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A review of strategies for infarct size reduction during acute myocardial infarction☆

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ABSTRACT

Advances in medical and interventional therapy over the last few decades have revolutionized the treatment of acute myocardial infarction. Despite the ability to restore epicardial coronary artery patency promptly through percutaneous coronary intervention, tissue level damage may continue. The reported 30-day mortality after all acute coronary syndromes is 2 to 3%, and around 5% following myocardial infarction. Post-infarct complications such as heart failure continue to be a major contributor to cardiovascular morbidity and mortality. Inadequate microvascular reperfusion leads to worse clinical outcomes and potentially strategies to reduce infarct size during periods of ischemia–reperfusion can improve outcomes. Many strategies have been tested, but no single strategy alone has shown a consistent result or benefit in large scale randomised clinical trials. Herein, we review the historical efforts, current strategies, and potential novel concepts that may improve myocardial protection and reduce infarct size.

1. Introduction

Risk factor modification, in combination with prompt revascularization and optimal medical therapy, has led to a reduction in the morbidity and mortality associated with myocardial infarction (MI) [1]. However, one-month mortality following an infarct is still in the order of 2.5 to 5% and post-infarct conditions (e.g. myocardial dysfunction and heart failure) continue to be major contributors of morbidity and mortality and impact on health care economics worldwide [1,2]. Irrespective of strategies aimed at prompt revascularization of occluded epicardial arteries in the catheterization laboratory, thrombosis, embolization and release of harmful substances to the myocardium persist in the peri-infarct period. The associated reperfusion injury can result in further harm and adversely affect the long-term prognosis after MI by increasing the infarct size [1,2].

The microvascular status remains a strong prognostic marker [3]. Infarct size correlates with left ventricular (LV) systolic dysfunction, presence of arrhythmias, morbidity, and mortality following an acute MI [4]. The importance of infarct size and increase in LV volumes has been shown in acute ST-elevation MI (STEMI) treated with reperfusion therapy [4]. Various strategies can be used to measure the infarct size such as bio-markers, technetium-99 m sestamibi single-photon emission computed tomography (SPECT) myocardial perfusion imaging, and cardiac magnetic resonance imaging (CMR) [5]. Strategies to reduce infarct size during periods of ischemia–reperfusion can lead to improved LV function [6,7].

Herein, we review the currently available therapies for myocardial protection (i.e., for the prevention of injury associated with an acute MI and reperfusion), while highlighting novel and cost-effective strategies to reduce infarct size.

2. Pathogenesis

2.1. Ischemic cascade

The myocardial territory supplied by the infarct-related artery (IRA) undergoes biochemical changes at the cellular level. Myocardial cells enter a state of ischaemia, switching the metabolism to anaerobic form, which leads to accumulation of lactate, cellular acidosis, increased intracellular calcium, and production of reactive oxygen species (ROS), all contributing to apoptosis.

2.2. Microvascular obstruction

Microvascular obstruction (MVO) is the inability of a previously ischemic myocardium to be reperfused despite having achieved patency of the epicardial vessel supplying the region of myocardium [8].

The incidence of MVO can be as high as 67% in patients presenting with STEMI and treated with primary percutaneous coronary intervention (PPCI), despite achieving thrombolysis in myocardial

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infarction grade 3 (TIMI 3) flow in the epicardial coronary artery [9]. MVO is associated with major adverse cardiac events (MACE) rates of 30% at 1 month and 60% at 12 months [10–12]. MVO results from a combination of an inflammatory state, endothelial dysfunction, apoptotic cell death, and associated vasoconstriction in the myocardial bed [13,14].

2.3. Reperfusion injury

Reperfusion injury may occur during the restoration of flow in occluded coronary arteries. This injury is thought to be due to free radicals, calcium build-up, acidosis, inflammation and accumulation of neutrophils. All these changes lead to the opening of the mitochondrial permeability transition pore (MPTP) and cell death.

The reperfusion era has seen great strides in the therapeutic strategies leading to improved survival of patients presenting with an acute MI [10,11] and there are continued efforts to reduce the reperfusion-associated injury.

2.4. No-reflow phenomenon

No-reflow phenomenon is defined as inadequate myocardial perfusion through a given segment of the coronary circulation without angiographic evidence of mechanical vessel obstruction [15]. No-reflow is possibly due to MVO alongside other mechanisms such as myocardial stunning, ischaemia-reperfusion injury, autonomic dysfunction and microvascular constriction, free radical-induced myocardial injury as well as neutrophil and platelet micro-aggregates causing luminal obstruction of the microvasculature [16]. No-reflow phenomenon has been linked to larger infarct size and poorer outcomes [17].

