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An Exploratory Factor Analysis of Inflammatory and Coagulation Markers Associated with Femoral Artery Atherosclerosis in the San Diego Population Study

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Abstract

Background and Aims—Several biomarkers of inflammation and coagulation have been implicated in lower extremity atherosclerosis. We utilized an exploratory factor analysis (EFA) to identify distinct factors derived from circulating inflammatory and coagulation biomarkers then examined the associations of these factors with measures of lower extremity subclinical atherosclerosis, including the ankle-brachial index (ABI), common and superficial femoral intima-media thickness (IMT), and atherosclerotic plaque presence, burden, and characteristics.

Methods—The San Diego Population Study (SDPS) is a prospective, community-living, multi-ethnic cohort of 1103 men and women averaged age 70. Regression analysis was used to assess cross-sectional associations between the identified groupings of biomarkers (factors) and the ABI and femoral artery atherosclerosis measurements.

Results—Two biomarker factors emerged from the factor analysis. Factor 1 consisting of Creactive protein (CRP), interleukin (IL)-6, and fibrinogen was significantly associated with

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higher odds (OR=1.99, $p<0.01$) of a borderline ABI value (0.91–0.99), while Factor 2 containing Ddimer and pentraxin (PTX)-3 was significantly associated with higher common femoral artery (CFA) IMT (β=0.23, $p<0.01$) and lower ABI (β=−0.03, $p<0.01$).

Conclusions—Two groupings of biomarkers were identified via EFA of seven circulating biomarkers of inflammation and coagulation. These distinct groups are differentially associated with markers of lower extremity subclinical atherosclerosis. Our findings suggest that high inflammatory and coagulation burden were better markers of more severe lower-extremity disease as indicated by low ABI rather than early atherosclerotic lesion development in the femoral artery.

Keywords

Ankle-brachial index; inflammation; peripheral artery disease; plaque; subclinical atherosclerosis

INTRODUCTION

Atherosclerosis is a chronic inflammatory disease that is the underlying disease process responsible for the majority of cardiovascular disease (CVD) morbidity and mortality (1–4). Peripheral artery disease (PAD), one manifestation of atherosclerosis, affects an estimated 8.5 million individuals in the U.S. (5). PAD is associated with declines in functional status, increased risk of cardiovascular events, as well as cardiovascular and all-cause mortality (6–8).

Subclinical measures of atherosclerosis allow for the assessment of different stages of atherosclerosis development and for the identification of individuals at risk of cardiovascular events or complications. The ankle-brachial index (ABI), which is the clinical criterion used to diagnose PAD (ABI≤0.90), is associated with reduced functional performance even in cases of a borderline ABI (0.91–0.99) suggesting that significant lower extremity atherosclerosis may occur before the ABI is considered abnormal (9). Higher femoral artery intima-media thickness (IMT) is associated with PAD in patients with coronary heart disease (10) while plaque identified in the femoral artery is associated with reduced functional performance, and an increased risk of cardiovascular events (11–13). Similarly, greater femoral plaque burden is associated with symptomatic PAD and worse functional performance (13, 14).

Research investigating the inflammatory mechanisms contributing to atherosclerosis has identified several circulating biomarkers of inflammation and coagulation, including C-reactive protein (CRP), soluble intracellular adhesion molecule (sICAM)-1, interleukin (IL)-6, fibrinogen, D-dimer, Lipoprotein(Lp)-a, and pentraxin(PTX)-3, as independent predictors of cardiovascular risk (15–20). However, less is known about the potential associations or involvement of these biomarkers in various stages of the development and progression of atherosclerotic disease in the lower extremities.

Our study had two objectives. First, we used an exploratory factor analysis (EFA) to identify the underlying structure of seven circulating markers of inflammation and coagulation. Next, we measured the associations of the derived biomarker groupings (factors) with measures of

subclinical atherosclerosis: the ABI and IMT, plaque presence, burden, and characteristics in the common and superficial femoral arteries of healthy older adults.

