Published in final edited form as:
Am J Cardiol. 2009 July 1; 104(1): 92–96. doi:10.1016/j.amjcard.2009.02.053.

Relation of Multiple Inflammatory Biomarkers to Incident Atrial Fibrillation

Renate B. Schnabel, MD, MSc[a,m], **Martin G. Larson, ScD**[a,b], **Jennifer F. Yamamoto, BS**[a,c], **Sekar Kathiresan, MD**[j,l], **Jian Rong, MS**[a], **Daniel Levy, MD**[a,h], **John F. Keaney Jr., MD**[k], **Thomas J. Wang, MD**[j], **Ramachandran S. Vasan, MD**[a,d,e,f], and **Emelia J. Benjamin, MD, ScM**[a,d,e,f]

[a]NHLBI's Framingham Study, Framingham, MA

[b]Boston University's Department of Mathematics and Statistics Department, School of Medicine, Boston, MA

[c]Department of Mathematics and Statistics, Boston University Public School of Health, Boston, MA

[d]Department of Biostatistics, Boston University Public School of Health, Boston, MA

[e]Evans Memorial Medicine Department, School of Medicine, Boston, MA

[f]Section of Preventive Medicine, School of Medicine, Boston, MA

[h]Center for Population Studies, National Heart, Lung, and Blood Institute, Bethesda, MD

[j]Cardiology Division, Massachusetts General Hospital, Harvard Medical School, Boston, MA

[k]University of Massachusetts Medical School, Massachusetts Institute of Technology, Cambridge, MA

[l]Broad Institute of Harvard and Massachusetts Institute of Technology, Cambridge, MA

[m]Department of Medicine II, Johannes Gutenberg-University, Mainz, Germany

Abstract

Basic and clinical studies suggest that inflammation predisposes to atrial fibrillation (AF). We assessed the association of 12 circulating inflammatory biomarkers [C-reactive protein, fibrinogen, interleukin-6, intercellular adhesion molecule-1, lipoprotein-associated phospholipase A2 (mass and activity), monocyte chemoattractant protein-1, myeloperoxidase, CD40 ligand, osteoprotegerin, P-selectin, tumor necrosis factor receptor II] with incident AF in 2863 Framingham Offspring Study participants (mean age 60.7 years, SD=9.4, 55% women). During follow-up (median 6 years), 148 participants (43% women) developed incident AF. In multivariable proportional-hazards models, the inflammatory biomarker panel was associated with incident AF (p=0.03). With stepwise selection (p<0.01 for entry and retention), log-transformed osteoprotegerin was associated with incident AF

Address correspondence: Emelia J. Benjamin, MD, ScM, Professor of Medicine and Epidemiology, **Boston University Schools of Medicine and Public Health, The Framingham Heart Study**, 73 Mount Wayte Avenue, Framingham, MA 01702-5827, Phone: 617-638-8968; Fax:508-626-1262; emelia@bu.edu.

Disclosures
The authors report no conflicts of interest.

(hazard ratio [HR] per standard deviation 1.30, 95% confidence interval [CI] 1.08–1.56, p=0.006). Adjusting for interim myocardial infarction or heart failure attenuated the association between osteoprotegerin and incident AF (HR 1.18, 95% CI 0.98–1.43, p=0.09). In conclusion, circulating osteoprotegerin concentration was significantly associated with incident AF in our community-based sample, possibly mediated by interim cardiovascular events.

Keywords

atrial fibrillation; inflammation; epidemiology; cohort

Both clinical and experimental evidence supports a contribution of inflammation to the development and persistence of AF, although the exact mechanisms are not well understood. A consistent finding in manifest AF is elevated inflammatory activity at the atrial tissue level. [1] In most published studies, patients with AF have higher circulating inflammatory marker concentrations compared to referents.2–5 Investigators also have reported that the highly proinflammatory state induced by cardiopulmonary bypass surgery leads to increased C-reactive protein (CRP) concentrations, which may be etiologically related to incident AF.[4] Prospective studies report an association between the nonspecific inflammatory marker CRP and recurrent6, [7] and incident AF.[4]

METHODS

Participants

For the Framingham Offspring cohort, 5124 individuals were recruited in the early 1970s and were followed routinely.[8] The 7th examination cycle (1998–2001) was attended by 3539 participants who were eligible for analysis. For the present investigation, we excluded individuals with any missing inflammatory biomarker measurements (n=483), incomplete or missing follow-up (n=22), prevalent AF (n=132), and missing covariate data (n=39), leaving 2863 attendees for analysis. The study protocols were approved by the Boston University Medical Center Institutional Review Board. Written informed consent was obtained from all participants at each examination. The authors had full access to the data and take responsibility for its integrity. All authors have read and agreed to the manuscript as written.

