

<https://doi.org/10.48047/AFJBS.6.14.2024.10652-10665>



African Journal of Biological Sciences

Journal homepage: <http://www.afjbs.com>



Research Paper

Open Access

An Overview on Management of No-Reflow

Ghada Ibrahim Mohammed, Wael Ali Ali Mohammed Khalil, Shadi Mohamed Awny Kharboush, Radwa Mohammed Mohamed Khalil

Department of Cardiology, Faculty of Medicine, Zagazig University, Egypt

***Corresponding author: Shadi Mohamed Awny Kharboush ,**

Email: Shadikharboush@gmail.com

Volume 6, Issue 14, Aug 2024

Received: 07 July 2024

Accepted: 22 July 2024

Published: 15 Aug 2024

[doi:10.48047/AFJBS.6.14.2024.10652-10665](https://doi.org/10.48047/AFJBS.6.14.2024.10652-10665)

Abstract:

The lack of reperfusion of myocardium after prolonged ischaemia that may occur despite opening of the infarct-related artery is termed “no reflow”. No reflow or slow flow occurs in 3–4% of all percutaneous coronary interventions, and is most common after emergency revascularization for acute myocardial infarction. In this setting no reflow is reported to occur in 30% to 40% of interventions when defined by myocardial perfusion techniques such as myocardial contrast echocardiography. No reflow is clinically important as it is independently associated with increased occurrence of malignant arrhythmias, cardiac failure, as well as in-hospital and long-term mortality. Previously the no-reflow phenomenon has been difficult to treat effectively, but recent advances in the understanding of the pathophysiology of no reflow have led to several novel treatment strategies. These include prophylactic use of vasodilator therapies, mechanical devices, ischaemic postconditioning and potent platelet inhibitors. As no reflow is a multifactorial process, a combination of these treatments is more likely to be effective than any of these alone. In this review we discuss the pathophysiology of no reflow and present the numerous recent advances in therapy for this important clinical problem.

Keywords: No-Reflow, ischaemic, Myocardial Infarction.

Introduction:

Despite being recognized for many years, the effectiveness of therapies for no-reflow (NR) observed in animal models has only partially translated to human patients, showing benefits on surrogate endpoints but not on outcomes like cardiovascular mortality. Currently, the primary treatment for NR involves intracoronary drugs that induce vasodilation in the coronary arteries. Studies have indicated potential efficacy for vasodilators such as

adenosine, calcium channel blockers, and sodium nitroprusside, either alone or in combination, as well as antiplatelet drugs like glycoprotein IIB/IIIA inhibitors [1].

In addition to these pharmacologic treatments, non-pharmacologic strategies have been explored in various trials. These include coronary post-conditioning, remote ischemic conditioning, and tools designed to reduce thrombotic material embolization and enhance coronary flow. However, no single or combined therapy has yet been clearly linked to improved clinical outcomes by reducing ischemia/reperfusion injury. [2].

❖ Pharmacological Treatment

1. B-Blockers

The effect of this class of drugs has been primarily studied in terms of cardiomyocyte protection and infarct extension. However, in some animal models, administering metoprolol before reperfusion has shown to reduce infarct size and the incidence of no-reflow (NR) by inhibiting neutrophil-platelet aggregate formation, demonstrating an anti-inflammatory effect. [3].

In the METOCARD-CNIC study (Effect of Metoprolol in Cardio-protection During an Acute Myocardial Infarction), administering metoprolol before primary percutaneous coronary intervention (pPCI) demonstrated a time-dependent reduction in infarct size, prevention of adverse left ventricular remodeling, preservation of systolic function, and a decrease in the rate of re-hospitalization for heart failure. [4].

A sub analysis of this study also documented an interaction between metoprolol and neutrophil count with a modulating effect of metoprolol on neutrophil impact on MVO. [5]. However, the EARLY-BAMI trial (Early-Beta Blocker Administration Before Reperfusion Primary PCI in Patients With ST-Elevation Myocardial Infarction) provided less promising results, as it did not show a reduction in infarct size at one month in patients who received intravenous metoprolol before pPCI. [6].

