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EDITORIAL COMMENT

Periprocedural Myocardial Infarction

The "SCAI" Is the Limit*

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Percutaneous coronary intervention (PCI) is performed in more than 1 million patients per year, enhancing quality of life and, in the case of acute coronary syndromes (ACS), improving survival free from myocardial infarction (MI). Nonetheless, adverse events may accompany the PCI procedure itself, the most frequent of which is periprocedural myonecrosis, which if extensive can result in left ventricular dysfunction and death. With high-sensitivity troponin assays, periprocedural myonecrosis may be detected in nearly 80% of PCI patients (1). The extent of myonecrosis that is prognostically relevant is a matter of long-term debate. Because cardiac regeneration occurs very slowly if at all (2), some argue that any loss of myocardium is regrettable, a position difficult to oppose. However, many biomarker elevations post-PCI are unassociated with electrocardiographic changes or left ventricular dysfunction. Overreacting to abnormal biochemical measures that have no clinical relevance may provoke unnecessary tests (imaging, repeat cardiac catheterization) and medications (with side effects), needlessly increase hospitalization duration and costs, and result in undesirable psychological (and even medicolegal) consequences of informing patients that they have had a "heart attack" from the procedure. Conversely, accurate diagnosis, risk stratification, and appropriate treatment of patients who have had clinically relevant complications are essential to optimize outcomes after an untoward event. Is there a threshold of cardiac biomarker elevation post-PCI representing a periprocedural MI (PMI) substantial enough to worsen prognosis?

Surprisingly, despite decades of research, a definitive answer has proven elusive. Indeed, the academic community cannot even agree on the definition of PMI. Three major working groups have defined PMI differently, requiring different thresholds of biomarker elevations, with or without symptoms or electrocardiographic changes or angiographic or imaging evidence of ischemia or myocardial loss (3–5). Also unsettled is the preferred post-PCI biomarker, whether creatine kinase-MB (CK-MB) (which has the strongest proven linkage to subsequent mortality) or troponins (which are now more widely used). Are angiographic complications, ST-segment changes, or imaging evidence of infarction also required for prognostic relevance? Again, the subject is poorly understood (although PMI with new pathological Q waves is particularly ominous) (6). And almost all prior studies have only explored the relationship between PMI and subsequent mortality. The implications of post-PCI biomarker elevations on heart failure symptoms and hospitalization, arrhythmias, and angina are unknown.

In 2013, the Society of Cardiac Angiography and Interventions (SCAI) proposed a definition for a clinically relevant PMI on the basis of studies that established an independent relationship between biomarker elevations and morality (5). CK-MB was the biomarker of choice, as it had the strongest evidence for this relationship. Specifically, peak post-PCI CK-MB ≥10 times the upper limit of normal (ULN) represented the threshold at which mortality was independently increased (or ≥5 times the ULN with new pathological Q waves). In the absence of meaningful troponin data, a 7:1 quantitative ratio of troponin to CK-MB was proposed as conservatively representing bioequivalence on the basis of cardiac magnetic resonance imaging and clinical studies

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(5,7,8). Thus, a troponin elevation of ≥70 times the ULN (or ≥35 times the ULN with new Q waves) was also offered as indicating a clinically relevant PMI. These definitions assume normal pre-PCI biomarker levels; elevated baseline troponins (whether chronic or due to ACS) obfuscate interpretation of further elevations and by themselves portend a worse prognosis (9,10). The SCAI document concluded by noting that these recommendations were on the basis of the best available evidence, and emerging data would engender revisions of the proposed criteria.

Since the SCAI publication, there have been few new investigations exploring the relationship between PMI and outcomes. Idris et al. (11) reported that the SCAI thresholds were prognostically more accurate than lesser degrees of peak biomarker elevations. In a pooled database study of 23,604 patients from 11 studies, post-PCI CK-MB >3 times the ULN was an independent correlate of long-term mortality (12). Unfortunately, categorical analysis was not provided to determine the threshold at which this effect emerged. Moreover, 58% of patients presented with ACS, many of whom had baseline biomarker elevations, complicating interpretation of further biomarker increases.