All participants underwent regular cardiovascular health status assessments at the Framingham Study clinic every 4 to 8 years. Routine biennial telephone-administered health history updates were performed. Disease risk factors were documented in questionnaires and during physician-administered interviews and physical examinations. Valvular heart disease was considered present if the physician auscultated ≥3 out of 6 systolic, or any diastolic murmur. Current smoking, alcohol consumption, and medication use were indicated by self-report. Diabetes was defined as elevated glucose ≥126 mg/dL or use of hypoglycemic drugs. Systolic blood pressure was determined as the average of 2 measurements performed by a physician. The participants' physician office visits and hospitalization records were routinely collected.

The diagnosis of AF was made if atrial fibrillation or flutter was present on an electrocardiogram derived from hospital or outpatient records or on a Framingham Study clinic tracing. Biennial health history update calls included a routine question as to whether the participant had experienced interim AF. If AF was reported at the main examination or on the health history update, outside records were routinely sought. All incident AF cases underwent a review by 2 of 3 Framingham cardiologists (RS, DL, EJB). If AF was recorded by history only, 2 investigators had to agree that the evidence for the presence of AF was compelling (cardioversion or institution of anticoagulant or antiarrhythmic medication).

Fasting blood samples obtained from participants were processed promptly, centrifuged and frozen at −80°C. The twelve circulating inflammatory markers comprised: plasma CD40 ligand, CRP, fibrinogen, lipoprotein-associated phospholipase A2 activity and mass, osteoprotegerin, P-selectin, and tumor necrosis factor receptor-II, and serum intercellular adhesion molecule-1, interleukin-6, monocyte chemoattractant protein-1, and myeloperoxidase. Details of specimen type, measurement kit and measurement properties have been published before.[9] All mean intra-assay coefficients of variation were less than 7%.

Biomarkers were natural logarithmically transformed for analyses and standardized (mean of 0, standard deviation 1). We used multivariable Cox proportional hazards regression models to relate inflammatory biomarkers to incident AF.[10] We adjusted for AF risk factors including age, sex, body mass index, systolic blood pressure, current smoking, diabetes, alcohol consumption category (less than 1 drink per week; 1–7 drinks/week in women or 1–14 drinks/week in men; and >7 drinks/week in women or >14 drinks/week in men), hypertension treatment, left ventricular hypertrophy on the ECG, heart valve disease (heart murmur), history of myocardial infarction and heart failure.

To test the overall inflammation hypothesis, we added all 12 biomarkers to the covariates and used a likelihood ratio test with 12 degrees of freedom. Our primary model forced in clinical covariates, and used a stepwise selection procedure to select biomarkers associated with AF with 2-sided $p<0.01$ for entry and retention. Similar to prior Framingham multimarker papers, we used a more conservative threshold for significance to account for multiple testing.[9] Regression coefficients are presented per 1 SD increase in natural logarithm transformed biomarkers. For the marker selected by the stepwise method, we a) estimated Kaplan Meier survival by tertile; b) conducted a log rank test for trend with tertiles scored as integers; c) estimated unadjusted cumulative incidence of AF by tertile to visually examine the association over time. A C-statistic was calculated for the baseline model and for the model additionally including the retained biomarker.[11] The proportional hazards assumption was examined using a Kolmogorov-type supremum test based on cumulative sums of martingale-based residuals over follow-up times and covariate values.[12]

In addition, bivariate correlation coefficients for the (log) inflammatory biomarkers were calculated. Finally, we present the data for each biomarker analyzed separately.

