Optimized Treatment of ST-Elevation Myocardial Infarction

The Unmet Need to Target Coronary Microvascular Obstruction as Primary Treatment Goal to Further Improve Prognosis

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Abstract: **Primary percutaneous coronary intervention is nowadays the preferred reperfusion strategy for patients with acute ST-segment–elevation myocardial infarction, aiming at restoring epicardial infarct-related artery patency and achieving microvascular reperfusion as early as possible, thus limiting the extent of irreversibly injured myocardium. Yet, in a sizeable proportion of patients, primary percutaneous coronary intervention does not achieve effective myocardial reperfusion due to the occurrence of coronary microvascular obstruction (MVO). The amount of infarcted myocardium, the so-called infarct size, has long been known to be an independent predictor for major adverse cardiovascular events and adverse left ventricular remodeling after myocardial infarction. Previous cardioprotection studies were mainly aimed at protecting cardiomyocytes and reducing infarct size. However, several clinical and preclinical studies have reported that the presence and extent of MVO represent another important independent predictor of adverse left ventricular remodeling, and recent evidences support the notion that MVO may be more predictive of major adverse cardiovascular events than infarct size itself. Although timely and complete reperfusion is the most effective way of limiting myocardial injury and subsequent ventricular remodeling, the translation of effective therapeutic strategies into improved clinical outcomes has been largely disappointing. Of importance, despite the presence of a large number of studies focused on infarct size, only few cardioprotection studies addressed MVO as a therapeutic target. In this review, we provide a detailed summary of MVO including underlying causes, diagnostic techniques, and current therapeutic approaches. Furthermore, we discuss the hypothesis that simultaneously addressing infarct size and MVO may help to translate cardioprotective strategies into improved clinical outcome following ST-segment–elevation myocardial infarction.** **(*Circ Res*. 2019;125:245-258. DOI: 10.1161/CIRCRESAHA.119.315344.)**

Key Words: myocardial infarction ■ myocardial reperfusion ■ myocardium ■ percutaneous coronary intervention ■ ventricular remodeling

Advances in the treatment of patients with acute ST-segment–elevation myocardial infarction (STEMI) have resulted in a decline in mortality over the past 4 decades,[1] with 1-year cardiac mortality in all-comers patients with STEMI treated with primary percutaneous coronary intervention (PCI) reaching a plateau of ≈7% to 8%.[2] However, although national system delays for patients undergoing primary PCI have been significantly improved over recent years, in-hospital mortality has remained substantially unchanged.[3,4] Moreover, morbidity caused by the development of post–myocardial infarction (MI) left ventricular (LV) remodeling and heart failure remains significant and is on the rise.[5] In particular, 1 in 5 patients may be hospitalized with heart failure within 12 months of presenting with an anterior STEMI.[5]

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Nonstandard Abbreviation and Acronyms

AIDA STEMI	Abciximab Intracoronary versus intravenous Drug Application in STEMI
ANP	atrial natriuretic peptide
CMR	cardiac magnetic resonance
IMH	intramyocardial hemorrhage
IMR	index of microvascular resistance
LV	left ventricular
MACE	major adverse cardiovascular events
MI	myocardial infarction
MVO	microvascular obstruction
OxAMI-PICSO	Oxford Acute Myocardial Infarction–Pressure-Controlled Intermittent Coronary Sinus Occlusion
PCI	percutaneous coronary intervention
PICSO	pressure-controlled intermittent coronary sinus occlusion
RESTORE-MI	Restoring Microcirculatory Perfusion in ST-Elevation Myocardial Infarction
SECURE-PCI	Statins Evaluation in Coronary Procedures and Revascularization
STEMI	ST-segment–elevation myocardial infarction
STR	ST-segment resolution
TIMI	Thrombolysis In Myocardial Infarction

Infarct size has long been known to be an independent predictor of adverse LV remodeling after MI.[6] In addition to infarct size, several clinical and preclinical studies have reported that the presence and extent of microvascular obstruction (MVO) represents an important independent predictor of adverse LV remodeling,[7,8] and recent evidence supports the notion that MVO may be more predictive of major adverse cardiovascular events (MACE) than infarct size itself.[9]

Although timely and complete reperfusion is the most effective way of limiting myocardial injury and subsequent ventricular remodeling,[10] most other effective therapeutic strategies for reducing infarct size or MVO have not been translated into improved clinical outcomes, despite tremendous research efforts in this field.[5,11] There is currently only one study demonstrating improved clinical outcome (cardiac mortality, hospitalization for heart failure) with remote ischemic conditioning (RIC) in patients with STEMI.[12] Several explanations, including imperfect study design and true lack of efficacy, have been proposed to be responsible for the difficulties in translation.[13] For example, in the field of cardioprotection, preclinical data may be inadequate, and study design problems relate to patient selection or inappropriate timing and mode of delivery of the cardioprotective agent.[14] Moreover, previous cardioprotection studies were mainly aimed at protecting cardiomyocytes and reducing infarct size, neglecting other targets notably the coronary microcirculation.[10,11,15] On the contrary, infarct size and MVO represent 2 complementary therapeutic targets for cardioprotection trials.[16]

In this review, we discuss the hypothesis that an integrated therapeutic approach simultaneously addressing both infarct size and MVO may help to effectively translate cardioprotective strategies into improved clinical outcome for patients with STEMI.

Mechanisms Underlying MVO During STEMI

MVO refers to the inability to reperfuse the coronary microcirculation (microvessels, <200 μm diameter) in a previously ischemic region, despite opening of the epicardial vessel.[17,18] Mechanisms underlying myocardial injury and MVO are multiple and interacting[18] (Figure 1). Ischemic injury represents a well-known mechanism responsible for cardiomyocyte death, and when ischemia lasts >3 hours, the adverse effects of ischemia-associated injury become all the more pronounced.[19–22] However, besides effects on cardiomyocytes, ischemia/reperfusion injury may also damage other cell types, in particular, endothelial cells. Notably, apoptosis of endothelial cells seems to precede cardiomyocyte cell apoptosis during ischemia/reperfusion injury.[23] Initial studies in the dog using electron microscopic analysis after 90 minutes of coronary artery occlusion followed by reperfusion revealed severe capillary damage, endothelial protrusions, and blebs that appeared to block the capillary lumen, and endothelial gaps with extravascular erythrocytes that in turn may favor the occurrence of intramyocardial hemorrhage (IMH).[24] MVO is caused by further obliteration of vessel lumen by neutrophil-platelet aggregates, which in turn produce large amount of vasoconstrictors and inflammatory mediators.[18,24] Furthermore, intense interstitial myocardial edema occurring upon reperfusion compresses capillaries and small arterioles, further decreasing flow through these dysfunctional vessels.[25]

