JACC: CARDIOVASCULAR IMAGING VOL. 5, NO. 2, 2012

ISSN 1936-878X/$36.00

PUBLISHED BY ELSEVIER INC.

DOI:10.1016/j.jcmg.2011.11.008

Prediction of Coronary Artery Calcium Progression in Individuals With Low Framingham Risk Score

The Multi-Ethnic Study of Atherosclerosis

Tochi M. Okwuosa, DO,* Philip Greenland, MD,† Gregory L. Burke, MD, MSc,‡ John Eng, MD,§ Mary Cushman, MD, MSc,‖ Erin D. Michos, MD, MHS,¶ Hongyan Ning, MD, MS,† Donald M. Lloyd-Jones, MD, ScM†

Detroit, Michigan; Chicago, Illinois; Winston-Salem, North Carolina; Baltimore, Maryland; and Burlington, Vermont

OBJECTIVES This study sought to determine whether novel markers not involving ionizing radiation could predict coronary artery calcium (CAC) progression in a low-risk population.

BACKGROUND Increase in CAC scores over time (CAC progression) improves prediction of coronary heart disease (CHD) events. Due to radiation exposure, CAC measurement represents an undesirable method for repeated risk assessment, particularly in individuals with low predicted risk (Framingham Risk Score [FRS] <10%).

METHODS From 6,814 participants in MESA (Multi-Ethnic Study of Atherosclerosis), 2,620 individuals were classified as low risk for CHD events (FRS <10%) and had follow-up CAC measurement. In addition to traditional risk factors (RFs), various combinations of novel marker models were selected on the basis of data-driven, clinical, or backward stepwise selection techniques.

RESULTS Mean follow-up was 2.5 years. CAC progression occurred in 574 participants (22% overall; 214 of 1,830 with baseline CAC = 0 and 360 of 790 with baseline CAC >0). Addition of various combinations of novel markers to the base model (c statistic = 0.711) revealed improvements in discrimination of approximately only 0.005 each (c statistics 0.7158, 0.7160, and 0.7164) for the best-fit models. All 3 best-fit novel marker models calibrated well but were similar to the base model in predicting individual risk probabilities for CAC progression. The highest prevalence of CAC progression occurred in the highest compared with the lowest probability quartile groups (39.2% to 40.3% vs. 6.4% to 7.1%).

CONCLUSIONS In individuals at low predicted risk according to FRS, traditional risk factors predicted CAC progression in the short term with good discrimination and calibration. Prediction improved minimally when various novel markers were added to the model. (J Am Coll Cardiol Img 2012;5:144–53) © 2012 by the American College of Cardiology Foundation

From the *Wayne State University School of Medicine, Division of Cardiology, Detroit, Michigan; †Northwestern University, Feinberg School of Medicine, Departments of Preventive Medicine and Medicine, Chicago, Illinois; ‡Wake Forest University School of Medicine, Division of Public Health Sciences, Winston-Salem, North Carolina; §Johns Hopkins University School of Medicine, Russell H. Morgan Department of Radiology and Radiological Science, Baltimore, Maryland; ‖University of Vermont Department of Medicine, Burlington, Vermont; and the ¶Johns Hopkins University School of Medicine, Division of Cardiology, Baltimore, Maryland. This research was supported by contracts N01-HC-95159 through N01-HC-95169 from the National Heart, Lung, and Blood Institute, Bethesda, Maryland. All authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received October 27, 2011; accepted November 1, 2011.

The Framingham Risk Score (FRS) has been validated as a useful tool in the estimation of 10-year risk of coronary heart disease (CHD) (1). However, events may still occur among those predicted to be at low (<10%) 10-year CHD risk (2–4) and could amount to a significant number given the large size of this group (75% of the population) (5–7). As such, identification of factors associated with CHD events in low-risk persons is imperative. Because of limitations of the FRS for risk prediction in individuals, much effort has been targeted toward improving identification of persons at risk for coronary events.

The coronary artery calcium (CAC) Agatston score predicts coronary events beyond the FRS risk factors (3,4,8) and is predictive of coronary events even in individuals with low FRS (2,9). Some expert panels recommend some CAC screening in persons at lower risk for CHD events (10,11). However, due to ionizing radiation exposure as well as associated cancer risks and costs, computed tomography (CT) scanning likely represents an undesirable method of repeated screening for CHD, particularly among persons at low risk. This fact therefore underscores the need for alternative methods of risk assessment, not involving radiation in this population. To this effect, a recent cross-sectional study by our group (12) demonstrated that in individuals at low risk according to FRS, a model containing traditional cardiovascular risk factors had excellent discrimination for CAC ≥300. This model was only modestly improved with the addition of novel markers (individually or in combination).

Studies have linked CAC progression to coronary events, increased all-cause mortality, and an unfavorable prognosis (13–16) and have even suggested CAC progression to be a better predictor of CVD risk than baseline CAC score (17). Serial assessment of CAC scores has been proposed for monitoring progression of atherosclerosis and for assessing the effectiveness of medical therapies aimed at reducing cardiac risk (17). Although baseline CAC score likely reflects previous coronary atherosclerotic plaque burden, CAC progression probably provides insight into ongoing current disease activity. Although past studies suggest that the most consistent predictors of CAC progression (regardless of risk level) are age and initial CAC burden (18–21), other factors (including novel risk markers) associated with CAC progression have not been routinely examined. Identification of factors involved in atherosclerosis development and progression could help identify factors that can be modified, prevented, or both, and may be useful to identify those among the lower predicted-risk strata who actually will experience events.

The objective of this study was to identify novel markers or traditional cardiovascular risk factors that are associated with CAC progression (incident or increased CAC scores) among low-risk participants (FRS <10%) who, due to the large size of the group, make up a significant proportion of CHD/CVD events observed in the general population.

