Comparison of Novel Risk Markers for Improvement in Cardiovascular Risk Assessment in Intermediate-Risk Individuals

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Context Risk markers including coronary artery calcium, carotid intima–media thickness, ankle-brachial index, brachial flow–mediated dilation, high-sensitivity C-reactive protein (CRP), and family history of coronary heart disease (CHD) have been reported to improve on the Framingham Risk Score (FRS) for prediction of CHD, but there are no direct comparisons of these markers for risk prediction in a single cohort.

Objective We compared improvement in prediction of incident CHD/cardiovascular disease (CVD) of these 6 risk markers within intermediate-risk participants (FRS >5%-<20%) in the Multi-Ethnic Study of Atherosclerosis (MESA).

Design, Setting, and Participants Of 6814 MESA participants from 6 US field centers, 1330 were intermediate risk, without diabetes mellitus, and had complete data on all 6 markers. Recruitment spanned July 2000 to September 2002, with follow-up through May 2011. Probability-weighted Cox proportional hazard models were used to estimate hazard ratios (HRs). Area under the receiver operator characteristic curve (AUC) and net reclassification improvement were used to compare incremental contributions of each marker when added to the FRS, plus race/ethnicity.

Main Outcome Measures Incident CHD defined as myocardial infarction, angina followed by revascularization, resuscitated cardiac arrest, or CHD death. Incident CVD additionally included stroke or CVD death.

Results After 7.6-year median follow-up (IQR, 7.3-7.8), 94 CHD and 123 CVD events occurred. Coronary artery calcium, ankle-brachial index, high-sensitivity CRP, and family history were independently associated with incident CHD in multivariable analyses (HR, 2.60 [95% CI, 1.94-3.50]; HR, 0.79 [95% CI, 0.66-0.95]; HR, 1.28 [95% CI, 1.00-1.64]; and HR, 2.18 [95% CI, 1.38-3.42], respectively). Carotid intima–media thickness and brachial flow–mediated dilation were not associated with incident CHD in multivariable analyses (HR, 1.17 [95% CI, 0.95-1.45] and HR, 0.95 [95% CI, 0.78-1.14]). Although addition of the markers individually to the FRS plus race/ethnicity improved AUC, coronary artery calcium afforded the highest increment (0.623 vs 0.784), while brachial flow–mediated dilation had the least (0.623 vs 0.639). For incident CHD, the net reclassification improvement with coronary artery calcium was 0.659, brachial flow–mediated dilation was 0.024, ankle-brachial index was 0.036, carotid intima–media thickness was 0.102, family history was 0.160 and high-sensitivity CRP was 0.079. Similar results were obtained for incident CVD.

Conclusions Coronary artery calcium, ankle-brachial index, high-sensitivity CRP, and family history were independent predictors of incident CHD/CVD in intermediate-risk individuals. Coronary artery calcium provided superior discrimination and risk reclassification compared with other risk markers.

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Current trends in primary prevention of cardiovascular disease (CVD) emphasize the need to treat individuals based on their global cardiovascular risk.[1] Accordingly, practice guidelines recommend approaches to classify individuals as high, intermediate, or low risk using the Framingham Risk Score (FRS) or other similar CVD risk prediction models.[2,3] However, there is increasing recognition of the imprecision of these classifications such that the intermediate-risk group actually represents a composite of higher-risk individuals for whom more aggressive (ie, drug) therapy might be indicated. The intermediate-risk group also contains lower-risk individuals in whom CVD might be managed with lifestyle measures alone. This recognition has motivated researchers to identify markers that could offer greater discrimination of higher- and lower-risk patients within the intermediate-risk group.

Risk markers that have shown promise in improving risk discrimination include carotid intima–media thickness (CIMT), coronary artery calcium (CAC)

For editorial comment see p 816.

