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Utility of Nontraditional Risk Markers in Atherosclerotic Cardiovascular Disease Risk Assessment

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ABSTRACT

BACKGROUND The improvement in discrimination gained by adding nontraditional cardiovascular risk markers cited in the 2013 American College of Cardiology/American Heart Association cholesterol guidelines to the atherosclerotic cardiovascular disease (ASCVD) risk estimator (pooled cohort equation [PCE]) is untested.

OBJECTIVES This study assessed the predictive accuracy and improvement in reclassification gained by the addition of the coronary artery calcium (CAC) score, the ankle-brachial index (ABI), high-sensitivity C-reactive protein (hsCRP) levels, and family history (FH) of ASCVD to the PCE in participants of MESA (Multi-Ethnic Study of Atherosclerosis).

METHODS The PCE was calibrated (cPCE) and used for this analysis. The Cox proportional hazards survival model, Harrell's C statistics, and net reclassification improvement analyses were used. ASCVD was defined as myocardial infarction, coronary heart disease–related death, or fatal or nonfatal stroke.

RESULTS Of 6,814 MESA participants not prescribed statins at baseline, 5,185 had complete data and were included in this analysis. Their mean age was 61 years; 53.1% were women, 9.8% had diabetes, and 13.6% were current smokers. After 10 years of follow-up, 320 (6.2%) ASCVD events occurred. CAC score, ABI, and FH were independent predictors of ASCVD events in the multivariable Cox models. CAC score modestly improved the Harrell's C statistic (0.74 vs. 0.76; $p = 0.04$); ABI, hsCRP levels, and FH produced no improvement in Harrell's C statistic when added to the cPCE.

CONCLUSIONS CAC score, ABI, and FH were independent predictors of ASCVD events. CAC score modestly improved the discriminative ability of the cPCE compared with other nontraditional risk markers.
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ABBREVIATIONS AND ACRONYMS

ABI = ankle-brachial index

ACC = American College of Cardiology

AHA = American Heart Association

ASCVD = atherosclerotic cardiovascular disease

CAC = coronary artery calcium

CHD = coronary heart disease

CI = confidence interval

cPCE = calibrated pooled cohort equation

CT = computed tomography

DM = diabetes mellitus

FH = family history

hsCRP = high-sensitivity C-reactive protein

MI = myocardial infarction

NRI = net reclassification improvement

PCE = pooled cohort equation

In the recently published guidelines on assessment of cardiovascular risk and treatment of blood cholesterol to reduce atherosclerotic risk in adults (1,2), the American College of Cardiology (ACC) and the American Heart Association (AHA) introduced a new risk prediction tool using pooled cohort equations (PCEs) for primary atherosclerotic cardiovascular disease (ASCVD) (1). The ACC/AHA cholesterol guidelines also recommend the use of additional markers to improve ASCVD risk assessment and medical decision making, especially in individuals in whom the decision to initiate statins is unclear (2). The additional markers mentioned included low-density lipoprotein cholesterol, other genetic hyperlipidemias, family history (FH) of premature ASCVD, high-sensitivity C-reactive protein (hsCRP) levels, coronary artery calcium (CAC) score, lifetime ASCVD risk, and ankle-brachial index (ABI).

The ACC/AHA cholesterol guidelines did not cite data or provide evidence concerning what the yield would be when using these risk markers as additional tests for primary ASCVD risk assessment (2). To address this gap, the present report describes the improvement in discrimination afforded by the addition of the CAC score, hsCRP levels, ABI, and FH of premature ASCVD, over and beyond the PCE, for 10-year ASCVD events in asymptomatic adult participants in MESA (Multi-Ethnic Study of Atherosclerosis).

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METHODS

The MESA study design has been published previously (3). Briefly, MESA is a prospective population-based cohort study investigating the prevalence, correlates, and progression of subclinical cardiovascular disease in persons without known cardiovascular disease at baseline. The full cohort includes 6,814 women and men aged 45 to 84 years recruited from 6 U.S. communities (Baltimore, Maryland; Chicago, Illinois; Forsyth County, North Carolina; Los Angeles County, California; northern Manhattan, New York; and St. Paul, Minnesota). MESA included 38% white, 28% African-American, 22% Hispanic, and 12% Chinese adults. Demographic characteristics, medical history, and anthropometric and laboratory data for the present study were gathered from the first examination (July 2000 to August 2002). The MESA study was approved by the institutional review boards of each study site, and written informed consent was obtained from all participants.