METHODS

MESA (Multi-Ethnic Study of Atherosclerosis) is a prospective cohort study examining measures of subclinical atherosclerosis, progression of subclinical atherosclerosis, and conversion to clinical events. Details of the study design, as well as inclusion/exclusion criteria and baseline characteristics, have been described previously (8). Briefly, at baseline the cohort included 6,814 participants (3,213 men and 3,601 women) aged 45 to 84 years from 4 different racial/ethnic groups (38% white, 28% African American, 22% Hispanic, and 12% Chinese) in 6 U.S. communities (Baltimore, Maryland; Chicago, Illinois; Forsyth County, North Carolina; Los Angeles, California; New York, New York; and St. Paul, Minnesota). The participants were free of clinical cardiovascular disease at first examination (July 2000 to August 2002). The institutional review boards at all participating centers approved the study, and all participants gave informed consent. The study was powered to detect relationships between risk factors with a prevalence of ≥10% in the cohort, and the presence of coronary calcium with an odds ratio of ≥1.5.

ABBREVIATIONS AND ACRONYMS

AIC = Akaike information criterion
BMI = body mass index
CAC = coronary artery calcium
CHD = coronary heart disease
CIMT = carotid intima-media thickness
CRP = C-reactive protein
CT = computed tomography
FRS = Framingham Risk Score
LDLpn = low-density lipoprotein (LDL) particle number
SBP = systolic blood pressure
sICAM = soluble intercellular adhesion molecule-1

For the current study, we included men and women aged ≤79 years at baseline, categorized as being at low 10-year risk for CHD events (FRS <10%) (1). The present analyses excluded participants with coronary risk equivalents (non-low risk) according to National Cholesterol Education Program–Adult Treatment Panel III definitions, including a diagnosis of diabetes, peripheral arterial disease (ankle-brachial index <0.9), carotid artery disease (≥50% carotid artery stenosis), history of abdominal aortic aneurysm, severe kidney disease (glomerular filtration rate <30 ml/min/1.73 m^2 based on the Modification of Diet in Renal Disease

[22] equation). Other exclusion criteria are detailed in Figure 1.

Baseline examination, laboratory data, cardiac CT, and carotid ultrasonography ascertainment have been described elsewhere (8,23). Carotid ultrasound was performed using high-resolution B-mode ultrasound. We used the common carotid artery measurements in our data analysis. CAC was measured at baseline MESA examination 1 (2000 to 2002) for all participants. Follow-up CAC measurements were performed on one-half of the cohort (randomly selected) at the second examination (2002 to 2004) and the other half at the third examination (2004 to 2005) at an average of 1.7 and 3.3 years after the baseline examination, respectively. FRS was calculated using age, total and high-density lipoprotein (HDL) cholesterol levels, current smoking status, systolic blood pressure (SBP), and the use of antihypertensive medication using the risk prediction functions from the National Cholesterol Education Program–Adult Treatment Panel III guidelines (24).

Definitions. Body mass index (BMI) was defined as weight in kilograms divided by height in meters squared. Medication use was derived from medication lists and clinical staff entry of prescribed medications. Aspirin use was defined as ≥3 days per week at baseline. Physical activity was measured using a semiquantitative questionnaire adapted from the Cross-Cultural Activity Participation Study (25).

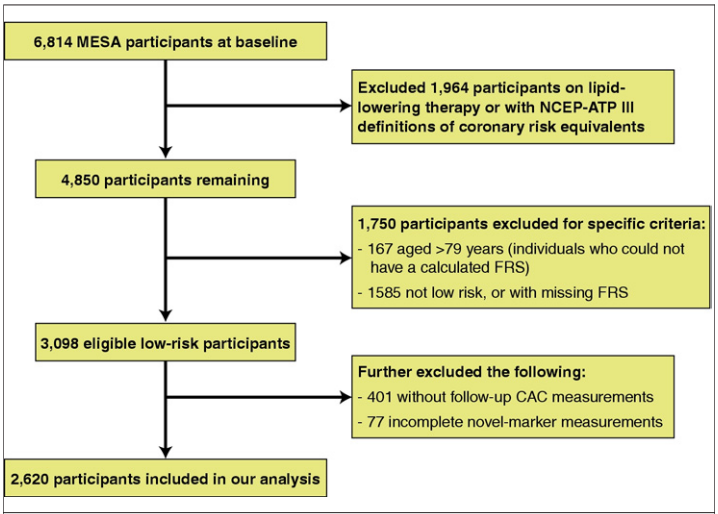


Figure 1. Study Flow Diagram

The exclusion criteria for the study analysis are detailed in this flow diagram. CAC = coronary artery calcium; FRS = Framingham Risk Score; MESA = Multi-Ethnic Study of Atherosclerosis; NCEP-ATP III = National Cholesterol Education Program–Adult Treatment Panel III.

Because there is no agreed on definition for CAC progression in the literature, we used the CAC progression definition described by Berry et al. in a previous MESA study (26): among those with CAC = 0 at baseline, CAC progression or "incident CAC" was defined as CAC >0 at follow-up. For those with presence of any CAC at baseline, CAC progression or "increased CAC" was defined as either an annualized change of 10 Agatston units at follow-up among participants with 0 < CAC < 100 at baseline; or an annualized percentage change (annualized change in CAC score divided by the baseline CAC score) ≥10% among participants with CAC ≥100 at baseline. This method allows for a categorical definition of CAC progression (progression versus no progression).

Statistical analysis. All analyses were performed using SAS software, version 9.2 (SAS Institute, Cary, North Carolina). A 2-tailed value of $p < 0.05$ was considered statistically significant. Baseline characteristics were compared according to CAC progression status using general linear models for continuous variables and cross-tabulations for categorical variables. Biomarkers and one subclinical measure of vascular disease (novel markers) were evaluated and include low-density lipoprotein particle number (LDLpn), urine albumin, C-reactive protein (CRP) using a high-sensitivity assay, D-dimer, factor VIIIc, total homocysteine, fibrinogen, cystatin C, soluble intercellular adhesion molecule (sICAM)-1, and carotid intima-media thickness (CIMT). sICAM had values missing at random, which were filled in using multiple imputation techniques in secondary analyses (27). Logistic regression was used to obtain odds ratios per 1 SD higher baseline value of individual novel markers. This analysis was conducted with CAC progression overall, and with incident and increased CAC separately. The first model adjusted for age only; the second model adjusted for traditional cardiovascular risk factors including age, sex, race/ethnicity, SBP, diastolic blood pressure, hypertension treatment, total and HDL cholesterol, current smoking, BMI, physical activity, and family history of heart attack (base model for remainder of analyses).

