

## Clinical Decision Making

# Consideration of a New Definition of Clinically Relevant Myocardial Infarction After Coronary Revascularization: An Expert Consensus Document From the Society for Cardiovascular Angiography and Interventions (SCAI)

Issam D. Moussa,<sup>1\*</sup> MD, Lloyd W. Klein,<sup>2</sup> MD, Binita Shah,<sup>3</sup> MD, Roxana Mehran,<sup>4</sup> MD, Michael J. Mack,<sup>5</sup> MD, Emmanouil S. Brilakis,<sup>6</sup> MD, John P. Reilly,<sup>7</sup> MD, Gilbert Zoghbi,<sup>8</sup> MD, Elizabeth Holper,<sup>9</sup> MD, and Gregg W. Stone,<sup>10</sup> MD

Numerous definitions have been proposed for the diagnosis of myocardial infarction (MI) after coronary revascularization. The universal definition for MI designates post procedural biomarker thresholds for defining percutaneous coronary intervention (PCI)-related MI (type 4a) and coronary artery bypass grafting (CABG)-related MI (type 5) which are of uncertain prognostic importance. In addition, for both MI types cTn is recommended as the biomarker of choice, the prognostic significance of which is less well validated than CK-MB. Widespread adoption of a MI definition not clearly linked to subsequent adverse events such as mortality or heart failure may have serious consequences for the appropriate assessment of devices and therapies, may affect clinical care pathways, and may result in misinterpretation of physician competence. Rather than employing an MI definition sensitive for small degrees of myonecrosis (the occurrence of which, based on contemporary large-scale studies, are unlikely to have important clinical consequences), it is instead recommended that a threshold level of biomarker elevation which has been strongly linked to subsequent adverse events in clinical studies be used to define a “clinically relevant MI.” The present document

<sup>1</sup>Mayo Clinic, Jacksonville, Florida

<sup>2</sup>Division of Cardiology, Department of Medicine, Rush University, Chicago, Illinois

<sup>3</sup>Division of Cardiology, New York University School of Medicine, New York

<sup>4</sup>Mount Sinai Medical Center, New York

<sup>5</sup>Baylor HealthCare System, Dallas, Texas

<sup>6</sup>VA North Texas Healthcare System and UT Southwestern Medical School, Dallas, Texas

<sup>7</sup>Oschner Clinic, New Orleans, Louisiana

<sup>8</sup>Stern Cardiovascular Foundation, Memphis, Tennessee

<sup>9</sup>Medical City Dallas Hospital, Dallas, Texas

<sup>10</sup>Columbia University Medical Center, New York Presbyterian Hospital and The Cardiovascular Research Foundation, New York City, New York

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Additional Supporting Information may be found in the online version of this article.

\*Correspondence to: Issam D. Moussa, MD, FSCAI, FACC, Division of Cardiovascular Diseases, Mayo Clinic, 4500 San Pablo Road, Jacksonville, FL 32224. E-mail: moussa.issam@mayo.edu

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introduces a new definition for "clinically relevant MI" after coronary revascularization (PCI or CABG) which is applicable for use in clinical trials, patient care, and quality outcomes assessment. © 2013 Wiley Periodicals, Inc.

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## INTRODUCTION

Numerous definitions for the diagnosis of MI after coronary revascularization are in use [1]. A standardized MI definition would provide uniformity for comparing clinical trial results, for assessing patient outcomes and for guiding quality improvement initiatives. In 2007, a "universal definition" for MI following coronary revascularization was proposed [2] and recently revised in 2012 [3]. In this document, a PCI-related MI (type 4a) was defined as an increase in cTn to  $>5\times$  the 99th percentile of the URL during the first 48 hr following PCI (in patients with normal baseline cTn concentrations), plus either (i) evidence of prolonged ischemia as demonstrated by prolonged chest pain, or (ii) ischemic ST segment changes or new pathological Q waves, or (iii) angiographic evidence of a flow limiting complication, or (iv) 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  $>10\times$  the 99th percentile URL during the first 48 hr following CABG (in patients with normal baseline cTn concentrations), plus either (i) new pathological Q waves or new LBBB, or (ii) angiographically documented new graft or new native coronary artery occlusion, or (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality. cTn were considered the preferred biomarker for 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 [2,3].

