Troponins are recommended as the biomarkers of choice for the detection of myocardial infarction (MI) by the Universal Definition. This is well accepted for the diagnosis of type 1 or spontaneous MI, in which any elevation in the setting of ischemia is required but not for the diagnosis of type 4a or MI associated with percutaneous coronary intervention (PCI), in which an isolated 3× the upper reference limit elevation is required. Creatine kinase MB (CKMB) is widely favored because a number of studies support a relationship between CKMB elevation after PCI and long-term mortality with the cut-point appearing to be about 8 to 10× elevation of CKMB.\footnote{Standing Joint Committee for Clinical Pathology. International Federation for Clinical Chemistry (IFCC) Web-site, 2012.}

In a meta-analysis of 4 studies with 2359 patients undergoing PCI, increases in troponin of >3 times upper reference limit were found in 14.5% and were associated at 18-month follow-up with increased events (death, MI, repeat target vessel PCI, and coronary artery bypass grafting) (odds ratio [OR], 2.25; 95% confidence interval [CI], 1.26–4.00).\footnote{McDermott AC, et al. Am Heart J 2009; 158: 17–24.} However, none of the studies used a 99th percentile cutoff with a sensitive troponin assay to define a normal baseline.

The situation is complex because PCI may reduce the risk of death in high-risk patients, and the risk of a small amount of myocardial injury related to PCI may be balanced by the success of the PCI. On the other hand, PCI in a low-risk patient, if associated with myocardial injury, may be associated with an adverse prognosis. Furthermore, increased biomarker release may be a trade-off for optimal stent implantation and related to the amount of underlying atherosclerosis. The prognostic importance of isolated biomarker level elevations remains controversial, with several studies showing that only elevation of pre-PCI biomarkers and not post-PCI levels affect survival.\footnote{White HD, et al. Am J Cardiol 2009; 103: 554–61.}

In this issue of Circulation: Cardiovascular Interventions, Pervaiz and colleagues\footnote{Pervaiz S, et al. Circ Cardiovasc Interv 2012; 5: 142–145.} report from the SPIRIT IV (Clinical Evaluation of the XIENCE V Everolimus Eluting Coronary Stent System) trial, where they randomly assigned 3687 patients with stable coronary artery disease to undergo stenting with either everolimus- or paclitaxel-eluting stents. Serial CKMB or troponin levels were obtained before and after stenting. The primary objective was to evaluate the Universal Definition, using either troponin or CKMB (3× upper limit of normal, ULN) versus a historic protocol definition based on 2× elevation of CK with elevated CKMB. Troponins were elevated at baseline in 8.8%. Protocol MI occurred in 58 patients (1.6%) and Universal Definition MI in 287 patients (7.8%).

There were 69 deaths at 2.3 years: none in patients with a protocol MI, 4 in patients with a Universal Definition MI, and 65 in patients without an MI. No association was present between periprocedural MI and mortality by either definition.

A detailed analysis of the correlation of CKMB and troponin and relative value of each biomarker is not possible from this data set because both biomarkers were not collected systematically and troponins were only available in 30% of patients. Using the Universal Definition, CKMB levels were elevated >3× in 5.4% and troponins elevated in 18.7%. The confidence limits for the association of troponins with mortality are wide and include a 64% increase in mortality (OR, 0.60; 95% CI, 0.22–1.64).

The troponins used were not defined in this study. There are >20 different troponin assays, some of which are not "clinically useful" or guideline-compliant.\footnote{Rump RM, et al. Am J Cardiol 2008; 101: 11F–15F.} Results may have been different if higher-sensitivity troponin assays had been used.

The low mortality rate was probably due to a combination of excellent stenting, high rates of medical treatment, and perhaps lower-risk patients. It would take many thousands of patients to show that a small loss of myocytes is prognostically adverse with such excellent outcomes.

