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SPECIAL ARTICLE
Ischaemic heart disease

Pathophysiology, prevention, and management of coronary microvascular obstruction

A clinical consensus statement of the ESC Working Group on Coronary Pathophysiology & Microcirculation, the ESC Working Group on Thrombosis, and the European Association of Percutaneous Cardiovascular Interventions (EAPCI) of the ESC

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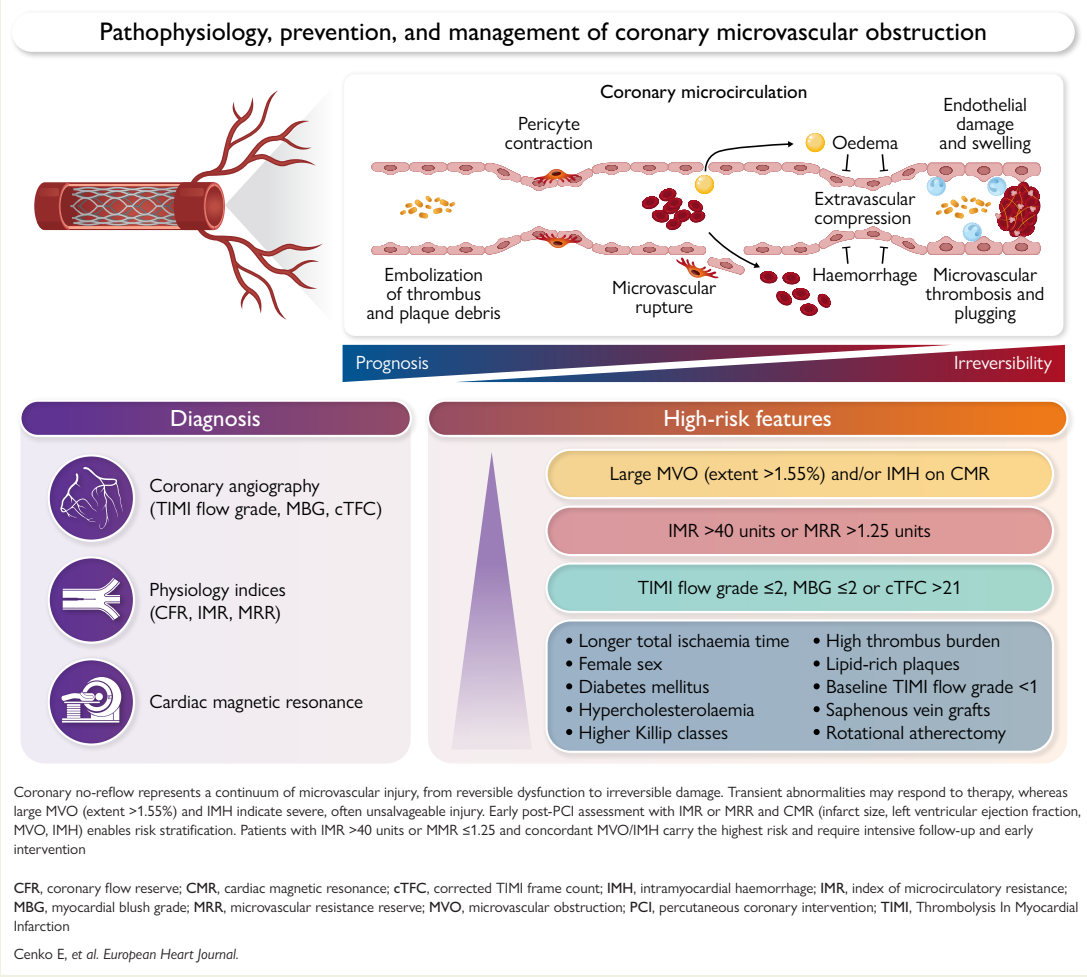
Graphical Abstract



Coronary no-reflow represents a continuum of microvascular injury, from reversible dysfunction to irreversible damage. Transient abnormalities may respond to therapy, whereas large MVO (extent >1.55%) and IMH indicate severe, often unsalvageable injury. Early post-PCI assessment with IMR or MRR and CMR (infarct size, left ventricular ejection fraction, MVO, IMH) enables risk stratification. Patients with IMR >40 units or MMR ≤1.25 and concordant MVO/IMH carry the highest risk and require intensive follow-up and early intervention

CFR, coronary flow reserve; **CMR**, cardiac magnetic resonance; **cTFC**, corrected TIMI frame count; **IMH**, intramyocardial haemorrhage; **IMR**, index of microcirculatory resistance; **MBG**, myocardial blush grade; **MRR**, microvascular resistance reserve; **MVO**, microvascular obstruction; **PCI**, percutaneous coronary intervention; **TIMI**, Thrombolysis In Myocardial Infarction

Cenko E, *et al. European Heart Journal.*

Abstract

Although prompt primary percutaneous coronary intervention (PCI) reduces mortality in patients with ST-elevation myocardial infarction (STEMI), the burden of post-infarction heart failure remains considerable and is expected to increase. A major contributory factor is suboptimal myocardial reperfusion, which persists in up to 60% of cases even with timely revascularization. This is largely driven by microvascular obstruction and ischaemia–reperfusion injury, culminating in the no-reflow phenomenon, a critical prognostic factor associated with impaired infarct healing, adverse left ventricular remodelling, and increased risk of heart failure and death. No-reflow is a complex and heterogeneous phenomenon, identifiable through different invasive and noninvasive technologies. When observed post-PCI, after excluding residual epicardial stenosis, it indicates poor microvascular perfusion and necessitates urgent management. Identifying patients at high risk and implementing early targeted interventions are essential to improving outcomes. Pharmacological therapies, including intracoronary adenosine and nitroprusside, have shown unclear benefit in improving microvascular flow. Non-pharmacological strategies, such as ischaemic postconditioning, intracoronary supersaturated oxygen therapy, stent-retriever thrombectomy, and mechanical left ventricular unloading, have demonstrated promise but require further validation in large-scale clinical trials. This clinical consensus statement summarizes current strategies for the prevention and treatment of no-reflow and underscores the need for improved risk stratification and novel microvasculature-targeted therapies. Addressing this persistent and significant unmet clinical need is crucial for improving care for STEMI patients and for mitigating its long-term complications, including heart failure and mortality.

Keywords coronary no-reflow phenomenon • microvascular injury • microvascular obstruction • intramyocardial haemorrhage • ischemia-reperfusion injury • distal embolization • interstitial oedema • ST-segment elevation myocardial infarction • percutaneous coronary intervention • coronary blood flow • index of microcirculatory resistance • prognosis

Introduction

Coronary no-reflow refers to the failure to restore myocardial tissue perfusion following successful epicardial recanalization. First described in experimental models in 1966[1,2] and later in clinical settings following myocardial infarction (MI) reperfusion in 1985,[3] no-reflow represents a significant challenge in contemporary cardiovascular medicine. Temporary arterial occlusion or subocclusion is a prerequisite for its occurrence. A clear distinction must be made between the two clinical manifestations of the no-reflow phenomenon. On one end of the spectrum, there is a complete interruption of blood flow from the epicardial artery to the myocardial tissue, observed as a slow back-and-forth movement of contrast agent within the vessel without distal progression. On the other hand, epicardial flow may appear normal, yet tissue perfusion remains impaired, reflecting underlying microvascular obstruction (MVO) or microvascular injury (MVI) (*Figure 1*).[4]

Prior research has classified coronary no-reflow into two distinct pathophysiological entities: 'angiographic no-reflow' and 'MI reperfusion no-reflow'.[5] This clinical consensus statement aims to examine the proposed mechanisms underlying no-reflow, explore diagnostic techniques for its accurate identification, and discuss therapeutic strategies for its management, both in cases with and without normal epicardial flow. Given their shared prognostic implications, the authors advocate maintaining the term 'no-reflow' across various clinical scenarios. Regardless of the underlying cause, suboptimal myocardial tissue perfusion is associated with an increased risk of adverse outcomes, including death and left ventricular (LV) dysfunction. Addressing no-reflow remains a critical goal in optimizing post-reperfusion outcomes in MI patients.

Definition and epidemiology

No-reflow is defined as inadequate myocardial tissue perfusion following successful recanalization of the culprit epicardial coronary artery, in the absence of coronary dissection, vasospasm, or side branch loss. Persistent no-reflow is linked to higher complication rates and mortality. Its incidence varies widely [from ~3% in stable elective percutaneous coronary intervention (PCI) to as high as 40%–60% in high-risk settings] and is more frequent

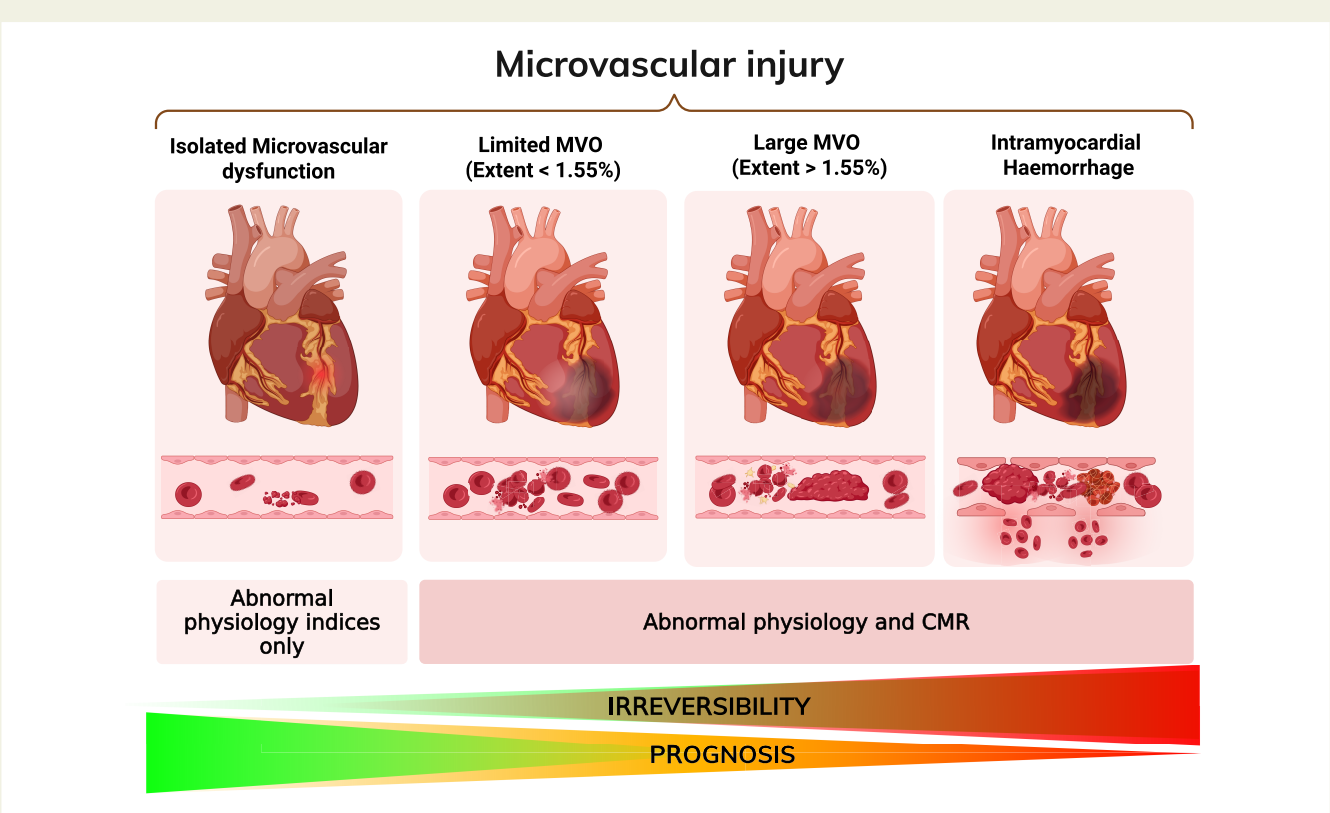


Figure 1 Pathophysiological spectrum of coronary no-reflow post-ST-elevation myocardial infarction: from reversible dysfunction to irreversible structural damage. Coronary no-reflow is not a categorical phenomenon (present or absent) but rather a dynamic condition representing a spectrum, ranging from functional, potentially reversible microvascular dysfunction, reflected by isolated abnormalities, to structural anatomical derangement, identified by concordant abnormalities in invasive physiology indices and on CMR. The term 'microvascular injury' offers a broader framework to capture this continuum of pathophysiological scenarios. Within anatomical derangement, the severity of microvascular disarray varies, with greater MVO extent (threshold >1.55%) and the presence of IMH, as a major predictor of adverse clinical outcomes, indicating more severe injury. This distinction has important clinical implications: while early microvascular dysfunction may be reversible and targeted by preventive and therapeutic strategies, extensive anatomical injury, particularly with haemorrhage, may represent an unsalvageable condition with currently available therapies. CMR, cardiac magnetic resonance; IMH, intramyocardial haemorrhage; MVI, microvascular injury; MVO, microvascular obstruction

