

Acute coronary syndromes and multivessel coronary artery disease

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KEYWORDS

Acute coronary syndrome;
Multivessel coronary
artery disease;
Non-culprit lesion;
Complete revascularization;
Percutaneous coronary
intervention

Patients with acute coronary syndromes (ACS) and multivessel coronary artery disease are frequently encountered during clinical practice and those patients are at higher risk of subsequent acute cardiovascular events. In patients presenting with both ST-segment elevation myocardial infarction and non-ST-segment elevation acute coronary syndromes, complete revascularization is associated with decreased risk of major adverse cardiovascular events. Nevertheless, the optimal timing of the intervention and treatment modality are still in discussions. Furthermore, non-culprit lesions assessment based on stenosis severity, either on visual or on functional evaluation, may not provide information about vulnerable plaques prone to thrombosis. Therefore, insights from intracoronary imaging could further identify high-risk plaque and patients at higher risk of future adverse events. This article aims to provide an overview of current guideline recommendations, envisioning future perspectives for the treatment of patients with ACS and multivessel disease.

Introduction

Acute coronary syndromes (ACS) represent one of the most common causes of hospitalization, mortality, and morbidity worldwide,^{1,2} despite the spreading of new pharmacotherapies and technological innovations. Percutaneous coronary intervention (PCI) of the culprit lesion, aiming at restoring blood flow in the infarct-related artery (IRA), is the cornerstone of treatment of patients presenting with ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation acute coronary syndromes (NSTEMI).² Among patients presenting with ACS, the ones affected by multivessel coronary artery disease (MVD), defined by the presence of $\geq 50\%$ stenosis in two or more major epicardial vessels, result in the worst prognosis, compared to those with one-vessel disease only.³

To date, there has been a debate whether to routinely revascularize the non-culprit lesions (NCL) or to manage

them conservatively, according to guidelines directed therapy. In fact, it is not possible to estimate if a preventive intervention could actually reduce the occurrence of subsequent events, since, at the time of ACS index procedure, the clinical relevance of NCLs about inducible ischaemia, angina or plaques vulnerability is still unknown. Therefore, the management of NCL in ACS—if it is to achieve complete revascularization and how to select NCLs, the timing, and modality of intervention—has been recently addressed in randomized clinical trials and observational studies, supporting clinicians in decision-making.

In this article, current indications for management of patients presenting with ACS and MVD are provided.

Timing and completeness of revascularization in patients with ST-segment elevation myocardial infarction

The standard procedure to treat patients presenting with STEMI requires primary PCI of the culprit lesion.¹

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In the PRAMI trial, the authors randomized patients presenting with STEMI and MVD to receive culprit-lesion-only-PCI or culprit-lesion-PCI and preventive-PCI of NCL. The result revealed that the occurrence of composite primary endpoint—death, non-fatal myocardial infarction (MI) and refractory angina—was higher in the patients that received culprit-lesion-only PCI, than in the ones who underwent preventive-PCI too, at a mean follow-up of 23 months (23% vs. 9%, respectively; HR in preventive-PCI group, 0.35; 95% confidence interval (CI), 0.21-0.58, $P < 0.001$). The timing of treatment of NCL was not investigated in this trial.⁴

In the CvLPRIT trial, angiography-guided complete revascularization yielded a 55% reduction in the composite primary endpoint when compared to a culprit-only strategy.⁵ In the DANAMI-3-PRIMULTI trial, the authors tested a strategy of complete fractional flow reserve (FFR)-guided NCLs revascularization in patients presenting with STEMI compared to a culprit-lesion-only strategy. At a median follow-up of 27 months, complete FFR-guided revascularization reduced the risk of major adverse cardiac events (MACE) compared with patients with no further intervention (13% vs. 22%, respectively, HR 0.56, 95% CI 0.38-0.83; $P = 0.004$). This result is mainly driven by fewer repeat revascularization.⁶

