Tommasino *et al. Vessel Plus* 2024;8:24
DOI: 10.20517/2574-1209.2023.138

Vessel Plus

Review

Open Access

Multivessel disease in patient with acute myocardial infarction: current treatment strategies and future perspectives

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How to cite this article: Tommasino A, Dell'Aquila F, Cesario V, Tempestini F, Casenghi M, Giovannelli F, Rigattieri S, Barbato E, Berni A. Multivessel disease in patient with acute myocardial infarction: current treatment strategies and future perspectives. *Vessel Plus* 2024;8:24. https://dx.doi.org/10.20517/2574-1209.2023.138

Received: 20 Oct 2023 **First Decision:** 28 Apr 2024 **Revised:** 11 May 2024 **Accepted:** 16 May 2024 **Published:** 23 May 2024

Academic Editor: Giuseppe Andò **Copy Editor:** Fangling Lan **Production Editor:** Fangling Lan

Abstract

Patients who present with acute myocardial infarction (AMI) often suffer from coronary multivessel disease (MVD). This condition is associated with an increased mortality rate; it is, therefore, important to improve clinical outcomes through appropriate treatment strategies. Over the past decades, extensive research in AMI and MVD patients has consistently shown that complete revascularization is superior to treatment of the only culprit lesion. Another controversial issue concerns the most appropriate timing for percutaneous coronary intervention in non-culprit lesions. Fractional flow reserve (FFR) is considered the best method for identifying ischemic coronary lesions in the context of acute coronary syndromes, but the detection of vulnerable plaques in non-culprit vessels could further improve clinical outcomes. Intravascular imaging goes beyond physiology and it is potentially useful to recognize patients who are vulnerable, despite negative FFR. Therefore, we analyzed the most relevant studies that have investigated the relationship between physiological indexes and plaque vulnerability. However, ongoing trials aim to clarify how coronary physiology can be combined with the benefits of intracoronary imaging.

Keywords: Multivessel disease, acute myocardial infarction, fractional flow reserve, intravascular imaging

INTRODUCTION

Patients who present with acute myocardial infarction (AMI) often have coronary multivessel disease (MVD). They have a poorer prognosis compared to stable patients. Improving clinical outcomes through an appropriate treatment approach is crucial[1].

We aim to review the data on the benefits of complete revascularization in patients with AMI and MVD and to investigate the methods used to assess non-culprit lesions (NCLs).

COMPARISON OF FUNCTIONAL-GUIDED AND ANGIOGRAPHY-GUIDED STRATEGIES IN THE MANAGEMENT OF NON-CULPRIT LESIONS

An overview of the main studies that investigated the role of complete revascularization in patients with AMI and MVD is summarized in Table 1.

Over the last decades, numerous studies have been carried out on patients with AMI and multivessel disease.

These trials aimed to address two fundamental questions: whether performing complete revascularization leads to improved survival and when is the optimal time to perform the procedure.

While the latter question has still not been definitively answered, a broad consensus has emerged regarding the former, stating that complete revascularization is superior to performing percutaneous coronary intervention (PCI) specifically at the culprit lesion.

The first study to address this issue was the PRAMI trial, which was conducted between 2008 and 2013[2]. The investigators randomized 465 patients with ST-elevation myocardial infarction (STEMI) with MVD who underwent primary PCI (P-PCI) to a strategy of "preventive" (as the authors defined) revascularization of NCLs or "no preventive" revascularization.

The study was stopped after a median follow-up period of 2 years. It showed that preventive PCI for bystander stenosis (visual assessment by angiography) reduced the incidence of MACE compared to a "no-preventive" strategy.

The CULPRIT trial was conducted in seven centers in the UK and enrolled 296 patients with STEMI[3]. The aim was to compare complete revascularization on initial admission (either at the time of P-PCI or before discharge with culprit-only PCI). Non-infarct-related arteries (IRAs) were treated during the initial procedure in 64% of patients in the complete revascularization group. Intracoronary imaging and Fractional flow reserve (FFR) were not used to assess lesion severity.

At 1 year, the primary endpoint (PE) showed a significant reduction in the group who received complete revascularization (10.0%) compared to the IRA-only cohort (21.2%). While there was no significant reduction in death or MI, it is noted that all components of PE did not decrease significantly.

Contextually, in the DANAMI 3-PRIMULTI trial, 627 patients with STEMI and MVD were randomized to receive either complete revascularization with an FFR-guided strategy before discharge or no further PCI[4]. The primary endpoint (PE) was met by 22% of patients who underwent PCI limited to IRA alone and by 13% of patients who underwent comprehensive invasive treatment of non-culprit lesions. No significant

Table 1. This table summarizes the main studies, cited in the text, that investigated the role of complete revascularization in patients with MI and MVD, its timing with respect to the index procedure and the role of Functionally-Guided *vs.* Angiography-Guided strategies in non-culprit lesions management

