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Vittorio Zuccarelli [1], Stefano Andreaggi [1,2], Jason L Walsh [1,3], Rafail A. Kotronias [1,3], Chu Miao [1,3], Jonathan Vibhishanan [1,3], Adrian P. Banning [1,3,4] and Giovanni Luigi De Maria [1,3,4,*]

[1] Oxford Heart Centre, Oxford University Hospitals NHS Trust, Oxford OX3 9DU, UK
zuccarellivittorio@gmail.com (V.Z.); rafail.kotronias@cardiov.ox.ac.uk (R.K.);
jason.walsh@queens.ox.ac.uk (J.W.); miao.chu@cardiov.ox.ac.uk (C.M.);
jonathan.vibhishanan@ouh.nhs.uk (J.V.)

[2] Division of Cardiology, Department of Medicine, University of Verona, Verona, Italy;
stefano.andreaggi@gmail.com (S.A.)

[3] Division of Cardiovascular Medicine, Radcliffe Department of Medicine, University of Oxford, Oxford UK

[4] National Institute for Health Research (NIHR) Oxford Biomedical Research Centre, Oxford;
adrian.banning@ouh.nhs.uk (A.P.B).

[*] Correspondence: giovanniluigi.demaria@ouh.nhs.uk

Abstract: Primary percutaneous coronary intervention (pPCI) has revolutionized the prognosis of ST-segment elevation myocardial infarction (STEMI) and is the gold standard treatment. As a result of its success, the number of pPCI centres has expanded worldwide. Despite decades of advancements, clinical outcomes in STEMI patients have plateaued. Out-of-hospital cardiac arrest and cardiogenic shock remain a major cause of high in-hospital mortality, whilst the growing burden of heart failure in long-term STEMI survivors presents a growing problem. Many elements aiming to optimize STEMI treatment are still subject to debate or lack sufficient evidence. This review provides an overview of the most contentious current issues in pPCI in STEMI patients, with an emphasis on unresolved questions and persistent challenges.

Keywords: ST-elevation myocardial infarction; primary percutaneous coronary intervention; coronary no-reflow

1. Introduction

ST-segment elevation myocardial infarction (STEMI) occurs when an atherosclerotic plaque ruptures or erodes, triggering the coagulation cascade and platelet activation resulting in intraluminal thrombus formation and coronary artery occlusion, leading to myocardial necrosis. STEMI constitutes a life-threatening medical emergency due to the imminent risk of arrhythmic events, mechanical complications and acute and long-term risk of heart failure.

In 1977, Dr Grüntzig performed the first successful percutaneous transluminal coronary angioplasty (PTCA) in stable coronary artery disease, demonstrating the feasibility of catheter-based revascularization [1]. In 1983, Dr. Hartzler introduced primary angioplasty in the treatment of acute myocardial infarction (MI) [2]. Despite initial enthusiasm, early trials investigating balloon angioplasties following thrombolytic therapy did not demonstrate superiority over thrombolytic therapy alone [3,4]. However, primary PTCA alone was subsequently shown to be superior to thrombolytic therapy alone in terms of mortality, re-infarction, stroke and major bleeding [5,6]. Angioplasty faced three main issues at the time: intravascular thrombosis, vascular occlusion due to elastic recoil, and neointimal proliferation leading to restenosis [7,8].

In 1991 these challenges were addressed with the introduction of bare-metal stents (BMS), providing a metal scaffold aiming to reduce restenosis and re-occlusion following PTCA [9]. BMS demonstrated its superiority over balloon angioplasty alone [10,11]. Subsequently, several trials including STENT-PAMI, FRESCO and CADILLAC established coronary stenting as the standard of care reperfusion strategy for MI to reduce restenosis, re-occlusion, and recurrent ischemia [12–14]. Despite the excitement surrounding BMS, intimal hyperplasia leading to in-stent restenosis remained a significant issue. In the early 2000s, the first drug-eluting stents (DES) were introduced. Following this, several studies confirmed the safety and efficacy of pPCI using BMS and DES in STEMI [15–17] Over the 2010s DES technology was improved with better platforms and antiproliferative drugs leading to lower rates of restenosis [18,19]. As a result of these advancements, pPCI became established as the gold standard strategy for treating STEMI compared to thrombolysis leading to a proliferation of catheterization laboratories around the world.