In contrast, other molecules such as carvedilol and Nebivolol have demonstrated protection of the coronary microcirculation in preclinical studies [7].

Current guidelines from ESC recommend the use of intravenous beta-blockers in STEMI patients undergoing pPCI without signs of acute heart failure and with systolic blood pressure > 120 mmHg (recommendation class IIa, level of evidence A) [2].

2. Calcium Channel Blockers

Calcium channel blockers (CCBs) (verapamil, diltiazem, nifedipine) are used to treat no-reflow through various mechanisms. Through channel binding on vascular smooth muscle, cardiac myocytes, and nodal cells, they result in smooth muscle relaxation and coronary vasodilation. Several studies, with numerous limitations of selection and

measurements, have demonstrated benefits in NR treatment for verapamil and diltiazem with better outcomes in those treated intracoronary [8, 9].

3. Adenosine

Adenosine is a purine nucleoside with a short half-life (<2 s) and numerous pleiotropic effects including vasodilation of the coronary microcirculation via binding to A₂ receptors and smooth muscle relaxation. It also has anti-inflammatory properties against neutrophils and inhibition of platelet aggregation, promotes ischemic preconditioning by limiting reperfusion injury, and exhibits anti-apoptotic and pro-angiogenic effects. Side effects include bradycardia with atrioventricular block, hypotension, dyspnea, bronchospasm, and flushing [10].

The REOPEN-AMI (Intracoronary Nitroprusside Versus Adenosine in Acute Myocardial Infarction) trial documented a significant improvement in MVO and peak troponin compared with placebo or sodium nitroprusside, leading to a reduction in major cardiovascular events and favorable left ventricular remodeling at 1 year after the event. [11].

4. Sodium Nitroprusside

Sodium nitroprusside is a non-selective drug metabolized to its active form, nitric oxide that acts as a potent vasodilator in the coronary and peripheral microcirculation and by inhibiting platelet aggregation. Its latency of action appears to be more prolonged than other vasodilators [12]

Furthermore, in comparison with drugs such as Tirofiban, it has demonstrated a lower rate of adverse events, an improvement in TIMI frame count, a more rapid resolution of ST-segment elevation, and a higher rate of left ventricular ejection fraction without achieving a significant difference in TIMI grade [7]

5. Epinephrine

Among the pharmacological alternatives available is also intracoronary epinephrine, a drug with limited experience compared to others, but which has recently shown encouraging results for the treatment of NR refractory to other therapies or where these could not be used. [13]

In 2020, the RESTORE trial, a multicenter observational study, was published to evaluate the safety and efficacy of epinephrine in NR during STEMI compared with conventional therapy. Navarese et al. documented a significant improvement in coronary flow, left ventricular ejection fraction, ST-segment resolution, and clinical events at 30 days in STEMI patients with refractory NR compared with the control group [14].

More recently, the COAR trial, an open-labeled study that randomized patients to intracoronary epinephrine vs. adenosine, was published, demonstrating improved end coronary flow and relative safety of epinephrine in normotensive patients with acute coronary syndrome. Nevertheless, the main side effect of epinephrine is the risk of developing malignant arrhythmias [15]

6. Nicorandil

Nicorandil is a vasodilator drug that acts through potassium channels and intracellular cGMP concentrations. It is used for the treatment of angina pectoris during acute coronary syndromes in Japan and some other Asian and European countries because it showed improved coronary perfusion and lower no-reflow rates in a previous meta-analysis [16]

7. Antiplatelet Therapy

Regarding major antiplatelet drugs, The PLEIO study, recently showed superior recovery of microcirculation function in patients treated with Ticagrelor compared with Clopidogrel [17].

