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REVIEW

Novel therapeutic concepts

Pathophysiology of ST-segment elevation myocardial infarction: novel mechanisms and treatments

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Despite major advances in mechanical and pharmacological reperfusion strategies to improve acute myocardial infarction (MI) injury, substantial mortality, morbidity, and socioeconomic burden still exists. To further reduce infarct size and thus ameliorate clinical outcome, the focus has also shifted towards early detection of MI with high-sensitive troponin assays, imaging, cardioprotection against pathophysiological targets of myocardial reperfusion injury with mechanical (ischaemic post-conditioning, remote ischaemic pre-conditioning, therapeutic hypothermia, and hypoxemia) and newer pharmacological interventions (atrial natriuretic peptide, cyclosporine A, and exenatide). Evidence from animal models of myocardial ischaemia and reperfusion also demonstrated promising results on more selective anti-inflammatory compounds that require additional validation in humans. Cardiac stem cell treatment also hold promise to reduce infarct size and negative remodelling of the left ventricle that may further improves symptoms and prognosis in these patients. This review focuses on the pathophysiology, detection, and reperfusion strategies of ST-segment elevation MI as well as current and future challenges to reduce ischaemia/reperfusion injury and infarct size that may result in a further improved outcome in these patients.

Keywords Acute myocardial infarction • Pathophysiology • Treatment

Introduction: definition of the disease

Pathophysiologically, acute myocardial infarction (MI) is commonly defined as a cardiomyocyte death due to a prolonged ischaemia resulting from an acute imbalance between oxygen supply and demand.[1] The 'clinical' definition of MI was recently updated, focusing on the values of serum markers of cardiac necrosis, such as cardiac troponin (cTn). Patients presenting with suspected acute coronary syndrome (ACS) in the emergency department will undergo clinical evaluation, 12-lead electrocardiogram, and complemented by measurements of cTnI or T in order to directly identify and quantify cardiomyocyte injury.[2] An increase and/or decrease in a patient's plasma of cTn with at least one cTn measurement >99th percentile of the upper normal reference signifies MI (ischaemic chest pain at rest with cardiomyocyte necrosis), while the absence of such high plasma levels in cTn refers to unstable angina (ischaemic chest pain at rest or at minimal exertion without cardiomyocyte necrosis).[3] The relatively low sensitivity of conventional cTn assays at the time of patient presentation due to a delayed elevation in circulating cTn levels commonly requires serial sampling for >6 h. Conversely, primary reperfusion therapy without troponin assessment is recommended in all patients with symptoms of ≤12 h duration and persistent ST-segment elevation or (presumed) new left bundle branch block. In addition, there is general agreement that reperfusion therapy should be considered if there is clinical and/or electrocardiographic evidence of ongoing ischaemia, even if, according to the patient, symptoms started >12 h before as the exact onset of symptoms is often unclear.[4] With the introduction of high-sensitive cTn, however, 3 h rule-out protocols in the emergency department are commonly applied. Furthermore, large observational multi-centre studies have demonstrated an excellent performance of a 2 h rule-out protocol that combines hs-cTn values with clinical information[5,6] and a 1-h rule-out protocol only based on hs-cTn

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values,[7] but needing further clinical validation. The need of a standardized definitions of ST-segment elevation myocardial infarction (STEMI) and non-STEMI are critical for diagnosis, clinical triage, and research purposes. A first consensus definition of MI stated that any necrosis in the setting of myocardial ischaemia should be labelled as MI.[1] The second and third universal definitions updated both clinical and pathophysiological aspects, including MI types[8,9] that can be secondary to ischaemic imbalance (Type 2 MI, e.g. due to vasospasm, endothelial dysfunction, coronary embolism, anaemia, respiratory failure, arrhythmias, hypertension, and hypotension) and the sudden cardiac death suggestive for MI but without available biomarker values (Type 3 MI) (*Table 1*). In addition, novel entities, such as the procedure-related MI, due to percutaneous coronary intervention (Type 4a), stent thrombosis (Type 4b), and coronary artery bypass grafting (Type 5), were considered (*Table 1*). The universal definition of MI substantially impacted on the diagnosis and treatment of the disease. Conversely, the prevention of MI requires a more comprehensive understanding of the pathophysiological aspects in vulnerable patients.[10] The present review aims at updating the relevance of a pathophysiological approach for imaging and treatments in MI models and patients.

Pathophysiology of MI: from 'vulnerable plaque' to 'vulnerable patient'

The rupture or erosion of a coronary atherosclerotic plaque is the more frequent underlying condition for MI occurrence. In the last 20 years, a strong debate on the structural characteristics of a vulnerable plaque (a plaque more prone to rupture) has been performed without a conclusive statement. In addition, the identification of a vulnerable plaque in animal models and human atherogenesis remains controversial. More recently, the concept of 'vulnerable patients', considering different entities (i.e. plaque characteristics, circulating biomarkers, and the response of the injured myocardium), was recently suggested as a better strategy to assess the risk of MI (*Figure 1*). In fact, as subclinical process characterized by dynamic, non-linear, and unpredictable course, the attempt to prospectively identify specific morphological features predictive of plaque rupture, erosion, and clinical event are likely to be unrealistic. Rather, current pathophysiological paradigm considers MI as the result of a 'perfect storm' scenario in which a coronary arterial stimulus for clinically relevant thrombosis overlaps a pro-thrombotic milieu at the site of plaque rupture or erosion (*Figure 1*).[11] The majority of scientists traditionally consider thin-cap fibroatheroma (TCFA) as a lesion at higher risk of rupture but the association with MI might be far less strong than generally assumed. In the large prospective clinical study Providing Regional Observations to Study Predictors of Events in the Coronary Tree, which followed-up 697 patients treated for ACS, nearly half of the 3 years recurrent cardiovascular events observed was ascribed to TCFAs as assessed at baseline by virtual histology intravascular ultrasound.[12] Indeed, cycles of plaque rupture and healing have been recognized as fairly frequent events that contribute to coronary narrowing and changes of plaque morphology without clinical symptoms.[13] On the contrary, transition to symptomatic plaque rupture involves only a small fraction of moderately severe vulnerable plaques that undergo rapid progression in the weeks to months before MI.[14] Since high luminal stenosis is likely to be associated with greater atherosclerotic burden, this latter might explain the high rate of event rather than stenosis itself. This consideration may also agree with recent investigation of Buffon and colleagues, challenging the concept of 'single' vulnerable plaque. By measuring neutrophil myeloperoxidase content in cardiac and femoral circulations, the authors demonstrated that widespread coronary inflammation observed in patients with unstable angina was independent of the location of the culprit lesion.[15] However, also intraplaque inflammation was described as a critical process in atherogenesis and plaque evolution.[16] In addition to macrophages, Th1 cells and smooth muscle cells, recently B lymphocyte subsets, dendritic cells, and neutrophils were described to actively influence plaque vulnerability in both human and animal models.[16]

Recently, additional systemic mediators increasing the risk of MI are identified in auto-antibodies.[17] IgG (instead of IgM that were considered as protective) against modified low-density lipoproteins, phosphorylcholine, apolipoprotein A-1 (apoA-1), heat shock proteins, and phospholipids were associated with an increased cardiovascular risk. Notably, the anti-apoA-1 IgG were described as active mediators of plaque vulnerability that may be proven useful for prognostication of MI.[18]

Pathophysiological mechanisms of myocardial ischemic/reperfusion injury

After the occlusion of an epicardial artery, mechanical or pharmacological re-establishment of the blood flow (reperfusion) may save part of hypoperfused myocardial area. However, in the early phases, reperfusion itself may cause injury. In fact, reperfusion might trigger recruitment and activation of inflammatory cells in the systemic circulation and within the myocardial ischaemic area that might increase myocardial injury. Few days later, these inflammatory mechanisms are thought to become beneficial allowing scare formation and stabilization. Reperfusion-induced injury therefore might be a selective target to improve post-infarction function and negative remodelling of the left ventricle. The first inflammatory cells infiltrating the ischaemic myocardium are neutrophils. These cells are recruited in the area at risk (AAR) very early after reperfusion (within 30 min), while resident macrophages disappear. Although neutrophils are needed to ensure an effective scar formation and to prevent adverse remodelling, they may in turn accelerate and perpetuate myocardial injury.[19] Pro-inflammatory environment due to reactive oxygen species (ROS) generation and cytokines release induces a positive feedback loop that enhances neutrophil recruitment and prolongs their life-span. However, 3–7 days after MI, neutrophil infiltrate resolves and granulocytes undergo apoptosis. Timely resolution of neutrophil inflammation is a critical step for optimal healing of the infarcted heart and multiple inhibitory signals have evolved for negative regulation of the inflammatory cascade following tissue injury.[20] Because of their regulated recruitment and different functional properties, monocyte subpopulations have been suggested as master regulators of the inflammatory reaction, alongside regulatory T cells and dying

Table 1 Classification of myocardial infarction according to clinical criteria and cardiac troponin raise/fall reported in the third (2012) universal definition of myocardial infarction

Criteria	Classification
	Type 1 spontaneous
Troponin threshold	Rise or fall, with at least one value above 99th percentile
Time frame	Not defined
Additional criteria	– Symptoms of ischaemia – ECG patterns – Imaging evidence – Angiographic evidence of coronary thrombus
	Type 2 MI secondary to ischemic imbalance
Troponin threshold	Rise or fall, with at least one value above 99th percentile
Time frame	Not defined
Additional criteria	– Symptoms of ischaemia – ECG patterns – Imaging evidence – Angiographic evidence of coronary thrombus
	Type 3 Cardiac death due to MI
Troponin threshold	Not defined
Time frame	Not defined
Additional criteria	– Symptoms of ischaemia – ECG patterns – Angiographic evidence of coronary thrombus – Cardiac death
	Type 4a MI related to PCI
Troponin threshold	One value >3× the 99th percentile with the normal baseline value
Time frame	Within 48 h after PCI
Additional criteria	– Symptoms of ischaemia – ECG patterns – Angiographic evidence of peri-procedural complication – Imaging evidence
	Type 4b MI related to stent thrombosis
Troponin threshold	Rise or fall, with at least one value above 99th percentile
Time frame	Not defined
Additional criteria	Stent thrombosis detected by coronary angiography in setting of myocardial ischaemia
	Type 4c MI related to restenosis
Troponin threshold	Rise or fall, with at least one value above 99th percentile
Time frame	Not defined
Additional criteria	– No significant obstructive CAD following stent deployment – No stenosis dilatation after angioplasty
	Type 5 MI related to CABG
Troponin threshold	One value >10× the 99th percentile with the normal baseline value
Time frame	Within 48 h after CABG
Additional criteria	– Symptoms of ischaemia – ECG patterns – Angiographic evidence of new graft or new coronary artery occlusion – Imaging evidence

MI, myocardial infarction; ECG, electrocardiography; PCI, percutaneous coronary intervention; cTn, cardiac troponin; CAD, coronary artery disease; CABG, coronary artery bypass grafting.

neutrophils. Cytokines and growth factor-rich environment dynamically regulate monocyte polarization, fibroblast activity, matrix metabolism, and angiogenesis, thus orchestrating reparative response. The myocardial salvage is dependent on many other factors including total ischaemic time, extension of the AAR (the area submitted to ischaemia), haemodynamic status during ischaemia,

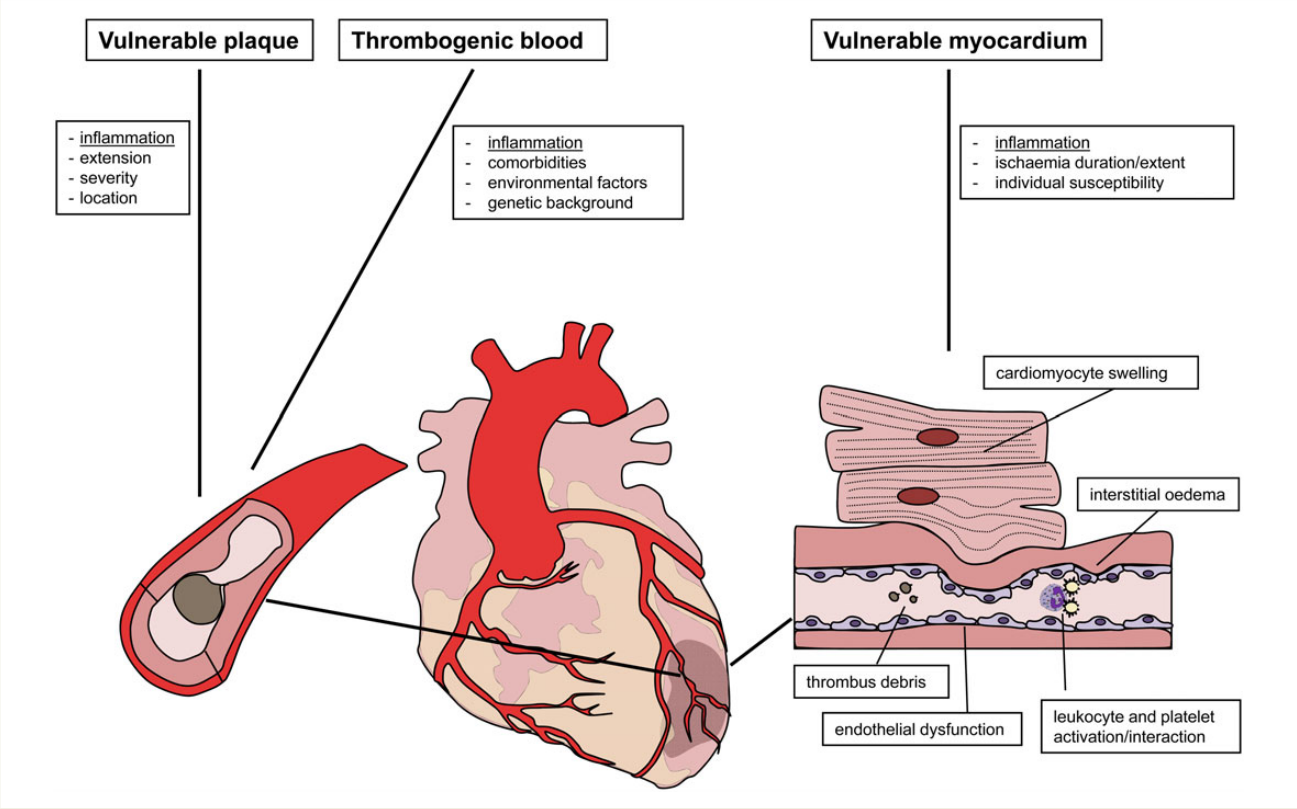

Figure 1 Critical determinants of myocardial infarction injury. The overlapping of vulnerable plaque and thrombogenic blood are critical determinants for myocardial infarction occurrence and extension. In addition, myocardium vulnerability, which is largely due to coronary microvascular dysfunction, contributes to extension and severity of ischaemic injury. In the most severe form (known as no-reflow), structural and functional impairment sustain vascular obstruction. Endothelial dysfunction triggers leukocyte and platelet activation/interaction, whereas thrombus debris may worsen the obstruction. Furthermore, cardiomyocyte swelling, interstitial oedema, and tissue inflammation promote extravascular compression.

and residual blood flow through collateral vessels. Interestingly, a severe form of coronary microvascular dysfunction (known as no-reflow) (NR) may also occur. It is defined as the ineffective reperfusion of previously ischaemic myocardial tissue despite a proper recanalization of corresponding epicardial artery.[21] No-reflow has an incidence of 5–50% after percutaneous coronary intervention and accounts, at least in part, for the residual mortality observed in reperfused ST-segment elevation acute MI. No-reflow may be sustained by structural and functional impairment of coronary microcirculation and extravascular compression. Endothelial swelling induced by ischaemia may itself obstruct microcirculation. In addition, ischaemic endothelium represents a pro-thrombogenic environment where neutrophils and platelets generate obstructive micro-aggregates. Reduced amount of nitric oxide production from ischaemic endothelium, autonomic dysfunction mediated by α-adrenergic receptor, and embolization of thrombus debris further worsen microvascular obstruction. On the other hand, extravascular compression characterized by interstitial oedema and haemorrhages is due to the massive leukocyte extravasation secondary to the opening of endothelial gaps and the overexpression of adhesion molecules. Also myocardial cell swelling and myofibrillar hyper-contraction may contribute to compression on intramural vessels (*Figure 1*). However, whether cardiomyocyte damage is causal for coronary microvascular dysfunction or both are consequence of ischaemia/reperfusion (I/R) injury remains unclear. Cardiomyocytes have traditionally been viewed as target of I/R injury, with a prevalent necrotic cell death characterized by unregulated pathophysiological mechanisms leading to microvascular destruction, haemorrhage, and sterile inflammation. Instead, accumulating evidence suggests that necrotic process may be tightly regulated by the activation of receptor-interacting protein kinases 1 and 3 (necroptosis), whereas apoptosis and autophagy further contribute to myocardial cell death in I/R injury. Although it is unclear to what extent each kind of cell death contributes to the infarct size, a crosstalk between necrosis, apoptosis, and autophagy requires further investigations. Nowadays, the damage-associated molecular patterns, toll-like receptors (TLRs), and nucleotide-binding domain leucine-rich repeat containing receptors (NLRs) appear as hot-topic regulators of reperfusion injury.[22] Once activated, downstream signalling of TLRs (including My88- and TRIF-dependent pathways) promotes nuclear translocation of NF-κB thus inducing production of pro-inflammatory cytokines and expression of co-stimulatory molecules. In particular, TLR4 has been demonstrated to promote immune response by stimulating neutrophil homing and recruitment into injured myocardium.[23] Similarly, among different NLRs, the