Novel markers were added individually to the base model to assess their independent associations with CAC presence. Using this approach, various models were fitted to estimate the associations of combinations of novel markers with CAC progression (incident plus increased CAC) using data-driven methods (combination of measures signifi-

cantly associated with CAC in multivariable analysis from this and our prior study [12]), mechanistic approaches/clinically available covariates (combination of measures from each major biologic/pathophysiological group), and backward stepwise selection statistical techniques. Thus, the base model made up of traditional risk factors was combined with several novel marker combinations to create the best-fit models: fibrinogen, sICAM, factor VIIIc, CIMT (model 1); LDLpn, CRP, fibrinogen, urine albumin, sICAM (model 2); and an unbiased statistical approach using a backward stepwise selection model including all potential variables, with $p < 0.10$ selected for model retention (model 3). Incident CAC and increased CAC were also assessed separately.

P values obtained using likelihood ratio tests were used to determine the level of significance of each model relative to the base model; Akaike information criterion (AIC) assessed the level of informativeness of each model, with lower values indicating greater informativeness; and the c statistic measured the discriminative power of each model, with higher values indicating better fit. Receiver-operating characteristic curves were then plotted for the base model, as well as the combination models exhibiting the greatest levels of discrimination for advanced CAC (best-fit models).

RESULTS

Baseline characteristics. Among 6,814 MESA participants, 2,620 aged ≤79 years were classified as low 10-year FRS CHD risk and had follow-up CT scans (overall mean age 56.9 ± 8.7 years; women 58.6 ± 9.0 years; men 52.5 ± 6.1 years). Overall mean follow-up between CAC measurements was 2.5 years. Among 1,830 participants with baseline CAC = 0, a total of 214 (11.7%) developed CAC (incident CAC), whereas among 790 participants with baseline CAC >0, a total of 360 (45.6%) had increased CAC. The 478 participants who were excluded because of missing novel marker and follow-up CAC measurements had higher SBP, BMI, and triglyceride levels and included more smokers, but they had similar baseline FRS and CAC scores when compared with those without missing data.

Almost all of the lifestyle and traditional risk factors were associated with CAC progression univariately except race/ethnicity, sex, HDL cholesterol, current smoking, and physical activity (Table 1). Baseline FRS, CAC score, and absence of CAC were significantly associated with CAC progression. Higher mean values of all the novel markers were significantly associated with CAC progression (Table 2).

Table 1. Baseline Characteristics and CAC Progression Among Low-Risk Participants

	No CAC Progression (n = 2,046)	CAC Progression (n = 574)	p Value
Age (yrs)	55.9 ± 8.3	60.4 ± 9.2	<0.01
Female	72.5	74.4	0.38
Race/ethnicity			0.08
White	39.3	45.1	
Black	26.1	24.7	
Chinese	13.3	11.9	
Hispanic	21.3	18.3	
SBP (mm Hg)	118.2 ± 18.3	124.9 ± 19.2	<0.01
DBP (mm Hg)	69.9 ± 10.0	71.4 ± 10.1	<0.01
BMI (kg/m^2)	27.7 ± 5.5	28.8 ± 6.2	<0.01
Total cholesterol (mg/dl)	195.3 ± 33.1	200.7 ± 38.0	<0.01
HDL (mg/dl)	55.4 ± 15.4	54.1 ± 14.8	0.07
LDL (mg/dl)	117.1 ± 29.8	120.5 ± 32.0	0.02
Triglycerides (mg/dl)	114.3 ± 63.6	127.3 ± 67.8	<0.01
Current smoking	9.04	10.45	0.31
HTN treatment	17.3	31.0	<0.01
Family history of CHD	35.8	48.4	<0.01
Mean baseline FRS (%)	3.0 ± 2.5	4.1 ± 2.5	<0.01
Mean baseline CAC score (in CAC >0)	23.0 ± 178.0	106.8 ± 228.8	0.01
Median baseline CAC score (in CAC >0)	18.7	80.7	<0.01
CAC = 0	79.0	37.3	<0.01
Education			0.03
Less than high school	12.5	15.8	
High school	16.2	17.4	
College or bachelor	50.1	50.2	
Graduate school or professional	21.2	16.6	
Physical activity*	924.7 ± 2,608.7	1,000.0 ± 2879.1	0.55
Marital status (married)	62.4	53.7	<0.01
Income ($)			<0.01
<25,000	23.0	29.6	
25,000–50,000	28.5	31.6	
50,000–75,000	20.0	15.0	
>75,000	28.5	23.8	
Health insurance	89.6	91.5	<0.01
Medications use			
Aspirin	10.6	14.4	0.01
ACEI/ARB use	7.5	13.8	<0.01
Beta-blocker	4.7	6.3	0.14
Nitrates	0.05	0.17	0.34
Calcium blocker	6.0	10.8	<0.01
Estrogen use (women)	30.0	30.3	0.91

Values are mean ± SD or %. *Physical activity is defined as vigorous physical activity total (MET [min]/week, Monday through Sunday).

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BMI = body mass index; CAC = coronary artery calcium; CHD = coronary heart disease; DBP = diastolic blood pressure; FRC = Framingham Risk Score; HDL = high-density lipoprotein; HTN = hypertension; LDL = low-density lipoprotein; MET = metabolic equivalent; SBP = systolic blood pressure.

