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Cellular and molecular approaches to enhance myocardial recovery after myocardial infarction

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ABSTRACT

Reperfusion therapy has resulted in significant improvement in post-myocardial infarction morbidity and mortality in over the last 4 decades. Nonetheless, it is well recognized that simply restoring patency of the epicardial artery may not stop or reverse damage at microvascular level, and myocardial salvage is often suboptimal. Numerous efforts have been undertaken to elucidate the mechanisms underlying extensive myonecrosis to facilitate the discovery of therapies to provide additional and incremental benefits over current therapeutic pathways. To date, conclusively effective strategies to promote myocardial recovery have not yet been established. Novel approaches are investigating the foundational cellular and molecular bases of myocardial ischemia and irreversible injury. Herein, we review the emerging concepts and proposed therapies that may improve myocardial protection and reduce infarct size. We examine the preclinical and clinical evidence for reduced infarct size with these strategies, including anti-inflammatory agents, intracellular ion channel modulators, agents affecting the reperfusion injury salvage kinase (RISK) and nitric oxide signaling pathways, modulators of mitochondrial function, anti-apoptotic agents, and stem cell and gene therapy. We review the potential reasons of failures to date and the potential for new strategies to further promote myocardial recovery and improve prognosis.

Contents

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1. Introduction

The success achieved over the last 4 decades in reducing the morbidity and mortality associated with acute myocardial infarction (AMI) has been attributed to a combination of timely reperfusion strategies and adjunctive medical therapies [1]. Although primary percutaneous coronary intervention (PCI) has significantly improved mortality and morbidity in patients with ST-elevation myocardial infarction (STEMI), myocardial dysfunction and heart failure resulting from AMI is still distressingly frequent. Despite timely restoration of epicardial coronary artery patency by PCI, myocardial recovery is often suboptimal resulting in extensive myonecrosis. As such, new approaches are needed to enhance myocardial function after STEMI [2,3]. Effective therapies must be addressed to the underlying mechanisms determining infarct size after early reperfusion, including microvascular dysfunction and release of reactive oxygen species (ROS) and other cellular and humoral mediators.

2. Pathophysiology of post reperfusion myocardial injury

The determinants of myocardial injury post reperfusion in STEMI are incompletely understood, and are likely to be multifactorial. Acute thrombotic occlusion of an epicardial coronary artery leads to myocardial ischaemia which if not reversed quickly results in myonecrosis. Reperfusion using fibrinolytic agents or primary PCI can reestablish blood flow and theoretically halt the wavefront of myonecrosis that spreads from the subendocardium to the subepicardium. However, atherothrombotic material can embolise to the distal microvasculature and cause microvascular obstruction (MVO), impairing myocardial recovery. Restoration of blood flow itself may also directly extend the degree of myonecrosis, a phenomenon termed 'myocardial reperfusion injury'. Reperfusion injury accounts for up to 50% of the final infarct size in animal studies [4]. Reperfusion injury involves a variety of complex cellular and molecular mechanisms including activation of free radicals, intracellular calcium accumulation, acidosis, inflammation and neutrophil infiltration [5, 6]. As a consequence of these metabolic alterations, the mitochondrial permeability transition pores (mPTP) opens and the process of apoptosis is initiated [7].

Antioxidants in the human body serve as defence mechanisms to preserve homeostasis [8]. During AMI and after reperfusion these endogenous agents are less effective and there is accumulation of various substances including xanthine oxidase, hypoxanthine and others. Restoration of flow (either spontaneously through endogenous fibrinolysis or through reperfusion therapy) with increased downstream oxygen delivery leads to formation of reactive oxygen species (ROS) [9]. A potentially important target of ROS is the tetrahydrobiopterin–eNOS complex, which may be dissociated by oxidation, resulting in peroxynitrite formation and reduced NO availability [10]. These alternations can potentially damage DNA, proteins, carbohydrates, and lipids.

Although the process of cell death starts from within the cardiac myocyte, the microvasculature, inflammatory cells, and platelets all play a role in promoting (or preventing) cell death [6, 11]. The sequence of events and role of MPTP opening during reperfusion injury and its relationship to sarcolemmal rupture, calpain activation, high oscillating Ca^{2+} in the presence of ATP and development of contracture, leading to apoptosis, are not well understood (Fig. 1).

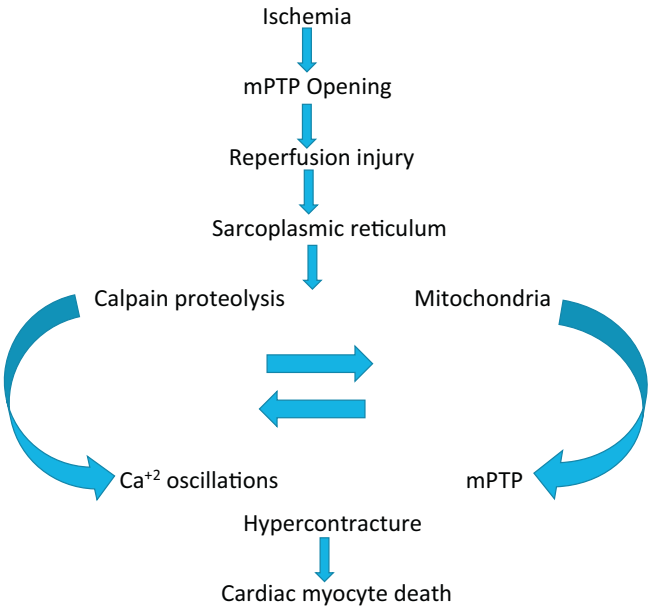

Fig. 1. Pathophysiology of reperfusion injury.

In this review, we provide an overview of novel concepts and therapies based on cellular and molecular disturbances in STEMI that may be applied to reduce infarct size (Fig. 2). We also describe the possible reasons why many promising therapies have thus far failed, and why future approaches may succeed.

3. Agents to reduce inflammation

Vascular inflammation is thought to play an important role in coronary artery plaque initiation, progression, rupture and thrombosis [12]. The Prospective Physicians Health Study (PHS) demonstrated that men with high baseline levels of C-reactive protein (CRP) measured with a high sensitivity assay are more likely to develop adverse cardiac events than those with normal levels [13]. It is also well established that during the acute inflammatory state that accompanies AMI chemokines and neutrophils are released into circulation [14, 15]. Thus, agents targeting the inflammatory cascade may reduce infarct size [Table 1]. A variety of anti-inflammatory agents have been studied for this purpose but despite promising results in experimental studies, most agents have failed to demonstrate reductions in infarct size or improved clinical outcomes in human trials (Table 1) [16, 17].

