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Biomarkers in acute coronary syndrome

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ABSTRACT

Background: Biomarkers play an important role in the diagnosis and risk stratification of patients with ischemic heart disease. Currently, troponin continues as the reference biomarker in acute coronary syndromes. However, there are other biomarkers that have shown additional value in improving sensitivity and prognostic information. Several promising molecules are reviewed, some related to cardiomyocyte structure and others working as inflammatory and renal function markers.
Conclusions: Although many biomarkers have been shown useful in some studies, further prospective studies are needed to establish their accurate usefulness in routine clinical practice.

1. Introduction

Over the past years biomarkers have become a fundamental tool for the evaluation and management of numerous diseases. Cardiology, and more specifically, acute coronary syndrome, is no stranger to this. Currently, several molecules have demonstrated their value in improving the diagnosis and prognostic classification of patients with acute myocardial infarction. However, available biomarkers are not perfect and interpretation requires careful consideration of the specific clinical scenario [1].

This review aims to analyze the value of biomarkers in acute coronary syndromes (ACS) with a special look on new candidates that could contribute in the near future to the role reserved at present almost exclusively to troponins.

2. Brief historical overview: from AST to troponin

The use of biomarkers in the diagnosis of acute myocardial infarction (AMI) begins in 1954 when Karmen et al. first reported elevation of aspartate aminotransferase (AST) in the serum of patients with AMI [2]. Later, limitations of AST as a biomarker were recognized due to its lack of specificity for myocardial tissue. One year later, Wroblewski proposed the use of lactate dehydrogenase (LDH) in the diagnosis of AMI [3].

The 1960s marked the beginning of creatine kinase (CK) as a better biomarker as it was demonstrated to be more cardiac-specific and clinically useful due to its kinetics after AMI [4]. In the following years the development of new laboratory techniques was essential to describe the CK-MB isoenzyme as the molecule that showed the highest diagnostic accuracy [5]. The World Health Organization (WHO) officially recognized the major role of CK-MB and other enzyme determinations in AMI diagnosis in 1979, when diagnostic criteria included demonstration of typical rising and falling of CK, CK-MB, LDH, or AST activities along with clinical and electrocardiographic features [6,7].

The need to find molecules with higher sensitivity and specificity for the diagnosis of AMI and the development of new methods of detection made the emergence of cardiac troponins (cTn) possible at the end of 1980s [8]. A new era was born in the diagnosis of AMI because of its clinical sensitivity and myocardial-specificity, placing cTn as first-line biomarkers in the definition of ACS. Medical community moved from a clinical–electrocardiographic–biochemical approach to AMI definition to a biomarker-centered definition in which cTn have a central role [9].

3. Biomarkers in current standard of care

3.1. Troponins

Troponins are cardiac proteins important for actin and myosin interaction, modulating sarcomeric contractile function in response to cytosolic calcium and protein phosphorylation. The troponin complex is composed of three regulatory proteins: cTnC, cTnI, and cTnT [10].

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Troponins T and I have unique cardiac isoforms, whereas cardiac muscle and skeletal muscle share troponin C isoforms, rendering this protein unsuitable for diagnostic use. Troponins T and I are currently the gold standard for the detection of myocardial injury and are key to clinical decision making in ACS [11–14].

The Third Universal Definition of Myocardial Infarction requires a detection of a typical rise and fall in serum cTn with at least one value above the 99th percentile of the upper reference limit (URL) and with at least one of the following: (I) Symptoms of ischemia, (II) new or presumed new significant ST-segment–T wave (ST–T) changes or new left bundle branch block (LBBB), (III) development of pathological Q waves, (IV) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality, and (V) identification of an intracoronary thrombus by angiography or autopsy. Values of cTn should be measured with a coefficient of variation of 10% or less [15].

The detection of abnormal cTn levels after myocardial injury occurs generally 2–4 h after the initial insult. The development of what is known as high-sensitivity assays has increased the sensitivity of cTn in the first few hours after coronary occlusion. It is possible that early, small and non-sustainable releases of cTn represent reversible injury mobilizing cytosolic or free cTn, while continuous and severe damage inducing cell death provokes membrane rupture with liberation of a structurally bound pool with longer detection periods. This concept could explain why brief episodes of ischemia, tachyarrhythmias, heart failure, takotsubo syndrome and even induction of mental stress can induce variable amounts of cTnI release.

The crucial role of cTn in the routine assessment of suspected myocardial infarction goes beyond diagnostic purposes. Elevation of cTn levels is an important independent prognostic marker as shown in several clinical trials and one meta-analysis [16–18]. Moreover, cTn is key in determining the choice of invasive or conservative strategies after ACS. The TACTICS-TIMI-18 trial enrolled 2200 patients with non-ST elevation myocardial infarction that were randomly assigned to an early invasive, with routine coronary angiography within the first 48 h or a more conservative approach, with only ischemia-driven revascularization. Abnormal cTnI helped to define the subgroup of patients who had a greater benefit from an early invasive management [19].