MATERIALS AND METHODS

Participants

The San Diego Study Population (SDPS) is a prospective, multi-ethnic cohort study of lower extremity PAD and venous disease in men and women that has been described in detail elsewhere (21, 22). Briefly, employees of the University of California, San Diego and their significant others, all of whom resided in San Diego County, were recruited to participate in the study. Participants were selected randomly within strata of age, sex, and race/ethnicity. Women and racial/ethnic minorities (African-American, Hispanic, and Asian) were over-sampled. The present study includes 1001 SDPS participants who had both a femoral artery ultrasound and blood draw in order to measure inflammatory and coagulation biomarkers completed at a clinical exam between 2007–2011. All participants provided signed informed consent at baseline and follow-up, and the University of California-San Diego Institutional Review Board Committee on Investigations Involving Human Subjects approved the study.

Ultrasound Measurements

Doppler ultrasound scans were conducted using an Acuson Aspen (Siemens, Inc) to obtain images of three 10 mm segments of the right and left common and superficial femoral arteries: one at the common femoral artery (CFA) just proximal to the bifurcation, one at the bifurcation of the CFA and one at the SFA distal to the bifurcation. Five-second image clips were obtained for these segments at an angle of insonation of 90 degrees.

The measurement of femoral IMT and assessment of femoral plaque presence in the SDPS have previously been described in detail elsewhere (23). Briefly, the posterior (far) wall of the left and right common and superficial femoral arteries was used in order to determine average common and superficial IMT using semi-automated Carotid Analyzer software from the Vascular Research Tools 5 Suite (Medical Imaging Applications LLS, Coralville, IA). Plaque presence was defined as a participant having plaque in at least one arterial segment (left SFA, right SFA, left CFA, or right CFA) and total number of plaques was defined as the sum of all plaques across the four segments. In some segments, visualization of plaque was limited due to artifact. Focal structures fitting the Mannheim consensus in these images were classified as “probable plaques”.

Plaque area and grey-scale median (GSM) were determined by one ultrasound reader using the aforementioned software. Area of each plaque was calculated by the software after tracing by the reader and outlining by the software. Total plaque area was defined as the sum of plaque area across the four arterial segments. GSM, a continuous measure of plaque echogenicity, was calculated by the software for each plaque. Normalization, which minimizes the effect of different ultrasound machine gain settings, was performed manually by the reader selecting a dark area of blood from the lumen and the brightest area of the adventitial layer. Mean GSM was calculated by averaging the GSM values for all identified plaques. The within-reader intraclass correlation coefficients (ICC) for plaque area and GSM

were 0.95 and 0.99, respectively, according to a reliability study using femoral images at the University of Pittsburgh Ultrasound Research Lab. Calcification was subjectively identified by the vascular sonographers after assessing each plaque for highly echogenic areas and acoustic shadowing.

Ankle Brachial Index

With the participant in the supine position, systolic blood pressure (SBP) was measured twice in both arms, as well as both the anterior and posterior tibial and dorsalis pedis arteries using a Doppler probe (Acuson Aspen, Siemens, Inc). The maximum of the average posterior tibial or dorsalis pedis SBP was divided by the maximum of the average left and right arm SBP to calculate ABI. The lower of the left and right leg's ABI was considered the index ABI.

Inflammatory and Coagulation Biomarkers

Nephelometric assays (Siemens Healthcare, Erlange, Germany) were used to measure CRP and fibrinogen from EDTA plasma, and Lp(a) in serum. Inter-assay coefficients of variation (CVs) were 4.1–5.1%, 3.2–4.7%, and 5.2–8.2% for CRP, fibrinogen, and Lp(a), respectively. sICAM-1 was measured in EDTA plasma using a non-allele specific enzyme-linked immunosorbent assay (ELISA) (R&D Systems, Minneapolis, MN) with a CV range of 10.3–11.0%. An ELISA was also used to measure PTX-3 in EDTA plasma and IL-6 in serum with CVs of 9.3–14.9% and 4.2–6.3%, respectively. Finally, D-dimer was measured in EDTA plasma using an Evolution Coagulation Analyzer (Diagnostica Stago, Parsippany, NJ) with a CV range of 2.7–24.7%.

