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Timing and completeness of revascularisation in acute coronary syndromes

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INTRODUCTION

Acute coronary syndrome (ACS) represents one of the primary causes of mortality and loss of disability-adjusted life years worldwide despite recent pharmacological and technological innovations.¹ Percutaneous coronary intervention (PCI) of the culprit vessel remains the standard of care for patients presenting with ACS.¹ Nevertheless, multivessel coronary disease is found in up to 60% of patients presenting with ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation acute coronary syndrome (NSTEMI), and is associated with worse clinical outcomes and increased mortality.²

The optimal timing to undergo coronary angiography and the best strategy for treatment of non-culprit lesions have been subject to controversies for the past two decades and are yet to be determined. Therefore, the aim of this article was to provide a practical overview on available evidence on timing and completeness of revascularisation in patients presenting with ACS.

PATIENTS PRESENTING WITH NSTEMI

Invasive coronary angiography plays a pivotal role in the management of patients presenting with NSTEMI.¹ Invasive coronary angiography allows (1) confirmation of the diagnosis, (2) identification of the culprit lesion and (3) establishment of the optimal myocardial revascularisation modality. Culprit lesions can be identified by the presence of morphological features suggestive of plaque rupture, such as intraluminal fillings associated with thrombus, plaque ulcerations, plaque irregularities and dissections.³ In case of diagnostic uncertainty, intracoronary imaging may facilitate the identification of hallmarks of the culprit lesion (ie, luminal discontinuity, plaque disruption and presence of thrombus) (figure 1).⁴

When to revascularise patients presenting with NSTEMI

A routine invasive strategy has been shown to improve clinical outcomes (refractory angina and late myocardial infarction), reduce recurrent ACS and rehospitalisations as compared with a selective invasive strategy (ie, undergoing coronary angiography in case of recurrent symptoms, evidence of ischaemia or obstructive coronary artery disease with non-invasive imaging techniques).^{5,6} In addition, a trend towards a decreased mortality associated with an early invasive strategy has been shown in an individual patient data meta-analysis.⁷ This benefit was more pronounced in patients with elevated cardiac biomarkers, diabetes, a Global

Learning objectives

- ▶ To discuss the most appropriate timing of invasive angiography and culprit-lesion revascularisation in patients presenting with acute coronary syndrome (ACS).
- ▶ To summarise the indication to revascularise non-culprit lesions in patients with ACS with multivessel disease.
- ▶ To evaluate the most appropriate strategy and timing for complete revascularisation in patients with ACS with multivessel disease.

Registry of Acute Coronary Events risk score of >140 and an age of 75 years or older.⁷ However, a routine invasive strategy, compared with a selective invasive strategy, has been shown to increase the risk of periprocedural myocardial infarction and bleeding.⁶ These findings should be interpreted with caution in the context of contemporary increasing use of transradial access, as more recent meta-analyses have not shown an increased bleeding risk with an invasive strategy as compared with a selective invasive approach.⁸ In addition, the differentiation between the evolution of the index myocardial infarction and a periprocedural ischaemic complication is very difficult if not impossible. Periprocedural myocardial infarction has not been consistently defined across the included studies and its clinical impact is of debatable relevance, depending on the considered definition.

Against this background, a routine invasive strategy is recommended in patients with an established diagnosis of NSTEMI with a timing based on individual risk stratification, as summarised in figure 2 and table 1.⁹ Whereas, a selective invasive strategy or non-invasive imaging to guide invasive coronary angiography should be limited to low-risk patients (ie, patients with low-to-intermediate likelihood of coronary artery disease, normal or inconclusive cardiac troponin and/or ECG) (figure 2).⁹

The recently published European Guidelines for the management of patients with NSTEMI have established a class I level A indication to undergo coronary angiography within 24 hours of hospital admission to high-risk patients presenting with NSTEMI.⁹ Despite the 24-hour benchmark might seem arbitrary (as different studies have included a different interval time to define early invasive strategy), when assessing the relationship between median difference in time to angiography and clinical outcomes, a significant association in post hoc metaregression with regard to non-fatal myocardial infarction was found in the individual patient data

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Figure 1 Role of intracoronary imaging to define the plaque aetiology during non-ST-segment elevation acute coronary syndrome in patients with angiographically intermediate lesions. **Intraluminal thrombus with high signal attenuation.

meta-analysis performed by Jobs *et al.*⁷ This might imply that an early-as-possible rather than a <24-hour approach could represent the best strategy, easing the pressure on the infrastructure. However, baseline risk assessment remains the key, as benefit with an early invasive strategy is strongly associated with patient's risk profile.

Should we perform a complete revascularisation in patients presenting with NSTEMACS and multivessel disease?

