Translational Medicine @ UniSa

Volume 26 | Issue 1 Article 4

February 2024

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REVIEW

Invasive and Non-invasive Assessment of Non-culprit Coronary Lesions in Patients with ST-segment Elevation Myocardial Infarction

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Abstract

The angiographic evidence of coronary multivessel disease (MVD) increases significantly the risk of recurrent ischemic events in patients with ST-segment elevation myocardial infarction (STEMI).

Recent evidence suggests that a complete revascularization strategy should be considered the standard of care in these patients and performed for significant non-culprit lesions (NCLs) after careful assessment of the individual risk-benefit ratio. However, the optimal timing and the modality for the assessment of NCLs is not fully standardized.

This brief review aims to summarise the management of MVD in patients with STEMI and to provide an overview of the principal techniques used to guide revascularisation in this high-risk clinical setting.

Keywords: Acute coronary syndrome, Non-culprit lesion, Multivessel disease, Intracoronary imaging, IVUS, OCT, Functional assessment, Coronary computed tomography angiography

1. Introduction

About half of patients with ST-segment elevation myocardial infarction (STEMI) exhibits coronary multivessel disease (MVD), defined as the presence of two or more epicardial coronary arteries with obstructive luminal narrowing [1]. The angiographic evidence of MVD has achieved increasing clinical interest in the last decades due to the robust evidence of its association with recurrent ischemic events and mortality [2–5].

Current guidelines recommend routine revascularization of non-culprit lesions (NCLs), defined as any coronary lesion not responsible for the acute coronary syndrome (ACS), during the index percutaneous coronary intervention (PCI) procedure or within 45 days in haemodynamically stable patients [6].

The decision to perform coronary revascularisation needs to be carefully evaluated against the risks of the procedure and the patient's comorbidities, especially in the case of complex coronary lesions [7–11].

Therefore, the identification of really significant NCLs is central to the decision-making process. No one technique fits all patients, but the integration of invasive and non-invasive techniques is currently considered the most rational approach by the interventional cardiology community [12,13].

This short review aims to summarise the management of MVD in patients with STEMI and to provide an overview of the techniques used to guide revascularisation decisions.

2. Treatment of non-culprit lesions

Robust evidence of NCLs treatment in patients with ACS and MVD demonstrated the safety and effectiveness of complete revascularization and its value in reducing the risk of long-term adverse

Received 4 December 2023; revised 16 March 2024; accepted 20 March 2024.
Available online 2 May 2024

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https://doi.org/10.37825/2239-9747.1050

events (Table 1) [14–18]. The Preventive Angioplasty in Myocardial Infarction (PRAMI) trial included 465 patients with STEMI and MVD, who were randomized to immediate angiography-guided multivessel complete revascularization versus culprit-only lesion primary PCI [7]. The study demonstrated the benefit of immediate multivessel PCI with a significant reduction of the composite endpoint including cardiovascular death, non-fatal myocardial infarction or refractory angina at three years follow-up, as compared to culprit-only lesion PCI [14].

Consistently with this study, the Complete versus Lesion-only Primary PCI (CvLPRIT) trial showed a significantly lower risk for the composite of all-cause mortality, recurrent myocardial infarction, heart failure, and ischemia-driven revascularization at one-year follow-up in patients with STEMI and MVD undergoing early angiography-guided complete revascularization compared to culprit-only lesion PCI [15]. Also, the Treatment of Culprit Lesion Only or Complete Revascularization (DANAMI-3 PRIMULTI), the FFR Guided Revascularization Versus Conventional Strategy in Acute STEMI Patients With MVD (COMPARE-ACUTE) and the Complete vs. Culprit-only Revascularization to Treat Multi-vessel Disease After Early PCI for STEMI (COMPLETE) trials demonstrated the benefit of complete revascularization guided by early fractional flow reserve (FFR) or coronary angiography compared to culprit-only lesion primary PCI [16–18].

