Clinical utility of novel biomarkers in acute myocardial infarction

Thomas Stiermaier[1,2], Holger Thiele[1,2], Ingo Eitel[1,2]

[1]Department of Cardiology, Angiology, Intensive Care Medicine, Medical Clinic II, University Heart Center of Lübeck, Lübeck, Germany; [2]German Center for Cardiovascular Research (DZHK), partner site Hamburg/Kiel/Lübeck, Lübeck, Germany

Correspondence to: Ingo Eitel, MD. Medical Clinic II, University Heart Center Lübeck, University Hospital Schleswig-Holstein, Ratzeburger Allee 160, 23538 Lübeck, Germany. Email: ingo.eitel@uksh.de.

Over the past decades, biomarkers of myocardial injury, particularly cardiac troponin (cTn), creatine kinase and its isoenzyme creatine kinase myocardial band, have been extremely valuable for the diagnosis and clinical decision making in patients with suspected acute coronary syndrome (ACS). These established markers of necrosis were recently complemented by numerous novel biomarkers reflecting causes and consequences of myocardial infarction (e.g., inflammation, endothelial dysfunction, or hemodynamic stress). Therefore, research efforts have been directed to determine the additional diagnostic and prognostic value of these novel biomarkers.

While the diagnosis and management of ST-elevation myocardial infarction is solely based on clinical and electrocardiographic findings, the identification of patients with non-ST-elevation myocardial infarction (NSTEMI) requires a more sophisticated approach including the measurement of cTn and other biomarkers of myocardial necrosis (1,2). In patients with NSTEMI, levels of cTn usually rise rapidly within 1 hour after symptom onset and remain elevated for a variable period of time (1). Advances in technology have led to an improvement in cTn assays and have refined the ability to detect and quantify myocardial injury. By using conventional, non-high-sensitive cTn (hs-cTn) assays elevated troponin concentrations in the peripheral blood may be detected delayed which necessitates serial testing to ascertain the diagnosis in most cases. Novel biomarkers were thought to bridge this "troponin-blind" gap and enable immediate decision making in patients presenting with acute chest pain.

Copeptin has emerged as one of these promising biomarkers that may overcome this lack of sensitivity within the first hours after symptom onset although non-specific to myocardial injury. It is released in response to endogenous and/or hemodynamic stress and a dual-marker strategy with conventional cTn and copeptin showed a high negative predictive value for the early rule-out of NSTEMI including a reduction of the average time-to-diagnosis, therefore adding incremental value to conventional cTn assays (3,4). However, the introduction of hs-cTn assays in clinical routine significantly increased the diagnostic performance of cTn and facilitates to rule out myocardial infarction within 1 hour (1). An additional diagnostic value of copeptin to hs-cTn has not been convincingly established (5,6). Consequently, current guidelines recommend the routine use of copeptin for the early rule-out of NSTEMI only if hs-cTn assays are not available (1).

In view of the limited diagnostic gain in addition to hs-cTn, the focus shifted to the prognostic value of novel cardiac biomarkers. In the British Medical Bulletin, Feistritzer and colleagues provide a systematic review of selected biomarkers reflecting myocardial injury, inflammation/fibrosis, and hemodynamics (7). The authors illustrate the pathophysiological background and the prognostic utility of hs-cTn, natriuretic peptides, copeptin, galectin-3, corin, fetuin-A, adiponectin and micro-RNAs. Scientific advances created numerous other markers that may reflect further aspects of coronary artery disease (e.g., plaque

destabilization/rupture or platelet activation) but would exceed the scope of this review (8). In the context of prognostic utility, growth differentiation factor 15 (GDF-15) showed promising results as an independent predictor of mortality and a potential tool to guide therapy and should therefore be mentioned additionally (8,9). However, although most of these novel biomarkers can improve risk stratification in patients with acute myocardial infarction to some extent, the question regarding their actual role in clinical routine arises (8). As nicely illustrated by Feistritzer and colleagues, the obligatory measurement of hs-cTn already provides substantial prognostic information and is pivotal for patient management (7). In addition, only natriuretic peptides were extensively validated and have proven prognostic utility on top of cTn although without definitive treatment implications (10). Other novel biomarkers have not yet shown useful regarding therapeutic decision making and their incremental prognostic value over and above established biomarkers and risk scores is only marginal. Similarly, multi-marker approaches involving several novel biomarkers failed to clearly outperform the prognostic usefulness of cTn (11). Therefore, guidelines for the management of patients with acute myocardial infarction do not recommend their routine assessment (1,2).

