Soluble Urokinase Plasminogen Activator Receptor Level Is an Independent Predictor of the Presence and Severity of Coronary Artery Disease and of Future Adverse Events

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Soluble Urokinase Plasminogen Activator Receptor Level Is an Independent Predictor of the Presence and Severity of Coronary Artery Disease and of Future Adverse Events

Danny J. Eapen, MD; Pankaj Manocha, MD; Nima Ghasemzadeh, MD; Riyaz S. Patel, MD; Hatem Al Kassem, MD; Muhammad Hammadah, MD; Emir Veledar, PhD; Ngoc-Anh Le, PhD; Tomasz Pielak, BS; Christian W. Thorball, BS; Aristea Velegraki, PhD; Dimitrios T. Kremastinos, MD, PhD; Stamatios Lerakis, MD; Laurence Sperling, MD; Arshed A. Quyyumi, MD

Introduction—Soluble urokinase plasminogen activator receptor (suPAR) is an emerging inflammatory and immune biomarker. Whether suPAR level predicts the presence and the severity of coronary artery disease (CAD), and of incident death and myocardial infarction (MI) in subjects with suspected CAD, is unknown.

Methods and Results—We measured plasma suPAR levels in 3367 subjects (67% with CAD) recruited in the Emory Cardiovascular Biobank and followed them for adverse cardiovascular (CV) outcomes of death and MI over a mean 2.1±1.1 years. Presence of angiographic CAD (≥50% stenosis in ≥1 coronary artery) and its severity were quantitated using the Gensini score. Cox’s proportional hazard survival and discrimination analyses were performed with models adjusted for established CV risk factors and C-reactive protein levels. Elevated suPAR levels were independently associated with the presence of CAD (P<0.0001) and its severity (P<0.0001). A plasma suPAR level ≥3.5 ng/mL (cutoff by Youden’s index) predicted future risk of MI (hazard ratio [HR]=3.2; P<0.0001), cardiac death (HR=2.62; P<0.0001), and the combined endpoint of death and MI (HR=1.9; P<0.0001), even after adjustment of covariates. The C-statistic for a model based on traditional risk factors was improved from 0.72 to 0.74 (P=0.008) with the addition of suPAR.

Conclusion—Elevated levels of plasma suPAR are associated with the presence and severity of CAD and are independent predictors of death and MI in patients with suspected or known CAD. (J Am Heart Assoc. 2014;3:e001118 doi: 10.1161/JAHA.114.001118)

Key Words: biomarker • cardiovascular outcomes • coronary heart disease • C-reactive protein • inflammation

The development of atherosclerosis and subsequent plaque rupture is a highly complex process that involves interplay of multiple mechanistic pathways, including those involving inflammation and immunity. Soluble urokinase plasminogen activator receptor (suPAR), an emerging biomarker that represents activation of both of these pathways, has been implicated in atherogenesis by orchestrating cellular adhesion, migration, and proliferation during development of atherosclerotic plaque.1 Increased plasma and intraplaque suPAR levels have been observed in subjects with symptomatic carotid plaques, suggesting that suPAR may be associated with the vulnerable plaque phenotype.2 Increased suPAR levels have also been associated with incident cardiovascular (CV) disease (CVD) in the “healthy” population, even after adjustment for Framingham risk variables and C-reactive protein (CRP).3,4 Moreover, in individuals presenting with ST-elevation myocardial infarction (STEMI), elevated suPAR level was an independent predictor of all-cause mortality and recurrent myocardial infarction (MI).5

Whether suPAR levels predict presence, absence, and severity of coronary artery disease (CAD), and whether the level is a measure of long-term risk of adverse CVD events in subjects at risk for CAD remains unknown, and is the aim of this study. We hypothesized that higher suPAR levels will be associated with the presence and severity of CAD and with incident adverse CVD events.
Methods