This is in line with a previous meta-analysis that demonstrated a greater benefit of Ticagrelor over Clopidogrel in reducing NR and incidence of MACE without significantly increasing the risk of bleeding [18]

Among novel antiplatelet agents, we are awaiting data from the Platelet Inhibition to Target Reperfusion Injury (PITRI) trial, which evaluated the ability of Cangrelor, administered before reperfusion, to reduce the size of acute myocardial infarction and MVO by CMR [19]

Glycoprotein IIB/IIIA inhibitors are potent antiplatelet agents that inhibit platelet aggregation and have demonstrated benefit in the era before the routine use of dual antiplatelet therapy. To date, there have been no studies showing convincing benefits of glycoprotein IIB/IIIA inhibitors in addition to standard therapy [20].

However, the On-TIME-2 (Ongoing Tirofiban in Myocardial Infarction Evaluation 2) study showed that prehospital initiation of bolus Tirofiban could result in ST-segment resolution and improve clinical outcome after pPCI. [21].

Additional conflicting data are those regarding the route of administration, intracoronary or intravenous. Although the **CICERO trial** (Comparison of Intracoronary Versus Intravenous Abciximab Administration During Emergency Reperfusion of ST-Segment Elevation Myocardial Infarction) and **INFUSE-AMI study** (Intracoronary Abciximab and Aspiration Thrombectomy in Patients with Large Anterior Myocardial

Infarction) reported benefits in terms of reduction of infarct area after intra-coronary administration of Abciximab, the **AIDA STEMI study** (Abciximab Intracoronary versus intravenous Drug Application in STEMI) documented similar rates of major adverse cardiovascular events after 90 days and 1 year between the two modalities of administration. [22].

In a series of 71 STEMI cases treated with pPCI, the combined use of glycoprotein IIB/IIIA inhibitors along with aspiration and balloon inflation resulted in decreased NR rates [23].

Finally, according to current ESC guidelines, GP IIb/IIIa inhibitors should be considered (class of recommendation IIa, level of evidence C) if there is evidence of NR or thrombotic complication.

8. Intracoronary Fibrinolysis

The role of fibrinolytic therapy is also still under study. In fact, although some initial encouraging data documented benefits, in terms of myocardial reperfusion, subsequent studies have not confirmed these data [24].

Recently, however, a meta-analysis by Alyamani et al. showed that a targeted thrombolytic IC approach seems safe and able to increase the efficacy of pPCI. [25]

9. Statins

Statin therapy, probably through pleiotropic effects independent of the effect on lipid metabolism, also seems to have beneficial effects in the treatment and prevention of NR. In the **STATIN STEMI study** (Efficacy of High-Dose AtorvaSTATIN Loading Before Primary Percutaneous Coronary Intervention in ST-Elevation Myocardial Infarction), high doses of statins improved angiographic MVO but not infarct extension, compared with low doses. [26]

Data was also confirmed by the **SECURE-PCI study** (Statins Evaluation in Coronary Procedures and Revascularization), which showed an almost 50% reduction in cardiovascular events at 30 days with high-dose atorvastatin compared with placebo. In addition, statin therapy already on board at the time of the event reduced NR rates, improved myocardial functional recovery at follow-up, and reduced the extent of infarction compared with naive patients. [27].

❖ Non-Pharmacological Treatment

1. Ischemic Conditioning

Ischemic preconditioning is the most powerful endogenous mechanism capable of reducing the extent of myocardial infarction by cycles of coronary balloon occlusion and reperfusion [28].

However, although the recent CONDI-2/ERIC-PPCI study did not demonstrate the efficacy of ischemic preconditioning on clinical endpoints as already shown in other large trials. [29]

A recent randomized trial showed encouraging results regarding the incidence of NR by prolonged balloon inflation during stent deployment. Although ischemic post-conditioning has been shown to reduce no-reflow in small studies [30].