NLRP3 inflammasome has been identified as mediator of inflammatory response in reperfused myocardium.[24] Danger signals such as potassium efflux, lysosomal destabilization, or mitochondrial ROS lead to assembly NLRP3 inflammasome that include NLRP3, apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC) and the cysteine protease caspase-1. Activated NLRP3 inflammasome binds and activates caspase-1, known as the enzyme which converts to the active form interleukin (IL)-β, probably the most important signal amplifier due to its potent ability to induce secretion of other cytokines.[24] In addition, inflammasome-mediated caspase-1 activation may induce a high-inflammatory form of cell death, known as pyroptosis, characterized by both apoptotic and necrotic features. Caspase-1 and ASC deletion in mice were shown to suppress inflammatory responses to I/R injury, including leukocyte recruitment and cytokine/chemokine expression. Finally, defective coronary blood flow further contributes to cardiac injury even in patients with TIMI Grade 3 flow after primary angioplasty or stenting. This phenomenon, identified through a partial or no ST-segment resolution, may be the result of tissue and microvascular injury remodelling and has been associated with adverse cardiac remodelling and increased mortality rate.[25,26]

Imaging of myocardial infarction

The non-invasive assessment of the infarct size in the post-infarct period plays a central role in patient management and prognostication.[27] Although electrocardiography, cardiac enzyme levels, and non-contrast echocardiography are used in clinical routine in order to identify and characterize acute MI.[3,28–30] They do not directly visualize the extent and severity of myocardial necrosis. While there are profound advances in contrast echocardiography, strain, and strain rate imaging in the assessment of the infarct size,[31] it is not yet widely used in clinical routine.[32] Applying contrast echocardiography, however, affords a reliable evaluation of the myocardial flow or perfusion that is increasingly used for an accurate visualization and delineation of the extent of MI.[33–35] Contrast agents carrying gas-filled microbubbles are injected intravenously that results into myocardial opacification as they pass through the coronary microcirculation. Myocardial necrosis again reflects ultrasound beams more intensely than unaltered myocardium that is signified by a hyperechoic signal. In addition, applying second-harmonic imaging with the use of a mechanical index of 0.5 renders an optimal differentiation between myocardial necrotic and normal regions. The gas-filled microbubbles also enable an improved delineation of endo- and epicardial border of the myocardium enabling for the quantification of the transmural extent of the scar tissue. For more than a decade, myocardial perfusion scintigraphy with ^{99m}Tc-sestamibi SPECT has been used to quantify resting perfusion defects as an estimate of non-reversible tissue injury after MI providing valuable incremental prognostic information in these patients.[36] With the advent of delayed gadolinium enhancement magnetic resonance imaging (DE-MRI), a more direct visualization of myocardial necrosis became feasible.[37] The high spatial resolution of cardiac MRI with up to 1.5 mm in-plane resolution when compared with ~10 mm of SPECT perfusion imaging affords the direct visualization of the transmural thickness of the scar tissue. Cardiac DE-MRI therefore systematically detects small subendocardial infarcts (≈85%) that are commonly missed by conventional SPECT perfusion imaging (*Figure 2*).[38] Conversely, DE-MRI may overestimate the infarct zone by ≈10–20%.[39] The latter observations may be related to gadolinium accumulation not only in the necrotic area but also in surrounding myocardial oedema in particular in patients with acute MI. An increase in volume for the contrast agent gadolinium due to myocyte necrosis, oedema, and inflammation-induced increases in capillary permeability may account for a reported 10–20% overestimation of acute MI.[39,40] Acute infarction-related myocardial oedema may last between 4 weeks and 6 months as characterized by T2-weighted cardiac MR imaging (*Figure 3A*).[41] In particular, myocardial oedema is maximal and constant over the first week after MI. In this respect, DE-MRI imaging affords a stable window for the retrospective analysis of the area at risk, while the assessment of the infarct size may be hampered to some extent (*Figure 3B*). Myocardial regions with high signal intensity in DE-MRI in fact may regress over time associated with recovery in function providing direct proof that DE detection with MRI in the acute setting does not necessarily conform to myocardial necrosis or irreversible injury and, at the same time, may underestimate salvaged myocardium to some degree.[41] T2-weighted MR images were reported to signify the initial area at risk for myocardial necrosis in occluded vessels, if no timely restoration of myocardial flow was achieved, by delineating the peri-infarction oedema.[42,43] Conceptually, by subtraction of T2 from T1-weighted DE-MRI images, the true extent of myocardial necrosis in an ACS may be unravelled.[41,43] More recent investigations, however, question this concept by outlining that a bright myocardial signal on T2-weighted MR images does not only reflect only myocardial oedema but also necrosis as described by DE-MRI.[44,45] For the time being, DE-MRI may be seen as gold standard for an accurate delineation and characterization of chronic MI,[37] while a bright signal on T1-weighted and DE-MR images may reflect both the area at risk and/or myocardial necrosis in the setting of an acute MI.[44,46] Notably, first pass myocardial perfusion MRI with gadolinium contrast may provide additional important information on the severity of MI by visualizing the extent of infarct-related microvascular obstruction after successful restoration of coronary flow. This so-called no-reflow phenomenon signifies either no or inadequate reperfusion in the area of MI that carries independent and predictive information on subsequent cardiovascular outcome. Specifically, In patients with STEMI, the presence and magnitude of microvascular obstruction was associated with the occurrence of mayor adverse cardiovascular events (adjusted HR 3.74 [95% CI 2.21–6.34]; $P < 0.001$).[47] Combining first pass myocardial perfusion and DE-MRI is also a unique means to visualize in one study session infarct size, myocardial salvage, microvascular obstruction, and intra-myocardial haemorrhage as it has been demonstrated in the AIDA STEMI (Abciximab i.v. vs. i.c. in STEMI) cardiac magnetic resonance sub-study.[48] Another modality to indirectly assess the extent and severity of myocardial necrosis is ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG-PET). ^{18}F-FDG-PET evaluates the presence of myocardial viability predominantly in myocardial regions with wall motion abnormalities such as akinesis and dyskinesis.[49] By visualization of extent of glucose metabolism of myocytes with ^{18}F-FDG uptake in dysfunctional segments, ^{18}F-FDG-PET provides indirect information

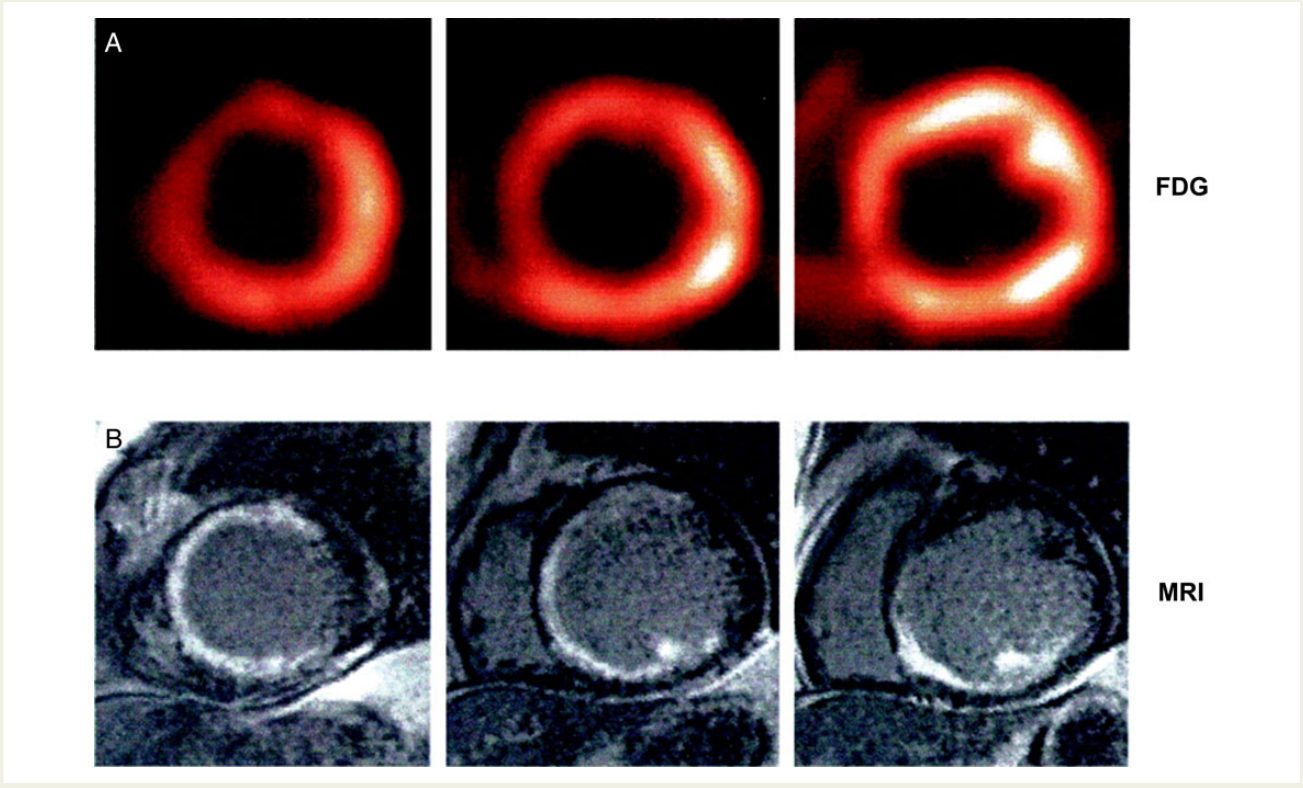

Figure 2 (*A*) Top panel with short-axis view (apical, mid-ventricular, and basal) of a fluorodeoxyglucose positron emission tomography viability study in a patient with old infarction. (*B*) Bottom panel with corresponding images of gadolinium-delayed enhancement magnetic resonance imaging signifying hyperenhancement of the subendocardial myocardial infarction. As can be seen, in the area of reduced fluorodeoxyglucose uptake on positron emission tomography, there is delayed gadolinium enhancement on magnetic resonance imaging. Owing the higher spatial resolution of magnetic resonance imaging, there is a distinction between widely transmural, subendocardial, and papillary defects can be performed. (With kind permission from reference: Klein *et al.*[40]).

on the extent of myocardial necrosis.[40] Since the uptake of ^{18}F-FDG should not be confounded by the presence of myocardial oedema, it may be the more optimal approach to identify indirectly the extent of myocardial necrosis by delineating the presence of myocardial viability in acute MI.[49] Nevertheless, ^{18}F-FDG-PET has also been apt to some criticism as ^{18}F-FDG may not only be taken up by viable myocardial cells but also by penetrating macrophages associated with acute MI.[50] With the introduction of PET/MRI, however, a further improvement of the identification and characterization of both, area at risk and infarct size, in acute MI appears feasible but needing further clinical validation.[51] Similar to DE-MRI, delayed iodinated contrast enhancement of myocardium can be acquired with multislice computed tomography (CT) with extracellular contrast retention as another approach to assess the infarct size in acute MI anatomical marker of nonviable myocardium.[52] Although this approach with CT and contrast enhancement may be useful for the identification of myocardial scar tissue, for the time being at least, it does not appear to be accurate enough for clinical use to differentiate between scar and viable myocardium in ischaemic cardiomyopathy patients when compared with ^{18}F-FDG-PET imaging.[53] Taken together, direct visualization of myocardial necrosis plays an important role in determining patient management and prognostic outcome. Although there are multiple imaging modalities to visualize the extent and severity of MI DE-MRI is considered to be the most accurate method by which to assess myocardial necrosis in the chronic state. Assessment of the infarct size in the acute MI, however, remains a challenge for DE-MRI, while ^{18}F-FDG-PET imaging may be of help to provide an indirect estimation of the extent of the infarct size. With the advent of PET/MRI, however, a further refinement of area at risk and infarct size is likely to ensue.[51]

Targeting pathophysiological pathways in myocardial infarction: new therapeutic strategies

Promising treatments in animal models

Reasonable therapeutic targets in the early stages of reperfusion injury may become essential for cardiac repair so that early report on potential anti-inflammatory therapy were later challenged by experimental studies on knockout mice. Also spatial activity of anti-inflammatory intervention may have a critical role, considering that distinct signals may occur within infarcted and border zone. Furthermore, translation from mouse model to human beings presents several limitations. In humans, MI is usually triggered by sudden plaque

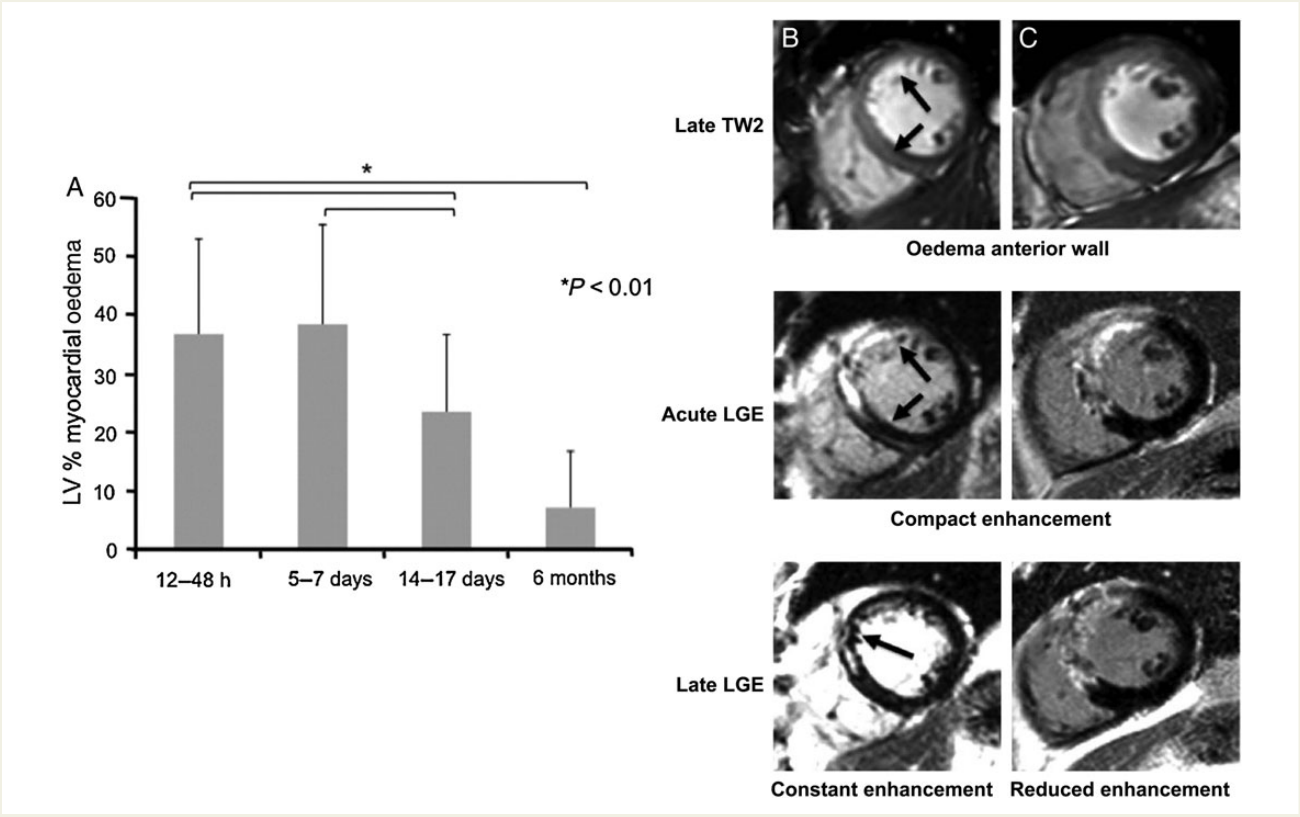

Figure 3 (*A*) Myocardial infarction and time course of oedema. Mean percentage of left ventricular volume positive for myocardial oedema at each time point. The volume of oedema remained stable in the first week after the event with a significant decrease at 15–17 days with near resolution by 6 months (with kind permission from reference Dall'Armellina *et al.*[41]). (*B* and *C*) Representative cardiac magnetic resonance images. In the column B, T2-weighted image (upward row) shows oedema in the anterior wall; the acute late gadolinium enhancement shows compact enhancement (middle row), which is reduced in size by 6 months (bottom row). In another example (column C), oedema imaging confirms acute injury (upward row). Late gadolinium enhancement present in the acute phase persists without significant alteration to the 6-month time point (middle and bottom row) (with kind permission from reference: Dall'Armellina *et al.*).

erosion/rupture in subjects characterized by middle-advanced age, comorbidities (diabetes, hypertension, and dyslipidaemia), gender differences, poly-pharmacological treatments, and genetic background. All these factors contribute to final infarct size, in addition to the ischaemic pre-conditioning, eventually due to previous episodes of angina or prior coronary microembolization. On the contrary, MI is experimentally induced in anesthetized, young, healthy mice subjected to sudden coronary occlusion and reperfusion. Furthermore, the high heart rate and the small size of mouse heart ensure oxygen and nutrients supply by diffusion, so that no >70% of the AAR is actually infarcted. Concerning clinical outcome, ventricular arrhythmias are a very common cause of death in humans, whereas their incidence is very low in mice. *Table 2* summarizes the most recent animal studies investigating promising pathophysiological treatments to reduce reperfusion injury. Specifically, we included pre-clinical studies testing compounds not yet translated in human beings.[54–75] In this regard, CC and CXC chemokine inhibition has been largely investigated as potential strategy to reduce reperfusion-related inflammation (*Figure 4*).[76,77] However, although the inhibitors of CCL5/CCR5 (Maraviroc) and CXCL12/CXCR4 (Plerixafor) have already been approved by EMEA for clinical use in HIV infection and stem cell mobilization, respectively, the evidence in MI was disappointing. The greatest concerns arose from immunological side effects, especially in prolonged treatment. On the other hand, promising results are expected by non-selective chemokine inhibitors. The activation of cannabinoid receptor 2 (CB_2) showed cardioprotective effect, potentially related to a down-regulation of chemokine expression, and suppression of oxidative stress and apoptosis.[78] Reduction of infarct size has been described in mice treated with CB_2 agonists, which were also effective in preventing arterial restenosis after percutaneous intervention (PCI) (*Table 2*).[79] Similarly, also adipocytokines have been suggested as potential target. By suppressing the enzymatic activity of intracellular and extracellular nicotinamide phosphoribosyltransferase (Nampt, also called 'visfatin'), acute treatment with the compound FK866 reduced infarct size (*Table 2*).[65] Treatment with anti-inflammatory adipocytokines chemerin and omentin prevented reperfusion injury by suppressing leukocyte recruitment and cardiomyocyte apoptosis.[66,67] Finally, inhibitors of NADPH oxidase and free radical scavenger have so far provided interesting result. As reported in *Table 2*, beneficial effects on reperfused myocardium induced by Ebselen, Fasudil, and Edaravone seem to confirm

