Indian Heart Journal 73 (2021) 395–403

Contents lists available at ScienceDirect

Indian Heart Journal

journal homepage: www.elsevier.com/locate/ihj

Editorial

Myocardial preservation during primary percutaneous intervention: It's time to rethink?

Keywords:
Myocardial preservation
Primary PCI

Primary Percutaneous Coronary Intervention (PPCI) plays the most important role in the management of ST Segment elevation myocardial infarction (STEMI). It is more effective than thrombolytic therapy (TT) for the treatment of STEMI.[1] Timely reperfusion either by TT or PPCI is the key factor for limiting infarct size, preserving left ventricular ejection fraction (LVEF) and decreasing mortality.[2] To achieve maximum myocardial salvage it is important to restore the full patency of large epicardial coronary arteries, but it is also necessary to maintain blood flow in microcirculation of the reperfused bed. Myocardial damage during STEMI is primarily due to ischemia, but paradoxically, reperfusion also play an important role. A clear understanding of ischemic and reperfusion injury may help to improve myocardial protection during PPCI. The ischemic injury can be minimized by early revascularization, however limiting reperfusion injury require more insight into its pathophysiology. Reperfusion injury can lead to reperfusion arrhythmias, myocardial stunning, microvascular obstruction (MVO) leading to no-flow and sometime lethal cellular injury.[3] Usually every effort was made by interventionist to maintain the epicardial patency, they often forget that in spite of fully open epicardial artery, effective reperfusion may not have reached to the myocardial tissue and restoration of blood flow to ischemic tissue is incomplete. This often mitigate the full benefit of PPCI. Treatments for MVO that were shown to be effective in pre-clinical research have often failed to translate into effective clinical therapies. Current review will emphasize the importance of myocardial preservation during PPCI.

1. No-flow

During PPCI successful opening of epicardial infarction related artery, but incomplete restoration of blood flow to ischemic myocardial tissue is called no-flow. This is because of severe MVO. No-flow because of procedure failure (i.e. incomplete lesion dilatation, coronary spasm, dissection or in situ thrombosis) should be carefully excluded from true no-flow. No-flow phenomenon is dynamic by nature and may spontaneously resolve itself over time. The phenomenon of no-flow was first confirmed in animal models of brain ischaemia,[4,5] then in canine ischemic heart.[6] It was first demonstrated in human heart with use of myocardial contrast echocardiography (MCE) and changes of myocardial blush grade (MBG).[7,8]

The reported incidence of no-flow during PPCI is quite variable. In some series it is between 1 and 3% cases.[9,10] However higher incidence has been reported 5–25 %.[11–16] This depend upon the definition which was used in various studies. Some define TIMI grade $\leq$2 and some included patients with TIMI grade $\leq$1 as no-flow. When MVO was assessed within 7 days after reperfusion by PPCI using cardiac magnetic resonance imaging (CMR) microvascular obstruction was present in upto 56.9 % of patients.[17] Early detection, preventive measures and treatment of no-flow may alter the final outcome of PPCI.

2. Mechanism of No-flow

No flow during PPCI is caused by a combination of multiple mechanisms. The four important mechanism is describes below.

1 Microembolization:

Microembolization from erosion or rupture of atherosclerotic plaque occurs in approximately 25 % of all PCIs.[18] Its incidence ranges from 0 % to 70 %, in part depending on the method of its assessment[19] and it seems to be predominating cause of no-flow. It occurs frequently with preexisting kidney disease, acute coronary syndrome, complex and lengthy lesions, increased number and duration of balloon inflations, use of rotablation and use of stent rather than POBA.[19] Plaque erosion is more prone to distal embolization when compared with plaque rupture.[20] A study done with doppler guide wire had shown that average PCI generates approximately 25 emboli particles which are not sufficient to cause MVO in human. When the number increases to >25–200 or the size of micro-emboli is > 200 μm, it can lead to severe MVO and no-flow.[21] Although this is more common in venous graft, but can occurs in native coronary arteries.[22] Microparticles content of embolized material are also important. Embolized material are found to be biologically active and may aggravate reperfusion injury beyond its mechanical obstructive effect on the microcirculation. During PPCI generation of micro emboli is strongly associated with thrombus burden, increased myocardial damage, MVO and no-flow.[20,22]

2 Ischemia mediated injury:

https://doi.org/10.1016/j.ihj.2021.07.008

Complete absence of blood supply to the myocardium leads to depletion of residual oxygen of the myocardium within seconds. Anaerobic metabolism is activated which is able to produce sufficient ATP for basal cell activity for a short time. As the duration of ischemia increase there is accumulation of many inflammatory and bioactive products which further slows down ATP production. Further ion pumps in the sarcolemma and sarcoplasmic reticulum cease to function, leading to calcium overload into the cell which further damage mitochondria and cell in the ischemic zone. Once ATP is completely depleted, cardiomyocytes undergo ischemic contracture and death through a process of oncosis and necrosis. However, even before this step, programmed cell death pathways may be activated which include apoptosis, necroptosis or pyroptosis.[23]

Prolonged ischemia is known to causes specific changes in endothelium. Ischemia followed by reperfusion lead to endothelial cell and microvascular damage. Endothelial cells showed large intraluminal protrusions, decreased pinocytic vesicles, large endothelial gaps with extra vascular erythrocytes and fibrin deposit, which leads to endothelial and capillary dysfunction leading to MVO.[24] Myocardial cell swelling with marked interstitial edema is one of the early morphologic changes which compresses capillaries and small arterioles leading to MVO.[24,25] The most important clinical predictor of ischemia related injury is ischemia duration and ischemic extent.[20,26]

3 Reperfusion injury:

After prolong ischemia when reperfusion starts, ischemia mediated injury is potentiated by reperfusion injury which may lead to further myocardial necrosis. Calcium paradox, i.e. the readmission of calcium after a short period of calcium-free or low-flow (ischemic) plays important role in immediate damage to the myocyte. Calcium overload lead to damage to the sarcolemma and the sarcoplasmic reticulum, mitochondria and subsequently myocytes.[27] Platelets leukocyte aggregates in microvasculature produces large amount of vasoconstrictors, oxidants, proteolytic enzymes and pro inflammatory mediators. Abrupt pH restoration (pH Paradox) during reperfusion and production of radical oxygen species (Oxygen Paradox and Oxidative Stress) lead to opening of mitochondrial membrane permeability transition pores, calcium overload of cells, mitochondrial swelling, and cell membrane disruption results in further coronary vascular dysfunction and MVO.[27,28] Release and accumulation of many bioactive factors from endothelium and coronary plaque e.g. neutrophils, proteolytic enzymes, prostacyclin, endothelin-1, tissue factors, and microparticles may further increase functional impairment of coronary microvascular.[28–30] Reperfusion after ischemia often lead to intramyocardial haemorrhage. Endothelial damage, activation of inflammation and coagulation pathway further aggravate the haemorrhage.[31]

4 Susceptibility of coronary microcirculation to injury:

Traditional and non-traditional risk factors play a role in epicardial and microvascular endothelial dysfunction. Aging, hypertension, diabetes, dyslipidaemia, insulin resistance, and chronic inflammatory diseases has shown to impaired coronary flow reserve.[32,33] Diabetes and hypercholesterolemia may precipitate no-flow.[34,35] Individual genetic susceptibility may also plays role in the modulation of no-flow.[36] Hyperglycemia may contribute to no-flow irrespective of previous glycemic control and lead to larger infarct size and worse functional recovery in STEMI patients with successful reperfusion.[37] Pre-infarction angina is associated with reduced no-flow leading to preservation of the microvasculature.[26,38]

3. Predictors of no flow

Longer time to reperfusion and thrombus burden at a lesion site is a major predictor for distal embolization and no-flow.[12,39,40] The extent of the ischemic area is another determinant of no-reflow.[26] Another risk factor for no-flow is Saphenous vein graft intervention.[41–43] A positive relationship between acute increase myocardial wall thickness and occurrence of no-flow was proposed.[44] Several studies have demonstrated that platelets play an important role in no-flow. Platelet reactivity on admission,[45] mean platelet volume on admission[46] and plasma levels of thromboxane-A2[47] might be associated with the no-flow. Depletion of antioxidants,[48] Endothelin-1 levels on admission[49,50] and increase neutrophil count[51] may be associated with the no-flow phenomenon and MVO in STEMI. Elevated C-reactive protein was associated with impaired reperfusion in the myocardium with STEMI.[52] SYNTAX score can identify patients at risk for developing no-flow.[53] Soluble suppression of tumorigenicity (sST2) was found to be one of the independent predictors of the no-flow phenomenon in STEMI patients undergoing PPCI.[54]

4. Diagnosis of no flow

Galiuto[55] proposed a pathological classification of no-flow, based upon pathophysiology and therapeutic options of no-flow. (1) Structural no-flow which is largely irreversible and caused by prolonged ischemia leading to damage and loss of capillary integrity with endothelial swelling and odema thus causing severe MVO. The extent of lesion depends upon the severity and duration of ischemia. (2) Functional no-flow which is largely reversible and in which patency of microvasculature is compromised due to spasm, micro embolization and reperfusion injury etc.

