10%), intermediate (10-year risk of 10% to 20%), and high (10-year risk of >20%) risk [16]. Although the FRS is widely used as the primary CVD risk assessment, it has some limitations. The FRS could predict, only modestly, coronary heart disease (CHD) events with a C-statistic value of approximately 0.70 [17,18] and could not classify younger populations nor women as precisely as high-risk cohorts could, despite substantial risk factor burden [19–21]. Thus, additional tests of cardiovascular risk such as CAC scoring have been evaluated as possible ways to improve global CHD risk assessment.

The CAC score itself is a strong predictor of CHD and CVD events. Budoff et al. [22] reported the clinical importance of a CAC score of 0. MESA participants with a CAC score of 1 to 10 experienced CHD events with a hazard ratio (HR) of 3.66 compared with those with a CAC score of 0 after adjusting for age, sex, race, and CHD risk factors [22]. A CAC score of 0 is considered a stronger negative risk predictor for all CHD/CVD events among negative atherosclerotic risk markers such as carotid intima-media thickness <25th percentile, absence of carotid plaque, brachial flow-mediated dilation >5% change, ankle-brachial index >0.9 and <1.3, hs-CRP <2 mg/l, homocysteine <10 μmol/l, N-terminal pro-brain natriuretic peptide <100 pg/m, no microalbuminuria, no family history of CHD, absence of metabolic syndrome, and healthy lifestyle [23]. Thus, asymptomatic populations with a CAC score of 0 could be considered to have very low risk of CHD. Among 1,850 MESA participants with a CAC score of 0 as a baseline, those with a persistent CAC score of 0 were significantly more likely to be younger, female, and have fewer traditional risk factors; however, there was no single risk factor or specific low-risk phenotype [24]. A CAC score of 0 may be predominantly influenced by the long-term maintenance of low-risk factors of CVD or genetic factors rather than the absence of any specific risk factors in late adulthood [24]. In contrast, populations with a great CAC burden and serial CAC progression have significant risk of CHD. Detrano et al. [5] reported that the adjusted risk of a coronary event increased by a factor of 7.73 among participants with a CAC score between 101 and 300, and by 9.67 among participants with a CAC score >300, compared with the participants with a CAC score of 0 (Figure 1). Moreover, Budoff et al. [25] reported the clinical importance of CAC progression for predicting future CHD events. Compared with participants with no increase in CAC score, any increase in CAC score was associated with greater risk for CHD events during the median 7.6-year follow-up. Among the participants with a CAC score of 0, CAC progression of 5 units per year was associated with an adjusted HR of 1.4 (95% CI: 1.0 to 1.9) for total CHD and an adjusted HR of 1.5 (95% CI: 1.1 to 2.1) for hard CHD. Among the participants with a CAC score >0, CAC progression of a 100-unit change per year was associated with an adjusted HR of 1.2 (95% CI: 1.1 to 1.4) for total CHD and an adjusted HR of 1.3 (95% CI: 1.1 to 1.5) for hard CHD [25]. Silverman et al. [26] reported CAC having a great impact on prognosis regardless of traditional risk factors including smoking, high low-density lipoprotein cholesterol, low high-density lipoprotein cholesterol, hypertension, and diabetes within 7.1 years' follow-up. Compared with individuals with >3 risk factors and a CAC score of 0, those with 0 risk factors and a CAC score >300 had 3.5× higher CHD event rates (3.1 per 1,000 person-years vs. 10.9 per 1,000 person-years) [26]. In terms of coronary artery stenosis, Rosen et al. [27] reported relationships between baseline extent of CAC and the severity of coronary stenosis using coronary angiography. The average CAC scores were 161.3 ± 268.2, 462.7 ± 608.5, 961.7 ± 986.9, 1351.4 ± 1180.1, and 658.3 ± 607.4 for patients without significant stenosis, 1-vessel disease, 2-vessel disease, 3-vessel disease, and left main trunk disease, respectively ($p < 0.001$) [27]. Furthermore, a closer