For the present analysis, participants were excluded who had missing data related to traditional or additional risk factors or to follow-up; also excluded were those who were using statins at baseline. Our analyses were restricted to participants age 40 to 75 years because they were identified in the guidelines as having the strongest data indicating a benefit from statin therapy for primary prevention.

CONVENTIONAL RISK FACTORS. As part of the baseline examination, clinical teams collected information on traditional and additional putative cardiovascular risk factors. Current smoking was defined as having smoked a cigarette in the past 30 days. Medication use was based on medication inventory. Diabetes mellitus (DM) was defined as self-reported history of diabetes, use of diabetes medication, or a fasting glucose level ≥126 mg/dl. Resting blood pressure was measured 3 times in the seated position, with the average of the second and third readings recorded. Hypertension was defined as a systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or use of antihypertensive medication. Body mass index was calculated as weight (in kilograms) divided by height (in meters squared). Total and high-density lipoprotein cholesterol were measured from blood samples obtained after a 12-h fast; low-density lipoprotein cholesterol was estimated by using the Friedewald equation (4).

ADDITIONAL GUIDELINE-RECOMMENDED RISK MARKERS. Determining the presence of genetic hyperlipidemias, as recommended in the guidelines (2), was not assessed in the present analysis because this information was not collected in MESA. Also, we did not assess lifetime ASCVD risk because it can only be calculated in adults age 20 to 59 years, and many MESA participants are age >59 years. In addition, to create the lifetime risk calculator, only cohorts with >15 years of follow-up were included, which is beyond the duration of follow-up in MESA.

FH OF ASCVD. In MESA, we did not specifically define FH of ASCVD as premature (i.e., before the age of 55 years for men and 65 years for women). Instead, such a history was obtained by asking participants whether any member in their immediate family (first-degree relatives [parents, siblings, or children]) had experienced a fatal or nonfatal myocardial infarction (MI) or stroke. Age at onset of the event was not specified, and it is therefore unknown whether the events were premature.

LEVELS OF hsCRP. The levels of hsCRP were measured by using the BNII nephelometer (N High

Sensitivity CRP, Dade Behring, Inc., Deerfield, Illinois) at the Laboratory for Clinical Biochemistry Research (University of Vermont, Burlington, Vermont). Analytical intra-assay coefficients of variation ranged from 2.3% to 4.4%, and interassay coefficients of variation ranged from 2.1% to 5.7%, with a detection level of 0.18 mg/l.

CAC SCORE. Details of the MESA computed tomography (CT) scanning and interpretation methods have been reported by Carr et al. (5). Scanning centers assessed CAC by using chest CT scans with either a cardiac-gated electron-beam CT scanner (Chicago, Los Angeles, and New York field centers) or a multidetector CT system (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). The mean Agatston score was used for the 2 scans in all analyses (6). Intraobserver and interobserver agreements were excellent ($\kappa = 0.93$ and $\kappa = 0.90$, respectively).

ANKLE-BRACHIAL INDEX. Details of the MESA ABI measurement protocol have been published by Criqui et al. (7). Briefly, systolic blood pressure measurements in the bilateral brachial, dorsalis pedis, and posterior tibial arteries were obtained in the supine position by using a hand-held 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 the ABI was evaluated by using measurements of 43 participants by 2 technicians. The inter-reader and intrareader correlation coefficients were 0.845 and 0.937, respectively, with an intrareader and inter-reader coefficient of variation of 5.14% and 3.27%. Participants with an ABI $\geq$ 1.4 were excluded.

