Age as a Modulator of Inflammatory Cardiovascular Risk Factors

Erdembileg Anuurad, Byambaa Enkhmaa, Zeynep Gungor, Wei Zhang, Russell P. Tracy, Thomas A. Pearson, Kyoungmi Kim, Lars Berglund

Objective—Levels of acute phase reactants are affected by age. The extent to which cardiovascular risk associated with aging is due to an increase in the inflammatory burden is not known. We assessed the relationship with age of inflammatory markers, representing (1) systemic (C-reactive protein, fibrinogen, and serum amyloid-A) and (2) vascular (lipoprotein-associated phospholipase A2 and pentraxin-3) inflammation.

Methods and Results—We determined lipoprotein-associated phospholipase A2 mass and activity, C-reactive protein, fibrinogen, serum amyloid-A, and pentraxin-3 levels and other cardiovascular disease risk factors in 336 whites and 224 African Americans. Levels of systemic inflammatory markers increased significantly with age in both ethnic groups (P<0.05 for all), whereas trend patterns of vascular inflammatory markers did not change significantly with age for either group. In multivariate regression models adjusting for confounding variables, age remained independently associated with a composite Z score for systemic but not vascular inflammation (β=0.250, P<0.001, and β=0.276, P<0.001, for whites and African Americans, respectively).

Conclusion—We report an increase in the systemic but not vascular inflammatory burden over age. Levels of both categories of inflammatory markers over age were similar across ethnicity after adjustment for confounders. Our results underscore the importance of age in evaluating inflammatory markers to assess cardiovascular risk. (Arterioscler Thromb Vasc Biol. 2011;31:00-00.)

Key Words: aging ■ coronary artery disease ■ epidemiology ■ risk factors

Over the past decade there has been a growing appreciation that inflammation plays a critical role at every stage of the atherosclerotic process, from lesion initiation to the rupture of atherosclerotic plaque.1 In support of this concept, many prospective studies demonstrate a positive association between risk for cardiovascular disease (CVD) and plasma levels of C-reactive protein (CRP)2,3 or fibrinogen.4,5 More recently, other markers, such as lipoprotein-associated phospholipase A2 (Lp-PLA2), were considered informative with regard to vascular inflammation and have shown to be associated with CVD.6–8 Notably, the weak correlation between Lp-PLA2 and CRP suggests that these inflammatory markers may reflect differences in underlying mechanisms.9 Furthermore, ethnic differences in levels of circulating inflammatory markers have been reported, potentially related to demographic or lifestyle factors.10

Although traditional cardiovascular risk factors are useful for predicting cardiovascular events in younger populations, their predictive value decreases with age.11 Therefore, one could speculate that presence of a low-grade inflammation may play a more substantial role in the pathogenesis of CVD in older compared with younger adults. However, information about the distribution pattern of inflammatory markers over the age spectrum is limited, and previous studies have yielded conflicting results. Thus, studies among healthy subjects failed to detect any significant difference in the production of interleukin-1 and interleukin-6 between young, middle-aged, and older participants.12 Other studies among healthy volunteers found an increase in circulating levels of IL-6, CRP, serum amyloid-A (SAA), and other inflammatory markers with age.13–14 Furthermore, as we have demonstrated previously, compared with whites, African Americans had higher levels of systemic inflammatory markers but lower levels of vascular inflammatory markers.15 To address the question to what extent inflammatory markers are affected by aging, we investigated 2 sets of inflammatory markers, one set representing general, systemic inflammation (CRP, fibrinogen, and SAA) and the other representing vascular inflammation (Lp-PLA2 mass, activity, and pentraxin-3 [PTX-3]) across the age spectrum in African Americans and whites.
Specifically, we hypothesized that the presence of heterogeneity in the relationship of systemic and vascular inflammatory markers with age would aid our understanding of their predictive ability in the assessment of cardiovascular risk.