Completeness of revascularisation can be determined either on an anatomical (ie, successful revascularisation of all lesions of $\geq 50\%$ diameter stenosis) or functional basis (ie, successful revascularisation of all lesions determining myocardial ischaemia in invasive or non-invasive diagnostic tests). In the AUCITY trial, patients with NSTEMACS with a residual SYNTAX score of ≥ 9 were associated with higher rates of major adverse cardiac event (MACE) and death at 1 year compared with patients with complete anatomical revascularisation (22.4% vs 16.3%; $p < 0.001$ and 4.8% vs 1.4%; $p < 0.001$, respectively).¹⁰ However, whether multivessel PCI offers incremental benefit over culprit-only PCI for patients presenting with NSTEMACS and multivessel disease is unclear as data come only from observational studies. A recent observational cohort study, including 21 857 patients with NSTEMACS and multivessel disease, has shown that single-stage complete revascularisation reduced the risk of all-cause mortality compared with culprit-only vessel PCI (adjusted HR=0.90, 95% CI 0.85 to 0.97) at a median follow-up of 4.1 years.¹¹ Ongoing large-scale randomised clinical trials will provide further evidence about the clinical impact of complete

revascularisation in patients with NSTEMACS with multivessel disease (table 2).

Coronary artery bypass grafting represents another revascularisation alternative for patients presenting with NSTEMACS. However, there are no randomised data comparing PCI to coronary artery bypass grafting in this clinical setting. Therefore, current European Society of Cardiology (ESC) guidelines recommend to apply, in stabilised patients with NSTEMACS, the same criteria to guide the choice of revascularisation modality as in patients presenting with chronic coronary syndromes.⁹

Based on this, reasonable incomplete revascularisation (ie, revascularisation of all haemodynamically significant flow-limiting lesions without revascularisation of lesions with $\geq 50\%$ diameter stenosis in the absence of ischaemia on invasive or non-invasive tests) in patients presenting with NSTEMACS should be attempted tailoring the need, strategy and timing on patient's comorbidities, coronary anatomy and lesion functional evaluation (figure 2).⁹

When should we complete the revascularisation in patients presenting with NSTEMACS and multivessel disease?

The only randomised clinical trial assessing the best timing to complete the revascularisation in patients with NSTEMACS with multivessel disease has been the SMILE trial.¹² Patients were randomised in a 1:1 fashion to complete revascularisation during a single procedure or to culprit lesion-only revascularisation, followed by revascularisation of the remaining lesions during the index hospitalisation. Single-stage revascularisation was associated with lower rates of major adverse cardiovascular and

Figure 2 Timing and revascularisation strategy in patients presenting with NSTEMACS. *It is reasonable to consider a physiology-guided strategy to complete revascularisation in patients with NSTEMACS with multivessel disease. NSTEMACS, non-ST-segment elevation acute coronary syndrome; NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention.

cerebrovascular events—that is, a composite of cardiac death, death, reinfarction, rehospitalisation for unstable angina, repeat coronary revascularisation and stroke—at 1-year follow-up (HR 0.549, 95% CI 0.363 to 0.828, $p=0.004$), mainly driven by higher rates of target vessel revascularisation in the multistage group. Given the lack of robust

data, a single-stage revascularisation seems reasonable in patients with good clinical conditions, low-intermediate coronary anatomy complexity (ie, lack of chronic total occlusions (CTOs), severely calcified lesions and bifurcations requiring ≥ 2 stents) and haemodynamic stability (ie, mechanical haemodynamic support not required upfront) (figure 2).

Table 1 Risk stratification of patients presenting with NSTEMACS

Very high risk	High risk	Low risk
Cardiogenic shock	Established NSTEMACS diagnosis	None of the previous characteristics
Haemodynamic instability	Dynamic new contiguous ST/T-segment changes	
Acute heart failure related to NSTEMACS	Resuscitated cardiac arrest without ST-segment elevation or cardiogenic shock	
Mechanical complication of MI	GRACE risk score >140	
Life-threatening arrhythmias		
Recurrent/refractory chest pain		
ST-segment depression >1 mm/6 leads plus ST-segment elevation aVr and/or V1		

GRACE, Global Registry of Acute Coronary Events; MI, myocardial infarction; NSTEMACS, non-ST-segment acute coronary syndrome.