3. Assessing infarct size

An electrocardiogram is the earliest and perhaps the easiest way to gain information regarding infarct size. Infarct size can be estimated from the extent of ST-segments deviations (elevation and depression) as well from the number of leads affected. ECG can be used to assess the efficacy of various reperfusion therapies. However, this is imprecise and has been shown not to correlate well with imaging studies [18,19]. Attempts at quantifying final infarct size by using formulae to calculate the myocardium at risk, such as Aldrich score was employed in the thrombolytic era [20]. Infarct size can be measured using biomarkers or imaging. Peak levels of creatine kinase isoenzyme MB (CK-MB) and troponin have been studied [21–25]. Although biomarkers are useful in giving a rough estimate of the infarct size, their use is limited because of reperfusion affecting the enzyme kinetics and difficulty in determining peak values [5]. There is a significant correlation between individual time-point, peak, and area-under time-concentration curve (AUC) of these biomarkers determined infarct size in comparison with SPECT. The AUC and peak levels of troponin I at 72 h have strong predictive correlation as compared to troponin T [26]. It is important to note that it is less practical to generate AUC curves from troponins, as opposed to CK, as they are elevated for a longer time and hence a peak value of a troponin measured at a specific time can be a more useful in in daily practice [27]. A single point measurement can be as useful in infarct size estimation as compared to a measurement derived from the area under the curve.

Imaging modalities such as Tc99 Sestamibi SPECT imaging and CMR have been widely studied [28–30]. SPECT Sestamibi imaging has been used as endpoints in several randomized trials [31,32]. It is good at detecting transmural infarcts. However, CMR with superior spatial resolution has improved ability to detect smaller, sub-endocardial infarcts and has emerged as the gold standard in assessing infarct size [33,34]. CMR is also able to evaluate other useful parameters such as microvascular obstruction (MVO), salvaged myocardium, and myocardium at risk and predict ventricular dysfunction [35,36]. In addition CMR indices have been shown to provide independent prognostic information [37]. Echocardiographic assessment of global and regional left ventricular function can be used but these are indirect measurements and influenced by variety of factors [38]. Advanced echocardiographic techniques such as global longitudinal strain by 2D speckle tracking and wall motion score index have been studied and shown to correlate with infarct size of CMR [39,40]. These techniques may prove to be quick and easy methods to assess infarct size and predict prognosis at the bedside. The various methods commonly employed to assess infarct size has been summarized in Table 1.

The index of microcirculatory resistance (IMR) was developed as an invasive measure of microvascular status, utilizing a pressure and temperature sensitive guidewire [41,42]. In a recently published trial involving 283 STEMI patients, IMR greater than 40 was associated with larger infarct size on CMR [43]. This may be a useful tool to risk stratify patients in the cardiac catheterization laboratory.

4. Therapies for infarct size reduction

There are various potential strategies for infarct size reduction [Figure 1]. Efforts to minimize the myocardial damage can be started even before the patients' presentation to hospital, and various mechanical and pharmacological agents can be tried during the hospital stay and continued even after discharge to have best clinical outcomes. These efforts for emerging therapies are ongoing, and large-scale randomized clinical trials are needed to investigate the clinical applicability of various strategies.

4.1. Mechanical interventions

4.1.1. Primary angioplasty and timing of stenting

Primary percutaneous coronary intervention (PPCI) is the current gold standard worldwide for the treatment for STEMI, with strong evidence supporting the benefits of PPCI over thrombolysis [44]. When compared to fibrinolysis, PPCI leads to better ST segment elevation resolution, arterial patency, and reduced infarct size [45]. However, PCI of an athero-thrombotic lesion during STEMI, can lead to distal embolization of debris, further augmenting MVO, infarct size, and other harmful sequelae [46]. Therefore, various interventions can be used in an attempt to reduce this risk.

In order to minimize the damage associated with stenting, a strategy of delaying the stenting tested. There were initial results from a small study showing benefit in a delayed stenting strategy in patients with the patent infarct related artery [47]. This was followed by the larger randomized DEFER-STEMI study (Randomized Trial of Deferred Stenting Versus Immediate Stenting to Prevent No- or Slow-Reflow in Acute ST-Segment Elevation Myocardial Infarction), which also supported a strategy of deferred stenting with lesser no-reflow/slow flow, fewer thrombotic events and increased myocardial salvage [48]. However, the Danish Study of Optimal Acute Treatment of Patients with ST-segment Elevation Myocardial Infarction: DEFER and the Mechanical Intervention Approach in Acute ST-Segment-Elevation Myocardial Infarction: The MIMI Study failed to show the benefit of such strategy [49,50]. The Deferred versus conventional stent implantation in patients with ST-segment elevation myocardial infarction (DANAMI 3-DEFER) study was a large open-label randomized controlled trial that randomized patients to immediate and delayed stenting strategies. This study also failed to show any difference in the occurrence of death, heart failure, myocardial infarction, or repeat revascularization [51].

