*Heart Metab.* (2015) 67:4-8

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

**Kai C. Wollert, MD**
**Division of Molecular and Translational Cardiology, Department of Cardiology and Angiology, Hannover Medical School, Hannover, Germany**

Correspondence: Kai C. Wollert, Hans Borst Center for Heart and Stem Cell Research, Hannover Medical School, 30625 Hannover, Germany
E-mail: wollert.kai@mh-hannover.de

**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 (cTn) T or cTnI, measured serially with high-sensitivity as-

## 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; **lncRNA:** 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

says, are the preferred biomarkers to rule in or rule out MI in the acute setting.[1] Moreover, risk stratification is critically important after initial medical contact to target patients at high risk for adverse events toward potentially lifesaving therapies. Patients at low risk also need early identification to allow saving of resources by early discharge and further evaluation in outpatient settings. Risk stratification is especially important in patients presenting without ST-segment elevation on their ECG (non–ST-segment elevation ACS, NSTE-ACS), because the timing of angiography and revascularization should be planned based on the individual patient's risk profile.[2,3] In patients presenting with ST-segment elevation MI (STEMI), reperfusion therapy needs to be initiated as soon as possible and should not be delayed while awaiting the results of cTn measurement. Risk stratification is less important in these patients, because it does not inform management decisions.[4]

## 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.[2-4] 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.[5] 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 nontroponin 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).[6] 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.[7] However, a recent study tempered speculations about the usefulness of cardiomyocyte-enriched miRNAs as diagnostic or prognostic markers in ACS.[8] lncRNAs constitute a novel class of RNAs that regulate gene expression and protein function. Unlike miRNAs, plasma concentrations of lncRNAs are very low. A recent study quantified five lncRNA species in blood leukocytes in patients with acute MI. Although four lncRNA species were differentially expressed in patients, there was a large overlap between patients and controls, and none of the investigated lncRNAs emerged as a promising diagnostic biomarker.[9] Since humans express >95 000 different lncRNAs, more promising lncRNA biomark-

ers may be discovered in the future.[10] Using metabolomic tools, multiple small-molecule metabolites can be measured in biological specimens, including plasma. In a small study, a metabolic signature of early myocardial injury was defined in patients undergoing alcohol septal ablation treatment for hypertrophic obstructive cardiomyopathy.[11] Because circulating metabolites may represent diverse tissue origins, the potential value of metabolic profiling for diagnostic or prognostic purposes in ACS will have to be further defined.[12]

## 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,[2] or maybe even within 1 hour,[5] 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.[13,14] 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.[15] 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.[2] The ability of the GRACE score to discriminate outcome groups leaves room for improvement, however.[16] All biomarkers listed in *Table I* have been related to an adverse prognosis in NSTE-ACS. However, the incremental information provided by these biomarkers beyond the GRACE score and high-sensitivity cTn, information that is already available in all patients as part of routine care, varies considerably. In a recent head-to-head comparison of nine circulating biomarkers, growth differentiation factor 15 (GDF-15) and, to a

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

***Table I*** *Protein and peptide biomarkers in acute coronary syndrome.*
**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 help 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

1. Thygesen K, Mair J, Giannitsis E, et al. How to use high-sensitivity cardiac troponins in acute cardiac care. *Eur Heart J*. 2012;33(18):2252-2257.
2. Hamm CW, Bassand JP, Agewall S, et al. ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: The Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J*. 2011;32(23):2999-3054.
3. Windecker S, Kolh P, Alfonso F, et al. 2014 ESC/EACTS Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). *Eur Heart J*. 2014;35(37):2541-2619.
4. Steg PG, James SK, Atar D, et al. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J*. 2012;33(20):2569-2619.
5. Mueller C. Biomarkers and acute coronary syndromes: an update. *Eur Heart J*. 2014;35(9):552-556.
6. Giannitsis E, Katus HA. Cardiac troponin level elevations not related to acute coronary syndromes. *Nat Rev Cardiol*. 2013;10(11):623-634.
7. Tijsen AJ, Pinto YM, Creemers EE. Circulating microRNAs as diagnostic biomarkers for cardiovascular diseases. *Am J Physiol Heart Circ Physiol*. 2012;303(9):H1085-H1095.
8. Widera C, Gupta SK, Lorenzen JM, et al. Diagnostic and prognostic impact of six circulating microRNAs in acute coronary syndrome. *J Mol Cell Cardiol*. 2011;51(5):872-875.
9. Vausort M, Wagner DR, Devaux Y. Long noncoding RNAs in patients with acute myocardial infarction. *Circ Res*. 2014;115(7):668-677.
10. Skroblin P, Mayr M. "Going long": long non-coding RNAs as biomarkers. *Circ Res*. 2014;115(7):607-609.
11. Lewis GD, Wei R, Liu E, et al. Metabolite profiling of blood from individuals undergoing planned myocardial infarction reveals early markers of myocardial injury. *J Clin Invest*. 2008;118(10):3503-3512.