Abbreviations

ACS	acute coronary syndrome
CCTA	coronary computed tomography angiography
CMR	cardiac magnetic resonance
FFR	fractional flow reserve
IVUS	intravascular ultrasound
MLA	minimal lumen area
MVD	multivessel coronary disease
NCLs	non-culprit lesions
NHPRs	non-hyperaemic pressure ratios
NIRS	near-infrared spectroscopy
NSTEMI	non-ST-segment elevation myocardial infarction
OCT	optical coherence tomography
PCI	percutaneous coronary intervention
STEMI	ST-segment elevation myocardial infarction
TFCA	tin-cap fibroatheroma

The mechanisms underlying the association between NCLs and adverse cardiac events are complex and multifactorial. In the acute phase of STEMI, the release of inflammatory substances promotes instability of NCLs and microcirculatory endothelial damage potentially leading to thrombosis, plaque rupture and myocardial ischemia [19–23]. After the acute phase, NCLs may undergo disease progression, especially in patients with multiple and not optimally controlled cardiovascular risk factors such as diabetes, high cholesterol levels, hypertension, smoking, and chronic kidney disease [24–29].

The optimal timing to complete myocardial revascularization is controversial, since some trials

Table 1. Randomized clinical trials comparing complete revascularization vs. culprit-only lesion revascularization strategies.

Study, years	Sample size	NCLs severity	Primary outcome	Main result
PRAMI, 2013	465	angiographic diameter stenosis >50%	MACE: CV death, non-fatal MI, refractory angina at 23 months FU	Complete multivessel PCI of NCLs was associated with reduced risk of MACE compared to culprit-only PCI
CvLPRIT, 2015	296	Angiography diameter stenosis >70% or >50% in 2 views	MACE: Death, MI, any repeat revascularization, HF at 12 months FU.	Complete multivessel PCI was associated with lower risk of MACE compared to culprit-only PCI
DANAMI-3 PRIMULTI, 2015	627	Angiography diameter stenosis >90% or Angiography diameter stenosis >50% and FFR<0.80	MACE: Death, re-infarction, ischemia-driven revascularization at 27 months FU.	Complete multivessel PCI guided by FFR reduced the risk of MACE compared with no further invasive intervention after primary PCI
COMPARE-ACUTE, 2017	885	Angiography diameter stenosis>50% and FFR<0.80	MACE: Death, non-fatal MI, revascularization, cerebrovascular events at 12 months FU	Complete multivessel PCI guided by FFR reduced the risk of MACE compared to culprit-only PCI
COMPLETE, 2019	4041	Angiography diameter stenosis >70% or angiography diameter stenosis between 50% and 69% and FFR <0.80	Coprimary outcome 1. Composite of CV death and MI 2. Composite of CV death, MI, and ischemia-driven revascularization at 36 months FU	Complete multivessel PCI reduced the risk of both coprimary outcome compared to culprit-only PCI

CV, cardiovascular; FFR, fractional flow reserve; FU, follow-up; HF, heart failure; MI, myocardial infarction; MACE, major adverse cardiac events; MVD, multivessel disease; NCLs, non-culprit lesions; PCI, percutaneous coronary intervention.

treated NCLs during index PCI [14,15] and others planned revascularization in staged procedure [16,18].

The Direct Complete Versus Staged Complete Revascularization in Patients Presenting With Acute Coronary Syndromes and Multivessel Disease (BIOVASC) trial enrolled 764 patients with ACS, who were randomized to immediate vs staged complete multivessel PCI. The study showed that complete revascularisation at index PCI was not inferior to staged PCI in terms of the composite of all-cause mortality, myocardial infarction, any unplanned ischemia-driven revascularization, or cerebrovascular events. Moreover, immediate complete PCI of NCLs was associated with a reduction in myocardial infarction and unplanned ischaemic-driven revascularisation [30].

Consistently with this study, MULTivessel Immediate versus STAged RevaScularization in Acute Myocardial Infarction (MULTISTARS AMI) trial compared the safety and efficacy of immediate vs staged complete revascularisation in haemodynamically stable patients with STEMI and MVD. The results showed that achieving complete revascularisation during index PCI was not inferior to staged PCI in terms of mortality and ischaemic events [31].