STEMI represents one third of all admissions for acute coronary syndromes [20]. The global prevalence of STEMI is estimated at 4% in individuals <60-years-old and 9.5% in individuals >60-years-old [21]. In the last thirty years, STEMI presentations have declined in incidence in high-income nations [22], largely due to increased awareness of cardiovascular risk factors and widespread primary prevention strategies. Specifically, in the US, between 1997 and 2005, the incidence rate of STEMI has decreased from 121 to 77 per 100.000 people [23].

Despite improvements in STEMI care, no overall improvement in mortality was seen in the first two decades of this century. However, once adjusting for co-morbidities and high-risk features such as cardiac arrest on presentation there was a significant decrease in risk-adjusted mortality. This demonstrates that patients presenting to the catheterization laboratory have become sicker over time [23]. Data coming from European registries established that in high-income European countries, 1-year mortality in pPCI-treated patients decreased substantially from 2003 to 2018, with the largest absolute mortality decline occurring in the first 30 days[5]. The pooled in-hospital mortality rate for patients with ST-elevation myocardial infarction ranges between 4% and 12%. Additionally, mortality at the one-year follow-up is estimated to be around 10% [24,25]. A recent meta-analysis, which included 91 cohort studies involving around 200,000 patients, identified advanced age, out-of-hospital cardiac arrest, cardiogenic shock, delay in symptoms-to-balloon and door-to-balloon time as the main predictors of death [26].

There is little doubt that a major contributor to this steep decline in mortality comes from prompt mechanical restoration of the infarct-related artery (IRA) via primary percutaneous coronary intervention (pPCI). In 1993 the PAMI trial first demonstrated the superiority of pPCI over thrombolysis, with lower in-hospital and 6-month rates of death and re-infarction, as well as a reduced incidence of intracranial bleeding [27].

Despite this progress, challenges persist in STEMI care, some of which have not been fully addressed. At a broad level, improving overall in-hospital mortality remains a major challenge. Further, the growing burden of heart failure in STEMI survivors is a growing challenge, which significantly impacts long-term survival and quality of life, placing strain on healthcare systems [28].

This review seeks to identify and explore specific challenges in optimising STEMI care and delineate new avenues of investigation in STEMI care in the years ahead (Figure 1).

2. Ischaemic Time: Can We Make It Shorter?

The extent of myocardial ischemia is one of the main determinants of infarct size, as clearly demonstrated in both experimental models [29] and clinical practice [30,31].

The concept of Door-to-Balloon Time (DTB), defined as the time-interval between arrival to hospital and coronary flow restoration via pPCI, has emerged as a key quality indicator of performance for ambulance networks and hospitals. However, a national study in the United States showed no improvement in mortality despite an average reduction in DTB from 83 to 67 minutes [32].

Symptom-to-Balloon (STB) has since emerged as a more reliable mortality predictor [33,34]. Past literature has reported a clear relationship between mortality and time delay from symptom onset to

fibrinolysis [35] and pPCI [36] in STEMI patients. Observational studies have shown that most of the time delay in STB is represented by the time interval between symptom onset and hospital arrival, with factors such as advanced age, diabetes and initial admission to a non-PCI centre identified as main predictors of prolonged STB time [37].

In response efforts have aimed to reduce prehospital admission delays in STEMI. Pre-hospital ECG diagnosis and direct transfer to the catheterization laboratory has resulted in significantly shorter STB time [38]. Equally, the value of earlier symptom recognition and seeking of medical attention (e.g., pain to first medical contact), have been recognized as important areas to invest. Despite efforts to promote early symptom recognition through media campaigns, certain populations still exhibit reluctance to seek prompt medical assessment for heart attack symptoms, leading to poorer outcomes [39,40]. Sociodemographic factors, such as lower education levels, advanced age, and rural residency, contribute to delays in seeking medical attention. This suggests that policymakers should target these populations. Implementing tailored educational programmes and enhancing accessibility to healthcare services in these groups, aiming to mitigate delays in seeking care.

Notably, the financial impact associated with myocardial infarction is high, as a result of increasing sophistication of acute care, hospital stay in intensive care environments, frequent readmissions and long-term comorbidities [41]. Consequently, considerable effort and resources are now essential in primary prevention to raise awareness in the public and to further improve pPCI networks. This is a major challenge as national healthcare services, acute and emergency departments and ambulance services are already over-stretched and working at maximum capacity and at the limits of financial sustainability.