We assessed potential effect modification of the selected biomarker-AF association by age and sex. To further explore whether the association of inflammatory biomarkers with incident AF was mediated by interim events we conducted analyses adjusting for time-dependent myocardial infarction or heart failure. A secondary model was performed excluding prevalent myocardial infarction and heart failure at baseline. For the single marker analyses we examined what effect size we could detect at 80% power. Analyses were conducted with SAS version 8.1 (Cary, North Carolina, http://www.sas.com/presscenter/guidelines.html) statistical software version.

RESULTS

During follow-up through 2007 (median 6.2 years, maximum 8.0 years), 148 incident AF cases (43% women) were identified. Table 1 shows baseline characteristics of the study sample. In brief, the cohort was middle-aged to elderly and about half of the participants were women. At baseline, heart valve disease, myocardial infarction, and heart failure were uncommon and observed in less than 5% of participants. *Of individuals with cardiovascular disease at baseline 38 (11.8%) developed AF, whereas of those without baseline cardiovascular disease 110 (4.3%) developed AF in follow-up*.

Adjusting for established risk factors, the inflammatory biomarkers added as a group were associated with incident AF (p=0.03). In stepwise selection, only osteoprotegerin was significantly associated with AF and had a 30% increased risk of incident AF (hazard ratio [HR] per SD increment in log-marker 1.30, 95% confidence interval [CI] 1.08–1.56, p=0.006). No other inflammatory marker met the p<0.01 entry criterion. Cumulative incidence of AF was highest for individuals in the third tertile of osteoprotegerin (Figure 1). The C-statistic did not change appreciably between the multivariable model with (C-statistic=0.810, 95% CI 0.777–0.844) or without osteoprotegerin (0.808, 95% CI 0.775–0.841) .

For the variable heart murmur, we saw a nominal departure from the proportional hazards assumption (p=0.028). However, when adjusting for the variable (heart murmur yes/no), the estimates for all covariates were similar to those observed without adjustment.

In models excluding prevalent myocardial infarction or heart failure at baseline, osteoprotegerin was similarly associated with AF (HR 1.27, 95% CI 1.05–1.55, p=0.02) compared to the final model including and adjusting for prevalent disease. The final model did not show a statistically significant interaction between osteoprotegerin and age or sex for the risk of incident AF. If occurrence of interim myocardial infarction and heart failure (n=87) was introduced as a time-dependent covariate, the panel of circulating biomarkers (p=0.14), and osteoprotegerin (HR 1.18, 95% CI 0.98–1.43, p=0.09) were not statistically significantly associated with AF.

Pairwise correlation analysis revealed minor to moderate correlations between inflammatory biomarkers. Modest bivariate correlations were observed between osteoprotegerin and CRP (r=0.15), fibrinogen (r=0.14), intercellular adhesion molecule-1 (r=0.18), interleukin-6 (0.20), monocyte chemoattractant protein-1 (r=0.12), and tumor necrosis factor receptor-II (r=0.31) (all p<0.0001). No significant correlations were observed for osteoprotegerin with the other inflammatory markers. Maximum correlation coefficients were seen for CRP and fibrinogen (r=0.52) and CRP and interleukin-6 (r=0.47).

Because different investigators have examined varying inflammatory biomarkers in relation to AF, in secondary analyses we examined the multivariable-adjusted relation of the biomarkers analyzed individually in relation to incident AF (Table 2). We had 80% power to detect a hazard ratio of 1.27 per SD at p<0.05 and 1.37 at p<0.005 level for individual biomarkers. Lipoprotein-associated phospholipase A2 mass showed a borderline significant association with incident AF (p=0.02, Table 2). We did not observe significant associations between incident AF and CRP (HR 1.05; 95% CI 0.87–1.26; p=0.61) or interleukin-6 (HR 1.08; 95% CI 0.91–1.29; p=0.36).[13]

DISCUSSION

We examined the association of 12 circulating inflammatory biomarkers with incident AF in a contemporary community-based middle-aged to elderly cohort. The biomarker osteoprotegerin was significantly associated with incident AF. The relation between osteoprotegerin and incident AF was attenuated, and no longer achieved statistical significance in models accounting for interim myocardial infarction and heart failure, suggesting that interim cardiovascular events may partially mediate the osteoprotegerin–AF association.

