

## Soluble Urokinase-Type Plasminogen Activator Receptor: A Useful Biomarker for Coronary Artery Disease and Clinical Outcomes?

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While coronary artery disease (CAD) is a leading cause of death and disability worldwide, causal pathways for the progression of underlying atheromatous coronary plaque formation remain poorly understood.<sup>1</sup> Numerous clinical characteristics and associated laboratory findings (ie, elevated LDL-C levels) have been firmly linked with an increased likelihood of developing atherosclerosis. Some of these variables are modifiable, such as obesity, smoking, hypercholesterolemia, hypertension, and lack of exercise, while other demographic factors such as age, sex, and family history cannot be changed.<sup>2,3</sup> Risk assessment at the individual patient level, however, should not relate to simply accounting for the number of risk factors but rather should focus upon how to delineate the complex interplay among many established clinical and laboratory risk factors. With numerous recent advances, novel biomarkers have been identified from plasma samples of patients with possible or suspected CAD. One such biomarker that looks to be promising is the inflammatory protein—soluble urokinase-type plasminogen activator receptor (suPAR).

In the current issue of the *Journal of the American Heart Association*, Eapen et al<sup>4</sup> present the findings of a study that assessed the association of plasma suPAR with the presence and severity of CAD as well as the role of suPAR as a predictive marker for death and myocardial infarction (MI) (over a mean of  $\approx 2$  years) in 3367 patients undergoing cardiac catheterization. In this study, suPAR levels were associated with both the presence and severity of CAD, and with an increased risk of subsequent death or myocardial infarction (MI) (hazard ratio [HR]: 1.9), cardiac death (HR:

2.62), and MI (HR: 3.20). The addition of suPAR levels to a prediction model that incorporated traditional risk factors modestly improved the discriminatory capabilities of the model (the C statistic changed from 0.72 to 0.74).

Urokinase-type plasminogen activator (uPA) and its cell surface-receptor (uPAR) regulate cellular functions linked to adhesion and migration and are involved in the tissue remodeling processes.<sup>5</sup> The soluble form (suPAR) is present in the serum and other bodily fluids, and the soluble receptor accounts for 10% to 20% of the total receptor in vascular endothelial and smooth muscle cells.

Numerous observational studies have shown systemic levels of suPAR to be associated with an increased risk of cancer, various infectious and inflammatory diseases, rheumatoid arthritis, and hepatic fibrosis.<sup>6</sup> Furthermore, elevated levels of suPAR have been shown to have prognostic value for patients with neoplasms, systemic inflammatory diseases, and those with various infectious diseases.<sup>6</sup>

In a Danish population-based cohort (n=2602) elevated baseline suPAR levels were independently associated with an increased likelihood of cardiovascular disease, as well as diabetes, cancer, and all-cause mortality.<sup>7</sup> In this study, elevated suPAR levels appeared to be more strongly related with these outcomes in men compared with women, and in younger compared with older participants. Sehestedt et al showed in a population-based study of patients without a history of cardiovascular disease (n=2038) that elevated suPAR levels were associated with subclinical organ damage as well as cardiovascular events (a composite of cardiovascular death, MI, and stroke) during a median follow-up of more than 10 years.<sup>8</sup> In another population-based study, the prognostic implications of elevated suPAR levels was assessed together with the Framingham risk score; and the study found that suPAR levels improve the overall risk prediction when combined with hs-CRP (high sensitivity C-reactive protein).<sup>9</sup> Besides the aforementioned population-based studies, data from experimental studies also indicate that suPAR from vascular cells is up-regulated by pro-atherogenic and pro-angiogenic growth factors and cytokines that accumulate in the vessel wall, which suggests a link with suPAR, atherosclerosis, and the subsequent development of symptomatic CAD.<sup>5</sup>

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These salient observations correlate with the results from an epidemiologic study of patients with acute ST-elevation myocardial infarction treated with primary percutaneous coronary intervention, which demonstrated that elevated suPAR levels were significantly associated with the risk of death or re-infarction.<sup>10</sup> Collectively, these studies have demonstrated the potential of elevated suPAR levels for improving the risk prediction of patients with an increased risk for developing CAD and for those with established, symptomatic CAD.

Within this context, the findings of the current work by Eapen et al<sup>4</sup> add further to the developing body of evidence that supports elevated suPAR levels as a novel risk factor for CAD. The aforementioned studies with suPAR levels have either been based on healthy community-based populations with relatively low incidence of CAD, or used a very specific study population of symptomatic CAD patients such as those with STEMI. The findings of the study by Eapen et al can be applied to a much broader population of patients undergoing cardiac catheterization, and as such are representative for a wide spectrum of patients with clinical indications for diagnostic cardiac catheterization. Interestingly, the predictive capabilities of suPAR levels were similar for patients with versus without an acute MI as the indication for catheterization.

Despite these findings, there are a number of concerns with the present analysis. First, only baseline suPAR levels were measured and assessed so the prognostic implications of dynamic changes in serial suPAR levels could not be ascertained. Second, while the sample size of the study cohort undergoing cardiac catheterization is large (>3000), the estimated volume of patients undergoing this procedure over a 6-year period across a number of large hospitals would be expected to be much higher. Third, the ascertainment, collection, and verification of non-fatal MI events were not described in great detail, so the internal and external validity of this endpoint is uncertain without such information. Finally, the rationale for including patients with insignificant CAD identified during cardiac catheterization in the study was not discussed, which is puzzling especially given the differential association of suPAR levels with death or MI in those with versus without significant CAD (higher risk with insignificant CAD).

As the search for more accurate and reproducible methods of risk stratification for patients with suspected or confirmed CAD continues, the accumulated data on suPAR levels suggest that this laboratory-based biomarker may provide modest, additive benefit for predicting the risk of future

cardiovascular events. The next phase in the journey for improved risk stratification will involve integration of this promising biomarker with many other biomarkers and clinical characteristics to develop improved, dynamic models that can delineate risk at multiple time points along the decades-long pathway of disease progression for CAD.

## Disclosures

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