Table 2 Experimental studies investigating new therapeutic strategies for treatments of myocardial infarction

Author	Year	Animal	Model	Treatment	Outcome
CB_2 agonists and antagonists					
Montecucco *et al.*[54]	2009	Mouse	Reperfusion after 30 min of ischaemia	CB2 selective agonist JWH-133 (20 mg/kg) 5 min before reperfusion	Treatment reduced the infarct size ($P < 0.05$). Additional findings were reduction of oxidative stress and neutrophil infiltration. Treatment also inhibited TNF-α induced chemotaxis and integrin CD18/CD11b (Mac-1) upregulation on human neutrophils
Defer *et al.*[55]	2009	Mouse	Reperfusion after 1 h of ischaemia	JWH-133 (3 mg/kg) 5 min before reperfusion	Treatment reduced infarct size ($P < 0.05$). *In vitro*, CB_2 activation was shown to inhibit cardiomyocyte and fibroblast death
Wang *et al.*[56]	2012	Mouse	Reperfusion after 30 min of global ischaemia Permanent ligation	HU308 (2 mg/kg) and/or AM630 (2 mg/kg) before ligation (1 and 2 h respectively)	In both models, pre-treatment with HU308 reduced infarct size and serum levels of ROS and TNF-α ($P < 0.01$ for all)
Li *et al.*[57]	2013	Mouse	Reperfusion after 30 min of ischaemia	JWH-133 (1, 10 or 100 nmol/L) and/or AM6301 (1 μmol/L) 5 min before ligation	Treatment with JWH-133 reduced infarct size ($P < 0.05$) promoting LV function recovery. Furthermore, treatment prevented mPTP opening
Wang *et al.*[58]	2014	Mouse	Permanent ligation	AM1241 (20 mg/daily) for 7 days after ligation	Treatment increase CPC, enhancing cardiomyocyte proliferation. In addition AM1241 significantly decrease serum levels of MDA, TNF-α and IL-6
Feng *et al.*[59]	2015	Rabbit	Reperfusion after 90 min of ischaemia	CBD (100 μg/kg) 2 doses before reperfusion	After 24 h, treated group showed a marked reduction of serum cTnI, cardiac leukocyte infiltration, and myocellular apoptosis ($P < 0.05$). In addition, treatment decreased microvascular obstruction ($P < 0.05$), thus reducing infarct size and improving systolic wall thickening ($P < 0.05$)
DPP-4 inhibitors					
Hocher *et al.*[60]	2013	Rat	Reperfusion after 30 min of ischaemia	BI 14361 (3 mg/kg daily) for a week or Linagliptin (3 mg/kg daily) 4 weeks before to 8 weeks after surgery	In both models, treatment significantly reduced infarct size ($P < 0.05$) without improving cardiac function but increasing myocardial recruitment of CPC.
Hausenloy *et al.*[61]	2013	Rat	Reperfusion after 30 min of ischaemia	Sitagliptin (100 mg/kg/day) for 2 weeks before surgery	Treatment was effective in reducing infarct size ($P < 0.05$)
Chinda *et al.*[62]	2014	Rat	Reperfusion after 30 min of ischaemia	Vildagliptin (2 mg/kg)	Vildagliptin was effective in reducing infarct size ($P < 0.05$) also preventing cardiac dysfunction. This effect was associated with improved mitochondrial function and reduced ROS generation ($P < 0.05$)
Inthachai *et al.*[63]	2015	Rat	Permanent ligation	Vildagliptin (3 mg/kg) for 8 weeks starting 3 days after surgery	At the end of treatment, vildagliptin significantly reduced infarct size also improving %FS as compared to non-treated rats. This effects were also associated with reduced oxidative stress and cardiac fibrosis ($P < 0.05$ for all)
Connelly *et al.*[64]	2015	Diabetic rat	Permanent ligation	Saxagliptin (10 mg/kg/day) and/or AMD3100 (1 mg/kg/day) for the 2 weeks before surgery	Saxagliptin increased rat overall survival ($P = 0.02$), also improving LV systolic dysfunction (assessed by %FS; $P < 0.001$) and chamber dilatation ($P < 0.05$) at day 2 after surgery. Due to the cleavage activity on CXCL12, Saxagliptin reduced cardiomyocyte hypertrophy. Accordingly, co-administration with AMD3100 abolished these beneficial effects

Continued

Table 2 ***Continued***

Author	Year	Animal	Model	Treatment	Outcome
Adipocytokines					
Montecucco *et al.*[65]	2013	Mouse	Reperfusion after 30 min of ischaemia	Nampt inhibitor (FK866 30 mg/kg)	FK866 was effective in reducing infarct size ($P < 0.01$). As additional findings, treatment inhibited neutrophil recruitment within infarcted heart and serum levels of CXCL2. *In vitro*, FK866 was shown to suppress the release of CXCL2 by peripheral monocyte and Jurkat cells
Chang *et al.*[66]	2015	Mouse	Reperfusion after 45 min of ischaemia	Chemerin-15 (0.3 ng/kg)	Treatment reduced the infarct size ($P < 0.05$). Additional findings were reduction of neutrophil infiltration and cardiomyocyte apoptosis as well as prevalence of M2 macrophage polarization within infarcted heart
Kataoka *et al.*[67]	2014	Mouse	Reperfusion after 60 min of ischaemia	Omentin (0.1 μg/g)	Treatment reduced the infarct size ($P < 0.01$) regardless of mouse sex. Omentin administration also reduced cardiomyocyte apoptosis ($P < 0.01$) via AMPK pathway
Antioxidants					
Baljinnyam *et al.*[68]	2006	Rabbit	Reperfusion after 30 min of ischaemia	Ebselen (30 or 100 mg/kg) infusion 24 h before surgery ± H_2O_2 during the first minute of reperfusion	Ebselen reduced infarct size as compared with control group, but also dose-dependently abolished the increasing in infarct size due to H_2O_2 administration ($P < 0.05$ for both models). These findings were associated with preserved glutathione levels and enhanced HSP72 expression
Jiang *et al.*[69]	2013	Rat	Reperfusion after 60 min of ischaemia	Fasudil (5 min infusion of 500 μg/kg/min)	Compared with control group, treatment reduced cardiomyocyte apoptosis and the infarct size ($P < 0.05$ for both). Fasudil was shown to increase Bcl-2 expression and Akt phosphorylation, whereas Bax and caspase-3 expression were suppressed
Zhang *et al.*[70]	2013	Rat	Reperfusion after 45 min of ischaemia	Edaravone (60 μL) ± lactic acid (60 μL) during surgery	After 24 h reperfusion, Edaravone reduced infarct size in both models ($P < 0.05$). Significant improvement also included serum markers of myocardial injury, oxidative stress, and apoptosis rate ($P < 0.05$ for all)
Fu *et al.*[71]	2013	Dog	Reperfusion after 60 min of ischaemia	HLF low (5 mg/kg) or high (10 mg/kg) dosage i.v.	Treatment was useful in reducing the activity of MPO, IL-1 and TNF-α. HLF and also increased GRK2 expression
Other					
Asanuma *et al.*[72]	2014	Dog	Reduced perfusion pressure in the LAD to one-third of the baseline value	Carperitide (0.025–0.2 μg/ kg/min into the coronary artery	At 10 min after treatment, an increase of coronary blood flow was observed. This change was also characterized by increased FS, cardiac NO, and pH levels in coronary venous blood flow
Shinlapawittayatorn *et al.*[73]	2014	Pig	Reperfusion after 60 min of LAD occlusion	VNS (30 min after LAD occlusion or at reperfusion). associated to ischaemia ± atropine or reperfusion	VNS applied 30 min after LAD occlusion, but not at reperfusion, markedly reduced ventricular fibrillation incidence and infarct size, improved cardiac function; attenuated cardiac mitochondrial depolarization, swelling, and cytochrome *c* release; as well as ROS generation. These beneficial effects of VNS were abolished by atropine

Continued

Table 2 *Continued*

Author	Year	Animal	Model	Treatment	Outcome
Uitterdijk *et al.*[74]	2015	Swine	Reperfusion after 45 min of LAD occlusion	VNS started 5 min prior to reperfusion and continued until 15 min of reperfusion	After 2 h, treated group had significantly reduced infarct size. These effects were accompanied by reductions in neutrophil and macrophage infiltration ($P < 0.05$). Interestingly, in the presence of NO-synthase inhibitor, VNS no longer attenuated infarct size and area of NR
Koudstaal *et al.*[75]	2015	Pig	reperfusion after 75 min of LCx occlusion	Nec-1 (1.0 mg/kg or 3.3 mg/kg) 10 min prior to reperfusion	At dose of 3.3 mg/kg, Nec-1significantly reduced infarct size ($P = 0.016$). In line, cardiac function was characterized by significantly higher LVEF ($P = 0.015$) and preserved contractility at 24-h follow-up ($P = 0.032$)

CB_2, cannabinoid receptor 2; JWH-133, CB_2 receptor agonist; TNF-α, tumour necrosis factor-α; CD, cluster of differentiation; Mac-1, integrin-1α; HU308, CB_2 receptor agonist; AM630, CB_2 selective inverse agonist; ROS, reactive oxygen species; mPTP, mitochondrial permeability transition pore; CPC, circulating progenitor cells; AM1241, peripheral cannabinoid CB_2 receptor agonist; MDA, malondialdehyde; IL, interleukin; CBD, cannabidiol; cTnI, cardiac troponin I; AMPK, 5′ adenosine monophosphate-activated protein kinase; DPP-4, dipeptidyl peptidase-4; CPC, circulating progenitor cells; FS, fractional shortening; LV, left ventricular; CXCL, chemokine (C-X-C motif) ligand; AMD3100, plerixafor (CXCR4 inhibitor); AMPK, 5′ adenosine monophosphate-activated protein kinase; HSP, heat shock protein; HLF, Hawthorn leaves flavonoids; MPO, myeloperoxidase; GRK2, G-protein-coupled receptor kinases; LAD, left anterior descending coronary artery; FS, fractional shortening; NO, nitric oxide; VNS, vagal nerve stimulation; LCx, left circumflex coronary artery; Nec-1, necrostatin-1.

previous evidence from experimental models of cerebral reperfusion injury, but further studies are required.[68–70]

Evidence from clinical studies

Fibrinolytic therapy

Pre-hospital fibrinolytic therapy (FT) to primary PCI is an attractive concept that has proofed to be safe and effective in several trials.[80,81] This reperfusion strategy decreases the time to treatment by ~60 min and may decrease mortality by ≈17%.[82,83] Conversely, one-third of patients may not necessarily respond FT and a relative delay or reperfusion may occur with subsequent PCI.[84] The STREAM trial emphasizes a reperfusion strategy combining pre-hospital FT with immediate transfer of the patient to a tertiary centre for rescue-PCI in non-responders to FT and for early diagnostic angiography and secondary PCI within 6–24 h after initiation of FT. Overall, early reperfusion strategy with pre-hospital FT followed by PCI is regarded as the optimal reperfusion strategy as stated in recent guidelines.[85,4 84] Current guidelines recommend that FT should be initiated within 30 min of first medical contact when primary PCI cannot be performed within 90 min or within an acceptable period of delay.[4,27] When primary PCI is not available, then FT is a viable option. Fibrinolytic therapy cautiously applied within 12 h of symptom onset substantially reduces mortality and morbidity.[86] It is important to bear in mind that the reduction of mortality is greater when FT begins within 1–2 h from the onset of symptoms, whereas the benefits decrease by half for patients treated between 7 and 12 h.[87] Fibrin-specific agents such as tenecteplase, alteplase, and retaplase rather than a non-fibrinic agent like streptokinase are preferred for FT. When compared with streptokinase, these fibrin-specific agents are antigenic and achieve higher patency rates of the infarct-related artery of ~85% vs. 60–70%.[88–90] Prior to FT aspirin and clopidogrel should be given to dissolve or inhibit thrombocyte aggregation. In this regard, the ISIS-2 trial reported similar efficacy of aspirin and streptokinase alone, whereas combined therapy provided an additive effect.[91] Later, the CLARITY-TIMI 28 trial indicated the association of aspirin and clopidogrel to FT as the gold standard to improve patency rate and reduce ischaemic complication in STEMI patients treated with FT.[92] This dual antiplatelet therapy should be continued for a minimum of 1 year in order to avoid late in-stent thrombosis with associated increase in mortality rate up to 45% and non-fatal MI rate of another 30–40%.[93,94]

The role of more recently introduced antiplatelet agents like prasugrel and ticagrelor, that both antagonize the P2Y12 receptor, as an adjunct to thrombolytic therapy for fibrinolysis in STEMI holds promise, but large-scale trials are still needed to draw more definite conclusions (*Table 3*).[95–117] Unfractionated heparin, and more recently low-molecular-weight heparins (LMWH), such as enoxaparin and fondaparinux, are increasingly used. The OASIS trial signified a relevant advantage of fondaparinux and unfractionated heparin over placebo with regard to death or reinfarction at 30 days. However, the use of fondaparinux in primary PCI appears not recommended due to the higher rate of catheter thrombosis.[118] The role of LMWH in STEMI still needs to be better defined in upcoming research trials. More recently, the adjunct use of Bivalirudin in STEMI patients with primary PCI was investigated the recent HORIZON-AMI trial, and marked 30 days cardiovascular event outcome improvement for Bivalirudin over heparin plus clopidogrel (9.2 vs. 22%) was noted (*Table 3*).[100] Such observations may suggest an emerging role of Bivalirudin in STEMI patients who are undergoing primary PCI. Failed FT may be indicated by ongoing chest pain, lack of >50% ST segment resolution and the absence of reperfusion arrhythmias at 60–90 min after application of fibrinolytic agents. A failure of FT is commonly associated with a TIMI flow < 3 in the infarct artery (R110) and 'rescue' PCI have been demonstrated to be beneficial.[119] Six months event-free survival was 84.6% in the group with rescue-PCI when compared with 70.1% among those patients

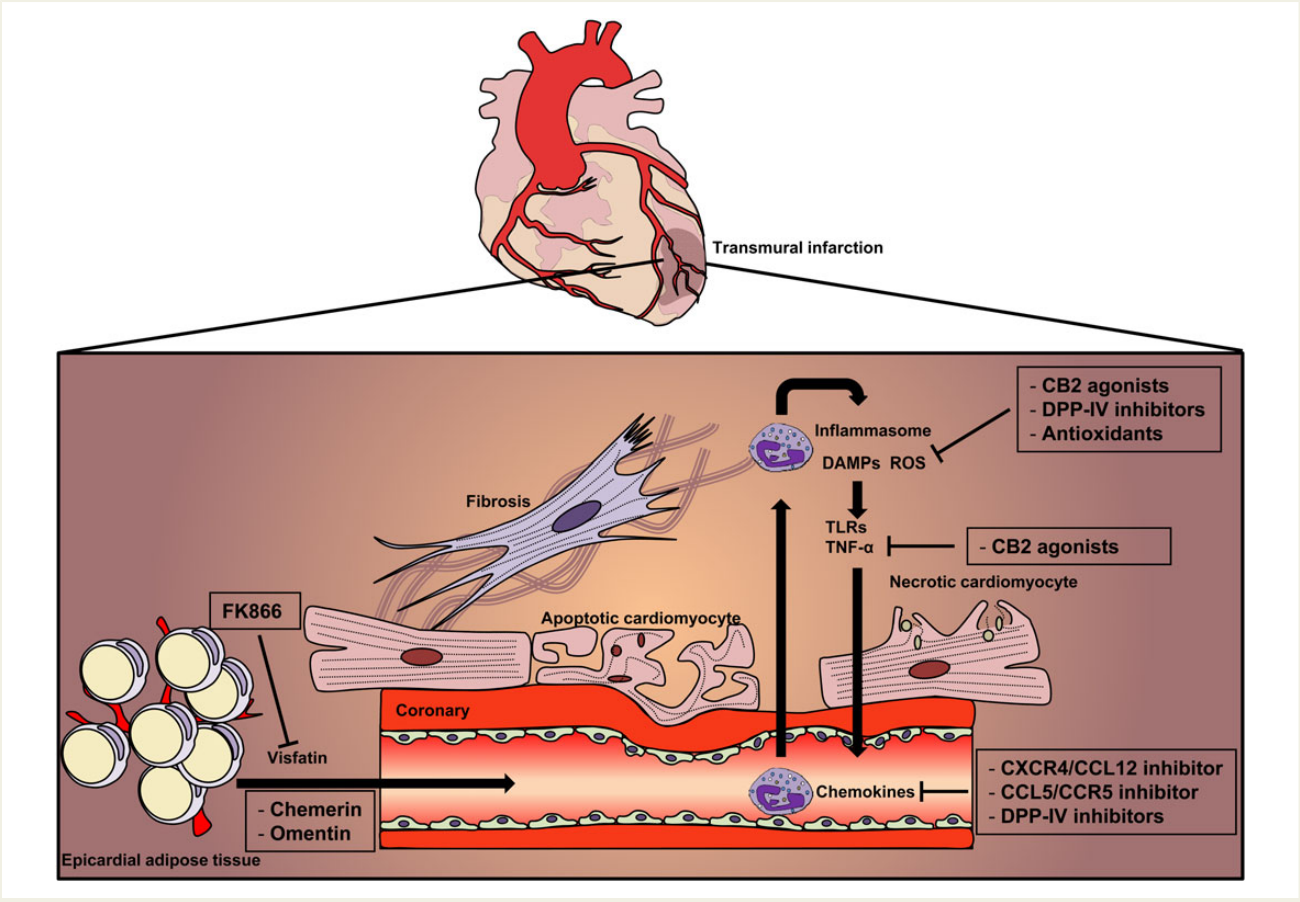

Figure 4 Anti-inflammatory therapy in myocardial infarction: pre-clinical evidence. Cardiomyocyte death triggers a massive inflammatory burst that plays a critical role in reprefusion injury following myocardial infarction. Whereas antioxidants selectively reduce reactive oxygen species, cannabinoid receptor 2 agonists, and dipeptidyl peptidase-4 inhibitors were shown to significantly reduce oxidative stress and chemokine expression. Selective inhibition of chemokine axes CXCR-4/CCL12 and CCR5/CCL5 have so far provided controversial results. Finally, targeting adipokines may be a promising strategy, effective in reducing chemokine expression and cardiomyocyte apoptosis.

