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Conference Paper

Update on the Universal Definition of Acute Myocardial Infarction in the Light of New Data

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This Conference Paper is based on a presentation given by K. Thygesen at "Clinical Decisions in Acute Patients: ACS–POCT–Hypertension and Biomarkers" held from 19 October 2012 to 20 October 2012 in Berlin, Germany.

At the 2012 European Society of Cardiology (ESC) Conference in Munich, the updated Universal Definition of myocardial infarction was presented for the first time and was then published simultaneously in five medical journals (European Heart Journal, Circulation, Journal of American College of Cardiology, Nature Reviews Cardiology, Global Heart). Major changes in this updated version include the differentiation between myocardial ischemia and myocardial injury, which gives credit to the relatively large number of patients with troponin positive test results, especially when measured with high sensitivity assays, in patients without myocardial ischemia. Another important topic is the revised criteria for the diagnoses of acute myocardial ischemia related to percutaneous coronary intervention (PCI) and coronary arterial bypass grafting (CABG).

1. Introduction

The first clinical descriptions of myocardial infarction are only around 100 years old. From this first description it took some time until the first working group was set up by the World Health Organization (WHO) in 1959 to define the disease "acute myocardial infarction (AMI)" in order to study disease prevalence [1]. This definition was based on patient symptoms and ECG findings. Later definitions of the WHO described AMI as a combination of two of three characteristics: typical symptoms (i.e., chest discomfort), enzyme rise, and a typical ECG pattern involving the development of Q waves, but still myocardial infarction was mainly an ECG-based diagnosis [2]. Due to technological advances in the fields of more sensitive biomarkers and imaging techniques and due to a need for a more precise and comparable definition, The Joint European Society of Cardiology/American College of Cardiology Committee published its first consensus document for the redefinition of myocardial infarction in the year 2000 [3], with a more pronounced biochemical approach demanding an elevation of cardiac biomarkers before myocardial infarction could be diagnosed and a more prospective approach considering rather ST-T-changes than Q-wave development for categorization. With this definition, the "STEMI" was born.

The task force was then joined by the American Heart Association (AHA) and the World Health Federation to become the global task force for the definition of acute myocardial infarction.

This definition was updated by the same task force in 2007 [4], giving cardiac troponins a much higher significance than in the 2000 definition. Additionally, different types of myocardial infarction were defined. By now, cardiologists around the world had become used to using cardiac biomarkers and particularly troponin for the diagnosis of AMI. This year at the ESC, the task force presented their latest update on the universal definition of acute myocardial infarction [5].

This paper gives an overview on the updated definition and highlights and critically reviews the most important and prominent changes. The complete update was published simultaneously in 5 journals at the time of our symposium and was presented for the first time only a few weeks before.

2. Methods and Results

2.1. Universal Definition of Acute Myocardial Infarction Update. The general definition of acute myocardial infarction is a definition of the underlying pathology and remains unchanged. Acute myocardial infarction is thus defined as myocardial necrosis due to prolonged myocardial ischemia. Ideally, to diagnose the two components of the definition myocardial necrosis and myocardial ischemia, two different biomarkers, indicating each of these components, should be available. Unfortunately, while cardiac troponins are very specific markers of myocardial cell necrosis, good markers of ischemia are currently lacking. Thus, other criteria have to support the diagnosis of AMI. These basic criteria for the AMI diagnosis were not altered in the new definition, except for a small amendment regarding the identification of an intracoronary thrombus by angiography or autopsy, which was added as a relevant criterion. Table 1 shows the criteria for acute myocardial infarction and the definition for the different types of myocardial infarction as published in the 2012 definition [5, 6].

The recommendation for the use of biomarkers remained unchanged. Troponin I and T are the preferred markers for the diagnosis of AMI, but in countries where troponins are not available yet other markers like CK and CK-MB are also acceptable [7].

The most prominent changes in the new definition cover the distinction between myocardial ischemia and myocardial injury and the new criteria to define myocardial infarction in the setting of cardiac interventions like PCI and CABG.

2.1.1. Myocardial Injury versus Myocardial Ischemia. The distinction between injury and ischemia is important because troponin release, even though it is specific for cardiac tissue damage, can be caused by underlying mechanisms other than ischemia. Every injury of the myocardium results in necrosis of at least some myocardial cells, and therefore, causes a troponin release [8].

Thus, elevation of cardiac troponin first of all indicates myocardial necrosis with cell death. This cell death can be caused by myocardial ischemia and is then defined as myocardial infarction. In cases where the myocardial necrosis is unrelated to ischemia, the new definition speaks of myocardial injury. Myocardial injury can be caused by a variety of diseases and conditions which are listed in the task force update.