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scores, brachial flow–mediated dilation (FMD), ankle-brachial index (ABI), high-sensitivity C-reactive protein (CRP), and family history of coronary heart disease (CHD).[4-9] A recent American College of Cardiology Foundation/American Heart Association statement on the use of markers to improve cardiovascular risk prediction beyond the FRS gave family history a class I recommendation; CIMT, CAC, ABI, and high-sensitivity CRP received class II recommendations, while the American College of Cardiology Foundation/American Heart Association recommended against the use of brachial FMD (class III).[10] However, these recommendations were limited by the relative paucity of published data and the fact that the published studies of individual risk markers were performed in different cohorts with different composite outcomes, analytic methodologies, and inadequate statistical power to detect improvements of risk prediction beyond commonly used risk-prediction algorithms. Moreover, there are no comprehensive head-to-head comparisons of these risk markers in a single population cohort similar to the US population. Determining the relative improvements in prediction afforded by various risk markers, especially when considering intermediate-risk individuals as classified by the FRS, could help determine the most efficient strategy for identifying select, intermediate-risk participants for more aggressive primary prevention interventions, including the use of aspirin and lower targets for drug treatments of low-density lipoprotein (LDL) cholesterol and blood pressure.

In this report, we assess the improvements in prediction accuracy and reclassification to high- and low-risk categories using CIMT, CAC, FMD, ABI, high-sensitivity CRP, and family history of CHD in asymptomatic adults classified as intermediate risk (FRS standards) who participated in the Multi-Ethnic Study of Atherosclerosis (MESA).

METHODS

Study Population and Data Collection

The study design for the MESA study has been published elsewhere.[11] In brief, MESA is a prospective cohort study to investigate the prevalence, correlates, and progression of subclinical CVD in individuals without known CVD at baseline.

The full cohort includes 6814 women and men aged 45 to 84 years without known CVD, recruited from 6 US communities (Baltimore, Maryland; Chicago, Illinois; Forsyth County, North Carolina; Los Angeles County, California; northern New York City, New York; and St Paul, Minnesota). Self-reported race/ethnicity was collected to explore the possible racial/ethnic differences in the development and progression of atherosclerosis. The race/ethnic breakdown of MESA participants was 38% white, 28% black, 22% Hispanic, and 12% Chinese adults. Participants with diabetes were excluded because it is considered to be a CHD risk equivalent. Diabetes was defined as self-reported history of diabetes mellitus, diabetes medication use, or a fasting glucose level of 126 mg/dL or greater (for mmol/L, multiply by 0.0555). Demographics, medical history, and anthropometric and laboratory data for the present study were taken from the first examination (July 2000 to August 2002). Current smoking was defined as having smoked a cigarette in the last 30 days. Use of antihypertensive and other medications was based on review of prescribed medication containers. Resting blood pressure was measured 3 times in the seated position and the average of the second and third readings was recorded. Hypertension was defined as a systolic blood pressure of at least 140 mm Hg, diastolic blood pressure of at least 90 mm Hg, or use of medication prescribed for hypertension. Body mass index was calculated as weight in kilograms divided by height in meters squared. Total cholesterol and high-density lipoprotein (HDL) cholesterol were measured from blood samples obtained after a 12-hour fast. LDL cholesterol was estimated using the Friedewald equation.[12] High-sensitivity CRP was measured using the BNII nephelometer (N High Sensitivity CRP; Dade Behring Inc) at the Laboratory for Clinical Biochemistry Research (University of Vermont, Burlington). Analytical intra-assay coefficient of variations ranged from 2.3% to 4.4%, and inter-assay coefficient of variation ranged from 2.1% to 5.7% with a detection level of 0.18 mg/L. Family history of CHD was obtained by asking participants whether any member in their immediate family (parents, siblings, and children) experienced fatal or nonfatal myocardial infarction. The MESA study was approved by the institutional review boards of each study site and written informed consent was obtained from all participants.

Measurement of ABI

Protocol for ankle-brachial index measurement in MESA was reported by Criqui et al.[9] Briefly, systolic blood pressure measurements in the bilateral brachial, dorsalis pedis, and posterior tibial arteries were obtained in the supine position using a handheld Doppler instrument with a 5-mHz probe. To avoid potential bias from subclavian stenosis, the higher of the brachial artery pressures was used as the denominator. For each lower extremity, the ABI numerator used was the highest pressure (dorsalis pedis or posterior tibial) from that leg. Reproducibility of ABI was evaluated using measurements of 43 participants by 2 technicians. The interreader and intrareader correlation coefficients were 0.845 and 0.937, with the intrareader and interreader coefficients of variation being 5.14% and 3.27%.