Assessment of post-PCI and post-CABG biomarkers that are strongly related to subsequent adverse patient outcomes is undoubtedly worthwhile. Conversely, applying undue significance to peri-procedural biomarker elevations without prognostic relevance may have unintended consequences on patient care, physician and systems evaluation of PCI quality, and for the development and appropriate assessment of new therapies. Uncertainty among healthcare providers regarding the interpretation of elevated cardiac biomarkers after successful revascularization can lead to prolonged hospital stay and unnecessary diagnostic or therapeutic interventions which may result in iatrogenic complications and increased costs. Lastly, adoption of a MI def-

inition not based on meaningful correlation with adverse consequences in clinical trials may result in false conclusions regarding the relative risk-benefit ratio of comparative therapeutic strategies. The present working group was thus tasked by SCAI Publication committee with developing a definition of peri-procedural MI which, based on the preponderance of the best scientific evidence, has clearly been shown to have important prognostic significance, hence termed a "clinically relevant" MI. This document is endorsed by SCAI publication committee, SCAI board of trustees, and SCAI executive committee.

The present document will emphasize the definition of MI after PCI procedures, but also refer to MI after CABG. The present consensus recommendations are based heavily on data from the largest, contemporary studies. The reader should view this document as the best attempt of the writing committee to inform and guide clinical practice and clinical trial design in an area where the evidence base, while substantial, is evolving.

## Pathophysiology of Peri-Procedural Myonecrosis, and the Potential for Confounding

The pathophysiology of myocardial necrosis following revascularization procedures is multifactorial [4–8] (Table SI, Supporting Information Electronic Appendix). The mechanisms and risk factors associated with post-PCI myonecrosis vary according to the definition of myonecrosis (e.g., troponin vs. CK-MB elevations, and the selected threshold for abnormality) and the patient population studied. Lee et al. [6] reported that a post-PCI MI (defined as cTn I elevation to  $>3X$  URL) was predicted by treatment of type B2/C lesions and a thin-cap fibroatheroma as assessed by optical coherence tomography. Other studies have shown a strong association between post-procedural cardiac biomarker release and large atherosclerotic plaque burden, large thrombus burden, coronary calcification, and lesion eccentricity, as detected by angiography and intravascular ultrasound imaging [7–9]. As the extent and complexity of coronary atherosclerosis is also an independent predictor of mortality after PCI [10,11], the association between post-PCI biomarker elevation and mortality may be an epiphenomenon; that is, the linkage is explained by the impact of the extent of atherosclerosis and lesion complexity on mortality, not the biomarker

elevation itself [12]. Thus, multivariable analysis incorporating both clinical and angiographic variables, along with biomarker elevations is necessary to determine whether the biomarker elevation per se is an independent correlate of mortality.

Angiographically evident complications are not always associated with sizable post-PCI biomarker elevations, and biomarker elevations can occur without angiographic complications [5,13]. Muschart et al. [5] identified an angiographic cause of post-PCI CK-MB >ULN (sidebranch occlusion, distal embolization, slow flow or no-reflow, intraprocedural stent thrombosis, or coronary perforation) in only 60% of cases. Whether periprocedural biomarker elevations of any level correlate with subsequent adverse events when angiographic complications are absent is questionable. Among 5,850 patients from six stent trials, even large biomarker elevations (CK-MB >8x ULN) had no prognostic impact unless associated with overt angiographic complications, questioning the relevance of isolated measures of myonecrosis [14]. The frequency of peri-procedural MI depends on the type of cardiac biomarker being measured (cTn vs. CK-MB), the frequency and timing of biomarker determinations, and the threshold that defines a MI [15]. Moreover, in most clinical studies, the upper range of cardiac biomarkers has been defined as a multiple of the ULN of the local laboratory assay. In contrast, the universal definition recommends evaluating biomarker elevations based on the 99th percentile limit of the reference value distribution [99th upper reference limit (URL)] [2,3], which is an even more sensitive measure. However, use of the URL is problematic because most assays do not have the sensitivity to consistently measure cTn in the blood of apparently healthy individuals, with a high proportion of the values being below the method's detection limit. Moreover, the 99th URL for cTn can vary depending on the reference population used, and its sample size. A marked difference can also be observed between the 99th URL obtained using plasma versus that obtained with serum. Finally, interferences with cTn measurement may occur with assays having increased analytical sensitivity [16]. As a result of these limitations, most laboratories have established a normal reference range defined as the set of values within which 95% of the normal population falls. Most prior studies have used this locally derived ULN when examining the prognostic relevance of CK-MB and troponin elevations.