3.1. Specific anti-inflammatory agents studied to reduce infarct size

3.1.1. Pexelizumab

The activation of the complement system may increase the extent of myonecrosis after coronary artery thrombosis [23]. Pexelizumab is a monoclonal antibody that binds the complement component 5 (C5). Anti-C5 therapy in the setting of MI has shown to inhibit cell apoptosis and necrosis leading to reduction in infarct size in the preclinical setting [18]. In the small COMMA (COMplement inhibition in Myocardial infarction treated with Angioplasty) trial, pexelizumab failed to reduce infarct size, but was associated with a reduction in mortality [18]. Conversely, in the large scale Apex-AMI trial (Pexelizumab for Acute ST-Elevation Myocardial Infarction in Patients Undergoing Primary Percutaneous Coronary Intervention), pexelizumab reduced infarct size at 90 days and improved left ventricular ejection fraction (LVEF) in a cardiac magnetic resonance imaging (CMRI) sub-study, but did not reduce mortality [16,19]. As a result of these conflicting results, and given the negative clinical results of the pivotal Apex-AMI trial, pexelizumab development for AMI has not progressed [24].

3.1.2. Fibrin-Derived Peptide, FX06

Fibrin-Derived Peptide, FX06 is a naturally occurring peptide derived from human fibrin that competes with E1 fragments of fibrin for binding to an endothelial specific molecule, VE-cadherin. FX06 has been shown to have anti-inflammatory properties, and decreased myocardial infarct size in animal models by mitigating reperfusion injury [25, 26]. Unfortunately, no difference in infarct size as measured by CMRI or troponin-I levels was evident with its use in the FIRE (Efficacy of FX06 in the Prevention of Myocardial Reperfusion Injury) trial [17].

3.1.3. Colchicine

Colchicine, an anti-inflammatory agent, was evaluated in STEMI patients for infarct size reduction [20]. A colchicine regimen of 1.5 mg followed by 0.5 mg 1 h later and 0.5 mg twice daily for 5 days was evaluated with infarct size assessed by CMRI. There was no benefit in infarct size reduction in the colchicine group [20]. Additionally, in a small study colchicine failed to demonstrate a reduction in peak CRP values post-acute MI as compared to placebo [27, 28].

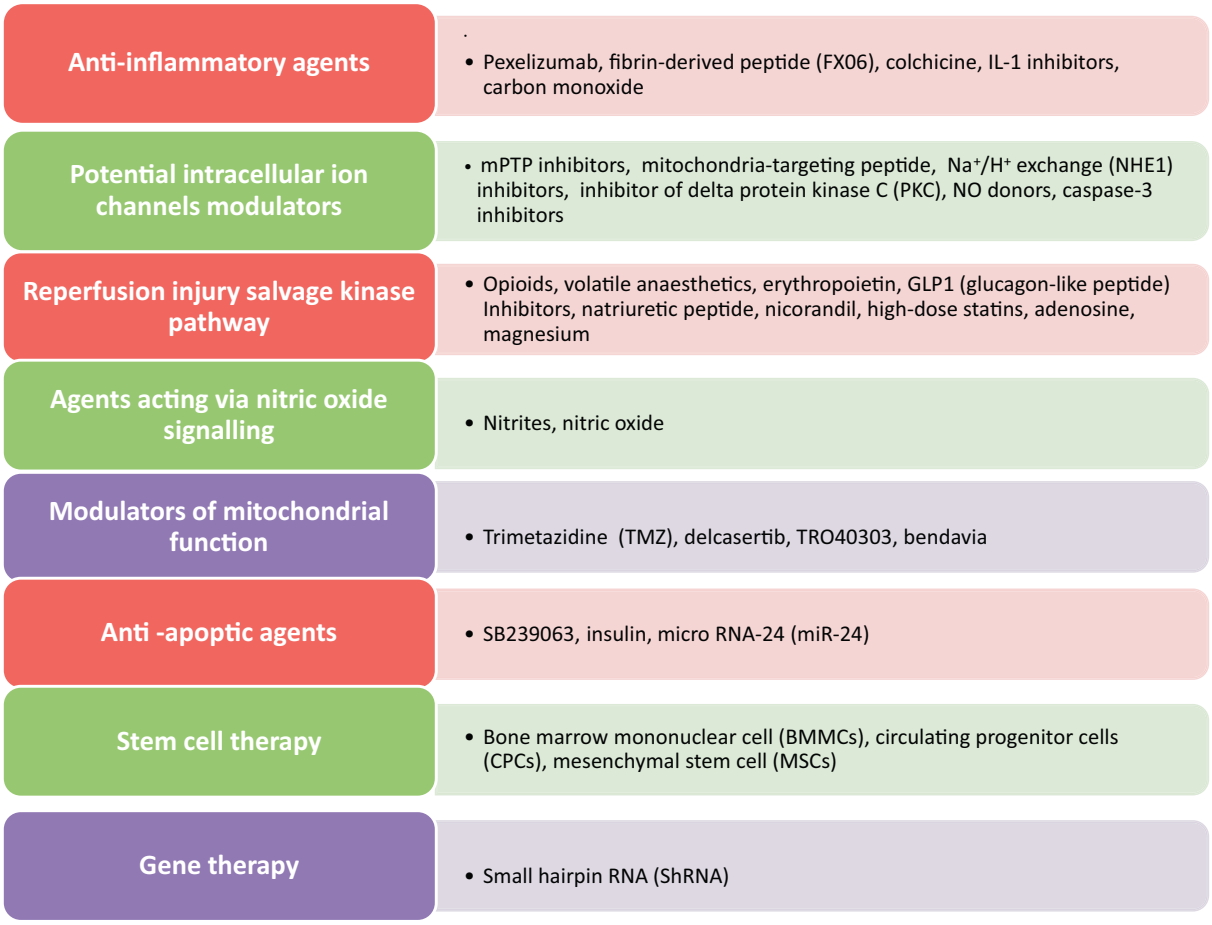

Fig. 2. Emerging strategies for myocardial protection.

Table 1
Anti-inflammatory agents investigated to reduce infarct size.