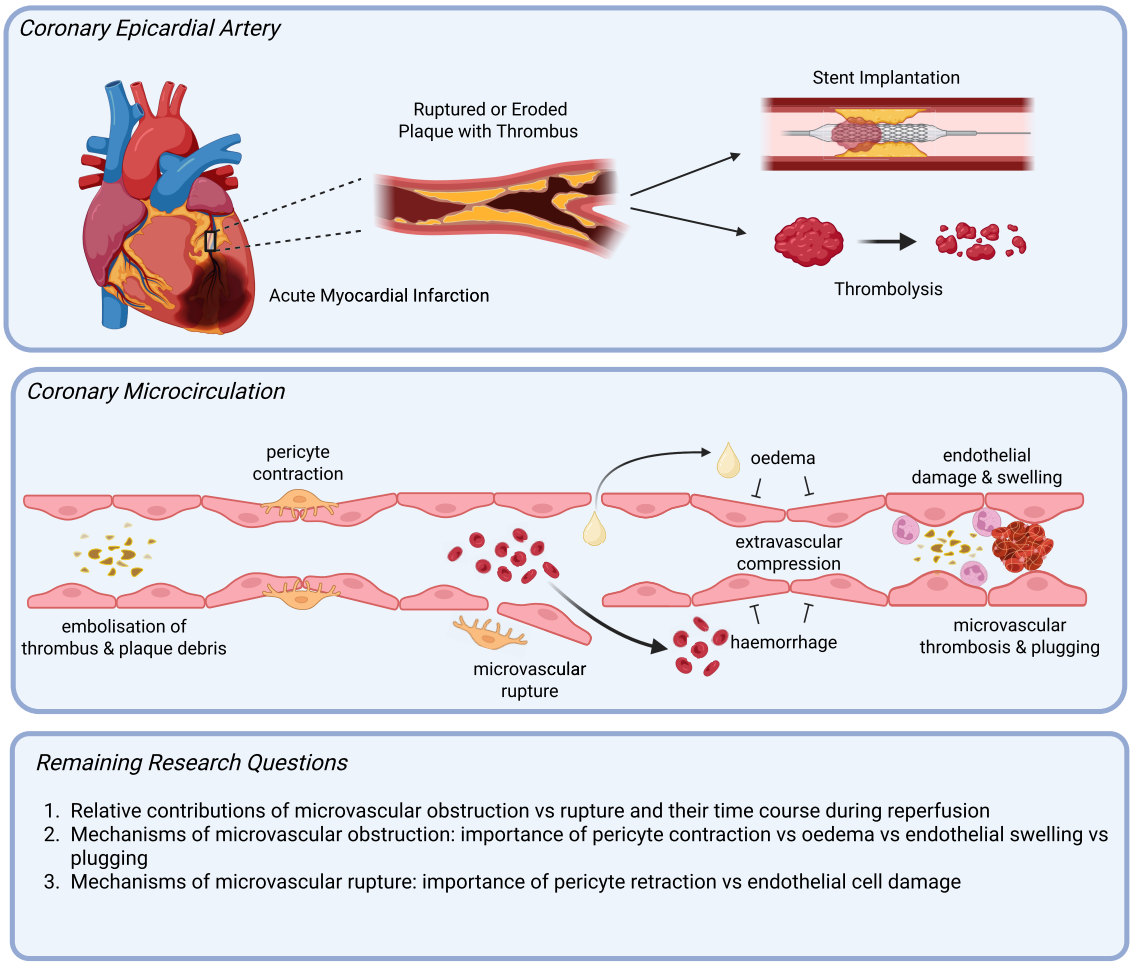


Figure 2 Mechanisms of the coronary no-reflow phenomenon include distal microvascular obstruction due to embolization of thrombus and plaque debris, and microvascular dysfunction that persists even after achieving epicardial patency with stent implantation. Current models attribute this failure to restore tissue-level perfusion to a complex interplay of structural and functional abnormalities within the coronary microcirculation. Functional mechanisms such as microvascular spasm, pericyte contraction, and endothelial damage or swelling initiate the process, while severe structural injury involves microvascular obstruction, rupture, and intramyocardial haemorrhage. These primary insults are further exacerbated by resultant oedema and extravascular compression, which together significantly impair microvascular perfusion.

during PCI for ST-elevation MI (STEMI) and degenerated saphenous vein grafts (SVG) and after rotational atherectomy.[6–8]

There is no uniform definition of no-reflow. While some rely on angiographic features, such as Thrombolysis In Myocardial Infarction (TIMI) flow Grade ≤2, myocardial blush grade (MBG) ≤ 2, or high corrected TIMI frame count (cTFC), others focus on tissue-level evidence of MVO using advanced imaging techniques.[9–13] Recent modalities like cardiac magnetic resonance (CMR), myocardial perfusion imaging, and invasive physiological indices have advanced our ability to detect suboptimal reperfusion post-acute MI. Given the evolving understanding, we propose the following consensus definition for clinical and research purposes: 'The coronary no-reflow phenomenon is defined as inadequate myocardial tissue perfusion despite successful epicardial coronary artery recanalization, in the absence of mechanical obstruction, and resulting from microvascular dysfunction or injury, including mechanisms such as distal embolization, endothelial disruption, and microvascular spasm' (*Figures 1* and *2*).

Mechanisms of no-reflow

Originally, no-reflow was attributed to obstruction of the distal microvasculature by small thrombi dislodged during PCI, which became lodged in microvessels.[14,15] However, persistent contractile dysfunction after achieving vessel patency and TIMI flow Grade 3 following pharmacological or mechanical acute MI interventions prompted further investigation. It was subsequently proposed that the failure to restore myocardial perfusion could result from structural and functional abnormalities in the coronary microcirculation, such as microvascular spasm, MVO, intramyocardial haemorrhage (IMH), and microvascular dysfunction, with endothelial damage being a key contributing factor (*Figure 2*).[14]

Distal embolization and microvascular dysfunction

Plaque rupture[16] or PCI, especially stenting, can cause distal embolization of atherothrombotic material.[17,18] Disruption of the

endothelial barrier facilitates distal embolization, inflammation, and vasoconstriction, as well as microvascular spasm. Distal embolization, in turn, contributes to increased microvascular resistance, obstructed capillaries, and perpetuation of no-reflow. Platelet-derived microvesicles and exosomes may exacerbate this dysfunction.[19,20] Inflammatory mediators from platelets and injured cardiomyocytes exacerbate oxidative stress and MVI, leading to oedema, haemorrhage, and further obstruction. Inflammation directly contributes to no-reflow through leukocyte plugging and myocardial oedema.[21]

Microvascular endothelial ischaemia–reperfusion injury

No-reflow is closely associated with ischaemia–reperfusion injury. Early, often reversible, endothelial damage includes glycocalyx loss and endothelial swelling, impairing nitric oxide production and promoting vasoconstriction, thrombosis, and inflammation.[14,15] Reperfusion injury triggers proinflammatory pathways and increases vascular sensitivity to vasoconstrictors like endothelin and angiotensin II.[22] Vagal nerve stimulation has shown benefit in animal models by reducing immune cell infiltration.[23] However, clinical trials, such as that testing colchicine, have yet to demonstrate preventive efficacy.[24]

Microvascular vasospasm

Sympathetic reflexes that induce adrenergic macrovascular and microvascular constriction can contribute to no-reflow.[25] Endothelial dysfunction, platelet activation, and pericyte contraction all promote vasospasm. Sympathetic reflexes further drive micro- and macrovascular constriction, while endothelin-1, thromboxane A2, serotonin, and angiotensin II are key vasoconstrictors.[26–29] Neural degeneration and cardiac denervation after MI also impair coronary vasomotion, increasing vasoconstrictive tone and worsening perfusion.[30,31] Interestingly, vasoconstriction may limit microthrombus spread, potentially serving a protective role by preventing detrimental metabolites or microthrombi from reaching viable myocardium and the systemic circulation.[15]

Myocardial necrosis

No-reflow is associated with larger infarcts but likely develops in parallel rather than causing necrosis.[32] Experimental data suggest cardiomyocyte death precedes MVI.[33,34] Hypothermia reduces no-reflow without affecting infarct size, supporting the concept that no-reflow contributes more to healing and remodelling than to the extent of necrosis itself.[35–37]

Diagnosis

Accurate and early diagnosis of coronary no-reflow is essential for improving patient outcomes. Several diagnostic modalities have been employed for this purpose, ranging from traditional angiographic assessments to advanced imaging and physiological evaluation techniques. *Tables 1* and *2* provide an overview of the techniques used to demonstrate no-reflow. *Figure 3* outlines a hierarchical three-level diagnostic schema to identify no-reflow.

Angiographic assessment

Coronary angiography remains the primary method for assessing no-reflow in the catheterization laboratory (*Table 1*). While angiographic parameters provide a rapid and practical assessment, they lack sensitivity in detecting microvascular dysfunction and may fail to identify cases where no-reflow and MVO or MVI are present with TIMI flow Grade 3.[38] Therefore, angiographic parameters alone are insufficient for diagnosis. The only exception is SVG-PCI, where angiography-based indices remain the sole validated method for detecting no-reflow in the catheterization laboratory (*Table 1* and *Figure 4*).

Recent advancements in computational angiography-derived indices, such as angiography-derived index of microvascular resistance (IMR_{angio})[38] and other pressure–flow-based measures, offer promising alternatives for assessing microvascular dysfunction. These indices integrate aortic pressure and contrast flow dynamics to estimate microvascular resistance, providing a noninvasive surrogate for invasive physiological measurements. Although some of these methods have been validated, limited availability and the need for specialized expertise currently limit their application in routine clinical practice.

Coronary physiology indices

Coronary physiology indices provide a quantitative assessment of coronary flow and pressure, circumventing the limitations of traditional angiographic parameters. Unlike angiography-based indices, these measurements enable direct evaluation of microvascular resistance and function, offering higher sensitivity and specificity for detecting MVI. An impaired coronary flow reserve (CFR <2.0) post-PCI is associated with a worse prognosis across various clinical settings.[39] Coronary flow reserve is associated with clinical and mechanistic outcomes. However, its dependence on resting measurements makes it vulnerable to haemodynamic fluctuations (e.g. blood pressure, contractility, heart rate) common during acute situations, reducing its reproducibility. As a result, assessment of alternative indices that directly measure minimal microvascular resistance have gained attention. Three validated indices are commonly used:

Hyperaemic microvascular resistance (hMR)

Defined as the ratio of hyperaemic distal coronary pressure to Doppler-derived average peak velocity, hMR correlates with infarct size, MVO, LV remodelling, and prognosis. An hMR >2.5 mmHg/m/s is considered abnormal, while values >3.0 mmHg/m/s predict adverse clinical outcomes.[40] Doppler-derived assessments are accurate but limited by technical challenges, such as suboptimal Doppler tracings, which occur in up to 30% of cases.[41] Furthermore, hMR calculations typically assume a linear relationship between coronary pressure and flow. However, blood flow approaches zero at a positive pressure level, known as zero flow pressure. This nonlinearity becomes particularly important in the setting of severe microvascular dysfunction and may lead to underestimation of true microvascular resistance. Although adjusting for zero flow pressure could theoretically improve hMR accuracy, it requires multiple flow–pressure measurements and is not routinely performed in clinical practice.

