

## REVIEW ARTICLE

## Reperfusion Strategies in Acute Myocardial Infarction: State of the Art

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### Abstract

ST elevation myocardial infarction (STEMI) is a highly prevalent condition worldwide. Reperfusion therapy is strongly associated with the prognosis of STEMI and must be performed with a high standard of quality and without delay. A systematic review of different reperfusion strategies for STEMI was conducted, including randomized controlled trials that included major cardiovascular events (MACE), and systematic reviews in the last 5 years through the PRISMA (*Preferred Reporting Items for Systematic Reviews and Meta-Analysis*) methodology. The research was done in the PubMed and Cochrane Central Register of Controlled Trials databases, in addition to a few manual searches. After the exclusion criteria were applied, 90 articles were selected for this review. Despite the reestablishment of IRA patency in PCI for STEMI, microvascular lesions occur in a significant proportion of these patients, which can compromise ventricular function and clinical course. Several therapeutic strategies – intracoronary administration of nicorandil, nitrates, melatonin, antioxidant drugs (quercetin, glutathione), anti-inflammatory substances (tocilizumab [an inhibitor of interleukin 6], inclacumab, P-selectin inhibitor), immunosuppressants (cyclosporine), erythropoietin and ischemic pre- and post-conditioning and stem cell therapy – have been tested to reduce reperfusion injury, ventricular remodeling and serious cardiovascular events, with heterogeneous results: These therapies

### Keywords

Acute Myocardial Infarction/therapy; Myocardial Reperfusion; Myocardial Stunning; Ventricular Remodeling; Morbidity and Mortality.

need confirmation in larger studies to be implemented in clinical practice

### Prevalence

The worldwide prevalence of ischemic heart disease is approximately 111 million cases, with 7.3 million cases of fatal acute myocardial infarction (AMI) in 2015. The inadequate treatment of patients with AMI is associated with significant increases in morbidity and mortality.<sup>1</sup>

### Objectives

The objective of this systematic review is to evaluate the evidence of different reperfusion therapies in ST-segment elevation AMI (STEMI), selecting mainly randomized controlled trials and systematic reviews that address major cardiovascular clinical outcomes.

### Methods

The review was carried out in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA). We searched the PubMed database for the terms “acute myocardial infarction” and “reperfusion therapy”, which yielded 9,885 results. After applying the following search filters – type of abstract: “text and full text”; type of article: “meta-analysis, review, systematic review and randomized clinical trial”, and date of publication: “last 5 years”, and language: “English” – 127 articles were obtained. In addition, research was conducted at the Cochrane Central Register of Controlled Trials using the terms “acute myocardial infarction” and “reperfusion therapy”, in English, between 2018 and 2020, which revealed 64 clinical trials, already excluding duplicates. Of the 191

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articles, nine articles were selected manually and added to the review, as they were considered of high relevance to the topic. Of the 200 articles, 92 were removed after analysis of the abstracts and, after reading the full texts, 18 (12 in PubMed and 6 in the Cochrane database) of the 108 remaining were excluded for not addressing reperfusion, yielding a total of 90 references, which were included in this review.

## Results

### Revascularization Strategies

The invasive strategy is the treatment of choice for reperfusion of patients with high-risk non-ST elevation AMI (STEMI).<sup>1,2</sup> Delays in reperfusion therapy for patients with STEMI cause significant impairments in myocardial reperfusion.<sup>3</sup>

Patients with acute coronary syndrome (ACS), who had transient ST elevation, were analyzed before reperfusion, and no differences were found in the size of the infarction or in the rates of serious ischemic events.<sup>4</sup>

Hospital interventions for qualitative improvement in the care of patients with STEMI can improve myocardial reperfusion.<sup>5</sup> Difficulties in implementing reperfusion therapy include: delay in seeking care, absence of adequate pre-hospital emergency systems, absence of trained emergency services, inadequate hospital structure, absence of quality improvement and rehabilitation programs.<sup>6</sup>

### Thrombolytics

Thrombolytics are indicated for patients with STEMI in the first 12 hours of symptom onset, in cases where percutaneous coronary intervention (PCI)-related delay would be 120 minutes or more. Thrombolytics can be administered in the first 30 minutes of first medical contact, with no contraindications. Streptokinase is associated with higher mortality rates and lower reperfusion rates as compared with tissue plasminogen activator (tPA) and its recombinant forms – alteplase, tenecteplase (TNK) and reteplase. Therefore, a fibrin-specific agent should be chosen, since, although the administration of TNK in a single bolus is equivalent to accelerated tPA, in terms of reducing mortality in 30 days, it is safer in reducing non-cerebral hemorrhages and preventing blood transfusions, with easier administration.<sup>1,3</sup>

