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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 (PCI) is nowadays the preferred reperfusion strategy for patients with acute ST-segment elevation myocardial infarction (STEMI), 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 PCI does not achieve an 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 (MACE) and adverse left ventricular (LV) remodelling 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 represents another important independent predictor of adverse LV remodelling, and recent evidences support the notion that MVO may be more predictive of MACE than infarct size itself. Although timely and complete reperfusion is the most effective way of limiting myocardial injury and subsequent ventricular remodelling, there are currently no other effective therapeutic strategies that have been translated into improved clinical outcomes. 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 STEMI.

Keywords

Coronary microvascular obstruction; myocardial infarction; primary PCI; STEMI.

Introduction

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 patients with STEMI reaching a plateau of ≈7-8% (2,3). However, although national system delays for patients undergoing primary percutaneous coronary interventions (PCI) have been significantly improved over recent years, in-hospital mortality has remained substantially unchanged (4,5). Moreover, morbidity caused by development of post–myocardial infarction (MI) left ventricular (LV) remodelling and heart failure remains significant and is on the rise (3). In particular, 1 in 5 patients may be hospitalised with heart failure within 12 months of presenting with an anterior STEMI (3).

Infarct size has long been known to be an independent predictor of adverse LV remodelling 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 remodelling (7), and recent evidences support the notion that MVO may be more predictive of major adverse cardiovascular events (MACE) than infarct size itself (8).

Although timely and complete reperfusion is the most effective way of limiting myocardial injury and subsequent ventricular remodelling (9), there are currently no other effective therapeutic strategies for reducing infarct size or MVO that have been translated into improved clinical outcomes, despite tremendous research efforts in this field (5,10). There may be several explanations including imperfect study design and true lack of efficacy. For example, in the field of cardioprotection, preclinical data may be inadequate, and study design problems relate to patient selection and/or inappropriate timing and mode of delivery of the cardioprotective agent (11). Moreover previous cardioprotection studies were mainly aimed at protecting cardiomyocytes and reducing infarct size, neglecting other targets notably the coronary microcirculation (10,11). On the contrary, infarct size and MVO represent two complementary therapeutic targets for cardioprotection trials.

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

Mechanisms underlying MVO during STEMI

Microvascular obstruction refers to the inability to reperfuse the coronary microcirculation (microvessels, <200 μm diameter) in a previously ischemic region, despite opening of the epicardial vessel (12,13). Mechanisms underlying myocardial injury and MVO are multiple and interacting (13) (Figure 1). Ischemic injury represents a well-known mechanism responsible for cardiomyocyte death, and when ischemia lasts >3 h, the adverse effects of ischemia-associated injury become all the more pronounced (14-17). 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 (18). Initial studies in the dog using electron microscopic analysis after 90 min 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 favour the occurrence of intramyocardial haemorrhage (IMH) (19). MVO is caused by further obliteration of vessel lumen by neutrophil-platelet aggregates, which in turn produce large amount of vasoconstrictors and inflammatory mediators (13,19). Furthermore, intense interstitial myocardial edema occurring upon reperfusion compresses capillaries and small arterioles, further decreasing flow through these dysfunctional vessels (20).

Distal embolization is another important mechanism contributing to both myocardial injury and MVO. Coronary micro-embolization in experimental models causes regional contractile dysfunction. Of note, myocardial perfusion starts falling when microspheres obstruct >50% of coronary capillaries (21). Thus, the small number of emboli during primary PCI in the setting of STEMI, although not affecting 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 (22). Moreover, in patients with STEMI, the coronary neutrophil extracellular traps (NETs) burden correlates negatively with ST-segment resolution (STR) and positively with infarct size, thus suggesting that NETs may propagate thrombosis and inflammation distally into the infarcted myocardium and contribute to myocyte death during atheroembolism (23). Finally, oxidative stress and ischemia *per se* reduce the bioavailability of nitric oxide, further contributing to the dysfunction of the myocardial microcirculation (13).

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 (24). Genetic factors may modulate adenosine-induced vasodilation (i.e. 1976T.C polymorphism of the adenosine 2A receptors gene was suspected to be related with a higher prevalence of MVO) (13). Moreover, 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 with an increased risk of coronary microvascular dysfunction in men (25). Another factor modulating individual susceptibility to MVO is the presence of ischemic preconditioning (IPC), which not only protects the myocardium but might also protect the coronary microcirculation (13). Accordingly, pre-infarction angina might help preventing cardiomyocyte death and MVO by inducing IPC. Importantly, beneficial effect of pre-infarction angina may be blunted in humans due to risk factors or drugs therapy affecting unfavourably IPC (26).

Finally, pre-existing microvascular dysfunction, particularly in patients with multiple cardiovascular risk factors, may be associated with an increased risk of developing MVO (13). Indeed, pre-existent microvascular dysfunction might represent an important pathogenetic component of MVO, as previous studies demonstrated that coronary blood flow is reduced by 50% in the non-culprit coronary arteries during acute MI, before and after primary PCI, thus confirming a

global rather than a regional myocardial microcirculatory impairment (27). Moreover, 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 (28). Moreover, in diabetic patients, 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 (29) and hyperglycemia causes the plugging of leukocytes in the microvasculature of the myocardium and increases pro-coagulable properties of platelets (30). Also dyslipidemia may predispose to MVO. Indeed, hypercholesterolemia may impair vascular wall function and structure, interfering with endothelial function (31), along with a possible role in the delayed healing after ischemia/reperfusion injury (32). Moreover, hypercholesterolemia may cause a near-complete abrogation in vascular nitric oxide (NO) bioavailability, elevated oxidative stress, and a pro-inflammatory milieu, conditions associated with an impaired vascular reactivity (31). Hypertension is also involved in the predisposition to MVO. Indeed, hypertension is linked to endothelial dysfunction, along with ultra-structural remodeling of cardiac microvessels, that can cause a progressive impairment of flow-mediated vasodilation. Also advanced age has been shown to be an independent predictor of MVO (33).

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 (13). Indeed, MVO can be assessed using different techniques and at different time points after STEMI.

CMR represents the reference standard technique for in-vivo MVO detection and quantification (13,34). 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) (34). Early and late MVO are assessed approximately 1 and 15 minutes after gadolinium injection, respectively. Since 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 post-infarction adverse events, however, is low. In contrast, late MVO reflects severely disturbed microcirculation and is strongly associated with clinical outcome (34). 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 inter-study comparisons and collaborative research with data merging. The international standardization of post-infarction 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 (34,35). MVO can be also detected at coronary angiography (defined as Thrombolysis In Myocardial Infarction [TIMI] flow grade <3 or 3 with a myocardial blush grade [MBG] 0 to 1), by myocardial contrast echocardiography, as an incomplete STR on ECG (13), or directly by invasive measurement of the index of microvascular resistance (IMR) using a diagnostic guidewire (13). This technique is appealing since 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 (i.e. infusion of glycoprotein IIb/IIIa inhibitors, intracoronary thrombolysis or vasodilators). On the other hand, 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. 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 myocardial haemorrhage (36).

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 (37). 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 (37). However, recent evidence suggests that MVO may be more predictive of clinical outcome after primary PCI than infarct size itself (38) (Figure 2). Indeed, in a patient-level meta-analysis of 1025 patients from 8 studies, Van Kranenburg and colleagues (39) 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. (40) confirmed the prognostic value of MVO over MI size for mortality and hospitalisation 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 hospitalisation. Moreover, 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 (40). Similar findings were obtained by Symons et al. in a longitudinal study of 810 patients after a median follow-up of 5.5 years (41).

It is well known that patients with larger MI are more likely to develop MVO (11,35). However, pathophysiologic mechanisms through which MVO adversely impacts 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 (35,42) (Figure 3).

Animal and human studies demonstrated that, in contrast to the non-reperfused myocardium, microvascular reperfusion injury is associated with IMH (43,44). 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, while no IMH was observed in animals with permanent coronary occlusion (45). CMR studies demonstrated that IMH occurs in ~40% of STEMI patients (35), and while MVO is present in all patients with IMH, hemorrhage does not have to present with MVO (46). 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 sub-acute phase, a prolonged inflammation favouring the occurrence of adverse LV remodelling (42,47). Indeed, CMR studies showed that IMH was closely related to the development of adverse LV remodelling and worse clinical outcomes (48) and a study by Carrick et al. (42) showed that IMH was more closely associated with adverse clinical outcomes than MVO (49). On the other hand, the occurrence of MVO in the acute phase after STEMI may limit the delivery of endogenous promoters responsible for post-infarction remodelling, as well as macrophages required for phagocytosis of cellular debris needed for optimal infarct healing (50). In conclusion, beyond cardiomyocyte injury, MVO may contribute to a worse prognosis by blunting a “positive” inflammatory response in the acute phase and, through development of IMH and residual iron deposits, stimulating a prolonged intramyocardial inflammatory reaction that in turn could promote LV remodelling.

Current therapeutic approaches addressing infarct size reduction and MVO

Several pharmacological and non-pharmacological therapies have been evaluated in the last decades in cardioprotection studies (see Table 1).

Drugs

Beta-blockers

Most of the clinical studies have evaluated the effect of ß-blockers on infarct size and cardiomyocyte protection, but only few pre-clinical studies have explored possible effects on MVO. Data from a large-animal MI model found that intravenous administration of the ß1-selective blocker, metoprolol, prior to reperfusion, reduced MI size (51), 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 (52). Moreover, pre-clinical studies showed that the third generation ß-blockers like carvedilol and nebivolol are able to protect the coronary microcirculation and thereby reduce infarct size (53,54).

In the METOCARD-CNIC trial, which enrolled 270 patients with anterior STEMI, intravenous metoprolol (3x5mg) administered in the ambulance prior to primary PCI reduced MI size, prevented LV adverse remodelling, preserved LV systolic function, and lowered hospital readmissions for heart failure (55,56). Of note, the cardioprotective effect of metoprolol was time-dependent (57). Moreover, a subanalysis of the METOCARD-CNIC trial (52) 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 (that is, not receiving metoprolol), while in patients receiving i.v. 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 i.v. 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 failed to report a reduction in MI size at 1-month (assessed by CMR) with IV metoprolol (2x5mg) administered just before primary PCI in STEMI patients presenting within 12 h of symptom onset (58). The reasons for the neutral results of the EARLY BAMI trial vs. the METOCARD-CNIC trial may include: dosing (10 vs. 15 mg), timing

(most benefit observed with metoprolol given soon after STEMI onset) and patient population (all-comers vs. anterior STEMI) (10). Of note, current ESC STEMI guidelines propose that IV beta-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 mmHg (Class of recommendation IIa, level of evidence A) (5).