Materials and Methods

Subjects

Subjects were recruited from a patient population scheduled for diagnostic coronary arteriography either at Harlem Hospital Center in New York City or at the Mary Imogene Bassett Hospital in Cooperstown, NY. The study design, including exclusion and inclusion criteria, has been described previously. Briefly, a total of 648 patients, self-identified as white (n=344), African American (n=232), or other (n=72) were enrolled. Exclusion criteria for this study included the use of lipid-lowering drugs, as well as hormone replacement therapies. The present report is based on findings in 560 subjects (336 whites, 224 African Americans); 16 subjects were excluded because of incomplete data. The study was approved by the institutional review boards at Harlem Hospital, the Mary Imogene Bassett Hospital, Columbia University College of Physicians and Surgeons, and University of California Davis, and informed consent was obtained from all subjects.

Clinical and Biochemical Assessment

Blood pressure was measured with a random-zero mercury sphygmomanometer. Waist circumference was calculated as the average of 2 measurements taken after inspiration and expiration at the midpoint between the lowest rib and iliac crest. Participants were asked to fast for 12 hours, and blood samples were drawn approximately 2 to 4 hours before the catheterization procedure. Serum and plasma samples were separated and stored at −80°C before analysis. Concentrations of total and high-density lipoprotein (HDL) cholesterol and glucose (Roche, Somerville, NJ) were determined using standard enzymatic procedures. HDL cholesterol levels were measured after precipitation of apolipoprotein B–containing lipoproteins with dextran sulfate. The low-density lipoprotein (LDL) cholesterol levels were calculated with the formula of Friedewald et al. High-sensitivity C-reactive protein levels were measured using an enzyme-linked immunosorbent assay, standardized according to the World Health Organization First International Reference Standard (coefficient of variation [CV] 8.9%). Fibrinogen levels were measured by the clot-rate method of Clauss (CV 3.0%). Insulin levels were assessed using a Coat-A-Count RIA kit (DPC Diagnostic Products Co, Los Angeles, CA). Homeostasis model assessment–insulin resistance (HOMA-IR) was calculated using the updated model available from the Oxford Centre for Endocrinology and Diabetology.

PTX-3 was measured by PTX-3 (human) Detection Set from Alexis Biochemicals (Axxora, LLC) (CV 10.2%). Plasma SAA concentrations were measured by enzyme-linked immunosorbent assay using a commercially available kit (Innitrogen, Inc, Carlsbad, CA) (CV 5.4% to 10.3%). Lp-PLA2 mass was assayed using a microplate-based enzyme linked immunosorbent assay (CV 4.8% to 7.2%), and Lp-PLA2 activity was measured with a colorimetric activity method (diaDexus, Inc, South San Francisco, CA) (CV 6.5% to 7.8%). All biochemical assessments were made in duplicate.

Statistics

Analysis of data were done with SPSS statistical analysis software (SPSS Inc, Chicago, IL). Results are expressed as means±SE. Levels of triglycerides, insulin, HOMA-IR, Lp-PLA2 mass, and activity and the cardiovascular score were logistically transformed to achieve normality for statistical analysis. Proportions were compared between groups using the χ^2 test or the Fisher exact test, as appropriate. Group means were compared using the Student t test. Gender-adjusted Pearson’s partial correlation coefficients were calculated for age and inflammatory markers across ethnicities. To construct a composite score of multiple markers, we first calculated a Z-score for each inflammatory marker (Z=(x−μ)/σ), where x is an individual marker value, μ is the mean marker value, and σ is the standard deviation of marker values. Using the individual Z-scores, we next calculated a composite Z score for systemic inflammation (ie, Z score [systemic]=Average [Z-CRP, Z-Fibrinogen, Z-SAA]) and for vascular inflammation (Z score [vascular]=Average [0.5 Z-Lp-PLA2 mass, 0.5 Z-Lp-PLA2 activity, Z-PTX-3]). As we used Lp-PLA2 mass and activity to calculate a composite Z score for vascular inflammation, these 2 parameters were given a coefficient of 0.5 in the formula. Multivariate linear regression analysis was performed to explore the independent association of age with the composite Z scores, adjusted for confounding variables. Two-tailed probability values less than 0.05 were considered statistically significant.