Covariates

Age, sex, race/ethnicity, cigarette smoking habits, as well as prevalent CVD (MI, stroke, angioplasty, or revascularization) were determined via self-report. Diabetes was ascertained via self-report of the use of anti-diabetic medications or insulin and physical activity level was determined by asking participants to rate their perceived activity level compared to others their age.

Height (centimeters) and weight (kilograms) were obtained in order to calculate body mass index (BMI) as kg/m^2. Blood pressure was obtained from the right arm using a standard manual sphygmomanometer after five minutes of rest. Hypertension was defined as SBP ≥140 mmHg, diastolic blood pressure (DBP) ≥90, or anti-hypertensive medication use. Total and high density lipoprotein (HDL) cholesterol were measured from non-fasting blood samples using a Roche Cobas 6000 analyzer (Roche Diagnostics Corporation, Indianapolis, IN). Low density lipoprotein (LDL) was calculated using the Friedewald equation (24). Estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI equation, and a Roche Cobas 6000 analyzer (Roche Diagnostics Corporation, Indianapolis, IN) was utilized to measure serum creatinine levels via isotope dilution mass spectrometry (25).

Statistical Analysis

An exploratory factor analysis was performed using maximum likelihood methods with direct oblimin rotation on Pearson correlation matrix using PROC Factor in SAS 9.3 (SAS

Institute, Cary, NC). We compared the model fit and interpretability of models with one- through four-factor solutions, and retained the two-factor solution based on model fit statistics and parallel analysis. Estimated factor scores were obtained via the SCORE option in PROC Factor based on the biomarkers with loadings ≥|0.3|, and were categorized based on tertiles of the distribution.

Differences in categorical and continuous participant characteristics were compared using Chi-square and Kruskal-Wallis tests, respectively, among those with and without femoral plaque and across tertiles of the factor scores. Logistic regression was used to assess the associations between the factor score tertiles with plaque presence and calcification. Linear regression was used to determine associations between the factor score tertiles and average CFA IMT, average SFA IMT, total plaque area and average GSM, and zero-inflated Poisson regression was used to determine associations between the factor score tertiles and total number of plaques. Minimally adjusted models included age, sex, and race/ethnicity, while fully adjusted models also included ABI, BMI, SBP, total cholesterol, eGFR, diabetes, smoking status, statin use, and self-reported activity level. Finally, linear regression was used in order to measure the association of factor tertiles with ABI among individuals with ABI <1.4. Those with ABI ≥ 1.4 were excluded considering an ABI of this level typically is indicative of severe arterial stiffening. Logistic regression was used to measure the association between continuous factor scores with likelihood of being in an abnormal ABI category (Low ABI ≤0.90, Borderline ABI 0.91–0.99, High ABI>1.30) compared to the normal ABI category of 1.00–1.30. Sensitivity analyses were conducted excluding the “probable” plaques (22%), but the results did not differ.

RESULTS

A total of 1001 participants were included in the EFA based on the complete availability of biomarker data. Characteristics of the 67 excluded participants did not differ from those in the analysis. Participants with femoral plaque were older, more likely to be male, had higher SBP, and lower BMI compared to those without plaque (Table 1). Two factors were derived from the EFA (Supplemental Table 1). Factor 1 was comprised of CRP, IL-6, and fibrinogen with factor loadings ranging from 0.49–0.83. Factor 2 was comprised of D-dimer and PTX-3 with factor loadings ranging from 0.43–0.48. sICAM-1 and Lp(a) did not load on either factor.