However, larger randomized trials of POST, DANAMI-3-iPOST, POSTEMI, and LIPSIA CONDITIONING have not supported its choice in clinical practice [31]

2. Thrombus Aspiration

Thrombus aspiration or coronary filters are tools designed to reduce distal embolization injury, which is one of the etio-pathogenetic mechanisms of NR. However, the routine use of thrombus aspiration, initially associated with better clinical outcomes in STEMI patients has been progressively downgraded because of its inability to reduce 30-day mortality in trials in subsequent years. It is even contraindicated as a routine maneuver in the most recent ESC guidelines (recommendation class III). [32];

Another mechanical approach to reduce distal embolization during STEMI consists of the placement of filters, devices placed before stent deployment, which, however, have never documented an effective improvement in microvascular flow, infarct extension, or clinical outcomes [33].

Among the devices tested, we also find the pressure-controlled intermittent coronary sinus occlusion (PICSO). This is a device of transient occlusion of the flow in the coronary sinus with the aim of increasing cardiac venous pressure and thus improve the perfusion of the microcirculation [34]

3. Future Perspectives

Among the techniques being tested in recent years, we can list therapeutic hypothermia, which has shown favorable results in animals but controversial results in humans [35]

Another technique is **hyper-oxemic reperfusion**, recently approved by the FDA, which consists of the administration of supersaturated oxygen for 90 min after completion of PCI in patients with STEMI. This technique, evaluated in the AMIHOT I and AMIHOT II studies, documented a reduction in final infarct size in spite, however, of an increase in bleeding. [36].

Therefore, in a more recent trial, the IC-HOT study, an infusion of hyper-oxygenated blood at the origin of the left main with a duration of about 60 min was used. [37].

New therapeutic targets could also be those represented by the modulation of the inflammatory response. Possibly, a “tailored” anti-inflammatory approach in patients with evidence of myocardial edema at CMR could benefit this subgroup of individuals. [38]

Finally, other possible “cellular” approaches could be represented by pericytes, which are responsible for vasomotility in the coronary microcirculation and by stem cells, exploiting the photobiostimulatory effects of low-level laser therapy that promotes the recruitment of mesenchymal stem cells into the myocardium. [39].

Assessment of the efficacy of revascularization

- **TIMI Flow Grading (TFG)** is an angiographic tool used to assess myocardial perfusion after PCI. The TIMI flow score ranges from 0 to 3, with 0 indicating no flow and 3 indicating normal flow. [40]
 - **Grade 0** (no perfusion): There is no antegrade flow beyond the point of occlusion.
 - **Grade 1** (penetration without perfusion): The contrast material passes beyond the area of obstruction but “hangs up” and fails to opacify the entire coronary bed distal to the obstruction for the duration of the cine-angiographic filming sequence.
 - **Grade 2** (partial perfusion): The contrast material passes across the obstruction and opacifies the coronary bed distal to the obstruction. The rate of entry of the contrast material into the vessel distal to the obstruction or the rate of clearance from the distal bed is perceptibly slower than its entry into or clearance from comparable areas not perfused by the previously occluded vessel—e.g., the opposite coronary artery or the coronary bed proximal to the obstruction.
 - **Grade 3** (complete perfusion): Antegrade flow into the bed distal to the obstruction occurs as promptly as antegrade flow into the bed proximal to the obstruction, and clearance of contrast material from the involved bed is as rapid as clearance from an uninvolved bed in the same vessel or the opposite artery.
- **Myocardial Blush Grading (MBG)**

MBG is a simple visual angiographic assessment of myocardial perfusion in the infarct area after PCI. It seems to be of additional value, especially in patients with restored epicardial blood flow because MBG reflects the extent of damage of the microvascular bed.