3. Primary PCI in STEMI Patients Complicated by Cardiogenic Shock

The incidence of cardiogenic shock in patients admitted with myocardial infarction ranges between 3–13% [42]. Despite a widespread implementation of early revascularization with subsequent mortality reduction, cardiogenic shock remains the leading cause of death in STEMI patients [43,44]. Data from Randomized Controlled Trials (RCTs) such as the SHOCK-trial, IABP-Shock II and CULPRIT-Shock, highlights that mortality between 30-days and 1-year in these patients ranges from 6.7% to 12% [45–47].

RCTs have proven that an invasive approach with early revascularization in STEMI patients with cardiogenic shock reduces the overall and cardiovascular mortality at long-term follow-up [48,49]. Real-world data from multicentre registries have equally confirmed the benefit of early invasive management along with reduction of time between first medical contact and pPCI [49–51].

Most of the STEMI patients with cardiogenic shock have multi-vessel coronary artery disease (CAD). Multivessel CAD constitutes an independent predictor of in-hospital mortality [52]. How and to what extent to revascularize STEMI patients with multivessel CAD and cardiogenic shock is still matter of debate. Although achieving a complete coronary revascularization improves myocardial perfusion and cardiac output, multivessel PCI is strongly related to increased procedural time and higher rates of procedural complications, which have a magnified impact in a patient in cardiogenic shock [53].

The CULPRIT-Shock trial demonstrated that early revascularization of the IRA alone in the index procedure, followed by staged completion of revascularization, improved 30-day survival rates and reduced the need for renal replacement therapy compared to immediate multi-vessel PCI at the index procedure [45]. However, long-term outcomes showed no significant difference in mortality between the two strategies at one year [54]. Interestingly, the IRA-only PCI group had higher rates of heart failure rehospitalisation and repeat revascularization at one year [55]. The trial experienced a notable rate of crossover between groups, indicating the difficulty in achieving complete revascularization, particularly in patients with chronic total occlusion [55].

Data from real-world registries have started to highlight that STEMI patients complicated by cardiogenic shock can benefit from complete revascularization in terms of all-cause death and non-IRA repeat revascularization both at short and long-term follow-up [56,57]. These results underscore

the fragmented and contrasting evidence on the topic, calling for additional RCTs to help better define patient selection criteria, optimal approaches and timing for complete revascularization in STEMI complicated by cardiogenic shock. Additionally, the impact of functionally significant non-culprit vessel disease on the prognosis of cardiogenic shock after myocardial infarction remain to be investigated, as does the impact of occurrence and extent of microvascular obstruction in this category of patients.

A further matter of debate relates to the role of temporary mechanical circulatory support (MCS).

The IABP-SHOCK II trial has confirmed no significant prognostic benefits associated with the use of an intra-aortic balloon pump (IABP) in STEMI patients in cardiogenic shock undergoing pPCI [58–60]. However significant variability in timing of IABP insertion and revascularization protocols with significant crossover rates (ca 10%) between groups should be noted.

Early implantation of a micro-axial pump (Impella CP) as mechanical circulatory support is independently associated with improved survival, in the context of shock before initiation of inotropes or vasopressors and without delaying reperfusionl [61]. Furthermore, survival has been reported to decline in proportion to time delay between shock onset and MCS initiation, decreasing from 65% when MCS is implemented <1.25 hours to 26% when MCS is started after 4.25 hours [61]. Despite demonstrating a superior hemodynamic profile compared to IABP, data from RCTs have failed to show differences in short- and long-term mortality between IABP and Impella in patients with STEMI and cardiogenic shock [62]. Moreover, the use of Impella has been associated with a higher rate of bleeding complications.

Encouraging data emerged from the most recent RCT, the DanGer Shock trial, involving patients with STEMI complicated by CS randomized to receive a microaxial flow pump (Impella CP) plus standard care or standard care alone. The use of Impella CP led to a lower risk of death from any cause at 3-months even though patients in Impella-arm experienced a significantly higher rate of device related complications, in terms of major bleedings, limb-ischaemia, haemolysis, device failure or worsening aortic regurgitation, and higher rate of renal replacement therapy [63].

Which MCS for which STEMI patient remains unanswered. The SCAI-shock (Society for Cardiovascular Angiography & Interventions) classification, the phenotype of cardiac failure and vascular access anatomy certainly all play a role in choosing the most appropriate modality of hemodynamic support. Further, the timing of MCS insertion has been recognized as an independent predictor of prognosis. Promising data, despite coming from observational studies, reported that the combination of Impella-supported pPCI and of complete revascularization in STEMI patients in cardiogenic shock, translated into a reduction in short-term mortality, in particular in those patients in whom Impella was started before pPCI [64].