More recently, the INNOVATION Study (Impact of Immediate Stent Implantation Versus Deferred Stent Implantation on Infarct Size and Microvascular Perfusion in Patients With ST-Segment–Elevation Myocardial Infarction) randomized 114 patients to immediate stenting or deferred stenting. The overall infarct size and MVO were not significantly different between the groups [52]. However, in anterior wall MI,

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deferred stenting strategy seemed to have beneficial effects on infarct size and MVO.

MVO assessed by CMR after MI has been shown to be related to ischaemic time (time between symptom onset and successful restoration of blood flow) as opposed to the mode of reperfusion therapy, highlighting the importance of early reperfusion in reducing MVO [53].

There is convincing evidence that early revascularization with primary PCI helps in infarct size reduction. A strategy of deferred stenting cannot be recommended at this stage.

4.1.2. Distal protection devices

Embolic protection devices (EPD) are intended to capture and remove debris generated during the various interventional procedures, with the ultimate aim of reducing myocardial damage. Various EPDs have been used in an attempt to reduce adverse distal embolization [54–61]. In contrast to their benefit in vein graft interventions, the evidence regarding the utility of these devices in preserving myocardium viability during STEMI has been disappointing [Table 2].

4.1.3. Thrombectomy

Thrombectomy during acute MI has shown conflicting results. There is some evidence that manual thrombectomy can reduce infarct size and preserve microvascular integrity as assessed by CMR [62]. On the other hand, a meta-analysis suggested that it may be associated with harm [63]. The Intracoronary Abciximab and Aspiration Thrombectomy in Patients with Large Anterior Myocardial Infarction (INFUSE-AMI) trial showed no benefit in infarct size reduction [64]. Initially, there was much enthusiasm with the publication of the TAPAS (Thrombus Aspiration during Percutaneous Coronary Intervention in Acute Myocardial Infarction Study) trial that showed benefits of using routine thrombus aspiration, not only in improving reperfusion as assessed by TIMI blush grade, but also in reducing mortality [65,66]. It led to changes in guideline recommendation in favor of mechanical thrombectomy. Later, the larger TASTE (Thrombus Aspiration in ST-Elevation Myocardial Infarction in Scandinavia) trial showed no improvement in both 30-day and 1-year mortality with routine aspiration thrombectomy [67]. Finally, TOTAL (Trial of Routine Aspiration Thrombectomy with PCI versus PCI Alone in Patients with STEMI) trial proved that routine manual thrombectomy in STEMI patients did not improve clinical outcomes [68]. A sub-study of TOTAL demonstrated that routine thrombectomy during PPCI has no beneficial impact on myocardial blush grade or post-PCI TIMI flow grade. There was reduced distal embolization associated with thrombectomy group in comparison to PCI alone group [69].

TAPAS trial was a relatively small single centre trial with the very high use of GP2b3a inhibitors. It was underpowered to detect differences in the secondary endpoints. Some of the differences between the three trials are summarized in Table 3.

The contradictory findings between TAPAS and the other two trials may be due to some of the differences such as the use of GP2b3a inhibitors, direct stenting and use of balloon predilatation. TASTE and TOTAL trials were conducted in different eras with significant differences in anti-thrombotic pharmacotherapies, increased use of radial access for PCI and improved stent technology. Ultimately, the discrepancy between the trials underscore the importance of performing clinical trials with sufficient power, once smaller trials suggest an effect of intervention or medication.

Recently, a meta-analysis using individual patient level data from TAPAS, TASTE and TOTAL trials, concluded that routine thrombus aspiration did not improve clinical outcomes [70]. However, in those patients with highest thrombus burden, thrombus aspiration was associated with reduced cardiovascular death at the expense of higher risk of stroke or transient ischaemic attack (TIA).

There are clear limitations to the current technology available in aspiration thrombectomy, such as iatrogenic thrombus embolization during the crossing of the lesion with a guide wire, difficulty in treating large organized thrombi, potential displacement of thrombi into other vessels and systemic circulation during removal of the aspiration catheter. It is possible that as technology improves, especially if the risk of stroke is mitigated, mechanical thrombectomy may prove a useful strategy in infarct size reduction.