3. Invasive assessment

3.1. Coronary physiology

Although previous studies have demonstrated the potential benefit of invasive functional assessment for PCI guidance in patients with stable ischemic heart disease [32,33], this evidence cannot be extended to patients with ACS.

FFR is the most used technique to evaluate the functional severity of coronary lesions during adenosine-induced hyperemia. Non-hyperaemic pressure ratios (NHPRs) provide an alternative method for evaluating the ratio between distal coronary pressure and aortic pressure across coronary lesions during the wave-free period of the resting cardiac cycle without the need for hyperaemic stimuli [34].

In the acute or subacute phase of ACS, the release of inflammatory mediators, distal embolization, vasoconstriction of microcirculation and increased left ventricular tele-diastolic pressure may promote a transient change in coronary physiology and thus affect measurements of both hyperaemic- and non-hyperaemic-based indexes [35–39].

Two randomized clinical trials investigated the role of complete revascularization guided by invasive functional vs angiography strategy in patients with ACS and MVD (Table 2) [38,40].

The FLOW Evaluation to Guide Revascularization in Multi-vessel ST-elevation Myocardial Infarction (FLOWER-MI) trial enrolled 1171 patients with STEMI and MVD, who were randomized to receive complete revascularization guided by FFR or angiography alone. At one-year, complete revascularization guided by FFR did not show significant benefit compared to revascularization guided by angiography alone [38]. However, the unexpected very low rate of adverse events during follow-up makes the results of this study not conclusive [38]. More recently, the Fractional flow reserve versus angiography-guided strategy in acute myocardial infarction with multivessel disease (FRAME-AMI) trial demonstrated a lower risk of the composite of death, myocardial infarction, or repeat revascularization in patients with ACS and MVD undergoing complete revascularization guided by FFR compared to PCI guided by angiography strategy [40].

Therefore, the implementation of physiology to guide PCI decisions of NCLs remains controversial.

3.2. Intravascular imaging

The assessment of NCLs using intravascular imaging techniques can help to identify plaque characteristics associated with a higher risk of rupture including a high percentage of lipids, necrotic core, and thin fibrous cap (tin-cap fibroatheroma, TCFA), in patients with STEMI and MVD (Table 2) [41–43].

Currently, the main catheter-based imaging techniques are: intravascular ultrasound (IVUS), near-infrared spectroscopy (NIRS) and optical coherence tomography (OCT).

IVUS is an intravascular coronary imaging technique based on the use of ultrasounds with high penetration depth, which allows the assessment of the plaque burden and of the minimal lumen area (MLA) [42]. The Providing Regional Observations to Study Predictors of Events in the Coronary Tree (PROSPECT) study enrolled 697 patients with ACS, who underwent three-vessel IVUS for the assessment of NCLs. The authors showed that the presence of plaque burden $\geq$70%, the presence of TCFA and an MLA $\leq$4 mm [2] were independent predictors of adverse events [19].

The assessment of lipid-rich plaques may be facilitated through NIRS, which is an intravascular coronary imaging technique used to estimate the lipid pool extension in coronary lesions [43,44]. In Near-infrared spectroscopy predicts cardiovascular outcome in patients with coronary artery disease

Table 2. Studies providing the invasive and non-invasive assessment of NCLs in patients with multivessel coronary disease.