The patient with no-flow has persistent chest pain, tachycardia, and hypotension. Although MVO is reversible in about 50 % of patients, persistent no-flow and MVO should be considered with persistent chest pain post PPCI. Surface ECG gives clue to diagnosis. Lack of ST Segment resolution (complete resolution defined as a 50–70 % decrease of sum of ST segment) is considered as an established marker of no-flow.[56–58]

Assessment of no-flow in catheterization laboratory is a common practice. During PCI no flow phenomenon is define by Thrombolysis In Myocardial Infarction (TIMI) flow grade. TIMI flow grade 0 to 2, is associated with no-flow.[59] The TIMI Flow is widely used for acute success and short or long term clinical outcomes after PPCI and thrombolysis.[58]

However newer technique has shown than epicardial TIMI flow grade 3 may be an incomplete measure of reperfusion success and still MVO and poor outcome is seen.[60] Corrected TIMI frame Count (CTFC) more objectively assess coronary circulation. However has not reached wide acceptance in assessing MVO.[61,62] An alternative method to assess micro vascular perfusion is the TIMI myocardial perfusion grade (TIMI-MPG), graded on a scale of 0–3.[63]

TIMI myocardial perfusion grades, flow grades, frame count all has shown to predict outcome in PPCI.[64]

Myocardial Blush Grade (MBG) measures the relative “blush” or intensity of the contrast reaching in the myocardial tissue and the rapidity by which it clears. Intensity of the myocardial blush and faster clearance is suggestive of better microvascular perfusion. Its scale is described as 0,1,2, 3 with higher scores means better perfusion.[65] MBG is mainly influenced by microvascular patency and is less dependent on the amount of muscle necrosis.[66] After PPCI significant number of patients with TIMI 3 flow has MBG of

0–1, which is suggestive of no-flow. MBG can better describe the effectiveness of myocardial reperfusion and is an independent predictor of long-term mortality, independent of Killip class, TIMI grade flow, LVEF and other clinical variables.[65,67] Patients treated by either PPCI[68] or thrombolysis[57] integration of MBG and STR, not only MBG, was found to be of greater prognostic utility. A very good outcomes in patients with an MBG 2 to 3 and STR >70 %, very poor outcomes in patients with MBG 0 to 1 and STR<70 %.

Noninvasive imaging techniques such as Myocardial contrast echocardiography (MCE): and Cardiac magnetic resonance imaging (CMR) provide a more direct assessment of myocardial perfusion. Lack of intramyocardial contrast opacification is predictive of no-flow.[69] No-flow at MCE was found to be the better predictor of adverse LV remodeling than MBG, TIMI grade flow and STR.[70]

CMR at present it is a gold standard for assessment and diagnosis of no-flow. It can accurately characterize the presence and spatial extent of no-flow regions. It is useful in discriminating areas of necrosis with and without no-flow. It can also predict left ventricular remodeling and patient outcome in STEMI.[17,71,72]

5. Consequences of No-flow

Clinically it is important because no-flow predicts poor outcomes after PPCI.[13,14,73,74] It is associated with nonresolving chest pain and persistent ST-T changes. Major consequences of no-flow are larger infarct size, poor LVEF, LV dilatation, ventricular arrhythmia[75–77] and adverse LV remodeling.[78] No-flow phenomenon after PPCI predicts an increased risk of death and reinfarction,[14,75,76] even after 5 years.[77] No-flow is a progressive phenomenon and its presentation may be delayed.

6. Prevention and treatment strategies

Well controlled blood sugar levels improve long term prognosis in STEMI.[79] Chronic hyperglycemia plays a key role in coronary vascular endothelium dysfunction.[80] The no-flow phenomenon was found more in patients with hyperglycemia leading to larger infarct size and worse functional recovery.[37] So control diabetes plays important preventive strategies. Before PPCI acute intensive statin therapy has shown to significantly reduces post-procedural no-flow phenomenon.[81] Prevention of distal embolization during PPCI is important for prevention of no-flow. Stent deployment at nominal pressure rather than at high pressure and direct stenting[82] has shown to minimize distal embolization. Use of cover stents thought to prevent distal embolization and has shown to improve MBG and corrected TIMI frame count[83] but this has not translated in improve clinical outcome in randomized studies.[84,85] The concept of defer stenting has also not shown to be beneficial.[86]

Use of thrombectomy both (mechanical or manual) have shown mixed results. Initial studies with mechanical thrombectomy devices has shown some benefit in form of better post-procedural STR and reduced MVO, MBG, TIMI flow.[87–92] However larger trials and meta-analysis has not found it beneficial.[93–95] Similar mixed result was shown with manual thrombectomy, initial small studies has shown improved clinical outcome,[95–99] subsequently two large studies and a meta-analysis has shown no significant benefit of routine thrombus aspiration during PPCI.[100–102] However subsequent meta-analysis has shown that thought in routine thrombus aspiration during PPCI for STEMI did not improve clinical outcomes. In the high thrombus burden group, the trends toward reduced cardiovascular death was seen.[103] Based on available data, current guideline stated that routine use of thrombus aspiration before PPCI is not recommended, however, a selective and bailout aspiration thrombectomy in patients with large residual thrombus burden after opening the vessel with a guide wire or a balloon may be considered.[104]

Distal/proximal protection devices thought is certain cases are useful in prevention no-flow, the long term outcome has mixed results. Embolic protection devices are shown to be useful during SVG PCI.[105,106] Similar benefit may be translated during PPCI of SVG. Embolic protection devices has not shown to improve microvascular flow, reperfusion success, survival or re-infarction rates in patients undergoing native-artery PPCI.[107–112]

Strategies of reducing total ischemic time might reduce the prevalence of the no-reflow phenomenon. Pharmacologic drugs reducing myocardial oxygen consumption and free radical scavengers may prevent reperfusion induce cell necrosis thus metabolic status of the ischemic myocardium at the end of the ischemic period might improve outcome thus prevent no-flow phenomenon[113]

Beneficial effects of carvedilol,[114] fosinopril or valsartan[115] on coronary no-flow have been demonstrated. Glycoprotein IIb/IIIa antagonists also improves myocardial perfusion when started during primary PCI and infused for 12 h thereafter.[116] Use of intravascular ultrasound can accurately identify lesion-specific features such as plaque composition and thrombus burden which may influence the risk of no-flow.[117,118] Shortened door-to-balloon time is associated with less myocardial damage, a lower incidence of no-flow.[119]

Several drugs have been shown to reduce the incidence of no-flow. Pharmacotherapy for the treatment of no-flow has focused primarily on two strategies: local vasodilator therapy and local antiplatelet therapy. Evidence for a beneficial effect of various drugs on no-flow exists. For prevention of no flow as adjuvant therapy use of these agent have been limited because of lack of there effect of hard end point like LV function and mortality. However as a treatment of no-flow several drugs have been recommended, Adenosine,[120] Calcium channel blockers (diltiazem, nicardipine or verapamil),[121–123] nitroprusside (SNP),[124] Intracoronary epinephrine,[125] nicorandil[126] are the current standard of care for the treatment of no-flow.

Adenosine in some studies and few meta-analysis has shown to exhibited significantly greater myocardial salvage, post procedure coronary flow and better in-hospital outcome as adjuvant therapy with PPCI.[127–131] Adenosine as adjunctive therapy appears to improve many clinical outcomes in patients with AMI after PCI, but there is no evidence that adenosine can reduce mortality rates.[132] However no much clinical benefit was shown in some large trials and meta-analysis.[133–136] Even high-dose intracoronary adenosine and SNP during PPCI did not reduce infarct size, Furthermore adenosine may adversely affect mid-term clinical outcome and should not be used as adjuvant therapy during PPCI to prevent reperfusion injury.[137] Continuous infusion is better than bolus use has been shown in animal study.[138]

Calcium channel blockers (CCB) attenuate microvascular spasm but also reduce ischemia and infarct size by lowering blood pressure and heart rate. In the microvasculature verapamil inhibit platelet aggregation and thrombus formation[139] and showed a direct effect on calcium flux across the sarcolemmal membrane or within intracellular compartments. Intracoronary administration of verapamil after PPCI can attenuate microvascular dysfunction.[140] Verapamil therapy is effective in animal models of coronary ischemia.[141] In small metanalysis adenosine and verapamil as treatments for no-flow during PPCI has shown to reduce all-cause mortality, non-fatal myocardial infarction or the incidence of angiographic no-flow (TIMI flow grade < 3 and MBG 0 to1).[142] Nicardipine, a vasoselective dihydropyridine CCB, offers more potent and prolonged vasodilation with less serious side effects than verapamil. Nicardipine has shown to be useful to prevent no-flow during rotational atherectomy[122] and percutaneous

interventions in vein grafts[123] with minimal myocardial depressant effect.[143]

Nitroprusside and nitroglycerin are nitric oxide donors that vasodilate conductance vessels >200 μm. Microvessels are unable to metabolize nitroglycerin to nitric oxide; in contrast, nitroprusside does not require metabolism. Nitroprusside has been extensively studied and found to be useful for management of no-flow phenomenon[144] and also as an adjunct therapy during PPCI for prevention of no flow.[145,146] Nitroglycerin has been also studied and in small trials and case reports shown benefit in preventing no-flow and coronary perfusion during PPCI. But not been studied in large randomized trials. It is less effective that verapamil and diltaizen.[147]

Intravenous nicorandil as adjuvant therapy during PPCI improved myocardial perfusion, prevent no-flow and cardiac function[147–150] and also long term clinical outcome.[147,150] However, a randomized trial found no reduction in infarct size with nicorandil versus placebo but intravenous atrial natriuretic peptide had shown to lower infarct size, fewer reperfusion injuries, and better clinical outcomes than controls.[151] Pharmacological post-conditioning by intravenous administration of cyclosporine, a direct MPTP blocker has also been studied for preventing reperfusion injury and reduce myocardial infarct size but was not found to be better than those with placebo.[152] Niu X et al[153] performed a network meta-analysis to assess the effect of 7 intracoronary agents (adenosine, anisodamine, diltiazem, nicorandil, nitroprusside, urapidil, and verapamil) on the no-flow phenomenon in patients with STEMI undergoing PPCI. They found that only addition of anisodamine was associated with improved post-procedural TIMI flow grade, more occurrences of STR, and improvement of LVEF. The cardioprotective effect of anisodamine conferred a MACE-free survival benefit. Additionally, nitroprusside was shown to improve coronary flow and clinical outcomes. Compared with standard care, adenosine, nicorandil, and verapamil improved coronary flow but not shown to improve cardiac function and clinical outcomes. Intracoronary administration of anisodamine appears to improve myocardial reperfusion, cardiac function, and clinical outcomes in patients with STEMI undergoing PPCI.