One way to distinguish myocardial ischemia from myocardial injury is the presence of biomarker dynamics [6, 9–11]. In the acute setting of myocardial ischemia, biomarker levels will change over time, and the definition thus requires a biomarker rise and/or fall. In chronic conditions and diseases causing myocardial injury, biomarker levels will be more continuously elevated. In these patients, even though troponin levels are elevated, patients should not be diagnosed

Table 1: Criteria for and different types of acute myocardial infarction as defined in Thygesen et al. 2012 [6].

Criteria for the Definition of Acute Myocardial Infarction
The term myocardial infarction (MI) should be used when there is evidence of myocardial necrosis in a **clinical setting** consistent with **acute myocardial ischemia**.
Detection of a rise or fall of cardiac biomarker values (preferably cardiac troponin) with at least one value above the 99th percentile URL together with at least one of the following: (i) symptoms of ischemia, (ii) new significant ST changes or LBBB, (iii) development of pathological Q-waves, (iv) imaging evidence, (v) intracoronary thrombus.
Type 1: Spontaneous myocardial infarction
MI related to atherosclerotic plaque rupture with resulting intraluminal thrombus in the coronary artery.
Type 2: Myocardial infarction secondary to an ischemic imbalance
MI where a condition other than CAD contributes to an imbalance between oxygen supply and demand.
Type 3: Myocardial infarction resulting in death when biomarkers are unavailable
Cardiac death with symptoms of myocardial ischemia and presumed new ECG changes but death occurring before biomarkers results are available or before biomarkers could rise.
Type 4a: Myocardial infarction related to PCI
MI associated with PCI arbitrarily defined by (i) an elevation of cTn >5 times the 99th percentile URL in patients with normal cTn baseline values, (ii) a rise of cTn >20% in patients with elevated baseline cTn values plus (i) symptoms suggestive of ischemia, (ii) new ischemic ECG changes, (iii) angiographic evidence, or (iv) imaging evidence.
Type 4b: Myocardial infarction related to stent thrombosis
MI related to stent thrombosis is detected by coronary angiography or autopsy in the—setting of myocardial ischemia plus (i) a rise or fall of cardiac biomarkers above the 99th percentile URL.
Type 5: Myocardial infarction related to CABG:
MI related to CABG is arbitrarily defined by (i) an elevation of cTn >10 times the 99th percentile URL in patients with normal cTn baseline values plus (i) new pathological Q-waves or LBBB, (ii) angiographic evidence, or (iii) imaging evidence.

with myocardial infarction but with myocardial ischemia in the setting of other underlying diseases.

The different etiologies of myocardial ischemia were classified as the different types of myocardial infarction. A spontaneous atherosclerotic plaque rupture causes the classic type 1 AMI, which is defined as "spontaneous myocardial infarction related to atherosclerotic plaque rupture, ulceration, fissuring, erosion, or dissection with resulting intraluminal thrombus in one or more of the coronary arteries leading to decreased myocardial blood flow or distal platelet emboli with ensuing myocyte necrosis."

In patients where there is an imbalance of oxygen supply and oxygen demand, which can be the case a many diseases and conditions, the definition speaks of type 2 myocardial infarction secondary to ischemic imbalance. Even though the definition is more explicit than in the 2007 publication, the description of this type of AMI was not finalized and still requires clearer criteria. Type 2 MI can occur in patients with stable coronary artery disease where other circumstances cause the supply-demand imbalance, but also in patients with endothelial dysfunction, vasospasm, or even completely normal coronary arteries. These patients should not be treated with antiplatelet medication, and it is important to be able to correctly diagnose this type of AMI.

2.1.2. Myocardial Infarction Related to Percutaneous Coronary Intervention (PCI) (4a) and CABG (4b). Type 4a AMI was discussed very intensely and controversially by the task force, and the result of these discussions is a markedly changed consensus definition. In the 2007 definition, MI 4a required a biomarker increase greater than 3 times the 99th percentile URL in patients with normal preprocedural troponin levels. In the updated version a 5-fold increase of cardiac biomarkers above the 99th percentile URL is regarded significant in the setting of PCI (Figure 1). In patients where the initial troponin is already elevated, a 20% change is required to define AMI type 4a. Additionally, after the new definition, MI 4a can only be diagnosed in patients with either symptoms suggestive of MI or new ischemic ECG changes or angiographic-imaging evidence of an MI. Any elevations in the setting of PCI below the 5-fold 99th percentile cutoff or without clinical evidence of ischemia should not be called myocardial infarction but myocardial injury.

In type 5 AMI associated with CABG, the biomarker cutoff for the diagnosis was changed from a 5-fold to a 10-fold 99th percentile increase (Figure 1). This, too, caused a controversial discussion. Both changes in type 4 and 5 definitions have to be seen in the light of the increasing use of high-sensitivity troponin assays which would have resulted in a very high percentage of patients with type 4 and 5 myocardial infarction when applying the 2007 definition.