Table 2. Mean Novel Marker Levels and CAC Progression

	Mean Novel Marker Levels		
	No CAC Progression (n = 2,046)	CAC Progression (n = 574)	p Value
LDLpn (nmol/l)	1,257.0 ± 352.3	1,307.6 ± 382.7	<0.01
Urine albumin (mg/dl)	0.9 ± 2.76	1.6 ± 11.0	<0.01
hs-CRP (mg/l)	3.6 ± 5.1	4.5 ± 6.7	<0.01
D-dimer (μg/ml)	0.29 ± 0.56	0.36 ± 0.62	<0.01
Factor VIIIc (%)	93 ± 34	99 ± 37	<0.01
tHcy (μmol/l)	8.4 ± 3.6	8.9 ± 3.1	<0.01
Fibrinogen (mg/dl)	335 ± 70	349 ± 71	<0.01
Cystatin C (mg/l)	0.82 ± 0.15	0.87 ± 0.16	<0.01
C-IMT (mm)	0.79 ± 0.16	0.84 ± 0.16	<0.01
sICAM-1 (ng/ml)*	263 ± 74	281 ± 76	<0.01

Values are mean ± SD. *n for sICAM-1 = 962 without CAC progression, 256 with CAC progression. hs-CRP = high-sensitivity C-reactive protein; CIMT = carotid intima-media thickness; LDLpn = low-density lipoprotein particle number; sICAM = soluble intercellular adhesion molecule, tHcy = total homocysteine.

Univariate and multivariable models for CAC progression relative to novel markers. Table 3 displays unadjusted and adjusted odds ratios for associations of baseline individual novel markers with CAC progression. There was a significant positive association of most of the individual novel markers with CAC progression in the univariate and age-adjusted models, which were no longer significant after adjustment for traditional risk factors. When incident CAC and increased CAC were examined separately, only CRP was associated with increased CAC, whereas LDLpn, fibrinogen, cystatin C, sICAM, and CIMT were associated with incident CAC after adjusting for age. There were no sex or race interactions found in any of the models.

Combination novel markers in the prediction of CAC progression. Selected novel marker combinations were chosen on the basis of data-driven methods, clinical/mechanistic approaches, and backward stepwise selection processes and assessed for their ability to predict CAC progression. Models with the best informativeness and discrimination for CAC progression are displayed in Table 4. Model 1 was the best-fit model from previous data from our group (12), model 2 was the best-fit model for clinical/mechanistic relevance, and model 3 reflects the statistical backward selection process for CAC progression (incident and increased CAC combined). The base model, composed of traditional risk factors, discriminated incident CAC better than increased CAC (c statistic = 0.688 vs. 0.645, respectively). For overall CAC progression, the c statistic for the base model was 0.711 (AIC = 2,524.65). All 3 best-fit models showed little or no improvement (in discrimination and informative-

Table 3. Standardized ORs for Annualized CAC Progression (Incident and Increased CAC) Relative to Novel Markers

Novel Markers	CAC Progression			Incident CAC			Increased CAC		
	Unadjusted OR per 1 SD	Adjusted OR per 1 SD*	Adjusted OR per 1 SD†	Unadjusted OR per 1 SD	Adjusted OR per 1 SD*	Adjusted OR per 1 SD†	Unadjusted OR per 1 SD	Adjusted OR per 1 SD*	Adjusted OR per 1 SD†
LDLpn (nmol/l)	1.15 (1.05–1.26)	1.21 (1.10–1.33)	0.93 (0.79–1.11)	1.17 (1.02–1.34)	1.20 (1.04–1.38)	0.88 (0.69–1.13)	1.08 (0.94–1.24)	1.14 (0.99–1.32)	1.02 (0.79–1.32)
Urine albumin (mg/dl)	1.15 (0.99–1.32)	1.18 (1.01–1.38)	1.11 (0.95–1.30)	1.16 (1.04–1.29)	1.16 (0.98–1.37)	1.10 (0.92–1.33)	1.59 (0.98–2.59)	1.55 (0.95–2.53)	1.34 (0.81–2.20)
CRP (mg/l)	1.16 (1.07–1.26)	1.13 (1.04–1.23)	1.07 (0.98–1.18)	1.14 (1.01–1.29)	1.12 (0.99–1.27)	0.98 (0.84–1.15)	1.24 (1.07–1.44)	1.21 (1.04–1.41)	1.16 (0.99–1.35)
D-dimer (μg/ml)	1.14 (1.02–1.27)	1.07 (0.98–1.16)	1.07 (0.98–1.17)	1.08 (0.97–1.21)	1.07 (0.97–1.18)	1.07 (0.96–1.20)	1.11 (0.95–1.30)	1.07 (0.92–1.24)	1.06 (0.91–1.23)
Factor VIIIc (%)	1.19 (1.09–1.30)	1.09 (0.99–1.19)	1.08 (0.98–1.20)	1.13 (0.98–1.31)	1.07 (0.92–1.24)	1.06 (0.91–1.23)	1.09 (0.96–1.24)	1.04 (0.91–1.18)	1.03 (0.89–1.18)
tHcy (μmol/l)	1.15 (1.04–1.27)	1.08 (0.99–1.19)	1.02 (0.93–1.12)	1.04 (0.93–1.16)	1.02 (0.90–1.15)	0.97 (0.81–1.16)	1.10 (0.95–1.27)	1.07 (0.92–1.24)	1.03 (0.88–1.20)
Fibrinogen (mg/dl)	1.21 (1.10–1.32)	1.11 (1.01–1.22)	1.03 (0.92–1.15)	1.25 (1.09–1.44)	1.20 (1.04–1.38)	1.03 (0.87–1.22)	1.10 (0.95–1.26)	1.04 (0.90–1.19)	0.94 (0.80–1.10)
Cystatin C (mg/l)	1.34 (1.23–1.47)	1.19 (1.08–1.31)	1.01 (0.91–1.12)	1.29 (1.13–1.47)	1.21 (1.05–1.39)	1.00 (0.86–1.17)	1.20 (1.04–1.38)	1.13 (0.97–1.30)	1.03 (0.87–1.21)
sICAM-1 (ng/ml)	1.26 (1.10–1.43)	1.23 (1.07–1.41)	1.15 (0.99–1.34)	1.28 (1.06–1.55)	1.27 (1.04–1.54)	1.15 (0.92–1.44)	1.09 (0.89–1.33)	1.08 (0.88–1.32)	1.05 (0.84–1.30)
Imputed sICAM-1 (ng/ml)	1.22 (1.07–1.40)	1.20 (1.04–1.38)	1.12 (0.94–1.34)	1.32 (1.11–1.58)	1.04 (1.02–1.06)	1.21 (0.98–1.50)	1.17 (0.93–1.48)	1.16 (0.93–1.45)	1.13 (0.88–1.46)
CIMT (mm)	1.36 (1.25–1.49)	1.16 (1.05–1.28)	1.02 (0.92–1.13)	1.29 (1.12–1.49)	1.18 (1.02–1.38)	1.04 (0.88–1.22)	1.15 (1.00–1.31)	1.04 (0.90–1.20)	0.94 (0.81–1.09)

