International Journal of Cardiology 166 (2013) 487–493

Contents lists available at SciVerse ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Association of novel biomarkers with future cardiovascular events is influenced by ethnicity: Results from a multi-ethnic cohort

Vikas Veeranna [a,b], Sandip K. Zalawadiya [b], Ashutosh Niraj [a,b], Abhimanyu Kumar [c], Brian Ference [a,b], Luis Afonso [a,b,*]

[a] Division of Cardiology, Wayne State University, Detroit Medical Center, Detroit, MI, United States
[b] Department of Internal Medicine, Wayne State University, Detroit Medical Center, Detroit, MI, United States
[c] Department of Applied Mathematics, University of Akron, Akron, OH, United States

ARTICLE INFO

Article history:
Received 11 March 2011
Received in revised form 27 October 2011
Accepted 24 November 2011
Available online 10 January 2012

Keywords:
Inflammation
Biomarkers
Cardiovascular disease
Coronary artery disease
Ethnicity
CRP
Fibrinogen
Interleukin
Epidemiology
Cardiovascular disease
Risk factors
Stroke
Atherosclerosis
Death
Outcome

ABSTRACT

Background: We sought to define the influence of ethnicity on associations between novel biomarkers and cardiovascular disease (CVD) events among Multi-Ethnic Study of Atherosclerosis (MESA) study participants, a community based population of asymptomatic US adults.
Methods: Baseline (log transformed) levels of biomarkers namely C-reactive protein (CRP), fibrinogen, interleukin-6 (IL-6), D-dimer, plasmin–antiplasmin complex (PAP) and factor VIII were used to predict the cumulative incidence of all CVD events in an ethnicity stratified study cohort from Cox-proportional hazard analysis where models were adjusted for relevant confounders.
Results: Ethnic cohorts included 2362 Caucasians, 1601 African Americans, 1353 Hispanics, and 751 Chinese. At mean 4.6 years of follow-up, 286 CVD events were identified with cumulative incidence of 11.3% in Caucasians, 9.8% in African Americans, 11.3% in Hispanics and 6.9% in Chinese.
Biomarker risk association with CVD events incidence was significantly influenced by ethnicity with positive association (HR, 95% CI, p value) being shown for: CRP among Caucasians only (1.23, 1.04–1.47, <0.01) IL-6 among African Americans only (1.69, 1.15–2.48, <0.01) and fibrinogen among Caucasians (3.05, 1.21–7.69, 0.02), African Americans (3.51, 1.09–11.2, 0.03) and Hispanics (4.16, 1.23–14.1, 0.02) only. None of the biomarkers were able to predict CVD in Chinese. Association between above biomarkers and CVD was bi-directional: cases with CVD events had higher mean levels of biomarkers; cases in higher quartiles of biomarkers had increased cumulative incidence of CVD events.
Conclusion: Study results from a vast, ethnically diverse, asymptomatic US adult population suggest that biomarker association with incident CVD events is significantly influenced by ethnicity.

1. Introduction

Cardiovascular disease (CVD) is the leading cause of mortality in the United States, accounting for more than one third of all deaths [1]. Based on the prior population study results, e.g. the Framingham Score [2] and the Prospective Cardiovascular Münster (PROCAM) Score [3], identifying the population at risk for future CVD events has traditionally centered on well validated CVD risk factors including age, gender, diabetes, dyslipidemia and smoking. However, data suggest that a considerable number of those at risk cannot be identified on the basis of traditional risk factors alone [4,5]. Accordingly, this significant 'residual risk' for future CVD in the population, has prompted a search for alternative markers of cardiovascular risk [6,7].

Since inflammatory processes accompany all stages of atherosclerosis, the major harbinger of CVD events, measurement of plasma concentrations of circulating inflammatory biomarkers and their role in predicting CVD events has received considerable attention [8,9]. However, the large majority of these studies have either been performed in predominantly Caucasian cohorts, restricted by gender or included individuals with pre-existing cardiac disease, limiting the applicability of these data to other minority groups. For a host of less well understood reasons, ethnic groups appear to be predisposed to develop coronary heart disease (CHD) and CVD at disparate rates, as evident from the higher prevalence of these diseases in certain populations, including African-Americans, Mexican Americans and Pacific Asians [10]. The need to obtain more health information on ethnic minority groups in the contemporary era has been recognized and reflected in the policies governing funding by the National Institutes of Health that mandate the inclusion of minorities in clinical research [11].