### Percutaneous Coronary Intervention (PCI) x Thrombolysis

In STEMI without previous fibrinolytic therapy, PCI is the best strategy for reperfusion of AMI when performed by experienced operators, ideally within the first 90 minutes of admission. Although thrombolysis allows early vascular reperfusion, with an average rate of infarct-related artery (IRA) patency of 50%, in PCI the rates are greater than 90%, with a reduction in the incidence of reinfarction.<sup>7</sup>

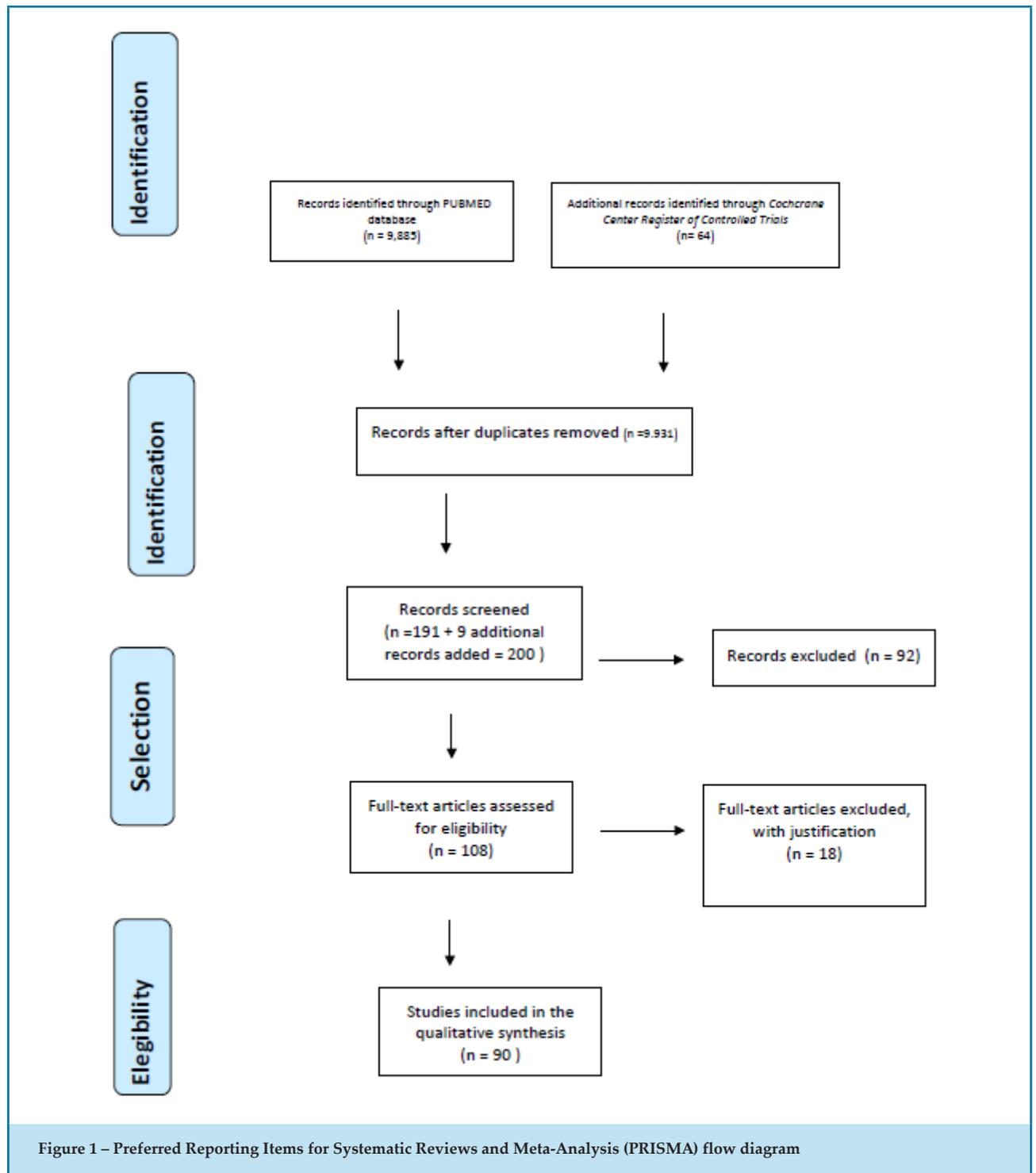
### Pharmacoinvasive Therapy

When a delay to primary PCI is suspected, fibrinolytic therapy should be immediately followed by the transfer, between 2 hours and 24 hours, to a coronary intervention center, for coronary angiography and PCI of the IRA, a strategy called “pharmacoinvasive therapy”, or for rescue angioplasty if there are no signs of reperfusion.<sup>1,2</sup> Although a superiority of the pharmacoinvasive strategy over thrombolysis with Tenecteplase has been shown, no differences were found after 8 years regarding major cardiovascular events (MACE).<sup>8</sup> Compared with primary PCI, the pharmacoinvasive strategy showed no differences in the occurrence of MACE in 30 days.<sup>9,10</sup> The pharmacoinvasive strategy using streptokinase reduced the size of the infarction and MACE, compared to conventional thrombolysis.<sup>11</sup> The effectiveness of the pharmacoinvasive strategy does not depend on initial troponin levels,<sup>12</sup> and the radial access was considered safe and effective in the pharmacoinvasive strategy.<sup>13</sup>

The EARLY-MYO Study demonstrated that in patients with STEMI presenting less than 6 h after symptom onset and expected delay to PCI, the pharmacoinvasive strategy with half-dose of alteplase was not inferior to PCI in complete epicardial and myocardial reperfusion evaluated defined as thrombolysis in myocardial infarction (TIMI) grade 3, TIMI perfusion grade 3 and resolution of the ST segment  $\geq 70\%$  in 60 minutes.<sup>14</sup> In patients who admitted within 6 hours of STEMI and underwent PCI, intracoronary administration of low doses of alteplase had no effect on the degree of microvascular obstruction or on clinical outcomes.<sup>15</sup>

