Providing Evidence for Subclinical CVD in Risk Assessment

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ABSTRACT

When the MESA (Multi-Ethnic Study of Atherosclerosis) began, the Framingham risk score was the preferred tool for 10-year global coronary heart disease risk assessment; however, the Framingham risk score had limitations including derivation in a homogenous population lacking racial and ethnic diversity and exclusive reliance on traditional risk factors without consideration of most subclinical disease measures. MESA was designed to study the prognostic value of subclinical atherosclerosis and other risk markers in a multiethnic population. In a series of landmark publications, MESA demonstrated that measures of subclinical cardiovascular disease add significant prognostic value to the traditional Framingham risk variables. In head-to-head studies comparing these markers, MESA established that the coronary artery calcium score may be the single best predictor of coronary heart disease risk. Results from MESA have directly influenced recent prevention guidelines including the recommendations on risk assessment and cholesterol-lowering therapy. The MESA study has published its own risk score, which allows for the calculation of 10-year risk of coronary heart disease before and after knowledge of a coronary artery calcium score.

The Framingham Heart Study, the first major longitudinal cohort study of cardiovascular disease (CVD) in the United States, identified and described the major traditional risk factors for coronary heart disease (CHD): high cholesterol; high blood pressure; smoking; and diabetes [1,2]. Recognizing that these risk factors acted synergistically, Framingham investigators developed risk equations for the calculation of 10-year risk that became the basis for global risk assessment for over 25 years [3]. In 2001, the ATPIII (Third Adult Treatment Panel) of the National Cholesterol Education Program adopted a version of the 10-year Framingham risk score for CHD (FRS) in their guidelines, which solidified the role of global risk assessment in the decision to treat asymptomatic individuals free of known CHD with lipid-lowering therapy [4].

The MESA (Multi-Ethnic Study of Atherosclerosis), following the original Framingham cohort by approximately 50 years, began enrollment in an era when the traditional CHD risk factors were well known [5]. MESA was distinct in its aim to study the prevalence, burden, progression, and clinical significance of *subclinical* CVD (Figure 1). At the time MESA was conceived, it was not at all clear whether routine measurement of subclinical cardiac or vascular disease would add clinical value and predict risk beyond the FRS. Therefore, the initial objectives in MESA sought to investigate whether new risk markers, especially those representing subclinical atherosclerosis, added prognostic value when combined with the FRS or with the individual traditional risk factors [6].

It was reassuring that the traditional risk factors were not only associated with subclinical disease in MESA, but that they predicted the progression of subclinical disease. In a paper by Kronmal et al. [7] in 2007, MESA investigators demonstrated that age, male sex, white race/ethnicity, hypertension, body mass index, diabetes, and family history not only predicted incident coronary artery calcium (CAC) over 2.4 years of follow-up, but also the progression of existing CAC. These data were recently replicated over the 10-year follow-up [8]. Coupled with data demonstrating that subclinical disease predicts CHD events [9], MESA helped solidify subclinical disease as a true precursor lesion on the causal pathway between risk factors and hard events. Other MESA studies have established a wide range of more novel risk factors, ranging from air pollution to lifestyle variables to insulin resistance, as predictors of both subclinical disease progression and CHD events [10-14].

The FRS itself predicts CAC progression. In 2011, DeFilippis et al. [15] demonstrated a 40% higher risk of incident CAC per 5% higher absolute FRS risk, and a mean Agatston score of 7 increase per 5% higher FRS among those with existing CAC. However given concerns about possible limitations of the FRS [16], including lack of race and ethnic diversity in the derivation sample and the absence of certain newly identified risk factors, competing risk scores including the Reynolds risk score (RRS) were also studied. The 2008 RRS added family history and high-sensitivity C-reactive protein (hsCRP) to the risk algorithm along with the traditional Framingham risk factors [17].

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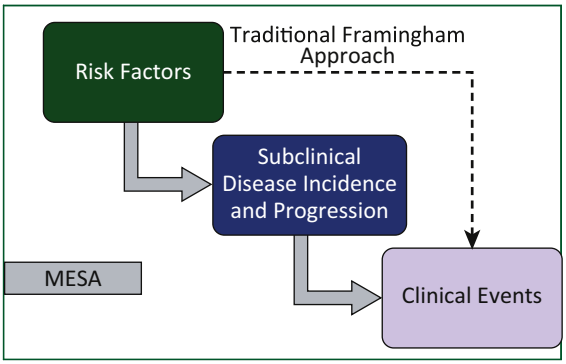

FIGURE 1. The design of MESA (Multi-Ethnic Study of Atherosclerosis) allows the study of the associations among risk factors, subclinical disease burden and progression, and clinical events.

The DeFilippis et al. [15] paper showed that when the FRS and RRS were discordant, the RRS better predicted CAC incidence and progression.

ADDING TO THE FRAMINGHAM RISK FACTORS

Many novel risk markers have been proposed to improve CHD risk prediction when added to the traditional Framingham risk factors. In MESA, these most prominently have included measures of subclinical CVD (CAC, carotid intima media thickness, carotid plaque, and ankle brachial index), vascular function (flow-mediated dilation), inflammation (especially hsCRP), and family history of CHD.