The Multi-Ethnic Study of Atherosclerosis (MESA) study participants included a substantial proportion of previously understudied

* Corresponding author at: Internal Medicine, Division of Cardiology, Wayne State University, Detroit, MI 48201, United States. Tel.: +1 313 745 2620.
E-mail address: lafonso@med.wayne.edu (L. Afonso).

0167-5273/$ – see front matter © 2012 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.ijcard.2011.11.034

minority groups whose prevalence of risk factors and CVD risk attributable to specific risk factors have been shown or hypothesized to differ from that of the majority of the population. To date, no study has systematically explored the predictive value of novel markers for future CVD events in ethnically stratified cohorts. This gap in knowledge was highlighted in the recent U.S. Preventive Services Task Force recommendation statement for nontraditional risk factors in coronary heart disease risk assessment [7]. We therefore sought to define the effect of ethnicity on associations between novel biomarkers and incident CVD events in this community-based multi-ethnic population of US adults free of CVD.

2. Methods

2.1. Study population

After obtaining Institutional Review Board approval, we undertook a post-hoc analysis of the MESA Limited Access Dataset, obtained from the National Heart, Lung and Blood Institute (NHLBI). None of the authors are affiliated with the NHLBI or part of the MESA Study. A detailed description of the study design, methods and objectives has been published previously [12-14]. In brief, MESA Is a population based study with subjects without a prior history of clinical CVD of four ethnicities from six US communities, n = 6814, aged 45–84 years and was designed to identify the characteristics of subclinical cardiovascular disease and the risk factors that predict progression to clinically overt cardiovascular disease or progression of the subclinical disease.

Demographic information was obtained using standard questionnaires. After excluding patients with missing data, we identified a total of 6067 healthy adults: 2863 men and 3204 women. Ethnic sub-cohorts included 2362 Caucasians, 1601 African Americans, 1353 Hispanics, and 751 Chinese.

2.2. Measurement of serum/plasma biomarkers

All the biomarkers analyzed in our study were measured in the entire cohort at baseline. C-reactive protein (CRP) and fibrinogen were determined by BNII nephelometer (N high sensitivity CRP and N antiserum to human fibrinogen; Dade Behring Inc., Deerfield, IL). Interleukin-6 (IL-6) was measured by ultra-sensitive ELISA (Quantikine HS Human IL-6 Immunoassay; R&D Systems, Minneapolis, MN). Analytical CVs for CRP, fibrinogen, and IL-6 were 3.6%, 2.7% and 6.3%, respectively. Factor VIII coagulant activity was measured using the Sta-R analyzer (STA-Deficient VIII; Diagnostica Stago, Parsippany, NJ, USA). D-dimer was quantified by immuno-turbidometric methods on the Sta-R analyzer (Liatest D-DI; Diagnostica Stago, Parsippany, NJ, USA). Plasmin–antiplasmin Complex (PAP) was measured by a two-site enzyme-linked immunosorbent assay (ELISA) that utilizes two monoclonal antibodies [15], blood sample collection and measurements were made in duplicate, in random order and in a blinded fashion.

2.3. Incidence of CVD events as primary end point

For this study analysis, the primary end point was the first incidence of all cardiovascular disease (CVD) events which was defined as a composite endpoint of myocardial infarction (MI), resuscitated cardiac arrest, definite angina, probable angina (if followed by revascularization), stroke, stroke death, coronary heart disease (CHD) death, other atherosclerotic death, other CVD death as per the MESA steering committee recommendations. A more detailed description of the MESA follow-up methods is available at http://www.mesa-nhlbi.org.

Over a mean of 4.6 years of follow-up, a total of 286 CVD events were identified. Cumulative incidence for CVD events during the same time period were 11.3% in Caucasians, 9.8% in African Americans, 11.3% for Hispanics and 6.9% for Chinese.