Measurement of the CAC Score

CT scanning and interpretation methods in MESA have were reported by Carr et al.[13] Scanning centers assessed CAC by chest computed tomography (CT) with either a cardiac-gated electron-beam CT scanner (Chicago, Los Angeles County, and New York City field centers) or a multidetector CT sys-

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Table 1. Baseline Characteristics of Participants in the Multi-Ethnic Study of Atherosclerosis at Intermediate Framingham Risk (N = 1330)[a]

Variables	Mean (SD)
Age, y	63.8 (9.5)
Women, No. (%)	443 (33.3)
Race/ethnicity, No. (%)	
White	475 (35.7)
Chinese	225 (16.9)
Black	292 (22.0)
Hispanic	338 (25.4)
Body mass index[b]	27.9 (4.7)
Cigarette smoking status, No. (%)	
Never	616 (46.3)
Former	494 (37.1)
Current	220 (16.5)
Cholesterol, mg/dL	
Total	196.9 (34.6)
LDL	122.4 (30.3)
HDL	46.5 (11.9)
Triglycerides, mg/dL	140.7 (77.0)
Blood pressure, mm Hg	
Systolic	129.9 (19.8)
Diastolic	74.4 (9.8)
Heart rate, beats/min	61.9 (9.2)
Statin use, No. (%)	187 (14.1)
Blood pressure medication use, No. (%)	508 (38.2)
Coronary calcium score, median (IQR)[c]	7.0 (0-111.7)
Brachial flow–mediated dilation, median (IQR), %	3.60 (2.1-5.4)
Carotid intima–media thickness, median (IQR), mm	0.86 (0.76-0.98)
Ankle-brachial index, median (IQR)	1.14 (1.07-1.20)
High-sensitivity CRP, median (IQR), mg/L	1.62 (0.79-3.68)
Family history of premature CHD, No. (%)	567 (42.6)
Framingham Risk Score, median (IQR), %	8.8 (6.5-12.2)

Abbreviations: CHD, coronary heart disease; CRP, C-reactive protein; HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein.

SI conversion factors: To convert CRP from mg/L to nmol/L, multiply by 9.524; HDL, LDL, and total cholesterol from mg/dL to mmol/L, multiply by 0.0259; triglycerides from mg/dL to mmol/L, multiply by 0.0113.

[a] Data are reported as mean (SD) unless otherwise indicated.

[b] Body mass index is calculated as weight in kilograms divided by height in meters squared.

[c] Indicates Agatston.

tem (Baltimore, Forsyth County, and St Paul field centers). Certified technologists scanned all participants twice over phantoms of known physical calcium concentration. A radiologist or cardiologist read all CT scans at a central reading center (Los Angeles Biomedical Research Institute at Harbor–UCLA, Torrance, California). We used the mean Agatston score for the 2 scans in all analyses[14] Intraobserver and interobserver agreements were excellent (κ=0.93 and κ=0.90).

Measurement of Brachial FMD

Methods for measuring and interpreting brachial FMD in MESA were reported by Yeboah et al.[8] Intrareader reproducibility for baseline diameter, maximum diameter, and percent FMD was evaluated by comparing an original and a blinded quality control reread of ultrasounds from 40 MESA participants. The intraclass correlation coefficients were 0.99, 0.99, and 0.93, respectively. Intraparticipant variability was evaluated by comparing results from repeated examinations of 19 participants on 2 days, 1 week apart. The intraclass correlation coefficients for baseline diameter, maximum diameter, and percent FMD were 0.90, 0.90, and 0.54, respectively. Percent technical error of measurement was 1.39% for baseline diameter measurement, 1.47% for maximum diameter measurement, and 28.4% for percent FMD measurement.

Measurement of CIMT

Methods for measuring and interpreting CIMT were reported by Polak et al.[15] The mean of maximum intima-media thickness of the common carotid artery was used. Reproducibility was assessed by blinded replicate readings of CIMT performed by 2 readers. One reader reread 66 studies for a between-reader correlation coefficient of 0.84 (n=66), and a second reader reread 48 studies for a correlation coefficient of 0.86. The rescan and the reread coefficients of variation were 7.07% and 3.48%.

