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An Overview on Management of No-Reflow

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Abstract:

Primary percutaneous angioplasty (pPCI), represents the reperfusion strategy of choice for patients with STEMI according to current international guidelines of the European Society of Cardiology. Coronary no-reflow is characterized by angiographic evidence of slow or no anterograde epicardial flow, resulting in inadequate myocardial perfusion in the absence of evidence of mechanical vessel obstruction. No reflow (NR) is related to a functional and structural alteration of the coronary microcirculation. Although NR has been a known phenomenon for many years, the efficacy of therapies in animal models has only partially translated to humans with benefits on surrogate endpoints but no impact on endpoints such as cardiovascular mortality. To date, the main treatment of NR is based on the use of intracoronary drugs that can result in vasodilation in the coronary arteries. Several studies have shown possible efficacy for vasodilator drugs, such as adenosine, calcium channel blockers, and sodium nitroprusside, used singularly or in combination, and antiplatelet drugs such as glycoprotein IIB/IIIA inhibitors. Alongside these, nonpharmacologic treatment strategies such as coronary post-conditioning, remote ischemic conditioning, or tools to reduce the embolization of thrombotic material and increase coronary flow have also been investigated in several trials, but there is still no therapy, single or in combination, aimed at reducing ischemia/reperfusion injury that is clearly associated with improved clinical outcomes.

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

Introduction:

Coronary no-reflow (CNR) is characterized by insufficient myocardial tissue perfusion in segments of the coronary circulation affected by thrombotic occlusion, despite the absence of mechanical obstruction evident on angiography. Coronary no-reflow predominantly occurs in patients with ST-segment elevation myocardial infarction (STEMI) following reperfusion therapy, more frequently than in other forms of cardiac ischemia. This condition is a highly dynamic phenomenon, developing progressively over hours and potentially persisting for days to weeks post-reperfusion **(1)**.

The term "no-reflow" was not originally used to describe the phenomenon, which was first observed outside the coronary context. This observation occurred during a case of arterial embolectomy performed by G. Jefferson in 1934, where a patient presented with acute brachial artery occlusion. Although the embolectomy was successfully executed, the patient developed ischemic symptoms within two and a half hours, manifesting as moderate forearm flexor muscle contracture. This initial observation was not an isolated incident; similar conditions were noted in other cases, such as femoral artery embolectomy. The phenomenon resurfaced in 1940 while investigating Volkmann’s ischemic contracture syndrome, characterized by post-traumatic muscle ischemia and infarction. It was hypothesized that post-ischemic contracture results from prolonged blood flow interruption, leading to muscle infarction if unchecked. Since Volkmann's original description, extensive literature has emerged regarding the pathophysiology, clinical presentation, diagnosis, and treatment of this

potentially devastating condition. This review will focus on key aspects of upper extremity compartment syndromes, emphasizing pathophysiological theories, clinical manifestations, and treatment protocols.

In 1948, Harman provided a comprehensive description of what would later be termed the "no-reflow" phenomenon in the skeletal muscle of albino male rabbits. The study involved inducing ischemia through the application of tourniquets, followed by their release. Angiographic assessment, along with the use of bromophenol blue dye, was employed to evaluate the rate of dye penetration and elimination in the ischemic muscles. The results indicated that blood circulation in the ischemic muscles remained extremely sluggish even after the occlusion was removed. Harman established a correlation between the duration of ischemia and the rate of dye elimination from the ischemic muscle. Histological analysis of the ischemic lesions revealed tightly packed erythrocytes within capillaries and accumulation of interstitial fluid post-occlusion, while ruling out thrombi as a contributing factor to the phenomenon **(2)**. In the following years, the no-reflow phenomenon was observed in various experimental ischemia/reperfusion models in kidney **(3)**, adrenal gland **(4)**, brain **(5, 6)**, myocardium **(7)**, and skin **(8)**.