EVENT ASCERTAINMENT. A detailed description of the event ascertainment procedures and the adjudication process in MESA has been published (8). Briefly, every 9 to 12 months since the baseline examination, MESA participants (or, when necessary, their proxies) are contacted to inquire about hospital admissions, diagnosis of cardiovascular disease, and death that may have occurred. Hospital and other documentation of possible cardiovascular events and deaths are subsequently obtained. These documentations are sent to at least 2 MESA morbidity and mortality committee members for adjudication using a standard protocol. This committee included cardiologists, physician epidemiologists, and neurologists. All possible events with disagreements after adjudication by at least 2 MESA morbidity and mortality members were discussed and voted on by the committee during their monthly meetings. For the purposes of this study, incident ASCVD was defined as adjudicated MI, coronary heart disease (CHD)-related death, and fatal and nonfatal stroke as described by the MESA protocol.

STATISTICAL ANALYSIS. Baseline characteristics are presented as mean $\pm$ SD for continuous variables and percentages for categorical variables. Analyses were performed to address 2 specific questions, as discussed in the following text.

1. Are the additional risk markers independent predictors of ASCVD events? Additional markers were treated as continuous variables (with the exception of FH). Normalizing log transformation was used for hsCRP and CAC+1. Cox proportional hazards analysis was used to assess the association between each of the markers (CAC score, ABI, hsCRP levels, and FH) and incident ASCVD in univariable and multivariable models adjusting for age, sex, race/ethnicity, total and high-density lipoprotein cholesterol, DM, cigarette use, body mass index, systolic blood pressure, and antihypertensive medication use. These potential confounders were chosen based on their association with incident ASCVD in previous studies and also in our univariate analysis.

2. Do the additional risk markers improve discrimination over and beyond the calibrated PCEs? The PCE was known to overestimate risk in MESA (9). Thus, to avoid overstating the contribution of the additional risk factors in improving the PCE risk estimates, the PCE was recalibrated to the MESA data. Calibration was accomplished by including the PCE in a Cox model predicting ASCVD events (10); this approach created a calibrated pooled cohort equation (cPCE), which used the baseline survival estimate from the MESA data and thus reduced the risk overestimation presented in the original PCE/score. These cPCEs were used in all subsequent analyses. Ten-year cPCE was calculated for each participant, including subjects with type 2 DM. The cPCE included race-specific risk estimates for black and white subjects only; risk estimates for Hispanic and Chinese participants were calculated by using the cPCE for white subjects, as suggested in the new guidelines.

Discrimination was assessed by using Harrell's C statistic for the cPCE with and without each additional risk marker (11,12). Cross-tabulation of the cPCE with and without each additional risk marker

TABLE 1 Baseline Characteristics

	<7.5% cPCE (n = 4,185)	≥7.5% cPCE (n = 1,000)	Total Cohort (N = 5,185)
Age, yrs	58.2 ± 8.6	73.6 ± 6.6	61.2 ± 10.3
Female	2,380 (56.9)	371 (37.1)	2,751 (53.1)
Race/ethnicity			
White	1,606 (38.4)	363 (36.3)	1,969 (38)
Chinese	518 (12.4)	107 (10.7)	625 (12.1)
Black	1,117 (26.7)	285 (28.5)	1,402 (27.0)
Hispanic	944 (22.6)	245 (24.5)	1,189 (22.9)
Diabetes mellitus	236 (5.6)	270 (27.0)	506 (9.8)
Cholesterol, mg/dl			
Total	196.2 ± 35.1	197.2 ± 37.9	196.4 ± 35.7
LDL*	119.3 ± 31.2	121.2 ± 32.0	119.7 ± 31.4
HDL	51.6 ± 15.0	48.4 ± 14.4	51.0 ± 15.0
Triglycerides	126.6 ± 75.5	142.7 ± 125.8	129.7 ± 87.7
BMI, kg/m^2	28.2 ± 5.6	28.0 ± 4.9	28.2 ± 5.4
Blood pressure, mm Hg			
Systolic	121.0 ± 18.5	145.0 ± 21.9	125.6 ± 21.4
Diastolic	71.3 ± 10.1	75.1 ± 11.0	72.1 ± 10.4
Cigarette smoking			
Never	2,177 (52.0)	447 (44.7)	2,624 (50.6)
Former	1,457 (34.8)	397 (44.7)	1,854 (35.8)
Current	551 (13.2)	156 (15.6)	707 (13.6)
Antihypertensive medication use	1,092 (26.1)	591 (59.1)	1,683 (32.5)
CAC score, agatston	0 (0–24.2)	94.5 (4.7–374.5)	0 (0–63.6)
hsCRP, mg/l	1.9 (0.8–4.3)	2.1 (1.0–4.1)	1.9 (0.8–4.3)
ABI	1.1 (1.1–1.2)	1.1 (1.0–1.2)	1.1 (1.1–1.2)

