

Combining invasive coronary physiology with cardiovascular magnetic resonance for long-term risk-stratification in ST-segment Elevation Myocardial Infarction: ready for clinical application?

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Timely reperfusion by primary percutaneous coronary intervention (PPCI) is the most effective treatment for limiting myocardial infarct (MI) size and improving clinical outcomes in ST-segment elevation myocardial infarction (STEMI) patients. However, despite prompt PPCI, the presence of acute myocardial reperfusion injury can attenuate the benefits of timely reperfusion and contribute up to 50% of the final infarct size in STEMI patients(1). A prognostically important component of acute myocardial reperfusion injury is coronary microvascular dysfunction (CMD), which occurs in up to 60% of PPCI-treated STEMI patients and manifests as angiography no-reflow at time of PPCI, an increase in index microvascular resistance (IMR) on invasive coronary physiology, or the presence of microvascular obstruction (MVO) and intramyocardial hemorrhage (IMH) on cardiovascular magnetic resonance (CMR)(1).

Angiographic no-reflow (post-PCI Thrombolysis in Myocardial Infarction (TIMI) flow grade ≤ 2) has previously been shown to be a strong predictor of clinical outcomes in STEMI patients(1), and MVO and IMH are associated with larger MI size, adverse left ventricular (LV) remodelling, and worse clinical outcomes post-STEMI(2). IMR can directly interrogate the coronary microvascular circulation immediately post-PPCI(1). An $IMR > 40U$ immediately post-PPCI in STEMI patients has consistently been shown to be strongly associated with MVO, IMH(3), adverse LV remodelling(3) and poorer long-term clinical outcomes(4,5).

Of note, both IMR and MVO has been shown to be dynamic in the first few days following PPCI. Cuculi et al(6) showed that there was a reduction in IMR from $37 \pm 22U$ to $31 \pm 21U$ within 24 hours in a small cohort of STEMI patients. Carrick et al(2) previously demonstrated that the extent of MVO by CMR remained similar from 4-12 hours post-PPCI to day 2 and then reduced in size by day 10. The dynamic nature of IMR and MVO, may therefore explain why the Oxford Acute Myocardial Infarction (OxAMI) investigators previously found that up to a third of patients had discordance between $IMR > 40U$ and the presence of MVO (7).

In this issue of *JACC: Cardiovascular Imaging*, the OxAMI investigators have extended their studies to evaluate the long-term prognostic implications of CMD defined as high IMR ($>40U$) and/or the presence of MVO on CMR performed within 2 days(8). In a cohort of 198 STEMI patients, those with either $IMR > 40U$ or MVO (Group 2) had similar outcomes for the primary composite endpoint of all-cause mortality, new heart failure, cardiac arrest, sustained ventricular tachycardia/fibrillation and cardioverter defibrillator implantation at 1 year, when compared to those with $IMR \leq 40U$ and no MVO (Group 1), whereas those with both $IMR > 40U$ and MVO (Group 3) had worse outcomes when compared to Groups 1 and 2(8). However, after long-term follow-up (median time of 40 months), those in Groups 2 and 3 experienced similarly poorer clinical outcomes than Group 1, and this was driven by new heart failure. The authors suggest that both IMR and MVO should be considered in the early risk-stratification of STEMI patients(8). Of note, patients with persistent angiographic no-reflow (13.6% of patients having post-PCI TIMI flow grade ≤ 2) were also included, and post-PCI TIMI flow was also a strong independent predictor of outcomes, after adjusting for high IMR and/or MVO.

The study by Scarsini et al(8) is of great interest and relevance given that optimizing risk-stratification of reperfused STEMI patients has been a topic of ongoing research. However, there are a few observations to take into consideration that may help put their research findings into perspective. Undertaking both IMR and CMR in PPCI-treated STEMI patients to detect CMD may be challenging and they depend on the availability of technical expertise and suitable facilities. More importantly, whether CMD should be defined in a dichotomised manner as $IMR > 40U$ and/or the presence of MVO is highly debatable. An alternative approach may have been to define “clinically important CMD” as $IMR > 40U$ and/or the presence of a prognostically significant extent of MVO, as previously shown by Stiermaier et al(9) (1.4% of the LV) and an approach used by the OxAMI investigators in a previous manuscript (1.55% of

the LV)(10). Last but not least, whether high IMR and/or MVO provide additive long-term prognostication value over existing clinical risk scores such as the Global Registry of Acute Coronary Events (GRACE) and TIMI STEMI risk scores was not evaluated in this study.

The clinical utility of performing either IMR immediately post-PPCI or CMR 2 days post-PPCI may not be so attractive for long-term risk-stratification unless treatments are available to target and reduce CMD and improve clinical outcomes in STEMI patients with $IMR > 40U$ or MVO, respectively(1). If the use of IMR is to only provide long-term risk stratification, the CMR risk score(9) which includes MI size, LV ejection fraction and MVO has already been shown to provide incremental prognostic value over clinical risk factors in reperfused STEMI patients. However, more research is required to assess whether a CMR-only approach or a hybrid approach (invasive coronary physiology + CMR) as used by Scarsini et al(8) performs better, and would be easier and more cost-effective for clinical implementation.

Currently, neither IMR nor MVO are used as part of routine clinical practice for risk-stratification. However, in centers where the technique and expertise is available and based on our knowledge so far, a hypothetical and pragmatic approach for the clinician to early risk stratification would be to use post-PCI TIMI flow, IMR and MVO in a step-wise manner to identify a high-risk cohort in the first 48 hours post-PPCI, and this may negate the need for all patients to have IMR and MVO assessment as illustrated in Figure 1. IMR has previously been shown to have similar prognostic value as $< 50\%$ ST-segment resolution (STR) on the electrocardiogram at 60 minutes(3), and whether $< 50\%$ STR and/or MVO would have performed equally well to high IMR and/or MVO was not evaluated in this study and it is possible that $< 50\%$ STR may be a potential alternative, when IMR is not available or feasible. Similarly, IMH may be an alternative to MVO to detect CMD by CMR post-STEMI, in cases when gadolinium contrast is contraindicated or scan time needs to be kept to a minimum(11).

To conclude, the OxAMI investigators should be congratulated for their study, as it is the first to provide prognostic insights into combining invasive coronary physiology and CMR for early risk stratification post-PPCI. Their study provides a platform for further research on how angiographic, electrocardiographic and invasive coronary physiology parameters, and CMR indices could add prognostic value to existing GRACE or TIMI STEMI risk scores to further streamline the risk-stratification of STEMI patients treated by PPCI.

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Figure 1: Hypothetical and pragmatic approach to early risk-stratification of STEMI patients (based on the findings of the study by Scarsini et al(9)).

Clinicians may consider using a step-wise approach as shown in this figure to identify those at high risk and who could be targeted with tailored additional therapy and/or closer follow-up.