Distal embolization is another important mechanism contributing to both myocardial injury and MVO. Coronary microembolization in experimental models causes regional contractile dysfunction. Of note, baseline myocardial perfusion starts falling when microspheres obstruct >50% of coronary capillaries.[26] Thus, the small number of emboli during primary PCI in the setting of STEMI, although not affecting baseline myocardial perfusion may create a local reacting milieu with release of inflammatory and vasoactive substances from coronary plaque, such as endothelin-1, tissue factor, and microparticles, which have the potential to increase the severity of the functional impairment of the coronary circulation.[27,28] Moreover, in patients with STEMI, the coronary neutrophil extracellular traps burden correlates negatively with ST-segment resolution (STR) and positively with infarct size, thus suggesting that neutrophil extracellular traps may propagate thrombosis and inflammation distally into the infarcted myocardium and contribute to myocyte death during atheroembolism.[29] Finally, oxidative stress, ischemia per se, and soluble substances released from the ruptured plaque[27] reduce the bioavailability of nitric oxide, further contributing to the dysfunction of the myocardial microcirculation.[18] Distal embolization occurring during primary PCI probably represents only a part of the phenomenon, along with spontaneous distal embolization arising from ruptured or eroded plaques during the natural course of an acute coronary syndrome, and this may explain the negative results deriving from trials with distal filter protection devices.[31] However, the role of distal embolization during primary PCI is not so negligible, and a different approach may be probably useful to prevent MVO occurrence. Indeed, in the MASTER trial (Safety and Efficacy Study of MGuard Stent After a Heart Attack), patients with STEMI were randomized to conventional stent implantation or Mesh-covered embolic protection stent, and superior rates of epicardial coronary flow and

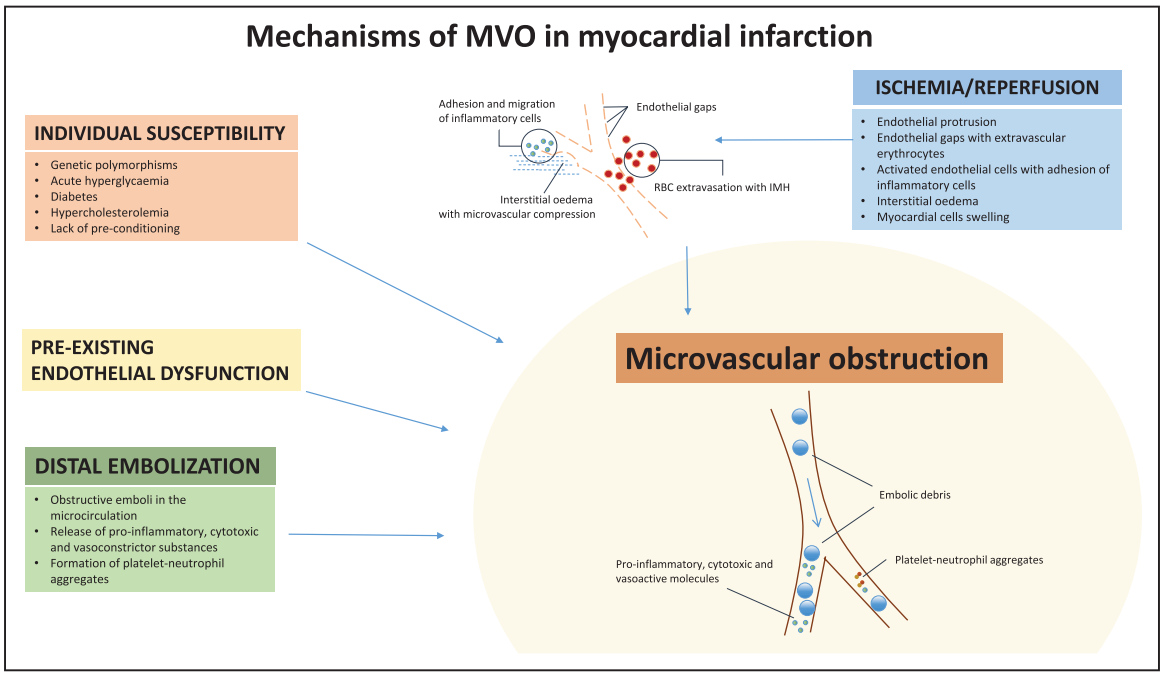

Figure 1. Pathogenic mechanisms involved in coronary microvascular obstruction (MVO) and cardiomyocyte death.

complete STR were found in the Mesh-covered stent group. Of importance, this benefit was particularly evident among patients with a higher thrombus burden.[32]

Another pathogenic mechanism causing MVO is represented by individual susceptibility to microvascular dysfunction, related to the function, as well as to the structure and the density of the microcirculation.[33] Genetic factors may modulate adenosine-induced vasodilation (ie, 1976T.C polymorphism of the adenosine 2A receptors gene was suspected to be related with a higher prevalence of MVO).[18] Genetic variations within defined regions of *VEGFA* and *CDKN2B-AS1* genes have been shown to be associated with coronary microvascular dysfunction, whereas sex-specific allelic variants within *MYH15, VEGFA*, and *NT5E* genes seem to be related to an increased risk of coronary microvascular dysfunction in men.[34] Another factor modulating individual susceptibility to MVO is the presence of ischemic preconditioning, which not only protects the myocardium but might also protect the coronary microcirculation.[18] Accordingly, preinfarction angina might help preventing cardiomyocyte death and MVO by inducing ischemic preconditioning.[18] Importantly, the beneficial effect of preinfarction angina may be blunted in humans because of risk factors or drugs therapy affecting unfavorably ischemic preconditioning.[35]

Finally, preexisting microvascular dysfunction, particularly in patients with multiple cardiovascular risk factors, may be associated with an increased risk of developing MVO.[18] Indeed, preexistent microvascular dysfunction might represent an important pathogenetic component of MVO, as previous studies demonstrated that coronary blood flow is reduced by 50% in the nonculprit coronary arteries during acute MI, before, and after primary PCI, thus confirming a global rather than a regional myocardial microcirculatory impairment.[36] Also, known cardiovascular risk factors have been shown to predispose to MVO. In particular, acute hyperglycemia, which was independent on previous glycemic control evaluated by glycosylated hemoglobin A1c levels, is associated with a higher risk of developing MVO, therefore, suggesting a direct detrimental effect on reperfusion injury.[37] Moreover, in patients with diabetes mellitus, disturbances in glucose metabolism per se may also have a negative impact on myocardial reperfusion, as elevated levels of free fatty acids during hyperglycemia reduce endothelium-derived vasodilation of the myocardial vasculature[38] and hyperglycemia causes the plugging of leukocytes in the microvasculature of the myocardium and increases procoagulable properties of platelets.[39] In addition, dyslipidemia may predispose to MVO. Indeed, hypercholesterolemia may impair vascular wall function and structure, interfering with endothelial function,[40] along with a possible role in the delayed healing after ischemia/reperfusion injury.[41] Also, hypercholesterolemia may cause a near-complete abrogation in vascular nitric oxide bioavailability, elevated oxidative stress, and a proinflammatory milieu, conditions associated with an impaired vascular reactivity.[40] Hypertension is also involved in the predisposition to MVO. Indeed, hypertension is linked to endothelial dysfunction, along with ultrastructural remodeling of cardiac microvessels, that can cause a progressive impairment of flow-mediated vasodilation. Advanced age has also been shown to be an independent predictor of MVO.[42]

Diagnostic Techniques for MVO Assessment

Patients presenting with STEMI may develop MVO, with a variable prevalence ranging from 5% up to 60%, according to the methods used to assess the phenomenon and to the population under study.[18] Indeed, MVO can be assessed using different techniques and at different time points after STEMI.