Table 2 Selected ongoing trials evaluating the timing, completeness and revascularisation strategies in patients presenting with ACS

Study	NCT number	Design	Clinical setting	Treatment group	Control group	Primary outcome	Included patients (N)	Completion date*
BIOVASC	03621501	Multicentre open-label non-inferiority RCT	Patients with STEMI and NSTEMI with MVD	Immediate complete revascularisation (angiography/physiology guided)	Staged complete revascularisation (angiography/physiology guided)	All-cause death, MI, unplanned ischaemia-driven revascularisation and cerebrovascular events	1525	2021
FIRE	03772743	Multicenter prospective open-label RCT	Patients with STEMI and NSTEMI MVD aged ≥ 75 years	Functional complete revascularisation	IRA-only revascularisation	All-cause death, any MI, stroke or coronary revascularisation	1385	2021
FULL-REVASC	02862119	Multicentre prospective open-label RCT	STEMI/very high-risk NSTEMI with MVD	FFR-guided complete revascularisation during index hospital admission	Conservative management of non-culprit lesions during index hospital admission	All-cause death and MI	4052	2021
IMODERN	03298659	Multicentre prospective open-label RCT	Patients with STEMI with MVD	Immediate iFR-guided complete revascularisation	Deferred stress perfusion CMR-guided revascularisation	All-cause death, MI and hospitalisation for HF	1146	2021
OPTION STEMI	04626882	Multicentre prospective open-label RCT	Patients with STEMI with MVD	Immediate FFR revascularisation of non-IRA lesions with diameter stenosis 50%–70% by visual estimation†	In-hospital FFR revascularisation of non-IRA lesions with diameter stenosis 50%–70% by visual estimation†	All-cause death, MI or unplanned revascularisation	784	2024
Quantitative fractional ratio-guided revascularisation	04259853	Multicenter prospective RCT	Patients with STEMI with MVD	QFR-guided complete revascularisation	Angiography-guided complete revascularisation	All-cause death, MI, any revascularisation, hospitalisation for HF, stroke or major bleeding	1016	2022
RAPID-NSTEMI	03707314	Multicentre prospective open-label RCT	High-risk patients with NSTEMI	Immediate angiography	Standard of care angiography	All-cause death, MI and admission for HF	2314	2021
SAFE STEMI for Seniors	02939976	Multicentre prospective unblinded RCT	Patients with STEMI aged ≥ 60 years	iFR-guided complete revascularisation	IRA-only revascularisation	CvLPRIT-MACE‡ Infarct-related artery MACE§	875	2024
ISENIOR-RITA	03052036	Multicentre prospective open-label RCT	Patients with type I NSTEMI aged ≥ 75 years	Invasive angiography and coronary revascularisation	Optimal medical therapy	CV death or non-fatal MI	1668	2022
SLIM	03562572	Multicentre prospective RCT	Patients with NSTEMI with MVD	Immediate FFR-guided complete revascularisation	Usual care non-IRA lesions by discretion of the physician	All-cause death, MI, any revascularisation and stroke	414	2021

*Estimated primary completion date.

†Non-IRA lesion which have $\geq 70\%$ diameter stenosis by visual estimation will be revascularised without FFR evaluation.

‡CvLPRIT MACE: all-cause mortality, recurrent MI, heart failure (requiring hospitalisation or 12-hour emergency room visit) or ischaemia-driven revascularisation for all treated arteries.

§Infarct-related artery MACE: cardiac death, infarct artery target-vessel MI, or ischaemia-driven index infarct-related vessel revascularisation by percutaneous or surgical methods.

CMR, cardiovascular magnetic resonance; CV, cardiovascular; CvLPRIT, Complete Versus Lesion-Only Primary PCI Trial; FFR, fractional flow reserve; HF, heart failure; iFR, instantaneous wave-free ratio; IRA, infarct-related artery; MACE, major adverse cardiac event; MI, myocardial infarction; MVD, multivessel disease; NCT, National Clinical Trial; NSTEMI, non-ST-segment elevation acute coronary syndrome; RCT, randomised controlled trial; STEMI, ST-segment elevation myocardial infarction.

However, large dedicated randomised clinical trials are required to add further knowledge on the best timing to complete the revascularisation in patients with NSTEMACS (table 2).

How should we guide the revascularisation strategy in patients presenting with NSTEMACS and multivessel disease?

A personalised approach for revascularisation of patients with NSTEMACS with physiological assessment of non-culprit lesions might represent the cornerstone to improve clinical outcomes. However, evidence is scarce and mainly coming from subgroup analyses of registries and randomised clinical trials, as powered dedicated randomised trials have not yet been published (table 2). In a subgroup analysis of the FAME trial, which included 328 patients with unstable angina or NSTEMACS, the use of fractional flow reserve (FFR) to guide PCI in multivessel disease resulted in an absolute MACE risk reduction of 5.1% compared with an angiography guidance. Of note, none of the myocardial infarctions at follow-up in the FFR-guided group occurred on previously deferred lesions.¹³ The FAMOUS-NSTEMI trial randomised 350 patients with NSTEMACS with ≥ 1 coronary stenosis of $\geq 30\%$ of the lumen diameter assessed visually to undergo FFR-guided or angiography-guided coronary revascularisation. An angiography-guided strategy resulted in higher rates of coronary revascularisation without any impact on clinical outcomes at 12-month follow-up.¹⁴

