Conference Paper

Cardiovascular Biomarkers in ACS: State of the Art 2012

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In the setting of an acute coronary syndrome cardiac troponins are well established for the diagnosis of myocardial infarction. In particular, diagnostic protocols using high-sensitivity troponin assays are being recommended for earlier diagnosis of MI by the European Society of Cardiology (ESC) guidelines on the management of ACS without ST segment elevation. In addition to accurate detection of myocardial necrosis, cardiac troponins give complementary information on short- and long-term prognosis and facilitate the identification of patients who derive benefits from a more aggressive anticoagulation and/or early invasive therapy versus conservative therapy. Other cardiac biomarkers may help to improve earlier diagnosis or improve risk stratification. Their role is currently under investigation. The present state-of-the-art paper gives an overview on the role of cardiac troponins including recent recommendations on the use of high-sensitivity assays from the third version of the Joint ESC/ACCF/AHA/WHF infarct definition “Universal MI definition” and the ESC guidelines. In addition, an overview on the role of novel cardiac biomarkers in earlier diagnosis or risk stratification is provided.

1. Introduction

Coronary artery disease is one of the leading causes of death worldwide [1]. Better understanding of the pathomechanism of disease, use of more potent drugs, and improved diagnosis have helped to reduce CV mortality although total numbers of MI increase. Nowadays cardiac troponins are the preferred biomarkers for detection of myocardial cell necrosis and are essential for the diagnosis of myocardial infarction [2, 3]. The revised ESC/ACC definition of MI that had replaced the WHO definition of MI in the year 2000 [4] is now available in its third updated version [5]. This definition is supported by all major cardiology societies and by the WHO referred to as the third Universal MI definition. More recently, novel highly sensitive cTn assays are being increasingly used in clinical practice due to their superior analytical sensitivity allowing the detection of minute myocardial damage [6, 7]. Current ESC guidelines endorse earlier diagnostic algorithms using such hsTn assays [8]. However, increasing rates of patients with detectable cTn levels, not due to an ACS, also started to confuse clinicians [9]. This paper gives an overview on the present role of cTn and hsTn assays in diagnosis, risk

stratification, and guidance of therapy and provide a state-of-the-art overview on new promising biomarkers for earlier or rapid rule-out of MI and for prognostic assessment.

2. Universal MI Definition and Cardiac Troponin

Cardiac biomarkers play a central role for the diagnosis and management of patients with an ACS. It is well established that cardiac troponins are the preferred biomarkers for diagnosis of myocardial infarction due to their absolute cardiospecificity and due to their ability to detect minute cardiomyocyte necrosis [2, 3]. Accordingly, cardiac troponins have been implemented in contemporary definitions of MI [4, 5]. The third version of the redefinition of MI was published in the year 2012 [5]. In this updated version, cardiac troponin continues to be the preferred biomarker of myocardial necrosis. An elevation of cTn exceeding the 99th percentile of a healthy reference population is diagnostic for an MI, provided that cTn shows a rise and/or a fall signaling an acute rather than a chronic elevation and only in the presence of myocardial ischemia.

Criteria for MI (3rd Version of the Joint ESC/ACCF/AHA/WHF Infarct Definition). The term acute myocardial infarction (MI) should be used when there is evidence of myocardial necrosis in a clinical setting consistent with acute myocardial ischemia. Under these conditions any one of the following criteria meets the diagnosis for MI (adapted from [5]).

Detection of a rise and/or a fall of cardiac biomarker values (preferably cardiac troponin (cTn)) with at least one value above the 99th percentile 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 in the ECG,
- (iv) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality,
- (v) identification of an intracoronary thrombus by angiography or autopsy.

As compared to the second version of the Universal MI definition, the criteria for a context of myocardial ischemia have been extended. Now detection of an intracoronary thrombus on coronary angiography or autopsy has been added to the list of criteria that includes symptoms, ECG changes, new wall motion abnormalities, or detection of loss of viable myocardium. In addition, 5 subtypes of MI have been defined according to their putative pathomechanism [5]. Strict adherence to the diagnostic criteria of the third version of the MI definition ensures a proper interpretation of troponin results given that troponin is due to myocardial cell necrosis but not obligatory due to myocardial ischemia [10]. The list of conditions that may cause an acute or chronic elevation of troponin in the absence of myocardial infarction is seemingly endless [10]. Discrimination of a type II MI, that is, characterized by myocardial ischemia arising from an imbalance of oxygen demand and supply from myocardial injury unrelated to the myocardial ischemia, is difficult as myocardial ischemia may be involved in some cases, and the definite reason for myocardial injury remains illusive in many conditions.