The MBG score ranges from 0 to 3, with 0 meaning no myocardial blush or contrast density; 1, minimal myocardial blush or contrast density; 2, moderate myocardial blush or contrast density but less than that obtained during angiography of a contralateral or ipsilateral non-infarct related coronary artery; 3, normal myocardial blush or contrast density, comparable with that obtained during angiography of a contralateral or ipsilateral non-infarct-related coronary artery. [41]

- **Comparison of Myocardial Blush Grades With TIMI Flow Grades**

Myocardial blush grade was related to TIMI flow. However, the majority of patients with myocardial blush grade ≤ 2 had “normal” TIMI flow. The patients with TIMI 3 flow but low blush grades can be regarded as having no reflow in a comparable way as patients who lack myocardial contrast on their echocardiogram after intracoronary injection of sonicated microbubbles. [42, 43]

Multivariate logistic regression analyses showed that the myocardial blush grade was related to long-term mortality independent of TIMI flow. Therefore, an angiographic variable that takes the extent of myocardial reperfusion into account is of additional prognostic value.

- **Integrating the Assessment of Epicardial and Myocardial Perfusion**

There is the need for a simple, broadly applicable angiographic metric that takes into account indices of epicardial and myocardial perfusion both before and after PCI to arrive at a single perfusion grade. The **Angiographic Perfusion Score (APS)** is the sum of the TFG (0 to 3) added to the MPG (0 to 3) before and after PCI which makes a total possible grade of 0 to 12 scale. [44]

According to the study by Gibson et al. 2004, failed perfusion can be defined as an APS of 0 to 3; partial perfusion, 4 to 9; and full perfusion, 10 to 12. Among STEMI patients in their study, the APS is associated with larger SPECT infarct sizes and with the incidence of death or MI, as follows: failed, 16.7%; partial, 2.5%; and full, 2.4% ($P=0.039$). No patient with an APS score of “full” died, whereas mortality was 11.1% among patients with an APS score of “failed” ($P=0.03$). Such an APS, which combines grades of epicardial and tissue level perfusion before and after PCI or at the end of diagnostic cardiac catheterization to arrive at a single angiographic variable that is

associated with infarct size and 30 day death or MI, may prove valuable in clinical risk stratification. [44]

References:

1. Faruk Akturk, I., Arif Yalcin, A., Biyik, I., Sarikamis, C., Turhan Caglar, N., Erturk, M.,...Oner, E. (2014). Effects of verapamil and adenosine in an adjunct to tirofiban on resolution and prognosis of noreflow phenomenon in patients with acute myocardial infarction. *Minerva Cardioangiol*, 62(5), 389-397.
2. Ibanez, B., James, S., Agewall, S., Antunes, M. J., Bucciarelli-Ducci, C., Bueno, H.,...Group, E. S. C. S. D. (2018). 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J*, 39(2), 119-177.
3. Ibanez, B., Prat-González, S., Speidl, W. S., Vilahur, G., Pinero, A., Cimmino, G.,...Badimon, J. J. (2007). Early metoprolol administration before coronary reperfusion results in increased myocardial salvage: analysis of ischemic myocardium at risk using cardiac magnetic resonance. *Circulation*, 115(23), 2909-2916.
4. Ibanez, B., Macaya, C., Sánchez-Brunete, V., Pizarro, G., Fernández-Friera, L., Mateos, A.,...Fuster, V. (2013). 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*, 128(14), 1495-1503.
5. Niccoli, G., Montone, R. A., Ibanez, B., Thiele, H., Crea, F., Heusch, G.,...Eitel, I. (2019). Optimized Treatment of ST-Elevation Myocardial Infarction. *Circ Res*, 125(2), 245-258.
6. Roolvink, V., Ibáñez, B., Ottervanger, J. P., Pizarro, G., van Royen, N., Mateos, A.,...van 't Hof, A. W. J. (2016). Early Intravenous Beta-Blockers in Patients With ST-Segment Elevation Myocardial Infarction Before Primary Percutaneous Coronary Intervention. *J Am Coll Cardiol*, 67(23), 2705-2715.
7. Zhao, Y. J., Fu, X. H., Ma, X. X., Wang, D. Y., Dong, Q. L., Wang, Y. B.,...Jiang, Y. F. (2013). Intracoronary fixed dose of nitroprusside via thrombus aspiration catheter for the