Index of microcirculatory resistance (IMR)

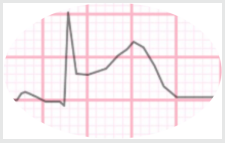
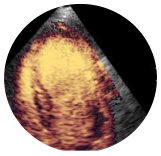
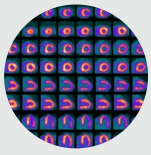
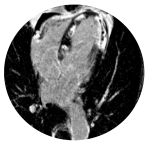
Derived from bolus thermodilution, IMR is calculated as the product of mean transit time and distal coronary pressure under hyperaemic conditions. It is widely applicable, requiring only a

Table 1 Semiquantitative angiography-based indices of microvascular obstruction

Type	Subtype	Name	Definition/formula	Reference threshold
Angiography-based indices		TIMI	TIMI 0: no antegrade flow beyond the occlusion TIMI 1: contrast dye beyond obstruction but fails to opacify the coronary bed TIMI 2: antegrade flow and clearance of contrast dye from the infarct-related artery slower than in the non-infarct-related artery TIMI 3: antegrade flow and clearance of contrast dye from the infarct-related artery occur as in the non-infarct-related artery	> 2
		cTFC	Number of frames required for dye to reach a distal coronary artery landmark, which is vessel specific. Value to be divided by 1.7 for left anterior descending artery	21 ± 3
		MBG	MBG 0/1: Minimal or no opacification of the myocardium supplied by the infarct-related artery MBG 2: Moderate myocardial blush, fainter if compared to blush in the non-infarct-related artery MBG 3: Normal myocardial blush, comparable with that in the non-infarct-related artery	>2
Pressure–wire based coronary physiology indices	Doppler based	CFVR	$APV_{Hyperaemia}/APV_{resting}$	>2.5
		hMR	$Pd_{hyperaemia}/APV_{Hyperaemia}$	< 2.5 mmHg/m/s
	Bolus thermodilution	CFR	$Transit\ Time_{resting}/Transit\ Time_{hyperaemia}$	> 2.5
		IMR	$Pd_{hyperaemia} \times TransitTime_{hyperaemia}$	<25 units < 40 units in STEMI
	Continuous thermodilution	Q	$Qi \times 1.08 \times \frac{Ti}{T}$	Interpatient variability
		R	Pd/Q	Interpatient variability
		MRRa	$\frac{CFR}{FFR} \times \frac{Parest}{Pahyperaemia}$	≤ 1.25 in STEMI
Angiography-derived coronary physiology indices		IMR_{angio}	$Pa_{hyperaemia} \times aQFR \times \frac{n\ frames\ hyperaemia}{frame\ rate}$	< 40
		$NH\text{-}IMR_{angio}$	$Pa_{resting} \times cQFR \times \frac{n\ frames}{frame\ rate}$	< 40
		ca IMR	$Pa_{hyperaemia} \times caFFR \times \frac{vessel\ length}{K \times Vdiastole}$	< 40
		cAngio IMR	$[Pa_{resting} - (0.1 \times Pa_{resting})] \times cQFR \times \frac{vessel\ length}{V\ hyperaemia}$	< 25 (not tested in STEMI)

APV, average peak velocity; aQFR, adenosine quantitative flow ratio; caFFR, coronary angiography-derived fractional flow reserve; CFR, coronary flow reserve; cQFR, contrast quantitative flow ratio; cTFC, corrected TIMI frame count; CFVR, coronary flow velocity reserve; hMR, hyperaemic microvascular resistance; IMR: index of microcirculatory resistance; k, constant; MBG, myocardial blush grade; MRR, microvascular resistance reserve; $NH\text{-}IMR_{angio}$, non-hyperaemic angiography-derived IMR; Pa, aortic pressure; Pd, distal coronary pressure; Q, absolute flow; Qi, saline infusion rate; R, absolute resistance; STEMI, ST-elevation myocardial infarction; T, blood-saline mixture temperature; Ti, saline infused temperature; TIMI, Thrombolysis In Myocardial Infarction; Vdiastole, diastolic flow velocity; Vhyperaemia, hyperaemic flow velocity.
[a]MRR can also be calculated using Doppler flow velocity or bolus thermodilution.

Table 2 Noninvasive modalities to assess coronary no-reflow

Modality	Advantages	Limitations
ST-segment resolution 	• STR <70% (sum STR in multiple leads) or <50% (single-lead STR) at 60–90 min postreperfusion therapy is a prognostic indicator of mortality and a marker of coronary no-reflow phenomenon for patients with STEMI • Continuous ECG recording improves accuracy in detecting reperfusion changes. Useful for monitoring reperfusion dynamics across multiple time points • Clinical availability • Widely available • Easily repeatable • Cost-effective • Safe	• Integrates both epicardial and myocardial reperfusion, limiting its specificity for coronary no-reflow • Discordance with angiographic indices of coronary no-reflow (complete STR does not always confirm TIMI 3 flow, particularly in anterior MI). • Conflicting evidence on correlation with IMR • Sex differences may confound interpretation with discordance between STR and angiographic outcomes in women • Infarct size and poor ECG quality can limit STR reliability • Single-point ECG snapshots may miss the dynamic evolution of ST-segment changes
Myocardial contrast echocardiography 	• Evaluation of myocardial perfusion; • Detects MVO and predicts long-term outcomes • CFR reflects microvascular function and predicts adverse remodelling • Low cost • Lack of radiation exposure • Bedside • Ease of use	• Operator dependency • Lack of experience • Lack of reproducibility • Image quality is dependent on subject characteristics
Positron emission tomography 	• Evaluates myocardial perfusion • Provides absolute quantitative MBF at rest and during hyperaemia • Detects MVO and predicts adverse remodelling • Offers absolute flow quantification, valuable in FFR-CFR • Evaluate viable myocardium	• High cost • Lack of availability • Radiation exposure • Requires a vasodilator agent to induce hyperaemia
Magnetic resonance imaging 	• Gold standard to assess infarct size, MVO, and IMH • Strong prognostic value for adverse remodelling and outcomes • Offers long-term risk stratification • Lack of radiation exposure • Reproducibility • Quantitative and qualitative data	• Lack of availability • Intermediate/high cost • Time-consuming

CFR, coronary flow reserve; ECG, electrocardiogram; FFR, fractional flow reserve; IMH, intramyocardial haemorrhage; IMR, index of microcirculatory resistance, MBF, myocardial blood flow; MI, myocardial infarction; MVO, microvascular obstruction, STEMI, ST-elevation myocardial infarction; STR, ST-segment resolution; TIMI, Thrombolysis In Myocardial Infarction.

pressure wire with thermistors. Index of microcirculatory resistance is a valuable tool for assessing microvascular resistance and stratifying risk in STEMI patients following primary PCI with the additional potential to guide therapeutic strategies targeting microvascular dysfunction and reperfusion injury. An IMR >40 units is strongly associated with adverse short- and long-term outcomes in STEMI patients undergoing primary PCI.[38,42] A collaborative pooled analysis of individual patient data from six cohorts confirmed this, showing a 2.81-fold increase in the hazard ratio for 5-year cardiac mortality and approximately twofold higher hazard of all-cause mortality or hospitalization for heart failure during long-term follow-up.[43] These findings underscore the prognostic value of IMR for both short- and long-term outcomes in STEMI patients. Additionally, the feasibility IMR pre-stenting has been demonstrated, aiding in the prediction of MVO post-stent deployment.[44] It remains the only index validated in observational studies to guide infarct size/MVO-targeted therapies and determine accelerated discharge pathways for low-risk STEMI patients.[45,46] However, IMR has some operator dependence, which may impact reproducibility.[47] Moreover, wire-based assessments in STEMI patients face practical challenges, including prolonged procedural time, the need for dedicated pressure wires, additional intracoronary instrumentation, administration of hyperaemic agents, and increased procedural costs. To circumvent these limitations, IMR_{angio} has emerged as an alternative. IMR_{angio} estimates microcirculatory resistance based on computational flow dynamics from standard coronary angiograms, without requiring a pressure wire or vasodilators. Angiography-derived index of microvascular resistance has shown good correlation with wire-based IMR measurements in

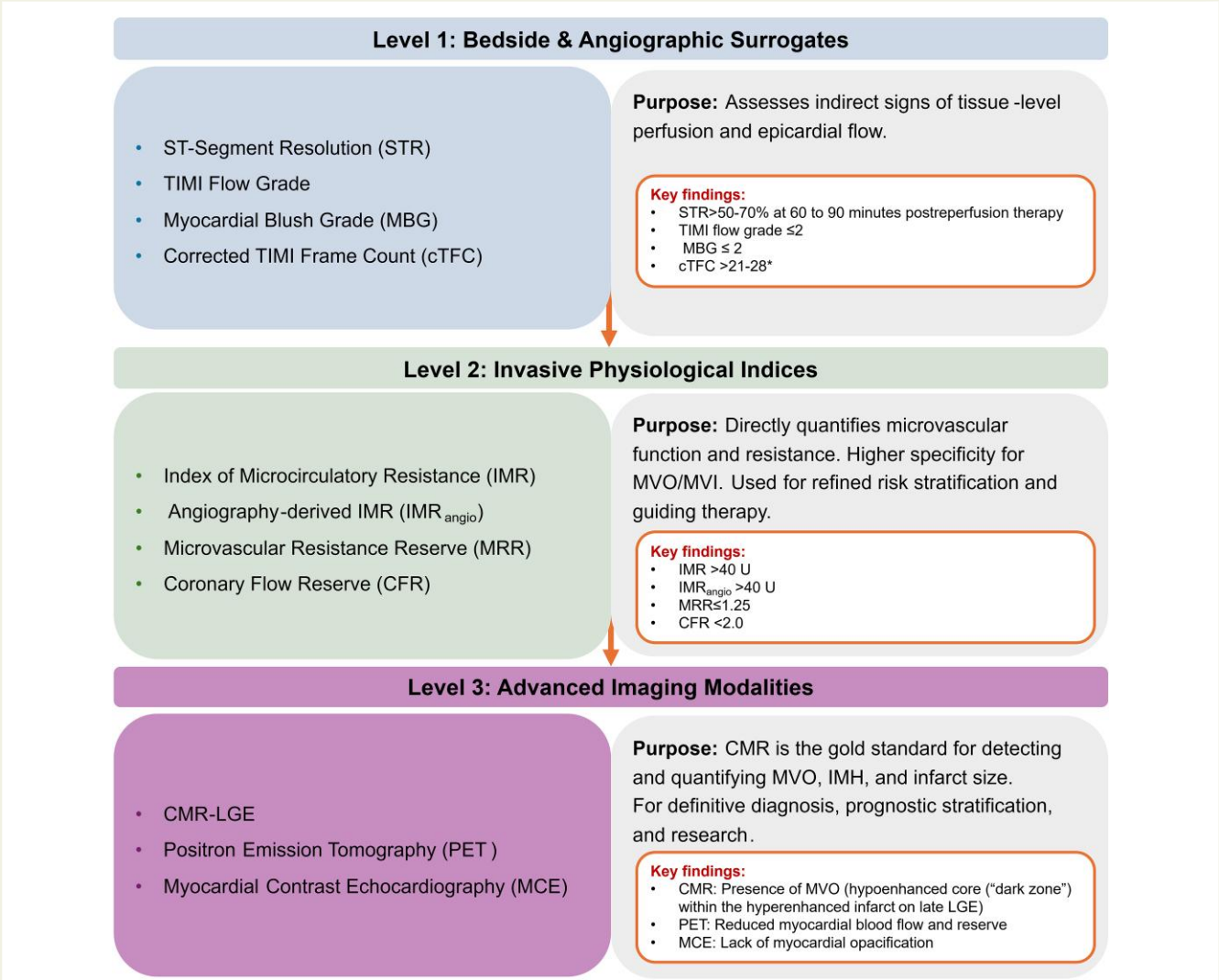


Figure 3 Hierarchical diagnostic framework for microvascular assessment. Level 1 includes bedside and angiographic surrogates for rapid initial evaluation. Level 2 incorporates invasive physiological indices for direct quantification of microvascular function, and Level 3 encompasses advanced imaging modalities for definitive tissue characterization and risk stratification. This structured approach facilitates the selection of diagnostic tools based on clinical context, resource availability, and the need for precision

both the acute and subacute phases of STEMI, across culprit and non-culprit vessels, offering a noninvasive approach for microvascular assessment in this high-risk population.[48]

Microvascular resistance reserve (MRR)

Microvascular resistance reserve is a novel physiological index that quantifies the reduction in microvascular resistance from rest to hyperaemia. It is defined as the ratio of true resting microvascular resistance to hMR, incorporating an adjustment factor to account for epicardial resistance.[49] As a result, MRR is independent of epicardial stenosis and provides a coronary microcirculation-specific analogue to CFR.[50]

Microvascular resistance reserve was originally derived using continuous thermodilution, the only volumetric technique capable of quantifying absolute coronary blood flow and resistance. This method utilizes a dedicated microcatheter (RayFlow) for controlled saline infusion and has demonstrated superior reproducibility and accuracy compared to bolus thermodilution, offering potential advantages over other invasive indices such as hMR and IMR.[51] Importantly, MRR can also be calculated using Doppler flow velocity or bolus thermodilution, increasing its clinical applicability across different platforms. Among patients with STEMI, an MRR ≤1.25 is associated with a fourfold increase in the hazard for all-cause mortality or heart failure hospitalization over a median 3-year follow-up.[52] Even modest preservation of vasodilatory capacity, evidenced by a 25% reduction in microvascular resistance with hyperaemia, immediately after primary PCI, has been shown to carry prognostic significance for survival, over a follow-up period of 5 years.