Ascertainment of Incident CHD and CVD

Follow-up took place through May 2011. CVD events were adjudicated by a MESA study committee that included cardiologists, physician epidemiologists, and neurologists. A detailed description of the adjudication process was previously reported.[8] For the purposes of this study, we define incident CHD as myocardial infarction, CHD death, resuscitated cardiac arrest, or definite or probable angina if followed by coronary revascularization. Incident CVD additionally included stroke or CVD death as defined by the MESA protocol (available at http://www.mesa-nhlbi.org). Thus CHD is a subset of CVD.

Statistical Analysis

The study population was limited to MESA participants classified as intermediate risk (estimated 10-y CHD risk of >5%-<20%) based on the Framingham risk equation.[3] The intermediate-risk range was chosen to make our results comparable to other studies that have reported data on intermediate-risk participants using some of the risk markers under consideration.[4-6] Descriptive data are presented as mean (SD) for continuous variables or frequencies of participants for categorical variables. CAC scores were expressed as ln (CAC+1). Family history was entered into models as a categorical variable (yes/no), high-sensitivity CRP had a highly skewed distribution and was log transformed; all other variables were expressed as continuous variables. Weighted analyses were done to reflect the sampling from the overall MESA cohort. Probability-weighted Cox proportional hazard analysis with robust variance estimates was used to assess the association between each of the markers (CAC, FMD, CIMT, ABI, high-sensitivity CRP, and family history of CHD) and incident CHD or CVD in univariable and multivariable models while adjusting for age, sex, race/ethnicity, total and HDL cholesterol, cigarette smoking status, body mass index, blood pressure medication use, and hydroxmethyl glutaryl coenzyme A–reductase inhibitor use. These confounders were chosen based on their association with the outcomes of interest (incident CHD/

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CVD) in the current analysis and prior published data.

We assessed the improvement in discrimination by comparing the area under the receiver operator characteristic curves (AUC) in models with and without each novel risk marker, using the method of DeLong et al.[16] The FRS (derived using age, sex, total cholesterol, HDL cholesterol, smoking status, systolic blood pressure, and blood pressure medication use), a general clinical practice tool, plus race/ethnicity, served as the baseline model. ROC curves were developed using a probability-weighted Cox model. We assessed the classification of risk using the net reclassification improvement (NRI):

NRI=[*Prob* (being correctly reclassified to a higher-risk category/event)

–*Prob* (being incorrectly reclassified to a lower-risk category/event)]

+[*Prob* (being correctly reclassified to a lower-risk category/nonevent)

–*Prob* (being incorrectly classified to a higher-risk category/nonevent)].[17]

The NRI captures the relative improvement in classification associated with the additional predictive variable, while explicitly balancing trade off between changes in sensitivity and specificity. NRI is the sum of 2 percentages with different denominators and hence, is reported as a proportion (possible range, –2.0 to 2.0). At the time of these analyses, the mean observed follow-up in MESA was 7.5 years (maximum follow-up, 9 y). To account for the fact that actual follow-up was less than 10 years, we redefined the risk in terms of 7.5-year risk when calculating the NRI, using a logistic regression model with probability weighting to reflect the sampling from the overall cohort. Based on the new model, intermediate 7.5-year risk categories for CHD and CVD were defined as 2.0% to 15.4% and 3.4% to 21.1%. With the addition of each novel risk marker to the base model, participants were considered to be reclassified to high risk if their estimated risks for CHD and CVD were greater than 15.4% and 21.1%, and reclassified to low risk if their estimated risks were lower than 2.0% and 3.4% for CHD and CVD. As a sensitivity analysis, we repeated our evaluation of ABI and the imaging markers using the Reynolds score (RS, calculated separately for men and women)[6,18] instead of the FRS to define these risk groups. This score incorporates family history and log-transformed high-sensitivity CRP in addition to other risk factors. A 2-tailed *P* value of less than .05 was considered significant. All statistical analyses were performed using SAS version 9.2 (SAS Institute).

Table 2. Association of Several Novel Risk Markers With Incident Coronary Heart Disease (No. of Events = 94)[a]

	Univariable		Multivariable[b]	
Marker	HR (95% CI)[c]	*P* Value	HR (95%CI)[c]	*P* Value
ABI	0.78 (0.66-0.93)	.005	0.79 (0.66-0.95)	.01
Brachial FMD	0.82 (0.66-1.03)	.09	0.93 (0.74-1.16)	.52
CAC[d]	2.72 (2.09-3.55)	<.001	2.60 (1.94-3.50)	<.001
Carotid IMT	1.33 (1.12-1.59)	.001	1.17 (0.95-1.45)	.13
Family history	2.39 (1.54-3.70)	<.001	2.18 (1.38-3.42)	.001
High-sensitivity CRP[d]	1.26 (1.01-1.57)	.05	1.28 (1.00-1.64)	.05

Abbreviations: ABI, ankle-brachial index; CAC, coronary calcium score; CRP, C-reactive protein; FMD, flow-mediated dilation; IMT, intima-media thickness; HR, hazard ratio.