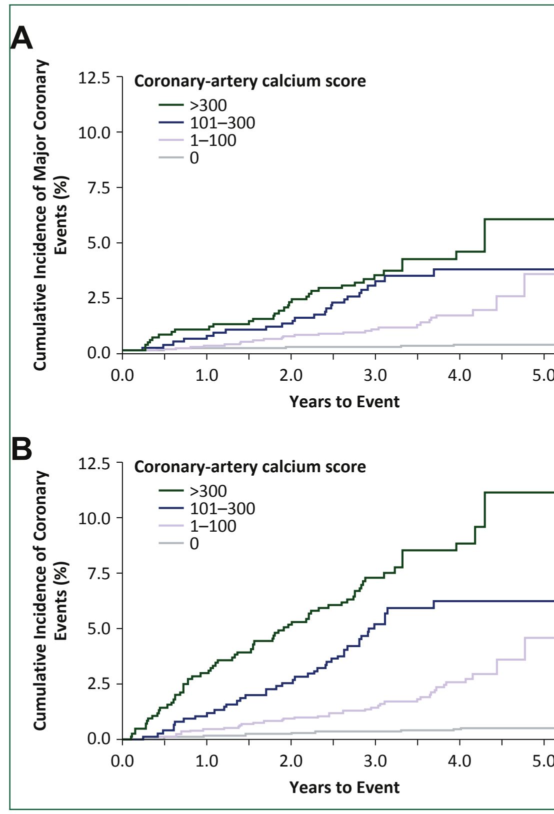

FIGURE 1. (A) Shows the rates for major coronary events (myocardial infarction and death from coronary heart disease), and (B) shows the rates for any coronary event. The differences among all curves are statistically significant ($p < 0.001$). Reprinted with permission from Detrano et al. [5], copyright Massachusetts Medical Society.

relationship was evident between CAC burden and the need for future revascularization. Within 8.5-year median follow-up, the revascularization rates per 1,000 per year for CAC scores of 1 to 100, 101 to 400, and >400 were 4.9, 11.7, and 25.4, respectively [28]. Blaha et al. [29] evaluated whether CAC may further stratify JUPITER (Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin)-eligible individuals (low-density lipoprotein cholesterol <130 mg/dl and hs-CRP ≥2.0 mg/dl) in MESA study participants during median 5.8-year follow-up. The presence of CAC was associated with a 4.29-fold increased risk of CHD (95% CI: 1.99 to 9.25) and a 2.57-fold increased risk of CVD (95% CI: 1.48 to 4.48), whereas hs-CRP was not associated with either CHD or CVD after multivariate adjustment [29].

Different CAC score cutoffs have been examined to distinguish the high-risk population in MESA. Currently, CAC scores of 1 to 100, 101 to 300, and >300 are the most common used cutoffs points for increasing CHD risk [5,30]. Moreover, some studies from MESA have revealed the significant association between CAC score and cerebrovascular diseases [31,32]. Gibson et al. [32] reported that CAC score was an independent risk factor of cerebrovascular disease and improves the ability of prediction for it by the Framingham stroke risk score. Log-transformed CAC score was associated with the increased risk for cerebrovascular disease after adjusting for traditional risk factors (HR: 1.13; 95% CI: 1.07 to 1.20; $p < 0.0001$) [32]. MESA has established that the CAC score itself is a strong risk marker for future cerebrovascular events.

THE UTILITY OF A CAC SCORE IN COMBINATION WITH OTHER RISK FACTORS

CAC score assessment in combination with the FRS is useful compared with just FRS (Table 1) [3,5,33–37]. Detrano et al. [5] reported the clinical value of CAC score in combination with the traditional risk factors. The areas under the curve (AUC) for receiver-operating characteristics analysis for the predictive value of major adverse coronary events and any coronary events increased from 0.79 to 0.83 ($p = 0.006$) and from 0.77 to 0.82 ($p < 0.001$), respectively [5]. Lakoski et al. [38] stated the significant role of CAC score in subsequent risk for CHD and CVD events among 3,601 asymptomatic women classified as low risk based on FRS in the MESA population. Compared with women with CAC score 0 in the low-risk category with FRS, those with a CAC score >0 in the low-risk category with FRS showed significant risk of CHD events (HR: 6.5; 95% CI: 2.6 to 16.4) and CVD events (HR: 5.2; 95% CI: 2.5 to 10.8) [38]. This result showed the possibility of a CAC score improving risk prediction obtained from FRS, especially in the female population, which was considered as a limitation. Polonsky et al. [3] also reported the clinical significance of the CAC score for risk stratification in addition to traditional risk factors in each category. Compared with factors alone, calculated by including models of FRS and race/ethnicity, the risk prediction of CHD events showed a significant improvement after including CAC scores (net reclassification improvement 0.25; 95% CI: 0.16 to 0.34; $p < 0.001$). The AUC analysis for the prediction of CHD events was 0.76 (95% CI: 0.72