The use of mechanical and aspiration thrombectomy has limited impact on infarct size reduction and is not recommended for routine use.

4.1.4. M guard stents

Polyethylene terephthalate micronet mesh-covered stent (M guard, Inspire-MD, Israel) was designed to prevent distal embolization by facilitating the capture of thrombus behind the mesh covering the stent. M guard has shown superior rates of epicardial coronary flow and complete ST-segment resolution in comparison to bare metal stent [71].

However, one trial revealed higher target lesion revascularization (TLR) rates associated with M guard stents, raising questions about their long-term safety profile [72]. Nonetheless, there is compelling evidence from clinical trials as well as registries showing improved outcomes in acute MI patients treated with this stent [73].

Table 1
Methods to assess infarct size. ECG- electrocardiogram, SPECT- single photon emission computed tomography.

Method	Advantages	Disadvantages
ECG	Easily available. Available in an emergency.	It provides an indirect measure of infarct size that can be quantitative by utilization of various scores.
Biomarkers	Easily available. Available in an emergency	Need for repeated sampling for peak levels, affected by reperfusion. True troponin AUCs is not a practical approach.
Echocardiographic techniques	Easily available. Available in emergency	Operator dependent, not widely used outside the research setting.
Tc99 Sestamibi SPECT imaging	Can assess full thickness infarcts. Not available in an emergency	The low spatial resolution, hence misses sub-endocardial infarcts; need for radioactive tracer with limited shelf life and use of ionizing radiation.
Cardiac MRI	Current gold standard; high spatial resolution; can detect sub-endocardial infarcts better. not available in an emergency	Not widely available, cannot be used in patients with metal implants or those who have claustrophobia. Not available in the emergency setting.
Index of micro-circulatory resistance (IMR)	The numerical value for myocardial resistance Correlates with infarct size on CMR. Useful for prompt decision-making in the catheterisation laboratory.	Invasive technique Requires adenosine to induce hyperaemia.

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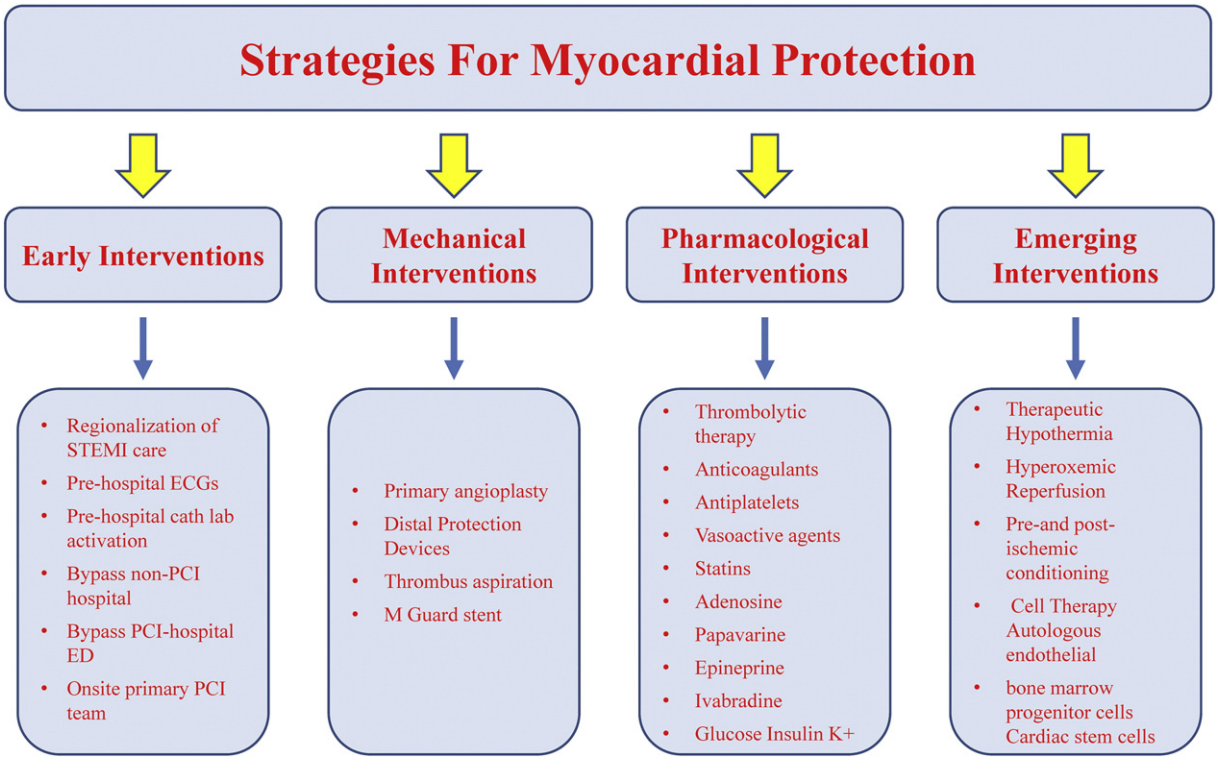

Fig. 1. Various potential strategies for infarct size reduction.

