

EDITORIAL

# Is Platelet Reactivity a Therapeutic Target to Limit Microvascular Obstruction?

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**D**espite advances in treatment for ST-segment-elevation myocardial infarction (STEMI), microvascular obstruction is a prognostically significant complication for which there is no treatment.<sup>1,2</sup> Microvascular obstruction occurs in approximately half of patients who present with STEMI,<sup>3</sup> and is associated with the appearance of no- or slow-flow on the postprimary percutaneous coronary intervention (PCI) angiogram. Microvascular obstruction can also be revealed by cardiac magnetic resonance imaging, and is represented by a hypointense core within the late gadolinium contrast-enhanced infarct zone.

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**See Article by Massalha et al.**

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Microvascular obstruction represents microvascular damage and limited tissue perfusion. If microvascular perfusion is not restored, capillary degradation transitions to myocardial hemorrhage, which promulgates adverse left ventricular remodeling and adverse cardiac outcomes.<sup>3</sup> The multifactorial causes of microvascular obstruction can be divided into extrinsic and intrinsic mechanisms.<sup>4</sup> Ischemia followed by reperfusion subjects the myocardium to injury. Myocyte edema results in capillary compression, which perpetuates local ischemia leading to more myocyte death. Microvasculature spasm, plugging by distal embolization of thrombus or

atherosclerotic debris, and luminal invasion by white cells, red cells, and platelets all contribute to microvascular obstruction. Damage to endothelial cells is caused by intracellular calcium overload, increased mitochondrial permeability, and local acute inflammatory response. The resulting endothelial cell swelling further obstructs the microvasculature.<sup>4</sup>

Microvascular obstruction develops from the sub-endocardium and follows the wavefront of ischemia toward the epicardium, and the size of microvascular obstruction is positively associated with the size of infarction. If coronary reperfusion is not achieved quickly, microvascular obstruction will establish, leading to hemorrhagic transformation within the infarct core. On the other hand, the restoration of microvascular perfusion within the infarct zone should salvage reversibly ischemic cardiomyocytes and limit edema and microvascular obstruction. Currently, there are no proven interventions that can prevent microvascular obstruction at the time of primary PCI or treat microvascular obstruction that is established.

The T-TIME (Trial of Low-Dose Adjunctive Alteplase During Primary PCI; URL: <https://www.clinicaltrials.gov>; Unique identifier: NCT02257294) trial investigated the use of low-dose intracoronary alteplase to prevent and treat microvascular obstruction in patients undergoing primary PCI for STEMI.<sup>5</sup> The trial hypothesized that intracoronary alteplase would limit distal embolization of coronary thrombus, as well as the generation

**Key Words:** Editorials ■ adenosine di-phosphate ■ arachidonic acid ■ dual antiplatelet therapy ■ microvascular obstruction ■ platelet aggregation ■ ST-segment-elevation myocardial infarction

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The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

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of microvascular thrombi, and therefore limit the occurrence and extent of microvascular obstruction. Unexpectedly, there was no difference in microvascular obstruction at 4 days post-STEMI in patients who had received 10 mg of alteplase, 20 mg of alteplase, or placebo.<sup>5</sup> The T-TIME trial underlines the therapeutic challenges and uncertainty still posed by microvascular obstruction.