TABLE 1. Area under the ROC curve for risk factors alone and risk factors alone plus CAC

First Author [Ref.]	N	Specific Subjects	Follow-up, yrs	Event	AUC for Risk Factors Alone	AUC for Risk Factors Plus CAC	p Value
Detrano et al. [5]	6,722		3.9	Major coronary event	0.79	0.83	0.006
				Any coronary event	0.77	0.82	<0.001
Polonsky et al. [3]	5,931	Nondiabetic	5.8	CHD event	0.76	0.81	<0.001
Gepner et al. [33]	6,779		9.5	CVD event	0.756	0.776	<0.001
				CHD event	0.752	0.784	<0.001
Yeboah et al. [34]	6,814		7.6	CHD event	0.623	0.784	<0.001
				CVD event	0.627	0.752	<0.001
Malik et al. [35]	6,603	Neither metabolic nor diabetic	6.4	CHD/CVD event	0.73	0.80	<0.001
		Metabolic		CHD/CVD event	0.73	0.79	<0.001
		Diabetic		CHD/CVD event	0.72	0.78	<0.001
Criqui et al. [36]	3,398	>0 CAC score at baseline	7.6	CHD event	0.668	0.696	0.02
				CVD event	0.669	0.688	0.02
Yeboah et al. [37]	5,185		10	ASCVD event	0.74	0.78	0.001

ASCVD, atherosclerosis cardiovascular disease; AUC, area under the curve; CAC, coronary artery calcification; CHD, coronary heart disease; CVD, cardiovascular disease; ROC, receiver-operating characteristic.