### Importance of Pre-Procedure Cardiac Biomarker Elevation

Prior studies in which pre-PCI and post-PCI cTn elevations were analyzed have reported that only pre-

procedure cTn elevations are correlated with subsequent mortality (Table SII, Supporting Information Electronic Appendix). In an analysis of 5,487 patients undergoing nonemergent PCI at the Mayo Clinic [17], an abnormal pre-PCI cTnT level independently predicted death (median follow-up of 28 months), but the occurrence of PCI-related myonecrosis did not, whether defined by >3x elevation in cTn or CK-MB. In a separate study, baseline cTn was >ULN in 6.0% of 2,382 patients undergoing elective PCI, and was an independent predictor of in-hospital death or MI [18]. Thus, interpretation of post-PCI biomarker elevations may be erroneous if baseline levels are not assessed.

The accurate diagnosis of post-PCI MI is challenging among patients with baseline biomarker elevations. The 2012 universal definition states that "If the baseline cTn values are elevated and are stable or falling, then a rise of >20% is required for the diagnosis of a type 4a MI, as with reinfarction" [3]. These recommendations were based on recent data from the TRITON-TIMI 38 which suggest that, when PCI is delayed after MI until biomarker concentrations are falling or have normalized, re-elevation of cardiac biomarker values may have long-term significance [19]. The diagnosis of peri-PCI MI in this study, however, was preferentially based on CK-MB measures, and residual confounding cannot be excluded, as discussed in the next section. As such, the prognostic relevance of post-PCI biomarkers in the patient with a recent ACS have not been sufficiently validated to be applied clinically.

### cTn Versus CK-MB Elevation After Coronary Revascularization

cTn is a more sensitive and specific biomarker for myonecrosis than is CK-MB [20,21], and CK-MB is no longer measured at some institutions. This transition was made prior to thorough understanding of the prognostic implications of cTn elevations after coronary revascularization. Numerous studies have suggested a stronger association with post-PCI CK-MB and subsequent cardiovascular events than with cTn elevation (Table SIII, Supporting Information Electronic Appendix). Furthermore, the greater sensitivity of cTn for myonecrosis markedly increases the rate of type 4a MI. Among 4,930 patients undergoing elective coronary stenting, MI occurred in 7.2% using a CK-MB criteria of  $\geq 3x$  ULN and in 24.3% using a cTn criteria of  $\geq 3x$  ULN [22]. Lastly, changes in myocyte membrane permeability resulting from prolonged myocardial ischemia and other causes is sufficient for the release of cTn from the free cytosolic pool of myocytes without structural damage, explaining troponin elevations during rapid atrial pacing, supraventricular

tachycardia and noncardiac conditions, including exercise and renal disease [23].

The recommendation to use cTn rather than CK-MB and a cutoff of 3x the 99th percentile URL for the diagnosis of post-PCI MI in the original universal definition of MI was described as arbitrary by the authors [2]. The revised universal definition has raised the cTn cutoff to 5x the 99th percentile URL and added the requirement for clinical, ECG or angiographic changes for the diagnosis of post-PCI MI, likely increasing the specificity for MI [3]. Although these revisions are a step in the right direction, they are still admittedly arbitrary and do not sufficiently weigh the contemporary evidence base from which the criteria for a “clinically relevant MI” (one associated with an adverse prognosis) should be derived.

The relationship between biomarker elevations after revascularization and mortality is controversial, and the evidence base for this association has evolved over the last 15 years. When analyzed as a continuous variable above a threshold, a small incremental risk with cardiac biomarker elevation is noted (Table SIII, Supporting Information Electronic Appendix). However, this type of analysis is misleading because it lumps large biomarker elevations with small elevations. When analyzed in categories of incrementally increasing biomarker elevations, most contemporary PCI studies have reported associations between peri-procedural myonecrosis and mortality only for very large infarcts (Table SIII, Supporting Information Electronic Appendix). Among 7,147 patients undergoing PCI at Washington Hospital Center, 37.3% had a post-PCI CK-MB >ULN; however, only Q-wave MI or non-Q-wave MI with a peak CK-MB of >8x ULN correlated with increased 2-year mortality [24]. Among 3,478 patients undergoing stent implantation at the Cleveland Clinic, post-PCI CK-MB >ULN was detected in 24%; only CK-MB >10x ULN was significantly associated with increased 1-year mortality [25]. In the EVENT registry ( $n = 6,347$ ), only CK-MB  $\geq 50$  mg/ml ( $\sim 10x$  ULN) was associated with increased 30-day and 1-year mortality after nonemergent PCI [26]. In the 3,687 patient SPIRIT IV trial, CK-MB >3x ULN and cTn >3x ULN were present in 5.4% and 19.7% of stented patients, respectively; there was no relationship between any level of either biomarker and 2-year mortality, even >10x ULN [27]. Some have argued that small peri-procedural MIs will only have clinical impact with long-term follow-up. However, there was no relationship between protocol-defined MI and 5-year mortality among 5,467 patients with ACS in whom PCI was performed from three randomized trials [28].