Cardiac magnetic resonance (CMR) represents the reference standard technique for in vivo MVO detection and quantification.[18,43] On contrast-enhanced CMR MVO is identified as a dark hypointense core within the areas of hyperenhancement on

either early gadolinium enhancement (referred to as early MVO) or conventional late gadolinium enhancement (referred to as late MVO).[43] Early and late MVO are assessed ≈1 and 15 minutes after gadolinium injection, respectively. Because the presence and extent of MVO diminish over time, early MVO is more sensitive to less pronounced, subtle microvascular injury. Its prognostic value for the prediction of postinfarction adverse events, however, is low. In contrast, late MVO reflects severely disturbed microcirculation and is strongly associated with clinical outcome.[43] Apart from the impact of different imaging techniques, CMR measurements of MVO are also affected by the timing of image acquisition after infarction due to the dynamic course of microvascular injury. Therefore, STEMI trials require predefined CMR protocols for the entire study population to ensure the validity of the acquired data. The imaging protocols in previous studies, however, were quite heterogeneous, which hampers interstudy comparisons and collaborative research with data merging. The international standardization of postinfarction CMR imaging protocols is currently elaborated and urgently needed to overcome the mentioned drawbacks and further strengthen CMR as the reference method to evaluate myocardial damage.[43,44] MVO can be also detected at coronary angiography (defined as TIMI [Thrombolysis In Myocardial Infarction] flow grade <3 or 3 with a myocardial blush grade 0 to 1), by myocardial contrast echocardiography, as an incomplete STR on ECG or directly by invasive measurement of the index of microvascular resistance (IMR) using a diagnostic guidewire.[18] This technique is appealing because IMR can be measured immediately during primary PCI identifying in the catheterization laboratory high-risk patients with an increased IMR requiring a more intensive therapy targeting MVO. Indeed, patients with a high value of IMR (>40 U) at the time of primary PCI might likely benefit from a more aggressive therapeutic approach (ie, infusion of glycoprotein IIb/IIIa inhibitors, intracoronary thrombolysis, or vasodilators). However, patients with low values of IMR (<40 U) will not be subjected to aggressive therapies with the unnecessary risk of adverse events, such as bleeding.[45] At the same time, it should be noted that, among the available methods, IMR has the highest predictive accuracy for identifying patients at risk of IMH.[19]

Correlation Between Infarct Size and MVO

Evidence derived from trials and meta-analyses has demonstrated that morbidity and mortality after STEMI are closely related to infarct size. In particular, a recent meta-analysis of 2632 patients from 10 randomized controlled trials showed that infarct size measured by CMR or single-photon emission computed tomography, within a month after primary PCI, was strongly associated with 1-year hospitalization for heart failure and all-cause mortality.[6] Of note, for every 5% increase in MI size, there was a 20% increase in the relative hazard ratio for 1-year hospitalization for heart failure and all-cause mortality.[6] However, recent evidence suggests that MVO may be more predictive of clinical outcome after primary PCI than infarct size itself.[46] Indeed, in a patient-level meta-analysis of 1025 patients from 8 studies, van Kranenburg et al[47] showed that the presence of MVO was an independent predictor of MACE at 2 years in patients with STEMI, whereas MI size was not independently associated with adverse events. Moreover, a more recent patient-level meta-analysis from 7 randomized controlled trials (n=1688) by de Waha et al[9] confirmed the prognostic value of MVO over MI size for mortality and hospitalization for heart failure at 1 year. Of note, in the fully adjusted model, every 1% absolute increase in MVO extent was independently associated with a 14% relative increase in 1-year all-cause mortality and an 8% increase in 1-year heart failure hospitalization. Anterior infarct location, baseline TIMI flow, and symptom-to-device time were not significant predictors of outcomes in these adjusted models, suggesting that their prognostic impact may be mediated through larger areas of MVO.[9] Similar findings were obtained by Symons et al[48] in a longitudinal study of 810 patients after a median follow-up of 5.5 years.

It is well known that patients with larger MI are more likely to develop MVO.[11,44] Indeed, myocardial necrosis extends from the center of the area-at-risk to the peripheral zone after coronary occlusion. The functional border zone is in the marginal zone of the risk area, and myocardial perfusion due to the diffusion from the normal peripheral myocardium plays an important role in preserving myocardial viability in this area. If the risk area is too large to be perfused with collateral or diffusive blood flow, the size of infarction would be greater leading also to a greater area of MVO.[49] However, pathophysiologic mechanisms through which MVO adversely impacted prognosis and demonstrated a superior prognostic value over MI size are likely multiple and not completely understood. Indeed, beyond cardiomyocyte injury, severe microvascular damage after STEMI has been shown to be associated with extravasation of red blood cells leading to IMH[44,50] (Figure 2). Animal and human studies demonstrated that, in contrast to the nonreperfused myocardium, microvascular reperfusion injury is associated with IMH.[51,52] Two possible mechanisms link MVO and IMH. The first mechanism suggests that hemorrhage leads to myocardial swelling and compression on the microvasculature, which in turn worsens MVO. In the second plausible mechanism, it is the microvascular injury and obstruction that lead to endothelial damage and subsequent leakage of blood cells to the interstitium. Of note, IMH was found to be associated with the duration of ischemia and necrosis, and represented a hallmark of reperfusion, whereas no IMH was observed in animals with permanent coronary occlusion.[53] CMR studies demonstrated that IMH occurs in ≈40% of patients with STEMI,[44] and although MVO is present in all patients with IMH, IMH does not have to present with MVO.[54] Of importance, recent data revealed that IMH occurring in the acute phase after primary PCI leads to residual myocardial iron deposition that has been shown to induce, in the subacute phase, a prolonged inflammation favoring the occurrence of adverse LV remodeling.[50,55] Indeed, CMR studies showed that IMH was closely related to the development of adverse LV remodeling and worse clinical outcomes[7] and a study by Carrick et al[50] showed that IMH was more closely associated with adverse clinical outcomes than MVO.[56] However, the occurrence of MVO in the acute phase after STEMI may limit the delivery of endogenous promoters responsible for postinfarction remodeling, as well as macrophages required for phagocytosis of cellular debris needed for optimal infarct healing.[57] In conclusion, beyond cardiomyocyte injury, MVO may contribute to a worse prognosis by blunting a positive inflammatory response in the acute phase and, through the development of IMH and residual iron deposits, stimulating a prolonged intramyocardial inflammatory reaction that in turn could promote adverse LV remodeling.