Adenosine

Adenosine is an endogenous nucleoside characterized by a short half-life (<2 s) and by pleiotropic effects (59). 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 (59,60). Moreover, adenosine mimics IPC limiting reperfusion injury (59), and it exhibits antiapoptotic effects and may stimulate angiogenesis (59). 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 STEMI patients presenting within 3 h of symptom onset (61,62). In the REOPEN-AMI trial, 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 remodelling at 1-year follow-up (63,64). However, the REFLO-STEMI trial enrolling 247 patients presenting within 6 h of symptom onset failed to confirm these results (65). In fact, compared with controls, intracoronary adenosine was associated similar amount of MVO, but with an increase in infarct size and MACE at 30 days and 6 months, and LV ejection fraction was reduced. Interestingly, 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 (66).

Exenatide

Experimental studies in diabetic rats demonstrated that exenatide, a synthetic version of the glucagon-like-peptide-1 (GLP-1) analogue, exendin-4, might protect the coronary microcirculation against oxidative stress, apoptosis, and the resultant microvascular barrier dysfunction in diabetes (67), Moreover, the GLP-1 receptor is also present on cardiomyocytes and infusion of GLP-1 has been shown to activate anti-apoptotic pathways and increase myocardial metabolic efficiency in preclinical and clinical studies (68,69). Of importance. exenatide reduced MI size when administered prior to reperfusion (70) in studies with animal MI model, and two small proof-of-concept clinical studies in STEMI patients have reported beneficial effects with exenatide initiated prior to primary PCI (71,72), with the most benefit observed in those STEMI patients presenting within 132 min of symptom onset (73). However, these findings did not translate into improved long-term clinical outcomes, and a recent study by Roos et al. (74) failed to find any beneficial effect of exenatide on infarct size normalized for area-at-risk (AAR). The ongoing Exenatide for Myocardial Protection During Reperfusion Study is also testing the effect of IV exenatide on final MI size at 3 months over AAR at 72 h post-randomization (assessed by CMR). However, it should be noted that, currently, no studies have hitherto evaluated the effect of exenatide on MVO.

Statins

In the STATIN STEMI trial enrolling 171 patients with STEMI administration of high doses of statins prior to primary PCI has been found to improve angiographic MVO but not to reduce infarct size when compared with low doses (75). Moreover, a post hoc analysis from the SECURE-PCI (Statins Evaluation in Coronary Procedures and Revascularization) trial, 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 h 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.

Atrial natriuretic peptide

Experimental studies demonstrated that atrial natriuretic peptide (ANP) may supress endothelin-1 production in endothelial cells (79) with possible favourable effects on MVO (80). On the contrary, another animal study demonstrated that ANP may enhance myocardial inflammatory infiltration in the early phase after MI, thus worsening MVO (81). Of importance, the J-WIND trial has demonstrated a reduction in enzymatic infarct size in STEMI patients treated with an infusion of carperitide (an ANP agonist) prior to primary PCI (82). However, the effect of ANP on MVO has never been investigated in clinical studies (13).

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 (83). However, a sub-analysis of PLATO trial, did not find differences with regard to myocardial perfusion between clopidogrel and ticagrelor (84) and in the large ATLANTIC study, pre-hospital administration of ticagrelor, in patients with acute STEMI, did not improve pre-PCI coronary reperfusion as assessed by STR (85). The REDUCE-MVI trial did not find any differences in MVO or infarct size between ticagrelor and prasugrel (86). Currently, the PITRI trial is ongoing and is testing if intravenous cangrelor administered prior to reperfusion will reduce the incidence of MVO and limit infarct size in STEMI patients treated with primary PCI (87). Moreover, results from clinical studies evaluating pre-hospital 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 pre-stent era and prior to 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. Indeed, the FINESSE trial demonstrated that upstream administration of abciximab with half-dose reteplase significantly reduces infarct size but does not have any overall clinical benefit in primary study endpoint at 90 days as well as in mortality at 1 year (88). A pooled meta-analysis of 16 randomized trials involving 10,085 patients found similar rates of 30-day mortality and re-infarction whereas the risk of major bleeding complications was significantly increased in the glycoprotein IIb/IIIa group (89). On the other hand, the On-TIME-2 trial showed that a routine pre-hospital initiation of high-bolus dose tirofiban might improve STR and clinical outcome after PCI (90). Finally, Amier *et al*. (91) 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 since higher local concentrations and increased levels of platelet receptor occupancy can be achieved with intracoronary compared to standard intravenous application (92). The INFUSE-AMI (Intracoronary abciximab and aspiration thrombectomy in patients with large anterior myocardial infarction) study reported a significant reduction of infarct size assessed with CMR imaging after intracoronary administration of abciximab compared to no abciximab in 452 STEMI patients with large anterior infarctions (93). The Abciximab Intracoronary versus intravenous Drug Application in STEMI (AIDA STEMI) trial was the only investigation, which was powered for clinical outcomes and directly compared both routes of administration in 2,065 STEMI patients (94). Intracoronary, as compared to intravenous abciximab, resulted in a similar rate of MACE (all-cause death, re-infarction, or new congestive heart failure) after 90 days and 1 year (94,95). 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 (96). Of note, glycoprotein IIb/IIIa inhibitors represent the only therapy to treat MVO proposed in the current ESC 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) (5).

Mitochondria-targeted approaches

Cyclosporine-A has been advocated as a cardioprotective drug by inhibiting MPTP opening during ischemia-reperfusion injury. Of interest, an initial proof-of-concept clinical study suggested a benefit deriving from an IV bolus of Cyclosporine-A, administered prior to reperfusion, by reducing infarct size and occurrence of adverse LV remodelling (3,75). However, two subsequent large multicentre randomized clinical trials have failed to demonstrate a reduction in MI size or improved clinical outcomes with Cyclosporine-A administered prior to primary PCI in STEMI patients (3,97,98). Of interest, the recent NACIAM trial (99) demonstrated that IV administration of high-dose of N-acetylcysteine (NAC, 29 g over 48h), an antioxidant drug, combined with low-dose 48 h infusion of nitroglycerin reduced infarct size. The cardioprotective effect of NAC was mainly attributed to the ability to scavenge reactive oxygen species (ROS), especially at the level of mitochondria. On the other hand, the LIPSIA-NACC trial demonstrated no benefit of a lower dose of NAC (2.4 g over 48 h) compared with placebo in terms of myocardial salvage index assessed by CMR (100).

Ischemic conditioning

Experimental studies over the last three decades demonstrated a cardioprotective role for ischemic conditioning (10,11). In particular, remote ischemic conditioning (RIC), using one or more cycles of brief limb ischemia and reperfusion, has been found in both small and large animal MI models to reduce infarct size (101). Moreover, several clinical studies have shown a reduced infarct size or increased myocardial salvage in STEMI patients undergoing RIC and treated with primary PCI, as assessed by both serum cardiac enzyme release and cardiac imaging (SPECT, CMR) (102-105) and this benefit was associated with an improvement of T2-weighted edema volume assessed by CMR and STR (103). Moreover, cardioprotection by combined intrahospital RIC and postconditioning in addition to primary PCI significantly reduced the rate of MACE and new congestive heart failure after STEMI (106). However, a recent study by Verouhis et al. (107),

enrolling 93 anterior STEMI patients did not demonstrate a reduced infarct size as a percentage of the AAR (assessed by CMR at 4–7 days). The CONDI trial randomized 333 STEMI patients 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 MACCE (108) and a lowered economic deriving from reduced hospitalisations for heart failure (108). Some limitations of this trial include comparatively few primary outcome events (n=49). Of note, statin use was associated with an increased efficacy of RIC to reduce infarct size (110). However, these studies were underpowered for clinical outcome analyses, and the ongoing CONDI-2/ERICPPCI trial, which will investigate the effect of RIC on cardiac death and hospitalisation for heart failure at 1-year in reperfused STEMI patients, will shed further light on this topic.

Intracoronary fibrinolysis

In a proof-of-concept randomized controlled trial, Sezer et al. 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 (110), instigating other clinical trials, such as T-TIME (NCT02257294), OPTIMAL (NCT02894138), RESTORE-MI (ACTRN12618000778280), STRIVE (NCT03335839) and a trial of intracoronary tenecteplase vs. abciximab (2010-022725-16). Two of these trials have recently reported (112,113). The T-TIME investigators tested the hypothesis that a strategy involving low dose intra-coronary fibrinolytic therapy with alteplase (10 mg or 20 mg) infused during 5–10 min early after coronary reperfusion and before stenting would prevent and reduce MVO. 1527 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 enrolment be discontinued due to futility. The amount (mean, standard deviation) of MVO did not differ between the groups [2.32 (4.31) vs. 2.61 (4.49) vs. 3.48 (5.83) %

LV mass); p=0.43] (111). In the trial led by Morales-Ponce *et al*. (113), 76 patients with anterior STEMI were randomized to treatment with either intra-coronary tenecteplase or intravenous abciximab. At 4 months, infarct size measured by CMR was not different between the groups. In RESTORE-MI, enrolment 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

Despite initial promising results, routine manual thrombus aspiration performed during primary PCI failed to demonstrate a clinical benefit in STEMI patients. Indeed, the TASTE trial randomized 7,244 patients with STEMI to manual thrombus aspiration or to conventional primary PCI. Death from any cause after 30 days occurred in 2.8% and in 3.0% of patients, respectively (114). After 1 year, no mortality benefit was associated with manual thrombus aspiration (115). Moreover, the TOTAL trial showed that, in patients with STEMI undergoing primary PCI, routine manual thrombectomy when compared with PCI alone did not reduce the risk of cardiovascular death, recurrent MI, cardiogenic shock, or NYHA class IV heart failure within 180 days but was associated with an increased rate of stroke within 30 days (116). On the other hand, the JETSTENT study, including patients with angiographic evidence of a large thrombus burden, evaluated the Angiojet mechanical thrombectomy device showing an acute improvement in STR and a lower MACE rate at 1-year in the Angiojet group compared with the direct stenting group (117).

Moreover, pressure-controlled intermittent coronary sinus occlusion (PICSO) may improve microvascular perfusion after primary PCI and has been shown to reduce infarct size both in experimental and small clinical studies (118). However, evidence of improved clinical outcome is still lacking.

Finally, hypothermia induced by cold saline and endovascular cooling failed to show a reduction of IS and MVO (13).

Future therapeutic approaches and gaps in knowledge

It is evident that most of the cardioprotection studies performed in the last decades mainly addressed infarct size as endpoint, 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.

