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## Role of Soluble Endothelial Cell–Selective Adhesion Molecule Biomarker in Albuminuria and Kidney Function Changes in Patients With Coronary Artery Disease:

The Heart and Soul Study

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### Abstract

**Objective**—Endothelial dysfunction is a possible mechanism to explain the association between atherosclerosis and kidney disease. This study evaluated circulating soluble endothelial cell–selective adhesion molecule (sESAM), a marker of endothelial dysfunction, as a risk factor for kidney function decline and albuminuria.

**Approach and Results**—In the Heart and Soul Study, we measured sESAM from baseline serum samples and defined elevated levels of sESAM by the highest quartile (quartile 4 [Q4]: >65.4 ng/mL). We evaluated the associations of high sESAM with baseline estimated glomerular filtration rate (eGFR) and ratio of urine albumin to creatinine (ACR), and with longitudinal changes in eGFR and ACR. Among 990 participants with sESAM measurements, median sESAM was 54.5 ng/mL (interquartile range, 45.3–65.8). After multivariable adjustment, elevated levels of sESAM were strongly and independently associated with baseline reduced eGFR <60 mL/min per 1.73 m<sup>2</sup> (odds ratio [OR], 11.44; *P*<0.0001) and ACR ≥30 mg/g (OR, 5.23; *P*<0.0001). Associations of sESAM (Q4 versus quartile 1 [Q1]) with change in ACR ( $\beta$ =54.47; *P*<0.0001) were also significant after full adjustment. The association with change in eGFR (1.56%; *P*=0.0049) was not statistically significant after application of the Bonferroni correction for multiple markers. In unadjusted models, sESAM was associated with rapid kidney function loss, defined as 3% annual eGFR decline (OR, 2.28; *P*=0.0003), although this was attenuated by adjustment (OR, 2.11; *P*=0.0095).

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**Disclosures**

None.

**Conclusions**—sESAM is associated with albuminuria and reduced kidney function in both cross-sectional and longitudinal analyses. These findings implicate endothelial dysfunction as a potential contributor to the elevated kidney disease risk in persons with cardiovascular disease.

### Keywords

albuminuria; atherosclerosis; kidney diseases

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Clinical cardiovascular disease (CVD) is independently associated with kidney function decline and development of chronic kidney disease (CKD), defined by estimated glomerular filtration rate (eGFR)  $<60$  mL/min per  $1.73$  m<sup>2</sup>.<sup>1</sup> Mechanisms explaining the higher risk of CKD in this population are incompletely understood.<sup>2</sup> Albuminuria occurs in many individuals with CVD<sup>3</sup> and may be the result of a defect in the endothelial surface monolayer.<sup>4</sup> Endothelial dysfunction is observed in early stages of atherosclerosis and contributes to its progression to more advanced disease.<sup>5,6</sup> Because endothelial dysfunction in atherosclerosis is a systemic process,<sup>7</sup> its effects on renal vasculature may contribute to the development and progression of CKD among patients with atherosclerotic CVD.<sup>7</sup>

Endothelial dysfunction is associated with impaired endothelium-dependent vasodilation and has been observed in persons with proinflammatory or prothrombotic states, including dyslipidemia, coronary artery disease, congestive heart failure, and peripheral artery disease.<sup>5,8</sup> Abnormal endothelial function has also been described in early kidney disease<sup>9,10</sup> and may be responsible for albuminuria,<sup>4</sup> although the role of glomerular endothelial cells in the onset of albuminuria remains controversial.<sup>11</sup> Endothelial dysfunction can be assessed by brachial artery flow-mediated dilation,<sup>12</sup> but this measurement is methodologically challenging.<sup>8</sup> Identification of specific serum markers of endothelial function is an active area of research<sup>13</sup>; one example is endothelial cell-selective adhesion molecule (ESAM), which is expressed in vascular endothelial cells.<sup>14</sup> Increased expression of ESAM is associated with susceptibility to atherosclerosis.<sup>15</sup> In the Dallas Heart Study, a population-based cohort, circulating soluble ESAM (sESAM) was associated with subclinical CVD assessed by coronary artery calcium, abdominal aortic wall thickness, aortic plaque burden, and aortic compliance.<sup>15</sup> sESAM is also expressed at the glomerulus.<sup>16</sup> The association of this selective endothelial function marker with kidney disease in patients with preexisting atherosclerotic heart disease is unknown.