receiving conservative treatment, or 68.7% undergoing repeat FT.[119] Conversely, such rescue-PCI after failed FT may be associated with relatively higher rates of stroke and peri-procedural bleeding.[120] As regards STEMI patients who responded successfully to FT, elective catheterization should be performed routinely or ischaemia guided between 3 and 24 h post-therapy.[84,99,121] Fibrinolytic agents have also been used as adjunct to primary PCI with or without glycoprotein IIb/IIIa inhibitor. This so-called facilitated PCI was based on the consideration that combined treatment will promote higher and faster rates of reperfusion of the infarcted region. The ASSENT-4 PCI randomized trial evaluated this at first sight attractive concept of a facilitated PCI that, however, did not proof to be successful.[122] The trial was ended prematurely as a marked increase in mortality rate in patients with facilitated PCI vs. primary PCI was observed. In another randomized trial,[123] neither combination-facilitated PCI (reteplase + abciximab) nor abciximab-facilitated PCI proved to be superior to primary PCI in patients with acute MI to improve 90 days outcome, but it was associated with increased rates of major bleedings. In view of these findings, facilitated PCI at least for the time being is not pursued any more.[27] As most patients with STEMI have a large thrombus burden, it appears intriguing that thrombectomy may improve coronary flow, prevent distal embolization, reduce microvascular obstruction, no reflow phenomenon and thereby should further improve PCI-related outcome. Recent, The Thrombus Aspiration in ST-elevation Myocardial Infarction in Scandinavia[124] and Trial of Routine Aspiration Thrombectomy with PCI vs. PCI Alone in Patients with STEMI Undergoing Primary PCI[125] trials could not demonstrate reduction in mortality and morbidity if adjunct thrombus aspiration was performed during primary PCI.

Advances in stent employment with primary percutaneous intervention

Bare-metal stent (BMS) employment during primary PCI has become routine practice as it reduces the rates of reinfarction and target vessel revascularization but not mortality.[86,126,127] In recent years, drug-eluting stents (DES) have more and more outperformed BMS for both elective and primary PCI as they significantly reduce restenosis rates and the need for reintervention.[128] Of note, the first-generation DES like Taxus and Cypher, when compared with BMS, has been reported to increase the risk of very late stent thrombosis with MI and fatal outcome, particular in patients with large

Table 3 Clinical trials investigating new therapeutic strategies for treatments of myocardial infarction

Author	Year	Study design (number of patients)	Treatment (follow-up)	Results
Fibrinolytic therapy				
Wallentin *et al.*[95]	2009	Double-blind, randomized trial (18 624 patients with ACS)	Ticagrelor (180 mg loading dose, 90 mg twice daily thereafter) or clopidogrel (300–600 mg loading dose, 75 mg daily thereafter)	When compared with clopidogrel, ticagrelor significantly reduced vascular death risk [HR 0.84 (95% CI 0.77–0.92); $P < 0.001$), without increasing the rate of overall major bleeding
Montalescot *et al.*[96]	2009	Double-blind, randomized trial (3534 patients with STEMI undergoing PCI)	Prasugrel (60 mg loading, 10 mg maintenance) or clopidogrel (300 mg loading, 75 mg maintenance)	When compared with clopidogrel prasugrel is more effective in preventing ischaemic events [HR 0.79 (95% CI 0.65–0.97); $P = 0.025$], without an apparent excess in bleeding
Morrow *et al.*[97]	2009	Double-blind, randomized trial (13 608 patients with STEMI undergoing PCI)	Prasugrel (60 mg loading, 10 mg maintenance) or clopidogrel (300 mg loading, 75 mg maintenance)	When compared with clopidogrel prasugrel is more effective in reducing the overall risk of MI [HR 0.79 (95% CI 0.67–0.85); $P < 0.001$], and involve both procedure-related and non-procedural MI bleeding
Steg *et al.*[98]	2010	Double-blind, randomized trial (7544 patients with STEMI undergoing PCI)	Ticagrelor (180 mg loading, 90 mg twice daily maintenance) or clopidogrel (300 mg loading, 75 mg maintenance)	When compared with clopidogrel ticagrelor is more effective in reducing the risk of MI ($P = 0.03$), and stent thrombosis ($P = 0.03$)
Bøhmer *et al.*[99]	2010	Double-blind, randomized trial (266 patients with STEMI and >90 min delay to PCI)	Rescue-PCI or conservative treatment	Rescue-PCI did not improve the composite outcome but significantly reduced the rate of death, reinfarction, and stroke ($P = 0.01$).
Stone *et al.*[100]	2015	Double-blind, randomized trial (5800 patients with ACS)	Bivalirudin (0.75 mg/kg i.v. bolus, followed by 1.75 mg/kg/h infusion) or heparin (60 IU/kg i.v. bolus) ± GPI (30 days)	Bivalirudin reduced rates of major bleeding [RR 0.53 ([95% CI 0.43–0.66); $P < 0.001$], thrombocytopenia [RR 0.48 (95% CI 0.33–0.71); $P = 0.002$], and cardiac mortality [RR 0.70 (95% CI 0.50–0.97); $P = 0.03$]. However, bivalirudin was associated with increased acute stent thrombosis rates [RR: 6.04 (95% CI 2.55–14.31); $P < 0.001$].
Stent employment with primary PCI				
Sabate *et al.*[101]	2012	Double-blind, randomized trial (1498 patients with STEMI up to 48 h after the onset of symptoms requiring PCI)	Everolimus-eluting stent or bare-metal stents	The use of everolimus-eluting stent in the setting of STEMI did not reduce the risk of adverse events. However, everolimus-eluting stent was associated with higher procedure success rate (97.5 vs. 94.6%; $P = 0.005$) and reduced risk of stent thrombosis (0.5 vs. 1.9%; $P = 0.019$)
Dewilde *et al.*[102]	2013	Double-blind, randomized trial (573 patients receiving oral anticoagulants and undergoing PCI)	Clopidogrel alone (300–600 mg loading dose, 75 mg daily thereafter) or clopidogrel plus aspirin (80–100 mg/day) in addition to anticoagulant therapy (1 year)	Use of clopidogrel without aspirin was associated with a significant reduction in bleeding complications [HR: 0.36 (95% CI 0.26–0.50); $P < 0.001$] without increase in the rate of thrombotic events
de Belder *et al.*[103]	2014	Double-blind, randomized trial (800 patients ≥80 years with STEMI undergoing stent placement)	Drug-eluting stent or bare-metal stents	Both stents offer good clinical outcome. Drug-eluting stents were associated with a lower rate of MI (8.7 vs. 4.3%; $P = 0.01$) and target vessel revascularization (7.0 vs. 2.0%; $P = 0.001$) without increased risk of bleeding
Kočka *et al.*[104]	2014	Double-blind, randomized trial (142 patients with STEMI undergoing PCI)	Bioresorbable vascular scaffold implantation	Bioresorbable vascular scaffold implantation has been demonstrated to be feasible and safe. However, event-free survival was not different when compared with the control group
Pharmacological cardioprotection in STEMI				
Atar *et al.*[105]	2009	Double-blind, randomized trial (234 patients with STEMI undergoing PCI)	FX06 (two i.v. bolus administration of 200 mg each during PCI; the first immediately before the guidewire passed the occlusion and the second 10 later)	On Day 5, the necrotic zone was significantly reduced in the FX06 group ($P < 0.025$) without significant differences in TnI levels. After 4 months, there were no longer significant differences in scar size

Continued

Table 3 *Continued*

Author	Year	Study design (number of patients)	Treatment (follow-up)	Results
Botker *et al.*[106]	2010	Double-blind, randomized trial (142 patients with STEMI undergoing PCI)	Remote conditioning (intermittent arm ischaemia through four cycles of 5-min inflation and 5-min deflation of a blood-pressure cuff).	Myocardial salvage was greater in the remote conditioning group ($P = 0.033$)
Lønborg *et al.*[107]	2012	Double-blind, randomized trial (172 patients with STEMI undergoing PCI)	Exenatide (0.12 μg/min for 15 min and then reduced to 0.043 μg/min for 6 h) or placebo i.v. (90 ± 21 days)	Exenatide induced a significantly larger salvage index as assessed by CMR (0.71 ± 0.13 vs. 0.62 ± 0.16; $P = 0.003$). However, no difference was observed in left ventricular function or 30-day clinical events. No adverse effects were reported
Lincoff *et al.*[108]	2014	Double-blind, randomized trial (1176 patients with anterior or inferior STEMI undergoing PCI)	Placebo or delcasertib (i.v. infusion of 50, 150, or 450 mg/h initiated before PCI and continued for ∼2.5 h) (3 months)	Treatment failed to reduce biomarkers of myocardial injury
Sloth *et al.*[109]	2014	Double-blind, randomized trial (333 patients with STEMI undergoing PCI)	PCI with or without remote ischaemic conditioning (intermittent arm ischaemia through four cycles of 5-min inflation) (3.8 years)	Ischaemic conditioning was associated with reduced risk of MACCE [13.5 vs. 25.6%; HR 0.49 (95% CI 0.27–0.89); $P = 0.018$) and all-cause mortality [HR 0.32 (95% CI 0.12–0.88); $P = 0.027$]
Atar *et al.*[110]	2015	Double-blind, randomized trial (163 patients with STEMI undergoing PCI)	TRO40303 (i.v. bolus administration of 6 mg/kg each during PCI; before the guidewire passage, prior to balloon inflation and stenting)	There were no significant differences in the biochemical evaluation and CMR-assessed infarct size and cardiac function between TRO40303 and placebo. However, a greater number of adjudicated safety events occurred in the TRO40303 group
Cung *et al.*[111]	2015	Double-blind, randomized trial (791 patients with STEMI undergoing PCI)	Cyclosporine (i.v. bolus administration of 2.5 mg/kg before recanalization)	The rate of composite adverse CV events between cyclosporine and control group was similar [59.0 vs. 58.1%; OR 1.04 ([95% CI 0.78–1.39); $P = 0.77$]. Moreover, cyclosporine did not reduce the incidence of the separate outcomes
Stem cells				
Traverse *et al.*[112]	2011	Double-blind, randomized trial (87 patients with LVEF ≤ 45% post-MI undergoing PCI)	Intracoronary infusion of autologous BMCs (150×10^6) or placebo infused 2–3 weeks after PCI (6 months)	Infusion of autologous BMCs did not improve global or regional function, assessed as changes in global (LVEF) and regional (wall motion) LV function in the infarct and border zone
Traverse *et al.*[113]	2012	Double-blind, randomized trial (120 patients with LVEF ≤ 45% post-MI undergoing PCI)	Intracoronary infusion of autologous BMCs (150×10^6) or placebo infused 3 or 7 days after PCI (6 months)	BMCs at either 3 or 7 days after the event failed to improve recovery of global or regional left ventricular function
Chugh *et al.*[114]	2012	Double-blind, randomized trial (33 patients with LVEF ≤ 40% before CABG)	Intracoronary infusion of autologous CSCs (1×10^6) or placebo infused a mean of 113 days after surgery (12 months)	After infusion of autologous CSCs, CMR showed a significant reduction of infarct size (−30.2% at 12 months; $P = 0.039$), and increase of LV liable mass (+31.5 ± 11.0 g at 12 months; $P = 0.035$)
Makkar *et al.*[115]	2012	Double-blind, randomized trial (31 patients with LVEF of 25–45% after AMI)	Intracoronary infusion of autologous CSCs ($12.5–25 \times 10^6$) or placebo infused within 90 days after AMI (1 year)	Infusion of autologous CSCs was associated with decreased scar size ($P = 0.004$), increased viable myocardium ($P < 0.05$), and improved regional function ($P = 0.036$) of infarcted myocardium without rising significant safety concerns
Nasseri *et al.*[116]	2014	Double-blind, randomized trial (60 patients with IHD and LVEF < 35% undergoing CABG)	Intracoronary infusion of autologous $CD133^+$ BMC ($12.5–25 \times 10^6$) or placebo infused within 90 days after AMI (6 months)	By cardiac MRI, the $CD133^+$ group showed improved myocardial perfusion at rest ($P < 0.001$), and scar mass decreased ($P = 0.05$).
Mathiasen *et al.*[117]	2015	Double-blind, randomized trial (55 patients with severe ischaemic HF and LVEF ≤ 50%)	Intra-myocardial injection of 10–15 injections of MSCs (0.2 mL) or placebo (6 months)	Treatment with MSCs reduced LVESV ($P = 0.001$) also improving LVEF ($P < 0.001$), stroke volume ($P < 0.001$), and myocardial mass ($P = 0.001$)

ACS, acute coronary syndrome; HR, hazard ratio; CI, confidence interval; STEMI, ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; MI, myocardial infarction; i.v., intravenous; GPI, glycoprotein IIb/IIIa inhibitor; RR, relative risk; CV, cardiovascular; MACCE, major adverse cardiac and cerebrovascular events; CMR, cardiac magnetic resonance; OR, odds ratio; LVEF, left ventricular ejection fraction; BMCs, bone marrow mononuclear cells; LV, left ventricular; CABG, coronary artery bypass grafting; CSCs, cardiac stem cells; AMI, acute myocardial infarction; IHD, ischaemic heart disease; HF, heart failure; MSCs, mesenchymal stromal cells; LVESV, left ventricular end-systolic volume.

DES.[129,130] When the newer generation of DES like Xience, Promeus, and Endeavour was compared with BMS, no risk increase of acute or late stent thrombosis was noted any more (*Table 3*).[101,103,131] The further development of DES with bioresorbable vascular scaffolds may avoid permanent rigid metallic structure in coronary arteries. Bioresorbable vascular scaffolds have been demonstrated to be safe and effective in chronic stable coronary artery disease as well as in STEMI (*Table 3*).[104,132–134] Stent implantation in patients taking oral anticoagulation and presenting with STEMI constitutes a significant challenge as it results in a triple therapy significantly increasing the risk of major bleedings. A recent study puts forth that in primary PCI warfarin plus clopidogrel had lower bleeding complications than warfarin, clopidogrel, plus aspirin, while the rate of stent thrombosis was not increased (*Table 3*).[102] The study, however, was not sufficiently powered to investigate the risk of stent thrombosis, so that further large-scale studies in this direction are warranted.