A physiology-guided strategy leads to the use of fewer coronary stents, shorter procedural times, reduced amount of contrast and similar overall healthcare costs during the index hospitalisation.¹⁴ The reduced number of implanted stents has the potential to decrease the rates of periprocedural and long-term complications (ie, periprocedural myocardial infarction, acute kidney injury and stent thrombosis) which have a negative prognostic impact, especially in elderly patients.^{15–17} In addition, the presence of a residual angiographically assessed burden of coronary artery disease after physiology-guided complete PCI has shown to have no impact on prognosis in patients presenting with ACS and multivessel disease.¹⁸ Therefore, it is reasonable to consider a physiology-guided strategy to complete revascularisation in patients with NSTEMACS with multivessel disease (figure 2).

PATIENTS PRESENTING WITH STEMI

Despite progressive improvements in reperfusion therapy strategies, antithrombotic drugs and secondary prevention during the past four decades, in-hospital mortality following STEMI remains substantial—ranging from 4% to 12% among different registries.¹⁹ Emergency medical system-based STEMI networks are pivotal to shorten ischaemia time, maximise efficiency and improve patients' clinical outcomes.

When to revascularise patients presenting with STEMI

Primary PCI remains the gold-standard reperfusion strategy in patients with STEMI within 12 hours from symptom onset. However, if time from STEMI diagnosis to mechanical reperfusion is expected to be ≥ 120 min, fibrinolysis followed by coronary angiography within 24 hours is recommended.²⁰ Data supporting the extent to which PCI-related time delay diminishes the advantages of PCI over fibrinolysis must be interpreted with caution, as they mainly come from post hoc analyses. In the most recent STREAM trial, 1892 patients who presented with early STEMI (within 3 hours from symptoms onset) and were unable to undergo primary PCI within 1 hour were randomised to undergo either primary PCI or fibrinolytic therapy followed by early angiography. No significant differences in clinical outcomes were shown between both strategies. However, the rate of intracranial haemorrhage in the fibrinolysis group was five times higher than in the primary PCI group (1.0% vs 0.2%, $p=0.04$).²¹ In patients with time from symptom onset of >12 hours but <48 hours, routine primary PCI should be considered despite evidence supporting this strategy is limited. The BRAVE-2 trial randomised 365 patients with STEMI who were assessed between 12 and 48 hours from symptom onset to undergo PCI or conservative management. At 4-year follow-up, mortality in the PCI group was lower than in the conservative arm (adjusted HR 0.55, 95% CI 0.31 to 0.97, $p=0.04$).²² However, the trial was not powerful to demonstrate a difference in mortality. Conversely, in patients presenting >48 hours after symptom onset, routine PCI should not be performed unless there is clinical or electrocardiographic evidence of ongoing ischaemia (figure 3).²⁰

Should we complete the revascularisation in patients presenting with STEMI and multivessel disease?

Individual randomised clinical trials comparing complete versus culprit-only PCI in patients with STEMI with multivessel disease have shown a reduction in unplanned revascularisation with a strategy of complete revascularisation after primary PCI.²³ Some trials have also demonstrated a reduction in myocardial infarction.^{24–25} However, none of the individual trials were adequately powered to detect reductions in mortality and current ESC guidelines assigned a IIa class level A recommendation to complete the revascularisation in patients with STEMI with multivessel disease.¹ Nevertheless, recently published meta-analyses performed after publication of the COMPLETE trial, have shown a reduction in the risk of cardiovascular death favouring a complete revascularisation strategy.^{26–28} This advantage is mechanistically explained by a significant reduction in the risk of myocardial infarction.

Based on this evidence, a full revascularisation should be attempted in patients with STEMI with

Figure 3 Timing and revascularisation strategy in patients presenting with STEMI. *Selective PCI is indicated in case of clinical and/or electrocardiographic evidence of ischaemia. **Either a functional or angiography-derived evaluation on non-culprit lesions can be performed to complete revascularisation. STEMI, ST-elevation myocardial infarction; PCI, percutaneous coronary intervention.

multivessel disease, given the favourable prognosis impact (figure 3). However, up to 15% of patients presenting with STEMI have a concurrent CTO. These patients have usually been excluded from randomised clinical trials or, as in the COMPLETE trial, CTO PCI (which only represented the 2%) has been performed by expert operators only when there was a high likelihood of success.^{23 24 29} The EXPLORE trial is the only study so far evaluating the impact of CTO PCI of a non-infarct-related artery after primary PCI. A total of 304 patients were randomised to early PCI of the CTO (within 1 week) or conservative treatment. Procedural success rate was only 73%, and at 4-month follow-up, no differences were found between groups for coprimary outcomes: mean left ventricular ejection fraction ($44.1\% \pm 12.2\%$ vs $44.8 \pm 11.9\%$, $p=0.6$) and left ventricular end-diastolic volume (215.6 ± 62.5 mL in the CTO PCI arm vs 212.8 ± 60.3 mL in the no-CTO PCI arm, $p=0.70$).³⁰ Although patients who underwent PCI of left anterior descending coronary artery CTO had significantly higher ejection fractions compared with those patients who were treated with medical therapy alone.