Further evidence needs to be built to clarify the role of MCS in this clinical scenario. Ongoing trials, such as the ANCHOR trial (NCT04184635) and RECOVER IV (NCT05506449), will help to shed more light on this highly debated topic[81].

4. Anticoagulant Treatment in the Acute Phase – When Should Be Started?

Anticoagulation plays a key role in the initial treatment of STEMI patients managed with an invasive strategy. Unfractionated heparin has been established as the standard of care in patients with STEMI undergoing PPCI due to its favourable risk/benefit profile. However, there is a notable absence of high-quality evidence regarding pre-treatment with UFH, defined as intravenous administration of UFH at 70-100 units/kg once the diagnosis of STEMI has been confirmed and before arrival in the catheterization laboratory, in patients with STEMI undergoing primary PCI. This is reflected in current European-American guidelines where UFH is endorsed for use during PCI, but there are no clear recommendations for UFH pre-treatment prior to arrival in the catheterization laboratory.

In the literature, only observational studies and non-randomized clinical trials dealt with this topic [65,66]. At present, there is no conclusive evidence on absolute risk difference between anticoagulation pre-treatment and anticoagulation during PPCI[85]. Much of the evidence supporting the potential benefits of UFH pre-treatment has been derived from trials involving medically

managed patients with unstable angina or non-ST-segment elevation MI. Heparin pre-treatment has been related to a lower risk of intracoronary thrombus, lower rate of total vessel occlusion, and enhanced reperfusion success with a significant impact on 1-year survival [67,68], without a significant increase in rate of major bleeding [69]. The ongoing trial UFH-STEMI, which compares final TIMI flow in patients randomized 1:1 to early UFH administration at first medical contact versus administration after coronary angiography, will shed new light on this topic.

Alternatively, enoxaparin and bivalirudin could be considered in patients with STEMI undergoing PPCI. Enoxaparin has been demonstrated to be superior to UFH in decreasing clinical ischaemic outcomes such as CV death, MI complications and PCI failure, without significant differences in major and minor bleeding [70]. Recently, an RCT including East-Asian patients, has proven that in STEMIs undergoing primary PCI, anticoagulation with bivalirudin followed by a post-PCI high-dose infusion for 2–4 hours, significantly reduced the composite endpoint of all-cause mortality and major bleeding at 30-days, compared with UFH [71].

5. Antiplatelet Therapy Timing in Primary PCI: What and When?

Antiplatelet agents are the cornerstone in the acute treatment of STEMI and the choice of antiplatelet regimen should take both the patient's thrombotic and bleeding risk profile into account. In addition to aspirin, a potent P2Y12 receptor inhibitor (prasugrel or ticagrelor) is recommended as the default strategy for patients with acute coronary syndrome [72,73]. According to European and American Guidelines, clopidogrel should only be used when prasugrel or ticagrelor are contraindicated or as an alternative when bleeding risk is high, such as the elderly or after fibrinolysis [74,75].

Debate persists on the optimal timing for loading doses of P2Y12 receptor inhibitors. The ATLANTIC trial compared ticagrelor administration before coronary angiography during ambulance transfer versus in-hospital before angiography for STEMI patients. The trial found no significant improvement in primary endpoints, such as ST-segment elevation resolution or TIMI flow, with pre-treatment [76]. Further, real-world multicentre registry data support the lack of benefit in terms of hard cardiovascular outcomes like all-cause mortality, myocardial infarction, or stent thrombosis at 30 days [77].

In NSTEMI the ACCOAST trial showed that prasugrel pre-treatment did not reduce the incidence of thrombotic complications in either the overall population or among patients undergoing PCI, with a lack of protection against ischemic events consistently shown across all pre-specified subgroups, including diabetic and elderly patients [78]. Additionally, the COMPARE-CRUSH trial investigated the impact of pre-treatment with crushed verses whole prasugrel prior to pPCI. No notable difference in TIMI-3 initial flow or complete ST-segment resolution one hour after pPCI was evident between groups [79]. Comparable results were confirmed at 1-year follow-up with no difference in terms of clinical outcomes [80]. However, a sub-analysis of this trial highlighted that pre-hospital administration of crushed prasugrel significantly improved postprocedural TIMI 3 flow rates in STEMI patients with an ECG-based large myocardial area at risk [81]. Hence, these findings may be hypothesis-generating in support of the use of prasugrel pre-treatment in high-risk ST-elevation myocardial infarction (STEMI) patients undergoing primary percutaneous coronary intervention (pPCI).

