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ORIGINAL RESEARCH

Cardio-Renal Biomarker Soluble Urokinase-Type Plasminogen Activator Receptor Is Associated With Cardiovascular Death and Myocardial Infarction in Patients With Coronary Artery Disease Independent of Troponin, C-Reactive Protein, and Renal Function

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BACKGROUND: Risk stratification among patients with coronary artery disease (CAD) is of considerable interest due to the potential to guide secondary preventive therapies. Thus, we evaluated the predictive value of soluble urokinase-type plasminogen activator receptor (suPAR) levels for cardiovascular mortality and nonfatal myocardial infarction in patients with CAD.

METHODS AND RESULTS: Plasma levels of suPAR were measured in a cohort of 1703 patients with documented CAD as evidenced by coronary angiography—including 626 patients with acute coronary syndrome and 1077 patients with stable angina pectoris. Cardiovascular death and/or nonfatal myocardial infarction were defined as main outcome measures. During a median follow-up of 3.5 years, suPAR levels reliably predicted cardiovascular death or myocardial infarction in CAD, evidenced by survival curves stratified for tertiles of suPAR levels. In Cox regression analyses, the hazard ratio for the prediction of cardiovascular death and/or myocardial infarction was 2.19 (P<0.001) in the overall cohort and 2.56 in the acute coronary syndrome cohort (P<0.001). Even after adjustment for common cardiovascular risk factors, renal function and the biomarkers C-reactive protein, N-terminal pro-B-type natriuretic peptide and high-sensitivity troponin I suPAR still enabled a reliable prediction of cardiovascular death or myocardial infarction with a hazard ratio of 1.61 (P=0.022) in the overall cohort and 2.22 (P=0.005) in the acute coronary syndrome cohort.

CONCLUSIONS: SuPAR has a strong and independent prognostic value in secondary prevention settings, and thereby might represent a valuable biomarker for risk estimation in CAD.

Key Words: biomarker ■ coronary artery disease ■ prognosis ■ soluble urokinase-type plasminogen activator receptor

Stratification for subsequent coronary events among patients with coronary artery disease (CAD) is of considerable interest due to the potential to guide secondary preventive therapies.[1–3]

Soluble urokinase-type plasminogen activator receptor (suPAR) is the circulating form of a glycosylphosphatidylinositol–anchored 3-domain membrane protein.[4] It is expressed on a variety of cells, which

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CLINICAL PERSPECTIVE

What Is New?

- Little has been known about the prognostic value of soluble urokinase-type plasminogen activator receptor in patients with coronary artery disease.
- This study found that soluble urokinase-type plasminogen activator receptor was reliably associated with cardiovascular death and/or myocardial infarction in coronary artery disease patients, and this association appears to be independent of high-sensitivity troponin I and N-terminal pro-B-type natriuretic peptide.

What Are the Clinical Implications?

- Soluble urokinase-type plasminogen activator receptor could be a novel and strong prognostic biomarker for adverse cardiovascular events in coronary artery disease patients and might facilitate tailoring secondary preventive therapies in these patients.

Nonstandard Abbreviations and Acronyms

CAD	coronary artery disease
MI	myocardial infarction
SAP	stable angina pectoris
suPAR	soluble urokinase-type plasminogen activator receptor
HR	hazard ratio
ACS	acute coronary syndrome
CRP	C-reactive protein
NT-proBNP	N-terminal pro-B-type natriuretic peptide
hs-TnI	high-sensitivity troponin I
eGFR	estimated glomerular filtration rate
CKD-EPI	chronic kidney disease epidemiology collaboration

play a critical role in all stages of atherogenesis, especially progression of atherosclerosis and plaque vulnerability and destabilization.[5,6] Until now, it has mainly been evaluated in renal disease, where it was independently associated with incident chronic kidney disease and an accelerated decline in the estimated glomerular filtration rate (eGFR).[4] Beyond being a risk marker, most recent cutting-edge studies even evidenced a leading role in the pathogenesis of inflammatory and immune-mediated renal diseases.[7–9]

As there is mounting evidence for multiple pathophysiological connections between cardiovascular and renal diseases, and since inflammatory and immunological processes play a critical role in atherosclerosis, it seems plausible that suPAR, a marker for immune activation and inflammation, may provide prognostic information in CAD beyond established risk factors.[5,10,11] Therefore, it was the aim of this study to assess the association of circulating suPAR levels with subsequent adverse cardiovascular events in a secondary prevention cohort of 1703 patients with documented CAD.