12. Shah SH, Kraus WE, Newgard CB. Metabolomic profiling for the identification of novel biomarkers and mechanisms related to common cardiovascular diseases: form and function. *Circulation*. 2012;126(9):1110-1120.
13. Mockel M, Searle J, Hamm C, et al. Early discharge using single cardiac troponin and copeptin testing in patients with suspected acute coronary syndrome (ACS): a randomized, controlled clinical process study. *Eur Heart J*. 2015;36(6):369-376.
14. Body R, Carley S, McDowell G, et al. The Manchester Acute Coronary Syndromes (MACS) decision rule for suspected cardiac chest pain: derivation and external validation. *Heart*. 2014;100(18):1462-1468.
15. Fox KA, Anderson FA Jr, Dabbous OH, et al. Intervention in acute coronary syndromes: do patients undergo intervention on the basis of their risk characteristics? The Global Registry of Acute Coronary Events (GRACE). *Heart*. 2007;93(2):177-182.
16. D'Ascenzo F, Biondi-Zoccai G, Moretti C, et al. TIMI, GRACE and alternative risk scores in Acute Coronary Syndromes: a meta-analysis of 40 derivation studies on 216,552 patients and of 42 validation studies on 31,625 patients. *Contemp Clin Trials*. 2012;33(3):507-514.
17. Widera C, Pencina MJ, Bobadilla M, et al. Incremental prognostic value of biomarkers beyond the GRACE (Global Registry of Acute Coronary Events) score and high-sensitivity cardiac troponin T in non-ST-elevation acute coronary syndrome. *Clin Chem*. 2013;59(10):1497-1505.
18. Morrow DA, Scirica BM, Sabatine MS, et al. B-type natriuretic peptide and the effect of ranolazine in patients with non-ST-segment elevation acute coronary syndromes: observations from the MERLIN-TIMI 36 (Metabolic Efficiency With Ranolazine for Less Ischemia in Non-ST Elevation Acute Coronary-Thrombolysis In Myocardial Infarction 36) trial. *J Am Coll Cardiol*. 2010;55(12):1189-1196.
19. Wallentin L, Lindholm D, Siegbahn A, et al. Biomarkers in relation to the effects of ticagrelor in comparison with clopidogrel in non-ST-elevation acute coronary syndrome patients managed with or without in-hospital revascularization: a substudy from the Prospective Randomized Platelet Inhibition and Patient Outcomes (PLATO) trial. *Circulation*. 2014;129(3):293-303.
20. Bonaca MP, Morrow DA, Braunwald E, et al. Growth differentiation factor-15 and risk of recurrent events in patients stabilized after acute coronary syndrome: observations from PROVE IT-TIMI 22. *Arterioscler Thromb Vasc Biol*. 2011;31(1):203-210.
21. O'Malley RG, Bonaca MP, Scirica BM, et al. Prognostic performance of multiple biomarkers in patients with non-ST-segment elevation acute coronary syndrome: analysis from the MERLIN-TIMI 36 trial (Metabolic Efficiency With Ranolazine for Less Ischemia in Non-ST-Elevation Acute Coronary Syndromes-Thrombolysis In Myocardial Infarction 36). *J Am Coll Cardiol*. 2014;63(16):1644-1653.
22. Kirchhof P, Sipido KR, Cowie MR, et al. The continuum of personalized cardiovascular medicine: a position paper of the European Society of Cardiology. *Eur Heart J*. 2014;35(46):3250-3257.