We investigated the associations between sESAM and kidney outcomes among ambulatory individuals with stable coronary heart disease in the Heart and Soul Study cohort. We evaluated a comprehensive array of kidney outcomes, including baseline reduced eGFR and ratio of albumin to creatinine (ACR), change in eGFR, change in ACR, incident reduced eGFR  $<60$  mL/min per  $1.73$  m<sup>2</sup>, and rapid kidney function decline. Understanding these associations may help to delineate the role of endothelial dysfunction in kidney disease onset, particularly among patients with established CVD.

### Materials and Methods

The Materials and Methods section is available in the online-only Supplement.

## Results

### Participant Characteristics

Among 990 individuals with ischemic heart disease and serum measurements of sESAM at baseline, mean age was 66.7 ( $\pm 11$ ) years, 81% were men, 60% were white, 70% had hypertension, and 26% had diabetes mellitus. Mean  $eGFR_{\text{creatinine-cystatin C (cr-cys)}}$  at baseline was 70.6 ( $\pm 22.2$ ) mL/min per 1.73 m<sup>2</sup>, and the prevalence of  $eGFR_{\text{cr-cys}} < 60$  mL/min per 1.73 m<sup>2</sup> at baseline was 31%. Individuals in the highest quartile of sESAM were more likely to be older, men, and white, and to have much lower baseline eGFR and higher baseline ACR and modestly lower high-density lipoprotein and low-density lipoprotein levels (Table 1).

### Associations of sESAM With Baseline Reduced eGFR and Albuminuria

sESAM was strongly associated with  $eGFR < 60$  mL/min per 1.73 m<sup>2</sup> at baseline. After full adjustment, the highest quartile had 11-fold increased odds of  $eGFR < 60$  mL/min per 1.73 m<sup>2</sup> (Table 2). Similarly, the highest quartile had 5-fold increased odds of baseline urine ACR  $\geq 30$  mg/g (Table 2). These associations remained strong after additional adjustment for ACR and were attenuated by adjustment for eGFR. These findings were especially strong among black individuals (adjusted odds ratio [OR] for  $eGFR < 60$ : 70;  $P < 0.0001$ ; adjusted OR for ACR  $\geq 30$ : 16;  $P = 0.0001$ ).

### Associations With Change in Urine ACR

Compared with the lowest quartile, adjusted mean increase in ACR from baseline to year 5 was 54 mg/g higher among patients in the highest sESAM quartile (Table 3). The adjusted mean increase in ACR was similar among individuals with preserved and reduced eGFR. Our sensitivity analysis using proportional odds and ordinal categories of ACR change gave similar results (OR, 2.55;  $P = 0.0171$ ).

### Associations With Changes in Kidney Function

The highest quartile of sESAM compared with the lowest was associated with a loss in  $eGFR_{\text{cr-cys}}$  of 1.56% per year after full adjustment ( $P = 0.0049$ ; Figure). This association was minimally affected by additional adjustment for ACR (1.36%;  $P = 0.0166$ ). These results were not statistically significant at the experiment-wide  $P = 0.0017$ .

In unadjusted models, when compared with the lower 3 quartiles, the highest quartile of sESAM was associated with rapid loss in kidney function, defined as a loss of  $eGFR_{\text{cr-cys}}$  of  $> 3\%$  per year (Table 4). Adjusted models were not significant after applying the 29-marker Bonferroni correction to the  $P$  value. sESAM was not associated with incident reduced  $eGFR < 60$  mL/min per 1.73 m<sup>2</sup> (adjusted OR, 1.32;  $P = 0.56$ ).