In summary, IMR >40 units, either alone or in combination with CFR <2.0 and MRR ≤1.25, has been validated for the diagnosis of coronary microvascular dysfunction in the setting of

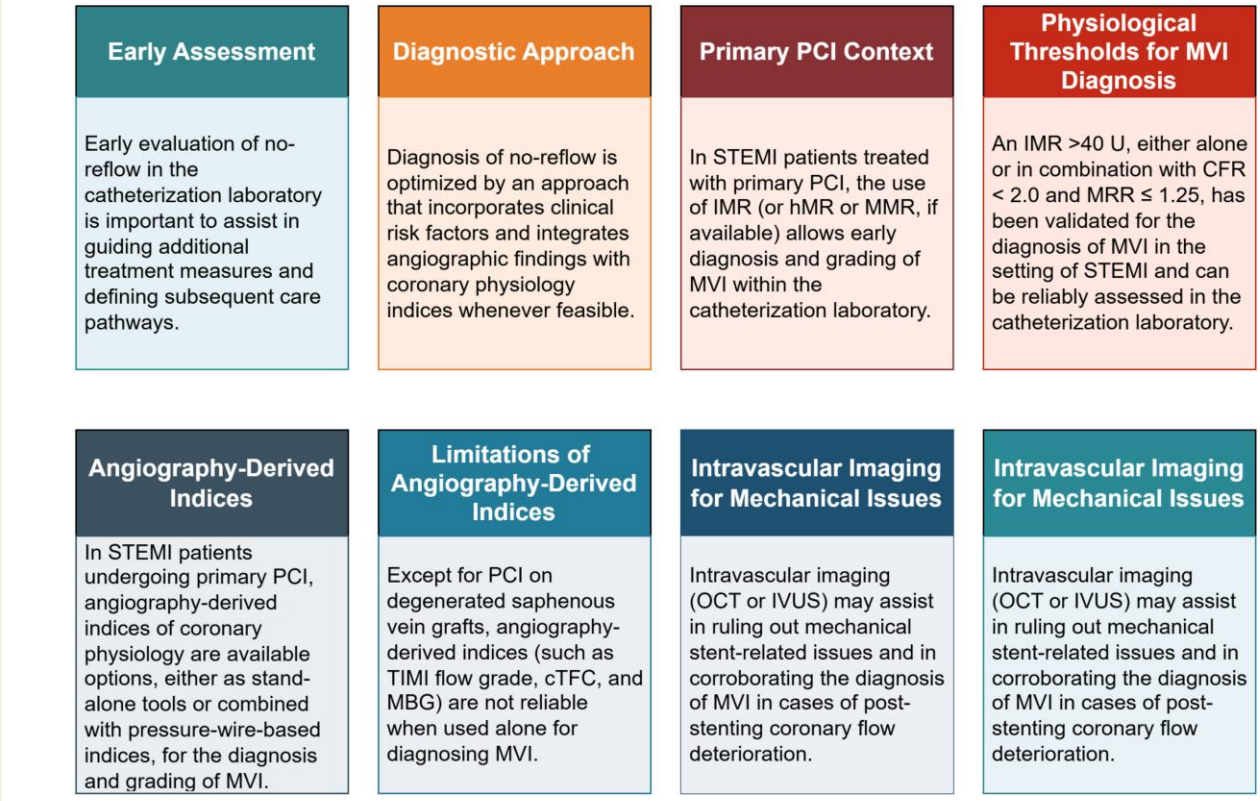


Figure 4 Advice for diagnosis and evaluation of coronary no-reflow in the catheterization laboratory. cTFC, corrected TIMI frame count; IMR, index of microcirculatory resistance; IVUS, intravascular ultrasound; MBG, myocardial blush grade; MMR, microvascular resistance reserve; MVI, microvascular injury; OCT, optical coherence tomography; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction; TIMI, Thrombolysis In Myocardial Infarction

STEMI and can be reliably assessed in the catheterization laboratory and also provides important prognostic information for early risk stratification (*Figure 5*).

Intravascular imaging and no-reflow

Intravascular ultrasound (IVUS) and optical coherence tomography (OCT) do not directly diagnose no-reflow but help identify coronary plaque features that predispose to its occurrence.[53] Features such as large lipidic/necrotic cores, attenuated plaque, plaque rupture, and a substantial thrombotic burden are well-established contributors to MVO, primarily through an increased risk of distal embolization.[54,55] Coronary plaque burden and morphology are key determinants of no-reflow in acute MI. Intravascular imaging studies have linked larger plaque volumes,[56] higher plaque rupture prevalence,[57] and extensive thrombus burden to higher risk of no-reflow risk. Optical coherence tomography has shown a superior accuracy than angiography in defining and quantifying the true thrombotic burden in the culprit artery of the STEMI patients.[58] Equally, OCT findings confirm that lipid-rich plaques predict no-reflow in STEMI. This finding is consistent with IVUS data correlating plaque attenuation with impaired post-PCI coronary flow.[57] Concentric plaques, due to their heightened thrombogenicity, further elevate this risk by promoting microcirculatory embolization.[57] Recent research has identified cholesterol crystals at culprit sites as independent predictors of no-reflow, improving lipid arc-based risk assessment.[59] While the exact mechanism(s) remain unclear, cholesterol crystals likely enhance embolization and thrombogenicity, exacerbating MVO.[60]

Intravascular imaging can aid in the differential diagnosis of no-reflow during PCI, particularly in cases of abrupt loss of antegrade flow following stent implantation or post-dilatation. In such scenarios, the absence of mechanical stent-related complications (e.g. distal edge dissections) and the presence of protruding atherothrombotic material through stent struts are hallmarks of distal embolization, a key mechanism underlying the no-reflow phenomenon.

Given these insights, intravascular imaging represents an essential tool in the context of coronary revascularization.[61,62] In selected high-risk cases or when the culprit lesion is unclear, IVUS or OCT can provide valuable insights, helping to assess no-reflow risk or confirm its diagnosis alongside angiography and coronary physiology indices (*Figure 4*).

ST-segment resolution

ST-segment resolution (STR), assessed 60–90 min after reperfusion, is a low-cost, bedside marker of myocardial reperfusion and an independent predictor of mortality[63] (*Table 2*). In fibrinolysis-treated patients, failure to achieve ≥50% STR mandates rescue PCI as per current guidelines.[61] Recent trials

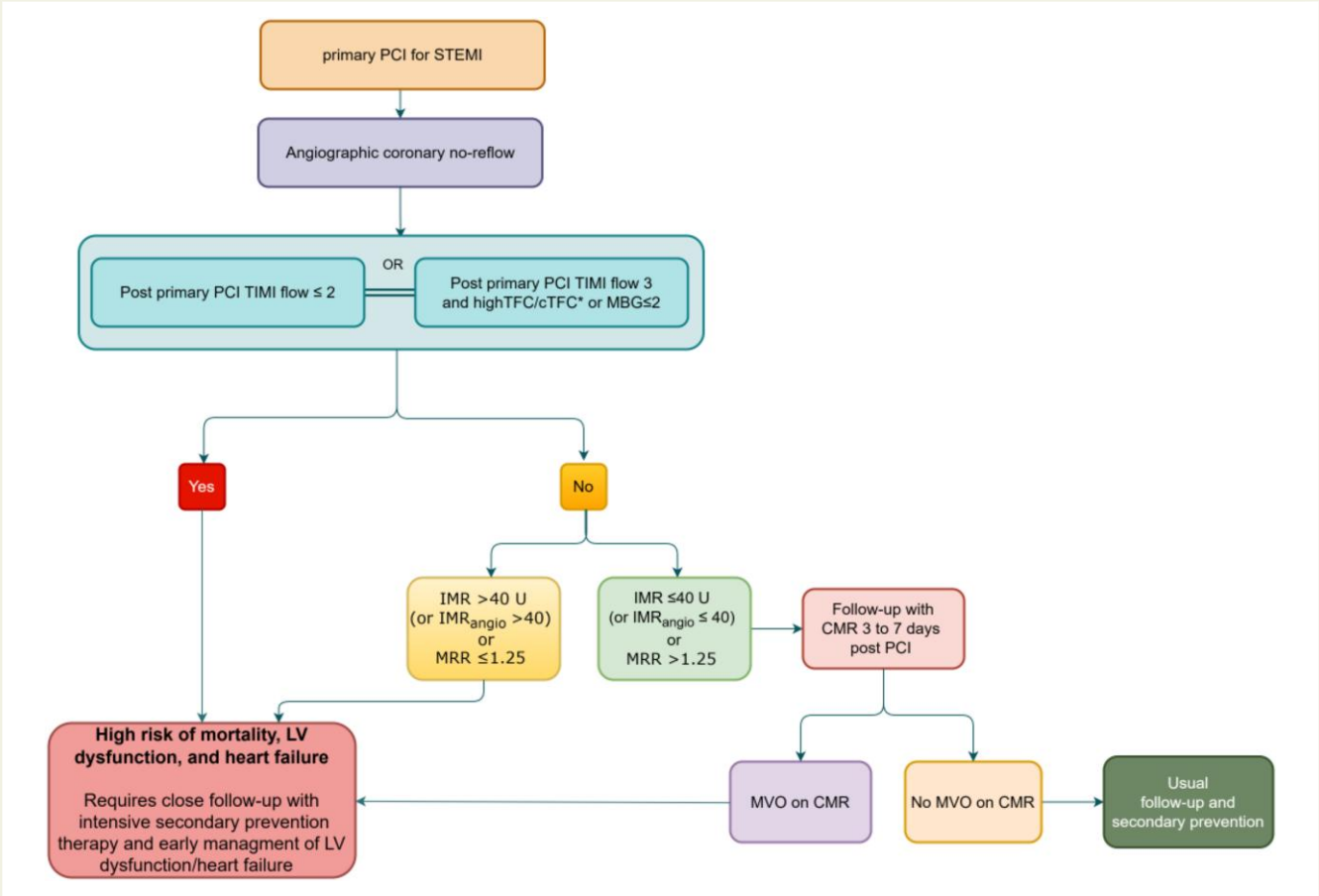


Figure 5 Proposed algorithm for early risk stratification of patients with STEMI post primary PCI (based on[38,42,52]). An approach to early risk stratification could incorporate post-PCI angiographic markers of no-reflow, IMR, and MVO assessment to identify high-risk patients within the first 7 days after primary PCI, potentially limiting the need for routine IMR and CMR evaluation in all patients. Post-PCI TIMI flow, cTFC, MBG, IMR, and MVO are dynamic markers of MVI post-STEMI. Patients with preserved IMR, even in the presence of MVO, may experience infarct size regression, whereas an IMR >40 units may reflect irreversible MVI. Acutely measured IMR likely captures both reversible microcirculatory stunning and irreversible injury, potentially influenced by pre-existing coronary microvascular dysfunction. MVO, particularly when associated with IMH, represents a robust marker of microvascular injury and poor prognosis. Immediate post-primary PCI IMR (or MMR) assessment combined with early CMR detection of MI size, LVEF, and MVO provides complementary strategies to identify clinically significant post-ischaemic microvascular dysfunction, stratify risk, and guide long-term management. The presence of both IMR >40 units (or MMR ≤1.25) and MVO indicates high short- and long-term risk, whereas the presence of IMR >40 units (or MMR ≤1.25) alone or MVO alone identifies patients at elevated long-term risk. These patients warrant intensive care, including close follow-up, optimized secondary prevention therapy, and early intervention for LV dysfunction and heart failure to improve outcomes. Integrating IMR and MVO assessments offers superior prognostic precision compared to either marker in isolation and supports a move towards personalized, precision-based cardiovascular care. CMR, cardiac magnetic resonance; cTFC, corrected TIMI frame count; IMH, intramyocardial haemorrhage; IMR, index microvascular resistance; IMRangio, angiography-derived index of microcirculatory resistance; LV, left ventricular; MBG, myocardial blush grade; MVO, microvascular obstruction; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction; TIMI, Thrombolysis In Myocardial Infarction

confirm its utility. In the STREAM-2 trial, STR was superior with a pharmaco-invasive strategy, with comparable final TIMI flow Grade 3, underlining its incremental value.[64] Poor STR was associated with longer ischaemic times, higher thrombus burden, and impaired coronary flow before and after PCI.[65] ST-segment resolution also inversely correlates with IMR, indicating its relevance in microvascular assessment.[66]

Limitations include discordance with angiographic markers; up to 20% of anterior STEMI patients may show complete STR despite TIMI flow Grade ≤2, while one-third of those with MBG ≥2 lack STR.[63,67] Sex-related differences, infarct size, ECG artefacts, and timing of assessment may further affect reliability.[63,68] Nevertheless, STR remains a widely available tool that complements angiographic, physiological, and imaging-based assessments of reperfusion.