Platelet inhibition with glycoprotein IIb/IIIa inhibitors (GPIIb/IIIa) may reduce downstream embolization and generation of thrombus thus reduce release of vasoactive and chemotactic mediators from platelets.[154] Role of GPIIb/IIIa platelet receptor antagonists have some promise but are not currently routinely used in clinical practice for the prevention or treatment of no-reflow.[155–157] However glycoprotein IIb/IIIa receptor antagonist in combination with other therapy during PPCI has shown better outcome and decrease the incidence of no-flow[158–160] By contrast, glycoprotein IIb/IIIa receptor antagonists have failed to mitigate the impact of distal embolization in SVG intervention.[161] Intracoronary thrombolysis in a small randomized trial, immediately following PPCI improved microvascular integrity and tissue perfusion.[162] The role of oral anticoagulant has also been studied in animal model which failed to show a benefit of intravenous dabigatran treatment for no-flow.[163] Administration of Glucagon-like peptide (GLP)-1 analog liraglutide 30 min before PPCI is found to reduce no-flow.[164]

At present administration of an intracoronary vasodilator (adenosine, calcium channel blockers, nitroprusside not nitroglycerin, nicorandil or epinephrine) is reasonable to treat PPCI related no-flow or MVO but not as adjuvant therapy for the prevention of no-flow.[165]

Use of intermittent low-pressure balloon inflations in the infarct-related artery after direct stenting (Myocardial post-conditioning) decreases infarct size and improves microvascular perfusion.[166–169] Remote ischemic preconditioning by intermittent inflations of a blood pressure cuff on the upper limb before reperfusion improved ST-segment resolution, myocardial edema levels, myocardial salvage index and incidence of major adverse cardiac and cerebrovascular events but non-significant beneficial effect on infarct size, TIMI flow grade III or LVEF following PPCI.[170,171] Pharmacological pre- and postconditioning may be achieved by administration of exenatide, an antiapoptotic glucagonlike peptide-1 analogue, which also activates prosurvival kinases and found beneficial in reducing infarct size.[172] Aqueous oxygen hyperoxemic intracoronary perfusion was found to improve microvascular blood flow and decrease infarct size in canine model.[173] Intracoronary delivery of supersaturated oxygen in patients undergoing PPCI results in a significant reduction in infarct size with non-inferior rates of major adverse cardiovascular events at 30 days.[174] Induced hypothermia may have cardioprotective effect in STEMI and has shown to decrease no-flow.[175–177]

Glucose-insulin-potassium has shown mixed results. It was not found to be beneficial in STEMI[178,179] however it reduce infarct size and serious arrhythmias when administered in the ambulance to patients with STEMI that will receive PPCI.[180]

7. Conclusion

Despite improvements in treatment strategies and awareness STEMI remains an important cause of morbidity and mortality and its incidence is rising. Early reperfusion, is the most effective strategy and only proven strategy for reducing infarct size and improving clinical outcome. The process of myocardial reperfusion itself, however, can lead to severe injury to the myocardium, thereby reducing the beneficial effects of reperfusion. Despite the convincing experimental evidence of many strategies to minimize the reperfusion injury, it has not translated in improving clinical outcome. Reduction of reperfusion injury remains a neglected therapeutic target by interventionist, even though it is highly needed. Today, the only realistic strategy to reduce reperfusion injury in STEMI patients remains early reperfusion. No-flow and MVO following PPCI is a multifactorial phenomenon with variable etiologies in different clinical settings and is quite frequent during PPCI. This is associated with poor both acute and long term outcome. Prevention of no-flow and MVO following PPCI is beneficial in reducing cardiac injury and improving clinical outcome. Prevention and treatment are of prime importance because maximum gain of revascularization occurs with normal epicardial coronary flow with no microvasculature damage. Several preventive measures in animal model and small studies have effectively decrease the degree of MVO and improve clinical outcome in the setting of PPCI. Unfortunately, there is limited data comparing the efficacy of various strategies. There is also no large randomized trials to guide selection of various therapies for prevention of no-flow in clinical setting. Key strategies for prevention of no-flow is early revascularization, short door-to-balloon times, keep stent length minimal, deployment of stent at nominal pressures, direct stenting, high dose statin and proper antiplatelet and anticoagulation therapy. Manual thrombus aspiration can be used when there is angiographic evidence of large thrombus burden. Distal/proximal protection devices have not been proved beneficial.

Treatment of no-reflow have not been studied in large randomized trials so there are no definite recommendation. However in absence of alternative proven therapy administration of vasodilators should be considered mainly adenosine, verapamil, nicorandil, nitroprusside and epinephrine. Distal intracoronary infusion via infusion catheter is better than over guiding catheter injection because it causes less systemic hemodynamic effects. Although other may be beneficial in individual patients, we do not currently recommend the routine use of other pharmacological and mechanical interventions.

Conflicts of interest

None declared.