- prevention of the no-reflow phenomenon following primary percutaneous coronary intervention in acute myocardial infarction. *Exp Ther Med*, 6(2), 479-484.
8. Huang, R. I., Patel, P., Walinsky, P., Fischman, D. L., Ogilby, J. D., Awar, M.,...Savage, M. P. (2006). Efficacy of intracoronary nicardipine in the treatment of no-reflow during percutaneous coronary intervention. *Catheter Cardiovasc Interv*, 68(5), 671-676.
 9. Wang, L., Cheng, Z., Gu, Y., & Peng, D. (2015). 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, 382086.
 10. Grygier, M., Araszkievicz, A., Lesiak, M., & Grajek, S. (2013). Role of adenosine as an adjunct therapy in the prevention and treatment of no-reflow phenomenon in acute myocardial infarction with ST segment elevation: review of the current data. *Kardiol Pol*, 71 2, 115-120.
 11. Niccoli, G., Rigattieri, S., De Vita, M. R., Valgimigli, M., Corvo, P., Fabbiochi, F.,...Crea, F. (2013). Open-label, randomized, placebo-controlled evaluation of intracoronary adenosine or nitroprusside after thrombus aspiration during primary percutaneous coronary intervention for the prevention of microvascular obstruction in acute myocardial infarction: the REOPEN-AMI study (Intracoronary Nitroprusside Versus Adenosine in Acute Myocardial Infarction). *JACC Cardiovasc Interv*, 6(6), 580-589.
 12. Parham, W. A., Bouhasin, A. P., Ciaramita, J. P., Khoukaz, S., Herrmann, S. C., & Kern, M. J. (2004). Coronary Hyperemic Dose Responses of Intracoronary Sodium Nitroprusside. *Circulation: Journal of the American Heart Association*, 109, 1236-1243.
 13. Aksu, T., Guler, T. E., Colak, A., Baysal, E., Durukan, M., Sen, T., & Guray, U. (2015). Intracoronary epinephrine in the treatment of refractory no-reflow after primary percutaneous coronary intervention: a retrospective study. *BMC Cardiovasc Disord*, 15, 10.
 14. Navarese, E. P., Frediani, L., Kandzari, D. E., Caiazzo, G., Cennamo, A. M., Cortese, B.,...Kubica, J. (2021). 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*, 97(4), 602-611.

15. Khan, K. A., Qamar, N., Saghir, T., Sial, J. A., & Kumar, D. (2022). Comparison of Intracoronary Epinephrine and Adenosine for No-Reflow in Normotensive Patients With Acute Coronary Syndrome (COAR Trial). 15(2), e011408.
16. Iwakura, K., Ito, H., Okamura, A., Koyama, Y., Date, M., Higuchi, Y.,...Fujii, K. (2009). Nicorandil treatment in patients with acute myocardial infarction: a meta-analysis. *Circ J*, 73(5), 925-931.
17. Park, K., Cho, Y. R., Park, J. S., Park, T. H., Kim, M. H., & Kim, Y. D. (2019). Comparison of the Effects of Ticagrelor and Clopidogrel on Microvascular Dysfunction in Patients With Acute Coronary Syndrome Using Invasive Physiologic Indices. *Circ Cardiovasc Interv*, 12(10), e008105.
18. Dai, W., Ye, Z., Li, L., & Su, Q. (2018). 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*, 12, 2039-2049.
19. Bulluck, H., Chan, M. H. H., Bryant, J. A., Chai, P., Chawla, A., Chua, T. S.,...Hausenloy, D. J. (2019). Platelet inhibition to target reperfusion injury trial: Rationale and study design. *Clin Cardiol*, 42(1), 5-12.
20. De Luca, G., Navarese, E., & Marino, P. (2009). Risk profile and benefits from Gp IIb-IIIa inhibitors among patients with ST-segment elevation myocardial infarction treated with primary angioplasty: a meta-regression analysis of randomized trials. *Eur Heart J*, 30(22), 2705-2713.
21. Dudek, D., Dziewierz, A., Brener, S. J., Abizaid, A., Merkely, B., Costa, R. A.,...Stone, G. W. (2015). Mesh-Covered Embolic Protection Stent Implantation in ST-Segment–Elevation Myocardial Infarction. *Circulation: Cardiovascular Interventions*, 8(2), e001484.
22. Shakoor, M. T., Ayub, S., & Dhakam, S. (2014). Complications of intracoronary abciximab bolus-only versus standard protocol during percutaneous coronary intervention in acute coronary syndrome. *Int J Cardiol Heart Vessel*, 3, 64-67.
23. Potdar, A., & Sharma, S. (2015). The 'MAP strategy' (Maximum aspiration of atherothrombus and adjunctive glycoprotein IIb/IIIa inhibitor utilization combined with