Values are mean ± SD, n (%), or median (interquartile range). *Low-density lipoprotein (LDL) sample size = 5,123 (due to missing values).

ABI = ankle-brachial index; BMI = body mass index; CAC = coronary artery calcium; cPCE = calibrated pooled cohort equation; HDL = high-density lipoprotein; hsCRP = high-sensitivity C-reactive protein.

was performed to calculate the net reclassification improvement (NRI). Bootstrapping was used to calculate 95% confidence intervals (CIs) (13). The NRI analyses for events and nonevents were calculated separately, as previously recommended. The NRI analyses were conducted by using the 7.5% ASCVD risk cutoff, per the ACC/AHA guidelines (2 categories). Three categories of ASCVD risk (0% to 5%, 5% to 7.5%, and >7.5%) were also used as a sensitivity analysis. The improvement in Harrell's C statistics and NRI of the additional risk markers were directly compared. In a subsequent analysis, the Framingham risk score (14) was recalibrated as described for the PCE, and the improvement in reclassification afforded by the addition of these additional risk markers (CAC score, ABI, hsCRP levels, and FH) was assessed by using Harrell's C statistics and an NRI analysis; incident CHD was used as the outcome of interest. The statistical analysis was performed by using Stata version 12.0 (StataCorp LP, College Station, Texas).

TABLE 2 ASCVD Event Hazard Associated With Additional Risk Markers

	Univariable			Multivariable*		
	HR	95% CI	p Value	HR	95% CI	p Value
CAC (ln + 1, per 1.98 SD)	2.06	1.86–2.29	<0.001	1.58	1.40–1.79	<0.001
hsCRP (ln, per 1.17 SD)	1.23	1.10–1.37	<0.001	1.12	0.99–1.27	0.077
Family history of ASCVD	1.57	1.26–1.95	<0.001	1.37	1.09–1.71	0.007
ABI (per 0.11 SD)	0.69	0.63–0.75	<0.001	0.87	0.79–0.94	0.001

Total population = 5,185; number of events = 320. *Multivariable Cox model adjusted for age, sex, race/ethnicity, diabetes mellitus, total cholesterol, HDL cholesterol, BMI, systolic blood pressure, cigarette smoking status, and antihypertensive medication use.

ASCVD = atherosclerotic cardiovascular disease; CI = confidence interval; HR = hazard ratio; ln = natural logarithm; SD = standard deviation; other abbreviations as in Table 1.