Coronary artery calcium

In the first landmark MESA paper, Detrano et al. [18] reported on the relationship between CAC and CHD events in the 4 race/ethnicity groups in MESA. Over a median follow-up of 4 years, CAC was associated with a graded increase in risk of both hard and all CHD events (Figure 2) [18]. In multivariable models controlling for the traditional risk factors, a CAC score of 1 to 100 was associated with a nearly 4-fold higher risk of hard events (95% confidence interval [CI]: 1.72 to 8.79), whereas a CAC score >300 was associated with a nearly 7-fold higher hard event risk (95% CI: 2.93 to 15.99) compared with those who had a CAC score of 0. Each doubling of CAC was associated with a 20% increased risk of events (95% CI: 1.12 to 1.29). Similar trends were noted for each of the 4 race/ethnic groups, and there was no interaction between CAC and race/ethnicity. In the overall population as well as for each racial/ethnic group, CAC improved discrimination for incident CHD. Overall, there was a significant increase in the C-statistic from 0.79 to 0.83 after addition of CAC to a model with only traditional risk factors [18].

To better understand the impact of CAC on CHD risk classification, Polonsky et al. [19] calculated the

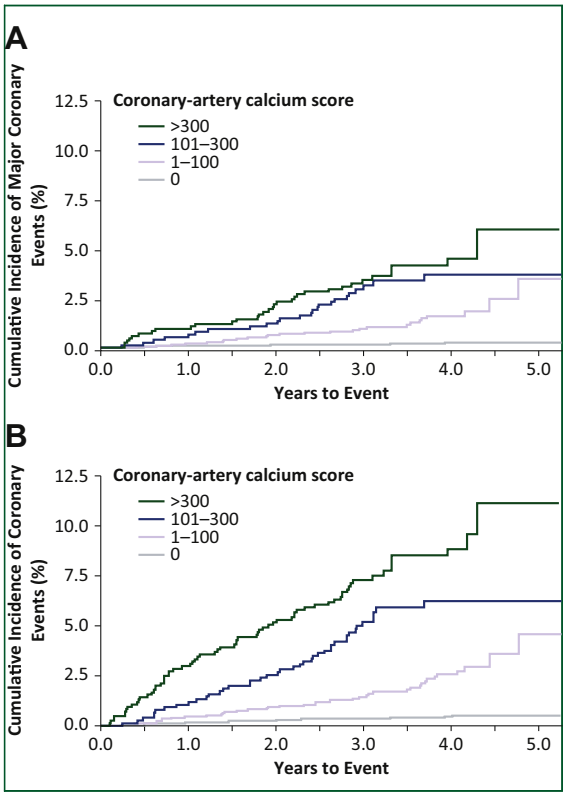

FIGURE 2. Unadjusted Kaplan-Meier cumulative-event curves for coronary events among participants with coronary artery calcium scores of 0, 1 to 100, 101 to 300, and >300. Reprinted with permission from Detrano et al. [18], copyright Massachusetts Medical Society.

net reclassification improvement (NRI) using models with traditional risk factors before and after addition of the CAC score. In an analytic sample of 5,878 individuals, the addition of CAC resulted in an overall NRI of 0.25 (95% CI: 0.16 to 0.34), whereby 728 individuals were reclassified to a higher risk category and 814 to a lower risk category. This translated to a higher proportion of individuals classified as either high or low risk (77% vs. 69%). Importantly, the addition of CAC to the model resulted in an additional 23% of participants who had events and an additional 13% of those who did not experience events to be classified as high or low risk, respectively [19]. Several other MESA papers have supported these general findings [20-25].

The legacy of MESA in the field of risk prediction has perhaps been most solidified by these results for CAC, driving the current shift in the risk assessment paradigm from a purely risk factor—based enterprise to a multifaceted approach including measurement of subclinical disease.

Carotid intima-media thickness and carotid plaque

While the strongest results have been observed for CAC, MESA has provided additional insight about other markers. Polak et al. [26] used baseline ultrasound measurements of the carotid arteries to study the association of different plaque indices (carotid intima-media thickness [cIMT] and carotid plaque stenosis) and incident CVD over a follow-up of 7.8 years. Each metric was significantly associated with CHD and CVD risk and modestly improved the area under the curve (AUC) when added to a baseline model with risk factors only. Only carotid plaque causing >25% narrowing at the carotid bulb was associated with a higher risk of stroke (hazard ratio [HR]: 1.60; 95% CI: 1.08 to 2.35), but this did not improve discrimination when compared with risk factors only. Importantly, different plaque metrics resulted in improved reclassification depending on the outcome of interest. For CHD, the NRI was small but significant for all metrics except for the maximum internal carotid artery IMT >1.5 mm, and the largest NRI was observed for mean of the maximum IMT. For CVD events, the NRI was significant only for the mean of the maximum internal carotid artery IMT, whereas NRI values were not significant for any metric for stroke [26].

Flow-mediated dilation

Yeboah et al. [27] assessed the predictive value of brachial flow-mediated dilation (FMD) for incident cardiovascular events over 5 years of follow-up. An increase in 1 SD of FMD was significantly associated with decreased CVD risk (HR: 0.80; 95% CI: 0.63 to 0.97) independent of the FRS. Similarly, FMD was inversely associated with incident CHD and CVD death in fully adjusted models. In race-stratified analyses, FMD was no longer significantly associated with incident CVD after full adjustment. Addition of FMD to the FRS did not improve overall global discrimination of incident CVD as measured by the C-statistic. However, FMD correctly reclassified 52% of participants with no incident CVD event but also incorrectly reclassified 23% of subjects who developed CVD; the overall NRI was 29% ($p < 0.001$) [27].