In this analysis, the 99th percentile, as recommended by the Universal Definition, was not available for CKMB or troponins; as in most trials, the ULN, as defined by the local investigators, was used. Different sites, despite using the same assays, may define different cut-points that may differ from the manufacturer’s recommendations and that may be an order of magnitude 10× different. Use of a value at the 10% coefficient of variation, which is higher than the 99th percentile value, will have a decreased prognostic effect.\footnote{White HD, et al. Am J Cardiol 2009; 103: 554–61.}

The manufacturer’s 99th percentile should be used as recommended by the Universal Definition, which is available on the International Federation for Clinical Chemistry (IFCC) Web-
Importance of a Stable Biomarker Baseline

As mentioned above, it has been controversial as to whether troponin release after PCI carries any prognostic relevance if the baseline level is not stable. In a recent study, 37% of patients undergoing elective PCI had elevation of troponins at baseline. When cardiac biomarkers are rising before PCI, the curve of biomarker release may overlap with the curve of biomarker release after an ischemic complication of PCI, and the ability to discriminate between the curves is limited. Indeed, it may be impossible to distinguish rises due to the PCI from the original myocyte necrosis, and the Universal Definition states that type 4a MI cannot be assessed when biomarkers are rising or unknown at the time of PCI.

In a recent analysis from the TRITON (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel) trial, which required patients with elevated baseline biomarkers to have stable or falling levels and a new 50% rise, there was an association between type 4a MI as defined by 3X CKMB elevation and cardiovascular mortality at 180 days of 3.2% (adjusted HR, 2.4; 95% CI, 1.6–3.7). However, because of the lower sensitivity and late rise of CKMB as compared with troponins, an unstable baseline may not have been detected.

Criteria for a New Definition

The Universal Definition for type 1 or spontaneous MI requires elevated troponin levels in the setting of ischemia. The diagnosis is based on the pathophysiology, and there is no requirement for the diagnosis to have prognostic significance. Type 4a MIs have less of a mortality risk than spontaneous MIs, and there is a clamoring for the definition to have prognostic importance; thus, there is a need for the definition to have a clinically relevant mortality risk. This can be achieved in several ways: requiring associated complications, by reverting to CKMB, or raising the troponin cut-point.

Need for Associated Ischemia or Angiographic Complications

The definition of type 4a MI should be symmetrical with the definitions for type 1 and type 5 requiring similar ischemic symptoms, ischemic ECG changes, or imaging abnormalities. Chest discomfort is common even after a successful PCI, and symptoms must be standardized and similar to those required for a type 1 MI, for example, ≥20 minutes of ischemic chest discomfort or an ischemic surrogate. The ECG and imaging requirements to be similar should require ≥0.5 mm ST depression and new loss of viability.

Myocardial necrosis can result from ischemia associated with PCI complications such as side branch occlusion, distal embolization of thrombus or plaque, poor flow, and coronary dissection. It would seem reasonable to require these ischemic complications as well as biomarker elevation to make the biomarker elevations clinically relevant. However, there are no studies able to inform as to what the risk is when these factors are present.

Some studies have noted that type 4a MIs are only associated with increased mortality when they are unsuccessful or associated with the development of Q waves. In a pooled analysis of 6 stent trials, increased mortality was confined to unsuccessful procedures defined as final diameter stenosis >50%, TIMI flow <3, dissection, repeat revascularization, or stent thrombosis within 24 hours.

In a study of 10,315 patients, 55% of whom underwent atherectomy, the development of Q waves was the most powerful predictor of death. However, the development of Q waves is rare after PCI, and they take several days to develop. In the CHAMPION PLATFORM study, they occurred in only 0.2% of patients undergoing PCI.

Why Use Troponins Instead of CKMB?

There are number of reasons to use troponins rather than CKMB. The variability in CKMB mass assays is considerable, with 2- to 3-fold variability, whereas troponins are more sensitive and specific markers of myocyte necrosis than CKMB and have nearly absolute specificity for myocardial tissue. Troponins, and particularly high-sensitivity troponins, increase earlier than CKMB. Because they are more sensitive, troponin levels may be elevated in acute coronary syndromes (ACS) due to multiple microemboli with the areas of myocyte necrosis being too small to be seen on MRI, whereas CKMB elevations that are larger may be associated with large confluent scars. Troponins have been shown to be better for prognosis than CKMB in ACS, and troponins identify patients at higher risk despite CKMB levels being normal.