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In this issue of *JACC: Cardiovascular Interventions,* the study by Lee et al. (13) re-examines this issue in a novel population, 1,058 patients undergoing successful PCI of chronic total occlusions, lesions prone to periprocedural myonecrosis because of extensive atherosclerotic burden, itself a predictor of PMI (14). PMI, defined as a post-procedural CK-MB increase to >3 times the upper reference limit of the assay occurred in 11.4% of patients, a higher prevalence than typically reported after PCI of nonoccluded coronary segments (5,8,12). At median 4.4-year follow-up, PMI was an independent predictor of subsequent mortality, but only when peak CK-MB was >10 times the upper reference limit (hazard ratio: 2.67; 95% confidence interval: 1.13 to 6.30; $p = 0.026$). Thus, the "SCAI is the limit"; this latest report reinforces the SCAI definition of a clinically relevant MI as a post-PCI CK-MB rise to ≥10 times the ULN (or upper reference limit) as the prognostically important threshold.

This study had some limitations. Only 1 CK-MB level was mandated post-PCI, likely underestimating peak CK-MB in some patients, adding imprecision. Q waves developed in 0.9% of patients; how this affected prognosis and biomarker thresholds was not reported. The main analysis was performed after successful PCI; periprocedural myonecrosis may have a greater impact after failed PCI. ACS was present in one-quarter of patients and was also a multivariable predictor of PMI. A different PMI definition was used with elevated baseline biomarkers; whether this affected the results is unknown. With "only" 1,058 patients, the study was underpowered to exclude an association between lower levels of peak CK-MB and a small mortality increase. Finally, troponins were not routinely collected, precluding analysis of troponin-defined PMI. These limitations notwithstanding, this well-done study adds to the weight of evidence that only large post-PCI biomarker elevations (i.e., extensive myonecrosis) are prognostically important.

Future studies are encouraged to evaluate the PMI-prognosis relationship in other patient populations, especially with troponins. Outcomes other than death should be examined, including angina, heart failure, left ventricular function, exercise performance, and quality-of-life measures. Such studies should ideally be prospectively performed, large (n = >5,000), and have routine frequent biomarker draws (every 8 h, 3 times). Multivariable adjustment is necessary to account for the numerous clinical, angiographic, and procedural covariates also associated with mortality. Nonetheless, unmeasured confounders strongly related to both myonecrosis and mortality (e.g., the extent of atherosclerosis) (14) are unavoidable. Thus, these studies can only establish associations between PMI and outcomes, not causality.

Widespread adoption of a clinically relevant MI definition has important implications for trials investigating new therapies as well as for patient care. For example, both periprocedural and spontaneous MIs are typically counted as "MI" events. Combining clinically meaningless biomarker elevations with prognostically important spontaneous MIs dilutes the relevance of the MI endpoint and may obscure appropriate interpretation. For example, most studies of PCI versus medical therapy in stable CAD have been neutral in regards to MI event rates. But PCI results in increased PMI and reduced rates of non-PMI, the latter correlating with a trend toward improved long-term survival with PCI (15,16). In the FAME II trial, death or MI after 8 days (excluding PMI) was significantly reduced with PCI versus medical therapy (17). Had that been the primary endpoint, the trial interpretation would have been markedly strengthened. Future trials should incorporate different myonecrosis thresholds for PMI and non-PMI, using only clinically relevant definitions of each to avoid obscuring meaningful outcomes. Finally, whether

serial routine biomarker assessments after PCI is necessary in clinical practice requires additional study. Because a SCAI-defined clinically relevant PMI occurs in only about 1% to 3% of PCI patients (depending on procedural complexity) (5,13), many sites draw biomarkers only in case of angiographic complications, prolonged symptoms, or electrocardiographic changes. Although intuitive and cost saving, prospective studies are warranted to demonstrate the safety of this approach.

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