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EDITORIAL COMMENT

Myocardial Infarction After Percutaneous Coronary Intervention and Coronary Artery Bypass Graft Surgery

Time for a Unifying Common Definition*

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Elevation of cardiac biomarkers (cardiac troponin [cTn] and creatinine kinase MB fraction [CK-MB]) is common after percutaneous coronary intervention (PCI) and coronary artery bypass graft surgery (CABG). Defining the threshold of cardiac biomarkers elevation that constitutes a myocardial infarction (MI) and the prognostic impact of these events on long-term outcomes has been a subject of intense controversy for some time.

An early attempt to define PCI-related and CABG-related MI was made by the 2nd Universal Definition of MI (UDMI) study group (1). Because of its greater specificity for cardiac myonecrosis compared with CK-MB, cTn was designated as the preferred biomarker, with substitution of CK-MB allowed in the absence of cTn. PCI-related MI was defined by cTn elevation >3 times the 99th percentile of the upper reference limit (URL), without requiring any clinical, electrocardiographic (ECG), or imaging indicators of myocardial injury. CABG-related MI was defined by elevation of cTn >5 times the 99th percentile URL but also required clinical, ECG, or imaging indicators of myocardial injury. The 3rd UDMI (2) increased the threshold of cTn elevation to ≥5 times the 99th percentile URL to define a post-PCI MI, and now also required the presence of clinical, ECG, or imaging indicators of myocardial injury. However, it also adopted a more stringent definition for CABG-related MI (elevation of cTn [or CK-MB] to ≥10 times the 99th percentile URL plus clinical, ECG, or imaging indicators of myocardial injury).

An expert consensus document by the Society for Cardiac Angiography and Interventions (SCAI) introduced a biomarker-based definition for periprocedural MI that was "clinically relevant," that is, having been associated with subsequent mortality in large-scale studies (3). In contrast to the UDMI in which cTn was the preferred biomarker, SCAI recommended CK-MB as the preferred biomarker (because CK-MB had the strongest data correlating its elevation with prognosis). SCAI also proposed a unifying common definition for PCI-related and CABG-related MI: a CK-MB rise to ≥10 times the local laboratory upper laboratory normal (ULN) (not requiring clinical, ECG, or imaging evidence of MI), or to ≥5 times the ULN in patients with new pathologic Q-waves. When CK-MB is not available, SCAI defined PCI-related and CABG-related MI by cTn elevation to ≥70 times the local laboratory ULN, or ≥35 times the ULN with new Q-waves. The 7:1 ratio used by the SCAI group for bioequivalence of cTn:CK-MB was based on cardiac magnetic resonance imaging (cMRI) studies supporting this ratio for infarct size assessment (3). Moreover, low and intermediate levels of cTn elevation after PCI do not result in detectable myocardial necrosis. A threshold of ~40 times the 99th percentile URL of cTn is required for cMRI-detectable post-PCI myocardial necrosis (4).

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Few studies have prospectively validated the UDMI or SCAI definitions of periprocedural MI in terms of its

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impact on prognosis. In this regard, in the present issue of the *JACC: Cardiovascular Interventions* Cho et al. (5) report a study in which 7,697 patients with multivessel disease who underwent PCI (n = 4,514) or CABG (n = 3,183) between 2003 and 2013 with normal baseline CK-MB and who had serial measurement of CK-MB was available were evaluated. They assessed the prevalence and prognostic significance of periprocedural MI after both PCI and CABG according to the 2nd and 3rd UDMI and the SCAI definitions. Patients were followed for major cardiovascular events for a median of 4.7 years.

WHAT CAN BE LEARNED FROM THIS NOVEL AND VALUABLE STUDY?

THE RATE OF PERIPROCEDURAL MI WITH PCI AND CABG VARIES MARKEDLY WITH THE DEFINITION. The post-PCI MI rates with the 2nd UDMI, 3rd UDMI, and SCAI definition were 18.7%, 3.2%, and 5.5%, respectively. The markedly lower MI rate with the 3rd UDMI compared with the 2nd UDMI may be attributed to both the increase in CK-MB threshold from 3 times to 5 times the 99th percentile URL, and by the 3rd UDMI requiring concurrent clinical, ECG, or imaging evidence of MI. The SCAI post-PCI rate was slightly higher than the 3rd UDMI rate despite using a higher CK-MB threshold, presumably because concurrent clinical, ECG, or imaging evidence of MI was not required.