Pharmacological cardioprotection in ST-segment elevation myocardial infarction

Pharmaceutical interventions have been put forth to mediate some cardioprotection against reperfusion injury, including calcium-channel blockers, antioxidants, and anti-inflammatory agents, while these pharmaceutical approaches of cardioprotection did not translate into a clinical benefit with improved clinical outcome.[135–139] More recently, much hope was projected into protein kinase C (PKC) isoenzyme modulated cardioprotection.[140,141] In a multi-centre, double-blinded trial the effect of Delcasertib a selective inhibitor of delta-PKC on infarct size and clinical outcome in 1010 patients undergoing primary PCI for anterior STEMI (*Table 3*).[108] No significant differences among the treatment groups in secondary endpoints of infarct size, electrocardiographic ST-segment and time to stable ST recovery, or left ventricular ejection fraction (LVEF) at 3 months were noted. Although the trial was not sufficiently powered for clinical endpoints, there was no improved outcome as regards death, heart failure, or serious ventricular arrhythmia.[108] Similarly, the use of peptides has so far provided controversial results. In the F.I.R.E. (Efficacy of FX06 in the Prevention of Myocardial Reperfusion Injury) trial, the administration of FX06 (a cleavage product of human fibrin) substantially reduced infarct size early after STEMI, but no significant difference with placebo was observed in the scar size after 4 months.[105] Similarly, inhibiting mitochondrial permeability transition pore by the peptide TRO40303, as tested in the MITOCARE trial, failed to reduce reperfusion injury also inducing a not negligible number of adjudicated safety events.[110] In this regard, there is great expectation for the results of EMBRACE STEMI, Phase 2a, randomized, double-blind, placebo-controlled trial designed for testing the mitochondrial targeting peptide Bendavia in patients undergoing primary PCI within 4 h of symptom onset for a first-time anterior STEMI occluding proximal or mid-left anterior descending artery.[142] Conversely, mechanical interventions such as ischaemic post-conditioning, remote ischaemic pre-conditioning, therapeutic hypothermia and hypoxemia,[106,109,137,143,144] but also more recently introduced pharmacologic interventions with atrial natriuretic peptide and exenatide hold promise for cardioprotection against myocardial perfusion injury but require confirmation in larger clinical trials (*Table 3*).[107,136,144] With regard to cyclosporine, a potential role in reducing infarct size was suggested in two small pilot trials.[145,146] However, the Cyclosporine and Prognosis in Acute MI Patients (CIRCUS) trial that included 791 patients recently demonstrated that cyclosporine did not improve 1-year clinical outcome after STEMI. Specifically, the treatment failed to reduce incidence of both single and composite outcome including recurrent infarction, unstable angina, and stroke.[111] Contrariwise, the results of the Cardiovascular Risk Reduction Study, which investigates the anti-inflammatory properties of Canakinumab (a human monoclonal antibody neutralizing IL-1β) might be associated with a significant reduction of recurrent MI. Specifically, the purpose of this trial is to test Canakinumab in patients undergone MI at least 1 month prior to recruitment and having high serum levels of high-sensitivity C-reactive protein (CRP).[147] Also first promising results of the IL-6 inhibitor tocilizumab was reported as a potential treatment against reperfusion injury. In patients with MI, treatment with tocilizumab was correlated with a significant decrease in CRP and cTn release.[148] Finally, many large trials supported the early start of therapy with inhibitors of the renin–angiotensin–aldosterone system. The ISIS-4 first showed a reduction of 5-week mortality in captopril-treated patients when compared with placebo. Furthermore, this beneficial effect was greater in certain high-risk groups, such as those presenting with a history of previous MI or with heart failure.[149]

Stems cells in clinical trials

Various approaches of stem cell treatment have been investigated to confine myocardial damage and potentially regenerate myocardium in acute MI.[150,151] In general, the effects of two populations of stem cells on regeneration and left ventricular function such as adult bone marrow mononuclear cells (BMCs) and cardiac stem cells are being investigated in patients with MI and/or ischaemic cardiomyopathy. Adult BMCs from the bone marrow aspirates carry ∼0.5–3.0% haematopoietic and mesenchymal progenitor cells. These progenitor cells from the bone marrow, when injected intracoronarily or directly into the myocardium, release growth factors and cytokines that appears to confine myocardial inflammation and infarct size.[150,151] These cells have some ability to replicate but they cannot transform into myocytes. Conversely, they release mediators that recruit endogenous stem cells from the patient for repair or limitation of cardiac injury. Several non-randomized and small-sized clinical investigation have reported that intracoronary injection of autologous un fractionated BMCs in acute MI may lead to a mild but statistically significant increase of ≈2–3% in LVEF associated with a reduction in the size of the infarction of ≈5.5% (*Table 3*).[112,113,150,152–154] These initial results raised questions about the optimal cell for acute MI treatment, the optimal timing of cell injection, the viability of stem cells prior and after injection into patients, and the best parameter to monitor and guide the success of stem cell treatment for cardiac repair. In this direction, the LateTIME trial[112] investigated in a randomized double-blind; placebo-controlled fashion whether the application of adult BMCs 2–3 weeks after anterior wall MI would be safe and effective in confining infarct size and increasing left ventricular function. The infarct volume, global and regional left ventricular function were determined by gadolinium magnetic resonance imaging (MRI) prior to intracoronary injection and 6 months after injection. Alterations of infarct size, LVEF, wall motion in the infarct zone, and wall motion

in the border zone of the infarction, did not differ significantly between treatment and placebo group. The following TIME trial[113] again evaluated also in a double-blind, placebo-controlled design the effect of intracoronary application of autologous BMCs or placebo in 120 patients 3–7 days after predominantly acute MI of the anterior wall. This trial was based on a prior REPAIR AMI trial that noted a 5.1% increase in LVEF after application of BMCs to patients 5–7 days after acute MI.[155] The TIME trial,[113] however, could not confirm the observation REPAIR AMI trial. Magnetic resonance imaging-determined changes of infarct size, LVEF, wall motion in the infarct zone, and wall motion in the border zone of the infarction after the 6 months follow-up were not significantly different between treatment and placebo group.[155] Another randomized trial, the SWISS study[156] evaluated the impact of 140–160 million autologous BMCs injected at a median of 6 days or in a delayed fashion 24 days after acute MI. Cardiac MRI in these patients was performed at baseline prior to cell infusion and 4 months after the injection of BMCs into the infarct-related coronary artery. Magnetic resonance imaging results were compared with control patients treated with optimal medical care. At 4 months after intracoronary application, no significant changes in infarct size, left ventricular wall thickening, or increase in left ventricular function in patients treated early with BMC at 5–7 days or delayed 3–4 weeks after acute MI when compared with control patients, respectively. The reasons for the failure of these randomized, double–blind, and placebo-controlled clinical investigations[112,113,156] assessing the effect of intracoronary administration of BMCs on myocardial infarct size and left ventricular function in patients with acute MI remains uncertain but are thought to be related, at least in part, to small size of the infarction and extent of remodelling at baseline, concomitant effect of optimal conservative medical treatment and recovery of myocardial stunning,[157,158] heterogeneity and dose of BMC population, red blood cell contamination of BMC affecting the viability, migration ability, and efficacy of BMCs,[159] inhibiting effects of heparin on migration and homing of BMCs,[160,161] and substantial non-homing of BMCs in the myocardium.[162,163]

On the other hand, cardiac stem cells constitute specific undifferentiated progenitor cells commonly located in the right atrial appendage and the ventricular apices of the heart. Such cardiac stem cells have paracrine effects, while recruiting stem cells from the patient and potentially trans-differentiating into myocytes for cardiac repair. Cardiac stem cells are multipotent progenitor cells and add to the physiological turnover of myocytes and vascular endothelial cells in the heart. As there is one cardiac stem cell per 1000 cardiac myocytes,[164] endogenous cardiac stem cells are not capable to repair heart injury caused by MI. Two recent clinical trials have investigated the effects of major autologous cardiac stem cells for myocardial repair and regeneration in acute MI (*Table 3*).[114,115,165,166] The open-labelled Cardiac Stem Cell Infusion in Patients with Ischemic Cardiomyopathy (SCIPIO) trial assessed the effect of autologous C-kit-positive cardiac stem cells on left ventricular function and infarct size,[114,165] C-kit-positive stem cells were isolated during coronary artery bypass surgery from the right atrial appendages of ischaemic cardiomyopathy patients with an LVEF $<$ 40%. Following 4 months, a maximum of 1 million cardiac stem cells were injected into the saphenous vein grafts and coronary arteries supplying the infarcted region. After follow-up of 2 years, MRI-determined LVEF increased by 11.9% and scar tissue decreased by ~20.4 g in the stem cell treatment group of 12 individuals with ischaemic cardiomyopathy. It is thought that C-kit cardiac stem cells chemoattracted patient native stem cells to areas of myocardial injury and also to transdifferentiate to myocytes for cardiac regeneration. Another viable option is the use of cardiosphere-derived cells (CDCs).[167] The effects of autologous CDCs have been evaluated in the open-labelled Cardiosphere-derived Autologous Stem Cells to Reverse Ventricular Dysfunction (CADUCEUS) trial.[115,166] In 17 patients, after MI with LVEFs of 25–45% underwent endomyocardial biopsies of the right ventricular septum and CDCs were obtained from cultures of the endomyocardial biopsy and the cells were propagated. Subsequently, 12.5–25 million CDCs were injected into the infarct-related artery 1.5–3 months after their MI. After a 1 year follow-up, MRI-determined scar tissue decreased in the mean by 11.9 g in the CDC-treated patients but only by 1.7 g in the control patients. While the LVEF in the CDC-treated group did not increase significantly, regional wall function of the infarcted segments increased and correlated well with the decrease in size of MI.[115,166] Overall, the SCIPIO and CADUCEUS trials[114,115,165,166] outline that the intracoronary application of CDCs may indeed reduce the size of MI associated with a significant improvement of left ventricular function that, however, needs to be further clinically tested in large-scale and randomized trials. New development in stem cell treatment of MI is on the horizon such as intramyocardial transplantation of CD133+ BMCs, or autologous culture expanded mesenchymal stromal cells, and transplantation of embryogenic stem cells-derived cardiac progenitor cells within a tissue-engineered construct, that constitute a further enrichment of stem cell treatment of acute MI to stimulate further advancements in this critical research field and clinical applications (*Table 3*).[116,117,168]

Conclusion

Over the past decade, major advances in the early detection and reperfusion strategies of acute MI have led to a substantial reduction in morbidity and mortality. To further optimize the clinical outcome in these patients, many efforts have been geared towards cardioprotection against myocardial reperfusion injury with mechanical (ischaemic post-conditioning, remote ischaemic pre-conditioning, therapeutic hypothermia and hypoxemia) and pharmacologic interventions (atrial natriuretic peptide, cyclosporine A, and exenatide). Although mechanical and pharmacologic cardioprotection in acute MI in the animal models and initial observational trials hold promise, these concepts of cardioprotection need to be further firmly tested in randomized clinical trials. In addition, stem cell therapy with BMC in acute and chronic MI have yielded promising results but still needing confirmation in larger randomized trials. The SCIPIO trial with autologous C-kit-positive cardiac stem cells and the CADUCEUS trials with cardiosphere-derived autologous stem cells application in acute MI signify reduced infarct size and improved left ventricular function that may shift the pendulum in favour of stem cell trials to further improve outcome in these patients.

Authors' contributions

F.M., F.C., T.H.S.: handled funding and supervision; F.M., F.C., T.H.S.: acquired the data; F.M., F.C., T.H.S.: conceived and designed the

research; F.M., F.C., T.H.S.: drafted the manuscript; F.M., F.C., T.H.S.: made critical revision of the manuscript for key intellectual content.

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References

1. Myocardial infarction redefined – a consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. *Eur Heart J* 2000;**21**:1502–1513.
2. Haaf P, Reichlin T, Twerenbold R, Hoeller R, Rubini Gimenez M, Zellweger C, Moehring B, Fischer C, Meller B, Wildi K, Freese M, Stelzig C, Mosimann T, Reiter M, Mueller M, Hochgruber T, Sou SM, Murray K, Minners J, Freidank H, Osswald S, Mueller C. Risk stratification in patients with acute chest pain using three high-sensitivity cardiac troponin assays. *Eur Heart J* 2014;**35**:365–375.
3. Rubini Gimenez M, Twerenbold R, Reichlin T, Wildi K, Haaf P, Schaefer M, Zellweger C, Moehring B, Stallone F, Sou SM, Mueller M, Denhaerynck K, Mosimann T, Reiter M, Meller B, Freese M, Stelzig C, Klimmeck I, Voegele J, Hartmann B, Rentsch K, Osswald S, Mueller C. Direct comparison of high-sensitivity-cardiac troponin I vs. T for the early diagnosis of acute myocardial infarction. *Eur Heart J* 2014;**35**:2303–2311.
4. Task Force on the management of STseamiotESoC, Steg PG, James SK, Atar D, Badano LP, Blomstrom-Lundqvist C, Borger MA, Di Mario C, Dickstein K, Ducrocq G, Fernandez-Aviles F, Gershlick AH, Giannuzzi P, Halvorsen S, Huber K, Juni P, Kastrati A, Knuuti J, Lenzen MJ, Mahaffey KW, Valgimigli M, van 't Hof A, Widimsky P, Zahger D. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J* 2012;**33**:2569–2619.
5. Than M, Cullen L, Aldous S, Parsonage WA, Reid CM, Greenslade J, Flaws D, Hammett CJ, Beam DM, Ardagh MW, Troughton R, Brown AF, George P, Florkowski CM, Kline JA, Peacock WF, Maisel AS, Lim SH, Lamanna A, Richards AM. 2-Hour accelerated diagnostic protocol to assess patients with chest pain symptoms using contemporary troponins as the only biomarker: the ADAPT trial. *J Am Coll Cardiol* 2012;**59**:2091–2098.
6. Cullen L, Mueller C, Parsonage WA, Wildi K, Greenslade JH, Twerenbold R, Aldous S, Meller B, Tate JR, Reichlin T, Hammett CJ, Zellweger C, Ungerer JP, Rubini Gimenez M, Troughton R, Murray K, Brown AF, Mueller M, George P, Mosimann T, Flaws DF, Reiter M, Lamanna A, Haaf P, Pemberton CJ, Richards AM, Chu K, Reid CM, Peacock WF, Jaffe AS, Florkowski C, Deely JM, Than M. Validation of high-sensitivity troponin I in a 2-hour diagnostic strategy to assess 30-day outcomes in emergency department patients with possible acute coronary syndrome. *J Am Coll Cardiol* 2013;**62**:1242–1249.
7. Reichlin T, Schindler C, Drexler B, Twerenbold R, Reiter M, Zellweger C, Moehring B, Ziller R, Hoeller R, Rubini Gimenez M, Haaf P, Potocki M, Wildi K, Balmelli C, Freese M, Stelzig C, Freidank H, Osswald S, Mueller C. One-hour rule-out and rule-in of acute myocardial infarction using high-sensitivity cardiac troponin T. *Arch Intern Med* 2012;**172**:1211–1218.
8. Thygesen K, Alpert JS, White HD. Universal definition of myocardial infarction. *Eur Heart J* 2007;**28**:2525–2538.
9. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, Katus HA, Apple FS, Lindahl B, Morrow DA, Chaitman BA, Clemmensen PM, Johanson P, Hod H, Underwood R, Bax JJ, Bonow RO, Pinto F, Gibbons RJ, Fox KA, Atar D, Newby LK, Galvani M, Hamm CW, Uretsky BF, Steg PG, Wijns W, Bassand JP, Menasche P, Ravkilde J, Ohman EM, Antman EM, Wallentin LC, Armstrong PW, Januzzi JL, Nieminen MS, Gheorghiade M, Filippatos G, Luepker RV, Fortmann SP, Rosamond WD, Levy D, Wood D, Smith SC, Hu D, Lopez-Sendon JL, Robertson RM, Weaver D, Tendera M, Bove AA, Parkhomenko AN, Vasilieva EJ, Mendis S. Third universal definition of myocardial infarction. *Eur Heart J* 2012;**33**:2551–2567.
10. Townsend N, Nichols M, Scarborough P, Rayner M. Cardiovascular disease in Europe - epidemiological update 2015. *Eur Heart J* 2015. doi: 10.1093/eurheartj/ehv428.
11. Arbab-Zadeh A, Fuster V. The myth of the "vulnerable plaque": transitioning from a focus on individual lesions to atherosclerotic disease burden for coronary artery disease risk assessment. *J Am Coll Cardiol* 2015;**65**:846–855.
12. Stone GW, Maehara A, Lansky AJ, de Bruyne B, Cristea E, Mintz GS, Mehran R, McPherson J, Farhat N, Marso SP, Parise H, Templin B, White R, Zhang Z, Serruys PW. A prospective natural-history study of coronary atherosclerosis. *N Engl J Med* 2011;**364**:226–235.
13. Kubo T, Maehara A, Mintz GS, Doi H, Tsujita K, Choi SY, Katoh O, Nasu K, Koenig A, Pieper M, Rogers JH, Wijns W, Bose D, Margolis MP, Moses JW, Stone GW, Leon MB. The dynamic nature of coronary artery lesion morphology assessed by serial virtual histology intravascular ultrasound tissue characterization. *J Am Coll Cardiol* 2010;**55**:1590–1597.
14. Ahmadi A, Leipsic J, Blankstein R, Taylor C, Hecht H, Stone GW, Narula J. Do plaques rapidly progress prior to myocardial infarction? The interplay between plaque vulnerability and progression. *Circ Res* 2015;**117**:99–104.
15. Buffon A, Biasucci LM, Liuzzo G, D'Onofrio G, Crea F, Maseri A. Widespread coronary inflammation in unstable angina. *N Engl J Med* 2002;**347**:5–12.
16. Libby P, Tabas I, Fredman G, Fisher EA. Inflammation and its resolution as determinants of acute coronary syndromes. *Circ Res* 2014;**114**:1867–1879.
17. Carbone F, Nencioni A, Mach F, Vuilleumier N, Montecucco F. Evidence on the pathogenic role of auto-antibodies in acute cardiovascular diseases. *Thromb Haemost* 2013;**109**:854–868.
18. Montecucco F, Vuilleumier N, Pagano S, Lenglet S, Bertolotto M, Braunersreuther V, Pelli G, Kovari E, Pane B, Spinella G, Pende A, Palombo D, Dallegri F, Mach F, Roux-Lombard P. Anti-Apolipoprotein A-1 auto-antibodies are active mediators of atherosclerotic plaque vulnerability. *Eur Heart J* 2011;**32**:412–421.
19. Carbone F, Nencioni A, Mach F, Vuilleumier N, Montecucco F. Pathophysiological role of neutrophils in acute myocardial infarction. *Thromb Haemost* 2013;**110**:501–514.
20. Frangogiannis NG. Regulation of the inflammatory response in cardiac repair. *Circ Res* 2012;**110**:159–173.
21. Durante A, Camici PG. Novel insights into an "old" phenomenon: the no reflow. *Int J Cardiol* 2015;**187**:273–280.
22. Vilahur G, Badimon L. Ischemia/reperfusion activates myocardial innate immune response: the key role of the toll-like receptor. *Front Physiol* 2014;**5**:496.
23. Montecucco F, Braunersreuther V, Burger F, Lenglet S, Pelli G, Carbone F, Fraga-Silva R, Stergiopulos N, Monaco C, Mueller C, Pagano S, Dallegri F, Mach F, Vuilleumier N. Anti-apoA-1 auto-antibodies increase mouse atherosclerotic plaque vulnerability, myocardial necrosis and mortality triggering TLR2 and TLR4. *Thromb Haemost* 2015;**114**:410–422.
24. Takahashi M. NLRP3 inflammasome as a novel player in myocardial infarction. *Int Heart J* 2014;**55**:101–105.
25. de Lemos JA, Antman EM, Giugliano RP, McCabe CH, Murphy SA, Van de Werf F, Gibson CM, Braunwald E. ST-segment resolution and infarct-related artery patency and flow after thrombolytic therapy. Thrombolysis in Myocardial Infarction (TIMI) 14 investigators. *Am J Cardiol* 2000;**85**:299–304.
26. Nicolau JC, Maia LN, Vitola J, Vaz VD, Machado MN, Godoy MF, Giraldez RR, Ramires JA. ST-segment resolution and late (6-month) left ventricular remodeling after acute myocardial infarction. *Am J Cardiol* 2003;**91**:451–453.
27. Huber K, Gersh BJ, Goldstein P, Granger CB, Armstrong PW. The organization, function, and outcomes of ST-elevation myocardial infarction networks worldwide: current state, unmet needs and future directions. *Eur Heart J* 2014;**35**:1526–1532.
28. Mockel M, Searle J, Hamm C, Slagman A, Blankenberg S, Huber K, Katus H, Liebetrau C, Muller C, Muller R, Peitsmeyer P, von Recum J, Tajsic M, Vollert JO, Giannitsis E. Early discharge using single cardiac troponin and copeptin testing in patients with suspected acute coronary syndrome (ACS): a randomized, controlled clinical process study. *Eur Heart J* 2015;**36**:369–376.
29. Gorcsan J III, Sogaard P, Bax JJ, Singh JP, Abraham WT, Borer JS, Dickstein K, Gras D, Krum H, Brugada J, Robertson M, Ford I, Holzmeister J, Ruschitzka F. Association of persistent or worsened echocardiographic dyssynchrony with unfavourable clinical outcomes in heart failure patients with narrow QRS width: a subgroup analysis of the EchoCRT trial. *Eur Heart J* 2015. doi:10.1093/eurheartj/ehv418.
30. Roffi M, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F, Bax JJ, Borger MA, Brotons C, Chew DP, Gencer B, Hasenfuss G, Kjeldsen K, Lancellotti P, Landmesser U, Mehilli J, Mukherjee D, Storey RF, Windecker S. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2015. doi:10.1093/eurheartj/ehv320.
31. Plana JC, Mikati IA, Dokainish H, Lakkis N, Abukhalil J, Davis R, Hetzell BC, Zoghbi WA. A randomized cross-over study for evaluation of the effect of image optimization with contrast on the diagnostic accuracy of dobutamine echocardiography in coronary artery disease The OPTIMIZE Trial. *JACC Cardiovasc Imaging* 2008;**1**:145–152.
32. Lancellotti P, Price S, Edvardsen T, Cosyns B, Neskovic AN, Dulgheru R, Flachskampf FA, Hassager C, Pasquet A, Gargani L, Galderisi M, Cardim N, Haugaa KH, Ancion A, Zamorano JL, Donal E, Bueno H, Habib G. The use of echocardiography in acute cardiovascular care: recommendations of the