## Discussion

In a cohort of individuals with known ischemic heart disease, we found higher levels of sESAM to be strongly associated with baseline reduced eGFR and higher ACR. sESAM was significantly associated with worsening ACR after full multivariable adjustment and with

rapid kidney function loss in unadjusted models only. sESAM was not significantly associated with annual eGFR loss after application of Bonferroni correction for multiple markers tested on the same platform on which sESAM was measured. Higher sESAM may indicate early endothelial dysfunction that precedes kidney function decline among individuals with established CVD.

This is the first study to our knowledge to examine the relationship between sESAM and changes in kidney function in individuals with established atherosclerosis. CKD is a frequent complication of CVD<sup>17-19</sup> and accelerates risk of cardiovascular mortality in this population.<sup>20</sup> Previous work by Gold et al<sup>21</sup> has shown that sESAM is associated cross-sectionally with CKD. It is possible that sESAM is associated with CKD and kidney function decline in our study only as a result of reduced kidney filtration of this molecule. However, we adjusted for baseline kidney function and for known confounders, and our associations remained significant. Furthermore, the strong association of sESAM with ACR and change in ACR was independent of kidney filtration function assessed by eGFR, which implicates endothelial dysfunction in glomerular capillary disruption and consequent increases in ACR.<sup>4</sup>

sESAM regulates vascular permeability, and sESAM may regulate albumin extravasation at the level of the glomeruli in hyperglycemia.<sup>11</sup> In a longitudinal study of 88 individuals with type 2 diabetes mellitus, Kacso et al<sup>22</sup> found an increase in albuminuria over 12 to 24 months in individuals with lower sESAM levels. This finding is in contrast to our study. However, our study was larger and included only 26% diabetic subjects, and these relationships may differ in the absence of overt hyperglycemia.<sup>11</sup> Our study detected a much larger magnitude of change in ACR and had a longer follow-up time. Furthermore, the Kacso study<sup>22</sup> did not observe associations of sESAM with a change in eGFR. Decreased sESAM expression may play a role in early diabetic nephropathy,<sup>11</sup> and our study could not address different stages of diabetes mellitus. Our study adjusted for the presence of diabetes mellitus, and our associations remained strong.

Our findings are of interest for several reasons. Although this study focused on the association of CVD with development and progression of CKD, the increased cardiovascular risk in individuals with preexisting CKD is substantial, and the mediators remain incompletely characterized.<sup>23</sup> Candidate mechanisms for CKD to CVD risk association include inflammation, abnormal bone mineral calcification, and other conditions associated with CKD.<sup>24,25</sup> Endothelial dysfunction is considered a prodromal phase of atherosclerosis in CKD. However, atherosclerosis often precedes CKD diagnosis,<sup>26</sup> and efforts to identify early parallel processes of vascular dysregulation may be a useful framework for identifying common mechanisms for both diseases. As a marker of endothelial function, sESAM may help to explain the early pathogenesis of kidney abnormalities in the setting of known CVD.

Our study has several strengths. The Heart and Soul Study cohort is a unique cohort in which to examine the relationship between CVD and CKD. This cohort has robust measurements of sESAM and repeated measures of eGFR and ACR in 990 individuals. The coefficients of variation of biomarker measurement were not perfect but were comparable to

those of other studies and are low for a new biomarker.<sup>27</sup> Also, our samples were all measured in concert, minimizing risks of drift among biomarker samples.

Our study has several limitations. First, the endothelial function biomarkers are only available on baseline serum samples. Although we have robust measurements of kidney function at baseline and at 5 years of follow-up, this cohort has a relatively low prevalence and incidence of kidney disease. We had inadequate power to stratify by race, and there were relatively few women in this cohort. Exploratory analyses suggest that further investigations into racial differences may be revealing, especially in light of higher prevalence of apolipoprotein L1 risk variants among the black population.<sup>28</sup> Finally, we were underpowered to detect associations with more severe changes in kidney function, such as rapid kidney function loss, decline in eGFR >50%, incident end-stage renal disease, or increase in ACR >50%. Application of the Bonferroni correction suggests that our results for changes in eGFR may be attributable to chance.