References

1. Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. *Lancet*. 2003 Jan 4;361(9351):13–20. https://doi.org/10.1016/S0140-6736(03)12113-7.
2. Menees DS, Peterson ED, Wang Y, et al. Door-to-balloon time and mortality among patients undergoing primary PCI. *N Engl J Med*. 2013;369:901–909.
3. Ferrari R, Biscaglia S, Malagù M, Bertini M, Campo G. Can we improve myocardial protection during ischaemic injury? *Cardiology*. 2016;135(1):14–26. https://doi.org/10.1159/000444847.
4. Ames III A, Wright RL, Kowada M, et al. Cerebral ischemia, II: the no-reflow phenomenon. *Am J Pathol*. 1968;52:437–447.
5. Asano T, Sano K. Pathogenetic role of no-reflow phenomenon in experimental subarachnoid hemorrhage in dogs. *J Neurosurg*. 1977;46:454–466.
6. Kloner RA, Ganote CE, Jennings RB. The “no-reflow” phenomenon after temporary coronary occlusion in the dog. *J Clin Invest*. 1974;54:1496–1508.
7. Galiuto L, Lombardo A, Maseri A, et al. Temporal evolution and functional outcome of no-reflow: sustained and spontaneously reversible patterns following successful coronary recanalization. *Heart*. 2003;89:731–737.
8. Hoffmann R, Haager R, Arning J, et al. Usefulness of myocardial blush grade early and late after primary coronary angioplasty for acute myocardial infarction in predicting left ventricular function. *Am J Cardiol*. 2003;92:1015–1019.
9. Mehta RH, Harjai KJ, Boura J, et al. Primary Angioplasty in Myocardial Infarction (PAMI) Investigators. Prognostic significance of transient no-reflow during primary percutaneous coronary intervention for ST-elevation acute myocardial infarction. *Am J Cardiol*. 2003 Dec 15;92(12):1445–1447. https://doi.org/10.1016/j.amjcard.2003.08.056.
10. Harrison RW, Aggarwal A, Ou FS, et al. American College of Cardiology National Cardiovascular Data Registry. Incidence and outcomes of no-reflow phenomenon during percutaneous coronary intervention among patients with acute myocardial infarction. *Am J Cardiol*. 2013 Jan 15;111(2):178–184. https://doi.org/10.1016/j.amjcard.2012.09.015.
11. Nair Rajesh G, Jayaprasad N, Madhavan S. Predictors and prognosis of no-reflow during primary percutaneous coronary intervention. *SAVE Proc*. 2018 Dec 27;32(1):30–33. https://doi.org/10.1080/08998280.2018.1509577.
12. 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 Oct;122(4):1322–1332. https://doi.org/10.1378/chest.122.4.1322.
13. Brosh D, Assali AR, Mager A, et al. Effect of no-reflow during primary percutaneous coronary intervention for acute myocardial infarction on six-month mortality. *Am J Cardiol*. 2007 Feb 15;99(4):442–445. https://doi.org/10.1016/j.amjcard.2006.08.054.
14. 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 Oct;36(4):1202–1209. https://doi.org/10.1016/s0735-1097(00)00865-2.
15. Eeckhout E, Kern MJ. The coronary no-reflow phenomenon: a review of mechanisms and therapies. *Eur Heart J*. 2001;22(9):729–739.
16. Rezkalla SH, Kloner RA. Coronary no-reflow phenomenon: from the experimental laboratory to the cardiac catheterization laboratory. *Cathet Cardiovasc Interv*. 2008 Dec 1;72(7):950–957. https://doi.org/10.1002/ccd.21715.
17. de Waha S, Patel MR, Granger CB, et al. Relationship between microvascular obstruction and adverse events following primary percutaneous coronary intervention for ST-segment elevation myocardial infarction: an individual patient data pooled analysis from seven randomized trials. *Eur Heart J*. 2017 Dec 14;38(47):3502–3510. https://doi.org/10.1093/eurheartj/ehx414.
18. Skyschally A, Leineweber K, Gres P, Haude M, Erbel R, Heusch G. Coronary microembolization. Basic Res Cardiol;101:373– 382.
19. Herrmann J. Peri-procedural myocardial injury: 2005 update. *Eur Heart J*. 2005;26:2493–2519.
20. Niccoli G, Scalone G, Lerman A, Crea F. Coronary microvascular obstruction in acute myocardial infarction. *Eur Heart J*. 2016 Apr 1;37(13):1024–1033. https://doi.org/10.1093/eurheartj/ehv484.
21. Okamura A, Ito H, Iwakura K, et al. Detection of embolic particles with the Doppler guide wire during coronary intervention in patient with acute myocardial infarction: efficacy of distal protection device. *J Am Coll Cardiol*. 2005;45:212–215.
22. Heusch G, Kleinbongard P, Bose D, et al. Coronary microembolization: from bedside to bench and back to bedside. *Circulation*. 2009;120:1822–1836.
23. Davidson SM, Adameová A, Barile L, et al. -CARDIOPROTECTION COST Action (CA16225). Mitochondrial and mitochondrial-independent pathways of myocardial cell death during ischaemia and reperfusion injury. *J Cell Mol Med*. 2020 Apr;24(7):3795–3806. https://doi.org/10.1111/jcmm.15127.
24. Kloner RA, Ganote CE, Jennings RB. The "no-reflow" phenomenon after temporary coronary occlusion in the dog. *J Clin Invest*. 1974 Dec;54(6):1496–1508. https://doi.org/10.1172/JCI107898.
25. Tranum-Jensen J, Janse MJ, Fiolet WT, Krieger WJ, D'Alnoncourt CN, Durrer D. Tissue osmolality, cell swelling, and reperfusion in acute regional myocardial ischemia in the isolated porcine heart. *Circ Res*. 1981 Aug;49(2):364–381. https://doi.org/10.1161/01.res.49.2.364.
26. 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 Aug;38(2):472–477. https://doi.org/10.1016/s0735-1097(01)01405-x.
27. Ferrari R, Curello S, Cargnoni A, et al. Metabolic changes during post-ischaemic reperfusion. *J Mol Cell Cardiol*. 1988;20:119–133.
28. Bekkers SC, Yazdani SK, Virmani R, Waltenberger J. Microvascular obstruction: underlying pathophysiology and clinical diagnosis. *J Am Coll Cardiol*. 2010 Apr 20;55(16):1649–1660. https://doi.org/10.1016/j.jacc.2009.12.037.
29. Bonderman D, Teml A, Jakowitsch J, et al. Coronary no-reflow is caused by shedding of active tissue factor from dissected atherosclerotic plaque. *Blood*. 2002 Apr 15;99(8):2794–2800. https://doi.org/10.1182/blood.v99.8.2794.
30. wakura K, Ito H, Kawano S, et al. Prediction of the no-reflow phenomenon with ultrasonic tissue characterization in patients with anterior wall acute myocardial infarction. *Am J Cardiol*. 2004 Jun 1;93(11):1357–1361. https://doi.org/10.1016/j.amjcard.2004.02.030. A5.
31. Robbers LF, Eerenberg ES, Teunissen PF, et al. Magnetic resonance imaging-defined areas of microvascular obstruction after acute myocardial infarction represent microvascular destruction and haemorrhage. *Eur Heart J*. 2013 Aug;34(30):2346–2353. https://doi.org/10.1093/eurheartj/eht100.
32. Herrmann J, Lerman A. The endothelium: dysfunction and beyond. *J Nucl Cardiol*. 2001 Mar-Apr;8(2):197–206. https://doi.org/10.1067/mnc.2001.114148.
33. Lerman A, Holmes DR, Herrmann J, Gersh BJ. Microcirculatory dysfunction in ST-elevation myocardial infarction: cause, consequence, or both? *Eur Heart J*. 2007;28:788–797.
34. Collet JP, Montalescot G. The acute reperfusion management of STEMI in patients with impaired glucose tolerance and type 2diabetes. *Diabetes Vasc Dis Res*. 2005;2:136–143. https://doi.org/10.3132/dvdr.2005.021.
35. Golino P, Maroko PR, Carew TE. The effect of acute hypercholes-terolemia on myocardial infarct size and the no-reflow phenomenon during coronary occlusion-reperfusion. *Circulation*. 1987;75:292–298.
36. 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.
37. 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;41:1–7.
38. Karila-Cohen D, Czitrom D, Brochet E, et al. Decreased no-reflow in patients with anterior myocardial infarction and pre-infarction angina. *Eur Heart J*. 1999 Dec;20(23):1724–1730. https://doi.org/10.1053/euhj.1999.1714.
39. Dong-bao L, Qi H, Zhi L, Shan W, Wei-ying J. Predictors and long-term prognosis of angiographic slow/no-reflow phenomenon during emergency percutaneous coronary intervention for ST-elevated acute myocardial infarction. *Clin Cardiol*. 2010 Dec;33(12):E7–E12. https://doi.org/10.1002/clc.20634.
40. Limbruno U, De Carlo M, Pistolesi S, et al. Distal embolization during primary angioplasty: histopathologic features and predictability. *Am Heart J*. 2005 Jul;150(1):102–108. https://doi.org/10.1016/j.ahj.2005.01.016.
41. Hoffmann R, Hamm C, Nienaber CA, et al. German Cypher Registry. Implantation of sirolimus-eluting stents in saphenous vein grafts is associated with high clinical follow-up event rates compared with treatment of native vessels. *Coron Artery Dis*. 2007 Nov;18(7):559–564. https://doi.org/10.1097/MCA.0b013e3282ef5b40.
42. Soverow J, Lee MS. Saphenous vein graft intervention: status report 2014. *J Invasive Cardiol*. 2014 Dec;26(12):659–667. PMID: 25480996.
43. Hashemi-Jazi M, Hosseini SM, Gholamrezaei A. Factors associated with the no-reflow phenomenon following percutaneous intervention of saphenous vein coronary bypass grafts. *ARYA Atheroscler*. 2017 Sep;13(5):221–229. PMID: 29371868.
44. 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 May;25(9):794–803. https://doi.org/10.1016/j.ehj.2004.01.006.
45. Campo G, Valgimigli M, Gemmati D, et al. Value of platelet reactivity in predicting response to treatment and clinical outcome in patients undergoing primary coronary intervention: insights into the STRATEGY Study. *J Am Coll Cardiol*. 2006 Dec 5;48(11):2178–2185. https://doi.org/10.1016/j.jacc.2005.12.085.
46. Huczek Z, Kochman J, Filipiak KJ, et al. Mean platelet volume on admission predicts impaired reperfusion and long-term mortality in acute myocardial infarction treated with primary percutaneous coronary intervention. *J Am Coll Cardiol*. 2005 Jul 19;46(2):284–290. https://doi.org/10.1016/j.jacc.2005.03.065.
47. Niccoli G, Giubilato S, Russo E, et al. Plasma levels of thromboxane A2 on admission are associated with no-reflow after primary percutaneous coronary intervention. *Eur Heart J*. 2008 Aug;29(15):1843–1850. https://doi.org/10.1093/eurheartj/ehn325.