[a] There were 43 myocardial infarctions, 3 resuscitated cardiac arrests, 44 cases of angina followed by revascularization, and 14 deaths due to coronary heart disease that occurred during follow-up. An individual may have experienced more than 1 event but only the first event was included for the composite number of events used in this analysis.

[b] Multivariable models were adjusted for age, sex, race/ethnicity, systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, smoking status, body mass index (calculated as weight in kilograms divided by height in meters squared), blood pressure medication use, and statin use.

[c] For continuous risk markers, HRs are standardized per unit SD change in the marker.

[d] CAC was expressed as ln (CAC + 1) and high-sensitivity CRP was log transformed.

RESULTS

Study Cohort

The final study population included 1330 participants without diabetes mellitus, with an FRS of more than 5% to less than 20%, and with complete data on all 6 of the novel risk markers. The median (IQR) for the FRS of the cohort at baseline was 8.8% (6.5%-12.2%). The baseline characteristics of the study population are shown in TABLE 1.

After a median follow-up of 7.6 years (IQR, 7.3-7.8; maximum follow-up, 9 y), 94 participants (7.1%) experienced a CHD event and 123 (9.2%) experienced a CVD event. Specific events were: 43 with myocardial infarction, 3 with resuscitated cardiac arrest, 14 with CHD death, 44 with angina followed by revascularization, and 31 participants with stroke.

Association of Risk Markers With Incident CHD and CVD

In the univariable probability-weighted Cox proportional hazard analyses, each of the novel risk markers was associated with incident CHD; however, after adjusting for confounders, the associations with CIMT and FMD were no longer significant (TABLE 2). Among all of the risk markers, CAC had the strongest association. Similarly, for incident CVD in univariable analyses, each of the novel risk markers was associated with events except high-sensitivity CRP. However, after adjusting for confounders, the associations between CIMT and FMD were no longer significant (eTable 1). CAC also had the strongest association in the multivariable models for CVD.

Improvement of Discrimination by Addition of Novel Risk Markers to the FRS

For CHD/CVD events, the addition of each of the 6 risk markers to the baseline model improved the AUC. CAC showed the highest increment while FMD showed the least increment (FIGURE) for incident CHD. CAC also showed the highest increment while high-sensitivity CRP showed the least increment for incident CVD (Figure).

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Classification of Risk

Using TABLE 3 (FRS+CAC variable) as an example, 51.1% of participants who had CHD (events) and 54.9% of those who did not have CHD (nonevents) during follow-up period were reclassified either to low or high risk by the addition of CAC to the FRS(+race/ethnicity). Applying the NRI formula that considers both those correctly reclassified as well as those incorrectly reclassified, a net 25.5% of the events group were reclassified to high risk appropriately, while a net 40.4% of the nonevents group were appropriately reclassified into the low-risk group by the addition of CAC to FRS(+race/ethnicity). The NRI for the addition of CAC to FRS (+race/ethnicity) is therefore calculated by adding 0.255 to 0.404 (0.255+0.405=0.659).

The addition of CAC to the FRS (+race/ethnicity) resulted in the highest NRI (0.659) and the greatest absolute number of correctly reclassified participants (n=625) (Table 3), while the addition of FMD resulted in the lowest NRI (0.024) and the fewest total number of correctly reclassified individuals. Carotid IMT, ABI, CRP, and family history afforded modest NRIs for CHD events (Table 3). CAC also provided the greatest NRI and total number of correctly reclassified participants for CVD events (Figure and TABLE 4). Among the non-CAC risk markers, family history performed the best for CHD risk reclassification (NRI=0.160), while ABI performed the best for CVD risk reclassification (NRI=0.068).