Further trials are needed to test the concept of covered stent platforms in STEMI.

4.2. Pharmacological therapies

4.2.1. Thrombolytic therapy

Although thrombolysis is a well validated and widely used therapy, it restores coronary perfusion in only 60–80% of cases [74,75].

Large-scale clinical trials have demonstrated infarct size reduction and improvement in regional and global LV function in patients where intravenous thrombolytic therapy has been successful [76]. It has been reported that intracoronary thrombolysis with primary PCI leads to improved myocardial perfusion and TIMI blood flow as shown in data from a pilot study [77] and a randomized trial demonstrating that intracoronary streptokinase administration immediately after PCI significantly improves infarct size and left ventricular volumes and function [78].

There is convincing evidence that a timely administration of intravenous thrombolytic therapy can help reduce the infarct size. Further studies are needed to test the effect of intracoronary fibrinolysis.

4.2.2. Anticoagulant therapy antiplatelet therapy

A wide variety of anti-coagulant and antiplatelet agents have been used in the treatment of acute myocardial infarction.

These agents have a potential role in infarct size reduction by having an impact on the no-reflow phenomenon and MVO, associated with embolization of particles during acute MI. There is a combination of fibrin and blood cells in the formation of these thrombi and hence logically we need a combination of antiplatelet and anticoagulants. The thrombi formation is a combination of activation of blood coagulation cascade as well as platelets. These mechanisms are linked to each other in a vicious cycle as, thrombin, is an enzyme generated by blood coagulation that leads to platelet activation.

The thrombo-embolic state during no reflow is composed of platelet aggregates with associated fibrin strands [79–81].

Different antiplatelet agents with their potential role in infarct size reduction are listed in Table 4. A high loading dose (600 mg) of clopidogrel has been shown to be more effective than low dose (300 mg) in reducing the CMR measured infarct size in patients undergoing PPCI for STEMI [82]. In a small study, upstream treatment with clopidogrel compared to those clopidogrel loading after reaching the catheterization laboratory was noted to have reduced MVO

Table 2
Trials of embolic protection devices.

Trial (year)	Number	Device	Findings
EMERALD (2005) [54]	501	Guard wire plus	No reduction in infarct size.
MICADO (2007) [55]	154	Guide wire	Better TIMI perfusion grade
ASPARAGUS (2007) [56]	341	Guide wire plus	No reduction in infarct size
PREMIAR (2007) [57]	140	Spider X	No benefit on myocardial perfusion/ejection fraction.
PROMISE (2005) [58]	200	Filter wire-EX	No improvement in perfusion
UPFLOW (2007) [59]	100	Filter wire-EX	No improvement in perfusion
DEDICATION (2008) [60]	626	Filter wire-EZ & Spider X	No improvement in perfusion
PREPARE (2009) [61]	284	Proxis embolic protection system	Rapid ST segment resolution. No difference in myocardial reperfusion.

The data suggest that distal protection devices have no clear beneficial role in infarct size reduction.

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Table 3
Differences between major thrombectomy trials..

Characteristic	TAPAS	TASTE	TOTAL
Number of patients randomized	1071	7244	10,732
Study design	Single-centre RCT	Swedish multicentre RCT	Multi-national multicentre RCT
Direct stenting	62%	15%	17%
GP2b3a use	92%	17%	40%
Primary end point	Post-procedural myocardial blush grade of 0 or 1	All-cause mortality at 30 days	CV death, recurrent MI, cardiogenic shock or NYHA IV heart failure at 180 days
Secondary endpoints	TIMI flow grade of 3, complete resolution of ST-segment elevation, the absence of persistent ST-segment deviation, TVR, reinfarction, death & MACE at 30 days	30-day rates of hospitalization for recurrent MI, stent thrombosis, TVR, TLR, and the composite of all-cause mortality or recurrent MI and during index admission, complications of PCI, stroke, heart failure, and length of stay in the hospital	Stent thrombosis or TVR within 180 days and cardiovascular death within 180, safety outcome of stroke within 30 days
Reperfusion	Improved	Not reported	Improved
Stroke at 30 days	Not reported	No difference	Increased
1-year mortality	Reduced	No difference	No difference
1-year recurrent MI, Stent thrombosis, TVR	No difference	No difference	No difference

