

Defining acute myocardial infarction

Kai M. Eggers, MD, PhD

Department of Medical Sciences, Cardiology, Uppsala University, Uppsala, Sweden

Correspondence: Kai M. Eggers, Department of Medical Sciences, Cardiology, Uppsala University, S-751 85 Uppsala, Sweden
E-mail: kai.eggers@ucr.uu.se

Abstract

The definition of myocardial infarction (MI) has evolved over the last decades, from rather simple criteria in the first World Health Organization documents, to a five-category classification in the 2007 and 2012 universal definitions. In particular, the introduction of sensitive and cardiac-specific biomarkers in clinical practice has had a clear impact in this regard, as well as a more differentiated perspective on the pathophysiology of myocardial injury, in particular in the setting of invasive coronary procedures. The implications of the revisions of the definition criteria of MI have been important as they have affected our perception of MI as a disease state. In addition, they have contributed to an improved identification of at-risk patients warranting customized treatment regimens. However, several aspects of the definition criteria of MI are still debated and will likely be subject to modifications in forthcoming updates of the universal definition. ■ *Heart Metab.* 2015;67:34-38

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The evolution of the criteria to define myocardial infarction

The criteria to define myocardial infarction (MI) have been modified several times over the last decades, and this has had important clinical, epidemiological, and research implications. The aim of this review is to summarize the evolution of the diagnostic criteria of MI and the consequences of these changes on clinical management.

The first guidelines to define MI were published by the World Health Organization (WHO) in 1959 (*Figure 1*).¹ A revision, the first universal definition of MI, followed in 1979.² These guidelines emphasized the presence of two of three possible criteria: clinical symptoms compatible with MI, typical electrocardiography (ECG) changes, and elevated circulating biomarkers of myocardial injury, which at that time were

mainly total creatine kinase (CK) and myocardial CK (CK-MB).

Following the introduction of cardiac troponin (cTn) into clinical practice, it soon became clear that “unstable angina” patients, ie, those with normal CK-MB, had an increased cardiac risk if cTn was elevated.³ Considering this issue, together with concerns over the limited cardiac specificity of CK-MB, the National Academy of Clinical Biochemistry (NACB) issued, in 1999, the first guidelines for the use of cardiac markers in acute coronary syndrome (ACS) that included cTn.⁴ At that time, two cutoff values were suggested: the 97.5th percentile of a healthy reference population to define unstable angina with minimal myocardial injury, and a receiver operator characteristics (ROC) curve-derived cutoff for definite MI. However, this approach maintained at its core the insensitive and nonspecific criteria

Abbreviations

ACC: American College of Cardiology; **ACS:** acute coronary syndrome; **CK:** creatine kinase; **cTn:** cardiac troponin; **ESC:** European Society of Cardiology; **MI:** myocardial infarction; **WHO:** World Health Organization

predicated on CK-MB and was, especially from today's perspective, suboptimal.

In 2000, the Joint European Society of Cardiology (ESC)/American College of Cardiology (ACC) Committee redefined the diagnostic criteria of MI. Given its superior sensitivity and specificity, cTn was recommended as the biomarker of choice with a significant rise and/or fall in serially measured concentrations and at least one value above the 99th percentile. In addition, the presence of either ischemic symptoms, ischemic ECG changes, or coronary artery intervention was required.⁵ Importantly, these criteria lowered the diagnostic cTn concentration cutoff from a ROC-derived value and increased it from the 97.5th percentile recommended by the NACB.⁴ The 99th percentile was chosen as it is approximately three standard deviations from the mean, which was thought to protect against false-positive values. The ESC/ACC Committee also stated that the acceptable imprecision at the 99th percentile should be $\leq 10\%$, because of concerns regarding the analytic variability in biochemical determinations.

The ESC/ACC consensus document had several major clinical implications. First, the use of cTn levels became the cornerstone of the diagnosis of MI. Second, the increased sensitivity of cTn relative to CK-MB resulted in a 30% to 80% increase in the prevalence of MI⁶⁻⁸ and a more reliable identification

of at-risk patients^{6,7} in need of more aggressive therapies.⁹ Finally, the call for rigorous and high analytical precision has driven assay technical development.