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 US, which mention the lack of a 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, e.g. 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 (119) with an increase over the first 48 hours after infarction followed by a stable period for several days and complete resolution within weeks to months might also provide mechanistic insights into the causes of microvascular dysfunction. 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.

In particular, 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 (13). Moreover, the persistence of an inflammatory process in the chronic phase after MI may contribute to the occurrence of adverse ventricular remodelling and worse clinical outcomes (120). Of note, statins represent one of the treatments able to attenuate inflammation in the context of MI, and probably the positive results of previous 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 (120). 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 remodelling (121). Of note, a small randomized, double-blind, placebo-controlled study (122) using iron chelation with deferoxamine (500 mg immediately before primary PCI followed by a 12-h infusion) to target ischemia-reperfusion injury in patients with STEMI treated by primary PCI, failed to show a significant difference in the primary endpoint 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 administration of iron chelation therapy in all unselected STEMI patients. 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 (123). 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 (123).

Finally, as multiple cellular players and different signalling pathways are involved in determining both infarct size and the occurrence of MVO, a multi-targeted approach using a combination of therapies may be a more effective way to obtain an effective cardioprotection that translate into improved clinical outcome. Accordingly, recent studies evaluating a multi-targeted approach showed promising results (99,105, 106, 124).

References

1. Nabel EG, Braunwald E. A tale of coronary artery disease and myocardial infarction. N Engl J Med. 2012;366:54–63.
2. Pedersen F, Butrymovich V, Kelbæk H, Wachtell K, Helqvist S, Kastrup J, Holmvang L, Clemmensen P, Engstrm T, Grande P, Saunamki K, Jorgensen E. Short- and long-term cause of death in patients treated with primary PCI for STEMI. J Am Coll Cardiol. 2014;64:2101–2108.
3. Cung TT, Morel O, Cayla G, Rioufol G, Garcia-Dorado D, Angoulvant D, Bonnefoy-Cudraz E, Guerin P, Elbaz M, Delarche N, Coste P, Vanzetto G, Metge M, Aupetit JF, Jouve B, Motreff P, Tron C, Labeque JN, Steg PG, Cottin Y, Range G, Clerc J, Claeys MJ, Coussement P, Prunier F, Moulin F, Roth O, Belle L, Dubois P, Barragan P, Gilard M, Piot C, Colin P, De PF, Morice MC, Ider O, Dubois-Rande JL, Unterseeh T, Le BH, Beard T, Blanchard D, Grollier G, Malquarti V, Staat P, Sudre A, Elmer E, Hansson MJ, Bergerot C, Boussaha I, Jossan C, Derumeaux G, Mewton N, Ovize M. Cyclosporine before PCI in patients with acute myocardial infarction. N Engl J Med 2015;373:1021–1031.
4. Menees DS, Peterson ED, Wang Y, Messenger JC, Rumsfeld JS, Gurm HS. Door-to-balloon time and mortality among patients undergoing primary PCI. N Engl J Med 2013;369:901–909.
5. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, Caforio ALP, Crea F, Goudevenos JA, Halvorsen S, Hindricks G, Kastrati A, Lenzen MJ, Prescott E, Roffi M, Valgimigli M, Varenhorst C, Vranckx P, Widimský P; ESC Scientific Document Group . 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J. 2018;39:119-177.

6. Stone GW, Selker HP, Thiele H, Patel MR, Udelson JE, Ohman EM, Maehara A, Eitel I, Granger CB, Jenkins PL, Nichols M, Ben-Yehuda O. Relationship between infarct size and outcomes following primary PCI: patient-level analysis from 10 randomized trials. J Am Coll Cardiol. 2016;67:1674–1683.

7. Hamirani YS, Wong A, Kramer CM, Salerno M. Effect of microvascular obstruction and intramyocardial hemorrhage by CMR on LV remodelling and outcomes after myocardial infarction: a systematic review and meta-analysis. J Am Coll Cardiol Cardiovasc Imaging. 2014;7:940–952.

8. de Waha S, Patel MR, Granger CB, Ohman EM, Maehara A, Eitel I, Ben-Yehuda O, Jenkins P, Thiele H, Stone GW. Relationship between microvascular obstruction and adverse events following primary percutaneous coronary intervention for ST-segment elevation myocardial infarction: an individual patient data pooled analysis from seven randomized trials. Eur Heart J. 2017;38:3502–3510.

9. Heusch G, Libby P, Gersh B, Yellon D, Böhm M, Lopaschuk G, Opie L. Cardiovascular remodeling in coronary artery disease and heart failure. Lancet 2014;383:1933–1943.

10. Hausenloy DJ, Chilian W, Crea F, Davidson SM, Ferdinandy P, Garcia-Dorado D, van Royen N, Schulz R, Heusch G. The coronary circulation in acute myocardial ischaemia/reperfusion injury - a target for cardioprotection. Cardiovasc Res. 2018 Nov 14. doi: 10.1093/cvr/cvy286. [Epub ahead of print].

11. Hausenloy DJ, Botker HE, Engstrom T, Erlinge D, Heusch G, Ibanez B, Kloner RA, Ovize M, Yellon DM, Garcia-Dorado D. Targeting reperfusion injury in patients with ST-segment elevation myocardial infarction: trials and tribulations. Eur Heart J. 2017;38:935-941.

12. Kloner RA, Ganote CE, Jennings RB. The "no-reflow" phenomenon after temporary coronary occlusion in the dog. J Clin Invest. 1974;54:1496-508.

13. Niccoli G, Scalone G, Lerman A, Crea F. Coronary microvascular obstruction in acute myocardial infarction. Eur Heart J. 2016;37:1024-33.

14. Carrick D, Haig C, Ahmed N, Carberry J, Yue May VT, McEntegart M, Petrie MC, Eteiba H, Lindsay M, Hood S, Watkins S, Davie A, Mahrous A, Mordi I, Ford I, Radjenovic A, Oldroyd KG, Berry C. Comparative Prognostic Utility of Indexes of Microvascular Function Alone or in Combination in Patients With an Acute ST-Segment-Elevation Myocardial Infarction. Circulation. 2016;134:1833-1847.

15. Fröhlich GM, Meier P, White SK, Yellon DM, Hausenloy DJ. Myocardial reperfusion injury: looking beyond primary PCI. Eur Heart J. 2013;34:1714-22.

16. Ibáñez B, Heusch G, Ovize M, Van de Werf F. Evolving therapies for myocardial ischemia/reperfusion injury. J Am Coll Cardiol. 2015 Apr 14;65(14):1454-71.

17. Heusch G, Gersh BJ. The pathophysiology of acute myocardial infarction and strategies of protection beyond reperfusion: a continual challenge. Eur Heart J. 2017;38:774-784.

18. Heusch G, Boengler K, Schulz R. Inhibition of mitochondrial permeability transition pore opening: the holy grail of cardioprotection. Basic Res Cardiol 2010;105:151–154.

19. Scarabelli T, Stephanou A, Rayment N, Pasini E, Comini L, Curello S, Ferrari R, Knight R, Latchman D. Apoptosis of endothelial cells precedes myocyte cell apoptosis in ischemia/reperfusion injury. Circulation. 2001;104:253-6.

20. Reffelmann T, Kloner RA. The no-reflow phenomenon: a basic mechanism of myocardial ischemia and reperfusion. Basic Res Cardiol 2006;101:359–372.

21. Bekkers SC, Yazdani SK, Virmani R, Waltenberger J. Microvascular obstruction: underlying pathophysiology and clinical diagnosis. J Am Coll Cardiol 2010;55:1649–1660.

22. Heusch G, Kleinbongard P, Bose D, Levkau B, Haude M, Schulz R, Erbel R. Coronary microembolization: from bedside to bench and back to bedside. Circulation 2009;120:1822–1836.

23. Stakos DA, Kambas K, Konstantinidis T, Mitroulis I, Apostolidou E, Arelaki S, Tsironidou V, Giatromanolaki A, Skendros P, Konstantinides S, Ritis K. Expression of functional tissue

factor by neutrophil extracellular traps in culprit artery of acute myocardial infarction. Eur Heart J 2015;36:1405–1414.

24. Niccoli G, Burzotta F, Galiuto L, Crea F. Myocardial no-reflow in humans. J Am Coll Cardiol 2009;54:281–292.

25. Yoshino S, Cilluffo R, Best PJ, Atkinson EJ, Aoki T, Cunningham JM, de Andrade M, Choi BJ, Lerman LO, Lerman A. Single nucleotide polymorphisms associated with abnormal coronary microvascular function. Coron Artery Dis 2014;25:281–289.

26. Niccoli G, Altamura L, Fabretti A, Lanza GA, Biasucci LM, Rebuzzi AG, Leone AM, Porto I, Burzotta F, Trani C, Crea F. Ethanol abolishes ischemic preconditioning in humans. J Am Coll Cardiol 2008;51:271–275.

27. Gibson CM, Cannon CP, Murphy SA, Ryan KA, Mesley R, Marble SJ, et al. Relationship of TIMI myocardial perfusion grade to mortality after administration of thrombolytic drugs. Circulation 2000;101:125-30.

28. Iwakura K, Ito H, Ikushima M, Kawano S, Okamura A, Asano K, et al. Association between hyperglycemia and the no-reflow phenomenon in patients with acute myocardial infarction. J Am Coll Cardiol 2003;41:1-7.

29. Lind L, Fugmann A, Branth S, Vessby B, Millgård J, Berne C, et al. The impairment in endothelial function induced by non-esterified fatty acids can be reversed by insulin. Clin Sci (London) 2000;99:169-74.

30. Gresele P, Guglielmini G, De Angelis M, Ciferri S, Ciofetta M, Falcinelli E, et al. Acute, short-term hyperglycemia enhances shear stress-induced platelet activation in patients with type II diabetes mellitus. J Am Coll Cardiol 2003;41:1013-20.

31. Hayakawa H, Raij L. Relationship between hypercholesterolaemia, endothelial dysfunction and hypertension. J Hypertens 1999;17:611-19.

32. Stapleton PA, Goodwill AG, James ME, D'Audiffret AC, Frisbee JC. Differential impact of familial hypercholesterolemia and combined hyperlipidemia on vascular wall and network remodeling in mice. Microcirculation 2010;17:47-58.

33. Kirma C, Izgi A, Dundar C, Tanalp AC, Oduncu V, Aung SM, et al. Clinical and procedural predictors of no-reflow phenomenon after primary percutaneous coronary interventions: experience at a single center. Circ J 2008;72:716-21.