European Association of Cardiovascular Imaging and the Acute Cardiovascular Care Association. *Eur Heart J Cardiovasc Imaging* 2015;**16**:119–146.
33. Caldas MA, Tsutsui JM, Kowatsch I, Andrade JL, Nicolau JC, Ramires JF, Mathias W Jr. Value of myocardial contrast echocardiography for predicting left ventricular remodeling and segmental functional recovery after anterior wall acute myocardial infarction. *J Am Soc Echocardiogr* 2004;**17**:923–932.
34. Partington SL, Kwong RY, Dorbala S. Multimodality imaging in the assessment of myocardial viability. *Heart Fail Rev* 2011;**16**:381–395.
35. Lancellotti P, Price S, Edvardsen T, Cosyns B, Neskovic AN, Dulgheru R, Flachskampf FA, Hassager C, Pasquet A, Gargani L, Galderisi M, Cardim N, Haugaa KH, Ancion A, Zamorano JL, Donal E, Bueno H, Habib G. The use of echocardiography in acute cardiovascular care: recommendations of the European Association of Cardiovascular Imaging and the Acute Cardiovascular Care Association. *Eur Heart J Acute Cardiovasc Care* 2015;**4**:3–5.
36. Hachamovitch R, Rozanski A, Shaw LJ, Stone GW, Thomson LE, Friedman JD, Hayes SW, Cohen I, Germano G, Berman DS. Impact of ischaemia and scar on the therapeutic benefit derived from myocardial revascularization vs. medical therapy among patients undergoing stress-rest myocardial perfusion scintigraphy. *Eur Heart J* 2011;**32**:1012–1024.
37. Kim RJ, Wu E, Rafael A, Chen EL, Parker MA, Simonetti O, Klocke FJ, Bonow RO, Judd RM. The use of contrast-enhanced magnetic resonance imaging to identify reversible myocardial dysfunction. *N Engl J Med* 2000;**343**:1445–1453.
38. Wagner A, Mahrholdt H, Holly TA, Elliott MD, Regenfus M, Parker M, Klocke FJ, Bonow RO, Kim RJ, Judd RM. Contrast-enhanced MRI and routine single photon emission computed tomography (SPECT) perfusion imaging for detection of subendocardial myocardial infarcts: an imaging study. *Lancet* 2003;**361**:374–379.
39. Ibrahim T, Nekolla SG, Hornke M, Bulow HP, Dirschinger J, Schomig A, Schwaiger M. Quantitative measurement of infarct size by contrast-enhanced magnetic resonance imaging early after acute myocardial infarction: comparison with single-photon emission tomography using Tc99m-sestamibi. *J Am Coll Cardiol* 2005;**45**:544–552.
40. Klein C, Nekolla SG, Bengel FM, Momose M, Sammer A, Haas F, Schnackenburg B, Delius W, Mudra H, Wolfram D, Schwaiger M. Assessment of myocardial viability with contrast-enhanced magnetic resonance imaging: comparison with positron emission tomography. *Circulation* 2002;**105**:162–167.
41. Dall'Armellina E, Karia N, Lindsay AC, Karamitsos TD, Ferreira V, Robson MD, Kellman P, Francis JM, Forfar C, Prendergast BD, Banning AP, Channon KM, Kharbanda RK, Neubauer S, Choudhury RP. Dynamic changes of edema and late gadolinium enhancement after acute myocardial infarction and their relationship to functional recovery and salvage index. *Circ Cardiovasc Imaging* 2011;**4**:228–236.
42. Tilak GS, Hsu LY, Hoyt RF Jr, Arai AE, Aletras AH. In vivo T2-weighted magnetic resonance imaging can accurately determine the ischemic area at risk for 2-day-old nonreperfused myocardial infarction. *Invest Radiol* 2008;**43**:7–15.
43. Ugander M, Bagi PS, Oki AJ, Chen B, Hsu LY, Aletras AH, Shah S, Greiser A, Kellman P, Arai AE. Myocardial edema as detected by pre-contrast T1 and T2 CMR delineates area at risk associated with acute myocardial infarction. *JACC Cardiovasc Imaging* 2012;**5**:596–603.
44. Kim HW, Van Assche L, Jennings RB, Wince WB, Jensen CJ, Rehwald WG, Wendell DC, Bhatti L, Spatz DM, Parker MA, Jenista ER, Klem I, Crowley AL, Chen EL, Judd RM, Kim RJ. Relationship of T2-weighted MRI myocardial hyperintensity and the ischemic area-at-risk. *Circ Res* 2015;**117**:254–265.
45. Heusch P, Nensa F, Heusch G. Is MRI really the gold standard for the quantification of salvage from myocardial infarction? *Circ Res* 2015;**117**:222–224.
46. Heusch G, Botker HE, Przyklenk K, Redington A, Yellon D. Remote ischemic conditioning. *J Am Coll Cardiol* 2015;**65**:177–195.
47. 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.
48. Eitel I, Wohrle 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**:1447–1454.
49. Ghosh N, Rimoldi OE, Beanlands RS, Camici PG. Assessment of myocardial ischaemia and viability: role of positron emission tomography. *Eur Heart J* 2010;**31**:2984–2995.
50. Lautamaki R, Schuleri KH, Sasano T, Javadi MS, Youssef A, Merrill J, Nekolla SG, Abraham MR, Lardo AC, Bengel FM. Integration of infarct size, tissue perfusion, and metabolism by hybrid cardiac positron emission tomography/computed tomography: evaluation in a porcine model of myocardial infarction. *Circ Cardiovasc Imaging* 2009;**2**:299–305.
51. Nensa F, Poeppel T, Tezgah E, Heusch P, Nassenstein K, Mahabadi AA, Forsting M, Bockisch A, Erbel R, Heusch G, Schlosser T. Integrated FDG PET/MR imaging for the assessment of myocardial salvage in reperfused acute myocardial infarction. *Radiology* 2015;**276**:400–407.
52. Mahnken AH, Koos R, Katoh M, Wildberger JE, Spuentrup E, Buecker A, Gunther RW, Kuhl HP. Assessment of myocardial viability in reperfused acute myocardial infarction using 16-slice computed tomography in comparison to magnetic resonance imaging. *J Am Coll Cardiol* 2005;**45**:2042–2047.
53. Dwivedi G, Al-Shehri H, deKemp RA, Ali I, Alghamdi AA, Klein R, Scullion A, Ruddy TD, Beanlands RS, Chow BJ. Scar imaging using multislice computed tomography versus metabolic imaging by F-18 FDG positron emission tomography: a pilot study. *Int J Cardiol* 2013;**168**:739–745.
54. Montecucco F, Lenglet S, Braunersreuther V, Burger F, Pelli G, Bertolotto M, Mach F, Steffens S. CB(2) cannabinoid receptor activation is cardioprotective in a mouse model of ischemia/reperfusion. *J Mol Cell Cardiol* 2009;**46**:612–620.
55. Defer N, Wan J, Souktani R, Escoubet B, Perier M, Caramelle P, Manin S, Deveaux V, Bourin MC, Zimmer A, Lotersztajn S, Pecker F, Pavoine C. The cannabinoid receptor type 2 promotes cardiac myocyte and fibroblast survival and protects against ischemia/reperfusion-induced cardiomyopathy. *FASEB J* 2009;**23**:2120–2130.
56. Wang PF, Jiang LS, Bu J, Huang XJ, Song W, Du YP, He B. Cannabinoid-2 receptor activation protects against infarct and ischemia-reperfusion heart injury. *J Cardiovasc Pharmacol* 2012;**59**:301–307.
57. Li Q, Guo HC, Maslov LN, Qiao XW, Zhou JJ, Zhang Y. Mitochondrial permeability transition pore plays a role in the cardioprotection of CB2 receptor against ischemia-reperfusion injury. *Can J Physiol Pharmacol* 2014;**92**:205–214.
58. Wang Y, Ma S, Wang Q, Hu W, Wang D, Li X, Su T, Qin X, Zhang X, Ma K, Chen J, Xiong L, Cao F. Effects of cannabinoid receptor type 2 on endogenous myocardial regeneration by activating cardiac progenitor cells in mouse infarcted heart. *Sci China Life Sci* 2014;**57**:201–208.
59. Feng Y, Chen F, Ting Y, Xia Q, Liu Y, Huang G, Zhang J, Oyen R, Ni Y. Pharmacologic effects of cannabidiol on acute reperfused myocardial infarction in rabbits: evaluated with 3.0 T cardiac magnetic resonance imaging and histopathology. *J Cardiovasc Pharmacol* 2015. doi:10.1097/FJC.0000000000000287.
60. Hocher B, Sharkovska Y, Mark M, Klein T, Pfab T. The novel DPP-4 inhibitors linagliptin and BI 14361 reduce infarct size after myocardial ischemia/reperfusion in rats. *Int J Cardiol* 2013;**167**:87–93.
61. Hausenloy DJ, Whittington HJ, Wynne AM, Begum SS, Theodorou L, Riksen N, Mocanu MM, Yellon DM. Dipeptidyl peptidase-4 inhibitors and GLP-1 reduce myocardial infarct size in a glucose-dependent manner. *Cardiovasc Diabetol* 2013;**12**:154.
62. Chinda K, Sanit J, Chattipakorn S, Chattipakorn N. Dipeptidyl peptidase-4 inhibitor reduces infarct size and preserves cardiac function via mitochondrial protection in ischaemia-reperfusion rat heart. *Diab Vasc Dis Res* 2014;**11**:75–83.
63. Inthachai T, Lekawanvijit S, Kumfu S, Apaijai N, Pongkan W, Chattipakorn SC, Chattipakorn N. Dipeptidyl peptidase-4 inhibitor improves cardiac function by attenuating adverse cardiac remodelling in rats with chronic myocardial infarction. *Exp Physiol* 2015;**100**:667–679.
64. Connelly KA, Advani A, Zhang Y, Advani SL, Kabir G, Abadeh A, Desjardins JF, Mitchell M, Thai K, Gilbert RE. Dipeptidyl peptidase-4 inhibition improves cardiac function in experimental myocardial infarction: Role of stromal cell-derived factor-1alpha. *J Diabetes* 2015. doi:10.1111/1753-0407.12258.
65. Montecucco F, Bauer I, Braunersreuther V, Bruzzone S, Akhmedov A, Luscher TF, Speer T, Poggi A, Mannino E, Pelli G, Galan K, Bertolotto M, Lenglet S, Garuti A, Montessuit C, Lerch R, Pellieux C, Vuilleumier N, Dallegri F, Mage J, Sebastian C, Mostoslavsky R, Gayet-Ageron A, Patrone F, Mach F, Nencioni A. Inhibition of nicotinamide phosphoribosyltransferase reduces neutrophil-mediated injury in myocardial infarction. *Antioxid Redox Signal* 2013;**18**:630–641.
66. Chang C, Ji Q, Wu B, Yu K, Zeng Q, Xin S, Liu J, Zhou Y. Chemerin15-ameliorated cardiac ischemia-reperfusion injury is associated with the induction of alternatively activated macrophages. *Mediators Inflamm* 2015;**2015**:563951.
67. Kataoka Y, Shibata R, Ohashi K, Kambara T, Enomoto T, Uemura Y, Ogura Y, Yuasa D, Matsuo K, Nagata T, Oba T, Yasukawa H, Numaguchi Y, Sone T, Murohara T, Ouchi N. Omentin prevents myocardial ischemic injury through AMP-activated protein kinase- and Akt-dependent mechanisms. *J Am Coll Cardiol* 2014;**63**:2722–2733.
68. Baljinnyam E, Hasebe N, Morihira M, Sumitomo K, Matsusaka T, Fujino T, Fukuzawa J, Ushikubi F, Kikuchi K. Oral pretreatment with ebselen enhances heat shock protein 72 expression and reduces myocardial infarct size. *Hyperten Res* 2006;**29**:905–913.
69. Jiang ZH, Zhang TT, Zhang JF. Protective effects of fasudil hydrochloride postconditioning on acute myocardial ischemia/reperfusion injury in rats. *Cardiol J* 2013;**20**:197–202.

