EDITORIAL COMMENT

Measuring Troponin Elevation After Percutaneous Coronary Intervention
Ready for Prime Time?*

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Since the description by Klein et al. (1) of an unexpected rise in plasma creatine kinase muscle-brain fraction (CK-MB) following percutaneous transluminal angioplasty, debate has ensued concerning the mechanisms, meaning, and importance of this phenomenon. Postulated mechanisms for its occurrence have included transient balloon-induced ischemia, side branch occlusion, and embolization of platelet-fibrin aggregates along with atherosclerotic debris. Data extracted from several large databases have indicated that when levels of CK-MB release are high, the relationship with ensuing events, particularly mortality, is clear; the largest of these databases (those with the most statistical power) have also indicated that the long-term relative risk of mortality is increased even when the levels of enzyme elevation are relatively low (2). A study by Kong et al. (3) suggested that the diffuse nature of microinfarction represented by CK-MB elevation might provide the substrate for sudden cardiac death as a mechanism of mortality. Other authors, however, have suggested that CK-MB elevation may be most important as a covariate of lesion complexity and the extent of coronary atherosclerosis (4). Now that the troponins and other markers of myocardial necrosis have become available, similar questions about their importance and the extent of coronary atherosclerosis (4) may be most important as a covariate of lesion complexity and the extent of coronary atherosclerosis (4).

The e-Cypher Investigators recently reported that among a broad population of more than 14,000 patients undergoing PCI, 1,949 had normal baseline CK-MB and troponin T and had their post-procedure troponin levels evaluated; 383 (19.6%) of these patients had elevation in troponin T but not CK-MB after the procedure. This occurred despite nearly 50% use of glycoprotein (GP) IIb/IIIa antagonists and 90% stent placement. As expected, the degree of underlying illness in these patients was greater than in patients in whom circulating troponin T was undetectable. The number of in-hospital events was relatively small, and only at about the first year was the rate of death or myocardial infarction observed to be higher in the troponin-positive group. At 3 years, mortality in this seemingly low-risk group of patients was 13%, compared with 7% in patients without troponin T elevation (partial hazard ratio 1.2, 95% confidence interval 1.02 to 1.40). Among the variables studied, troponin T elevation was found to be an independent predictor of long-term mortality. Commonly quoted rates of myocardial infarction after PCI, as defined using CK-MB, range from 6% to 10%, depending on the underlying risk of the patient population. The data of Prasad et al. (7) indicate that infarction (based on European Society of Cardiology/American College of Cardiology standards, which include troponin elevation [8]) occurs in an additional 20% of patients. These figures are concordant with observations made in multicenter registries (EVENT [A Multicenter Registry for the Evaluation of Drug Eluting Stents and Ischemic Events] Investigators, 2006). Clearly, myocardial infarction after PCI is more common than is readily believed. As the number of markers available to detect myocyte injury continues to grow, and as the sensitivity for detecting them increases, the observed rates will likely increase.

What do these findings mean? The answer is 2-fold. First, it must be recognized that clinical events continue to occur after patients who have had successful PCI are discharged from the hospital. Although hospital mortality is low, mortality continues to accrue after hospital discharge. The e-Cypher Investigators recently reported that among a broad population of more than 14,000 patients undergoing placement of a sirolimus-eluting stent in late 2004 and 2005, mortality rose from 0.6% at 30 days to 1.4% at 6 months and 2.2% at 1 year (9). Although CK-MB elevation has been a useful surrogate for mortality, not all deaths during follow-up can be predicted on the basis of CK-MB elevation; some authors have argued that rather than a surrogate, it should be viewed as one of many risk factors (4). Because the attributable risk associated with CK-MB elevation greater than 3-fold is approximately 14% (10), it is almost certain that additional factors are involved. Additional markers may be useful to help refine risk estimates.