Agent	Clinical evidence	Time of infarct size assessment	Primary endpoints	Secondary endpoints	Findings	*n*
Pexelizumab	COMMA trial	90 days	Infarct size	Composite of death, new or worsening heart failure, shock or stroke.	No major impact on infarct size [18]	960
	Apex-AMI trial	3–5 days and 90 days	Infarct size	Left ventricular ejection fraction(LVEF), median peak creatine kinase(CK), thrombolysis in Myocardial Infarction (TIMI) flow, death, heart failure or shock.	Reduced infarct size at 90 days and improved LVEF in the cardiac magnetic resonance (CMRI) sub-study [16, 19]	5745
FX06	FIRE trial	5 and 40 days	Infarct size	Size of necrotic core zone and MVO, infarct size at 4 months, left ventricular function, troponin I levels, and safety.	No major impact on infarct size [17]	234
Colchicine	Pilot Study	5 days	Creatine kinase-MB (CKMB); In subgroups - absolute myocardial infarct volume, determined by LGE, was the primary outcome.	Maximal high-sensitivity troponin T.	Smaller infarct size by both CMRI and biomarker levels [20, 21]	151
IL-1 Inhibitors	MRC-ILA Heart Study	14 days	High-sensitivity C-reactive protein level; levels of von Willebrand factor (vWF) and IL-6, troponin; infarct size estimated by CMRI; and burden of ischaemia by continuous ECG monitoring		No reduction in infarct size [22]	

COMMA trial, (COMplement inhibition in Myocardial infarction treated with Angioplasty). Apex-AMI trial, (Pexelizumab for Acute ST-Elevation Myocardial Infarction in Patients Undergoing Primary Percutaneous Coronary Intervention). FIRE trial, (Efficacy of FX06 in the Prevention of Myocardial Reperfusion Injury) Trial. MRC-ILA Heart Study (Investigation of the effect of Interleukin-1 receptor antagonist (IL-1ra) on markers of inflammation in non-ST elevation acute coronary syndromes).

Studies of colchicine in MI were not powered to for clinical outcomes. The ongoing Colchicine and Spironolactone in Patients with STEMI/SYNERGY Stent: CLEAR-SYNERGY (OASIS-9) trial is designed to detect an effect on clinical outcomes in an adequately powered trial involving 4000 patients (NCT03048825).

3.1.4. Interleukin-1 (IL-1)

Myocardial infarction has a well-established inflammatory component. [29, 30] Interleukin-1 (IL-1) is a cytokine released from macrophages and monocytes and plays an important role in the inflammatory cascade [31]. Interleukin-1 has been detected in human coronary arteries with atherosclerosis [32, 33] and also been found in high concentration after coronary intervention. It is a potential target to reduce neointimal proliferation [34]. IL-1 is an early mediator of the inflammatory cascade and is actively involved in mobilisation of various components of inflammation. Alongside these inflammatory components glucocorticoids are released, playing a vital role in the stress response during myocardial infarction. [35, 36]

IL-1 is expressed in the coronary arteries of patients with coronary artery disease [37]. IL-1 has been shown to drive the rise in CRP in acute coronary syndromes(ACS) [22]. Inhibitors of IL-1 have reduced infarct size in both preclinical and some clinical studies [38, 39]. In a mouse model, treatment with an IL-1β blocking monoclonal antibody prevented further deterioration in LV function after acute MI [38]. A randomized controlled trial in a pig model demonstrated significant infarct size reduction and preservation of LV function with MCC950 treatment, a selective NLRP3-inflammasome inhibitor [40]. In the randomized MRC-ILA Heart Study (Investigation of the effect of Interleukin-1 receptor antagonist (IL-1ra) on markers of inflammation in non-ST elevation acute coronary syndromes), a recombinant IL-1 receptor antagonist resulted in increased rates of recurrent MI within 12 months [22]. However this trial was underpowered and a larger study evaluating longer term IL-1 inhibition is ongoing [41].

3.2. Carbon monoxide

Carbon monoxide (CO) is a toxic substance given its ability to bind haemoglobin thereby displacing oxygen [42, 43]. While CO poisoning is associated with cardiovascular complications, including myocardial necrosis [44, 45]; there is some evidence that CO in small doses may have cardioprotective effects [46–48]. At low levels, CO inhibits the expression of pro-inflammatory cytokines (including TNF-α, IL-1β, MIP-1β) and increases the expression of the anti-inflammatory cytokine IL-10 through a MAP kinase pathway [49, 50].

Various CO-releasing molecules (CORM) have been developed for infarct size reduction [51, 52,53]. CORM administration reduced infarct size in mice without any effect on arterial blood pressure, heart rate and carboxyhaemoglobin levels [54]. CORMs have also been shown to favourably influence post-infarction LV remodelling in a mouse model of LAD ligation [55]. In another experiment pre-treating mice with CORM-3, 24–72 h prior to coronary occlusion reduced infarct size [56]. These data support a potential role for CORMs in limiting ischaemic myocardial damage after coronary occlusion and reperfusion, warranting further development of these agents.

3.3. Possible reasons for failure of anti-inflammatory agents

Anti-inflammatory agents have reduced infarct size in preclinical studies but have thus far failed to show benefit in clinical trials. It may be that the pathophysiologic and cellular processes of AMI in mice, rodents and rabbit models differ substantially from humans. Preclinical studies mostly involve healthy and young animals without atherosclerosis that mount a robust inflammatory response, unlike some patients with chronic comorbidities.

One possible reason that therapies for infarct size reduction have failed in humans is that their targets were often non-specific. Specific agents targeting individual molecules may be more effective. Such targets may be identified from human genome-wide associated studies (HGWAS) [57]. In this regard coronary artery disease and AMI are associated with abnormal metabolic pathways that are often genetically regulated [58, 59]. The lessons learned from gene-targeted cancer therapies can be translated to applications to reduce the infarct size [60]. Diagnostic imaging modalities such as FDG-PET may be used to develop goal-directed therapies [61]. A number of pre-clinical efforts in this regard are already underway and may translate to human patients in the near future [62].

3.4. Regulation of intracellular ion channels

3.4.1. mPTP inhibitors and cyclosporine

Opening of the mitochondrial permeability transition pore (mPTP) has been shown to be centrally involved in reperfusion injury, and inhibitors of mPTP opening may prevent or reduce apoptosis and myonecrosis and enhance the cellular recovery (Fig. 3) [63, 64]. The immunosuppressive agent cyclosporine is one such inhibitor of mPTP