34. Bulluck H, Dharmakumar R, Arai AE, Berry C, Hausenloy DJ. Cardiovascular Magnetic Resonance in Acute ST-Segment-Elevation Myocardial Infarction: Recent Advances, Controversies, and Future Directions. Circulation. 2018;137:1949-1964.

35. Bulluck H, Hammond-Haley M, Weinmann S, Martinez-Macias R, Hausenloy DJ. Myocardial Infarct Size by CMR in Clinical Cardioprotection Studies: Insights From Randomized Controlled Trials. JACC Cardiovasc Imaging. 2017;10:230-240.

36. Carrick D, Haig C, Ahmed N, Carberry J, Yue May VT, McEntegart M, Petrie MC, Eteiba H, Lindsay M, Hood S, Watkins S, Davie A, Mahrous A, Mordi I, Ford I, Radjenovic A, Oldroyd KG, Berry C. Comparative Prognostic Utility of Indexes of Microvascular Function Alone or in Combination in Patients With an Acute ST-Segment-Elevation Myocardial Infarction. Circulation. 2016;134:1833-1847.

37. Stone GW, Selker HP, Thiele H, Patel MR, Udelson JE, Ohman EM, Maehara A, Eitel I, Granger CB, Jenkins PL, Nichols M, Ben-Yehuda O. Relationship between infarct size and outcomes following primary PCI: patient-level analysis from 10 randomized trials. J Am Coll Cardiol. 2016;67:1674–1683.

38. Eitel I, de Waha S, Wöhrle J, Fuernau G, Lurz P, Pauschinger M, Desch S, Schuler G, Thiele H. Comprehensive prognosis assessment by CMR imaging after ST-segment elevation myocardial infarction. J Am Coll Cardiol. 2014;64:1217-26.

39. van Kranenburg M, Magro M, Thiele H, de Waha S, Eitel I, Cochet A, Cottin Y, Atar D, Buser P, Wu E, Lee D, Bodi V, Klug G, Metzler B, Delewi R, Bernhardt P, Rottbauer W,

Boersma E, Zijlstra F, van Geuns RJ. Prognostic value of microvascular obstruction and infarct size, as measured by CMR in STEMI patients. JACC Cardiovasc Imaging. 2014;7:930–939.

40. de Waha S, Patel MR, Granger CB, Ohman EM, Maehara A, Eitel I, Ben-Yehuda O, Jenkins P, Thiele H, Stone GW. Relationship between microvascular obstruction and adverse events following primary percutaneous coronary intervention for ST-segment elevation myocardial infarction: an individual patient data pooled analysis from seven randomized trials. Eur Heart J. 2017;38:3502–3510.

41. Symons R, Pontone G, Schwitter J, Francone M, Iglesias JF, Barison A, Zalewski J, de Luca L, Degrauwe S, Claus P, Guglielmo M, Nessler J, Carbone I, Ferro G, Durak M, Magistrelli P, Lo Presti A, Aquaro GD, Eeckhout E, Roguelov C, Andreini D, Vogt P, Guaricci AI, Mushtaq S, Lorenzoni V, Muller O, Desmet W, Agati L, Janssens S, Bogaert J, Masci PG. Long-Term Incremental Prognostic Value of Cardiovascular Magnetic Resonance After ST-Segment Elevation Myocardial Infarction: A Study of the Collaborative Registry on CMR in STEMI. JACC Cardiovasc Imaging. 2018;11:813-825.

42. Carrick D, Haig C, Ahmed N, McEntegart M, Petrie MC, Eteiba H, Hood S, Watkins S, Lindsay MM, Davie A, Mahrous A, Mordi I, Rauhalammi S, Sattar N, Welsh P, Radjenovic A, Ford I, Oldroyd KG, Berry C. Myocardial hemorrhage after acute reperfused ST-segment-elevation myocardial infarction: relation to microvascular obstruction and prognostic significance. Circ Cardiovasc Imaging. 2016;9:e004148.

43. Bresnahan GF, Roberts R, Shell WE, Ross J, Sobel BE. Deleterious effects due to hemorrhage after myocardial reperfusion. Am J Cardiol 1974;33:82-6.

44. Ganame J, Messalli G, Dymarkowski S, et al. Impact of myocardial haemorrhage on left ventricular function and remodelling in patients with reperfused acute myocardial infarction. Eur Heart J 2009;30:1440-9.

45. Garcia-Dorado D, Théroux P, Solares J, et al. Determinants of hemorrhagic infarcts. Histologic observations from experiments involving coronary occlusion, coronary reperfusion, and reocclusion. Am J Pathol 1990;137:301-11.

46. Zia MI, Ghugre NR, Connelly KA, et al. Characterizing myocardial edema and hemorrhage using quantitative T2 and T2* mapping at multiple time intervals post ST-segment elevation myocardial infarction. Circ Cardiovasc Imaging 2012;5:566-72.

47. Bulluck H, Rosmini S, Abdel-Gadir A, White SK, Bhuva AN, Treibel TA, Fontana M, Ramlall M, Hamarneh A, Sirker A, Herrey AS, Manisty C, Yellon DM, Kellman P, Moon JC, Hausenloy DJ. Residual myocardial iron following intramyocardial hemorrhage during the convalescent phase of reperfused ST-segment-elevation myocardial infarction and adverse left ventricular remodeling. Circ Cardiovasc Imaging. 2016;9:e004940.

48. Hamirani YS, Wong A, Kramer CM, Salerno M. Effect of microvascular obstruction and intramyocardial hemorrhage by CMR on LV remodelling and outcomes after myocardial infarction: a systematic review and meta-analysis. JACC Cardiovasc Imaging. 2014;7:940–952.

49. Reinstadler SJ, Stiermaier T, Reindl M, Feistritzer HJ, Fuernau G, Eitel C, Desch S, Klug G, Thiele H, Metzler B, Eitel I. Intramyocardial haemorrhage and prognosis after ST-elevation myocardial infarction. Eur Heart J Cardiovasc Imaging. 2018 Aug 24. doi: 10.1093/ehjci/jey101. [Epub ahead of print]

50. Wu KC. CMR of microvascular obstruction and hemorrhage in myocardial infarction. J Cardiovasc Magn Reson 2012;14:68.

51. Ibanez B, Prat-Gonzalez S, Speidl WS, Vilahur G, Pinero A, Cimmino G, Garcia MJ, Fuster V, Sanz J, Badimon JJ. Early metoprolol administration before coronary reperfusion results in increased myocardial salvage: analysis of ischemic myocardium at risk using cardiac magnetic resonance. Circulation 2007;115:2909–2916.

52. García-Prieto J, Villena-Gutiérrez R, Gómez M, Bernardo E, Pun-García A, García-Lunar I, Crainiciuc G, Fernández-Jiménez R, Sreeramkumar V, Bourio-Martínez R, García-Ruiz JM, Del Valle AS, Sanz-Rosa D, Pizarro G, Fernández-Ortiz A, Hidalgo A, Fuster V, Ibanez B. Neutrophil stunning by metoprolol reduces infarct size. Nat Commun. 2017;8:14780.

53. Sorrentino SA, Doerries C, Manes C, Speer T, Dessy C, Lobysheva I, Mohmand W, Akbar R, Bahlmann F, Bester C, Schaefer A, Hilfiker-Kleiner D, Luscher TF, Balligand JL, Drexler H, Landmesser U. Nebivolol exerts beneficial effects on endothelial function, early endothelial progenitor cells, myocardial neovascularization, and left ventricular dysfunction early after myocardial infarction beyond conventional 1- blockade. J Am Coll Cardiol 2011;57:601–611.

54. Zhao JL, Yang YJ, Pei WD, Sun YH, Zhai M, Liu YX, Gao RL. Carvedilol reduces myocardial no-reflow by decreasing endothelin-1 via activation of the ATPsensitive K+ channel. Perfusion 2008;23:111–115.

55. Ibanez B, Macaya C, Sanchez-Brunete V, Pizarro G, Fernandez-Friera L, Mateos A, Fernandez-Ortiz A, Garcia-Ruiz JM, Garcia-Alvarez A, Iniguez A, Jimenez-Borreguero J, Lopez-Romero P, Fernandez-Jimenez R, Goicolea J, Ruiz-Mateos B, Bastante T, Arias M, Iglesias-Vazquez JA, Rodriguez MD, Escalera N, Acebal C, Cabrera JA, Valenciano J, Perez de PA, Fernandez-Campos MJ, Casado I, Garcia-Rubira JC, Garcia-Prieto J, Sanz-Rosa D, Cuellas C, Hernandez-Antolin R, Albarran A, Fernandez-Vazquez F, de la Torre-Hernandez JM, Pocock S, Sanz G, Fuster V. Effect of early metoprolol on infarct size in ST-segment-elevation myocardial infarction patients undergoing primary percutaneous coronary intervention: the effect of Metoprolol in Cardioprotection During an Acute Myocardial Infarction (METOCARD-CNIC) Trial. Circulation 2013;128:1495–1503.

56. Pizarro G, Fernandez-Friera L, Fuster V, Fernandez-Jimenez R, Garcia-Ruiz JM, Garcia-Alvarez A, Mateos A, Barreiro MV, Escalera N, Rodriguez MD, de MA, Garcia-Lunar I, Parra-Fuertes JJ, Sanchez-Gonzalez J, Pardillos L, Nieto B, Jimenez A, Abejon R, Bastante

T, Martinez dV, V, Cabrera JA, Lopez-Melgar B, Guzman G, Garcia-Prieto J, Mirelis JG, Zamorano JL, Albarran A, Goicolea J, Escaned J, Pocock S, Iniguez A, Fernandez-Ortiz A, Sanchez-Brunete V, Macaya C, Ibanez B. Long-term benefit of early pre-reperfusion metoprolol administration in patients with acute myocardial infarction: results from the METOCARD-CNIC trial (Effect of Metoprolol in Cardioprotection During an Acute Myocardial Infarction). J Am Coll Cardiol 2014;63:2356–2362.

57. García-Ruiz JM, Fernández-Jiménez R, García-Alvarez A, Pizarro G, Galán-Arriola C, Fernández-Friera L, Mateos A, Nuno-Ayala M, Aguero J, Sánchez-González J, García-Prieto J, López-Melgar B, Martínez-Tenorio P, López-Martín GJ, Macías A, Pérez-Asenjo B, Cabrera JA, Fernández-Ortiz A, Fuster V, Ibáñez B. Impact of the Timing of Metoprolol Administration During STEMI on Infarct Size and Ventricular Function. J Am Coll Cardiol. 2016;67:2093-2104.