When should we complete the revascularisation in patients presenting with STEMI and multivessel disease?

Complete revascularisation can be achieved either at the time of primary PCI or during a staged procedure, which can be planned during the index hospitalisation or during a new hospitalisation after hospital discharge.

In the COMPLETE trial, the largest randomised trial evaluating complete versus culprit-only revascularisation in patients with STEMI, recurrent events were reduced with a complete revascularisation during long-term follow-up. The benefit of complete revascularisation on cardiovascular death or myocardial infarction was consistent, irrespective of PCI of the non-culprit lesion was performed during index hospitalisation (median time 1 day; HR 0.77, 95% CI 0.59 to 1.00) or after hospital discharge (median time 23 days; HR 0.69, 95% CI 0.49 to 0.97, interaction $p=0.62$). In addition, the benefit of complete revascularisation on hard clinical outcomes emerged over the long term as shown at landmark analysis: HR of 0.86 (95% CI 0.59 to 1.24) during the first 45 days and 0.69 (95% CI 0.54 to 0.89) from 45 days to the end of follow-up for intended non-culprit lesion PCI versus culprit-only PCI.³¹ These findings underscore the concept that early events after STEMI are more related to the culprit lesion than to the non-culprit lesions and that the benefit of complete revascularisation accrues mainly over time; prevailing the importance of completing the revascularisation irrespective of the timing (in-hospital vs post-discharge).

PCI of non-culprit lesions during primary PCI represents another alternative strategy in patients with STEMI with multivessel disease. Notwithstanding, this strategy might be associated with an increased risk of (1) overestimation of the angiographical severity of non-infarct-related artery due to heightened vascular tone and (2) contrast nephropathy due to higher contrast volume use.^{32 33} Therefore, multivessel

revascularisation during primary PCI should be only considered in the presence of multiple highly unstable lesions with angiographical signs of possible thrombus or lesion disruption, and in case of persistent signs and symptoms of ischaemia after culprit-lesion PCI (figure 3).¹

Insights into the best timing to complete the revascularisation in patients with STEMI with multivessel disease will be provided by ongoing randomised clinical trials (table 2)

How should we guide the revascularisation in patients presenting with STEMI and multivessel disease?

Although the majority of patients with STEMI included in trials evaluating the impact of complete revascularisation on clinical outcomes have undergone an angio-guided revascularisation strategy, a physiology-guided revascularisation of non-culprit lesions in patients with STEMI with multivessel disease has been shown effective and safe.^{23 29}

The DANAMI-3-PRIMULTI study randomised 627 patients with STEMI and multivessel disease to culprit lesion only PCI versus FFR-guided complete revascularisation. At a median follow-up of 27 months, the primary endpoint (a composite of all-cause mortality, non-fatal reinfarction and ischaemia-driven revascularisation) occurred more frequently in the culprit-only PCI group (HR 0.56, 95%CI 0.38 to 0.83, $p=0.004$).²⁹ The Compare-Acute trial has also demonstrated the benefit of an FFR-guided complete revascularisation strategy, as compared with a culprit-only PCI approach in reducing a composite endpoint of all-cause mortality, non-fatal myocardial infarction, any revascularisation and stroke (HR 0.46, 95%CI 0.33 to 0.64, $p<0.001$) in patients with STEMI and multivessel disease. Moreover, a cost analysis of the aforementioned trial has shown a benefit of the FFR-guided complete revascularisation strategy, which can reduce the cost per patient by up to 21% at 1 year (€8150€ vs €10 319) and by 22% at 3 years (€8653 vs €11 100) as compared with a culprit-only PCI strategy.³⁴

The recently published FLOWER-MI clinical trial randomised 1171 patients with STEMI and multivessel disease to complete revascularisation guided by FFR or angiography. At 1-year follow-up, the primary outcome (a composite of death from any cause, non-fatal myocardial infarction or unplanned hospitalisation leading to urgent revascularisation) occurred in 5.5% in the FFR-guided group and in 4.2% in the angio-guided group (HR 1.32, 95%CI 0.78 to 2.23, $p=0.31$), showing that an FFR-guided strategy as compared with an angio-guided was not superior in reducing the risk of the primary endpoint. Although no statistically significant differences for individual components of the primary endpoint were found between groups, a numerically higher rate of non-fatal myocardial infarction (3.1% vs 1.7%, HR 1.77, 95%CI 0.82 to 3.84) and urgent revascularisation (2.6% vs 1.9%, HR 1.34, 95%CI 0.62 to 2.92) was found in the FFR-guided group.³⁵ Insights for these findings