Myocardial contrast echocardiography

Myocardial contrast echocardiography (MCE) allows direct, bedside assessment of myocardial perfusion using microbubble

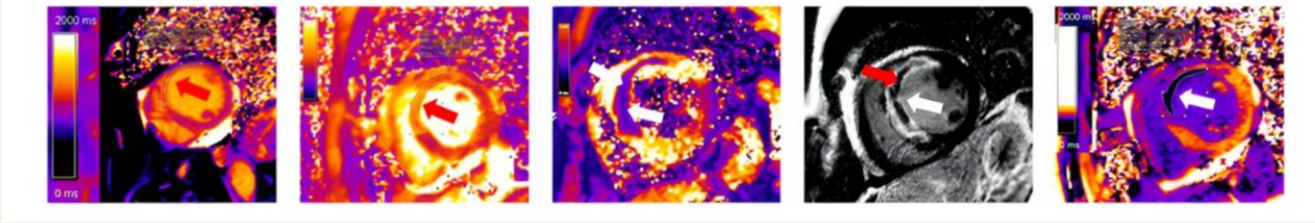


Figure 6 Detection of microvascular obstruction and intramyocardial haemorrhage on T2 myocardial mapping following acute anteroseptal ST-elevation myocardial infarction: correlation with native T1, T2, LGE, and post-contrast T1 myocardial maps*: (*A*) native T1 myocardial map (mid short axis): demonstrates transmural prolongation of native T1 time in the anterior and anteroseptal segments, indicative of transmural myocardial oedema; (*B*) T2 myocardial map (mid short axis): shows transmural prolongation of T2 time in the anterior and anteroseptal segments, confirming the presence of transmural myocardial oedema; (*C*) T2 myocardial map (mid short axis)*: reveals transmural shortening of T2* time in the anterior and anteroseptal segments, consistent with intramyocardial haemorrhage; (*D*) LGE PSIR (mid short axis): displays transmural LGE in the anterior and anteroseptal segments (white arrow), indicating myocardial necrosis, with coexisting MVO (red arrow). (*E*) Post-contrast T1 myocardial map (mid short axis): depicts transmural shortening of post-contrast T1 time in the anterior and anteroseptal segments, further supporting myocardial necrosis. LGE, late gadolinium enhancement; MVO, microvascular obstruction; PSIR, phase sensitive inversion recovery

contrast agents and ultrasound (*Table 2*).[69] A lack of contrast opacification in the myocardium indicates MVO, representing no-reflow.[70] Myocardial contrast echocardiography-detected scarring predicts long-term cardiac outcomes.[71] Functional MVI can also be evaluated with Doppler-derived CFR and diastolic deceleration time, both predictive of severe microvascular damage, adverse remodelling, and outcomes.[72,73] Nonetheless, MCE's clinical application is limited by operator dependency, image quality, reproducibility, and quantification challenges.[74] Doppler CFR is further constrained by technical limitations, including dependence on beam angle and lack of vessel diameter assessment.

Nuclear imaging

Nuclear techniques such as single-photon emission computed tomography (SPECT) and positron emission tomography (PET) are valuable for assessing myocardial perfusion after STEMI (*Table 2*). Early studies showed that absent ^{201}Tl uptake post-thrombolysis indicated microvascular, not myocardial, dysfunction, a finding supported by ^{99m}Tc-based SPECT imaging.[3,75] Tracers such as ^{99m}Tc-sestamibi and ^{99m}Tc-tetrofosmin offer higher specificity than MCE after PCI.[76,77] More recently, PET imaging with [^{13}N]-ammonia and [^{18}F]-FDG enables precise quantification of myocardial blood flow (MBF). In STEMI, reduced hyperaemic MBF and myocardial perfusion reserve (MPR) correlate with MVO on CMR.[78] Positron emission tomography also reveals partial microvascular recovery post-PCI. Notably, PET's ability to detect MBF and MPR abnormalities, even in patients with normal TIMI flow Grade 3, has shown prognostic implications. A higher PET-derived hMR index (≥2.5) post-PCI is associated with worse LV remodelling and reduced ejection fraction at follow-up. While limited by cost and access, PET remains a powerful tool in complex cases, including FFR-CFR discordance or viability assessment. As technology improves, PET's role in diagnosing no-reflow and guiding therapy is likely to expand.

Cardiac magnetic resonance

Cardiac magnetic resonance is the gold-standard noninvasive modality for diagnosing coronary no-reflow, offering high-resolution transmural perfusion imaging, detailed tissue characterization, and unparalleled sensitivity for detecting MVO, IMH, and infarct size post-STEMI (*Table 2* and *Figure 6*). Contrast-enhanced CMR distinguishes viable from infarcted myocardium based on gadolinium distribution.[79] Microvascular obstruction is classified as 'early' or 'late' based on the timing of imaging relative to gadolinium administration. Late MVO is a stronger predictor of adverse outcomes than early MVO, correlating with larger infarct size, adverse LV remodelling, and poorer short-, medium-, and long-term clinical outcomes, independent of infarct size.[80–82] Given its prognostic significance, late MVO detection has become a key imaging target, with late gadolinium enhancement (LGE)-CMR playing a central role in long-term risk stratification and evaluation of cardioprotective strategies. A strong graded relationship exists between MVO extent and 1-year mortality or heart failure hospitalization, with a threefold higher hazard ratio in patients with greater MVO burden (>1.55%) and concomitant IMH, indicating more severe injury.[6,83]

The timing of CMR imaging significantly affects the detection of MVO and IMH, as the post-MI myocardium undergoes dynamic changes influenced by blood flow restoration, ischaemic duration, and cardioprotective interventions. Although no definitive consensus exists, current evidence suggests that the optimal window for post-MI CMR is between 3 and 7 days after reperfusion therapy, when LGE and MVO findings are relatively stable and offer strong prognostic value.[84–86] However, the lack of standardized scan timing may introduce variability in interpretation and potential biases in outcome assessment. Additionally, widespread clinical application is limited by high costs, long acquisition times, restricted availability, and patient-related factors such as claustrophobia, ferromagnetic implants, or noncompatible device and the risks associated with gadolinium in renal impairment.

Radiomics and artificial intelligence approaches

Radiomics and artificial intelligence (AI) are emerging as promising applications to predict and quantify MVO.[87] By applying

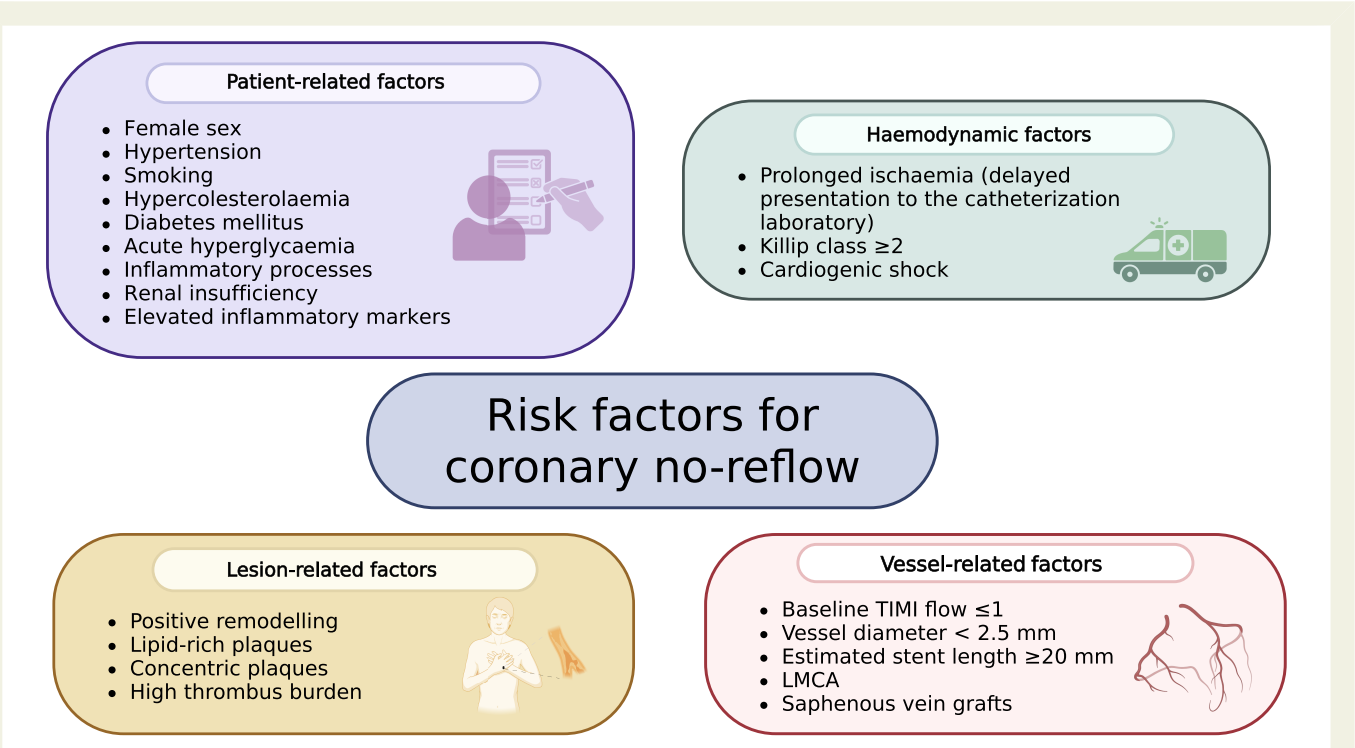


Figure 7 Risk factors for the development of coronary no-reflow. LMCA, left main coronary artery; TIMI, Thrombolysis In Myocardial Infarction

advanced computational algorithms, radiomics enables the extraction of high-dimensional quantitative features, including texture, shape, and signal–intensity patterns, that are imperceptible to the human eye.

Contrast-sparing strategies, particularly radiomics applied to non-contrast cine CMR with LGE as reference, have generated signatures and nomograms that accurately discriminate MVO presence, offering diagnosis and risk stratification in patients with contraindications to contrast media.[87,88]

The advent of photon-counting computed tomography (PCCT) has expanded myocardial imaging capabilities by enabling simultaneous high-resolution coronary assessment and myocardial tissue characterization through PCCT with late iodine enhancement.[89,90] In STEMI patients, PCCT shows excellent concordance with CMR for infarct size and MVO quantification (intraclass correlation coefficient ≈0.96–0.98), with MVO visualized on iodine-derived extracellular volume maps as hypodense cores within hyperdense infarction, closely matching CMR-LGE and without systematic bias.[89] Photon-counting computed tomography represents a promising integrated, noninvasive platform for combined coronary and myocardial evaluation, particularly in late-presenting STEMI, where MVO and viability assessment are clinically relevant.