MATERIAL AND METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request due to restrictions in informed consent.

Study Population

In the AtheroGene cohort, a total of 3800 patients, who underwent coronary angiography at the Department of Medicine II of the Johannes Gutenberg-University Mainz or the Bundeswehr-Zentralkrankenhaus Koblenz between June 1999 and March 2000, were recruited.[12,13] Exclusion criteria were evidence of hemodynamically significant valvular heart disease, surgery, or trauma within the previous month, known cardiomyopathy, known cancer, febrile conditions, or use of oral anticoagulant therapy within the previous 4 weeks. Patients with missing information on the clinical presentation, missing laboratory measurements, or lack of information on the cause of death were excluded. Additionally, missing samples and low sample volumes led to exclusion. Thus, the analyses were performed in 1703 subjects. Baseline characteristics were not relevantly different between the subcohort and the overall cohort.

The study was conducted according to the Declaration of Helsinki and approved by the Ethic Board of the Johannes Gutenberg-University Mainz and of the Physicians' chamber of the State Rhineland-Palatinate (Germany) under the number 837.057.99. All participants gave written informed consent.

Data Collection

At baseline, all participants were subjected to a standardized questionnaire containing sociodemographic information and medical history. In addition, information was taken from the patients' hospital charts. Coronary artery disease was diagnosed if the coronary angiogram showed at least one stenosis >30% in a major coronary artery. Unstable angina was diagnosed according to Braunwald.[14] Acute myocardial infarction was either ST-segment elevation with significant elevation in at least 2 contiguous leads or non–ST-segment–elevation myocardial

infarction (MI) based on clinic and positive in-house troponin concentrations. The final diagnosis of acute coronary syndrome (ACS; unstable angina, non–ST-segment–elevation MI, or ST-segment–elevation MI) was made retrospectively on the basis of on the judgment of 2 physicians, with access to the history and nature of the presenting symptoms, medical history, results of physical examination, and all of the medical records available from index hospitalization (including the results of troponin testing).

Median follow-up after discharge was 3.5 years. Information was obtained from the patients using a mailed standardized questionnaire. Information regarding adverse cardiovascular disease events and treatment since discharge from the in-hospital rehabilitation clinic was obtained from the primary care physicians also by means of a standardized questionnaire. If a subject had died during follow-up, the death certificate was obtained from the local public health department and the main cause of death was coded according to the *International Classification of Diseases, Ninth Revision* (*ICD-9,* pos. 390–459) and Tenth Revision (*ICD-10,* pos. I0–I99 and R57.0). Adverse cardiovascular disease events were defined either as cardiovascular disease as the main cause of death (as stated in the death certificate), nonfatal MI. All nonfatal adverse events were reported by the primary care physicians.

Laboratory Methods

Within the recruiting sites, blood samples were obtained before angiography and application of heparin in a fasting state under standardized conditions and stored at –80°C until analysis.

Plasma levels of suPAR were determined with the suPARnostic standard enzyme-linked immunosorbent assay (ViroGates, Birkerød, Denmark). The intra-assay variation was 2.75%, and the interassay variation 9.17%. High-sensitivity-assayed troponin I (hs-TnI) was measured using the Architect immunoassay (ARCHITECT i1000SR, Abbott Diagnostics, Chicago, IL). The intra-assay variation was 6.68%, and the interassay variation 4.26%. CRP (C-reactive protein) was determined by a highly sensitive, latex particle-enhanced immunoassay (detection range, 0–20 mg/L; Roche Diagnostics, Mannheim, Germany). The measurement of NT-proBNP (N-terminal pro-B-type natriuretic peptide) was performed by electrochemiluminescence sandwich immunoassay (Roche Diagnostics, Mannheim, Germany). Serum creatinine was determined by standardized routine laboratory method. The Chronic Kidney Disease Epidemiology Collaboration equation was applied to calculate the eGFR.[15] All biomarkers were measured in a blinded fashion.