### Electrocardiogram on Reperfusion

The reduction in QRS duration immediately after and 60 minutes after reperfusion was associated with its success, but the presence of QRS fragmentation had



an inverse correlation.<sup>16</sup> Incomplete resolution of ST-segment depression (reciprocal image of ST elevation) 90 minutes after PCI was correlated with larger infarctions and MACE.<sup>17</sup> The absence of ST resolution was poor prognostic factor after primary PCI, but complete resolution of the ST elevation was associated with an

increased risk of ST elevation at the time of discharge.<sup>18</sup> The complete resolution ( $\geq 70\%$ ) of the ST elevation, 60 minutes after PCI, was associated with greater reduction of MACE; however, the presence of diabetes mellitus and delay in reaching the hospital were deleterious to reperfusion.<sup>19</sup> Distortion of the terminal portion of the

QRS was associated with cardiac dysfunction.<sup>20</sup> The presence of Q wave on the initial ECG was associated with mortality, regardless of the time interval to peripheral PCI.<sup>21</sup> Early HR elevation  $\geq 100$  bpm was an independent prognostic marker.<sup>22</sup> Reperfusion arrhythmias, defined by accelerated idioventricular rhythm and ventricular extrasystoles with long periods of coupling, are well tolerated and may be related to the infarction size and reperfusion injury.<sup>23</sup> The peak of plasma troponin T occurs after 12 hours of type 1 AMI and after 6 hours of AMI successfully reperfused, with a second peak after 24 hours.<sup>24</sup>

Coronary flow (TIMI flow grades 0 or 1) before PCI is an independent risk factor for microcirculatory obstruction and size of AMI.<sup>25</sup>

### Thrombectomy in PCI

Embolization of thrombus fragments in PCI can lead to microcirculatory obstruction, with impacts on myocardial remodeling and prognosis.<sup>26</sup> In patients with a high thrombotic load in the IRA undergoing PCI, there was an improvement in coronary flow after the intervention with aspiration catheter, but without differences in the VCTs.<sup>26</sup> There were no differences regarding the effectiveness of coronary reperfusion between manual and mechanical methods.<sup>27</sup> The procedure should be reserved for patients with high thrombotic burden, and its routine use is not recommended, since it did not reduce MACE and increased the risk of stroke.<sup>1</sup>