3. Statistical analysis

Distribution of baseline characteristics among different ethnic groups was compared using chi-square test for categorical variables (presented as percentages) and one-way ANOVA test for continuous variables (presented as mean ± SD). All covariates were tested for normality by visual inspection using frequency distribution curves. Log transformations were performed to normalize biomarkers (IL-6, PAP, fibrinogen, CRP, D-dimer, CRP, factor VIII). Ethnicity stratified utility of novel biomarkers (as a continuous variable, log-transformed; i.e. IL-6, PAP, fibrinogen, CRP, D-dimer, factor VIII) to predict incident CVD events was estimated though a Cox proportional hazards model (incident CVD events occurred as dependent binary categorical variable: either yes or no).

Unadjusted and adjusted multivariate Cox proportional hazard models were generated for each ethnic cohort as follows: Model 1: biomarkers alone and Model 2: Model 1 + traditional CV risk factors analogous to Framingham Heart Study i.e. age, gender, systolic blood pressure (continuous variable) + use of anti-hypertension medications (categorical) + total cholesterol (continuous variable) + serum high density lipoprotein cholesterol (continuous variable) + history of smoking (categorical variable). The variables were added to the Cox proportional hazard model based on the known clinical significance rather than on purely their statistical significance. For relevant ethnic cohorts, cumulative incidence for all CVD events (calculated as incidence of at least one CVD event at a mean 4.6 years of follow up divided by population at risk, i.e. equal to one fourth of each ethnic cohort and expressed as %) was plotted against the four quartile levels of biomarkers in ethnic sub cohorts. On other hand, a box plot display was plotted for relevant ethnic subgroups showing distribution of biomarkers against cases with or without CVD events.

Difference in the above cohorts was compared using ANOVA analysis for continuous variables and chi-square test for categorical variables. Two-tailed p-values <0.05 were considered statistically significant. All statistical analysis was performed using Stata Version 10 (STATACorp, College Station, TX, USA).

4. Results

4.1. Baseline characteristics

Significant ethnic differences were observed in the demographics and cardiovascular risk factor covariates (Table 1). In general, Caucasians were more likely to be dyslipidemic, active smokers, physically active; and less likely to be obese, diabetic and hypertensive. African-Americans were more likely to be obese, diabetic, hypertensive, smokers, physically active and had lower serum total cholesterol, triglycerides and creatinine levels. Hispanics were younger in age, more likely to be diabetic, had worse lipid profiles and were less physically active. The Chinese cohort was characterized by the lowest mean BMI (with least prevalence of obesity), and was less likely to be diabetic and physically active. Overall use of aspirin and statins was less prevalent among Hispanics and Chinese.

The ethnicity-stratified prevalence distribution of studied biomarkers is tabulated in Table 2. Biomarker distribution was not homogenous among ethnic sub cohorts. In the case of IL-6, fibrinogen and CRP, Hispanics and African Americans had the highest levels. In contrast, the highest levels of PAP, D-dimer and factor VIII, were observed in African-Americans. Overall, the Chinese population displayed the lowest level of all biomarkers except for factor VIII. The population distribution for each ethnic cohort was also analyzed according to quartiles of biomarkers. African-Americans in general had higher proportions of cases falling under higher quartiles of each biomarker (IL-6, PAP, fibrinogen, D-dimer, CRP, factor VIII), while the Chinese cohort had a higher proportions of cases distributed in the lower quartiles for almost all biomarkers (IL-6, PAP, fibrinogen, D-dimer, CRP) except factor VIII. The Caucasian cohort had the most homogenous distribution across quartiles of biomarkers, while Hispanics displayed a larger distribution towards higher quartiles of IL-6, fibrinogen and CRP.

4.2. Influence of ethnicity on association of inflammatory marker and future CVD events

An ethnicity-stratified crude and adjusted multivariate Cox proportional hazard model analysis was performed to characterize the predictive role of novel biomarkers for ALL CVD events across ethnic sub cohorts. CRP remained a predictor of incident CVD on unadjusted and adjusted analysis among Caucasians. However, for other ethnic cohorts (African American, Hispanics and Chinese), no association was observed between CRP and CVD.