# No Reflow Phenomenon in ST-segment elevation myocardial infarction (STEMI)

1st author
Rekha V
Department of Cardiovascular Technology
Manipal College of Health Professions
Maniapl Acadamy of Higher Education
Manipal, Udupi District, Karnataka , India
Ph no: +91 9663682484
Email: rekha.v@manipal.edu

Contribution : Drafting the work and revisied it critically for important intellectual content AND Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

**Corresponding author**
Dr. Padmakumar R
Departnment of Cardiology
Kasturba Medical College
Maniapl Acadamy of Higher Education
Manipal, Udupi District, Karnataka , India
Ph no: +91 9900921428
Email: padma.kumar@manipal.edu

Contribution: Substantial contributions to the conception of the work AND Final approval of the version to be published

Next author
Dr. Sudhakar Rao
Departnment of Cardiology
Kasturba Medical College
Maniapl Acadamy of Higher Education
Manipal, Udupi District, Karnataka , India

Contribution: served as scientific advisors AND critically reviewed the study proposal

Next author
Dr. Krishnananda Nayak
Department of Cardiovascular Technology
Manipal College of Health Professions
Maniapl Acadamy of Higher Education
Manipal, Udupi District, Karnataka , India

Contribution: served as scientific advisors AND critically reviewed the study proposal

**Key Messages**

1. Coronary no-reflow (NR) significantly lead to increased mortality and LV dysfunction. Although it is a known phenomenon and has been studied for several years, there is currently no treatment that has demonstrated clear efficacy in terms of reduction of clinical adverse events. Hence we have reviewed the treatment options available for no reflow phenomenon.
2. However, in absence of alternative proven therapy administration of vasodilators should be considered mainly adenosine, verapamil, nicorandil, nitroprusside and epinephrine.
3. Also Manual thrombus aspiration can be used when there is angiographic evidence of large thrombus burden thereby improving the angiographic outcomes.

## No Reflow Phenomenon in ST-segment elevation myocardial infarction (STEMI)

### Abstract

**Objective :**
Primary PCI (PPCI) is the preferred reperfusion strategy STEMI patients. Coronary no-reflow (NR) is characterized by inadequate myocardial perfusion without angiographic evidence of mechanical obstruction. NR significantly lead to increased mortality and LV dysfunction. The objective of the review is to provide a comprehensive overview of the pathogenesis, predictors, diagnosis, and management of NR.

**Design:**
Data were reviewed from various scientific databases including primary and secondary sources to contribute various phenomenon of NR.

**Results:**
NR has been reported in up to 60% of STEMI patients with optimal coronary reperfusion. NR phenomenon remains a significant contributor to the morbidity and mortality burden of STEMI. NR is caused by a functional/structural change in the coronary circulation, with distal embolization, ischemia, reperfusion injury, and individual sensitivity to microvascular damage being the key pathophysiological mechanisms. Leukocyte infiltration, vasoconstriction, activation of inflammatory pathways, and cellular edema are other contributors of NR. A combined approach involving pharmacological and non-pharmacological interventions may be the best way to improve the prognosis of NR. These interventions aim to minimize the thrombus burden, augment microvascular function, mitigate reperfusion or regenerate the damaged myocardium. PPCI-related NR can be treated with certain drugs like adenosine and nicorandil. In the high thrombus burden, thrombectomy and/or embolic protection devices should be used to prevent NR

**Conclusion:**
Early detection, preventive measures, and treatment of no-reflow may alter the outcome of PCI. Reducing infarct size with early revascularization and pharmacological therapy is one of the most effective approaches to lowering the occurrence of NR.

**Keywords:** myocardial infarction; no-reflow; percutaneous coronary intervention; acute coronary syndrome

## INTRODUCTION

Cardiovascular disease (CVD) is frequent and one of the leading causes of death worldwide. The most severe form of acute coronary syndrome is ST-segment elevation myocardial infarction (STEMI)[1,2]. Primary percutaneous coronary intervention (PPCI) is the preferred reperfusion strategy for treating acute ST-segment elevation myocardial infarction[1,3,4]. The major objectives are restoring arterial patency in the epicardial artery and establishing microvascular reperfusion. Up to 95% of occluded coronary vessels can be reopened in the setting of STEMI. Despite restoring epicardial flow following PPCI, a considerable proportion of patients still have reduced myocardial perfusion, termed the no-reflow phenomenon (NR)[5]. According to Kloner et al. [6], NR is defined as suboptimal myocardial reperfusion through a portion of the coronary circulation without angiographic evidence of mechanical vessel obstruction. No reflow, also known as thrombolysis in myocardial infarction (TIMI) flow grade and myocardial blush grade between 0 to1, is characterized by abnormal epicardial blood flow despite resolution of coronary obstruction[7]. Ito et al. [8] in 1992 described the no-reflow phenomena in patients with acute myocardial infarction when perfusion is not restored despite the patency of the epicardial coronary artery. The incidence of the no-reflow phenomenon is highly variable in the literature, ranging from 5% to 65%[9,10].

No-reflow is a challenging complication of percutaneous coronary intervention. Its presence is related to a higher risk of major adverse cardiac events (MACE). It may lead to a higher incidence of early post-infarction complications, ventricular function reduction, repeat hospitalizations for heart failure, and higher mortality[9,11–14]. In a study of 4264 patients who had PCI, 135 (3.1%) experienced no-reflow and had a fivefold more significant risk of myocardial infarction and a fourfold increased risk of mortality[15]. Another study found that 66 individuals who underwent no-reflow following PCI had a 10-fold greater risk of myocardial infarction and mortality than normal flow[16]. Clinically, patients with reflow can experience hemodynamic instability, ischemic symptoms, and ST elevation. Left ventricular systolic dysfunction, reduced left ventricular ejection fraction, left ventricular remodeling, malignant ventricular arrhythmias, heart failure, and cardiac rupture have all been associated with no-reflow[17]. In patients with STEMI undergoing primary PCI, NR has also been proven to be an independent predictor of 1-year mortality, with a 3-fold increase in the adjusted risk of death[17]. These findings highlight the need to identify, prevent or treat NR as a critical risk marker for cardiovascular events as soon as possible.

The specific mechanisms causing no-reflow are unclear. However, they might involve distal microvascular embolization and reperfusion-related injury. Platelets, neutrophils, endothelial cells, tissue factors, and vasoconstrictors are the inflammatory components implicated in the no-reflow process[12,18]. Despite ongoing advancements in PCI protocols, no-reflow remains a continual concern. It is critical to prevent, diagnose, and treat no-reflow to enhance outcomes following PCI. This review aims to provide an overview of no-reflow pathophysiology, diagnosis, predictors, and treatment options.

**Classification:**

No-reflow can be classified as interventional or reperfusion no-reflow depending on the duration of the preceding myocardial ischemia.

*Interventional no-reflow*
Following non-infarct PCI, interventional no-reflow occurs in cardiac muscle that has not been subjected to chronic ischemia prior to the procedure. It has an unanticipated onset and clinically manifests as acute ischemia with chest pain and electrocardiographic alterations. Patients with interventional no-reflow complicating PCI are reported to have increased risks of myocardial infarction and death [16].

*Reperfusion no-reflow*
In the case of acute myocardial infarction, reperfusion no-reflow occurs after PCI for reperfusion of an infarct-related coronary artery. Reperfusion no-reflow is preceded by ischemic cell injury. It is restricted to the permanently injured necrotic zone and may worsen the following reperfusion. It may manifest clinically as unresolved ST-resolution and ongoing chest pain. No-reflow reperfusion is an independent predictor of poor clinical outcomes following an acute myocardial infarction and is associated with higher mortality rate[19].

**Diagnosis of the no-reflow phenomenon:**
Various procedures can be employed alone or in combination to diagnose re-reflow. This is a brief overview of the many modalities for diagnosing no-reflow.

*Coronary angiography*
This is the simplest way to identify no-reflow in the cath lab. During coronary angiography, TIMI blood flow grades are used to assess the quality of coronary flow. The clearance of radiographic dye in the coronary arteries is measured using this approach. Patients with TIMI 0 or 1 flow are deemed to have failed reperfusion, whereas those with TIMI 3 flow are thought to have, had effective reperfusion. Coronary angiography is still an essential and straightforward approach to detecting any clinical type of no-reflow if it is used with prudence [1,8,20].