Trial	Number of pts*	Design	Population	Intervention	Control	Primary outcomes
PRAMI	465	Multicenter, single-blind, randomized study	STEMI pts with a bystander lesion > 50% based on angiography	"Preventive" PCI of non-culprit lesion	No "preventive" PCI	Death from cardiac causes, nonfatal MI, or RA
DANAMI-3-PRIMULTI	627	Open-label, randomized controlled trial	STEMI pts with multivessel disease	PCI FFR-guided of non-culprit lesion before discharge	No further invasive treatment	Composite of all-cause mortality, nonfatal reinfarction, ischemia-driven revascularization
CULPRIT	296	Multicenter, open-label, randomized trial	STEMI pts with multivessel disease	In-hospital complete revascularization	IRA-only revascularization	All-cause mortality, recurrent MI, HF, and ischemia-driven revascularization at 1 year
COMPLETE	4,041	Multinational, randomized trial	STEMI pts with multivessel disease	PCI angio or FFR-guided of non-culprit lesion before or after discharge	No further invasive treatment	Cardiovascular death or MI at 3 years
BIOVASC	1,525	International, prospective, open-label, non-inferiority, randomized trial	STEMI and NSTEMI pts with multivessel disease	Complete revascularization during the index procedure	Complete revascularization within 6 weeks	Composite of all-cause mortality, MI, any unplanned ischemia-driven revascularization, or cerebrovascular events at 1 year
FIRE	1,445	Investigator-initiated, multicenter, prospective, superiority, randomized trial	STEMI and NSTEMI pts with multivessel disease	Physiology-guided complete revascularization during the index hospitalization	No further invasive treatment	Composite of death, MI stroke, or any revascularization at 1 year
FUTURE	927	Prospective, randomized, open-label superiority trial	Multivessel CAD pts (46% of ACS)	FFR in all stenotic (≥ 50%) coronary arteries. Revascularization (PCI or surgery) was indicated for FFR ≤ 0.80 lesions	Traditional strategy without FFR	Composite of major adverse cardiac or cerebrovascular events at 1 year
FLOWER-MI	1,163	Investigator-initiated, randomized, open-label, multicenter trial with blinded end-point evaluation	STEMI pts with multivessel disease	Complete revascularization guided by FFR	Complete revascularization guided by angiography	Composite of death from any cause, nonfatal MI, or unplanned hospitalization leading to urgent revascularization at 1 year
FRAME-AMI	562	Investigator-initiated, randomized, open-label, multicenter trial	AMI pts with MVD	FFR-guided PCI (FFR ≤ 0.80) of non-IRA lesions	Angiography-guided PCI (diameter stenosis of > 50%) of non-IRA lesions	Composite of time to death, MI, or repeat revascularization
FRAME-AMI - post hoc analysis	552 lesions in 443 pts		Post hoc QFR analysis of non-IRA lesions of AMI pts enrolled in the FRAME-AMI trial			MACE, a composite of cardiac death, MI, and repeat revascularization

MI: Myocardial infarction; AMI: acute myocardial infarction; STEMI: ST-segment elevation myocardial infarction; NSTEMI: non-ST-elevation myocardial infarction; MVD: multivessel disease; RA: refractory angina; HF: heart failure; pts: patients; PCI: percutaneous coronary intervention; FFR: fractional flow reserve; IRA: infarct-related artery; MACE: major adverse cardiac events; QFR: quantitative flow ratio; CAD: coronary artery disease. *: randomized patients.

differences were found regarding all-cause mortality and non-fatal MI. The need for successive revascularization of non-IRA lesions decreased significantly, which puts the study results in a positive perspective.

The "first era" of studies, conducted from 2008 to 2015, began to demonstrate the safety and benefit of complete revascularization of non-culprit lesions as opposed to managing them with medication[5]. However, they were unable to demonstrate significant benefits on hard endpoints such as mortality. Therefore, large, randomized trials have been called for by the cardiology community to definitively prove this and accurately quantify the nature and magnitude of these benefits.

The most comprehensive study to date addressing this evidence gap is the COMPLETE, in which Metha *et al.* randomized 4,041 patients with STEMI and MVD[6]. The study compared two approaches: complete revascularization and PCI of the culprit lesion alone. Complete revascularization by PCI was performed either during the index admission or within 45 days after discharge. NCLs were classified as angiographically significant if they had a vessel diameter stenosis of at least 70% on visual assessment, or if they had a stenosis between 50% and 69% along with a FFR value < 0.80. The authors were able to achieve PE and thus demonstrate the effects of complete revascularization on the reduction of cardiovascular events. At three-year follow-up, PE occurred in 7.8% of patients in the complete revascularization group, compared to 10.5% in the culprit-lesion-only group ($P = 0.004$). The benefit was primarily due to the 32% reduction in the risk of suffering a new, non-fatal MI. In addition, complete revascularization led to an improvement in health status. Patients who underwent complete revascularization showed significant improvements in Seattle Angina Questionnaire Summary Score and residual angina[7] at the end of the study. Interestingly, optical coherence tomography (OCT) was performed as a substudy in 93 patients with at least two NCLs[8]. Investigator analysis revealed that 39% of patients had a thin-cap fibroatheroma (TCFA). Among the non-obstructive stenosis, a TCFA was found in 27% of cases. In addition, "high-risk" plaque features such as a wider lipid arch and macrophage infiltration were more common in obstructive lesions. This finding raises the hypothesis that the benefits of routine PCI for NCLs in STEMI patients may be due to the "stabilization" of vulnerable plaques prone to complications. This theory is consistent with previous studies like the PROSPECT trial, which have partially demonstrated and theorized similar concepts[9-11].

COMPLETE provided the answer to the benefit of bystander stenosis revascularization and provided the timing for it (between 1 and 45 days). The latest guidelines of the European Society of Cardiology on acute coronary syndromes (ACS) also clearly recognized this advice and assigned an indication class I with evidence level A[12].