Across the tertiles of Factors 1 and 2, average CFA and SFA IMT increased and ABI decreased significantly in univariate analyses. Approximately 25% (246) of the participants had at least one plaque present. Plaque presence, burden, and characteristics did not differ significantly across the tertiles of Factor 1. However, individuals in the higher tertiles of Factor 2 were significantly more likely to have plaque and a greater number of plaques.

There were no significant differences in plaque characteristics across the factor tertiles in univariate analysis. There were no statistically significant associations between Factor 1 and CFA IMT, SFA IMT, plaque presence, or plaque burden (Table 3). However, individuals in the highest tertile of Factor 2 had a significantly higher CFA IMT (β=0.234 p<0.001) and SFA IMT (β=0.031 p<0.001) compared to those in the lowest tertile. The relationship

between Factor 2 and CFA IMT was independent of demographics and CVD risk factors. Notably, in unadjusted models, the highest tertile of Factor 2 was significantly associated with increased odds of femoral plaque presence (OR=2.19 95% CI=1.48–3.25) and an increased total number of plaques (OR=2.36 95% CI=1.66–3.36) compared to the lowest tertile. Neither of these associations remained statistically significant following adjustment for covariates. There were no statistically significant associations between either factor and plaque characteristics (Supplemental Table 3).

Among those with ABI <1.4, the highest tertile of Factor 2 was negatively associated with ABI even after adjustment for covariates (β=−0.027 p<0.01) (data not shown). Notably, higher Factor 1 scores were associated higher odds of having a borderline ABI (OR=1.99, 95% CI=1.25–3.19) compared to a normal ABI (Figure 1). Higher Factor 2 scores were associated with higher odds of having a low (OR=3.51, 95% CI=1.81–6.79), borderline (OR=2.18, 95% CI=1.16–4.10), or high ABI (OR=1.93, 95% CI=1.05–3.56), but these associations were no longer significant after adjustment for covariates.

DISCUSSION

In this multi-ethnic, community-living cohort of predominately healthy men and women, we found that inflammatory and coagulation factors identified via an EFA were differentially associated with various measures of lower extremity subclinical atherosclerosis. Specifically, the factor composed of CRP, IL-6, and fibrinogen (Factor 1) was independently associated with higher odds of having a borderline low ABI (0.91–0.99), but was not consistently associated with other subclinical measures. A second factor composed of D-dimer and PTX-3 (Factor 2) was consistently associated with markers of PAD including higher CFA IMT and lower ABI among those with ABI <1.4. Before adjustment for covariates, Factor 2 was also associated with higher SFA IMT, likelihood of femoral plaque, plaque burden, and odds of having a low, borderline, or high ABI.

Factor 1 seems likely to represent a non-specific inflammatory process. The grouping of CRP and IL-6 was expected considering CRP is synthesized in response to IL-6 secretion, and both are generalized markers of inflammation predictive of CVD (15–17, 26). Fibrinogen is a glycoprotein that contributes to platelet aggregation and is converted to fibrin in order to form clots (27, 28). Like CRP, fibrinogen is an acute phase reactant synthesized by hepatocytes that is associated with risk of CHD and stroke (18, 27). The composition of Factor 2 (D-dimer and PTX-3) is seemingly less straight-forward. PTX-3 is an activator of the classical complement pathway thought to be secreted by vascular cells under stress (20). High levels of PTX-3 have been observed within coronary artery thrombi, and some evidence suggests that PTX-3 may increase the expression of Tissue Factor (TF), an activator of the coagulation cascade (29, 30). D-dimer, a fibrin degradation product, is a marker of thrombogenesis that is present in the blood following the activation of the coagulation cascade (31, 32). Thus, the grouping of these biomarkers within Factor 2 is likely indicative of a thrombogenic process and the concomitant vascular perturbation.

