

# Why all the struggle about CK-MB and PCI?

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## Introduction

Cardiovascular medicine has, in general, enthusiastically embraced new technologies and used them per appropriate guidelines. However, one area in which this has not been as much the case has been with cardiac troponin (cTn). There has been reluctance to use cTn at the suggested 99th percentile of the upper reference range (URL).<sup>1</sup> Part of this reluctance reflects a lack of comfort with the large number of increases seen with such a sensitive probe that challenge clinicians.<sup>2</sup> However, the reluctance to utilize cTn properly has distorted the utility of cTn in many areas,<sup>1,2</sup> but perhaps it has caused the greatest confusion in the area of post-PCI biomarker increases as attested to by recent articles.<sup>3–5</sup> In this area, the reluctance to give up the paradigms of the past and to use cTn per guidelines has led to confusion and inaccurate conclusions in articles published even in our most prestigious journals. This editorial from a group of researchers knowledgeable in this area attempts to articulate some of the difficulties with the interpretations thus far posed and suggest how proper use of cTn can achieve a better understanding in this important area. It does not and cannot answer all of the questions going forward but progress is only possible if we understand and properly interpret the data that presently exist.

A recent article in this area published in JACC<sup>3</sup> is an excellent example of the problems in this area. It was followed by an editorial that misconstrues most of the important concepts.<sup>4</sup> The article utilized MR imaging post-PCI to visualize areas of cardiac injury putatively related to the procedure. Because they used a good and sensitive cTn assay and the recommended cut-off values, they found that more increases in CK-MB were associated findings of delayed hyperenhancement than with cTn. However, they then concluded that CK-MB increases were more significant. The problems with this logic are several. First, it is not surprising that increases of CK-MB are more apt to be detected by MR imaging; CK-MB is much less sensitive than cTn and so more myocardial injury is required and thus MR imaging detects larger areas of hyperenhancement. The authors acknowledge this in the results section by indicating that higher cTn values would have provided similar results to

CK-MB. Does that mean that the increases of cTn not seen were not related to cardiac injury? Of course not! MR imaging is less sensitive than cTn and therefore patients with small increase in cTn may not manifest hyperenhancement. The only challenge to this assertion utilized a very insensitive cTn assay and an excessively high cut-off value<sup>6</sup> that was unmasked by calling the authors (A.S.J. personal communication). In addition, if plaque emboli are the aetiology of the injury, it may be sufficiently diffuse that it does not cause hyperenhancement because the areas of injury are not sufficiently confluent.<sup>7</sup> Finally, we have no data to suggest that MR detectable defects worsen prognosis more than non detectable ones.

Most importantly, we contend that present data do not support the contention that post-PCI biomarker increases imply an adverse prognosis when the analysis includes the baseline cTn value used as suggested by guidelines.<sup>8</sup> This later point underlies the confusion articulated in the JACC editorial.<sup>4</sup> The concept of post-PCI injury developed prior to the development of cTn. The initial studies suggested that if one had a normal CK-MB at baseline and then an increase post-intervention, it was associated with an adverse prognosis.<sup>9</sup> We do not take issue with the design or interpretation of those studies, but would point out that there was controversy at the time about how minor amounts of necrosis could cause an adverse prognosis.<sup>10</sup> In hindsight, those concerns were more right than wrong and now the use of cTn has helped us to understand the reason for the results that were reported. In most of the initial studies, the likelihood of a stable baseline value was presumed but, in retrospect, it is clear that was improbable because so many of the patients presented acutely. Now, with acute presentations, in many patients cTn measurements are already rising.<sup>11</sup> Knowing that cTn is rising confirms what is difficult to ascertain with CK-MB; that it, too, likely is rising. Thus, what was called a normal CK-MB in these studies belied the fact that the value was already starting to rise, albeit slowly and from a relatively low baseline.

Cardiac troponin solves this problem but only if one interprets the values properly. If one uses high cut-off values for the baseline, this effect may be missed. However, once it is recognized that the baseline value is rising, it becomes clear that distinguishing

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subsequent rises from the initial insult from those due to PCI is impossible regardless which biomarker one uses. The use of the proper reference value at baseline is essential to detect this situation. Some data suggest that most post-PCI increases are due to increases induced prior to the PCI because it is almost exclusively those who have increased cTn at baseline who manifest marked increases (greater than three-fold) of either cTn or CK-MB post-PCI.<sup>11</sup> Thus, perhaps most of the myocardial injury is related to the initial insult although it is hard to exclude an additional component due to re-perfusion of an already injured area or due to new interventional complications.<sup>12,13</sup> An appreciation of this fact has been lost in many studies because so many studies have not used the recommended cut-off values at baseline (see below). One could of course argue that any increase is adverse, but the critical question is at what level, if any, does it become clinically significant (see below).