Statistical Analysis

The study population was described with respect to various sociodemographic and medical characteristics using quartiles for continuous variables and absolute and relative frequencies for binary variables. Comparisons between the ACS and stable angina pectoris (SAP) cohorts were performed using the Mann–Whitney test for continuous variables and the chi-squared test for binary variables. Spearman correlation coefficients were calculated to describe associations of suPAR with conventional cardiovascular risk factors; renal function according to eGFR; and the biomarkers hs-TnI, CRP, and NT-proBNP.

For displaying survival curves, subjects were grouped according to tertiles of suPAR levels. The log-rank test was used to test the null hypothesis of equality of survival curves versus the alternative hypothesis that at least 2 of the curves are different. Pairwise comparisons of survival curves were also performed. The relation of suPAR concentrations, used after log transformation, with cardiovascular mortality and nonfatal MI during follow-up was assessed by Cox proportional hazards analyses adjusted for age (years) and sex. In additional models, the age and sex adjustment was extended to conventional cardiovascular risk factors (body mass index, diabetes mellitus, smoking status, dyslipidemia, hypertension—Model 2); the biomarkers CRP, NT-proBNP, and hs-TnI and renal function according to eGFR (Model 3); and a combined adjustment for both cardiovascular risk factors and the biomarkers and renal function mentioned above (Model 4). The proportional hazards assumption was examined graphically and with formal tests using the methods described by Grambsch and Thernau,[16] and no evidence of violation was found. Multiple imputation was used to fill the missing values. Twenty imputed data sets were created using multivariate imputations by chained equations, as proposed by Buuren and Groothuis-Oudshoorn.[15–17]

All computations were performed with R version 3.6.1 (http://www.r-project.org/). A P value of <0.05 was considered statistically significant. P values were not adjusted for multiple comparisons.

RESULTS

A total of 1703 individuals with evident CAD and available suPAR measurements were included in this analysis. In Table 1, the main sociodemographic and laboratory characteristics at baseline are presented, differentiated by the presenting diagnosis of ACS or SAP. The mean age of patients with SAP was 64 years and, similarly, 63 years in ACS. The majority of participants were male—78.6% in the SAP cohort and 76%

Table 1. Characteristics of the Study Patients With Coronary Heart Disease

	All	SAP	ACS	
n	1703	1077	626	*P* Value
Age, y*	64.0 (56.0–69.0) NA: 0 (0)	64.0 (56.0–69.0) NA: 0 (0)	63.0 (55.0–69.0) NA: 0 (0)	0.074
Male, N (%)	1335 (78.4) NA: 0 (0)	847 (78.6) NA: 0 (0)	488 (78.0) NA: 0 (0)	0.790
BMI, kg/m²*	27.3 (25.0–30.0) NA: 0 (0)	27.3 (25.1–30.1) NA: 0 (0)	27.3 (24.9–29.5) NAs: 0 (0)	0.330
Diabetes mellitus, N (%)	351 (20.6) NA: 0 (0)	240 (22.3) NA: 0 (0)	111 (17.7) NA: 0 (0)	0.029
Current smoker, N (%)	322 (18.9) NA:1 (0.1)	180 (16.7) NA: 0 (0)	142 (22.7) NA: 1 (0.2)	0.003
Dyslipidemia, N (%)	1247 (73.2) NA: 0 (0)	836 (77.6) NA: 0 (0)	411 (65.7) NA: 0 (0)	<0.001
Hypertension, N (%)	1315 (77.2) NA: 0 (0)	885 (82.2) NA: 0 (0)	430 (68.7) NA: 0 (0)	<0.001
NT-proBNP, pg/mL*	210.9 (92.4–592.0) NA: 36 (2.1)	156.0 (78.0–383.0) NA: 20 (1.9)	386.3 (152.5–1142.5) NA: 16 (2.6)	<0.001
CRP, mg/L*	3.0 (1.4–7.4) NA: 36 (2.1)	2.3 (1.2–5.1) NA: 22 (2.0)	5.0 (2.0–13.8) NA: 14 (2.2)	<0.001
Hs-TnI, ng/L*	7.2 (3.6–28.7) NA: 218 (12.8)	5.2 (3.1–10.2) NA: 102 (9.5)	72.2 (7.3–1788.2) NA: 116 (18.5)	<0.001
suPAR, ng/mL*	3.1 (2.3–4.0) NA: 0 (0)	3.1 (2.3–4.0) NA: 0 (0)	3.0 (2.3–4.0) NA: 0 (0)	0.770

