Advances in the understanding of the molecular basis of inflammation, atherogenesis, and plaque instability have led to the identification of a number of molecules that are posited to play a critical role in various aspects of atherosclerotic lesions and/or their liability, which can be measured quantitatively in plasma. Intercellular cell adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-1) are two important members of the immunoglobulin gene superfamily that play important but different roles in the adhesion of leukocytes to the vascular endothelium. VCAM-1, which is the endothelial ligand for α4β1 (very late antigen 4 [VLA-4]), has been postulated to play the more critical role in monocyte adherence to endothelial cells under flow conditions. ICAM-1 ligands include CD11a/CD18 (LFA-1) and CD11b/CD18 (Mac-1), which are present on monocytes, lymphocytes, and neutrophils. Increased expression of ICAM-1 and VCAM-1 is observed in atherosclerotic lesions, and mice deficient in either ICAM-1 or VCAM-1 have reduced response to experimental atherosclerotic stimuli (eg, apolipoprotein E deletion). In the mouse, a deficiency of VCAM-1 seems to play a more important role in the initiation of atherosclerosis than does a deficiency of ICAM-1.

Although membrane-bound forms of either adhesion molecule are difficult to measure in vivo, soluble forms can be detected in the serum or plasma and are increased in many conditions with an inflammatory component. The levels of soluble ICAM-1 (sICAM-1) in apolipoprotein E–deficient mice increases over time in parallel with the progression of atherosclerosis, providing evidence in a murine model that sICAM-1 may correlate with the burden of atherosclerosis.

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On the basis of this information, a number of clinical investigators have measured levels of sICAM-1 or soluble VCAM-1 (sVCAM-1) as potential biomarkers to see whether they are associated with either the burden or liability of atherosclerosis. In this issue of Circulation, Pradhan et al have shown that levels of sICAM-1 were higher in individuals that have shown a relationship between sICAM-1 and incident coronary heart disease (CHD).

The opinions expressed in this editorial are not necessarily those of the editors or of the American Heart Association.

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for lipid and nonlipid risk factors, including C-reactive protein, the odds ratio for the highest quartile of sICAM-1 compared with the lowest quartile was 3.9 (95% confidence interval [CI] 1.7 to 8.6, P trend 0.001). In contrast, there was no relationship between sVCAM-1 and peripheral arterial disease. This study confirms the results of 4 large prospective studies of healthy individuals that have shown a relationship between sICAM-1 and incident coronary heart disease (CHD) which was attenuated in one study after adjustment for socioeconomic status. Another trial has shown that in stable patients with CHD, levels of sICAM-1 were associated with increased risk for future CHD events. In contrast, no relationship has been found between VCAM-1 and incident CHD in several of these studies.

Previous studies have also shown that there is no relationship between sVCAM-1 and increased intimal-medial thickness of the carotid artery as assessed by ultrasound. In marked contrast to these findings is a report by Blankenberg et al, which showed that in a cohort of patients documented to have coronary artery disease, level of sVCAM-1 was the best predictor of death from CHD after adjustment for other clinical risk factors.

Interpretation of these studies with regard to the importance of either ICAM-1 or VCAM-1 in various stages or beds of atherosclerosis is clouded by lack of knowledge as to what cellular and molecular factors determine the steady-state levels of either of these adhesion molecules in plasma. ICAM-1 and VCAM-1, like many genes that play an important role in inflammation, have careful regulation at many levels. Increased production of sICAM-1 or sVCAM-1 detected in the plasma component could be due to increased transcription, alterations of mRNA stability, changes in translation, production of alternatively spliced forms that are secreted, and/or enhanced proteolytic cleavage from the cell surface. Human leukocyte elastase has been shown to cleave ICAM-1 from several cell types in vitro, and this proteolytic cleavage can be inhibited by α1-antitrypsin. The membrane-anchored form of VCAM-1 can be cleaved from lymphocytes in vitro by proteolytic cleavage involving a metalloprotease. Levels of sICAM-1 and sVCAM-1 increase by ~10% immediately after exercise in patients with peripheral arterial disease and claudication but do not change after exercise in control subjects.

Whether this increase is due to activation of proteases by leukocytes or the endothelium or to other mechanisms is unknown. Finally, whereas VCAM-1 expression is primarily endothelial, macrophages and endothelial cells synthesize and express ICAM-1 in response to inflammatory stimuli.

Although many studies have measured the levels of soluble adhesion molecules, we unfortunately have almost no information as to what regulates the production of sICAM-1 or sVCAM-1 in human or animal models of disease. In addition, no
studies have specifically examined the variables that regulate catabolism of soluble cell adhesion molecules in vivo. Levels of sVCAM-1 are increased in diabetic patients with microalbuminuria. High levels of sVCAM-1 are associated with elevated urinary albumin excretion and chronic renal disease. Clearly, it would be important to know whether the kidney plays an important role in the catabolism of sVCAM-1 or sICAM-1. Indeed, our lack of knowledge may be important in understanding discrepancies between trials. For example, in the study by Blankenberg et al., which showed that level of sVCAM-1 was strongly associated with high levels of cardiovascular mortality, no adjustment was made for proteinuria or renal disease. If one were to calculate the levels of sICAM-1 and sVCAM-1 in the total serum, it is unlikely that this mass could come from an isolated inflammatory focus unless the level is integrated over a long period. Indeed, high levels of sICAM-1 or sVCAM-1 may have different prognostic value if due to increased production versus decreased catabolism.

Although our lack of knowledge limits the interpretation of clinical studies, the consistent association between increased levels of sICAM-1 and incident CHD does support the concept that improved understanding of the molecular basis of atherosclerosis may identify new biomarkers associated with the disease that can be measured quantitatively in plasma or serum. The current approach of studying one or two candidate molecules at a time is unlikely to identify clinically useful biomarkers for atherosclerosis, just as the “candidate” gene approach almost always failed to identify the genetic basis of a clinical disorder. The tremendous breakthroughs in genetics that were obtained by systematically searching the genome may be paralleled in the development of biomarkers by new technological advances that allow us to systematically examine changes in gene expression in atherosclerosis at both the mRNA and protein levels. Protein profiling in plasma by new proteomics techniques has recently shown great potential in the field of cancer. The National Heart, Lung, and Blood Institute’s proteomics initiative should rapidly advance application to cardiovascular disease.

If we do identify new biomarkers for atherosclerosis, how will they be used clinically? Although the first reflexive response is to assume that these biomarkers will be therapeutic targets, that will probably not be the case, if we judge by the few currently used biomarkers in cancer therapy. Instead, biomarkers for cardiovascular disease will most probably be used to identify high-risk patients who may benefit from specific therapies and to track response to antiatherosclerotic therapy in a manner similar to the current use of prostate-specific antigen in prostate cancer.

The article in this issue of Circulation and the others cited provide substantial evidence that increased levels of sICAM-1 are associated with atherosclerosis in multiple arterial beds, whereas levels of VCAM-1 in healthy individuals are not associated with clinical atherosclerosis. An explanation for these disparate results will require a better understanding of the mechanism by which soluble cell adhesion molecules are related to plaque burden and/or liability. Future studies must clarify such issues as cell and tissue of origin, mechanism of generation of soluble forms (secretion, proteolysis), clearance and catabolism of these potential forms, and potential bioactivity of soluble adhesion molecules and their role in the disease process. With this type of information, large population studies and clinical trials can be better designed to determine whether increased levels of these molecules give additive information to current risk assessment approaches and whether patients with elevated levels of soluble adhesion molecules would benefit from any specific therapy.

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Soluble Adhesion Molecules and the Search for Biomarkers for Atherosclerosis
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