70. Zhang G, Sun Y, Wang Y, Li X, Li T, Su S, Xu L, Shen H. Local administration of lactic acid and a low dose of the free radical scavenger, edaravone, alleviates myocardial reperfusion injury in rats. *J Cardiovasc Pharmacol* 2013;**62**:369–378.
71. Fu JH, Zheng YQ, Li P, Li XZ, Shang XH, Liu JX. Hawthorn leaves flavonoids decreases inflammation related to acute myocardial ischemia/reperfusion in anesthetized dogs. *Chin J Integr Med* 2013;**19**:582–588.
72. Asanuma H, Sanada S, Asakura M, Asano Y, Kim J, Shinozaki Y, Mori H, Minamino T, Takashima S, Kitakaze M. Carperitide induces coronary vasodilation and limits infarct size in canine ischemic hearts: role of NO. *Hypertens Res* 2014; **37**:716–723.
73. Shinlapawittayatorn K, Chinda K, Palee S, Surinkaew S, Kumfu S, Kumphune S, Chattipakorn S, KenKnight BH, Chattipakorn N. Vagus nerve stimulation initiated late during ischemia, but not reperfusion, exerts cardioprotection via amelioration of cardiac mitochondrial dysfunction. *Heart Rhythm* 2014;**11**:2278–2287.
74. Uitterdijk A, Yetgin T, te Lintel Hekkert M, Sneep S, Krabbendam-Peters I, van Beusekom HM, Fischer TM, Cornelussen RN, Manintveld OC, Merkus D, Duncker DJ. Vagal nerve stimulation started just prior to reperfusion limits infarct size and no-reflow. *Basic Res Cardiol* 2015;**110**:508.
75. Koudstaal S, Oerlemans MI, Van der Spoel TI, Janssen AW, Hoefer IE, Doevendans PA, Sluijter JP, Chamuleau SA. Necrostatin-1 alleviates reperfusion injury following acute myocardial infarction in pigs. *Eur J Clin Invest* 2015;**45**: 150–159.
76. Montecucco F, Lenglet S, Braunersreuther V, Pelli G, Pellieux C, Montessuit C, Lerch R, Deruaz M, Proudfoot AE, Mach F. Single administration of the CXC chemokine-binding protein Evasin-3 during ischemia prevents myocardial reperfusion injury in mice. *Arterioscler Thromb Vasc Biol* 2010;**30**:1371–1377.
77. Montecucco F, Braunersreuther V, Lenglet S, Delattre BM, Pelli G, Buatois V, Guilhot F, Galan K, Vuilleumier N, Ferlin W, Fischer N, Vallee JP, Kosco-Vilbois M, Mach F. CC chemokine CCL5 plays a central role impacting infarct size and post-infarction heart failure in mice. *Eur Heart J* 2012;**33**:1964–1974.
78. Carbone F, Mach F, Vuilleumier N, Montecucco F. Cannabinoid receptor type 2 activation in atherosclerosis and acute cardiovascular diseases. *Curr Med Chem* 2014;**21**:4046–4058.
79. Molica F, Matter CM, Burger F, Pelli G, Lenglet S, Zimmer A, Pacher P, Steffens S. Cannabinoid receptor CB2 protects against balloon-induced neointima formation. *Am J Physiol Heart Circ Physiol* 2012;**302**:H1064–H1074.
80. Bonnefoy E, Lapostolle F, Leizorovicz A, Steg G, McFadden EP, Dubien PY, Cattan S, Boullenger E, Machecourt J, Lacroute JM, Cassagnes J, Dissait F, Touboul P, Comparison of A, Prehospital Thromboysis in Acute Myocardial Infarction study g. Primary angioplasty versus prehospital fibrinolysis in acute myocardial infarction: a randomised study. *Lancet* 2002;**360**:825–829.
81. Morrow DA, Antman EM, Sayah A, Schuhwerk KC, Giugliano RP, deLemos JA, Waller M, Cohen SA, Rosenberg DG, Cutler SS, McCabe CH, Walls RM, Braunwald E. Evaluation of the time saved by prehospital initiation of reteplase for ST-elevation myocardial infarction: results of The Early Retavase-Thrombolysis in Myocardial Infarction (ER-TIMI) 19 trial. *J Am Coll Cardiol* 2002; **40**:71–77.
82. Bjorklund E, Stenestrand U, Lindback J, Svensson L, Wallentin L, Lindahl B. Prehospital thrombolysis delivered by paramedics is associated with reduced time delay and mortality in ambulance-transported real-life patients with ST-elevation myocardial infarction. *Eur Heart J* 2006;**27**:1146–1152.
83. Westerhout CM, Bonnefoy E, Welsh RC, Steg PG, Boutitie F, Armstrong PW. The influence of time from symptom onset and reperfusion strategy on 1-year survival in ST-elevation myocardial infarction: a pooled analysis of an early fibrinolytic strategy versus primary percutaneous coronary intervention from CAPTIM and WEST. *Am Heart J* 2011;**161**:283–290.
84. Armstrong PW, Gershlick AH, Goldstein P, Wilcox R, Danays T, Lambert Y, Sulimov V, Rosell Ortiz F, Ostojic M, Welsh RC, Carvalho AC, Nanas J, Arntz HR, Halvorsen S, Huber K, Grajek S, Fresco C, Bluhmki E, Regelin A, Vandenberghe K, Bogaerts K, Van de Werf F, STREAM Investigative Team. Fibrinolysis or primary PCI in ST-segment elevation myocardial infarction. *N Engl J Med* 2013;**368**:1379–1387.
85. O'Gara PT, Kushner FG, Ascheim DD, Casey DE Jr, Chung MK, de Lemos JA, Ettinger SM, Fang JC, Fesmire FM, Franklin BA, Granger CB, Krumholz HM, Linderbaum JA, Morrow DA, Newby LK, Ornato JP, Ou N, Radford MJ, Tamis-Holland JE, Tommaso CL, Tracy CM, Woo YJ, Zhao DX, Anderson JL, Jacobs AK, Halperin JL, Albert NM, Brindis RG, Creager MA, DeMets D, Guyton RA, Hochman JS, Kovacs RJ, Kushner FG, Ohman EM, Stevenson WG, Yancy CW, American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2013;**61**:e78–e140.
86. Kristensen SD, Laut KG, Fajadet J, Kaifoszova Z, Kala P, Di Mario C, Wijns W, Clemmensen P, Agladze V, Antoniades L, Alhabib KF, De Boer MJ, Claeys MJ, Deleanu D, Dudek D, Erglis A, Gilard M, Goktekin O, Guagliumi G, Gudnason T, Hansen KW, Huber K, James S, Janota T, Jennings S, Kajander O, Kanakakis J, Karamfiloff KK, Kedev S, Kornowski R, Ludman PF, Merkely B, Milicic D, Najafov R, Nicolini FA, Noc M, Ostojic M, Pereira H, Radovanovic D, Sabate M, Sobhy M, Sokolov M, Studencan M, Terzic I, Wahler S, Widimsky P, on behalf of the European Association for Percutaneous Cardiovascular Interventions. Reperfusion therapy for ST elevation acute myocardial infarction 2010/2011: current status in 37 ESC countries. *Eur Heart J* 2014;**35**:1957–1970.
87. Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomised trials of more than 1000 patients. Fibrinolytic Therapy Trialists' (FTT) Collaborative Group. *Lancet* 1994;**343**:311–322.
88. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 2002;**324**:71–86.
89. A clinical trial comparing primary coronary angioplasty with tissue plasminogen activator for acute myocardial infarction. The Global Use of Strategies to Open Occluded Coronary Arteries in Acute Coronary Syndromes (GUSTO IIb) Angioplasty Substudy Investigators. *N Engl J Med* 1997;**336**:1621–1628.
90. Lundergan CF, Reiner JS, McCarthy WF, Coyne KS, Califf RM, Ross AM. Clinical predictors of early infarct-related artery patency following thrombolytic therapy: importance of body weight, smoking history, infarct-related artery and choice of thrombolytic regimen: the GUSTO-I experience. Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries. *J Am Coll Cardiol* 1998;**32**:641–647.
91. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. *Lancet* 1988; **2**:349–360.
92. Sabatine MS, Cannon CP, Gibson CM, Lopez-Sendon JL, Montalescot G, Theroux P, Claeys MJ, Cools F, Hill KA, Skene AM, McCabe CH, Braunwald E. Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation. *N Engl J Med* 2005;**352**:1179–1189.
93. Pfisterer M, Brunner-La Rocca HP, Buser PT, Rickenbacher P, Hunziker P, Mueller C, Jeger R, Bader F, Osswald S, Kaiser C, BASKET-LATE Investigators. Late clinical events after clopidogrel discontinuation may limit the benefit of drug-eluting stents: an observational study of drug-eluting versus bare-metal stents. *J Am Coll Cardiol* 2006;**48**:2584–2591.
94. Pfisterer ME. Late stent thrombosis after drug-eluting stent implantation for acute myocardial infarction: a new red flag is raised. *Circulation* 2008;**118**:1117–1119.
95. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, Horrow J, Husted S, James S, Katus H, Mahaffey KW, Scirica BM, Skene A, Steg PG, Storey RF, Harrington RA, Investigators P, Freij A, Thorsen M. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2009;**361**:1045–1057.
96. Montalescot G, Wiviott SD, Braunwald E, Murphy SA, Gibson CM, McCabe CH, Antman EM. Prasugrel compared with clopidogrel in patients undergoing percutaneous coronary intervention for ST-elevation myocardial infarction (TRITON-TIMI 38): double-blind, randomised controlled trial. *Lancet* 2009;**373**:723–731.
97. Morrow DA, Wiviott SD, White HD, Nicolau JC, Bramucci E, Murphy SA, Bonaca MP, Ruff CT, Scirica BM, McCabe CH, Antman EM, Braunwald E. Effect of the novel thienopyridine prasugrel compared with clopidogrel on spontaneous and procedural myocardial infarction in the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction 38: an application of the classification system from the universal definition of myocardial infarction. *Circulation* 2009;**119**: 2758–2764.
98. Steg PG, James S, Harrington RA, Ardissino D, Becker RC, Cannon CP, Emanuelsson H, Finkelstein A, Husted S, Katus H, Kilhamn J, Olofsson S, Storey RF, Weaver WD, Wallentin L. Ticagrelor versus clopidogrel in patients with ST-elevation acute coronary syndromes intended for reperfusion with primary percutaneous coronary intervention: A Platelet Inhibition and Patient Outcomes (PLATO) trial subgroup analysis. *Circulation* 2010;**122**:2131–2141.
99. Bohmer E, Hoffmann P, Abdelnoor M, Arnesen H, Halvorsen S. Efficacy and safety of immediate angioplasty versus ischemia-guided management after thrombolysis in acute myocardial infarction in areas with very long transfer distances results of the NORDISTEMI (NORwegian study on DIstrict treatment of ST-elevation myocardial infarction). *J Am Coll Cardiol* 2010;**55**:102–110.
100. Stone GW, Mehran R, Goldstein P, Witzenbichler B, Van't Hof A, Guagliumi G, Hamm CW, Genereux P, Clemmensen P, Pocock SJ, Gersh BJ, Bernstein D, Deliargyris EN, Steg PG. Bivalirudin versus heparin with or without glycoprotein IIb/IIIa inhibitors in patients with STEMI undergoing primary percutaneous coronary intervention: pooled patient-level analysis from the HORIZONS-AMI and EUROMAX trials. *J Am Coll Cardiol* 2015;**65**:27–38.
101. Sabate M, Cequier A, Iniguez A, Serra A, Hernandez-Antolin R, Mainar V, Valgimigli M, Tespili M, den Heijer P, Bethencourt A, Vazquez N, Gomez-Hospital JA, Baz JA, Martin-Yuste V, van Geuns RJ, Alfonso F, Bordes P,

Tebaldi M, Masotti M, Silvestro A, Backx B, Brugaletta S, van Es GA, Serruys PW. Everolimus-eluting stent versus bare-metal stent in ST-segment elevation myocardial infarction (EXAMINATION): 1 year results of a randomised controlled trial. *Lancet* 2012;**380**:1482–1490.

102. Dewilde WJ, Oirbans T, Verheugt FW, Kelder JC, De Smet BJ, Herrman JP, Adriaenssens T, Vrolix M, Heestermans AA, Vis MM, Tijsen JG, van 't Hof AW, ten Berg JM, WOEST Study Investigators. Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: an open-label, randomised, controlled trial. *Lancet* 2013; **381**:1107–1115.
103. de Belder A, de la Torre Hernandez JM, Lopez-Palop R, O'Kane P, Hernandez Hernandez F, Strange J, Gimeno F, Cotton J, Diaz Fernandez JF, Carrillo Saez P, Thomas M, Pinar E, Curzen N, Baz JA, Cooter N, Lozano I, Skipper N, Robinson D, Hildick-Smith D, XIMA Investigators. A prospective randomized trial of everolimus-eluting stents versus bare-metal stents in octogenarians: the XIMA Trial (Xience or Vision Stents for the Management of Angina in the Elderly). *J Am Coll Cardiol* 2014;**63**:1371–1375.
104. Kocka V, Maly M, Tousek P, Budesinsky T, Lisa L, Prodanov P, Jarkovsky J, Widimsky P. Bioresorbable vascular scaffolds in acute ST-segment elevation myocardial infarction: a prospective multicentre study 'Prague 19'. *Eur Heart J* 2014;**35**: 787–794.
105. Atar D, Petzelbauer P, Schwitter J, Huber K, Rensing B, Kasprzak JD, Butter C, Grip L, Hansen PR, Suselbeck T, Clemmensen PM, Marin-Galiano M, Geudelin B, Buser PT. Effect of intravenous FX06 as an adjunct to primary percutaneous coronary intervention for acute ST-segment elevation myocardial infarction results of the F.I.R.E. (Efficacy of FX06 in the Prevention of Myocardial Reperfusion Injury) trial. *J Am Coll Cardiol* 2009;**53**:720–729.
106. 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.
107. 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.
108. Lincoff AM, Roe M, Aylward P, Galla J, Rynkiewicz A, Guetta V, Zelizko M, Kleiman N, White H, McErlean E, Erlinge D, Laine M, Dos Santos Ferreira JM, Goodman S, Mehta S, Atar D, Suryapranata H, Jensen SE, Forster T, Fernandez-Ortiz A, Schoors D, Radke P, Belli G, Brennan D, Bell G, Krucoff M, Investigators PA. Inhibition of delta-protein kinase C by delcasertib as an adjunct to primary percutaneous coronary intervention for acute anterior ST-segment elevation myocardial infarction: results of the PROTECTION AMI Randomized Controlled Trial. *Eur Heart J* 2014;**35**:2516–2523.
109. Sloth AD, Schmidt MR, Munk K, Kharbanda RK, Redington AN, Schmidt M, Pedersen L, Sorensen HT, Botker HE, Investigators C. 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.
110. Atar D, Arheden H, Berdeaux A, Bonnet JL, Carlsson M, Clemmensen P, Cuvier V, Danchin N, Dubois-Rande JL, Engblom H, Erlinge D, Firat H, Halvorsen S, Hansen HS, Hauke W, Heiberg E, Koul S, Larsen AI, Le Corvoisier P, Nordrehaug JE, Paganelli F, Pruss RM, Rousseau H, Schaller S, Sonou G, Tuseth V, Veys J, Vicaut E, Jensen SE. Effect of intravenous TRO40303 as an adjunct to primary percutaneous coronary intervention for acute ST-elevation myocardial infarction: MITOCARE study results. *Eur Heart J* 2015;**36**:112–119.
111. 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 Poli F, Morice MC, Ider O, Dubois-Rande JL, Unterseeh T, Le Breton H, 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.
112. Traverse JH, Henry TD, Ellis SG, Pepine CJ, Willerson JT, Zhao DX, Forder JR, Byrne BJ, Hatzopoulos AK, Penn MS, Perin EC, Baran KW, Chambers J, Lambert C, Raveendran G, Simon DI, Vaughan DE, Simpson LM, Gee AP, Taylor DA, Cogle CR, Thomas JD, Silva GV, Jorgenson BC, Olson RE, Bowman S, Francescon J, Geither C, Handberg E, Smith DX, Baraniuk S, Piller LB, Loghin C, Aguilar D, Richman S, Zierold C, Bettencourt J, Sayre SL, Vojvodic RW, Skarlatos SI, Gordon DJ, Ebert RF, Kwak M, Moye LA, Simari RD, Cardiovascular Cell Therapy R. Effect of intracoronary delivery of autologous bone marrow mononuclear cells 2 to 3 weeks following acute myocardial infarction on left ventricular function: the LateTIME randomized trial. *JAMA* 2011;**306**: 2110–2119.
113. Traverse JH, Henry TD, Pepine CJ, Willerson JT, Zhao DX, Ellis SG, Forder JR, Anderson RD, Hatzopoulos AK, Penn MS, Perin EC, Chambers J, Baran KW, Raveendran G, Lambert C, Lerman A, Simon DI, Vaughan DE, Lai D, Gee AP, Taylor DA, Cogle CR, Thomas JD, Olson RE, Bowman S, Francescon J, Geither C, Handberg E, Kappenman C, Westbrook L, Piller LB, Simpson LM, Baraniuk S, Loghin C, Aguilar D, Richman S, Zierold C, Spoon DB, Bettencourt J, Sayre SL, Vojvodic RW, Skarlatos SI, Gordon DJ, Ebert RF, Kwak M, Moye LA, Simari RD, Cardiovascular Cell Therapy Research N. Effect of the use and timing of bone marrow mononuclear cell delivery on left ventricular function after acute myocardial infarction: the TIME randomized trial. *JAMA* 2012;**308**:2380–2389.
114. Chugh AR, Beache GM, Loughran JH, Mewton N, Elmore JB, Kajstura J, Pappas P, Tatooles A, Stoddard MF, Lima JA, Slaughter MS, Anversa P, Bolli R. Administration of cardiac stem cells in patients with ischemic cardiomyopathy: the SCIPIO trial: surgical aspects and interim analysis of myocardial function and viability by magnetic resonance. *Circulation* 2012;**126**(11 Suppl. 1):S54–S64.
115. Makkar RR, Smith RR, Cheng K, Malliaras K, Thomson LE, Berman D, Czer LS, Marban L, Mendizabal A, Johnston PV, Russell SD, Schuleri KH, Lardo AC, Gerstenblith G, Marban E. Intracoronary cardiosphere-derived cells for heart regeneration after myocardial infarction (CADUCEUS): a prospective, randomised phase 1 trial. *Lancet* 2012;**379**:895–904.
116. Nasseri BA, Ebell W, Dandel M, Kukucka M, Gebker R, Doltra A, Knosalla C, Choi YH, Hetzer R, Stamm C. Autologous CD133+ bone marrow cells and bypass grafting for regeneration of ischaemic myocardium: the Cardio133 trial. *Eur Heart J* 2014;**35**:1263–1274.
117. Mathiasen AB, Qayyum AA, Jorgensen E, Helqvist S, Fischer-Nielsen A, Kofoed KF, Haack-Sorensen M, Ekblond A, Kastrup J. Bone marrow-derived mesenchymal stromal cell treatment in patients with severe ischaemic heart failure: a randomized placebo-controlled trial (MSC-HF trial). *Eur Heart J* 2015;**36**: 1744–1753.
118. Yusuf S, Mehta SR, Chrolavicius S, Afzal R, Pogue J, Granger CB, Budaj A, Peters RJ, Bassand JP, Wallentin L, Joyner C, Fox KA, Group O-T. Effects of fondaparinux on mortality and reinfarction in patients with acute ST-segment elevation myocardial infarction: the OASIS-6 randomized trial. *JAMA* 2006;**295**:1519–1530.
119. Gershlick AH, Stephens-Lloyd A, Hughes S, Abrams KR, Stevens SE, Uren NG, de Belder A, Davis J, Pitt M, Banning A, Baumbach A, Shiu MF, Schofield P, Dawkins KD, Henderson RA, Oldroyd KG, Wilcox R, Investigators RT. Rescue angioplasty after failed thrombolytic therapy for acute myocardial infarction. *N Engl J Med* 2005;**353**:2758–2768.
120. Wijeysundera HC, Vijayaraghavan R, Nallamothu BK, Foody JM, Krumholz HM, Phillips CO, Kashani A, You JJ, Tu JV, Ko DT. Rescue angioplasty or repeat fibrinolysis after failed fibrinolytic therapy for ST-segment myocardial infarction: a meta-analysis of randomized trials. *J Am Coll Cardiol* 2007;**49**:422–430.
121. Borgia F, Goodman SG, Halvorsen S, Cantor WJ, Piscione F, Le May MR, Fernandez-Aviles F, Sanchez PL, Dimopoulos K, Scheller B, Armstrong PW, Di Mario C. Early routine percutaneous coronary intervention after fibrinolysis vs. standard therapy in ST-segment elevation myocardial infarction: a meta-analysis. *Eur Heart J* 2010;**31**:2156–2169.
122. Assessment of the Safety and Efficacy of a New Treatment Strategy with Percutaneous Coronary Intervention (ASSENT-4 PCI) investigators. Primary versus tenecteplase-facilitated percutaneous coronary intervention in patients with ST-segment elevation acute myocardial infarction (ASSENT-4 PCI): randomised trial. *Lancet* 2006;**367**:569–578.
123. Ellis SG, Tendera M, de Belder MA, van Boven AJ, Widimsky P, Janssens L, Andersen HR, Betriu A, Savonitto S, Adamus J, Peruga JZ, Kosmider M, Katz O, Neunteufl T, Jorgova J, Dorobantu M, Grinfeld L, Armstrong P, Brodie BR, Herrmann HC, Montalescot G, Neumann FJ, Effron MB, Barnathan ES, Topol EJ, Investigators F. Facilitated PCI in patients with ST-elevation myocardial infarction. *N Engl J Med* 2008;**358**:2205–2217.
124. Vlaar PJ, Svilaas T, van der Horst IC, Diercks GF, Fokkema ML, de Smet BJ, van den Heuvel AF, Anthonio RL, Jessurun GA, Tan ES, Suurmeijer AJ, Zijlstra F. Cardiac death and reinfarction after 1 year in the Thrombus Aspiration during Percutaneous coronary intervention in Acute myocardial infarction Study (TAPAS): a 1-year follow-up study. *Lancet* 2008;**371**:1915–1920.
125. Kumbhani DJ, Bavry AA, Desai MY, Bangalore S, Bhatt DL. Role of aspiration and mechanical thrombectomy in patients with acute myocardial infarction undergoing primary angioplasty: an updated meta-analysis of randomized trials. *J Am Coll Cardiol* 2013;**62**:1409–1418.
126. Windecker S, Kolh P, Alfonso F, Collet JP, Cremer J, Falk V, Filippatos G, Hamm C, Head SJ, Juni P, Kappetein AP, Kastrati A, Knuuti J, Landmesser U, Laufer G,