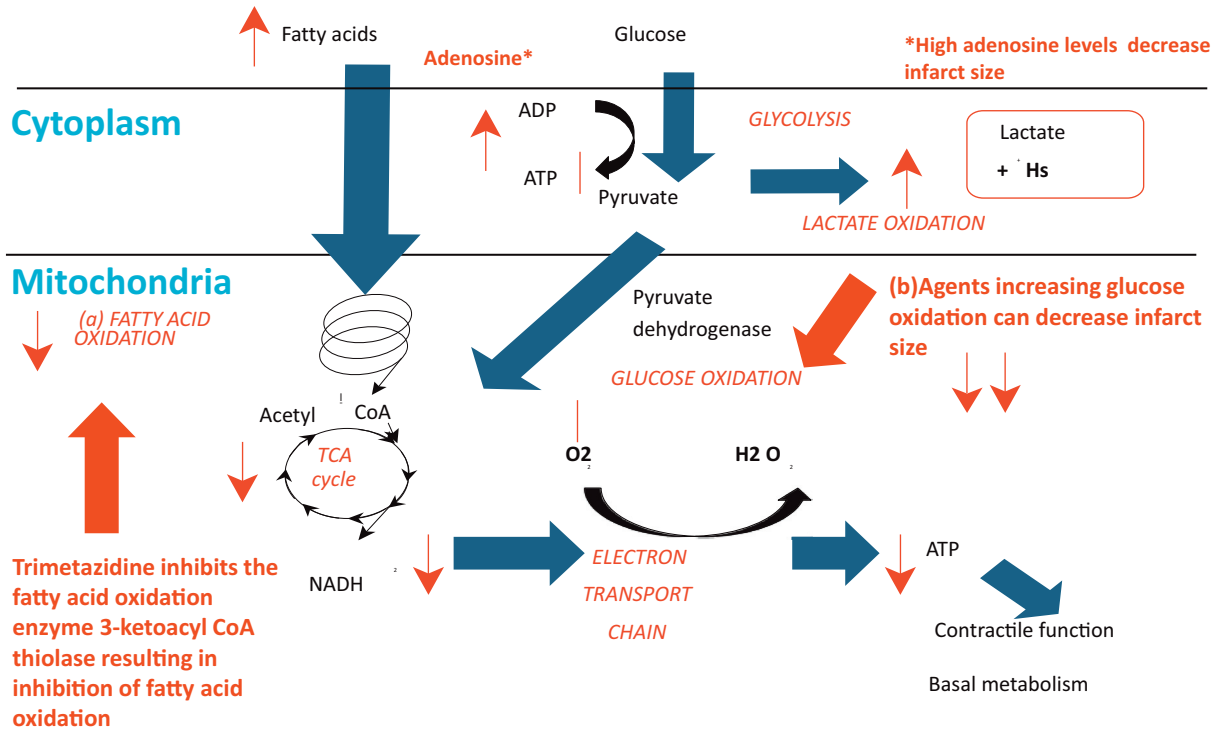

Fig. 3. Mechanisms of agents affecting fatty acid and glucose oxidation.

opening. Small-scale studies have shown that cyclosporine therapy at the time of acute MI reperfusion may reduce infarct size and mitigate pathologic LV remodelling [21,65]. In a meta-analysis of 20 in vivo experimental studies in animal models (involving four species), cyclosporine was found to be beneficial in reducing infarct size. However, a beneficial response was not present in porcine models raising concerns in regards to the cardioprotective potential in humans [66].

In the randomized CIRCUS (Does Cyclosporine Improve Clinical Outcome in ST-Elevation Myocardial Infarction Patients) trial, intravenous cyclosporine (2.5 mg/kg Ciclomulsion) failed to reduce infarct size or improve event-free survival [67]. It was hypothesized that the negative results of this study may have been due to the formulation of cyclosporine used (CicloMulsion, NeuroVive Pharmaceuticals). However, the CYCLE (CYCLosporinE A in Reperfused Acute Myocardial Infarction) trial, in which the alternative formulation (Sandimmune, Novartis) was given as a single intravenous bolus before primary PCI in anterior STEMI patients, also was negative, demonstrating no effect on ST-segment resolution, infarct size, LV remodelling or clinical outcomes [68].

mPTP is a non-selective pore and cyclosporine A is not specific for cyclophilin D, also binding cytosolic cyclophilin A [69]. Argaud et al. demonstrated that the specific mPTP inhibitor NIM811, a remodelling derivative devoid of activity on calcineurin, increased the resistance of mPTP to Ca^{2+} overload and limited infarct size when given at the time of reflow [70]. Clinical studies are thus required to determine whether specific inhibitors of the mPTP will more consistently reduce infarct size and improve outcomes [71]. CAPRI (Ciclosporin to Reduce Reperfusion Injury in Primary PCI) trial is a single centre, double-blind randomized trial, currently recruiting patients for the study and aiming to evaluate the effectiveness of IV Ciclosporin on reducing reperfusion injury in patients undergoing primary PCI.

3.4.2. Na^+/H^+ exchange (NHE1) inhibitors

In experimental models reducing intracellular Calcium (Ca^{2+}) overload by blocking the sarcolemmal Ca^{2+} ion channel, the mitochondrial Ca^{2+} uniporter, or the sodium-hydrogen exchanger decreases myocardial infarct size [72]. Cariporide, a specific benzoyl-guanidine Na^+/H^+ exchange (NHE1) inhibitor, has been shown to have cardioprotective effects [73]. Specific inhibition of Na^+/H^+ exchange using HOE-642 can potentially retard myocardial remodelling and improve diastolic function [74]. However, clinical benefits of cariporide in humans were not present in the ESCAMI (evaluation of the safety and cardioprotective effects of eniporide in acute myocardial infarction) and CASTEMI (CAldaret in ST-elevation Myocardial Infarction) trials [75, 76]. At this time there is limited evidence that agents regulating intracellular ions and cytosolic calcium may reduce infarct size or improve clinical outcomes (Table 2).

3.4.3. Potential reasons for failure of modulators of intracellular ions

Various agents (e.g. cyclosporine, TRO40303 and MTP-131) reported benefit in pre-clinical models but not in human clinical trials. Most of these molecules were tested before validation of molecular and cellular targets. These agents were also administered to patients treated with antiplatelet agents which may themselves have cardioprotective properties [80, 81]. Delivering the compound at the right time and at the right dose to achieve adequate therapeutic levels also remains a challenge. Compounds with better bioavailability may improve outcomes through regulation of intracellular ions and cytosolic calcium. Intracoronary administration may be more effective than systemic administration.

3.5. Agents impacting the reperfusion injury salvage kinase pathway

In preclinical studies the reperfusion injury salvage kinase (RISK) pathway has been shown to have a significant cardioprotective effect. This is achieved by a variety of pathways that includes the activation of mPTP as well.

A variety of agents have shown to activate the RISK pathway and potentially reduce infarct size [Table 3].

3.5.1. Opioids

Morphine has been tested as a cardioprotective agent in preclinical as well as in clinical studies [118, 119]. In a prospective randomized trial, intracoronary morphine failed to reduce infarct size as assessed

Table 2
Agents with cellular targets to reduce infarct size.