ACS indicates acute coronary syndrome; BMI, body mass index; CRP, C-reactive protein; hs-TnI, high-sensitivity troponin I; NA, not available; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SAP, stable angina pectoris; and suPAR, soluble urokinase-type plasminogen activator receptor.
*Median 25th and 75th quartile cut point.

in the ACS cohort. As expected, hs-TnI, CRP, and NT-proBNP levels were higher in patients with ACS than in SAP patients, whereas dyslipidemia was present in 77.6% of the SAP cohort compared with 65.7% in the ACS cohort. SuPAR levels were significantly higher in subjects with a future event compared with event-free subjects. Median suPAR levels were comparable in subjects with ACS and SAP (3.0 ng/mL versus 3.1 ng/mL). Figure 1 shows the distribution of circulating suPAR levels in all SAP and ACS patients. In Tables S1 through S3, the range of suPAR values for the different populations is presented.

During a median follow-up of 3.5 years, 123 (7.2%) cardiovascular deaths or nonfatal MI were documented, 60 (5.6%) among SAP patients and 63 (10.1%) in the ACS cohort.

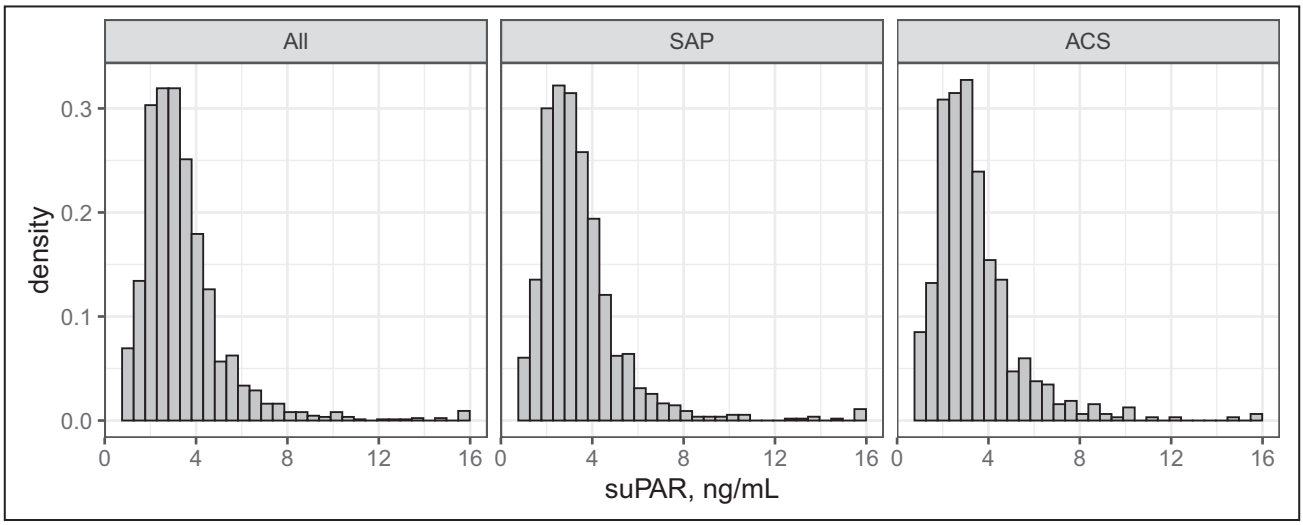

Figure 1. Distribution of circulating soluble urokinase-type plasminogen activator receptor (suPAR) levels in all (All), stable angina pectoris (SAP) and acute coronary syndrome patients (ACS).

Table 2. Spearman Correlations of Selected Variables With suPAR in the Overall Cohort

	Age	Male	BMI	Diabetes Mellitus	Smoker	Dyslipidemia	Hypertension	NT-proBNP	CRP	hs-TnI	eGFR (CKD-EPI)
Correlation	0.20	−0.13	0.07	0.16	0.11	0.03	0.04	0.21	0.21	0.11	−0.27
P Value	<0.001	<0.001	0.007	<0.001	<0.001	0.210	0.140	<0.001	<0.001	<0.001	<0.001

BMI indicates body mass index; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; hs-TnI, high-sensitivity troponin I; NT-proBNP, N-terminal pro-B-type natriuretic peptide; and suPAR, soluble urokinase-type plasminogen activator receptor.

