VARC3 criteria: adding prognosis to injury

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How to best define periprocedural myocardial infarction (PPMI) in the setting of transcatheter aortic valve replacement (TAVR) remains challenging. PPMI is inevitable with transapical TAVR as a result of direct myocardial mechanical trauma. It is the mainstay with other vascular approaches consequent to hypotension, valve delivery mechanical trauma, calcific embolization, acute bleedings or valvular prosthetic coronary artery obstruction, occurring in frail patients commonly burdened with underlying coronary artery disease (1). The valve academic research consortium (VARC) was precisely initiated to provide with standardized consensus definitions, paving the way for randomized controlled trials (RCT) and observational studies ever since. Back in 2011, the VARC-1 defined PPMI as an acute ischemic event associated with documented and clinically significant myocardial necrosis occurring within 72h of the procedure(2). Cardiac necrosis was defined by the continuous elevation of cardiac biomarkers on consecutive samples, preferably, creatinine kinase-MB (CK-MB) (**Figure 1**). In 2012, the VARC criteria were updated and PPMI characterization was simplified, with only one post-procedural abnormal sample required, while the threshold values were adjusted to account for different use of CK-MB or cardiac troponin (cTn) (3). Interestingly enough, this updated definition of PPMI was not consistently associated with adverse outcomes following TAVR, suggesting that different thresholds could be considered(4,5).

Following numerous controversies on MI definition in RCT, the VARC-3, released in 2021, proposed a pragmatic and exhaustive interpretation on myocardial lesions adapted from the 4th universal, SCAI and ARC-2 definitions(6). PPMI is rendered as occurring within 48h of the procedure with a clear distinction between type 4a, subsequent to percutaneous coronary intervention (PCI)-related MI, when performed, and type 5, subsequent to SAVR or TAVR. Both types now include increased thresholds of cardiac biomarkers to characterize myocardial injury, with 10 and 70 times the upper reference limit for CK-MB and cTn respectively, to

account for the large use of high-sensitivity cTn (hs-cTn), or half the amount if associated with clear electrical, angiographic or imaging signs of myocardial injury.

In this issue of the journal, Real and coauthors provide the first external validation of the updated VARC 3 PPMI definition, using a prospective international cohort study(7). They included 1394 consecutive patients undergoing TAVR from 2015 to 2022, as this time period corresponds to the implementation of hs-cTn in both participating centers. In this cohort, 193 (14%) patients presented PPMI according to VARC-3 criteria, versus 817 (59%) according to VARC-2 criteria. Interestingly, the occurrence of PPMI according to VARC-3 criteria was associated with an increased all-cause mortality at both 30 days and one year (HR: 2.69, 95%CI: 1.50 to 4.82, and HR: 1.54, 95%CI: 1.04 to 2.27, respectively), as well as cardiovascular (CV) mortality at one year, conversely to the VARC-2 criteria for PPMI which were not significantly associated with neither all-cause nor CV death. Consistently, the authors reported the optimal cut-off value of hs-cTn elevation to define PPMI to be 82-fold, which is much in range of the VARC-3 rather than the VARC-2 criteria. Of note, it should be noted that the impact on mortality of the VARC-3 criteria PPMI is quite similar to what has been reported following post-PCI, with consistent definition of PPMI(8).

What conclusion should we draw from this study? First, it validates the VARC-3 PPMI criteria with the use of a hs-cTn troponin threshold that is adapted to current clinical practice. Second, PPMI is rarer with this updated definition but more impactful in term of prognosis. Much more remains to be done to better assess if PPMI is a marker of risk or a risk factor with potential preventable upstream actions. Indeed, the only independent determinants of VARC-3 PPMI in the present study were female sex and peripheral artery disease. The Direct Transcatheter Aortic Valve Implantation (DIRECTAVI) reported the use of systematic balloon aortic valvuloplasty prior to Edward Sapien 3 valve implantation to increase the risk of VARC-2 PPMI by 2.8 fold(9,10). In the present study, both pre and post-dilatation were

associated with a higher risk of VARC-3 PPMI, albeit not reaching statistical significance with p-values of 0.053 and 0.059 respectively, warranting further investigation. Consistently the impact of the occurrence of PPMI on post-TAVR left ventricle ejection fraction evolution should be investigated in larger dedicated studies to confirm the statistically significant, yet potentially clinically irrelevant, observed improvement in the present study. Finally, pre-TAVR CT features might be key players further adding prognosis to injury with potentially preventive approaches.

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Figure 1

Definition of peri-procedural myocardial infarction		
VARC 1 **2011**	**VARC 2** **2012**	**VARC 3** **2021**
Based on 1st universal definition		Based on 4th universal, modified SCAI and ARC-2 definitions
Delay = within 72h of procedure		Delay = within 48h of procedure
New ischemic symptoms or signs **AND** ≥2 samples separated by ≥6h **WITH** 20% increase of cardiac biomarker in second sample **AND** peak value of cardiac biomarkers>20URL **OR** >5 URL with new Q-waves	New ischemic symptoms or signs **AND** ≥1 sample with CK-MB>5URL **OR** cTn(I or T) >15URL If at baseline	CK-MB≥10ULN or ≥5ULN with new Q-waves **OR** cTn(I or T) ≥ 70ULN **OR** cTn(I or T) ≥ 35ULN **WITH** new Q-waves or LBBB or flow-limiting angiographic complications or lose of myocardium on imaging

VARC: Valve academic research consortium; URL: upper reference limit; ULN: upper limit of normal; CK-MB: creatinine kinase-MB; cTN: cardiac troponin; LBBB: left bundle branch block; SCAI: society of cardiovascular angiography and intervention; ARC: academic research consortium