Ankle brachial index

Criqui et al. [28] evaluated the association of high and low ankle brachial index (ABI) with incident cardiovascular events over a mean follow-up of 5.3 years. Both high (ABI ≥1.4) and low (ABI <1) were associated with higher risk of CVD (HR: 1.82; 95% CI: 0.98 to 3.34, and HR: 1.78; 95% CI: 1.32 to 2.39, respectively) after adjusting for traditional risk factors. After additional adjustment for markers of inflammation, thrombosis, subclinical CVD, and kidney function, only low ABI remained a significant predictor of CVD (HR: 1.46; 95% CI: 1.06 to 2.00). In analyses of ABI as a continuous variable, excluding ABI ≥1.4, a 0.1-unit increment in ABI was associated with an 11% lower risk of CVD (95% CI: 0.81 to 0.97) after adjusting for traditional risk factors. Interaction testing between ABI and each of sex and race/ethnicity was not significant. Similarly, both low and high ABI were associated with CHD events independent of traditional risk factors (HR: 1.87 [$p = 0.001$] and 2.15 [$p = 0.029$], respectively). Results for stroke were not significant. Addition of ABI to traditional risk factors increased the C-statistic from 0.78 to 0.79 ($p = 0.022$) and the integrated discrimination improvement demonstrated a significant role for ABI for reclassification of events and nonevents ($p = 0.003$) [28].

Inflammation

Jenny et al. [29] examined the cross-sectional association between inflammatory markers and coronary atherosclerosis measured by presence of CAC. Compared with the lowest quartile of hsCRP, there was a 13% higher risk of CAC >0 in the highest quartile (95% CI: 1.06 to 1.19) in age, sex, and ethnicity adjusted models. For interleukin 6, the corresponding relative risk was 22% (95% CI: 1.15 to 1.30) and 18% (95% CI: 1.11 to 1.24) for fibrinogen. After adjustment for FRS variables, the relative risk estimates were attenuated and were as follows: 1.05 (95% CI: 0.99 to 1.12) for hsCRP, 1.12 (95% CI: 1.06 to 1.20) for interleukin 6, and 1.09 (95% CI: 1.02 to 1.16) for fibrinogen. Similar trends were noted in sex- and ethnicity-stratified analyses [29].

HsCRP is the most clinically accepted inflammatory biomarker and has been the subject of many important papers from MESA. For example, Yeboah et al. [30] demonstrated that hsCRP was mildly associated with incident CHD but not CVD over a median follow-up of 7.6 years in multivariable models that controlled for traditional risk factors (HR: 1.28; 95% CI: 1.00 to 1.64, and HR: 1.15; 95% CI: 0.92 to 1.45, respectively). Other studies suggested that the association of hsCRP with subclinical atherosclerosis was at least moderately attenuated by adjustment for obesity, and after stratification, there was a stronger association between obesity and cIMT as compared to hsCRP and cIMT [31].

Family history of coronary heart disease

Nasir et al. [32] examined the cross-sectional association of a family history (FH) of premature CHD with prevalence of CAC. After adjustment for the FRS, FH of premature CHD was associated with a 78% higher odds ratio (OR) of CAC >0 (95% CI: 1.48, 2 to 13). The corresponding OR for CAC ≥75th percentile was 2.00 (95% CI: 1.66 to 2.41). The association of FH of late-onset CHD and CAC was weaker than FH of premature CHD. In race/ethnicity-stratified analyses, FH of premature CHD was associated with a higher prevalence of CAC ≥75th percentile in both low and intermediate FRS categories. When considering the relationship to the affected family member, FH of premature CHD in a sibling had a stronger association with CAC >0 when

compared with a parent only, whereas FH in both parents and siblings had the strongest association (OR: 1.90; 95% CI: 1.49 to 2.40; OR: 1.48: 95% CI: 1.15 to 1.91; and OR: 3.23; 95% CI: 1.85 to 5.63, respectively). The association of CHD risk factors and CAC did not differ according to FH of premature CHD status [32]. Among individuals with a CAC score of 0, a positive FH of CHD portended a greater 10-year risk of CVD and CHD events when compared with those without a FH of CHD [33].

HEAD-TO-HEAD COMPARISONS OF NOVEL RISK MARKERS—A PRIMARY CONTRIBUTION OF MESA

MESA uniquely allowed head-to-head comparison of the strength of novel markers for a variety of outcomes.

Folsom et al. [34] compared CAC and cIMT for the prediction of cardiovascular events over approximately 5 years of follow-up. In multivariable models adjusted for traditional risk scores and both CAC and cIMT (modeled continuously), CAC was a stronger predictor of CVD and CHD than cIMT. The HR (95% CI) of CVD and CHD per standard deviation increase of CAC versus cIMT were (HR: 2.1; 95% CI 1.8 to 2.5 vs. HR: 1.3; 95% CI 1.1 to 1.4, and HR: 2.3; 95% CI: 1.9 to 2.8 vs. HR: 1.1; 95% CI: 1.0 to 1.3). Only cIMT was significantly associated with incident stroke (HR: 1.3; 95% CI: 1.1 to 1.7) whereas the HR (95% CI) for CAC was 1.1 (0.8 to 1.4). Similar results were obtained in analyses using categorical CAC and cIMT. In analyses of discrimination, CAC was better able to discriminate CVD events than cIMT was. Addition of CAC to traditional risk factors improved the C-statistic from 0.772 (95% CI: 0.74 to 0.80) to 0.808 (95% CI: 0.78 to 0.83), whereas addition of cIMT led to an increase to 0.782 (95% CI: 0.75 to 0.81). The C-statistic after including both cIMT and CAC was 0.811 (95% CI: 0.78 to 0.84). Similar trends were obtained for CHD such that addition of CAC to risk factors alone increased the C-statistic from 0.771 (95% CI: 0.74 to 0.80) to 0.823 (95% CI: 0.79 to 0.85), whereas addition of cIMT increased it to 0.782 (95% CI: 0.75 to 0.82). Similarly, addition of both cIMT and CAC had a similar effect on the C-statistic as did addition of CAC only (AUC: 0.824; 95% CI: 0.79 to 0.85) [34].

