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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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Listen to this manuscript's audio summary by *JACC* Editor-in-Chief Dr. Valentin Fuster.

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