might be found in a substudy of the REDUCE-MVI randomised clinical trial that included 73 patients with STEMI who, after successful primary PCI, non-culprit intracoronary haemodynamic assessment was performed and repeated at 1-month follow-up. Instantaneous wave-free ratio did not change significantly between the acute phase and 1-month follow-up (mean 0.93 (SD 0.07) vs mean 0.94 (SD 0.06), $p=0.12$), whereas FFR decreased significantly (mean 0.88 (SD 0.07) vs mean 0.86 (SD 0.09), $p=0.001$) and coronary flow reserve increased significantly (mean 2.9 (SD 1.4) vs mean 4.1 (SD 2.2), $p<0.001$).³⁶ These results might be explained by an increased hyperemic microvascular resistance and a blunted adenosine responsiveness during the acute phase, associated with infarct size.

Both an angio-guided and a physiology-guided approach are suitable to complete revascularisation in patients presenting with STEMI and multivessel disease (figure 3). Further evidence about the clinical impact of different revascularisation strategies in patients with STEMI with multivessel disease will be provided by a great number of ongoing randomised clinical trials (table 2).

Finally, the role of intracoronary imaging has been recently assessed in the COMPLETE-OCT substudy where 93 patients randomised to non-culprit PCI were included with the aim to determine the prevalence of thin-cap fibroatheroma by OCT (the primary morphology feature defining a vulnerable plaque). Obstructive lesions (defined as those with >70% diameter stenosis by visual estimation) more commonly contained vulnerable plaque morphology compared with non-obstructive lesions (35.4% vs 23.2%, $p=0.022$), with about 47% of patients having at least one obstructive non-culprit lesion thin-cap fibroatheroma.³⁷ These findings highlight the increased frequency of vulnerable plaques in patients with STEMI and hint at the future need to use intracoronary imaging to guide the revascularisation of non-culprit lesions in patients with STEMI with multivessel disease.

PATIENTS PRESENTING WITH CARDIOGENIC SHOCK

Emergency revascularisation has been shown to reduce mortality in patients with ACS complicated with cardiogenic shock.¹ However, one out of three patients does not survive to hospital discharge.³⁸ The best strategy to treat non-culprit lesions, present in up to 80% of patients with cardiogenic shock, has been subject to controversies during the past years. The CULPRIT-SHOCK trial randomised 706 patients with acute myocardial infarction and cardiogenic shock to undergo culprit-only PCI or immediate multivessel PCI. In the multivessel PCI group, complete revascularisation was achieved in 81% of patients. Cross-over rates between groups was 12.5% in the culprit lesion-only PCI and 9.4% in the multivessel PCI arm. Patients allocated to the culprit lesion-only PCI group showed lower rates of the primary endpoint (ie, a composite of death or renal replacement) at 30 days (45.9% vs 55.4%,

$p=0.01$). In addition, a post hoc landmark analysis revealed a difference between the two groups in mortality within the first 30 days (relative risk, 0.84; 95% CI, 0.72 to 0.98), but mortality was similar in the two groups thereafter (relative risk 1.08, 95% CI 0.60 to 1.93).³⁹

Therefore, in patients with cardiogenic shock and multivessel disease, PCI should be confined to the culprit lesion in the acute emergency setting, whereas revascularisation of significant additional lesions to achieve complete (anatomical or ischaemic) revascularisation in a staged procedure after haemodynamic stabilisation is a reasonable strategy.

CONCLUSIONS

Patients presenting with ACS and multivessel disease have worse clinical outcomes and increased mortality compared with patients with a single-vessel

disease. The optimal timing and best strategy to complete the revascularisation of non-culprit lesions remain controversial. In patients presenting with NSTEMI and STEMI, a complete revascularisation of non-culprit lesions should be the strategy of choice, either during the index hospitalisation or early after hospital discharge, depending on individual patients' risk profiles and physicians' preferences, whereas in patients with cardiogenic shock, PCI should be limited to the culprit-lesion during the acute emergency setting, eventually completing the revascularisation after clinical stabilisation.