The BIOVASC[13] trial enrolled 1,525 patients with ACS and MVD (≥ 70% stenosis by angiography or positive physiological indicators) who were randomized into two groups (immediate *vs*. deferred complete revascularization performed within 6 weeks). The main endpoint at one-year follow-up was observed in 7.6% of patients with immediate revascularization and in 9.4% of patients with staged complete revascularization. This study demonstrates the benefits of immediate, comprehensive revascularization in patients with ACS, which included a significant proportion of NSTEMI patients (60% of the cohort). The improved outcomes observed in the patients with immediate revascularization were primarily due to a significant reduction in MI and unplanned revascularizations due to ischemia. Notably, the number of myocardial infarctions decreased by 59 % and unplanned revascularizations by 39%. Interestingly, these events were not categorized as procedure-related (type 4) but were spontaneous events of MI, mainly type 1, manifesting in the early phase, within six weeks of discharge. As we mentioned earlier, the inflammatory milieu that characterizes the clinical setting of ACS could predispose bystander lesions to complications

leading to clinical manifestations. This could explain the observed results regarding the reduction of acute events with immediate complete revascularization.

The COMPARE-ACUTE trial investigated the role of FFR-guided complete revascularization *vs.* no revascularization of the NCL arteries in 885 patients with STEMI and MVD undergoing primary PCI. Smits *et al.* randomly assigned these patients into a 1:2 ratio group to receive either complete revascularization of the NCL coronary arteries using FFR or no complete revascularization of the NCL[14].

Although the FFR technique was used in both cohorts in this study, the FFR data were not reported to the patients or their cardiologists in the latter group. In addition, in the group receiving PCI for the CL coronary artery only, clinically recommended elective revascularization procedures performed within 45 days of the first PCI were not considered events.

The primary endpoint, which includes death, non-fatal myocardial infarction, revascularization, and cerebrovascular events at 12 months, showed a significant decrease in the complete revascularization group. This decrease is likely due to fewer subsequent revascularization procedures, highlighting the benefit of complete revascularization with FFR-guided PCI for NCL arteries in this patient group.

Recently, Biscaglia *et al.* presented the results of the FIRE study, a randomized, multicenter trial[15]. The investigators randomly assigned patients with an MI, both STEMI and NSTEMI, with MVD to undergo either physiologically guided (by FFR or quantitative flow ratio measurements) complete revascularization of NCLs during the same admission or to receive no additional revascularization. The main feature of this study is that it focuses on a specific population: Only patients aged 75 years and older were included[16]. This target group generally has a higher prevalence of comorbidities and is more prone to frailty compared to younger patients. In addition, they often have high-risk features such as HF and shock associated with multivessel and complex coronary artery disease[17]. At 1-year follow-up, complete revascularization was found to have a lower incidence of the primary outcome than patients in whom revascularization focused only on the culprit lesion (15.7% *vs.* 21.0%). The results underline the concept that complete revascularization is critical for patients with ACS and extend the benefits of this treatment approach to older patients, who now represent a growing and highly vulnerable population. Evaluation of NCLs with coronary physiology, as performed in this trial, offers the benefit of reducing unnecessary PCIs by approximately 50%. However, the "dark side of the moon" is that it carries the risk of leaving potentially vulnerable plaques, which, as mentioned above, are high-risk factors for potential ischemic events.

Conversely, some studies have questioned the role of FFR compared to angiography in guiding revascularization in multivessel disease. In the FUTURE trial[18], FFR-guided treatment failed to reduce the risk of MACE. The trial was concluded early due to the increased mortality rate in the FFR group compared to the angiography-guided group (4.3% *vs.* 1.8%, $P = 0.038$). However, in the final analysis, which included all data, the mortality endpoint was no longer significant ($P = 0.06$). Although the trial was not explicitly designed to study multivessel disease in AMI patients, nearly 50% of the study population had an ACS.

The FLOWER-MI trial showed no benefit of FFR-guided over angiography-guided PCI[19]. The study involved 1,163 patients presented with ACS who had angiographic stenosis of at least 50% in at least one no-culprit artery. There was no significant difference in PE between the two groups, neither after 1 nor after 3 years.

A detailed analysis of the structure of the study is crucial for understanding its results. First, the FLOWER-MI randomization has a certain similarity to the FAME trial. The trial had the statistical power to detect only a 5.5% absolute reduction in the incidence of the primary endpoint, and no significant differences were observed in all predefined clinical outcomes between the FFR and angiography groups. In the FFR group, 7 of 9 deaths (78%) were non-cardiac compared to 3 of 10 (30%) in the angiography group. In addition, the incidence of non-fatal MI was increased in the FFR group, and despite fewer PCI procedures, the periprocedural MI rate (type 4a) was tripled.

Recently, Lee *et al.* published a post-hoc analysis[20] of the FRAME-AMI trial[21] that focused on the assessment of clinical outcomes based on quantitative flow ratios (QFR)[22] in non-IRA PCI. Patients who underwent non-IRA PCI had a higher incidence of adverse events at 3.5 years of follow-up than those who deferred non-IRA PCI, even with a QFR > 0.80 (12.9% *vs.* 3.1%).

In addition, the analysis revealed that unnecessary non-IRA PCI (QFR > 0.80) was performed in 30% of AMI patients when revascularization was guided solely by angiography.

INTRACORONARY AND NON-INVASIVE IMAGING IN THE MANAGEMENT OF NON-CULPRIT LESIONS

An overview of the main studies that investigated the role of intracoronary and non-invasive imaging in the management of NCLs in AMI patients with MVD is summarized in Table 2.

Although FFR is recognized as the best method for diagnosing ischemic lesions in stable CAD, there is currently no proven superior advice strategy in the context of ACS, highlighting the need for large-scale studies. Identification of vulnerable plaques in non-disease vessels could provide additional benefits in improving clinical outcomes.

Several studies have examined the relationship between physiological indexes and plaque vulnerability [Table 2][23-25].