This demonstration of the no-reflow phenomenon across different animal models and organs led Majno et al. to propose that no-reflow following an ischemic insult may represent a generalizable phenomenon **(9)**.

The term "no-reflow phenomenon" was first introduced by Guido Majno et al. in 1967 in a Letter to the Editor published in the Lancet, describing the failure to achieve reperfusion in rabbit brain regions subjected to ischemia via arterial ligation, despite restored blood flow **(9)**.

Approximately six months later, a supportive publication appeared in the February issue of the American Journal of Pathology, utilizing electron microscopy to elucidate various morphological characteristics of the no-reflow phenomenon at the capillary level. These characteristics included capillary obstruction due to cellular swelling, bleb formations from endothelial cells, aggregates of platelets and red blood cells, and extravascular compression of the microcirculation **(6)**.

In 1974, Kloner et al., in collaboration with Robert Jennings, conducted the first study linking coronary ischemia, specifically myocardial infarction, to the no-reflow phenomenon following coronary occlusion in anesthetized dogs subjected to ischemia for 40 to 90 minutes **(10)**.

Ischemia was induced by clamping the circumflex coronary artery, followed by the release of the clamp and subsequent reperfusion. Utilizing electron microscopy, the authors provided a detailed characterization of the ultrastructural alterations in the vasculature and functioning myocardium that underlie the pathophysiology of coronary no-reflow (CNR) to this day **(10, 11)**.

Pharmacological Treatment

1. B-Blockers

The effect of this class of drugs has been primarily studied in terms of cardiomyocyte protection and infarct extension. In some animal models, however, metoprolol, before reperfusion, reduced the size of the infarct area and the occurrence of NR with an anti-inflammatory action through inhibition of neutrophil-platelet aggregate formation **(12)**. In the METOCARD-CNIC (Effect of Metoprolol in Cardioprotection During an Acute Myocardial Infarction) study, metoprolol, administered before pPCI and through a time-dependent action, reduced the extent of infarction, prevented adverse left ventricular remodeling, preserved systolic function, and reduced the rate of rehospitalization for heart failure **(13)**. 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 **(14)**.

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) **(15)**.

2. Calcium Channel Blockers

Calcium channel blockers (CCBs) (verapamil, diltiazem, nicardipine) 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. In particular, nicardipine has documented better outcomes in combination with rotational atherectomy for the prevention of no-reflow **(16)**.

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 **(17)**.

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 **(18)**.

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 **(19, 20)**. 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 **(21)**.

Although there are no data to support the preventive capacity of NR, nitroprusside, at 6-month follow-up, documented lower rates of revascularization, myocardial infarction, or death compared with placebo-treated patients. However, further studies are needed for a more accurate assessment of the ability of nitroprusside to prevent NR **(22)**.

6. 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 **(23, 24)**. 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 **(25)**.

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 **(26)**.

7. Antiplatelet Therapy

With regard to the major antiplatelet drugs, no NR or myocardial perfusion benefits were documented from sub-analysis of the PLATO (Study of Platelet Inhibition and Patient Outcomes) in the ATLANTIC

(Administration of Ticagrelor in the Cath Lab or in the Ambulance for New ST Elevation Myocardial Infarction to Open the Coronary Artery) study and in the REDUCE-MVI (Reducing Micro Vascular Dysfunction in Acute Myocardial Infarction by Ticagrelor) study **(27-29)**. The PLEIO study, however, recently showed superior recovery of microcirculation function in patients treated with ticagrelor compared with clopidogrel **(30)**. 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 **(31)**.

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 **(32)**.

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 **(15)**.

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 **(33)**. Among them, the randomized T-TIME trial recently demonstrated that low-dose intracoronary alteplase does not improve MVO **(34)**. Therefore, at present, current data do not support its use as adjuvant therapy to improve NR **(14)**. 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 **(35)**.