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The second part of the answer lies in the additional prognostic information obtained from examining additional markers after PCI. In principle, it is likely that an association can be found between elevation of any abnormal protein in the blood after PCI and worse outcomes. Most studies that have examined the significance of troponin elevation were relatively small and did not include long-term follow-up. In the largest of these studies, Kini et al. (11) observed that approximately 25% of patients with normal post-procedure CK-MB had elevations in the levels of troponin I. In contrast with the present study, follow-up was for 12 months; CK-MB was the most powerful predictor of events during this period. Unlike the observations made by Prasad et al. (7), only elevations of troponin exceeding 5-fold predicted events during follow-up. Interestingly, the estimated hazard ratios for troponin I elevation (1.1 to 1.4, depending on the level of elevation) were very similar to those of Prasad et al. (7).

At the current time, the findings of Prasad et al. (7) should be viewed as proof of principle rather than as a dictum for altering practice. Over the last 15 years, a wealth of information has accumulated concerning the prognostic information surrounding CK-MB elevation. This body of knowledge does not yet exist for the troponins. The latest iteration of American College of Cardiology/American Heart Association guidelines for PCI now assigns a class I indication for determination of CK-MB or troponin after PCI complicated by evidence of ischemia and a class IIa indication for routine collection of either marker (12). During preparation for a number of clinical trials and registries, we have learned that about half of the PCI centers in the U.S. have adopted the latter practice. However, because there is no specific therapy for such patients (other than aspirin, clopidogrel, and statins, which are routinely used in post-PCI patients anyway) the utility of the test for clinical decision making rather than for informational purposes remains in question. The recognition of CK-MB elevation as an important prognostic indicator, and its acceptance as a surrogate for catastrophic clinical events was instrumental in the development of “adjunctive” therapies designed to reduce the rate of periprocedural infarction.

Post hoc analyses of these treatments has confirmed the relationship between reductions in enzyme release with reduction in mortality (13,14). Perhaps the recognition that troponin T elevations occur after otherwise uncomplicated procedures and are associated with a 20% increase in long-term mortality ought to prompt the development of new strategies, both short- and long-term. As has been the case with CK-MB, it is likely that there will be controversy as to whether the association is causal or is an index of underlying risk. Several steps are needed to address this issue. First, the findings reported in the present study need to be replicated. Data accumulated from large registries of stent implantation as well as upcoming stent trials offer the opportunity to confirm or refute these findings. Because CK-MB is usually collected in these studies, including troponin, determination would involve little additional effort. Second, new trials of therapies designed to reduce periprocedural infarction (defined using CK-MB) should also include data collection concerning the frequency of troponin elevation and the effect of the treatment on it. Correlation of clinical outcomes with changes in troponin-defined infarction should follow. Such observations would be useful in determining whether troponin is a useful surrogate for mortality after PCI. Formal rules are evolving for acceptance of an end point as a valid surrogate (15), and these will need to be applied to newly recognized biomarkers.

At least one novel experimental use also exists for troponin measurement after PCI. Data from a number of sources indicate that endothelialization is delayed after placement of drug-eluting stents compared with bare-metal stents (16); there has been concern about the effect of this phenomenon on subacute and late stent thrombosis (17). It is also possible that delayed endothelialization exposes the recipients of drug-eluting stents to a longer risk period for microinfarction. Although periprocedural infarction is generally stated to occur within <24 h after stent placement, it is worth noting that measurement of CK-MB is rarely performed after this period. Current assessments are inadequate to test this hypothesis, and asking patients to return to the hospital for daily measurements of CK-MB is clearly impractical. Because troponin levels remain elevated in the blood for days to weeks, 1 or 2 late measurements of troponin several days after hospital discharge might help shed light on this situation. All these steps would be useful in determining whether troponin is useful as a surrogate for mortality after PCI.

The present report should help refocus the stage light on post-procedural infarction. We now know that it happens, even in the context of modern techniques (i.e., well-developed technical skills, aggressive use of GP IIb/IIIa antagonists, clopidogrel, and modern stents). If we are to continue to reduce the long-term morbidity and mortality in patients who have had interventions, we will need to recognize that there are new markers of risk that merit our attention.

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