### Stents at Primary PCI

There was a reduction in the target vessel revascularization rate, in favor of drug-eluting stents in relation to conventional stents in PCI, in addition to MACE reduction,<sup>27</sup> leading to the recommendation of eluted stent implantation as a preferred strategy.<sup>28</sup> The option of late stent implantation in PCI, with the objective of reducing microvascular obstruction, had no effect in reducing MACE, but increased the rate of revascularization of the target vessel.<sup>29</sup>

### Antiplatelet Therapy

The loading dose of acetyl salicylic acid (162 mg to 325 mg) should be administered shortly after the diagnosis of AMI, followed by low maintenance doses (75-100 mg) indefinitely, as they are equally effective as larger doses for MACE reduction, but causing less bleeding.<sup>1</sup>

### P2Y<sub>12</sub> Inhibitors

Clopidogrel is an irreversible inhibitor of the adenosine diphosphate (ADP) platelet receptor P2Y<sub>12</sub>, being recommended in acute coronary syndromes (ACSs), regardless of the performance of primary PCI. The addition of clopidogrel reduces the risk of CVMS in patients with SCASST, treated or not with PCI.<sup>30,31</sup> In patients with STEMI treated with thrombolysis, clopidogrel also significantly reduces MACE, without increasing hemorrhagic outcomes.<sup>32,33</sup> A loading dose of clopidogrel (300 mg) is recommended in patients <75 years of age, after fibrinolysis.<sup>34</sup>

Clopidogrel requires conversion of hepatic cytochromes to the active form. The activity of the C19 allele has great variation in the population, increasing the risks of thrombotic events. Clopidogrel has a relatively small antiplatelet potency and a slow onset of action, which is a disadvantage, especially in patients treated with PCI, who have considerable thrombotic burden. The onset of action of ticagrelor and prasugrel is, respectively, 30 minutes and 60 minutes.<sup>7</sup> Prasugrel was shown to be superior to clopidogrel in patients with ACS undergoing PCI, with reductions in the rates of death from cardiovascular causes, infarction, stroke, and a 52% relative reduction for stent thrombosis. However, rates of major bleeding and life-threatening bleeding were greater in patients receiving prasugrel compared with clopidogrel. There were no benefits in patients with cerebrovascular disease, individuals older than 75 years or those with a body weight less than 60Kg.<sup>35</sup> Ticagrelor, a direct-acting and reversible P2Y<sub>12</sub> inhibitor, with a shorter duration of action, was superior to clopidogrel in ACS, both in invasive and conservative strategies, with a decrease in MACE and mortality (by 22%) rates, but higher rate of major bleeding not related to CABG. Although not significantly, there was a higher incidence of sinus pauses and dyspnea in patients taking ticagrelor than in those taking clopidogrel.<sup>36</sup> Another study obtained favorable results for ticagrelor administered before PCI.<sup>37</sup>

Morphine prolongs gastric emptying and delays the onset of action of prasugrel, ticagrelor and clopidogrel.<sup>7</sup> In the absence of contraindications, ticagrelor and prasugrel are recommended, preferably, in ACSs.<sup>1,2,38</sup>

There were no differences in reperfusion rates before PCI when ticagrelor was initiated in the ambulance (prehospital treatment) than in the catheterization laboratory; but prehospital treatment reduced rates of stent thrombosis and MACE.<sup>39</sup> Diabetics had lower rates

of reperfusion and a higher incidence of MACE, with a large increase in stent thrombosis.<sup>40</sup> The comparative analysis of the administration of clopidogrel, prasugrel or ticagrelor in the emergency room in patients treated with PCI, showed a superiority of prasugrel and ticagrelor over clopidogrel, regarding reperfusion rates pre- and post-PCI.<sup>41</sup> In STEMI, the administration of intravenous agents that are extremely fast and potent, such as cangrelor, may be advantageous for patients who have not received P2Y12, patients with hemorrhagic complications or for whom surgery is indicated.<sup>7,38</sup> In patients with STEMI, when compared with ticagrelor, cangrelor produced greater inhibition of P2Y12 receptors, but there were no differences regarding coronary microvascular function and infarct size.<sup>42,43</sup> The TREAT study compared clopidogrel with ticagrelor after fibrinolytic therapy, with no differences in the incidence of VCT or severe bleeding after one year, which suggests the use of ticagrelor 24 hours after STEMI, initially treated with chemical thrombolysis.<sup>44</sup>

