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ST elevation myocardial infarction and multi-vessel coronary artery disease: complete or incomplete revascularisation?

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SOUHRN

Nejnovější doporučené postupy pro léčbu infarktu myokardu s elevací úseku ST se jednoznačně vyslovují ve prospěch urychleného mechanického otevření uzavřené infarktové (culprit) koronární tepny. Probíhá však intenzivní diskuse ohledně léčby koronárních tepen se stenózami, které však nejsou tepnami, jejichž uzávěr vedl k akutnímu infarktu myokardu. Přestože údaje z retrospektivních studií a registrů naznačují, že by řešení mělo být ve druhém čase, je podle výsledků nedávno publikované randomizované studie výsledný stav pacientů při úplné revaskularizaci po dané primární PCI lepší. V našem článku se zabýváme touto spornou otázkou na základě analýzy nejnovějších a nejvýznamnějších publikací a předkládáme osobní názor podložený zkušenostmi z klinické praxe v našem centru.

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ABSTRACT

The most recent guidelines for the treatment of ST elevation myocardial infarction strongly support a prompt mechanical reopening of the occluded culprit coronary artery. However, there is a great debate regarding how to treat the bystander non-culprit coronary artery disease. While data from retrospective studies and registries suggest that it should be treated in a second staged procedure, a recent randomised study has suggested a better outcome for patients receiving complete revascularisation during the index primary PCI. In this paper we aim to address this controversial point, analysing the most recent and important scientific publications and trying to give a personal point of view according to the clinical practice in our institution.

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Introduction

ST elevation myocardial infarction (STEMI) represents the most challenging scenario among the spectrum of acute coronary syndromes: if the urgent flow restoration of the occluded coronary artery significantly reduces complications, decreases mortality and improves outcomes, conflicting data exist regarding the best management of bystander non-culprit lesions.

According to the available literature, the prevalence of significant multi-vessel coronary disease among patients with STEMI varies from 30% to 60% [1–4].

In the following pages we aim to address this controversial point, analysing the most recent and important scientific publications and trying to give a personal point of view according to the clinical practice in our institution.

What do the guidelines say

The 2012 European Society of Cardiology (ESC) guidelines on management of STEMI states that “Primary percutaneous coronary intervention (PCI) should be limited to the culprit vessel with the exception of cardiogenic shock and persistent ischaemia after PCI of the supposed culprit lesion – Class IIa of recommendation, Level of evidence A” [5].

The same approach is indicated by the more recent American Heart Association (AHA) guidelines, according to which “PCI is indicated in a noninfarct artery at a time separate from primary PCI in patients who have spontaneous symptoms of myocardial ischemia (Class I, Level C)”. Lower class of recommendation is given in case of “patients with intermediate or high-risk findings on noninvasive testing”, for whom “PCI is reasonable in a noninfarct artery at a time separate from primary PCI (Class IIa, Level C)” [6].

An important aspect to be taken into account, though, is that the recommendations coming from the cited guidelines are on the basis of retrospective or observational studies, while evidence from randomized studies are poor.

Data from retrospective studies and registries

Multi-vessel PCI in the same setting is worse than single-vessel PCI

To date, the largest dataset comes from the United States National Cardiovascular Data Registry. Cavender et al. [7] retrospectively analysed 31,681 patients with STEMI and multi-vessel coronary disease undergoing primary PCI between 2004 and 2007. The authors compared the outcome of patients undergoing multi-vessel PCI during the index catheterisation (N = 3134) with patients undergoing single-vessel PCI of the infarct related artery (IRA) (N = 25,802), after excluding patients who underwent staged PCI or left main PCI (N = 2745). Of note, the analysis included patients with cardiogenic shock, for whom current guidelines suggest, if possible, complete revascularisation. The overall in-hospital mortality rate was greater in patients undergoing multi-vessel PCI than the single-vessel PCI of the IRA group (7.9% vs 5.1%, $p < 0.01$). Interestingly, the same result was found considering only

the patients with cardiogenic shock, after adjusting for potential confounders (OR 1.54 [1.22–1.95 95% CI], $p < 0.01$). Adjusted analysis for patients without cardiogenic shock failed to prove a statistically significant increased mortality risk in the multi-vessel PCI group vs the single-vessel PCI group. Similar results come from another STEMI registry, the EUROTRANSFER, a multi-center European registry [8].