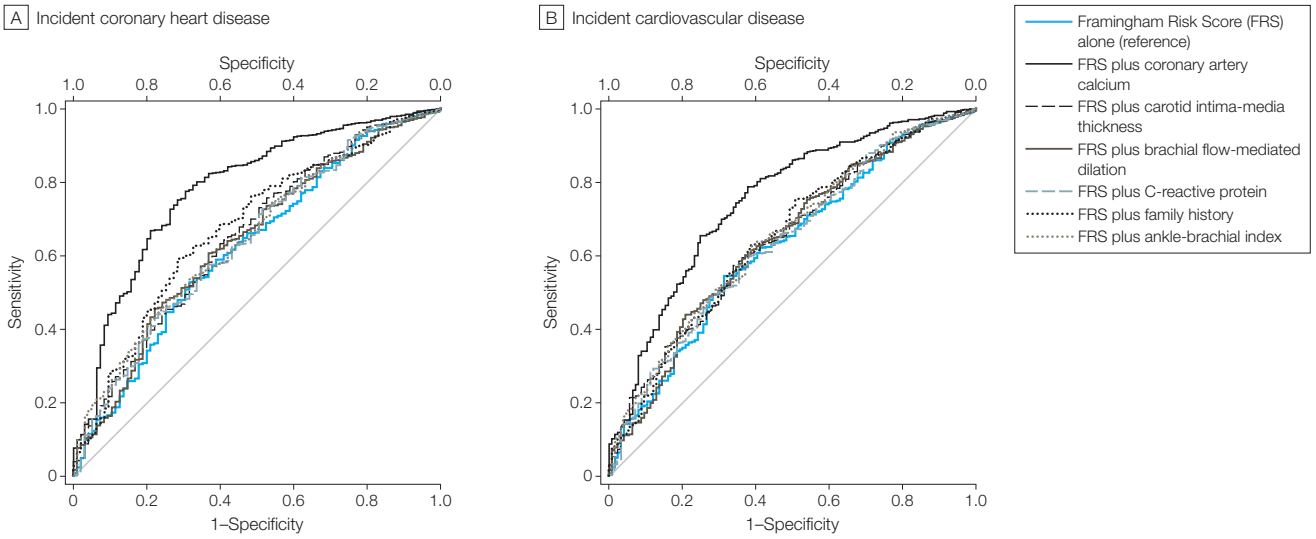
The respective AUCs were 0.642 for the RS alone, 0.766 for RS plus CAC, 0.643 for RS plus CIMT, 0.648 for RS plus ABI, and 0.642 for RS plus FMD for incident CHD in the present cohort. The NRIs were 0.528 for RS plus CAC, 0.003 for RS plus CIMT, 0.002 for RS plus ABI, and 0 for RS plus FMD over RS alone for incident CHD. Similarly the AUCs were 0.645 for FRS alone, 0.742 for RS plus CAC, 0.645 for RS plus CIMT, 0.656 for RS plus ABI, and 0.646 fpr RS plus FMD for incident CVD. The NRIs were 0.415 for RS plus CAC, 0 for RS plus CIMT, 0.008 for RS plus ABI, and 0.007 for RS plus FMD over RS alone for incident CVD.

COMMENT

The current study shows that among 6 of the most promising novel risk markers, CAC provides the highest improvement in discrimination over the FRS and RS in individuals classified as intermediate risk. The present study provides additional support for the use of CAC as a tool for refining cardiovascular risk prediction in individuals classified as intermediate risk by the FRS or the RS. To our knowledge, this is the first study to compare directly the improvement in risk prediction provided by the novel markers included in the present study in a multiethnic cohort with intermediate Framingham or Reynolds risk.

Previous studies showed that CIMT, CAC, brachial FMD, ABI, high-sensitivity CRP and family history of CHD improve the classification of risk over the FRS, but to varying degrees. Direct comparisons between studies should be made with caution because

Figure. Receiver Operator Characteristic Curves Showing Area Under the Curve for Incident Coronary Heart Disease and Incident Cardiovascular Disease in Intermediate-Risk MESA Participants



