Using biomarkers to obtain mechanistic insight and guide management in acute coronary syndrome

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Abstract
Patients presenting with symptoms suggestive of an acute coronary syndrome (ACS) are heterogeneous in terms of their clinical background, preexisting cardiovascular disease, comorbidities, and risk of adverse outcomes. Despite this clinical diversity, cardiac troponin is the only biomarker that is routinely measured in ACS. Conceptually, testing for additional biomarkers may provide mechanistic insight and enable more personalized and more effective management decisions. Most nontroponin biomarkers are produced in multiple tissues, in response to multiple stressors, and in acute as well as in chronic disease states. The information provided by circulating biomarkers is therefore complex and not related to single disease pathways. Nonetheless, several potential indications for nontroponin biomarkers are emerging, where they may be used in a pragmatic fashion for diagnosis, risk stratification, and therapeutic decision making in ACS. ■ Heart Metab. 2015;67:4-8

Keywords: acute coronary syndrome; acute myocardial infarction; biomarker; cardiac troponin; diagnosis; patient management; prognosis

Diagnosis, risk stratification, and therapeutic decision making in ACS

Patients presenting with symptoms suggestive of an acute coronary syndrome (ACS) are heterogeneous in terms of their clinical background, preexisting cardiovascular disease, comorbidities, and risks of ischemic complications, heart failure, or death. In many patients with an initial suspicion of ACS, the diagnosis will eventually be ruled out, and the patients will be found to have other cardiac or noncardiac diagnoses. Patients with suspected ACS therefore constitute a diagnostic, prognostic, and therapeutic challenge. The purpose of early triage is the rapid diagnosis of acute myocardial infarction (MI) and the identification of other urgent conditions. The diagnosis of acute MI is based on the presence of ischemic symptoms, electrocardiogram (ECG) findings, and the documentation of a concentration rise and/or fall of a circulating biomarker of cardiac necrosis. Cardiac troponin (cTnI) T or cTnI, measured serially with high-sensitivity as-
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Abbreviations
ACS: acute coronary syndrome; BNP: B-type natriuretic peptide; cTn: cardiac troponin; GDF-15: growth differentiation factor 15; h-FABP: heart-type fatty acid-binding protein; IL-6: interleukin 6; hs-CRP: high-sensitivity C-reactive protein; IMA: ischemia-modified albumin; IncRNA: long noncoding RNA; MI: myocardial infarction; miRNA: microRNA; MPO: myeloperoxidase; MR-proADM: midregional proadrenomedullin; MR-proANP: midregional proatrial natriuretic peptide; NSTE-ACS: non–ST-segment elevation acute coronary syndrome; NT-proBNP: N-terminal pro–B-type natriuretic peptide; PAPP-A: pregnancy-associated plasma protein A; STEMI: ST-segment elevation myocardial infarction; TnT: cardiac troponin T; TnI: cardiac troponin I; VAP: ventilation assistive pressure; WCC: white blood cell count;

Information provided by biomarkers is complex and not related to single disease pathways

Currently, cTn is the only biomarker recommended for diagnosis, risk stratification, and therapeutic decision making in ACS. However, there is a continued interest in using additional circulating biomarkers to obtain mechanistic insight and to further improve the management of patients with ACS. A large number of protein and peptide biomarkers reflecting different pathophysiological mechanisms have been investigated (examples are highlighted in Table I). While the categorization of biomarkers into distinct pathophysiological classes provides a conceptual framework, it is also an oversimplification. Most non troponin biomarkers are produced in multiple tissues and in response to multiple stressors, and virtually all biomarkers integrate information from different disease pathways. Moreover, it can be difficult to distinguish between acute biomarker elevations caused by the ACS and chronic elevations related to underlying cardiovascular and noncardiovascular disease, situations that may require different therapeutic responses (eg, inflammation or matrix remodeling related to chronic atherosclerosis and/or heart failure vs an acute plaque rupture/erosion event and/or infarct healing). In addition, biomarker concentrations are not only determined by their synthesis and release, but also by their catabolism and clearance. As an example, elevated cTn levels reflect not only ischemic and nonischemic cardiomyocyte necrosis, but are also related to ventricular strain, hypertrophy, and failure (similar to the natriuretic peptides), inflammation (eg, elevated levels in sepsis), and renal dysfunction (reduced clearance). Interpretation of cTn levels in patients with suspected ACS therefore requires careful consideration of the clinical context and serial measurements to distinguish acute from chronic and ischemic from nonischemic elevations.

