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. Percutaneous coronary intervention (PCI) of the culprit vessel remains the standard of care for patients presenting with ACS. 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 (NSTEACS), and is associated with worse clinical outcomes and increased mortality.

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 NSTEACS

Invasive coronary angiography plays a pivotal role in the management of patients presenting with NSTEACS. 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. 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).

When to revascularise patients presenting with NSTEACS

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). In addition, a trend towards a decreased mortality associated with an early invasive strategy has been shown in an individual patient data meta-analysis. This benefit was more pronounced in patients with elevated cardiac biomarkers, diabetes, a Global Registry of Acute Coronary Events risk score of >140 and an age of 75 years or older. However, a routine invasive strategy, compared with a selective invasive strategy, has been shown to increase the risk of periprocedural myocardial infarction and bleeding. 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. 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 NSTEACS with a timing based on individual risk stratification, as summarised in figure 2 and table 1. 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).

The recently published European Guidelines for the management of patients with NSTEACS have established a class I level A indication to undergo coronary angiography within 24 hours of hospital admission to high-risk patients presenting with NSTEACS. 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.
meta-analysis performed by Jobs et al. 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 NSTEACS and multivessel disease?
Completeness of revascularisation can be determined either on an anatomical (ie, successful revascularisation of all lesions of ≥50% diameter stenosis) or functional basis (ie, successful revascularisation of all lesions determining myocardial ischaemia in invasive or non-invasive diagnostic tests).

In the ACUITY trial, patients with NSTEACS 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). However, whether multivessel PCI offers incremental benefit over culprit-only PCI for patients presenting with NSTEACS and multivessel disease is unclear as data come only from observational studies. A recent observational cohort study, including 21 857 patients with NSTEACS 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. Ongoing large-scale randomised clinical trials will provide further evidence about the clinical impact of complete revascularisation in patients with NSTEACS with multivessel disease (table 2).

Coronary artery bypass grafting represents another revascularisation alternative for patients presenting with NSTEACS. 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 NSTEACS, the same criteria to guide the choice of revascularisation modality as in patients presenting with chronic coronary syndromes.

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

When should we complete the revascularisation in patients presenting with NSTEACS and multivessel disease?
The only randomised clinical trial assessing the best timing to complete the revascularisation in patients with NSTEACS with multivessel disease has been the SMILE trial. 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
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).

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

**Table 1** Risk stratification of patients presenting with NSTEACS

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

GRACE, Global Registry of Acute Coronary Events; MI, myocardial infarction; NSTEACS, non-ST-segment acute coronary syndrome.
### Table 2: Selected ongoing trials evaluating the timing, completeness and revascularisation strategies in patients presenting with ACS