In conclusion, in the STEMI clinical setting, the higher degree of thrombotic burden in the IRA could lead to speculation about a higher benefit from an early administration of a potent P2Y12 inhibitor, but evidence in this regard is missing.

5. Intravenous/Intracoronary Antiplatelet Agents: Do They Still Have a Role?

Peri-interventional intravenous/intracoronary antiplatelet agents typically include glycoprotein IIb/IIIa inhibitors (GPI). Most of the trials evaluating GPI in PCI-treated patients pre-dated the routine use of last generation P2Y12 inhibitors and most of these trials included mainly NSTEMI patients [82–84]. Data from initial studies showed a clinical benefit of routine GPI administration in the setting of primary PCI [85,86].

However, more recent data does not support the routine use of GPI. The On-TIME 2 trial, randomized patients to pre-hospital administration of tirofiban or placebo after a loading dose of clopidogrel, showing no additional significant survival benefit nor reduction in re-infarction at 1-yr, despite a lower rate of stent thrombosis in the active arm [87]. Similarly, the BRAVE-3 trial, showed that routine abciximab administration after a loading dose of clopidogrel did not achieve a reduction in infarct size nor improved survival rate at 30 days, compared to placebo [88]. Prolonged infusions of GPI is common practice, however clinical studies show that a bolus-only strategy reduces vascular/bleeding complications with a similar MACE rate compared to prolonged infusion in PCI [89,90]. However, there is no evidence in pPCI for a bolus-only strategy.

Route of GPI infusion (intracoronary verses intravenous) have been investigated. The AIDA-STEMI trial found no disparity in primary outcomes (death, new MI, new-onset heart failure) at 3 months between patients receiving intracoronary versus intravenous abciximab[110]. Similarly, the Cardiac-MRI sub study and the CICERO trial supported these findings, showing comparable results in terms of infarct size, myocardial salvage index, microvascular obstruction, and ejection fraction between the two routes [91]. Conversely, the INFUSE-AMI trial showed a significant reduction of infarct size in the intracoronary abciximab arm, possibly driven by patient selection as the study only included patients presenting early (time < 4 h) with large anterior STEMIs [92].

Currently European and American guidelines underscore that there is no strong evidence for routine use of GPI in STEMI patients and that their use should be considered for bailout if there is evidence of no-reflow or thrombotic complications.

6. Intravascular Imaging of the Infarct-Related Artery

The role of intravascular imaging in pPCIs is another potential under-explored field. STEMI patients are typically under-represented in RCTs exploring the role of intracoronary imaging in PCI optimization [93–95].

Despite this, there is large scope and impact that intracoronary imaging can have in STEMI care. Intracoronary imaging before stent implant could play a role in defining mechanism of plaque instability, defining presence of significant calcified plaque requiring additional lesion preparation and assessing and quantifying the thrombotic burden. This last aspect could be helpful in defining whether further thrombus-modification techniques (device or drug-based) should be applied and whether stenting deferral should be considered to avoid severe distal embolization and no reflow [96].

Post-PCI intravascular imaging can reveal stent under-expansion, malposition or edge dissections, which occur in up to one third of STEMI cases [97]. OCT studies have clearly shown a high rate of stent under expansion and stent malposition in STEMI patient follow-up. The increased vascular tone and the presence of thrombus during the index procedure, can indeed contribute to stent under-sizing and malposition as thrombus resorbs and normal vascular tone is restored [98,99].

Primary PCI is often perceived as a fast procedure and sometimes stent optimization is sacrificed in the name of speed, especially when dealing with a sick patient. As evidence is accumulating on the clinical benefit and cost-effectiveness of intracoronary imaging in routine PCI, there should be a call to investigate if there is added benefit to utilising intracoronary imaging in the context of pPCI.

7. DEB/DCB in STEMI

Drug coated balloons (DCBs) and drug eluting balloons (DEBs) have shown safety and efficacy in treating in-stent restenosis, small-vessel disease, and high-bleeding risk cohorts [100–102]. DEB-only PPCI is emerging as a feasible and safe treatment option for patient's ineligible for drug-eluting stents [103]. A recent study indicated no disparity in mortality or target lesion revascularization between DCBs and DES in pPCI patients [104]. DCBs could be beneficial in lesions with a large thrombotic burden, when employing a deferred stenting approach.