Several therapeutic trials are targeting microvascular obstruction<sup>6–15</sup> (Table). We would like to highlight some of them. The EURO-ICE (European Intracoronary Cooling Evaluation in Patients With STEMI; URL: <https://www.clinicaltrials.gov>; Unique identifier: NCT03447834) trial is comparing selective intracoronary hypothermia using cooled saline with standard of care in patients who present with an anterior STEMI.<sup>9</sup> The presence and extent of microvascular obstruction and intramyocardial hemorrhage are secondary end points. The PiCSO (Pressure-Controlled Intermittent Coronary Sinus Occlusion) PiCSO-AMI-I (in Acute Myocardial Infarction; URL: <https://www.clinicaltrials.gov>; Unique identifier: NCT03625869) trial is assessing the efficacy and safety of an intermittent coronary sinus occlusion device in patients with anterior STEMI. The hypothesis is that increased coronary sinus pressure will maintain microcirculatory patency and redistribute blood flow to areas of ischemic myocardium when used in conjunction with standard PCI.<sup>8</sup> There are 2 trials assessing the effect of the timing of PCI in patients with STEMI.<sup>6,7</sup> The Evaluate Early Invasive Strategy for Patients With STEMI Presenting 24 to 48 Hours From Symptom Onset (URL: <https://www.clinicaltrials.gov>; Unique identifier: NCT04962178) trial will assess immediate stenting versus optimal medical therapy in patients who present within 24 to 48 hours of symptom onset.<sup>6</sup> Comparatively, the LATE-MI (Late Reperfusion With Percutaneous Coronary Intervention in Patients With STEMI; URL: <https://www.clinicaltrials.gov>; Unique identifier: NCT02445885) trial will investigate immediate versus deferred stenting for patients presenting within 12 to 36 hours of onset of symptoms.<sup>7</sup> There are several trials investigating the effects of intracoronary therapy, including cangrelor (PITRI [Platelet Inhibition to Target Reperfusion Injury] trial; URL: <https://www.clinicaltrials.gov>; Unique identifier: NCT03102723),<sup>10</sup> and alteplase (OPTIMAL [Optimal Coronary Flow After PCI for Myocardial Infarction—A Pilot Study; URL: <https://www.clinicaltrials.gov>; Unique identifier: NCT02894138] trial).<sup>11</sup> RESTORE-MI (Restoring Microcirculatory Perfusion in STEMI; URL: <https://www.australianclinicaltrials.gov.au>; Unique identifier: ACTRN12618000778280) is a phase 3 trial of low- or very-low-dose tenecteplase in patients who have had PCI for STEMI and have an index of microvascular resistance >32.<sup>13</sup> A similar stratification is implemented in the OPTIMAL trial. The

EMPRESS-MI (Empagliflozin to Prevent Worsening of Left Ventricular Volumes and Systolic Function After Myocardial Infarction; URL: <https://www.clinicaltrials.gov.au>; Unique identifier: NCT05020704) trial will investigate empagliflozin 10 mg daily in patients with reduced left ventricular ejection fractions post-STEMI or non-STEMI, to determine the effect on change in left ventricular end-systolic volume from index event to 6 months using cardiac magnetic resonance imaging.<sup>16</sup> The extent of microvascular obstruction will also be assessed.

In the search for therapeutic strategies for microvascular obstruction, Massalha et al correlated platelet reactivity post-STEMI with the extent of microvascular obstruction ~5 days after admission.<sup>17</sup> The results are now published in this issue of the *Journal of the American Heart Association (JAHA)*.<sup>17</sup> One hundred five patients presenting with first STEMI were included in the study (mean age, 57 years [10 years]; 91% men). Patients were treated with primary PCI and dual antiplatelet therapy (DAPT), with glycoprotein IIa/IIIb use and thrombus aspiration decided by the treating clinician. Platelet reactivity was assessed using arachidonic acid- and adenosine diphosphate-induced platelet aggregation. Infarct size and microvascular obstruction were assessed by late gadolinium enhancement imaging, using a 5 SD above remote region cutoff. Major adverse cardiac events were assessed at 1 year.