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 **(36)**. In the STATIN STEMI (Efficacy of High-Dose AtorvaSTATIN Loading Before Primary Percutaneous Coronary Intervention in ST-Elevation Myocardial Infarction) study, high doses of statins improved angiographic MVO but not infarct extension, compared with low doses **(37)**.

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 **(38)**. However, although the recent CONDI-2/ERIC-PPCI study did not demonstrate the efficacy of ischemic preconditioning on clinical endpoints **(39)**, as already shown in other large trials **(40)**, a recent randomized trial showed encouraging results regarding the incidence of NR by prolonged balloon inflation during stent deployment **(41)**.

2. Thrombus Aspiration

Thrombus aspiration or coronary filters are tools designed to reduce distal embolization injury, which is one of the etiopathogenetic mechanisms of NR **(42)**.

However, the routine use of thrombus aspiration, initially associated with better clinical outcomes in STEMI patients **(14)**, has been progressively downgraded because of its inability to reduce 30-day mortality in trials in subsequent years **(43, 44)**; it is even contraindicated as a routine maneuver in the most recent ESC guidelines (recommendation class III) **(15)**.

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 **(42)**.

The pressure-controlled intermittent coronary sinus occlusion (PICSO) was tested. 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 **(45)**. The OxAMI-PICSO (Oxford Acute Myocardial Infarction-

Pressure-Controlled Intermediate Coronary Sinus Occlusion) trial tested the use of PICSO prior to stent release in patients with IMR > 40, demonstrating less extension of infarction at 6 months in patients treated with PICSO compared with the control group **(46)**.

3. other techniques

Therapeutic hypothermia, which has shown favorable results in animals but controversial results in humans **(47)**.

Another technique is hyperoxemic 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 **(48)**.

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 **(36)**.

Finally, other possible "cellular" approaches could be represented by pericytes, which are responsible for vasomotility in the coronary microcirculation **(49)**, and by stem cells, exploiting the photobiostimulatory effects of low-level laser therapy that promotes the recruitment of mesenchymal stem cells into the myocardium **(50)**.

References:

1. **Ndrepepa, G. and Kastrati, A. (2023):** Coronary No-Reflow after Primary Percutaneous Coronary Intervention—Current Knowledge on Pathophysiology, Diagnosis, Clinical Impact and Therapy. Journal of Clinical Medicine, 12(17), 5592.
2. **Harman, J. W. (1948):** The significance of local vascular phenomena in the production of ischemic necrosis in skeletal muscle. *The American journal of pathology*, *24*(3), 625.
3. **Flores, J., DiBona, D. R., Beck, C. H. and Leaf, A. (1972):** The role of cell swelling in ischemic renal damage and the protective effect of hypertonic solute. *The Journal of clinical investigation*, *51*(1), 118-126.
4. **Kovacs, K., Carroll, R. and Tapp, E. (1966):** Temporary ischaemia of the rat adrenal gland. *The Journal of Pathology and Bacteriology*, *91*(1), 235-240.
5. **Ames 3rd, A., Wright, R. L., Kowada, M., Thurston, J. M. and Majno, G. (1968):** Cerebral ischemia. II. The no-reflow phenomenon. *The American journal of pathology*, *52*(2), 437.
6. **Chiang, J., Kowada, M., Ames 3rd, A., Wright, R. L. and Majno, G. (1968):** Cerebral ischemia. III. Vascular changes. *The American journal of pathology*, *52*(2), 455.
7. **Krug, A., De Rochemont, W. D. M. and Korb, G. (1966):** Blood supply of the myocardium after temporary coronary occlusion. *Circulation Research*, *19*(1), 57-62.
8. **Willms-Kretschmer, K. and Majno, G. (1969):** Ischemia of the skin. Electron microscopic study of vascular injury. *The American journal of pathology*, *54*(3), 327.
9. **Majno, G., Ames, A., Chiang, J. and Wright, R. L. (1967):** No reflow after cerebral ischaemia. *The Lancet*, *290*(7515), 569-570.
10. **Kloner, R. A., Ganote, C. E. and Jennings, R. B. (1974a):** The "no-reflow" phenomenon after temporary coronary occlusion in the dog. The Journal of clinical investigation, 54(6), 1496-1508.
11. **Kloner, R. A., Ganote, C. E., Whalen Jr, D. A. and Jennings, R. B. (1974b):** Effect of a transient period of ischemia on myocardial cells: II. Fine structure during the first few minutes of reflow. The American journal of pathology, 74(3), 399.