Implementation of DEB/DCBs in PPCI is certainly a new line of research and numerous studies are underway with the results eagerly awaited.

8. Invasive Strategy in Late-Presenting ST-Segment Elevation Myocardial Infarction: How Late Is Too Late?

The incidence of late STEMI presenters seeking medical attention more than 12 hours after symptom onset ranges between 10 and 20%, according to registries [105,106]. This subgroup of patients is known to have a higher rate of hemodynamic instability, a worse chance of systolic function recovery and higher rates of acute heart failure [107].

European and American guidelines are concordant in recommending routine immediate angiography and pPCI in STEMI patients admitted within 12 hours of symptoms onset. The value of a routine pPCI strategy in late-presenting STEMI patients (>12 h after symptom onset) is still not fully established.

Randomised clinical trials have established that STEMI patients presenting 12-48h after symptom onset and without persistent symptoms of ongoing ischemia, might still benefit from reperfusion therapy as reflected by lower rates of in-hospital death and re-infarction, compared to a conservative management strategy [108]. Similarly, real-world data from multicentre registries have highlighted that late STEMI presenters invasively managed, show a lower mortality rate both in-hospital and at five years of follow up [106].

On the other hand, different results have emerged in very late STEMI presenters (total ischaemic time >48h). Haemodynamically stable patients without ongoing ischemia symptoms despite persistent occlusion of the culprit artery get no clinical benefit in terms of mortality and hard cardiovascular endpoints from an invasive strategy [109–111].

There is evidence showing that, despite late presenters having a larger infarct size than early presenters, a significant amount of myocardial salvage is achievable in later presenters (beyond 12h from symptom onset) [112]. Advanced imaging modalities such as cardiac magnetic resonance imaging (Cardiac-MRI) may play a key role in stratifying late-presenters, defining upfront who could benefit from revascularisation and hence who should be considered for an invasive strategy, possibly irrespectively of overall ischaemic time. Indeed, there is initial evidence suggesting that STEMI patients with symptoms onset within 12-72 h and signs of ongoing ischemia, benefited from early revascularisation in terms of myocardial salvage, despite having larger final infarct size and higher rate of MVO [113].

Additionally, novel CMR mapping techniques may allow better characterization and quantification of severity of myocardial injury as well as the extent of recoverable myocardium [114,115]. This could pave the way to a new line of research looking into a multi-parametric assessment for risk-stratification of late presenters aiding in defining those requiring revascularisation and detecting early those with an increased chance of long-term heart failure and mechanical/arrhythmic complications.

9. Coronary No-Reflow: How to Diagnose It?

Despite pPCI restoring patency of the infarct related artery in STEMI patients, up to 40-50% experience the "no-reflow" phenomenon due to coronary microvascular dysfunction (CMD) [116]. The no reflow phenomenon remains one of the most common complications in pPCI, significantly impacting outcomes, increasing infarct size, mortality risk and heart failure readmission [117,118]. No reflow arises from complex interactions including ischemic and reperfusion-related injuries, along with embolization of athero-thrombotic material. Early diagnosis, risk stratification, and effective prevention/treatment of no reflow pose ongoing challenges for clinicians and researchers [119,120].

Diagnosing no reflow, early detection of patients at higher risk of no reflow and preventing/treating no reflow are the still open challenges that clinicians and researchers are called to address in the near future.

No reflow phenomenon is usually defined on angiography as occurrence of Thrombolysis in Myocardial Infarction (TIMI) flow < 3 or TIMI 3 in the presence of suboptimal myocardial blush grade (MBG < 2). However, the angiographic no reflow represents only the tip of the iceberg, as invasive angiography is suboptimal in detecting the occurrence of microvascular injury, with TIMI flow and

MBG being limited by their semi-quantitative nature, poor reproducibility and low accuracy [118,121].

The gold standard method to define the occurrence of microvascular injury in STEMI patients is Cardiac Magnetic Resonance (cMRI), which can detect and quantify infarct size, occurrence of microvascular obstruction and intra-myocardial haemorrhage, which results from an advanced and irreversible degree of microvascular injury [122]. All these are parameters are strongly related with clinical outcomes in STEMI patients[123,124]. Cardiac-MRI is, however, limited by its availability/accessibility and costs. Furthermore, a cMRI-based diagnosis of microvascular injury is typically late (2-3 days after the index event) and outside the time window when additional therapy can be offered in the catheterization laboratory during or immediately after pPCI.