3. High-Sensitivity Troponin Assays

In an attempt to improve precision of conventional cTn assays at the lower detection range, manufacturers refined their assays that are now able to detect more than 2-fold lower troponin concentrations with an acceptable imprecision of less than 10% at the 99th percentile [11]. Now, hsTn assays can measure cardiac troponin in the majority of healthy individuals [12]. Improved analytical sensitivity of cTn also enabled earlier diagnosis of MI and detection of more infarcts at the cost of a declining number of unstable angina [13]. Based on findings from large clinical trials, ESC guidelines for management of NSTEMI-ACS promote the use of hsTn assays

and recommend the implementation of an earlier rule-in and rule-out algorithm [8]. Accordingly, patients presenting with suspected ACS without ST-segment elevation need a cTn measurement on presentation. If cTn is still below the 99th percentile, retesting after 3 or 6 hours is recommended unless the time from the onset of symptoms to the presentation is longer than 6 hours [14]. An increase of cTn above the 99th percentile with a percent change of 50% or more qualifies for a diagnosis of NSTEMI. Smaller percent changes may signal a relevant differential diagnosis. It is anticipated that the majority of patients with suspected ACS will present with a baseline elevation of cTn [7]. Rule-in of NSTEMI requires repeat measurement of cTn to discriminate between a chronic and an acute change. By arbitrary convention, a change in either the direction of 20% or more serves as the kinetic criterion [14]. Patients with a very high cTn level on presentation have a high pretest probability of NSTEMI as a differential diagnosis is less likely [8]. These patients should undergo coronary angiography without an obligatory need to retest after 3 or 6 hours.

4. Earlier Detection of MI

One of the most attractive applications of hsTn assays is earlier rule-out of MI. While earlier guidelines recommended to repeat troponin testing 6 to 9 hours after presentation, the new algorithm recommends a repeat testing after 3 hours and optionally after 6 hours [8]. Study findings suggest that other earlier markers of ischemia such as myoglobin or heart type FABP do not provide additional information and thus may be obviated [15]. There is also emerging evidence that rule-out of an MI can be accomplished safely within 1 or 2 hours using a hsTn assay [16, 17]. Such protocols would accelerate diagnostic workup, reduce observation times in overcrowded chest pain units or EDs, and allow a cost-effective and safe discharge of patients and avoid unnecessary hospitalization. However, such algorithms need to be validated prospectively in broad unselected patient cohorts with suspected ACS [18].

5. Other Promising Biomarkers for Early Diagnosis

There is accumulating evidence indicating that copeptin, the stable fragment of vasopressin, can improve rapid rule-out of MI when measured together with a conventional [19, 20] or a hsTn assay [21]. Following an index event such as a small infarct copeptin is rapidly released from the hypothalamus and will be detectable in blood in patients with a later rise of cTn. Patients with a negative copeptin and cTn on presentation are unlikely to develop a NSTEMI at serial testing [19]. The performance of copeptin is excellent in combination with a conventional cTnT or cTnI assay where negative predictive value is >99% [19, 20]. The added benefit of copeptin to a hsTn assay is smaller but still significant [21].

6. Prognosis

An obstacle with hsTn assays is that the higher sensitivity results in a substantially higher rate of patients with

analytically true positive troponin results not due to ACS reflecting acute or chronic myocardial injury [22]. It may be challenging to discriminate between NSTEMI and noncoronary cardiac or extracardiac reasons of elevated cTn. Nevertheless, an elevated cTn is associated with an adverse outcome regardless whether the underlying reason is NSTEMI or non-ACS [23]. The reasons for troponin elevations in the absence of myocardial ischemia are not fully understood but may be associated with a higher burden of atherosclerosis [24], more complex coronary lesions [25], depressed LV function, associated cardiac comorbidities, and severely impaired renal function [26]. Thus, elevated cTn may represent a surrogate parameter integrating prognostic informations from associated diseases.