To assess the correlation of suPAR with common cardiovascular risk factors like diabetes mellitus, smoking status, and arterial hypertension, as well as with the biomarkers hs-TnI, CRP, and NT-proBNP, Spearman correlation coefficients (*R*) were calculated (Table 2). Only weak correlations were found, with a maximum correlation coefficient of 0.11 for hs-TnI, 0.21 for NT-proBNP and CRP (each $P<0.001$), and 0.20 ($P<0.001$) for age. The strongest correlation was observed for eGFR with a correlation coefficient of −0.27.

In Cox regression analyses, the hazard ratio for the prediction of cardiovascular death and/or MI during follow-up (in Model 1) was 2.19 (95% CI, 1.52–3.17; $P<0.001$) for suPAR used after log transformation in the overall cohort (Table 3), 2.56 (95% CI, 1.53-4.27; $P<0.001$) in the ACS cohort (Table 4) and 1.90 (95% CI: 1.11–3.25; $P=0.019$) in the SAP cohort (Table S4). The prognostic value of suPAR remained clear after adjustment for either conventional cardiovascular risk factors (Model 2) or the established biomarkers CRP, NT-proBNP, and hsTnI and renal function according to eGFR (Model 3) both in the overall and the ACS cohort. Even in fully adjusted Cox regression analyses adjusted for common cardiovascular risk factors; renal function; and the biomarkers CRP, NT-proBNP, and hs-TnI (Model 4), suPAR still predicted cardiovascular death and/or nonfatal MI with a hazard ratio of 1.61 ($P=0.022$) in the overall cohort and a hazard ratio of 2.22 ($P=0.005$) in the ACS cohort. Compared with the results of the combined end point, the hazard ratios of cardiovascular death are larger and those of nonfatal MI smaller (Tables S5 through S7). Accordingly, survival curves stratified for tertiles of circulating suPAR levels, both in the overall cohort ($P<0.001$) and in the ACS cohort ($P<0.001$), evidenced the prognostic relevance of suPAR (Figure 2). In the SAP cohort, the differences in survival curves lacked statistical significance (Figure S1). In the ACS cohort, however, suPAR tertiles strongly stratified for future coronary events.