The same clinical topic is also discussed in the COMPARE-ACUTE trial, in which investigators randomized patients successfully treated with primary PCI to receive either a complete revascularization of NCLs guided by FFR or no other intervention. Once again, the treatment of NCLs conferred better outcomes at 12 months follow-up, since 8% of events in the complete revascularization group occurred compared with 21% in the IRA-only PCI (HR, 0.35; 95% CI, 0.22-0.55; $P < 0.001$).⁷

Since none of the aforementioned trials demonstrated different mortality between complete and incomplete revascularization, current 2017 European Society of Cardiology (ESC) guidelines assigned a class IIa level A recommendation to complete revascularization in patients with STEMI and MVD.¹

Later, the composite coprimary 'hard' endpoint of cardiovascular death and MI has been addressed in the COMPLETE trial. Mehta *et al.* randomized patients with STEMI and MVD to undergo either PCI of angiographically significant NCLs or no further intervention. It was found that complete revascularization was superior to culprit-only-PCI in reducing the risk of cardiovascular death or MI (7.8% vs. 10.5%, respectively, HR, 0.74; 95% CI, 0.60-0.91; $P \leq 0.001$).⁸

It is also noteworthy that the benefit of complete revascularization was maintained either when performing PCI during index hospitalization or early after hospital discharge, but not later than 45 days.⁹

Thus, prompt revascularization of further coronary lesions during primary PCI could be considered if signs and symptoms of ischaemia are still ongoing. If not, the approach to NCLs could be staged during the hospitalization. In this way, it is possible to avoid the risk of overestimation of lesion severity given high adrenergic vascular tone and the risk of contrast nephropathy during index procedure.

In all the above-mentioned trials, lesion severity was assessed either by angiographic or functional guidance.

Recently, a strategy of complete revascularization guided by either angiography or FFR in STEMI patients

has been evaluated and an FFR-guided strategy failed to improve outcomes over an angiography-guided strategy with respect to the risk of death, MI or urgent revascularization at 1 year.¹⁰

As opposed, according to the findings from FRAME-AMI trial (presented at ESC Congress 2022), among patients with acute MI and MVD, an FFR-guided complete revascularization was superior to an angiography-guided one, with significant reduction in death and MI.

Therefore, complete revascularization after primary PCI should be achieved since it confers prognostic advantages, reducing cardiac death, spontaneous MI, and predicting unplanned revascularization. Either a strategy of anatomic or functional complete revascularization seems to be beneficial, while the higher the degree of residual untreated lesion the higher the risk of subsequent events.¹¹

Timing and completeness of revascularization in patients with NSTEMI

In patients with NSTEMI, invasive coronary angiography allows both confirmation of diagnosis and definition of treatment modality. The timing of invasive strategy is based on individual risk stratification. Compared to STEMI patients, those with NSTEMI are generally older and have more diffuse coronary disease, sometimes without a clear culprit lesion.¹² Coronary artery by-pass grafting (CABG) may represent an alternative modality of revascularization in stabilized patients applying the same criteria as in patients with chronic coronary syndromes.²

Since the early trials, an invasive strategy, involving extensive revascularization, has been proved to be superior in reducing cardiovascular death and recurrent MI as compared to a conservative approach.¹³ In the ACUITY trial, higher rates of MACE were recorded among patients with residual SYNTAX SCORE ≥ 9 , compared with those who underwent complete anatomical revascularization (22.4% vs. 16.3% respectively, $P < 0.001$).¹¹ In an observational cohort study, patients with NSTEMI and MVD managed with single-staged complete revascularization procedure showed lower mortality rates compared to those undergoing culprit-lesion-only-PCI at a median follow-up of 4.1 years, despite a higher rate of in-hospital mortality.¹⁴

In contrast with the STEMI setting, there is only one randomized trial exploring revascularization timing in NSTEMI patients. In fact, results from the SMILE trial showed less major adverse cardiovascular and cerebrovascular events in patients undergoing single-stage coronary revascularization compared with those undergoing complete coronary revascularization in multistage PCI during the index hospitalization (HR 0.55, 95% CI 0.36-0.83, $P = 0.004$), mainly driven by a significant reduction in repeat revascularization with single-stage multivessel PCI.¹⁵