12. **Ibanez, B., Prat-González, S., Speidl, W. S., Vilahur, G., Pinero, A., Cimmino, G., et al. (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.

13. **Ibanez, B., Macaya, C., Sánchez-Brunete, V., Pizarro, G., Fernández-Friera, L., Mateos, A., et al. (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.

14. **Niccoli, G., Montone, R. A., Ibanez, B., Thiele, H., Crea, F., Heusch, G., et al. (2019):** Optimized treatment of ST-elevation myocardial infarction: the unmet need to target coronary microvascular obstruction as primary treatment goal to further improve prognosis. *Circulation Research*, *125*(2), 245-258.

15. **Ibanez, B., James, S., Agewall, S., Antunes, M. J., Bucciarelli-Ducci, C., Bueno, H., et al. (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). *European heart journal*, *39*(2), 119-177.

16. **Fischell, T. A., Haller, S., Pulukurthy, S. and Virk, I. S. (2008):** Nicardipine and adenosine "flush cocktail" to prevent no-reflow during rotational atherectomy. *Cardiovascular Revascularization Medicine*, *9*(4), 224-228.

17. **Grygier, M., Araszkiewicz, A., Lesiak, M. and 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. *Kardiologia Polska (Polish Heart Journal)*, *71*(2), 115-120.

18. **Niccoli, G., Rigattieri, S., De Vita, M. R., Valgimigli, M., Corvo, P., Fabbiocchi, F., et al. (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: Cardiovascular Interventions*, *6*(6), 580-589.

19. **Parham, W. A., Bouhasin, A., Ciaramita, J. P., Khoukaz, S., Herrmann, S. C. and Kern, M. J. (2004):** Coronary hyperemic dose responses of intracoronary sodium nitroprusside. *Circulation*, *109*(10), 1236-1243.

20. **Wang, H. J., Lo, P. H., Lin, J. J., Lee, H. and Hung, J. S. (2004):** Treatment of slow/no-reflow phenomenon with intracoronary nitroprusside injection in primary coronary intervention for acute myocardial infarction. *Catheterization and Cardiovascular Interventions*, *63*(2), 171-176.

21. **Zhao, Y. J., Fu, X. H., Ma, X. X., Wang, D. Y., Dong, Q. L., Wang, Y. B., et al. (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. *Experimental and Therapeutic Medicine*, *6*(2), 479-484.

22. **Amit, G., Cafri, C., Yaroslavtsev, S., Fuchs, S., Paltiel, O., Abu-Ful, A., et al. (2006):** Intracoronary nitroprusside for the prevention of the no-reflow phenomenon after primary percutaneous coronary intervention in acute myocardial infarction. A randomized, double-blind, placebo-controlled clinical trial. *American Heart Journal*, *152*(5), 887-e889.

23. **Skelding, K. A., Goldstein, J. A., Mehta, L., Pica, M. C. and O'Neill, W. W. (2002):** Resolution of refractory no-reflow with intracoronary epinephrine. *Catheterization and Cardiovascular Interventions*, *57*(3), 305-309.

24. **Aksu, T., Guler, T. E., Colak, A., Baysal, E., Durukan, M., Sen, T., et al. (2015):** Intracoronary epinephrine in the treatment of refractory no-reflow after primary percutaneous coronary intervention: a retrospective study. *BMC Cardiovascular Disorders*, *15*, 1-7.

