JSCAI
The official journal of the Society for Cardiovascular Angiography & Interventions

Editorial

# Periprocedural Myocardial Infarction: Is the Debate Over?

Usman Baber, MD, MS *

*Cardiovascular Section, University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma*

The clinicopathologic construct of myocardial infarction (MI), as articulated by the Fourth Universal Definition (UDMI), requires biochemical evidence of myocardial injury, objective signs of ischemia, and a putative underlying mechanism.[1] In this regard, the definition of spontaneously occurring MI has remained relatively constant across iterations of the UDMI and is aligned with clinical practice guidelines. By contrast, the diagnostic criteria and prognostic impact of MI occurring after percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) surgery, or periprocedural MI (pMI), remain unsettled. Salient and unresolved issues vis à vis pMI include the optimal cardiac biomarker and associated thresholds that reliably distinguish injury from infarction, links between pMI and clinical outcomes, and the need for ancillary (ie, non-biomarker) evidence to substantiate the diagnosis of MI. Although several definitions for pMI have been proposed by professional societies and other stakeholders,[1–3] differences across schema yield inconsistencies in the incidence and impact of pMI.

Not surprisingly, this lack of consensus has important implications for clinical practice, the design and interpretation of clinical trials, and regulatory approval. For example, the effect of CABG vs PCI among patients with left main coronary artery disease shifted from a neutral to beneficial effect with use of a more sensitive cardiac biomarker (creatine kinase myocardial band [CK-MB] vs cardiac troponin [cTn]) and lower diagnostic threshold to diagnose pMI.[4] From a regulatory standpoint, the safety and efficacy of novel devices may vary substantially according to the definition and, by extension, the incidence of pMI, thereby impacting commercial approval.[5] Hence, achieving consensus on the definition of pMI has emerged as an important clinical priority not only for practicing clinicians but also clinical trialists and regulators.

In this regard, 2 articles in this issue of *JSCAI* contribute novel and incremental insights to the evolving framework of pMI. In one report, Wang et al[6] evaluated the incidence and impact of pMI among patients with left main coronary artery disease presenting with acute coronary syndrome and undergoing PCI (n = 350). The assessment of pMI was performed in an independent fashion using Society for Cardiovascular Angiography & Interventions (SCAI), Fourth UDMI, and Academic Research Consortium (ARC) 2 definitions. Each approach differs in preferred biomarker, threshold, and need for adjunctive criteria (electrocardiographic, imaging, or angiographic) to diagnose pMI. The rates of pMI were highest with Fourth UDMI, intermediate with ARC-2, and lowest with SCAI (19.4%, 12.3%, and 8.6%, respectively). Over a median follow-up of 3.1 years, the adjusted risk for cardiovascular death associated with SCAI-defined pMI was much higher (adjusted hazard ratio [aHR], 6.34) than corresponding estimates for ARC-2 (aHR, 2.82) or Fourth UDMI (aHR, 2.65). These results extend similar findings reported in more stable cohorts[7] and highlight the lower rate but higher risk associated with SCAI-defined pMI, which prioritizes the more specific cardiac biomarker CK-MB as compared with ARC-2 or Fourth UDMI. Interestingly, the authors found no association between any degree of myocardial injury using cTn and mortality, a result that is discordant with several prior reports that might reflect differences in troponin assays or patient case-mix.[4,8]

In a separate report, Gaudino et al[9] conducted a study-level meta-analysis comprising randomized trials comparing PCI vs CABG (n = 12) to explore associations between pMI, death, and quality of life. Most trials (n = 8) relied on CK-MB to diagnose pMI, and 5 studies defined pMI as cardiac biomarker elevation >5 times the upper reference limit. The authors plotted the treatment effect (PCI vs CABG) on risks for both pMI and each respective outcome to assess correlations. To formally evaluate the utility of pMI as a surrogate marker for mortality, the authors also calculated a coefficient of determination ($R^2$), with values >0.7 fulfilling the prespecified criteria for validity. Over a weighted mean follow-up of 5.6 years, pMI was positively associated with risk for all-cause death ($R^2$, 0.72), with a stronger association observed for trials requiring a higher biomarker threshold to diagnose pMI ($R^2$, 0.93). Importantly, pMI was inversely associated with changes in quality of life ($R^2$, 0.99).