A, Receiver operator characteristic curves showing area under the curve for FRS alone, 0.623; FRS plus coronary artery calcium, 0.784 ($P<.001$); FRS plus intima-media thickness, 0.652 ($P=.01$); FRS plus flow-mediated dilation, 0.639 ($P=.06$); FRS plus high-sensitivity C-reactive protein, 0.640 ($P=.03$); FRS plus family history, 0.675 ($P=.001$); and FRS plus ankle-brachial index, 0.650 ($P=.01$). B, Receiver operator characteristic curves showing area under the curve for FRS alone, 0.623; FRS plus coronary artery calcium, 0.784 ($P<.001$); FRS plus intima-media thickness, 0.652 ($P=.01$); FRS plus flow-mediated dilation, 0.639 ($P=.06$); FRS plus high-sensitivity C-reactive protein, 0.640 ($P=.03$); FRS plus family history, 0.675 ($P=.001$); and FRS plus ankle-brachial index, 0.650 ($P=.01$). MESA indicates Multi-Ethnic Study of Atherosclerosis.

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they were conducted in different cohorts, did not have uniform definitions of the primary outcome, and had varying duration of follow-up. Nambi et al[4] showed in the Atherosclerosis Risk In Communities study that CIMT improved the AUC from 0.742 to 0.750, and had a net clinical NRI of 0.167. Polonsky et al[5] showed in a larger subset of the MESA study that CAC is an independent predictor of CHD, improved the AUC from 0.76 to 0.81, and has a net clinical NRI of 0.55 in the intermediate-risk stratum. Yeboah et al[8] showed that brachial FMD is an inde-

Table 3. Net Reclassification Improvement (NRI) for Incident Coronary Heart Disease Events With Addition of Novel Risk Markers to the Framingham Risk Score in Intermediate-Risk MESA Participants (N = 1330)

Variable	% Reclassified	Risk Category, No. of Events FRS Events (n = 94) FRS Nonevents (n = 1236) Low	Intermediate	High	% Net Correct Reclassification	NRI
FRS plus carotid IMT						.102
Events	7.4	0	87	7	7.4	
Nonevents	5.3	50	1170	16	2.8	
FRS plus CAC						.659
Events	51.1	12	46	36	25.5	.
Nonevents	54.9	589	557	90	40.4	
FRS plus brachial FMD						.024
Events	0.0	0	94	0	0	
Nonevents	3.2	35	1196	5	2.4	
FRS plus ABI						.036
Events	4.3	1	90	3	2.1	
Nonevents	4.0	34	1186	16	1.5	
FRS plus high-sensitivity CRP						.079
Events	4.3	0	90	4	4.3	
Nonevents	5.2	54	1172	10	3.6	
FRS plus family history						.160
Events	8.5	0	86	8	8.5	
Nonevents	11.2	116	1097	23	7.5	

Abbreviations: ABI, ankle-brachial index; CAC, coronary calcium score; CRP, C-reactive protein; FMD, flow-mediated dilation; FRS, Framingham Risk Score; IMT, intima-media thickness; MESA, Multi-Ethnic Study of Atherosclerosis.

Table 4. Net Reclassification Improvement (NRI) for Incident Cardiovascular Disease Events With Addition of Novel Risk Markers to the Framingham Risk Score in Intermediate-Risk MESA Participants (N = 1330)

Variable	% Reclassified	Risk Category, No. of Events FRS Events (n = 123) FRS Nonevents (n = 1207) Low	Intermediate	High	% Net Correct Reclassification	NRI
FRS plus carotid IMT						.060
Events	3.3	0	119	4	3.3	
Nonevents	3.8	39	1161	7	2.7	
FRS plus CAC						.466
Events	36.6	16	78	29	10.6	
Nonevents	45.7	493	655	59	36.0	
FRS plus brachial FMD						.023
Events	2.4	3	120	0	–2.4	
Nonevents	5.6	62	1140	5	4.7	
FRS plus ABI						
Events	4.1	0	118	5	4.1	.068
Nonevents	4.6	44	1151	12	2.7	
FRS plus high-sensitivity CRP						.037
Events	1.6	0	121	2	1.6	
Nonevents	3.2	32	1168	7	2.1	
FRS plus family history						.040
Events	2.4	1	120	2	0.8	
Nonevents	4.9	49	1148	10	3.2	

Abbreviations: ABI, ankle-brachial index; CAC, coronary calcium score; CRP, C-reactive protein; FMD, flow-mediated dilation; FRS, Framingham Risk Score, IMT, intima-media thickness; MESA, Multi-Ethnic Study of Atherosclerosis.