48. Matsumoto H, Inoue N, Takaoka H, et al. Depletion of antioxidants is associated with no-reflow phenomenon in acute myocardial infarction. *Clin Cardiol*. 2004 Aug;27(8):466–470. https://doi.org/10.1002/clc.4960270809.
49. Niccoli G, Lanza GA, Shaw S, et al. Endothelin-1 and acute myocardial infarction: a no-reflow mediator after successful percutaneous myocardial revascularization. *Eur Heart J*. 2006 Aug;27(15):1793–1798. https://doi.org/10.1093/eurheartj/ehl119.
50. Eitel I, Nowak M, Stehl C, et al. Endothelin-1 release in acute myocardial infarction as a predictor of long-term prognosis and no-reflow assessed by contrast-enhanced magnetic resonance imaging. *Am Heart J*. 2010 May;159(5):882–890. https://doi.org/10.1016/j.ahj.2010.02.019.
51. Takahashi T, Hiasa Y, Ohara Y, et al. Relation between neutrophil counts on admission, microvascular injury, and left ventricular functional recovery in patients with an anterior wall first acute myocardial infarction treated with primary coronary angioplasty. *Am J Cardiol*. 2007 Jul 1;100(1):35–40. https://doi.org/10.1016/j.amjcard.2007.02.049.
52. Hoffmann R, Suliman H, Haager P, et al. Association of C-reactive protein and myocardial perfusion in patients with ST-elevation acute myocardial infarction. *Atherosclerosis*. 2006 May;186(1):177–183. https://doi.org/10.1016/j.atherosclerosis.2005.07.011.
53. Magro M, Nauta ST, Simsek C, et al. Usefulness of the SYNTAX score to predict "no reflow" in patients treated with primary percutaneous coronary intervention for ST-segment elevation myocardial infarction. *Am J Cardiol*. 2011 Mar 1;109(5):601–606. https://doi.org/10.1016/j.amjcard.2011.10.013.
54. Somuncu MU, Akgun T, Cakır MO, et al. The elevated Soluble ST2 predicts No-reflow phenomenon in ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention. *J Atheroscler Thromb*. 2019 Nov 1;26(11):970–978. https://doi.org/10.5551/jat.48413.
55. Galiuto L. Optimal therapeutic strategies in the setting of post-infarct no reflow: the need for a pathogenetic classification. *Heart*. 2004 Feb;90(2):123–125. https://doi.org/10.1136/hrt.2003.020800.
56. Schröder R. Prognostic impact of early ST-segment resolution in acute ST-elevation myocardial infarction. *Circulation*. 2004;110:506–510.
57. Giugliano RP, Sabatine MS, Gibson CM, et al. Combined assessment of thrombolysis in myocardial infarction flow grade, myocardial perfusion grade, and ST-segment resolution to evaluate epicardial and myocardial reperfusion. *Am J Cardiol*. 2004 Jun 1;93(11):1362–1367. https://doi.org/10.1016/j.amjcard.2004.02.031. A5-6.
58. Allencherril J, Jneid H, Atar D, et al. Pathophysiology, diagnosis, and management of the No-reflow phenomenon. *Cardiovasc Drugs Ther*. 2019 Oct;33(5):589–597. https://doi.org/10.1007/s10557-019-06901-0.
59. The TIMI. Study group. The thrombolysis in myocardial infarction [TIMI] trial. Phase I findings. *N Engl J Med*. 1985;312:932–936.
60. Roe MT, Ohman EM, Maas AC, et al. Shifting the open-artery hypothesis downstream: the quest for optimal reperfusion. *J Am Coll Cardiol*. 2001 Jan;37(1):9–18. https://doi.org/10.1016/s0735-1097(00)01101-3.
61. Ohara Y, Hiasa Y, Takahashi T, et al. Relation between the TIMI frame count and the degree of microvascular injury after primary coronary angioplasty in patients with acute anterior myocardial infarction. *Heart*. 2005;91(1):64–67.
62. Gibson CM, Murphy SA, Rizzo MJ, et al. Relationship between TIMI frame count and clinical outcomes after thrombolytic administration. Thrombolysis in Myocardial Infarction (TIMI) Study Group. *Circulation*. 1999;99(15):1945–1950.
63. Gibson CM, Cannon CP, Murphy SA, et al. Relationship of TIMI myocardial perfusion grade to mortality after administration of thrombolytic drugs. *Circulation*. 2000 Jan 18;101(2):125–130. https://doi.org/10.1161/01.cir.101.2.125.
64. Gibson CM, Cannon CP, Murphy SA, Marble SJ, Barron HV, Braunwald E. TIMI Study Group. Relationship of the TIMI myocardial perfusion grades, flow grades, frame count, and percutaneous coronary intervention to long-term outcomes after thrombolytic administration in acute myocardial infarction. *Circulation*. 2002 Apr 23;105(16):1909–1913. https://doi.org/10.1161/01.cir.0000014683.52177.b5.
65. van 't Hof Aw. Liem A, Suryapranata H, Hoorntje JC, de Boer MJ, Zijlstra F. Angiographic assessment of myocardial reperfusion in patients treated with primary angioplasty for acute myocardial infarction: myocardial blush grade. Zwolle Myocardial Infarction Study Group. *Circulation*. 1998 Jun 16;97(23):2302–2306. https://doi.org/10.1161/01.cir.97.23.2302.
66. Porto I, Burzotta F, Brancati M, et al. Relation of myocardial blush grade to microvascular perfusion and myocardial infarct size after primary or rescue percutaneous coronary intervention. *Am J Cardiol*. 2007 Jun 15;99(12):1671–1673. https://doi.org/10.1016/j.amjcard.2007.01.045.
67. Kampinga MA, Nijsten MW, Gu YL, et al. Is the myocardial blush grade scored by the operator during primary percutaneous coronary intervention of prognostic value in patients with ST-elevation myocardial infarction in routine clinical practice? *Circ Cardiovasc Interv*. 2010 Jun 1;3(3):216–223. https://doi.org/10.1161/CIRCINTERVENTIONS.109.916247.
68. Sorajja P, Gersh BJ, Costantini C, et al. Combined prognostic utility of ST-segment recovery and myocardial blush after primary percutaneous coronary intervention in acute myocardial infarction. *Eur Heart J*. 2005 Apr;26(7):667–674. https://doi.org/10.1093/eurheartj/ehi167.
69. Hayat SA, Senior R. Myocardial contrast echocardiography in ST elevation myocardial infarction: ready for prime time? *Eur Heart J*. 2008 Feb;29(3):299–314. https://doi.org/10.1093/eurheartj/ehm621.
70. Galiuto L, Garramone B, Scarà A, et al. AMICI Investigators. The extent of microvascular damage during myocardial contrast echocardiography is superior to other known indexes of post-infarct reperfusion in predicting left ventricular remodeling: results of the multicenter AMICI study. *J Am Coll Cardiol*. 2008 Feb 5;51(5):552–559. https://doi.org/10.1016/j.jacc.2007.09.051.
71. Albert TSE, Kim RJ, Judd RM. Assessment of no-reflow regions using cardiac MRI. *Basic Res Cardiol*. 2006;101:383–390. https://doi.org/10.1007/s00395-006-0617-0.
72. Wu KC, Zerhouni EA, Judd RM, et al. Prognostic significance of microvascular obstruction by magnetic resonance imaging in patients with acute myocardial infarction. *Circulation*. 1998 Mar 3;97(8):765–772. https://doi.org/10.1161/01.cir.97.8.765.
73. Jaffe R, Dick A, Strauss BH. Prevention and treatment of microvascular obstruction-related myocardial injury and coronary no-reflow following percutaneous coronary intervention: a systematic approach. *JACC Cardiovasc Interv*. 2010 Jul;3(7):695–704. https://doi.org/10.1016/j.jcin.2010.05.004.
74. Eeckhout E, Kern MJ. The coronary no-reflow phenomenon: a review of mechanisms and therapies. *Eur Heart J*. 2001 May;22(9):729–739. https://doi.org/10.1053/euhj.2000.2172.
75. Bolognese L, Carrabba N, Parodi G, et al. Impact of microvascular dysfunction on left ventricular remodeling and long-term clinical outcome after primary coronary angioplasty for acute myocardial infarction. *Circulation*. 2004 Mar 9;109(9):1121–1126. https://doi.org/10.1161/01.CIR.0000118496.44135.A7.
76. 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 Feb 1;3(1):27–33. https://doi.org/10.1161/CIRCINTERVENTIONS.109.896225.
77. Ndrepepa G, Tiroch K, Fusaro M, et al. 5-year prognostic value of no-reflow phenomenon after percutaneous coronary intervention in patients with acute myocardial infarction. *J Am Coll Cardiol*. 2010 May 25;55(21):2383–2389. https://doi.org/10.1016/j.jacc.2009.12.054.
78. Niccoli G, Spaziani C, Crea F. REOPEN-AMI Investigators. Left ventricular remodeling and 1-year clinical follow-up of the REOPEN-AMI trial. *J Am Coll Cardiol*. 2014 Apr 15;63(14):1454–1455. https://doi.org/10.1016/j.jacc.2013.10.042.
79. Malmberg K, Rydén L, Efendic S, et al. Randomized trial of insulin-glucose infusion followed by subcutaneous insulin treatment in diabetic patients with acute myocardial infarction (DIGAMI study): effects on mortality at 1 year. *J Am Coll Cardiol*. 1995 Jul;26(1):57–65. https://doi.org/10.1016/0735-1097(95)00126-k.
80. Di Carli MF, Janisse J, Grunberger G, Ager J. Role of chronic hyperglycemia in the pathogenesis of coronary microvascular dysfunction in diabetes. *J Am Coll Cardiol*. 2003 Apr 16;41(8):1387–1393. https://doi.org/10.1016/s0735-1097(03)00166-9.
81. Li XD, Yang YJ, Hao YC, et al. Effect of pre-procedural statin therapy on myocardial no-reflow following percutaneous coronary intervention: a meta analysis. *Chin Med J*. 2013;126(9):1755–1760. PMID: 23652063.
82. Loubeyre C, Morice MC, Lefèvre T, et al. 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. https://doi.org/10.1016/s0735-1097(01)01701-6.
83. Lindefjeld DS, Guarda E, Méndez M, et al. Microvascular coronary flow comparison in acute myocardial infarction angioplasty treated with a mesh covered stent (MGUARD stent) versus bare metal stent: MICAMI-MGUARD. *Cardiovasc Revascularization Med*. 2013;14(1):4–8.
84. Stone GW, Abizaid A, Silber S, et al. Prospective, randomized, multicenter evaluation of a polyethylene terephthalate micronet mesh-covered stent (MGuard) in ST-segment elevation myocardial infarction: the MASTER trial. *J Am Coll Cardiol*. 2012 Nov 6;60(19):1975–1984.
85. Stone GW. The MASTER II trial Comparison of the MGuard embolic protection stent with standard stent in acute myocardial infarction. In: *The International Conference for Innovations Meeting*. Tel Aviv: Israel; 2014.
86. Kelbæk H, Høfsten DE, Køber L, et al. Deferred versus conventional stent implantation in patients with ST-segment elevation myocardial infarction (DANAMI 3-DEFER): an open-label, randomised controlled trial. *Lancet*. 2016 May 28;387(10034):2199–2206. https://doi.org/10.1016/S0140-6736(16)30072-1.
87. Young JJ, Cox DA, Stuckey T, et al. Prospective, multicenter study of thrombectomy in patients with acute myocardial infarction: the X-Tract AMI registry. *J Intervent Cardiol*. 2007;20(1):44–50. https://doi.org/10.1111/j.1540-8183.2007.00223.x.
88. Lefèvre T, Garcia E, Reimers B, et al. X AMINE ST Investigators. X-sizer for thrombectomy in acute myocardial infarction improves ST-segment resolution: results of the X-sizer in AMI for negligible embolization and optimal ST resolution (X AMINE ST) trial. *J Am Coll Cardiol*. 2005 Jul 19;46(2):246–252. https://doi.org/10.1016/j.jacc.2005.04.031.
89. Antoniucci D, Valenti R, Migliorini A, et al. Comparison of rheolytic thrombectomy before direct infarct artery stenting versus direct stenting alone in patients undergoing percutaneous coronary intervention for acute myocardial infarction. *Am J Cardiol*. 2004 Apr 15;93(8):1033–1035. https://doi.org/10.1016/j.amjcard.2004.01.011.
90. Beran G, Lang I, Schreiber W, et al. Intracoronary thrombectomy with the X-sizer catheter system improves epicardial flow and accelerates ST-segment resolution in patients with acute coronary syndrome: a prospective,