Gepner et al. [35] compared the predictive use of CAC, carotid plaque, and cIMT for incident CVD, CHD, and stroke/transient ischemic attack. CAC presence was the strongest predictor of CVD events after adjustment for traditional risk factors (HR: 3.12; 95% CI: 2.44 to 3.99). Presence of carotid plaque was also significantly associated with incident CVD (HR: 1.61; 95% CI: 1.17 to 2.21). Carotid plaque/cIMT $\geq$75th percentile was a better predictor of CVD than carotid plaque only was (HR: 2.06; 95% CI: 1.46 to 2.91). CAC presence was a stronger predictor of CHD events (HR: 4.48; 95% CI: 3.24 to 6.17) than CVD. CAC presence, carotid plaque presence, and carotid plaque/cIMT $\geq$75th percentile independently predicted stroke/transient ischemic attack (HR: 1.54; 95% CI: 1.09 to 2.18, HR: 1.40; 95% CI: 1.35 to 1.45, and HR: 1.86; 95% CI: 1.10 to 3.13, respectively). In analyses of discrimination of incident CVD, addition of CAC presence to traditional risk factors increased the C-statistic from 0.756 to 0.776 ($p < 0.001$). Addition of carotid plaque presence increased the C-statistic to 0.760 ($p = 0.033$), whereas cIMT $\geq$75th percentile, compared with traditional risk factors alone, did not have an effect on the C-statistic ($p = 0.110$). The improvement in discrimination for carotid plaque/cIMT $\geq$75th percentile was similar to carotid plaque alone. The results were similar for incident CHD. For combined stroke/transient ischemic attack, only the addition of carotid plaque led to a statistically significant improvement in the AUC (C-statistic = 0.787, $p = 0.045$). In reclassification analyses, only CAC presence resulted in a statistically significant improvement in NRI for CVD and CHD events [35].

Criqui et al. [28] studied the joint association of ABI and CAC with incident CVD by analyzing the relationship of ABI and CVD risk within strata of CAC. Among those with CAC = 0, incidence rates were low regardless of ABI group. In those with CAC >0, ABI was found to have a U-shaped association within CAC groups (1 to 100 and >100). In analyses using ABI as a continuous variable, ABI was inversely related to the CVD event rate among those with presence of CAC [28].

Blaha et al. [36] studied the prognostic significance of CAC in MESA participants who met the JUPITER (Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin) trial entry criteria (low-density lipoprotein cholesterol >130 mg/dl, and hsCRP $\geq$2 mg/l). Among those with CAC = 0, CHD and CVD event rates were low (0.8 and 3.7 events per 1,000 person-years, respectively), whereas event rates were high for CAC >100 (20.2 and 26.4 events per 1,000 person-years). Importantly, over a median follow-up of 5.8 years, hsCRP did not predict CHD (HR: 0.98; 95% CI: 0.62 to 1.57) or CVD events (HR: 1.15; 95% CI: 0.78 to 1.68) after adjusting for basic demographics. Presence of CAC, however, was significantly associated with both CHD (HR: 6.65; 95% CI: 2.99 to 14.78) and CVD (HR: 3.06; 95% CI: 1.82 to 5.13) in similarly adjusted models. CAC prevalence, and increasing CAC burden, remained significant predictors of events after full adjustment. This comparative effectiveness study helped conclude that CAC is a stronger predictor of CHD and CVD risk than hsCRP [36].

Yeboah et al. [30] compared novel risk markers in MESA participants who were at intermediate risk of CHD (FRS >5% to <20%) to determine which marker most improved risk prediction. All risk markers were associated with incident CHD; however, after adjusting for traditional risk factors, cIMT and FMD were no longer significant. Among the risk markers, CAC had the strongest association (HR: 2.60; 95% CI: 1.94 to 3.50). Similar results were obtained for CVD except that hsCRP was not significant in univariable analyses. Addition of each of the 6 risk markers to FRS improved the AUC; the C-statistic for risk factors

alone was 0.623. CAC showed the highest increment whereas FMD showed the least increment for incident CHD (C-statistic = 0.784 and 0.639, respectively). CAC also showed the highest increment whereas hsCRP showed the least increment for incident CVD (Figure 3). For incident CHD, CAC resulted in the highest NRI of 0.659. The respective NRI was 0.024 for FMD, 0.036 for ABI, 0.102 for cIMT, 0.160 for FH of CHD, and 0.079 for hsCRP. Similar results were obtained for incident CVD [30].

ASSESSING RISK SCORE PERFORMANCE: THE POOLED COHORT EQUATIONS AND 2013 ACC/AHA PREVENTION GUIDELINES

In 2013, the American College of Cardiology (ACC) and the American Heart Association (AHA) published a new set of prevention guidelines, and for the first time since 2001, a new risk score was introduced. As opposed to the FRS, which was derived solely from the original Framingham Heart Study cohort, the new pooled cohort equations (PCE) score was derived from 4 cohorts representing a mix of white and African American participants. Instead of CHD as the outcome, the PCE modeled the 10-year risk of both CHD and stroke (so-called atherosclerotic cardiovascular disease [ASCVD]). However, the risk factors included in the PCE (except for race) are exactly the same as those in the FRS [37].

MESA, although not a part of the derivation dataset, played a major role in risk score evaluation. In a limited validation exercise, the guideline writers themselves noted moderate discrimination (C-statistic for men and women ranging from 0.70 to 0.71 in whites, and 0.67 to 0.77 in African Americans) and just fair calibration of the PCE in MESA, with a trend toward overestimation of risk [37].

