Editorial Commentary

Complete revascularisation in STEMI: consider the benefits but do not forget the risks!

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Multivessel disease is a common scenario in ST elevation myocardial infraction (STEMI) patients and up to 50% of them may have additional angiographically severe lesions in non-culprit coronaries (1,2). Patients with extensive disease in vessels other than the infract related artery (IRA) are known to have inferior prognosis compared with the patients with single-vessel disease (3,4). While the benefits of treating the culprit artery and restoring coronary flow have been extensively and conclusively documented, the evidence of whether to treat other angiographically significant lesions in asymptotic patients outside the IRA or not is less convincing. Indeed, it may be argued that complete revascularisation of significant non-IRA might prevent recurrent ischaemia and adverse cardiac events, while a common counterargument is that this approach might cause periprocedural myocardial infarction (MI) potentially leading to larger infract size and worst prognosis.

Four major randomised trials have tried to assess the risks and benefits of complete versus incomplete revascularisation in STEMI patients undergoing primary PCI (*Table 1*). Preventive angioplasty in acute myocardial infarction (PRAMI) trial assigned 465 multivessel disease patients to undergo either preventive PCI (234 patients) or no preventive PCI (231 patients). At an average follow-up of 23 months, preventive PCI in the non-IRA with stenosis ≥50% (i.e., based on lumen narrowing assessed at the time of index angiogram) was associated with lower rates of the compound primary endpoint of death, myocardial infraction, or refractory angina (9% versus 23%) (HR 0.35, 95% CI: 0.21–0.58; P<0.001) (5). Notably, this is the only study, which observed a strong trend towards a possible mortality benefit in patients who underwent angiography-based complete revascularisation and a significant reduction of recurrent MI.

In complete versus lesion-only PRimary PCI pilot study (CvLPRIT) trial, 296 patients have been assigned to either complete revascularisation (n=150) or culprit lesion only primary PCI (n=146). The timing of complete revascularization was after the primary PCI (P-PCI) or during the same hospital stay and as in PRAMI the decision to revascularise or not the non-culprit lesions was based on angiography. The primary endpoint was a compound of death, recurrent MI, heart failure, and ischemia-driven revascularization. The complete revascularisation group was associated with lower rates of the primary endpoint within a 12-month period (10.0 % versus 21.2%) (HR 0.45, 95% CI: 0.24–0.84; P=0.009) (6). In this study, the benefit of complete revascularisation was apparently driven by each component of the primary endpoint being numerically even if not statistically significant lower in the experimental group.

The third Danish study of primary PCI in patients with ST-elevation MI and multivessel disease: treatment of culprit lesion only or complete revascularization

(DANAMI-3-PRIMULTI) was the third randomised study to become available. In this study, 627 patients were assigned to only IRA-only revascularisation or FFR-guided complete revascularisation. The primary endpoint at a mean follow up of 27 months, was a compound of all-cause mortality, non-fatal myocardial re-infarction, and ischaemia-driven revascularization of lesions other than the IRA artery and occurred in 68 (22%) patients who had IRA PCI only and in 40 (13%) patients who had complete revascularization (HR 0.56, 95% CI: 0.38–0.83; P=0.004). This advantage was driven mainly by a reduction in repeat revascularization (7), without a cleat impact on mortality or MI rates.

Finally, the Fractional Flow Reserve-Guided Multivessel Angioplasty in Myocardial Infarction (Compare-Acute) trial enrolled 885 patients with STEMI and multivessel disease to FFR-guided complete revascularisation or culprit lesion only treatment. A reduction of the primary endpoint (death, MI, revascularization, or stroke) was observed with multivessel PCI (HR 0.35, 95% CI: 0.22–0.55; P<0.001), which was driven mainly by a reduction in the need for revascularization at a later time point by non-IRA FFR-guided revascularization (8).

A recent meta-analysis of 10 trials (but not included the Compare-Acute study) demonstrated that complete revascularization was related with a lower risk of MACE (RR 0.57, 95% CI: 0.42–0.77). This benefit was driven by a lower risk of urgent revascularization (RR 0.44, 95% CI: 0.30–0.66), while there was no significant difference in mortality (RR 0.76, 95% CI: 0.52–1.12) or spontaneous MI (RR 0.54, 95% CI: 0.23–1.27) (9).

The recent 2018 ESC/EACTS Guidelines on myocardial revascularization (10) recommend that routine complete revascularization should be considered in patients with multivessel disease during the same hospital stay (Class IIA, Level of evidence A). Similarly, the 2015 ACC/AHA/SCAI recommendations (11), suggest that non-IRA PCI may be considered in selected hemodynamically stable patients with STEMI and multivessel disease, either during primary PCI or as a staged procedure.

Whether complete revascularisation after STEMI in multivessel disease patients improves LV function and volumes remains unclear. In addition, the risks of inducing peri-procedural MI when attempting at completing revascularisation has not been well documented so far.