Yang *et al.* investigated the relationship between physiological indexes and coronary plaque features detected by cardiac computed tomography angiography (CCTA)[26]. Indicators of significant disease were both resting pressure and hyperemic pressure, as well as coronary flow reserve, identified by a large plaque burden and a small minimal lumen area (MLA). Positive remodeling was associated with impaired microvascular resistance[27]. In addition, CCTA algorithms identified several plaque metrics and remodeling indexes in predicting FFR ≤ 0.80, indicating a complex interplay between coronary plaque morphology and functional significance[28].

In the FLAVOUR, a prospective, randomized, open-label trial, treatment strategy guided by FFR was not inferior to IVUS-guided concerning the PE in patients with intermediate coronary stenosis[29].

Retrospective studies suggested a positive relationship between ischemic FFR values and the presence of vulnerable plaques and showed an increased prevalence of OCT-derived TCFA in lesions characterized by low coronary pressure and low indexes, supporting the safety of deferring treatment of FFR-negative lesions[10,30]. However, in some high-risk patients, the decision-making process based on FFR appears to be associated with an increased incidence of MACE.

Table 2. This table summarizes the main studies, cited in the text, that investigated the role of intracoronary and non-invasive imaging in the management of non-culprit lesions in AMI patients with MVD

Study	Number of pts*	Design	Population	Intervention	Control	Primary outcomes
Prospect	697	Multicenter prospective registry	ACS pts with multivessel disease	Three-vessel imaging IVUS and virtual histology guided	No	Composite of all-cause death, cardiac arrest, MI, or rehospitalization due to UA
Prospect-II	898	Sponsored, multicenter, prospective trial	Recent (within past 4 weeks) STEMI pts with MVD	Three-vessel imaging (IVUS) and NIRS	No	Composite of cardiac death, MI, UA or progressive angina
Prospect-adsorbe	182	Sponsored randomized trial	ACS pts with MVD	NIRS-IVUS imaging of the prox 6-10 cm of all 3 coronary arteries	ABSORB BVS + GDMT *vs.* GDMT alone	Cardiac death, target vessel-related MI or clinically-driven TLR at 24 months
FLAVOUR	1,682	Prospective, randomized, open-label, multinational trial, non-inferiority trial	Pts with intermediate stenosis (40% to 70%)	FFR or IVUS used to determine whether to perform PCI and to assess PCI success	No further invasive treatment	Composite of death, MI or revascularization at 24 months
CLIMA	1,003	Prospective observational, multicenter registry	Consecutive patients undergoing assessment of proximal LAD atherosclerosis by OCT		No further invasive treatment	Composite of cardiac death and target LAD segment MI
COMBINE-FFR	550	Prospective, multicenter international study	DM pts that undergo angiography for any indication with ≥ 1 lesion (non-culprit) ≥ 40- ≤ 80% diameter stenosis where FFR and OCT have been performed			Target-lesion related MACE (cardiac death, target vessel MI, clinically driven TLR or hospitalization due to UA) at 18 months in pts with target lesions with FFR > 0.80 + NO-TCFA or ≥ 1 TCFA
PECTUS	419	International, multicenter, prospective, observational cohort study	Pts with MI + OCT performed in FFR-negative (FFR > 0.80) non-culprit lesions			Composite of all-cause mortality, nonfatal MI, or unplanned revascularization at 2-year follow-up in pts with and without a high-risk plaque

ACS: Acute coronary syndromes; IVUS: intravascular ultrasound; MI: myocardial infarction; UA: unstable angina; STEMI: ST-segment elevation myocardial infarction; MVD: multivessel disease; pts: patients; NIRS: near-infrared spectroscopy; BVS: bioresorbable vascular scaffolds; GDMT: guideline-directed medical therapy; TLR: target lesion revascularization; CAD: coronary artery disease; LAD: left anterior descending artery; OCT: optical coherence tomography; FFR: fractional flow reserve; MACE: major adverse cardiac events; TCFA: thin-cap fibroatheroma; DM: diabetes mellitus; PCI: percutaneous coronary intervention. *: finally included patients.

The COMBINE OCT-FFR trial prospectively investigated the impact of high-risk plaques (OCT-detected TCFA) within a high-risk population with intermediate, FFR-negative lesions deemed to be managed by optimal medical therapy[11]. The primary endpoint occurred in 13.3% of patients who were FFR-negative but had TCFA, compared with 3.1% of patients who were both FFR-negative and did not have TCFA. This was attributed to a significantly increased rate of TV MI, clinically driven TLR, and unstable angina. TCFA positivity was found to be a predictor of PE, along with MI and a smaller MLA. In diabetic patients, TFCA accounts for 25% of FFR-negative lesions, with a 5-fold increased rate of MACE at follow-up and is responsible for > 80% of MACE. As the authors point out, the study was too weak to detect differences in low-incidence endpoints such as cardiac mortality, and most participants were diagnosed

with CAD. Interestingly, however, the presence of TCFA was strongly associated with both acute plaque destabilization and progressive plaque progression leading to angina.

According to the PROSPECT study[9], most vulnerable plaques were stable and rarely caused ACS, with only about 5% of IVUS-detected TCFA leading to MACEs. TCFA may cause even fewer events in lower-risk patients. Indeed, the impact of plaque rupture is determined not only by plaque morphology, but also by the interaction of pro- and anti-thrombotic factors that contribute to the recognized process of plaque healing.