CKMB is now not available in an increasing number of hospitals. With CKMB becoming obsolete, troponin will become the gold standard and CKMB will no longer have a role in defining after PCI injury in clinical practice.

What Should the Clinically Relevant Cut-Point Be?

It is important to define what level of periprocedural injury has an impact on survival. Cut-points for a large MI could also be defined based on the amount of troponin rise to see a fall in ejection fraction to 40%. Because of the difference in sensitivities between CKMB and troponins, different multiples of the 99th percentile will be required to have a similar prognosis. An absolute amount of myocyte necrosis could also be defined as a criterion.
In the small MICASA (Myocardial Injury following Coronary Artery Surgery versus Angioplasty) study categorization of a type 4a MI associated with a 3× elevation of CKMB (%) required a troponin elevation of >40× 99th percentile.\textsuperscript{19} In the EVENT (Evaluation of Drug Eluting Stents and Ischemic Events) registry,\textsuperscript{20} troponin levels had to be elevated 20× ULN to be equivalent to the 1-year mortality (5.8%) associated with 3× elevation of CKMB. It is notable that in this population of 4930 patients undergoing elective PCI (and therefore expected to mostly have stable baseline biomarkers), the 1-year mortality for a 3× elevation in troponins was 4.3%, that is, 95% increase over the 2.1% mortality of patients without biomarker elevation and an absolute increase in mortality of 2.2%. However the mortality rate didn’t increase until an inflection point of 20 times ULN. For similar mortality rates as with 5× CKMB the troponin levels had to be >35× ULN.

In an analysis of 10 119 patients undergoing PCI from the EARLY ACS and SYNERGY trials for patients with stable or failing baseline troponin levels, there was a 7% increase in the adjusted HR of 1-year death per 10× ULN increase in troponin levels (HR, 1.07; 95% CI, 1.03–1.1; \(P=0.004\)). An elevation of troponin >60× ULN had a similar adjusted mortality risk (5%) as a 3× CKMB elevation.\textsuperscript{21}

Currently there is only one high-sensitivity (hs) assay available (not yet approved in the United States). As the hsTroponin T assay (99th percentile = 14 ng/L) can be related to the 4th generation troponin T assay (the contemporary cut-point of 0.03 \(\mu\)g/L = 50 ng/L hsTroponin), an increase of 3× elevation of the contemporary troponin T(150 ng/L) equates to an increase in hsTroponin T of approximately 11× (and 5× contemporary troponin T[250 ng/L] of approximately 18× hsTroponin T).

Implications for Clinical Trials

In a PCI trial, a core laboratory can measure the same biomarker, which, although troponins are preferred, could still be CKMB. Biomarker cut-points could be defined to reflect clinically relevant 1-year mortality rates and could be at a level to reflect the HR of a type 1 MI. The use of a core laboratory would be challenging in a long-term trial with type 1 and type 4a MIs occurring at multiple outlying hospitals. However, when PCI was performed at an outlying hospital, the type of assay used could be defined and the 99th percentile obtained from the IFCC Website. This will also become increasingly important for defining spontaneous MIs with vastly different sensitivities with the different assays. Complications of PCI should be readily extracted from the angiographic report.

Conclusions

Definitions for periprocedural myocardial injury and infarction have been arbitrary. A clinically meaningful cut-point of biomarker elevation, either relative or absolute, should relate to a relative or absolute increase in mortality. This need not be related to mortality rates found with various CKMB cut-points.

To make the definitions more clinically relevant, the biomarker cut-point for MI should be raised to at least >5× the 99th percentile, and associated ischemic features and/or angiographic complications should be required for the diagnosis of MI. In the absence of a >5× troponin elevation, or the absence of ischemia and angiographic complications, elevations of troponins above the 99th percentile, but below the defined cutpoint should be defined as myocardial injury, and not MI.

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References


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