Values are OR (95% confidence interval). *Age-only adjustment. †Adjusted by age, sex, race/ethnicity, SBP, DBP, HTN treatment, total cholesterol, HDL cholesterol, current smoking, BMI, physical activity, and family history of heart attack. CRP = C-reactive protein; OR = odds ratio; other abbreviations as in Tables 1 and 2.

ness) over the base model. Nevertheless, model 1 showed the best discrimination (c statistic = 0.7164; AIC = 2,518.03), model 3 exhibited the greatest informativeness (c statistic = 0.7158; AIC = 2,513.01), and model 2 had both characteristics (c statistic = 0.7160; AIC = 2,517.55, respectively) (all $p < 0.01$). Accordingly, the ROC curves for these 4 models overlapped substantially (Fig. 2).

The predictive utility of the models were further assessed by comparing 3 best-fit combination models with the base model for their applicability in the prediction of an individual's risk for CAC progression. This analysis was done by first dividing this low-risk cohort into quartiles of CAC progression. The first quartile included participants with lowest CAC progression, whereas the fourth quartile represented those with highest CAC progression. We then estimated the probabilities of CAC progression using each of our models and divided these into quartiles also, going from the lowest (in the first quartile) to highest probability (in the fourth quartile). In so doing, we compared observed CAC progression in the study population with the estimated probabilities of CAC progression using each of our models (Fig. 3). For all 4 models, participants with the highest estimated probabilities (the 4th quartile groups) had very high prevalence of CAC progression compared with the lowest quartile groups (39.2% to 40.3% vs. 6.4% to 7.1%). In addition, most of the participants with CAC progression were from the highest probability quartile groups. The model-estimated probabilities for the 3 best-fit models were similar to those for the base model.

For individual measures, sICAM improved the c statistic of the base model by 0.004 ($p < 0.01$); CRP did not show any improvement over the base model ($p = 0.15$). However, baseline CAC score (for those with CAC >0 at baseline) improved the base model c statistic by 0.028 (c statistic = 0.739). It is noteworthy that in these low-risk participants, age (chi-square = 107) was the primary risk factor that drove the fit and informativeness of the base model (data not shown). Other risk factors worth noting included use of antihypertensive medications (chi-square = 20), HDL cholesterol (chi-square = 18), and family history of heart attack (chi-square = 14).

When we used a more restrictive definition (as proposed by Chung et al. [28]) for CAC progression among those with CAC >0 at baseline, we found similar results: traditional risk factors remained associated with CAC progression, and there was minimal improvement with addition of novel markers to the base model. Thirteen intercurrent events occurred between baseline and follow-up CT scanning for CAC measurement. There was no change in model output results when data were reanalyzed with the exclusion of intercurrent events.

Table 4. Novel Marker Combinations Used to Predict CAC Progression

Combination Novel Marker Model	OR per 1 SD (95% CI)	c Statistic	AIC	LR Test p Value
Base model*		0.7110	2,524.65	
Model 1		0.7164	2,518.03	<0.01
Fibrinogen	1.06 (1.05–1.07)			
sICAM	1.11 (0.81–1.52)			
Factor VIIIc	1.05 (0.89–1.25)			
CIMT	1.06 (1.02–1.10)			
Model 2		0.7160	2,517.55	<0.01
LDLpn	0.91 (0.76–1.08)			
CRP	1.06 (0.96–1.18)			
Fibrinogen	0.98 (0.87–1.11)			
Urine albumin	1.11 (0.95–1.31)			
sICAM	1.17 (0.96–1.43)			
Model 3 (backward stepwise selection)		0.7158	2,513.01	
sICAM	1.18 (0.97–1.43)			
Factor VIIIc	1.09 (0.99–1.20)			
Age	1.08 (1.06–1.09)			
Sex	1.53 (1.17–2.00)			
Race/ethnicity	0.87 (0.80–0.95)			
DBP	1.02 (1.01–1.03)			
Antihypertensive medication use	1.76 (1.39–2.23)			
Total cholesterol	1.01 (1.00–1.01)			
HDL	0.99 (0.98–0.99)			
Smoking	1.42 (0.98–2.06)			
BMI	1.03 (1.01–1.05)			
Physical activity	1.00 (1.00–1.00)			
Family history of heart attack	1.45 (1.19–1.78)			
sICAM	1.17 (0.96–1.43)	0.7150	2,515.21	<0.01
CRP alone	1.07 (0.97–1.18)	0.711	2,524.66	0.15
Ln baseline CAC score (for those with baseline CAC >0, n =790)	1.59 (1.43–1.77)	0.739		

*Base model includes age, sex, race/ethnicity, SBP, DBP, antihypertensive medication use, current smoking, total and HDL cholesterol, family history of heart attack, BMI, and physical activity. †The rest of models are adjusted for the base model.
AIC = Akaike information criterion; CI = confidence interval; Ln = natural log; LR = likelihood ratio; other abbreviations as in Tables 1, 2, and 3.