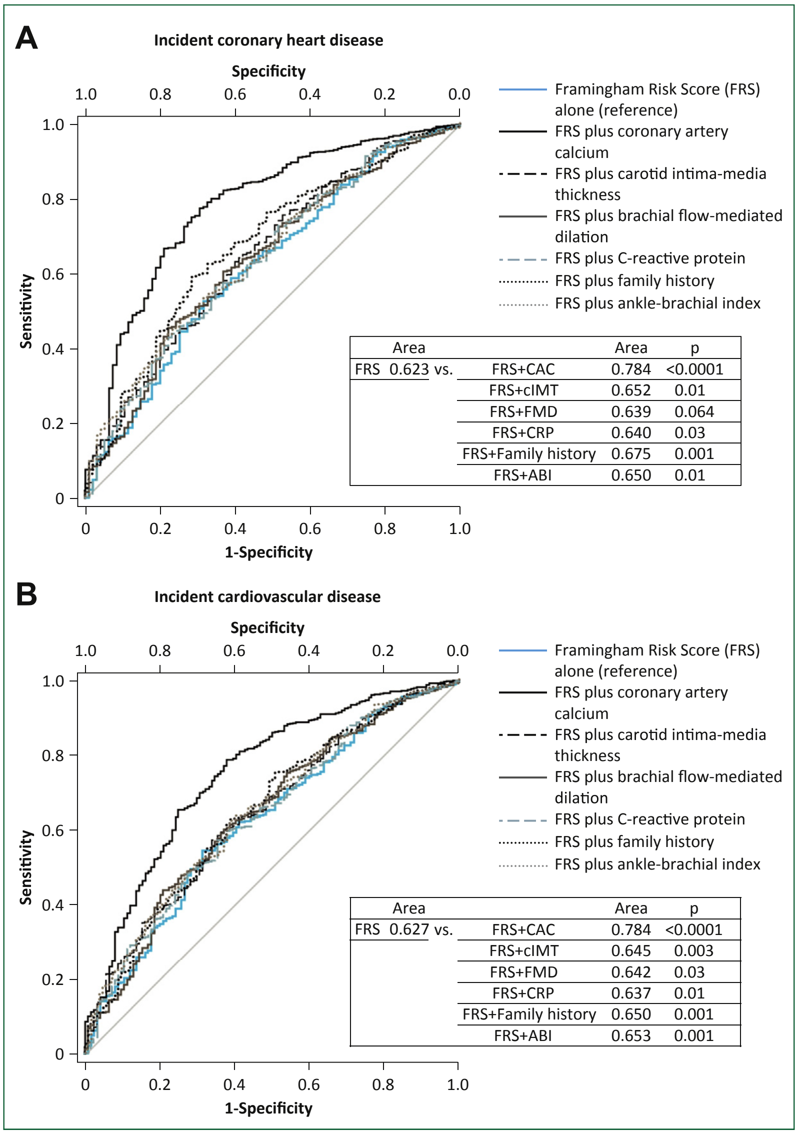

FIGURE 2. Receiver operator characteristic curves showing area under the curve for FRS alone versus FRS plus CAC, FRS plus IMT, FRS plus FMD, FRS plus CRP, FRS plus family history, and FRS plus ABI for incident coronary artery disease (A) and cardiovascular (B) in MESA intermediate-risk participants. ABI, ankle-brachial index; CAC, coronary artery calcification; cIMT, carotid intima-media thickness; CRP, high-sensitivity C-reactive protein; FMD, flow-mediated dilation; FRS, Framingham risk score; IMT, intima-media thickness; MESA, Multi-Ethnic Study of Atherosclerosis. Reprinted with permission from Yeboah et al. [34].

to 0.79) using only traditional risk factors, which increased to 0.81 (95% CI: 0.78 to 0.84) ($p < 0.001$) with the model after the addition to CAC score [3]. Pletcher et al. [39] reported CAC score could be used to improve the pre-test CHD risk estimate in each individual clinical scenario. The most interesting clinical scenario was the interpretation of the intermediate CAC score groups (1 to 100). In scenarios in which a high CAC score was expected, a moderately elevated CAC score of 1 to 100 was reassuring (reducing the risk from a pre-test CHD risk estimate of 10% to post-test risk estimate of 6% in a healthy older Caucasian man). However, when a low or 0 CAC score was expected, even with identical pre-test CHD risk, the same CAC score of 1 to 100 may be alarmingly high (increasing the risk from a pre-test CHD risk estimate of 10% to a post-test risk estimate of 20% in a middle-aged African American women with multiple risk factors) [39]. Moreover, a CAC score could have a superior diagnostic value for CHD and CVD compared with risk markers such as carotid intima-media thickness [33,40], brachial flow-mediated dilation, hs-CRP, a family history of CHD, and ankle-brachial index in a nondiabetic population with intermediate-risk MESA participants. The CAC score could highly improve the operating AUC for incident CHD after combining it with FRS and race/ethnicity among the 6 risk markers (Figure 2) [34]. CAC screening can also improve CHD and CVD risk stratification in diabetic individuals [35]. Malik et al. [35] reported that even when diabetes was present, if the CAC score was not significant, CHD or CVD event rates were as low as in those without diabetes: 0.1% of annual rate for CHD and 0.2% for CVD. They also showed a 10-fold variation in CHD event rates in those with diabetes or metabolic syndrome ranging from a CAC score of 0 to a CAC score >400. From AUC analysis, the CAC score addition to the adjusted models including traditional risk factors showed strong incremental predictive value for CHD compared with the adjusted models alone (0.78 vs. 0.72, $p < 0.0001$) in diabetic populations [35]. Martin et al. [41] reported the possibility of CAC in reclassification of population by the addition of a number of traditional lipid abnormalities including low-density lipoprotein cholesterol $\geq$130 mg/dl, high-density lipoprotein cholesterol <40 mg/dl for men or <50 mg/dl for women, and triglycerides $\geq$ 150 mg/dl. Participants with a CAC score >100 and no lipid abnormalities, showed higher event rates of CVD compared with the patients who had no CAC and 3 lipid abnormalities (22.7 vs. 5.9 per 1,000 people per year). Individuals without any lipid abnormalities by traditional definitions could be evaluated more accurately by adding a CAC score [41]. Recently, a report that focused on each component of the CAC score, including volume and density of CAC, was published [36]. Compared with base model containing the FRS, race/ethnicity, and statin use, adding the CAC volume score and CAC density score to this base model significantly improved the predictive ability of CHD in the AUC analyses from 0.668 to 0.771 ($p = 0.006$). Similarly, the AUC for CVD increased from 0.669 to 0.704 ($p < 0.001$). Furthermore, the CAC density score showed a significantly stronger predictive value compared with the CAC volume score for CHD and CVD [36]. The 2010 ACC/AHA guidelines have incorporated CAC for cardiovascular risk assessment in asymptomatic adults at intermediate risk (10% to 20% 10-year FRS risk: Class IIa indication), for people with diabetes (Class IIa indication) and at low-intermediate risk (6% to 10% 10-year FRS risk: Class IIb indication).

