

The management of non-culprit coronary lesions in patients with acute coronary syndrome

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About 50% of patients diagnosed with ST-segment elevation myocardial infarction have multivessel disease on coronary angiography. Recent evidence has shown that a staged percutaneous coronary intervention (PCI) strategy of non-culprit lesions, achieving complete revascularization, significantly reduces the rate of recurrent cardiovascular events compared with a PCI strategy limited to culprit lesion. Although functional evaluation of intermediate coronary stenoses by functional flow reserve (FFR) or instantaneous wave-free ratio (iFR) is widely used to detect residual myocardial ischaemia, the reliability of the study of non-culprit lesions in the acute phase of heart attack is controversial. On the other hand, the excess of new events in patients with acute coronary syndrome in whom PCI was deferred on the basis of FFR/iFR compared to patients with stable CAD could be due to both an inadequate functional evaluation and an intrinsic higher risk, related to the presence of untreated vulnerable plaques. In this context, intra-coronary imaging has shown that the presence of vulnerability features in non-culprit plaques is associated with an increased rate of ischaemic recurrence.

Introduction

Over 50% of patients diagnosed with ST-segment elevation myocardial infarction (STEMI) have multivessel disease on coronary angiography. The most recent guidelines indicate percutaneous revascularization of lesions not responsible for the acute event (the so-called ‘non-culprit’) with a recommendation Class IIb. On the other hand, numerous trials have documented the usefulness and safety of a complete revascularization strategy. In particular, the COMPLETE trial¹ demonstrated that a staged percutaneous procedure (percutaneous coronary intervention; PCI) strategy of non-culprit lesions results in a 26% reduction in the composite risk of death from heart disease and acute myocardial infarction (AMI) at an average follow-up of 3 years, compared to a PCI strategy of only the lesion responsible for the acute event (‘culprit’).

However, the decision as to which non-culprit lesion to treat with PCI rather than conservative treatment is controversial. In particular, how and when to perform a functional evaluation of an intermediate coronary stenosis (stenosis diameter 40-70%) in patients with acute coronary syndrome (ACS) is still a matter of debate.² This consideration has a significant clinical impact, as intermediate stenoses in non-culprit vessels represent ~70% of the lesions in patients with STEMI and multivessel coronary artery disease and, on the other hand, coronary angiography is not able to evaluate reliably the ‘functional criticality’ of these lesions. In addition, coronary angiography does not allow identifying plaque vulnerability features that could suggest an increased probability of ischaemic recurrence. In this context, intra-coronary imaging can facilitate the identification of high-risk patients who could benefit from the revascularization of non-culprit lesions.

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The role of invasive functional assessment

Pathophysiological caveats for the use of the fractional flow reserve and instantaneous wave-free ratio in patients with acute coronary syndrome

Numerous evidences support the use of the physiological evaluation of ischaemia by means of the functional flow reserve, commonly known as fractional flow reserve (FFR) or the instantaneous wave-free ratio (iFR) in order to guide revascularization, especially in patients with stable CAD. However, the reliability of the functional evaluation in the acute phase of the ACS is, to date, controversial.²

Recent randomized clinical trials^{3,4} have shown that the use of the FFR to guide decisions related to the percutaneous treatment of non-culprit lesions in acute STEMI is safe and effective. In particular, COMPARE-ACUTE and DANAMI3-PRIMULTI have shown that complete revascularization by PCI guided by FFR reduces the rate of ischaemic recurrence with a median follow-up of 12 and 27 months, respectively compared to PCI of culprit lesion alone. Specifically, the difference between the two groups was due to a lower rate of urgent revascularization procedures, while cardiac death and recurrence of AMI did not differ significantly.

However, multiple issues remain unresolved. First, the FFR was measured during primary PCI in the COMPARE-ACUTE study and a median of 2 days after primary PCI in the DANAMI3-PRIMULTI study; in fact, it is not yet clear how and when to interrogate an intermediate non-culprit stenosis in patients with ACS.