58. Roolvink V, Ibanez B, Ottervanger JP, Pizarro G, van RN, Mateos A, Dambrink JH, Escalera N, Lipsic E, Albarran A, Fernandez-Ortiz A, Fernandez-Aviles F, Goicolea J, Botas J, Remkes W, Hernandez-Jaras V, Kedhi E, Zamorano JL, Navarro F, Alfonso F, Garcia-Lledo A, Alonso J, van LM, Nijveldt R, Postma S, Kolkman E, Gosselink M, de Smet B, Rasoul S, Piek JJ, Fuster V, van ‘t Hof AW. Early intravenous beta-blockers in patients with ST-segment elevation myocardial infarction before primary percutaneous coronary intervention. J Am Coll Cardiol 2016;67:2705–2715.

59. Cohen MV, Downey JM. Adenosine: trigger and mediator of cardioprotection. Basic Res Cardiol 2008;103:203–15.

60. Zhao Z-Q, Sato H, Williams MW, Fernandez AZ, Vinten-Johansen J. Adenosine A2-receptor activation inhibits neutrophil-mediated injury to coronary endothelium. Am J Physiol 1996;271:H1456–64.

61. Ross AM, Gibbons RJ, Stone GW, Kloner RA, Alexander RW. A randomized, double-blinded, placebo-controlled multicenter trial of adenosine as an adjunct to reperfusion in the

treatment of acute myocardial infarction (AMISTAD-II). J Am Coll Cardiol 2005;45:1775–1780.

62. Kloner RA, Forman MB, Gibbons RJ, Ross AM, Alexander RW, Stone GW. Impact of time to therapy and reperfusion modality on the efficacy of adenosine in acute myocardial infarction: the AMISTAD-2 trial. Eur Heart J 2006;27:2400–2405.

63. Niccoli G, Rigattieri S, De Vita MR, Valgimigli M, Corvo P, Fabbiocchi F, Romagnoli E, De Caterina AR, La Torre G, Lo Schiavo P, Tarantino F, Ferrari R, Tomai F, Olivares P, Cosentino N, D'Amario D, Leone AM, Porto I, Burzotta F, Trani C, Crea F. Open-label, randomized, placebo-controlled evaluation of intracoronary adenosine or nitroprusside after thrombus aspiration during primary percutaneous coronary intervention for the prevention of microvascular obstruction in acute myocardial infarction: the REOPEN-AMI study (intracoronary nitroprusside versus adenosine in acute myocardial infarction). JACC Cardiovasc Interv 2013;6:580–589.

64. Niccoli G, Spaziani C, Crea F; REOPEN-AMI Investigators. Left ventricular remodelling and 1-year clinical follow-up of the REOPEN-AMI trial. J Am Coll Cardiol 2014;63:1454–1455.

65. Nazir SA, McCann GP, Greenwood JP, Kunadian V, Khan JN, Mahmoud IZ, Blackman DJ, Been M, Abrams KR, Shipley L, Wilcox R, Adgey AA, Gershlick AH. Strategies to attenuate micro-vascular obstruction during P-PCI: the randomized reperfusion facilitated by local adjunctive therapy in ST-elevation myocardial infarction trial. Eur Heart J. 2016;37:1910-9.

66. Bulluck H, Sirker A, Loke YK, Garcia-Dorado D, Hausenloy DJ. Clinical benefit of adenosine as an adjunct to reperfusion in ST-elevation myocardial infarction patients: An updated meta-analysis of randomized controlled trials. Int J Cardiol 2015;202:228–237.

67. Wang D, Luo P, Wang Y, Li W, Wang C, Sun D, Zhang R, Su T, Ma X, Zeng C, Wang H, Ren J, Cao F. Glucagon-like peptide-1 protects against cardiac microvascular injury in diabetes via a cAMP/PKA/Rho-dependent mechanism. Diabetes. 2013 May;62(5):1697-708.

68. Bose AK, Mocanu MM, Carr RD, Brand CL, Yellon DM. Glucagon-like peptide 1 can directly protect the heart against ischemia/reperfusion injury. Diabetes. 2005;54:146-51.

69. Nikolaidis LA, Mankad S, Sokos GG, Miske G, Shah A, Elahi D, Shannon RP. Effects of glucagon-like peptide-1 in patients with acute myocardial infarction and left ventricular dysfunction after successful reperfusion. Circulation. 2004 Mar 2;109(8):962-5.

70. Timmers L, Henriques JP, de Kleijn DP, Devries JH, Kemperman H, Steendijk P, Verlaan CW, Kerver M, Piek JJ, Doevendans PA, Pasterkamp G, Hoefer IE. Exenatide reduces infarct size and improves cardiac function in a porcine model of ischemia and reperfusion injury. J Am Coll Cardiol 2009;53:501–510.

71. Lonborg J, Vejlstrup N, Kelbaek H, Botker HE, Kim WY, Mathiasen AB, Jorgensen E, Helqvist S, Saunamaki K, Clemmensen P, Holmvang L, Thuesen L, Krusell LR, Jensen JS, Kober L, Treiman M, Holst JJ, Engstrom T. Exenatide reduces reperfusion injury in patients with ST-segment elevation myocardial infarction. Eur Heart J 2012;33:1491–1499.

72. Woo JS, Kim W, Ha SJ, Kim JB, Kim SJ, Kim WS, Seon HJ, Kim KS. Cardioprotective effects of exenatide in patients with ST-segment-elevation myocardial infarction undergoing primary percutaneous coronary intervention: results of exenatide myocardial protection in revascularization study. Arterioscler Thromb Vasc Biol 2013;33:2252–2260.

73. Lonborg J, Kelbaek H, Vejlstrup N, Botker HE, Kim WY, Holmvang L, Jorgensen E, Helqvist S, Saunamaki K, Terkelsen CJ, Schoos MM, Kober L, Clemmensen P, Treiman M, Engstrom T. Exenatide reduces final infarct size in patients with ST segment-elevation myocardial infarction and short-duration of ischemia. Circ Cardiovasc Interv 2012;5:288–295.

74. Roos ST, Timmers L, Biesbroek PS, Nijveldt R, Kamp O, van Rossum AC, van Hout GP, Stella PR, Doevendans PA, Knaapen P, Velthuis BK, van RN, Voskuil M, Nap A, Appelman Y. No benefit of additional treatment with exenatide in patients with an acute myocardial infarction. Int J Cardiol 2016;220:809–814.

75. Kim JS, Kim J, Choi D, Lee CJ, Lee SH, Ko YG, Hong MK, Kim BK, Oh SJ, JeonDW, Yang JY, Cho JR, Lee NH, Cho YH, Cho DK, Jang Y. Efficacy of high-dose atorvastatin loading before primary percutaneous coronary intervention in ST-segment elevation myocardial infarction: the STATIN STEMI trial. JACC Cardiovasc Interv 2010;3:332–339.

76. Berwanger O, Santucci EV, de Barros E Silva PGM, Jesuíno IA, Damiani LP, Barbosa LM, Santos RHN, Laranjeira LN, Egydio FM, Borges de Oliveira JA, Dall Orto FTC, Beraldo de Andrade P, Bienert IRC, Bosso CE, Mangione JA, Polanczyk CA, Sousa AGMR, Kalil RAK, Santos LM, Sposito AC, Rech RL, Sousa ACS, Baldissera F, Nascimento BR, Giraldez RRCV, Cavalcanti AB, Pereira SB, Mattos LA, Armaganijan LV, Guimarães HP, Sousa JEMR, Alexander JH, Granger CB, Lopes RD; SECURE-PCI Investigators. Effect of Loading Dose of Atorvastatin Prior to Planned Percutaneous Coronary Intervention on Major Adverse Cardiovascular Events in Acute Coronary Syndrome: The SECURE-PCI Randomized Clinical Trial. JAMA. 2018;319:1331-1340.

77. Iwakura K, Ito H, Kawano S, Okamura A, Kurotobi T, Date M, Inoue K, Fujii K. Chronic pre-treatment of statins is associated with the reduction of the no-reflow phenomenon in the patients with reperfused acute myocardial infarction. Eur Heart J 2006;27:534–539.

78. Marenzi G, Cosentino N, Cortinovis S, Milazzo V, Rubino M, Cabiati A, De Metrio M, Moltrasio M, Lauri G, Campodonico J, Pontone G, Andreini D, Bonomi A, Veglia F, Bartorelli A. Myocardial Infarct Size in Patients on Long-Term Statin Therapy Undergoing Primary Percutaneous Coronary Intervention for ST-Elevation Myocardial Infarction. Am J Cardiol. 2015;116:1791-7.

79. Emori T, Hirata Y, Imai T, Eguchi S, Kanno K, Marumo F. Cellular mechanism of natriuretic peptides-induced inhibition of endothelin-1 biosynthesis in rat endothelial cells. Endocrinology. 1993;133:2474-80.

80. Niccoli G, Lanza GA, Shaw S, Romagnoli E, Gioia D, Burzotta F, Trani C, Mazzari MA, Mongiardo R, De Vita M, Rebuzzi AG, Lüscher TF, Crea F. Endothelin-1 and acute

myocardial infarction: a no-reflow mediator after successful percutaneous myocardial revascularization. Eur Heart J. 2006;27:1793-8.

81. Chen W, Spitzl A, Mathes D, Nikolaev VO, Werner F, Weirather J, Špiranec K, Röck K, Fischer JW, Kämmerer U, Stegner D, Baba HA, Hofmann U, Frantz S, Kuhn M. Endothelial Actions of ANP Enhance Myocardial Inflammatory Infiltration in the Early Phase After Acute Infarction. Circ Res. 2016;119:237-48.

82. Kitakaze M, Asakura M, Kim J, Shintani Y, Asanuma H, Hamasaki T, Seguchi O, Myoishi M, Minamino T, Ohara T, Nagai Y, Nanto S, Watanabe K, Fukuzawa S, Hirayama A, Nakamura N, Kimura K, Fujii K, Ishihara M, Saito Y, Tomoike H, Kitamura S. Human atrial natriuretic peptide and nicorandil as adjuncts to reperfusion treatment for acute myocardial infarction (J-WIND): two randomised trials. Lancet 2007;370:1483–1493.

83. Yang XM, Liu Y, Cui L, Yang X, Liu Y, Tandon N, Kambayashi J, Downey JM, Cohen MV. Platelet $P2Y_{12}$ blockers confer direct postconditioning-like protection in reperfused rabbit hearts. J Cardiovasc Pharmacol Ther 2013;18:251–262.