More recently, circulating microRNAs (miRNAs), long noncoding RNAs (lncRNAs), and metabolites have been added to the growing list of potential ACS biomarkers. miRNAs are short noncoding RNA species that function in posttranscriptional regulation of gene expression. miRNAs may circulate in plasma and exhibit remarkable stability to degradation. Based on their tissue selectivity, cardiomyocyte-enriched miRNAs have been proposed as potential diagnostic markers for acute MI. However, a recent study tempered speculations about the usefulness of cardiomyocyte-enriched miRNAs as diagnostic or prognostic markers in ACS. IncRNAs constitute a novel class of RNAs that regulate gene expression and protein function. Unlike miRNAs, plasma concentrations of IncRNAs are very low. A recent study quantified five IncRNA species in blood leukocytes in patients with acute MI. Although four IncRNA species were differentially expressed in patients, there was a large overlap between patients and controls, and none of the investigated IncRNAs emerged as a promising diagnostic biomarker. Since humans express >95,000 different IncRNAs, more promising IncRNA biomark-
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Emerging biomarker applications in ACS

Using serial cTn measurements with high-sensitivity assays, the diagnosis of acute MI can be ruled out or ruled in, in most patients within 3 hours, or maybe even within 1 hour, from initial presentation. Recent studies indicate that it may be safe to more rapidly discharge low-to-intermediate risk patients with suspected ACS based on a single measurement of high-sensitivity cTnT and copeptin or heart-type fatty acid-binding protein (h-FABP) on admission. If confirmed in prospective, interventional studies, these biomarker-guided strategies have the potential to further shorten the length of stay in the emergency department in low risk patients without ACS.

Management decisions in NSTE-ACS should be based on a rapid and accurate assessment of risk. Physicians relying on a “subjective” assessment of risk may fail to consider important prognostic factors, and physicians’ underestimation of risk may result in high-risk patients paradoxically receiving less intensive therapies. The European Society of Cardiology (ESC) guidelines therefore recommend a standardized approach that uses the Global Registry of Acute Coronary Events (GRACE) score to calculate risk and guide management decisions.

Table I  Protein and peptide biomarkers in acute coronary syndrome.

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Biomarker characteristics</th>
<th>Primary disease pathways</th>
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</thead>
<tbody>
<tr>
<td>Established</td>
<td></td>
<td></td>
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<tr>
<td>cTn</td>
<td>Cardiomyocyte-specific protein released upon myocyte strain and cell death</td>
<td>Cardiomyocyte injury</td>
</tr>
<tr>
<td>Under investigation (examples)</td>
<td></td>
<td></td>
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<tr>
<td>BNP, NT-proBNP</td>
<td>Peptides released upon ventricular strain, ischemia, and hypertrophy</td>
<td>Ventricular strain</td>
</tr>
<tr>
<td>Copeptin</td>
<td>Peptide released together with the neurohypophysial hormone vasopressin</td>
<td>Hemodynamic stress, osmotic stress</td>
</tr>
<tr>
<td>Cystatin C</td>
<td>Ubiquitously expressed protease inhibitor and marker of renal dysfunction</td>
<td>Renal dysfunction, inflammation</td>
</tr>
<tr>
<td>Galectin-3</td>
<td>Widely expressed, pleiotropic carbohydrate-binding protein</td>
<td>Inflammation, wound repair</td>
</tr>
<tr>
<td>GDF-15</td>
<td>Stress-inducible TGF-β-related cytokine, weakly expressed under healthy conditions</td>
<td>Inflammation, aging, tissue injury</td>
</tr>
<tr>
<td>h-FABP</td>
<td>Widely expressed cytoplasmic protein enriched in striated muscles</td>
<td>Myocyte ischemia and injury</td>
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<tr>
<td>hs-CRP</td>
<td>Hepatic acute phase protein induced during acute and chronic inflammation</td>
<td>Inflammation</td>
</tr>
<tr>
<td>IL-6</td>
<td>Proinflammatory cytokine</td>
<td>Inflammation</td>
</tr>
<tr>
<td>IMA</td>
<td>Serum protein, N-terminus is modified upon tissue (cardiac) ischemia</td>
<td>Tissue ischemia</td>
</tr>
<tr>
<td>MPO</td>
<td>Inflammatory cell-derived secreted enzyme</td>
<td>Inflammation</td>
</tr>
<tr>
<td>MR-proADM</td>
<td>Midregional fragment of proadrenomedullin, expressed by various tissues including the vasculature and the heart</td>
<td>Hemodynamic stress, inflammation</td>
</tr>
<tr>
<td>MR-proANP</td>
<td>Midregional fragment of proatrial natriuretic peptide, produced mainly in the atria of the heart</td>
<td>Hemodynamic stress, volume overload</td>
</tr>
<tr>
<td>PAPP-A</td>
<td>Metalloproteinase secreted during inflammation and wound healing</td>
<td>Inflammation</td>
</tr>
<tr>
<td>Soluble ST2</td>
<td>Soluble isoform of the IL-33 receptor, induced during T-cell activation, inflammation and fibrosis</td>
<td>Hemodynamic stress, inflammation</td>
</tr>
</tbody>
</table>