2.1.3. Myocardial Infarction Related to Percutaneous Coronary Intervention (PCI) (4a), and CABG (5). Mainly in order to improve endpoint definition in clinical trials, a third type of intervention-related MI was added in the updated version, type 4c MI related to restenosis. This type caused a very controversial discussion in the task force, and it was decided not to add this type into the main section but to include it in the clinical trial section.

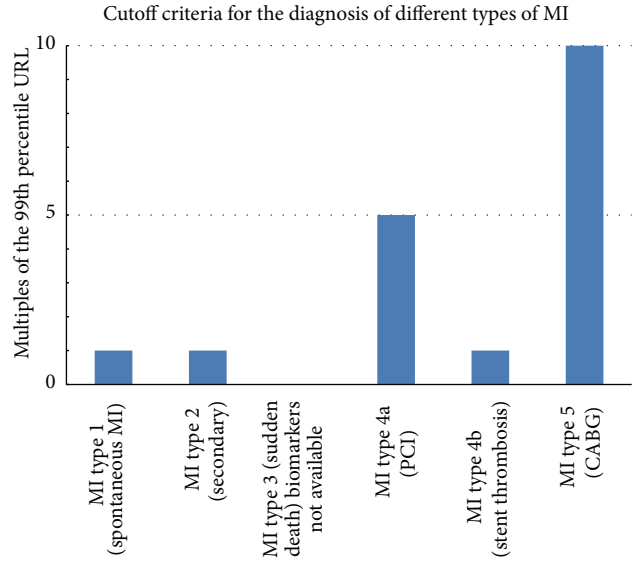

Figure 1: Cutoff criteria for the diagnosis of different types of myocardial infarction (PCI:percutaneous coronary intervention, CABG: coronary artery bypass graft).

Reinfarction and recurrent MI had already been defined in the 2007 definition but were now clarified, adapting the definition to that of the WHO. Reinfarction is defined as AMI that occurs within 28 days after the index MI. If an AMI occurs after these 28 days, it is termed recurrent MI.

2.1.4. Age-and Gender-Dependent ECG Changes. An important change in the new definition is the introduction of gender-and age-dependent criteria for ST-elevations in the ECG. This is especially important in women where ST-elevations have been found to be less prominent than those in men [12]. The criteria for ST-depression remain unchanged.

3. Discussion

The new definition has a more academic, sophisticated approach than previous versions and may be challenging for clinicians who actually have to diagnose and treat patients with acute myocardial infarction. There are three main take-home messages every clinician should be aware of.

(i) Try to distinguish myocardial injury and myocardial infarction. There has been a tendency to interpret any troponin elevation as myocardial infarction. This is not correct. Troponin should never stand alone but should always be seen in the clinical setting. Many troponin elevations, especially below certain cut-points and troponin elevations without a rise and fall, are myocardial injuries and should be called this.

(ii) It has been made more difficult to diagnose procedure-related myocardial infarction after some criticism with the older definitions that the

cutoffs had been set too low. Still, the prognostic meaning of postinterventional troponin rises remains unclear due to the lack of data [13].

(iii) Clinicians should be aware of the different types of myocardial infarction, but the discussions around this classification are probably not finished yet. In particular type 2 myocardial infarction needs to be discussed more, and, criteria which allow to distinguish between this type of MI and myocardial injury have to be set up.

3.1. Clinical Documentation/ICD-Codes. One important issue is the translation of the new definition into the clinical documentation in ICD codes which has an impact on reimbursement. In particular myocardial injury has no match in the ICD-coding system.

Currently ICD-11 is being prepared by the WHO, but the process of developing and implementing a new coding system is usually very slow. Even if the WHO was approached with a request to include myocardial injury into their system, it would not be available for several years.

Additionally, the WHO is usually quite critical towards biochemical markers because they are relatively expensive and cannot be afforded by all countries in the world. The WHO, therefore, still recommends using symptoms and ECG for the diagnosis of AMI. The WHO has accepted the definitions set up by the global task force but clearly stated that they only apply to wealthier countries [7]. Therefore, it may be a very long way until myocardial injury is represented in the ICD-coding system.

3.2. Impact on the Number of AMI Diagnoses. After the new definition of myocardial infarction and the use of troponin was introduced in the year 2000, the numbers of myocardial infarctions increased [14–16]. This caused some controversies, but today there is a high acceptance of using troponin for the diagnosis of AMI. Now, with the increasing use of high-sensitivity troponin, the same effect can be expected again [17]. This will probably lead to discussions but needs to be weighed up against the chance of a standardized and well-established patient management. Increase of the diagnosis of AMI is not just an artificial increase of something that is not really there but is a true reflection of the disease prevalence and will be accompanied by an improvement of morbidity and mortality.