Neumann FJ, Richter DJ, Schauerte P, Sousa Uva M, Stefanini GG, Taggart DP, Torracca L, Valgimigli M, Wijns W, Witkowski A. 2014 ESC/EACTS guidelines on myocardial revascularization. *EuroIntervention* 2015;**10**:1024–1094.
127. Nordmann AJ, Hengstler P, Harr T, Young J, Bucher HC. Clinical outcomes of primary stenting versus balloon angioplasty in patients with myocardial infarction: a meta-analysis of randomized controlled trials. *Am J Med* 2004;**116**:253–262.
128. Kastrati A, Dibra A, Spaulding C, Laarman GJ, Menichelli M, Valgimigli M, Di Lorenzo E, Kaiser C, Tierala I, Mehilli J, Seyfarth M, Varenne O, Dirksen MT, Percoco G, Varricchio A, Pittl U, Syvanne M, Suttorp MJ, Violini R, Schomig A. Meta-analysis of randomized trials on drug-eluting stents vs. bare-metal stents in patients with acute myocardial infarction. *Eur Heart J* 2007;**28**:2706–2713.
129. Pfisterer M, Brunner-La Rocca HP, Rickenbacher P, Hunziker P, Mueller C, Nietlispach F, Leibundgut G, Bader F, Kaiser C, Basket. Long-term benefit-risk balance of drug-eluting vs. bare-metal stents in daily practice: does stent diameter matter? Three-year follow-up of BASKET. *Eur Heart J* 2009;**30**:16–24.
130. Raber L, Wohlwend L, Wigger M, Togni M, Wandel S, Wenaweser P, Cook S, Moschovitis A, Vogel R, Kalesan B, Seiler C, Eberli F, Luscher TF, Meier B, Juni P, Windecker S. Five-year clinical and angiographic outcomes of a randomized comparison of sirolimus-eluting and paclitaxel-eluting stents: results of the Sirolimus-Eluting Versus Paclitaxel-Eluting Stents for Coronary Revascularization LATE trial. *Circulation* 2011;**123**:2819–2828, 6 p following 2828.
131. Byrne RA, Serruys PW, Baumbach A, Escaned J, Fajadet J, James S, Joner M, Oktay S, Juni P, Kastrati A, Sianos G, Stefanini GG, Wijns W, Windecker S. Report of a European Society of Cardiology-European Association of Percutaneous Cardiovascular Interventions task force on the evaluation of coronary stents in Europe: executive summary. *Eur Heart J* 2015. doi:10.1093/eurheartj/ehv203.
132. Ormiston JA, Serruys PW, Regar E, Dudek D, Thuesen L, Webster MW, Onuma Y, Garcia-Garcia HM, McGreevy R, Veldhof S. A bioabsorbable everolimus-eluting coronary stent system for patients with single de-novo coronary artery lesions (ABSORB): a prospective open-label trial. *Lancet* 2008;**371**:899–907.
133. Serruys PW, Ormiston JA, Onuma Y, Regar E, Gonzalo N, Garcia-Garcia HM, Nieman K, Bruining N, Dorange C, Miquel-Hebert K, Veldhof S, Webster M, Thuesen L, Dudek D. A bioabsorbable everolimus-eluting coronary stent system (ABSORB): 2-year outcomes and results from multiple imaging methods. *Lancet* 2009;**373**:897–910.
134. Onuma Y, Serruys PW, Perkins LE, Okamura T, Gonzalo N, Garcia-Garcia HM, Regar E, Kamberi M, Powers JC, Rapoza R, van Beusekom H, van der Giessen W, Virmani R. Intracoronary optical coherence tomography and histology at 1 month and 2, 3, and 4 years after implantation of everolimus-eluting bioresorbable vascular scaffolds in a porcine coronary artery model: an attempt to decipher the human optical coherence tomography images in the ABSORB trial. *Circulation* 2010;**122**:2288–2300.
135. Babu GG, Walker JM, Yellon DM, Hausenloy DJ. Peri-procedural myocardial injury during percutaneous coronary intervention: an important target for cardioprotection. *Eur Heart J* 2011;**32**:23–31.
136. Frohlich GM, Meier P, White SK, Yellon DM, Hausenloy DJ. Myocardial reperfusion injury: looking beyond primary PCI. *Eur Heart J* 2013;**34**:1714–1722.
137. Heusch G. Cardioprotection: chances and challenges of its translation to the clinic. *Lancet* 2013;**381**:166–175.
138. Bainey KR, Armstrong PW. Clinical perspectives on reperfusion injury in acute myocardial infarction. *Am Heart J* 2014;**167**:637–645.
139. Schindler TH, Bax JJ. Assessment of coronary artery plaque with non-contrast and T1-weighted magnetic resonance: promise for clinical use? *Eur Heart J* 2015. doi:10.1093/eurheartj/ehv246.
140. Chen L, Hahn H, Wu G, Chen CH, Liron T, Schechtman D, Cavallaro G, Banci L, Guo Y, Bolli R, Dorn GW II, Mochly-Rosen D. Opposing cardioprotective actions and parallel hypertrophic effects of delta PKC and epsilon PKC. *Proc Natl Acad Sci USA* 2001;**98**:11114–11119.
141. Inagaki K, Chen L, Ikeno F, Lee FH, Imahashi K, Bouley DM, Rezaee M, Yock PG, Murphy E, Mochly-Rosen D. Inhibition of delta-protein kinase C protects against reperfusion injury of the ischemic heart in vivo. *Circulation* 2003;**108**:2304–2307.
142. Chakrabarti AK, Feeney K, Abueg C, Brown DA, Czyz E, Tendera M, Janosi A, Giugliano RP, Kloner RA, Weaver WD, Bode C, Godlewski J, Merkely B, Gibson CM. Rationale and design of the EMBRACE STEMI study: a phase 2a, randomized, double-blind, placebo-controlled trial to evaluate the safety, tolerability and efficacy of intravenous Bendavia on reperfusion injury in patients treated with standard therapy including primary percutaneous coronary intervention and stenting for ST-segment elevation myocardial infarction. *Am Heart J* 2013;**165**:509–514 e7.
143. Botker HE. Mitochondrial care in acute myocardial infarction. *Eur Heart J* 2015;**36**:77–79.
144. Ibanez B, Heusch G, Ovize M, Van de Werf F. Evolving therapies for myocardial ischemia/reperfusion injury. *J Am Coll Cardiol* 2015;**65**:1454–1471.
145. Piot C, Croisille P, Staat P, Thibault H, Rioufol G, Mewton N, Elbelghiti R, Cung TT, Bonnefoy E, Angoulvant D, Macia C, Raczka F, Sportouch C, Gahide G, Finet G, Andre-Fouet X, Revel D, Kirkorian G, Monassier JP, Derumeaux G, Ovize M. Effect of cyclosporine on reperfusion injury in acute myocardial infarction. *N Engl J Med* 2008;**359**:473–481.
146. 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 remodeling after reperfused myocardial infarction. *J Am Coll Cardiol* 2010;**55**:1200–1205.
147. Ridker PM, Thuren T, Zalewski A, Libby P. Interleukin-1beta inhibition and the prevention of recurrent cardiovascular events: rationale and design of the Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS). *Am Heart J* 2011;**162**:597–605.
148. Kleveland O, Kunszt G, Bratlie M, Ueland T, Amundsen B, Aakhus S, Damaas JK, Aukrust P, Wiseth R, Gullestad L. The interleukin-6 receptor antagonist tocilizumab reduces inflammation and myocardial damage in non-ST elevation myocardial infarction - a randomized, double-blind, placebo controlled study. *Eur Heart J* 2015;**36**(abstract supplement):27.
149. ISIS-4: a randomised factorial trial assessing early oral captopril, oral mononitrate, and intravenous magnesium sulphate in 58,050 patients with suspected acute myocardial infarction. ISIS-4 (Fourth International Study of Infarct Survival) Collaborative Group. *Lancet* 1995;**345**:669–685.
150. Henning RJ. Stem cells for cardiac repair: problems and possibilities. *Future Cardiology* 2013;**9**:875–884.
151. Leistner DM, Zeiher AM. Novel avenues for cell therapy in acute myocardial infarction. *Circ Res* 2012;**110**:195–197.
152. Assmus B, Honold J, Schachinger V, Britten MB, Fischer-Rasokat U, Lehmann R, Teupe C, Pistorius K, Martin H, Abolmaali ND, Tonn T, Dimmeler S, Zeiher AM. Transcoronary transplantation of progenitor cells after myocardial infarction. *N Engl J Med* 2006;**355**:1222–1232.
153. Schachinger V, Erbs S, Elsasser A, Haberbosch W, Hambrecht R, Holschermann H, Yu J, Corti R, Mathey DG, Hamm CW, Suselbeck T, Assmus B, Tonn T, Dimmeler S, Zeiher AM, Investigators R-A. Intracoronary bone marrow-derived progenitor cells in acute myocardial infarction. *N Engl J Med* 2006;**355**:1210–1221.
154. Meyer GP, Wollert KC, Lotz J, Steffens J, Lippolt P, Fichtner S, Hecker H, Schaefer A, Arseniev L, Hertenstein B, Ganser A, Drexler H. Intracoronary bone marrow cell transfer after myocardial infarction: eighteen months' follow-up data from the randomized, controlled BOOST (BOne marrOw transfer to enhance ST-elevation infarct regeneration) trial. *Circulation* 2006;**113**:1287–1294.
155. Schachinger V, Erbs S, Elsasser A, Haberbosch W, Hambrecht R, Holschermann H, Yu J, Corti R, Mathey DG, Hamm CW, Suselbeck T, Werner N, Haase J, Neuzner J, Germing A, Mark B, Assmus B, Tonn T, Dimmeler S, Zeiher AM, Investigators R-A. Improved clinical outcome after intracoronary administration of bone-marrow-derived progenitor cells in acute myocardial infarction: final 1-year results of the REPAIR-AMI trial. *Eur Heart J* 2006;**27**:2775–2783.
156. Surder D, Manka R, Lo Cicero V, Moccetti T, Rufibach K, Soncin S, Turchetto L, Radrizzani M, Astori G, Schwitter J, Erne P, Zuber M, Auf der Maur C, Jamshidi P, Gaemperli O, Windecker S, Moschovitis A, Wahl A, Buhler I, Wyss C, Kozerke S, Landmesser U, Luscher TF, Corti R. Intracoronary injection of bone marrow-derived mononuclear cells early or late after acute myocardial infarction: effects on global left ventricular function. *Circulation* 2013;**127**:1968–1979.
157. Meyer GP, Wollert KC, Lotz J, Pirr J, Rager U, Lippolt P, Hahn A, Fichtner S, Schaefer A, Arseniev L, Ganser A, Drexler H. Intracoronary bone marrow cell transfer after myocardial infarction: 5-year follow-up from the randomized-controlled BOOST trial. *Eur Heart J* 2009;**30**:2978–2984.
158. Solomon SD, Skali H, Anavekar NS, Bourgoun M, Barvik S, Ghali JK, Warnica JW, Khrakovskaya M, Arnold JM, Schwartz Y, Velazquez EJ, Califf RM, McMurray JV, Pfeffer MA. Changes in ventricular size and function in patients treated with valsartan, captopril, or both after myocardial infarction. *Circulation* 2005;**111**:3411–3419.
159. Assmus B, Tonn T, Seeger FH, Yoon CH, Leistner D, Klotsche J, Schachinger V, Seifried E, Zeiher AM, Dimmeler S. Red blood cell contamination of the final cell product impairs the efficacy of autologous bone marrow mononuclear cell therapy. *J Am Coll Cardiol* 2010;**55**:1385–1394.
160. Seeger FH, Rasper T, Fischer A, Muhly-Reinholz M, Hergenreider E, Leistner DM, Sommer K, Manavski Y, Henschler R, Chavakis E, Assmus B, Zeiher AM, Dimmeler S. Heparin disrupts the CXCR4/SDF-1 axis and impairs the functional capacity of bone marrow-derived mononuclear cells used for cardiovascular repair. *Circ Res* 2012;**111**:854–862.
161. Heeschen C, Lehmann R, Honold J, Assmus B, Aicher A, Walter DH, Martin H, Zeiher AM, Dimmeler S. Profoundly reduced neovascularization capacity of bone marrow mononuclear cells derived from patients with chronic ischemic heart disease. *Circulation* 2004;**109**:1615–1622.
162. Hofmann M, Wollert KC, Meyer GP, Menke A, Arseniev L, Hertenstein B, Ganser A, Knapp WH, Drexler H. Monitoring of bone marrow cell homing into the infarcted human myocardium. *Circulation* 2005;**111**:2198–2202.

163. Templin C, Zweigerdt R, Schwanke K, Olmer R, Ghadri JR, Emmert MY, Muller E, Kuest SM, Cohrs S, Schibli R, Kronen P, Hilbe M, Reinisch A, Strunk D, Haverich A, Hoerstrup S, Luscher TF, Kaufmann PA, Landmesser U, Martin U. Transplantation and tracking of human-induced pluripotent stem cells in a pig model of myocardial infarction: assessment of cell survival, engraftment, and distribution by hybrid single photon emission computed tomography/computed tomography of sodium iodide symporter transgene expression. *Circulation* 2012;**126**:430–439.
164. Beltrami AP, Barlucchi L, Torella D, Baker M, Limana F, Chimenti S, Kasahara H, Rota M, Musso E, Urbanek K, Leri A, Kajstura J, Nadal-Ginard B, Anversa P. Adult cardiac stem cells are multipotent and support myocardial regeneration. *Cell* 2003;**114**:763–776.
165. Bolli R, Chugh AR, D'Amario D, Loughran JH, Stoddard MF, Ikram S, Beache GM, Wagner SG, Leri A, Hosoda T, Sanada F, Elmore JB, Goichberg P, Cappetta D, Solankhi NK, Fahsah I, Rokosh DG, Slaughter MS, Kajstura J, Anversa P. Cardiac stem cells in patients with ischaemic cardiomyopathy (SCIPIO): initial results of a randomised phase 1 trial. *Lancet* 2011;**378**:1847–1857.
166. Malliaras K, Makkar RR, Smith RR, Cheng K, Wu E, Bonow RO, Marban L, Mendizabal A, Cingolani E, Johnston PV, Gerstenblith G, Schuleri KH, Lardo AC, Marban E. Intracoronary cardiosphere-derived cells after myocardial infarction: evidence of therapeutic regeneration in the final 1-year results of the CADUCEUS trial (CArdiosphere-Derived aUtologous stem CElls to reverse ventricULar dySfunction). *J Am Coll Cardiol* 2014;**63**:110–122.
167. Chimenti I, Smith RR, Li TS, Gerstenblith G, Messina E, Giacomello A, Marban E. Relative roles of direct regeneration versus paracrine effects of human cardiosphere-derived cells transplanted into infarcted mice. *Circ Res* 2010;**106**:971–980.
168. Menasche P, Vanneaux V, Fabreguettes JR, Bel A, Tosca L, Garcia S, Bellamy V, Farouz Y, Pouly J, Damour O, Perier MC, Desnos M, Hagege A, Agbulut O, Bruneval P, Tachdjian G, Trouvin JH, Larghero J. Towards a clinical use of human embryonic stem cell-derived cardiac progenitors: a translational experience. *Eur Heart J* 2015;**36**:743–750.