The post-CABG MI rates with the 2nd UDMI, 3rd UDMI, and SCAI definition were 2.9%, 1.9%, and 18.3%, respectively. The markedly lower MI rates with either UDMI definition compared with the SCAI definition presumably reflects the difficulty in ascertaining associated evidence of MI in the post-surgical patient. Ischemic chest pain may be misconstrued as sternal wall pain (or not assessable in intubated patients), 12-lead ECGs may not be easily collected, and angiographic complications are not routinely visualized (in contrast to PCI). Consistent with this explanation, prior studies have reported that whereas 42% to 82% of patients undergoing CABG have cTn elevation ≥5 times the URL (6), only 4% to 7% have the additional ECG evidence needed to meet the criteria for a post-CABG UDMI event (7). Several studies using cMRI also support the concept that the UDMI underestimates the frequency of myocardial necrosis after CABG, finding that 28% to 44% of post-CABG patients have detectable myonecrosis (8). The marked variation in PCI-related and CABG-related MI rates based on definition would imply that the interpretation of trials comparing the 2 revascularization modalities may markedly vary depending on the definition applied.

THE PROGNOSTIC IMPACT OF THE 3 PERIPROCEDURAL MI DEFINITIONS VARY. After multivariable adjustment for differences in baseline characteristics, all 3 definitions of periprocedural MI were associated with increased 5-year composite rates of cardiovascular death or spontaneous MI, but only the SCAI definition of periprocedural MI was significantly associated with 5-year all-cause mortality. This pattern held when analyzed separately in the PCI and CABG strata.

This observation is of interest because it suggests the utility of a higher biomarker threshold not requiring associated clinical, ECG, angiographic, or imaging evidence of MI. Prior studies have confirmed the prognostic correlation of a 10 times CK-MB threshold for correlation with mortality (3). Since publication of the SCAI consensus document, the Asan group reported that after multivariable adjustment a peak CK-MB level of >10 times the URL was predictive of long-term mortality after PCI of chronic total occlusions, whereas lesser post-PCI CK-MB elevations were not (9). The FREEDOM investigators recently demonstrated that CK-MB elevations >~7 to 10 times the URL significantly predicted subsequent mortality at median 3.6 years follow-up after CABG in patients with multivessel disease and diabetes (10). In the present study, adjusted hazard ratios for periprocedural MI using the 2nd and 3rd UDMI were directionally predictive of 5-year mortality, but in contrast to the SCAI definition were not statistically significant, likely because of inclusion of smaller MIs with lesser CK-MB elevations that are not as strongly predictive of outcome as larger MIs. Thus, these data support prior findings (3,9) that only large periprocedural MIs as reflected by high peak thresholds of CK-MB elevation (as defined by the SCAI definition) predict mortality at 5 years. Moreover, the present dataset also suggests that requiring clinical, ECG, angiographic, or imaging evidence of MI (as in the UDMI) may miss capturing important periprocedural MIs that are associated with subsequent death. Finally, it should be noted that the adjusted hazard ratios for the effect of SCAI MI definition on 5-year mortality were roughly similar for both PCI and CABG, supporting the use of this common definition in trials comparing the 2 revascularization modalities.

A major limitation of the present study is that cTn levels were not collected. Thus, we are unable to determine the rates and prognostic impact of the 2nd and 3rd UDMI using cTn, their preferred biomarker.

However, given the greater sensitivity of cTn compared with CK-MB, it is highly likely that using cTn with the same thresholds would have greatly increased the rates of periprocedural MI after both PCI and CABG. Moreover, because cTn-based MIs indicate substantially less myonecrosis compared with CK-MB-based MIs for the same threshold multiple, including smaller infarctions with cTn-based MIs would have decreased the overall prognostic significance of periprocedural MI events.

The time has come to adopt a unifying common definition for PCI-related and CABG-related MI (for both clinical trial use and clinical practice). In this regard the SCAI definition is simple to implement, uses the same criteria for PCI and CABG, avoids ascertainment bias, and has been associated with subsequent mortality for both PCI and CABG. We do agree that further studies with cMRI would be useful to demonstrate whether the extent of myonecrosis after PCI and CABG is similar for any given post-procedural biomarker elevation. Absent this demonstration, the roughly comparable adjusted hazard for 5-year mortality after MI for both PCI and CABG using the SCAI definition supports using this common biomarker threshold for both revascularization modalities.

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