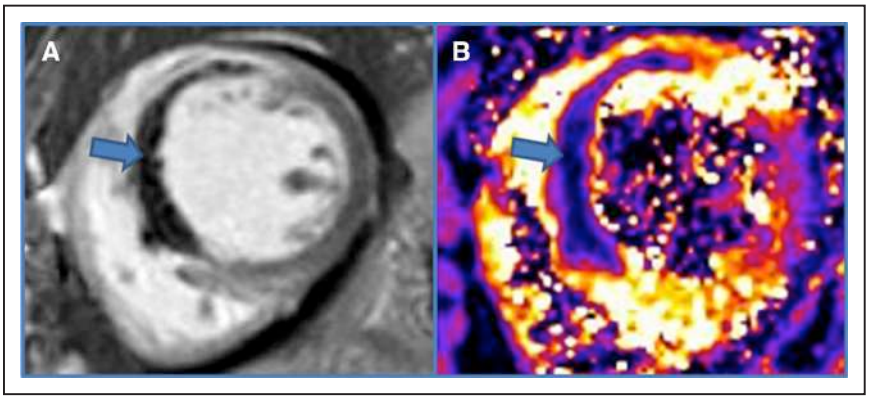

Figure 2. Visualization of microvascular obstruction (MVO) and intramyocardial hemorrhage (IMH) by cardiac magnetic resonance (CMR). Visualization of MVO (**A**) and IMH (**B**; arrows) on short-axis late gadolinium-enhanced (**A**) and T2* mapping (**B**). CMR images were performed 4 d after acute ST-segment–elevation myocardial infarction due to occlusion of the left anterior descending artery.

Current Therapeutic Approaches Addressing Infarct Size Reduction and MVO

Several pharmacological and nonpharmacological therapies have been evaluated in the past decades in cardioprotection studies (Table 1).

Drugs

β-Blockers

Most of the clinical studies have evaluated the effect of β-blockers on infarct size and cardiomyocyte protection, but only few preclinical studies have explored possible effects on MVO. Data from a large-animal MI model found that intravenous administration of the β1-selective blocker, metoprolol, before reperfusion, reduced MI size[58] and reduced the occurrence of MVO by modulating the inflammatory response during the acute phase of MI and inhibiting the formation of neutrophil-platelet aggregates.[59] Indeed, metoprolol has been shown to impair neutrophil migration by preventing the morphological changes needed to initiate intercellular interactions and subsequent tissue infiltration.[59] Moreover, preclinical studies showed that the third generation β-blockers like carvedilol and nebivolol are able to protect the coronary microcirculation and thereby reduce infarct size.[60,61]

In the METOCARD-CNIC trial (The Effect of Metoprolol in Cardioprotection During an Acute Myocardial Infarction), which enrolled 270 patients with anterior STEMI, intravenous metoprolol (3×5 mg) administered in the ambulance before primary PCI reduced MI size, prevented LV adverse remodeling, preserved LV systolic function, and lowered hospital readmissions for heart failure.[62,63] Of note, the cardioprotective effect of metoprolol was time-dependent.[64] Moreover, a subanalysis of the METOCARD-CNIC trial[59] demonstrated a significant interaction between metoprolol treatment and the correlation between leukocyte count and MVO. In particular, a significant positive correlation between neutrophil count and the extent of MVO was only present in control patients (ie, not receiving metoprolol), whereas in patients receiving intravenous metoprolol before reperfusion, there was no sign of association between total leukocyte or neutrophil counts and the extent of MVO, suggesting that the administration of intravenous metoprolol during ongoing MI does not affect the circulating levels of leukocytes but modulates the impact of neutrophils on MVO.

On the contrary, the EARLY BAMI trial (Early-Beta Blocker Administration Before Reperfusion Primary PCI in Patients With ST-Elevation Myocardial Infarction) failed to report a reduction in MI size at 1-month (assessed by CMR) with intravenous metoprolol (2×5 mg) administered just before primary PCI in patients with STEMI presenting within 12 hours of symptom onset.[65] The reasons for the neutral results of the EARLY BAMI trial versus the METOCARD-CNIC trial may include dosing (10 versus 15 mg), timing (most benefits observed with metoprolol given soon after STEMI onset), and patient population (all-comers versus anterior STEMI).[11] Of note, current European Society of Cardiology STEMI guidelines propose that intravenous β-blockers should be considered at the time of presentation in patients undergoing primary PCI without contraindications, with no signs of acute heart failure, and with a systolic blood pressure >120 mm Hg (class of recommendation IIa, level of evidence A).[4]

Adenosine

Adenosine is an endogenous nucleoside characterized by a short half-life (<2 s) and by pleiotropic effects.[66,67] Of importance, adenosine is a potent direct vasodilator of coronary microcirculation through stimulation of A2 receptors, and it also exhibits anti-inflammatory properties against neutrophils and inhibits platelet aggregation.[68] Moreover, adenosine mimics ischemic preconditioning limiting reperfusion injury,[66] and it exhibits antiapoptotic effects and may stimulate angiogenesis.[66] Clinical studies of acute MI with adenosine administered at the time of reperfusion have displayed mixed results in terms of improvement of MVO and MI size, with post hoc analyses suggesting beneficial effects in patients with STEMI presenting within 3 hours of symptom onset.[69,70] In the REOPEN-AMI trial (Intracoronary Nitroprusside Versus Adenosine in Acute Myocardial Infarction), high dosages of intracoronary adenosine, given after thrombus aspiration through the aspiration catheter, demonstrated a significant improvement of MVO, assessed by STR, and enzymatic infarct size when compared with placebo or sodium nitroprusside, which translated into a reduction of MACE and a better LV remodeling at 1-year follow-up.[71,72] However, the REFLO-STEMI trial (Reperfusion Facilitated by Local Adjunctive Therapy in ST-Elevation Myocardial Infarction) enrolling 247 patients presenting within 6 hours of symptom onset failed to confirm these results.[73] In fact, compared with controls, intracoronary adenosine was associated with similar extent of MVO, but with an increase in infarct size and MACE at 30 days and 6 months, and LV ejection fraction was reduced. The reason why results were so different between REOPEN-AMI and REFLO-STEMI trials is not clear. Probably, higher dosage of intracoronary adenosine