The TRITON-TIMI-38 investigators did report a relationship between type 4a MI (defined as CK-MB

>3x URL on two samples or >5x on a single sample) and 6-month cardiovascular mortality [19]. However, this risk was not adjusted for the complexity of underlying CAD or treated lesions. Similarly, multivariable analysis to account for recent MI, unstable angina, thrombotic or complex lesions, vein graft intervention, and various device usages was not performed in many of the earlier studies examining the relationship between peri-procedural biomarker elevation and mortality. As previously discussed, mortality after CK-MB elevation may reflect the underlying extent of atherosclerosis and lesion complexity requiring treatment rather than the biomarker elevation per se [12]. Similarly, procedural urgency and multivessel PCI is more common in patients with small post-PCI cTn elevations, suggesting complex and extensive atherosclerosis as underlying the mortality associated with microinfarcts rather than minor myocardial injury [29]. The association of low-level biomarker elevations with mortality in early studies was always difficult to reconcile with traditional concepts relating large infarctions and depressed global cardiac function as major determinants of prognosis. Conversely, nearly all large-scale, contemporary studies have shown that only a substantial amount of myonecrosis, typically associated with CK-MB >10x ULN or new Q-wave infarction, is required to adversely impact survival.

The requirement for a large biomarker increase to signify a clinically relevant MI after PCI contrast with type I (spontaneous) MI, in which even minor elevations of cTn have repeatedly and strongly been associated with high rates of death and subsequent MI during follow-up [17]. The adverse prognosis following type I MI is not only due to the immediate impact of myocardial injury, but also reflects the consequences of plaque rupture occurring in an uncontrolled setting. Multifocal plaque instability and persistent systemic inflammation are also often present and increase the risk of future events [30–32]. Conversely, peri-procedural myonecrosis is induced by a single procedure in a controlled setting, and in most cases its consequences (if any) are immediately addressed.

### Insight From Cardiac Magnetic Resonance Imaging Studies

cMRI is increasingly being used to evaluate the extent of coronary hypoperfusion and myonecrosis [33,34]. Large compared to small or absent cMRI defects are strongly associated with subsequent mortality [33]. cMRI studies have demonstrated poor discrimination of cTn elevations for myocardial injury. Using late gadolinium enhancement (LGE), Lim et al. [35] reported the sensitivity, specificity and positive



predictive value of cTn I-defined MI  $>3x$  the 99th percentile URL to be 100, 22, and 19%, respectively. The analogous findings using CK-MB-defined MI  $>3x$  the 99th percentile URL were 60, 93, and 60%, respectively, demonstrating that cTn is overly sensitive and identifies many patients without objective evidence of cMRI-detected myocardial injury. While small levels of cTn elevation may represent myonecrosis not detectable by cMRI, the prognostic significance of such small elevations has not been demonstrated. The authors further reported that changing the cTn I threshold for MI diagnosis to  $40x$  the 99th percentile URL would greatly enhance specificity (93%) without reducing sensitivity (100%). This  $\sim 13x$  bioequivalence ratio of cTn:CK-MB is even greater than the  $\sim 7$ -fold ratio reported from the EVENT registry in which a cTn threshold  $>20x$  ULN was associated with similar mortality rates as a  $>3x$  CK-MB increase [22]. These data confirm that very different thresholds for CK-MB and cTn after PCI must be considered to represent similar levels of myonecrosis.

