Editorial

Microvascular obstruction in ST elevation myocardial infarction patients undergoing primary percutaneous coronary intervention: another frontier to conquer?

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Over the past decades, a significant reduction in mortality due to ST elevation myocardial infarction (STEMI) has been observed worldwide (1,2). Prompt restoration of the epicardial coronary blood flow with timely primary percutaneous coronary intervention (PCI), as well as adjunctive pharmacological therapies have largely reduced the myocardial infarct size and improved short- and long-term outcomes (3,4). Nevertheless, residual cardiovascular risk persists after STEMI. Efforts are therefore underway to enhance the implementation of existing evidence-based treatments (4,5) and generate novel therapies that prevent and mitigate PCI complications, such as microvascular obstruction (MVO) and the clinical no-reflow phenomenon. No-reflow occurs when the flow in the epicardial coronary artery (or graft) is restored but remains suboptimal at the myocardial or microcirculatory level. This is manifested during coronary angiography as slow contrast flow despite successful resolution of the epicardial artery occlusion. Earlier studies have suggested that the incidence of no-reflow is variable and ranges from 5–50% (6). The main underlying pathophysiology of no-reflow is believed to be MVO, which appears to have many putative pathways including: distal embolization, vasospasm, microvascular damage related to ischemia/infarction, and ischemia-reperfusion injury, coupled with a predisposition (genetic and/or acquired) of the coronary microcirculation to injury (6). To date, several studies have shown that the presence of MVO is associated with worse outcomes, independent of the infarct size. However, these reports were small sized, had methodological flaws and inconsistent findings, and lacked power to provide definitive evidence (7-10).

It is in this context that the study by de Waha *et al.* should be viewed (11). The investigators conducted a comprehensive patient-level meta-analysis inclusive of seven randomized clinical trials (RCTs) and 1,688 STEMI patients who underwent primary PCI followed by early imaging with cardiac magnetic resonance (CMR) (11). CMR using late gadolinium enhancement was performed at a median of 3 days. Overall, MVO was diagnosed in ~57% of patients and was more common among diabetic patients, those who had a longer symptom-to-device duration, and those with occlusion of the left anterior descending artery (LAD), and baseline Thrombolysis In Myocardial Infarction (TIMI) flow 0/1. At a median follow-up of 1-year, there was a stepwise increase in the risk of all-cause mortality and hospitalization for heart failure with the increasing degree of MVO. Consistent with prior smaller studies (7,8), MVO was independently associated with all-cause mortality,

even after adjusting for infarct size. Multiple putative mechanisms may explain the graded association between MVO severity and adverse events, as discussed by the investigators. Interestingly, MVO remained an independent predictor of mortality but not of HF hospitalization after forcing infarct size into the multivariable analyses. This may espouse the plausible theory that infarct tissue heterogeneity and consequent re-entrant lethal arrhythmias may be key pathogenetic factors. This is however difficult to ascertain in the absence of granular data on the various etiologies of all-cause mortality. Despite the limitations arising from pooling data across several trials with variable inclusion and exclusion criteria, the present study is the largest report to date examining the clinical impact of MVO. In addition, an independent core laboratory evaluated the CMR data, the clinical end points were adjudicated by an independent committee in each trial, and the findings were further corroborated in different patient subgroups, all of which add to the robustness of the study findings.

Overall, de Waha *et al.* (11) demonstrated that MVO is not only more prevalent than previously believed but is also conclusively associated with adverse outcomes. Their seminal contribution raises numerous questions regarding its clinical implications: should a CMR be routinely performed after STEMI to diagnose MVO? How do clinicians prevent and treat MVO? What long-term strategies should be implemented in these patients?

While CMR using late gadolinium enhancement is currently the most sensitive non-invasive imaging modality to assess coronary MVO (7,12,13), it is costly and its overall value as a routine strategy remains unproven. Serial cardiac troponin measurements and left ventricular function assessment (4,5), preferably with a non-invasive modality such as an echocardiogram, should be implemented in all STEMI patients and are clinically-useful surrogates of infarct size. Moreover, MVO can be diagnosed by a myriad of other clinical (e.g., incomplete resolution of ST segment elevation) and angiographic measures (e.g., TIMI myocardial perfusion grade 0 or 1), although these are less sensitive measures and do not provide a reliable quantitative assessment of MVO as CMR.

The study by de Waha *et al.* (11) identified multiple factors associated with MVO, of which many are modifiable. Achieving prompt reperfusion is of paramount importance and constant attempts should be undertaken to improve timeliness of reperfusion for STEMI patients presenting to either PCI-capable or non-PCI-capable hospitals (4,5). Optimal blood glucose control prior to primary PCI was shown to lower the risk of no-reflow (14). Although hyperlipidemia was not associated with MVO in the current study, a prior meta-analysis found that statin use prior to primary PCI was associated with a lower risk of no-reflow (15). Additional approaches such as aspiration thrombectomy, deferred stenting strategy, and ischemic pre-conditioning have been shown to reduce the risk of no-reflow; however, the improvement in angiographic measures with these strategies did not translate into improvement in clinical outcomes (16-18). In a patient level meta-analysis of three large RCTs, aspiration thrombectomy was associated with a trend towards reduced cardiovascular mortality in STEMI patients with high thrombus burden (19). Notably, the 2015 ACC/AHA/SCAI Focused Update on primary PCI gave a class IIb recommendation for the selective and bailout use of aspiration thrombectomy (20). It is therefore reasonable to attempt aspiration thrombectomy when heavy thrombus is visualized after primary PCI. Pharmacological interventions with intracoronary or intragraft vasodilators (e.g., verapamil, nicardipine, adenosine, nitroprusside) delivered into the distal epicardial vessel are advocated, although evidence supporting their use is derived from few small studies (21). Fibrinolytic agents and anticoagulation therapy have not been shown to reduce the incidence of no-reflow in animal models (22,23), but a small pilot study showed that intracoronary low-dose streptokinase administered post-PCI might improve myocardial reperfusion in STEMI patients (24). Glycoprotein IIb/IIIa receptor inhibitors can also be used as a bail out strategy on top of dual antiplatelet therapy (preferably with a novel oral $P2Y_{12}$ receptor inhibitor) (4). Some experimental studies demonstrated that the initiation of therapeutic hypothermia minutes after restoring flow in a proximally-occluded coronary artery significantly reduced the incidence of no-reflow, but did not affect infarct size (25). Overall, there is a paucity of effective therapies for MVO in STEMI patients and research validating novel therapies in this arena is urgently needed.

The identification of STEMI patients with MVO is important because of its prognostic value and potential therapeutic implications. Secondary prevention therapies, such as neuroendocrine inhibitors (e.g., beta blockers, ACE-I/ARB) and high-intensity statin therapy, are recommended by guidelines and constitute performance measures that should be implemented in all STEMI patients (4,5). Based on the current study findings, clinicians may argue that STEMI patients with MVO are at higher intermediate-term risk and may benefit from closer

longitudinal follow-up and more aggressive up-titration of evidence-based therapies, although this remains to be proven in future prospective studies.

In summary, the meta-analysis by de Waha *et al.* (11) is a valuable contribution which demonstrates that MVO is a prevalent condition and has important prognostic implications in STEMI patients undergoing primary PCI. The findings of this study should direct our attention to focus on the development and validation of therapies that specifically target MVO and no-reflow and on the evaluation of their long-term impact.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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