ELSEVIER

Atherosclerosis 193 (2007) 401–407

ATHEROSCLEROSIS

www.elsevier.com/locate/atherosclerosis

Implications of C-reactive protein or coronary artery calcium score as an adjunct to global risk assessment for primary prevention of CHD

Susan G. Lakoski [a,*], Mary Cushman [b], Roger S. Blumenthal [c], Richard Kronmal [d], Donna Arnett [e], Ralph B. D'Agostino Jr. [f], Robert C. Detrano [g], David M. Herrington [a]

[a] *Department of Internal Medicine/Cardiology, 12 Wake Forest University School of Medicine, Medical Center Blvd., Winston-Salem, NC 27157, United States*
[b] *Departments of Medicine and Pathology, University of Vermont, Burlington, VT, United States*
[c] *Ciccarone Preventive Cardiology Center, Johns Hopkins University School of Medicine, Baltimore, MD, United States*
[d] *Collaborative Health Studies Coordinating Center, University of Washington, Seattle, WA, United States*
[e] *Department of Epidemiology, University of Alabama at Birmingham, Birmingham, AL, United States*
[f] *Department of Public Health Sciences, Wake Forest School of Medicine, Winston-Salem, NC, United States*
[g] *Division of Cardiology, Los Angeles Biomedical Research Institute, Torrance, CA, United States*

Received 27 March 2006; received in revised form 15 June 2006; accepted 6 July 2006
Available online 17 August 2006

Abstract

Background: C-reactive protein (CRP) or coronary artery calcium (CAC) score have been suggested to identify a higher risk subset of intermediate-risk individuals, who potentially could be considered for more aggressive therapy. In the Multi-Ethnic Study of Atherosclerosis (MESA), we estimated the proportion of intermediate-risk participants whose risk status might change based on additional testing using CRP and/or CAC score.
Methods: Framingham 10-year CHD risk scores (FRS) were calculated and cross tabulations were used to determine the percent of individuals at intermediate-risk by FRS with a CRP >3 mg/L and/or CAC score >100 AU. Similar analyses were performed using the gender-specific 75th percentile for CRP and CAC.
Results: Of the 30% of participants ($N = 1450$) classified as intermediate-risk by FRS, 30% had a CRP >3 mg/L and 33% had a CAC score >100 AU. Among intermediate-risk women, 49% had a CRP >3 mg/L compared to 27% of intermediate-risk men ($p < 0.0001$) while the same percent of intermediate-risk women and men (33%) had a CAC score >100 AU. Eleven percent or less of men or women had both a high CRP and CAC score whether conventional or gender-specific cut points were used. When the percent of intermediate-risk individuals with an elevated CRP and/or CAC score in MESA were applied to NHANES III data, over a million intermediate-risk individuals would move to high risk status if CRP or CAC screening directed treatment strategies were uniformly adopted in the U.S.
Conclusion: There were differences in the number of intermediate-risk individuals reclassified as high risk depending on the screening test used, the cut points selected, and the demographics of the individuals being screened. These data highlight current limitations of broadly using risk markers such as CRP and CAC score in an intermediate-risk population.

Keywords: C-reactive protein; Coronary artery calcium score; Risk factors; Framingham risk score

Abbreviations: AHA, American Heart Association; ATP III, Third Report of the National Cholesterol Education Program (NCEP) expert panel on detection evaluation and treatment of high blood cholesterol in adults; BMI, body mass index; CAC, coronary artery calcium; CDC, centers for disease control and prevention; CHD, coronary heart disease; CRP, C-reactive protein; CT, computed tomography; EBT, electron-beam computed tomography; FRS, Framingham risk score; JUPITER, justification for the use of statins in primary prevention: an intervention trial evaluating rosuvastatin; MESA, Multi-Ethnic Study of Atherosclerosis; MDCT, multidector computed tomography scanner; MI, myocardial infarction; NHANES III, National Health and Nutrition Examination Survey III

* Corresponding author. Tel.: +1 336 716 0489; fax: +1 336 716 9188.
E-mail address: slakoski@wfubmc.edu (S.G. Lakoski).

0021-9150/$ – see front matter © 2006 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.atherosclerosis.2006.07.006

1. Introduction

Risk stratification has become an important feature of contemporary strategies for primary prevention of coronary heart disease. ATP III guidelines recommend the Framingham risk score (FRS) to classify individuals into low, intermediate, and high risk categories based on their absolute 10-year risk for myocardial infarction (MI) or coronary heart disease (CHD) death [1]. Several studies have shown that newer risk markers such as C-reactive protein (CRP) or coronary artery calcium (CAC) score, as assessed by computed tomography (CT), could identify a higher risk subset of intermediate-risk individuals and potentially alter clinical-decision making [2–4]. However, it is unclear how many intermediate-risk individuals would actually be re-classified as high risk based on additional screening with CRP and/or CAC score.