*Myocardial contrast echocardiography (MCE)*
MCE is regarded as one of the most effective methods for predicting no-reflow. In both the experimental and clinical settings, myocardial contrast echocardiography studies have been utilized to portray myocardial infarction reperfusion no-reflow and its detrimental clinical consequences. Individuals with no-reflow on MCE were shown to have a considerably higher rate of congestive heart failure and pericardial effusion than patients with normal flow. Even in patients with angiographic TIMI flow grade 3 following PCI, noninvasive measurement of myocardial perfusion using myocardial contrast echocardiography may reveal microvascular no-reflow[1,20].

*Coronary Magnetic resonance imaging (CMRI)*
CMRI is the most sensitive and specific method for determining the amount of no-reflow. The best time to get an MRI with the most predictive value is one week after myocardial infarction, although it may also be done 48–72 hours following PCI. CMRI is used to determine the size of infarcts and intramural hemorrhage. In contrast-enhanced MRI or multi-detector computed

tomography, tissue hypo-enhancement suggests poor myocardial perfusion and corresponds with evidence of microvascular blockage. The excellent spatial resolution of contrast-enhanced MRI enables the evaluation of the transmural extent of the no-reflow phenomena and necrosis in the infarct site [1,20,21].

*Myocardial blush*

Myocardial blush grade (MBG) assesses myocardial microvasculature and tissue reflow by angiography[17]. The qualitative evaluation of myocardial contrast density is done using computerized myocardial blush grade analysis. The following are the grades that are used: Grade 0: no visible tissue perfusion; grade 1: myocardial blush is evident but not cleared by the microvasculature; grade 2: myocardial blush clears slowly; grade 3: myocardial blush clears within three cardiac cycles of washout. The infarct size is more extensive in TIMI perfusion grades 0 and 1 than in grades 2 and 3. The measurement of myocardial blush in patients with TIMI 3 flow allows for additional risk classification.

*Intracoronary pressure measurements*

This measures the blood pressure with in the coronary arteries, are used as part of a thorough assessment of coronary stenoses. Results from this diagnostic test can provide a clear indication as to whether the reduction in blood flow at the site of stenosis is sufficiently severe to warrant an intervention.

*Intracoronary Doppler*

According to intracoronary Doppler measurements, the no-reflow phenomenon features a distinct coronary blood flow pattern with three primary components: systolic retrograde flow, decreased systolic antegrade flow, and rapid deceleration of diastolic flow.Because of severe microvascular constriction, Iwakura and colleagues[22] hypothesized that the intra-myocardial blood pool in individuals with no-reflow is significantly diminished. This scenario would explain the fast diastolic flow deceleration because the myocardial blood pool is rapidly filled during diastole. Some of the pooled blood is discharged back into the epicardial coronary artery capacitor during systole, resulting in a retrograde systolic flow. Recognizing this distinct pattern can aid in determining whether or not PCI is necessary.

*Virtual histology intravascular ultrasound*

Imaging resolution is improving all the time. Intravascular ultrasonography can aid in the differential diagnosis of angiographic no-reflow since it allows for the precise study of epicardial vessel integrity. In individuals with acute myocardial infarction, virtual histology intravascular ultrasonography links the angiographic no-reflow phenomenon to culprit lesions with a high plaque load or marble-like images.

*Electrocardiography*

Since ST-segment resolution on electrocardiography measures myocardial tissue reperfusion, persistent ST-segment elevation in acute myocardial infarction might indicate microvascular obstruction and no-reflow. Rapid reduction in ST-segment elevation after reperfusion treatment has been reported to imply early, complete, and quick restoration of myocardial tissue perfusion. Successful tissue perfusion is also indicated by early T-wave inversion.

*Myocardial scintigraphy*
It is considered the first evidence of the no-reflow phenomenon in humans and is highly burdensome; therefore, it is not recommended in emergency clinical settings.

*Nuclear magnetic imaging and positron emission tomography*
These have several limitations, including high prices, technical complexity, and invasiveness. Their use is restricted to highly specialized clinics and research centers.

*Biochemical markers*
Serial measurements of serum myoglobin, creatine kinase-MB, or troponin I/T at baseline and 60 or 90 minutes following reperfusion therapy have been found to be effective in assessing infarct-related arterial patency. Following PCI, early raise and fall in serum cardiac biomarkers indicate myocardial necrosis due to tissue hypo-perfusion and ischemia[23].

**Pathophysiology of no-reflow:**
Understanding its pathogenesis is key to managing the no-reflow phenomenon and preventing adverse outcomes. Structure damage to the microvasculature reduces the amount of blood flow to the cardiac myocytes after a prolonged coronary occlusion and restoration of coronary blood flow, leading to inadequate healing of the cardiac scar. In acute myocardial infarction, the goal of reperfusion therapy with percutaneous coronary intervention is to restore optimum blood flow in the infarct-related artery (IRA) to provide adequate blood supply to the ischemic but still viable myocardium while reducing infarct size and mortality. Despite a patent IRA, myocardial reperfusion is not accomplished in no-reflow[24].
No-reflow was described for the first time by Kloner et al. [6] in 1974 in a canine experimental model of myocardial ischemia-reperfusion[25]. Several experimental and clinical studies over the last three decades have discovered several predisposing factors for the no-reflow phenomena and provided a variety of explanatory mechanisms and strategies to overcome it in the clinical setting. NR is believed to be caused by microvascular blockage due to distal embolization of thrombus or debris, vasoconstriction, activation of the inflammatory cascade, neutrophil plugging, platelet aggregation, toxic free-radical production, and myocardial edema[1,7,12,13,20,26,27]. The release of potent vasoconstrictors from degranulating platelets, including serotonin, α-adrenergic, and angiotensin II, has also been linked to no-reflow-associated vasoconstriction [4].

Pre-existing microvascular obstruction and/or endothelial dysfunction may impact the degree of microvascular obstruction following elective and infarct-related PCI. This might explain why diabetes and hyperlipidemia are associated with the no-reflow phenomena.

The following different pathogenic mechanisms can cause No-reflow.
*Distal athero-thrombotic embolization*
In humans, micro-embolism during PCI is the most common cause of no-reflow. When embolic microspheres block more than 50% of coronary capillaries, myocardial perfusion reduces irreversibly[24,28]. During PCI, emboli of various sizes can come from atherosclerotic plaques of coronary thrombus. Pre-arterioles can be obstructed by emboli, resulting in no-reflow. Distal

embolization is particularly significant in circumstances when there is a lot of debris, such as after SVG PCI.

*Ischemia-related injury*

No-reflow starts with the initial severe ischemic insult. Prolonged ischemia can lead to endothelial dysfunction. Endothelial protrusions and membrane-bound bodies are morphological alterations that can fill capillaries to luminal obliteration. Furthermore, after ischemia, endothelial gaps with extravascular erythrocytes are prevalent. A decrease often follows these morphological results in regional myocardial blood flow inside the previously ischemic zone, which might lead to no-reflow. Furthermore, cardiac cell enlargement can generate interstitial edema, leading to microvascular compression. Kloner et al.[6] reported that temporary ligation of a coronary artery in dogs for more than 90 minutes caused ischemic anatomical changes in the capillaries of the ischemic zone.

*Reperfusion-related injury*

Reperfusion is used to reverse the adverse consequences of ischemia. On the other hand, reperfusion may worsen endothelial injury when ischemia lasts longer than 3 hours. The ischemia-related injury is made worse by reperfusion injury. Microvascular dysfunction is frequently associated with reperfusion of ischemic tissues, as seen by decreased endothelium-dependent dilatation in arterioles, leukocyte trafficking, and plasma protein extravasation in postcapillary venules. Following reperfusion, activated endothelial cells in all segments of the microcirculation release more oxygen radicals but less nitric oxide. As a result of the imbalance, inflammatory mediators are produced and released, and the biosynthesis of adhesion molecules that mediate leukocyte-endothelial cell attachment is increased. TNF-α, IL-1β, selectin, and endothelin-1 (ET-1) appear to have a role in the reperfusion-related injury and no-reflow phenomenon. Myocytes might also suffer irreparable injury as a result of reperfusion.

