Future of Biomarkers in Acute Coronary Syndromes
Moving Toward a Multimarker Strategy

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Clinicians have become increasingly sophisticated in their application of cardiac biomarkers in the management of acute coronary syndromes (ACS). In the 1950s, clinical investigators first reported that proteins released from necrotic cardiac myocytes could be detected in the serum and could aid in the diagnosis of acute myocardial infarction. The ensuing 40 years witnessed progressive improvement in the cardiac tissue-specificity of biomarkers of myocardial necrosis and a corresponding enhancement in the clinical sensitivity and specificity of their use for establishing the diagnosis of acute myocardial infarction. Over the past decade, the emergence of convincing evidence for the value of cardiac troponin in guiding therapy has dramatically accelerated the integration of cardiac biomarkers into clinical decision-making for patients with ACS. Concurrently, advances in our understanding of the pathogenesis and consequences of acute coronary atherothrombosis have stimulated the development of new biomarkers and created the opportunity for an expanded role of multiple biomarkers, some old and others new, in the classification and individualization of treatment for ACS. The report by James et al in the present issue of Circulation adds substantially to the accumulating evidence that a multimarker strategy, employing a pathobiologically diverse set of biomarkers, is likely to add importantly to cardiac-specific troponin alone in the risk assessment of patients with ACS.

Characterizing the Pathogenesis of ACS
ACS is a complex syndrome with multiple causes, analogous to anemia or hypertension. As such, treatment is likely to be most effective when directed at the underlying cause of the disease. Five principal causes of ACS have been described; these include (1) plaque rupture with acute thrombosis, (2) progressive mechanical obstruction, (3) inflammation, (4) secondary unstable angina, and (5) dynamic obstruction (coronary vasoconstriction). It is rare that any of these contributors exists in isolation. However, patients with ACS may vary substantially with respect to the mixture of contributions from each of these major mechanisms and are likely to benefit from different therapeutic strategies. For example, coronary vasodilators (nitrates and calcium channel antagonists) are most useful in patients with predominantly dynamic obstruction. Moreover, the risk of subsequent death and/or recurrent ischemic events among patients with ACS also varies widely, depending on the presence or absence of irreversible myocyte injury, the hemodynamic consequences of ischemia and/or infarction, and the extent and tempo of atherosclerotic vascular disease.

With the emergence of novel, sensitive biomarkers of inflammation, myocyte necrosis, vascular damage, and hemodynamic stress, it is becoming possible to characterize noninvasively the participation of different contributors in any individual patient. For example, detection of cardiac troponin in the blood of patients with non–ST-elevation ACS is not only indicative of myocardial necrosis, but it is also associated with the presence of intracoronary thrombus and distal embolization of platelet microaggregates. These pathobiological links to elevated levels of cardiac troponin are likely to underlie, at least in part, the value of this biomarker in targeting potent antithrombin and antiplatelet therapy. As a second example, high-sensitivity testing for C-reactive protein (CRP) has emerged as a convenient tool for detecting low-level systemic inflammation that portends a higher risk of developing atherothrombotic vascular disease and poor short- and long-term prognosis in patients after ACS. Although the precise mechanistic links between inflammation and risk in ACS are not conclusively established, it is plausible that elevated levels of circulating markers of inflammation reflect an intensification of focal inflammatory processes that destabilize vulnerable plaques. In addition, growing evidence implicates CRP as a mediator, in addition to a marker, of atherothrombosis.

The present work by James et al highlights 2 additional biomarkers, a natriuretic peptide and creatinine clearance, that may provide additional pathophysiological insight and add to a strategy for comprehensive risk assessment.