Our findings suggest that coagulation burden, compared to inflammatory burden, may be a better indicator of subclinical PAD in older adults. This is consistent with the evidence

documenting a hypercoaguable state among those with PAD (33) as well as the established relationship between circulating coagulation markers and PAD severity (15). Our null findings regarding the relationships between the EFA-derived factors and femoral plaque suggest that high inflammatory or coagulation burden were better markers of more severe lower-extremity disease as indicated by low ABI rather than early atherosclerotic lesion development in the femoral artery. Although we did not find any significant associations between our factors and plaque measures, many of the biomarkers assessed in our study have been previously associated with plaque (34–36). The majority of these prior studies examine relationships between circulating biomarkers and atherosclerosis in the carotid or coronary arteries, or among participants who are already clinically diagnosed with some form of CVD. Our study included predominately active, healthy adults among whom only 25% had femoral plaque, 3% had PAD, and 9% had CVD. The relatively low burden of lower extremity atherosclerosis in our sample likely contributed to our null findings. It is also worth noting that participants with plaque on average had lower BMI compared to those without plaque. We believe this observation is partially explained by the fact that participants with plaque were older and more likely to be male compared to those without plaque. Additionally, higher BMI among the plaque-free participants may be indicative of better overall health considering BMI has been shown to be protective among some older cohorts (37). Further studies utilizing these techniques in populations with more advanced CVD or atherosclerosis in alternative arterial beds like the carotid artery where plaque is more likely to be characterized as high risk (38) are warranted to help elucidate the mechanisms through which circulating markers of inflammation and coagulation may influence atherosclerotic processes.

We chose to utilize an EFA approach in the present analysis because due to the complex nature of atherosclerosis, many biomarkers of inflammation and coagulation are interdependent. EFA is a technique that allows for the identification of underlying constructs, or factors, among a group of items with no *a priori* hypothesis (39, 40). It is not a data reduction technique, and therefore, can help address concerns regarding multicollinearity without sacrificing information. The identification of groupings of circulating inflammatory and coagulation markers, or latent processes to which these markers contribute may not only provide insight into the relationships among these biomarkers, but may aid in the characterization of patients who are at greatest risk (41). These types of techniques can shed light on the underlying biological relationships among biomarkers, and therefore, may prove particularly useful for the study of complex, multifaceted processes like atherosclerosis.

There are several limitations of the present study worth mentioning. B-mode ultrasound is a non-invasive and efficient method of measuring plaque in the general population, but is limited in its ability to characterize plaque. The measures collected here (e.g. GSM) may not have been sufficiently sensitive to identify associations between the biomarker factors and plaque characteristics in this population with relatively little femoral plaque. Additionally, the cross-sectional nature of this investigation limits our ability to draw conclusions regarding the causal relationships, or lack thereof, between the biomarker factors and plaque measures. Finally, only seven biomarkers were included in our analysis. The consideration

of additional biomarkers in the EFA may have yielded additional factors that incorporated sICAM-1 and Lp(a), which did not load on either of the factors identified in our analysis.

Conclusions

Two factors emerged following an EFA of circulating biomarkers of inflammation and coagulation in relation to peripheral arterial disease: Factor 1 composed of CRP, IL-6 and fibrinogen, and Factor 2 composed of D-dimer and PTX-3. Individuals with high levels of Factor 1 had higher odds of having a borderline low ABI. Factor 2 was associated with lower ABI among those with ABI <1.4, and with higher CFA IMT independent of ABI. We did not find any associations between either factor with measures of femoral plaque presence, burden, or characteristics after adjusting for covariates. These results indicate that in our community-living, multi-ethnic sample of healthy older adults, high inflammatory burden and coagulation burden were better markers of more severe lower-extremity disease as indicated by low ABI rather than early atherosclerotic lesion development assessed by ultrasound in the femoral artery.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Highlights