Deep learning-based LGE-CMR segmentation has been extended to MVO. However, MVO remains more challenging to delineate than infarct size, with substantial human–AI disagreement (55.6% vs. 11.3%; $P < .001$). Model generalizability requires external validation and sensitivity analyses, given the impact of acquisition-related variability.[91]

Beyond imaging, AI-enhanced ECG models show promise for MVO detection in anterior STEMI (area under the curve, 0.83; specificity, 94%), but limited sensitivity, restricted populations, and retrospective designs currently preclude clinical implementation, highlighting the need for prospective validation.[92]

Outcomes

The no-reflow phenomenon is strongly linked to worse clinical outcomes.[7,8] Patients with no-reflow experience more haemodynamic complications, a greater need for temporary mechanical circulatory support,[93] and higher in-hospital mortality (12.6% vs. 3.8%)[8] compared with those with TIMI flow Grade 3. No-reflow in STEMI patients carries a worse prognosis than in non-STEMI cases, reflecting the greater vulnerability of the STEMI population.[94]

Over the long term, no-reflow survivors show adverse LV remodelling, larger infarcts, higher B-type natriuretic peptide levels, and lower ejection fraction over a mean follow-up of 46 months.[95] Five-year mortality is significantly higher in no-reflow patients (18.2% vs. 9.5%).[96] Even transient no-reflow, resolving during PCI, is associated with increased in-hospital and 6-month mortality (13% and 31%, respectively).[97] Observational data confirm elevated long-term all-cause mortality (22% vs. 14%) compared with patients who maintain normal flow.[98]

Predictors of no-reflow

Risk factors for no-reflow align with those for cardiovascular disease, older age, diabetes, hypertension, smoking, and inflammation.[7,55,68,99] Female sex, higher Killip class, longer ischaemic time, and lesion- or vessel-related characteristics (*Figure 7*) also

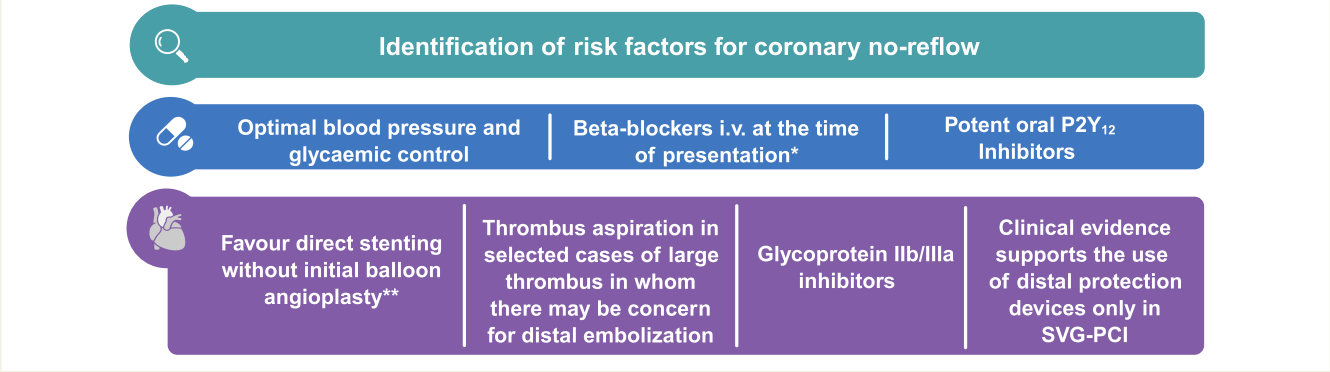


Figure 8 Proposed algorithm for the prevention of the coronary no-reflow phenomenon. *In patients without signs of acute heart failure, systolic blood pressure >120/80 mmHg, and no other contraindications. **Intracoronary imaging can provide valuable guidance during the procedure. Exceptions to direct stenting: cases of significant calcification, fibrotic lesions, or vessel tortuosity requiring lesion modification before stenting. SVG-PCI, saphenous venous graft percutaneous coronary intervention

increase risk.[7,55,68,100,101] Recognizing these factors early allows for targeted preventive measures during PCI.

Total ischaemic time and door-to-balloon time

Total ischaemic time is a critical determinant of no-reflow and myocardial injury.[102,103] In the HORIZONS-AMI trial, longer total ischaemic time duration independently predicted impaired myocardial perfusion regardless of the patient's risk profile. For those presenting within 2 h of symptom onset, faster door-to-balloon time (DBT) improved outcomes, suggesting that early intervention is crucial for improved reperfusion and survival.[104] A pooled analysis of over 3000 STEMI patients from 10 randomized trials undergoing primary PCI confirmed prior observations, showing that infarct size and MVO, as assessed by CMR, were strongly associated with total ischaemic time, but not with DBT.[105] A time-dependent relationship between total ischaemic time and no-reflow, and highlighted sex differences in post-PCI TIMI flow rates, was confirmed in another study.[68] Women had a higher incidence of suboptimal flow (8.8% vs. 5.0% in men) and a longer median total ischaemic time (280 min vs. 240 min). With similar DBT, women exhibited higher no-reflow rates, suggesting potential delays before hospital arrival. The study further showed that women had a consistently higher risk of suboptimal TIMI flow regardless of total ischaemic time, suggesting underlying factors like microvascular disease and endothelial dysfunction. In summary, although faster DBT improves early outcomes, limiting total ischaemic time is more impactful for long-term myocardial recovery.

Preventive strategies

Although several interventions have been tested to prevent no-reflow in STEMI patients undergoing primary PCI, the optimal approach remains unclear. *Figure 8* provides a summary of preventive measures to minimize the occurrence of no-reflow.

Pharmacological cardioprotective measures

Statins are a cornerstone of secondary prevention. Observational and small trial data suggest that early high-dose statins may reduce no-reflow and improve myocardial function, likely *via* pleiotropic effects beyond lipid lowering.[106–108] Beyond lipid-lowering and anti-inflammatory effects, statins may also contribute to plaque stabilization and reduce distal cholesterol embolization, thereby potentially mitigating one of the mechanistic pathways leading to no-reflow. The SECURE-PCI trial showed that early atorvastatin reduced 30-day major adverse cardiovascular events (MACE) in STEMI patients undergoing PCI, without affecting low-density lipoprotein cholesterol levels, suggesting benefit from rapid anti-inflammatory and plaque-stabilizing effects, including potential reduction of distal cholesterol embolization.[109–111] Recent preclinical studies suggested that intravenous administration of atorvastatin, during ongoing STEMI or at the time of reperfusion, more effectively reduces infarct size, preserves cardiac function, and attenuates adverse remodelling compared to oral administration initiated shortly after reperfusion, highlighting its potential for further investigation.[112–114]

Pre-reperfusion intravenous beta-blockers, particularly metoprolol, may reduce MVO and arrhythmias in STEMI, especially in patients with TIMI flow Grade ≤1.[115–118] However, trials were underpowered for clinical outcomes, and current guidelines suggest they may be considered in select patients without contraindications.[61]

A meta-analysis supports nicorandil for reducing no-reflow via K^+_{ATP} agonism.[119]

Preclinical studies suggest that sodium–glucose cotransporter 2 inhibitors and glucagon-like peptide-1 (GLP-1) analogues reduce infarct size and improve cardiac function through endothelial, anti-inflammatory, and metabolic mechanisms.[120–124] The EMMY trial[125] showed improved remodelling with empagliflozin, but DAPA-MI[126] and EMPACT-MI[127] found no significant reduction in death or heart failure hospitalization. Small randomized trials suggest GLP-1 analogues may improve myocardial salvage.[128,129] In one study, the myocardial salvage index, measured by CMR from the area at risk and final infarct

size, was significantly higher in the liraglutide group compared to placebo.[129] Additionally, favourable effects were observed on nitric oxide levels and LV ejection fraction over time. These benefits suggest a potential role for GLP-1 analogues in reducing reperfusion injury and improving myocardial recovery, although no significant differences in MACE have been reported to date.

Preventive antithrombotic strategies

While ticagrelor may offer microvascular benefits in small studies,[130–132] the ATLANTIC trial found no improvement in pre-PCI reperfusion with prehospital ticagrelor vs. clopidogrel.[133] In REDUCE-MVI, ticagrelor and prasugrel were comparable in preventing MVI.[134] Adding cangrelor to ticagrelor did not reduce infarct size or MVO in the PITRI trial.[135] Glycoprotein IIb/IIIa inhibitors (e.g. tirofiban, abciximab) may improve STR and reduce thrombus burden in high-risk cases,[136] but routine use is not recommended with potent $P2Y_{12}$ inhibitors due to bleeding risk and limited added benefit.[61] They remain an option for bail-out therapy in no-reflow or high-risk PCI.[61]

Thrombus aspiration and mechanical approaches for angiographic no-reflow

Several emerging technologies have been investigated to prevent no-reflow in high-risk STEMI patients with occluded coronary arteries. Thrombus aspiration has been evaluated in multiple studies, with a meta-analysis of 14 trials demonstrating a 37% relative reduction in the risk of no-reflow.[137] However, an individual patient data meta-analysis of the TAPAS, TASTE, and TOTAL trials did not demonstrate a clinical benefit from routine thrombus aspiration during PCI in STEMI patients. Notably, in a subgroup of patients with a high thrombus burden, a 20% relative reduction in cardiovascular death was observed, though accompanied by an increased risk of cerebrovascular events.[138] Consequently, current clinical guidelines do not recommend the routine use of thrombus aspiration, citing limited clinical benefit, lack of robust peer-reviewed data, and concerns regarding stroke risk.[61]

Direct stenting, which traps disrupted plaque and thrombus between the stent and the vessel wall, has shown potential in reducing no-reflow compared to conventional stenting. A meta-analysis of 12 trials reported a 52% reduction in the odds of no-reflow with direct stenting.[139] Deferred stenting (delaying stent deployment after achieving stable distal flow) has been proposed as a strategy to reduce no-reflow and improve clinical outcomes such as cardiovascular mortality, reinfarction, stroke, and stent thrombosis in STEMI patients. The DEFER-STEMI trial, a randomized mechanistic study in high-risk patients, showed that deferred stenting (4–16 h) reduced no/slow-reflow, increased myocardial salvage, and improved reperfusion.[140] Subsequent larger trials provided less favourable results. The DANAMI-3–DEFER trial found no significant difference in the composite endpoint of all-cause mortality, heart failure hospitalization, recurrent MI, or unplanned revascularization between deferred (48 h) and immediate stenting (hazard ratio, 0.99; 95% confidence interval, 0.76–1.29). Angiographic no-reflow rates were also similar (23% vs. 24%).[141] The DANAMI-3–DEFER CMR substudy confirmed these findings, showing no benefit of routine deferred stenting on infarct size, MVO, or myocardial salvage.[142] Likewise, the MIMI and INNOVATION pilot trials did not support the use of deferred stenting and even suggested a potential detrimental effect on MVO.[143,144] Subsequent meta-analysis aligned with these results, reporting no differences in MACE, though some studies observed improved LV function over the long term[145] or reduced no/slow-reflow with higher rates of MBG 3 in the deferred stenting group.[146] Whether deferred stenting is superior to the conventional approach remains uncertain. Based on current evidence, it may be most appropriate for select patients with a high thrombus burden, rather than routine use.

Some authors suggest that direct stenting without predilatation or avoiding high-pressure post-dilatation may help reduce distal embolization.[147–149] However, data from the NHLBI Dynamic Registry found no significant difference in angiographic no-reflow rates among 1358 acute MI patients who underwent post-dilatation (1.7% vs. 1.3%; $P = .53$), although there was a nearly twofold increase in the propensity score-adjusted risk of death or MI.[150] In contrast, a randomized pilot trial of 120 patients comparing prolonged stent inflation (>30 s, mean inflation pressure 13.4 atm) with conventional inflation demonstrated a significantly lower incidence of no-reflow (0% vs, 30%; $P = .002$) and reduced MVO on CMR (6.7% vs, 50%) in the prolonged inflation group.[151] These findings suggest that prolonged inflation may optimize stent expansion and allow more time for thrombotic material to become effectively trapped between the stent and the vessel wall, potentially reducing distal embolization.

Distal embolic protection devices

The term 'embolic protection devices' (EPDs) refers to the group of devices designed to prevent distal embolization of atherothrombotic debris, including friable lipid-rich plaque and platelet clumping during percutaneous interventions. The lack of benefit of distal embolic protection during PCI for STEMI in native coronary arteries has been addressed in three major RCTs. All RCTs demonstrated no significant benefit in improving microvascular perfusion, improving reperfusion success, reducing infarct size, or increasing event-free survival.[18,152,153] Based on these results, there is no approved or guideline-based indication for the use of EPDs in the native coronary arteries. In contrast, the benefits of the EPDs shown in the SAFER trial changed the standard of care for SVG-PCI.[154] The trial demonstrated higher procedural success and a lower composite rate of death, MI, emergency coronary artery bypass grafting, or target lesion revascularization at 30 days with the thrombectomy device. Additionally, EPDs provided similar benefits against MACE, regardless of whether glycoprotein IIb/IIIa inhibitors were used. Nevertheless, EPD utilization remains suboptimal in the real-world practice of SVG-PCI. Several factors may explain this gap. First, SVG interventions constitute a small proportion of total PCI cases, limiting operator experience with these devices. Second, the complexity of some EPDs may hinder widespread adoption. Finally, only the SAFER trial used a superiority design, and while it met its primary composite endpoint, no mortality benefit was observed at 30 days. This lack of a significant impact on in-hospital death may have limited their perceived utility. Further trials are needed to evaluate EPDs in contemporary practice and establish standardized guidelines for their use.