randomized, controlled study. *Circulation*. 2002 May 21;105(20):2355–2360. https://doi.org/10.1161/01.cir.0000016350.02669.1d.
91. De Carlo M, Aquaro GD, Palmieri C, et al. A prospective randomized trial of thrombectomy versus no thrombectomy in patients with ST-segment elevation myocardial infarction and thrombus-rich lesions: MUSTELA (MUltidevice Thrombectomy in Acute ST-Segment ELevation Acute Myocardial Infarction) trial. *JACC Cardiovasc Interv*. 2012 Dec;5(12):1223–1230. https://doi.org/10.1016/j.jcin.2012.08.013.
92. Topaz O, Ebersole D, Das T, et al. CARMEL multicenter trial. Excimer laser angioplasty in acute myocardial infarction (the CARMEL multicenter trial). *Am J Cardiol*. 2004 Mar 15;93(6):694–701. https://doi.org/10.1016/j.amjcard.2003.11.050.
93. Migliorini A, Stabile A, Rodriguez AE, et al. JETSTENT Trial Investigators. Comparison of AngioJet rheolytic thrombectomy before direct infarct artery stenting with direct stenting alone in patients with acute myocardial infarction. The JETSTENT trial. *J Am Coll Cardiol*. 2010 Oct 12;56(16):1298–1306. https://doi.org/10.1016/j.jacc.2010.06.011.
94. Ali A, Cox D, Dib N, et al. Rheolytic thrombectomy with percutaneous coronary intervention for infarct size reduction in acute myocardial infarction: 30-day results from a multicenter randomized study. *J Am Coll Cardiol*. 2006;48(2):244–252.
95. Kumbhani DJ, Bavry AA, Desai MY, Bangalore S, Bhatt DL. Role of aspiration and mechanical thrombectomy in patients with acute myocardial infarction undergoing primary angioplasty: an updated meta-analysis of randomized trials. *J Am Coll Cardiol*. 2013 Oct 15;62(16):1409–1418. https://doi.org/10.1016/j.jacc.2013.04.025.
96. Vlaar PJ, Svilaas T, van der Horst IC, et al. Cardiac death and reinfarction after 1 year in the Thrombus Aspiration during Percutaneous coronary intervention in Acute myocardial infarction Study (TAPAS): a 1-year follow-up study. *Lancet*. 2008 Jun 7;371(9628):1915–1920. https://doi.org/10.1016/S0140-6736(08)60833-8.
97. De Luca G, Dudek D, Sardella G, Marino P, Chevalier B, Zijlstra F. Adjunctive manual thrombectomy improves myocardial perfusion and mortality in patients undergoing primary percutaneous coronary intervention for ST-elevation myocardial infarction: a meta-analysis of randomized trials. *Eur Heart J*. 2008 Dec;29(24):3002–3010. https://doi.org/10.1093/eurheartj/ehn389.
98. Burzotta F, Trani C, Romagnoli E, et al. Manual thrombus-aspiration improves myocardial reperfusion: the randomized evaluation of the effect of mechanical reduction of distal embolization by thrombus-aspiration in primary and rescue angioplasty (REMEDIA) trial. *J Am Coll Cardiol*. 2005 Jul 19;46(2):371–376. https://doi.org/10.1016/j.jacc.2005.04.057.
99. Elfekky EM, Penjameen MN, Nassar AI, Elias RR. Outcome of manual thrombus aspiration for patients undergoing primary PCI for acute STEMI showing large thrombus burden. *Egypt Heart J*. 2021 Jan 12;73(1):8. https://doi.org/10.1186/s43044-020-00122-9.
100. Fröbert O, Lagerqvist B, Olivecrona GK, et al. TASTE Trial. Thrombus aspiration during ST-segment elevation myocardial infarction. *N Engl J Med*. 2013 Oct 24;369(17):1587–1597. https://doi.org/10.1056/NEJMoa1308789. Epub 2013 Aug 31. Erratum in: N Engl J Med. 2014 Aug 21;371(8):786.
101. Jolly SS, Cairns JA, Yusuf S, et al. TOTAL Investigators. Randomized trial of primary PCI with or without routine manual thrombectomy. *N Engl J Med*. 2015 Apr 9;372(15):1389–1398. https://doi.org/10.1056/NEJMoa1415098.
102. Islam Y Elgendy, Huo Tianyao, Bhatt Deepak L, Bavry Anthony A. Is aspiration thrombectomy beneficial in patients undergoing primary percutaneous coronary intervention? Meta-analysis of randomized trials. *Circulation: Cardiovascular Interventions*. 2015;8, e002258. https://doi.org/10.1161/CIRCINTERVENTIONS.114.002258.
103. Jolly SS, James S, Džavík V, et al. Thrombus aspiration in ST-segment-elevation myocardial infarction: an individual patient meta-analysis: thrombectomy trialists collaboration. *Circulation*. 2017 Jan 10;135(2):143–152. https://doi.org/10.1161/CIRCULATIONAHA.116.025371.
104. Ibanez B, James S, Agewall S, et al. ESC Scientific Document Group. 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*. 2018 Jan 7;39(2):119–177. https://doi.org/10.1093/eurheartj/ehx393.
105. Coolong A, Baim DS, Kuntz RE, et al. Saphenous vein graft stenting and major adverse cardiac events: a predictive model derived from a pooled analysis of 3958 patients. *Circulation*. 2008 Feb 12;117(6):790–797. https://doi.org/10.1161/CIRCULATIONAHA.106.651232.
106. Stone GW, Rogers C, Hermiller J, et al. FilterWire EX Randomized Evaluation Investigators. Randomized comparison of distal protection with a filter-based catheter and a balloon occlusion and aspiration system during percutaneous intervention of diseased saphenous vein aorto-coronary bypass grafts. *Circulation*. 2003 Aug 5;108(5):548–553. https://doi.org/10.1161/01.CIR.0000080894.51311.0A.
107. Bavry AA, Kumbhani DJ, Bhatt DL. Role of adjunctive thrombectomy and embolic protection devices in acute myocardial infarction: a comprehensive meta-analysis of randomized trials. *Eur Heart J*. 2008 Dec;29(24):2989–3001. https://doi.org/10.1093/eurheartj/ehn421.
108. Stone GW, Webb J, Cox DA, et al. Enhanced Myocardial Efficacy and Recovery by Aspiration of Liberated Debris (EMERALD) Investigators. Distal microcirculatory protection during percutaneous coronary intervention in acute ST-segment elevation myocardial infarction: a randomized controlled trial. *J Am Med Assoc*. 2005 Mar 2;293(9):1063–1072. https://doi.org/10.1001/jama.293.9.1063.
109. Dangas G, Stone GW, Weinberg MD, et al. EMERALD Investigators. Contemporary outcomes of rescue percutaneous coronary intervention for acute myocardial infarction: comparison with primary angioplasty and the role of distal protection devices (EMERALD trial). *Am Heart J*. 2008 Jun;155(6):1090–1096. https://doi.org/10.1016/j.ahj.2007.12.003.
110. Muramatsu T, Kozuma K, Tsukahara R, et al. ASPARAGUS Trial Investigators. Comparison of myocardial perfusion by distal protection before and after primary stenting for acute myocardial infarction: angiographic and clinical results of a randomized controlled trial. *Cathet Cardiovasc Interv*. 2007 Nov 1;70(5):677–682. https://doi.org/10.1002/ccd.21190.
111. Kelbaek H, Terkelsen CJ, Helqvist S, et al. Randomized comparison of distal protection versus conventional treatment in primary percutaneous coronary intervention: the drug elution and distal protection in ST-elevation myocardial infarction (DEDICATION) trial. *J Am Coll Cardiol*. 2008 Mar 4;51(9):899–905. https://doi.org/10.1016/j.jacc.2007.10.047.
112. Haeck JD, Koch KT, Gu YL, et al. Proximal embolic protection in patients undergoing primary angioplasty for acute myocardial infarction (PREPARE): core lab adjudicated angiographic outcomes of a randomised controlled trial. *Neth Heart J*. 2010 Nov;18(11):531–536. https://doi.org/10.1007/s12471-010-0829-7.
113. Opie LH. Reperfusion injury and its pharmacologic modification. *Circulation*. 1989 Oct;80(4):1049–1062. https://doi.org/10.1161/01.cir.80.4.1049. PMID: 2571429.
114. 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 Feb 14;115(3):334–341. https://doi.org/10.1016/j.ijcard.2006.03.017.
115. Zhao JL, Yang YJ, You SJ, et al. Pretreatment with fosinopril or valsartan reduces myocardial no-reflow after acute myocardial infarction and reperfusion. *Coron Artery Dis*. 2006 Aug;17(5):463–469. https://doi.org/10.1097/00019501-200608000-00010.
116. Petronio AS, De Carlo M, Ciabatti N, et al. Left ventricular remodeling after primary coronary angioplasty in patients treated with abciximab or intracoronary adenosine. *Am Heart J*. 2005 Nov;150(5):1015. https://doi.org/10.1016/j.ahj.2005.07.012.
117. Amano H, Ikeda T, Toda M, et al. Plaque composition and no-reflow phenomenon during percutaneous coronary intervention of low-echoic structures in grayscale intravascular ultrasound. *Int Heart J*. 2016;57:285–291.
118. Suda A, Namiuchi S, Kawaguchi T, et al. A simple and rapid method for identification of lesions at high risk for the no-reflow phenomenon immediately before elective coronary stent implantation. *Heart Ves*. 2016;31:1904–1914.
119. Magro M, Springeling T, van Geuns RJ, Zijlstra F. Myocardial 'no-reflow' prevention. *Curr Vasc Pharmacol*. 2013 Mar 1;11(2):263–277. PMID: 23506503.
120. Grygier M, Araszkiewicz A, Lesiak M, Grajek S. 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*. 2013;71(2):115–120. https://doi.org/10.5603/KP.2013.0002.
121. Fischell TA, Maheshwari A. Current applications for nicardipine in invasive and interventional cardiology. *J Invasive Cardiol*. 2004 Aug;16(8):428–432. PMID: 15282420.
122. Fischell TA, Haller S, Pulukurthy S, Virk IS. Nicardipine and adenosine "flush cocktail" to prevent no-reflow during rotational atherectomy. *Cardiovasc Revascularization Med*. 2008;9:224–228.
123. Fischell TA, Subraya RG, Ashraf K, Carter AJ, Perry B, Haller SD. "Pharmacologic" distal protection using prophylactic, intragraft nicardipine to prevent no-reflow and non-Q was MI during SVG interventions. *J Invasive Cardiol*. 2007;19:58–62.
124. Wang HJ, Lo PH, Lin JJ, Lee H, Hung JS. Treatment of slow/no-reflow phenomenon with intracoronary nitroprusside injection in primary coronary intervention for acute myocardial infarction. *Cathet Cardiovasc Interv*. 2004 Oct;63(2):171–176. https://doi.org/10.1002/ccd.20149.
125. Aksu T, Guler TE, Colak A, et al. Intracoronary epinephrine in the treatment of refractory no-reflow after primary percutaneous coronary intervention: a retrospective study. *BMC Cardiovasc Disord*. 2015 Feb 19;15:10. https://doi.org/10.1186/s12872-015-0004-6.
126. Iwakura J, Ito H, Okamura A, et al. Nicorandil treatment in patients with acute myocardial infarction: a meta-analysis. *Circ J*. 2009;73:925–931.
127. Garratt KN, Holmes Jr DR, Molina-Viamonte V, et al. Intravenous adenosine and lidocaine in patients with acute myocardial infarction. *Am Heart J*. 1998 Aug;136(2):196–204. https://doi.org/10.1053/hj.1998. v136.89910.
128. Navarese EP, Buffon A, Andreotti F, et al. Adenosine improves post-procedural coronary flow but not clinical outcomes in patients with acute coronary syndrome: a meta-analysis of randomized trials. *Atherosclerosis*. 2012;222:1–7.
129. Claeys MJ, Bosmans J, De Ceuninck M, et al. Effect of intracoronary adenosine infusion during coronary intervention on myocardial reperfusion injury in patients with acute myocardial infarction. *Am J Cardiol*. 2004;94(9–13):23.
130. 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;101:2154–2159.
131. Polimeni A, De Rosa S, Sabatino J, Sorrentino S, Indolfi C. Impact of intracoronary adenosine administration during primary PCI: a meta-analysis. *Int J*