RCT - randomized controlled trial, MI - Myocardial infarction, TVR - target vessel revascularisation, TLR - target lesion revascularisation, MACE - major adverse cardiac events, CV - cardiovascular.

although the infarct sizes were not different [83]. The newer generation of antiplatelet agents has shown promising results in clinical studies. The recently published CV-TIME trial randomized 76 STEMI patients to receiving clopidogrel or ticagrelor loading doses prior to Primary PCI. The index of microcirculatory resistance (IMR) measured immediately afterwards, wall motion score index assessed by echocardiography and peak cardiac enzyme (CK) levels were assessed, all of which were in favor of ticagrelor [84]. A post hoc analysis of the Complete Versus Lesion-Only PRImary PCI Trial-CMR (CvLPRIT-CMR) substudy found that newer antiplatelet agents (ticagrelor and prasugrel) were associated with reduced infarct size compared with clopidogrel in patients undergoing primary PCI [85]. Animal studies suggest that the benefit seen with ticagrelor as compared to clopidogrel was dependent on adenosine-receptor activation with downstream upregulation of endothelial nitric oxide synthase and Cyclo-oxygenase-2 activity [86]. Ticagrelor is also thought to have potential protective effects against ischemia–reperfusion injury, which is mediated by adenosine, due to its action on the adenosine transporter type 1 equilibrative nucleoside transporter (ENT1) leading to increased concentration of adenosine, particularly at sites of ischemia and tissue injury [87]. The ability of chronic ticagrelor use in reducing infarct size has been tested in a pre-clinical setting in comparison to clopidogrel [88]. The clinical benefits seen in the PLATO (The multicenter, randomized, placebo-controlled Platelet inhibition and patient Outcomes) trial [89] could potentially be due to cardio protective properties of ticagrelor. Prasugrel has less data supporting its role in infarct size reduction. There is evidence that prasugrel inhibits platelet–leukocyte interactions and may reduce platelet-mediated inflammatory responses [90].

There is conflicting evidence for the potential role of various anticoagulant therapies in infarct size reduction [91–94]. Newer antiplatelet agents, in particular ticagrelor seem to reduce infarct size as compared to clopidogrel.

4.2.3. Vasoactive agents

Vasoactive agents have shown potential in infarct size reduction by having an impact on the acute ischemic injury. These vasoactive agents can decrease the myocardial oxygen demand and increase the oxygen supply, and thereby have an impact on anaerobic metabolism and enhance the supply of nutrient agents at the site of ischemia and reperfusion [95,96].

Nitrates have potential to limit or prevent the vasoconstrictive impacts of various chemicals at the site of inflammation and myocardial injury. The potential antiplatelet effects of nitrates can prevent re-occlusion and re-thrombosis [97].

Calcium channel blockers have vasodilator properties as well as cytoprotective impact by reducing the impact of calcium into the damaged myocardial cells [98].

Beta blockers are thought to reduce the reperfusion associated injury. These agents reduce the myocardial oxygen demand and have a potential beneficial role in the supply–demand imbalance of severe myocardial ischaemia leading to infarction. There is limited evidence for the use of vasodilators such as alpha blockers, beta blockers, calcium channel blockers and nitrates/nitrite donors in reducing the infarct size [Table 4].

4.2.4. Statin therapy

Statin (HMG-CoA reductase inhibitor) therapy has been shown to be cardio-protective by reducing inflammation and atherosclerosis via cholesterol-dependent pathways as well as other pleiotropic effects independent of its cholesterol lowering properties [113]. One of the potential mechanisms is by increasing the NO synthetase and hence potential to reduce atherosclerosis [114]. Statin therapy has shown to inhibit the endothelial exocytosis and hence they have a beneficial effect on protecting the myocardium and reducing the infarct size [115].

The ability to reduce the infarct size and cardio-protection is demonstrated in various animal models as well in clinical settings [116–118]. Statin therapy has acute cardio-protective benefits that are independent of its cholesterol lowering properties. This acute impact may be decreased during chronic use; however chronic statin therapy still plays cardio protective roles by lowering the lipid load. Statins have been reported to exert beneficial effects on the nitric oxide pathway and reduce cardiac cell death in a number of cardiovascular disease states. It has also been suggested that simvastatin reduces no-reflow by activating the mitochondrial K(ATP) channel [119].

There is convincing clinical evidence confirming the cardio protective effect of statin pre-treatment in patients undergoing PCI [120,121].