- Femoral artery intima-media thickness is greater among adults with high coagulation burden
- Inflammatory and coagulation burden are associated with lower ankle-brachial index
- Femoral plaque presence and characteristics not related to inflammatory and coagulation burden

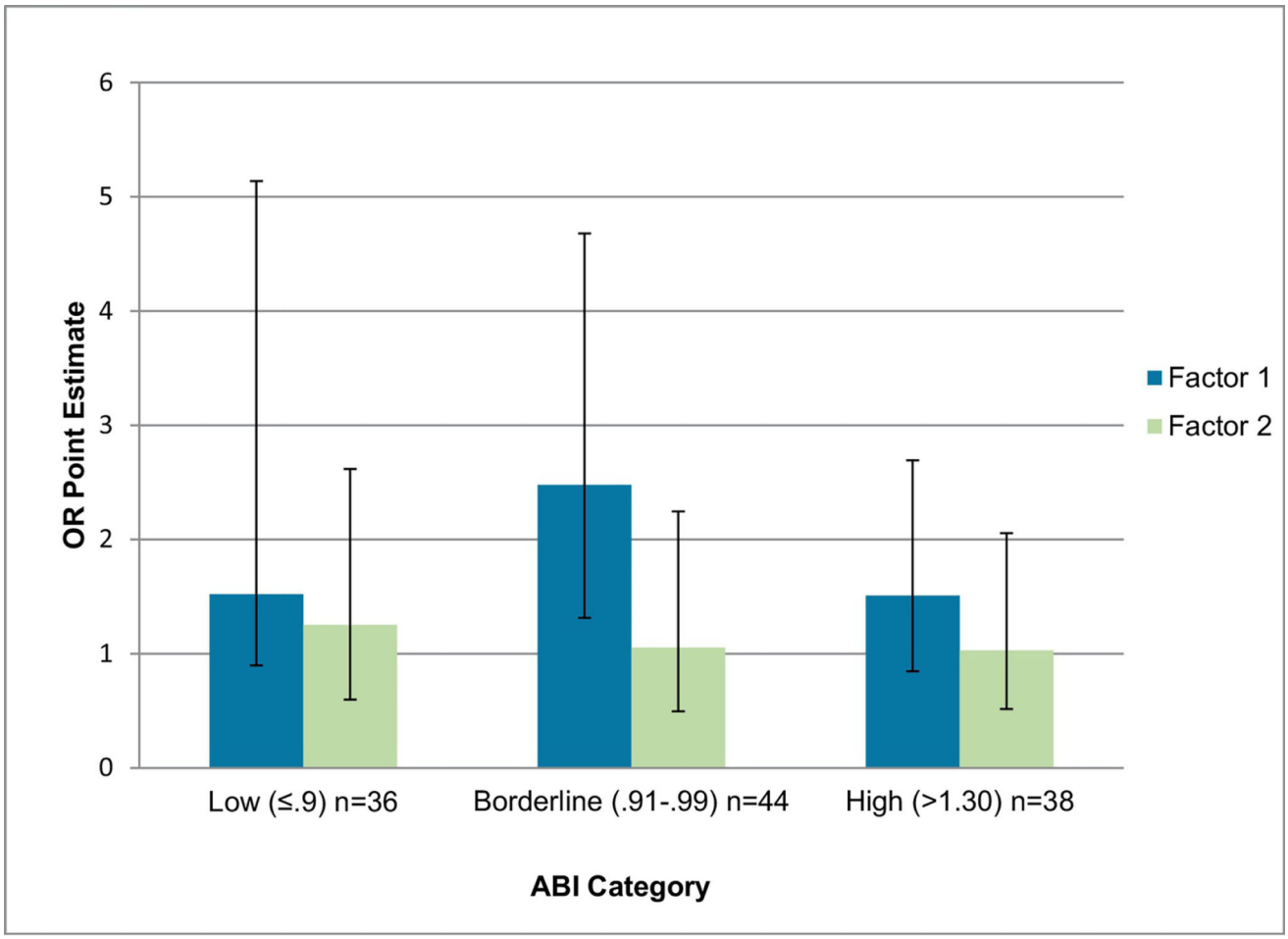

Figure 1.