*Individual susceptibility*

No-reflow predisposition can be inherited or acquired. Microvascular dysfunction has recently been related to genetic variation and sex-specific allelic variant genes[29]. Diabetes, hyperlipidemia, and hypertension have been linked to impaired microvascular reperfusion after primary PCI and increased reperfusion damage[30,31].

**Predictors of no-reflow**

Several recent studies looked into clinical predictors of no-reflow in STEMI patients with primary PCI. WBC count, thrombus grade/score, age ≥ 60 years, mean platelet volume (MPV), the time between the start of chest pain and PCI (≥4 h), hyperglycemia, and elevated serum creatinine were some of the predictors [24,32,33]. In recent research by Topark et al. [34], the platelet lymphocyte ratio (PLR) on admission was found to be a robust predictor of no-reflow. A recent metanalysis by Fajar et al. [35] reported that increased risks of no-reflow were associated with advanced age, male, family history of coronary artery disease, smoking, diabetes mellitus, hypertension, delayed reperfusion, Killip class ≥2, elevated blood glucose, increased creatinine, elevated creatine kinase (CK), higher heart rate, decreased left ventricular ejection fraction (LVEF), collateral flow ≤1, longer lesion length, multivessel disease, reference luminal diameter, initial thrombolysis in myocardial infarction (TIMI) flow, and high thrombus burden[20,35,36].

*Predictors of distal embolization*

The presence of a thrombus at a coronary artery lesion site is a substantial risk factor for distant embolization. Yip et al. [37] reported angiographic morphologic features of infarct-related arteries as independent predictors of no-reflow in 800 patients undergoing primary PCI. The following characteristics were included in the thrombus burden score: (1) an angiographic thrombus with a greatest linear dimension greater than three times the reference lumen diameter; (2) cutoff pattern (lesion morphology with a sharp cutoff without taper before the occlusion); (3) presence of accumulated thrombus (>5 mm of linear dimension) proximal to the occlusion; (4) presence of floating thrombus proximal to the occlusion; (5) persistent contrast medium distal to the obstruction [37].

*Predictors of ischemia-related injury*

The occurrence of the no-reflow phenomena is influenced by the time it takes to get treatment in PCI. The longer the reperfusion duration, the higher the prevalence of no-reflow. Turschner et al. [38] postulated a link between myocardial thickness and the occurrence of no-reflow. They found that prolonged ischemia followed by reperfusion causes increased myocardial thickness due to tissue edema, leading to no-reflow. According to Iwakura et al. [22], the size of the ischemic area is another predictor of no-reflow.

*Predictors of reperfusion-related injury*

Platelets have been shown to play a role in no-reflow. According to Campo et al., platelet reactivity on admission was associated with no-reflow prevalence. Niccoli et al. [28] proposed that thromboxane-A2 (TxA2) plasma levels indicate no-reflow. ET-1, a potent vasoconstrictor, appears to have a crucial role in no-reflow and may be a reliable predictor of no-reflow. The neutrophil count, linked to microvascular damage following initial PCI, is another readily available predictor.

*Predictors of individual susceptibility*

Acquired and hereditary factors might influence the development of the no-reflow phenomena. Iwakura et al39 discovered a link between hyperglycemia and the no-reflow phenomena in patients with acute myocardial infarction. In addition, evidence showed a link between C-reactive protein and myocardial perfusion in STEMI patients. According to Vignali et al. [40] the 1976T>C polymorphism of the adenosine 2A receptor gene has been associated with a greater prevalence of no-reflow

**Prevention and management of the no-reflow phenomenon**

Existing and under-development no-reflow prevention/treatment strategies primarily focus on reducing thrombus burden, improving microvascular function, reducing reperfusion injury, and enabling the regeneration of injured myocardium. There are two approaches for preventing and treating no-reflow: pharmacological and non-pharmacological. The no-reflow phenomena have yet to be treated with a standard, single treatment. Since there are so many mechanisms involved, a single treatment strategy is unlikely to be helpful in all situations; therefore prevention is essential.

*Prevention of distal embolization*

There is a substantial probability of no-reflow with PCI in thrombus-containing lesions. Loubeyre et al[41] found that patients who received direct stenting had better reperfusion than those who received standard primary PCI. Direct stenting after thrombus aspiration has been supported by Dudek et al[42] (PIHRATE Trial), resulting in improved microvascular perfusion. The use of thrombectomy and distal protection devices to prevent distal embolization is a more advanced technological method. The REMEDIA study was the first randomized experiment to evaluate the role of thrombectomy using a simple manual aspiration catheter. Compared to routine primary PCI, this trial showed that manual thrombectomy was safe and resulted in greater myocardial perfusion. A sub study of the REMEDIA trial found that thrombus aspiration decreased no-reflow substantially. The TAPAS trial was the first to indicate that manual thrombus aspiration improves myocardial perfusion and reduces mortality at a 12-month follow-up[24].

The M-guard stent is designed to prevent distal embolization and prevent no reflow after PCI. M-guard stenting has been shown to improve cardiac reperfusion and reduce no-reflow in STEMI patients with a significant thrombus load in several trials like MASTER I, MASTER II, MAGICAL, REWARD MI trials [24]

*Prevention by Deferred Stenting stratergy : A primer*

The strategy of deferred stenting represents a radical change in the management of patients with STEMI during PCI especially if they have a high thrombus burden. The stent placement is delayed by a finite interval after the index procedure when stable distal flow has been restored by PCI or thrombolysis. This time of deferment has multiple benefits – gradual clearing of the thrombus, improvement of microvascular flow, reduction of vasospasm, prevention of distal embolisation, avoidance of slow flow/no reflow and attenuated periprocedural MIs.

*Prevention of ischemia-related injury*

The prevalence of the no-reflow phenomena might be reduced by strategies that reduce overall ischemia time. Pharmacologic medications that lower myocardial oxygen consumption and thereby the degree of ischemia may improve the prognosis. Carvedilol, fosinopril, and valsartan have been shown to have beneficial benefits on coronary no-reflow[43,44].

*Prevention & treatment of the reperfusion-related injury*

Several studies have shown that medications that reverse endothelial dysfunction or platelet and neutrophil activation can be used as a preventative and/or therapy option for reperfusion no-reflow.

*Prevention of individual susceptibility*

Unfortunately, genetic susceptibility to a microcirculatory injury cannot be addressed at present. However, with diabetes and hypercholesterolemia, susceptibility could be controlled. The DIGAMI research found that infarct size was reduced following a peri-procedural blood glucose drop. According to Iwakura et al[39], chronic statin medication is related to a decreased prevalence of no-reflow in patients with or without hypercholesterolemia.

**Pharmacotherapy**

Improved myocardial perfusion is becoming a focus of reperfusion treatment, which may speed up the healing process by promoting functional recovery of viable muscle, reducing infarct size, and improving the supply of blood-borne components. According to clinical recommendations, platelet IIb/IIIa receptor inhibitors, nitrates, adenosine, and thrombus extraction can all be used to prevent and treat the no-reflow phenomenon. Refer to table 1 for commonly used pharmacologic therapies and their dosages for the treatment of No-Reflow

**Table 1: Pharmacologic Therapies and their dosages for the treatment of No-Reflow** [1,12,20]

| **Medication** | **Route** | **Dose** |
|---|---|---|
| Adenosine | Intracoronary<br><br>Intravenous | 100–200 µg bolus<br>70 µg/kg/min |
| Verapamil | Intracoronary | 100–500 µg bolus (max 1 mg) |
| Diltiazem | Intracoronary | 400 µg bolus (max 5 mg) |
| Nicardipine | Intracoronary | 200 µg bolus (max 1 mg) |
| Nitroprusside | Intracoronary | 60–100 µg bolus |
| Epinephrine | Intracoronary | 80–100 µg bolus |
| Nicorandil | Intracoronary | 4-6mg bolus |
| GP IIb/IIIa inhibitors | Intravenous | |
| 1. Abciximab<br><br>2. Eptifibatide<br><br>3. Tirofiban | 1. 0.25 mg/kg bolus, then 0.125 µg/kg/min (max 10 µg/min) infusion for 12 h<br>2. 180 µg/kg bolus, then further 180 µg/kg bolus 10 min later, then 2µg/kg/min infusion for up to 18 h<br>3. 25µg/kg over 3min, then 0.15 µg/kg/min infusion for up to 18h | |

*Antithrombotic drugs*

Glycoprotein IIb/IIIa (GP IIb/IIIa) receptor antagonists improved outcomes in acute coronary syndrome patients undergoing PCI, particularly those with pre-procedural TIMI 0 or 1 flow [1]. Abciximab, tirofiban, and eptifibatide have been used to prevent and treat no-reflow. Tirofiban was found to enhance myocardial perfusion and reduce infarct size when given before coronary reperfusion. According to Petronio et al[45]. abciximab enhances myocardial perfusion during primary PCI. Stone et al[46] reported that bolus intracoronary abciximab administered to the infarct lesion site significantly decreased infarct size at 30 days in patients with large anterior STEMI and underwent primary PCI with bivalirudin anticoagulation.