3.3. Need for New Biomarkers. There is a real clinical need for biochemical markers of ischemia. Some years ago, researchers set their hope on IMA, but the marker was too sensitive and identified too many patients with alleged ischemia.

Another clinical need is a biochemical marker of thrombosis, which would make diagnosis of a myocardial infarction type 2 much easier.

Additional biomarkers like copeptin, which are as such very unspecific, might help adding information on rule-out and identify severe cases earlier [18].

References

[1] "EPIDEMIOLOGY of hypertension and coronary-artery disease," *British Medical Journal*, vol. 2, no. 5145, p. 182, 1959.

[2] E. Rapaport, R. Bernard, and E. Corday, "Nomenclature and criteria for diagnosis of ischemic heart disease. Report of the Joint International Society and Federation of Cardiology/World Health Organization Task Force on standardization of clinical nomenclature," *Circulation*, vol. 59, no. 3, pp. 607–609, 1979.

[3] J. S. Alpert, E. Antman, F. Apple et al., "Myocardial infarction redefined—a consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction," *European Heart Journal*, vol. 21, no. 18, pp. 1502–1513, 2000.

[4] K. Thygesen, J. S. Alpert, and H. D. White, "Universal definition of myocardial infarction," *European Heart Journal*, vol. 28, no. 20, pp. 2525–2538, 2007.

[5] K. Thygesen, J. S. Alpert, A. S. Jaffe et al., "Third universal definition of myocardial infarction," *European Heart Journal*, vol. 33, no. 20, pp. 2551–2567, 2012.

[6] K. Thygesen, J. Mair, E. Giannitsis et al., "How to use high-sensitivity cardiac troponins in acute cardiac care," *European Heart Journal*, vol. 33, no. 18, pp. 2252–2257, 2012.

[7] S. Mendis, K. Thygesen, K. Kuulasmaa et al., "World Health Organization definition of myocardial infarction: 2008–09 revision," *International Journal of Epidemiology*, vol. 40, no. 1, pp. 139–146, 2011.

[8] A. S. Jaffe, L. Babuin, and F. S. Apple, "Biomarkers in acute cardiac disease: the present and the future," *Journal of the American College of Cardiology*, vol. 48, no. 1, pp. 1–11, 2006.

[9] A. H. B. Wu, A. S. Jaffe, F. S. Apple et al., "National academy of clinical biochemistry laboratory medicine practice guidelines: use of cardiac troponin and B-type natriuretic peptide or N-terminal proB-type natriuretic peptide for etiologies other than acute coronary syndromes and heart failure," *Clinical Chemistry*, vol. 53, no. 12, pp. 2086–2096, 2007.

[10] F. S. Apple, L. A. Pearce, S. W. Smith, J. M. Kaczmarek, and M. M. Murakami, "Role of monitoring changes in sensitive cardiac troponin I assay results for early diagnosis of myocardial infarction and prediction of risk of adverse events," *Clinical Chemistry*, vol. 55, no. 5, pp. 930–937, 2009.

[11] A. H. B. Wu, "Interpretation of high sensitivity cardiac troponin I results: reference to biological variability in patients who present to the emergency room with chest pain: case report series," *Clinica Chimica Acta*, vol. 401, no. 1-2, pp. 170–174, 2009.

[12] P. W. Macfarlane, "Age, sex, and the ST amplitude in health and disease," *Journal of Electrocardiology*, vol. 34, supplement, pp. 235–241, 2001.

[13] A. Prasad and J. Herrmann, "Myocardial infarction due to percutaneous coronary intervention," *New England Journal of Medicine*, vol. 364, no. 5, pp. 453–464, 2011.

[14] R. W. Yeh, S. Sidney, M. Chandra, M. Sorel, J. V. Selby, and A. S. Go, "Population trends in the incidence and outcomes of acute myocardial infarction," *New England Journal of Medicine*, vol. 362, no. 23, pp. 2155–2165, 2010.

[15] N. I. Parikh, P. Gona, M. G. Larson et al., "Long-term trends in myocardial infarction incidence and case fatality in the national heart, lung, and blood institute's Framingham heart study," *Circulation*, vol. 119, no. 9, pp. 1203–1210, 2009.

[16] V. Salomaa, H. Koukkunen, M. Ketonen et al., "A new definition for myocardial infarction: what difference does it make?" *European Heart Journal*, vol. 26, no. 17, pp. 1719–1725, 2005.

[17] T. Reichlin, R. Twerenbold, M. Reiter et al., "Introduction of high-sensitivity troponin assays: impact on myocardial infarction incidence and prognosis," *American Journal of Medicine*, vol. 125, no. 12, pp. 1205–1213, 2012.

[18] J. Searle, O. Danne, C. Müller, and M. Mockel, "Biomarkers in acute coronary syndrome and percutaneous coronary intervention," *Minerva Cardioangiologica*, vol. 59, no. 3, pp. 203–223, 2011.