The impact of vulnerable plaques on adverse events appears to be strongest in high-risk patients (ACS, DM) or high-risk vulnerable plaques. A sub-analysis of DM patients from the PROSPECT study showed that patients with ≥ 1 TCFA had a 3-fold higher rate of MACE after 3 years[31]. In the CLIMA[10] registry, the combination of multiple OCT high-risk plaques present in a small subset of patients was a strong predictor of TV-MI and cardiac death at 12 months. In the PROSPECT II trial[32], evidence of plaque burden greater than 70 and a large lipid-rich core with intravascular ultrasound (IVUS) and near-infrared spectroscopy (NIRS) in NLCs were independent predictors of MACE[33].

Finally, the PECTUS study[34] included 419 ACS patients and investigated the incidence of MACE in the presence of high-risk plaques identified by intravascular imaging (OCT) and functional indexes. At a median follow-up of 2 years, patients with high-risk plaques without evidence of ischemia on FFR or other physiologic indexes had nearly twice the risk of adverse events as patients without high-risk plaques. This increased incidence of MACE was primarily due to unexpected revascularization, which occurred in 9.8% of patients with high-risk plaques and in 4.3% of patients without high-risk plaques. The authors concluded that FFR may not be superior to imaging in identifying lesions requiring treatment in ACS patients compared to patients with stable CAD. OCT has been shown to be an important tool for detecting high-risk NCLs in ACS. Approximately one-third of study participants had high-risk plaques, which are associated with an increased incidence of unfavorable treatment outcomes in subsequent years. PECTUS unites COMBINE OCT-FFR and other studies, showing that even when there is no evidence of ischemia by FFR or physiologic indexes, vulnerable plaque features can predict future events. The results point to a potential patient phenotype that is vulnerable to future events and emphasize the need for further research and attentive care of patients with acute coronary syndrome, especially those with vulnerable plaques.

COMPLETE REVASCULARIZATION IN CARDIOGENIC SHOCK PATIENTS

Cardiogenic shock (CS) is a life-threatening condition that often occurs as a complication of acute myocardial infarction (AMI), particularly in patients with multivessel disease. Despite advances in treatment, including immediate revascularization and PCI, the mortality rate remains unacceptably high. While complete revascularization is the preferred strategy for hemodynamically stable patients with AMI and multivessel CAD, its role in the setting of CS remains controversial. The CULPRIT-SHOCK[35] trial has shown that the culprit lesion-only (CLO)-PCI strategy achieves better outcomes compared with immediate multivessel PCI. However, several limitations of this trial were noted, and conflicting results from non-randomized studies suggest that complete revascularization may be beneficial in selected patients. Current best practice for the treatment of infarct-related CS in patients with multivessel CAD involves prompt diagnosis followed by timely CLO revascularization and the use of mechanical circulatory support (MCS) systems such as intra-aortic balloon pumps (IABP), Impella, and extracorporeal membrane oxygenation (ECMO). Observational studies suggest that early implantation of MCS prior to PCI, particularly with Impella, may improve clinical outcomes. However, randomized trials are needed to definitively determine the role and timing of MCS in AMI-related CS[36].

Future randomized trials are needed to determine optimal revascularization strategies and the role of MCS in patients with AMI-related CS and multivessel CAD.

In our practice, the current approach to the management of multivessel STEMI patients, including potential revascularization strategies and timing, must take into account the presence or absence of CS and assessment of the patient's ischemic risk [Figure 1].

In uncomplicated STEMI patients, high-risk ischemic patients are evaluated to determine if they are appropriate for PCI. If PCI is deemed appropriate, a decision is made regarding whether to perform complete revascularization during the index hospitalization (either guided by angiography/FFR/imaging). In low-risk patients, complete revascularization within 45 days may be considered (using angiography/FFR/imaging). If PCI is not suitable, coronary artery bypass grafting (CABG) is considered.

Patients with STEMI complicated by CS require pharmacologic and/or mechanical support. The flowchart suggests [Figure 1] that in this high-risk population, complete revascularization may be considered either the index hospitalization. However, as mentioned above, the optimal revascularization strategy for patients with cardiogenic shock is still under investigation.

DISCUSSION AND FUTURE PERSPECTIVES

Although pilot trials and prospective observational cohort studies suggest that PCI of plaques with "vulnerable" high-risk features is safe and effective, clinical trials have not yet conclusively demonstrated the consistent clinical benefits of full standard revascularization in ACS. Imaging techniques serve as a reminder that atherosclerotic cardiovascular disease is a dynamic process. Optimal medical therapy plays a central role in plaque modification and regression. Recently, several studies have addressed the question of how periprocedural OCT might impact PCI outcomes by improving stent implantation. The results have been mixed[37,38].

While FFR remains a fundamental decision-making tool for deciding whether to perform revascularization, its potential utility may be limited in ACS due to secondary coronary microvascular injury and dysfunction, particularly in the setting of STEMI. Previous studies have reported that metabolic changes can also occur in non-ischemic areas during myocardial ischemia. These changes are thought to be mediated by increased catecholamine levels, leading to a cascade of consequences, including increased oxygen demand, depletion of glycogen stores, impairment of myocardial oxidation-reduction enzymes, and disruption of normal mitochondrial function[39]. As a result, these metabolic and functional disorders may reduce the achievement of optimal microvascular conditions required for reliable FFR assessment in the setting of STEMI. This diagnostic challenge underscores the need for complementary imaging modalities to assess the functional significance of non-culprit lesions in STEMI patients with multivessel disease. Intravascular imaging techniques such as OCT and near-infrared spectroscopy (NIRS) have proven to be valuable tools for the detection of vulnerable plaques in non-culprit vessels. OCT provides high-resolution images of the coronary artery wall and enables the identification of thin-cap fibroatheroma and other high-risk plaque features. Studies have shown a correlation between OCT-derived plaque features and FFR values, suggesting that OCT can provide additional information beyond physiologic assessment.