In conclusion, elevated sESAM may indicate increased risk of progressive albuminuria and rapid kidney function loss in individuals with known atherosclerotic disease. The accelerated kidney function loss is independent of baseline reduced eGFR, albuminuria, hypertension, and diabetes mellitus. This study indicates a possible role for endothelial function in the development and progression of CKD among individuals with preexisting CVD. Future investigations should focus on the pathophysiology of atherosclerosis and endothelial dysfunction as determinants of kidney function decline.

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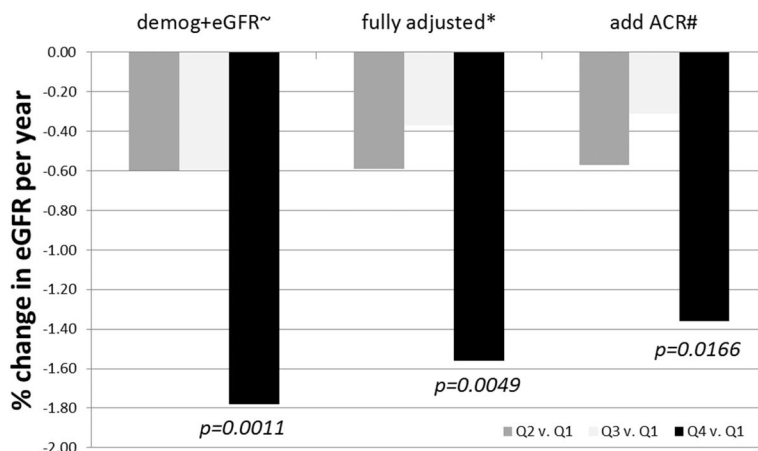


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### Significance

The risk of kidney disease in individuals with established cardiovascular disease is high. Mechanisms of onset of kidney disease are unclear and do not seem to be explained exclusively by traditional risk factors such as diabetes mellitus and hypertension. Endothelial dysfunction may be a pathogenic mechanism in the onset of kidney disease in systemic atherosclerosis. In the Heart and Soul Study, a cohort of individuals with established ischemic heart disease, we evaluated associations between soluble endothelial cell-selective adhesion molecule, a marker of endothelial dysfunction, and kidney function assessed by estimated glomerular filtration rate and albuminuria. Our findings suggest a role for endothelial dysfunction in the onset of kidney disease in this population.



**Figure.** Quartiles of soluble endothelial cell–selective adhesion molecule after sequential adjustment for demographics, covariates, and albumin-to-creatinine ratio and associations with annual percent change in estimated glomerular filtration rate. ~Adjusted for demographics and baseline eGFR only; \*Adjusted for age, race, sex, htn, BMI, smoking, T2DM, HDL, LDL, ACEI/ ARB, statins, CRP, baseline eGFR; #Above covariates plus ACR. Threshold *P*-value for significance=0.001724.