Study Population

Study participants were recruited as part of the Emory Cardiology Biobank and consisted of 3763 patients enrolled before undergoing elective or emergent cardiac catheterization across 3 Emory Healthcare sites between 2003 and 2009. Subjects with congenital heart disease, severe valvular heart disease, severe anemia, recent blood transfusion, myocarditis, active inflammatory diseases, and cancer were not enrolled in the Biobank registry. Patients aged 20 to 90 years were interviewed to collect information on demographic characteristics, medical history, medication use, and behavioral (lifestyle) habits. Risk-factor prevalence was determined by physician diagnosis and/or treatment for hypertension (HTN), hyperlipidemia, and diabetes. Smoking was classified as nonsmoker or “ever smoked” if there was a lifetime history of smoking at least 100 cigarettes. Blood pressure (BP), heart rate, weight, and height were measured. Medical records were reviewed to confirm self-reported history of MI and history of revascularization. After excluding individuals with heart transplantation (n = 170), as well as those with missing or incomplete angiographic data or serum and plasma samples (n = 226), 3367 subjects were eligible. The study was approved by the institutional review board at Emory University (Atlanta, GA). All subjects provided written informed consent at the time of enrollment.

Outcomes and Follow-up

Follow-up was conducted between 1 and 5 years for determination of the primary composite endpoint of all-cause death and nonfatal MI, as well as the secondary endpoint of cardiac death. This was performed by personnel blinded to the biomarker data through telephone interview, chart review, and linkage with the Social Security Death Index and state records. Cause of death was adjudicated by 2 cardiologists with a third arbitrator in case of disagreement. Cardiac death was defined as death attributable to an ischemic CV cause (fatal MI) or sudden death resulting from an unknown, but presumed, CV cause in high-risk patients. Medical records were accessed or requested to validate all self-reported events, including MI, which was again defined using standard international criteria for diagnosis of MI.6

Identification of CAD and Severity Scoring

All coronary angiograms were scored for luminal narrowing using a modified American Heart Association/American College of Cardiology classification.7 Patients were designated as having angiographically smooth normal coronary arteries, nonsignificant CAD (visible plaque resulting in <50% luminal stenosis), or significant CAD (at least 1 major epicardial vessel with ≥50% stenosis). Those with a history of coronary artery bypass grafting (CABG) were all labeled as having significant CAD. The severity of their CAD was calculated based on angiographic disease of their native vessels before revascularization. Quantitative angiographic scoring was performed using the Gensini score that quantifies CAD severity by a nonlinear points system for degree of luminal narrowing. The score has prognostic significance.8

Sample Collection

Fasting arterial blood samples for serum and plasma were drawn at cardiac catheterization and stored at −80°C (mean, 4.9 years). Serum high-sensitivity (hs)CRP measurements were determined using a sandwich immunoassay by FirstMark, Inc. (San Diego, CA), and plasma levels of suPAR were measured using commercially available kits according to the manufacturer’s instructions (suPARnostic kit; ViroGates, Copenhagen, Denmark). Minimum detectable hsCRP and suPAR was 0.1 mg/L and 0.1 ng/mL, respectively. Both CRP and suPAR have previously been shown to be stable in frozen samples.9,10

Statistical Analyses

Continuous variables are presented as means (±SD) and categorical variables as proportions (%). The Student t test, 1-way ANOVA, and Cochran-Mantel-Haenszel’s chi-squared test were used, as appropriate. Mann-Whitney’s U or Kruskall-Wallis’ nonparametric tests were performed on non-normally distributed variables. The relationship between biomarkers and outcomes was determined using the Cox’s proportional hazards regression in unadjusted models and in models adjusted for established risk factors that include clinically relevant covariates for CVD outcomes (age at baseline, gender, race, diagnosis of HTN, diabetes, dyslipidemia, use of statins, aspirin, clopidogrel, previous history of MI, acute MI at presentation, estimated glomerular filtration rate (eGFR), Gensini score, hsCRP, body mass index (BMI), left ventricular (LV) ejection fraction (LVEF), history of CABG, and smoking status. Continuous variables were normalized by calculating their respective z-scores ([value in individual − mean value in the study population]/SD). Missing covariate data for the fully adjusted model (range, 0% to 3%) was imputed and sensitivity analysis with unimputed data found results to be similar. The proportional hazards assumption for Cox’s models was evaluated by plots of Schoenfeld residuals and formal testing (a chi-square test calculated as the sum of Schoenfeld residuals). No significant violations of the assumption were found.
suPAR and CAD  Eapen et al

suPAR levels were evaluated both as continuous (natural log transformed) per SD and as categorical variables based on a cutpoint determined from Youden’s index calculated from Cox’s regression models (Figure 1). Briefly, Youden’s index is a global measure of a biomarker’s effectiveness that calculates to the maximum difference between sensitivity and 1-specificity. The cutpoint for outcomes of death and MI was determined to be 3.5 ng/mL. Analyses were performed on all participants and in subsets of those with and those without significant CAD.