In a subsequent paper by DeFilippis et al. [38], the MESA investigators conducted a comprehensive analysis of the discrimination and calibration of not just the PCE, but also the original FRS, the more popular ATPIII version of FRS, the RRS, and another Framingham risk formula for total CVD (Table 1). In MESA, the PCE displayed moderate discrimination, similar to that seen for the ATPIII FRS (C-statistic = 0.71 vs. 0.71). The PCE showed slightly better discrimination than did the ATPIII FRS in women (C-statistic = 0.71 vs. 0.67). Calibration for both scores was poor, with both the PCE and the ATPIII FRS overestimating 10-year CHD risk (discordance 78% and 115%, respectively). Overestimation was more notable in men (85% and 154%) than in women (67% and 46%) [38]. The DeFilippis et al. [38] paper clearly demonstrated that a traditional risk factor model alone had limited performance in MESA. Similar poor discrimination with the FRS was also noted by other MESA papers [30,39].

MESA AND THE CLINICIAN-PATIENT RISK DISCUSSION

A prominent feature of the new cholesterol treatment guidelines was the so-called Clinician-Patient Risk Discussion, a 2-way conversation between clinicians and patients about risk, potential benefits and harms of cholesterol therapy, and patient preferences [40]. Several studies from MESA directly influenced the details of the Clinician-Patient Risk Discussion, including recommended strategies for advanced risk stratification.

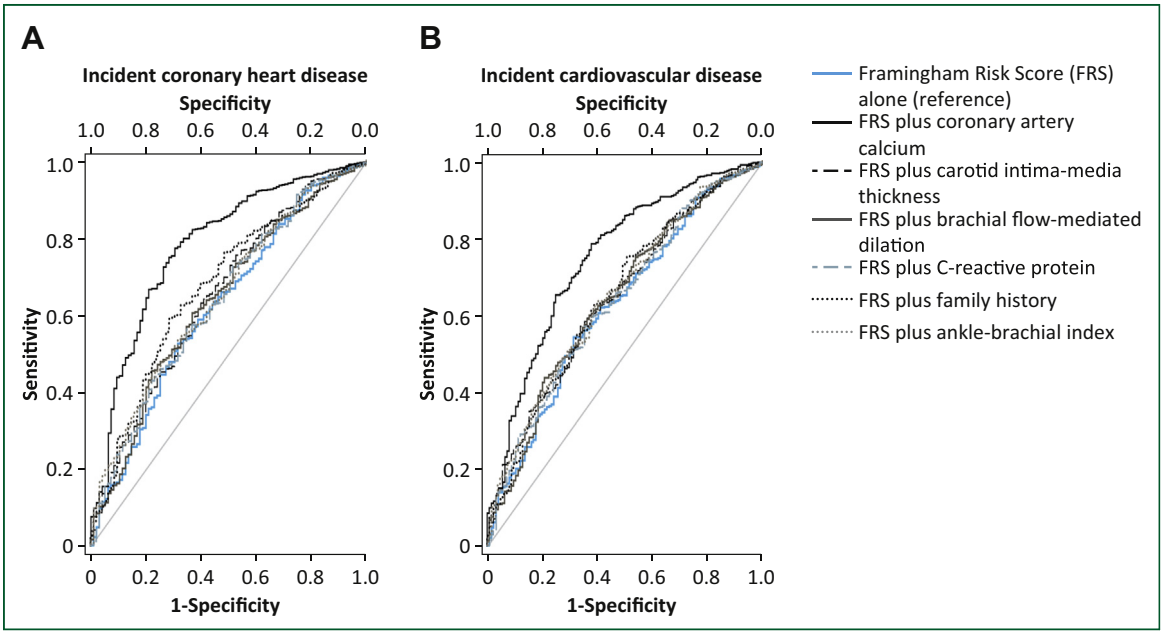

FIGURE 3. Receiver-operating characteristic curves showing area under the curve for Framingham risk score (FRS) alone and FRS in addition to novel risk markers. Reprinted with permission from Yeboah et al. [30].

TABLE 1. Calibration and discrimination of various risk scores undergoing validation in the MESA study

Risk Score	Predicted Events, n (%)	Observed Events, n (%)	Signed Absolute Difference	Discordance, %*	C-Statistic	Discrimination Slope
Total (n = 4,227)						
FRS-CHD†	397.6 (9.41)	263 (6.22)	3.18	51	0.68	0.05
FRS-CVD‡	561.3 (13.28)	448 (10.60)	2.68	25	0.71	0.09
ATPIII-FRS-CHD§	288.7 (6.83)	134 (3.17)	3.66	115	0.71	0.06
RRS‖	314.0 (7.43)	323 (7.64)	−0.21	−3	0.72	0.07
AHA-ACC-ASCVD¶	387.2 (9.16)	218 (5.16)	4.00	78	0.71	0.06
Men (n = 1,961)						
FRS-CHD†	251.1 (12.80)	164 (8.36)	4.44	53	0.69	0.05
FRS-CVD‡	358.7 (18.29)	261 (13.31)	4.98	37	0.71	0.09
ATPIII-FRS-CHD§	218.6 (11.15)	86 (4.39)	6.76	154	0.71	0.05
RRS‖	213.5 (10.89)	196 (9.99)	0.89	9	0.70	0.06
AHA-ACC-ASCVD¶	232.1 (11.84)	125 (6.37)	5.46	86	0.71	0.06
Women (n = 2,266)						
FRS-CHD†	146.5 (6.47)	99 (4.37)	2.10	48	0.60	0.01
FRS-CVD‡	202.6 (8.94)	187 (8.25)	0.69	8	0.70	0.05
ATPIII-FRS-CHD§	70.2 (3.10)	48 (2.12)	0.98	46	0.67	0.02
RRS‖	100.5 (4.44)	127 (5.60)	−1.17	−21	0.72	0.05
AHA-ACC-ASCVD¶	155.1 (6.84)	93 (4.10)	2.74	67	0.70	0.05

ACC = American College of Cardiology; AHA = American Heart Association; ASCVD = atherosclerotic cardiovascular disease; ATPIII = Adult Treatment Panel III; CHD = coronary heart disease; CVD = cardiovascular disease; FRS = Framingham risk score; MESA, Multi-Ethnic Study of Atherosclerosis; RRS = Reynolds risk score.