**Table 1**  
Baseline Characteristics by Quartile of Soluble Endothelial Cell–Selective Adhesion Molecule

|                                      | Q1 (0.4–45.1 ng/mL) | Q2 (45.1–53.8 ng/mL) | Q3 (53.8–65.3 ng/mL) | Q4 (65.4–130 ng/mL) | P Value |
|--------------------------------------|---------------------|----------------------|----------------------|---------------------|---------|
| Age, y*                              | 62 (10)             | 66 (10)              | 67 (11)              | 72 (10)             | 0.0001  |
| Men*                                 | 73%                 | 80%                  | 86%                  | 86%                 | 0.0001  |
| Race                                 |                     |                      |                      |                     |         |
| White                                | 44%                 | 60%                  | 67%                  | 69%                 | 0.0001  |
| Latino                               | 9%                  | 11%                  | 8%                   | 7%                  |         |
| Asian                                | 14%                 | 12%                  | 11%                  | 9%                  |         |
| Black                                | 28%                 | 15%                  | 12%                  | 11%                 |         |
| Other                                | 4%                  | 3%                   | 2%                   | 4%                  |         |
| Tobacco, pack-years*                 | 22 (22)             | 21.1 (22.5)          | 20.9 (21.7)          | 21.3 (23)           | 0.8596  |
| HDL, mg/dL*                          | 46 (14)             | 46 (13)              | 44 (15)              | 46 (14)             | 0.0374  |
| LDL, mg/dL*                          | 110 (35)            | 105 (31)             | 102 (35)             | 101 (34)            | 0.0012  |
| C-reactive protein, mg/L             | 4.4 (6.8)           | 4.5 (10.3)           | 3.9 (5.3)            | 5.5 (9.5)           | 0.2219  |
| Hypertension                         | 70.5%               | 64.8%                | 70.2%                | 75.6%               | 0.075   |
| Type 2 diabetes mellitus             | 23%                 | 24%                  | 29%                  | 29%                 | 0.276   |
| ACEI/ARB                             | 45.5%               | 50%                  | 56.6%                | 52.8%               | 0.092   |
| Statins                              | 59.5%               | 70%                  | 65%                  | 63%                 | 0.133   |
| eGFR, mL/min per 1.73 m <sup>2</sup> |                     |                      |                      |                     |         |
| cr*                                  | 76 (19)             | 68 (15)              | 65 (18)              | 52 (20)             | 0.0001  |
| cys*                                 | 85 (21)             | 77 (17)              | 70 (18)              | 54 (23)             | 0.0001  |
| cr-cys*                              | 86 (19)             | 77 (17)              | 70 (18)              | 52 (19)             | 0.0001  |
| cr-cys <60                           | 14.8%               | 16.0%                | 27.1%                | 58.1%               | 0.0001  |
| ACR, mg/g <sup>†</sup>               | 8.0 (4.4–13.8)      | 7.8 (4.1–13.9)       | 8.3 (4.9–17.1)       | 11.8 (6.9–54)       | 0.0001  |
| ACR 30 mg/g                          | 10.4%               | 9.5%                 | 12.3%                | 31.6%               | 0.0001  |

Values reported as \*mean (SD) or †median (IQR). ACEI indicates angiotensin-converting enzyme inhibitor; ACR, albumin-to-creatinine ratio; ARB, angiotensin receptor blocker; cr, creatinine; cys, cystatin C; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein; Q, quartile; and SD, standard deviation.

Table 2

Associations of Quartiles of Soluble Endothelial Cell-Selective Adhesion Molecule With Baseline CKD Assessed by eGFR and ACR

|   | Q1  | Q2        | Q3        | Q4         | P Overall |
|---|-----|-----------|-----------|------------|-----------|
| eGFR <60 mL/min per 1.73 m <sup>2</sup> |     |           |           |            |           |
| Unadjusted OR                           | Ref | 1.41      | 3.22      | 16.0       | <0.0001   |
| 99.83% CI                               |     | 0.59–3.36 | 1.46–7.11 | 7.43–34.41 |           |
| P value                                 |     | 0.2212    | <0.0001   | <0.0001    |           |
| Adjusted* OR                            | Ref | 1.12      | 2.56      | 11.44      | <0.0001   |
| 99.83% CI                               |     | 0.43–2.89 | 1.07–6.12 | 4.89–26.76 |           |
| P value                                 |     | 0.7454    | 0.0016    | <0.0001    |           |
| Adjusted* plus ACR                      | Ref | 1.12      | 2.53      | 9.58       | <0.0001   |
| 99.83% CI                               |     | 0.42–3.03 | 1.02–6.3  | 3.87–23.73 |           |
| P value                                 |     | 0.7177    | 0.0014    | <0.0001    |           |
| ACR 30 mg/g                             |     |           |           |            |           |
| Unadjusted OR                           | Ref | 0.75      | 1.12      | 3.52       | <0.0001   |
| 99.83% CI                               |     | 0.28–2.02 | 0.45–2.75 | 1.61–7.69  |           |
| P value                                 |     | 0.3557    | 0.7044    | <0.0001    |           |
| Adjusted* OR                            | Ref | 0.95      | 1.36      | 5.23       | <0.0001   |
| 99.83% CI                               |     | 0.31–2.89 | 0.47–3.93 | 1.96–13.91 |           |
| P value                                 |     | 0.8788    | 0.3598    | <0.0001    |           |
| Adjusted* plus eGFR                     | Ref | 0.82      | 1.05      | 2.83       | 0.0006    |
| 99.83% CI                               |     | 0.27–2.52 | 0.35–3.11 | 0.93–8.6   |           |
| P value                                 |     | 0.5888    | 0.8965    | 0.00334    |           |

Threshold *P* value for significance=0.0017. *P* overall gives results of test of heterogeneity. ACR indicates albumin-to-creatinine ratio; CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; OR, odds ratio; Q, quartile; and Ref, reference.