Table 1. Pharmacological Strategies to Reduce MVO and Limit Infarct Size

Drugs	Studies	Setting	End Points	Results	Potential Effect on Cardiomyocytes	Potential Effect on Microcirculation	References
β-blockers	METOCARD-CNIC: IV metoprolol up to 15 mg before reperfusion	STEMI	Infarct size (CMR at 5–7 d)	↓ infarct size	↓ O2 consumption	Inhibition of neutrophil-platelet coaggregation	Ibanez et al,[58] Ibanez et al,[62] Pizarro et al[63]
	EARLY BAMI: IV metoprolol 2 bolus of 5 mg before reperfusion	STEMI	Infarct size (CMR at 30 d)	No effect			Roolvink et al[65]
Adenosine	AMISTAD-II: 3-h infusion of adenosine 50 or 70 μg/(kg·min) started within 15 min either of the start of fibrinolysis or before coronary intervention	STEMI	Composite of chronic HF, Rehospitalization for HF and death at 6 mo; infarct size (technetium-99 m sestamibi)	No differences in clinical outcomes; ↓infarct size	↓ Afterload ↓ ATP breakdown ↓ Cellular Ca^{2+} influx ↓ Oxidative stress	↑ Coronary microvascular vasodilation ↓ Neutrophil adherence and neutrophil-mediated cellular damage ↓ Platelet aggregation ↓ Oxidative stress	Ross et al,[69] Kloner et al[70]
	REFLO-STEMI: intracoronary adenosine 2–3 mg during PCI	STEMI	Infarct size and MVO (CMR at 2–4 d)	No effect			Nazir et al[73]
	REOPEN-AMI: iIntracoronary adenosine (120 μg as fast bolus followed by 2 mg given in 2 min as slow bolus) during PCI after thrombus aspiration	STEMI	MVO (assessed as STR) and enzymatic infarct size	↓ Enzymatic infarct size and MVO			Niccoli et al[71]
Statins	SECURE-PCI: Atorvastatin 80 mg before and 24 h after a planned PCI	STEMI	Composite of all-cause mortality, myocardial infarction, stroke, and unplanned coronary revascularization at 30 d.	No effect	Unknown	↑ Microvascular dilation ↑ Endothelial function ↓ Platelet activation ↓ Inflammation ↓ Immune response	Berwanger et al[76]
	Hahn et al[133]: Atorvastatin 80 mg before PCI and for 5 d	STEMI	Infarct size (assessed by technetium Tc 99 m tetrofosmin)	No effect			Niccoli et al[18]
Atrial natriuretic peptide	J-WIND: IV carperitide 72 h infusion started before PPCI	STEMI	Infarct size (CKMB) and LVEF	↓ Infarct size ↑ LVEF	↓ End-diastolic pressure ↑ Coronary collateral blood flow ↑ Mitochondrial potassium ATP channel activation	↓ Neutrophils-induced endothelial cytotoxity	Kitakaze et al[84]
Intracoronary fibrinolytic therapy	T-TIME: Intracoronary alteplase 10 mg or 20 mg during PPCI (after reperfusion of the infarct-related coronary artery and before stent implant)	STEMI	MVO by CMR at day 2 to 7	No effect	Unknown	↓ Intracoronary clot	Mccartney et al[114]

(*Continued*)

Table 1. Continued

Drugs	Studies	Setting	End Points	Results	Potential Effect on Cardiomyocytes	Potential Effect on Microcirculation	References
P2Y12 inhibitor	PITRI: (ongoing) Cangrelor IV bolus followed by an infusion before PCI	STEMI	Myocardial infarct size by CMR at Day 2 to 7		↑ Prosurvival signaling pathway	Platelet inhibition	Bulluck et al[90]
	CvLPRIT-CMR: Clopidogrel vs Prasugrel or Ticagrelor before hospital arrival or in hospital at arrival	STEMI	Myocardial infarct size at CMR	↓ Infarct size (ticagrelor and prasugrel>clopidogrel)		Platelet inhibition*	Niccoli et al[18]
GP IIb/IIIa receptor inhibitors	ON-TIME 2: Prehospital intravenous tirofiban bolus administration	STEMI	MVO assessed by STR	↓ MVO	Unknown	Platelet inhibition	Van't Hof et al[93]
	INFUSE-AMI: Intracoronary abciximab at the time of PCI	STEMI	Infarct size at 30 d assessed by CMR	↓ Infarct size			Stone et al[96]

AMISTAD-II indicates Acute Myocardial Infarction Study of Adenosine; CKMB, creatine kinase myocardial band; CMR, cardiac magnetic resonance; CvLPRIT-CMR, Complete Versus Lesion-Only Primary Percutaneous Coronary Intervention Trial: Cardiovascular Magnetic Resonance Imaging Substudy; EARLY BAMI, Early-Beta Blocker Administration Before Reperfusion Primary PCI in Patients With ST-Elevation Myocardial Infarction; GP, glycoprotein; HF, heart failure; INFUSE-AMI, Intracoronary Abciximab and Aspiration Thrombectomy in Patients With Large Anterior Myocardial Infarction; IV, intravenous; J-WIND, Human Atrial Natriuretic Peptide and Nicorandil as Adjuncts to Reperfusion Treatment for Acute Myocardial Infarction; LVEF, left ventricular ejection fraction; METOCARD-CNIC, The Effect of Metoprolol in Cardioprotection During an Acute Myocardial Infarction; MVO, microvascular occlusion; On-TIME 2, Ongoing Tirofiban in Myocardial Infarction Evaluation 2; PCI, percutaneous coronary intervention; PITRI, Platelet Inhibition to Target Reperfusion Injury; PPCI, primary percutaneous coronary intervention; REFLO-STEMI, Reperfusion Facilitated by Local Adjunctive Therapy in ST-Elevation Myocardial Infarction; REOPEN-AMI, Intracoronary Nitroprusside Versus Adenosine in Acute Myocardial Infarction; SECURE-PCI, Statins Evaluation in Coronary Procedures and Revascularization; STEMI, ST-segment–elevation myocardial infarction; STR, ST-segment resolution; and T-TIME, A Trial of Low-Dose Adjunctive Alteplase During Primary PCI.

