The inflammatory etiology of atherosclerosis has prompted a search for biomarkers of inflammation that predict risk for coronary artery disease and its sequelae. Within the acute coronary syndromes (ACS), inflammatory biomarkers may provide independent information regarding pathophysiology, prognosis, and optimal therapeutic strategies. Based on the hypothesis that different pathophysiological processes provide nonoverlapping information regarding risk stratification and disease management, this review series addresses biomarkers for each step in the inflammatory process leading to ACS. Parts I and II reviewed cytokines, acute-phase reactants, and biomarkers of endothelial cell activation; this part reviews biomarkers of oxidative stress and angiogenesis; part IV addresses biomarkers of extracellular matrix degradation and platelet activation.

Markers of Oxidative Stress

Oxidative stress leading to modification of low-density lipoprotein (LDL) is a central paradigm of atherogenesis and plaque destabilization. The antioxidant hypothesis of atherosclerosis has been bolstered by recent results suggesting that markers of oxidative stress may have prognostic significance in ACS (Table).

Myeloperoxidase

Myeloperoxidase (MPO) is a heme protein produced by neutrophils and monocytes. MPO-dependent halides, tyrosyl radicals, and reactive nitrogen species can modify LDL and thereby promote subsequent foam cell formation. Patients with ACS have a reduction in intracellular neutrophil MPO across both left and right coronary beds, suggesting that widespread neutrophil activation may underlie ACS.2 In a prospective study, patients with ACS and elevated MPO levels had a statistically significant increase in the risk of death or myocardial infarction (MI) at 72 hours, 30 days, and 6 months.3 These differences in risk were attributable entirely to differences in mortality and MI during the first 72 hours. MPO levels were not related to levels of troponin T (TnT), C-reactive protein (CRP), or soluble CD40 ligand (sCD40L), suggesting that MPO provides independent prognostic information distinct from other established biomarkers. In a prospective study of patients presenting with chest pain, a single measurement of plasma MPO independently predicted risk of MI, even if the patient initially had undetectable TnT levels.4

These 2 studies, if replicated in future trials, argue that MPO is a pathophysiologically distinct, independent predictor of risk in ACS. The most important use of MPO may be early risk stratification of patients with non-ST-elevation MI (NSTEMI).

Oxidized LDL

Under conditions of high oxidant stress, lipoprotein phospholipids become progressively oxidized. These oxidant products cross link and fracture the apolipoprotein B molecule of LDL; the resulting adducts are referred to by the general term “oxidized LDL” (Ox-LDL).5 Macrophage uptake of Ox-LDL leads to foam cell formation and elaboration of proinflammatory cytokines that promote endothelial cell dysfunction, further immune cell activation, matrix metalloproteinase expression, and eventual plaque destabilization.6
Inflammatory Biomarkers in Acute Coronary Syndromes

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NSTEACS indicates non-ST elevation acute coronary syndromes.

The 2 most extensively studied biomarkers of LDL oxidation are malondialdehyde-modified LDL (MDA-LDL) and standardized ELISA tests against a heterogeneous group of Ox-LDL.7,8 Some studies also have measured levels of minimally modified LDL, which represents an intermediate oxidation product not recognized by macrophage scavenger receptors.9 All of these studies have shown a correlation between plasma levels of oxidized LDL products and the presence and/or severity of ACS compared with normal control subjects or patients with stable coronary artery disease. Some studies have suggested that MDA-LDL may be a more specific marker in ACS than other types of Ox-LDL because platelet activation may release aldehydes that preferentially oxidize LDL to MDA-LDL.7

Circulating levels of Ox-LDL were recently shown to be associated with the presence of coronary artery disease in patients undergoing elective coronary angiography10; no study has yet addressed outcomes specific to ACS. Data from the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) trial, however, showed that atorvastatin markedly decreased the total content of oxidized phospholipids associated with apolipoprotein B-100 in patients with ACS.11 In the future, prospective studies should be performed to ascertain whether decreased circulating levels of Ox-LDL correlate with outcomes in patients with ACS and whether circulating levels of Ox-LDL are independent of other markers such as cholesterol levels and CRP.

### A2 Phospholipases

A2 phospholipases (PLA2) cleave phospholipids into free fatty acids and lysophospholipids that are metabolized to generate numerous inflammatory mediators. Type II secretory PLA2 (sPLA2) promotes LDL oxidation and catalyzes phospholipid metabolism of LDL, thereby increasing the atherogenicity of LDL particles.12 Another PLA2 enzyme, lipoprotein-associated phospholipase A2 (Lp-PLA2), circulates bound to LDL.