Cardiol. 2016 Jan 15;203:1032–1041. https://doi.org/10.1016/j.ijcard.2015.11.086.
132. 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 (Baltim)*. 2015 Aug;94(32):e1279. https://doi.org/10.1097/MD.0000000000001279.
133. Mahaffey KW, Puma JA, Barbagelata NA, et al. Adenosine as an adjunct to thrombolytic therapy for acute myocardial infarction: results of a multicenter, randomized, placebo-controlled trial:the Acute Myocardial Infarction STudy of Adenosine (AMISTAD) trial. *J Am Coll Cardiol*. 1999;34:1711–1720.
134. Ross AM, Gibbons RJ, Stone GW, Kloner RA, Alexander RW. AMISTAD-II Investigators. A randomized, double-blinded, placebocontrolled multicenter trial of adenosine as an adjunct to reperfusion in the treatment of acute myocardial infarction (AMISTAD-II). *J Am Coll Cardiol*. 2005;45:1775–1780.
135. Kloner RA, Forman MB, Gibbons RJ, Ross AM, Alexander RW, Stone GW. Impact of time to therapy and reperfusion modality on the efficacy of adenosine in acute myocardial infarction: the AMISTAD-2 trial. *Eur Heart J*. 2006;27:2400–2405.
136. Fokkema ML, Vlaar P, Vogelzang M, et al. Effect of high-dose intracoronary adenosine administration during percutaneous coronary intervention in acute myocardial infarction — a randomized controlled trial. *Circ Cardiovasc Interv*. 2009;2:323–329.
137. Nazir SA, Khan JN, Mahmoud IZ, et al. The REFLO-STEMI (REperfusion Facilitated by LOcal adjunctive therapy in ST-Elevation Myocardial Infarction) trial: a randomised controlled trial comparing intracoronary administration of adenosine or sodium nitroprusside with control for attenuation of microvascular obstruction during primary percutaneous coronary intervention. *Southampton (UK): NIHR Journals Library*. 2016 Dec. PMID: 27929619.
138. Yetgin T, Uitterdijk A, Te Lintel Hekkert M, et al. Limitation of infarct size and No-reflow by intracoronary adenosine depends critically on dose and duration. *JACC Cardiovasc Interv*. 2015 Dec 28;8(15):1990–1999. https://doi.org/10.1016/j.jcin.2015.08.033.
139. Ikeda Y, Kikuchi M, Toyama K, Watanabe K, Ando Y. Inhibition of human platelet functions by verapamil. *Thromb Haemostasis*. 1981;45:158–161.
140. 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 Nov 1;30(5):1193–1199. https://doi.org/10.1016/s0735-1097(97)00277-5.
141. Kloner RA, DeBoer LW, Carlson N, Braunwald E. The effect of verapamil on myocardial ultrastructure during and following release of coronary artery occlusion. *Exp Mol Pathol*. 1982 Jun;36(3):277–286. https://doi.org/10.1016/0014-4800(82)90057-0.
142. Aung Naing K, Li L, Su Q, Wu T. Adenosine and verapamil for no-reflow during primary percutaneous coronary intervention in people with acute myocardial infarction. *Cochrane Database Syst Rev*. 2013 Jun 4;6(CD009503). https://doi.org/10.1002/14651858.CD009503.pub2. Update in: Cochrane Database Syst Rev. 2015;(5):CD009503.
143. Lambert CR, Pepine CJ. Effects of intravenous and intracoronary nicardipine. *Am J Cardiol*. 1989 Oct 17;64(15):8H–15H. https://doi.org/10.1016/0002-9149(89)90974-0.
144. Kobatake R, Sato T, Fujiwara Y, et al. Comparison of the effects of nitroprusside versus nicorandil on the slow/no-reflow phenomenon during coronary interventions for acute myocardial infarction. *Heart Ves*. 2011 Jul;26(4):379–384. https://doi.org/10.1007/s00380-010-0065-5.
145. Su Q, Li L, Naing KA, Sun Y. Safety and effectiveness of nitroprusside in preventing no-reflow during percutaneous coronary intervention: a systematic review. *Cell Biochem Biophys*. 2014 Jan;68(1):201–206. https://doi.org/10.1007/s12013-013-9690-9.
146. Zhao S, Qi G, Tian W, Chen L, Sun Y. Effect of intracoronary nitroprusside in preventing no reflow phenomenon during primary percutaneous coronary intervention: a meta-analysis. *J Intervent Cardiol*. 2014 Aug;27(4):356–364. https://doi.org/10.1111/joic.12133.
[147. Huang D, Qian J, Ge L, et al. REstoration of COronary flow in patients with no-reflow after primary coronary interVEntion of acute myocaRdial infarction (RECOVER). *Am Heart J*. 2012 Sep;164(3):394–401. https://doi.org/10.1016/j.ahj.2012.06.015.
148. Ishii H, Ichimiya S, Kanashiro M, et al. Impact of a single intravenous administration of nicorandil before reperfusion in patients with ST-segment-elevation myocardial infarction. *Circulation*. 2005 Aug 30;112(9):1284–1288. https://doi.org/10.1161/CIRCULATIONAHA.104.530329.
149. Qi Q, Niu J, Chen T, Yin H, Wang T, Jiang Z. Intracoronary nicorandil and the prevention of the No-reflow phenomenon during primary percutaneous coronary intervention in patients with acute ST-segment elevation myocardial infarction. *Med Sci Mon Int Med J Exp Clin Res*. 2018 May 4;24:2767–2776. https://doi.org/10.12659/MSM.906815.
150. Xu L, Wang L, Li K, Zhang Z, Sun H, Yang X. Nicorandil prior to primary percutaneous coronary intervention improves clinical outcomes in patients with acute myocardial infarction: a meta-analysis of randomized controlled trials. *Drug Des Dev Ther*. 2019 Apr 29;13:1389–1400. https://doi.org/10.2147/DDDT.S195918.
151. Kitakaze M, Asakura M, Kim J, et al. J-WIND investigators. Human atrial natriuretic peptide and nicorandil as adjuncts to reperfusion treatment for acute myocardial infarction (J-WIND): two randomised trials. *Lancet*. 2007 Oct 27;370(9597):1483–1493. https://doi.org/10.1016/S0140-6736(07)61634-1. Erratum in: Lancet. 2008 Dec 22;370(9605):2102.
152. Cung TT, Morel O, Cayla G, et al. Cyclosporine before PCI in patients with acute myocardial infarction. *N Engl J Med*. 2015;373:1021–1031.
153. 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 Jan 10;18(1):3. https://doi.org/10.1186/s12872-017-0722-z.
154. 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 Jan 21;43(2):276–283. https://doi.org/10.1016/j.jacc.2003.08.040.
155. Porto I, Ashar V, Mitchell AR. Pharmacological management of no reflow during percutaneous coronary intervention. *Curr Vasc Pharmacol*. 2006 Apr;4(2):95–100. https://doi.org/10.2174/157016106776359835.
156. Qin T, Xie L, Chen MH. Meta-analysis of randomized controlled trials on the efficacy and safety of intracoronary administration of tirofiban for no-reflow phenomenon. *BMC Cardiovasc Disord*. 2013;13:68. https://doi.org/10.1186/1471-2261-13-68.
157. Kandzari DE, Hasselblad V, Tcheng JE, et al. Improved clinical outcomes with abciximab therapy in acute myocardial infarction: a systematic overview of randomized clinical trials. *Am Heart J*. 2004 Mar;147(3):457–462. https://doi.org/10.1016/j.ahj.2003.08.011.
158. Zhou SS, Tian F, Chen YD, et al. Combination therapy reduces the incidence of no-reflow after primary per-cutaneous coronary intervention in patients with ST-segment elevations acute myocardial infarction. *J Geriatr Cardiol*. 2015;12:135–142.
159. Zeng Q, Zhang LD, Wang W. A meta-analysis of randomized controlled trials investigating tirofiban combined with conventional drugs by intracoronary administration for no-reflow prevention. *Anatol J Cardiol*. 2021 Jan;25(1):7–16. https://doi.org/10.14744/AnatolJCardiol.2020.99469.
160. Potdar A, Sharm S. 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*. 2015;67:S43–S46.
161. Roffi M, Mukherjee D, Chew DP, et al. Lack of benefit from intravenous platelet glycoprotein IIb/IIIa receptor inhibition as adjunctive treatment for percutaneous interventions of aortocoronary bypass grafts: a pooled analysis of five randomized clinical trials. *Circulation*. 2002 Dec 10;106(24):3063–3067. https://doi.org/10.1161/01.cir.0000041250.89627.a9.
162. Sezer M, Oflaz H, Goren T, et al. Intracoronary streptokinase after primary percutaneous coronary intervention. *N Engl J Med*. 2007;356:1823–1834.
163. Hale SL, Kloner RA. Dabigatran treatment: effects on infarct size and the no-reflow phenomenon in a model of acute myocardial ischemia/reperfusion. *J Thromb Thrombolysis*. 2015 Jan;39(1):50–54. https://doi.org/10.1007/s11239-014-1098-x.
164. Chen WR, Tian F, Chen YD, et al. Effects of liraglutide on no-reflow in patients with acute ST-segment elevation myocardial infarction. *Int J Cardiol*. 2016 Apr 1;208:109–114. https://doi.org/10.1016/j.ijcard.2015.12.009.
165. Levine GN, Bates ER, Blankenship JC, et al. 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention: a report of the American college of cardiology foundation/American heart association task force on practice guidelines and the society for cardiovascular angiography and interventions. *Circulation*. 2011 Dec 6;124(23):574–651. https://doi.org/10.1161/CIR.0b013e31823ba622.
166. Staat P, Rioufol G, Piot C, et al. Postconditioning the human heart. *Circulation*. 2005 Oct 4;112(14):2143–2148. https://doi.org/10.1161/CIRCULATIONAHA.105.558122.
167. Thibault H, Piot C, Staat P, et al. Long-term benefit of postconditioning. *Circulation*. 2008;117:1037–1044.
168. Mewton N, Thibault H, Roubille F, et al. Postconditioning attenuates no-reflow in STEMI patients. *Basic Res Cardiol*. 2013 Nov;108(6):383. https://doi.org/10.1007/s00395-013-0383-8. Epub 2013 Sep 11.
169. 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;87:406–423.
170. Rentoukas I, Giannopoulos G, Kaoukis A, et al. Cardioprotective role of remote ischemic periconditioning in primary percutaneous coronary intervention: enhancement by opioid action. *JACC Cardiovasc Interv*. 2010 Jan;3(1):49–55. https://doi.org/10.1016/j.jcin.2009.10.015.
171. Gong R, Wu YQ. Remote ischemic conditioning during primary percutaneous coronary intervention in patients with ST-segment elevation myocardial infarction: a systematic review and meta-analysis. *J Cardiothorac Surg*. 2019 Jan 21;14(1):14. https://doi.org/10.1186/s13019-019-0834-x.
172. Timmers L, Henriques JP, de Kleijn DP, et al. Exenatide reduces infarct size and improves cardiac function in a porcine model of ischemia and reperfusion injury. *J Am Coll Cardiol*. 2009 Feb 10;53(6):501–510. https://doi.org/10.1016/j.jacc.2008.10.033.
173. Spears JR, Prcevski P, Xu R, et al. Aqueous oxygen attenuation of reperfusion microvascular ischemia in a canine model of myocardial infarction. *Am Soc Artif Intern Organs J*. 2003 Nov-Dec;49(6):716–720. https://doi.org/10.1097/01.mat.0000094665.72503.3c.