84. Kunadian V, James SK,Wojdyla DM, Zorkun C, WuJ, Storey RF, Steg PG, Katus H, Emanuelsson H, Horrow J, Maya J, Wallentin L, Harrington RA, Gibson CM. Angiographic outcomes in the PLATO trial (platelet inhibition and patient outcomes). JACC Cardiovasc Interv 2013;6:671–683.

85. Montalescot G, Van't Hof AW, Lapostolle F, Silvain J, Lassen JF, Bolognese L, Cantor WJ, Cequier A, Chettibi M, Goodman SG, Hammett CJ, Huber K, Janzon M, Merkely B, Storey RF, Zeymer U, Stibbe O, Ecollan P, Heutz WM, Swahn E, Collet P, Willems FF, Baradat C, Licour M, Tsatsaris A, Vicaut E, Hamm CW; ATLANTIC Investigators. Prehospital ticagrelor in ST-segment elevation myocardial infarction. N Engl J Med 2014;371:1016–1027.

86. Van Leeuwen MAH et al. Evaluation of Microvascular Injury in Revascularized Patients with ST Elevation Myocardial Infarction Treated with Ticagrelor versus Prasugrel: The REDUCE-MVI Trial. Circulation 2018 Oct 30. [Epub ahead of print].

87. Bulluck H, Chan M, Bryant J, Chai P, Chawla A, Chua T, Chung YC, Gao F, Ho HH, Ho AFW, Hoe AJ, Syed Saqib I, Lee R, Han LS, Liew BW, Yun PLZ, Hock MOE, Paradies V, Roe MT, Teo L, Wong A, Wong E, Wong P, Watson T, Chan MY, Tan JW, Hausenloy DJ. Platelet Inhibition to Target Reperfusion Injury (The PITRI trial): Rationale and Study Design. Clin Cardiol. 2018 Nov 12. doi: 10.1002/clc.23110. [Epub ahead of print]

88. Ellis SG, Tendera M, de Belder MA, van Boven AJ, Widimsky P, Andersen HR, Betriu A, Savonitto S, Adamus J, Peruga JZ, Hamankiewicz M, Pluta W, Oldroyd K, Ecollan P, Janssens L, Armstrong P, Brodie BR, Herrmann HC, Montalescot G, Neumann FJ, Effron MB, Barnathan ES, Topol EJ; FINESSE Investigators. 1-year survival in a randomized trial of facilitated reperfusion: results from the FINESSE (facilitated intervention with enhanced reperfusion speed to stop events) trial. JACC Cardiovasc Interv 2009;2:909–916.

89. De Luca G, Navarese E, Marino P. Risk profile and benefits from Gp IIb-IIIa inhibitors among patients with ST-segment elevation myocardial infarction treated with primary angioplasty: a meta-regression analysis of randomized trials. Eur Heart J. 2009;30:2705-13.

90. Van't Hof AW, Ten Berg J, Heestermans T, Dill T, Funck RC, van Werkum W, Dambrink JH, Suryapranata H, van Houwelingen G, Ottervanger JP, Stella P, Giannitsis E, Hamm C; Ongoing Tirofiban In Myocardial infarction Evaluation (On-TIME) 2 study group. Prehospital initiation of tirofiban in patients with ST-elevation myocardial infarction undergoing primary angioplasty (On-TIME 2): a multicentre, double-blind, randomised controlled trial. Lancet 2008;372:537–546.

91. Amier RP, Tijssen RYG, Teunissen PFA, Fernández-Jiménez R, Pizarro G, García-Lunar I, Bastante T, van de Ven PM, Beek AM, Smulders MW, Bekkers SCAM, van Royen N, Ibanez

B, Nijveldt R. Predictors of Intramyocardial Hemorrhage After Reperfused ST-Segment Elevation Myocardial Infarction. J Am Heart Assoc. 2017;6(8). pii: e005651.

92. Desch S, Siegemund A, Scholz U, Adam N, Eitel I, de Waha S, Fürnau G, Lurz P, Wetzel S, Schuler G, Thiele H. Platelet inhibition and GP IIb/IIIa receptor occupancy by intracoronary versus intravenous bolus administration of abciximab in patients with ST-elevation myocardial infarction. Clin Res Cardiol. 2012;101:117-24.

93. Stone GW, Maehara A, Witzenbichler B, Godlewski J, Parise H, Dambrink JH, Ochala A, Carlton TW, Cristea E, Wolff SD, Brener SJ, Chowdhary S, El-Omar M, Neunteufl T, Metzger DC, Karwoski T, Dizon JM, Mehran R, Gibson CM; INFUSE-AMI Investigators. Intracoronary abciximab and aspiration thrombectomy in patients with large anterior myocardial infarction: the INFUSE-AMI randomized trial. JAMA 2012;307:1817-26.

94. Thiele H, Wöhrle J, Hambrecht R, Rittger H, Birkemeyer R, Lauer B, Neuhaus P, Brosteanu O, Sick P, Wiemer M, Kerber S, Kleinertz K, Eitel I, Desch S, Schuler G. Intracoronary versus intravenous bolus abciximab during primary percutaneous coronary intervention in patients with acute ST-elevation myocardial infarction: a randomised trial. Lancet. 2012;379:923-931.

95. Desch S, Wöhrle J, Hambrecht R, Rittger H, Birkemeyer R, Lauer B, Neuhaus P, Brosteanu O, Sick P, Pauschinger M, Kerber S, Kleinertz K, de Waha S, Eitel I, Schuler G, Thiele H. Intracoronary versus intravenous abciximab bolus in patients with ST-segment elevation myocardial infarction: 1-year results of the randomized AIDA STEMI trial. J Am Coll Cardiol. 2013;62:1214-5.

96. Eitel I, Wöhrle J, Suenkel H, Meissner J, Kerber S, Lauer B, Pauschinger M, Birkemeyer R, Axthelm C, Zimmermann R, Neuhaus P, Brosteanu O, de Waha S, Desch S, Gutberlet M, Schuler G, Thiele H. Intracoronary compared with intravenous bolus abciximab application during primary percutaneous coronary intervention in ST-segment elevation myocardial infarction: cardiac magnetic resonance substudy of the AIDA STEMI trial. J Am Coll Cardiol. 2013;61:1447-54.

97. Mewton N, Croisille P, Gahide G, Rioufol G, Bonnefoy E, Sanchez I, Cung TT, Sportouch C, Angoulvant D, Finet G, Andre-Fouet X, Derumeaux G, Piot C, Vernhet H, Revel D, Ovize M. Effect of cyclosporine on left ventricular remodelling after reperfused myocardial infarction. J Am Coll Cardiol 2010;55:1200–1205.

98. Ottani F, Latini R, Staszewsky L, La VL, Locuratolo N, Sicuro M, Masson S, Barlera S, Milani V, Lombardi M, Costalunga A, Mollichelli N, Santarelli A, De CN, Sganzerla P, Boi A, Maggioni AP, Limbruno U. Cyclosporine A in reperfused myocardial infarction: the multicenter, controlled, open-label CYCLE trial. J Am Coll Cardiol 2016;67:365–374.

99. Pasupathy S, Tavella R, Grover S, Raman B, Procter NEK, Du YT, Mahadavan G, Stafford I, Heresztyn T, Holmes A, Zeitz C, Arstall M, Selvanayagam J, Horowitz JD, Beltrame JF. Early Use of N-acetylcysteine With Nitrate Therapy in Patients Undergoing Primary Percutaneous Coronary Intervention for ST-Segment-Elevation Myocardial Infarction Reduces Myocardial Infarct Size (the NACIAM Trial [N-acetylcysteine in Acute Myocardial Infarction]). Circulation. 2017;136:894-903.

100. Thiele H, Hildebrand L, Schirdewahn C, Eitel I, Adams V, Fuernau G, Erbs S, Linke A, Diederich KW, Nowak M, Desch S, Gutberlet M, Schuler G. Impact of high-dose N-acetylcysteine versus placebo on contrast-induced nephropathy and myocardial reperfusion injury in unselected patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention. The LIPSIA-N-ACC (Prospective, Single-Blind, Placebo-Controlled, Randomized Leipzig Immediate PercutaneouS Coronary Intervention Acute Myocardial Infarction N-ACC) Trial. J Am Coll Cardiol. 2010 May 18;55(20):2201-9.

101. Heusch G, Botker HE, Przyklenk K, Redington A, Yellon D. Remote ischemic conditioning. J Am Coll Cardiol 2015;65:177–195.

102. Botker HE, Kharbanda R, Schmidt MR, Bottcher M, Kaltoft AK, Terkelsen CJ, Munk K, Andersen NH, Hansen TM, Trautner S, Lassen JF, Christiansen EH, Krusell LR, Kristensen

SD, Thuesen L, Nielsen SS, Rehling M, Sorensen HT, Redington AN, Nielsen TT. Remote ischaemic conditioning before hospital admission, as a complement to angioplasty, and effect on myocardial salvage in patients with acute myocardial infarction: a randomised trial. Lancet 2010;375:727–734.

103. Crimi G, Pica S, Raineri C, Bramucci E, De Ferrari GM, Klersy C, Ferlini M, Marinoni B, Repetto A, Romeo M, Rosti V, Massa M, Raisaro A, Leonardi S, Rubartelli P, Oltrona VL, Ferrario M. Remote ischemic post-conditioning of the lower limb during primary percutaneous coronary intervention safely reduces enzymatic infarct size in anterior myocardial infarction: a randomized controlled trial. JACC Cardiovasc Interv 2013;6:1055–1063.

104. White SK, Frohlich GM, Sado DM, Maestrini V, Fontana M, Treibel TA, Tehrani S, Flett AS, Meier P, Ariti C, Davies JR, Moon JC, Yellon DM, Hausenloy DJ. Remote ischemic conditioning reduces myocardial infarct size and edema in patients with ST-segment elevation myocardial infarction. JACC Cardiovasc Interv 2015;8:178–188.

105. Eitel I, Stiermaier T, Rommel KP, Fuernau G, Sandri M, Mangner N, Linke A, Erbs S, Lurz P, Boudriot E, Mende M, Desch S, Schuler G, Thiele H. Cardioprotection by combined intrahospital remote ischaemic perconditioning and postconditioning in ST-elevation myocardial infarction: the randomized LIPSIA CONDITIONING trial. Eur Heart J 2015;36:3049–3057.

106. Stiermaier T, Jensen JO, Rommel KP, de Waha-Thiele S, Fuernau G, Desch S, Thiele H, Eitel I. Combined Intrahospital Remote Ischemic Perconditioning and Postconditioning Improves Clinical Outcome in ST-Elevation Myocardial Infarction: Long-Term Results of the LIPSIA CONDITIONING Trial. Circ Res 2019 [Epub ahead of print].