*Vasodilators*

Vasodilators such as nitrates, verapamil, papaverine, nicardipine, adenosine, and sodium nitroprusside have been studied in several observational and randomized controlled studies to see if they might help improve microvascular function following an acute myocardial infarction[4]. Vasodilators are supposed to help with microvascular dysfunction by reducing microvessel spasm and modulating endothelial function; however, the outcomes are inconsistent.

Calcium channel blockers like verapamil, diltiazem, and nicardipine have been studied for their beneficial effects in no-reflow. These drugs block L-type channels in the myocardium's cell membrane, causing endothelial-dependent microvessel relaxation[1]. These also lower the myocardium's oxygen demand and the damage caused by oxygen free radicals. Verapamil, for example, has been demonstrated to increase $Ca^{2+}$ hemostasis in ischemic myocardium cells, whereas adenosine has been shown to inhibit neutrophil activation and endothelial damage in ischemic myocardial cells. Taniyama et al. [47] conducted a small randomized trial and found that intracoronary verapamil was linked with improved microvascular function in patients with their first STEMI compared to placebo. As a result, intracoronary verapamil has been successfully used to reverse no-reflow following primary PCI. Wang et al. [48] conducted a meta-analysis of 8 RCTs and found that verapamil and diltiazem both significantly reduced no re-flow[11].
According to Marzilli et al. [49], intracoronary injection of 4 mg of adenosine as an adjuvant to primary PCI in acute myocardial infarction resulted in a reduced rate of no-reflow compared to the control group. Adenosine reduced infarct size in the AMISTAD II trial; however, it was found to be harmful in the REFLO-STEMI study, although the dose of adenosine used in REFLO-STEMI was quite high (1–2 mg).Studies have reported that intracoronary adenosine could effectively prevent the no-reflow phenomenon in STEMI patients with primary PCI. A metanalysis by Gao et al[50] reported better ST-segment resolution and improved TIMI flow grade after adenosine but no definite improvement in LVEF or mortality.
Nicorandil, a nitrate-containing mitochondrial potassium-channel opener, has shown promise in individuals with acute myocardial infarction when administered before reperfusion[1,24]. Preload and afterload are reduced, coronary resistance arteries are dilated, myocyte Ca2+ excess is reduced, and neutrophil activation is reduced with this drug. In randomized studies, intravenous nicorandil infusion for 24 hours after primary PCI improved angiographic, functional, and clinical results compared to placebo. Intracoronary sodium nitroprusside administration was associated with considerable improvements in coronary flow and an increase in TIMI flow grade[24].

*Hormones*
According to the RESTORE trial, epinephrine administration improved coronary flow, ST-segment resolution, and left ventricular ejection fraction in STEMI patients with refractory no-reflow during primary PCI[51]. Skelding et al[52] evaluated 29 individuals who had been given intracoronary epinephrine for refractory no-reflow. The use of intracoronary epinephrine improved coronary flow significantly. According to Kitakaze et al[53], treatment with atrial-natriuretic peptide was also associated with a substantial decrease in infarct size, increased left ventricular ejection fraction, and improved myocardial perfusion.

*GP IIb/IIIa Inhibitors*
The overall effect of antithrombotics has been variable. Wohrle et al.[54] reported a significant improvement in patients with acute coronary syndrome undergoing PCI compared to the control group (10.2% vs. 20.2; $p<0.008$). Similarly, Lemos et al.[55] reported significant improvement among patients with preprocedural TIMI 0 or 1 flow (11.8% vs. 27.5%; $p<0.002$). An experimental study by Kunichika et al.[56] reported that administration of tirofiban before coronary perfusion was associated with improved myocardial perfusion and reduced infarct size. ADMIRAL trial[57] reported that intravenous abciximab is associated with a higher incidence

of TIMI 3 flow with an 80% reduction in adverse cardiac events compared to controls. Nevertheless, whether the improvement in coronary flow is mediated by platelet aggregation inhibition or by rapid establishment of epicardial artery recanalization remains unknown.

*Statins*

Statins, an HMG-CoA reductase, appears to affect the prevention of the no-reflow phenomenon[58]. STATIN STEMI[59] trial reported a significant improvement in angiographic microvascular obstruction with high dose statins compared to low dose statins. Similar results were observed in the SECURE-PCI trial[60]. The study reported a 50% reduction in cardiovascular events at one month with a high dose of atorvastatin when compared to a placebo.

*Ticagrelor*

Ticagrelor, a potential $P2Y_{12}$ inhibitor, appears to have a pleiotropic cardioprotective effect against acute myocardial reperfusion injury[61]. A meta-analysis by Dai et al.[62] reported a significant reduction in no-reflow during PCI with substantial improvement in thrombolysis in myocardial infarction after PCI. An observation study reported by Backer et al.[63] on 3497 STEMI patients showed no significant improvement in coronary reperfusion with ticagrelor compared to pre-hospital clopidogrel loading. However, in 2019, the PLEIO [64] study reported a significant recovery of microcirculation functions in patients with ticagrelor compared to clopidogrel.

**Thrombus Aspiration**

Thrombus aspiration is designed to reduce the etiopathogenetic mechanism of the no-reflow phenomenon[65]. Routine thrombus aspiration was initially associated with better clinical outcomes among patients with STEMI[66]. However, few studies [67,68] have reported its inability to reduce 30-day mortality. Per ESC guidelines, thrombus aspiration use is contraindicated as a routine maneuver[69]. Among the designed and tested, pressure-controlled intermittent coronary sinus occlusion (PICSO) showed promising results in improving microcirculation [70]. OxAMI-PICSO [71] trial reported a significant decrease in the extension of infarction in patients with STEMI at 6 months compared to the control group.

**Mechanical Therapy**

*Distal Embolic Protection Devices*

Filter wire and PercuSurge Guard Wire are the two clinically proven protective devices for patients undergoing PCI of saphenous vein graft lesions. Baim et al.[72] reported a significant reduction in major adverse cardiac events and no-reflow phenomenon with stenting over a conventional angioplasty guidewire. Zhou et al.[73] reported a significant improvement in TIMI and MBG score among patients who underwent PCI with PercuSurge Guard Wire. However, the randomized control trial reported by Stone et al[74] showed no significant difference in thrombotic and plaque debris among distal and control groups. Also, the author reported when compared to the control, the distal group showed no significant difference in major cardiac events at 6 months.

***Proximal Protection Device***

Proxis Embolic Protection System is a newly developed method to reduce distal embolization during primary PCI among STEMI patients. The catheter is deployed proximal to the target lesion, interrupting anterograde blood flow before crossing the lesion. European Registry reported significant achievement in retrograde blood flow during proximal occlusion among patients undergoing PCI for saphenous venous bypass graft and native coronary arterial lesions to capture embolic material[75]. However, Wang et al.[76] reported that due to the need of a landing zone the clinical use of proxis system is difficult in a small target vessel (<2.5mm). The author reported the landing zone as one of the limitations of proximal protection devices as most of the lesions are located in the proximal segments of native coronary arteries.