AGENTS	Cellular target	Clinical evidence	Time line for assessment of infarct size	Primary endpoints	Secondary endpoints	Findings	*n*
Cyclosporone	mPTP	CIRCUS study	1 year	A composite of all cause death, worsening of heart failure during the initial hospitalisation, rehospitalisation for heart failure, or adverse left ventricular remodelling at 1 year.		Did not prevent adverse left ventricular remodelling.No reduction in infarct size. [67]	791
		CYCLE trial	60 min, 4 days and 6 months	Incidence of ≥70% ST-segment resolution 60 min after TIMI flow grade 3	High-sensitivity cardiac troponin T (hs-cTnT) on day 4, left ventricular (LV) remodelling, and clinical events at 6-month follow-up.	No reduction in infarct size [68].	410
TRO40303	Indirect mPTP inhibitor	MITOCARE	3 days	Infarct size	Infarct size and clinical safety outcomes.	No significant infarct size reduction [77].	163
Bendavia	Mitochondria-targeting peptide	EMBRACE-STEMI	72 h and 4 + −1 days	Infarct size.	Infarct size.	No reduction in infarct size by biochemical analysis [78].	297
Cariporide	Na^+/H^+ exchange (NHE1) inhibitor	Rupprecht, Hans-Jürgen, et al.				Reduces reperfusion injury [73].	100
Eniporide	Specific NHE1 inhibitors	ESCAMI	0–72 h	Infarct size, area under the curve [AUC] (0 to 72 h). Clinical outcomes death, cardiogenic shock, heart failure, life-threatening arrhythmia.		No reduction in infarct size [75].	
Caldaret	NHE1 inhibitors	CASTEMI	7 and 30 days	Infarct size, area under the concentration–time curve (AUC) for total creatine kinase (CK) and its MB isoenzyme (CK-MB) to 72 h; for troponin T (TnT) and lactate dehydrogenase		Lack of cardio protection [76].	
Delcasertib	Inhibitor of delta Protein Kinase C(PKC)	PROTECTION - AMI	3 months	Infarct size	Infarct size, electrocardiographic ST-segment recovery, AUC or time to stable ST recovery, or LVEF.	No reduction in infarct size [79].	1010

CIRCUS study, Does Cyclosporine Improve Clinical Outcome in ST-Elevation Myocardial Infarction Patients trial. CYCLE trial, CYCLosporinE A in Reperfused Acute Myocardial Infarction. MITOCARE, Multicenter Multicentre, randomized, double-blind, placebo-controlled study to assess safety and efficacy of TRO40303 for reduction of reperfusion injury in STEMI patients undergoing primary PCI. NA, Not Available. EMBRACE-STEMI, Evaluation of the Myocardial Effects of Bendavia for Reducing Reperfusion Injury in Patients With Acute Coronary Events–STEMI. ESCAMI, evaluation of the safety and cardioprotective effects of eniporide in acute myocardial infarction. CASTEMI, CAldaret in ST-elevation Myocardial Infarction. PROTECTION – AMI, Inhibition of d-Protein Kinase C for Reduction of Infarct Size in Acute Myocardial Infarction. REVEAL, Intravenous erythropoietin in patients with ST-segment elevation myocardial infarction.

by CMRI. There was also no difference in myocardial salvage ST – segment resolution or peak CK-MB levels compared with control [120].

3.5.2. Volatile anaesthetics

Volatile anaesthetic agents may reduce infarct size by affecting the potassium ATP (KATP) channel, mitochondrial permeability transition pore (mPTP), reactive oxygen species (ROS) production, cytoprotective Akt and extracellular signal kinases (ERK) pathways. The evidence in regards to the cardioprotective role of these agents is controversial, although isoflurane, desflurane, and sevoflurane have demonstrated some cardioprotective potential [121–123]. A comparison of various agents during on-pump cardiac surgery has shown no significant difference in infarct size reduction [82]. Randomized clinical trials are required to examine whether these agents have meaningful cardioprotective effects in humans.

3.5.3. Erythropoietin

In animals studies erythropoietin administration before ischemic reperfusion injury conveyed significant myocardial protection through mechanisms involving reduction of caspase-3 activity and up-regulation of Bcl-2 in association with enhanced ERK-induced GATA-4 stability [104]. However, the cardioprotective effect of erythropoietin was not replicated in a clinical trial, REVEAL (The Reduction of Infarct Expansion and Ventricular Remodelling With Erythropoietin After Large Myocardial Infarction) [88].

3.5.4. Natriuretic peptides [Atrial (ANP) and B- type natriuretic peptide (BNP)]

There is some preclinical as well as clinical evidence that natriuretic peptides may reduce infarct size. Pre-clinical studies in rabbits have shown encouraging results when ANP was administered prior to myocardial reperfusion [110]. In the Japan-Working groups of acute myocardial Infarction for the reduction of Necrotic Damage by ANP (J-WIND-ANP) trial, an ANP analogue (Carperitide) was administered intravenously as an adjunct to primary PCI to patients with STEMI. Infarct size was reduced by 15% as assessed by 72 h AUC total CK [96]. These results warrant further human randomized trials.

3.5.5. GLP1 (Glucagon-like peptide) inhibitors

The glucagon-like peptide-1 (GLP-1) may have cardioprotective effects via regulation of blood glucose. These chemicals have insulin-like properties and affect glucose uptake, not needing administration of glucose in this regard. There is preclinical as well as clinical evidence for the use of GLP1 inhibitors to reduce infarct size. An IV infusion of exenatide started at least 15 min before primary PCI and continued for 6 h after primary PCI in STEMI reduced infarct size by 23% as demonstrated by

Table 3
Potential agents acting on RISK pathway and other cellular targets for infarct size reduction.

AGENTS	Cellular target	Clinical evidence	Time Frame for assessment of infarct	Primary end points	Secondary end points	Findings	n
Remifentanil infusion		During CABG				The possible beneficial impact on biomarkers of injury [82, 83].	200
Fentanyl		During CABG				Reduction in enzyme release in the treatment group [84].	150
Iso flurane		During CABG				Significant reduction in peak cTnI up to 36 h postoperatively in the isoflurane group [85, 86].	45
Exenitide	GLP 1	Lonborg et al.				Some beneficial effect of reducing the infarct size [87].	
Erythropoietin		REVEAL	2–6 days and 12 ± 2 weeks	Infarct size.		No significant reduction in infarct size [88].	
Adenosine		AMISTAD-I	6 ± 1 days	Infarct size	Myocardial salvage index and a composite of in-hospital clinical outcomes (death, reinfarction, shock, congestive failure or stroke).	Significant reduction in infarct size [89].	222
Adenosine		AMISTAD- II				Significant reduction in infarct size [90].	
		Fokkema et al.	30 to 60 min. 30 days			No effect on enzymatic infarct size. [91]	
Nitrite therapy		NIAMI trail	6–8 days. 6 months.	Infarct size	Plasma troponin I and CK area under the curve, left ventricular volumes (LV), and LVEF.	No reduction in infarct size [92].	
		Jones et al.	2 days	Infarct size.	Infarct size	No evidence of reduction in infarct size [93].	
		NOMI study				No beneficial effect on the infarct size. NCT01398384	
Magnesium		ISIS-4-A				No clinical benefit in infarct size reduction [94, 95].	
ANP/BNP		J-WIND-ANP	3 days and 6–12 months.	Infarct size		Some reduction in infarct size [96].	
Nicorandil		J-WIND-KATP	3,6 days. 12 months.	Infarct size.		No significant reduction in infarct size [96].	