It is well understood that, in patients with ACS, an increased cTn marks patients at accentuated risk.<sup>14</sup> cTn increases mark more adverse coronary anatomy, more unstable plaque, more thrombosis, more endothelial dysfunction, or all in combination.<sup>14</sup> Recently, similar data in patients with stable disease have been presented; i.e. increases of cTn are common and prognostically important with or without intervention.<sup>15,16</sup> Consequently, the information provided by cTn is available prior to PCI. Because CK-MB is less sensitive, increases lag behind cTn so some of CK-MB increases are only detectable post PCI. Appreciation of this prognostic information at baseline critically depends on the use of the proper cut-off value (the 99th percentile URL) because this value maximizes the prognostic value. Values above this and many below are indicative of myocardial injury because most assays cannot measure normal values.<sup>8</sup> If one uses a higher cut-off value, one diminishes this prognostic effect. A good example of this is a recent analysis using the value at the 10% coefficient of variation (CV) instead of the 99th percentile value. This value is higher than the 99th percentile URL. In a large cohort with baseline values <10% of the CV value, increases rising to above that value were reported to have prognostic importance.<sup>17</sup> However, these values are abnormal and likely were rising pre-PCI and there is known prognostic significance to this value as well.<sup>18</sup> With high-sensitivity assays, we now know that values in that range are well above the true normal values. Unfortunately, the use of cut-off values above the 99th percentile value to define a 'normal' baseline value is common practice. In one recent meta-analysis,<sup>5</sup> it was claimed that all the baseline values were 'normal,' but if one reviews the individual manuscripts, none of the papers cited used the 99th percentile value with a reasonably sensitive cTn assay. It was not until 2008 that an analysis using the 99th% URL was reported.<sup>19</sup> When the 99th percentile cutoff was used to determine a normal baseline, increases at baseline above this level provided substantial prognostic information but neither values of cTn nor CK-MB post-PCI regardless of their magnitude had prognostic significance. The only marginally significant analysis was the short-term analysis of patients with normal values (less than the 99th percentile value) at baseline and isolated increases of cTn post-PCI. The *P*-value for a short-term adverse prognostic sign was 0.05. However, 2/3 of the events in this group occurred secondary to non-cardiac causes in patients with severe non-

cardiac co-morbidities. There was no signal for cardiac complications. The recent analysis by Cavellini is similar despite the fact that they used a cut-off value slightly higher than the 99th percentile.<sup>20</sup> The lack of prognostic value of post-PCI biomarker increases also recently was reported from the Acuity trial.<sup>21</sup> What this means is that interventional cardiologists have been at least partially right in saying that a good intervention, even if associated with small amounts of necrosis, is not associated with an adverse prognosis. Most importantly, well-done interventions in the absence of baseline injury rarely results in marked increases in biomarkers. It is only when treating a recently damaged area that more marked increases occur and they may be due mostly to the initial insult and not the intervention. What is associated with an adverse prognosis is more severe disease, which is what an increased biomarker at baseline denotes. The necessary prognostic information is available at baseline if one uses the proper metrics. Thus, in our opinion, CK-MB no longer has a role in defining post-PCI injury. For now, cTn at baseline will provide all the prognostic information that is important. It is likely that there is some level of post-PCI cTn increase, where a peri-procedural complication harms patients but the frequency of those marked increases are likely infrequent and hard to study. One could argue that physicians should continue to monitor cTn post-procedures for quality control purposes but not prognosis.

As with any field, there are many questions posed by new data and/or new interpretations of older data. This is certainly the case here. We would point out the need to define the following:

- (1) There are data sets that could probe the frequency where a peri-procedural myocardial infarction (AMI) might have been diagnosed despite the fact that PCI was delayed.
- (2) Other investigators could reanalyse their data sets using contemporary assays and proper cut-off values to confirm or refute our synthesis.
- (3) We suspect that novel high-sensitivity cTn assays will support the prior data detailed. However, this will only happen if the proper metrics are used.
- (4) There are some patients who have stable increases of cTn either due to chronic disease or because they are on the down slope of the cTn time–concentration curve after an event. The impact of a subsequent rise after PCI has not yet been defined in this group.
- (5) It may well be that if identical interventions were done, it might be that those without any injury at all (no cTn change) might have a better prognosis since any loss of myocardium is probably adverse. However, it might take hundreds of thousands of patients to confirm this but it should be explored. Perhaps very large data sets will allow us to define some level at which elevated post-PCI values are prognostically important even when they occur from a normal baseline value.
- (6) Using post-PCI cTn increases to probe the effects of new adjunctive interventions might be a wise investment in the future.
- (7) We should ask if increases in cTn post-procedure is of importance in other developing catheter-based interventions?

In conclusion, it is time to move beyond the concept that post-PCI CK-MB values are useful. Furthermore, it is time to give up the

concept that post-PCI myocardial injury is an important endpoint. Some clinical trialists wish to retain it because it has served clinical trials well for many years. However, from a patient-oriented focus, prognostically, it is the increases of cTn at baseline that are important. Likely, further increases post-PCI are indicative of cardiac injury if the baseline value is normal but the data strongly support the idea that such increases rarely have prognostic importance. Should we call these biomarker increases AMIs despite the lack of prognostic significance? Should we measure biomarkers post-PCI? If we choose to, what criteria should we employ? Our focus should be on questions like this and not on trying to justify the retention of paradigms that no longer serve the clinical community well.

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