THE UTILITY OF CAC SCORE FOR PATIENT'S TREATMENT

In 2013, the ACC/AHA released the updated CVD prevention guidelines [42,43]. Of note, the 2013 guidelines changed the outcome (atherosclerosis cardiovascular disease [ASCVD]) to include stroke. Moreover, the guidelines moved away from the low-density lipoprotein cholesterol level and instead, recommended the use of a statin for individuals with a 10-year ASCVD risk >7.5%, which was lowered from the former threshold, and the numbers of eligible individuals for statin therapy increased greatly. With the new guidelines, many future ASCVD events could be decreased; however, it could lead to potential overestimation in patients with lower ASCVD risk [18,44,45]. DeFilippis et al. [18] showed the discriminative capability of the new 2013 guidelines in the 4,227 MESA participants. They revealed an overestimation of the new guidelines in cardiovascular events (predicted events 9.16% vs. observed events 5.16%) and 78% of discordance. Discordance between observed and expected risk was found throughout the risk continuum, including those at moderate risk [18]. It is easy to imagine that risk overestimation could lead to increased use of preventive medications such as statin therapy, potentially exposing some patients to the unnecessary risks of these drugs and resulting in increased health care costs. The CAC score could be suggested for evaluating individuals at intermediate risk when there is uncertainty about the role for lipid-lowering agents [37,45,46]. Nasir et al. [45] evaluated the utility of CAC score in reclassifying populations in ASCVD by each risk stratum in which statins were recommended according to the guidelines in 4,758 participants of the MESA population. According to these guidelines, 2,377 participants were recommended for moderate- to high-intensity statin therapy. However, 41% of the 2,377 participants had a CAC score of 0 with only 5.2 events per 1,000 people per year. Among 589 participants considered for moderate-intensity statin, 338 (57%) had a CAC score of 0, with an ASCVD event rate of only 1.5 per 1,000 people per year. From these results, almost 50% of the patients assigned statin treatment had low event rates and were actually low risk (<7.5% 10-year risk). Thus, a CAC score of 0 could reclassify approximately one-half of candidates as not eligible for statin therapy [45].

In contrast, in the 2013 ACC/AHA Guideline for Management of Blood Cholesterol [43], CAC scores of either ≥75th percentile for age and sex or ≥300 Agatston units were considered as high risk and warranted high-dose statins. Based on studies from MESA, a CAC score >100 was more predictive of events than was >75th percentile and achieved high cardiovascular risk, so we recommend use of a CAC score >100 as the cutpoint for aggressive statin therapy [30]. Kim et al. [47] reported significant risk reduction of atorvastatin in individuals with a CAC score >400. They demonstrated that atorvastatin reduced cardiovascular events by 42% in those with CAC score >400, with a needed-to-treat value of only 16 to reduce 1 myocardial infarction or death [47].

The CAC score can robustly identify individuals who could benefit from antiatherosclerotic therapies and also identify those who may not need any treatment.

SUMMARY

In this review, we described the usefulness of the CAC as the strongest predictor of incident coronary events and its ability to reevaluate risk from MESA. The prevalence and progression of CAC is different between race and ethnic categories and is associated with traditional atherosclerotic factors such as an advanced age, male sex, hypertension, dyslipidemia, diabetes, smoking status, adiposities such as body mass index, and family history of premature CHD. The CAC score itself is a reliable independent predictor of CHD compared with other traditional coronary artery risk factors including FRS components and could improve the operating AUC for incident CHD after combining it with traditional risk factors. A CAC score of 0 is a promising marker of very low risk of CHD. The most commonly used cutoff numbers of CAC for distinguishing the high-risk population of CHD are CAC score of 1 to 100, 101 to 300, and >300. Furthermore, the density of CAC obtained simultaneously with a CAC score could be a new risk predictive marker, and it shows a promising future of risk evaluation for CHD and CVD. CAC, in MESA, has been strongly associated with the development of stroke and combined endpoints of CHD/CVD. In MESA, the CAC score is able to reclassify low-to-intermediate risk groups and certain subgroups, especially women and young adults, most of whom may classify as low risk by FRS risk stratification. The clinical role of the CAC score has been solidified as a part of our 2013 cholesterol guidelines and is now under discussion as a universally covered service by the U.S. Preventive Services Task Force. The CAC score will likely play an increasingly important role in health care management.

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