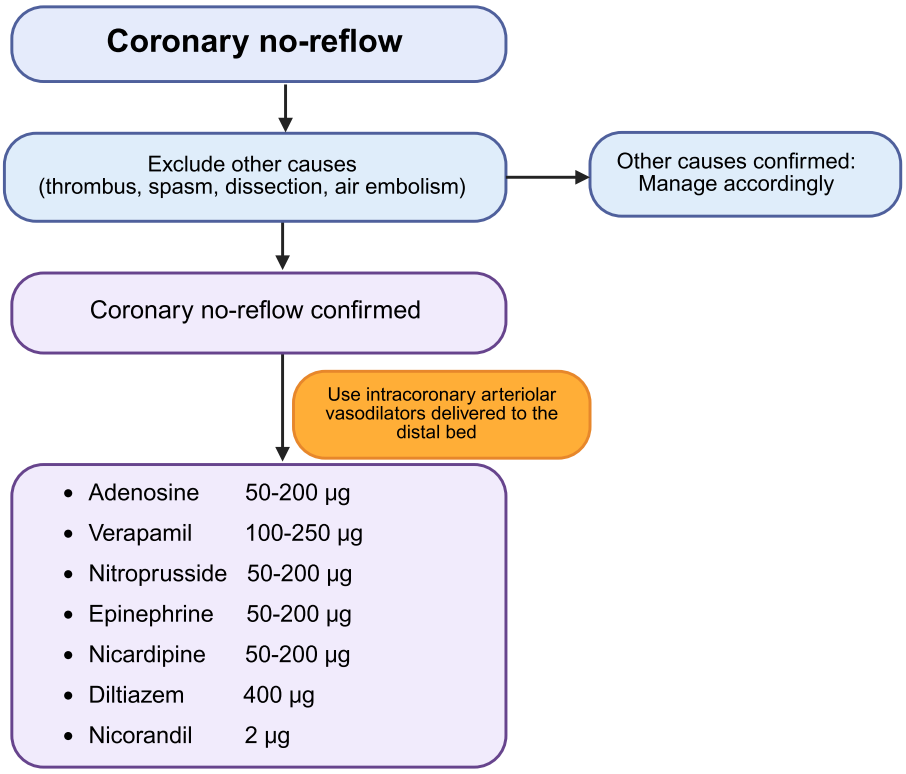


Figure 9 Proposed algorithm for the treatment of the coronary no-reflow phenomenon in the catheterization laboratory. Adenosine is contraindicated in patients with heart block. Similarly, verapamil and diltiazem, both non-dihydropyridine calcium channel blockers, are contraindicated in cases of cardiogenic shock or heart block. Nicardipine, a dihydropyridine calcium channel blocker, warrants caution or avoidance in severe aortic stenosis. Nitroprusside, a potent arterial and venous vasodilator, is unsuitable for patients with severe aortic stenosis or hypertrophic cardiomyopathy. Finally, epinephrine, though sometimes considered in refractory cases, is avoided in the setting of ventricular arrhythmias

Treatment of no-reflow

Pharmacological therapy for angiographic no-reflow

Various pharmacological agents, including heparin, intracoronary adenosine, nitrates, glycoprotein IIb/IIIa antagonists, and thrombolytics, have been suggested for treating no-reflow (*Figure 9*), but their therapeutic value remains limited. Heterogeneity in the pathophysiology of no-reflow, patient populations, adjunctive therapies, dosing, and drug-delivery methods makes study results difficult to interpret.

Adenosine

The AMISTAD and AMISTAD II trials demonstrated a reduction in infarct size in STEMI patients treated with high-dose (70 µg/kg/min) and prolonged (3-h) adenosine infusion. However, neither trial showed significant differences in clinical outcomes, such as heart failure, rehospitalization for congestive heart failure, or mortality, between patients receiving adenosine and those who did not.[155,156] The REOPEN-AMI trial investigated the effect of high-dose adenosine (120 µg fast bolus followed by 2 mg as slow bolus) or nitroprusside (60 µg fast bolus followed by 100 µg as slow bolus) in 240 patients with STEMI following intracoronary thrombus aspiration.[157] While STR >70% was higher in those treated with adenosine, no significant clinical benefit was observed at 30 days. However, the adenosine group showed favourable LV remodelling and a reduction in hospitalization for heart failure at 1 year as compared with controls.[157,158] In contrast, the REFLO-STEMI trial investigated the effects of high-dose intracoronary adenosine (1–2 mg) and nitroprusside (500 µg total) vs. controls in 247 STEMI patients undergoing primary PCI. Adenosine failed to reduce infarct size or MVO as measured by CMR when compared with controls. Per-protocol analysis showed that adenosine-treated patients had a larger infarct size, along with increased LV volumes and reduced ejection fraction, compared with controls. Additionally, the incidence of MACE was significantly higher in the adenosine group, primarily driven by heart failure at both 30 days and 6 months post-randomization.[159,160] Lastly, a meta-analysis of 11 RCTs reported that adenosine, when used as a treatment for no-reflow during primary PCI, was associated with a reduction in angiographic no-reflow (TIMI flow Grade ≤2).[161] However, this benefit was accompanied by an increased incidence of adverse events. Moreover, there was no evidence to suggest that adenosine reduced all-cause mortality, non-fatal MI, or the incidence of MBG ≤1.[161] It should be noted, however, that while these clinical trials primarily investigated adenosine administration after no-reflow was established, experimental studies have explored the potential benefits of earlier adenosine

administration, starting before reperfusion.[162] The optimal timing of adenosine administration relative to symptom onset and reperfusion, dose, as well as whether early administration might prove particularly beneficial for selected high-risk groups, such as patients with large anterior infarctions, high thrombus burden, or delayed reperfusion, remains to be determined. Overall, given the limited number of trials and participants, further research is necessary to draw definitive conclusions regarding the efficacy and safety of adenosine in this setting.

Nitroprusside is a potent vasodilator commonly used to increase epicardial coronary blood flow and myocardial perfusion when administered into the infarct-related artery, distal to the occlusion. In a small double-blind randomized trial involving 98 STEMI patients, selective intracoronary administration of nitroprusside (60 μg) immediately before primary PCI did not improve myocardial tissue reperfusion or coronary blood flow but did significantly reduce the composite endpoint of target vessel revascularization, MI, and death at 6 months compared to placebo.[163] In another study of 162 STEMI patients, selective intracoronary administration of a fixed dose of nitroprusside (100 μg) in combination with tirofiban improved coronary blood flow, myocardial perfusion, and LV function and also reduced the combined endpoint of cardiac mortality, MI, and target vessel revascularization at 6 months, relative to intracoronary tirofiban alone.[164] These findings were supported by a meta-analysis of seven clinical trials, which demonstrated that intracoronary nitroprusside may reduce the incidence of no-reflow and improve clinical outcomes.[165] However, the REOPEN-AMI (total dose, 160 μg)[157,158] and REFLO-STEMI (total dose, 500 μg)[159,160] trials failed to show a significant improvement in MVO with nitroprusside compared to controls. Similarly, both trials reported comparable rates of MACE between the nitroprusside and control groups. In summary, while existing data on intracoronary nitroprusside suggest potential benefit, the evidence is derived from relatively small studies with heterogeneous designs, limiting the generalizability of these findings.

Calcium channel blockers (CCBs) and other vasodilators

Calcium channel blockers may improve myocardial perfusion by relaxing vascular smooth muscle and promoting coronary vasodilation, potentially reducing infarct size. In a small trial of 40 AMI patients, intracoronary verapamil enhanced microvascular function and wall motion recovery at 24 days.[166] The RECOVER trial showed that intracoronary diltiazem or verapamil more effectively reversed no-reflow than nitroglycerine in 102 STEMI patients.[167] A meta-analysis of eight trials confirmed that these agents reduced no-reflow incidence, improved cTFC, and lowered 6-month MACE.[168] However, another meta-analysis of 181 STEMI patients showed no significant effect on LV function or MACE.[169] Thus, while promising, evidence for intracoronary CCBs remains limited and requires further validation.

Recent studies have explored intracoronary epinephrine (100–600 μg) for refractory no-reflow, suggesting improved coronary blood flow, though its impact on clinical outcomes still remains uncertain.[170–172] Similarly, nitroglycerine, while exerting potent epicardial vasodilatory effects, has shown limited efficacy in improving microvascular perfusion in no-reflow,[173–175] likely due to its dependency on enzymatic conversion and poor action in the microcirculation.[176]

Emerging pharmacological strategies

Anti-inflammatory therapy

Given the role of inflammation in reperfusion injury, the ASSAIL-MI trial investigated the effect of interleukin-6 receptor inhibition using tocilizumab (280 mg) in STEMI patients undergoing primary PCI within 6 h of symptom onset.[177] While no significant difference in infarct size was seen at 6 months overall, patients treated beyond 3 h showed improved myocardial salvage, indicating possible benefit in later reperfusion phases and warranting further study.[177]

Intracoronary fibrinolysis

Low-dose intracoronary fibrinolysis during primary PCI aims to improve myocardial perfusion by targeting microvascular thrombi. Early pilot studies using streptokinase and alteplase showed mixed results, with some improvement in perfusion but limited impact on long-term outcomes.[178,179] The larger T-TIME trial found no reduction in MVO with intracoronary alteplase (10 or 20 mg), and a *post hoc* analysis raised concerns about potential harm in patients with ischaemia time ≥4–6 h.[180–182] Similarly, the ICE-TIMI 49 pilot study with intracoronary tenecteplase showed no improvement in no-reflow markers, though thrombus burden and hyperaemia (a marker of distal embolization) tended to improve.[183] These findings were confirmed in the STRIVE three-arm trial, in which intracoronary low-dose alteplase (10 mg or 20 mg) failed to improve the composite of 30-day MACE or MVO in high-risk patients undergoing primary PCI for STEMI with large thrombus burden and was associated with a trend towards increased transient ventricular fibrillation during drug administration.[184] Overall, evidence does not currently support routine intracoronary fibrinolytics during PCI. These results align with long-standing evidence that the ultimate success of reperfusion is modulated by the timeliness, efficiency, and efficacy with which it is applied. Notably, the clinical benefit of fibrinolysis declines substantially beyond 3 h from symptom onset, underscoring the priority to minimize symptom-to-door delays.[185] Ongoing trials [RESTORE-MI (NCT03998319) and OPTIMAL (NCT02894138)] aim to clarify whether specific patient subgroups may benefit from this approach.

Emerging strategies for cardioprotection

SALINE technique

The SALINE technique involves a forceful intracoronary saline bolus through a thrombus aspiration catheter. In a small STEMI study, it improved TIMI flow and 3-year outcomes, likely by reducing interstitial oedema and optimizing coronary tone.[186]

Ischaemic conditioning

Techniques like ischaemic pre- and post-conditioning have shown myocardial salvage benefits in small trials such as LIPSIA CONDITIONING[187], but clinical impact remains uncertain due to limited sample sizes.[188]

Intracoronary supersaturated oxygen (SSO_2) therapy

Supersaturated oxygen may reduce oxidative stress and inflammation. Trials like AMIHOT I/II and IC-HOT showed limited benefits overall, with some improvement in patients with anterior STEMI presenting within 6 h of symptom onset. Follow-up

Table 3 Gaps in evidence in the diagnosis, prevention, and treatment of the coronary no-reflow phenomenon

Aspect	Current evidence	Identified gaps	Future directions
Incidence	• Observational data suggest that in severe coronary artery calcification, no-reflow is less frequent with intravascular lithotripsy than with rotational atherectomy • RCTs using intravascular lithotripsy alone reported no episodes of the no-reflow phenomenon.	• Could no-reflow be a more frequent occurrence in the context of intravascular lithotripsy? • Is no-reflow attributable to the intravascular lithotripsy technique itself, the complexity of the lesions in which it is used, the concurrent use of atherectomy devices, or does it represent a complication emerging with the broader adoption of the technology?	• Further studies on the incidence and potential prevention of no-reflow in the intravascular lithotripsy setting
Diagnosis and risk stratification	• CMR is the gold standard for MVO and no-reflow detection • IMR >40 and MMR <1.25 validated for prognosis • IVUS and OCT cannot directly diagnose no-reflow but identify plaque features linked to no-reflow, such as large lipid cores, plaque rupture, and high thrombus burden and that may influence the choice of strategy	• What is the optimal window for CMR assessment? • How can reperfusion efficacy be accurately assessed in the context of declining STEMI mortality? • What strategies can improve the detection and management of microvascular perfusion failure post-reperfusion therapy? • What are the barriers to widespread validation and adoption of IMR in routine clinical practice? • Does intracoronary physiology after primary PCI improve risk stratification or guide tailored therapies to reduce MVO and reperfusion injury post-STEMI? • How can we increase the clinical adoption of intravascular imaging and develop evidence-based protocols to guide therapy?	• Standardized CMR timing • Large-scale studies on intracoronary physiology and validation of angiography-derived metrics (e.g. IMR_{angio}) for enhanced risk stratification post-reperfusion integration into routine workflows. • Future research should focus on integrating plaque morphology into no-reflow risk prediction and evaluating imaging-guided therapeutic strategies in prospective trials. • Need to develop multimodal AI models and validate on large, diverse datasets. • Prospective trials using AI-guided risk stratification that combine imaging, labs, and clinical data
Emerging noninvasive approaches for MVO assessment	• AI-enhanced ECG: Machine-learning ECG models identify MVO in selected anterior STEMI patients	• How can sensitivity be improved to function as a reliable rule-out tool? • Can performance generalize beyond anterior STEMI in diverse populations?	• Large-scale, multicentre validation; enhanced algorithmic sensitivity • Integration of real-time MVO risk scores into clinical workflows to guide targeted therapies
	• Cine-CMR radiomics: non-contrast cine CMR radiomics predicts MVO using LGE as reference, generating signatures and nomograms that discriminate patients with and without MVO.	• How can models be validated externally? • Which features and algorithms are most reproducible?	• Standardization of radiomics pipelines, multicentre validation, and prospective studies linking features to clinical outcomes
	• PCCT with late iodine enhancement enables simultaneous coronary and myocardial assessment, with excellent concordance to CMR-LGE for infarct size and MVO	• Can findings be reproduced in larger, multicentre cohorts? • What is the long-term prognostic and cost-effectiveness value?	• Larger multicentre studies; protocol harmonization; outcome-driven validation; dose/cost optimization.
	• Radiogenomics: links imaging phenotypes, including radiomics/AI features, to underlying biology and omics data.	• How can limited datasets and lack of standardization be addressed? • Can MVO-specific radiogenomic markers be identified?	• Combine imaging features with genomics, transcriptomics, and proteomics to refine phenotyping and improve individualized prediction of microvascular injury and remodelling.