A prerequisite for a reliable FFR measurement is the achievement of the so-called 'maximal' hyperaemia due to the dilation of the microcirculation after intracoronary or intravenous administration of adenosine. However, patients with ACS may have an incomplete response to adenosine, as a consequence of both an increase in microvascular resistance and a reduction in the coronary flow reserve (CFR). Therefore, normal FFR values (>0.80) can be falsely negative due to submaximal hyperaemia.

In fact, an increased release of vasoconstrictor molecules occurs in ACS and it has been shown that adenosine is unable to eliminate α -adrenergic or endothelin-mediated coronary vasoconstriction or other powerful vasoconstrictors, such as angiotensin, thromboxane A₂, and serotonin. Furthermore, the non-culprit lesion can be associated with plaque rupture and distal embolization, which hinders the vasodilator response of the microcirculation.² Endothelial coronary dysfunction can pre-exist to the acute coronary event and may even contribute to its pathogenesis. Finally, the effects of an increase in left ventricular diastolic pressure, especially in the acute phase of ACS, can contribute to an alteration of myocardial perfusion and hyperaemic response.

In this context, the iFR has been proposed as an alternative to the FFR in patients with ACS. The iFR is calculated in a period of diastole in which alterations deriving from myocardial contraction or relaxation (the so-called 'wave-free period') are absent, a phase of the cardiac cycle in which the microvascular resistances are lower and more stable,

providing the optimal window for physiological measurements. Therefore, evaluation with iFR is performed in the absence of hyperaemic stimulation, thus avoiding any limitations regarding the incomplete response to adenosine.⁵ In addition, the iFR, when compared with the FFR, shows a stronger correlation with the CFR, suggesting that the iFR is more reliable in cases of dissociation between FFR and CFR, a situation that potentially occurs in ACSs.

Comparison between fractional flow reserve and instantaneous wave-free ratio in patients with acute coronary syndrome

A small study by Ntalianis *et al.*⁶ documented the reproducibility of assessments of non-culprit lesions with FFR in 101 patients diagnosed with AMI performed at the time of PCI of the culprit lesion and repeated after 35 ± 4 days. In another study,⁷ which enrolled 120 patients with STEMI and multivessel coronary artery disease, iFR was measured on non-culprit injury in the context of acute STEMI and then at a median of 16 days after showing a significant increase in iFR (0.89-0.91), which was particularly evident in patients with a longer period before the second iFR measurement.

Finally, van der Hoeven *et al.*⁸ evaluated iFR, FFR, CFR, and IMR in non-culprit lesions of 73 patients with STEMI in the acute phase and at 1-month follow-up. The authors demonstrated a numerical increase in the iFR from the first measurement to the follow-up, while the FFR decreased significantly (0.88-0.86; $P=0.001$). The CFR increased at follow-up (2.9-4.1; $P<0.001$) and the IMR decreased. In addition, the change in the FFR correlated with the size of the heart attack. The hyperaemic response to adenosine, determined by the difference between basal microvascular resistances and the IMR, was lower at the time of STEMI compared to the 1-month follow-up. These results suggest that in the context of acute STEMI a transient change in microcirculation and, more generally, in resting coronary haemodynamics, responsible for a flawed functional evaluation of non-culprit plaques, probably more significant in patients with large heart attacks (*Table 1*). Specifically, non-hyperaemic indices, such as iFR, can overestimate the severity of a non-culprit lesion in the acute phase of STEMI, while the FFR can underestimate it.

The role of intracoronary imaging

Numerous retrospective studies have documented that the majority of plaques responsible for acute coronary events are mild at baseline angiographic assessment. Therefore, coronary angiography alone is not a reliable tool for identifying stenosis at risk of instability.