DISCUSSION

Major study findings. In low-risk persons with FRS <10%, novel markers minimally improved the prediction of CAC progression beyond traditional cardiovascular risk factors. Individual novel marker levels were higher and were significantly associated with CAC progression in univariate

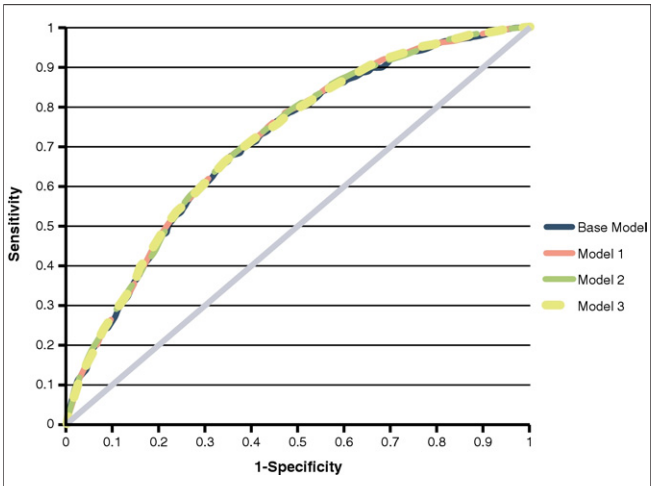


Figure 2. Area Under the ROC Curves

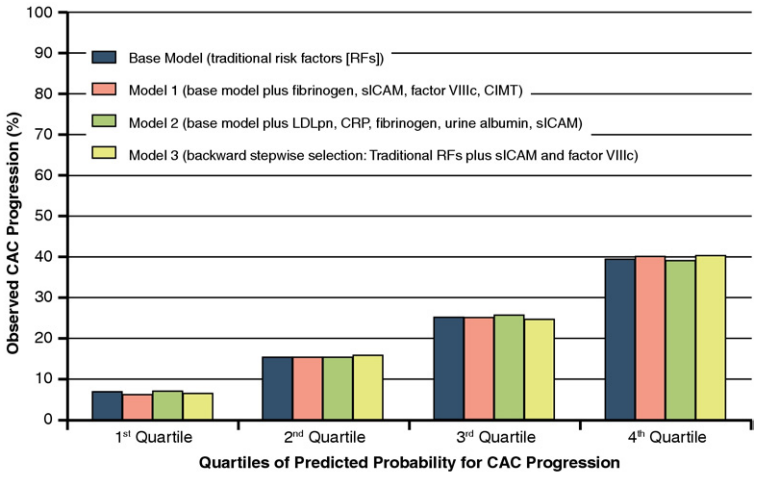
This compares the receiver-operating characteristic (ROC) curves for the base model with the best-fit models in the prediction of coronary artery calcium progression using combination novel markers. Base model: traditional risk factors (age, sex, race/ethnicity, systolic and diastolic blood pressure, hypertension treatment, total and high-density lipoprotein cholesterol, current smoking, body mass index, physical activity, and family history of heart attack). Model 1: base model plus fibrinogen, soluble intercellular adhesion molecule-1 (sICAM), factor VIIIc, and carotid intima-media thickness (CIMT). Model 2: base model plus low-density lipoprotein particle number (LDLpn), C-reactive protein, fibrinogen, urine albumin, and sICAM. Model 3: backward stepwise selection (traditional risk factors plus sICAM and factor VIIIc).

models. However, these associations became nonsignificant in multivariable models adjusting for age and other traditional risk factors in these already low-risk participants. Likewise, the novel marker combinations that significantly predicted CAC progression based on likelihood ratio tests very modestly improved the discrimination of the base model composed of traditional risk factors. Furthermore, although these best-fit models calibrated reasonably well, they were comparable to the base model in the prediction of an individual's risk of CAC progression. Findings were similar when incident CAC and increased CAC were examined separately.

Clinical implications. In this study of individuals classified as being at low 10-year risk for CHD events, 22% had CAC progression. Among those with CAC progression, 12% had incident CAC and 46% had increased CAC over a mean period of 2.5 years. Because CAC progression has been linked to CHD events (14–16), this finding represents a segment of the low-risk population at risk for CHD events over a short period of time who therefore may merit more intensive prevention efforts.

The findings of our study suggest that traditional risk factors still play a significant role in predicting disease progression, regardless of low-risk status. These findings are concordant with a previous cross-sectional study from our group (12), which showed that, even in people predicted to be at low risk for CHD events, traditional risk factors were still significantly associated with presence of any CAC and CAC ≥300. Traditional risk factors have previously been associated with CAC progression in all persons, no matter the risk level (15,19,29–32). However, to our knowledge, prediction of CAC progression using novel marker combinations has not previously been investigated, particularly in low-risk individuals. In addition, no studies have examined traditional risk factors in the prediction of CAC progression in low-risk persons.

Previous studies have shown that biomarkers do not substantially improve the prediction of CHD/CVD events beyond traditional risk factors (33–36). It is therefore not surprising that our study revealed that biomarkers do not predict CAC progression beyond traditional risk factors because these risk factors seem to create the inflammatory environment that generates changes in biomarker levels responsible for CAC progression. Cardiovascular risk factors, particularly those related to the metabolic syndrome (obesity, dyslipidemia, hypertension, and insulin resistance), as well as diabetes and smoking, lead to vascular injury with endothelial damage, oxidized lipid accumulation, and inflammation (24,37–39), which promote formation of atherosclerotic plaque (37,39,40). This process is considerably amplified by interactions between >1 risk factor (39). Calcification, which represents an advanced stage of atherosclerosis/plaque formation, is formed and regulated by this inflammatory milieu and is an active process, similar to bone formation, in which pericyte-like cells secrete a matrix scaffold that later becomes calcified (39). Progression of calcification likely represents the same process in a vessel with persistent inflammation and continued calcium formation. This inflammatory process is responsible for formation of inflammatory, thrombotic and endothelial dysfunction biomarkers and creates a vicious cycle leading to further atherosclerosis, which further worsens inflammation. As such, biomarkers should be considered risk markers (as they are termed) rather than risk factors, and efforts aimed at risk factor modification in low-risk individuals should be focused on traditional risk factors



CAC Progression Model	Probability Quartiles (%)			
	1st Quartile	2nd Quartile	3rd Quartile	4th Quartile
Base Model	7.87	15.40	24.10	40.27
Model 1	7.63	15.19	23.94	40.88
Model 2	7.64	15.17	23.95	40.88
Model 3	7.66	15.19	23.96	40.83

Figure 3. Calibration of Base Plus Novel Marker Best-Fit Models for CAC Progression

The models were assessed in their abilities to predict individual risk probabilities by comparing observed coronary artery calcium (CAC) progression in the study population with model-estimated probabilities of CAC progression. CRP = C-reactive protein; RF = risk factors; other abbreviations as in Figure 2.

that have been established as independent predictors of disease.