**Human Bone Marrow-Derived Cells**

An endothelial precursor is one of bone marrow's main constituents with phenotypic embryonic hemangioblasts phenotypic characteristics. Endothelial precursors are associated with developing new blood vessels at infarct and proliferate sites. Setting new ischemic myocardium by human bone marrow-derived endothelial precursor prevents cardiomyocyte apoptosis, which improves cardiac functions[77]. However, more randomized control trials are needed to evaluate the potential role of human bone marrow-derived cells on cardiac functions.

**Therapeutic Hypothermia**

Irreversible myocardial injury after AMI is divided into ischemic and reperfusion injury; however, both the insults share a common mechanism[78]. The longer the duration of coronary artery occlusion, the more the infarct size. Hence early perfusion significantly decreases infarct size and mortality[79]. Therapeutic hypothermia is based on cooling-induced cardioprotection. It reduces myocardium metabolic requirement and sodium-calcium overload. Therapeutic hypothermia was also found to increase cellular and mitochondrial membrane stability[80]. Gotberg et al.[81] reported a significant reduction in infarct size normalized to the myocardium at risk by 38% among patients in the hypothermia group compared to the control group. The study also reported a significant decrease in the hypothermia group's peak and cumulative release of troponin T. Nicgol et al.[82] performed a randomized control trial to evaluate the role of hypothermia on 30-day mortality, reinfarction, bleeding, sepsis, severe arrhythmia or renal failure as primary outcomes. The study reported a significant decrease in primary outcomes in the case group compared to the control. However, compared to control, a non-significant difference was observed concerning infarct size in the case group.

**Other potential therapies:**

*Exenatide, glucagon-like peptide-1 analog,* enhanced myocardial salvage at reperfusion in STEMI patients having initial PCI[83]

*Cyclosporine* inhibits the opening of mitochondrial permeability transition pore and was reported to reduce infarct size at reperfusion[84]

*Bendavia,* a mitochondria cytoprotective peptide (EMBRACE STUDY) reduced ischemic reperfusion injury[85]

*Fasudil,* a novel Rho-kinase inhibitor and potent vasodilator, has been shown to reduce the rate of NR in animal models. Recently, a clinical trial has been conducted to evaluate whether an

early intracoronary administration of Fasudil Hydrochloride during primary PCI of STEMI can improve epicardial and myocardial perfusion and clinical outcomes (NCT03753269)
*Metoprolol* in the METOCARD-CNIC study reduced the extent of infarction, prevented adverse left ventricular remodeling, preserved systolic function, and reduced the rate of re-hospitalization for heart failure[86]
*Anisodamine,* a muscarinic cholinergic antagonist, appears to improve myocardial reperfusion, cardiac function, and clinical outcomes in patients with STEMI undergoing PPCI. This was reported in a recent network metanalysis performed to assess the effect of 7 intracoronary agents (adenosine, anisodamine, diltiazem, nicorandil, nitroprusside, urapidil, and verapamil) on the no-reflow phenomenon in patients with STEMI undergoing PPCI[26]
*Alprostadil,* a prostaglandin E1 analog, may also be beneficial in treating NR[87]
*Dipyridamole,* a thromboxane synthase inhibitor, was found to be better than verapamil in a randomised study for the treatment of no-reflow during primary angioplasty[88]

Clinical trials are being conducted to develop safe and effective treatments to prevent and treat the no-reflow phenomena. Refer Table 2.

***Non-Pharmacological Treatment***
*Post-conditioning*
Ischemic preconditioning is the most effective endogenous mechanism capable of reducing the extent of myocardial infarction by cycles of coronary balloon occlusion and reperfusion. Zhao et al[44]. first described ischemic post-conditioning, a mechanical intervention performed at the onset of reperfusion that reduces infarct size following ischemia. This post-conditioning includes activation of extracellular signal-regulated kinase, the production of nitric oxide, the opening of mitochondrial potassium channels, and the inhibition of the opening of the mitochondrial permeability transition pore. A systematic review and meta-analysis reported that remote ischemic preconditioning appears to be an effective strategy for minimizing ischemia-reperfusion myocardial damage, and it may also minimize long-term clinical occurrences[1,24,89].

When no reflow is suspected, other causes of artery blockage, such as dissection, thrombus migration, and vasospasm, should be ruled out by imaging. After confirming vascular patency, use vasodilators, check the therapeutic activated clotting time, and give hemodynamic support if needed.

**Table 2: Ongoing clinical trials**

| **Clinical trials** | **Aim of the study** |
|---|---|
| *The EPIVER Randomized Controlled Trial* | To estimate the efficacy and safety of the intracoronary administration of adrenalin, verapamil, as well as their combination compared to standard treatment in patients with STEMI and refractory coronary no-reflow despite conventional treatment during percutaneous coronary intervention. |
| *The PiCSO-AMI-I trial* | To assess the effects of PICSO on infarct size in anterior STEMI. |
| *The PiCSO-AMI-V trial* | To assess adverse device effects rate at 30 days post index |

| | |
|---|---|
| | procedure |
| *The CHEETAH trial* | To assess the clinical utility of a next-generation mechanical aspiration catheter in thrombus aspiration. |
| *NCT04785209* | To predict no reflow in PPCI of STEMI patients using mean platelet volume together with STEMI clinical risk scores. |
| *NCT02054000* | To evaluate the acute effect of intracoronary administration of tirofiban on no-reflow phenomenon in patients with STEMI and occurrence of no-reflow phenomenon undergoing PPCI. |
| *NCT03264859* | To investigate the association between Neutrophil Gelatinase-associated Lipocalin (NGAL) plasma levels in ST-elevation myocardial infarction and the no-reflow phenomenon, adverse events during hospitalization and at 30-day follow-up. |

**Conclusion**

No reflow phenomenon is a challenging condition and may lead to worse outcomes, especially in patients presenting with STEMI. No-reflow is believed to be caused by microvascular obstruction triggered by various pathophysiological mechanisms. MCE, followed by coronary angiography, is the gold standard for diagnosing no-reflow.

There is currently no effective therapy for the no-reflow phenomenon. Early detection, preventive measures, and treatment of no-reflow may alter the outcome of PCI. Reducing infarct size with early revascularization and sufficient pharmacological therapy is one of the most effective approaches to lowering the occurrence of no-reflow.

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**Conflict of Interest**
Author's declare no conflict of interest

**Data availability**
Data openly avaible in the public repository that issues datasets with DOIs

**REFERENCES:**

1. Annibali G, Scrocca I, Aranzulla TC, Meliga E, Maiellaro F, Musumeci G. "No-Reflow" Phenomenon: A Contemporary Review. *J Clin Med*. 2022;11(8):2233. doi:10.3390/jcm11082233
2. Li H, Ge J. Cardiovascular diseases in China: Current status and future perspectives. *Int J Cardiol Heart Vasc*. 2015;6:25-31. doi:10.1016/j.ijcha.2014.10.002