DISCUSSION

The present study assessed the predictive value of circulating suPAR levels for cardiovascular death and secondary MI in a cohort of patients with documented CAD. This study demonstrated a statistically significant and clinically relevant impaired prognosis in patients with CAD with increasing suPAR levels. To our knowledge, this is the first study showing that suPAR levels significantly predict cardiovascular mortality and MI in a CAD cohort even after adjustment for cardiovascular risk factors; renal function; and the biomarkers CRP, NT-proBNP, and hs-TnI, which are all established factors for risk prediction in CAD. In general, the predictive power of suPAR was larger in the ACS cohort than in

Table 3. Association of Circulating suPAR Levels With Cardiovascular Death and/or Myocardial Infarction During Follow-Up in the Overall Cohort

Model	HR (95% CI)	*P* Value	N	N Events
1	2.19 (1.52–3.17)	<0.001	1703	123
2	2.03 (1.38–2.98)	<0.001	1703	123
3	1.74 (1.17–2.58)	0.007	1703	123
4	1.61 (1.07–2.42)	0.022	1703	123

Model 1: adjusted for age and sex. Model 2: adjusted for age, sex, BMI, diabetes mellitus, smoking status, dyslipidemia, and hypertension. Model 3: adjusted for age, sex, log(NT-proBNP), log(CRP), log(hs-TnI), eGFR (CKD-EPI). Model 4: age, sex, BMI, diabetes mellitus, smoking status, dyslipidemia, hypertension, log(NT-proBNP), log(CRP), log(hs-TnI), eGFR (CKD-EPI). BMI indicates body mass index; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; HR, hazard ratio; hs-TnI, high-sensitivity troponin I; NT-proBNP, N-terminal pro-B-type natriuretic peptide; and suPAR, soluble urokinase-type plasminogen activator receptor.

Table 4. Association of Circulating suPAR Levels With Cardiovascular Death and/or Myocardial Infarction During Follow-Up in the ACS Cohort

Model	HR (95% CI)	*P* Value	N	N Events
1	2.56 (1.53–4.27)	<0.001	626	24
2	2.37 (1.40–3.99)	0.001	626	24
3	2.35 (1.36–4.07)	0.002	626	24
4	2.22 (1.27–3.88)	0.005	626	24

Model 1: adjusted for age and sex. Model 2: adjusted for age, sex, BMI, diabetes mellitus, smoking status, dyslipidemia, and hypertension. Model 3: adjusted for age, sex, log(NT-proBNP), log(CRP), log(hs-TnI), eGFR (CKD-EPI). Model 4: age, sex, BMI, diabetes mellitus, smoking status, dyslipidemia, hypertension, log(NT-proBNP), log(CRP), log(hs-TnI), eGFR (CKD-EPI). BMI indicates body mass index; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; HR, hazard ratio; hs-TnI, high-sensitivity troponin I; NT-proBNP, N-terminal pro-B-type natriuretic peptide; and suPAR, soluble urokinase-type plasminogen activator receptor.