AMISTAD trial, In Acute Myocardial Infarction STudy of Adenosine. NA, Not available. ISIS-4-A, 4th International Study of Infarct Survival. NIAMI trail, Intravenous sodium nitrite in acute ST-elevation myocardial infarction. NOMI study, Nitric Oxide for inhalation to reduce reperfusion injury in acute ST-elevation Myocardial Infarction. J-WIND-ANP, Japan-Working groups of acute myocardial Infarction for the reduction of Necrotic Damage by ANP.

CMRI, and increased myocardial salvage [87, 124]. Subcutaneous exenatide prior to primary PCI in STEMI resulted in a 52% reduction in infarct size assessed by CMRI at 1 month [125]. However, these results were not replicated in a large double-blind, placebo-controlled randomized trial [126]. These conflicting results may be due to differences in the patient populations studied and/or different doses used in the varying trails. Further clinical trials with GLP-1 agents are warranted to investigate their potential to reduce infarct size and improve prognosis in STEMI.

3.5.6. Nicorandil

In J-WIND-KATP (Japan-Working groups of acute myocardial Infarction for the reduction of Necrotic Damage by ANP) trial, 545 patients were randomized to a 0.067-mg/kg bolus followed by 24-h infusion of 1.67 g/kg/min of nicorandil or placebo [96]. Nicorandil administration showed no difference in infarct size as measured by CK-MB release.

3.5.7. HMG-CoA reductase inhibitors

Statins have been shown to be cardioprotective with their effects not solely related to LDL reduction [100]. Increasing the availability of NO synthetase by statins may reduce the myocardial injury and hence may be cardioprotective [127, 128]. A beneficial role of statin therapy in infarct size reduction has been demonstrated in preclinical studies [111, 129]. To date, the acute use of statins to reduce infarct size and improve prognosis independent of their favourable effects on cholesterol metabolism has not been demonstrated.

3.5.8. Adenosine

During myocardial ischemia, adenosine is produced in cardiac myocytes by dephosphorylation of adenosine monophosphate (AMP); within seconds of ischemia the level of interstitial adenosine rises and causes arteriolar vasodilatation [130, 131]. Clinical studies with adenosine have reported conflicting results for infarct size reduction. In the Acute Myocardial Infarction STudy of ADenosine (AMISTAD) trial, adenosine given as an adjunct to thrombolytic therapy resulted in a 33% relative reduction in infarct size [89]. In the AMISTAD- II trial, intravenous adenosine (50 microgram/kg/min and 70 microg/kg/min doses) in patients with anterior STEMI receiving thrombolysis or primary PCI was associated with reduced infarct size, particularly with the high-dose [90]. However, a clinical benefit was not observed. Moreover, high dose intracoronary adenosine during primary PCI in AMI did not reduce enzymatic infarct size in another study [91]. Further studies with adenosine or adenosine analogues are warranted, especially at higher doses.

3.5.9. Magnesium

Neither regional nor systemic magnesium reduced infarct size in animal models [116]. Conflicting results of magnesium on infarct size reduction have been reported from small studies [132]. Some studies suggested magnesium sulfate may reduce infarct size when given before or at the time of reperfusion, rather than after coronary reperfusion [133]. However, in a large clinical trial magnesium sulfate provided no clinical benefit in infarct size reduction or survival [94].

3.6. Agents acting via nitric oxide signaling pathways

Nitrites and nitric oxides (NO) offer the potential to salvage jeopardized myocardium, and many NO donors have been tested for their ability to reduce infarct size. In experimental models, sodium nitrite has shown efficacy in reducing infarct size when used either pre occlusion or as a peri-conditioning agent [101, 102, 134]. In the randomized NIAMI (Intravenous sodium nitrite in acute ST-elevation myocardial infarction) trial, intravenous sodium nitrite failed to reduce infarct size in comparison to placebo [92]. The negative results may be attributable due to the fact that >90% of patients had received nitro-glycerine prior to reperfusion. Also, whether a higher dose or longer duration of infusion would have been effective.

In another trial, a 10 ml bolus of intracoronary sodium nitrite (1.8 μmol) was administered to patients undergoing primary PCI versus placebo just before balloon inflation. There was no evidence of a reduction in infarct size as assessed by creatine kinase and troponin T release and by CMRI measured on day two, although by chance total ischemia time was longer in the treatment group [93]. However, in a post hoc analysis of 66 patients with TIMI flow ≤1, nitrite administration was associated with a statistically significant reduction in infarct size and MACE and an improved myocardial salvage index. These findings need to be replicated in a larger randomized trial.

In the NOMI study (NCT01398384) inhaled nitric oxide at 80 ppm (parts per million) initiated prior to primary PCI and administered for 4 h did not reduce the primary endpoint of infarct size as assessed by CMRI at 48–72 h. Whether this negative effect is due to patient selection factors or prior dosing with intracoronary or intravenous nitro-glycerine or lack of effectiveness is speculative. Further clinical trials are warranted to explore the potential beneficial effect of administering intracoronary nitrites while the culprit artery is still occluded.

3.7. Strategies targeting mitochondrial function

During myocardial ischemia, there is a switch of mitochondrial energy metabolism; oxidation is decreased and glycolysis becomes the predominant source of energy production. Fatty acids are the principal substrate for residual oxidative metabolism. The increase in glycolysis and decrease in glucose oxidation results in the production of both lactate and hydrogen ions. Therapeutic agents to increase glucose oxidation can potentially decrease ischemic injury (Fig. 4). Various agents which target mitochondrial function have been studied in both preclinical and clinical setting to examine their potential to reduce infarct size.

3.7.1. Trimetazidine

Trimetazidine is an anti-ischemic agent that enhances mitochondrial glucose metabolism and inhibits fatty acid metabolism [135, 136]. It has an inhibitory action on the β-oxidation of fatty acids by blocking long-chain 3-ketoacyl-coenzyme A thiolase (LC 3-KAT), which enhances glucose oxidation.

Some preclinical and clinical evidence supports the potential cardioprotective role of trimetazidine [136, 137]. The anti-ischemic effects of Trimetazidine has been demonstrated in a small, randomized, double-blind study where it decreased the maximum ST-segment shift and delayed its onset in comparison to placebo treatment [138]. Trimetazidine in combination with PCI decreased cardiac troponin I release in comparison to placebo [139]. In another study trimetazidine improved symptoms, exercise capacity and reduced ischemia as assessed by SPECT (single photon emission computed tomography) [140].

In a large prospective, randomized, double-blind EMIP-FR (European Myocardial Infarction Project – Free Radical) trial, 19,725 patients with AMI within 24 h were enrolled, there was no difference between trimetazidine and placebo for the main endpoint of 35-day mortality [141, 142]. Thus, although there is some evidence that trimetazidine delays the onset of ischemia and may reduce infarct size, this agent has not shown to be of clinical benefit in large-scale trials.