A new line of investigation, for this reason, has aimed at assessing the role of pressure-sensor wire technologies to assess real-time, in the catheter laboratory during pPCI, the status of coronary microcirculation. This approach would aim to detect no-reflow early (when it is not angiographically apparent) and risk-stratify STEMI patients.

Among the many indices of coronary physiology, the index of microvascular resistance (IMR) is the one most explored in the STEMI setting. IMR is the product of distal coronary pressure and average transit time of 3 boluses of room-temperature saline injected in the coronary artery under assessment. Measurements are performed during steady-state hyperaemia[125].

IMR has been showed to be higher in patients with MVO[126]. IMR>40 has been associated with left-ventricular dysfunction, higher mortality and heart failure's hospitalizations[127,128]. However, at least one third of STEMI patients exhibit a discordance between cMRI-detected MVO and IMR [129]. Whilst a co-presence of both MVO and IMR>40 is associated with larger infarct size and strong cardiovascular events at long-term follow-up, patients with IMR<40, even in the presence of MVO, showed better clinical outcomes and a significant regression of CMR-based infarct size at six months follow-up[130]. IMR measurement has been shown to be feasible before stent insertion during pPCI, with the potential to define alone or in combination with other clinical/procedural parameters the risk of subsequent intra-procedural post-stenting no-reflow. Thus, IMR may be a possible tool to triage high risk patients to additional/alternative therapies in STEMI aiming to prevent no reflow [116,131,132].

Interestingly, beside its potential in defining high risk STEMI patients, IMR has actually proven to have a superior ability in defining low-risk patients with the potential to detect with high accuracy STEMI patients at low risk of intra-hospital complications who could possibly benefit from a shorter admission[133].

One of the limitations of IMR, as of many other coronary physiology indices, is represented by its invasive nature relying on instrumentation of the IRA with a pressure-sensor-wire. This is certainly a limiting factor towards a broader implementation of IMR in pPCI as it requires additional procedural time, costs and procedural risks. Various versions of angiography derived IMR have been proposed over the past few years, all showing good diagnostic accuracy in detecting an abnormal IMR (comparable to its invasive counterpart), and good correlations with clinical outcomes and MVO detection using cMRI in STEMI patients[134,135]. More recently, angiography-derived IMR (namely IMR$_{angio}$) has shown a 98% negative predictive value in ruling out occurrence of in-hospital and 30-day adverse events in STEMI patients, configuring itself as a promising tool to non-invasively risk stratify STEMI patients[136].

Implementation of these novel indices in the catheter laboratory to risk stratify STEMI patients early could perhaps identify patients at risk of no-reflow and guide treatment strategy in the upcoming years (Figure 2).

10. Coronary No-Reflow: How to Treat and Prevent It?

Prevention and treatment of coronary no reflow after pPCI represents a major outstanding challenge in STEMI care. Several strategies (device- and drug-based) have been tested over the past 20 years, but consistently with negative or neutral results. When it comes to additional therapy for no reflow prevention/therapy a typical pattern is consistently observed. Strategies with promising

initial results on surrogate outcomes in pilot/proof of concept studies, then fail to deliver when stress-tested in properly powered randomised clinical trials. It is likely that suboptimal patient-selection with an "all-comers" approach testing the routine implementation of additional therapies in STEMI patients, might have played a role in undermining the true ability of trials to prove the additional clinical benefit of new therapies during or after pPCI.

When it comes to device-based therapies, the only one so far demonstrating any efficacy is represented by intracoronary delivery of supersaturated oxygen (SSO2) (e.g., hyperoxemic blood with P_aO_2 760-1000 mmHg)). This approach has been shown in animal models to reduce oedematous capillary swelling and to improves microcirculatory function[137]. Safety and feasibility of SSO2 were demonstrated in the AMIHOT I study, whilst initial efficacy on infarct size reduction (assessed tc-99m sestamibi SPECT) was demonstrated in the AMIHOT II study. The AMIHOT III study (NCT04743245) is a post-market trial now underway, randomising 434 patients with anterior STEMI to 60 minutes of intracoronary SSO2 post pPCI versus conventional pPCI and powered to show superiority of the treatment arm for 1-year rate of net adverse clinical events.