- prolonged inflation of balloon/stent) for preventing no-reflow in patients with ST-segment elevation myocardial infarction undergoing percutaneous coronary intervention: A retrospective analysis of seventy-one cases. *Indian Heart J*, 67 Suppl 3(Suppl 3), S43-46.
24. Chen, L., Shi, L., & Tian, W. (2021). Intracoronary Thrombolysis in Patients With ST-Segment Elevation Myocardial Infarction: A Meta-Analysis of Randomized Controlled Trials. *72*(7), 679-686.
 25. Alyamani, M., Campbell, S., Navarese, E., Welsh, R. C., & Bainey, K. R. (2021). Safety and Efficacy of Intracoronary Thrombolysis as Adjunctive Therapy to Primary PCI in STEMI: A Systematic Review and Meta-analysis. *Can J Cardiol*, 37(2), 339-346.
 26. Choi, S. H., Kim, Y. H., Hebisch, M., Sliwinski, C., Lee, S., D'Avanzo, C.,...Kim, D. Y. (2014). A three-dimensional human neural cell culture model of Alzheimer's disease. *Nature*, 515(7526), 274-278.
 27. Pourhosseini, H., Lashkari, R., Aminorroaya, A., Soltani, D., Jalali, A., & Tajdini, M. (2019). Effects of high dose atorvastatin before elective percutaneous coronary intervention on highly sensitive troponin T and one year major cardiovascular events; a randomized clinical trial. *Int J Cardiol Heart Vasc*, 22, 96-101.
 28. Niccoli, G., Burzotta, F., Galiuto, L., & Crea, F. (2009). Myocardial no-reflow in humans. *J Am Coll Cardiol*, 54(4), 281-292.
 29. Hausenloy, D. J., Kharbanda, R. K., Møller, U. K., Ramlall, M., Aarøe, J., Butler, R.,...Bøtker, H. E. (2019). Effect of remote ischaemic conditioning on clinical outcomes in patients with acute myocardial infarction (CONDI-2/ERIC-PPCI): a single-blind randomised controlled trial. *Lancet*, 394(10207), 1415-1424.
 30. Rezkalla, S. H., Stankowski, R. V., Hanna, J., & Kloner, R. A. (2017). Management of No-Reflow Phenomenon in the Catheterization Laboratory. *JACC Cardiovasc Interv*, 10(3), 215-223.
 31. Ciofani, J. L., Allahwala, U. K., Scarsini, R., Ekmejian, A., Banning, A. P., Bhindi, R., & De Maria, G. L. (2021). No-reflow phenomenon in ST-segment elevation myocardial infarction: still the Achilles' heel of the interventionalist. *Future Cardiol*, 17(2), 383-397.
 32. Jolly, S. S., Cairns, J. A., Yusuf, S., Meeks, B., Pogue, J., Rokoss, M. J.,...Džavík, V. (2015). Randomized trial of primary PCI with or without routine manual thrombectomy.