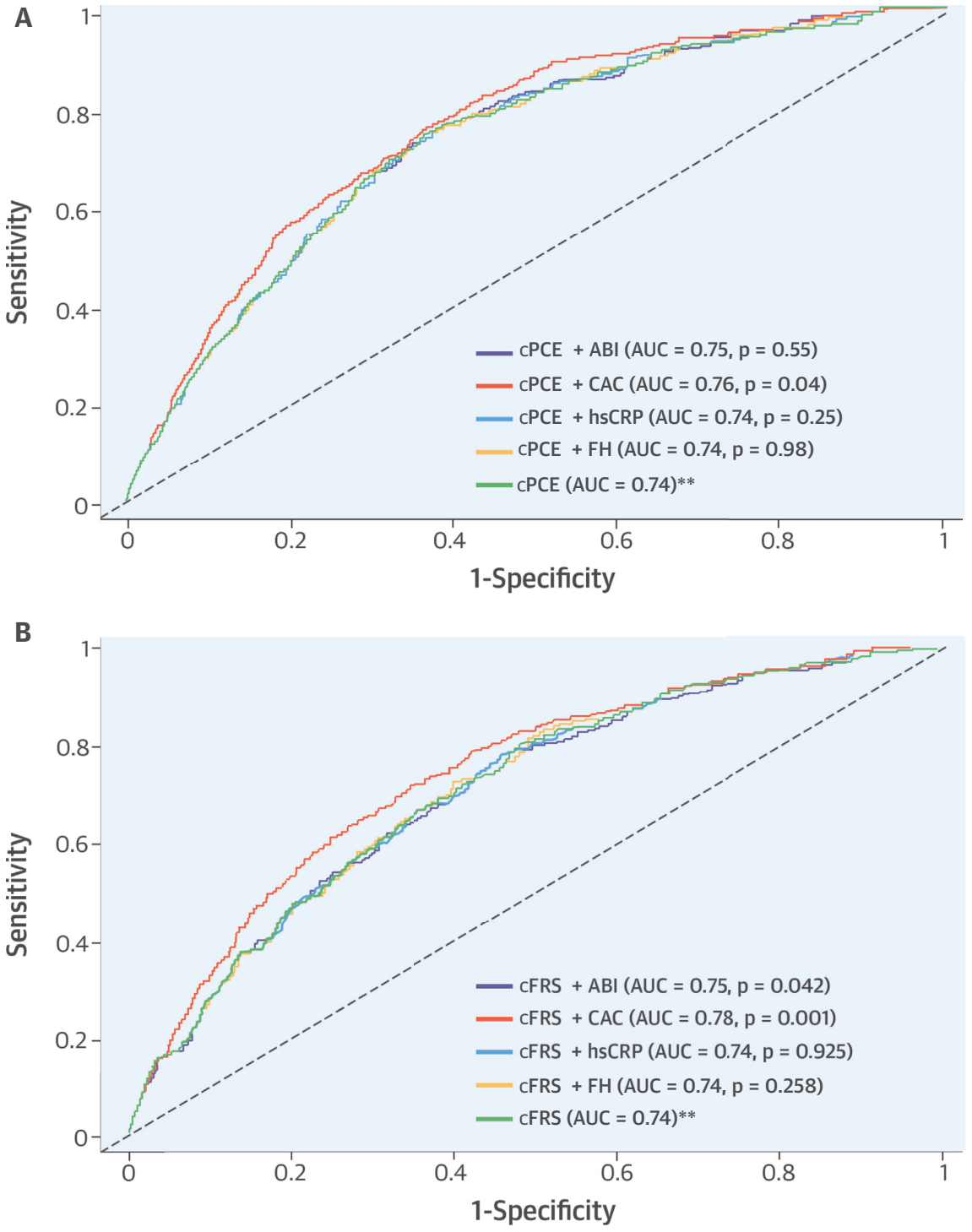
RESULTS

Of the 6,814 MESA participants, 1,629 (23.9%) were either prescribed statins, had an ABI ≥1.4, or had incomplete data and were therefore eliminated from the present analysis. In terms of baseline characteristics of the remaining 5,185 participants (Table 1), the mean age of the participants included in this analysis was 61.2 years; 53.1% were female; and 38% were white, 12.1% were Chinese, 27% were black, and 22.9% were Hispanic. After a mean follow-up of 10 years, 320 (6.2%) ASCVD events occurred; 139 (43.4%) were MIs, 132 (41.3%) were fatal or nonfatal strokes, and 49 (15.3%) were CHD-related death.

In terms of the added value of the additional risk markers, CAC score, ABI, and FH were each independent predictors of incident ASCVD events in multivariable Cox models (Table 2). Online Table 1 shows the hazard ratios and 95% CIs of the additional risk markers and the covariates in the multivariable Cox model. As to whether the markers improve discrimination beyond the cPCEs, the Central Illustration shows the comparative improvement in area under the curve/C statistics afforded by the addition of each of the additional risk markers to the cPCE for predicting incident ASCVD; the CAC score was the only additional risk marker to significantly improve discrimination.