Although robust clinical data are still lacking, physiological assessment of NCL could be a reasonable approach also in this setting.^{12,16} Using FFR to guide PCI in MVD resulted in a 5.1% risk reduction of MACE compared to angiography-guidance in a subgroup analysis of the FAME trial.¹⁷ It is also noteworthy that FFR deferred lesions were not responsible for MI at follow-up. In the

FAMOUS-NSTEMI, an FFR-guided coronary revascularization strategy compared to an angiography-guided one resulted in lower rates of revascularization without any impact on clinical outcomes at 12-month follow-up.¹⁸ Both trials included functional evaluation either of culprit or NCLs.

According to 2020 ESC guidelines on management of patients with NSTEMACS, complete revascularization should be achieved in patients with ACS and MVD.¹² Furthermore, when a functional complete revascularization is achieved, residual angiographic Syntax Score is not predictive of subsequent events.¹⁹ However, trials to further clarify the role of physiology guidance in patients with ACS and MVD are still ongoing (FIRE trial NCT 03772743, SLIM trial NCT 03562572).

Cardiogenic shock

Cardiogenic shock (CS) complicating ACS represents a challenging clinical scenario. According to current guidelines, emergency PCI of the culprit lesion is recommended, whereas routine immediately PCI of NCLs is contraindicated.^{2,12} These recommendations are based on the result of the CULPRIT-SHOCK trial, in which culprit-lesion-only-PCI in patients with ACS, CS, and MVD led to a significant reduction in all-cause death and in renal-replacement therapy at 30-days follow-up compared with immediate multivessel PCI.²⁰ A staged NCLs revascularization should be considered since residual Syntax Score is an independent predictor of mortality also in a CS setting.²¹

Despite the evidence, however, the use of short-term mechanical circulatory support (MCS) in patients with CS, such as Impella, has been increasing over the last years. Of note, data from registries identified Impella implantation before PCI and an extensive revascularization during the index procedure as predictors of improved

outcomes in patients with CS complicating ACS who undergo mechanically assisted PCI.²² Therefore, more data are needed to evaluate a strategy of complete revascularization in ACS-CS patients during a MCS-assisted PCI.

The role of intracoronary imaging

Functional evaluation is recommended to assess the hemodynamic relevance of angiographically intermediate stenosis and FFR-guided PCI should be considered in patients with MVD.² Functional assessment of NCLs in ACS is safe and it results in less repetitions of revascularization procedures, mainly avoiding inappropriate stenting and procedure-related issues (i.e. antithrombotic medications, peri-procedural-MI or stent failure). However, in the acute setting, the response to adenosine could be blunted and lesion severity may be underestimated by FFR. This should be considered when dealing with borderline value for significance.

Nevertheless, the observation that often atherosclerotic plaques, that lead to ACS, occur at sites of angiographically mild coronary-artery stenosis may drive to a paradigm shift from treating flow-limiting-ischæmia-generating lesions to looking for vulnerable plaques.²³ At this regard, thin-cap fibroatheroma (TCFA), lipid necrotic core, high atherosclerotic burden, macrophages infiltration, and reduced minimal lumen area are all well-recognized features of high-risk vulnerable plaques, as assessed by intracoronary imaging.²⁴ In an Optical Coherence Tomography (OCT) sub-analysis of the COMPLETE trial, obstructive NCLs showed higher vulnerable plaques morphology as compared to non-obstructive lesions, and this may explain the benefit in treating those lesions.²⁵ Moreover, the role of fibrous cap in predicting events has been tested in the COMBINE FFR-OCT trial, in which patients with non-flow limiting NCLs were divided into two groups on the basis of the presence of TCFA. The result shows that at 18 months of follow-up