Other findings. Concordant with our main study results from developed models, the backward stepwise selection process chose traditional risk factors as being the most predictive of CAC progression in these already low-risk participants, even when incident and increased CAC were examined separately. It is noteworthy that there were minimal differences in associations of novel markers with incident versus increased CAC. However, the predictive utility of traditional risk factors for CAC progression was better for both groups combined.

Similar to other studies (20,30,41), our study found that compared with traditional risk factors and novel markers, baseline CAC score (for those with baseline CAC >0) was the single most important predictor of CAC progression in low-risk persons, with an increment of ~0.03 in the c statistic analysis. This finding suggests that if initially assessed, those low-risk persons with higher baseline CAC scores might benefit from future repeat testing for CAC progression, particularly in a setting in which traditional risk factors do not provide clear directives for risk factor modification approaches, assuming that demonstration of CAC progression would change clinical decision-making.

CIMT—another subclinical measure of vascular disease, either singly, or in combination with biomarkers—did not improve the prediction of CAC progression beyond traditional risk factors. This finding is particularly noteworthy because even though CIMT is a noninvasive test, its measurement is dependent on technician and reader skills, and it is more costly than traditional risk factors plus/minus biomarkers.

It is noteworthy that the risk of cancer associated with radiation exposure from cardiac CT is a projected risk which is low on an individual level but becomes significant while screening at the population level. To this end, our study makes the argument for avoiding radiation from cardiac CT, but rather using traditional risk factors in screening for atherosclerosis development and progression, even in low-risk persons.

Study limitations. First, our results might have been different had we included other markers associated with CHD/CVD such as troponin I or B-type natriuretic peptide. However, these were not available within the MESA cohort at the time of the current study. Second, because of the

age range and selection criteria for FRS <10%, we were unable to stratify our findings according to age, race/ethnicity, or sex due to small sample size and limited power to make meaningful conclusions. Third, because there were few events in these low-risk participants in the MESA cohort after the second ascertainment of CAC (29 CHD events or 1.1% of our study sample), we were unable to compare prediction of clinical events between our various models. Finally, sICAM levels were imputed from sICAM measured in only one-third of study participants.

It should be noted that follow-up CAC measurements were obtained at a mean of 2.5 years after the baseline study. As such, our study only examines factors that predict CAC progression in low-risk participants in the short term. A study assessing longer-term CAC progression would be useful.

CONCLUSIONS

Traditional cardiovascular risk factors seem to play a significant role, with good discrimination and calibration, in the prediction of CAC progression in those at low 10-year CHD risk according to FRS. Individual or combinations of novel markers (including CIMT and CRP) only minimally improved this prediction when added to the model. Consequently, for FRS-predicted low-risk persons, efforts aimed at identifying those at risk for disease development and progression should be focused on these well-known traditional risk factors, rather than the novel markers assessed here. This finding represents an economical and effective method for CHD risk screening and management decisions in low-risk persons and could help avoid radiation risks, possibly increased costs, and discovery of incidental findings (42) (necessitating follow-up CT scans) associated with CAC measurement in lower-risk individuals.

Reprint requests and correspondence: Dr. Donald M. Lloyd-Jones, Department of Preventive Medicine and Medicine, Bluhm Cardiovascular Institute, Northwestern University, 680 North Lake Shore Drive, Suite 1400, Chicago, Illinois 60611. *E-mail: dlj@northwestern.edu.*

REFERENCES

1. Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. Circulation 1998;97:1837–47.
2. Lakoski SG, Greenland P, Wong ND, et al. Coronary artery calcium scores and risk for cardiovascular events in women classified as "low risk" based on Framingham risk score: the multi-ethnic study of atherosclerosis (MESA). Arch Intern Med 2007;167:2437–42.
3. Greenland P, LaBree L, Azen SP, Doherty TM, Detrano RC. Coronary artery calcium score combined with Framingham score for risk prediction in asymptomatic individuals (published correction appears in JAMA 2004;291:563). JAMA 2004;291: 210–5.
4. Taylor AJ, Bindeman J, Feuerstein I, Cao F, Brazaitis M, O'Malley PG. Coronary calcium independently predicts incident premature coronary heart disease over measured cardiovascular risk factors: mean three-year outcomes in the Prospective Army Coronary Calcium (PACC) project. J Am Coll Cardiol 2005;46: 807–14.
5. Naghavi M, Libby P, Falk E, et al. From vulnerable plaque to vulnerable patient: a call for new definitions and risk assessment strategies: Part II. Circulation 2003;108:1772–8.
6. Ford ES, Giles WH, Mokdad AH. The distribution of 10-year risk for coronary heart disease among US adults: findings from the National Health and Nutrition Examination Survey III. J Am Coll Cardiol 2004; 43:1791–6.
7. Ajani UA, Ford ES. Has the risk for coronary heart disease changed among U.S. adults? J Am Coll Cardiol 2006; 48:1177–82.
8. Detrano R, Guerci AD, Carr JJ, et al. Coronary calcium as a predictor of coronary events in four racial or ethnic groups. N Engl J Med 2008;358: 1336–45.
9. Kondos GT, Hoff JA, Sevrukov A, et al. Electron-beam tomography coronary artery calcium and cardiac events: a 37-month follow-up of 5635 initially asymptomatic low- to intermediate-risk adults. Circulation 2003;107:2571–6.
10. Naghavi M, Falk E, Hecht HS, et al. From vulnerable plaque to vulnerable patient--Part III: Executive summary of the Screening for Heart Attack Prevention and Education (SHAPE) Task Force report. Am J Cardiol 2006;98:2H–15H.
11. Greenland P, Alpert JS, Beller GA, et al. 2010 ACCF/AHA guideline for assessment of cardiovascular risk in asymptomatic adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2010;56:e50–103.
12. Okwuosa TM, Greenland P, Lakoski SG, et al. Factors associated with presence and extent of coronary calcium in those predicted to be at low risk according to Framingham risk score (from the Multi-Ethnic Study of Atherosclerosis). Am J Cardiol 2011; 107:879–85.
13. Budoff MJ, Hokanson JE, Nasir K, et al. Progression of coronary artery calcium predicts all-cause mortality. J Am Coll Cardiol Img 2010;3: 1229–36.
14. Raggi P, Callister TQ, Shaw LJ. Progression of coronary artery calcium and risk of first myocardial infarction in patients receiving cholesterol-lowering therapy. Arterioscler Thromb Vasc Biol 2004;24:1272–7.
15. Raggi P, Cooil B, Ratti C, Callister TQ, Budoff M. Progression of coronary artery calcium and occurrence of myocardial infarction in patients with and without diabetes mellitus. Hypertension 2005;46:238–43.