Natriuretic Peptides in Patients With ACS
B-type natriuretic peptide (BNP) is a 32 amino-acid peptide that is released predominantly from ventricular myocardium in response to increased ventricular wall stress. BNP is produced as a pro-hormone that is cleaved toward the N-terminal to produce BNP and the terminal portion, NT-proBNP. Both BNP and NT-proBNP have been shown to aid in the diagnosis of heart failure and to correlate with functional status among patients with CHF. Levels of BNP and NT-proBNP also correlate with left ventricular dilatation, remodeling, and dysfunction, as well as congestive heart failure and death among patients presenting with acute myocardial infarction. Including the present report, at least 5 studies have now demonstrated a robust association between BNP or NT-proBNP and the short- and long-term risk of death across the spectrum of non–ST-
elevation ACS,\textsuperscript{4,5,16–18} including patients without myocardial necrosis or clinical evidence of heart failure.\textsuperscript{4}

In some patients with ACS, elevated levels of BNP directly reflect the degree of left ventricular dysfunction resulting from acute myocardial infarction. However, the strong association between levels of BNP/NT-proBNP and mortality among patients without measurable myocyte necrosis (i.e., release of cardiac troponin) indicate that the level of BNP may reflect the extent or severity of the ischemic insult, even when irreversible injury has not occurred. Several additional observations support this hypothesis.\textsuperscript{13} Specifically, levels of BNP increase transiently after uncomplicated coronary angioplasty in the presence of stable intracardiac filling pressure, as well as after exercise-induced ischemia in patients with stable coronary artery disease.\textsuperscript{11} Together, these findings suggest that transient ischemia may induce BNP synthesis and release in proportion to the severity of myocardial ischemia. As such, BNP adds a new dimension to our ability to quantify the consequences of acute myocardial ischemia.

**Renal Dysfunction and the Risk of Cardiovascular Events**

The finding that the relationship between NT-proBNP and mortality is unaltered in the presence of renal dysfunction is an important and novel element of the report from James et al.\textsuperscript{8} Moreover, the observation that NT-proBNP and creatinine clearance provide complementary information with respect to mortality is noteworthy and points toward creatinine clearance as a valuable component of a multimarker approach to risk stratification in ACS. Prior studies have demonstrated that impaired renal function is associated with higher mortality in patients with ACS\textsuperscript{19–21} and have led to the incorporation of an assessment of renal function into several clinical tools for risk assessment. Patients with ST-elevation myocardial infarction and renal dysfunction are less likely to be treated with aspirin, \(\beta\)-blockers, fibrinolysis, and angioplasty,\textsuperscript{22} but they also remain at increased risk, even when aggressive treatment is administered.\textsuperscript{21} It has been proposed that creatinine clearance is an inverse integrated measure of the cumulative extent of vascular damage caused by a varied group of insults to the vascular endothelium (e.g., hypertension, dyslipidemia, hyperhomocysteinemia, and diabetes).\textsuperscript{23} As such, creatinine clearance (and/or microalbuminuria) may serve as a more direct measure of the end-organ consequences of vascular risk factors than as an assessment of the individual risk factors alone.

Other indicators of accelerated atherogenesis contribute additional information toward a cumulative assessment of risk for the individual patient. Patients with diabetes and the closely related metabolic syndrome are at 2- to 8-fold higher risk of first acute myocardial infarction, higher risk of death and recurrent ischemic events after presentation with ACS, and experience poorer outcomes after revascularization procedures. Hemoglobin A1c and blood glucose are obviously markers of this important risk factor.

**Putting It All Together: Implications for Prognosis and Therapy**

James et al\textsuperscript{8} have contributed importantly to the growing base of evidence demonstrating that combining a biomarker of hemodynamic stress (BNP or NT-proBNP) or of inflammation (high-sensitivity CRP) with a biomarker of necrosis (cardiac troponin) enhances risk assessment among patients with ACS.\textsuperscript{4,5,10,11,16–18} Specifically, elevated levels of CRP and BNP at presentation identify patients who are at higher mortality risk, irrespective of whether or not there is detectable elevation of troponin.\textsuperscript{4,10} Sabatine et al\textsuperscript{22} have shown that it is possible to use a simple multimarker approach combining each of these markers (BNP, CRP, cardiac troponin), assigning 1 point for each elevated marker, to improve risk stratification. With this simple strategy, a 6- to 13-fold gradient of mortality risk may be established between those without elevation of any marker and those in whom all 3 markers are elevated. The present report\textsuperscript{5} suggests that creatinine clearance will enhance risk assessment if included in a multimarker approach (Figure).