Results

Whites were slightly older and more obese as compared with African Americans (Table 1). There was no difference in the gender distribution, and a higher proportion of white women were postmenopausal. Levels of systemic inflammatory markers were higher in African Americans compared with whites, although the difference for SAA did not reach statistical significance. The opposite pattern was observed for markers of vascular inflammation: Lp-PLA2 mass, activity, and PTX-3 levels were significantly lower in African Americans compared with whites. Next we tested the correlations between markers of systemic and vascular inflammation within each ethnic group (Supplemental Table I, available online at http://atvb.ahajournals.org). Among systemic inflammatory markers, CRP, SAA, and fibrinogen were strongly correlated to each other, whereas these markers showed only a weak correlation with markers of vascular inflammation. For markers of vascular inflammation, Lp-PLA2 mass showed a moderate correlation with Lp-PLA2 activity but not with any other inflammatory marker. PTX-3 showed a weak or no correlation with other markers. The association of each marker of systemic and vascular inflammation with the presence of coronary artery disease (CAD) is

<table>
<thead>
<tr>
<th>Inflammatory markers</th>
<th>Whites (n=336)</th>
<th>African Americans (n=224)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP, mg/L</td>
<td>7.0±0.6</td>
<td>9.8±1.0</td>
<td>0.004</td>
</tr>
<tr>
<td>SAA, mg/L</td>
<td>82±8</td>
<td>111±13</td>
<td>0.284</td>
</tr>
<tr>
<td>Fibrinogen, mg/dL</td>
<td>328±5</td>
<td>383±7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lp-PLA2 mass, ng/mL</td>
<td>293±4</td>
<td>232±5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lp-PLA2 activity, nmol/min/mL</td>
<td>173±2</td>
<td>141±3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PTX-3, ng/mL</td>
<td>2.33±0.15</td>
<td>1.87±0.23</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data are expressed as mean±SEM. For CRP, SAA, Lp-PLA2 mass, Lp-PLA2 activity, and PTX-3 were logarithmically transformed to normalize the distribution of marker values before statistical analyses. CRP indicates C-reactive protein; SAA, serum amyloid A; Lp-PLA2, lipoprotein-associated phospholipase A2; PTX-3, pentraxin-3.
shown in Supplemental Table II. For both ethnic groups, fibrinogen levels and Lp-PLA2 activity were associated with the presence of CAD. Additionally, for African Americans, the presence of CAD was associated with higher CRP or SAA levels.

Pearson’s partial correlation coefficients between each inflammatory marker and age across ethnicity adjusted for gender are listed in Table 2. In both ethnic groups, systemic inflammatory markers were significantly and positively associated with age. In whites, among markers of vascular inflammation, Lp-PLA2 mass was positively associated with age, whereas no significant associations with age were seen for Lp-PLA2 activity or PTX-3. We did not observe any associations between markers of vascular inflammation and age among African Americans.

The trend pattern of each individual marker with age is shown in Figure 1. Among markers of systemic inflammation, CRP levels increased significantly (Figure 1A) with age in both ethnic groups ($P=0.012$ and $P=0.047$, for African Americans and whites, respectively). Similarly, in both groups, levels of fibrinogen and SAA increased significantly (Figure 1B and 1C) over age ($P<0.001$ and $P=0.003$ for African Americans, and $P<0.001$ and $P=0.001$ whites, respectively). In contrast, the trend patterns for vascular inflammatory markers (Lp-PLA2 activity and PTX-3) did not change with age for either ethnic group (Figure 1D and 1E), except a slight but significant increase of Lp-PLA2 mass with age among whites (Figure 1F).

To collectively compare systemic and vascular inflammatory markers, we developed a composite Z score based on the 3 respective markers in each category, as outlined in Materials and Methods. The relationship between age and the unadjusted composite Z score for systemic and vascular inflammation is shown in Figure 2A and 2B, respectively. Reflecting the findings for the individual markers, the composite Z score for systemic inflammation increased significantly with age in both ethnic groups ($P=0.001$ and $P<0.001$ for African Americans and whites, respectively), and the score levels were significantly higher in African Americans than in whites across the age spectrum (Figure 2A). In contrast, we did not observe any significant change over age for the composite vascular inflammation Z score for either group (Figure 2B). Furthermore, across age, the composite vascular inflammation Z score was significantly higher in whites compared with African Americans.