<table>
<thead>
<tr>
<th>Study</th>
<th>NCT number</th>
<th>Design</th>
<th>Clinical setting</th>
<th>Treatment group</th>
<th>Control group</th>
<th>Primary outcome</th>
<th>Included patients (N)</th>
<th>Completion date*</th>
</tr>
</thead>
<tbody>
<tr>
<td>BIVASC</td>
<td>03621501</td>
<td>Multicentre open-label non-inferiority RCT</td>
<td>Patients with STEMI and NSTEACS with MVD</td>
<td>Immediate complete revascularisation (angiography/physiology guided)</td>
<td>Staged complete revascularisation (angiography/physiology guided)</td>
<td>All-cause death, MI, unplanned ischaemia-driven revascularisation and cerebrovascular events</td>
<td>1525</td>
<td>2021</td>
</tr>
<tr>
<td>FIRE</td>
<td>03772743</td>
<td>Multicenter prospective open-label RCT</td>
<td>Patients with STEMI and NSTEACS MVD aged ≥75 years</td>
<td>Functional complete revascularisation</td>
<td>IRA-only revascularisation</td>
<td>All-cause death, any MI, stroke or coronary revascularisation</td>
<td>1385</td>
<td>2021</td>
</tr>
<tr>
<td>FULL-REVASC</td>
<td>02862119</td>
<td>Multicentre prospective open-label RCT</td>
<td>STEMI/very high-risk NSTEACS with MVD</td>
<td>FFR-guided complete revascularisation during index hospital admission</td>
<td>Conservative management of non-culprit lesions during index hospital admission</td>
<td>All-cause death and MI</td>
<td>4052</td>
<td>2021</td>
</tr>
<tr>
<td>iMODERN</td>
<td>03298659</td>
<td>Multicentre prospective open-label RCT</td>
<td>Patients with STEMI with MVD</td>
<td>Immediate iFR-guided complete revascularisation</td>
<td>Deferred stress perfusion CMR-guided revascularisation</td>
<td>All-cause death, MI and hospitalisation for HF</td>
<td>1146</td>
<td>2021</td>
</tr>
<tr>
<td>OPTION STEMI</td>
<td>04626882</td>
<td>Multicentre prospective open-label RCT</td>
<td>Patients with STEMI with MVD</td>
<td>Immediate FFR revascularisation of non-IRA lesions with diameter stenosis 50%–70% by visual estimation†</td>
<td>In-hospital FFR revascularisation of non-IRA lesions with diameter stenosis 50%–70% by visual estimation†</td>
<td>All-cause death, MI or unplanned revascularisation</td>
<td>784</td>
<td>2024</td>
</tr>
<tr>
<td>Quantitative fractional ratio-guided revascularisation</td>
<td>04259853</td>
<td>Multicentre prospective RCT</td>
<td>Patients with STEMI with MVD</td>
<td>QFR-guided complete revascularisation</td>
<td>Angiography-guided complete revascularisation</td>
<td>All-cause death, MI, any revascularisation, hospitalisation for HF, stroke or major bleeding</td>
<td>1016</td>
<td>2022</td>
</tr>
<tr>
<td>RAPID-NSTEMI</td>
<td>03707314</td>
<td>Multicentre prospective open-label RCT</td>
<td>High-risk patients with NSTEACS</td>
<td>Immediate angiography</td>
<td>Standard of care angiography</td>
<td>All-cause death, MI and admission for HF</td>
<td>2314</td>
<td>2021</td>
</tr>
<tr>
<td>SAFE STEMI for Seniors</td>
<td>02939976</td>
<td>Multicentre prospective unblinded RCT</td>
<td>Patients with STEMI aged ≥60 years</td>
<td>FFR-guided complete revascularisation</td>
<td>IRA-only revascularisation</td>
<td>CVLPRIT-MACE§</td>
<td>875</td>
<td>2024</td>
</tr>
<tr>
<td>ISENOR-RITA</td>
<td>03052036</td>
<td>Multicentre prospective open-label RCT</td>
<td>Patients with type 1 NSTEACS aged ≥75 years</td>
<td>Invasive angiography and coronary revascularisation</td>
<td>Optimal medical therapy</td>
<td>CV death or non-fatal MI</td>
<td>1668</td>
<td>2022</td>
</tr>
<tr>
<td>SLIM</td>
<td>03562572</td>
<td>Multicentre prospective RCT</td>
<td>Patients with NSTEACS with MVD</td>
<td>Immediate FFR-guided complete revascularisation</td>
<td>Usual care non-IRA lesions by discretion of the physician</td>
<td>All-cause death, MI, any revascularisation and stroke</td>
<td>414</td>
<td>2021</td>
</tr>
</tbody>
</table>

*Estimated primary completion date.
†Non-IRA lesion which have ≥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; CuVRIT, 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; NSTEACS, non-ST-segment elevation acute coronary syndrome; RCIT, 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 NSTEACS (table 2).

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

A personalised approach for revascularisation of patients with NSTEACS 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 NSTEACS, 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. The FAMOUS-NSTEMI trial randomised 350 patients with NSTEACS with ≥1 coronary stenosis of ≥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. 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. 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. In addition, the presence of a residual angiographically assessed burden of coronary artery disease after physiological-guided complete PCI has shown to have no impact on prognosis in patients presenting with ACS and multivessel disease. Therefore, it is reasonable to consider a physiology-guided strategy to complete revascularisation in patients with NSTEACS 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. 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. 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). 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). 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).

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. Some trials have also demonstrated a reduction in myocardial infarction. 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. 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. 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...
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%±12.2% vs 44.8±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.

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 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%±12.2% vs 44.8±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.

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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.

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.
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).

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.33 29

The DANAMI-3-PRMULTI 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 (£81506 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 angiography-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 angiography-guided was not inferior 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%, respectively).39
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 NSTEACS 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.

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 NSTEACS 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.

Key messages

Patients presenting with non-ST-segment elevation acute coronary syndrome (NSTEACS)
► In high-risk patients presenting with NSTEACS, coronary angiography should be performed as soon as possible, within 24 hours from hospital admission.
► Revascularisation of non-culprit lesion in patients with NSTEACS 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 NSTEACS 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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