25. **Navarese, E. P., Frediani, L., Kandzari, D. E., Caiazzo, G., Cenname, A. M., Cortese, B., et al. (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. *Catheterization and Cardiovascular Interventions*, *97*(4), 602-611.

26. **Iwakura, K., Ito, H., Okamura, A., Koyama, Y., Date, M., Higuchi, Y., et al. (2009):** Nicorandil Treatment in Patients With Acute Myocardial Infarction A Meta-Analysis. *Circulation Journal*, *73*(5), 925-931.

27. **Steg, P. G., James, S., Harrington, R. A., Ardissino, D., Becker, R. C., Cannon, C. P., et al. (2010):** Ticagrelor versus clopidogrel in patients with ST-elevation acute coronary syndromes intended for reperfusion with primary percutaneous coronary intervention: a Platelet Inhibition and Patient Outcomes (PLATO) trial subgroup analysis. *Circulation*, *122*(21), 2131-2141.

28. **Montalescot, G., Van't Hof, A. W., Lapostolle, F., Silvain, J., Lassen, J. F., Bolognese, L., et al. (2014):** Prehospital ticagrelor in ST-segment elevation myocardial infarction. *New England Journal of Medicine*, *371*(11), 1016-1027.

29. **van Leeuwen, M. A. H., van der Hoeven, N. W., Janssens, G. N., Everaars, H., Nap, A., Lemkes, J. S., et al. (2019):** Evaluation of Microvascular Injury in Revascularized Patients With ST-Segment–Elevation Myocardial Infarction Treated With Ticagrelor Versus Prasugrel: The REDUCE-MVI Trial. *Circulation*, *139*(5), 636-646.

30. **Park, K., Cho, Y.-R., Park, J.-S., Park, T.-H., Kim, M.-H. and 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. *Circulation: Cardiovascular Interventions*, *12*(10), e008105.

31. **Dai, W., Ye, Z., Li, L. and 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 design, development and therapy*, 2039-2049.

32. **Bulluck, H., Chan, M. H. H., Bryant, J. A., Chai, P., Chawla, A., Chua, T. S., et al. (2019):** Platelet inhibition to target reperfusion injury trial: Rationale and study design. *Clinical cardiology*, *42*(1), 5-12.

33. **Chen, L., Shi, L., Tian, W. and Zhao, S. (2021):** Intracoronary thrombolysis in patients with ST-segment elevation myocardial infarction: a meta-analysis of randomized controlled trials. *Angiology*, *72*(7), 679-686.

34. **McCartney, P. J., Eteiba, H., Maznyczka, A. M., McEntegart, M., Greenwood, J. P., Muir, D. F., et al. (2019):** Effect of low-dose intracoronary alteplase during primary percutaneous coronary intervention on microvascular obstruction in patients with acute myocardial infarction: a randomized clinical trial. *Jama*, *321*(1), 56-68.

35. **Alyamani, M., Campbell, S., Navarese, E., Welsh, R. C. and Bainey, K. R. (2021):** Safety and efficacy of intracoronary thrombolysis as adjunctive therapy to primary PCI in STEMI: a systematic review and meta-analysis. *Canadian Journal of Cardiology*, *37*(2), 339-346.

36. **Montone, R. A., Camilli, M., Del Buono, M. G., Meucci, M. C., Gurgoglione, F., Russo, M., et al. (2020):** "No-reflow": update su diagnosi, fisiopatologia e strategie terapeutiche. *Giornale Italiano di Cardiologia*, *21*(6), 4-14.

37. **Kim, J.-S., Kim, J., Choi, D., Lee, C. J., Lee, S. H., Ko, Y.-G., et al. (2010):** Efficacy of high-dose atorvastatin loading before primary percutaneous coronary intervention in ST-segment elevation myocardial infarction: the STATIN STEMI trial. *JACC: Cardiovascular Interventions*, *3*(3), 332-339.