The yield of screening intermediate-risk individuals using CRP or CAC score depends on the cut points used to classify those as high risk. AHA/CDC guidelines suggest a CRP cut point of 3 mg/L to define high risk [5] and a cut point of 3 mg/L has been shown to add incremental predictive value beyond FRS for prediction of cardiovascular events in intermediate-risk patients [2]. For CAC, there is a less clear consensus on appropriate cut points [6] although, a CAC score >100 AU has been shown to add predictive value beyond FRS as well [7]. However, both CRP concentration and CAC score vary by gender and ethnicity [8] and the impact of these factors on the performance of CRP and CAC score as screening tests is unclear.

The objective of the current analysis from the Multi-Ethnic Study of Atherosclerosis (MESA) was to estimate the proportion of intermediate-risk participants who might be reclassified as high risk based on additional testing using CRP or CAC score. Alternate gender-specific cut points for both CRP and CAC score were used to explore the implications of different strategies for screening intermediate-risk individuals. Yields from the MESA cohort were applied to data from NHANES III [9] to estimate the absolute number of intermediate-risk subjects in the U.S. whose risk status might change based on additional screening with CRP or CAC score.

2. Methods

The Multi-Ethnic Study of Atherosclerosis (MESA) was initiated in July 2000 to investigate the prevalence, correlates and progression of subclinical cardiovascular disease in individuals without known cardiovascular disease [10]. This prospective cohort study includes 6814 women and men ages 45–84 years old recruited from six U.S. communities (Baltimore, MD; Chicago, IL; Forsyth County, NC; Los Angeles County, CA; northern Manhattan, NY; and St. Paul, MN). There are 38% white ($N = 2624$), 28% African-American ($N = 1895$), 22% Hispanic ($N = 1492$), and 12% Chinese ($N = 803$) individuals.

Medical history, anthropometric measurements, and laboratory data for the present study were taken from the first examination of the MESA cohort (July 2000 to August 2002). Information about age, gender, ethnicity, and medical history were obtained by questionnaires. Current smoking was defined as having smoked a cigarette in the last 30 days. Alcohol use was defined as never, former, or current. Diabetes was defined as a fasting glucose >126 mg/dL or use of hypoglycemic medications. Use of antihypertensive and other medications were based on clinical staff entry of prescribed medications.

Resting blood pressure was measured three times in the seated position using a Dinamap model Pro 100 automated oscillometric sphygmomanometer (Critikon, Tampa, Florida) and the average of the 2nd and 3rd readings was recorded. Hypertension was defined as a systolic blood pressure $\geq$140 mmHg, diastolic blood pressure $\geq$90 mmHg, or use of medication prescribed for hypertension. Body mass index was calculated from the equation weight (kg)/height (m^2).

Total and HDL cholesterol were measured from blood samples obtained after a 12-h fast. LDL cholesterol was calculated with the Friedewald equation [11]. CRP was measured using the BNII nephelometer (N High Sensitivity CRP; Dade Behring Inc., Deerfield, IL) at the Laboratory for Clinical Biochemistry Research (University of Vermont, Burlington, VT). Analytical intra-assay CVs ranged from 2.3% to 4.4% and inter-assay CVs ranged from 2.1% to 5.7%.

Computed tomography scanning of the chest was performed either with an ECG-triggered (at 80% of the RR interval) electron-beam computed tomography scanner (Chicago, Los Angeles, and New York field centers; Imatron C-150, Imatron) [12] or with prospectively ECG-triggered scan acquisition at 50% of the RR interval with a multidetector computed tomography system [13] at acquired four simultaneous 2.5-mm slices for each cardiac cycle in a sequential or axial scan mode (Baltimore, Forsyth County, and St. Paul field centers; Lightspeed, General Electric or Siemens, Volume Zoom). Each participant was scanned twice. Scans were read centrally at the Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center to identify and quantify coronary calcification. CAC score among scanning centers and between participants were adjusted with a standard calcium phantom scanned simultaneously with each participant. The average Agatston score was used in all analyses [14]. Agreement with regard to presence of coronary calcification was high (κ-statistic 0.90–0.93 between and within readers), and the intraclass correlation coefficient for the Agatston score between readers was 0.99 [15]. Agreement between scans was good for both the electron-beam computed tomography (EBT) and the multidector computed tomography (MDCT) scanner [15].