Notwithstanding the common themes from the reports presented herein, substantial controversy surrounding the relevance and inclusion of pMI as an endpoint in clinical trials persists. One proposed solution is to remove pMI from composite outcome measures,[10,11] an approach that may be convenient but is also untenable for several reasons. For example, the current studies and earlier data confirm the strong links between pMI and both hard (ie, mortality) and soft (ie, quality of life) clinical outcomes. Moreover, depending on the definition used, the

DOIs of original articles: https://doi.org/10.1016/j.jscai.2023.100591, https://doi.org/10.1016/j.jscai.2022.100576.
*Keywords:* myocardial infarction; periprocedural; universal definition.
* Corresponding author: usman-baber@ouhsc.edu (U. Baber).

https://doi.org/10.1016/j.jscai.2023.100601
Received 31 January 2023; Accepted 1 February 2023
Available online 3 April 2023

mortality risk associated with pMI is comparable to that of spontaneous MI.[4,8] From a practical standpoint, the proportion of all MIs attributable to periprocedural events in contemporary trials is considerable. For example, among all MIs that occurred over 5 years in the Evaluation of XIENCE versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization (EXCEL) trial, a total of 79 (52.5%) were periprocedural events based upon the protocol definition of pMI.[12] Removing such early events from a composite outcome would lower anticipated event rates, which could compromise study power and result in longer follow-up periods or a larger sample size. In an era of costly and complex clinical trials, there is a greater incentive to include, not remove, such clinical events.

Although the debate over an ideal definition for pMI continues, the ARC-2 definition provides a reasonable compromise between SCAI and Fourth UDMI schemes. The former relies on CK-MB, which is rarely used in contemporary practice, whereas the latter requires only modest elevations in cTn with different thresholds for PCI and CABG. In contrast, ARC-2 defines pMI using higher biomarker thresholds consistent with a clinically meaningful degree of myonecrosis (cTn $\geq$35 times the upper reference limit) that are uniform for both PCI and CABG. Moreover, non-biomarker criteria for pMI are identical between revascularization approaches and include flow-limiting angiographic complications, development of new Q waves, and substantial loss of myocardium on imaging.[2] Although this approach should minimize ascertainment bias, angiography is routinely performed after PCI, not CABG. This distinction is clinically relevant, as angiographic complications are more common than ischemic electrocardiographic changes among patients with pMI.[7] Indeed, pMI rates after CABG are much more sensitive to the inclusion of additional ischemic evidence as compared with PCI.[4] Hence, the ARC-2 definition for pMI may be ideally suited to angiographic studies evaluating different stents or adjunctive PCI devices. In contrast, a biomarker-only approach may be more appropriate for valid comparisons between CABG and PCI.

Another important consideration in the debate surrounding pMI involves the appropriate analytic framework to evaluate such events. Composite outcomes are usually analyzed in a time to first event approach wherein outcomes are assigned equal weight irrespective of timing and event type; however, multiple studies have shown that the impact of MI varies by time (early vs late) and by mechanism (spontaneous vs periprocedural vs stent thrombosis).[13,14] One approach to account for this variability is to implement an event hierarchy that organizes outcomes by severity and then analyzes using a conventional approach or an alternative method (ie, win ratio).[15]

The articles by Wang et al[6] and Gaudino et al[9] remind us that pMI is a common and clinically meaningful event with substantial prognostic impact. Rather than continuing to debate the merits of various diagnostic schema, we should align behind the principles, thresholds, and criteria endorsed in ARC-2. Although no framework is perfect, this approach is a sensible compromise that should satisfy clinicians, trialists, and regulators.

## Declaration of competing interest

Usman Baber reports honoraria from Amgen, AstraZeneca, Boston Scientific, and Abbott.