Subsequently, the ESC/ACC Committee was expanded to include representatives from the American Heart Association and World Heart Federation. In 2007, this task force updated the universal definition of MI.¹⁰ Again, a combination of clinical symptoms, cardiac biomarkers (preferably cTn), and ischemic ECG changes were central to the definition of MI. However, because of pathological, clinical, and prognostic differences, several subtypes of MI were defined. Type 1 MI is caused by a sudden rupture of a coronary plaque. Type 2 MI, which accounts for up to 25% of all MI,^{8,11} is secondary to a myocardial oxygen supply/demand imbalance due to tachycardia, hypertension, etc, with or without underlying coronary artery disease. Also included in this category are patients who might have coronary endothelial dysfunction or vasospasm. Type 3 MI is the result of coronary thrombosis with sudden death before biomarker results are available. Type 4 MI is caused by complications of percutaneous coronary intervention (PCI): type 4A is a periprocedural MI, while type 4B is related to stent thrombosis. Type 5 MI is related to complications of coronary artery bypass surgery.

Interestingly, the universal definition did not considerably affect the prevalence of MI.⁸ However, the introduction of high-sensitivity cTn assays in the early 2010s resulted in a shift from unstable angina to MI and an increased prevalence of low-level cTn elevations in the setting of ischemic imbalance and critical illnesses (ie, type 2 MI).^{12,13} This was considered in the third universal definition of MI from 2012.¹⁴ In this revision, the classification into five MI subtypes was retained (Table 1). What was new was the reintroduction of the term myocardial injury, meant as an increase in cTn in nonischemic conditions such as acute ventricular stretch (Figure 2). Also, type 4A MI was defined more stringently, ie, by an elevation of cTn values >5 times the 99th percentile within 48 hours after PCI together with clinical or ECG criteria. The cTn cutoff was chosen acknowledging that small, not necessarily prognostically adverse, cTn elevations may be detected even after uncomplicated PCI.¹⁵ Similarly, the cTn cutoff to define type 5 MI was raised from 5 to 10 times the 99th percentile within 48 hours, acknowledging that biomarker elevations may occur as part of the surgical procedure itself. Finally,

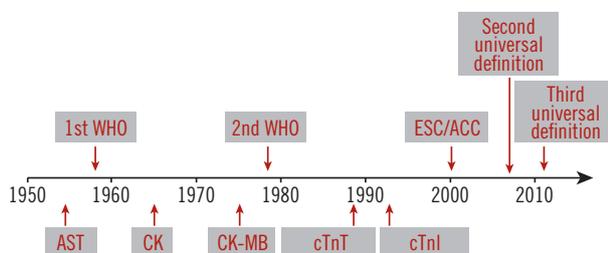


Fig. 1 Timeline displaying the introduction of diagnostic classifications of myocardial infarction and new circulating biomarkers of myocardial injury.

Abbreviations: ACC, American College of Cardiology; AST, aspartate transaminase; CK, creatine kinase; CK-MB, myocardial creatine kinase; cTn, cardiac troponin; ESC, European Society of Cardiology; WHO, World Health Organization.

Figure courtesy of Nick L. Mills

MI type	Definition	cTn cutoff
Type 1	Spontaneous MI	>99th percentile
Type 2	MI secondary to myocardial ischemic imbalance	>99th percentile
Type 3	MI resulting in sudden death before biomarker results are available	-
Type 4A	MI related to percutaneous coronary intervention	>5 times the 99th percentile*
Type 4B	MI related to stent thrombosis	>99th percentile
Type 5	MI related to coronary artery bypass grafting	>10 times the 99th percentile

Plus one additional criterion:

- Symptoms of myocardial ischemia;
- New ischemic ECG changes† or new left bundle branch block;
- Development of pathological Q-waves on the ECG;
- Identification of intracoronary thrombus by angiography or autopsy;
- Imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality.

Table 1 Third universal definition of myocardial infarction (MI). * If baseline cTn levels are elevated and are stable or falling, a rise of >20% is needed. † New or presumably new significant ST-segment/T-wave changes.

Abbreviations: cTn, cardiac troponin; ECG, electrocardiography; MI, myocardial infarction.

Data based on reference 14.

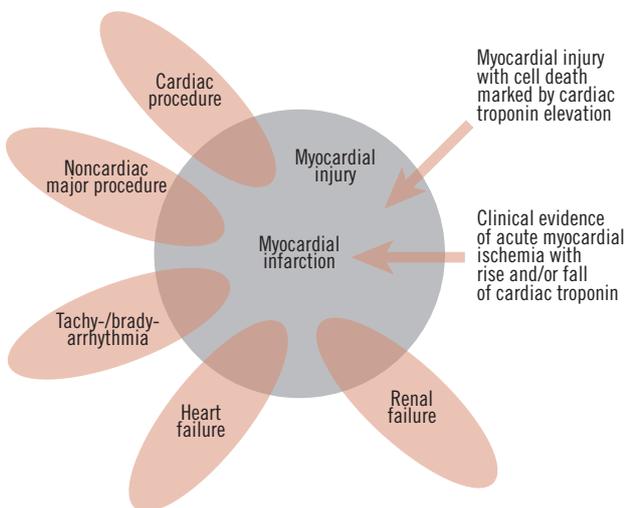


Fig. 2 Distinction between myocardial injury and myocardial infarction (MI) according to the third universal definition. This illustration shows various clinical entities, for example, renal failure, heart failure, tachy- or bradyarrhythmia, cardiac or noncardiac procedures that can be associated with myocardial injury with cell death marked by cardiac troponin (cTn) elevation. However, these entities can also be associated with MI in case of clinical evidence of acute myocardial ischemia with a rise and/or fall of cTn levels.