Mechanical unloading of the left ventricle before coronary reperfusion is another possibly ground-breaking concept. Animal models have shown that mechanical unloading before reperfusion could reduce left ventricular work and infarct size at 30 days by activating molecular pathways protecting against reperfusion injury [138,139]. In this regard, unloading with mechanical circulatory support (Impella CP) before reperfusion has proven to be safe and feasible in man. In the DTU-PILOT study, in anterior STEMI patients, delaying reperfusion to allow unloading first [140]. Whether unloading the ventricle before reperfusion can now translate into an actual benefit and reduction in infarct size in humans, is the object of the ongoing STEMI-DTU trial (NCT03947619) aiming at randomising 668 patients with anterior STEMI to 30 minutes of Impella before reperfusion versus conventional pPCI[141].

Prevention of distal embolization by dealing upstream with large thrombus burden has appeared from the start an obvious strategy associated with potential clinical benefit. However, after the initial positive results associated with manual thrombus aspiration[142], subsequent larger and ad hoc-powered powered randomized clinical trials have failed to demonstrate a clinical benefit associated with routine manual thrombus aspiration during pPCI [143,144].

Besides limitations related with patient selection bias, the reason why manual thrombus-aspiration might have failed to show some benefit could also be related with its actual ability at reducing thrombotic burden. The OCT-substudy of the TOTAL trial surprisingly showed no difference in post-PCI thrombus burden between the thrombus aspiration group and control group [145]. At the same time the rate of aspiration-failure remains high after manual – thrombus aspiration and a higher residual thrombus burden relates with more severe microvascular dysfunction [146]. A renewed interest in coronary thrombectomy has been reignited by advances made in stroke interventions with clot-retrievers. A few case-reports have suggested that these new devices could be superior at entangling large coronary thrombi, offering a circumferential interaction with the thrombus. The RETRIEVE-AMI study (NCT05307965) is currently ongoing aimed at assessing the difference in thrombus-burden reduction with stent-retriever thrombectomy compared to manual thrombus aspiration in STEMI [147].

A new generation of aspiration catheter (CatRX, Penumbra) has been developed which may offer greater thrombus extraction. The CatRX system provides steady and sustained aspiration, in contrast to manual aspiration which allows only short-lived suction that diminishes overtime. The CHEETAH registry has confirmed feasibility of this technique with promising results in terms of low rate of angiographic no-reflow [148]. Whether this technology can offer superior thrombus extraction to manual aspiration and/or an actual benefit in terms of infarct size or MVO reduction remains to be seen.

Evidence for drug therapy to prevent or treat no reflow is minimal. To date evidence is conflicting for several classes of medicine aiming to manage no reflow [149].To cite two examples: intracoronary thrombolytics were shown to be ineffective in the T-TIME trial [150], whilst

intracoronary adenosine in the REOPEN-AMI study did show benefit in that MVO was reduced compared to placebo [151].

It has been hypothesized that beside the agent adopted, the way it is delivered may also play a role. A new technology, the CoFI system (Corflow) consists of a dedicated infusion catheter, with a balloon at its tip to occlude coronary flow during infusion. This approach results in higher tissue-drug retention compared to coronary infusion via microcatheter or via guiding catheter. The system also has diagnostic capabilities. By measuring distal coronary pressure at increasing infusion-rates of saline it can provide an assessment of coronary microvascular function, with the potential to risk-stratify STEMI patients, integrating early detection of no-reflow with ad-hoc therapy. This technology remains however in early stages of development. The MOCA I study (NCT03654573) is collecting initial safety and feasibility data and preliminary data on the impact on infract size and MVO with intracoronary tirofiban using the CoFI system (Figure 3).

11. Conclusions

STEMI care has certainly evolved over the past three decades with the undoubted impact of pPCI on survival and quality of life for STEMI patients. However, STEMI care is far from optimal. This is reflected by the plateau in clinical outcomes in STEMI and increasing burden of heart failure in STEMI survivors.

Research in this field remains active and endeavours are underway to reduce symptom-to-balloon time, define novel/alternative care pathways and to explore additional diagnostic and therapeutic tools to prevent or deal with coronary no-reflow. This review has highlighted the main upcoming lines of investigation in the field and there is expectation and hope that results from ongoing research might reshape the landscape of STEMI care in the upcoming years.

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