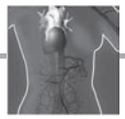
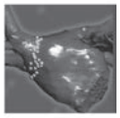


Redefining myocardial infarction following coronary revascularization: time for clarity?

"*A compilation of the best medical evidence to date does not support use of the universal definition as the optimal criterion to identify clinically relevant post-percutaneous coronary intervention myocardial infarction events.*"

KEYWORDS: cardiac biomarkers ■ coronary revascularization ■ myocardial infarction

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Myocardial infarction (MI) after coronary revascularization is very common and, at this time, we still do not have a clear definition. The universal definition for MI was published in 2007 and was revised in 2012. However, it has a lot of shortcomings and has not been correlated with clinical outcomes or prognostic significance. This definition used a postprocedural biomarker for defining percutaneous coronary intervention (PCI)-related MI (type 4a) and coronary artery bypass grafting (CABG)-related MI (type 5). cTn was recommended as the biomarker of choice, even though the prognostic significance of cTn is less well validated than CK-MB.

Assessment of post-PCI and -CABG biomarkers that are strongly related to subsequent adverse patient outcomes is clearly worthwhile. However, applying undue significance to periprocedural biomarker elevations without prognostic relevance will result in unintended consequences on patient care, and physician and systems quality evaluation. Elevated cardiac biomarkers, even after successful revascularization, can lead to prolonged hospital stay and unnecessary interventions. This, in turn, will result in iatrogenic complications and increased cost burden. Adoption of a MI definition not based on a meaningful correlation with adverse consequences in clinical trials may result in false conclusions and treatment options. Hence, it is time to determine a clearer and better definition that is clinically more relevant.

In 2007, a 'universal definition' for MI following coronary revascularization was proposed [1] and was recently revised in 2012 [2]. In this document, a PCI-related MI (type 4a) was defined as an increase in cTn to more than five-times the 99th percentile of the upper reference limits during the first 48 h following PCI (in patients with normal baseline cTn concentrations), plus either: evidence of prolonged ischemia as demonstrated by prolonged chest pain; ischemic ST-segment changes or new pathological Q waves; angiographic evidence of a flow-limiting complication; or imaging evidence of new loss of viable myocardium or new regional wall motion abnormality. MI associated with CABG (type 5) was defined as an increase in cTn to more than ten-times the 99th percentile upper reference limits during the first 48 h following CABG (in patients with normal baseline cTn concentrations), plus either: new pathological Q waves or new left bundle branch block; angiographically documented new graft or new native coronary artery occlusion; or imaging evidence of new loss of viable myocardium or new regional wall motion abnormality. cTn was considered the preferred biomarker for the detection of myonecrosis. However, the writing committee also noted that these definitions were arbitrarily chosen and of uncertain clinical relevance, and not grounded on substantial scientific evidence linking their occurrence to subsequent adverse outcomes [1].

Prior studies have reported that only preprocedure cTn elevations are correlated with subsequent mortality. In an analysis at the Mayo Clinic, an abnormal pre-PCI cTnT level independently predicted death; however, the occurrence of PCI-related myonecrosis did not, whether defined by more than three-times elevation in cTn or CK-MB [3]. In a separate study, baseline cTn >upper limits of normal (ULN) in patients undergoing elective PCI was an independent predictor of in-hospital death or MI [4]. Thus, interpretation of post-PCI biomarker elevations may be erroneous if baseline levels are not assessed.

Post-PCI MI (defined as cTn I elevation to more than three-times upper reference limits) was predicted by treatment of type B2/C lesions

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and a thin-cap fibroatheroma [5]. Other studies have demonstrated a strong association between postprocedural cardiac biomarker release and large atherosclerotic plaque burden, large thrombus burden, coronary calcification and lesion eccentricity, as detected by angiography, intravascular ultrasound imaging and optical coherence tomography [6–8]. Hence, the association between post-PCI biomarker elevation and mortality may be an epiphenomenon [9,10].

> *"The rationale for requiring a ≥ten-times increase in cardiac biomarkers for coronary artery bypass grafting versus a ≥five-times increase for percutaneous coronary intervention as recommended in the 2012 universal definition is not clearly substantiated."*

On the other hand, angiographically evident complications are not always associated with sizable post-PCI biomarker elevations, and biomarker elevations can occur without angiographic complications [11]. Muschart *et al.* identified that an angiographic cause of post-PCI CK-MB >ULN is present in only 60% of cases (side branch occlusion, distal embolization, slow flow or no-reflow, intraprocedural stent thrombosis or coronary perforation) [11]. Whether periprocedural biomarker elevations of any level correlate with subsequent adverse events when angiographic complications are absent is questionable.

Hence came the concept of 'clinically relevant MI'. A compilation of the best medical evidence to date does not support use of the universal definition as the optimal criterion to identify clinically relevant post-PCI MI events. This led to the 'expert consensus document' from the Society for Cardiovascular Angiography and Interventions. Moussa *et al.* summarized this very well in this document as described below [12]. Clinically relevant MI after coronary revascularization is defined as:

- In patients with normal baseline CK-MB, peak CK-MB to ≥ten-times ULN 48 h after PCI is used as a criterion. A lower threshold (≥five-times ULN) may be accepted in the patient in whom new pathologic Q waves in ≥2 contiguous leads (or new persistent left bundle branch block) develop post-PCI. If CK-MB levels are unavailable and cTn are normal at baseline, a reasonable cTn (I or T) value is measured 48 h after PCI and a cTn of ≥70-times ULN or ≥35-times ULN, with new pathologic Q waves in ≥2 contiguous leads or new persistent left bundle branch block is valid. This is based on the 7:1 troponin:CK-MB ratio noted to have approximate similar clinical implications [13];
- Accurately diagnosing post-PCI MI in the setting of elevated baseline biomarkers is problematic and requires assessment of serial biomarker levels. The following recommendations are made to diagnose post-PCI MI in acute coronary syndrome patients in whom the baseline level has not returned to normal. First, in patients with elevated cTn (or CK-MB) in whom the biomarker levels are stable or falling, there should be a new CK-MB elevation by an absolute increment of ≥ten-times ULN (or ≥70-times ULN for cTn I or T) from the previous nadir level. Second, in patients with elevated cTn (or CK-MB) in whom the biomarker levels have not been shown to be stable or falling, there should be a further rise in CK-MB or troponin beyond the most recently measured value by an absolute increment of ≥ten-times ULN in CK-MB or ≥70-times ULN in cTn plus new ST-segment elevation or depression in addition to signs consistent with a clinically relevant MI, such as new onset or worsening heart failure or sustained hypotension. Chest pain alone is not specific enough for substantial myonecrosis to be used as a criterion;
- The rationale for requiring a ≥ten-times increase in cardiac biomarkers for CABG versus a ≥five-times increase for PCI as recommended in the 2012 universal definition is not clearly substantiated [2]. Nonetheless, as a working definition, this threshold is supported to diagnose a clinically relevant MI post-CABG. However, CK-MB is the preferred biomarker, and if a cTn threshold must be used, ≥70-times is reasonable. The use of post-CABG ECGs, indices of hemodynamic instability and imaging studies demonstrating new wall motion abnormalities have been suggested to complement biomarker elevations post-CABG to improve specificity.

The currently recommended definition of a 'clinically relevant MI' is not perfect; however, it is clinically more useful and is based on the best scientific evidence presently available. Utilization of this definition in future randomized clinical trials of PCI would provide an opportunity to validate its premise. Additional investigation should focus on determining the threshold at

which cTn measurements have prognostic value after revascularization and whether there are important differences between cTnT and cTnI.

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