**Editorial**

**Circulating Biomarkers in Acute Coronary Syndromes**

**Something Different or More of the Same?**

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During the past 30 years, there have been significant advances in our treatment of cardiovascular disease, both in the acute setting and in the context of disease prevention. With regard to the former, the availability and safety of acute medical and revascularization strategies for myocardial infarction and unstable angina have reduced both the morbidity and mortality of acute coronary syndromes (ACS). Acute treatment options are typically resource intensive, however, and up to 50% of patients hospitalized for suspected ACS ultimately leave the hospital with other diagnoses. As a consequence, current guidelines for the management of ACS stress risk stratification as a means for directing invasive versus conservative approaches to patient management.

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The traditional clinical tools of risk stratification such as history, physical examination, and ECG have proven inadequate in the vast majority of cases. Not surprisingly, this need has spurred considerable investigation into circulating markers that better establish diagnoses and identify high-risk individuals appropriate for the most resource-intensive treatment. From this search, cardiac troponin measurements have emerged as important markers for both ACS diagnosis and identification of future coronary artery disease (CAD) events. More recently, circulating markers of inflammation such as C-reactive protein, CD40L, and myeloperoxidase have also proven effective in identifying patients with ACS.

In this issue of *Circulation*, Hayashida and colleagues have added soluble lectin-like oxidized LDL receptor-1 (sLOX-1) to this expanding list of markers that are associated with ACS. They examined 427 consecutive patients undergoing cardiac catheterization from a single center and measured sLOX-1 in serum. The presence or absence of CAD was determined by angiographic criteria, whereas the stability of CAD was determined clinically. An important referent group included patients hospitalized with severe noncardiac illness. Compared with other patients, individuals with ACS exhibited levels of sLOX-1 that were 4-fold higher. Consistent with this observation, serum levels of sLOX-1 in excess of 1.0 ng/mL had a significant predictive value for ACS that was superior to the predictive value of high-sensitivity-CRP in this cohort of patients. The authors conclude that sLOX-1 levels are a good marker for ACS.

The serum levels of sLOX-1 had several features that were noteworthy. Serum sLOX-1 levels tended to be elevated earlier in the hospital course of ACS than were troponin levels, suggesting that sLOX-1 could be particularly useful as an initial diagnostic marker. Moreover, sLOX-1 levels did not correlate with troponin, indicating the measurement of both could be complimentary rather than redundant. This is an important point because recent data suggest that complementary sets of prognostic markers provide superior information to any one marker alone. This notion that sLOX-1 may complement other diagnostic markers of ACS is consistent with observations that sLOX-1 levels are not correlated with traditional cardiovascular disease risk factors such as hypertension, diabetes, smoking, and LDL cholesterol. These observations suggest sLOX-1 may provide some information that is “missing” from traditional measures of cardiovascular risk.

Some elements of this study should be interpreted with caution. For example, the authors reported that CRP was less predictive than was sLOX-1 for the prediction of ACS in this study sample; however, the mean CRP values for the referent groups were in the high-risk range (>3.0 ng/mL). Given that low-level detection of CRP is typically required for prognostic significance, it is not surprising this study sample did not find CRP predictive of ACS. Consequently, the poor performance of CRP in this study may not be directly applicable to other study samples. Another consideration relates to the fact that Hayashida and colleagues reported results from a single center that were performed with an in-house ELISA. Although the intra-assay variation was reported to vary from 2.0% to 11.8%, we do not yet have a clear idea of the assay standardization. Issues of assay variation are not trivial. For example, the authors reported that CRP was less predictive than was sLOX-1 for the prediction of ACS in this study sample; however, the mean CRP values for the referent groups were in the high-risk range (>3.0 ng/mL). Given that low-level detection of CRP is typically required for prognostic significance, it is not surprising this study sample did not find CRP predictive of ACS. Consequently, the poor performance of CRP in this study may not be directly applicable to other study samples. Another consideration relates to the fact that Hayashida and colleagues reported results from a single center that were performed with an in-house ELISA. Although the intra-assay variation was reported to vary from 2.0% to 11.8%, we do not yet have a clear idea of the assay standardization. Issues of assay variation are not trivial because any useful biomarker must have well-established assays that lend themselves to use across varied patient settings and diagnostic laboratories. Fibrinogen levels serve as a case in point as they routinely predict future CAD events in both ambulatory and hospitalized patient populations, yet their widespread adoption has been hampered in part by the cumbersome nature of available assays. Focusing on this study, it is not yet clear whether the reported sample collection methods (storage at ~80°C) and assessment of sLOX-1 levels will prove to be easily adopted and standardized.

In this study, both sLOX-1 levels and troponin T were associated with ACS, although peak levels of these 2 markers
were not correlated. Given that troponin determinations are the current cornerstone of ACS diagnosis,\textsuperscript{2,12} it would have been of interest to formally compare serial troponin T and sLOX-1 levels in the diagnosis of ACS. Indeed, this oversight highlights an important issue that is of concern for future research on biomarkers. Given that we already have many established markers of CAD activity and future coronary heart disease risk, it will be imperative in the future to demonstrate the precise additive value of any newly discovered or proposed biomarkers over and above established practice. It is likely that clearing this hurdle will require validation of any proposed new biomarker in other prospective samples and clear demonstration of enhanced predictive value.

Successful incorporation of any new biomarker into clinical practice dictates that certain requirements be met (Figure). Simply adding more candidates to the growing list of biomarkers purported to be either diagnostic of CAD or predictive of future risk will not advance our ability to care for patients. We must undertake the extra effort required to establish the additive value of incorporating any proposed new biomarker into our diagnostic and risk-prediction schemes. This is particularly true because many available markers of cardiovascular disease and future CAD risk actually measure different facets of the same processes. For example, most markers of inflammation (cytokines, adhesion molecules, acute phase reactants) are highly correlated and thus their combination will tend to add little information. A similar argument applies to additional markers of myocardial necrosis. Therefore, in the future, it will be important to find markers or marker combinations that are not particularly correlated with one another in the hopes their joint use will be synergistic. One cogent example of this approach was recently demonstrated using a combination of markers for myocardial damage (troponin I), inflammation (C-reactive protein), and left ventricular dysfunction (B-type natriuretic peptide) by Sabatine and colleagues.\textsuperscript{8} Those investigators found that simply counting the number of elevated biomarkers at admission added considerably to the predictive value obtained with any single marker alone. The precise number of markers required to optimize our ability to positively and negatively predict future CAD risk, however, is not yet clear. Nevertheless, as we continue to expand our understanding of the molecular mechanisms of cardiovascular disease, it is likely we will have more potential markers to test in risk-prediction models.

In summary, Hayashida and colleagues have demonstrated that sLOX-1 levels identify patients with ACS and, perhaps,
future CAD risk. The extent to which these findings add to current risk prediction schemes is not yet known. As pointed out in the Figure, proof of the utility of sLOX-1 in CAD diagnosis and risk prediction will require considerable additional efforts, including testing its predictive utility in an external validation set and comparison with other validated risk stratification schemes in large, well-characterized populations. If these data subsequently determine the utility of sLOX-1, then it will also be imperative to explore the technical details of the assay and assess its applicability across the healthcare system.

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References


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