3.7.2. Delcasertib

Delcasertib is a peptide inhibitor of delta protein kinase C (PKC), a major mediator of the mitochondrial apoptotic pathway. Although delcasertib showed promise in preclinical studies, it was ineffective

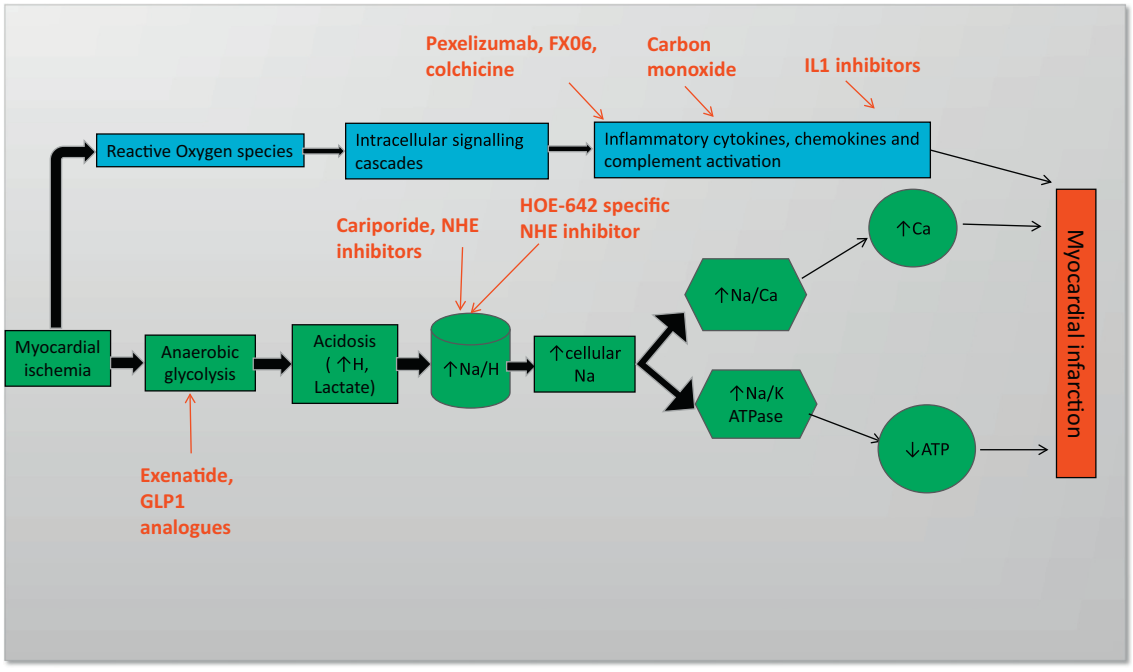

Fig. 4. Various agents and potential mechanisms to reduce infarct size.

Table 4
Various types of stem cells and studies assessing their impact on LV function.

Cell type	Trial	Participants (treatment/control)	Evidence of changes in LV function
BMMC	Strauer	10	No significant difference in LVEF [146].
BMMC/CPC	TOPCARE-MI	59	Some improvement in LVEF [147].
BMMC	Fernandez-Aviles	20	Some improvement in LVEF [148].
CD133-BMMC	Bartunek	16/19	Some improvement in LVEF [149].
MSC	Chen et al.	34/35	Some improvement in LVEF. [150]
BMMC	BOOST	30/30	Some improvement in LVEF [151].
BMMC	Janssens et al.	34/33	No significant improvement in LVEF [152].
BMMC	ASTAMI	50/47	No significant improvement in LVEF. [153]
BMMC	REPAIR-AMI	102/102	Some improvement of LVEF [154].

BMMC, Bone marrow mononuclear cells CPC, circulating progenitor cells. MSC, Mesenchymal stem cell. LVEF, Left Ventricular Ejection Fraction. TOPCARE-AMI, Transplantation of Progenitor Cells and Regeneration Enhancement in Acute Myocardial Infarction. ASTAMI, Autologous Stem-Cell Transplantation in Acute Myocardial Infarction. BOOST, Bone Marrow Transfer to Enhance ST-elevation Infarct Regeneration. LVEF, left ventricular ejection fraction. REPAIR-AMI, Reinfusion of Enriched Progenitor Cells and Infarct Remodelling in Acute Myocardial Infarction.

in the PROTECTION –AMI (Inhibition of delta-protein kinase C by delcasertib as an adjunct to primary percutaneous coronary intervention for acute anterior ST-segment elevation myocardial infarction) trial [79].[Table 2]The reasons for the neutral study may relate to patient selection, as 30%–40% of patients had TIMI flow of >1 before primary PCI. In addition, it may take up to 30 min for delcasertib to reach steady state. It is also possible that the dosing was inadequate, as lack of signs of toxicity raised the question of whether the dose used was sufficient.

3.7.3. TRO40303

TRO40303 is an indirect inhibitor of the mitochondrial permeability transition pore (mPTP) and has shown beneficial impact on infarct size reduction in preclinical settings. Conversely, in a large scale trial, MITOCARE (Multicentre, randomized, double-blind, placebo-controlled study to assess safety and efficacy of TRO40303 for reduction of reperfusion injury in STEMI patients undergoing primary PCI), no reduction in infarct size was present with TRO40303 treatment. [Table 2] There may be multiple reasons why this trial was negative. The sample size was small and the groups were imbalanced (higher initial mean CK, fewer patients with baseline TIMI 0 flow, more patients with TIMI 0/1 flow post-PCI, and older age in the TR040303 group). Dosing may also have been inadequate.

Table 5
Various animal models and agents tested for infarct size reduction.

Animal model	Agents	Findings
Mice studies	IL-1 Inhibitors	Preservation of LV function [38]
	Carbon monoxide	Reduced infarct size [54]
	Cyclosporine	Improved survival Improved LVEF [97]
	Delcasertib	Some reduction in infarct size [98, 99].
	Rosuvastatin	Some reduction in myocardial necrosis [100].
	Nitrite	Some reduction in infarct size [101, 102].
Rat studies	Pexelizumab	Reduction in infarct size [18].
	Fluvastatin	Significant reduction in infarct size [103].
	Erythropoietin	Significant myocardial protection under moderate hyperglycemic condition [104].
	Morphine	Significant reduction in infarct size [105].
	Morphine	Potential cardio protective role [106].
	Tramadol	May reduce the myocardial infarct size [107].
Rabbit studies	Simvastatin	Some reduction in infarct size [108]
	Adenosine	Reduction in infarct size [92, 109].
	ANP/BNP	Some reduction in infarct size [110]. Some reduction in infarct size [111].
	Eniporide	Some cardio protective effect [112].
	Bendavia	Reduced myocardial infarct size by ~50% when administered for either 1 or 3 h of reperfusion [113].
	NIM811	Some reduction in infarct size [70].
	Cyclosporine	Reduced infarct size. Apoptotic cell death reduced [114]
Dog studies	Adenosine	Significant reduction in myocardial perfusion injury [115]
	Magnesium	No significant reduction in infarct size [116].
Pig studies	FX06	Infarct size reduction [25, 26]
	IL-1 Inhibitor	Reduction in infarct size [40]
	Cariporide	Significantly reduced infarct size [117].