The investigators observed that only 74 (70%) patients had an optimal response to DAPT. A suboptimal response to DAPT, defined by arachidonic acid-induced platelet aggregation  $\geq 30\%$  and adenosine diphosphate-induced platelet aggregation  $\geq 50\%$ , was associated with greater microvascular obstruction as a percentage of left ventricular mass (3.2 [interquartile range [IQR], 0.9–5] versus 0.32 [IQR, 0.2–2],  $P=0.004$ ) and as a percentage of infarct size (8 [IQR, 2–14] versus 0.98 [IQR, 0–6],  $P=0.001$ ). This relationship persisted after adjustment for other clinically significant variables, including anterior infarct location, initial TIMI (Thrombolysis in Myocardial Infarction) flow, and symptom-to-balloon time. Patients with suboptimal DAPT response had higher peak troponins, lower ejection fraction, and a larger infarct size. In a 1-year follow-up, including 88% of the cohort, DAPT response was associated with major adverse cardiac events (hazard ratio, 3.2; 95% CI, 1.3–8.3;  $P=0.010$ ). There were no differences in baseline characteristics or treatments received, such as glycoprotein IIb/IIIa inhibitor therapy administered during the PCI procedure, which might have influenced DAPT responsiveness.

The investigators also found that patients treated with clopidogrel had higher levels of platelet activity when compared to those treated with third-generation antiplatelets ticagrelor or prasugrel. However, sensitivity analysis showed that the relationship between

**Table. Current Therapeutic Trials Investigating Microvascular Obstruction**

Clinical Trial	Identifier	Intervention(s)	Comparator	Population
Timing of PCI				
Evaluate Early Invasive Strategy for Patients With STEMI Presenting 24–48 Hours From Symptom Onset <sup>6</sup>	NCT04962178	Immediate PCI	Optimal medical therapy	STEMI patients presenting within 24–48 h of onset
LATE-MI (Late Reperfusion With Percutaneous Coronary Intervention in Patients With ST-Segment Elevation Myocardial Infarction) <sup>7</sup>	NCT02445885	Immediate PCI	Deferred PCI	STEMI patients presenting within 12–36 h of onset
Procedural techniques				
PICSO (Pressure-Controlled Intermittent Coronary Sinus Occlusion) PICSO-AMI-I (in Acute Myocardial Infarction) <sup>8</sup>	NCT03625869	Pressure-controlled intermittent coronary sinus occlusion	Standard care	Anterior STEMI
EURO-ICE (European Intracoronary Cooling Evaluation in Patients With ST-Elevation Myocardial Infarction) <sup>9</sup>	NCT03447834	Selective intracoronary hypothermia	Standard care	Anterior STEMI
Pharmacological, intracoronary				
PITRI (Platelet Inhibition to Target Reperfusion Injury) <sup>10</sup>	NCT03102723	Intracoronary cangrelor	Placebo	STEMI
OPTIMAL (Optimal Coronary Flow After PCI for Myocardial Infarction—A Pilot Study) <sup>11</sup>	NCT02894138	Intracoronary alteplase	Placebo	STEMI with IMR>30 in culprit vessel
RECOVERII (Effect of Low-Dose Intracoronary Reteplase on Myocardial Infarct Size During Primary Percutaneous Coronary Intervention) <sup>12</sup>	NCT04571580	Intracoronary reteplase 9 mg or 18 mg	Placebo	Anterior STEMI
RESTORE-MI (Restoring Microcirculatory Perfusion in ST-Elevation Myocardial Infarction) <sup>13</sup>	ACTRN12618000778280	Intracoronary tenecteplase	Placebo	STEMI with IMR >32 in culprit vessel
Pharmacological, oral				
PRESTIGE-AMI (Peri-Treatment of SGLT-2 Inhibitor on Myocardial Infarct Size and Remodeling Index in Patients With Acute Myocardial Infarction and High Risk of Heart Failure Undergoing Percutaneous Coronary Intervention) <sup>14</sup>	NCT04899479	SGLT2 inhibitor	Placebo	STEMI or non-STEMI
COVERT-MI (Colchicine for Left Ventricular Remodeling Treatment in Acute Myocardial Infarction) <sup>15</sup>	NCT03156816	Colchicine	Placebo	STEMI

IMR indicates index of microvascular resistance; PCI, percutaneous coronary intervention; SGLT2, sodium-glucose co-transporter 2; and STEMI, ST-segment–elevation myocardial infarction.

platelet reactivity and microvascular obstruction remained when type of P2Y12 (sodium-glucose cotransporter 2) inhibitor was adjusted for.

