Acute coronary syndromes (ACS), which include unstable angina, myocardial infarction, and sudden cardiac death, continue to be a significant public health problem in industrialized countries. A growing body of research is directed at understanding the etiology of ACS and at identifying biomarkers of high risk. The results from angiographic and angioscopic studies suggest that the disruption of an atherosclerotic plaque with subsequent thrombosis may represent a common, although not the only, pathogenetic mechanism for ACS (1).

The definitive reasons for plaque rupture are unknown, but inflammation appears to play a major role (2). Indeed, the main features that distinguish unstable from stable plaques include the presence of wide inflammatory infiltration, plaque fissures, and fresh thrombi (3). Early studies reported evidence of local activation of inflammatory cells in the shoulder region of coronary plaques, with release of proteolytic enzymes (metalloproteinases) that degrade the extracellular matrix and contribute to the fibrous cap weakening and plaque instability (1–3). More recently, however, it has been demonstrated that patients with ACS have widespread inflammation of the coronary tree as well as systemic activation of the inflammatory system (4, 5). These findings have stimulated the search for an ideal marker of plaque instability.

Liuzzo et al. (5) reported for the first time that systemic concentrations of C-reactive protein (CRP), a prototypic marker of inflammation, were increased in a population of patients with unstable angina and were associated with a high recurrence of cardiac events. Larger studies confirmed the predictive value of CRP in patients with known coronary artery disease as well as in healthy men and women (6, 7). In addition, direct proinflammatory and atherogenic effects of CRP have been reported in several studies showing that CRP binds oxidized LDL-cholesterol in the atherosclerotic plaques, activates complement, induces expression of adhesion molecules, and stimulates production of tissue factor (8). CRP is a general marker of inflammation, however, and is not specific for vascular inflammation, and there is no direct evidence that CRP is directly involved in the process of plaque rupture. These facts have led to the search for biomarkers that are specific for “plaque” or for vascular tissue, and for markers that have a plausible association with the mechanisms of plaque rupture.

In this issue of the Journal, Mueller et al. (9) report that plasma concentrations of pregnancy-associated plasma protein-A (PAPP-A) are higher in patients with symptomatic peripheral atherosclerotic disease (PAD) than in patients without atherosclerotic disease. The authors demonstrate that PAPP-A is a significant predictor of symptomatic PAD, even after adjustment for the traditional risk factors CRP and homocysteine. Interestingly, the odds ratio for PAD increased from 1.59 (95% confidence interval, 1.00–2.52) in the first quintile of PAPP-A to 2.86 (95% confidence interval, 1.78–4.59) in the fourth quintile. Moreover, the predictive value of PAPP-A was additional to those of LDL-cholesterol, homocysteine, glomerular flow rate, and, although to a lesser extent, CRP. The authors recognize limitations inherent with this kind of study, the main limiting factor being that the extent and activity of the atherosclerotic process can be only roughly assessed. This study, however, is important because it allows more comprehensive understanding of the role of PAPP-A in pathophysiology and as a biomarker.

PAPP-A is a high–molecular-mass (M, ~200 000), zinc-binding matrix metalloproteinase that is usually measured in the plasma of pregnant women to screen for fetal trisomy 21. The PAPP-A measured in the circulation during pregnancy is produced by the syncytiotrophoblast and is different from the PAPP-A that is present in atherosclerotic plaques and is produced by fibroblasts, vascular smooth muscle cells, and activated macrophages. In pregnancy, PAPP-A circulates in a heterotetrameric form consisting of 2 PAPP-A subunits covalently bound to 2 subunits of the proform of its endogenous inhibitor, the eosinophil major basic protein. Conversely, PAPP-A released in the atherosclerotic plaques consists of a homodimeric active form, not bound to the inhibitor (10).

The proteolytic activity of PAPP-A is directed specifically toward insulin-like growth factor (IGF)–binding proteins, and thus it allows the release of active IGF-I and promotes the proatherogenic effects of IGF-1 (10). In vitro, IGF-1 induces inflammatory cell activation and migration, LDL-cholesterol uptake, and release of inflammatory cytokines by macrophages, contributing to plaque progression and destabilization (10). In addition, it has been suggested that as a metalloproteinase, the PAPP-A produced by activated macrophages may be involved in degradation of the plaque extracellular matrix with consequent weakening of the fibrous cap. This might produce a more vulnerable plaque that is prone to rupture.

Bayes-Genis et al. (11) reported that PAPP-A was overexpressed in eroded and ruptured plaques from patients who died suddenly of cardiac causes, whereas it was only minimally present in stable plaques from patients with chronic stable angina. In addition, in the same study, increased plasma concentrations of PAPP-A were found in patients with ACS. Other studies have confirmed the presence of increased PAPP-A in patients with ACS (12, 13) and demonstrated that PAPP-A is an independent predictor of cardiac events. Finally, a significant association between increased concentrations of PAPP-A and complex coronary and carotid plaques has been described in patients with chronic stable angina and in asymptomatic hyperlipidemic persons (14, 15).

Although the studies summarized here indicate that PAPP-A may well represent a marker of plaque instability, it should be noted that beyond the degradation of IGF-1–binding proteins, no other proteolytic action has
been attributed to PAPP-A. Furthermore, emerging evidence suggests that IGF-1 might have a protective effect in atherosclerosis by inducing nitric oxide synthesis and endothelial cell migration, proliferation, and regeneration while inhibiting apoptosis of endothelial and vascular smooth muscle cells (16). As IGF may be cardioprotective, increased PAPP-A concentrations should also offer cardiovascular protection. Thus, it appears that the more our knowledge on cardiovascular diseases increases, the more complex the scenario becomes.

Indeed, although inflammatory infiltrates have been observed mainly in plaques of patients with ACS, inflammation is involved in all stages of atherosclerotic plaque development, from initiation to progression and complications. This suggests that PAPP-A, like many other inflammatory markers, is involved in plaque remodeling (1–3) and that the shift from stable to unstable coronary artery disease does not depend on the types of involved molecules, but on the magnitude of the inflammatory response. Indeed, circulating concentrations of PAPP-A in ACS were much higher than in the study by Mueller et al. (9). Similarly, CRP concentrations are much higher in ACS than in chronic stable angina. Because PAD represents the prototype of chronic atherosclerosis, increased concentrations of PAPP-A in these studies appear to be indicative of the atherosclerotic burden.

The report by Mueller et al. (9) therefore raises major questions: How far are we from the detection of the perfect marker of atherosclerosis and of ACS? Do we need different markers for different phases of the disease, or do we need different cutoffs? How important is it to find markers that are close to the pathophysiology of plaque rupture, when we know that the life of the plaque is a continuum and that plaque rupture is common also in asymptomatic persons and is not the only cause of ACS, with as many as 40% of cases of ACS arising from simple plaque erosion? An answer to these questions is perhaps also in the evidence that concentrations of “nonspecific markers”, such as CRP, creatinine, cystatin C, glucose, and leukocytes, represent the strongest predictors of cardiovascular death. However, as the question is still waiting for a definitive answer, all efforts in this direction are very welcome.

References