*Percentage discordance calculation: [(expected percentage − observed percentage)/observed percentage] × 100.

†Endpoints are myocardial infarction, death from CHD, and angina.

‡Endpoints are myocardial infarction, death from CHD, angina, stroke, transient ischemic attack, peripheral vascular disease, and heart failure.

§Endpoints are myocardial infarction and death from CHD.

‖Endpoints are myocardial infarction, death from CHD, stroke, and coronary revascularization.

¶Endpoints are myocardial infarction, death from CHD, and stroke.

Reproduced with permission from DeFilippis et al. [38].

Under the guidelines, clinicians may consider a number of additional risk markers in patients "for whom after quantitative risk assessment a risk-based treatment decision is uncertain." These include an abnormal CAC score (≥300 or ≥75th percentile for age/sex/race), hsCRP ≥2 mg/l, abnormal ABI, family history of premature CHD, and low-density lipoprotein cholesterol >160 mg/dl. cIMT was not included on the list (Class III recommendation), whereas the CAC score was described as single strongest predictor of risk [37].

Yeboah et al. [41] examined the utility of these risk markers to reclassify risk among individuals who are below the threshold for statin therapy. Using a calibrated version of the pooled cohort equation (cPCE), MESA participants with an initial cPCE <7.5% and elevated levels of additional risk markers whose new calculated risk was ≥7.5% were considered statin eligible. More than one-half of ASCVD events occurred among participants whose cPCE was <7.5% at baseline. Within this subgroup, 264 participants (6.8%) had a CAC score that exceeded the threshold recommended in the new guidelines and became statin eligible. Accordingly, the needed to screen to identify 1 potential statin-eligible participant (NNSI) for CAC was 14.7. The corresponding NNSI for the other markers was higher with 21.8 for a FH of ASCVD, 39.2 for hsCRP, 176 for ABI, and 193.3 for low-density lipoprotein cholesterol. Using ≥1 of the additional risk marker criteria, 431 of 3,882 of participants with an initial cPCE <7.5% (11.1%) became statin eligible (reclassified to ≥7.5% cPCE) [41].

In another pivotal study, Yeboah et al. [42] assessed whether the risk markers improved discrimination and reclassification of incident ASCVD beyond the cPCE. The markers that were studied only included CAC, hsCRP, ABI (all modeled continuously), and FH of ASCVD as these remained significant predictors of ASCVD over 10 years of follow-up independent of traditional risk factors. Whereas each of the risk markers improved the AUC when added to the cPCE, only CAC was significant. Furthermore, adding CAC to the cPCE resulted in a larger improvement in NRI compared with the other risk markers, but this was limited to an improvement in classification for events (event NRI: 0.178; 95% CI: 0.080 to 0.256; nonevent NRI: −0.059; 95% CI: −0.075 to −0.030). ABI yielded a very modest improvement but the highest nonevent NRI (event NRI: 0.013; 95% CI: −0.034 to 0.051; nonevent NRI: 0.004; 95% CI: −0.004 to 0.011). Similar analyses were conducted for incident CHD using the calibrated FRS (cFRS). CAC

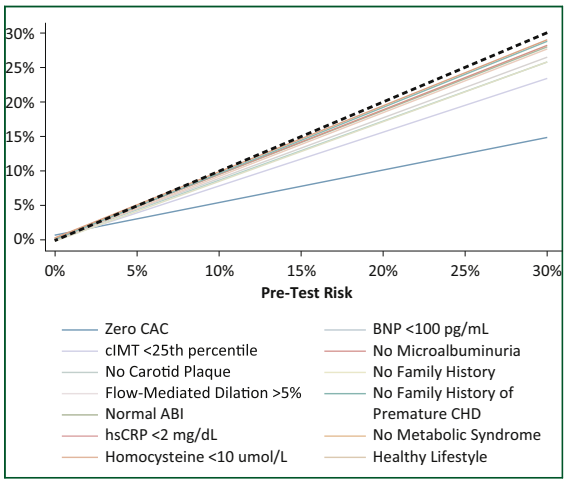

FIGURE 4. Relationship between pre-test and post-test cardiovascular disease risk after the knowledge of the negative result of each risk marker. ABI, ankle brachial index; BNP, B-type natriuretic peptide; CAC, coronary artery calcium; CHD, coronary heart disease; cIMT, carotid intima-media thickness; hsCRP, high-sensitivity C-reactive protein. Reprinted with permission from Blaha et al. [46].

was the only risk marker to significantly improve discrimination of CHD when added to the cFRS. Similar to ASCVD, addition of CAC resulted in a larger NRI compared to the other additional risk markers [42].

One of the most prominent criticisms of the PCE and the new cholesterol guidelines was the potential for overestimation and overtreatment [43]. The MESA study played a prominent role in describing how so-called negative risk factors can be used to down-classify risk in certain situations [21,36,44,45]. In a study of 13 negative risk factors, Blaha et al. [46] used risk factor—adjusted diagnostic likelihood ratios to demonstrate that a CAC score of zero was the strongest negative risk factor (0.41), followed by a normal carotid ultrasound (0.65) and a negative family history of CHD (0.76) (Figure 4) [46].