To address the impact of possible confounders on the relationship between age and composite $Z$ scores (systemic and vascular), we included the following variables in a multivariate regression model as covariates: gender, obesity (body mass index), insulin resistance (HOMA-IR), lipid levels (LDL and HDL cholesterol), and smoking. As seen in Figure 2C and 2D, irrespective of ethnicity, the adjusted $Z$ score for systemic inflammation increased significantly with age. No apparent increase was seen for the vascular inflammation $Z$ score. Furthermore, even after adjusting for the confounders, the trajectories of trend were not significantly different for the 2 ethnic groups (Figure 2C and 2D). In support of the trend pattern data, age remained independently associated with the composite Z score for systemic inflammation in both ethnic groups in multivariate linear regression models (Table 3, model 1). Age, gender, body mass index, HOMA-IR, LDL cholesterol, HDL cholesterol, and smoking together explained $\approx 12\%$ of the variability of the composite $Z$ score for systemic inflammation in whites (Table 3, model
1). For African Americans, age, gender, body mass index, HOMA-IR, LDL cholesterol, HDL cholesterol, and smoking explained 18% of the corresponding variability (Table 3, model 1). Again, we did not observe any significant association of age with the composite Z score for vascular inflammation in either ethnic group (Table 3, model 2). In whites, of the factors included in the model, only LDL cholesterol was significantly associated with the composite Z score for vascular inflammation (Table 3, model 2). In African Americans, none of the variables considered in the model significantly related to the composite vascular inflammation Z score.

Discussion

Age is an established cardiovascular risk factor and has quantitatively a strong impact on the Framingham risk score.29 Although the overall effect of age as a classic risk factor is well recognized, contribution of age to increasing cardiovascular risk remains unclear as yet. Risk associated with age could possibly reflect an accumulating burden of a number of contributing factors, and it is therefore tempting to suggest that inflammation may contribute to this burden. In the present study, we addressed the question of the extent to which inflammatory markers are associated with age, taking other established risk factors into account. Furthermore, we attempted to assess differences between markers representing a more general, systemic inflammation versus a vascular-focused inflammatory process. The main novel finding in our study was a constant increase of the systemic but not the vascular inflammatory burden over age and that this pattern was seen irrespective of ethnic background. Our findings underscore the importance of age in elevating inflammatory burden when assessing cardiovascular risk.

Although the notion that elevated inflammatory markers increase the risk of CVD has been increasingly recognized, underlying mechanisms and pathways remain to be elucidated. Notably, high levels of inflammatory markers are known to be associated with many factors contributing to an increased CVD risk, such as smoking, visceral obesity, sedentary lifestyle, and excessive alcohol consumption, sug-
gesting a considerable degree of complexity. Furthermore, an increase of inflammatory cytokines can potentially contribute to the progression of many chronic and degenerative diseases, such as atherosclerosis, cancer, obesity, diabetes, and congestive heart failure. Thus, the presence of these risk factors and CVD itself may in turn further stimulate the inflammatory process, resulting in a vicious cycle. In support of this, Ferrucci et al have demonstrated that increases in inflammatory markers with age are due, at least partly, to a progressive increase in the burden of cardiovascular risk factor and morbidity.31 On the other hand, inflammation is an integral and necessary part of the response to pathogens and constitutes an important part of the immune defense system. In view of these complex relationships, it is important to characterize the role of individual markers of inflammation in predicting risk of disease development.

Many prospective studies demonstrate a positive association between risk for CVD and markers of systemic inflammation, ie, acute phase reactants, such as CRP and fibrinogen.2–5 Furthermore, recently, more specific vascular inflammatory markers, such as Lp-PLA₂ and PTX-3, have been shown to be associated with CVD.6–8 However, the correlation between Lp-PLA₂ and CRP is weak, suggesting that markers of systemic and vascular inflammation may reflect different underlying mechanisms. We have previously studied the associations of CRP, fibrinogen, and Lp-PLA₂ with CAD risk across African Americans and whites.32–34 and our findings indicate an independent impact of vascular inflammation as contributory to CAD risk; suggesting that different sets of markers could provide complementary information as risk predictors.