16. Raggi P, Cooil B, Shaw LJ, et al. Progression of coronary calcium on serial electron beam tomographic scanning is greater in patients with future myocardial infarction. Am J Cardiol 2003;92:827–9.
17. McEvoy JW, Blaha MJ, Defilippis AP, et al. Coronary artery calcium progression: an important clinical measurement? A review of published reports. J Am Coll Cardiol 2010;56: 1613–22.
18. Hsia J, Klouj A, Prasad A, Burt J, Adams-Campbell LL, Howard BV. Progression of coronary calcification in healthy postmenopausal women. BMC Cardiovascular Disorders 2004; 4:21.
19. Elkeles RS, Godsland IF, Rubens MB, Feher MD, Nugara F, Flather MD. The progress of coronary heart disease in type 2 diabetes as measured by coronary calcium score from electron beam computed tomography (EBCT): the PREDICT study. Atherosclerosis 2008;197:777–83.
20. Min JK, Lin FY, Gidseg DS, et al. Determinants of coronary calcium conversion among patients with a normal coronary calcium scan: what is the "warranty period" for remaining normal? J Am Coll Cardiol 2010;55: 1110–7.
21. Anand DV, Lim E, Darko D, et al. Determinants of progression of coronary artery calcification in type 2 diabetes role of glycemic control and inflammatory/vascular calcification markers. J Am Coll Cardiol 2007;50: 2218–25.
22. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med 1999; 130:461–70.
23. Bild DE, Bluemke DA, Burke GL, et al. Multi-ethnic study of atherosclerosis: objectives and design. Am J Epidemiol 2002;156:871–81.
24. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). JAMA 2001;285:2486–97.
25. LaMonte MJ, Durstine JL, Addy CL, Irwin ML, Ainsworth BE. Physical activity, physical fitness, and Framingham 10-year risk score: the cross-cultural activity participation study. J Cardiopulm Rehabil 2001;21:63–70.
26. Berry JD, Liu K, Folsom AR, et al. Prevalence and progression of subclinical atherosclerosis in younger adults with low short-term but high lifetime estimated risk for cardiovascular disease: the coronary artery risk development in young adults study and multi-ethnic study of atherosclerosis. Circulation 2009; 119:382–9.
27. Schafer JL. Analysis of Incomplete Multivariate Data. 1st edition. London, United Kingdom: CRC Press, 1997.
28. Chung H, McClelland RL, Katz R, Carr JJ, Budoff MJ. Repeatability limits for measurement of coronary artery calcified plaque with cardiac CT in the Multi-Ethnic Study of Atherosclerosis. AJR Am J Roentgenol 2008;190: W87–92.
29. Kronmal RA, McClelland RL, Detrano R, et al. Risk factors for the progression of coronary artery calcification in asymptomatic subjects: results from the Multi-Ethnic Study of Atherosclerosis (MESA). Circulation 2007;115:2722–30.
30. Schmermund A. Progression of coronary calcium [in German]. Herz. 2001;26:278–86.
31. Taylor AJ, Bindeman J, Le TP, Bauer K, Byrd C, Feuerstein IM, et al. Progression of calcified coronary atherosclerosis: relationship to coronary risk factors and carotid intima-media thickness. Atherosclerosis 2008;197: 339–45.
32. Taylor AJ, Wu H, Bindeman J, et al. The relationship between the cardiometabolic syndrome and coronary artery calcium progression. J Clin Hypertens (Greenwich). 2009;11:505–11.
33. Wang TJ, Gona P, Larson MG, et al. Multiple biomarkers for the prediction of first major cardiovascular events and death. N Engl J Med 2006;355:2631–9.
34. Shlipak MG, Fried LF, Cushman M, et al. Cardiovascular mortality risk in chronic kidney disease: comparison of traditional and novel risk factors. JAMA 2005;293:1737–45.
35. Melander O, Newton-Cheh C, Almgren P, et al. Novel and conventional biomarkers for prediction of incident cardiovascular events in the community. JAMA 2009;302:49–57.
36. Folsom AR, Chambless LE, Ballantyne CM, et al. An assessment of incremental coronary risk prediction using C-reactive protein and other novel risk markers: the atherosclerosis risk in communities study. Arch Intern Med 2006;166:1368–73.
37. Rizzo M, Rizvi AA, Rini GB, et al. The therapeutic modulation of atherogenic dyslipidemia and inflammatory markers in the metabolic syndrome: what is the clinical relevance? Acta Diabetologica 2009;46:1–11.
38. Tracy RP. Inflammation, the metabolic syndrome and cardiovascular risk. Int J Clin Pract Suppl 2003:10–7.
39. Lusis AJ. Atherosclerosis. Nature 2000;407:233–41.
40. Berenson GS, Srinivasan SR, Bao W, Newman WP 3rd, Tracy RE, Wattigney WA. Association between multiple cardiovascular risk factors and atherosclerosis in children and young adults. The Bogalusa Heart Study. N Engl J Med 1998;338:1650–6.
41. Yoon HC, Emerick AM, Hill JA, Gjertson DW, Goldin JG. Calcium begets calcium: progression of coronary artery calcification in asymptomatic subjects. Radiology 2002;224: 236–41.
42. Machaalany J, Yam Y, Ruddy TD, et al. Potential clinical and economic consequences of noncardiac incidental findings on cardiac computed tomography. J Am Coll Cardiol 2009;54: 1533–41.

Key Words: coronary calcium ■ Framingham risk score ■ progression ■ risk factors.