Instead of labeling an elevated cTn in the absence of MI as a “false positive” finding one should rather search for the underlying etiology in order to provide an early and specific therapy.

The use of high-sensitivity cTn assays has further improved risk stratification by detecting patients at risk who were previously not detected by conventional cTn assays including small MIs [27] and patients in earlier stages of chronic pulmonary hypertension [28] or acute and chronic heart failure [29].

In ACS several other biomarkers have been identified to provide independent and additive prognostic information to cTn. These biomarkers included markers of inflammation such as CRP, IL-6, and fibrinogen, markers of hemodynamic stress or volume overload, that is, natriuretic peptides or MR-proadrenomedullin [30, 31], and indicators of impaired renal function such as creatinine, estimated GFR, or cystatin [32]. Little is known about the added value of these biomarkers when hsTn is used instead of conventional cTn. Recently, the utility of 14 novel biomarkers for prognostic assessment in ACS patients with undetectable conventional cTn level was investigated [33]. Along with hsTn an independent prognostic information was conferred only by GDF-15 and MR-proadrenomedullin. In another study, copeptin not only improved rapid rule-out of emerging NSTEMI when copeptin was low but also helped to identify patients at higher risk for adverse outcomes if copeptin levels were high [34].

Use of additional biomarkers or a panel of biomarkers appears attractive for the better understanding of the pathophysiological process behind ACS or other acute diseases and for a refined risk stratification (Figure 1). However, current guidelines preclude any recommendations for routine use because the incremental value over highly sensitive troponin tests has not been evaluated yet [8].

7. Guidance of Therapy

Cardiac troponins have been shown to help in the identification of patients who might benefit from more aggressive antithrombotic or antiplatelet therapies and derive more benefits from an early invasive strategy. For the former, cTn is regarded as a surrogate of a vulnerable or ruptured plaque with subsequent activation of platelets and clot formation. Accordingly, benefits of low molecular weight heparin [35, 36], GP IIb/IIIa inhibitors [37], and triple antiplatelet

Biomarkers for diagnosis and risk stratification in ACS

“However, the incremental value—particularly over highly sensitive troponin tests—has not been evaluated, thereby presently precluding any recommendations for routine use”

ESC guidelines 2011

FIGURE 1: Recommendation of ESC guidelines 2011 on biomarkers for diagnosis and prognostic assessment in ACS (adapted from [8]).

therapy [38] were found to be largely restricted to patients with elevated cTn but in present those with normal cTn values. Regarding the need and timing of coronary angiography and coronary intervention, large randomized trials and a meta-analysis on 7 trials including 9,212 patients demonstrated that patients clearly derived benefits from an invasive strategy if a cardiac marker particularly cTn was elevated [39]. Although there is evidence that benefits from early invasive therapy and concomitant administration of GPIIb/IIIa inhibition may be achieved in patients with any detectable cTn level [37], inappropriate precision of conventional cTn assays precluded an unequivocal conclusion. Taking the lowest concentration that could be measured with appropriate precision showed a consistent benefit of triple antiplatelet therapy using aspirin, 600 mg clopidogrel, and abciximab for ACS patients with cTn values exceeding $0.03 \mu\text{g/L}$, that is, the 10% CV cutoff [38].

In contrast, the GUSTO IV trial found an excess of death among patients at low estimated risk characterized by a normal cTn and a NT-pro BNP below an optimal cutoff [32]. Whether patients with a normal hsTn will benefit from more potent antiplatelets or an early invasive strategy remained illusive until recently. In the PLATO trial [40] more than 18,000 patients with NSTEMI-ACS or STEMI were randomized to clopidogrel or ticagrelor and were allocated to an invasive or conservative strategy at the discretion of their physicians. Patients with hsTn levels below the 99th percentile value had a similar rate of the primary efficacy endpoint consisting of a composite of CV death, nonfatal MI, or stroke.

Other biomarkers, particularly markers of inflammation such as IL-6 have been investigated for their utility to guide the decision for an early invasive strategy [41]. The role of natriuretic peptides to guide invasive strategy has remained controversial due to conflicting study findings [42, 43].

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