174. Stone GW, Martin JL, de Boer MJ, et al. AMIHOT-II Trial Investigators. Effect of supersaturated oxygen delivery on infarct size after percutaneous coronary intervention in acute myocardial infarction. *Circ Cardiovasc Interv*. 2009 Oct;2(5):366–375. https://doi.org/10.1161/CIRCINTERVENTIONS.108.840066.
175. Herring MJ, Dai W, Hale SL, Kloner RA. Rapid induction of hypothermia by the ThermoSuit system profoundly reduces infarct size and anatomic zone of no reflow following ischemia-reperfusion in rabbit and rat hearts. *J Cardiovasc Pharmacol Therapeut*. 2015;20:193–202.
176. Kang IS, Fumiaki I, Pyun WB. Therapeutic hypothermia for cardioprotection in acute myocardial infarction. *Yonsei Med J*. 2016 Mar;57(2):291–297. https://doi.org/10.3349/ymj.2016.57.2.291.
177. Kohlhauer M, Berdeaux A, Ghaleb B, Tissier R. Therapeutic hypothermia to protect the heart against acute myocardial infarction. *Arch Cardiovasc Dis*. 2016 Dec;109(12):716–722. https://doi.org/10.1016/j.acvd.2016.05.005.
178. Diaz R, Paolasso EA, Piegas LS, et al. ECLA (estudios Cardiolo' gicos Latinoame' rica) collaborative group. Metabolic modulation of acute myocardial infarction. The ECLA glucose-insulin-potassium pilot trial. *Circulation*. 1998;98:2227–2234.
179. Mehta SR, Yusuf S, Diaz R, et al. Effect of glucose-insulinpotassium infusion on mortality in patients with acute ST-segment elevation myocardial infarction: the CREATE-ECLA randomized controlled trial. *J Am Med Assoc*. 2005;293:437–446.
180. Selker HP, Beshansky JR, Sheehan PR, et al. Out-of-hospital administration of intravenous glucose-insulin-potassium in patients with suspected acute coronary syndromes: the IMMEDIATE randomized controlled trial. *J Am Med Assoc*. 2012;307:1925–1933.

Rakesh Yadav*, Satyavir Yadav, Kewal C. Goswami
Dept. of Cardiology, AIIMS, Ansari Nagar, New Delhi, 110029, India

Geetika Yadav
Division of NCD, ICMR, New Delhi, 110029, India

* Corresponding author.
E-mail address: rakeshyadav123@yahoo.com (R. Yadav).

Available online 28 July 2021