The definition of high-sensitivity cTn is not clearly established, but last generation assays can detect cTn in approximately 95% of normal individuals. Moreover, high-sensitivity cTn levels appear to be independent prognostic markers in elderly individuals and stable coronary artery disease [20–22]. Ongoing and future studies will help to establish whether cTn will move from a diagnostic tool almost exclusive of the acute setting to a valuable prognostic test also in office consultation.

Although cTn, especially cTnI, is highly specific for myocardial damage, they are not able to discern between ischemic or inflammatory or traumatic injury. Furthermore, there are several situations associated with cTn release that are not related to ACS (Table 1) [23].

Table 1
Causes of acute elevation of troponin in the absence of ACS.

Causes of acute elevation of troponin in absence of ACS	
1. Heart diseases	2. Others
Myocarditis	Hypotension/shock
Pericarditis	Pulmonary embolism
Tachyarrhythmia	Stroke
Acute heart failure	Acute aortic dissection
Radiofrequency catheter ablation	Sepsis
Cardiac contusion	Subarachnoid hemorrhage
Left ventricular hypertrophy	Acute lung edema
Cardiac Amyloidosis	Pulmonary hypertension
Electrical cardioversion	Chronic kidney disease
Heart surgery	Strenuous exercise
Percutaneous coronary intervention	Sympathomimetic drugs
Heart transplantation	Chemotherapy
Coronary vasospasm	
Electrical impulse of implantable cardioverter defibrillator	
Takotsubo cardiomyopathy	
Dilated cardiomyopathy	
Hypertrophic cardiomyopathy	
Endocarditis	

3.2. C-reactive protein (CRP)

Inflammation pathways play an important role in the pathogenesis of atherothrombosis and ACS [24]. CRP is an acute-phase inflammatory reactant marker that has been extensively studied as indicative of a higher cardiovascular risk among patients with established atherosclerosis. Ridker P et al. suggested that plasma concentration of CRP predicts the risk of future myocardial infarction and stroke [25]. Importantly, statins are capable of reducing CRP beyond cholesterol-lowering properties [26] and CRP could be a useful test to reclassify individuals considered at intermediate-risk for future cardiovascular complications.

ACS are commonly associated with elevated levels of CRP, probably reflecting widespread vascular inflammation. Several studies in non-ST elevation myocardial infarction have found that increased CRP values are independent prognostic markers of recurrent nonfatal myocardial infarction or cardiac death (GUSTO IV, PROVE IT-TIMI 22) [27,28]. In ST-elevation myocardial infarctions it might reflect the extent of myocardial injury. Despite some positive results, CRP has not been shown to be an independent predictor of events in all studies [29–31]. Given the current treatment of ACS, including double antiplatelet therapy, high intensity statin treatment and optimal revascularization strategies, the role of CRP in the routine prognostic assessment of ACS is not clear.

3.3. Cystatin-C

Cystatin C is a cysteine protease inhibitor involved in the catabolism of proteins. This protein is synthesized in all nucleated cells at a constant rate, and is freely filtered by the glomerulus with no reabsorption into the blood [32]. Although creatinine is the most used biomarker for the estimation of glomerular function, cystatin C is less influenced by other factors like diet, muscle mass, or body constitution [33]. Several studies have shown that cystatin C is more sensitive in identifying mild reductions of renal function than creatinine levels [34].

It is widely recognized that patients with renal impairment have a higher prevalence of cardiovascular disease with an associated higher mortality [35]. Considering the known prognostic impact of poor renal function in acute coronary syndrome patients, it seems reasonable to hypothesize that early stages of kidney dysfunction would provide additional prognostic information. Jernberg T. et al. were the first to demonstrate that measurement of cystatin-C substantially improves the early risk stratification of a large population with suspected or confirmed non-ST elevation ACS [36]. More recent studies confirm that cystatin-C concentration is independently correlated with cardiovascular risk, including myocardial infarction and cardiovascular death [37,38].

The utility of cystatin-C, instead of other renal function estimators, as a prognostic biomarker has been emerging in the past few years. However, it should be more fully explored in a wide spectrum of clinical scenarios, with current management strategies, before it becomes routine assessment.

4. Promising biomarkers in ACS

4.1. Copeptin

Copeptin is the C-terminal fragment of vasopressin precursor hormone (CT-proAVP) and is released together with vasopressin during precursor processing. The measurement of copeptin seems to be a clinically relevant method of reliably assessing AVP plasma concentrations, which cannot be determined directly in routine practice [39].

Copeptin is being evaluated both as a prognosis and diagnostic biomarker. Keller et al. tested whether determination of copeptin added diagnostic information to cardiac troponin in the early evaluation of patients with suspected myocardial infarction. In this study they analyzed levels of copeptin, cTnT, myoglobin, and creatine kinase-myocardial band, after 3 and 6 h of 1386 patients with suspected ACS. The results were that combined measurement of copeptin and cTnT on admission improved the sensibility of diagnosis of acute myocardial in the overall population and the combination of copeptin with a conventional cTnT provided a negative predictive value of 92.4% [40].