Table 1

Characteristics of Study Sample by Plaque Presence

Characteristic	Plaque N=246 (25%)	No Plaque N=755 (75%)	p-value
Age (years)	77 (69–83)	68 (61–76)	<0.0001
Sex (male)	97 (39%)	235 (31%)	0.0187
Race/Ethnicity			0.0002
Non-Hispanic White	177 (72%)	419 (56%)	
African-American	21 (9%)	96 (13%)	
Hispanic	19 (8%)	122 (16%)	
Asian	28 (11%)	105 (14%)	
Other	1 (0%)	13 (1%)	
Systolic BP (mmHg)	132 (120–146)	130 (118–140)	0.0013
Diastolic BP (mmHg)	72 (66–80)	76 (70–82)	0.0003
Pulse Pressure	60 (50–72)	52 (42–62)	<0.0001
Body Mass Index (kg/m2)	25 (23–28)	27 (23–30)	0.0179
Estimated GFR (min/mL/1.73m2)	74 (59–86)	83 (69–93)	<0.0001
Total Cholesterol (mg/dL)	190 (163–213)	197 (170–226)	0.0022
HDL Cholesterol (mg/dL)	58 (44–72)	57 (46–73)	0.5456
LDL Cholesterol (mg/dL)	104 (79–125)	107 (87–132)	0.0038
Smoking History			0.0351
Current	8 (3%)	27 (4%)	
Former	90 (37%)	210 (28%)	
Never	147 (60%)	513 (68%)	
Hypertension	184 (75%)	436 (58%)	<0.0001
Statin Use	97 (41%)	227 (31%)	0.0048
Cardiovascular Disease	36 (15%)	52 (7%)	0.0002
Diabetes	34 (14%)	63 (8%)	0.0043
Chronic Kidney Disease	65 (27%)	81 (11%)	<0.0001
Peripheral Artery Disease	24 (10%)	11 (1%)	<0.0001
Ankle Brachial Index	1.12 (1.04–1.18)	1.14 (1.09–1.19)	0.0001
Activity Level			0.8099
Much less active	8 (3%)	22 (3%)	
Somewhat less active	27 (11%)	65 (9%)	
About as active	62 (25%)	195 (26%)	
Somewhat more active	89 (36%)	272 (36%)	
Much more active	59 (24%)	198 (26%)	
CRP (mg/L)	1.2 (0.6–2.3)	1.0 (0.5–2.2)	0.1395
IL-6 (pg/mL)	2.0 (1.4–3.0)	1.7 (1.1–2.6)	<0.0001
ICAM-1 (ng/mL)	352.2 (294.3–429.4)	339.4 (284.9–409.8)	0.0469
Fibrinogen (mg/mL)	380.0 (331.0–428.0)	377.0 (330.0–423.0)	0.7490
D-dimer (ug/mL)	0.5 (.3–.8)	0.4 (0.2–0.6)	0.0021
Lp(a) (g/L)	0.1 (.0–.3)	0.1 (0.0–0.3)	0.4210

Characteristic	Plaque N=246 (25%)	No Plaque N=755 (75%)	p-value
PTX-3 (ng/mL)	1.3 (0.9–2.0)	1.2 (0.8–1.8)	0.0373

[a]. Median (25^{th}–75^{th} percentile) provided for all continuous variables, Kruskal-Wallis test used to compare groups.

[b]. N (%) provided for categorical variables, Chi-square test used to compare groups.