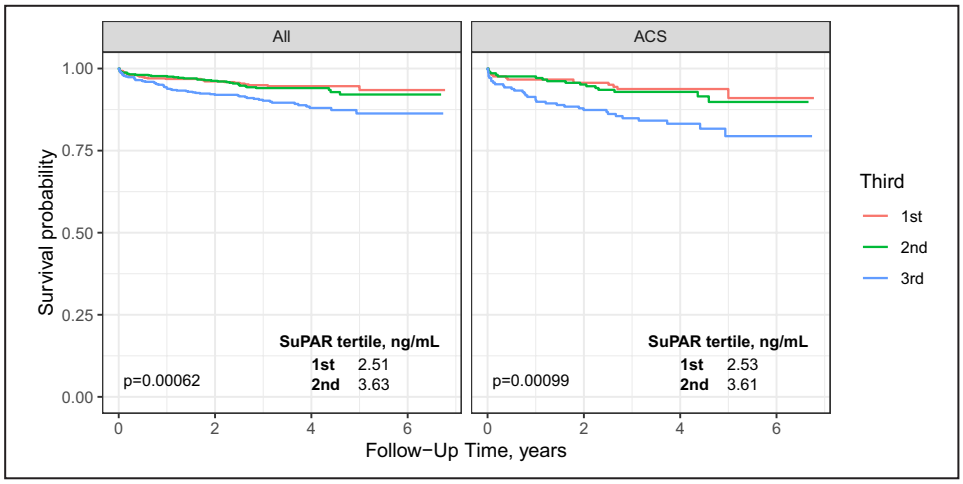

Figure 2. Survival curves for cardiovascular death and/or myocardial infarction according to soluble urokinase-type plasminogen activator receptor (suPAR) tertiles for the overall cohort (All) and the acute coronary syndrome cohort (ACS). The *P* value displayed on the graphics is for the log-rank test. *P* values for pairwise comparisons are first third vs second third, *P*=0.58; first third vs third third, *P*<0.001; second third vs third third, *P*=0.004 in all; and first third vs second third, *P*=0.620; first third vs third third, *P*=0.001; second third vs third third, *P*=0.006 in ACS patients.

SAP patients, which may be in part related to different event rates.

Pathophysiological Implications

Biomarkers are critical instruments in terms of risk prediction. Emerging data showed that new pathways and pathophysiological hypotheses yield biomarkers beyond the established ones.[18–22] Here, we assessed suPAR as a candidate biomarker for CAD and found significant association.

This concept is supported by an established pathophysiologic link between suPAR and atherosclerosis. Urokinase plasminogen activator is a serine protease that, on binding its receptor, urokinase plasminogen activator receptor, leads to the generation of plasmin.[18–22] Urokinase plasminogen activator is produced by vascular endothelial cells, smooth muscle cells, monocytes, macrophages, fibroblasts, and epithelial cells.[23] Urokinase plasminogen activator receptor plays a role in the development of atherosclerosis by orchestrating cellular adhesion, migration, and proliferation, and plasma suPAR likely reflects cellular shedding of a section of urokinase plasminogen activator receptor from either inflammatory or endothelial cells.[24] Atherosclerosis is an inflammatory disease. Its lesions are filled with macrophages, T cells, and other immune cells that can orchestrate and effect inflammatory responses.[25] In fact, the first lesions of atherosclerosis consist of macrophages and T cells. Unstable plaques are particularly rich in activated immune cells, suggesting that they may initiate plaque activation.[25] Elevated suPAR levels have typically been attributed to a state of inflammation.[26] The release of suPAR from activated neutrophils, monocytes, and endothelial cells is stimulated by proinflammatory cytokines.[27] In accordance, mounting experimental and clinical data suggest a key role of inflammation in the pathophysiology of atherogenesis.[28] SuPAR might represent an unknown link between physiological immune and inflammatory response processes and atherosclerotic processes. Furthermore, suPAR has been identified as immune-derived signaling molecule contributing to the pathogenesis of focal segmental glomerulosclerosis and probably other forms of chronic kidney disease.[29] SuPAR as a biomarker can reliably predict the incidence of chronic kidney disease.[4] Strong associations of chronic kidney disease with cardiovascular diseases have long been established.[30]

Interestingly, both kidneys and hearts were recently identified as organs of suPAR clearance in humans, supporting the concept of suPAR playing a key role not only in renal diseases but also in cardiac diseases such as CAD.[31]

Because suPAR is highly stable during storage and can be measured accurately even after repeated cycles of freezing and thawing, and since unlike CRP, suPAR levels appear to be free of circadian changes and are relatively stable during periods of acute stress, it seems to have a potential as a new cardiovascular biomarker and should be further evaluated.[31–33]

Strengths and Limitations

Strengths of this study include the large cohort size of 1703 patients and a median follow-up of 3.5 years. However, like all typical CAD populations, women are clearly underrepresented. Additionally, participant

acquisition was conducted from 1999 to 2000, so that demographic changes in CAD patient populations and altered therapy regimen might influence the transferability of the results to contemporary patient populations. Although we had a large sample of ACS patients, fatal cardiovascular disease events were limited in this study population. Furthermore, our study population only represents patients with CAD who underwent coronary angiography. This population might differ from CAD patients without the need for coronary intervention. Therefore, the predictive value of suPAR levels should also be assessed in those patients. Finally, Cox regression analyses should be interpreted with caution because of a possible overadjustment.