Table 3 presents the NRI analysis for events and nonevents when CAC score, hsCRP levels, FH, and ABI were added individually to the cPCE. The addition of the CAC score to the model resulted in a larger improvement in the classification of risk than the other risk markers but 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 provided 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). Using 3 ASCVD risk categories (0% to 5%, 5% to 7.5%, and >7.5%) instead of the 2 categories

CENTRAL ILLUSTRATION **Utility of Risk Markers for ASCVD Assessment: Receiver-Operating Characteristic Curves**



Yeboah, J. et al. J Am Coll Cardiol. 2016; 67(2):139–47.

To assess predictive accuracy and reclassification improvement of various risk markers for incident atherosclerotic cardiovascular disease (ASCVD), receiver-operating characteristic curves showing the area under the curve (AUC) were calculated for **(A)** calibrated pooled cohort equations (cPCEs) and **(B)** calibrated Framingham risk scores (cFRS) for study participants. Of the factors assessed, the coronary artery calcium (CAC) score modestly improved the discriminative ability of the cPCE. **Reference. ABI = ankle-brachial index; FH = family history; hsCRP = high-sensitivity C-reactive protein.

TABLE 3 NRI: Risk Markers Added to cPCE

	cPCE Alone			
	<7.5%	≥7.5 %	Row Total	NRI (95% CI)
cPCE + CAC				
Event (n = 320)				
<7.5%	107	19	126 (39.4)	0.178 (0.080 to 0.256)
≥7.5%	76	118	194 (60.6)	
Column total	183 (57.2)	137 (42.8)		
Nonevent (n = 4,865)				
<7.5%	3,506	202	3,708 (76.2)	-0.059 (-0.075 to 0.030)
≥7.5%	496	661	1,157 (23.8)	
Column total	4,002 (82.3)	863 (17.7)		
Total NRI for CAC				0.119 (0.080 to 0.256)
cPCE + hsCRP				
Event (n = 320)				
<7.5%	165	9	174 (54.4)	0.028 (-0.013 to 0.077)
≥7.5%	18	128	146 (45.6)	
Column total	183 (57.2)	137 (42.8)		
Nonevent (n = 4,865)				
<7.5%	3,882	98	3,980 (81.8)	-0.005 (-0.015 to 0.003)
≥7.5%	120	765	885 (18.2)	
Column total	4,002 (82.3)	863 (17.7)		
Total NRI for hsCRP				0.024 (-0.015 to 0.067)
cPCE + FH				
Event (n = 320)				
<7.5%	153	12	175 (54.6)	0.056 (0.007 to 0.118)
≥7.5%	30	125	155 (48.4)	
Column total	183 (57.2)	137 (42.8)		
Nonevent (n = 4,865)				
<7.5%	3,832	140	3,972 (81.6)	-0.006 (-0.019 to 0.003)
≥7.5%	170	723	893 (18.4)	
Column total	4,002 (82.3)	863 (17.7)		
Total NRI for FH				0.051 (0.000 to 0.109)
cPCE + ABI				
Event (n = 320)				
<7.5%	166	13	179 (55.9)	0.013 (-0.034 to 0.051)
≥7.5%	17	124	141 (44.1)	
Column total	183 (57.2)	137 (42.8)		
Nonevent (n = 4,865)				
<7.5%	3,910	113	4,023 (82.7)	0.004 (-0.004 to 0.011)
≥7.5%	92	750	842 (17.3)	
Column total	4,002 (82.3)	863 (17.7)		
Total NRI for ABI				0.017 (-0.031 to 0.058)

Values are n or n (%) unless otherwise indicated.
FH = family history; NRI = net reclassification improvement; other abbreviations as in Tables 1 and 2.

(sensitivity analysis) produced similar results (Online Table 2) for all the additional risk markers considered.

A total of 194 (3.7%) CHD events occurred. When considering the comparative improvement in area under the curve/C statistics afforded by adding each of the risk markers to the calibrated Framingham risk score for predicting incident CHD, the CAC score was the only factor to significantly improve discrimination (**Central Illustration**). **Table 4** displays the NRI analysis for events and nonevents when CAC score, hsCRP levels, FH, and ABI were added individually to the calibrated Framingham risk score. The addition of the CAC score resulted in a larger improvement in the classification of risk than the other additional risk markers but was limited to an improvement in classification of events.