The ability of the standard clinical model for predicting adverse events was calculated using the C-statistic from Cox’s regression models before and after the addition of suPAR. Using multivariate Cox’s models with the clinical covariates noted above, continuous net reclassification improvement (NRI) and integrated discrimination improvement (IDI) metrics were calculated. Average annual risks of events were computed by dividing observed number of events by the observed event-specific number of person-years of follow-up. P<0.05 from 2-sided tests were considered to indicate statistical significance.

Results

Baseline characteristics of the 3367 patients aged 63±12 years are included in Table 1. In univariate analysis, individuals with high suPAR levels were more likely to be older, female, have lower low-density lipoprotein (LDL) and high-density lipoprotein (HDL) levels and statin dose, an elevated hsCRP level, and a higher prevalence of diabetes, HTN, and dyslipidemia. Management strategy (medical management, revascularization, or other) after enrollment catheterization was not significantly different between the groups (Table 1).

Relationship of suPAR With Angiographic CAD

suPAR levels were lowest in subjects with angiographically normal (“clean”) coronary arteries (mean suPAR=3.1±1.6 ng/mL), compared to those with either insignificant coronary atherosclerosis (<50% stenosis; mean suPAR=3.3±1.9 ng/mL), or those with significant CAD (>50% stenosis; mean suPAR=3.5±1.9 ng/mL). The odds ratio (OR) for Ln suPAR as a continuous variable for presence of angiographic CAD compared to normal coronary arteries was 2.1, and for presence of significant CAD (≥50% luminal stenosis) compared to nonsignificant (<50% luminal stenosis) was 1.8 after adjustment for aforementioned covariates. Similarly, the Gensini score that measures severity of CAD was also significantly associated with suPAR levels (Table 2). In contrast, hsCRP was not significantly associated with any of these angiographic CAD indices.

Clinical and Demographic Predictors of Incident Adverse Outcomes

Over a median follow-up period of 2.3 years, 276 patients died (8.2%), 150 were cardiac deaths (4.9%), and 118 had an MI (3.5%; Table 1). Using Cox’s proportional hazard models that included all the aforementioned covariates, age (hazard ratio [HR], 1.2; P=0.003), diabetes (HR, 1.3; P=0.01), Gensini score (HR, 1.2; P=0.008), aspirin use (HR, 0.6; P=0.004), clopidogrel use (HR, 1.5; P=0.002), acute MI at presentation (HR, 1.5; P=0.009), LVEF (HR, 0.8; P<0.001), BMI (HR, 0.82; P=0.002), and hsCRP (HR, 1.3; P<0.001) were all independent predictors of the combined outcome of all-cause death and MI (Table 3).

Relationship Between suPAR Levels and Outcomes

Cox’s proportional hazard regression models, adjusted for aforementioned covariates, demonstrated that Ln suPAR had an HR of 3.16 (P<0.0001) and the cutpoint had an HR of 1.80 for the combined outcome of all-cause death and MI (Table 4; Figure 2A). A decrease in event-free survival was also observed with each increase in quartile of suPAR levels (Figure 2B). Significant associations were observed between Ln suPAR and the risk of cardiac death (HR=4.2; P<0.0001) and for the combined outcomes of cardiac death and MI (HR, 2.54; P<0.001). A trend toward significance was observed between Ln suPAR and risk of future MI (HR, 1.6; P=0.06). One-year risk of death and MI was 8.3% in those with an
elevated suPAR level (≥3.5 ng/mL), compared to 2.8% in those without an elevated level.