\* Adjusted for age, race, sex, hypertension, pack-years, type 2 diabetes mellitus, high-density lipoprotein, low-density lipoprotein, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, statins, and high-sensitivity C-reactive protein.

**Table 3**

Adjusted\* 5-Year Change in Albumin-to-Creatinine Ratio (mg/g) by Quartile of Soluble Endothelial Cell–Selective Adhesion Molecule

|                  | Entire Cohort (N=990) | eGFR 60 (N=678)      | eGFR <60 (N=303)     |
|------------------|-----------------------|----------------------|----------------------|
| Q1               | Ref                   | Ref                  | Ref                  |
| Q2               | 7.92 ( $P=0.4298$ )   | 2.26 ( $P=0.8255$ )  | 21.68 ( $P=0.6827$ ) |
| Q3               | 11.44 ( $P=0.3424$ )  | -0.91 ( $P=0.9358$ ) | 14.06 ( $P=0.7608$ ) |
| Q4               | 54.47 ( $P<0.0001$ )  | 40.35 ( $P=0.0041$ ) | 63.21 ( $P=0.1458$ ) |
| <i>P</i> overall | 0.0001                | 0.0143               | 0.2148               |

Threshold *P* value for significance=0.0017. *P* overall gives results of test of heterogeneity. ACR indicates albumin to creatinine ratio; eGFR, estimated glomerular filtration rate; Q, quartile; and Ref, reference.

\* Adjusted for age, race, sex, hypertension, pack-years, type 2 diabetes mellitus, high-density lipoprotein, low-density lipoprotein, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, statins, high-sensitivity C-reactive protein, and baseline ACR.

**Table 4**

Associations of Quartiles of Soluble Endothelial Cell–Selective Adhesion Molecule With Rapid Loss (>3% Per Year) in Kidney Function

|                  | Unadjusted OR; 99.83% CI; <i>P</i> Value | Adjusted* OR; 99.83% CI; <i>P</i> Value | Adjusted* Plus ACR; 99.83% CI; <i>P</i> Value |
|------------------|--|---|---|
| Q1               | Ref                                      | Ref                                     | Ref   |
| Q2               | 1.18; 0.44–3.12; 0.6018                  | 1.09; 0.38–3.13; 0.8056                 | 1.12; 0.37–3.36; 0.7489                       |
| Q3               | 1.16; 0.43–3.13; 0.6359                  | 0.94; 0.3–2.93; 0.8702                  | 0.99; 0.31–3.19; 0.9869                       |
| Q4               | 2.52; 0.99–6.41; 0.0019                  | 2.13; 0.65–7.01; 0.0465                 | 2.01; 0.58–6.93; 0.0783                       |
| <i>P</i> overall | 0.0043                                   | 0.0659                                  | 0.0157  |
| Q4 vs Q1–Q3      | 2.28; 1.11–4.65; 0.0003                  | 2.11; 0.86–5.22; 0.0095                 | 1.94; 0.76–4.93; 0.0265                       |

Threshold *P* value for significance=0.0017. *P* overall gives results of test of heterogeneity. ACR indicates albumin-to-creatinine ratio; CI, confidence interval; eGFR, estimated glomerular filtration rate; OR, odds ratio; Q, quartile; and Ref, reference.

\* Adjusted for age, race, sex, hypertension, pack-years, type 2 diabetes mellitus, high-density lipoprotein, low-density lipoprotein, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, statins, high-sensitivity C-reactive protein, and baseline eGFR.