In assessing the relationship of systemic and vascular inflammatory biomarkers with age, we observed that all markers of systemic inflammation increased significantly over age, for both African Americans and whites. In contrast, we did not observe any change in trend patterns of vascular inflammatory markers with age in either ethnic group. Furthermore, in univariate analysis, we noted ethnic differences in the relationship between age and some markers of systemic and vascular inflammation. To collectively test the overall effect and distribution of systemic and vascular inflammation over age, we constructed composite scores by combining Z scores of the 3 respective markers in each category. In agreement with the findings for the separate markers, we observed a significant increase of the composite Z score for systemic but not vascular inflammation with age in both ethnic groups. Age still remained independently associated with the composite Z score for systemic but not vascular inflammation in both ethnic groups, even after adjusting for confounding variables that potentially could affect the relationship between levels of inflammatory markers and age. Interestingly, the differences between African Americans and whites disappeared after adjustment for the confounders, suggesting that differences seen in the univariate analyses were likely due to differences in confounding factors between the ethnic groups rather than an inherent ethnic difference.

Our approach of using composite Z scores has several advantages: (1) it enables a comparison of individual inflammatory markers within each category at the same scale, (2) it provides a standardized way to assess the relative contribution of individual inflammatory markers to age, and (3) it makes it possible to collectively assess effects of systemic and vascular risk factors as a group over age. Furthermore, the use of the scoring system allowed us to document that an increase of systemic inflammation with age persisted even after adjusting for confounding factors. Notably, the confounding factors taken into account, together with age, explained only a minor fraction of the overall variability in systemic inflammatory scores (12% for whites and 18% for African Americans), suggesting that other factors beyond traditional cardiovascular risk factors (for example, environmental factors, genetic factors, or both) may play a larger role. Overall, our findings suggest that systemic inflammatory markers may reflect overall age-related inflammatory burden to a greater extent than vascular markers. One implication of this finding is that vascular inflammation may reflect more specifically to a localized atherogenic process but less to a more widespread inflammatory process.

We acknowledge some of the limitations of this study. In view of the complexity of the inflammatory process and the considerable arsenal of markers available, it is well recognized that a classification of systemic versus vascular inflammatory markers likely represents a relatively narrow and perhaps somewhat simplistic view. However, we nevertheless adopted this approach as an initial attempt to address the relationship of individual inflammatory markers with other cardiovascular risk factors. Furthermore, the cross-sectional study design does not allow us to evaluate the causative and longitudinal effect of age and other factors that might influence on levels of inflammatory markers. Subjects in our study were recruited from among patients scheduled for coronary angiography and are likely more typical of a high-risk patient group than the general population at large. However, the use of a high-risk population is particularly valuable in assessing inflammatory factors that might be enriched in this population and ultimately their effects on risk of CVD. We did study 2 race/ethnicity groups, but expanded studies are needed to investigate other ethnic background groups. Although our findings support the notion that systemic inflammatory burden measured as increased levels of inflammatory markers is persistently increased by age, additional studies are warranted to verify these results in more general populations, as well as in prospective studies.

In conclusion, the findings suggest an increase in the systemic but not vascular inflammatory burden over age. This observation has several potential implications: (1) the use of systemic inflammatory markers in assessment of cardiovascular risk may be more influenced by age-related processes than is the case for vascular markers; (2) we did not observe any differences in levels of inflammatory markers over age between the 2 ethnic groups when adjusting for confounding variables, including traditional risk factors; (3) age is an independent predictor of systemic inflammation, even after adjustment for other risk factors, and traditional cardiovascular risk factors may only explain a small fraction of the variability of inflammatory markers. Our results underscore the important influence of age on inflammatory markers in
identification of a high–cardiovascular-risk phenotype across ethnicity.

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Disclosures
None.

References
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Supplement Material

**Supplementary Table I.** Pearson’s correlation coefficients of markers of systemic and vascular inflammation with each other.