In the prespecified subgroups with nonsignificant CAD (<50% stenosis; n=1044) and in those with significant CAD (≥50% stenosis; n=2323), suPAR levels predicted combined outcomes of all-cause death and MI or cardiac death and MI (Table 4). Total death/MI rates were 5.2%, 6.2%, and 12.8% for angiographically normal, nonsignificant, and significant groups, respectively. We found no significant heterogeneity in the HR based on age, gender, race, and presence of individual risk factors, presentation with acute MI, severity of CAD, and eGFR values (Figure 3).
In a subset of patients (N=1368) with no previous history of CAD on enrollment (ie, excluding those with history of acute or previous MI, percutaneous coronary intervention [PCI], or CABG) there were 95 deaths/MI events. After adjusting for aforementioned covariates, an elevated suPAR level (≥3.5 ng/mL) predicts risk of future death/MI with an HR of 2.25 (P=0.0005).

### Discrimination Testing

The C-statistic significantly increased from 0.72 (base model with conventional risk factors) to 0.74 (P=0.008; for Ln suPAR) and 0.73 (P=0.04; for cutpoint) for outcomes of all-cause death and MI. The significant NRI of suPAR using the cutpoint for the combined outcomes of all-cause death and MI corresponded to a 6.3% rate of correctly reclassifying events and 28% rate of correctly reclassifying nonevents, respectively (Table 5). The relative IDI for this model was 4.1% for all-cause death and MI (Table 5). Similar improvements were observed for the combined outcomes of cardiac death and MI and in both subgroups with and without significant CAD. In all groups, more nonevents were correctly reclassified than were events.

### Discussion

Herein, for the first time, we demonstrate that elevated plasma suPAR levels are associated with the presence and severity of angiographic CAD. suPAR levels are higher in those with significant CAD compared to those with normal coronary arteries or insignificant CAD, and greater severity of CAD is associated with higher suPAR levels. Furthermore, we found that suPAR is a significant predictor of incident mortality and morbidity in patients with suspected or established CAD, as well as significantly improved discrimination of future death and MI risk over a standard clinical model, as evidenced by improvement in the C-statistic and NRI.

Urokinase plasminogen activator (uPA) is a serine protease that, on binding its receptor, urokinase plasminogen activator receptor (uPAR), leads to the generation of plasmin.1 uPA is produced by vascular endothelial cells, smooth muscle cells, monocytes, macrophages, fibroblasts, and epithelial cells.13 uPAR plays a role in development of atherosclerosis by orchestrating cellular adhesion, migration, and proliferation,1,14 and plasma suPAR likely reflects cellular shedding of a section of uPAR from either in smooth muscle cells, monocytes, macrophages, fibroblasts, and epithelial cells.13 uPAR plays a role in development of atherosclerosis by orchestrating cellular adhesion, migration, and proliferation,1,14 and plasma suPAR likely reflects cellular shedding of a section of uPAR from either in smooth muscle cells, monocytes, macrophages, fibroblasts, and epithelial cells.13 uPAR plays a role in development of atherosclerosis by orchestrating cellular adhesion, migration, and proliferation,1,14 and plasma suPAR likely reflects cellular shedding of a section of uPAR from either

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**Table 2.** Association of suPAR (Natural Log Transformed and Using Cutpoint) With CAD Indices

<table>
<thead>
<tr>
<th>suPAR (Ln)</th>
<th>Angiographically Abnormal vs. Normal OR (95% CI); P Value</th>
<th>Significant CAD vs. Nonsignificant CAD OR (95% CI); P Value</th>
<th>Gensini (Ln) Beta (95% CI); P Value</th>
</tr>
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<tbody>
<tr>
<td>suPAR ≥3.5 ng/mL</td>
<td>2.1 (1.61 to 2.84); &lt;0.0001</td>
<td>1.79 (1.40 to 2.29); &lt;0.0001</td>
<td>0.39 (0.24 to 0.54); &lt;0.0001</td>
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</table>

BMI indicates body mass index; CAD, coronary artery disease; CI, confidence interval; eGFR, estimated glomerular filtration rate; HTN, hypertension; LVEF, left ventricular ejection fraction; OR, odds ratio; suPAR, soluble urokinase plasminogen activator receptor.

