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Multi-vessel revascularization in ST-segment elevation myocardial infarction: where do we stand?

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A third to half of ST-segment elevation myocardial infarction (STEMI) patients present with angiographically significant lesions in non-culprit vessels.[1] There is solid evidence that timely reperfusion of the culprit vessel improves survival.[2] However, the management and revascularization strategy for stenosis in non-culprit vessels is still debated. Indeed, current guidelines were mostly based on observational data, which suggest possible harm of multi-vessel revascularization in STEMI patients. As such the AHA/ACC guidelines discouraged revascularization of non-culprit lesions (class III),[3] but recently changed the recommendation[4] to class IIb in accordance with the ESC guidelines, which were less stringent (class IIb).[5] The results of recently reported randomized trials have challenged these recommendations (*Table 1*).

Novel evidence

In the PRAMI trial,[6] 465 STEMI patients with multi-vessel disease, who were undergoing infarct-artery percutaneous coronary intervention (PCI), were randomized to either preventive PCI or no preventive PCI of non-culprit vessels. After a median follow-up of 23 months, the results were considered conclusive and the trial was stopped prematurely. The primary endpoint, a composite of death from cardiac causes, non-fatal myocardial infarction, or refractory angina, occurred considerably more often in patients without preventive PCI (hazard ratio in the preventive PCI group, 0.35; 95% confidence interval: 0.21–0.58; $P < 0.001$).

A similar result was observed in the CvLPRIT trial,[7] which randomized 296 STEMI patients to complete (64% ad-hoc and 36% staged during the same admission) or culprit-lesion-only revascularization. The primary endpoint, a composite of all-cause death, recurrent myocardial infarction, heart failure, and ischaemia-driven revascularization within 12 months, again occurred less often in completely revascularized patients (hazard ratio: 0.45; 95% confidence interval: 0.24–0.84; $P = 0.009$).

Recently, the PRAGUE-13 trial was presented at EuroPCR 2015 in Paris, France, and the results of the randomized DANAMI3-PRIMULTI trial[8] were published. In the PRAGUE-13 trial, 214 STEMI patients with double or triple vessel disease were randomly assigned to culprit-lesion-only PCI or complete revascularization (non-culprit vessel PCI as a staged procedure within 3–40 days after the index event). Patients with stable angina more than 1 month before primary PCI were not included in that trial. Contrary to the previous trials, the investigators found no significant difference in the primary endpoint, a composite of all-cause mortality, non-fatal myocardial infarction, and stroke, between complete vs. incomplete revascularization. Interestingly, none of the non-culprit lesions progressed to myocardial infarction during a median follow-up of 38 months.

Finally, in the larger DANAMI3-PRIMULTI trial,[8] 627 STEMI patients with multi-vessel disease were randomized after infarct-related artery PCI to either medical management or fractional flow reserve (FFR) guided complete revascularization. The primary endpoint, a composite of all-cause mortality, non-fatal myocardial infarction, or ischaemia driven revascularization of non-culprit lesions, occurred less often in patients with FFR-guided complete revascularization (hazard ratio: 0.56; 95% confidence interval: 0.38–0.83; $P = 0.004$). However, these results were mainly due to ischaemia driven revascularization and not related to a reduction of hard endpoints such as death or myocardial infarction.

However, a recent meta-analysis of randomized controlled trials of complete vs. infarct-related artery PCI in STEMI patients suggested a reduction in all-cause mortality with complete revascularization.[9] Unfortunately, the two most recently reported trials were not included in this meta-analysis.

Which lesions should be treated?

Most non-culprit lesions detected in STEMI patients are asymptomatic and do not cause any or little ischaemia. However, cardiologists may get carried away by the visual aspects of the stenosis and the instantaneous rewarding result of a successful PCI (i.e. *the oculo-stenotic reflex*). The primary goal of PCI, however, is reduction of ischaemia. If a lesion does not cause ischaemia, then PCI is not

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Table 1 Major randomized controlled trials comparing complete vs. culprit lesion only revascularization in patients presenting with ST-segment elevation myocardial infarction and multi-vessel coronary artery disease