### Recommendation for a Definition of “Clinically Relevant MI” After Coronary Revascularization

#### Patients with normal baseline cardiac biomarkers.

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. Rather, most contemporary studies support a post-PCI elevation of CK-MB to  $\geq 10x$  ULN as being clinically relevant. While there may be some incremental value of identifying very small post-PCI infarcts, specifically those that occur with angiographically evident complications, more study is required in this regard, with angiographic core laboratory verification of events. Similarly, almost all clinical studies to date have reported the impact of biomarker elevation in relation to a multiple of the ULN, not the 99th percentile of the URL. Thus, absent such studies, a clinically relevant MI occurring in the post-PCI period should be defined as that resulting in a CK-MB  $\geq 10x$  ULN. A lower threshold ( $\geq 5x$  ULN) may be accepted in the patient in whom new pathologic Q-waves in  $\geq 2$  contiguous leads (or new persistent LBBB) develop post-PCI, although further study is required to validate this threshold in the setting of new Q-waves.

A threshold post-PCI level of cTn above which long-term prognosis is affected has not been established, and thus CK-MB is strongly preferred to assess clinically relevant post-PCI MI events. If CK-MB levels are unavailable, a reasonable cTn (I or T) value to substitute to diagnose a type 4a MI would be cTn of  $\geq 70x$  ULN, based on the 7:1 troponin:CK-MB ratio

noted to have approximate similar clinical implications [22]. As discussed, this 7:1 ratio is a conservative estimate when examining the results from imaging studies [35]. Thus, in patients with normal baseline cTn and without an acute coronary syndrome (ACS) (i.e., rising biomarker levels are not suspected), a clinically relevant MI post-PCI is diagnosed by a new biomarker elevation of CK-MB to  $\geq 10x$  ULN or cTn (I or T) to  $\geq 70x$  ULN (or by CK-MB to  $\geq 5x$  ULN or cTn to  $\geq 35x$  ULN plus the development of new pathologic Q-waves in  $\geq 2$  contiguous leads or LBBB).

**Patients with elevated baseline cardiac biomarkers.** Accurately diagnosing post-PCI MI in the setting of elevated baseline biomarkers is problematic, and depends on whether the peak level has been documented. This requires assessment of serial biomarker levels. Often, however, cardiac catheterization is performed after only a single biomarker level is obtained, or when serial biomarkers show continued escalation, in which case diagnosing post-PCI MI on the basis of biomarker levels alone is impossible. Thus, based on the thresholds determined from large-scale studies in which baseline biomarkers were normal, the following recommendations are made to diagnose post-PCI MI in ACS patients in whom the baseline level has not returned to normal: (1) 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  $\geq 10x$  ULN (or  $\geq 70x$  ULN for cTn I or T) from the previous nadir level; (2) 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  $\geq 10x$  ULN in CK-MB or  $\geq 70x$  ULN in cTn plus new ST-segment elevation or depression *i* 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. We acknowledge, however, that further studies are required to refine the best diagnostic criteria in patients with elevated baseline biomarkers.

These criteria are summarized in Table I. Practical recommendations of a clinically relevant definition of MI for assessment of cardiac biomarkers after PCI, its use as a quality of care indicator, and its impact on clinical trial design are discussed in the electronic appendix.

### Post-CABG Myocardial Infarction

Applying the 2007 universal definition of post CABG MI (type 5), 42–82% of patients have cardiac biomarker

**TABLE I. Definition of Clinically Relevant MI After Both PCI and CABG Procedures**

1. In patients with normal baseline CK-MB	The peak CK-MB measured within 48 hours of the procedure rises to $\geq 10x$ the local laboratory ULN, or to $\geq 5x$ ULN with new pathologic Q-waves in $\geq 2$ contiguous leads or new persistent LBBB, OR in the absence of CK-MB measurements and a normal baseline cTn, a cTn (I or T) level measured within 48 hours of the PCI rises to $\geq 70x$ the local laboratory ULN, or $\geq 35x$ ULN with new pathologic Q-waves in $\geq 2$ contiguous leads or new persistent LBBB.
2. In patients with elevated baseline CK-MB (or cTn) in whom the biomarker levels are stable or falling	The CK-MB (or cTn) rises by an absolute increment equal to those levels recommended above from the most recent pre-procedure level.
3. In patients with elevated CK-MB (or cTn) in whom the biomarker levels have not been shown to be stable or falling	The CK-MB (or cTn) rises by an absolute increment equal to those levels recommended above plus new ST-segment elevation or depression plus signs consistent with a clinically relevant MI, such as new onset or worsening heart failure or sustained hypotension.

elevation  $\geq 5x$  the URL [36,37], but only 4–7% have the additional electrocardiographic evidence needed to meet the definition of post-CABG MI [38,39]. In the 2012 revised version of the universal definition the threshold for diagnosis of post CABG MI (type 5) was increased to  $>10x$  the 99th percentile of the URL from a normal baseline cTn value and in addition requires either (i) new pathologic Q-waves or new LBBB, or (ii) angiographically documented new graft or new native coronary artery occlusion, or (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality [3]. The implications of this change on the frequency and prognostic implications of post-CABG MI are unclear.