A post hoc analysis of the APEX-AMI (Assessment of Pexelizumab in Acute Myocardial Infarction) trial showed that PCI of the significant non-culprit lesion performed in the same setting of the index primary PCI has worse outcomes at 90 days follow-up than a single-vessel PCI of the IRA (12.5 vs. 5.6%, p [log-rank] < 0.001 for death and 17.4 vs. 12.0%, p [log-rank] = 0.020 for the composite endpoint of death/CHF/shock).

Different results come from a recently published analysis of the AMIS registry (Acute Myocardial Infarction in Switzerland) [9]. Even if the overall incidence of in-hospital mortality was significantly higher in the multi-vessel PCI group than in the group of single-vessel PCI of the IRA (7.3% vs 4.4%, $p < 0.001$), this difference disappeared after stratifying patients by risk (22.2% vs 21.7%, $p = 1.00$ in high risk patients and 2.0% vs 2.0% in low risk patients). Also, the study showed that multi-vessel disease STEMI patients who underwent complete revascularisation were more likely to have a higher risk profile (left-main involvement, out-of-hospital cardiac arrest or higher Killip class).

Staged multi-vessel PCI is better than one-time multi-vessel PCI

If registry data seem to be in favour of a single-vessel PCI of the IRA during the index procedure, a complete revascularisation seems to perform better when performed as a staged procedure.

A retrospective review of the New York State’s Percutaneous Coronary Interventions Reporting System analysed 4024 multi-vessel disease patients admitted with STEMI and undergoing primary PCI between 2003 and 2006 [10]. For patients without hemodynamic compromise, a single-vessel PCI of the IRA strategy was associated with lower in-hospital mortality than multi-vessel PCI during the index procedure (0.9% vs. 2.4%, $p < 0.04$). There was a lower mortality rate among patients who underwent staged PCI within 60 days after the index procedure than among patients undergoing single-vessel PCI of the IRA.

A recent analysis of an European registry, the Western Denmark Heart Registry, showed that multi-vessel PCI in the acute setting is associated with higher mortality than multi-vessel PCI performed in a staged fashion within 60 days after the index procedure [11]. Similar results came from a post hoc analysis of the HORIZONS-AMI trial, where multi-vessel PCI in the acute procedure was found to be significantly associated with higher 1-year mortality, cardiac mortality and stent thrombosis than a staged multi-vessel PCI [12].

Staged PCI for significant non-culprit lesions seems to guarantee better outcomes irrespective of when the staged procedure is performed. Indeed, Chen et al. [13] have demonstrated that in 561 multi-vessel disease STEMI patients a staged complete revascularisation significantly reduced 1-year mortality in comparison with single-

-vessel PCI of the infarct related artery (OR 0.29; 95% CI 0.15–0.53, $p < 0.0001$). The benefit was present when the staged PCI was performed either early (< 1 month from the index procedure) or late (< 6 months).

Data from randomised studies

Surprisingly, the data coming from the few randomised studies published so far go against the evidence cited in the previous paragraphs.

A 10-year-old study published by Di Mario et al. [14] showed that a multi-vessel treatment approach in the setting of primary PCI was safe in comparison with the approach of a single-vessel PCI of the IRA, with a similar rate of in-hospital major adverse cardiac events (0% in single-vessel PCI and 3.8% in multi-vessel PCI, $p = \text{NS}$). Nevertheless, the authors observed that, when only the culprit lesion was initially treated, the need for subsequent clinically driven revascularization remained low and no clinical or economical advantages were obtainable with a more aggressive initial approach. The absence of MACEs in the single-vessel PCI group and the low incidence in the multi-vessel PCI group don't reflect the common clinical practice and are explained by the very small population of the study ($N = 69$).