### GPIIb/IIIa (IGP) Inhibitors

PGIs (abciximab, tirofiban and eptifibatide) are potent and fast inhibitors. There is no evidence of the benefits of the administration of PGI with contemporary dual oral antiplatelet therapy in patients with ACS; however, as it can increase the bleeding risk, PGIs are recommended in situations where there is a significant thrombotic burden in PCI.<sup>7,37</sup> The inability to reperfuse a myocardial region, despite the opening of the IRA, is an independent prognostic factor, whose mechanisms are microembolization, reperfusion injury, endothelial dysfunction, myocardial edema, microcirculation vasospasm, and neutrophil aggregates.<sup>45</sup> Selective injection of tirofiban through a catheter showed improvement in reperfusion in patients with STEMI and high thrombotic load, but without differences in VCT.<sup>46</sup> The intracoronary (ic) injection of tirofiban was superior to intravenous administration regarding reperfusion parameters, left ventricular ejection fraction (LVEF), but with no differences in VCT or hemorrhagic outcomes.<sup>47</sup> Another study compared intralesional versus intracoronary administrations of PGI in patients with ACS and demonstrated a superiority of the first strategy.<sup>45</sup> The COCKTAIL II trial<sup>48</sup> also showed advantages of the intralesional administration of abciximab over intracoronary injection, in terms of better reperfusion.<sup>48</sup>

### Statins and Reperfusion

A meta-analysis of treatment with high-dose statins before PCI revealed improvement in reperfusion and a 47% reduction in MACE with atorvastatin in ACS patients, who had not received statins previously. No benefits were found with rosuvastatin.<sup>49</sup> A study showed that the administration of 80 mg of atorvastatin before PCI reduced the incidence of no-reflow and MACE, and increased survival.<sup>50</sup>

### Reperfusion Injury

Despite the restoration of the IRA patency in PPCI, microvascular lesions occur in a large proportion of these patients, which can compromise ventricular function and clinical outcome. The REDUCE-MVI trial showed no differences in microcirculatory resistance rates in patients undergoing PCI and treated with ticagrelor or prasugrel, resulting in similar infarction sizes.<sup>51</sup>

The ic administration of adenosine or sodium nitroprusside in patients with STEMI did not reduce the size of the infarction or the degree of microvascular obstruction.<sup>52</sup> The ic infusion of insulin-like growth factor after primary PCI improved ventricular remodeling.<sup>53</sup> Several trials have shown that both intravenous and ic administration of nicorandil in primary PCI improved reperfusion, left ventricular function and MACE<sup>54-57</sup> rates.

A meta-analysis of experimental studies demonstrated benefit with treatment with nitric oxide in reducing reperfusion injury and size of AMI.<sup>58</sup> The ic administration of nitrate reduced systemic inflammatory activity.<sup>59</sup> There was a reduction in the incidence of ventricular tachycardia with the use of ic nitrite in patients undergoing PCI.<sup>60</sup>

Liraglutide administered 30 minutes before PCI reduced the no-reflow rates and decreased the concentration of C-reactive protein, however, there was no difference in the incidence of ECVI.<sup>61</sup>

Intravenous or ic administration of melatonin was not associated with a reduction in the size of AMI and increased left ventricular remodeling;<sup>62</sup> however, when administration was early, it reduced the size of the infarction.<sup>63</sup>

The ic injection of morphine did not reduce the size of the AMI in patients undergoing PCI.<sup>64</sup> There was no reduction in the size of AMI in patients

treated with a mineralocorticoid receptor antagonist before reperfusion, but there was an improvement in left ventricular remodeling.<sup>65</sup>

There was no reduction in MACE with the administration of intravenous erythropoietin after reperfusion.<sup>66</sup> In addition, the ic injection of erythropoietin, before reperfusion, did not reduce the size of the AMI or the left ventricular remodeling.<sup>67</sup>

In patients undergoing PCI, intravenous injection of cyclosporine did not reduce MACE or left ventricular remodeling.<sup>68</sup> Other trials have also failed to demonstrate a favorable impact of intravenous cyclosporine administered prior to PCI.<sup>69-71</sup>

The intravenous infusion Quercetin (antioxidant) during reperfusion of ARI improved the clinical course of the disease, accelerating the onset of reperfusion.<sup>72</sup>

An experimental study showed attenuation of reperfusion myocardial injury with artesunate administration (an antimalarial substance).<sup>73</sup>

The infusion of Glutathione (antioxidant), before PCI, showed a reduction in the production of hydrogen peroxide and an increase in nitric oxide, which may improve cardiomyocyte survival.<sup>74</sup>