This study has strengths and limitations. First, selecting patients with first STEMI and no prior ischemic heart disease reduces confounding effects of chronic myocardial infarction. However, the investigators do not report how many patients were screened for eligibility. Second, contemporary cardiac magnetic resonance imaging techniques for measuring microvascular obstruction were used, but other forms of tissue characterization (eg, extracellular volume) were lacking. P2Y12 inhibitor treatment was given at the physicians' discretion, and this was accounted for in the statistical analysis, as well as other clinically important variables. The incidence of microvascular obstruction in this cohort, and therefore the effect of DAPT responsiveness on the incidence of microvascular obstruction, is not reported. In the methodology, the investigators state that P2Y12 inhibition could have been commenced at varying time points following the first medical contact to the PCI; however, the timing of P2Y12 inhibitor initiation is not reported. The authors highlight the ATLANTIC trial (Prehospital Ticagrelor in ST-Segment Elevation Myocardial Infarction; URL: <https://www.clinicaltrials.gov>; Unique identifier: NCT01347580), which showed that ticagrelor given before hospitalization prevented early stent thrombosis compared to when given in the hospital.<sup>18</sup> However, there is no difference in platelet reactivity between P2Y12 inhibition commenced before hospitalization versus in the hospital.<sup>19</sup> The most significant limitation is the small sample size and limited number of MACE leading to imprecision and the possibility of type 1 and type 2 errors. Accordingly, these observational findings are hypothesis generating.

There remains an unmet therapeutic need for the reduction of microvascular obstruction in reperfused STEMI. The study by Massalha and colleagues adds to the growing body of evidence aiming to target microvascular obstruction. These findings reveal platelet reactivity as a possible therapeutic target for reducing microvascular obstruction. The SGLT2 (sodium-glucose cotransporter 2) inhibitors have been found to reduce platelet reactivity,<sup>20</sup> which may go some way to explain their cardioprotective effects. Two upcoming trials, EMPRESS-MI and PRESTIGE-AMI (Peritreatment of SGLT2 Inhibitor on Myocardial Infarct Size and Remodeling Index in Patients With Acute Myocardial Infarction and High Risk of Heart Failure Undergoing Percutaneous Coronary Intervention; URL: <https://www.clinicaltrials.gov>; Unique identifier: NCT04899479), will investigate the use of SGLT2 inhibitors in patients with STEMI or non-STEMI and will assess microvascular obstruction using cardiac magnetic resonance imaging.<sup>14,16</sup> Patients recruited into PRESTIGE-AMI will commence an SGLT2 inhibitor

before coronary intervention, whereas in EMPRESS-MI, empagliflozin will be commenced within 14 days of hospital admission. Massalha et al hypothesize that early and effective platelet inhibition, achieved by chewing or subcutaneous administration of P2Y12 inhibitors, may lead to reduced microvascular obstruction.<sup>17</sup> The mechanisms of the cardiovascular effects of SGLT2 inhibitors are largely unknown; hence, the EMPRESS-MI and PRESTIGE-AMI trials are of great interest. For now, Massalha et al have identified platelet reactivity as a potential therapeutic target for the prevention of microvascular obstruction.

## ARTICLE INFORMATION

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### Disclosures

Dr Carberry reports that her employer, the University of Glasgow, has received research funding from Boehringer Ingelheim for her work relating to the EMPRESS-MI trial. Berry is supported by a British Heart Foundation Centre of Research Excellence award (RE/18/6134217) and funding from the Chief Scientist Office, United Kingdom Research and Innovation (COVID-HEART, reference MC/PC/20014), Engineering and Physical Sciences Research Council (EP/N014642/1; EP/S030875/1), and Wellcome Trust. The University of Glasgow, which employs Dr Berry, holds research and consultancy agreements with Abbot Vascular, AstraZeneca, Boehringer Ingelheim, Corvoventis, GSK, HeartFlow, Menarini, Neovasc, Novartis, Siemens Healthcare, and Valo Health. These companies had no involvement in this article.

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