Politi et al. [15] randomised 214 consecutive patients with STEMI and multi-vessel disease to undergo either complete revascularisation during the index catheterisation, or single-vessel PCI of the IRA or staged multi-vessel PCI and follow them up for 2.5 years. The patients undergoing single-vessel PCI were more likely to experience major adverse cardiac events (MACEs) at follow-up than the other groups (50% vs. 20% vs. 23.1%, $p < 0.001$). No difference in terms of MACEs was observed among patients with multi-vessel PCI, either in the same or in a staged procedure.

In 2013 was presented the "Randomized Trial of Preventive Angioplasty in Myocardial Infarction" (PRAMI) [16]. In this multi-center UK-based trial, the authors enrolled 465 patients with multi-vessel coronary disease undergoing primary PCI. To be considered eligible, patients had to present with one or more stenoses of $> 50\%$ in the non-culprit artery and had to be suitable either for the preventive or no-preventive approach, according to operator's discretion.

Patients have been randomised to receive either multi-vessel PCI in the same setting of the primary PCI (preventive PCI group, $N = 234$) or infarct related artery only PCI (no preventive PCI group, $N = 231$). After the randomization the patients have been followed up for a mean time of 23 months to evaluate the incidence of the primary composite outcome of death from cardiac causes, nonfatal myocardial infarction or refractory angina.

The trial has been stopped prematurely because of the increased incidence of the primary endpoint in the preventive PCI group (HR in the preventive PCI group, 0.35; 95% confidence interval [CI], 0.21–0.58; $p < 0.001$). The preventive PCI strategy performed better for all the single components of the primary endpoint, except for the cardiac death outcome, where the difference among groups was not statistically significant.

However, several controversial aspects of the trial need to be highlighted. First, the decision of considering eligible a patient was entirely left to operator's discretion and that might have caused bias due to inter-observer variability and different personal practice. Before randomisation, 286 patients have been excluded because of the presence of left-main or equivalent disease, chronic total occlusion in the non-infarct artery or due to a failure in re-opening the infarct related artery (as per study protocol), while 269 patients have been excluded because the non-infarct artery was considered "unsuitable for PCI". What are the features that led the operators to judge those arteries not suitable for PCI? Without this information the suspect of the presence of an operator discretion-based bias is high. Second, the authors did not report the distribution of important elements which are well-known predictors of poor prognosis in STEMI (Killip class, anemia, maximum elevation in enzymes, door-to-balloon time, left ventricular ejection fraction, and creatinine level) [17]. Third, there are no details regarding the characteristics of the coronary lesions in the non-culprit arteries (a critical stenosis left in the proximal left anterior descending artery has worse prognosis in comparison with a critical stenosis in the distal right coronary artery) [18]. Fourth, no data are available regarding the outcome of the non-invasive functional tests performed in 81 patients of the no preventive PCI group and in 39 patients of the preventive PCI group. Fifth, a careful look to the medical treatment reveals that the majority of patients had just one single anti-ischemic agent (mainly beta-blockers). Since one of the endpoint was the presence of refractory angina, it is possible that not all the patients have been treated with optimal anti-anginal medical treatment. Finally, the strategy proposed by PRAMI seems to be unfeasible in the daily practice, especially in high-volume centres. Indeed, performing a multi-vessel PCI can significantly increase the duration of the procedure and that might represent an issue in case of other impending emergencies. This is especially true during the night shifts, where the on-call team's performance can be lower and the back-up in case of complications might be sub-optimal.