Continued

Table 3 *Continued*

Aspect	Current evidence	Identified gaps	Future directions
Ischaemia time reduction	• Shorter total ischaemic time is strongly associated with better myocardial perfusion and clinical outcomes. • DBT alone does not correlate with infarct size/MVO • Sex-based disparities are not fully understood.	• What strategies can reduce total ischaemic time and address sex-specific disparities in reperfusion outcomes? • What strategies can improve patients' ability to recognize symptoms early and effectively reduce total ischaemic time?	• Need to develop sex-specific protocols. • Investigation and validation of emerging technologies, including wearable devices and vectorcardiography, to facilitate earlier symptom detection and enable timely medical intervention.
Statins	• Early high-dose statins may reduce MVO and improve myocardial function. • Mixed RCT result • Pleiotropic effects vs. lipid-lowering unclear.	• Do early high-dose statins reduce MVO, and how should timing and formulation be optimized?	• Larger trials to define timing and formulation (e.g. IV vs. oral)
Beta-blockers (IV)	• Metoprolol pre-PCI improves MVO and reduces arrhythmias • Trials are underpowered to detect clinical outcomes • Class effect unconfirmed.	• In which patients and settings does pre-reperfusion beta-blockade improve outcomes, and is the observed benefit specific to metoprolol?	• Clarify the benefit in TIMI 0–1 cases and define the ideal patient profile. • Clarify class–effect
SGLT2 inhibitors	• Preclinical cardioprotection • Modest benefit in post-MI LV remodelling in clinical studies • No significant reduction in heart failure/death in DAPA-MI and EMPACT-MI.	• Do SGLT2 inhibitors have a role in cardioprotection following MI?	• Define timing and patient selection for the acute MI setting.
GLP-1 analogues	• Small trials suggest reduced infarct size and improved LV function. • Inconsistent MACE reduction	• What is the role of GLP-1RA in cardioprotection?	• Larger trials powered for clinical endpoints and mechanism clarification.
Systemic inflammation	• IL-6 receptor inhibition (tocilizumab) improved myocardial salvage index in STEMI treated >3 h after onset, but no difference in infarct size at 6 months • No significant preventive benefit of colchicine given before PCI in STEMI	• Does anti-inflammatory therapy improve outcomes in STEMI, and how should timing and patient selection be optimized?	• Larger trials stratified by ischaemic time and inflammatory profile focused on infarct size, MVO, and long-term clinical events
Antiplatelets	• Ticagrelor/prasugrel show microvascular benefit in small trials • No benefit seen with cangrelor on top of a potent $P2Y_{12}$ antagonist • Inconsistent data on timing and combinations	• Given conflicting evidence on agent selection, timing, and combinations, what is the optimal antiplatelet strategy for preserving microvascular integrity in STEMI?	• Precision antithrombotic strategies and trials in high thrombus burden patients. • Stratified trials to identify responders, timing, and drug combinations.
Glycoprotein IIb/IIIa inhibitors	• Effective in some high-risk PCI and no-reflow bailout situations. • Routine use not supported • Limited data in patients on potent $P2Y_{12}$ blockers.	• What are the optimal and patient profiles for glycoprotein IIb/IIIa inhibitor use in the era of potent $P2Y_{12}$ inhibitors?	• Define optimal timing and indication, especially in high thrombus burden.

Continued

Table 3 *Continued*

Aspect	Current evidence	Identified gaps	Future directions
Pharmacological vasodilators	• Mixed data for adenosine, nitroprusside, CCBs, epinephrine • Lack of clear therapy response • Heterogeneous trial designs and small samples. • Limited benefit on hard outcomes	• Given conflicting evidence and unclear treatment–response profile, which pharmacological vasodilators are most effective for treating no-reflow?	• Head-to-head comparisons • Run therapy–response trials in AI-identified subgroups • Individualized therapy based on physiology/imaging
Intracoronary fibrinolysis	• T-TIME and STRIVE showed no benefit with possible harm in patients presenting with an ischaemic time < 6 h • Unclear benefit in specific subgroups	• Does intracoronary fibrinolysis have a role in selected STEMI subgroups, and what is the ideal therapeutic window for its use?	• Larger RCT to define patient selection, timing, and dosing
Deferred/direct stenting	• Mixed trial outcomes • Inconsistent benefit on infarct size or MVO with deferred stenting	• Which patient subgroups might benefit most from the deferred stenting?	• Studies targeting subgroups (e.g. high thrombus burden, delayed presentations)
Emerging strategies	• Sustained mechanical thrombectomy, stent-retriever-based thrombectomy, percutaneous microaxial flow pumps, SSO_2 therapy, SALINE technique, sonothrombolysis • Limited power, inconsistent protocols, endpoints often surrogate-based, no clear impact on MACE, and logistical complexity. • Bleeding, vascular complications, and haemolysis remain significant risks with percutaneous microaxial flow pump devices, with haemolysis sometimes requiring early device removal • Optimal timing and patient selection for initiation of percutaneous microaxial flow pumps for LV unloading remains undefined • Unclear role of pre-PCI sonothrombolysis	• What is the clinical role of non-pharmacological strategies in cardioprotection after STEMI? • In patients with high thrombus burden, does sustained mechanical aspiration or stent-retriever-based thrombectomy improve myocardial perfusion and clinical outcomes? • What are the optimal patient selection criteria (e.g. infarct location, ischaemic time, severely reduced LV ejection fraction, elevated LV end-diastolic pressure) to maximize the clinical benefits of SSO_2 therapy and how does total ischaemic time influence the efficacy of SSO_2 therapy post-PCI? • Can LV unloading and optimization of door-to-unload time further reduce infarct size and microvascular injury and improve clinical outcomes in patients with STEMI? • What is the role of sonothrombolysis in STEMI management, particularly when initiated before PCI?	• Larger RCTs with standardized protocols, investigating timing and combination strategies. • Validation of advanced thrombectomy strategies with larger RCTs using hard endpoints. • Further investigation into SSO_2 therapy, with a focus on timing and patient selection. • Large-scale randomized trials to define the role of early mechanical LV unloading in STEMI management and optimal patient selection criteria and establish standardized door-to-unload times. • Further studies on the role of sonothrombolysis in pre-PCI settings • Further mechanistic understanding and selection of patients more likely to benefit.

AI, artificial intelligence; CCB, calcium channel blocker; CMR, cardiac magnetic resonance; DAPA-MI, Dapagliflozin Effects on Cardiometabolic Outcomes in Patients with an Acute Heart Attack; DBT, door-to-balloon; EMPACT-MI, Study to Evaluate the Effect of Empagliflozin on Hospitalization for Heart Failure and Mortality in Patients with Acute Myocardial Infarction; GLP-1RA, glucagon-like peptide 1 receptor agonist; IL, interleukin; IMR, index of microcirculatory resistance; IMR_{angio}, angiography-derived IMR; IV, intravenous; IVUS, intravascular ultrasound; LGE, late gadolinium enhancement; LV, left ventricular; MACE, major adverse cardiovascular events; MI, myocardial infarction; MVO, microvascular obstruction; OCT, optical coherence tomography; PCCT, photon-counting computed tomography; PCI, percutaneous coronary intervention; RCT, randomized controlled trial; SGLT2, sodium–glucose cotransporter 2; SSO_2, supersaturated oxygen; STEMI, ST-elevation myocardial infarction; STRIVE, Adjunctive, Low-dose tPA in Primary PCI for STEMI; TIMI, Thrombolysis In Myocardial Infarction; T-TIME, A Trial of Low-dose Adjunctive alTeplase During prIMary PCI.

data suggest reductions in mortality and heart failure events[189–192] and significant reductions in MVO and infarct size.[193,194] Supersaturated oxygen is currently the only FDA-approved adjunct for no-reflow, with further validation awaited from the AMIHOT III trial (NCT04743245).

Advanced thrombectomy

Manual aspiration's limited efficacy may stem from poor patient selection and suboptimal thrombus removal, as evidenced by the OCT substudy of the TOTAL trial.[195] Novel strategies, including sustained mechanical aspiration[196] and thrombus retrieval devices such as stent-retriever-based thrombectomy,[197] already proven effective in stroke,[198] are emerging to address large thrombotic burden. The RETRIEVE-AMI trial reported a greater reduction in thrombus burden with stent-retriever thrombectomy.[58] Nevertheless, baseline imbalances in OCT-defined thrombus volume necessitate elucidation of these findings in larger studies adequately powered to assess effects on reperfusion indices.[58]

Left ventricular unloading pre-reperfusion

Mechanical LV unloading using microaxial flow pumps, such as the Impella CP, has emerged as a strategy to reduce infarct size by lowering myocardial oxygen demand, minimizing wall stress, and improving microvascular perfusion. Preliminary data from the Door-to-Unload in STEMI Pilot (DTU-STEMI Pilot) trial suggest that LV unloading 30 min before reperfusion may attenuate ischaemia–reperfusion injury and potentially limit infarct size and MVO extent in patients with anterior STEMI without cardiogenic shock.[199] The trial was limited by imbalances in total ischaemic time between randomized groups. Robust evidence from larger randomized trials is still lacking, and the routine use of microaxial flow pumps for no-reflow prevention or treatment remains investigational. The ongoing STEMI-DTU (NCT03947619) and UNLOAD-AMI trials (NCT04562272) are expected to further clarify the role of a door-to-unload strategy in improving outcomes in STEMI. Notably, elevated LV end-diastolic pressure may exacerbate MVO by increasing wall stress and compressing the subendocardial vasculature, thereby reducing coronary driving pressure during diastole. Mechanical LV unloading may help mitigate these effects by reducing LV end-diastolic pressure and myocardial wall tension, providing a mechanistic rationale for its potential role in no-reflow prevention.

Sonothrombolysis

Preclinical studies have shown that high mechanical index ultrasound impulses of short duration (3–4 μs) during intravenous microbubble infusion, sonothrombolysis, can restore both epicardial and microvascular flow in STEMI.[200,201] While early trials showed improved flow and function, a recent study found no benefit on infarct size or MACE.[202–206] Pre-hospital use is under exploration, but more data are needed to confirm clinical utility.[207]

Conclusions and perspectives

Coronary no-reflow remains a major challenge in STEMI management, contributing to adverse LV remodelling, heart failure, and increased mortality. Current evidence highlights the multifactorial nature of no-reflow, involving distal embolization, endothelial dysfunction, inflammation, and MVI. Although current pharmacological and non-pharmacological approaches have shown promise, their benefits remain limited and inconsistent, especially when applied to unselected patient populations. Intravascular physiology and imaging have emerged as useful tools for risk stratification, though their role in guiding treatment requires further validation. Future research (*Table 3*) should prioritize (i) patient-level data pooling to identify subgroups more likely to benefit from targeted therapies; (ii) defining standardized, reproducible endpoints (e.g. IMR/MMR, MVO quantification) for interventional trials; (iii) leveraging computational modelling and AI tools for noninvasive prediction of MVI; (iv) addressing pathophysiological knowledge gaps in women, elderly patients, and those with diabetes or renal dysfunction; and (v) developing trial designs that incorporate early haemodynamic assessment, mechanistic imaging, and adaptive enrichment strategies. Addressing the complex interplay of mechanisms underlying no-reflow is critical to improving long-term outcomes in patients with STEMI.

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Supplementary data

Supplementary data are not available at *European Heart Journal* online.

Declarations

Disclosure of Interest

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Data availability

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