Interleukin-1 receptor inhibitors (IL-1 inhibitors), Atrial (ANP) and B - type Natriuretic peptide (BNP), Fibrin-Derived Peptide, FX06.

3.7.4. Bendavia

Bendavia is another mitochondria-targeting peptide and similarly failed to replicate favourable preclinical results in clinical trials such as the EMBRACE-STEMI (Evaluation of Myocardial Effects of Bendavia for Reducing Reperfusion Injury in Patients With Acute Coronary Events) trial, in which treatment with MTP-131 was not associated with a decrease in myocardial infarct size as assessed by AUC_{0-72} of CK-MB [143]. In comparison to the MITOCARE study, EMBRACE-STEMI limited the inclusion of patients with only large anterior STEMI and administered the investigational drug for a prolonged time to ensure therapeutic effect. Despite these adjustments, MPT-131 did not show a reduction in infarct size. Thus, there is no current evidence supporting the use of mitochondrial function modulators for infarct size reduction.

3.7.5. Strategies to inhibit apoptosis (anti-apoptotic agents)

Apoptosis may play a crucial role in the pathophysiology of myocardial infarction, and inhibition of apoptosis in the early stages of reperfusion may reduce infarct size.

3.7.6. SB239063 and insulin

In experimental studies treatment with SB239063 and insulin markedly decreased myocardial apoptosis ($10.6 \pm 1.5\%$ and $7.9 \pm 0.9\%$ respectively, $P < 0.01$ vs. vehicle) and significantly reduced infarct size ($43 \pm 3.6\%$ and $35 \pm 2.9\%$, respectively, $P < 0.01$ vs. vehicle) [144].

3.7.7. MicroRNA-24 (miR-24)

The effects of MicroRNA-24 (miR-24) in inhibiting LV remodelling by suppressing cellular apoptosis via the phosphatase and tensin homolog (PTEN) have been studied in AMI rat models [145]. These studies suggest that Ad-miR-214 may protect against reperfusion injury and decrease myocardial cell apoptosis through a PTEN-mediated mechanism.

However, whether apoptosis is a primary or secondary event in the pathophysiology of AMI is controversial. Methods to assess apoptosis are also suboptimal. Currently available methods utilizing the terminal deoxynucleotidyl-transferase-mediated dUTP nick end-labelling (TUNEL) cannot differentiate the cell type that is undergoing apoptosis in a tissue sample comprising multiple types of cells. Ultimately, clinical trials will be required to determine whether anti-apoptotic agents provide beneficial effects in reducing infarct size and improving prognosis.

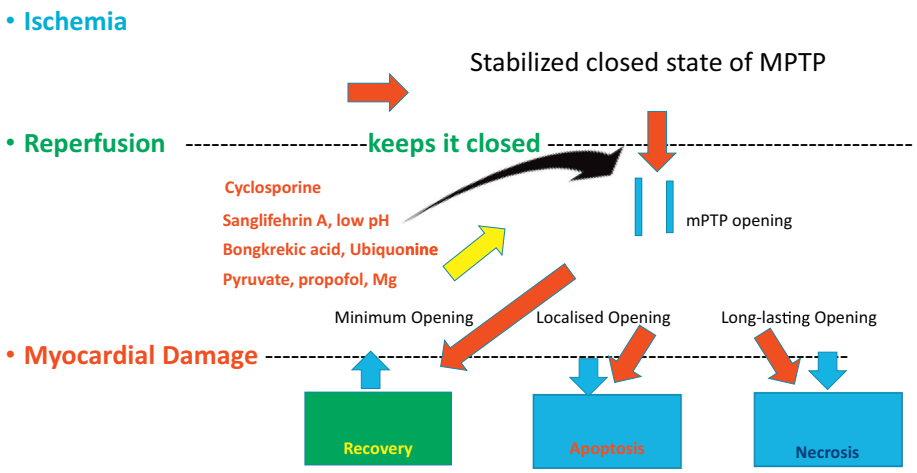

Fig. 5. Various agents acting on mPTP channels and mechanisms to reduce infarct size.

3.8. Stem cell and gene therapy to reduce infarct size

3.8.1. Stem cell therapy

Stem cell therapy to improve myocardial function after large STEMI has been extensively studied in phase I and II trials [Table 4].

Early experimental studies in animals suggested improvement in LV systolic function following cell therapy with bone marrow-derived mononuclear cells (BMMC) although with no effect on infarct size [155]. The BOOST (The Bone Marrow Transfer to Enhance ST-Elevation Infarct Regeneration Trial) suggested that intracoronary transfer of autologous bone marrow cells after acute MI could improve LV systolic function, a finding that was not supported by the Leuven trial [151,152]. The REPAIR-AMI (Reinfusion of Enriched Progenitor Cells and Infarct Remodelling in Acute Myocardial Infarction) trial reported a greater absolute increase in LVEF in the BMMC group than in the placebo group (2.5%; 95% CI, 0.5 to 4.5; P = 0.01) [154].

Allogeneic mesenchymal precursor cells (MPCs) have been safely delivered into the intra-coronary milieu after AMI in sheep, and improved myocardial function [156]. There is some evidence that a combination of human cardiac stem cells (hCSC) and bone marrow mesenchymal stem cells (hMSC) may reduce scar after MI and enhance restoration of systolic and diastolic function after MI [157].

However, clinical outcomes with stem cell therapy have been conflicting, likely explained by differences in patient characteristics and the cell type, number, timing and route of administration. Large-scale phase III trials are required to determine if this approach can durably improve LV function and prognosis after large MI.

3.8.2. Gene therapy

Gene therapy to enhance cardiac function is challenging due to the need for vectors and gene transcription and translation. Turunen MP et al. used "lentiviral" in vivo for delivery of small hairpin RNA (shRNA) into hearts in a murine infarction model. shRNA complementary to the promoter of vascular endothelial growth factor (VEGF-A) was able to up-regulate endogenous VEGF-A expression [158]. Infarct size reduction was noted in histological, multiphoton microscopic and MRI studies. Clinical studies are required to advance these preclinical observations.

4. Summary and future directions

Although numerous agents have been shown to reduce infarct size in preclinical models [Table 5], there is limited clinical evidence of benefit to date (Fig. 5) [159]. Emerging strategies effecting valid molecular and cellular targets require further study in humans. Rather than a "one size fits all" approach, individualized tailored therapies may be required for patients with select clinical, myocardial or genetic/cellular characteristics. Further study is also required to determine why beneficial animal studies have not translated into human effectiveness. Despite the numerous setbacks to date, there is a great clinical need to enhance myocardial recovery and LV function in patients with large MI to reduce the burden of heart failure and improve survival.

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