*Adjustment for established risk factors: age, race, sex, BMI, ever smoking, HTN, diabetes, aspirin use, statin use, hyperlipidemia, eGFR, and LVEF.
patients with severe sepsis and septic shock. There are no prospective data on interventions lowering suPAR levels; however, subjects on long-term treatment with beta-blockers were found to have lower levels of suPAR in their carotid endarterectomy specimens compared to those without beta-blocker use.

suPAR has been extensively studied in the infectious disease and critical care populations, but its relationship to CVD and associated outcomes has only been recently explored. The majority of these studies performed in Europe have examined the relationship between suPAR and incident CVD in healthy community-based populations. To our knowledge, there has been only one study in 354 patients with acute STEMI that demonstrated the prognostic utility of suPAR. In our study, we show the predictive value of plasma suPAR in a much larger population of patients with CAD and confirm the findings in those with acute MI. Interestingly, levels of suPAR were similar in those with (11% of the cohort) and without acute MI at presentation, and the HRs were similar for these 2 populations (Figure 3). Moreover, HRs did not change substantially when regression models were repeated after excluding patients

<table>
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<tr>
<th>Table 4. HRs (Natural Log Transformed [Ln], Cutpoint) for Outcomes of All-Cause Death and MI*</th>
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<tr>
<td>suPAR (Ln) HR (95% CI); P Value</td>
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<tr>
<td>Entire Cohort</td>
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<td>Nonsignificant CAD</td>
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BMI indicates body mass index; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio; HTN, hypertension; MI, myocardial infarction; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; suPAR, soluble urokinase plasminogen activator receptor.

*A adjustment for established risk factors: age, race, sex, BMI, ever smoking, HTN, diabetes, aspirin use, statin use, clopidogrel use, acute MI, previous MI, PCI history, Gensini score, hyperlipidemia, eGFR, LVEF, and CABG history.

Figure 2. A, Kaplan Meier Survival for outcomes of All-Cause Death and MI using suPAR cutpoint. Number of events listed next to each survival curve. B, Kaplan Meier Survival for all-cause death or MI by quartiles of suPAR. Number of events listed next to each survival curve. Mean suPAR levels listed next to each quartile.

Figure 3. Forest plot interaction of suPAR with clinical covariates.
presenting with an acute MI (data not shown). Our analysis shows that the value of suPAR in predicting future death and MI is independent of hsCRP levels, suggesting that these biomarkers reflect activation of different pathophysiological pathways. Importantly, suPAR added significantly to the statistical model performance for prediction of all-cause death and MI by improving the C-statistic and net reclassification indices, indicating that suPAR could be a valuable biomarker in risk stratification of patients with CAD.

Previous studies examining the role of multiple biomarkers in populations free of established CVD have demonstrated only slight improvement in predictive capacity (using C-statistic) when added to standard clinical models.22–24 We have previously shown that a pathway-specific aggregate biomarker score comprised of hsCRP (inflammation), fibrin degradation products (thrombosis), and heat shock protein 70 (cell stress) significantly predicts cardiac death and MI in a population with CAD.25 Whether suPAR will add to this biomarker aggregate score requires further investigation.

Our study has several strengths. Enrolled individuals included women (36% of total cohort), blacks, those with acute MI, and patients with a range of LV function, reflecting a population that is typical of those undergoing cardiac catheterization. This is different from many biomarker studies that are conducted retrospectively on highly select populations enrolled in clinical trials. Assays were performed at one time point by the same lab personnel, which minimized variability. C-statistic, NRI, and IDI were calculated using survival models that allowed for better model discrimination and overall predictive ability. Limitations of our study include a one-time measurement of biomarkers that may not reflect levels at future time points. Our results need to be further validated and should not be extrapolated to the general population without suspected or known CAD. Whether more-aggressive management in individuals with elevated suPAR levels translates to lower risk of developing CAD and improved event-free survival remains unknown and needs further investigation.

In conclusion, elevated suPAR levels are associated with an increased risk of CAD and of incident adverse CVD events, including death and MI, in the intermediate future. Whether treatment aimed at reducing activity of suPAR can positively alter disease course remains to be determined.

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Disclosures

Pielak and Thorball are employed by ViroGates (Denmark). Eapen and Quyumi had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

References


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/content/4/1/e000563.full.pdf
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