Although some studies have suggested that only large myocardial biomarker elevations after CABG are clinically important [40–42], others have demonstrated that even modest CK-MB elevations after CABG may be associated with increased mortality [43–48]. Most recently, a large patient-level meta-analysis demonstrated a doubling of short- and long-term mortality in patients in whom cardiac biomarker measurements within 24 hr after CABG rose to  $\geq 4$ – $5x$  ULN [49]. After multivariable adjustment, 30-day mortality was significantly increased in patients with a post-CABG CK-MB of  $>5x$  ULN and with a cTn  $>40x$  ULN; an exponential rise in mortality was seen with  $>40x$  and  $>100x$  increases in CK-MB and cTn above the ULN, respectively. Additional studies have suggested that early biomarker release (occurring within 1 hr post-CABG) may be a meaningful predictor of in-hospital mortality [50], while elevation in later samples (with 48 hr post-CABG) appear to be a stronger predictor of long-term mortality [51].

Modest-sized studies utilizing cMRI suggest that 28–44% of patients post CABG have detectable myonecrosis [50–52]. These studies have shown a moderate correlation between post-CABG cardiac biomarker elevation and the extent of new myocardial necrosis observed by LGE. Moreover, these studies have dem-

onstrated that new areas of LGE after CABG have greater prognostic impact when accompanied by biomarker elevation of  $\geq 5x$  ULN compared to  $<5x$  ULN.

Similar to the post-PCI population, the majority of the studies have evaluated the prognostic significance of post-CABG cardiac biomarker elevations using CK-MB. cTn measurements may be an overly sensitive marker of myocardial necrosis in this setting. Remppis et al. have shown that cTn release from nonstructurally bound cytosolic pools may lead to systemic troponin elevations without cardiomyocyte injury [53]. “Washout” of this cytosolic component of troponin, secondary to surgery-induced increased cell permeability without cellular death, could result in cTn rise in the first few hours after surgery without irreversible myocardial injury.

The rationale for requiring a  $\geq 10x$  increase in cardiac biomarkers for CABG versus a  $\geq 5x$  increase for PCI as recommended in the 2012 universal definition is not clearly substantiated [3]. Nonetheless, as a working definition we support this threshold to diagnose a clinically relevant MI post CABG. However, CK-MB is the preferred biomarker, and if a cTn threshold must be used,  $\geq 70x$  is reasonable. Thus, the recommendations for the preferred biomarker type and threshold after PCI and CABG are harmonized (Table I). While not currently recommended as part of this definition (given the absence of data), 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. Additional studies in this regard are warranted.

## LIMITATIONS AND FUTURE DIRECTIONS

The currently recommended definition of a clinically relevant MI, while admittedly imperfect, is based on the best scientific evidence presently available. Nonetheless, we acknowledge the need for further research,

and revision of this definition as new data becomes available. In particular, given the greater specificity of cTn for cardiac myonecrosis compared to CK-MB, additional investigation should focus on determining the threshold at which cTn measurements have prognostic value after PCI and CABG (and whether in this regard there are important differences between cTnT and cTnI).

One of the greatest barriers in interpreting the current data is the lack of patient-level, vessel-level and lesion-level characteristics, making it difficult to attribute post-PCI biomarker elevations to adverse events rather than representing a surrogate marker of higher risk patients. Future research should consider the relationship between plaque burden, coronary anatomy and complex intervention on the incidence of periprocedural MI. Until the issues surrounding diagnosis and prognosis associated with peri-procedural myonecrosis and adverse events can be resolved, our ability to effectively risk-stratify and optimally manage patients undergoing coronary revascularization will remain limited, and evaluation of the utility and cost-effectiveness of new therapies will be imperfect. It is our belief that the use of the definition of clinically relevant MI introduced in this document is a first step toward addressing these issues [54–99].

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