Pathological studies have shown that thrombotic occlusion after rupture of a lipid-rich atheroma with a necrotic nucleus covered by a thin fibrous layer of intimal tissue (the so-called 'thin cap fibro-atheroma', TCFA) is the most common cause of AMI and death from cardiac causes. Consequently, several prospective studies have been conducted with intravascular imaging techniques in order to detect the characteristics of high-risk coronary plaques *in vivo* (*Table 2*).

Table 1 Studies evaluating variation of pressure and flow in non-culprit lesions of patients with ACS

Study	Patients (n)	Value	Median time interval between measurement during the acute phase and follow-up	Results	Ref. No.
Ntalianis <i>et al.</i>	101 ACS (75 STEMI, 26 NSTEMI)	FFR	35 ± 4 days	No difference between acute FFR and FU measurement; 10% of patients went over the clinical cut-off FFR value	6
Thim <i>et al.</i>	120 STEMI	iFR	16 days	Concordance between acute and FU FFR value is 78%. No difference between acute and FU iFR value was observed for pts with FU recorded within 5 days of STEMI, concordance rate was 89%. For pts with iFR FU value recorded >16 days after STEMI, the acute phase iFR was lower than FU iFR with a concordance rate of 70%.	7
van der Hoeven <i>et al.</i>	98 STEMI	FFR	30 days	FFR value was significantly lower at FU. The acute submassimal hyperaemic response correlated well with the final infarct size.	8
		iFR		iFR value does not change between acute and FU measurement.	
		IMR CFR		IMR value is significantly lower at FU. CFR is significantly higher at FU.	

ACS, acute coronary syndrome; CFR, coronary flow reserve; FFR, fractional flow reserve; FU, follow-up; iFR, instantaneous wave-free ratio; IMR, microvascular resistance index; NSTEMI, non-ST-elevation myocardial infarction; STEMI, ST-elevation myocardial infarction.

Table 2 Intra-coronary imaging studies evaluating plaque characteristics of non-culprit lesions indicative of an increased risk of ischaemic recurrence

Study	Patients enrolled (n)	Imaging	Characteristics of the vulnerable plaque	Ref.
PROSPECT	697 ACS	IVUS	Thin cap fibro-atheroma, high atherosclerotic load ($\geq 70\%$) and small luminal area ($MLA \leq 4 \text{ mm}^2$).	9
Registry OCT del Massachusetts General Hospital	1474 (39% ACS)	OCT	Lipid rich plaque (defined as plaque with lipid arc of > 1 quadrant assessed with OCT)	10
Lipid-Rich Plaque	1271 (53.7% ACS)	NIRS	Lipid rich plaque	11
CLIMA	1003 (53.4% ACS)	OCT	Small luminal area ($MLA < 3.5 \text{ mm}^2$), thin cap thickness < 75 μm , circumferential extension of the lipid arch > 180° and macrophages assessed with OCT	12

ACS, acute coronary syndrome; IVUS, intracoronary ultrasound; MLA, minimal luminal area; NIRS, near infrared spectroscopy; OCT, optical coherence tomography.

The PROSPECT study,⁹ enrolling 697 patients with ACS who underwent intracoronary ultrasound (IVUS) of the three coronary vessels after PCI, showed that the simultaneous presence of three vulnerable plaque characteristics, such as TFCA, the high atherosclerotic burden ($\geq 70\%$), and a minimal luminal area ($MLA \leq 4 \text{ mm}^2$) were associated with an increase in the combined endpoint including cardiac death, target vessel AMI and hospitalization due to myocardial ischaemia [hazard ratio (HR) 11.05 (4.39-27.82), $P < 0.001$].