The OMEF[40] study showed a good correlation between MLA and the percentage of plaque burden on OCT and an FFR < 0.80; especially in proximal vessels, the best cut-off value to predict an FFR < 0.80 was MLA 3.1 mm^2. However, this multicenter study showed a worse outcome in patients who had a negative FFR, a lower MLA, and a higher %AS. Although the study included mainly stable patients, the results were also confirmed in the small cohort of patients with ACS.

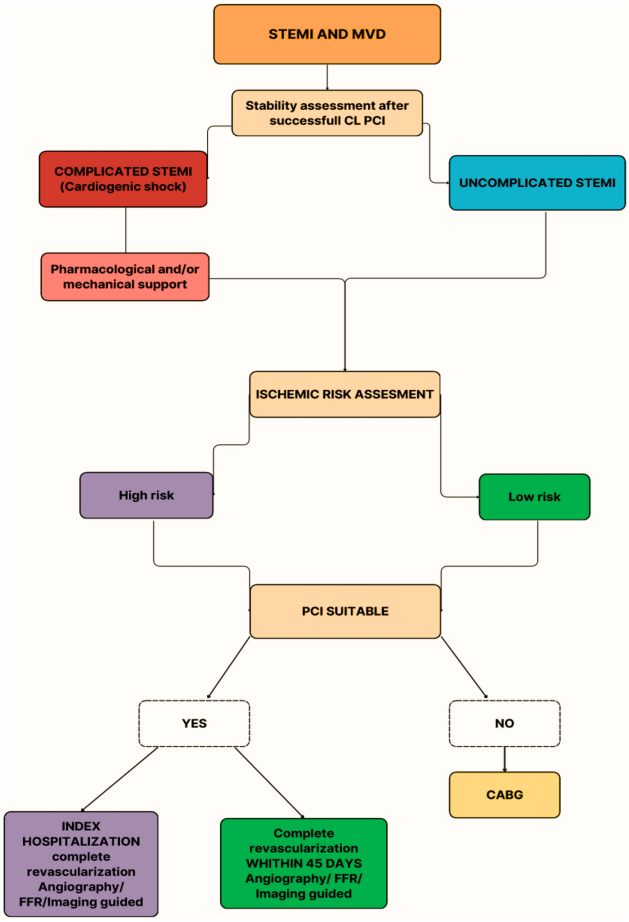

Figure 1. The flowchart provides a decision-making framework for managing STEMI and MVD based on patient stability, ischemic risk, and suitability for PCI or CABG. STEMI: ST-elevation myocardial infarction; MVD: multivessel coronary artery disease; PCI: percutaneous coronary intervention; FFR: fractional flow reserve; CABG: coronary artery bypass graft.

Recently, the PREVENT[41] trial showed a clear benefit of preventive PCI in vulnerable plaques (MLA < 4.0 mm^2 and plaque burden > 70%), in addition to OMT, with negative FFR. During a median follow-up of 4.3 years, patients who underwent preventive PCI consistently showed a significantly lower cumulative incidence of the composite primary endpoint and the composite patient-oriented risk of all-cause death, all myocardial infarction, or repeat revascularization. The results of the PREVENT trial offer new perspectives on the potential role of preventive PCI in this context and could help shape future clinical guidelines and decision-making processes, while the evidence for the treatment of vulnerable plaques in acute coronary syndromes remains controversial.

To date, the choice of optimal guidance technique for NCL revascularization should be based on patient characteristics and coronary anatomy [Figure 2]. Ongoing trials such as the COMPLETE-2 trial (ClinicalTrials.gov number: NCT05701358) are promising to resolve this dilemma and figure out how we can effectively combine coronary physiology with the benefits of intracoronary imaging.

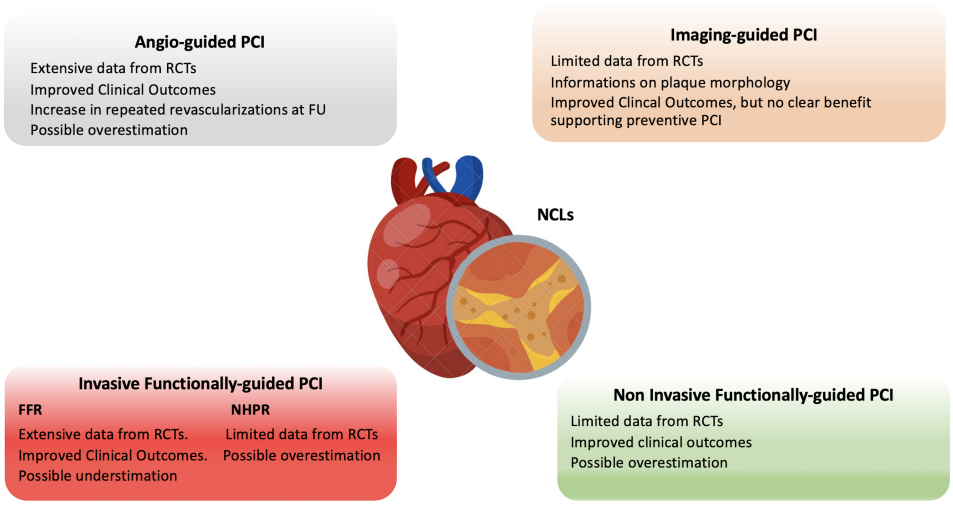

Figure 2. The figure outlines the strengths and limitations of angiography-guided, imaging-guided, invasive functionally-guided and non-invasive functionally-guided approaches to investigating NCLs during PCI procedures. NCLs: Non-culprit lesion; PCI: percutaneous coronary intervention; FFR: fractional flow reserve; NHPR: non-hyperemic pressure ratio.