*Ticagrelor also exerts adenosine-mediated effects.

used in the latter trial may lead to adverse events (possibly through cross-activation of other receptors) and probably should not be used to prevent MVO.[73] However, a meta-analysis of clinical studies undertaken in the primary PCI era has demonstrated a beneficial effect of intracoronary adenosine in terms of less heart failure following STEMI.[74]

Statins

In the STATIN STEMI trial (Efficacy of High-Dose AtorvaSTATIN Loading Before Primary Percutaneous Coronary Intervention in ST-Elevation Myocardial Infarction) enrolling 171 patients with STEMI, administration of high doses of statins before primary PCI has been found to improve angiographic MVO but not to reduce infarct size when compared with low doses.[75] A post hoc analysis from the SECURE-PCI trial (Statins Evaluation in Coronary Procedures and Revascularization), showed that the subgroup of 865 patients undergoing primary PCI had a nearly 50% reduction in 30-day MACE with high-dose atorvastatin (administered prior and 24 hours after primary PCI) compared with placebo.[76] At the same time, an ongoing statin therapy at the time of STEMI was associated to a lower rate of MVO, a better functional recovery of myocardial function after 6 months of follow-up[77] and a reduced infarct size[78] when compared with patients not on statin. Several studies suggested that the beneficial effects of acute statin treatment may be related to lipid-independent pleiotropic effects, such as improvement of endothelial function,[79] dilation of coronary microvessels, and anti-inflammatory and antithrombotic actions.[80]

Atrial Natriuretic Peptide

Experimental studies demonstrated that ANP (atrial natriuretic peptide) may suppress endothelin-1 production in endothelial cells[81] with possible favorable effects on MVO.[82] On the contrary, another animal study demonstrated that ANP may enhance myocardial inflammatory infiltration in the early phase after MI, thus worsening MVO.[83] Of importance, the J-WIND trial (Human Atrial Natriuretic Peptide and Nicorandil as Adjuncts to Reperfusion Treatment for Acute Myocardial Infarction) has demonstrated a reduction in enzymatic infarct size in patients with STEMI treated with an infusion of carperitide (an ANP agonist) before primary PCI.[84] However, the effect of ANP on MVO has never been investigated in clinical studies.[18]

Antiplatelet Therapy

Recent experimental data have suggested that the platelet P2Y12 inhibitors may reduce infarct size when administered at the onset of reperfusion, conferring a postconditioning-like protection.[85,86] However, a subanalysis of PLATO trial (The Study of Platelet Inhibition and Patient Outcomes) did not find differences with regard to myocardial perfusion between clopidogrel and ticagrelor,[87] and in the large ATLANTIC (Administration of Ticagrelor in the Cath Lab or in the Ambulance for New ST Elevation Myocardial Infarction to Open the Coronary Artery) study, prehospital administration of ticagrelor, in patients with acute STEMI, did not improve pre-PCI coronary reperfusion as assessed by STR.[88] The REDUCE-MVI trial (Reducing Micro Vascular Dysfunction in Acute Myocardial Infarction by

Ticagrelor) did not find any differences in MVO or infarct size between ticagrelor and prasugrel.[89] Currently, the PITRI trial (Platelet Inhibition to Target Reperfusion Injury) is ongoing and is testing if intravenous cangrelor administered before reperfusion will reduce the incidence of MVO and limit infarct size in patients with STEMI treated with primary PCI.[90]

Results from clinical studies evaluating prehospital administration of glycoprotein IIb/IIIa inhibitors have been mixed. Data initially suggesting improved outcome with the routine use of glycoprotein IIb/IIIa inhibitors were mostly derived from investigations in the prestent era and before the routine use of dual antiplatelet therapy. More contemporary studies did not exhibit benefits in patients receiving glycoprotein IIb/IIIa inhibitors in addition to primary PCI and dual antiplatelet therapy.[91–93] However, the On-TIME-2 trial (Ongoing Tirofiban in Myocardial Infarction Evaluation 2) showed that a routine prehospital initiation of high-bolus dose tirofiban might improve STR and clinical outcome after PCI.[93] On the contrary, Amier et al[94] in a retrospective post hoc analysis recently showed that anterior STEMI and the use of glycoprotein IIb/IIIa inhibitors were associated with the development of IMH. The route of glycoprotein IIb/IIIa inhibitor administration was also subject of clinical investigations because higher local concentrations and increased levels of platelet receptor occupancy can be achieved with intracoronary compared with standard intravenous application.[95] The INFUSE-AMI study (Intracoronary Abciximab and Aspiration Thrombectomy in Patients With Large Anterior Myocardial Infarction) reported a significant reduction of infarct size assessed with CMR imaging after intracoronary administration of abciximab compared with no abciximab in 452 patients with STEMI with large anterior infarctions.[96] The AIDA STEMI trial (Abciximab Intracoronary versus intravenous Drug Application in STEMI) was the only investigation that was powered for clinical outcomes and directly compared both routes of administration in 2065 patients with STEMI.[97] Intracoronary, as compared to intravenous abciximab, resulted in a similar rate of MACE (all-cause death, reinfarction, or new congestive heart failure) after 90 days and 1 year.[97,98] Consistently, the CMR substudy, which enrolled 795 patients, demonstrated no differences between groups with respect to myocardial damage and reperfusion injury, including a similar extent of MVO.[99] Of note, glycoprotein IIb/IIIa inhibitors represent the only therapy to treat MVO proposed in the current European Society of Cardiology STEMI guidelines, suggesting that they should be considered for bailout if there is evidence of no-reflow or a thrombotic complication (class of recommendation IIa, level of evidence C).[4]

Ischemic Conditioning

Experimental studies over the past 3 decades demonstrated a cardioprotective role for ischemic conditioning.[10,11,100] In particular, RIC, using ≥1 cycles of brief limb ischemia and reperfusion, has been found in both small and large-animal MI models to reduce infarct size[101] but did not reduce the area of now-reflow in a pig model of reperfused MI.[102] Several clinical studies evaluated a possible protective role of ischemic conditioning on MVO.[103–107] In particular, in the CONDI trial (Remote Ischaemic Conditioning Before Hospital Admission, as a Complement to Angioplasty, and Effect on Myocardial Salvage in Patients With Acute Myocardial Infarction), remote ischemic perconditioning with 4 cycles of 5-minute arm ischemia/5-minute reperfusion during transport in the ambulance reduced infarct size but did not improve coronary blood flow.[103] A study by White et al demonstrated that remote ischemic perconditioning with 4 cycles of 5-minute arm ischemia/5-minute reperfusion at hospital admission reduced both infarct size and edema on CMR.[105] Also, remote ischemic postconditioning by 3 cycles of lower limb ischemia/reperfusion reduced edema and infarct size at CMR, improved STR during reperfusion, but did not improve TIMI frame count or myocardial blush grading.[104] Finally, in the LIPSIA CONDITIONING trial (Cardioprotection by Combined Intrahospital Remote Ischaemic Perconditioning and Postconditioning in ST-Elevation Myocardial Infarction), postconditioning alone with 4 cycles of 30-s reocclusion/reperfusion failed to improve myocardial salvage and MVO by CMR, but combined postconditioning with remote ischemic perconditioning by 3 cycles of 5-minute upper arm ischemia/5-minute reperfusion improved myocardial salvage, albeit reduced MVO only nonsignificantly[106] that translated in a reduced rate of MACE and new congestive heart failure after STEMI.[107] However, in the recent National Heart, Lung, and Blood Institute–sponsored trial, Traverse et al[8] found no reduction in infarct size in patients with STEMI with ischemic postconditioning but reduced MVO and improved LV functional recovery. Similarly, a study by Mewton et al[108] demonstrated that ischemic postconditioning reduced MVO in patients with STEMI treated with primary PCI. However, Verouhis et al[109] enrolling 93 anterior patients with STEMI and using a highly variable protocol of RIC did not demonstrate a reduced infarct size as a percentage of the area-at-risk (assessed by CMR at 4–7 days). The CONDI trial randomized 333 patients with STEMI to receive RIC or not in the ambulance during transportation to primary PCI. In the per protocol analysis of 251 patients, mean myocardial salvage index was higher in patients treated with RIC. In a secondary analysis involving longer-term follow-up to 4 years, compared with control treatment, RIC was associated with reductions in all-cause mortality and major adverse cardiac and cerebrovascular events[110] and a lowered economic deriving from reduced hospitalization for heart failure.[111] Some limitations of this trial include comparatively few primary outcome events (n=49). Of note, statin use was associated with increased efficacy of RIC to reduce infarct size.[112] However, these studies were underpowered for clinical outcome analyses, and the ongoing CONDI-2/ERICPPCI trial (Effect of Remote Ischaemic Conditioning on Clinical Outcomes in STEMI Patients Undergoing PPCI), which will investigate the effect of RIC on cardiac death and hospitalization for heart failure at 1-year in reperfused patients with STEMI, will shed further light on this topic.