The Massachusetts General Hospital OCT registry,¹⁰ including 1474 PCI patients who underwent culprit

lesion evaluation with optical coherence tomography (OCT), documented that the rate of MACE related to non-culprit lesions was higher in patients with plaques rich in lipids (defined as plaque with lipid arc > 1 quadrant) compared to those without lipid-rich plaques (7.2% vs. 2.6%, respectively; $P = 0.033$) at a 2-year follow-up. Similarly, the Lipid-Rich Plaque study,¹¹ evaluating the extension of the lipid component by near infrared spectroscopy in 1271 patients (46.3% with stable angina), showed an 18% increase in MACE related to non-culprit lesions for each 100-unit increase in the lipid core maximum load index.

Finally, the recently published CLIMA study¹² enrolled 1003 patients undergoing OCT of the left anterior descending artery in the context of clinically indicated coronary angiography (53.4% with ACS). The presence of MLA <3.5 mm² [HR 2.1, 95% confidence interval (CI) 1.1-4.0], the thickness of the fibrous cap <75 μ m (HR 4.7, 95% CI 2.4-9.0), the circumferential extension of the lipid arch $>180^\circ$ (HR 2.4, 95% CI 1.2-4.8) and the presence of macrophages (HR 2.7, 95% CI 1.2-6.1) were associated with an increased risk of the primary endpoint, a compound of cardiac death and IMA of the target lesion. Furthermore, the simultaneous presence of these four OCT criteria in the same plaque, which occurred in 18.9% of patients with primary endpoint, was an independent predictor of events (HR 7.54, 95% CI 3.1-18.6).

The CLIMA study therefore broadened the conclusions reached by previous studies, underlining the clinical importance of local inflammation, assessed by the presence of macrophages and the thickness of the fibrous cap, as an additional high-risk characteristic, in addition to the presence and extension of the lipid components (Figure 1).

The role of non-invasive diagnostic techniques

The latest guidelines do not give a univocal recommendation as to the imaging technique of choice (echocardiography, SPECT, CMR, or PET) to detect residual ischaemia and myocardial viability in patients with STEMI, which will also depend on local availability and experience. However, in these patients, evaluation by stress echocardiography is difficult to apply due to the basic kinetic anomalies and the risk of ischaemic and/or arrhythmic complications when performed in the acute phase of STEMI.

Coronary flow reserve (CFVR) assessment with Doppler transthoracic echocardiography in patients with intermediate stenosis can be considered within 7 days of primary PCI when technically feasible and is associated with an excellent long-term clinical outcome if CFVR >2 .

Cardiac magnetic resonance-late gadolinium enhancement offer high diagnostic accuracy in evaluating the

transmural extent of scarred myocardial tissue, however, was not superior to other techniques in identifying vital myocardium and predicting contractile recovery.

PET is also an alternative non-invasive technique for evaluating perfusion and residual myocardial ischaemia, but its use in clinical practice is limited by availability and high costs.

Finally, Lee *et al.*,¹³ applying computerized tomography (CT) angiography to the study of non-culprit lesions in patients with ACS, suggested that the non-invasive haemodynamic evaluation using computational fluid dynamics allows identifying plaques with a high risk of instability. However, the diagnostic accuracy of FFR-CT in detecting residual ischaemia in patients with STEMI and multivessel disease is modest when compared with invasive FFR.

Therapeutic implications and future directions

In the European guidelines on myocardial revascularization, the use of FFR/iFR to identify hemodynamically significant stenoses is indicated with a recommendation Class I with level of evidence A. However, most of the knowledge has been acquired in the field of stable coronary artery disease, while there is limited evidence supporting the safety of PCI deferral based on invasive functional assessment in patients with ACS.

A subanalysis of the FAME study documented a higher prevalence of MACE at 2 years in 150 patients with ACS undergoing FFR-guided PCI (21.3%) compared to 359 patients with stable angina (16.4%).¹⁴ Similarly, a recent meta-analysis¹⁵ that brings together data from two major clinical studies, DEFINE-FLAIR and iFR-SWEDEHEART, compared the clinical outcomes of 4529 patients with coronary artery stenosis undergoing FFR or iFR guided revascularization, respectively, showing that in patients with SCA the deferral was associated with a higher 1-year MACE rate than in patients with stable CAD.