CONCLUSIONS

In conclusion, the treatment of STEMI patients with multivessel disease remains a complex challenge in clinical practice. While complete revascularization has been shown to be beneficial for clinical outcomes, the optimal timing and strategy for the assessment of non-culprit lesions is still controversial.

Based on current evidence, an integrated approach combining coronary physiology with intracoronary imaging seems to be the most promising strategy to optimize the treatment of STEMI patients with multivessel disease. However, further studies are needed to define the specific role of each diagnostic technique and to develop personalized decision algorithms based on the individual patient's risk profile and plaque characteristics.

The goal is to improve long-term clinical outcomes in this high-risk population by balancing the benefits of complete revascularization against the risks associated with treating non-culprit lesions in the acute phase. The integration of information from coronary physiology and intracoronary imaging and the advancement of therapeutic strategies will bring us closer to this goal and enable a personalized and evidence-based approach for each individual patient.

DECLARATIONS

Authors' contributions

Ideated the paper and was involved in the interpretation of the data and in the drafting of the manuscript: Tommasino A

Involved in the bibliographic research and the drafting of the manuscript: Cesario V, Tempestini F, Casenghi M, Giovannelli F, Rigattieri S

Involved in the revision of the manuscript and wrote the sections on cardiogenic shock and future perspectives; created the figures: Dell'Aquila F

Critically reviewed the manuscript: Barbato E, Berni A

Availability of data and materials
Not applicable.

Financial support and sponsorship
None.

Conflicts of interest
All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

REFERENCES
1. Rigattieri S, Biondi-Zoccai G, Silvestri P, et al. Management of multivessel coronary disease after ST elevation myocardial infarction treated by primary angioplasty. *J Interv Cardiol* 2008;21:1-7. DOI
2. Wald DS, Morris JK, Wald NJ, et al. Randomized trial of preventive angioplasty in myocardial infarction. *N Engl J Med* 2013;369:1115-23. DOI
3. Gershlick AH, Khan JN, Kelly DJ, et al. Randomized trial of complete versus lesion-only revascularization in patients undergoing primary percutaneous coronary intervention for STEMI and multivessel disease: the CvLPRIT trial. *J Am Coll Cardiol* 2015;65:963-72. DOI
4. Engstrøm T, Kelbæk H, Helqvist S, et al. Complete revascularisation versus treatment of the culprit lesion only in patients with ST-segment elevation myocardial infarction and multivessel disease (DANAMI-3 - PRIMULTI): an open-label, randomised controlled trial. *Lancet* 2015;386:665-71. DOI
5. Musto C, De Felice F, Rigattieri S, et al. Instantaneous wave-free ratio and fractional flow reserve for the assessment of nonculprit lesions during the index procedure in patients with ST-segment elevation myocardial infarction: the WAVE study. *Am Heart J* 2017;193:63-9. DOI
6. Mehta SR, Wood DA, Storey RF, et al. Complete revascularization with multivessel PCI for myocardial infarction. *N Engl J Med* 2019;381:1411-21. DOI
7. Mehta SR, Wang J, Wood DA, et al. Complete revascularization vs culprit lesion-only percutaneous coronary intervention for angina-related quality of life in patients with ST-segment elevation myocardial infarction: results from the COMPLETE randomized clinical trial. *JAMA Cardiol* 2022;7:1091-9. DOI
8. Pinilla-Echeverri N, Mehta SR, Wang J, et al. Nonculprit lesion plaque morphology in patients with ST-segment-elevation myocardial infarction: results from the COMPLETE trial optical coherence tomography substudys. *Circ Cardiovasc Interv* 2020;13:e008768. DOI
9. Stone GW, Maehara A, Lansky AJ, et al. A prospective natural-history study of coronary atherosclerosis. *N Engl J Med* 2011;364:226-35. DOI
10. Prati F, Romagnoli E, Gatto L, et al. Relationship between coronary plaque morphology of the left anterior descending artery and 12 months clinical outcome: the CLIMA study. *Eur Heart J* 2020;41:383-91. DOI
11. Roleder-Dylewska M, Gasior P, Hommels TM, et al. Morphological characteristics of lesions with thin cap fibroatheroma-a substudy from the COMBINE (OCT-FFR) trial. *Eur Heart J Cardiovasc Imaging* 2023;24:687-93. DOI
12. Byrne RA, Rossello X, Coughlan JJ, et al. 2023 ESC Guidelines for the management of acute coronary syndromes: developed by the task force on the management of acute coronary syndromes of the European Society of Cardiology (ESC). *Eur Heart J* 2023;44:3720-826. DOI
13. Diletti R, den Dekker WK, Bennett J, et al. Immediate versus staged complete revascularisation in patients presenting with acute coronary syndrome and multivessel coronary disease (BIOVASC): a prospective, open-label, non-inferiority, randomised trial. *Lancet* 2023;401:1172-82. DOI
14. Smits PC, Abdel-Wahab M, Neumann FJ, et al. Fractional flow reserve-guided multivessel angioplasty in myocardial infarction. *N Engl J Med* 2017;376:1234-44. DOI
15. Biscaglia S, Guiducci V, Escaned J, et al. Complete or culprit-only PCI in older patients with myocardial infarction. *N Engl J Med* 2023;389:889-98. DOI