Abbreviations: BNP, B-type natriuretic peptide; cTn, cardiac troponin; GDF-15, growth differentiation factor 15; h-FABP, heart-type fatty acid-binding protein; hs-CRP, high-sensitivity C-reactive protein; IL, interleukin; IMA, ischemia-modified albumin; MPO, myeloperoxidase; MR-proADM, midregional proadrenomedullin; MR-proANP, midregional proatrial natriuretic peptide; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PAPP-A, pregnancy-associated plasma protein A; TGF, transforming growth factor.
somewhat lesser extent, N-terminal pro–B-type natriuretic peptide (NT-proBNP) emerged as the most promising biomarkers adding prognostic information to GRACE and high-sensitivity cTnT.17 Both biomarkers reclassified patients in the appropriate directions and across risk thresholds, which may trigger changes in treatment decisions in the future. Notably, addition of more than one biomarker added little discriminatory information, perhaps because the GRACE score already reflects several disease pathways, including heart failure (Killip class), renal function (creatinine concentration), ischemia (ECG), and myocyte injury (cTn).17 More widespread use of risk scores and prognostic biomarkers in clinical practice will help to identify high-risk patients who have the most to gain, in absolute terms, from established therapies.

There are some recent examples where biomarkers may help to select NSTE-ACS patients for specific therapies. In an exploratory analysis of the MERLIN–TIMI 36 (Metabolic Efficiency with Ranolazine for Less Ischemia in Non–ST elevation acute coronary syndromes—Thrombolysis In Myocardial Infarction 36) trial, ranolazine reduced the risk of cardiovascular death, MI, or recurrent ischemia only in patients with elevated B–type natriuretic peptide (BNP) levels, but not in those without.18 In the PLATO (PLAtelet inhibition and patient Outcomes) trial, elevated high-sensitivity cTnT levels predicted substantial benefit of ticagrelor over clopidogrel, whereas the benefits of ticagrelor were limited in those patients with normal high-sensitivity cTnT concentrations. Furthermore, the magnitude of benefit of ticagrelor was related to the degree of elevation of GDF-15 and NT-proBNP.19

Recent studies have identified multiple biomarkers, including copeptin, GDF-15, midregional proadrenomedullin (MR-proADM), midregional proatrial natriuretic peptide (MR-proANP), and soluble ST2 that helps identify patients at increased risk of heart failure after an episode of ACS, independent of clinical indicators and BNP.20,21 Remarkably, most of these biomarkers were only weakly or moderately correlated with each other, emphasizing that these markers are induced by distinct stressors, and suggesting that multiple mechanisms contribute to the development of heart failure after ACS. In the future, these biomarkers may help select patients for therapies aimed at mitigating the risk of heart failure after ACS.20,21

The introduction of high-sensitivity cTn assays has resulted in an increased proportion of NSTE-ACS patients presenting with elevated cTn concentrations. Patients even with slight elevations of cTn (which could not be detected with previous less sensitive assays) are considered high risk and should undergo an early invasive strategy.2 As a result, current treatment recommendations for patients with NSTE-ACS have become more uniform, and less “personalized.” With a better understanding of the disease pathways reflected by circulating biomarkers, new treatment targets and a new taxonomy of ACS may emerge that will enable physicians to make more personalized and more effective treatment decisions.22

Dr Wollert is named as coinventor on a patent for the use of GDF-15 for cardiovascular applications and has a contract with Roche Diagnostics for the development of a GDF-15 assay. Dr Wollert has received research grant funding from Roche Diagnostics.

REFERENCES