These data clearly indicate that in patients with ACS, pressure-derived indices do not adequately identify the stenoses for which revascularization can be safely

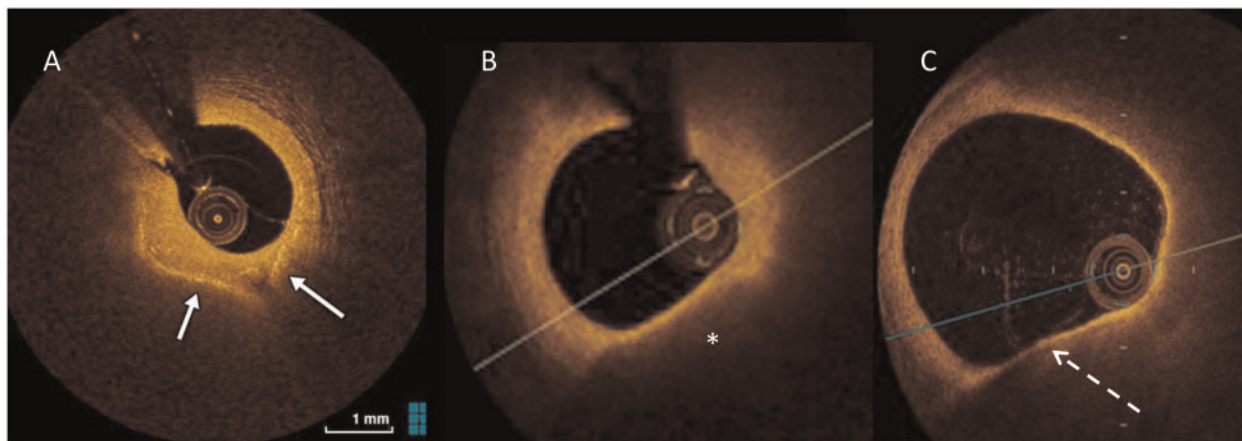


Figure 1 Characteristics of vulnerable plaques evaluated with optical coherence tomography. (A) Fibro-lipidic plaque with macrophage infiltration (white arrows). (B) Large lipid load (asterisk). (C) Thin cap fibro-atheroma (the dotted arrow indicates the thin cap).