107. Verouhis D, Sörensson P, Gourine A, Henareh L, Persson J, Saleh N, Settergren M, Sundqvist M, Tornvall P, Witt N, Böhm F, Pernow J. Effect of remote ischemic conditioning on infarct

size in patients with anterior ST-elevation myocardial infarction. Am Heart J. 2016;181:66-73.

108. Sloth AD, Schmidt MR, Munk K, Kharbanda RK, Redington AN, Schmidt M, Pedersen L, Sorensen HT, Botker HE. Improved long-term clinical outcomes in patients with ST-elevation myocardial infarction undergoing remote ischaemic conditioning as an adjunct to primary percutaneous coronary intervention. Eur Heart J 2014;35:168–175.

109. Sloth AD, Schmidt MR, Munk K, Schmidt M, Pedersen L, Sorensen HT, Enemark U, Parner ET, Botker HE. Cost-effectiveness of remote ischaemic conditioning as an adjunct to primary percutaneous coronary intervention in patients with STelevation myocardial infarction. Eur Heart J Acute Cardiovasc Care 2016; pii:2048872615626657. [Epub ahead of print].

110. Sloth AD, Schmidt MR, Munk K, Schmidt M, Pedersen L, Sorensen HT, Botker HE, Investigators C. Impact of cardiovascular risk factors and medication use on the efficacy of remote ischaemic conditioning: post hoc subgroup analysis of a randomised controlled trial. BMJ Open 2015;5:e006923.

111. Sezer M, Oflaz H, Gören T, Okçular I, Umman B, Nişanci Y, Bilge AK, Sanli Y, Meriç M, Umman S. Intracoronary streptokinase after primary percutaneous coronary intervention. N Engl J Med. 2007;356:1823-34.

112. McCartney P, Eteiba H, Maznyczka AM, et al on behalf of the T-TIME investigators. Effect of low-dose intracoronary alteplase during primary percutaneous coronary intervention on microvascular obstruction in patients with acute myocardial infarction: a randomized clinical trial. JAMA 2018; in press.

113. Morales-Ponce FJ, Lozano-Cid FJ, Martinez-Romero P, Gonzalez-Perez P, Sanchez-Brotons JA, Diaz-Torres I, Rodriguez-Yanez JC, Caro-Mateo P, Serrador-Frutos AM. Intracoronary Tenecteplase versus Abciximab as Adjunctive Treatment during Primary Percutaneous Coronary Intervention in Patients with Anterior Myocardial Infarction. EuroIntervention. 2018 Nov 13. pii: EIJ-D-18-00885. doi: 10.4244/EIJ-D-18-00885. [Epub ahead of print]

114. Fröbert O, Lagerqvist B, Olivecrona GK, Omerovic E, Gudnason T, Maeng M, Aasa M, Angerås O, Calais F, Danielewicz M, Erlinge D, Hellsten L, Jensen U, Johansson AC, Kåregren A, Nilsson J, Robertson L, Sandhall L, Sjögren I, Ostlund O, Harnek J, James SK; TASTE Trial. Thrombus aspiration during ST-segment elevation myocardial infarction. N Engl J Med. 2013;369:1587-97.

115. Lagerqvist B, Fröbert O, Olivecrona GK, Gudnason T, Maeng M, Alström P, Andersson J, Calais F, Carlsson J, Collste O, Götberg M, Hårdhammar P, Ioanes D, Kallryd A, Linder R, Lundin A, Odenstedt J, Omerovic E, Puskar V, Tödt T, Zelleroth E, Östlund O, James SK. Outcomes 1 year after thrombus aspiration for myocardial infarction. N Engl J Med. 2014;371:1111-20.

116. Jolly SS, Cairns JA, Yusuf S, Meeks B, Pogue J, Rokoss MJ, Kedev S, Thabane L, Stankovic G, Moreno R, Gershlick A, Chowdhary S, Lavi S, Niemelä K, Steg PG, Bernat I, Xu Y, Cantor WJ, Overgaard CB, Naber CK, Cheema AN, Welsh RC, Bertrand OF, Avezum A, Bhindi R, Pancholy S, Rao SV, Natarajan MK, ten Berg JM, Shestakovska O, Gao P, Widimsky P, Džavík V; TOTAL Investigators. Randomized trial of primary PCI with or without routine manual thrombectomy. N Engl J Med. 2015;372:1389-98.

117. Migliorini A, Stabile A, Rodriguez AE, Gandolfo C, Rodriguez Granillo AM, Valenti R, Parodi G, Neumann FJ, Colombo A, Antoniucci D. JETSTENT trial comparison of AngioJet rheolytic thrombectomy before direct infarct artery stenting with direct stenting alone in patients with acute myocardial infarction. The JETSTENT trial. J Am Coll Cardiol 2010;56:1298–1306.

118. van de Hoef TP, Nijveldt R, van der Ent M, Neunteufl T, Meuwissen M, Khattab A, Berger R, Kuijt WJ, Wykrzykowska J, Tijssen JG, van Rossum AC, Stone GW, Piek JJ. Pressure-controlled intermittent coronary sinus occlusion (PICSO) in acute ST-segment elevation myocardial infarction: results of the Prepare RAMSES safety and feasibility study. EuroIntervention. 2015;11:37-44.

119. Rochitte CE, Lima JA, Bluemke DA, Reeder SB, McVeigh ER, Furuta T, Becker LC, Melin JA. Magnitude and time course of microvascular obstruction and tissue injury after acute myocardial infarction. Circulation. 1998;98:1006-14.

120. Seropian IM, Toldo S, Van Tassell BW, Abbate A. Anti-inflammatory strategies for ventricular remodeling following ST-segment elevation acute myocardial infarction. J Am Coll Cardiol. 2014;63:1593-603.

121. Kali A, Kumar A, Cokic I, Tang RL, Tsaftaris SA, Friedrich MG, Dharmakumar R. Chronic manifestation of postreperfusion intramyocardial haemorrhage as regional iron deposition: a cardiovascular magnetic resonance study with ex vivo validation. Circ Cardiovasc Imaging. 2013;6:218–228.

122. Chan W, Taylor AJ, Ellims AH, Lefkovits L, Wong C, Kingwell BA, Natoli A, Croft KD, Mori T, Kaye DM, Dart AM, Duffy SJ. Effect of iron chelation on myocardial infarct size and oxidative stress in ST-elevation-myocardial infarction. Circ Cardiovasc Interv. 2012;5:270-8.

123. O'Farrell FM, Attwell D. A role for pericytes in coronary no-reflow. Nat Rev Cardiol. 2014;11:427-32.

124. Hausenloy DJ, Yellon DM. Combination Therapy to Target Reperfusion Injury After ST-Segment-Elevation Myocardial Infarction: A More Effective Approach to Cardioprotection. Circulation. 2017;136:904-906.

Table 1 Potential benefits of pharmacological strategies in reducing infarct size and clinical outcomes in STEMI patients

Drugs	Studies	Setting	Endpoints	Results	*Potential* effect on cardiomyocytes	*Potential* effect on microcirculation	Ref
Beta-blockers	METOCARD-CNIC *iv metoprolol up to 15mg before reperfusion*	STEMI	Infarct size (CMR at 5-7days)	↓ infarct size	↓ O2 consumption	Inhibition of neutrophil–platelet co-aggregation	41,42
	EARLY BAMI *iv metoprolol two bolus of 5mg before reperfusion*	STEMI	Infarct size (CMR at 30 days)	No effect			44
Adenosine	AMISTAD-II *3-h infusion of adenosine 50 or 70 microg/kg/min started within 15 min either of the start of fibrinolysis or before coronary intervention*	STEMI	Composite of chronic heart failure (HF), rehospitalization for HF and death at 6 months; infarct size (technetium-99m 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	45,46
	REFLO-STEMI *Intracoronary adenosine 1–2 mg during PCI*	STEMI	Infarct size and MVO (CMR at 2–4 days)	No effect			49
GLP-1 analogue *Exenatide*	Lønborg J et al. *i.v. infusion of exenatide started 15 min prior to PPCI and continued for 6 h*	STEMI	Salvage index (myocardial area at risk measured in the acute phase/final infarct size at CMR)	↓ Salvage index and infarct size	↑ Pro-survival signaling pathways ↓ Apoptosis ↑ Glucose uptake	↓ Macrophage migration ↑ Microvascular recruitment	52
	Woo *et al* *s.c. injection of Exenatide prior to PCI*	STEMI	Infarct size (CKMB, Tn and CMR)	↓ Infarct size			53

Statins	SECURE PCI *Atorvastatin 80mg before and 24 hours after a planned PCI*	STEMI	Composite of all-cause mortality, myocardial infarction, stroke, and unplanned coronary revascularization at 30 days.	No effect	Unknown	↑ Microvascular dilation ↑ Endothelial function ↓ Platelet activation ↓ Inflammation ↓ Immune response	57
	Hahn et al *Atorvastat 80mg before PCI and for 5 days after PCI*	STEMI	Infarct size (assessed by technetium Tc 99m tetrofosmin)	No effect			13
Atrial natriuretic peptide	J-WIND *iv carperitide 72 h infusion started prior to PPCI*	STEMI	Infarct size (CKMB) and LVEF	↓ Infarct size ↑ LEVF	↓ End-diastolic pressure ↑ Coronary collateral blood flow ↑ Mitochondrial potassium ATP channel activation	↓ Neutrophils-induced endothelial cytotoxity	60
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	89
P2Y12 inhibitor	PITRI (ongoing) *Cangrelor iv bolus followed by an infusion prior to PCI*	STEMI	Myocardial infarct size by CMR at Day 2 to 7		↑ Pro-survival signaling pathway	Platelet inhibition	65
	CvLPRIT-CMR *Clopidogrel versus 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‡	13

GP IIb/IIIa receptor inhibitors	INFUSE AMI *Intracoronary abciximab at the time of PCI*	STEMI	Infarct size at 30 days assessed by CMR	↓ Infarct size	Unknown	Platelet inhibition	71
Cyclosporin A	CYCLE *iv Ciclosporin-A-Sandimmune at the time of PCI*	STEMI	incidence of ≥70% ST-segment resolution 60 min after TIMI flow grade 3; (secondary endpoints included high-sensitivity cardiac troponin T)	No effect	↓ Apoptosis by reducing mitochondrial permeability	↑ Endothelial function	76
	CIRCUS *iv Cyclosporin A-Ciclomulsion at the time of PCI*	STEMI	Composite of death from any cause, worsening of HF, HF rehospitalization, or adverse LV remodeling at 1 year (by echo).	No effect			3
N-acetylcysteine	NACIAM Trial *iv N-acetylcysteine with background low-dose nitroglycerin at the time of PCI*	STEMI	Infarct size at CMR	↓ infarct size	↓ Oxidative stress (ROS scavenger)	↓ Oxidative stress (ROS scavenger)	77
	LIPSIA-NACC Trial *iv N-acetylcysteine*	STEMI	Myocardial salvage index at CMR	No effect			78

‡Ticagrelor also exerts adenosine-mediated effects.