16. Pavasini R, Biscaglia S, Barbato E, et al. Complete revascularization reduces cardiovascular death in patients with ST-segment elevation myocardial infarction and multivessel disease: systematic review and meta-analysis of randomized clinical trials. *Eur Heart J* 2020;41:4103-10. DOI
17. Damluji AA, Forman DE, Wang TY, et al. Management of acute coronary syndrome in the older adult population: a scientific statement from the American heart association. *Circulation* 2023;147:e32-62. DOI PubMed PMC
18. Rioufol G, Dérimay F, Roubille F, et al. Fractional flow reserve to guide treatment of patients with multivessel coronary artery disease. *J Am Coll Cardiol* 2021;78:1875-85. DOI
19. Puymirat E, Cayla G, Simon T, et al. Multivessel PCI guided by FFR or angiography for myocardial infarction. *N Engl J Med* 2021;385:297-308. DOI PubMed
20. Lee SH, Hong D, Shin D, et al. QFR assessment and prognosis after nonculprit PCI in patients with acute myocardial infarction. *JACC Cardiovasc Interv* 2023;16:2365-79. DOI
21. Lee JM, Kim HK, Park KH, et al. Fractional flow reserve versus angiography-guided strategy in acute myocardial infarction with multivessel disease: a randomized trial. *Eur Heart J* 2023;44:473-84. DOI
22. Tommasino A, Navarra E, Barbato E. A novel quantitative flow ratio in coronary bifurcations: a simpler way to a real-time functional provisional stenting strategy. *AsiaIntervention* 2023;9:99-100. DOI PubMed PMC
23. Usui E, Yonetsu T, Kanaji Y, et al. Optical coherence tomography-defined plaque vulnerability in relation to functional stenosis severity and microvascular dysfunction. *JACC Cardiovasc Interv* 2018;11:2058-68. DOI
24. Hoshino M, Usui E, Sugiyama T, Kanaji Y, Yonetsu T, Kakuta T. Prevalence of OCT-defined high-risk plaque in relation to physiological characteristics by fractional flow reserve and coronary flow reserve. *Rev Esp Cardiol* 2020;73:331-2. DOI
25. Yang S, Koo BK. Coronary physiology-based approaches for plaque vulnerability: implications for risk prediction and treatment strategies. *Korean Circ J* 2023;53:581-93. DOI PubMed PMC
26. Yang S, Koo BK, Narula J. Interactions between morphological plaque characteristics and coronary physiology: from pathophysiological basis to clinical implications. *JACC Cardiovasc Imaging* 2022;15:1139-51. DOI PubMed
27. Driessen RS, Stuijfzand WJ, Raijmakers PG, et al. Effect of plaque burden and morphology on myocardial blood flow and fractional flow reserve. *J Am Coll Cardiol* 2018;71:499-509. DOI
28. Yang S, Koo BK, Hoshino M, et al. CT angiographic and plaque predictors of functionally significant coronary disease and outcome using machine learning. *JACC Cardiovasc Imaging* 2021;14:629-41. DOI
29. Koo BK, Hu X, Kang J, et al. Fractional flow reserve or intravascular ultrasonography to guide PCI. *N Engl J Med* 2022;387:779-89. DOI PubMed
30. Lee JM, Choi KH, Koo BK, et al. Prognostic implications of plaque characteristics and stenosis severity in patients with coronary artery disease. *J Am Coll Cardiol* 2019;73:2413-24. DOI
31. Kedhi E, Kennedy MW, Maehara A, et al. Impact of TCFA on unanticipated ischemic events in medically treated diabetes mellitus: insights from the PROSPECT study. *JACC Cardiovasc Imaging* 2017;10:451-8. DOI
32. Erlinge D, Maehara A, Ben-Yehuda O, et al. Identification of vulnerable plaques and patients by intracoronary near-infrared spectroscopy and ultrasound (PROSPECT II): a prospective natural history study. *Lancet* 2021;397:985-95. DOI
33. Stone GW, Maehara A, Ali ZA, et al. Percutaneous coronary intervention for vulnerable coronary atherosclerotic plaque. *J Am Coll Cardiol* 2020;76:2289-301. DOI
34. Mol JQ, Volleberg RHJA, Belkacemi A, et al. Fractional flow reserve-negative high-risk plaques and clinical outcomes after myocardial infarction. *JAMA Cardiol* 2023;8:1013-21. DOI PubMed PMC
35. Thiele H, Akin I, Sandri M, et al. PCI strategies in patients with acute myocardial infarction and cardiogenic shock. *N Engl J Med* 2017;377:2419-32. DOI
36. Jentzer JC, Naidu SS, Bhatt DL, Stone GW. Mechanical circulatory support devices in acute myocardial infarction-cardiogenic shock: current studies and future directions. *JSCAI* 2023;2:100586. DOI
37. Ali ZA, Landmesser U, Maehara A, et al. Optical coherence tomography-guided versus angiography-guided PCI. *N Engl J Med* 2023;389:1466-76. DOI
38. Holm NR, Andreasen LN, Neghabat O, et al. OCT or angiography guidance for PCI in complex bifurcation lesions. *N Engl J Med* 2023;389:1477-87. DOI PubMed
39. Elbadawi A, Sedhom R, Ghoweba M, Etewa AM, Kayani W, Rahman F. Contemporary use of coronary physiology in cardiology. *Cardiol Ther* 2023;12:589-614. DOI PubMed PMC
40. Vergallo R, Lombardi M, Kakuta T, et al. Optical Coherence tomography measures predicting fractional flow reserve: the OMEF study. *JSCAI* 2024;3:101288. DOI
41. Ahn JM, Kang DY, Lee PH, et al. Preventive PCI or medical therapy alone for vulnerable atherosclerotic coronary plaque: rationale and design of the randomized, controlled PREVENT trial. *Am Heart J* 2023;264:83-96. DOI PubMed