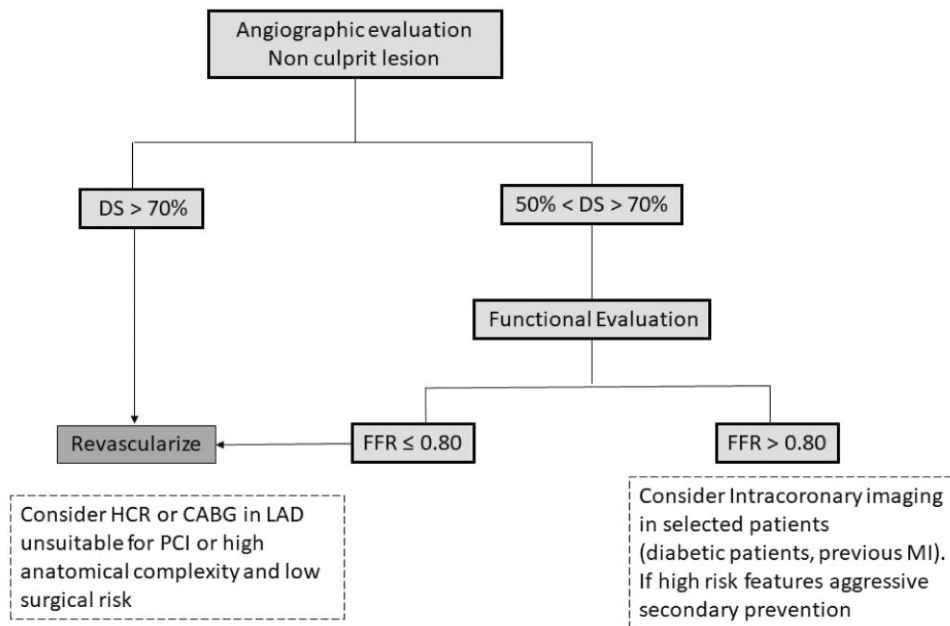


Figure 1 Diagnostic flowchart for non-culprit lesions assessment in acute coronary syndrome patients.

diabetic patients with TCFA had a higher incidence of MACE (13.3% and 3.1% in TCFA-positive vs. TCFA-negative groups, respectively, HR 4.65; 95% CI, 1.99-10.89; $P < 0.001$).²⁶

Therefore, intracoronary imaging could identify high-risk plaques in patients who may benefit from close surveillance and aggressive secondary prevention measures. Noteworthy, no data from randomized trials on preventive PCI for non-obstructive vulnerable plaques are available (Figure 1).

Hybrid coronary revascularization

When primary PCI is attempted in patients with ACS, coronary artery bypass grafting (CABG) could be an alternative in case of failure or complications of primary PCI, as an emergency procedure. On the other hand, CABG could be an option in stabilized patients with ACS and high anatomical complexity disease, who could not achieve complete revascularization through PCI. Concerns regarding bleeding risk in patients treated with potent antiplatelet therapy and recent MI may limit the indication to CABG in patients presenting with ACS after primary PCI.

An effective way to further reduce surgical risk is referring to off-pump CABG in left anterior descending artery patients treated with PCI in the right coronary artery or circumflex presenting with high anatomical complexity in left anterior descending artery, a so-called hybrid coronary revascularization. After primary PCI, CABG can be delayed, allowing safe discontinuation of antiplatelet therapy. This strategy may also be used in lesions with a risk of PCI failure such as chronic total occlusions.²⁷

Conclusions

Complete revascularization should be achieved in patients presenting with STEMI and NSTEMI, regardless of the timing and mode of selection of NCLs. Despite this, recurrence of events remains high in those patients, and insights from intracoronary imaging may help in identifying high-risk patients. In patients presenting with CS, immediate multivessel-PCI should be avoided. However, a personalized approach is preferred, based on patients' factors and anatomical findings. When PCI cannot be pursued, CABG and HCR remain an option in those patients.

Funding

None declared.

Conflict of interest: None declared.

Data availability

No new data were generated or analysed in support of this research.

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