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REFERENCES

- 1 Neumann F-J, Sousa-Uva M, Ahlsson A. ESC/EACTS guidelines on myocardial revascularization. *EuroIntervention* 2018;2019:1435–534.
- 2 Sorajja P, Gersh BJ, Cox DA, et al. Impact of multivessel disease on reperfusion success and clinical outcomes in patients undergoing primary percutaneous coronary intervention for acute myocardial infarction. *Eur Heart J* 2007;28:1709–16.
- 3 Goldstein JA, Demetriou D, Grines CL, et al. Multiple complex coronary plaques in patients with acute myocardial infarction. *N Engl J Med* 2000;343:915–22.
- 4 Johnson TW, Räber L, di Mario C, et al. Clinical use of intracoronary imaging. Part 2: acute coronary syndromes, ambiguous coronary angiography findings, and guiding interventional decision-making: an expert consensus document of the European Association of Percutaneous Cardiovascular Interventions. *Eur Heart J* 2019;40:2566–84.
- 5 Katritsis DG, Siontis GCM, Kastrati A, et al. Optimal timing of coronary angiography and potential intervention in non-ST-elevation acute coronary syndromes. *Eur Heart J* 2011;32:32–40.
- 6 Fanning JP, Nyong J, Scott IA, et al. Routine invasive strategies versus selective invasive strategies for unstable angina and non-ST elevation myocardial infarction in the stent era. *Cochrane Database Syst Rev* 2016;CD004815.
- 7 Jobs A, Mehta SR, Montalescot G, et al. Optimal timing of an invasive strategy in patients with non-ST-elevation acute coronary syndrome: a meta-analysis of randomised trials. *Lancet* 2017;390:737–46.

Key messages

Patients presenting with non-ST-segment elevation acute coronary syndrome (NSTEMI)

- In high-risk patients presenting with NSTEMI, coronary angiography should be performed as soon as possible, within 24 hours from hospital admission.
- Revascularisation of non-culprit lesion in patients with NSTEMI should be attempted either during acute procedure (in stable and low-anatomical complexity patients), during the index hospitalisation or after hospital discharge.
- It is reasonable to consider a physiology-guided revascularisation of non-culprit lesions in patients with NSTEMI with multivessel disease.

Patients presenting with ST-segment elevation myocardial infarction (STEMI)

- Percutaneous coronary intervention (PCI) of the culprit lesion in patients with STEMI must be performed as soon as possible in patients presenting within 48 hours from symptoms onset.
- In patients with STEMI presenting >48 hours after symptoms onset, PCI should be performed in case of clinical and/or electrocardiographic evidence of ischaemia.
- Revascularisation of non-culprit lesion in patients with STEMI should be attempted either during the index hospitalisation or early after hospital discharge.
- Both angio-guided and physiology-guided strategies are suitable to complete revascularisation in patients presenting with STEMI and multivessel disease.

Patients presenting with cardiogenic shock

- In patients with acute coronary syndrome complicated with cardiogenic shock, PCI should be confined to the culprit lesion in the acute emergency setting.