Intracoronary Fibrinolysis

In a proof-of-concept randomized controlled trial, Sezer et al[113] reported that intracoronary administration of a reduced dose (250 kU) of streptokinase via the guiding catheter at the end of primary PCI improves myocardial reperfusion, instigating other clinical trials, such as T-TIME (A Trial of Low-Dose Adjunctive Alteplase During Primary PCI; http://www.clinicaltrials.gov. Unique identifier: NCT02257294), OPTIMAL (Optimal Coronary Flow After PCI for Myocardial Infarction; http://www.clinicaltrials.gov. Unique identifier: NCT02894138), RESTORE-MI (Restoring Microcirculatory Perfusion in ST-Elevation Myocardial Infarction; Australian New Zealand Clinical Trials Registry Number: 12618000778280), STRIVE (Adjunctive, Low-Dose tPA in Primary PCI for STEMI; http://

www.clinicaltrials.gov. Unique identifier: NCT03335839), and a trial of intracoronary tenecteplase versus abciximab (EudraCT Number: 2010-022725-16). Two of these trials have recently reported.[114,115] The T-TIME investigators tested the hypothesis that a strategy involving low dose intracoronary fibrinolytic therapy with alteplase (10 or 20 mg) infused during 5 to 10 minutes early after coronary reperfusion and before stenting would prevent and reduce MVO. One thousand five hundred twenty-seven patients had been screened, and 440 (28.8%) had been randomized (placebo, n=151; alteplase 10 mg, n=144; alteplase 20 mg, n=145) when the Data and Safety Monitoring Committee recommended that enrollment be discontinued due to futility. The amount (mean, SD) of MVO did not differ between the groups (2.32 [4.31] versus 2.61 [4.49] versus 3.48 [5.83] % LV mass; *P*=0.43).[114] Of interest, an increase in prothrombin F_{1+2} concentrations was observed in the alteplase groups, despite achieving therapeutic anticoagulation with unfractionated heparin, and this undesired procoagulant effect of fibrinolytic therapy through thrombin activation may have led to microvascular thrombosis, limiting the efficacy of the intervention.[114] In the trial led by Morales-Ponce et al,[115] 76 patients with anterior STEMI were randomized to treatment with either intracoronary tenecteplase or intravenous abciximab. At 4 months, infarct size measured by CMR was not different between the groups. In RESTORE-MI, enrollment involves a stratified approach with patient selection based on an increased IMR (>32) measured at the end of PCI. RESTORE-MI and STRIVE were designed as phase 3 trials and are still ongoing.

Interventional Procedures

Initial studies demonstrated that the use of manual thrombus aspiration during primary PCI reduced MVO occurrence.[116] However, these promising results did not translate in a clinical benefit in subsequent randomized trials.[117–119] Thus, the routine use of manual aspiration is not recommended in the current guidelines.[4] However, in patients with angiographic evidence of a large thrombus burden, the use of the Angiojet mechanical thrombectomy device demonstrated an acute improvement in STR and a lower MACE rate at 1 year in the Angiojet group compared with the direct stenting group.[120]

The pressure-controlled intermittent coronary sinus occlusion (PICSO) during primary PCI represents another approach that may reduce MVO. Indeed, PICSO may improve microvascular perfusion by redistributing venous blood to the border zone of the ischemic myocardium, enhancing washout of deleterious agents from the microcirculation and inducing the release of vascular growth factors from the venous endothelium.[121,122] Of note, PICSO has been shown to reduce infarct size both in experimental and small clinical studies.[123] However, evidence of improved clinical outcome is still lacking.

Finally, hypothermia induced by cold saline and endovascular cooling failed to show a reduction of infarct size and MVO.[18]

Future Therapeutic Approaches and Gaps in Knowledge

It is evident that most of the cardioprotection studies performed in the past decades mainly addressed infarct size as end point, but they failed to translate the evidence of a reduced infarct size into improved clinical outcomes. Of note, cardiomyocyte death occurs as a result of the combined effect on multiple players within the cardiac tissue. In particular, the coronary microcirculation represents an important therapeutic target, and the effect of studied therapies on the occurrence of MVO was often not adequately assessed. Moreover, as discussed above, recent studies suggested a prognostic value of MVO over MI size. Thus, further studies specifically addressing the effect of therapies on MVO over infarct size are needed, and this remains an unmet medical need[16] (Table 2).

Although the discussed treatment options address specific mechanisms, which contribute to the occurrence of MVO, no approach clearly demonstrated superiority when applied in unselected patient cohorts with MI. Thus, the currently available data for the prevention and treatment approaches regarding MVO might best be described as weak or suggestive. This is also reflected in the current guidelines for Europe and the United States, which mention the lack of definitive proof of therapies to treat or prevent MVO. Therefore, future research efforts should be directed to evaluate potential benefits in high-risk subgroups, which are prone to develop MVO, for example, patients with high thrombus burden or spastic coronary arteries and in different time windows in the course of MI before, during, and after primary PCI. The dynamic pattern of MVO might also provide mechanistic insights into the causes of microvascular dysfunction. Indeed, MVO is maximal by 12 hours after reperfusion, remains stable for up to 72 hours, and then falls progressively in the days and weeks post-MI. By 10 days, MVO may have resolved in half of all patients initially affected. By 6 months, about 10% to 15% of patients may have persistent MVO, and these patients are typically those with concomitant myocardial hemorrhage.[51,124,125] A potential association between the timing of peak MVO or the length of its persistence with underlying mechanisms could enable targeted treatment approaches and should be evaluated in future studies (Table 2).