CONCLUSIONS

Our study demonstrates that suPAR levels predict mortality and nonfatal MI in secondary prevention settings, thereby possibly representing a valuable biomarker for risk estimation in CAD.

ARTICLE INFORMATION

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Disclosures

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Supplementary Materials

Tables S1–S7
Figure S1

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SUPPLEMENTAL MATERIAL

Table S1. Descriptive statistics for suPAR within suPAR thirds in all patients. The tertiles used to define the thirds were 2.51 ng/mL and 3.63 ng/mL.

Third	N	Minimum	Median (25th Percentile, 75th Percentile)
1st	568	1.12	2.00 (1.68, 2.26)
2nd	567	2.51	3.05 (2.78, 3.31)
3rd	568	3.63	4.52 (4.00, 5.67)

Table S2. Descriptive statistics for suPAR within suPAR thirds in SAP patients. The tertiles used to define the thirds were 2.50 ng/mL and 3.64 ng/mL.

Third	N	Minimum	Median (25th Percentile, 75th Percentile)
1st	360	1.12	2.00 (1.70, 2.28)
2nd	358	2.50	3.07 (2.80, 3.31)
3rd	359	3.64	4.50 (4.00, 5.58)

Table S3. Descriptive statistics for suPAR within suPAR thirds in ACS patients. The tertiles used to define the thirds were 2.53 ng/mL and 3.61 ng/mL.

Third	N	Minimum	Median (25th Percentile, 75th Percentile)
1st	209	1.12	1.99 (1.63, 2.25)
2nd	208	2.53	3.03 (2.75, 3.27)
3rd	209	3.62	4.58 (4.00, 5.85)

Table S4. Association of circulating suPAR levels with cardiovascular death and/or myocardial infarction during follow-up in the SAP cohort.

Model	HR (95% CI)	p-value	N	N events
1	1.90 (1.11-3.25)	0.019	1077	60
2	1.70 (0.96, 3.00)	0.068	1077	60
3	1.30 (0.72, 2.35)	0.38	1077	60
4	1.16 (0.64, 2.11	0.63	1077	60

HR, hazard ratio; CI, confidence interval
Model 1: adjusted for age, sex
Model 2: adjusted for age, sex, BMI, diabetes, smoking status, dyslipidemia, hypertension
Model 3: adjusted for age, sex, log(NT-proBNP), log(CRP), log(hs-TnI), eGFR (CKD-EPI)
Model 4: Age, sex, BMI, diabetes, smoking status, dyslipidemia, hypertension, log(NT-proBNP), log(CRP), log(hs-TnI), eGFR (CKD-EPI)

Table S5. Composition of events for combined cardiovascular death and non-fatal MI endpoint.

	Nonfatal MI	CVD Death
Overall	78	45
SAP	33	27
ACS	45	18

Table S6. Association of circulating suPAR levels with cardiovascular death during follow-up in the overall cohort.

Model	HR (95% CI)	p-value	N	N events
1	3.60 (2.12, 6.10)	<0.001	1703	53
2	3.27 (1.89, 5.68)	<0.001	1703	53
3	2.02 (1.12, 3.66)	0.020	1703	53
4	1.74 (0.96, 3.16)	0.067	1703	53

Table S7. Association of circulating suPAR levels with non-fatal MI during follow-up in the overall cohort.

Model	HR (95% CI)	p-value	N	N events
1	1.47 (0.91, 2.40)	0.12	1703	78
2	1.38 (0.84, 2.27)	0.21	1703	78
3	1.41 (0.85, 2.35)	0.18	1703	78
4	1.35 (0.80, 2.27)	0.26	1703	78

Figure S1. Survival curves for cardiovascular death and/ or myocardial infarction according to soluble urokinase-type plasminogen activator receptor (suPAR) tertiles in the stable angina pectoris cohort.