HMG-CoA reductase inhibitor therapy has shown a reduction in infarct size in preclinical as well as in clinical settings.

4.2.5. Adenosine and A2A receptor agonists

There is conflicting evidence regarding the role of adenosine as a myocardial protection agent during STEMI [122]. Adenosine has been shown to reduce infarct size, if given early (within 120 min) [123],

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Table 4
Anti-thrombotic and vasoactive pharmacological agents tested in myocardial protection in both pre-clinical and clinical studies.

Agents	Preclinical evidence	Clinical evidence	Number of subjects	Findings
Anticoagulants				
UFH	–	HORIZON AMI HORIZON AMI CMRI sub-study	51	No difference in infarct size, MVO, LVEF, or LV volume in comparison to bivalirudin [91] Infarct size reduction when used in addition to bivalirudin [92]
Enoxaparin	Dog model	–	71	Significant reduction in infarct size [93]
Fondaparinux	–	OASIS 5	20,078	Non-inferior to enoxaparin in prevention of cardiac death, and MI [94]
Bivalirudin	–	HORIZON AMI CMRI sub-study	51	No benefit in infarct size reduction as compared to Heparin [91]
Anti-platelet agents				
Aspirin /NCX4016 (NO-aspirin)	Pig model	–	19	NCX4016 (nitro-derivative of aspirin), reduces the extent of myocardial injury following ischaemia and reperfusion Aspirin has no beneficial role in infarct size reduction [99]
Thromboxane synthetase inhibitors. Benzylimidazole and OKY-046	Dog model	–	72	Reduced infarct size [100]
Clopidogrel	–	Observational study	198	High dose (600 mg) reduced myocardial infarct size and improved myocardial salvage compared with a 300-mg loading dose [82]
Ticagrelor	Rat model	–	32	Ticagrelor protects against reperfusion injury [88]
Cangrelor	Monkey model	–	31	Significantly decreased infarct size by an amount equivalent to that seen with ischemic post conditioning [101].
Prasugrel	–	INFUSE AMI	452	Showed better, TIMI 3 flow, lower corrected TIMI frame counts, and lower infarct size [102]
Abciximab	–	Prospective randomized trial	200	Improved recovery of microvascular perfusion and myocardium at risk [103].
		RELAX MI	210	Improved ventricular function recovery [104].
Tirofiban	–	On-TIME2	984	Improved ST-segment resolution and clinical outcomes. [105]
Vaso-active agents				
Alpha blockers				
Urapidil/Phentolamine	–	Multicentre, prospective, non-randomized trial	40	Attenuates vasoconstriction and post ischemic LV dysfunction [106]
Beta blockers				
Metoprolol	–	METOCARD-CNIC	270	Reduced infarct size and improved left ventricular ejection. [107,108]
	–	COMMIT	45,852	Reduces the risks of reinfarction and ventricular fibrillation [109].
Calcium channel blockers				
Diltiazem (Intracoronary)	Dog model	–	25	Increases the salvage of myocardium [110]
Nitrates/Nitrites/NO donors				
Sodium nitrite	–	NIAMI Trial	229	No benefit in infarct size reduction [111]
Tilarginine	–	TRIUMPH	398	No benefit in infarct size reduction [112]

whereas late administration (after 3 h) was not beneficial [124]. AMISTAD and AMISTAD II (A randomized, double-blinded, placebo-controlled multicentre trial of adenosine as an adjunct to reperfusion in the treatment of acute myocardial infarction) trials have shown infarct size reduction after administration of adenosine [125]. As an adjunct to PCI, there is some evidence that adenosine given prior to PCI reduces the 'no-reflow' phenomenon [126]. As previously described, ticagrelor has pleotropic effects on adenosine receptors and is thought to exert protective effects independent of the anti-platelet activity.

There is evidence that adenosine and related substances help in reducing the infarct size.

4.2.6. Papaverine

Papaverine is an opiate derivative that vasodilates by direct relaxation of arteriolar smooth muscle and coronary arteriolar bed [127]. Intracoronary administration of papaverine attenuated angiographic no-reflow better than nitro-glycerine [128].

4.2.7. Epinephrine

Intracoronary administration of epinephrine has shown improvement in TIMI flow without serious adverse hemodynamic or chronotropic effects [129].

4.2.8. Ivabradine

Ivabradine acts on the I_f ion current, expressed in the sinoatrial node, and has shown benefit in preclinical and clinical settings. The infarct size reduction is independent of bradycardia, and we need to explore this pleiotropic action in future trials [130].

Papaverine, Epinephrine and Ivabradine has limited evidence in infarct size reduction.