Table 2 Recommendations for future cardioprotection studies.

Strategy	Comment
MVO as a primary therapeutic target	Previous studies mainly focused on myocardial injury and infarct size as primary target for cardioprotection studies. However, future studies should evaluate systematically the effects of cardioprotective therapies on MVO, along with infarct size
Multi-targeted approach	Previous studies reported neutral results probably because they were based on a pharmacological strategy directed to a single target, an approach that may be ineffective given that ischemia/reperfusion injury is a complex process with different signalling cascades and multiple cellular players (cardiomyocytes, endothelial cells, fibroblasts, inflammatory cells, platelets). A multi-targeted approach with a combination of therapies may be a more effective approach to cardioprotection in the clinical setting.
Proper selection of enrolled patients	A proper selection of patients included in cardioprotective studies is crucial. In particular, patients less likely to benefit from cardioprotective therapies (i.e. patients spontaneously reperfused prior to PPCI, with small AAR or with ischaemic times >12 h) should be excluded, focusing on patients presenting with a large AAR >30% of the LV, usually involving proximal or mid left anterior descending coronary artery and with shorter ischaemic 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 if different mechanisms act in different manner in each patient, thus ensuring a personalized therapeutic approach (i.e. 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 oedema).
Standardization of imaging protocols and clinical endpoints	The imaging protocols in previous studies were quite heterogeneous, hampering inter-study comparisons and collaborative research with data merging. Thus, a standardization of post-infarction CMR imaging protocols is urgently needed to further strengthen CMR as the reference method to in cardioprotection studies. Moreover, only clinical endpoints that are relevant to

	cardioprotection should be considered (i.e. acute and chronic MI size, LV size and ejection fraction).

Legend: AAR: area-at-risk; CMR: cardiac magnetic resonance; LV: left ventricle; MVO: microvascular obstruction; PPCI: primary percutaneous coronary intervention.

Figure legends

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

Figure 2. Relationship and prognostic significance of infarct size and MVO. Reprinted with permission from Eitel *et al*. J Am Coll Cardiol 2014;64:1217-1226. Hazard ratios refer to the multivariate analysis of Eitel *et al*. J Am Coll Cardiol 2014;64:1217-1226.

Figure 3. Visualisation of MVO and IMH by CMR. Visualization of microvascular obstruction (A) and intramyocardial haemorrhage (B) (arrows) on short-axis late gadolinium-enhanced (A) and T2* mapping (B). Cardiac magnetic resonance images were performed 4 days after acute ST-elevation myocardial infarction due to occlusion of the left anterior descending artery.

Figure 1

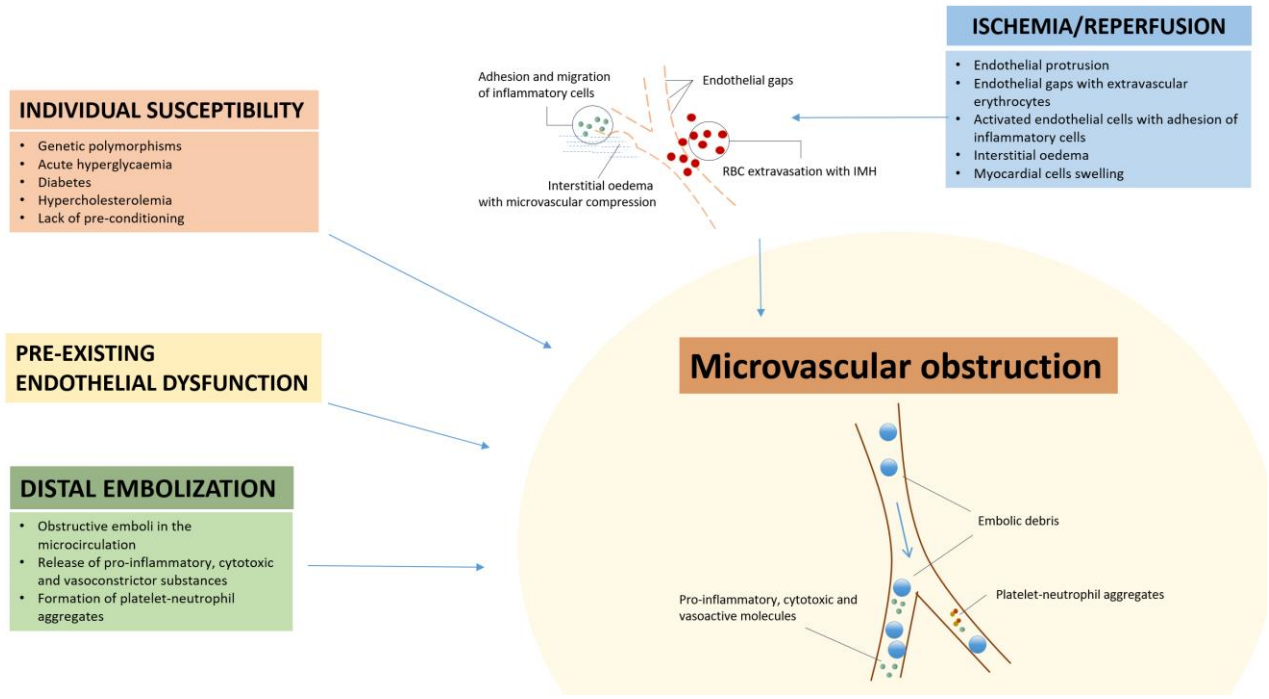

Figure 2

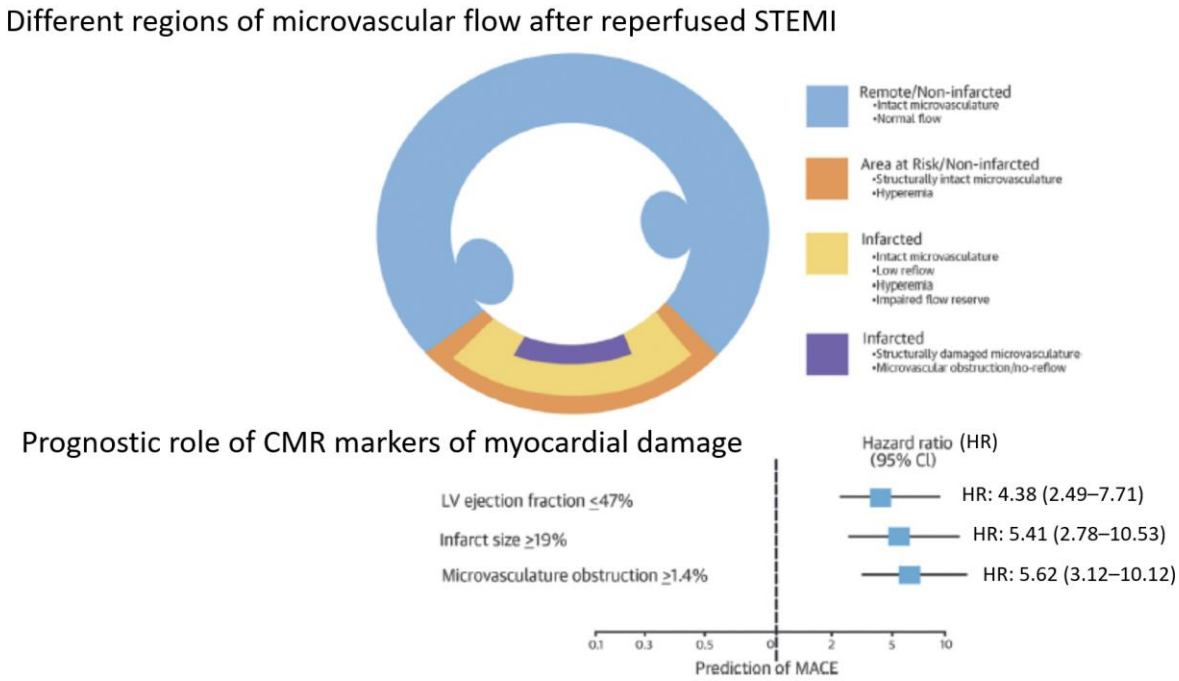
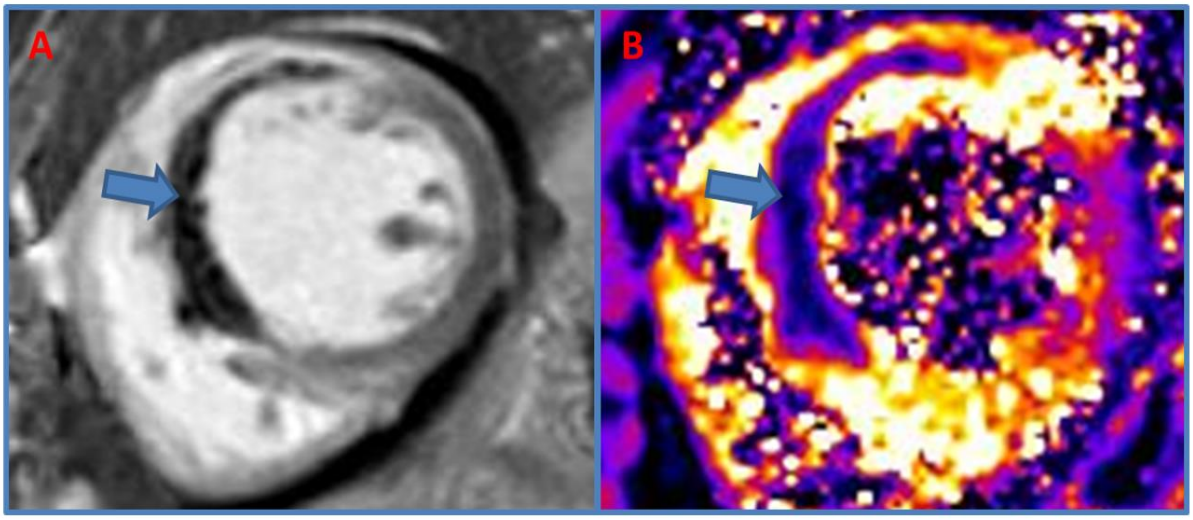
Figure 3