In particular, further studies are needed to evaluate if an invasive assessment of microvascular resistance by IMR during primary PCI may be useful to select patients requiring adjunctive therapies.[45] The OxAMI-PICSO (Oxford Acute Myocardial Infarction–Pressure-Controlled Intermittent Coronary Sinus Occlusion), an observational study that used IMR >40 to stratify patients for PICSO before stenting, demonstrated no difference in infarct size or MVO on CMR at 24 to 48 hours. However, final infarct size on CMR 6 months post-PCI was lower in the PICSO group.[126] Of importance, a precision-medicine approach using IMR is being examined in 3 ongoing STEMI studies.[45] A large randomized trial (http://www.clinicaltrials.gov. Unique identifier: NCT03581513) is evaluating deferred stenting in patients with STEMI on the basis of IMR prestenting. The primary outcome is the prevalence of heart failure, repeat MI, or target vessel revascularization at 1 year. Moreover, the RESTORE-MI, a phase 3 trial will use IMR as an inclusion criterion to stratify enrollment. In this study, 1660 patients will be enrolled, and IMR will be measured after primary PCI. Patients with IMR >32 will be eligible for progression into the trial (n=800), and those with IMR ≤32 will continue in a follow-up registry. The intervention is adjunctive intracoronary tenecteplase (one-third of the weight-based

Table 2. Recommendations for Future Cardioprotection Studies

Strategy	Comment
MVO as a primary therapeutic target	Previous reports mainly focused on myocardial injury and infarct size as primary targets in cardioprotection studies
	Future studies should evaluate systematically the effects of cardioprotective therapies on MVO, along with infarct size
Multitargeted approach	Previous studies reported neutral results, possibly because of focus on pharmacological strategies directed at individual pathways / targets
	Ischemia/reperfusion injury is a complex process with different signaling cascades and multiple cellular players (cardiomyocytes, endothelial cells, fibroblasts, inflammatory cells, platelets) and approaches directed to a single target may be ineffective
	A multitargeted approach with a combination of therapies may be a more effective for cardioprotection in the clinical setting
Targeted selection of at-risk patient groups	A targeted selection of patients at risk of MVO and potentially amenable to benefit from cardioprotective interventions is crucial
	Patients less likely to benefit from cardioprotective therapies (ie, patients spontaneously reperfused before PPCI, with small AAR or with ischemic times >12 h) should be excluded, focusing on patients presenting with a large AAR >30% of the LV, usually involving proximal or midleft anterior descending coronary artery and with shorter ischemic times (<4 h).
Personalized therapeutic approach based on the mechanism responsible for MVO	Assessment of dynamic changes in time course of MVO after STEMI may elucidate which are the different mechanisms involved in each case, thus ensuring a personalized therapeutic approach (ie, aggressive antithrombotic therapy in patients with MVO mainly due to distal embolization or anti-inflammatory therapy in patients with MVO deriving from extravascular compression from interstitial edema)
Standardization of imaging protocols and clinical end points	The imaging protocols implemented in previous studies were quite heterogeneous, hampering interstudy comparisons and collaborative research with data merging
	A standardization of postinfarction CMR imaging protocols is urgently needed to further strengthen CMR as the reference imaging method for cardioprotection studies
	Only clinical end points that are relevant to cardioprotection should be considered (ie, acute and chronic MI size, LV size. and ejection fraction)

AAR indicates area-at-risk; CMR, cardiac magnetic resonance; LV, left ventricle; MI, myocardial infarction; MVO, microvascular obstruction; PPCI, primary percutaneous coronary intervention; and STEMI, ST-segment–elevation myocardial infarction.

systemic dose) or placebo. Finally, the OPTIMAL study will randomize 80 patients with STEMI presenting within 12 hours of symptom onset with a poststenting IMR >30 to intracoronary alteplase (20 mg) or placebo, in an open-label design.

Modulation of inflammatory responses may represent a potential therapeutic target not fully explored. Indeed, acute ischemia-reperfusion injury during STEMI triggers an initial inflammatory reaction with the purpose to remove necrotic debris from the MI zone. However, a robust inflammatory response may lead to the occurrence of a significant interstitial myocardial edema that not only is a consequence of sustained myocardial ischemia/reperfusion injury but also contributes to MVO by compressing capillaries and small arterioles and further decreasing flow through this dysfunctional microcirculation.[18] Moreover, the persistence of an inflammatory process in the chronic phase after MI may contribute to the occurrence of adverse ventricular remodeling and worse clinical outcomes.[127] Of note, statins represent one of the treatments able to attenuate inflammation in the context of MI, and probably the positive results of previously reported studies may be in part due to their anti-inflammatory effect.[75–78] However, specific therapies addressing inflammation have been disappointing overall and newer treatments are needed.[127] Probably, a tailored anti-inflammatory approach in patients with evidence of significant myocardial edema at CMR may select patients that effectively benefit from this treatment.

Of interest, emerging data suggest that severe MVO and IMH at the time of primary PCI leads to residual myocardial iron during the chronic phase after MI, and it may be a source of prolonged inflammation and have an impact on adverse LV remodeling.[128] Of note, a small randomized, double-blind, placebo-controlled study[129] using iron chelation with deferoxamine (500 mg immediately before primary PCI followed by a 12-hour infusion) to target ischemia/reperfusion injury in patients with STEMI treated by primary PCI, failed to show a significant difference in the primary end point of MI size determined by CMR. However, deferoxamine effectively decreased serum iron levels and oxidative stress as measured by plasma F2-isoprostanes after primary PCI. Of note, a limitation of this study was the administration of iron chelation therapy in all unselected patients with STEMI. Further studies administering deferoxamine only in patients with evidence of IMH at CMR might produce different results.

Furthermore, pericytes are contractile cells on the walls of capillaries and are reported to be the second most common cell type in the heart, and they may represent a potential therapeutic target.[130] Indeed, pericytes can irreversibly constrict coronary capillaries after myocardial ischemia, reducing reperfusion and contributing to the occurrence of MVO, and intracoronary administration of adenosine, endothelin antagonists, and verapamil may be able to relax pericytes.[130]

Finally, as multiple cellular players and different signaling pathways are involved in determining both infarct size and the occurrence of MVO, a multitargeted approach using a combination of therapies may be a more effective way to obtain an effective cardioprotection that translates into improved clinical

outcome (Table 2). Accordingly, recent studies evaluating a multitargeted approach showed promising results.[106,107,131,132]

Conclusions

MVO identified by CMR is now a well-established adverse prognostic marker occurring in half of patients with STEMI undergoing successful primary PCI.[41,42] Efforts to date to further improve outcomes in these patients have been directed at reducing infarct size with limited success. There is an unmet need for future studies to evaluate whether targeting both infarct size and MVO using a combination of therapies would eventually be successful to further improve outcomes in this group of patients.

Disclosures

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