Study, years	Sample size	NCLs severity	Primary outcome	Main result
Coronary physiology				
FLOWER-MI, 2021	1171	Angiographic diameter stenosis >50% vs Angiography diameter stenosis >50% and FFR<0.80	MACE: Death, non-fatal MI, unplanned hospitalization leading to urgent revascularization at 12 months FU	Complete multivessel PCI guided by FFR did not show significant benefit compared to PCI guided by angiography alone
FRAME-AMI, 2022	562	Angiographic diameter stenosis >50% vs Angiography diameter stenosis >50% and FFR<0.80	MACE: Death, MI and repeat revascularization, at 41 months FU.	Complete multivessel PCI guided by FFR reduced the risk of MACE compared to PCI guided by angiography alone
Intravascular imaging				
PROSPECT, 2011	697	Three-vessel IVUS for the assessment of plaque features	MACE: CV death, cardiac arrest, MI, rehospitalization due to unstable or progressive angina at 36 months FU.	The presence of plaque burden ≥70%, TCFA and an MLA ≤4mm2 were independent predictors of MACE
ATHEROREMO-NIRS, 2014	203	NIRS for the assessment of lipid-rich plaques	MACE: Death, non-fatal MI, stroke, unplanned coronary revascularization at 12 months FU	The presence of lipid-rich plaques was associated with higher risk of MACE
CLIMA, 2020	1003	OCT for the assessment of plaque features	MACE: cardiac death and target segment myocardial infarction at 12 months FU	MLA<3.5 mm^2, fibrous cap thickness <75 μm, lipid arc circumferential extension>180, and macrophage infiltration were associated with a higher risk of MACE
COMBINE OCT-FFR, 2021	550	OCT detected TCFA in diabetes patients with negative FFR value	MACE: CV death, target vessel MI, clinically driven target lesion revascularization or hospitalization due to unstable or progressive angina at 18 months	The presence of TCFA was associated with higher risk of MACE
Non-invasive diagnostic tools				
PROMISE, 2018	4415	CCTA for the assessment of high-risk plaque features	MACE: death, myocardial infarction, or unstable angina at 25 months	Positive remodelling, low computed tomographic attenuation, or napkin-ring sign were associated with a higher risk of MACE
REDUCE-MVI sub-study, 2020	77	Stress perfusion CMR with adenosine Vs FFR<0.80	The agreement between CMR and invasive FFR in the assessment of NCLs at 1 month	The diagnostic performance of CMR was moderate when compared to invasive FFR assessment

CCTA, coronary computed tomography angiography; CMR, cardiac magnetic resonance; CV, cardiovascular; FFR, fractional flow reserve; FU, follow-up; IVUS, intravascular ultrasound; MI, myocardial infarction; MACE, major adverse cardiac events; MLA, minimal lumen area; MVD, multivessel disease; NCLs, non-culprit lesions; OCT, Optical coherence tomography; PCI, percutaneous coronary intervention; TFCA, tin-cap fibroatheroma.

(ATHEROREMO-NIRS) study, lipid-rich plaques were associated with cardiovascular adverse events during follow-up [44]. More recently, NIRS has been implemented in IVUS catheters to evaluate simultaneously the plaque burden and its lipid percentage [43]. Indeed, the high percentage of lipid in coronary lesion and the high plaque burden has been associated with a significantly higher risk of adverse cardiac events [43].

Optical coherence tomography (OCT) is characterized by higher spatial resolution and allows a more accurate estimation of the thickness of TCFA and the detection of plaque components [45]. In the Relationship between coronary plaque morphology of the left anterior descending artery and 12 months clinical outcome (CLIMA) study, the authors investigated the predictive value of specific plaque features identified by OCT. Among 1776 coronary

lesions, the presence of MLA<3.5 mm^2, fibrous cap thickness <75 μm, lipid arc circumferential extension>180, and macrophage infiltration were associated with a higher risk of cardiovascular events [46]. Also, in the Thin-cap fibroatheroma predicts clinical events in diabetic patients with normal fractional flow reserve (COMBINE OCT-FFR) trial, the presence of TCFA was associated with poor outcome in diabetic patients with negative FFR [47].

Therefore, intravascular imaging may help to identify characteristics of plaque vulnerability in NCLs and may improve the prognostic stratification in patients with STEMI and MVD. However, the optimal revascularization strategy for patients with vulnerable NCLs remains to be determined.