TABLE 4 NRI: Risk Markers Added to cFRS

	cFRS Alone				
	<10%	10%–20%	>20%	Row Total	NRI (95% CI)
cFRS + CAC					
Event (n = 194)					
<10%	132	5	0	137 (70.6)	0.119 (0.045 to 0.239)
10%–20%	26	18	2	46 (23.7)	
>20%	0	4	7	11 (5.7)	
Column total	158 (81.4)	27 (13.9)	9 (4.6)		
Nonevent (n = 4,991)					
<10%	4,540	63	8	4,611 (92.4)	-0.034 (-0.053 to 0.017)
10%–20%	230	101	11	342 (6.9)	
>20%	3	20	15	38 (0.8)	
Column total	4,773 (95.6)	184 (3.7)	34 (0.7)		
Total NRI for CAC					0.084 (0.024 to 0.196)
cFRS + hsCRP					
Event (n = 194)					
<10%	158	1	0	159 (82.0)	0.005 (-0.027 to 0.027)
10%–20%	1	24	1	26 (13.4)	
>20%	0	2	7	9 (4.6)	
Column total	159 (82.0)	27 (13.9)	8 (4.1)		
Nonevent (n = 4,991)					
<10%	4,749	16	0	4765 (95.5)	-0.002 (-0.007 to 0.001)
10%–20%	28	158	6	192 (3.8)	
>20%	0	3	31	34 (0.7)	
Column total	4,777 (95.7)	177 (3.5)	37 (0.7)		
Total NRI for hsCRP					0.003 (-0.028 to 0.026)
cFRS + FH					
Event (n = 194)					
<10%	150	6	0	156 (80.4)	0.010 (-0.032 to 0.074)
10%–20%	8	19	3	30 (15.5)	
>20%	0	3	5	8 (4.1)	
Column total	158 (81.4)	28 (14.4)	8 (4.1)		
Nonevent (n = 4,991)					
<10%	4,681	65	0	4,746 (95.1)	-0.007 (-0.013 to 0.002)
10%–20%	95	98	13	206 (4.1)	
>20%	0	17	22	39 (0.8)	
Column total	4,776 (95.7)	180 (3.6)	35 (0.7)		
Total NRI for FH					0.003 (-0.034 to 0.069)
cFRS + ABI					
Event (n = 194)					
<10%	152	4	0	156 (80.4)	0.041 (-0.010 to 0.108)
10%–20%	6	17	1	24 (12.4)	
>20%	1	6	7	14 (7.2)	
Column total	159 (82.0)	27 (13.9)	8 (4.1)		
Nonevent (n = 4,991)					
<10%	4,724	50	0	4,774 (95.7)	-0.003 (-0.008 to 0.004)
10%–20%	51	106	12	169 (3.4)	
>20%	6	18	24	48 (1.0)	
Column total	4,781 (95.8)	174 (3.5)	36 (0.7)		
Total NRI for ABI					0.039 (-0.011 to 0.109)

Values are n or n (%) unless otherwise indicated. Calibrated Framingham risk score (cFRS) for coronary heart disease events, which include myocardial infarction and coronary heart disease–related death.

Abbreviations as in Tables 1 to 3.

DISCUSSION

The goal of the present study was to assess the improvement in discrimination that would be gained by adding the recommended nontraditional risk markers to the 2013 cPCE. The present study found that among the 4 ACC/AHA-recommended nontraditional risk markers studied, the CAC score provides the highest (albeit, modest) improvement in discrimination over and beyond the cPCE (**Central Illustration**). The superiority of the CAC score seems to be consistent across all possible ASCVD strata. To our knowledge, this study is the first to assess whether nontraditional risk markers improve risk prediction afforded by the cPCE.