Results of the CHOPIN trial (Copeptin Helps in the early detection Of Patients with acute myocardial INfarction), have shown that adding copeptin to cTnI allowed safe rule out of AMI with a negative predictive value >99% in patients presenting early with a suspected ACS. In addition, the study suggests that the combination of abnormal copeptin and cTnI was an independent predictor of death at 180 days [41]. In the same line, Mockel M. et al. have demonstrated that patients who were troponin negative and also copeptin negative, using the initial blood sample, had virtually the same risk of having a major adverse cardiac event within 30 days (5.46%) as patients undergoing conventional serial blood samples to rule out myocardial infarction (5.50%) [42].

In conclusion, emerging data suggests that copeptin could provide additional value to cTn in the early rule-out patients presenting with suspected ACS.

4.2. Growth differentiation factor 15 (GDF-15)

GDF-15 is a member of the transforming growth factor beta cytokine superfamily that under physiologic conditions is only expressed by the placenta. GDF-15 plasma levels increase in response to stress and inflammation and it is involved in regulating apoptotic pathways needed for development, differentiation and tissue repair [43]. Focusing on the heart, GDF-15 is induced in the myocardium tissue after ischemia and for this reason it has been proposed as a biomarker of myocardial injury [44].

Several studies suggest that GDF-15 may be useful to risk stratification of patients presenting with symptoms of ACS. Schaub N et al. measured GDF-15, hs-cTn and BNP in 646 patients presenting to the emergency department with chest pain. GDF-15 predicted all-cause mortality independently and more accurately than hs-cTn and BNP [45]. Widera C. et al. determined that a single measurement of GDF-15 on admission of patients with NSTE-ACS markedly enhanced the predictive value of GRACE score [46].

Importantly, GDF-15 may be an important tool for identifying those patients that would benefit the most from an early invasive strategy in non-ST elevation-ACS. Wollert KC. et al., in a subgroup of FRagmin and Fast Revascularization during InStability in Coronary artery disease II (FRISC-II) trial, examined GDF-15 and other biomarkers and clinical parameters in patients included in. Patients presenting with highly elevated levels of GDF-15 (>1800 ng/l) in combination with cTn benefited from an invasive therapeutic strategy, while patients with lower levels of GDF-15 (<1200 ng/l) did not, even when presenting with ST-depression or cTnT >0.01 μg/L. Furthermore, elevated levels of GDF-15 were shown to be a strong independent predictor of death or recurrent myocardial infarction in patients treated with a conservative strategy instead of an invasive one. [47,48].

Although current data supports the potential role of GDF-15 as a diagnostic and prognostic biomarker in ACS, further prospective and randomized trials with contemporary treatment are needed to confirm these data.

4.3. Micro-RNAs

MicroRNAs (miRNAs) are non-coding RNA fragments of around 22 nucleotides with a key role in the regulation of mRNA coding for key proteins in the maintenance of cell integrity [49]. Over the past years, miRNAs have been postulated as important markers of different pathologic states, particularly the development of cancer-related processes [50,51]. Over 700 different human miRNAs have been described, although only a few of them have been detected and analyzed in AMI [52].

Myocardial infarction, as a damage and cell death process, sets in motion a number of genetic processes that aim repair and survival of the cardiomyocyte. Therefore, it seems intuitive to suggest that there would be changes in circulating levels of miRNA in the first few hours after beginning of symptoms and that it could be an extremely sensitive marker of AMI. van Rooij et al. described changes in miRNA expression in murine models during AMI [53]. More recently, D'Alessandra et al. analyzed plasma levels of miR-1, -133a, -133b, -499-5p, -122 and -375, in 17 healthy donors and 33 STEMI patients within few hours after the onset of myocardial infarction symptoms. Levels of miR-1, -133a, -133b, and miR-499-5p experienced a clear increase in the hours following infarction, while miR-122 and miR-375 experienced a drop in their plasma levels [54].

Up to date, approximately 20 miRNAs have been proposed as potential biomarkers of ACS. However, many of the studies have been carried out with small sample sizes and heterogeneous populations, leading to different results. Although miRNAs are promising candidates to an important role in the early diagnosis of myocardial infarction, more research is needed to determine its accuracy as a cardiac biomarker and its possible application in routine clinical practice.

5. Conclusion

Several biomarkers have been proposed as useful candidates to contribute to cTn as relevant tools for the diagnosis and risk stratification of myocardial infarction. The ideal biomarker should provide increased sensitivity especially over the first 3 h after onset of symptoms, greater precision regarding mechanisms of cardiomyocyte injury and sufficient prognostic information as to guide clinicians to the best management strategy. Until now, none of these novel biochemical tests is ready for prime time in routine clinical practice, but copeptin could be considered complementary to cTn for a rapid rule-out of patients presenting with compatible ACS symptoms. CRP or BNP values are more widely available, but despite providing additional refinement in risk stratification, it is doubtful that clinicians need its routine determination beyond traditional risk factors, medical history, electrocardiogram, cTn, stress test and coronary angiography. However, future studies should address possible contributions of these novel biomarkers and new advances in knowledge of myocardial damage and atherothrombotic pathways are eagerly awaited.

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