A paper by Nasir et al. [47] looked specifically at clinical situations where a finding of CAC = 0 might change clinician decision making for initiating lipid-lowering therapy. In MESA participants with 10-year ASCVD risk of between 5% and 20%, using the PCE, a finding of CAC = 0 was associated with observed ASCVD event rates below the guideline-treatment threshold of 7.5% (Figure 5) [47].

THE MESA CHD RISK SCORE

Despite the wealth of data supporting the superior predictive value of CAC and its potential value in clinical practice, until recently there was no tool for formally incorporating CAC into 10-year risk estimates. In 2016, the MESA CHD risk score was published in a paper by McClelland et al. [48] in the *Journal of the American College of Cardiology*. McClelland et al. [48] used the traditional risk factors as well as family history of CHD to fit 2 models for predicting the 10-year risk of hard CHD: 1 without CAC, and 1 adding CAC to the model. A striking feature of the results was the degree to which the predictive value of the traditional risk factors was reduced when CAC was added to the model (Table 2). Using just the traditional risk factors plus family history, the C-statistic was 0.75. After adding CAC, the C-statistic increased to 0.80. The MESA CHD risk score was validated in both the Dallas Heart Study and the Heinz-Nixdorf Recall study with similar discrimination (C-statistic = 0.82 and 0.78, respectively) and excellent calibration (Table 3).

Using the online MESA CHD risk score calculator [49], the clinician can now determine the estimated 10-year risk of patient before and after knowledge of the CAC score (Figure 6). Such information can be used to guide preventive pharmacotherapy and for enriching CAC score

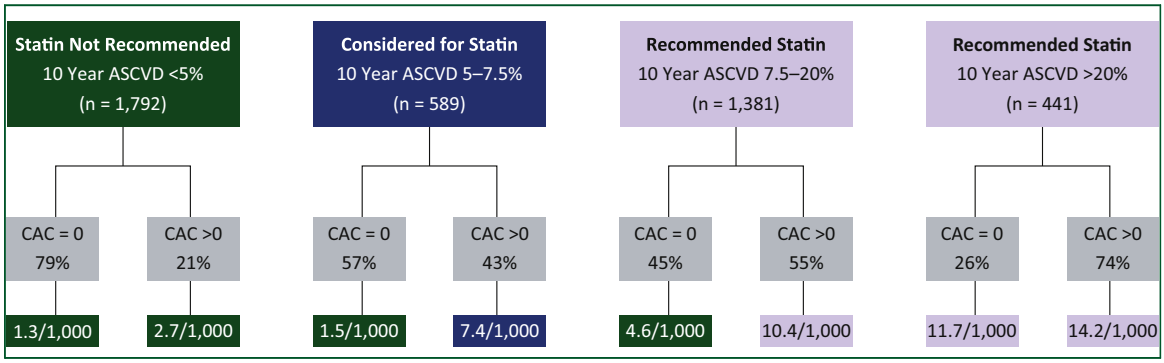

FIGURE 5. Impact of the absence of coronary artery calcium (CAC) in reclassifying risk below the threshold for statin consideration suggested by American College of Cardiology/American Heart Association cholesterol management guidelines, by estimated 10-year atherosclerotic cardiovascular disease (ASCVD) risk. Reprinted with permission from Nasir et al. [47]

TABLE 2. MESA 10-Year CHD risk prediction models without and with CAC

	Risk Factors Only			Risk Factors and CAC		
	Hazard Ratio	Beta Coefficient	p Value	Hazard Ratio	Beta Coefficient	p Value
Age, yrs	1.05	0.0455	<0.0001	1.02	0.0172	0.007
Male	2.12	0.7496	<0.0001	1.5	0.4079	<0.001
Race/ethnicity						
Non-Hispanic white	Ref	0	—	Ref	0	—
Chinese American	0.6	−0.5055	<0.01	0.71	−0.3475	0.07
African American	0.81	−0.2111	0.066	1.04	0.0353	0.7
Hispanic	0.83	−0.1900	0.11	0.98	−0.0222	0.88
Diabetes	1.68	0.5168	<0.0001	1.48	0.3892	0.002
Current smoker	1.61	0.4732	<0.001	1.45	0.3717	0.005
Total cholesterol, mg/dl	1.01	0.0053	<0.0001	1	0.0043	<0.001
HDL cholesterol, mg/dl	0.99	−0.0140	<0.001	0.99	−0.0114	0.003
Lipid-lowering medications	1.28	0.2473	0.003	1.13	0.1206	0.32
Systolic blood pressure, mm Hg	1.01	0.0085	0.0002	1.01	0.0066	0.004
Antihypertensive medications	1.4	0.3381	0.0013	1.26	0.2278	0.033
Family history of heart attack	1.57	0.4522	<0.0001	1.38	0.3239	<0.001
log (CAC + 1)	NA	NA	NA	1.32	0.2743	<0.0001
Baseline survival at 10 yrs	0.99963			0.99833		

CAC, coronary artery calcium; HDL, high-density lipoprotein; Ref, reference; other abbreviations as in Table 1.
Reproduced with permission from McClellend et al. [48].

reporting from computed tomography labs. A MESA CVD risk score is currently under development, which will allow separate modeling of CHD and stroke, rather than the composite outcomes chosen by the PCE.