N Engl J Med, 372(15), 1389-1398.

33. Annibali, G., Scrocca, I., Aranzulla, T. C., Meliga, E., Maiellaro, F., & Musumeci, G. (2022). "No-Reflow" Phenomenon: A Contemporary Review. *J Clin Med*, 11(8).
34. Egred, M., Bagnall, A., Spyridopoulos, I., Purcell, I. F., Das, R., Palmer, N.,...Zaman, A. (2020). Effect of Pressure-controlled intermittent Coronary Sinus Occlusion (PiCSO) on infarct size in anterior STEMI: PiCSO in ACS study. *Int J Cardiol Heart Vasc*, 28, 100526.
35. El Farissi, M., Mast, T. P., & van de Kar, M. R. D. (2022). Hypothermia for Cardioprotection in Patients with St-Elevation Myocardial Infarction: Do Not Give It the Cold Shoulder Yet! , 11(4).
36. Stone, G. W., Martin, J. L., de Boer, M. J., Margheri, M., Bramucci, E., Blankenship, J. C.,...Boscardin, W. J. (2009). Effect of supersaturated oxygen delivery on infarct size after percutaneous coronary intervention in acute myocardial infarction. *Circ Cardiovasc Interv*, 2(5), 366-375.
37. David, S. W., Khan, Z. A., Patel, N. C., Metzger, D. C., Wood, F. O., Wasserman, H. S.,...Stone, G. W. (2019). Evaluation of intracoronary hyperoxemic oxygen therapy in acute anterior myocardial infarction: The IC-HOT study. *Catheter Cardiovasc Interv*, 93(5), 882-890.
38. Montone, R., Camilli, M., Del Buono, M., Meucci, M. C., Gurgoglione, F., Russo, M.,...Niccoli, G. (2020). No-reflow: update on diagnosis, pathophysiology and therapeutic strategies. *Giornale italiano di cardiologia* (2006), 21, 4-14.
39. O'Farrell, F. M., & Attwell, D. (2014). A role for pericytes in coronary no-reflow. *Nat Rev Cardiol*, 11(7), 427-432.
40. Sarkar, A., Grigg, W. S., & Lee, J. J. (2024). TIMI Grade Flow. In *StatPearls*. StatPearls Publishing Copyright © 2024, StatPearls Publishing LLC.
41. van 't Hof, A. W., Liem, A., Suryapranata, H., Hoorntje, J. C., de Boer, M. J., & Zijlstra, F. (1998). Angiographic assessment of myocardial reperfusion in patients treated with primary angioplasty for acute myocardial infarction: myocardial blush grade. *Zwolle Myocardial Infarction Study Group. Circulation*, 97(23), 2302-2306.
42. Iliceto, S., Marangelli, V., Marchese, A., Amico, A., Galiuto, L., & Rizzon, P. (1996). Myocardial contrast echocardiography in acute myocardial infarction. *Pathophysiological*

background and clinical applications. *Eur Heart J*, 17(3), 344-353.

43. Ito, H., Maruyama, A., Iwakura, K., Takiuchi, S., Masuyama, T., Hori, M.,...Minamino, T. (1996). Clinical implications of the 'no reflow' phenomenon. A predictor of complications and left ventricular remodeling in reperfused anterior wall myocardial infarction. *Circulation*, 93(2), 223-228.
44. Gibson, C. M., Murphy, S. A., Morrow, D. A., Aroesty, J. M., Gibbons, R. J., Gourlay, S. G.,...Braunwald, E. (2004). Angiographic perfusion score: an angiographic variable that integrates both epicardial and tissue level perfusion before and after facilitated percutaneous coronary intervention in acute myocardial infarction. *Am Heart J*, 148(2), 336-340.