	PRAMI[6]	CvLPRIT[7]	DANAMI3-PRIMULTI[8]	PRAGUE-13
Sample size (n)	465	296	627	214
Median follow-up (months)	23	12	27	38
Primary endpoint (% complete vs. incomplete; HR with 95% CI)	9 vs. 23 0.35 (0.21–0.58)	10 vs. 21.2 0.45 (0.24–0.84)	13 vs. 22 0.56 (0.38–0.83)	16 vs. 13.9 1.35 (0.66–2.74)
All-cause mortality (% complete vs. incomplete; HR with 95% CI)	5 vs. 7 (ns, HR not reported)	1.3 vs. 4.1 0.32 (0.06–1.6)	4 vs. 5 1.4 (0.63–3.0)	5.7 vs. 6.5 0.91 (0.3–2.7)
Myocardial infarction (% complete vs. incomplete; HR with 95% CI)	3 vs. 8.6 0.32 (0.13–0.75)	1.3 vs. 2.7 0.48 (0.09–2.62)	5 vs. 5 0.94 (0.47–1.9)	10.4 vs. 7.4 1.71 (0.66–4.41)
Repeat revascularization (% complete vs. incomplete; HR with 95% CI)	6.8 vs. 19.9 0.30 (0.17–0.56)	4.7 vs. 8.2 0.55 (0.22–1.39)	5 vs. 17 0.31 (0.18–0.53)	Not published yet

CI, confidence interval; CvLPRIT, Complete vs. Lesion-only Primary PCI trial; DANAMI3-PRIMULTI, The third DANish study of optimal Acute treatment of patients with ST-segment elevation Myocardial Infarction: PRImary PCI in MULTIvessel disease; HR, hazard ratio; PRAMI, Preventive Angioplasty in Acute Myocardial Infarction trial.

beneficial, but rather increases costs and may indeed be harmful. While interventionalists focus on coronary arteries, the true target organ is not the blood vessel but the heart muscle. Percutaneous coronary intervention is justified, if the myocardium is ischaemic at rest or during exercise or any other stress, and PCI for this particular lesion is expected to reduce ischaemia with a favourable risk–benefit ratio.

If a STEMI patient with multi-vessel disease was asymptomatic before the index event, then the likelihood that the non-culprit lesion causes ischaemia is very slim (a fact considered in the inclusion criteria of the PRAGUE-13 trial). Of note, especially in intermediate grade lesions, angiographic assessment of coronary artery stenosis does not consistently predict myocardial ischaemia. Therefore, justification of PCI in previously asymptomatic non-culprit vessels has to be firmly based.

Fractional flow reserve is a technique to assess the haemodynamic significance of a stenosis based on physics.[10] It is applicable in patients with acute coronary syndromes and helps omit unnecessary PCI in non-flow-limiting lesions.[10] When the clinical situation permits a staged approach, other non-invasive ischaemia tests and imaging modalities such as perfusion MRI, nuclear scan, positron emission tomography, or stress echo may be performed to assess non-culprit vessel coronary artery stenosis.

When is the best timing for non-culprit lesion revascularization?

All the above-mentioned trials were not designed or sufficiently powered to assess differences in hard endpoints between staged vs. ad-hoc complete revascularization. As in some trials the time-event curves of complete vs. culprit-lesion-only revascularization started separating within days of the index procedure, this was taken as an argument for the superiority of ad-hoc complete revascularization. However, the exposure to additional nephrotoxic contrast dye, the risk of PCI complications in non-culprit vessels as well as the uncertainty of lesion significance and, on the other hand, the risk of access site-related complications during a staged procedure should be weighed against the potential benefits of complete revascularization.[11] Current guidelines recommend staged PCI (i.e. within days to weeks) of significant non-culprit lesions in patients with STEMI. However, in patients with ongoing ischaemia despite successful culprit lesion revascularization or in those with haemodynamic instability, there is widespread agreement that instantaneous complete revascularization should be performed (*Figure 1*).

Upcoming trials

The largest trial addressing this very issue is the currently recruiting COMPLETE trial (NCT01740479), which will randomize 3900 STEMI patients with multi-vessel disease in North America and Europe to culprit-lesion-only or staged complete revascularization. This study may definitely confirm or refute the hypothesis generated by the PRAMI[6] and CvLPRIT[7] trials; however, as non-culprit PCI will only be performed during staged procedures, the COMPLETE trial will not answer the question whether a single or staged revascularization procedure is preferable.

The COMPARE-ACUTE trial (NCT01399736) is based on FFR measurements in the non-culprit vessels, but aims at single procedure multi-vessel revascularization. Finally, the CROSS-AMI trial (NCT01179126) was designed to compare stress echo-guided revascularization vs. an angiography-based strategy.

Summary

In summary, current evidence suggests that it appears to be better to do something rather than nothing. However, the question of single vs. staged complete revascularization, the best timing of the staged PCI (during the index admission or within weeks) and the question of stratification for evidence of ischaemia remain to be answered in upcoming trials. Meanwhile, complete revascularization should not be routinely performed ad-hoc, but based on individual and careful patient and lesion assessments.