Other biomarkers, such as soluble CD40 ligand (a marker of platelet activation and a potential direct participant in plaque destabilization), metalloproteinases (enzymes that disrupt the integrity of the atheroma’s protective cap), and/or ischemia-modified albumin (a putative marker of myocardial ischemia), could be added to or replace the existing biomarkers in this paradigm if shown to contribute additional independent information. In particular, proteomic and genomic strategies for novel marker discovery are likely to extend this approach. Moreover, as point-of-care technology continues to advance, each of these biomarkers might be incorporated into a single cassette offering a rapidly and conveniently obtained multimarker profile to guide risk assessment and therapeutic decision-making.

**Limitations and Challenges**

Although the evidence that a multimarker approach can be valuable for comprehensive risk assessment is compelling, several limitations must be recognized. First, the relative risk relationships for the individual biomarkers and specific endpoints differ. For example, although BNP and NT-proBNP are potent predictors of mortality risk, they exhibit a weak association with recurrent ischemic events\textsuperscript{4,5}; similar data exist for CRP. Thus, the optimal weighting of each marker for assessment of mortality risk will differ from that for evaluating the risk of recurrent myocardial infarction. In addition, the ultimate test of a multimarker paradigm will be its value in therapeutic decision-making. Although the appropriate clinical responses to an elevated level of troponin in patients with suspected ACS is well
defined, to date we do not have a consistent base of evidence to
guide treatment in response to elevated levels of BNP or CRP in
this setting. Nevertheless, there is reason for optimism that
appropriate therapeutic responses to different patterns of biomar-
ker elevation in ACS will be defined.

An intense effort is underway to identify therapies that
modify the risk associated with inflammation and plaque
instability. Laboratory and clinical studies have revealed
anti-inflammatory effects of established treatments aimed at
other participants in atherothrombosis (eg, aspirin, statins,
angiotensin-converting enzyme inhibitors, and clopidogrel).
For example, clopidogrel decreases the expression of CD40
ligand and may have a greater impact on reducing ischemic
events after percutaneous coronary intervention in patients
with elevated markers of inflammation. Also, agonists of the
protein peroxisome proliferator-activated receptor (PPAR)-
r, such as fibric acid derivatives, can reduce the
expression of adhesion molecules on vascular endothelial
cells, inhibit T-lymphocyte function, improve vascular reac-
tivity, and reduce production of the potent procoagulant tissue
factor. Likewise, the family of insulin-sensitizing thiazo-
lidinediones that act through PPAR-γ are now appreciated to
exert anti-inflammatory actions; they reduce CRP and other
inflammatory mediators in patients with diabetes. They may
thereby slow the tempo of atherosclerosis in these patients.
Other therapies will no doubt emerge from specific targets
revealed by recent advances in vascular biology.

Similar investigation targeted at modifying the risk asso-
ciated with elevated levels of natriuretic peptides and im-
paired renal dysfunction is not as far advanced. Because BNP
levels are associated with left ventricular dysfunction as well
as the extent of coronary artery disease, it is reasonable to
hypothesize that early invasive evaluation and revasculariza-
tion will reduce the risk linked to higher levels of BNP.
However, the available data addressing this hypothesis have
not supported an interaction between BNP and the benefits of
early invasive management. Additional investigation is
needed to address the therapeutic implications of elevated
levels of BNP. Similarly, few data are available to guide specific interventions in patients with reduced creatinine
clearance, except that such patients seem to have a benefit
from an invasive strategy. It is possible that the most
effective treatments for this population are preventative.

Conclusions

The clinical application of cardiac biomarkers in ACS is no longer
limited to establishing or refuting the diagnosis of myocardial
necrosis. Cardiac biomarkers provide a convenient and noninvasive
means to gain insights into the underlying causes and consequences of ACS that mediate the risk of recurrent events and may be targets for specific therapeutic interventions. As our understanding of the pathogenesis of ACS advances and new markers and therapies are discovered, a multimarker paradigm using a combination of both established and new markers for risk assessment and clinical decision-making has the potential to improve substantially the outcomes in patients with ACS.

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