The pathophysiology of the inflammation-AF relation is an area of increasing scientific scrutiny. There is sound evidence from animal[14] and human[15] data that during ongoing atrial dysrhythmia higher levels of oxidative stress and inflammation can be measured locally and systemically, and atrial pro-inflammatory and pro-thrombotic gene expression is altered.[1] Atrial oxidative damage experienced during AF alters myofibrillar energetics and may lead to myocyte necrosis. Apoptosis and necrosis induce low-grade inflammation, paving the way for

structural alterations. The histological substrate of these processes are inflammatory and fibrotic changes of the atrial myocardium.[16] Inflammation thus may perpetuate adverse electrical and structural remodeling and promote disease chronicity. A more novel hypothesis is that enhanced inflammatory activity, as seen after cardiac surgery, may precede the onset of AF. This notion is supported by recent epidemiological findings[4] and our current results, which establish a temporal relation between inflammation and long-term AF incidence.

There are several possible interpretations for why we did not observe the previously reported[4] association between CRP concentrations and incident AF. Aviles and colleagues examined participants in the Cardiovascular Health Study and observed an adjusted HR for AF per 1-standard deviation in log CRP of 1.24 (95% CI 1.11 to 1.40; $P<0.001$).[4] Cardiovascular Health Study investigators examined a single inflammatory biomarker, had a significantly older participant mean age (73±5 years), a higher prevalence of cardiovascular disease, and many more incident AF events (n=897) than our study. It should be noted that our upper 95% confidence interval boundary was 1.26, which included the Cardiovascular Health Study's point estimate (1.24). We acknowledge that with 148 events our statistical power was modest for main effects and was underpowered for statistical interactions. Hence, we cannot exclude an interaction between inflammation and age (or prevalent cardiovascular disease) and risk of AF, accounting for the differences between the 2 studies.

Osteoprotegerin, a tumor necrosis factor receptor family member, which was not strongly correlated with any of the other measured inflammatory markers, has not been related to incident AF previously. Apart from its role in bone metabolism, osteoprotegerin has been associated with arterial calcification, endothelial function, and atherosclerosis[17] in animal models. Whereas osteoprotegerin itself exerts protective effects on vascular remodeling and calcification, elevated circulating concentrations seem to reflect a counterregulatory overproduction of the protein which thus becomes associated with adverse outcome.

Attributable to the influence on vascular wall composition, osteoprotegerin has been related to pulse wave velocity, an indicator of vascular stiffness.[18] Aortic stiffness mirrored by pulse pressure has been reported to predict incident AF.[19] In addition, osteoprotegerin may play a pathophysiological role in left ventricular remodeling and heart failure,[20–22] conditions, for which gene expression of osteoprotegerin is consistently increased[23] and which are both strongly related to future AF.

In our secondary analyses, including MI and CHF as time-dependent variables, the tests for the complete set of biomarkers and osteoprotegerin alone no longer reached statistical significance. The weakening of the apparent relation between inflammatory markers and AF is consistent with the concept that interim cardiovascular disease either is a confounder, or is part of the pathophysiological pathway connecting inflammation and the manifestation of AF.[20] If our findings are confirmed in other studies, further research is required to elucidate whether the risk association of osteoprotegerin with AF is attributable to mechanisms such as cardiovascular remodeling, and interim cardiovascular disease events, or whether there is a direct relation between osteoprotegerin and AF risk.

Our data were derived from a well-characterized community-based sample with extensive routine ascertainment of potential clinical confounders, strict quality control of inflammatory biomarker measurements and rigorous clinical ascertainment of the outcome. Due to the relatively small number of incident AF cases, we had modest power to detect relations of inflammatory markers to incident AF, particularly if the effect size was small. To reduce the burden of multiple testing, we à priori decided to run multivariable-adjusted models for the primary analyses. Since inflammatory biomarkers may lie in the pathophysiological pathway

from risk factors (e.g. body mass index) to incident AF, our models may be over-adjusted and mask relevant associations.