3. O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2013;127(4):e362-425. doi:10.1161/CIR.0b013e3182742cf6
4. Ramjane K, Han L, Jin C. The diagnosis and treatment of the no-reflow phenomenon in patients with myocardial infarction undergoing percutaneous coronary intervention. *Exp Clin Cardiol*. 2008;13(3):121-128.
5. Feher A, Chen SY, Bagi Z, Arora V. Prevention and treatment of no-reflow phenomenon by targeting the coronary microcirculation. *Rev Cardiovasc Med*. 2014;15(1):38-51. doi:10.3909/ricm0699
6. Kloner RA, Ganote CE, Jennings RB. The "no-reflow" phenomenon after temporary coronary occlusion in the dog. *J Clin Invest*. 1974;54(6):1496-1508. doi:10.1172/JCI107898
7. Rezkalla SH, Kloner RA. No-reflow phenomenon. *Circulation*. 2002;105(5):656-662. doi:10.1161/hc0502.102867
8. Ito H, Tomooka T, Sakai N, et al. Lack of myocardial perfusion immediately after successful thrombolysis. A predictor of poor recovery of left ventricular function in anterior myocardial infarction. *Circulation*. 1992;85(5):1699-1705. doi:10.1161/01.cir.85.5.1699
9. Rossington JA, Sol E, Masoura K, et al. No-reflow phenomenon and comparison to the normal-flow population postprimary percutaneous coronary intervention for ST elevation myocardial infarction: case-control study (NORM PPCI). *Open Heart*. 2020;7(2):e001215. doi:10.1136/openhrt-2019-001215
10. Soeda T, Higuma T, Abe N, et al. Morphological predictors for no reflow phenomenon after primary percutaneous coronary intervention in patients with ST-segment elevation myocardial infarction caused by plaque rupture. *Eur Heart J Cardiovasc Imaging*. 2017;18(1):103-110. doi:10.1093/ehjci/jev341
11. Sadeghian M, Mousavi SH, Aamaraee Z, Shafiee A. Administration of intracoronary adenosine before stenting for the prevention of no-reflow in patients with ST-elevation myocardial infarction. *Scand Cardiovasc J*. 2022;56(1):23-27. doi:10.1080/14017431.2022.2035807
12. Caiazzo G, Musci RL, Frediani L, et al. State of the Art: No-Reflow Phenomenon. *Cardiol Clin*. 2020;38(4):563-573. doi:10.1016/j.ccl.2020.07.001
13. Niu J, Tong J, Blevins JE. Oxytocin as an Anti-obesity Treatment. *Front Neurosci*. 2021;15:743546. doi:10.3389/fnins.2021.743546
14. Harrison RW, Aggarwal A, Ou F shu, et al. incidence and outcomes of no-reflow phenomenon during percutaneous coronary intervention among patients with acute myocardial infarction. *Am J Cardiol*. 2013;111(2):178-184. doi:10.1016/j.amjcard.2012.09.015

15. Resnic FS, Wainstein M, Lee MKY, et al. No-reflow is an independent predictor of death and myocardial infarction after percutaneous coronary intervention. *Am Heart J*. 2003;145(1):42-46. doi:10.1067/mhj.2003.36
16. Abbo KM, Dooris M, Glazier S, et al. Features and outcome of no-reflow after percutaneous coronary intervention. *Am J Cardiol*. 1995;75(12):778-782. doi:10.1016/s0002-9149(99)80410-x
17. Bouleti C, Mewton N, Germain S. The no-reflow phenomenon: State of the art. *Arch Cardiovasc Dis*. 2015;108(12):661-674. doi:10.1016/j.acvd.2015.09.006
18. Rezkalla SH, Kloner RA. Coronary no-reflow phenomenon: from the experimental laboratory to the cardiac catheterization laboratory. *Catheter Cardiovasc Interv*. 2008;72(7):950-957. doi:10.1002/ccd.21715
19. Morishima I, Sone T, Okumura K, et al. Angiographic no-reflow phenomenon as a predictor of adverse long-term outcome in patients treated with percutaneous transluminal coronary angioplasty for first acute myocardial infarction. *J Am Coll Cardiol*. 2000;36(4):1202-1209. doi:10.1016/s0735-1097(00)00865-2
20. Ciofani JL, Allahwala UK, Scarsini R, et al. No-reflow phenomenon in ST-segment elevation myocardial infarction: still the Achilles' heel of the interventionalist. *Future Cardiol*. 2021;17(2):383-397. doi:10.2217/fca-2020-0077
21. Jacquier A, Boussel L, Amabile N, et al. Multidetector computed tomography in reperfused acute myocardial infarction. Assessment of infarct size and no-reflow in comparison with cardiac magnetic resonance imaging. *Invest Radiol*. 2008;43(11):773-781. doi:10.1097/RLI.0b013e318181c8dd
22. Iwakura K, Ito H, Kawano S, et al. Predictive factors for development of the no-reflow phenomenon in patients with reperfused anterior wall acute myocardial infarction. *J Am Coll Cardiol*. 2001;38(2):472-477. doi:10.1016/s0735-1097(01)01405-x
23. Bonz AW, Lengenfelder B, Strotmann J, et al. Effect of additional temporary glycoprotein IIb/IIIa receptor inhibition on troponin release in elective percutaneous coronary interventions after pretreatment with aspirin and clopidogrel (TOPSTAR trial). *J Am Coll Cardiol*. 2002;40(4):662-668. doi:10.1016/s0735-1097(02)02014-4
24. Gupta S, Gupta MM. No reflow phenomenon in percutaneous coronary interventions in ST-segment elevation myocardial infarction. *Indian Heart J*. 2016;68(4):539-551. doi:10.1016/j.ihj.2016.04.006
25. Ndrepepa G, Tiroch K, Keta D, et al. Predictive factors and impact of no reflow after primary percutaneous coronary intervention in patients with acute myocardial infarction. *Circ Cardiovasc Interv*. 2010;3(1):27-33. doi:10.1161/CIRCINTERVENTIONS.109.896225
26. Niu X, Zhang J, Bai M, Peng Y, Sun S, Zhang Z. Effect of intracoronary agents on the no-reflow phenomenon during primary percutaneous coronary intervention in patients

with ST-elevation myocardial infarction: a network meta-analysis. *BMC Cardiovasc Disord*. 2018;18(1):3. doi:10.1186/s12872-017-0722-z

27. Jaffe R, Charron T, Puley G, Dick A, Strauss BH. Microvascular obstruction and the no-reflow phenomenon after percutaneous coronary intervention. *Circulation*. 2008;117(24):3152-3156. doi:10.1161/CIRCULATIONAHA.107.742312
28. Niccoli G, Scalone G, Lerman A, Crea F. Coronary microvascular obstruction in acute myocardial infarction. *Eur Heart J*. 2016;37(13):1024-1033. doi:10.1093/eurheartj/ehv484
29. Yoshino S, Cilluffo R, Best PJM, et al. Single nucleotide polymorphisms associated with abnormal coronary microvascular function. *Coron Artery Dis*. 2014;25(4):281-289. doi:10.1097/MCA.0000000000000104
30. Collet JP, Montalescot G. The acute reperfusion management of STEMI in patients with impaired glucose tolerance and type 2 diabetes. *Diab Vasc Dis Res*. 2005;2(3):136-143. doi:10.3132/dvdr.2005.021
31. Golino P, Maroko PR, Carew TE. The effect of acute hypercholesterolemia on myocardial infarct size and the no-reflow phenomenon during coronary occlusion-reperfusion. *Circulation*. 1987;75(1):292-298. doi:10.1161/01.cir.75.1.292
32. Danesh Sani SH, Eshraghi A, Shahri B, Vejdanparast M. No-Reflow Phenomenon in Patients with ST-Elevation Acute Myocardial Infarction, Treated with Primary Percutaneous Coronary Intervention: A Study of Predictive Factors. *Journal of Cardio-Thoracic Medicine*. 2014;2(4):221-226. doi:10.22038/jctm.2014.3491
33. Abdi S, Rafizadeh O, Peighambari M, Basiri H, Bakhshandeh H. Evaluation of the Clinical and Procedural Predictive Factors of no-Reflow Phenomenon Following Primary Percutaneous Coronary Intervention. *Res Cardiovasc Med*. 2015;4(2):e25414. doi:10.5812/cardiovascmed.4(2)2015.25414
34. Toprak C, Tabakci MM, Simsek Z, et al. Platelet/lymphocyte ratio was associated with impaired myocardial perfusion and both in-hospital and long-term adverse outcome in patients with ST-segment elevation acute myocardial infarction undergoing primary coronary intervention. *Postepy Kardiol Interwencyjnej*. 2015;11(4):288-297. doi:10.5114/pwki.2015.55599
35. Fajar JK, Heriansyah T, Rohman MS. The predictors of no reflow phenomenon after percutaneous coronary intervention in patients with ST elevation myocardial infarction: A meta-analysis. *Indian Heart J*. 2018;70 Suppl 3:S406-S418. doi:10.1016/j.ihj.2018.01.032
36. Yang L, Cong H, Lu Y, Chen X, Liu Y. Prediction of no-reflow phenomenon in patients treated with primary percutaneous coronary intervention for ST-segment elevation myocardial infarction. *Medicine (Baltimore)*. 2020;99(26):e20152. doi:10.1097/MD.0000000000020152