The recent publication of the Cardiac Magnetic Resonance Sub-study of the DANAMI-3-PRIMULTI (12) adds new pieces of the puzzle, which, however, does not yet come together. A non-randomly selected group of 280 patients (136 patients with IRA PCI and 144 with complete FFR-guided revascularization) underwent CMR before receiving (or not receiving) complete revascularisation and at 3 months. The final infract size, myocardial salvage index, LV ejection fraction (LVEF) and LV end-systolic volume (LVESV) remodelling were similar between the two groups. Interestingly, new non-culprit infarctions were numerically more common in the complete revascularization group [6 (4.5%) versus 1 (0.8%); P=0.12]. Therefore, this study may actually suggest that the risks of complete revascularisation, in terms of peri-procedural MI, may outweigh or at least counterbalance its possible benefit on LV function and volumes.

However, one may argue that three month-time frames is rather short to allow detecting significant different in LV remodelling. No proper sample size calculation was performed to justify the number of included patients; therefore, study power remains an issue. Moreover, whether FFR or angiography should be used to guide compete revascularisation is still unclear. In the early stage of acute MI, disturbed microvascular function might affect the reliability of FFR measurements. Microvascular dysfunction in the culprit territory is quite often due to distal thrombus embolization and vasoconstriction. This may lead to impaired hyperaemic flow in the non-culprit myocardium, possibly leading to underestimation of real FFR values in the acute setting. Studies using positron-emission tomography and Doppler flow have tested this hypothesis and presumed that during MI the non-infarcted myocardium is also affected (13,14). However, other studies suggest that FFR measurements in non-culprit vessels of patients with myocardial infraction are consistent and therefore FFR may be used to guide revascularization in the acute setting of a STEMI (15,16).

Prior to the DANAMI-3-PRIMULTI Cardiac Magnetic Resonance Sub-study, two similar sub-studies have been designed in order to assess the impact of multivessel PCI in LV parameters, using CMR (*Table 2*). In the CvLPRIT CMR sub-study, 203 patients (98 complete revascularization and 105 IRA-only) evaluated with CMR. There was no difference in the total median infarct size between the two groups. Notably, there were more non-IRA MIs in the complete revascularization group (22 of 98 versus 11 of 105; P=0.02) and also in this study there was no detectable effect of complete revascularisation on infarct size or LV volumes (17). 84 patients have been investigated with CMR within the PRAMI Trial (18). Consistently with

Table 1 Differences among randomized controlled trials evaluating multivessel revascularization in STEMI

Trial	Year	n	IRA only revascularization, n	Timing of non-IRA revascularization	Ad hoc complete revascularization, n	Staged complete revascularization, n	Trigger for non-IRA revascularization	Primary endpoint† (%)		F/U (months)
								Complete revascularization group	IRA only group	
PRAMI (5)	2013	465	231	During the P-PCI	234	N/A	Angiography driven (>50% stenosis)	9	23	23
CvLPRIT (6)	2015	296	146	Either during the P-PCI or before hospital discharge	97	42	Angiography driven (>70% stenosis)	10	21	12
DANAMI-3-PRIMULTI (7)	2015	627	313	2 days after P-PCI	N/A	314	FFR guided	13	22	27
Compare-Acute (8)	2017	885	590	Mainly during the P-PCI (some cases during the index hospitalization and preferably within 72 hours)	136	27	FFR guided	7.8	20.5	12

†, primary endpoints were: a compound of death, MI, or refractory angina in PRAMI , a compound of death, recurrent MI, heart failure, and ischemia-driven revascularization in CvLPRIT, a compound of all-cause mortality, non-fatal re-infarction, and ischaemia-driven revascularization in DANAMI-3-PRIMULTI and a compound of death, non-fatal MI, revascularization, and cerebrovascular events in Compare-Acute trial. STEMI, ST elevation myocardial infraction; P-PCI, primary PCI; IRA, infract related artery; F/U, follow-up.

Table 2 Differences among randomized controlled trials evaluating LV volumes, ejection fraction, remodelling and peri-procedural MI

First author	Year	n	CMR complete revascularization group	CMR IRA group	Baseline CMR	Follow up CMR	Baseline median total infract size (% LVM)		Follow up LVEF (%)		Periprocedural related MI (%)	
							Complete group	IRA group	Complete group	IRA group	Complete group	IRA group
McCann *et al.* (17)	2015	205	98	105	At a median of 3 days post P-PCI	9 months	13.5	12.6	49.7	50.8	23.8	11.2
Mangion *et al.* (18)	2016	84	42	42	During the first week post-MI	7 months (mean period)	14.6	15.6	54.4	51.7	4.8	0
Kyhl *et al.* (12)	2019	280	144	136	1-day post P-PCI	3 months	15%	16%	59%	58%	4.5	0.8

CMR, cardiovascular magnetic resonance; P-PCI, primary PCI; IRA, infract related artery; LVEF, left ventricular ejection fraction; MI, myocardial infraction; F/U, follow-up.

other evidence, the infarct size (% LV mass) at baseline and follow-up did not differ in the two study groups. However, in this study the incidence of peri-procedural MI in the preventive PCI group was uncommon (4.8%), may reflect the patient selection more than the real risks of competing revascularisation in an unselected patient population.

Therefore, no single study has so far shown an effect of complete revascularisation in STEMI patients on LV mechanics or remodelling whereas all studies have shown a sizable, yet variable, risk of peri-procedural MI. The prognostic implication of clinically silent CMR-detected MI is unclear. Yet, the benefit of complete revascularization in patients with STEMI and multivessel disease should be counterbalanced against a coexisting risk for periprocedural myocardial infraction.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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