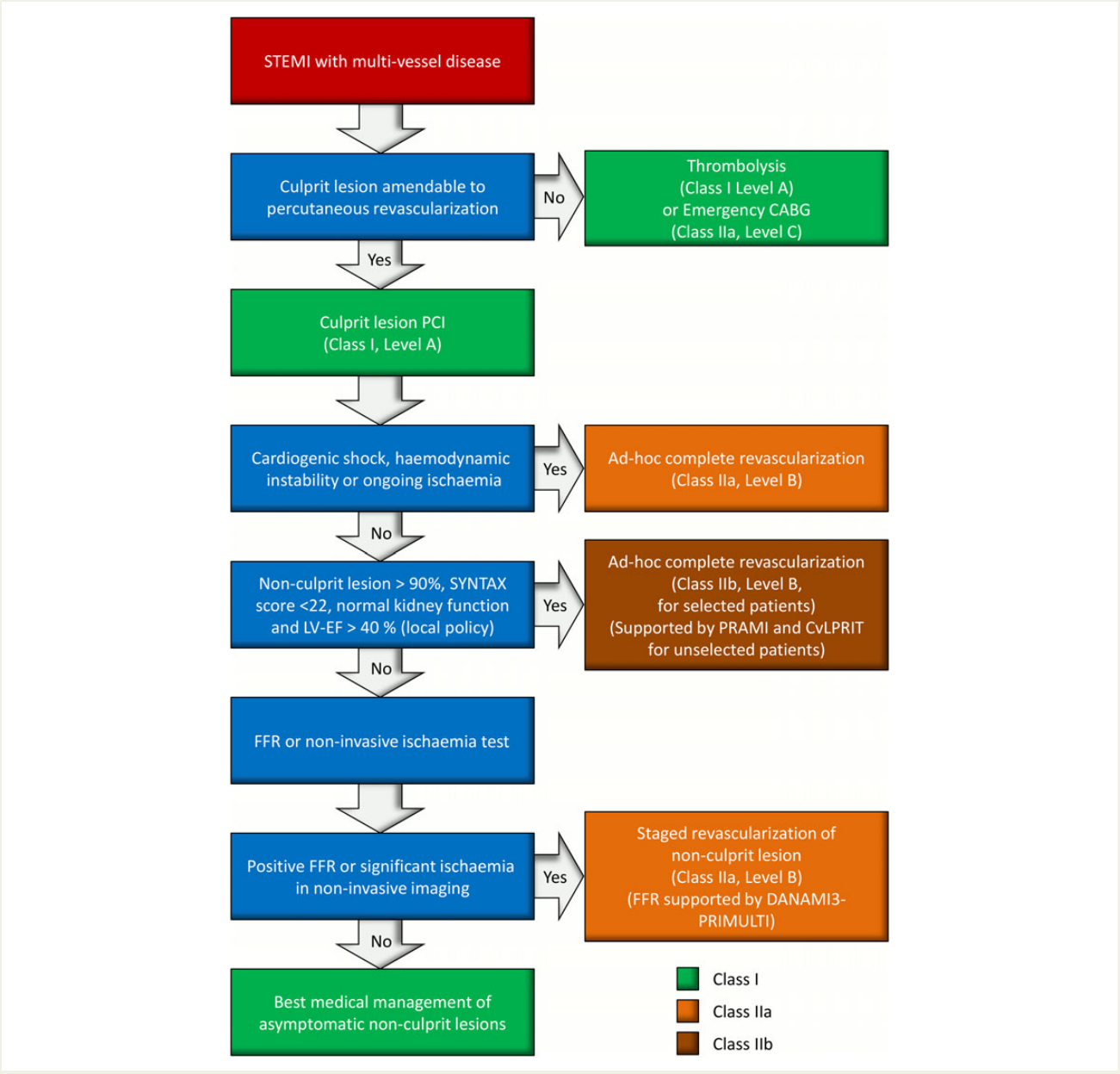

Figure 1 Proposed management algorithm for patients with ST-segment elevation myocardial infarction and multi-vessel coronary artery disease at the University of Zurich based on current evidence. Ad-hoc complete revascularization in patients with multi-vessel disease presenting with ST-segment elevation myocardial infarction is routinely performed in patients in cardiogenic shock, in haemodynamically unstable patients or when signs of ongoing ischaemia persist. In all other patients, the revascularization strategy is based on anatomical and clinical factors including lesion characteristics and evidence of ischaemia by invasive or non-invasive testing. Recommendation classes are based on current European Society of Cardiology guidelines.[5] CABG, coronary artery bypass grafting; FFR, fractional flow reserve; LV-EF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

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