4.2.9. Glucose, insulin, potassium (GIK)

The GIK has no beneficial role in myocardial protection [131]. The OASIS-6 (Organization for the Assessment of Strategies for Ischemic Syndromes-6) trial showed no beneficial impact [132]. The combined OASIS-6 and CREATE-ECLA trial had similar negative results. A meta-

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Table 5
Miscellaneous pharmacological agents used for infarct size reduction.

Agents	Evidence/Mechanisms
AdipoRon [145]	Protection against myocardial injury
Adiponectin [146]	Anti-inflammatory, anti-oxidant and anti-apoptotic
Apr Aliskiren [147]	Increases bradykinin and kallikrein levels
Bradykinin [148]	Inhibits apoptosis
BAY58 (guanylyl cyclase activator) [149]	Protection through post conditioning
Capsaicin [150]	Hypothermia induced protection
CTRP9 [151]	Reduction of adiponectin receptor 1
Cytochrome P450 inhibitors [152]	Role in Myocardial ischemia/reperfusion injury
Dark chocolate receptors [153]	Acts via-opioid receptor to produce cardiac protection
Epicatechin [154]	Improves mitochondrial function
Erythropoietin [155]	Renal nerve-mediated renal protection
Leptin [156]	Anti-inflammatory
Late sodium channel blockade [157]	Evidence in myocardial protection
Protein kinase C [158]	Ischemic post conditioning
Resvaratrol [159]	Antioxidant activity and upregulation of NO production
Sildenafil-mediated [160]	Up-regulating VEGF and Ang-1 system
Sevoflurane [27]	Infarct size reduction in cases of anterior MI.
Tadalafil [161]	Attenuates ischemic cardiomyopathy

analysis of 16 randomized trials did not reveal any mortality benefit for STEMI patients [133].

There is no role of GIK infusion in infarct size reduction.

4.2.10. Ischaemic conditioning

Ischaemic conditioning is a fascinating concept where intermittent occlusion of coronary arteries (local ischaemic conditioning) [134–136] or arteries to another part of the body or organ, commonly the upper limbs (remote conditioning) can lead to improved outcomes after myocardial injury. Remote ischaemic conditioning can be performed before an expected ischaemic insult (pre conditioning), during the evolution of an ischaemic insult (per-conditioning) or soon after the completion of an ischaemic insult (post conditioning) [137]. Although experts have proposed various theories, the exact mechanism is not fully known [137]. Remote ischaemic pre-conditioning has been shown to reduce infarct size in small trials [138,139] and larger trials and underway. A more recent meta-analysis also concluded that remote ischaemic pre-conditioning is effective and may reduce long-term clinical events [140]. There is, however, conflicting results from a large trial in patients undergoing CABG, where remote ischaemic pre-conditioning did not improve outcomes [141]. A trial studying post conditioning immediately after stenting during PCI did not show reduction in the incidence of peri-procedural myocardial injury or effect on long term outcome [142,143]. A recent systematic review and meta-analysis looking at a large body of evidence from a variety of clinical settings found that, the evidence does not support a clinically significant effect of ischaemic conditioning on all-cause mortality. Although, there was a suggestion that ischaemic conditioning may reduce myocardial ischaemia, stroke, and acute kidney injury, the authors concluded that the results were uncertain and that ischaemic conditioning cannot be recommended for routine use [144].

Ischaemic conditioning cannot be recommended as a strategy at present and large clinical trials are ongoing.

4.2.11. Miscellaneous agents used for infarct size reduction

A number of less commonly used pharmacotherapies have been tried in pre-clinical and clinical studies for infarct size reduction. They are summarized in Table 5.

4.3. Emerging strategies for infarct size reduction

There are continuous efforts and advances to help reduce the infarct size. Various emerging strategies [Fig. 1] have been evaluated in preclinical as well as in clinical settings with the potential to reduce the infarct size. A large number of these agents are in development and the list of potential strategies is likely to broaden. There are also experimental strategies being evaluated for prevention of adverse LV remodeling such as injectable bio-absorbable cardiac matrix. [162,163]

5. Summary

Numerous cardio-protective strategies have been tried to help reduce the infarct size. Although various agents have shown benefit in small proof of concept studies, identifying a single therapy specifically designed for infarct size reduction in large clinical studies has been unsuccessful so far. Keeping in view the available evidence in this field, clinicians can use their clinical acumen with evidence and can potentially employ a combination of various therapies tailored to individual high-risk patients to reduce the infarct size [164].

Further comparative, large scale, clinical studies and cost–benefit analysis are warranted to evaluate various cardio-protective strategies.

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