Previous studies showed that CAC score, ABI, hsCRP levels, and FH improve discrimination and classification of risk over the Framingham risk score but to varying degrees (15-18). Our group (19), as well as a report by the Rotterdam study (15), showed that among these 4 risk markers, CAC score provided the greatest improvement in discrimination across the whole CHD risk spectrum and also in those classified as intermediate risk according to the Framingham risk score. In the 2013 ACC/AHA guidelines (1), the primary outcome was expanded to ASCVD, which includes fatal and nonfatal stroke in addition to fatal and nonfatal MI. The PCE also includes variables for the presence or absence of DM and race (white or African American). The present study found that among the 4 recommended nontraditional risk markers, CAC score is superior for improving ASCVD risk prediction and may be useful in individuals in whom quantitative ASCVD risk-based treatment decision making may be uncertain.

The magnitude of improvement in discrimination afforded by the 4 nontraditional risk markers beyond the cPCE seems modest compared with what was reported in MESA using Framingham risk factors as the baseline model (16) but similar when the Framingham risk score was used (**Table 4**). For example, in the study by Polonsky et al. (16) in which the Framingham risk factors were used as the baseline model, CAC score had an event NRI of 0.23 and a nonevent NRI of 0.02 for incident CHD events. In the present study, when the calibrated Framingham risk score was used in the same cohort for incident CHD events, the CAC score had an event NRI of 0.119 and a nonevent NRI of -0.034. However, CAC scores, as well as some of the other risk markers, produced significant improvement in classification when the analysis was limited to those labeled as intermediate risk according to the Framingham risk score (19).

It should be noted that during the National Cholesterol Education Program/Adult Treatment Panel III era, these additional risk markers were only recommended for improvement in risk assessment in subjects with intermediate risk according to the Framingham risk score (20). Currently, these additional risk markers are recommended for improvement in ASCVD risk assessment in those who are not in 1 of the 4 statin-benefit groups and for whom the decision to initiate statin treatment is uncertain (2). It is plausible that despite the modest improvement in discrimination observed in the present study, these additional risk markers may still play significant roles for ASCVD risk assessment in a subgroup of the population. Studies on the improvement in discrimination afforded by these additional risk markers in subgroups of asymptomatic individuals (primary prevention) is needed, especially those for whom statin therapy is not recommended by the new ACC/AHA cholesterol guidelines (1).

Despite the finding of superior (albeit modest) discrimination when the CAC score was added to the PCE, its ultimate use in the clinical setting for risk assessment (especially after the introduction of the ASCVD risk estimator) demands consideration of additional variables such as cost-effectiveness, radiation exposure, and patient preference.

STUDY LIMITATIONS. Although participants who were taking statins during the baseline MESA examination were excluded from this analysis, some of the participants we did include were prescribed statins during follow-up. This approach may have affected our event rates and therefore our results. However, the sensitivity analysis, in which statin use during 10-year follow-up was accounted for in our models, did not significantly change either our point estimates or our conclusions. The MESA cohort is also not representative of the U.S. population. In addition, the calibrated versions of the PCE and the Framingham risk score are not currently available to clinicians. Therefore, although these tools are the most appropriate for statistical analysis, some caution may be needed when directly applying these results to clinical practice with the present PCE and Framingham risk score.

CONCLUSIONS

In this study of well-characterized individuals (including those who are nonwhite as well as white, who were followed up for 10 years), CAC score, ABI, and FH were each independently associated with incident ASCVD beyond traditional risk factors. The nontraditional risk factors resulted in varying degrees

of improvement in discrimination and reclassification of risk, including no improvement. Verification of our findings in other racial and ethnic groups, as well as in other patient cohorts, is needed.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: The nontraditional risk markers cited by the 2013 ACC/AHA cholesterol guidelines for ASCVD risk refinement and considered in this study provided modest degrees of improvement in discrimination over and beyond the cPCE, including no improvement.

TRANSLATIONAL OUTLOOK: Confirmation of our findings in other cohorts should consider the utility and the cost-effectiveness of using these risk markers for improving ASCVD risk assessment. The promise seen with the CAC score requires further study.

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KEY WORDS ankle-brachial index, coronary artery calcium, high-sensitivity C-reactive protein, pooled cohort equation

APPENDIX For supplemental tables, please see the online version of this article.