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pendent predictor of incident CVD, and that it did not improve the AUC of the FRS (0.74) but has a net clinical NRI, defined using the 10% to 20% Framingham risk, of 0.28. Fowkes et al[19] showed in a meta-analysis that ABI is an independent predictor of incident CVD, and improves the AUC from 0.646 to 0.655 and reclassification of the risk category and modification of treatment recommendations in approximately 19% of men and 36% of women. Wilson et al[20] showed in the Framingham Heart Study that high-sensitivity CRP is an independent predictor of incident CHD/CVD, it improved AUC from 0.795 to 0.865 and to 0.799, and it had an NRI of 0.118 and 0.056, respectively. Sivapalaratnam et al[7] showed in the EPIC-Norfolk study that family history of CHD is an independent predictor of incident CHD with a net clinical NRI of 0.021.

Recently, investigators from the Rotterdam study also performed a direct comparison of several novel risk markers, and also found that CAC provided the most robust improvement in risk prediction. Kavousi et al[21] compared the N-terminal fragment of prohormone B-type natriuretic peptide, Von Willebrand factor antigen, fibrinogen levels, homocysteine levels, uric acid levels, high-sensitivity CRP, leukocyte count, chronic kidney disease, CAC, CIMT, peripheral artery disease, and pulse wave velocity to the FRS using a similar definition of CHD and statistical approach to the current study. The authors found that CAC provided the highest increment in AUC and NRI over the FRS. It is noteworthy that the Rotterdam investigators found similar results to the current study, despite differences in the 2 study populations. All of the Rotterdam Study participants were white and approximately 13% of the cohort had diabetes mellitus.

Even though our study indicates considerable superiority of CAC over several risk markers for risk prediction of CHD and CVD, several other factors should be considered before making broad recommendations about incorporation of CAC into primary prevention screening strategies. One notable concern is that measurement of CAC exposes individuals to a small but nontrivial amount of ionizing radiation (approximately 0.9-1.1 mSv). Recent efforts have been made to standardize equipment and imaging protocols to reduce radiation exposure during CAC imaging[22]; however, the extent to which these recommendations have been implemented in general medical practice is not known. Previous studies suggest wide variations in radiation dose during CAC imaging by region/type of institution/protocol.[23] Even with the lowest possible radiation dose, there remains uncertainty about the magnitude of long-term cancer risks.[24] A small risk associated with the lowest possible radiation dose during CAC imaging could translate into a large number of avoidable cancers if CAC were to be uniformly applied to the estimated 23 million people in the United States currently classified as intermediate risk by the FRS.[25] Similarly, the benefits and risks associated with incidental findings detected during CAC imaging remain unclear. These indirect costs, in addition to the direct financial costs of CAC imaging, need to be weighed against the presumed benefits from better discrimination of participants at high risk for CHD and CVD events to best determine the role of CAC screening of patients with an intermediate risk for a CHD/CVD event. Thus, the ultimate decision regarding the optimum test to order should not be based solely on improvement in risk prediction afforded by a test but also cost effectiveness, acceptability to patients, and the potential risk and benefits associated with the test.[26]

The current study has limitations. We limited our analysis to the subset of MESA participants with complete data on all 6 risk markers, which decreased our sample size. Nevertheless, there were sufficient numbers of events to demonstrate clearly the superiority of CAC over the other measures in head-to-head ROC and NRI analyses. Finally, in MESA we did not specifically define family history of CHD as premature (ie, before the age of 55 for men and 65 for women). This may have influenced the association of family history with CHD and CVD.

CONCLUSIONS

CAC, ABI, high-sensitivity CRP, and family history were independent predictors of incident CHD/CVD beyond traditional risk factors, but had varying degrees of improvement in discrimination and classification of risk within intermediate-risk individuals. CAC had the highest improvement in both AUC and NRI when added to the FRS/RS. Additional research is warranted to explore further both the costs and benefits of CAC screening in intermediate-risk individuals.

Author Contributions: Dr Yeboah had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Yeboah, Burke, O'Leary, Carr, Herrington.
Acquisition of data: Burke, O'Leary, Carr, Greenland.
Analysis and interpretation of data: Yeboah, McClelland, Polonsky, Sibley, Carr, Goff, Greenland, Herrington.
Drafting of the manuscript: Yeboah.
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