Several aspects might explain why novel biomarkers have not yet found their way into clinical routine. Established biomarkers, basically hs-cTn and natriuretic peptides, as well as clinical scores such as the Global Registry of Acute Coronary Events (GRACE) or the Thrombolysis In Myocardial Infarction (TIMI) Risk Score enable excellent risk stratification, are widely available and cost effective (1). Moreover, imaging modalities provide further prognostic insights. Echocardiography to evaluate left ventricular function and contraction abnormalities is recommended in all patients with acute myocardial infarction (1,2). Cardiovascular magnetic resonance (CMR) imaging allows for a more detailed tissue characterization and is increasingly available in clinical routine. Parameters derived from these imaging modalities, particularly CMR, have demonstrated incremental prognostic information regarding hard clinical endpoints whereas many biomarkers have only been linked to impaired left ventricular function or adverse remodeling (12). Therefore, the combination of established biomarkers, clinical risk scores and imaging parameters facilitates a sufficient risk stratification from a clinician's point of view. Novel biomarkers have to outperform these markers regarding sensitivity, specificity and/or a quicker release kinetic while being similarly cost effective and easily

available to play a role in clinical practice. Since this is very difficult to achieve a potential alternative application of novel biomarkers is the guidance of treatment decisions to enable a more tailored patient management. However, a benefit of biomarker based approaches remains to be proven.

In summary, several novel biomarkers reflecting different pathophysiological aspects of acute myocardial infarction emerged during the last decade. However, few of them have proven valuable in clinical routine given the excellent diagnostic and prognostic performance of established evaluation strategies including cTn, clinical risk scores and imaging markers of myocardial damage. While cTn is highly specific for myocardial necrosis, it provides no information on the etiology of myocyte death. Thus, more research is necessary to determine new thresholds or additional helpful biomarkers to distinguish between etiologies in the heterogeneous field of ACS (e.g., in patients with atrial fibrillation, hypertension, Takotsubo syndrome, and/or kidney disease). Finally, an individualized biomarker-guided management according to cTn and other promising biomarkers like copeptin and/or GDF-15 (e.g., immediate coronary intervention in NSTEMI patients with high-risk biomarker features) should be addressed in upcoming ACS trials to evaluate if there is room for other novel biomarkers for clinical decision making next to cTn.

Acknowledgements

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Roffi M, Patrono C, Collet JP, et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). Eur Heart J 2016;37:267-315.
2. Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology (ESC), Steg PG, James SK, et al. ESC

Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Eur Heart J 2012;33:2569-619.

3. Maisel A, Mueller C, Neath SX, et al. Copeptin helps in the early detection of patients with acute myocardial infarction: primary results of the CHOPIN trial (Copeptin Helps in the early detection Of Patients with acute myocardial INfarction). J Am Coll Cardiol 2013;62:150-60.

4. Möckel 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;36:369-76.

5. Giannitsis E, Kehayova T, Vafaie M, et al. Combined testing of high-sensitivity troponin T and copeptin on presentation at prespecified cutoffs improves rapid rule-out of non-ST-segment elevation myocardial infarction. Clin Chem 2011;57:1452-5.

6. Karakas M, Januzzi JL Jr, Meyer J, et al. Copeptin does not add diagnostic information to high-sensitivity troponin T in low- to intermediate-risk patients with acute chest pain: results from the rule out myocardial infarction by computed tomography (ROMICAT) study. Clin Chem 2011;57:1137-45.

7. Feistritzer HJ, Klug G, Reinstadler SJ, et al. Novel biomarkers predicting cardiac function after acute myocardial infarction. Br Med Bull 2016;119:63-74

8. Hochholzer W, Morrow DA, Giugliano RP. Novel biomarkers in cardiovascular disease: update 2010. Am Heart J 2010;160:583-94.

9. Eitel I, Blase P, Adams V, et al. Growth-differentiation factor 15 as predictor of mortality in acute reperfused ST-elevation myocardial infarction: insights from cardiovascular magnetic resonance. Heart 2011;97:632-40.

10. Thygesen K, Mair J, Mueller C, et al. Recommendations for the use of natriuretic peptides in acute cardiac care: a position statement from the Study Group on Biomarkers in Cardiology of the ESC Working Group on Acute Cardiac Care. Eur Heart J 2012;33:2001-6.

11. 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;63:1644-53.

12. Eitel I, de Waha S, Wöhrle J, et al. Comprehensive prognosis assessment by CMR imaging after ST-segment elevation myocardial infarction. J Am Coll Cardiol 2014;64:1217-26.