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- 8 Bonello L, Laine M, Puymirat E, *et al.* Timing of Coronary Invasive Strategy in Non-ST-Segment Elevation Acute Coronary Syndromes and Clinical Outcomes: An Updated Meta-Analysis. *JACC Cardiovasc Interv* 2016;9:2267–76.
- *9 Collet J-P, Thiele H, Barbato E. ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: The Task Force for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J* 2020 (Published Online First: August 2020).
- 10 Généreux P, Palmerini T, Caixeta A, *et al.* Quantification and impact of untreated coronary artery disease after percutaneous coronary intervention: the residual SYNTAX (synergy between PCI with taxus and cardiac surgery) score. *J Am Coll Cardiol* 2012;59:2165–74.
- 11 Rathod KS, Koganti S, Jain AK, *et al.* Complete Versus Culprit-Only Lesion Intervention in Patients With Acute Coronary Syndromes. *J Am Coll Cardiol* 2018;72:1989–99.
- 12 Sardella G, Lucisano L, Garbo R, *et al.* Single-atagated compared with multi-staged PCI in multivessel NSTEMI patients: the SMILE trial. *J Am Coll Cardiol* 2016;67:264–72.
- 13 Sels J-WEM, Tonino PAL, Siebert U, *et al.* Fractional flow reserve in unstable angina and non-ST-segment elevation myocardial infarction experience from the FAME (fractional flow reserve versus angiography for multivessel evaluation) study. *JACC Cardiovasc Interv* 2011;4:1183–9.
- 14 Layland J, Oldroyd KG, Curzen N, *et al.* Fractional flow reserve vs. angiography in guiding management to optimize outcomes in non-ST-segment elevation myocardial infarction: the British Heart Foundation FAMOUS-NSTEMI randomized trial. *Eur Heart J* 2015;36:100–11.
- 15 Wang TY, McCoy LA, Bhatt DL, *et al.* Multivessel vs culprit-only percutaneous coronary intervention among patients 65 years or older with acute myocardial infarction. *Am Heart J* 2016;172:9–18.
- 16 Giacoppo D, Madhavan MV, Baber U, *et al.* Impact of contrast-induced acute kidney injury after percutaneous coronary intervention on short- and long-term outcomes: pooled analysis from the HORIZONS-AMI and acuity trials. *Circ Cardiovasc Interv* 2015;8:e002475.
- 17 Zeitouni M, Silvain J, Guedeney P, *et al.* Periprocedural myocardial infarction and injury in elective coronary stenting. *Eur Heart J* 2018;39:1100–9.
- 18 Kobayashi Y, Lonborg J, Jong A, *et al.* Prognostic value of the residual SYNTAX score after functionally complete revascularization in ACS. *J Am Coll Cardiol* 2018;72:1321–9.
- 19 Kristensen SD, Laut KG, Fajadet J, *et al.* Reperfusion therapy for ST elevation acute myocardial infarction 2010/2011: current status in 37 ESC countries. *Eur Heart J* 2014;35:1957–70.
- *20 Ibanez B, James S, Agewall S. 2017 ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation the task force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Societ. *Eur Hear J* 2017.
- 21 Armstrong PW, Gershlick AH, Goldstein P, *et al.* Fibrinolysis or primary PCI in ST-segment elevation myocardial infarction. *N Engl J Med* 2013;368:1379–87.
- 22 Ndrepepa G, Kastrati A, Mehilli J, *et al.* Mechanical reperfusion and long-term mortality in patients with acute myocardial infarction presenting 12 to 48 hours from onset of symptoms. *JAMA* 2009;301:487–8.
- 23 Smits PC, Abdel-Wahab M, Neumann F-J, *et al.* Fractional flow reserve-guided multivessel angioplasty in myocardial infarction. *N Engl J Med* 2017;376:1234–44.
- *24 Mehta SR, Wood DA, Storey RF. Complete revascularization with multivessel PCI for myocardial infarction. *N Engl J Med* 2019;NEJMoa1907775.
- *25 Wald DS, Morris JK, Wald NJ, *et al.* Randomized trial of preventive angioplasty in myocardial infarction. *N Engl J Med* 2013;369:1115–23.
- 26 Baine KR, Engström T, Smits PC, *et al.* Complete vs Culprit-Lesion-Only revascularization for ST-segment elevation myocardial infarction: a systematic review and meta-analysis. *JAMA Cardiol* 2020;5:1–9.
- 27 Pavalasini 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.
- 28 Sanz-Sánchez J, Chiarito M, Regazzoli D, *et al.* Impact of complete revascularization on mortality in patients with ST-segment elevation myocardial infarction and multivessel disease: an updated meta-analysis. *J Cardiovasc Med* 2020;21:988–90.
- 29 Engström 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.
- 30 Claessen BEPM, van der Schaaf RJ, Verouden NJ, *et al.* Evaluation of the effect of a concurrent chronic total occlusion on long-term mortality and left ventricular function in patients after primary percutaneous coronary intervention. *JACC Cardiovasc Interv* 2009;2:1128–34.
- 31 Wood DA, Cairns JA, Wang J, *et al.* Timing of Staged Nonculprit Artery Revascularization in Patients With ST-Segment Elevation Myocardial Infarction: COMPLETE Trial. *J Am Coll Cardiol* 2019;74:2713–23.
- 32 Hanratty CG, Koyama Y, Rasmussen HH, *et al.* Exaggeration of nonculprit stenosis severity during acute myocardial infarction: implications for immediate multivessel revascularization. *J Am Coll Cardiol* 2002;40:911–6.
- 33 Marenzi G, Assanelli E, Campodonico J, *et al.* Contrast volume during primary percutaneous coronary intervention and subsequent contrast-induced nephropathy and mortality. *Ann Intern Med* 2009;150:170–7.
- 34 Smits PC, Laforgia PL, Abdel-Wahab M, *et al.* Fractional flow reserve-guided multivessel angioplasty in myocardial infarction: three-year follow-up with cost benefit analysis of the Compare-Acute trial. *EuroIntervention* 2020;16:225–32.
- 35 Puymirat E, Cayla G, Simon T. Multivessel PCI guided by FFR or angiography for myocardial infarction. *N Engl J Med*.
- 36 van der Hoeven NW, Janssens GN, de Waard GA, *et al.* Temporal changes in coronary hyperemic and resting hemodynamic indices in Nonculprit vessels of patients with ST-segment elevation myocardial infarction. *JAMA Cardiol* 2019;4:736–44.
- 37 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 Substudies. *Circ Cardiovasc Interv* 2020;13:e008768.
- 38 Kolte D, Khera S, Aronow WS, *et al.* Trends in incidence, management, and outcomes of cardiogenic shock complicating ST-elevation myocardial infarction in the United States. *J Am Heart Assoc* 2014;3:e000590.
- *39 Thiele H, Akin I, Sandri M, *et al.* One-year outcomes after PCI strategies in cardiogenic shock. *N Engl J Med* 2018;379:1699–710.