After reference 14: Thygesen K et al. J Am Coll Cardiol. 2012;60(16):1581-1598. © 2012, European Society of Cardiology, American College of Cardiology Foundation, American Heart Association, Inc., and the World Heart Federation. Published by Elsevier Inc. All rights reserved.

a new category of type 4C MI (MI due to restenosis $\geq 50\%$ after an initially successful PCI) was created for reporting in clinical trials.

The evolution of the definitions of MI from rather simple criteria in the first WHO documents toward a differentiated five-category classification would not have been possible without medical and technical improvements. In particular, the availability of more sensitive and cardiospecific biomarkers has had a clear impact in this regard, but also the increasing use of invasive treatment strategies and a more differentiat-

ed perspective on the pathophysiology of myocardial injury. This has contributed to a better classification of patients, which, for example, is illustrated by the improved identification of cTn-positive high-risk acute coronary syndrome (ACS) following the introduction of the ESC/ACC criteria in 2000.⁶⁻⁹ Another example of improvement is the MI classification introduced in the 2007 universal definition.¹⁰ With this, it has become clear that type 2 MI is not a benign epiphenomenon in the setting of illnesses other than ACS, but rather an indicator of myocardial vulnerability and increased risk.¹¹

Steps ahead

Still, several aspects of the criteria to define MI are far from settled and there is much discussion regarding this. Below are listed some of the issues that are debated and might be subject to modification in the forthcoming updates of the universal definition:

1. There is a need to define the cTn cutoff in a more precise manner. The currently recommended 99th percentile lacks biological plausibility since cardiovascular risk is continuous and starts to rise at concentrations below this dichotomous cutoff.¹⁶ In addition, the 99th percentile is highly dependent on the composition of the population from which it is derived,¹⁷ which is the reason why corrections for age, gender, and/or race may be needed. In part, this could be mitigated if the populations used to derive the 99th percentile were defined and standardized.
2. The universal definition does not suggest criteria to define a significant change in cTn levels. Absolute

changes usually provide greater diagnostic utility than relative changes,¹⁸ but baseline concentrations and the biologic variability of cTn need to be taken into account.

3. The universal definition recommends cTn measurements at presentation and after 3 to 6 hours,¹⁴ but shorter sampling protocols using high-sensitivity assays have been suggested for ruling out MI.¹⁹ On the other hand, cTn levels may increase late,²⁰ which is the reason why sampling at >6 hours could be necessary if there is a high index of clinical suspicion.
4. The distinction between type 1 and type 2 MI may be challenging and requires careful judgment as the approaches to clinical management are different. In many cases, where there is a clear non-ACS-related cause of myocardial ischemia, eg, hypotension due to perioperative bleed, this distinction is not difficult. However, it may be complicated in other conditions, eg, cTn increase in acutely decompensated ischemic cardiomyopathy. This is a common source of anxiety among clinicians. Often, a subsequent test for inducible ischemia is helpful to decide whether there is underlying coronary artery disease or not, and to guide treatment and follow-up.
5. Even the distinction between MI and myocardial injury may cause problems. In general, a diagnosis of MI should not be made if the clinical setting is not of acute ischemia. However, there are conditions in which multifactorial causes for cTn elevation may exist, eg, septic shock with hypotension in a patient with known coronary artery disease.¹⁴ Nevertheless, the distinction between type 2 MI and myocardial injury with necrosis usually has less immediate therapeutic implications.
6. As outlined above, the cTn cutoffs to define type 4 and type 5 MI have been modified in the third universal definition.¹⁴ As biomarker elevations may occur as part of the interventions themselves, the discussion on this topic will likely continue.

Summary and outlook

The evolution of the criteria to define MI has had a major impact on the clinical management of patients with ACS. Still, there are issues that need further discussion and clarification. Further work is also required in relation to appropriate diagnosis-related coding so

that different types of MI can be reimbursed accordingly. It is thus evident that the diagnostic classification of patients with ACS is dynamic and will likely continue to evolve. ■

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