37. Yip HK, Chen MC, Chang HW, et al. Angiographic morphologic features of infarct-related arteries and timely reperfusion in acute myocardial infarction: predictors of slow-flow and no-reflow phenomenon. *Chest*. 2002;122(4):1322-1332. doi:10.1378/chest.122.4.1322
38. Turschner O, D'hooge J, Dommke C, et al. The sequential changes in myocardial thickness and thickening which occur during acute transmural infarction, infarct reperfusion and the resultant expression of reperfusion injury. *Eur Heart J*. 2004;25(9):794-803. doi:10.1016/j.ehj.2004.01.006
39. Iwakura K, Ito H, Ikushima M, et al. Association between hyperglycemia and the no-reflow phenomenon in patients with acute myocardial infarction. *J Am Coll Cardiol*. 2003;41(1):1-7. doi:10.1016/s0735-1097(02)02626-8
40. Vignali L, Talanas G, Saia F, et al. Genetic association between the 1976T_C polymorphism in the adenosine A2 receptor and angiographic no-reflow phenomenon (abstr). *Il giornale italiano di Cardiologia Invasiva*. 2007;3(Suppl 1):109.
41. Loubeyre C, Morice MC, Lefèvre T, Piéchaud JF, Louvard Y, Dumas P. A randomized comparison of direct stenting with conventional stent implantation in selected patients with acute myocardial infarction. *J Am Coll Cardiol*. 2002;39(1):15-21. doi:10.1016/s0735-1097(01)01701-6
42. Dudek D, Mielecki W, Burzotta F, et al. Thrombus aspiration followed by direct stenting: a novel strategy of primary percutaneous coronary intervention in ST-segment elevation myocardial infarction. Results of the Polish-Italian-Hungarian RAndomized ThrombEctomy Trial (PIHRATE Trial). *Am Heart J*. 2010;160(5):966-972. doi:10.1016/j.ahj.2010.07.024
43. Opie LH. Reperfusion injury and its pharmacologic modification. *Circulation*. 1989;80(4):1049-1062. doi:10.1161/01.cir.80.4.1049
44. Zhao J, Yang Y, you S, Cui C, Gao R. Carvedilol preserves endothelial junctions and reduces myocardial no-reflow after acute myocardial infarction and reperfusion. *Int J Cardiol*. 2007;115(3):334-341. doi:10.1016/j.ijcard.2006.03.017
45. Petronio AS, De Carlo M, Ciabatti N, et al. Left ventricular remodeling after primary coronary angioplasty in patients treated with abciximab or intracoronary adenosine. *American Heart Journal*. 2005;150(5):1015.1-1015.e9. doi:10.1016/j.ahj.2005.07.012
46. Stone GW, Maehara A, Witzenbichler B, et al. Intracoronary abciximab and aspiration thrombectomy in patients with large anterior myocardial infarction: the INFUSE-AMI randomized trial. *JAMA*. 2012;307(17):1817-1826. doi:10.1001/jama.2012.421
47. Taniyama Y, Ito H, Iwakura K, et al. Beneficial effect of intracoronary verapamil on microvascular and myocardial salvage in patients with acute myocardial infarction. *J Am Coll Cardiol*. 1997;30(5):1193-1199. doi:10.1016/s0735-1097(97)00277-5

48. Wang L, Cheng Z, Gu Y, Peng D. Short-Term Effects of Verapamil and Diltiazem in the Treatment of No Reflow Phenomenon: A Meta-Analysis of Randomized Controlled Trials. *Biomed Res Int*. 2015;2015:382086. doi:10.1155/2015/382086
49. Marzilli M, Orsini E, Marraccini P, Testa R. Beneficial Effects of Intracoronary Adenosine as an Adjunct to Primary Angioplasty in Acute Myocardial Infarction. *Circulation*. 2000;101(18):2154-2159. doi:10.1161/01.CIR.101.18.2154
50. Gao Q, Yang B, Guo Y, Zheng F. Efficacy of Adenosine in Patients With Acute Myocardial Infarction Undergoing Primary Percutaneous Coronary Intervention: A PRISMA-Compliant Meta-Analysis. *Medicine (Baltimore)*. 2015;94(32):e1279. doi:10.1097/MD.0000000000001279
51. Navarese EP, Frediani L, Kandzari DE, et al. Efficacy and safety of intracoronary epinephrine versus conventional treatments alone in STEMI patients with refractory coronary no-reflow during primary PCI: The RESTORE observational study. *Catheter Cardiovasc Interv*. 2021;97(4):602-611. doi:10.1002/ccd.29113
52. Skelding KA, Goldstein JA, Mehta L, Pica MC, O'Neill WW. Resolution of refractory no-reflow with intracoronary epinephrine. *Catheter Cardiovasc Interv*. 2002;57(3):305-309. doi:10.1002/ccd.10303
53. Kitakaze M, Asakura M, Kim J, et al. Human atrial natriuretic peptide and nicorandil as adjuncts to reperfusion treatment for acute myocardial infarction (J-WIND): two randomised trials. *Lancet*. 2007;370(9597):1483-1493. doi:10.1016/S0140-6736(07)61634-1
54. Lønborg J, Vejlstrup N, Kelbæk H, et al. Exenatide reduces reperfusion injury in patients with ST-segment elevation myocardial infarction. *Eur Heart J*. 2012;33(12):1491-1499. doi:10.1093/eurheartj/ehr309
55. Wohrle J, Grebe OC, Nusser T, Al-Khayer E, Schaible S, Kochs M, et al. reduction of major adverse cardiac events with intracoronary compared with intravenous bolus application of abciximab in patients with acute myocardial infarction or unstable angina undergoing coronary angioplasty. *Circulation.* 2003;107:1840–3.
56. De Lemos JA, Antman EM, Gibson CM, et al. Abciximab improves both epicardial flow and myocardial reperfusion in ST-elevation myocardial infarction. Observations from the TIMI 14 trial. *Circulation.* 2000;101:239–43.
57. Kunichika H, Ben-Yehuda O, Lafitte S, Kunichika N, Peters B, DeMaria AN. Effects of glycoprotein IIb/IIIa inhibition on microvascular flow after coronary reperfusion. A quantitative myocardial contrast echocardiography study. *J Am Coll Cardiol.* 2004;43:276–83.
58. Montalescot G, Barragan P, Wittenberg O, et al. Platelet glycoprotein IIb/IIIa inhibition with coronary stenting for acute myocardial infarction. *N Engl J Med.* 2001;344:1895–903.

59. Montone, R.A.; Camilli, M.; Del Buono, M.G.; Meucci, M.C.; Gurgoglione, F.; Russo, M.; Crea, F.; Niccoli, G. "No-reflow": Update su diagnosi, fisiopatologia e strategie terapeutiche. G. Ital. Cardiol. 2020, 21, 4S–14S

60. Kim, J.-S.; Kim, J.; Choi, D.; Lee, C.J.; Lee, S.H.; Ko, Y.-G.; Hong, M.-K.; Kim, B.-K.; Oh, S.J.; Jeon, D.W.; et al. Efficacy of high-dose atorvastatin loading before primary percutaneous coronary intervention in ST-segment elevation myocardial infarction: The STATIN STEMI trial. JACC Cardiovasc. Interv. 2010, 3, 332–339.

61. Berwanger, O.; Santucci, E.V.; de Barros E Silva, P.G.M.; de Andrade Jesuíno, I.; Damiani, L.P.; Barbosa, L.M.; Santos, R.H.N.; Laranjeira, L.N.; de Mattos Egydio, F.; Borges de Oliveira, J.A.; et al. Effect of Loading Dose of Atorvastatin Prior to Planned Percutaneous Coronary Intervention on Major Adverse Cardiovascular Events in Acute Coronary Syndrome: The SECURE-PCI Randomized Clinical Trial. JAMA 2018, 319, 1331–1340

62. Yang XM, Liu Y, Cui L, Yang X, Liu Y, Tandon N, Kambayashi J, Downey JM, Cohen MV (2013) Platelet P2Y(1)(2) blockers confer direct postconditioning-like protection in reperfused rabbit hearts. J Cardiovasc Pharmacol Ther 18:251–262.