In conclusion, PRAMI has the indisputable merit to be the biggest trial trying to address a topic for which very few randomised data are available. Nevertheless, we believe that, in presence of bystander angiographically significant coronary artery disease, the option of medical treatment only is not appropriate. It does not reflect the common clinical practice, where, if doubts regarding bystander lesions arise during the index procedure, patients are sent for functional tests to assess inducible ischemia rather than being left on medical treatment alone.

Data from meta-analyses

In 2011 Vlaar et al. retrospectively reviewed 40,280 with STEMI and multi-vessel coronary artery disease undergoing PCI. The following strategies have been evaluated: (1) IRA only PCI, (2) multivessel PCI in the index procedure and (3) staged PCI for the significant non-culprit lesions. The authors reported a clear benefit for the staged PCI strategy as regards the primary endpoint of short-term

mortality, compared with the single-vessel PCI of the IRA strategy (OR 3.03, 95% CI 1.41–6.51, $p < 0.005$) and with the multi-vessel PCI strategy (OR 5.31, 95% CI 2.31–12.21, $p < 0.0001$) [19].

A more recent meta-analysis confirmed this concept: in case of STEMI and multi-vessel disease, a complete revascularisation strategy during the primary PCI was associated with an increased in-hospital mortality (OR 1.35, 95% CI 1.19–1.54, $p < 0.001$). On the contrary, a multi-vessel PCI performed in a staged-fashion resulted in a reduced in-hospital mortality (OR 0.35, 95% CI 0.21–0.59; $p < 0.001$; p interaction < 0.001) [20].

Importantly, the above discussed meta-analyses did not include PRAMI results.

Our personal point of view

Finding the best treatment in the STEMI setting is challenging.

The presence of more potent antithrombotic agents along with a more diffuse adoption of the radial approach to reduce bleeding, opens new options to improve patients' outcomes. As regards the culprit lesion, the clinical context of STEMI and the extensive thrombotic burden may require a combination of mechanical and aggressive pharmacological approach. The recently published DEFER-STEMI trial [21] has proven an interesting concept. The authors have demonstrated that, after the mechanical flow restoration in the culprit artery, leaving the patients on GpIIb/IIIa inhibitors + low molecular weight heparin and deferring stenting in a second staged procedure reduced the risk of no-reflow and increased the myocardial salvage in comparison with an immediate stenting strategy. Nevertheless, 2 out of 52 patients in the deferred PCI group experienced a re-occlusion of the infarct related artery and this outcome highlights the major limitation of this strategy.

As regards the non-culprit lesions, if a complete revascularisation before the discharge seems to be an obvious strategy in case of a patient with a critical bystander proximal LAD stenosis and long-standing history of angina preceding the myocardial infarction (Fig. 1), the choice becomes more difficult in case of intermediate bystander coronary artery disease in patients with no

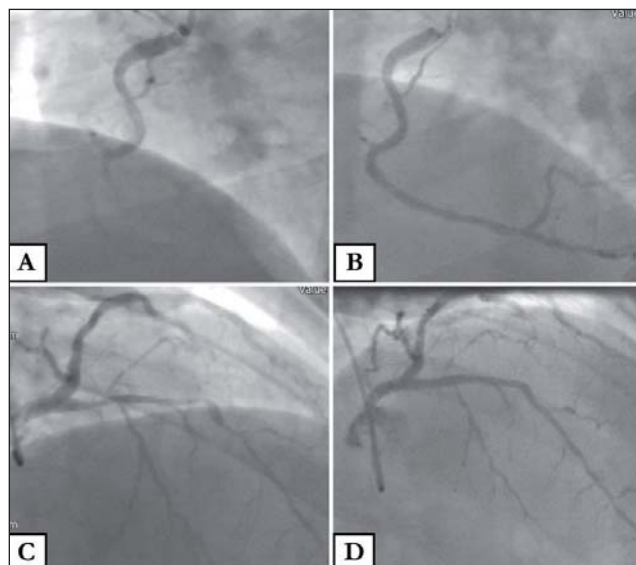


Fig. 1 – A 52-year-old man admitted with an inferior ST elevation myocardial infarction underwent a successful primary PCI to his right coronary artery (panels A and B). A bystander critical stenosis in the mid left anterior descending artery was then successfully treated with a staged PCI 5 days later after the index presentation (panels C and D).

previous cardiac history or symptoms. The key decisional factor in the latter case is represented, in case of asymptomatic patients, by the proof of inducible ischemia on functional tests, where the PCI option is superior to medical treatment only [22].