## Funding sources

This editorial was not supported by any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

## References

1. Thygesen K, Alpert JS, Jaffe AS, et al. Fourth universal definition of myocardial infarction (2018). *Circulation*. 2018;138(20):e618–e651. https://doi.org/10.1161/CIR.0000000000000617
2. Garcia-Garcia HM, McFadden EP, Farb A, et al. Standardized end point definitions for coronary intervention trials: the Academic Research Consortium-2 consensus document. *Circulation*. 2018;137(24):2635–2650. https://doi.org/10.1161/CIRCULATIONAHA.117.029289
3. Moussa ID, Klein LW, Shah B, et al. Consideration of a new definition of clinically relevant myocardial infarction after coronary revascularization: an expert consensus document from the Society for Cardiovascular Angiography and Interventions (SCAI). *J Am Coll Cardiol*. 2013;62(17):1563–1570. https://doi.org/10.1016/j.jacc.2013.08.720
4. Gregson J, Stone GW, Ben-Yehuda O, et al. Implications of alternative definitions of peri-procedural myocardial infarction after coronary revascularization. *J Am Coll Cardiol*. 2020;76(14):1609–1621. https://doi.org/10.1016/j.jacc.2020.08.016
5. Kereiakes DJ, Feldman RL, Ijsselmuiden AJJ, et al. Safety and effectiveness of the SVELTE fixed-wire and rapid exchange bioresorbable-polymer sirolimus-eluting coronary stent systems for the treatment of atherosclerotic lesions: results of the OPTIMIZE randomized study. *Circ Cardiovasc Interv*. 2021;14(9):e010609. https://doi.org/10.1161/CIRCINTERVENTIONS.121.010609
6. Wang H-Y, Xu B, Dou K, et al. Impact of periprocedural myocardial infarction after initial revascularization with left main PCI for patients with recent myocardial infarction. *J Soc Cariovasc Angiogr Interv Cardiovasc Interv*. 2023;2(2):100576.
7. Ueki Y, Otsuka T, Bär S, et al. Frequency and outcomes of periprocedural MI in patients with chronic coronary syndromes undergoing PCI. *J Am Coll Cardiol*. 2022;79(6):513–526. https://doi.org/10.1016/j.jacc.2021.11.047
8. Silvain J, Zeitouni M, Paradies V, et al. Procedural myocardial injury, infarction and mortality in patients undergoing elective PCI: a pooled analysis of patient-level data. *Eur Heart J*. 2021;42(4):323–334. https://doi.org/10.1093/eurheartj/ehaa885
9. Gaudino M, Di Franco A, Dimagli A, et al. Correlation between peri-procedural myocardial infarction, mortality, and quality-of-life in coronary revascularization trials: a meta-analysis. *JACC Cardiovasc Interv*. 2023;2(2):100591.
10. Cutlip DE. Procedural myocardial infarction: definitions everywhere, but not any that may fit. *J Am Coll Cardiol*. 2020;76(14):1640–1643. https://doi.org/10.1016/j.jacc.2020.08.024
11. Serruys PW, Hara H, Garg S, Onuma Y. Have we overdefined periprocedural myocardial infarction to the point of extinction? *JACC Cardiovasc Interv*. 2021;14(15):1635–1638. https://doi.org/10.1016/j.jcin.2021.06.006
12. Stone GW, Kappetein AP, Sabik JF, et al. Five-year outcomes after PCI or CABG for left main coronary disease. *N Engl J Med*. 2019;381(19):1820–1830. https://doi.org/10.1056/NEJMoa1909406
13. Chaitman BR, Alexander KP, Cyr DD, et al. Myocardial infarction in the ISCHEMIA trial: impact of different definitions on incidence, prognosis, and treatment comparisons. *Circulation*. 2021;143(8):790–804. https://doi.org/10.1161/CIRCULATIONAHA.120.047987
14. Généreux P, Giustino G, Witzenbichler B, et al. Incidence, predictors, and impact of post-discharge bleeding after percutaneous coronary intervention. *J Am Coll Cardiol*. 2015;66(9):1036–1045. https://doi.org/10.1016/j.jacc.2015.06.1323
15. Pocock SJ, Ariti CA, Collier TJ, Wang D. The win ratio: a new approach to the analysis of composite endpoints in clinical trials based on clinical priorities. *Eur Heart J*. 2012;33(2):176–182. https://doi.org/10.1093/eurheartj/ehr352