Table 2

Differences in Outcomes by Tertiles of Factor Scores

	Factor 1: CRP, IL-6, Fibrinogen				Factor 2: PTX-3, D-dimer			
	T1	**T2**	**T3**	**p-value**	**T1**	**T2**	**T3**	**p-value**
Average CFA IMT	0.73 (0.64–0.87)	0.75 (0.66–0.91)	0.77 (0.67–0.91)	0.008	0.71 (0.63–0.83)	0.74 (0.66–0.87)	0.79 (0.70–1.03)	<.0001
Average SFA IMT	0.57 (0.53–0.62)	0.58 (0.54–0.64)	0.59 (0.56–0.64)	<.0001	0.57 (0.53–0.61)	0.58 (0.53–0.63)	0.59 (0.56–0.63)	<.0001
ABI	1.15 (1.10–1.20)	1.13 (1.08–1.19)	1.12 (1.07–1.18)	<.0001	1.15 (1.12–1.20)	1.15 (1.12–1.20)	1.11 (1.04–1.18)	<.0001
Plaque Presence	68 (21%)	84 (25%)	94 (28%)	0.0921	62 (19%)	68 (21%)	116 (34%)	<.0001
Total # of Plaques				0.2481				0.0083
≤2	65 (96%)	74 (88%)	84 (89%)		59 (95%)	63 (93%)	101 (87%)	
>2	3 (4%)	10 (12%)	10 (11%)		3 (5%)	5 (7%)	15 (13%)	
Total Plaque Area	11.74 (8.19–36.86)	13.49 (9.32–24.62)	12.34 (8.41–21.26)	0.5148	14.16 (8.26–21.70)	12.02 (8.29–21.22)	12.61 (8.71–25.92)	0.6356
Average GSM	52.88 (39.83–59.78)	56.51 (42.73–73.33)	55.30 (44.18–68.12)	0.1956	49.62 (40.91–62.31)	56.51 (42.00–74.89)	55.54 (44.72–65.94)	0.1848
Calcification	19 (28%)	21 (25%)	26 (28%)	0.8963	13 (21%)	17 (25%)	36 (31%)	0.3253

a. Median (25^{th}–75^{th} percentile) provided for all continuous variables, Kruskal-Wallis test used to compare groups.

b. N (%) provided for categorical variables, Chi-square test used to compare groups.

Table 3

Associations of Biomarker Factor Score Tertiles with IMT, Plaque Presence, and Plaque Burden

	Outcome							
	Average CFA IMT		Average SFA IMT		Plaque Presence		# of Plaques	
Biomarker Factor	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2
	Factor 1: CRP, IL-6, Fibrinogen							
Tertile 1 (ref)	-	-	-	-	-	-	-	-
Tertile 2	0.03 (0.04)	0.03 (0.04)	0.01 (0.01)	0.00 (0.01)	0.13 (0.19)	−0.01(0.21)	0.21 (0.17)	0.15(.17)
Tertile 3	−0.03 (0.04)	0.02 (0.04)	0.02 (0.01)	0.01 (0.01)	0.05 (0.21)	0.21(0.23)	0.40 (0.18)	0.25(.18)
	Factor 2: PTX-3, D-Dimer							
Tertile 1 (ref)	-	-	-	-	-	-	-	-
Tertile 2	0.05 (0.04)	0.02 (0.04)	0.00 (0.01)	0.00 (0.01)	0.10 (0.20)	−0.25 (0.27)	0.23 (0.19)	0.01(.19)
Tertile 3	0.23 (0.04)[≠]	0.12 (0.04)[≠]	0.03 (0.01)[≠]	0.01 (0.01)	0.78 (0.20)[≠]	0.08 (0.24)	0.86 (0.18)[≠]	0.28(.20)

[a]. Beta estimates (se) provided.

[≠]indicates significant at the α=.05 level.

[b]. Model 1 is unadjusted.

[d]. Model 2 adjusts for age, sex, race/ethnicity, ABI, BMI, SBP, total cholesterol, eGFR, diabetes, smoking status, statin use, and activity level.