It was found that the monoclonal antibody against P-Selectin (Inclacumab), administered before PCI, reduced the size of the infarction. The ic administration of anisodamine improved reperfusion and reduced MACE.<sup>75</sup>

Also, interleukin-6 (IL-6) can participate in reperfusion injury. The IL-6 receptor antagonist, tocilizumab, was tested in STEMI, before coronary angiography, with a reduction in the systemic inflammatory response and troponin release.<sup>76</sup>

## Stem Cells

The administration of granulocyte-colony stimulating factor (G-CSF) did not influence the size of the AMI, left ventricular function or ECV in patients with AMI that underwent PCI.<sup>77</sup>

The ic infusion of autologous bone marrow stem cells (ABMC) 24 hours after PCI did not increase LVEF, but increased the rate of myocardial salvage.<sup>78</sup> The ic injection of primitive stromal cells after reperfusion increased the viability in the AMI territory and LVEF.<sup>79</sup> The TECAM trial<sup>80</sup> analyzed the ic injection of ABMC or subcutaneous G-CSF in the STEMI and showed no differences in left ventricular function.

A meta-analysis on ABMC to treat AMI showed that the ic infusion of ABMC led to an increase in LVEF and reduction of ventricular remodeling in up to 12 months, and was considered a safe and effective treatment in patients with AMI.<sup>81</sup>

In addition, a laser therapy applied to the tibia bone before and 24 and 72 hours after PCI reduced the troponin-T levels, with few adverse effects, but no differences were found in LVEF.<sup>82</sup>

## Ischemic Postconditioning

Ischemic postconditioning was assessed for recanalization of the IRA, through four repetitions of balloon occlusion, with no reductions in mortality and hospitalization rates for heart failure.<sup>83</sup> Another study on remote ischemic postconditioning in the upper limb, after PCI, demonstrated a reduction in the plasma release of CK-MB and an increase in LVEF and glomerular filtration rate.<sup>84</sup> Another study on ischemic postconditioning showed improvement in reperfusion and size of AMI.<sup>85</sup> Remote ischemic preconditioning uses brief cycles of cuff insufflation and deflation to protect the myocardium from reperfusion injury. A meta-analysis showed favorable results for this strategy, including higher myocardial salvage rate, reduced infarct size and reduced MACE.<sup>86</sup> The increase in plasma concentrations of the soluble tumor necrosis factor (TNF)-related apoptosis-inducing ligand (sTRAIL) after reperfusion was related to a reduction in the size of AMI and improvement in LVEF.<sup>87</sup> There were reductions in the size of AMI and reperfusion injury with ischemic postconditioning, in patients admitted for less than four hours.<sup>88</sup> A trial on remote ischemic preconditioning did not show changes in the rates of death and heart failure at 12 months of follow-up.<sup>89</sup>

## Multivessel Coronary Artery Disease

The AIDA STEMI trial analyzed patients with STEMI and multivessel coronary artery disease and found a higher prevalence of diabetes and advanced age when compared to patients with single-vessel disease. There were no differences in the reperfusion rates between the two groups, but those with multivessel disease had higher MACE rates over a year.<sup>90</sup>

## Conclusions

An effective reperfusion of STEMI, in a timely manner, defines the prognosis. Patients should be

selected for primary angioplasty or thrombolysis, followed by PCI in 24 hours (pharmacoinvasive therapy). Fibrin-specific agents are superior to streptokinase. Anticoagulant and dual antiplatelet therapy have evolved substantially in recent years, with a reduction in severe ischemic outcomes, such as death, reinfarction and stroke. The time factor and the experience of the interventionists are paramount in decision making for primary PCI. PCI has advanced in recent years, notably with the development of state-of-the-art drug-eluting stents. Even with an adequate opening of the IRA in PCI, there may be a failure in coronary microcirculatory reperfusion. Several clinical trials have tested different substances and different strategies, with inconclusive results regarding the improvement of tissue reperfusion, preservation of ventricular function and reduction of serious ischemic outcomes. Larger randomized controlled studies will be needed to test these therapeutic possibilities.

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## Author Contributions

Conception and design of the research: Rangel FO. Acquisition of data: Rangel FO. Analysis and interpretation of the data: Rangel FO. Writing of the manuscript: Rangel FO. Critical revision of the manuscript for intellectual content: Rangel FO.

## Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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## Study Association

This study is not associated with any thesis or dissertation work.

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