<table>
<thead>
<tr>
<th></th>
<th>CRP</th>
<th>SAA</th>
<th>Fibrinogen</th>
<th>Lp-PLA₂ mass</th>
<th>Lp-PLA₂ activity</th>
<th>PTX-3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Caucasians</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRP</td>
<td>-</td>
<td>0.728*</td>
<td>0.643*</td>
<td>0.069</td>
<td>-0.095</td>
<td>0.301*</td>
</tr>
<tr>
<td>SAA</td>
<td>0.728*</td>
<td>-</td>
<td>0.547*</td>
<td>-0.016</td>
<td>-0.158*</td>
<td>0.273*</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>0.643*</td>
<td>0.547*</td>
<td>-</td>
<td>0.035</td>
<td>-0.002</td>
<td>0.199*</td>
</tr>
<tr>
<td>Lp-PLA₂ mass</td>
<td>0.069</td>
<td>-0.016</td>
<td>0.035</td>
<td>-</td>
<td>0.447*</td>
<td>0.016</td>
</tr>
<tr>
<td>Lp-PLA₂ activity</td>
<td>-0.095</td>
<td>-0.158*</td>
<td>-0.002</td>
<td>0.447*</td>
<td>-</td>
<td>-0.138</td>
</tr>
<tr>
<td>PTX-3</td>
<td>0.301*</td>
<td>0.273*</td>
<td>0.199*</td>
<td>0.016</td>
<td>-0.138</td>
<td>-</td>
</tr>
</tbody>
</table>

|                  |         |         |            |               |                  |       |
| **African Americans** |       |         |            |               |                  |       |
| CRP              | -       | 0.662*  | 0.654*     | -0.003        | 0.148            | 0.147 |
| SAA              | 0.662*  | -       | 0.584*     | 0.083         | 0.140            | 0.209*|
| Fibrinogen       | 0.654*  | 0.584*  | -          | -0.020        | 0.116            | 0.203*|
| Lp-PLA₂ mass     | -0.003  | 0.083   | -0.020     | -             | 0.403*           | 0.055 |
| Lp-PLA₂ activity | 0.148   | 0.140   | 0.116      | 0.403*        | -                | 0.134 |
| PTX-3            | 0.147   | 0.209*  | 0.203*     | 0.055         | 0.134            | -     |

Data for CRP, SAA, Lp-PLA₂ and PTX-3 were logarithmically transformed to normalize the distribution of marker values before statistical analyses. *, correlation is significant at the 0.01 level;
Supplement Material

**Supplementary Table II.** Logistic regression analysis relating each marker of systemic and vascular inflammation to the presence of CAD across ethnicity.

<table>
<thead>
<tr>
<th>Inflammatory markers</th>
<th>Caucasians</th>
<th></th>
<th>African Americans</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>P</td>
<td>OR (95% CI)</td>
<td>P</td>
</tr>
<tr>
<td>CRP, mg/L</td>
<td>1.068 (0.882-1.293)</td>
<td>0.502</td>
<td>1.270 (1.014-1.591)</td>
<td>0.038</td>
</tr>
<tr>
<td>SAA, mg/L</td>
<td>1.086 (0.908-1.299)</td>
<td>0.365</td>
<td>1.212 (1.003-1.466)</td>
<td>0.047</td>
</tr>
<tr>
<td>Fibrinogen, mg/dL</td>
<td>1.003 (1.000-1.006)</td>
<td>0.030</td>
<td>1.003 (1.000-1.005)</td>
<td>0.025</td>
</tr>
<tr>
<td>Lp-PLA₂ mass, ng/mL</td>
<td>2.264 (0.946-5.416)</td>
<td>0.066</td>
<td>0.623 (0.242-1.599)</td>
<td>0.325</td>
</tr>
<tr>
<td>Lp-PLA₂ activity, nmol/min/mL</td>
<td>5.051 (2.029-12.578)</td>
<td>0.001</td>
<td>2.853 (1.038-7.841)</td>
<td>0.042</td>
</tr>
<tr>
<td>PTX-3, ng/mL</td>
<td>0.947 (0.705-1.273)</td>
<td>0.720</td>
<td>0.846 (0.625-1.146)</td>
<td>0.281</td>
</tr>
</tbody>
</table>

Data for CRP, SAA, Lp-PLA₂ and PTX-3 were logarithmically transformed to normalize the distribution of marker values before statistical analyses. CI, Confidence interval.