SUMMARY

MESA has moved the field of risk prediction forward, raising subclinical disease detection up to a standing alongside traditional risk factors as the preeminent tools for optimal risk prediction. The most important finding from MESA for risk prediction is the superior risk prediction provided by CAC. Whereas MESA has also made critical discoveries in advanced serum biomarkers (e.g., lipoprotein-associated phospholipase A2, homocysteine, interleukin 6, and others) [50], magnetic resonance imaging [51], and genetics [52], these have not reached clinical practice guidelines to date.

The future will bring an enhanced understanding of CAC [53]. For example, recent MESA studies have suggested that the rate of CAC progression adds additional prognostic value on top of traditional risk factors and the baseline CAC score [54]. A new study by Criqui et al. [55] has challenged the long-standing assumption that the density of CAC is a predictor of events; in fact, adjusted for the volume of CAC, increasing CAC density is a protective marker. The regional distribution of CAC also appears to have prognostic value. In studies by Silverman et al. [56] and Blaha et al. [57], a more diffuse distribution of CAC is association with more risk compared with a more concentrated pattern for a given absolute CAC score. Extracoronary calcification, which can also be detected on a CAC scan, appears to add prognostic value for CVD outcomes including stroke as well as all-cause mortality [58].

Whereas MESA had a significant impact on the 2013 ACC/AHA Prevention Guidelines, we expect there to be an even greater influence on the next guideline iteration. Coinciding with the call for precision medicine is the recognition that all preventive therapies should be matched to absolute risk to best maximize net benefit, including nonstatin lipid-lowering therapy, aspirin therapy, blood pressure therapy and intensification, and possible anti-inflammatory therapy. Studies from MESA have helped inform the balance between number needed to treat and number needed to harm of new and existing therapies [59].

TABLE 3. Validation of the MESA CHD risk score in the HNR and DHS cohorts

	MESA	HNR	DHS
Sample size, N	6,726	3,692	1,080
CHD events, n	422	274	58
Model with risk factors only			
Harrell C-statistic	0.75	0.72	0.782
Discrimination slope	0.052	0.053	0.046
Calibration slope	0.834	0.74	1.55
Model with risk factors and CAC			
Harrell C-statistic	0.8	0.779	0.816
Discrimination slope	0.086	0.095	0.078
Calibration slope	0.857	0.899	1.19

DHS, Dallas Heart Study; HNR, Heinz-Nixdorf Recall; other abbreviations as in Table 1.
Reproduced with permission from McClellend et al. [48].

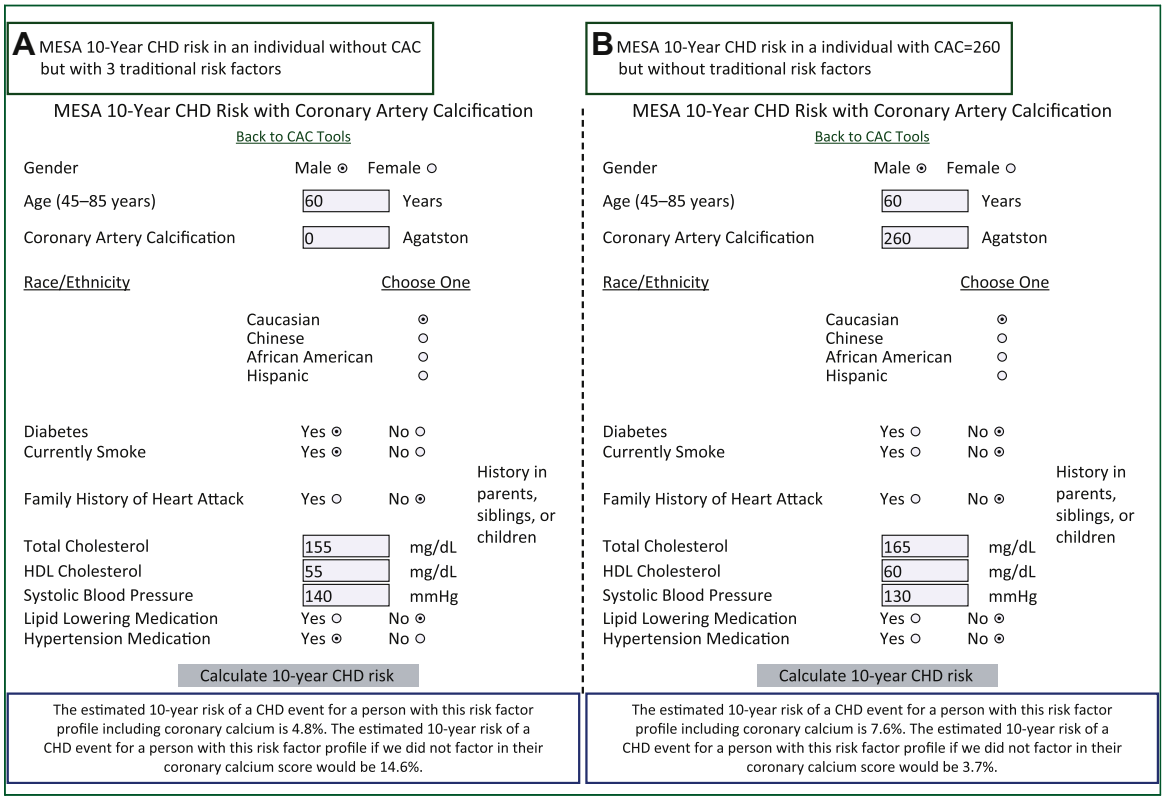

FIGURE 6. The MESA CHD risk score online calculator using 2 case examples. Abbreviations as in Figures 1, 4, and 5.

It is truly an exciting time for MESA, and arguably the greatest legacy of MESA is the paradigm shift toward routine consideration of subclinical disease measurement in clinical risk assessment.

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