38. **Niccoli, G., Burzotta, F., Galiuto, L. and Crea, F. (2009):** Myocardial no-reflow in humans. *Journal of the American College of Cardiology*, *54*(4), 281-292.

39. **Hausenloy, D. J., Kharbanda, R. K., Møller, U. K., Ramlall, M., Aarøe, J., Butler, R., et al. (2019b):** Effect of remote ischaemic conditioning on clinical outcomes in patients with acute myocardial infarction (CONDI-2/ERIC-PPCI): a single-blind randomised controlled trial. The Lancet, 394(10207), 1415-1424.

40. **Ciofani, J. L., Allahwala, U. K., Scarsini, R., Ekmejian, A., Banning, A. P., Bhindi, R., et al. (2021):** No-reflow phenomenon in ST-segment elevation myocardial infarction: still the Achilles' heel of the interventionalist. *Future cardiology*, *17*(2), 383-397.

41. **Ma, M., Wang, L., Diao, K.-y., Liang, S.-c., Zhu, Y., Wang, H., et al. (2022):** A randomized controlled clinical trial of prolonged balloon inflation during stent deployment strategy in primary percutaneous coronary intervention for ST-segment elevation myocardial infarction: A pilot study. *BMC Cardiovascular Disorders*, *22*(1), 30.

42. **Niccoli, G., Scalone, G., Lerman, A. and Crea, F. (2016):** Coronary microvascular obstruction in acute myocardial infarction. *European heart journal*, *37*(13), 1024-1033.

43. **Fröbert, O., Lagerqvist, B., Olivecrona, G. K., Omerovic, E., Gudnason, T., Maeng, M., et al. (2013):** Thrombus aspiration during ST-segment elevation myocardial infarction. *New England Journal of Medicine*, *369*(17), 1587-1597.

44. **Jolly, S. S., Cairns, J. A., Yusuf, S., Meeks, B., Pogue, J., Rokoss, M. J., et al. (2015):** Randomized trial of primary PCI with or without routine manual thrombectomy. *New England Journal of Medicine*, *372*(15), 1389-1398.

45. **Egred, M., Bagnall, A., Spyridopoulos, I., Purcell, I. F., Das, R., Palmer, N., et al. (2020):** Effect of Pressure-controlled intermittent Coronary Sinus Occlusion (PiCSO) on infarct size in anterior STEMI: PiCSO in ACS study. *IJC Heart & Vasculature*, *28*, 100526.

46. **De Maria, G. L., Alkhalil, M., Borlotti, A., Wolfrum, M., Gaughran, L., Dall'Armellina, E., et al. (2018):** 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. *EuroIntervention*, *14*(3), e352-e359.

47. **El Farissi, M., Mast, T. P., van de Kar, M. R. D., Dillen, D. M. M., Demandt, J. P. A., Vervaat, F. E., et al. (2022):** Hypothermia for Cardioprotection in Patients with St-Elevation Myocardial Infarction: Do Not Give It the Cold Shoulder Yet! *Journal of Clinical Medicine*, *11*(4), 1082.

48. **David, S. W., Khan, Z. A., Patel, N. C., Metzger, D. C., Wood, F. O., Wasserman, H. S., et al. (2019):** Evaluation of intracoronary hyperoxemic oxygen therapy in acute anterior myocardial infarction: the IC-HOT study. *Catheterization and Cardiovascular Interventions*, *93*(5), 882-890.

49. **O'Farrell, F. M. and Attwell, D. (2014):** A role for pericytes in coronary no-reflow. *Nature Reviews Cardiology*, *11*(7), 427-432.

50. **Elbaz-Greener, G., Sud, M., Tzuman, O., Leitman, M., Vered, Z., Ben-Dov, N., et al. (2018):** Adjunctive laser-stimulated stem-cells therapy to primary reperfusion in acute myocardial infarction in humans: safety and feasibility study.