A more comprehensive picture of the actions of osteoprotegerin might have been derived if measurements of the receptor activator of nuclear factor-kappa B ligand (RANKL) and its receptor (RANK) had been available to better reflect the osteoprotegerin-RANK-RANKL axis in relation to AF.[24] We provided data only on single occasion inflammatory biomarker measurements, which did not account for potential biomarker variability over time, although for some markers such variability is known to be relatively low.25 Participants with AF, especially asymptomatic ones, may have been missed, which might bias the study results towards the null. Finally, our data need confirmation in independent studies.

If inflammation can be established as a relevant AF risk factor as was shown for osteoprotegerin and incident heart failure and myocardial infarction,[20] it would be a potentially modifiable one. Lifestyle modifications like exercise, weight loss and diet can positively diminish pro-inflammatory states. In addition, drugs such as statins and renin angiotensin aldosterone blocking drugs have been noted to lower circulating osteoprotegerin concentrations,[26] and to reduce the risk of incident AF.[27, 28] The extent to which statins and renin-angiotensin aldosterone blocking drugs mechanistically reduce AF via modulation of inflammation or prevention of the development of the risk factors for AF (such as hypertension, diabetes, myocardial infarction and heart failure) remains to be determined.

Acknowledgments

Supported by NIH/NHLBI contract N01-HC-25195, 6R01-NS 17950, and NIH grants HL064753. HL076784, AG028321 (EJB), 1 RO1HL71039 (RSV); NIH Research career award K24 HL04334 (RSV); Deutsche Forschungsgemeinschaft (German Research Foundation) Research Fellowship SCHN 1149/1–1 (RS); 1K23HL083102, Doris Duke Charitable Foundation Clinical Scientist Development Award (SK). Lipoprotein-associated phospholipase A2 activity and mass measurements were provided to the Heart Study by GlaxoSmithKline at no cost.

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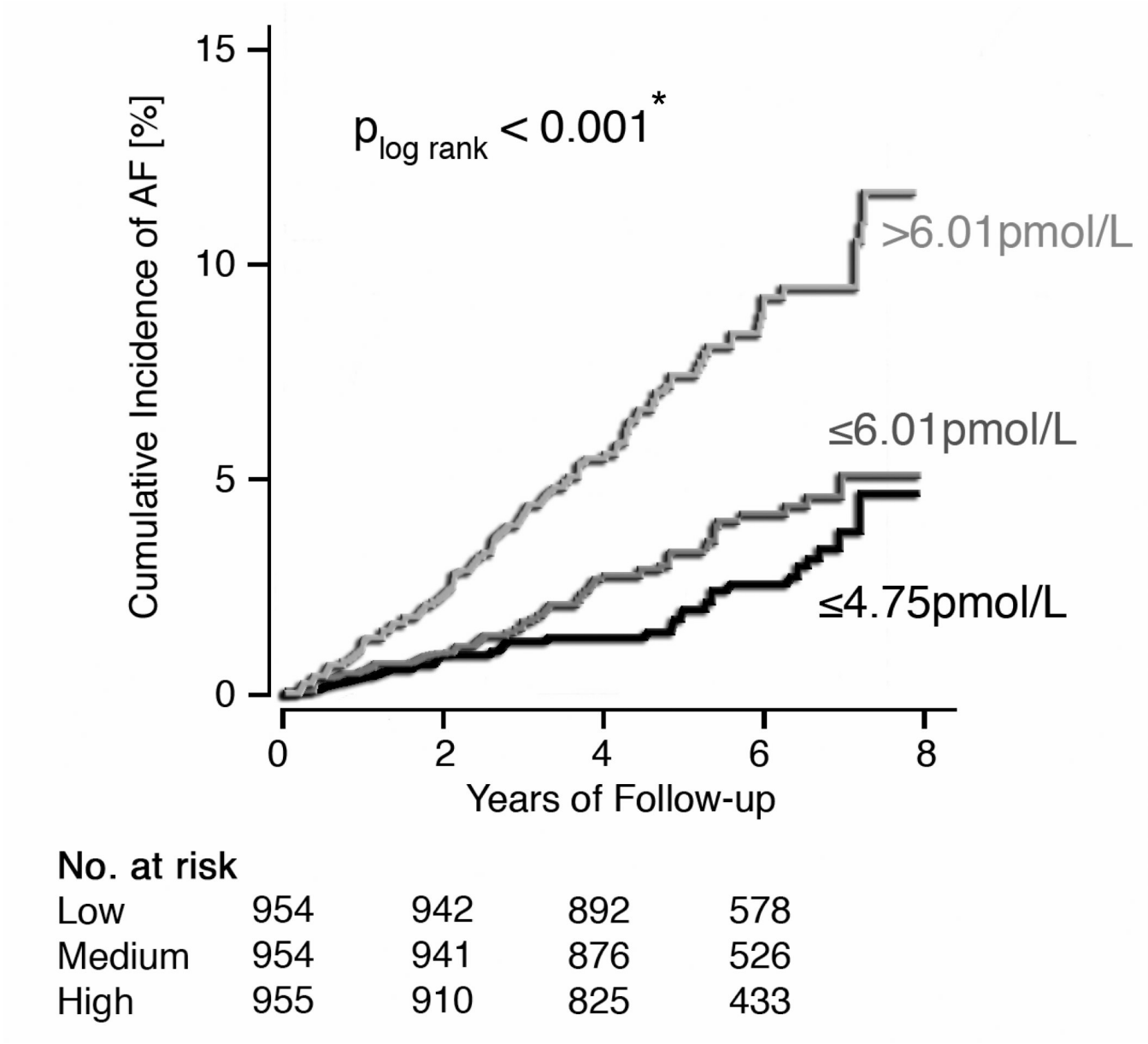