The decision is even more challenging because the visual angiographic inspection has been demonstrating its weakness as a predictor of either the functional significance or subsequent cardiovascular events in asymptomatic patients.

The FAME trial (Fractional Flow Reserve versus Angiography for Guiding Percutaneous Coronary Intervention) [23] has demonstrated the superiority of the fractional flow reserve-guided approach over the angiographic-guided approach in stable patients with multi-vessel coronary artery disease: 2-year rates of mortality or myocardial infarction were 12.9% in the angiography-guided group and 8.4% in the FFR-guided group ($p < 0.02$). Interestin-

Table 1 – Ongoing randomised studies in STEMI patients with multi-vessel PCI.^a

CVLPRIT (UK)	N = 300	Complete in-hospital revascularisation versus culprit only + conservative strategy
PRAGUE-13 (Czech Republic)	N = 400	Complete staged revascularisation versus culprit only + conservative strategy
CROSS-AMI (Spain)	N = 400	Complete staged revascularisation versus culprit only + stress echo guided revascularisation
COCUA (Korea)	N = 646	Complete acute revascularisation versus culprit only + staged revascularisation strategy
COMPARE-ACUTE (Europe and Asia)	N = 885	FFR guided complete (sub) acute revascularisation versus culprit only + conservative strategy
DANAMI-III (Denmark)	N = 2000	3 × 2 factorial design – culprit vessel PCI with DES versus culprit vessel thrombectomy with balloon angioplasty – primary PCI with or without post conditioning – complete revascularisation versus culprit only
COMPLETE (USA and Canada)	N = 3900	Complete revascularisation (acute or staged) versus culprit only + conservative strategy

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gly, 37% of the lesions judged significant on the angiographic assessment (> 50% of stenosis) had an FFR of less than 0.80.

An FFR-guided approach for non-culprit lesions in primary PCI and multi-vessel coronary artery disease could be a feasible and valid approach but needs to be validated by big randomised trials [24,25].

As shown by Stone et al. in the PROSPECT trial (Providing Regional Observations to Study Predictors of Events in the Coronary Tree) [26], over a follow-up of 3 years, only the 11.6% of 697 patients with acute coronary syndrome and bystander coronary artery disease developed a subsequent major adverse cardiovascular event caused by any of the non-culprit lesions. More importantly, the majority of these lesions were mild (less than 30% stenosis) on the basis of visual assessment at the index angiography.

In our centre, the treatment for STEMI patients with multi-vessel coronary artery disease doesn't differ from what is recommended by the current guidelines and follows a careful "patient-tailored" approach. Excluding the very complex cases with cardiogenic shock, we don't tend to perform a multi-vessel PCI during the index catheterisation, where we "just" aim to restore flow in the culprit artery and stabilise the culprit lesion.

The following step to treat by-stander coronary artery disease can be either completing the revascularisation during the index hospitalisation or re-assessing the angina burden at an early follow-up visit or, if needed, performing a functional test in order to guide any further intervention.

Future perspectives

Several ongoing randomised studies (Table 1) will definitely provide a great contribution to this topic [27]. Hopefully, they will give an answer to the current unmet needs in the the treatment of STEMI patients with multi-vessel coronary artery disease.

Conflict of interests

The authors have no relevant conflicts of interest to declare.

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Ethical statement

This research was done according to ethical standards.

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