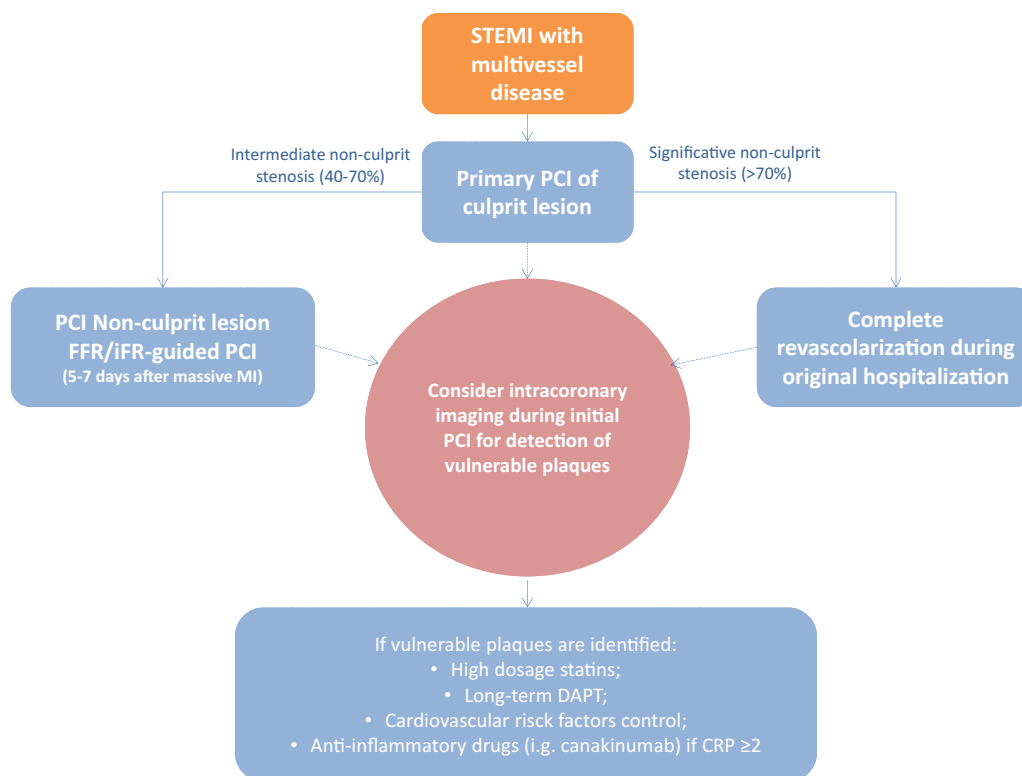


Figure 2 Diagnostic-therapeutic algorithm for the management of non-culprit lesions in patients with myocardial infarction with ST-segment elevation and multivessel coronary artery disease. FFR, fractional flow reserve; iFR, instantaneous wave-free ratio; PCI, percutaneous coronary intervention.

deferred. However, it is not clear whether the higher observed event rate is due to a higher intrinsic risk of patients with ACS or to an inadequate functional assessment of stenoses. Probably, the natural history of coronary lesions is different from their stable counterpart and the presence of vulnerable non-culprit plaques may have a role in determining the higher risk of ischaemic recurrence. The risk of plaque instability, therefore, is not strictly related to the presence of ischaemia detected by FFR or iFR, but to the underlying activity of the disease and this risk could be further amplified by the presence of systemic inflammation, which has been documented in patients with ACS. The combination of systemic evidence of inflammation and OCT findings in the culprit plaque (e.g. plaque rupture, macrophage infiltration, multifocal atherosclerosis) can identify patients with a higher risk of recurrence of ACS.

In this context, intracoronary imaging techniques can facilitate the identification of patients with high-risk non-culprit lesions (e.g. presence of TCFA, large lipid pool with a high atherosclerotic load, $MLA < 3.5\text{--}4\text{ mm}^2$, macrophages defined by the OCT).⁹⁻¹² However, so far, no studies have been conducted that have assessed the role of a 'preventive' PCI strategy for vulnerable plaque that does not result in myocardial ischaemia.

In contrast, several studies conducted with intracoronary imaging techniques have suggested that long-term aggressive therapy with high-dose statins or a combination of statins with ezetimibe helps stabilize non-culprit plaque with vulnerable characteristics. Furthermore, the use of ticagrelor or prasugrel compared to clopidogrel can also

reduce the risk of recurrence of ACS. Finally, patients with local or systemic signs of inflammatory activation are likely to benefit from blocking specific cytokine pathways, such as the interleukin-1 β pathway by administering canakinumab.

In conclusion, the decision to treat with PCI or to manage non-culprit plaques in patients with ACS with optimal medical therapy remains controversial (Figure 2). The assessment of the functional critical lesion with FFR or iFR must be performed in the subacute phase of the ACS (preferably after 5-6 days), especially after large myocardial infarcts, otherwise, it may be unreliable. At the same time, the role of FFR/iFR in improving the prognosis of patients with ACS is limited, since cardiovascular events may derive from functionally insignificant stenoses, but with characteristics of vulnerability. These characteristics can be identified with intra-coronary imaging, which together with the evaluation of inflammatory activity is useful for prognostic stratification, identifying high-risk patients, candidates therefore for a more aggressive lipid lowering and antiplatelet therapy and a strict control of cardiovascular risk factors.

Conflict of interest: none declared.

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