63. Dai, W.; Ye, Z.; Li, L.; Su, Q. Effect of preoperative loading dose ticagrelor and clopidogrel on no-reflow phenomenon during intervention in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention: A systematic review and meta-analysis. Drug Des. Devel. Ther. 2018, 12, 2039–2049.

64. Ratcovich H, Biasco L, Pedersen F, Helqvist S, Saunamaki K, Tilsted H et al. Prehospital administration of P2Y12 inhibitors and early coronary reperfusion in primary PCI: an observational comparative study. Thrombosis and Haemostasis. 2015;114(09):623-631.

65. Park, K., Cho, YR., Park, JS. *et al.* Design and Rationale for comParison Between ticagreLor and clopidogrEl on mIcrocirculation in Patients with Acute cOronary Syndrome Undergoing Percutaneous Coronary Intervention (PLEIO) Trial. *J. of Cardiovasc. Trans. Res.* **11,** 42–49 (2018). https://doi.org/10.1007/s12265-017-9783-8

66. Niccoli, G.; Scalone, G.; Lerman, A.; Crea, F. Coronary microvascular obstruction in acute myocardial infarction. Eur. Heart J. 2016, 37, 1024–1033.

67. Niccoli, G.; Montone, R.A.; Ibanez, B.; Thiele, H.; Crea, F.; Heusch, G.; Bulluck, H.; Hausenloy, D.J.; Berry, C.; Stiermaier, T.; et al. Optimized Treatment of ST-Elevation Myocardial Infarction. Circ. Res. 2019, 125, 245–258

68. Fröbert, O.; Lagerqvist, B.; Olivecrona, G.K.; Omerovic, E.; Gudnason, T.; Maeng, M.; Aasa, M.; Angerås, O.; Calais, F.; Danielewicz, M.; et al. Thrombus aspiration during ST-segment elevation myocardial infarction. N. Engl. J. Med. 2013, 369, 1587–1597.

69. Jolly, S.S.; Cairns, J.A.; Yusuf, S.; Meeks, B.; Pogue, J.; Rokoss, M.J.; Kedev, S.; Thabane, L.; Stankovic, G.; Moreno, R.; et al. Randomized trial of primary PCI with or without routine manual thrombectomy. N. Engl. J. Med. 2015, 372, 1389–1398

70. Ibanez, B.; James, S.; Agewall, S.; Antunes, M.J.; Bucciarelli-Ducci, C.; Bueno, H.; Caforio, A.L.P.; Crea, F.; Goudevenos, J.A.; Halvorsen, S.; et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Eur. Heart J. 2018, 39, 119–177.

71. Egred, M.; Bagnall, A.; Spyridopoulos, I.; Purcell, I.F.; Das, R.; Palmer, N.; Grech, E.D.; Jain, A.; Stone, G.W.; Nijveldt, R.; et al. Effect of Pressure-controlled intermittent Coronary Sinus Occlusion (PiCSO) on infarct size in anterior STEMI: PiCSO in ACS study. Int. J. Cardiol. Heart Vasc. 2020, 28, 100526.

72. De Maria, G.L.; Alkhalil, M.; Borlotti, A.; Wolfrum, M.; Gaughran, L.; Dall'Armellina, E.; Langrish, JP; Lucking, A.J.; Choudhury, R.P.; Kharbanda, R.K.; et al. Index of microcirculatory resistance-guided therapy with pressure-controlled intermittent coronary sinus occlusion improves coronary microvascular function and reduces infarct size in patients with ST-elevation myocardial infarction: The Oxford Acute Myocardial Infarction–Pressure-controlled Intermittent Coronary Sinus Occlusion study (OxAMIPICSO study). EuroIntervention 2018, 14, e352–e359.

73. Baim, Donald S et al. "Randomized trial of a distal embolic protection device during percutaneous intervention of saphenous vein aorto-coronary bypass grafts." *Circulation* vol. 105,11 (2002): 1285-90.

74. Zhou BQ, Tahk SJ. Effect of a distal protection device on epicardial blood flow and myocardial perfusion in primary percutaneous coronary intervention. J Zhejiang Univ Sci B. 2007 Aug;8(8):575-9

75. Stone GW, Webb J, Cox DA, et al. Distal microcirculatory protection during percutaneous coronary intervention in acute ST-segment elevation myocardial infarction: A randomized controlled trial. *JAMA.* 2005;293:1063–72.

76. Sievert H, Wahr DW, Schuler G, et al. Effectiveness and safety of the Proxis system in demonstrating retrograde coronary blood flow during proximal occlusion and in capturing embolic material. Am J Cardiol 2004;94:1134-9

77. Wang JC, Normand SL, Mauri L, et al. Coronary artery spatial distribution of acute myocardial infarction occlusions. Circulation 2004;110:278-84

78. Kocher AA, Schuster MD, Szabolcs MJ, et al. Neovascularization of ischemic myocardium by human bone-marrow-derived angioblasts prevents cardiomyocyte apoptosis, reduces remodeling and improves cardiac function. *Nat Med.* 2001;7:430–6.

79. McAlindon E, Bucciarelli-Ducci C, Suleiman MS, Baumbach A. Infarct size reduction in acute myocardial infarction. *Heart.* 2015;101:155–160.

80. Tekin K, Cagliyan CE, Tanboga IH, Balli M, Uysal OK, Ozkan B, et al. Influence of the timing of percutaneous coronary intervention on clinical outcomes in non-ST-elevation myocardial infarction. *Korean Circ J.* 2013;43:725–730.

81. Duncker DJ, Klassen CL, Ishibashi Y, Herrlinger SH, Pavek TJ, Bache RJ. Effect of temperature on myocardial infarction in swine. *Am J Physiol.* 1996;270(4 Pt 2):H1189–H1199

82. Götberg, Matthias et al. "A pilot study of rapid cooling by cold saline and endovascular cooling before reperfusion in patients with ST-elevation myocardial infarction." *Circulation. Cardiovascular interventions* vol. 3,5 (2010): 400-7.

83. Nichol, Graham et al. "Prospective, multicenter, randomized, controlled pilot trial of peritoneal hypothermia in patients with ST-segment- elevation myocardial infarction." *Circulation. Cardiovascular interventions* vol. 8,3 (2015): e001965.

84. Piot C, Croisille P, Staat P, et al. Effect of cyclosporine on reperfusion injury in acute myocardial infarction. *N Engl J Med*. 2008;359(5):473-481. doi:10.1056/NEJMoa071142

85. Chakrabarti AK, Feeney K, Abueg C, et al. Rationale and design of the EMBRACE STEMI study: a phase 2a, randomized, double-blind, placebo-controlled trial to evaluate the safety, tolerability and efficacy of intravenous Bendavia on reperfusion injury in patients treated with standard therapy including primary percutaneous coronary intervention and stenting for ST-segment elevation myocardial infarction. *Am Heart J*. 2013;165(4):509-514.e7. doi:10.1016/j.ahj.2012.12.008

86. Ibanez B, Macaya C, Sánchez-Brunete V, et al. Effect of early metoprolol on infarct size in ST-segment-elevation myocardial infarction patients undergoing primary percutaneous coronary intervention: the Effect of Metoprolol in Cardioprotection During an Acute Myocardial Infarction (METOCARD-CNIC) trial. *Circulation*. 2013;128(14):1495-1503. doi:10.1161/CIRCULATIONAHA.113.003653

87. Duan T, Zhang J, Kong R, Song R, Huang W, Xiang D. The effectiveness of alprostadil in treating coronary microcirculation dysfunction following ST-segment elevation myocardial infarction in a pig model. *Exp Ther Med*. 2021;22(6):1449. doi:10.3892/etm.2021.10884

88. Tanzilli G, Greco C, Pasceri V, et al. Dipyridamole versus verapamil for treatment of no-reflow during primary angioplasty. *Catheter Cardiovasc Interv*. 2010;76(6):787-793. doi:10.1002/ccd.22724
89. Ovize M, Baxter GF, Di Lisa F, et al. Postconditioning and protection from reperfusion injury: where do we stand? Position paper from the Working Group of Cellular Biology of the Heart of the European Society of Cardiology. *Cardiovasc Res*. 2010;87(3):406-423. doi:10.1093/cvr/cvq129