4. Non-invasive assessment

The timing and the modality for non-invasive evaluation of residual ischemia in patients with NCLs and recent STEMI is still a matter of debate and depends largely on the local availability and expertise [6].

In addition, coronary computed tomography angiography (CCTA) may be implemented to identify specific features of atherosclerotic plaques such as low-attenuation plaque, napkin-ring sign, positive remodeling and spotty plaque calcification, which are associated with a higher risk of further adverse events (Table 2) [48–51]. Ferencik and colleagues, in a secondary analysis of the PROMISE trial including 4415 patients, showed that high-risk plaques as defined by CCTA were associated with cardiovascular adverse events during follow-up. However, the study showed a low positive predictive value for CCTA which limits its clinical perspectives [52].

Currently, CCTA has been combined with computational fluid dynamics technologies to evaluate simultaneously both anatomical features and functional information of atherosclerotic plaques [53,54].

Lee et al. evaluated the prognostic significance of non-invasive hemodynamic parameters using CCTA in patients with NCLs and recent ACS. The study suggested that integrating non-invasive haemodynamic information with anatomical plaque characterization may improve the identification of NCLs with the highest risk of adverse events [55]. However, the diagnostic accuracy of non-invasive hemodynamic parameters by CCTA for detecting residual ischemia in patients with NCLs and recent ACS was only modest when compared to invasive physiology techniques [56].

Cardiac magnetic resonance (CMR) is another non-invasive imaging modality that allows simultaneous assessment of left ventricular morphology and function, tissue characterization, and stress myocardial perfusion [57,58].

A recent sub-study from the Reducing Micro Vascular Dysfunction in Acute Myocardial Infarction by Ticagrelor (REDUCE-MVI) trial including 77 patients demonstrated the usefulness of stress perfusion CMR with adenosine for detecting residual ischemia in patients with NCLs and recent ACS. However, the diagnostic performance of this non-invasive technique was moderate when compared to invasive FFR assessment at one month (Table 2) [59].

Currently, the main limitation to the implementation of non-invasive diagnostic tools for the assessment of NCLs in patients with recent STEMI is the modest positive predictive value for the identification of lesions associated with a higher risk of future adverse events compared to invasive techniques [56,59]. However, these methods are virtually risk-free and have the potential to avoid invasive examinations in patients with non-significant NCLs who do not require further coronary revascularization.

Future studies will determine whether non-invasive methods can be employed to guide the decision-making in STEMI patients with MVD.

5. Future perspectives

Currently, the optimal strategy for defining the anatomical and hemodynamic significance of NCLs to guide complete revascularisation decisions in patients with STEMI and coexisting NCLs remains to be determined.

Currently, the application of invasive physiology measurements to guide decisions on PCI of NCLs remains controversial. Therefore, the Physiology-guided vs Angiography-guided Non-culprit Lesion Complete Revascularization for Acute MI & Multivessel Disease (COMPLETE-2) study, a phase 3 trial, will investigate the prognostic role of physiology-guided complete revascularization compared to conventional angiography strategy in patients with MVD and recent ACS.

The Preventive PCI or medical therapy alone for vulnerable atherosclerotic coronary plaque (PREVENT) study will investigate the prognostic impact of preventive PCI in patients with high-risk plaque features quantified by intravascular imaging and negative value of FFR (FFR >0.80), compared to medical therapy alone.

6. Conclusions

In patients with STEMI, the prevalence of MVD is high and modern evidence supports the complete revascularization strategy during the index PCI procedure or at least within the first month to improve the patients' short- and long-term outcomes [6].

What is the best invasive or non-invasive modality for assessing the clinical relevance of NCLs remains an open question. In daily practice, the assessment of patients' comorbidities, hemodynamic status and coronary anatomy, together with the experience of the individual center in percutaneous treatment of complex lesions, directs patients toward dedicated pathways of clinical management.

Further evidence from large randomized trials is needed to establish a standardized approach in this complex clinical scenario.

Sources of funding

None.

Disclosure

None.

Conflicts of interest

The authors declare no conflict of interest.

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