Most studies of sPLA2 and Lp-PLA2 in patients with coronary artery disease have addressed the association between circulating levels of these markers and development of coronary heart disease13 or of ischemic events in patients with stable coronary artery disease.14 In a small study of patients with ACS, an elevated sPLA2 at presentation was associated with approximately 5-fold–increased probability of coronary events over the subsequent 2 years.15 A recent analysis of patients from the Global Registry of Acute Coronary Events (GRACE) found that elevated circulating sPLA2 activity was associated with a 3-fold increased risk of death or myocardial infarction, independent of other established risk markers.15a

Importantly, the risk associated with elevations in Lp-PLA2 levels is independent of CRP and, in the West of Scotland Coronary Prevention Study (WOSCOPS), was independent of statin use.13 This finding suggests that Lp-PLA2 may add novel prognostic information in ACS and that the anti-inflammatory mechanisms of statins may not affect sPLA2-mediated inflammatory pathways.

### Angiogenic Growth Factors

Angiogenic growth factor expression over the course of days to weeks after ACS may promote neovascularization and cardiac repair. Within atherosclerotic plaques, however, angiogenic factors promote neovascularization of the vasa vasorum and increase macrophage infiltration; these processes may lead to intraplaque hemorrhage and atherosclerosis.

### Vascular Endothelial Growth Factor

Vascular endothelial growth factor (VEGF) is a pleiotropic growth factor that regulates endothelial cell proliferation, permeability, migration, and survival. VEGF enhances...
plaque growth in animal models of atherosclerosis, although the relevance of these findings to human trials of therapeutic VEGF administration remains controversial.

In acutely ischemic myocardium, hypoxia triggers endothelial expression of VEGF mRNA transcripts within 48 hours. In the C7E3 Anti-platelet Therapy in Unstable Refractory Angina (CAPTURE) study, VEGF levels at presentation correlated with 72-hour risk of mortality or myocardial infarction. This effect remained significant at 6 months independently of other inflammatory biomarkers, including CRP, sCD40L, and MPO. The prognostic information provided by VEGF independently of other markers likely points toward an important role for angiogenesis in regulating myocardial repair and reperfusion after ACS.

**Placental Growth Factor**

Placental growth factor (PlGF) is a member of the VEGF family of growth factors. PlGF is expressed in many inflammatory cell types and recently has been identified as a crucial mediator of hematopoietic stem cell recruitment and later stages of angiogenesis.

In the CAPTURE study, PlGF levels >27.0 ng/L independently predicted death or nonfatal MI at 72 hours. Event rates continued to diverge at 6 months, with significant differences in rates of both nonfatal MI and mortality. PlGF provided prognostic value independently of cardiac TnT, CRP, and sCD40L and identified a group of patients without elevated cardiac TnT or sCD40L who were at additional risk for an adverse event.

In a large prospective study of patients presenting with chest pain but nondiagnostic ECGs, patients with ACS had increased levels of PlGF compared with patients with stable angina or noncardiac causes of chest pain. However, there was no difference in PlGF levels between patients with unstable angina and those with NSTEMI. In patients with no cardiac TnT elevation, patients with low levels of PI GF and sCD40L had significantly decreased 30-day risk compared with patients with elevation in one or both of these markers.

These initial basic and clinical studies provide an exciting starting point for clinical applications of PI GF. More studies are necessary to delineate the expression of PI GF in atherosclerotic plaques, the time course of expression in patients with coronary artery disease, and whether PI GF levels direct therapeutic decision making in ACS.

**Hepatocyte Growth Factor**

Hepatocyte growth factor (HGF) is a multipotent growth factor with significant angiogenic activity. Selective measurement of the coronary artery territory of patients 4 weeks after MI demonstrated that HGF levels were preferentially increased in the territory of the infarcted region. Furthermore, HGF levels correlated positively with ejection fraction and inversely with left ventricular end-diastolic volume index.

Increased HGF levels predict improved outcome after ACS, possibly because patients with high HGF levels are more likely to have visible collateral circulation at coronary angiography. In the CAPTURE study, increased HGF levels at presentation correlated with lower risk of death or MI at 72 hours. Patients with normal TnT levels but low HGF levels appear to be at increased risk of death, suggesting that HGF may be a useful marker for risk stratification in patients with ACS but no troponin elevation. Notably, however, HGF levels rise rapidly after heparin administration, an effect that may confound serial measurements of HGF.

**Disclosures**

Dr Morrow receives research grant support from Bayer Diagnostics, Beckman-Coulter, Biosite, Dade-Behring, and Roche Diagnostics; receives honoraria for educational presentations from Bayer, Beckman, and Dade-Behring; and serves on the advisory board of OrthoClinical Diagnostics. Dr Sa-batine receives research grant support from Roche. Dr Armstrong reports no conflicts.

**References**


Inflammatory Biomarkers in Acute Coronary Syndromes: Part III: Biomarkers of Oxidative Stress and Angiogenic Growth Factors
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Circulation. 2006;113:e289-e292
doi: 10.1161/CIRCULATIONAHA.105.595546
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2006 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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