Figure 1. Cumulative Incidence of AF by Osteoprotegerin Tertile

* Not defined à priori as a hypothesis.

Table 1

Baseline Characteristics of the Study Sample

Variable	Overall cohort (n=2863)
Age (years)	61±9
Female sex	55 %
Smoking	13 %
Body mass index (kg/m²)	28.1±5.3
Systolic blood pressure (mm Hg)	127±19
Hypertension treatment	33 %
Diabetes mellitus	12 %
Alcohol consumption, drinks per week	
<1	33 %
1–7 (women) or 1–14 (men)	50 %
>7 (women) or >14 (men)	17 %
Electrocardiographic left ventricular hypertrophy	<1 %
Auscultatory heart valve disease	2 %
Prevalent myocardial infarction	4 %
Prevalent heart failure	<1 %

Data are presented as mean±SD for continuous variables and percentage for dichotomous variables.

Am J Cardiol. Author manuscript; available in PMC 2010 July 1.

Table 2

Results from Multivariable-Adjusted Proportional Hazards Regression Models: Each Circulating Inflammatory Biomarker Modeled Separately

Variable	Mean±SD Nat. log Biomarker	Hazard Ratio per SD	95% Confidence Interval		P-Value
CD40 ligand	0.42±1.24	1.01	0.86	1.20	0.89
C-reactive protein	0.81±1.11	1.05	0.87	1.26	0.61
Fibrinogen	5.92±0.19	0.94	0.79	1.12	0.48
Intercellular adhesion molecule-1	5.51±0.25	1.08	0.91	1.28	0.39
Interleukin-6	1.06±0.71	1.08	0.91	1.29	0.36
Lipoprotein-associated phospholipase A2					
Activity	4.93±0.25	0.95	0.80	1.14	0.58
Mass	5.65±0.32	1.22	1.03	1.43	0.02
Monocyte chemoattractant protein-1	5.73±0.34	0.98	0.82	1.16	0.80
Myeloperoxidase	3.71±0.57	1.12	0.95	1.32	0.20
Osteoprotegerin	**1.68±0.31**	**1.30**	**1.08**	**1.56**	**0.006**
P-selectin	3.57±0.37	0.94	0.80	1.10	0.42
Tumor necrosis factor receptor II	7.62±0.30	1.15	0.98	1.34	0.09

Inflammatory biomarker concentrations are log-transformed measures.

Hazard ratios, per one standard deviation increase in log-biomarker concentration, are adjusted for age, sex, smoking, systolic blood pressure, hypertension treatment, body mass index, diabetes, alcohol consumption, electrocardiographic left ventricular hypertrophy, auscultatory valvular heart disease, myocardial infarction, heart failure (see text for definitions).